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New Functionalised 3-Hydroxypyridines

By

Richard William John Chubb

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Thesis submitted in accordance with the requirements of the University of Durham for the degree of Doctor of Philosophy

June 2001

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Finally I especially wish to thank Emma, Mark and my mother for their support, encouragement and love over the last two years.

To my parents

Abstract

This thesis is concerned with the synthesis and reactions of functionalised 3-hydroxypyridines, in particular 2-aryl- and 2-heteroaryl-3-hydroxypyridines by non-coupling methodology, from furan precursors. Chapter 1 reviews the synthesis and reactions of 3-hydroxypyridines. Chapter 2 describes the synthesis of 2-acylfurans *via* differing methods, which include acylation of the furan nucleus, Grignard reactions of furaldehydes and, most notably, reaction of lithiofurans with reagents containing a nitrile component. Chapter 3 concerns reaction of acylfurans with ammonia at high pressure and temperature to produce 3-hydroxypyridines. We have found that this ring expansion is able to withstand many differing substituents including bromine. Further development of the pyridine ring system involves reaction of the ring atoms or substituents, including protection of the hydroxy group.

This ring expansion was used in the development of a novel azabenzotriazole starting from a simple furan compound, and this is reported in Chapter 4.

The methodology described in this thesis is versatile and has allowed access to a range of novel pyridine derivatives in synthetically useful quantities which should be of interest in many areas of organic chemistry.

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CHAPTER 1

Introduction

1.1 Introduction

This project is concerned with the synthesis of novel highly functionalised pyridines from simple furan derivatives. Pyridines are key building blocks in the fine-chemical industry for pharmaceutical and agrochemical agents. There are many attractions in using the furan derivatives as starting materials;

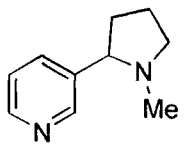
1. The rearrangement of 2-acylfurans and other derivatives into 3-hydroxypyridines is known to proceed in high yield, while being both cheap and easy to perform on the bench, or in large scale reaction vessels;
2. Highly functionalised furans can be easily synthesised or are commercially available;
3. The rearrangement of furans to 3-hydroxypyridines is versatile in both the number and type of subsituents on the rings.

1.2 Pyridines in Nature

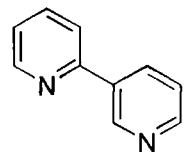
A number of pyridine compounds can be found in nature, principally among the alkaloids and the enzyme co-factors. Pyridine itself was first isolated in the pure state by Anderson[1] from bone oil in 1849. The established molecular formula showed it to be a tertiary base capable of forming quaternary salts.

1.2.1 Alkaloids

Only a few alkaloids are derived from a monocyclic aromatic pyridine system, the most notable being the tobacco alkaloids which comprise a group of ten bases of known structure and their oxygenated derivatives. This family of compounds includes nicotine (**1**)[2] and 2,3'-bipyridine (**2**)[3], both of which have been isolated from tobacco.



(1)

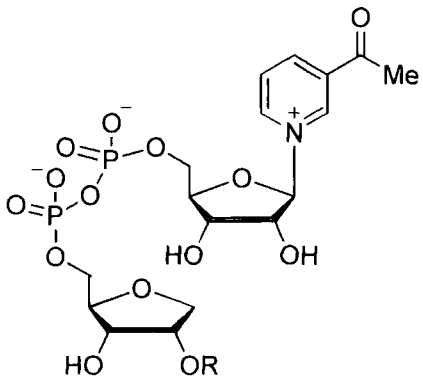


(2)

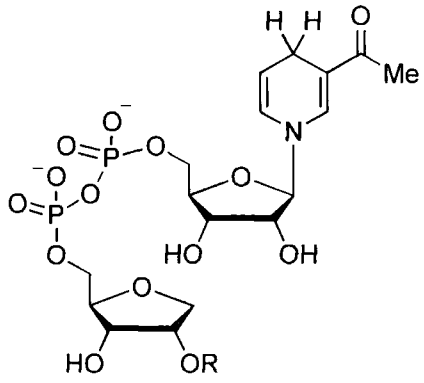
Nicotine (**1**) has been used as an anthelmintic, but it is more widely used as an agricultural insecticide, functioning as a contact poison when combined with oleic acid or a stomach poison with bentonite.[4] Interestingly, it has been recently reported that nicotine patches and gum may be beneficial to sufferers of Parkinson's and Alzheimer's diseases, which are neurodegenerative in their effects.[5]

1.2.2 Enzyme Co-factors

Enzyme co-factors have been found in all animal and plant tissues so far examined and are derived from either nicotinic acid or Vitamin B_6. Pyridine-3-carboxyamide (nicotinamide) occurs in the structure of the co-enzyme nicotinamide adenine dinucleotide (NAD^+) (**3a**) and the phosphate derivative ($NADP^+$) (**3b**). These act as oxidising agents giving the reduced forms NADH (**4a**) and NADPH (**4b**) respectively, in enzymatic processes.



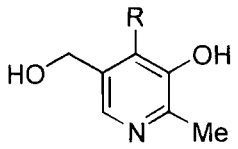
(**3a**) R=H
(**3b**) R=$PO(OH)_2$

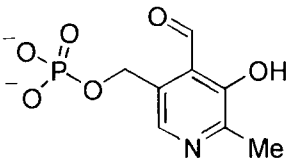


(**4a**) R=H
(**4b**) R=$PO(OH)_2$

The B_6 vitamins comprise a group of three compounds (**5a-c**) all of which are converted to pyridoxol phosphate (**6**) in tissue. The pyridine ring plays an important

role in metabolism in two ways. Firstly, as (**6**), in reactions of amino acids including racemisation, decarboxylation, transamination and elimination or replacement of substituents of the β or γ carbon atoms.[6] Secondly, as a co-enzyme, NAD^+ partakes in biological redox reactions.[7]





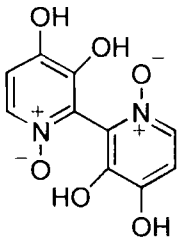
(**5a**) Pyridoxol R=CH_2OH
(**5b**) Pyridoxal R=CHO
(**5c**) Pyridoxamine R=CH_2NH_2

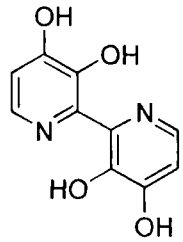
(**6**)

Pyridoxol (**5a**) was first isolated from rice bran as the hydrochloride salt by several co-workers.[8,9,10] Total synthesis by Harris and Fulkers[11] confirmed the assigned structure as that of a 2,4,5-trisubstituted-3-hydroxypyridine.

1.2.3 3-Hydroxypyridines

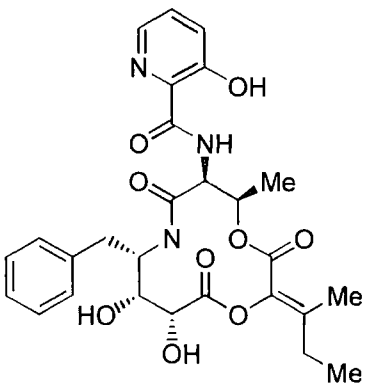
In 1952, a massive fatal poisoning occurred in Poland from the mushroom *Continarius Orellanus* Fries.[12] The toxic compound was identified as orellanine (**7**), which decomposes on heating to the non-toxic orelline (**8**). Antkowiak and Gessner[13] discovered that (**7**) is the *N*-oxide of (**8**), which has a 3,3',4,4'-tetrahydroxy-2,2'-bipyridyl structure. Tiecco *et al.*[12] achieved the total synthesis of orellanine starting from 3-hydroxypyridine.





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

The 3-hydroxypyridine ring system can be found in many alkaloids having biological activity of interest, for example the antibacterial agent pyridomycin (**9**).[14]



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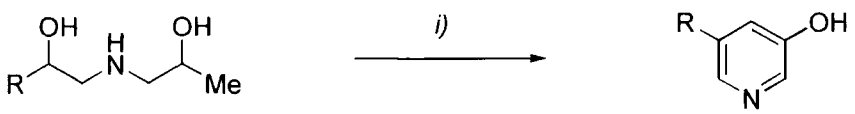
1.3 Synthesis of 3-Hydroxypyridines

1.3.1 Acyclic Precursors

1.3.1.1 Nitrogen Containing Chains

These involve a carbon-carbon bond formation as a necessity for the ring closure. 3-Hydroxypyridine (**11a**) and its 5-methyl derivative (**11b**) were prepared by vapour phase treatment of dialkanolamines (**10a**, **10b**), using a catalyst of copper, nickel and chromium in a hydrogen atmosphere at elevated temperatures (~350°C).[15] The yield for the reaction is low (~10%) when R=H, but if R=Me the yield increases (42%).



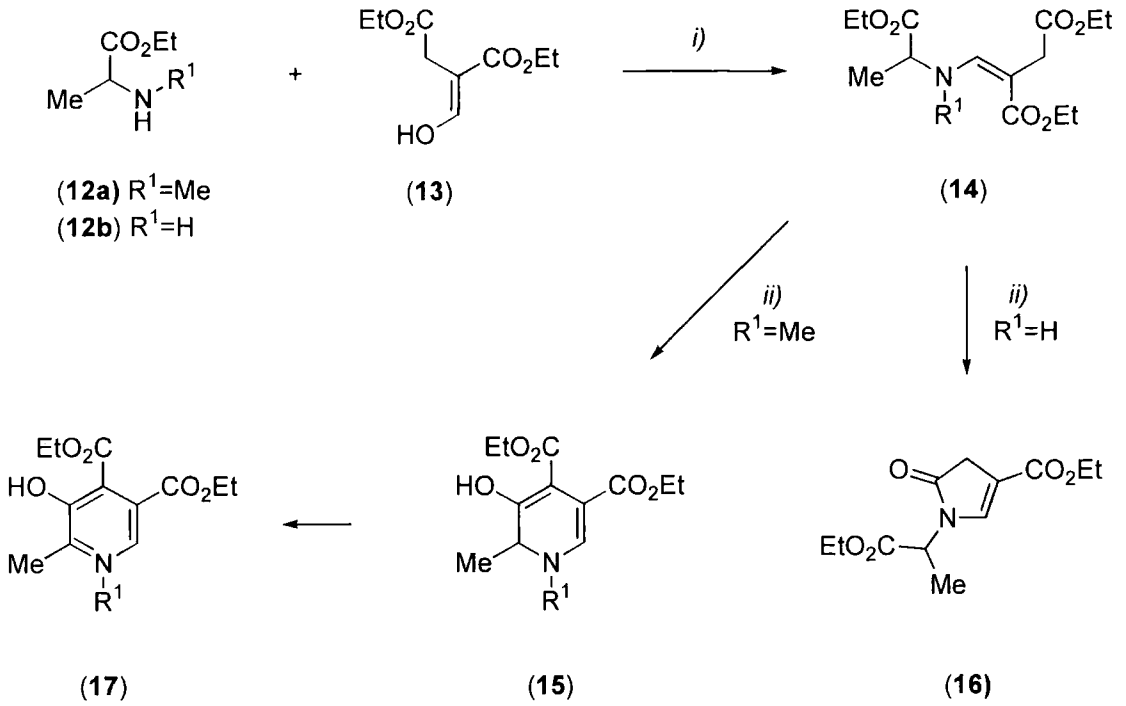
(**10a**) R=H
(**10b**) R=Me

(**11a**) R=H
(**11b**) R=Me

Scheme 1.1 *Reagents and Conditions: i) Cu catalyst (containing Ni and Cr), 350°C, H_2*

Several dihydropyridinols have also been prepared, *via* a method developed by Cohen,[16] which requires heating a mixture of an α-aminoester (**12a**, **12b**) and ethyl α–(hydroxymethylene)succinate (**13**). This leads to an ester (**14**), which cyclises in the presence of sodium, sodium ethoxide or sodamide (Dieckmann reaction) to give

the dihydropyridinol (**15**) or the lactam (**16**), depending on the alkyl group R^1. Further reaction of (**15**) gives the 3-hydroxypyridine (**17**) in 15% overall yield.

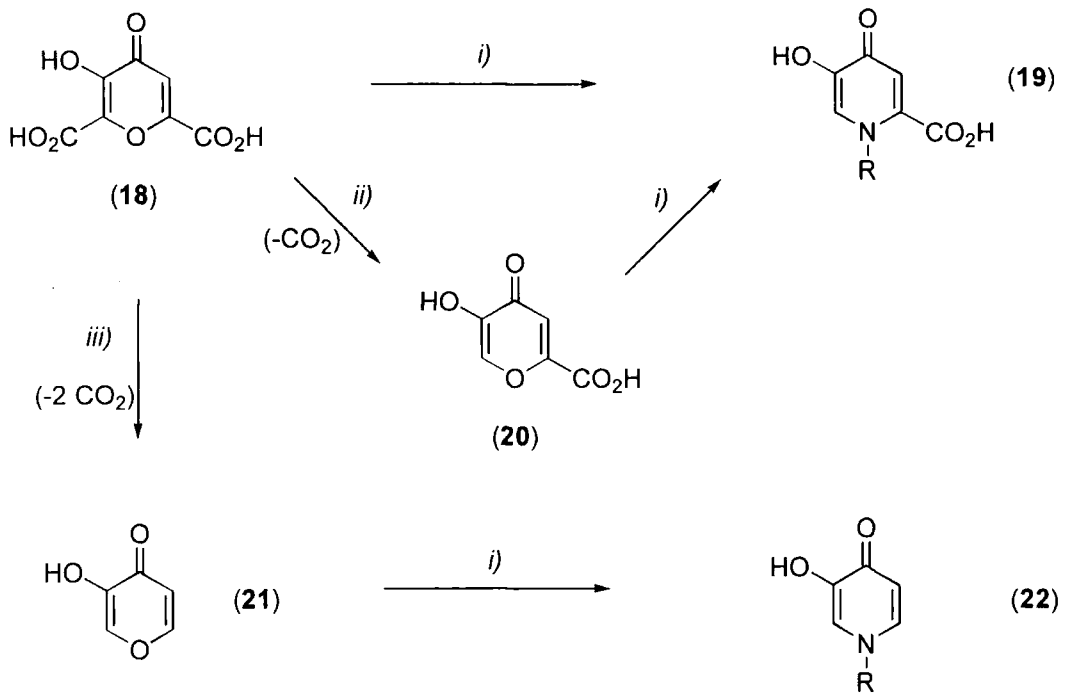


Scheme 1.2 *Reagents and Conditions: i) 90°C, 1h; ii) Reflux with Na, NaOEt or* $NaNH_2$ *in benzene*

1.3.2 Cyclic Precursors

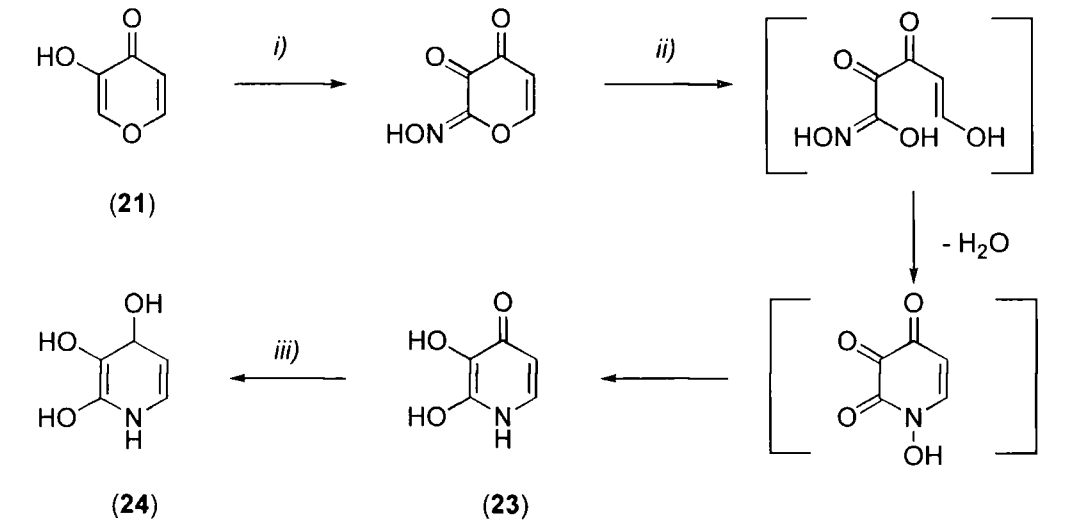
1.3.2.1 γ-Pyrones

Treatment of meconic acid (**18**) with concentrated ammonia[17] or alkylamines (R=CH_3, C_2H_5, *iso*-C_3H_7)[18,19] gives *N*-substituted comenamic acids (**19**), with one decarboxylation (15-40%). The yield can be increased by first decarboxylating, by heating in dilute hydrochloric acid, to give comenic acid (**20**), which can then be reacted with the amines producing higher yields (60-70%).[20] Complete decarboxylation to pyromeconic acid (**21**) and reaction with methyl-[21], ethyl-, propyl-, and *i*-propylamines[19], as well as 2-aminomethyl acetal[22], gives *N*-substituted-3-hydroxy-4-pyridones (**22**).



Scheme 1.3 *Reagents and Conditions: i) RNH_2, 110°C, 8-10h; ii) Dil. HCl, 40-50°C, 2h; iii) Conc. HCl, 80°C*

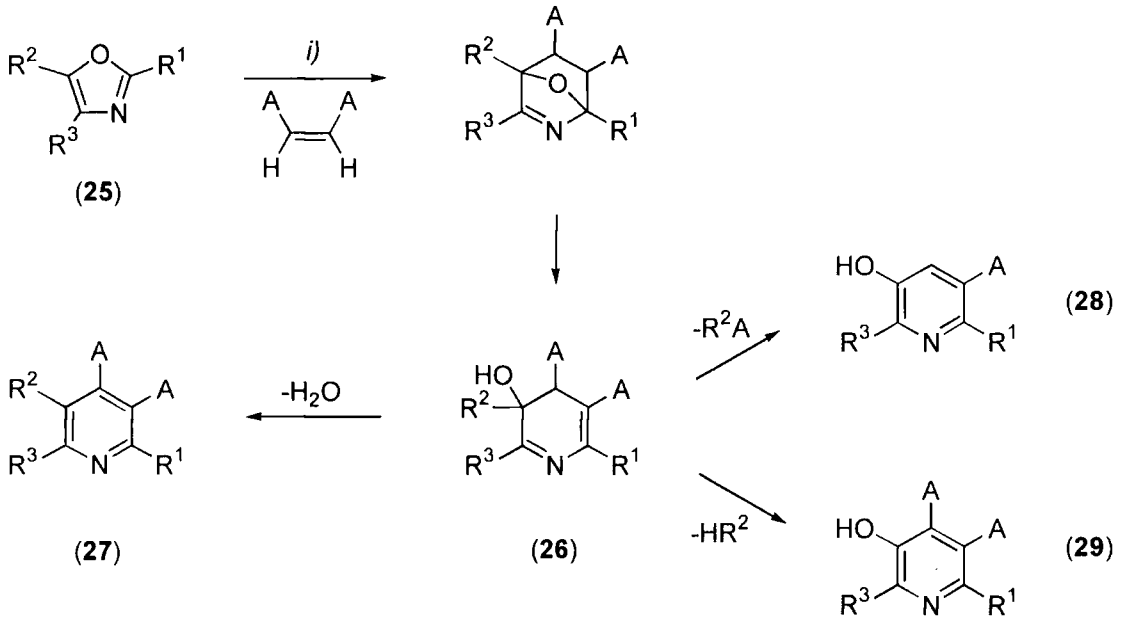
A unique reaction which does not require ammonia or amines to form the nitrogen ring is the nitrosation of pyromeconic acid (**21**).[23] The intermediate rearranged during reduction with sulfur dioxide to give 1,2-dihydroxy-4-(*1H*)-pyridone (**23**). Further reduction of (**23**) with tin and hydrochloric acid gave 2,3,4-pyridintriol (**24**) in 23% yield.



Scheme 1.4 *Reagents and Conditions: i) N_2O_3; ii) SO_2; iii) Sn, HCl*

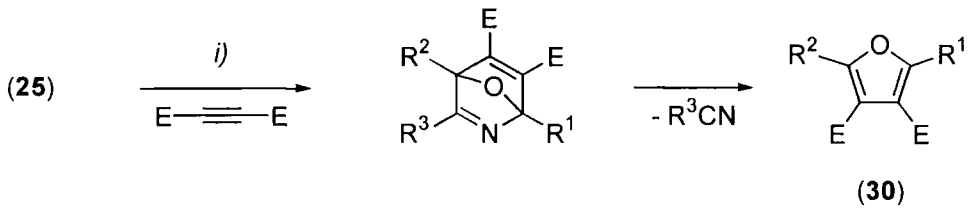
1.3.2.2 Cycloaddition Reactions

Certain oxazoles (**25**) react as 2-azadienes, giving adducts with dienophiles, which *via* various eliminations give pyridines.[24,25] These reactions were investigated in the course of research directed towards pyridoxine. The nature of the leaving group depends on the substituents but most commonly it is ethanol, as 5-ethoxyoxazoles are activated towards addition. The general order for activation of oxazoles to substitution is alkoxy > alkyl > 4-phenyl > acetyl > ethoxycarbonyl >> 2- or 5-phenyl. The cycloaddition is regioselective; reaction with acrylates or acrylonitriles leads to intermediate (**26**), which through elimination gives the 4-substituted pyridines (**27**) and (**29**) or the 4-hydropyridine (**28**).



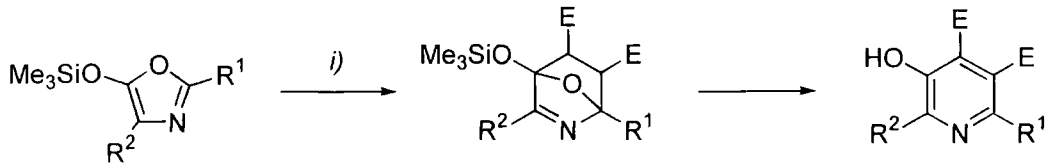
Scheme 1.5 *Reagents and Conditions: A=Electron withdrawing group; i) 90°C*

Reaction of (**25**) with alkynes leads to an intermediate which readily loses the nitrile fragment in the elimination step to give a tetrasubstituted furan derivative (**30**).[26]



Scheme 1.6 *Reagents and Conditions: E=CO_2Me; i) Toluene, 110°C*

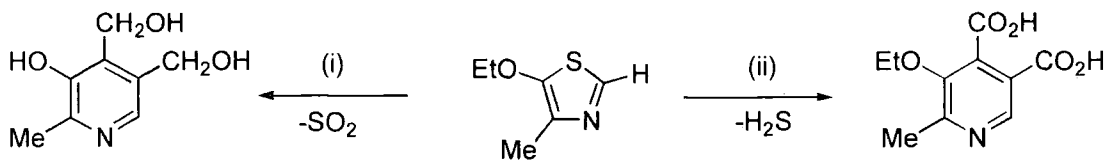
The trimethylsilyloxy substituent exemplifies a good leaving group: reaction of the oxazole (**31**) gives a high yield of the 3-hydroxypyridine (**32**),[27] which can be easily converted into pyridoxin derivatives.



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

Scheme 1.7 *Reagents and Conditions: i) Dimethyl maleate*

The thiazole (**33**) undergoes the analogous Diels-Alder reaction. The initial adduct is treated with dilute hydrochloric acid; loss of sulfur dioxide gives pyridoxine (**34**) and loss of hydrogen sulfide gives the corresponding 3-ethoxypyridine (**35**),[28] by analogy to the oxazole system.



(**34**) (**33**) (**35**)

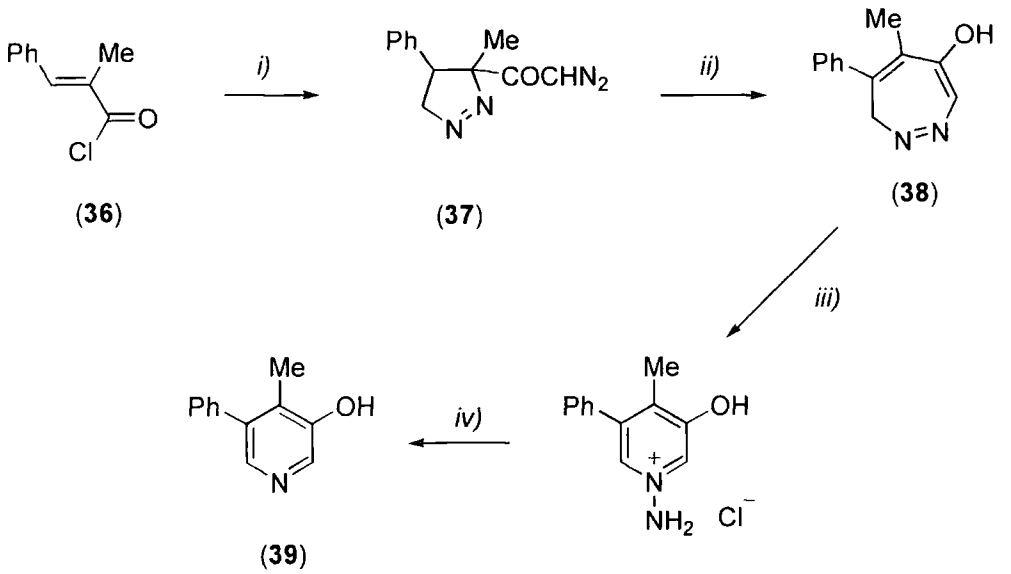
Scheme 1.8 *Reagents and Conditions: i) 2-Butyne-1,4-diol, $PhNO_2$, $AlCl_3$, 100°C, then HCl, H_2O; ii) Dimethyl maleate, 200°C, then HCl, H_2O*

1.3.2.3 7-Membered Rings

1.3.2.3.1 Diazepines

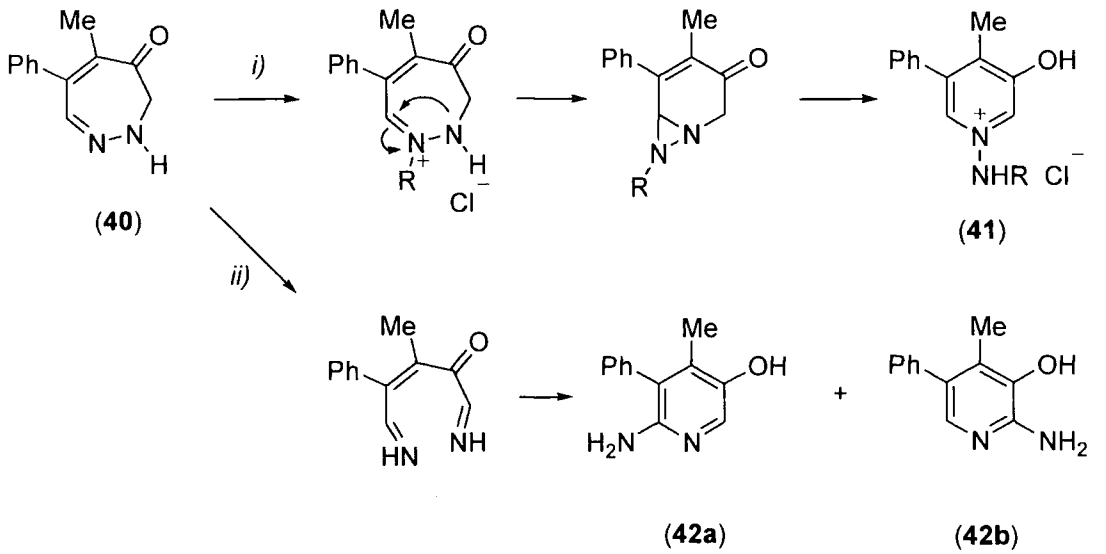
A novel scheme[29] to 3-hydroxypyridines starts from the reaction of acid chloride (**36**) with diazomethane giving 3-diazoacetyl-3-methyl-4-phenylpyrazoline (**37**), which is rearranged in acetic acid, with loss of nitrogen, to 4-hydroxy-5-methyl-6-phenyl-(*7H*)-1,2-diazepine (**38**). In warm hydrochloric acid (**38**) rearranges to the pyridinium

salt, which is deaminated with nitrous acid to give the free base, 3-hydroxy-4-methyl-5-phenylpyridine (**39**) in 42% overall yield.



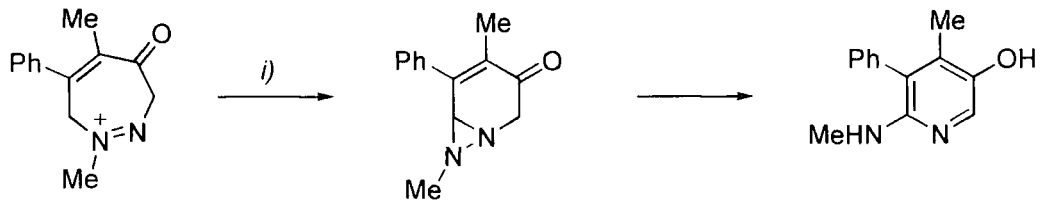
Scheme 1.9 *Reagents and Conditions: i) CH_2N_2; ii) Acetic acid, 70°C; iii) Warm HCl (20%), then 1 eq. NaOH; iv) HNO_2*

Diazepine-3-one derivative (**40**) undergoes rearrangment with carbocations to give the 3-hydoxypyridinium derivative (**41**). However, with bases it gives a mixture of products (**42a**, **42b**), arising from the ring closure of the intermediate diimine. The mechanisms are discussed at length.[30]



Scheme 1.10 *Reagents and Conditions: i) R^+; ii) Base*

The 1-methyldiazepine (**43**) is converted by photolysis into the same pyridine (**42a**) in 43% yield as that obtained by treatment with base. The intermediate (**44**) has been postulated.[31]

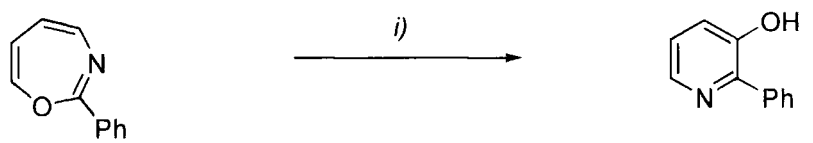


(**43**) (**44**) (**42a**)

Scheme 1.11 *Reagents and Conditions: i) hv*

1.3.2.3.2 Oxazepines

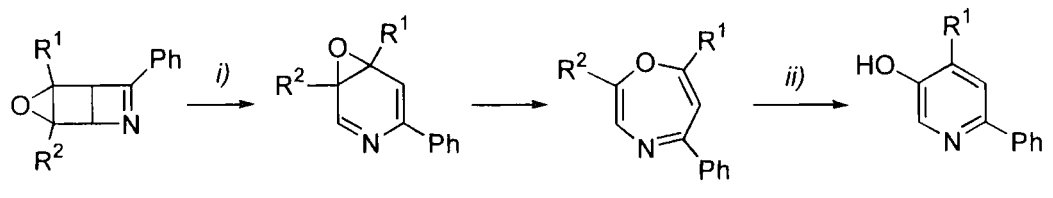
The 1,3-oxazepine (**45**) is thermally labile, 3-hydroxy-2-phenylpyridine (**46**) is the main product (23% yield); some N-formyl-2-phenylpyrrole (14%) is also obtained.[32]



(**45**) (**46**)

Scheme 1.12 *Reagents and Conditions: i) 450°C in benzene in a sealed tube*

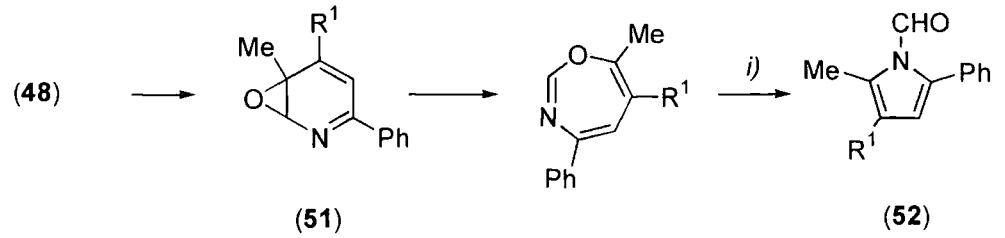
The 3-hydroxypyridine (**50**) has also been synthesised from the 1,4-oxazepine (**49**).[33] This 7-membered ring is made by irradiation of 2-azabicyclo[*2.2.0*]hex-5-ene (**47**), which is itself prepared from pyridine (by treatment with phenylmagnesium bromide in the presence of benzylchloroformate, followed by irradiation).[34]



(**47**) (**48**) (**49**) (**50**)

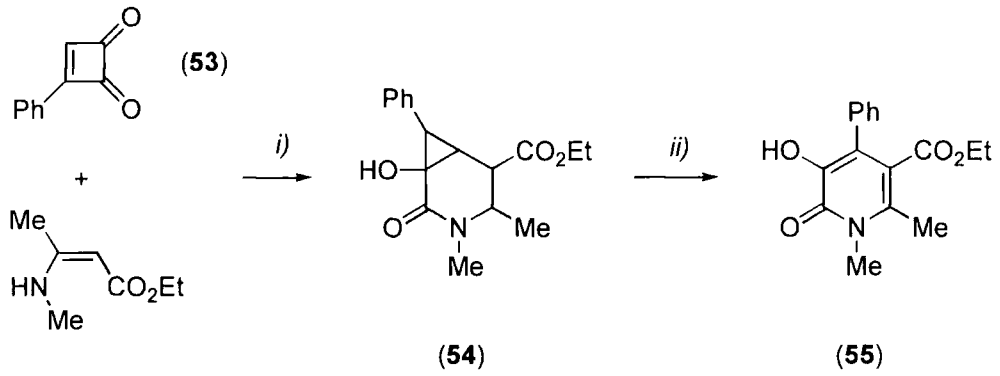
Scheme 1.13 *Reagents and Conditions: i) hv, CH_3CN, 15 min; ii) Toluene, 110°C*

If R^2 is hydrogen then heating of (**48**) gives the 7-membered ring (**49**). Further heating gives the 3-hydroxypyridine (**50**). However, if R^2 is a methyl group, the epoxide rearranges giving (**51**), on heating this gives the pyrrole (**52**).



Scheme 1.14 *Reagents and Conditions: i) Toluene, 100°C*

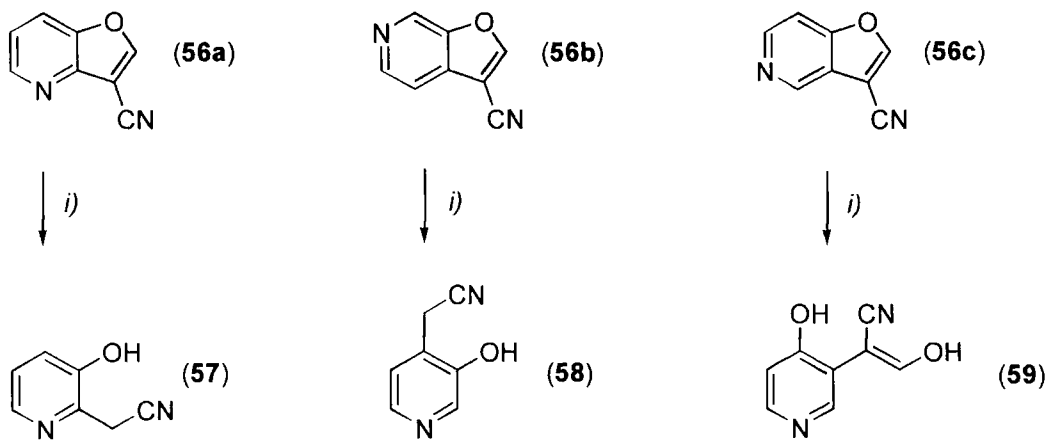
A similar reaction involves heating phenylcyclobutadione (**53**) with an enamine, giving the intermediate (**54**). Addition of base to (**54**) gives the 3-hydroxypyridin-2-one (**55**).[35]



Scheme 1.15 *Reagents and Conditions: i) 40-50°C; ii) NaOH*

1.3.2.4 Furopyridines

Nucleophilic substitution of 3-bromofuropyridines with copper cyanide in dimethylformamide gives the 3-cyano derivatives (**56a-c**). Alkaline hydrolysis[36] of (**56a**) gives 2-cyanomethyl-3-hydroxypyridine (**57**), (**56b**) gives 4-cyanomethyl-3-hydroxypyridine (**58**) and (**56c**) gives the 4-hydroxypyridine (**59**) in 66%, 68% and 85% yields, respectively.



Scheme 1.16 Reagents and Conditions: i) KOH, aq. Ethanol, 60°C

1.3.2.5 Synthesis From Pyridines

This is the most versatile route for the synthesis of hydroxypyridines. However, the 2- and 4-positions of pyridine are the most susceptible to nucleophilic attack: this conclusion can be reached by looking at the resonance structures of the intermediates. In the case of attack at the 2- and 4- positions the resulting negative charge can be delocalised onto the electronegative nitrogen, but attack at the 3-postion leads to this negative charge being distributed only on carbon. Thus displacements at the 3-position are very much slower.

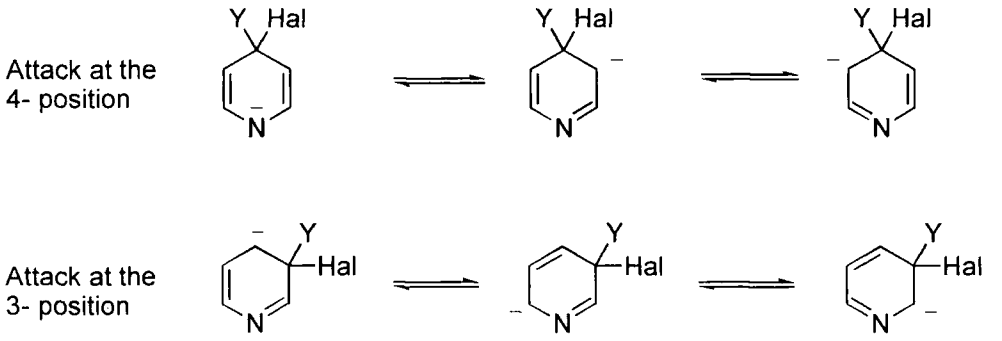


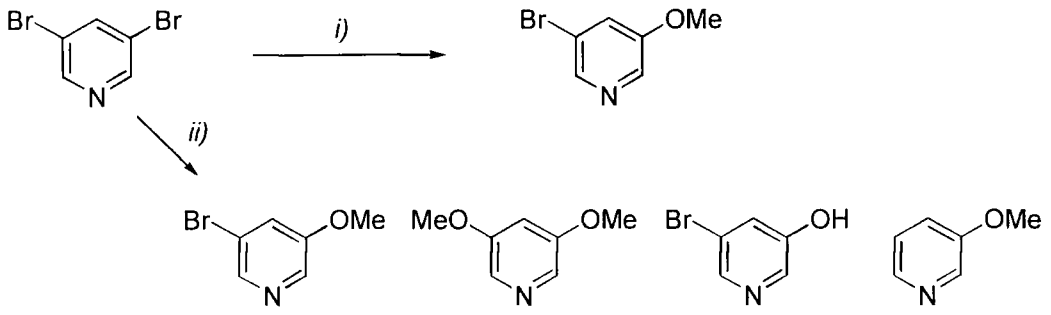
Fig. 1.1 Nucleophilic substitution of pyridine

1.3.2.5.1 Halo Compounds

3-Hydroxypyridine can be made, in 20% yield, from the 3-bromo derivative by reaction with aqueous sodium hydroxide at 200°C with copper sulfate as a catalyst.[37]

The less severe conditions for the reaction compared to the Dow process,[38] which makes phenol at 350°C, shows that the ring nitrogen does exert some activating influence on the 3-position, but much less than the 2- or 4- cases.

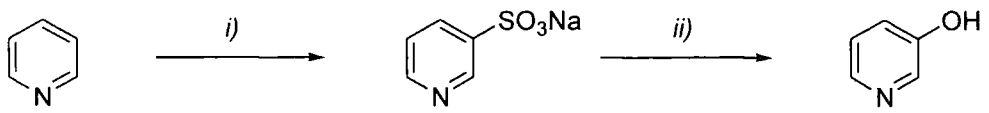
3,5- or 2,6-Dihalopyridines undergo displacement to give monohaloethers and diethers. Weidel and Blau[39] obtained 3,5-dimethoxypyridine (40%) and 5-methoxy-3-hydroxypyridine (10%) from the reaction of 3,5-dibromopyridine and sodium hydroxide in methanol. Subsequent repetition of the experiment led to isolation of 3-bromo-5-methoxypyridine.[40] When the reaction is performed in a sealed tube at 110°C, a number of products can be isolated, among them 3-bromo-5-hydroxypyridine (**60**) in 16% yield.[41]



Scheme 1.17 *Reagents and Conditions: i) CH_3ONa, CH_3OH, Cu, Reflux; ii) CH_3ONa, CH_3OH, Cu, 110°C*

1.3.2.5.2 Sulfonic Acids

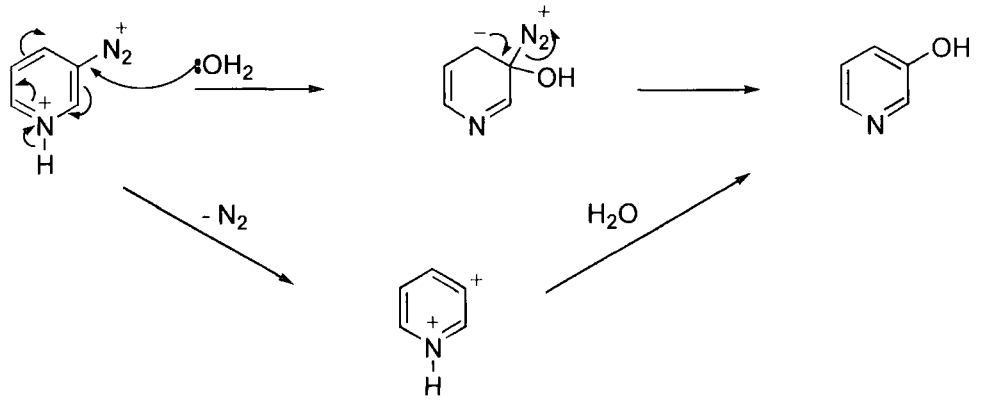
Alkali fusion of pyridinesulfonic acids is a useful synthesis of 3-hydroxypyridines; the weak base, sulfite ion, is easily displaced by the strong base, hydroxide ion. This is the conventional method for the synthesis of 3-hydroxypyridine[42,43] and most applicable to the 3-isomer due to difficulties in making the 2- or 4- sulfonic acids.



Scheme 1.18 *Reagents and Conditions: i) 100% H_2SO_4, $HgSO_4$, 330°C; ii) NaOH*

1.3.2.5.3 Amines

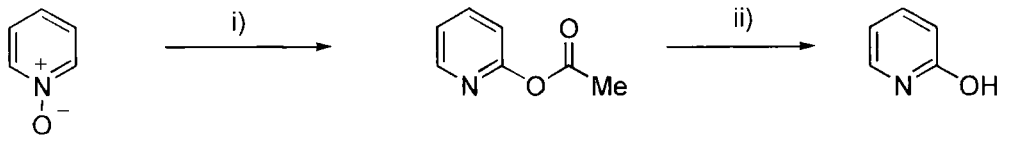
3-Aminopyridine can be converted to the 3-hydroxy derivative by diazotisation and hydrolysis.[44] The reaction probably involves displacement of the diazo group with water. Alternatively, the diazonium ion could lose nitrogen to give a carbocation which then can form the product by solvation. However, this leads to an intermediate with two positive charges in the ring, and without a group to stabilise them; making this mechanism highly unlikely.



Scheme 1.19

1.3.2.5.4 *N*-Oxides

The action of acetic anhydride on pyridine-1-oxide at 140-150°C leads predominately to 2-hydroxypyridine in high yield by way of the acetyl intermediate[45] (**Scheme 1.20**).



Scheme 1.20 *Reagents and Conditions: i) Acetic anhydride, 140-150°C; ii) H_2O*

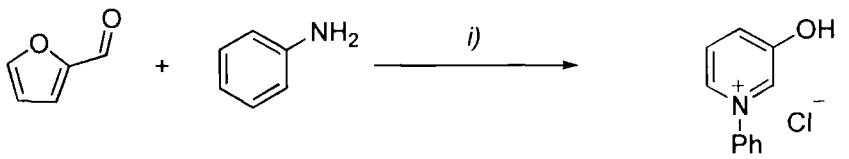
Isomeric 3-hydroxypyridine is occasionally isolated in low yields from rearrangments, in addition to the main products.[46,47] *p*-Toluenesulfonyl chloride and pyridine-1-oxide heated at 205°C[48] gives 3-hydroxypyridine as a major product; at lower temperatures only the 2-isomer is isolated.[49]

1.3.2.6 Furan Derivatives

Many furans are ring opened under certain conditions to give unsaturated 1,4-dicarbonyl compounds or their equivalent. Condensation with a nitrogen base intermolecularly can give rise to highly functionalised 3-hydroxypyridines.

1.3.2.6.1 Furaldehydes

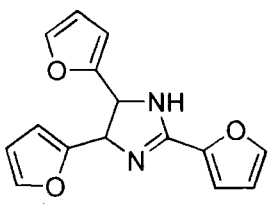
As early as 1905, a furan aldehyde was converted into a 3-hydroxypyridine by Zink *et al.*[50] Heating of an alcoholic solution of aniline and furfural gave 3-hydroxy-1-phenylpyridinium chloride (**61**).



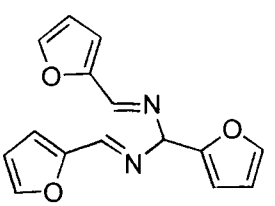
(**61**)

Scheme 1.21 *Reagents and Conditions: i) HCl, heat*

In 1938, Aso[51] reported the isolation of 3-hydroxy-6-methylpyridine in a low yield from reaction of 5-methylfurfural and ammonium sulfate at high temperatures. However, the reaction of furfural and ammonia at 10°C for 4 days produces only furfurin (**62**) and hydrofuramide (**63**)[52], at higher temperatures furfural gave only tars and resins.

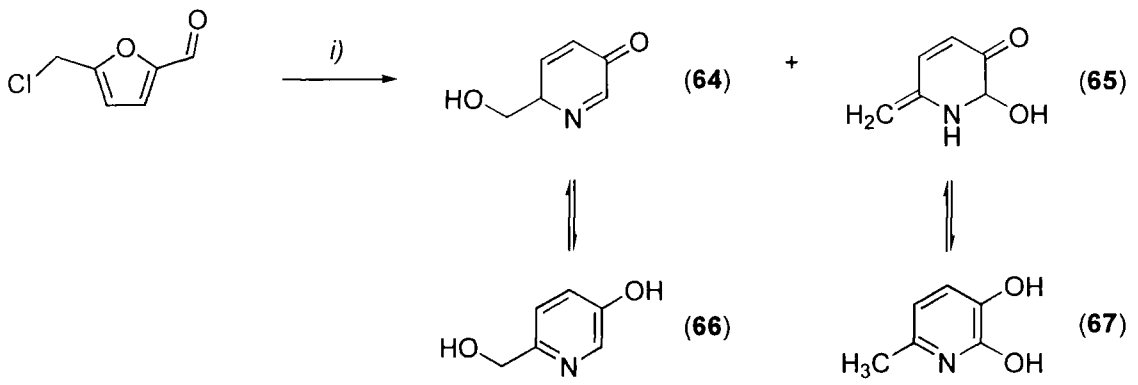


(**62**)



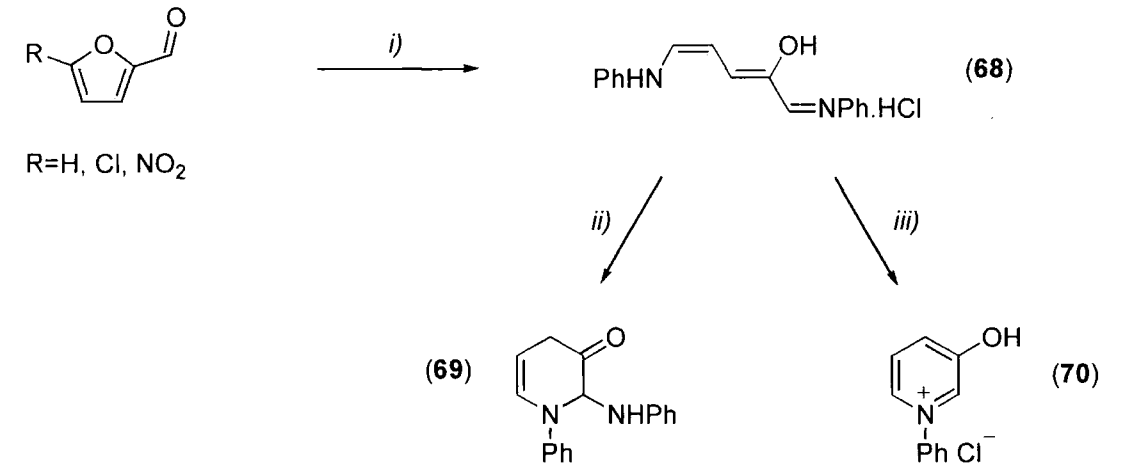
(**63**)

5-Chloromethylfurfural reacted with aqueous ammonium chloride at 160°C to give 5-hydroxy-2-pyridinemethanol (**66**) and 6-methyl-2,3-dihydroxypyridine (**67**).[53] The chloromethyl group being hydrolysed to the 5-hydroxymethyl-3-hydroxypyridine. Compound (**66**) comes from the intermediate (**64**), but the diol (**67**) is formed by the elimination of water at the 6-hydroxymethyl group rather than the 2-carbon.



Scheme 1.22 *Reagents and Conditions: i) NH_4Cl, H_2O, 160°C*

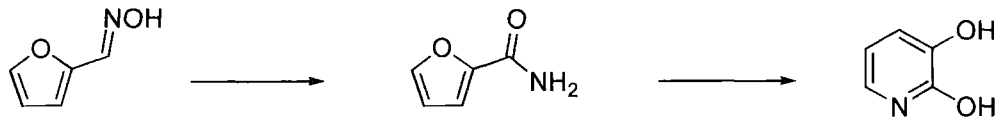
The reaction of furfural or its 5-nitro or 5-chloro derivatives with aromatic amines and their hydrochloride salt yields a Stenhouse dye (**68**).[54] Neutralisation of this salt with base produces a pyridine derivative (**69**).



Scheme 1.23 *Reagents and Conditions: i) $PhNH_2$, $PhNH_3^+Cl^-$; ii) OH^-; iii) Acetic acid, heat*

The aminopyridine derivative (**69**) can also be made by reaction of furfural and the amine if no acid or acid salt is present.[55] Heating of (**68**) in alcohol or acetic acid produces 1-phenyl-3-hydroxypyridinium chloride (**70**) in 37% yield.[56]

Aso[57] has shown that when furfural is treated with hydroxylamine hydrochloride or hydrazine sulfate at 155°C, 2,5-dihydroxypyridine (**72**) is obtained in low yield. He believed the aldoxime was converted to an amide (**71**), which was then hydrolysed and cyclised to give (**72**). This theory was supported by isolation of furoic acid from the reaction of furfural and the salt of hydroxyaminesulfonic acid, and conversion of furamide by acid at 160°C to (**72**) in low yield.[58,59].



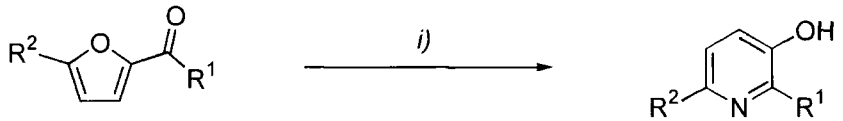
(**71**) (**72**)

Scheme 1.24

1.3.2.6.2 Ring Expansion of 2-Acylfurans

1.3.2.6.2.1 Mono Ketones

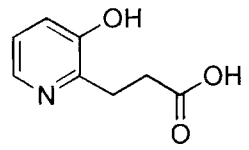
The reaction is similar to that of furaldehydes, but gives a 2-alkyl-3-hydroxypyridine. The first such reaction was reported by Leditschke,[61] in 1952, 2-phenylacylfuran (**73**) was reacted with ammonia to give 2-phenyl-3-hydroxypyridine (**74**) in 59% yield. Gruber[60] extended this work to various groups R^1 = alkyl or aryl, and also to other alkyl groups, R^2 on the ring.



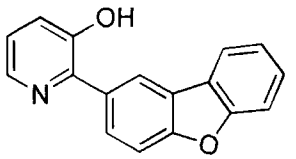
(**73**) R^1=Ph, R^2=H (**74**) R^1=Ph, R^2=H

Scheme 1.25 *Reagents and Conditions: i) NH_3 or NH_3/Ethanol, NH_4Cl*

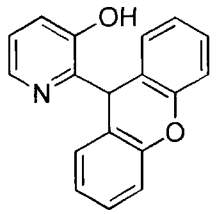
Many different alkyl groups have been used in the ring expansion. For example, simple alkyl or aryl groups by Gruber, who has examined alkyl chain substituents with a terminal carboxylic acid group, and found that the acid group in (**75**) withstood the reaction.[62] Leditscke found that the dibenzofuran (**76**) was stable[63], and Walter has incorporated the xanthene unit (**77**).[64]



(**75**)

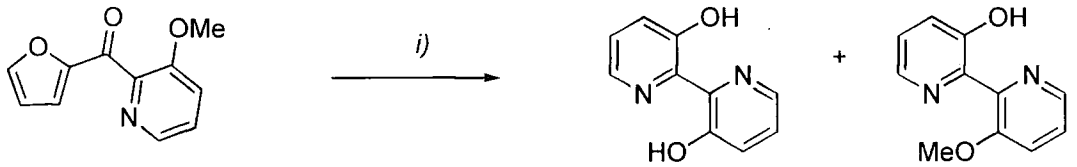


(**76**)



(**77**)

Reaction of a pyridyl ketone leads to bipyridyl compounds, which are normally made by cross-coupling reactions.[65] 2,2' and 2,4'-Bipyridines have been synthesised *via* this route.[66] The 2,2'-bipyridinol (**79**) was formed from the reaction of (**78**) with ammonia.[67]



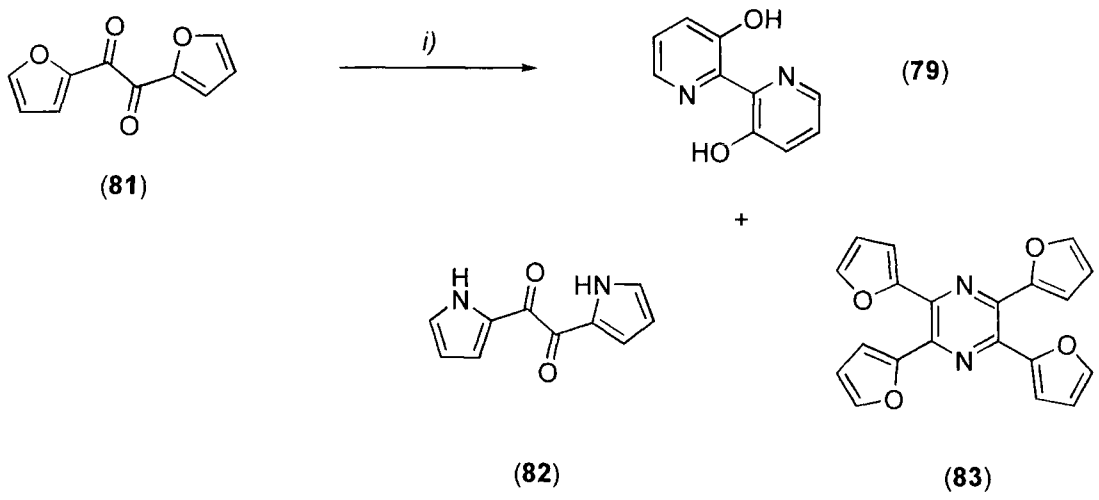
(**78**) (**79**) (**80**)

Scheme 1.26 *Reagents and Conditions: i) Ammonium acetate, 150°C, 2h*

The methoxy compound (**80**) was also reacted with dilute HCl to give the dihydroxy product (**79**), giving an overall yield for the reaction of 80%.

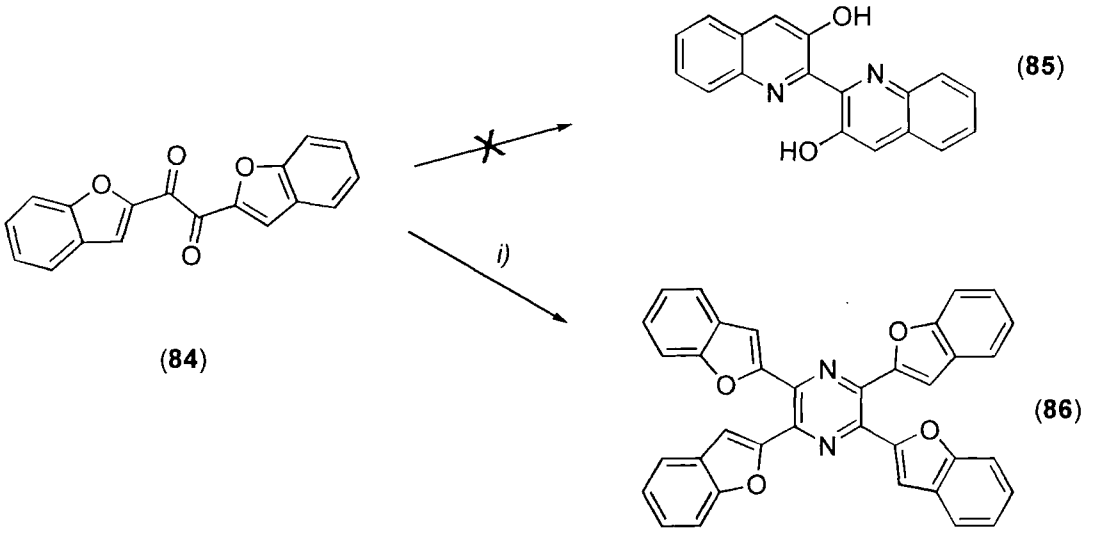
1.3.2.6.2.2 *Bis*-Ketones

The only reaction of a *bis*-ketone is that described by Langhals.[68] Furil (**81**) and ammonium chloride in methanol at 210°C, gave [*2,2'*]bipyridinyl-3,3'diol (**79**) in 32% yield. Traces of the pyrrole (**82**) and pyrazine (**83**) were also found in the reaction.



Scheme 1.27 *Reagents and Conditions: i) NH_4Cl, MeOH, 210°C*

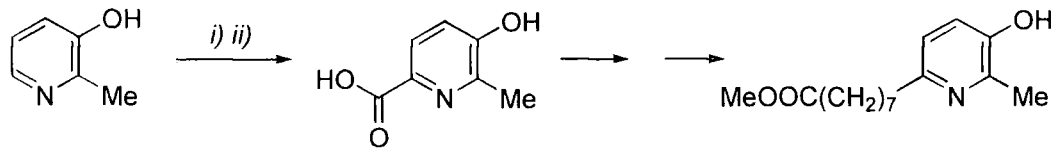
The reaction of 1,2-*bis*-benzofuran-2-yl-ethane-1,3-dione (**84**) did not give the *bis*-quinoline (**85**) but instead, the pyrazine (**86**) in 29% yield.[68]



Scheme 1.28 *Reagents and Conditions: i) NH_4Cl, MeOH, 210°C*

1.3.2.6.2.3 Synthetic Uses

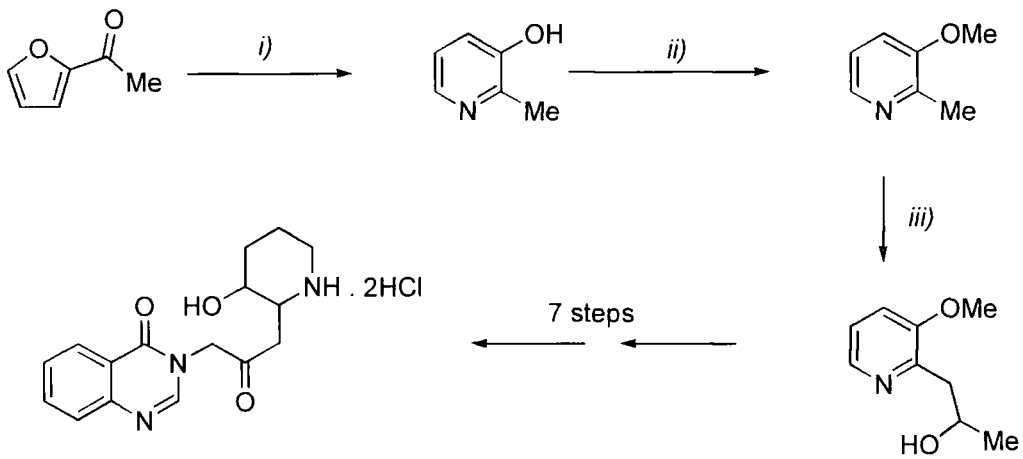
The reaction has also been widely used in the synthesis of natural products. Rapoport[69] used 2-acylfuran to form (**87**) then the carboxylic acid (**88**), as a starting point in the synthesis of carpyrinic acid (**89**), which comes from methyl carpamate, the chief papaya alkaloid, through catalytic dehydrogenation.



(**87**) (**88**) (**89**)

Scheme 1.29 *Reagents and Conditions: i)KOH; ii) K_2CO_3, CO_2, 250°C, 9h*

An antimalarial alkaloid (**91**) isolated from Hydrangea has been synthesised using this approach.[70] The key intermediate 2-(β-hydroxypropyl)-3-methoxypyridine (**90**) was synthesised from 2-acetylfuran in three steps, and another subsequent seven steps gave the alkaloid.



(**91**) (**90**)

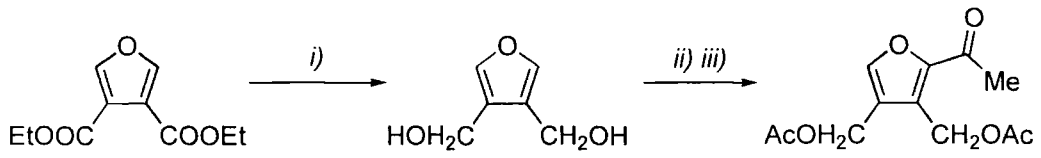
Scheme 1.30 *Reagents and Conditions: i) NH_4OH, 150°C; ii) Me_3PhNCl, DMF; iii) PhLi, Et_2O, Acetaldehyde*

The intermediate of major importance in the synthesis of pyridoxol (**5a**) is 2-acetyl-3,4-*bis*(acetoxymethyl)furan (**92**), which when reacted with ammonia should give acetoxymethyl groups on the pyridine ring at the 4- and 5- positions. This compound (**93**) could then easily be converted into pyridoxine.

(**92**) (**93**)

Scheme 1.31

Furan derivative (**92**) was made from 3,4-dimethanolfuran by a Friedel-Crafts reaction using acetic anhydride and zinc chloride. 3,4-Dimethanolfuran was synthesised from 3,4-dicarbethoxyfuran by reduction with lithium aluminium hydride. The diester was made using the Alder-Rickert[71] reaction, a procedure which was developed by reaction of furan and diethyl acetylenedicarboxylate, giving the adduct which was hydrogenated to give the diester. However, Williams *et al.*[72] did not report the reaction of the acylfuran with ammonia.

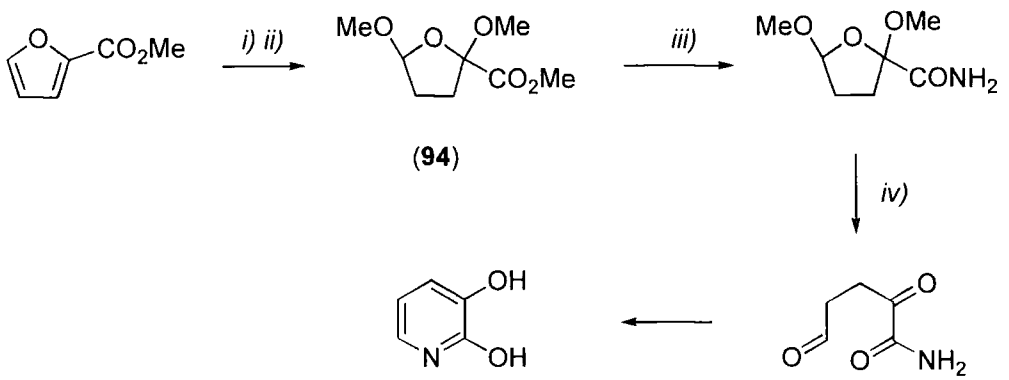


(**92**)

Scheme 1.32 *Reagents and Conditions: i) $LiAlH_4$, Et_2O, Reflux, 1h; ii) Ac_2O, NaOAc, reflux 1h; iii) $ZnCl_2$, Ac_2O*

1.3.2.6.3 Tetrahydrofurans

Treatment of 2-carbomethoxy-2,5-dimethoxytetrahydrofuran (**94**) with methanolic ammonia (to make the amide); and then with hot, aqueous acid (which hydrolyses the acetal and cyclises the intermediate) produced a 94% yield of 2,3-dihydroxypyridine.[73] The tetrahydrofuran (**94**) can be made from 2-methylfuroate in 62% yield.

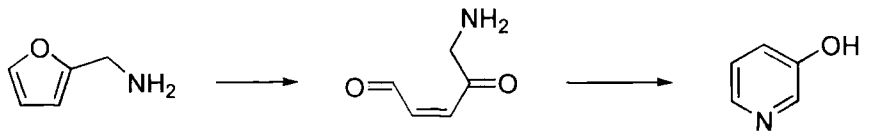


Scheme 1.33 *Reagents and Conditions: i) Electrolytic methoxylation; ii) H_2, Pd catalyst; iii) NH_3, MeOH, 25°C, 4 days; iv) H_2SO_4, Reflux, 20 min*

1.3.2.6.4 Dihydrofurans

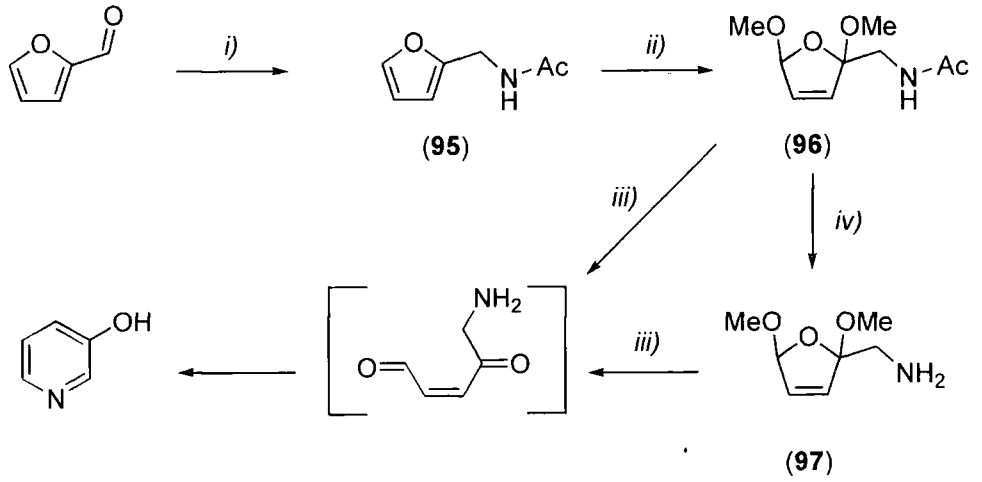
1.3.2.6.4.1 Furylamines

Under certain conditions the oxidation of furans can lead to an unsaturated 1,4-dicarbonyl compound. Furylamine oxidised in this way would give a dicarbonylamine, and as the double bonds are *cis*oid, intramolecular condensation should proceed to give the 3-hydroxypyridine (**Scheme 1.34**). Direct oxidation of the furan ring to a dicarbonyl compound is difficult, but Clauson *et al.*[74] achieved this by electrolytic methoxylation of the 2 and 5 positions of the ring giving a 2,5-dimethoxy,2,5-dihydrofuran, subsequent hydrolysis gives the dicarbonyl compound in 60-95% yield.



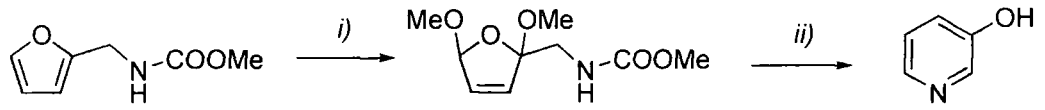
Scheme 1.34

Electrolytic methoxylation of the furylamine, however, gives a poor yield, probably due to interference of the amine in the reaction. However, 2-(acetamidomethyl)furan (**95**) gives an almost quantitative yield, 96%, at the methoxylation step. Alkaline hydrolysis of (**96**) to give 2,5-dimethoxy-2-(aminomethyl)-2,5-dihydrofuran (**97**), and boiling this product in hydrochloric acid gives 3-hydroxypyridine[75] (**Scheme 1.35**).



Scheme 1.35 Reagents and Conditions: i) NH_3, Ac_2O; ii) Electrolysis in MeOH; iii) HCl, H_2O; iv) NaOH, H_2O

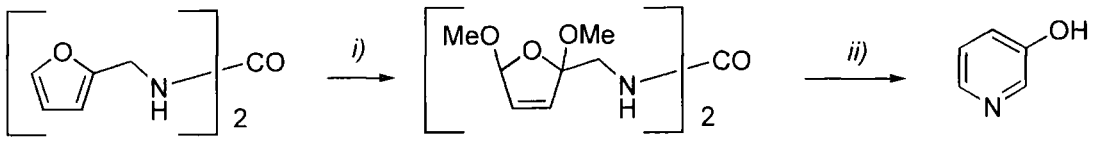
2,5-Dimethoxy-2-(acetamidomethyl)-2,5-dihydrofuran (**96**) boiled in hydrochloric acid gives a much lower yield of product (~50%), compared to 93% for the free amine (**97**).[75] This may be due to the fact that in the condensation step the molecule must lose acetic acid. Consistent with this assumption is the hydrolysis of the carbamate (**98**), which under the same conditions gives a higher yield of 3-hydroxypyridine, 76%[74] (**Scheme 1.36**).



(**98**)

Scheme 1.36 *Reagents and Conditions: i) Electrolysis in MeOH; ii) HCl, H_2O*

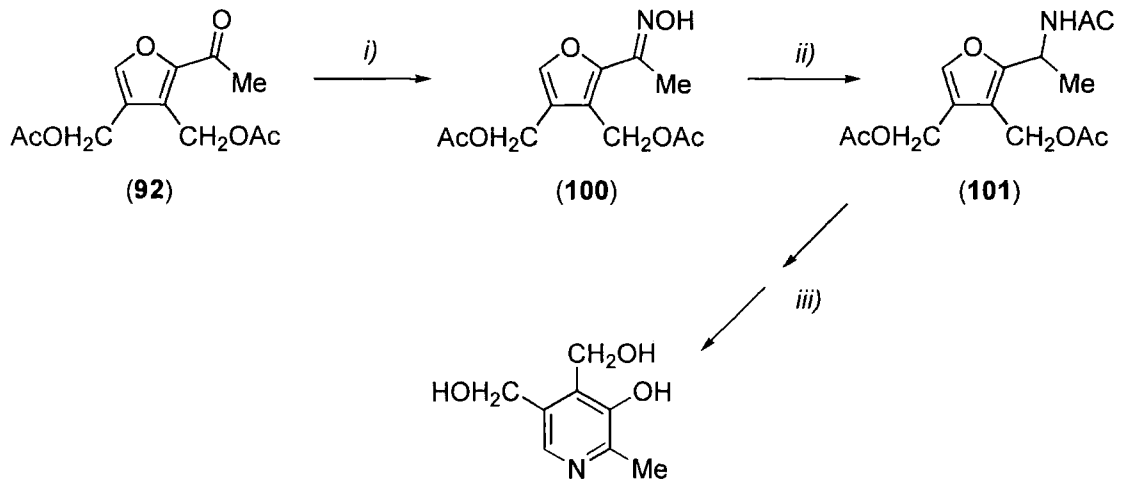
The overall yield from furylamine to 3-hydroxypyridine can be improved still further by proceeding through the *sym*-difurylurea (**99**)[74] (made from the reaction of furylamine and urea at 200°C), and the corresponding dimethoxydihydrofuran, leading to an overall yield of 85%.



(**99**)

Scheme 1.37 *Reagents and Conditions: i) Electrolysis in MeOH; ii) HCl, H_2O*

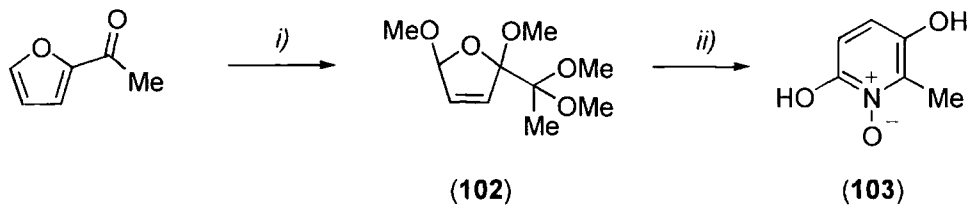
Clauson-Kaas[76] adapted the reaction to the synthesis of pyridoxine, with an overall yield of 76%. He made 2-acetyl-3,4-*bis*(acetoxymethyl)furan (**92**) using the same method as Williams[72] shown earlier (Scheme 1.36), but then reacted the acyl group with hydroxylamine hydrate to form an oxime (**100**). Reduction of the oxime with hydrogen using a Raney nickel catalyst, followed by acetylation gave 2-(acetamidomethyl)3,4-*bis*(acetoxymethanol)furan (**101**) which, *via* a three step synthesis, where none of the intermediates were isolated, gave pyridoxine (**Scheme 1.38**).



Scheme 1.38 *Reagents and Conditions: i) NH_2OH; ii) H_2, Raney Ni, Ac_2O; iii) Electrolysis in MeOH, then NaOH, H_2O, then HCl, H_2O*

1.3.2.6.4.2 Ketones

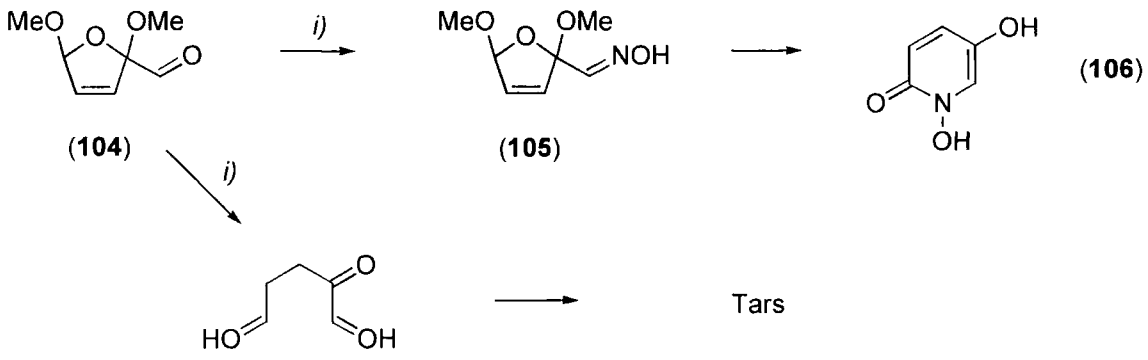
Converting 2-acetylfuran to the 2-acetylfuran dimethyl ketal with methyl orthoformate in methanol, then electrolysis gives (**102**). Allowing (**102**) to stand with methanolic hydroxylamine hydrochloride produced the N-oxide (**103**) in 57% yield.[77]



Scheme 1.39 *Reagents and Conditions: i) MeOH, $HC(OMe)_3$, reflux then electrolysis in MeOH; ii) $NH_2OH.HCl$, MeOH*

1.3.2.6.4.3 Furaldehydes

The methyl acetal of (**104**), when reacted with hydroxylamine hydrochloride gave only tars, but the free aldehyde gave (**106**). It is proposed that oxime intermediate (**105**), is formed first, before the dihydrofuran is hydrolysed to give (**106**).[78]

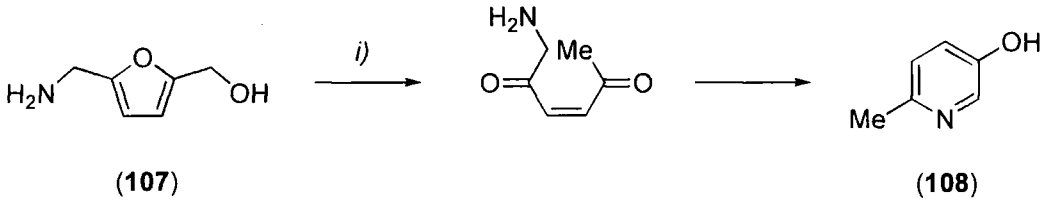


Scheme 1.40 *Reagents and Conditions: i) $NH_2OH.HCl$*

1.3.2.6.4.4 Furfuryl Alcohols

Furfuryl alcohol is transformed by the action of methanolic hydrogen chloride into a mixture of distillable products consisting of 2-, 3- (or 4-), 5-trimethoxytetrahydrosilvan, methyl levulinate, methyl levulinate dimethyl ketal and 2-(or 3-) methoxylevulinaldehyde dimethyl acetal.[79] It has been proved that this proceeds through *cis*-3-acetylacrolein or its equivalent.

Elming[80] found that 2-(hydroxymethyl)-5-(aminomethyl)furan (**107**) forms 3-hydroxy-6-methylpyridine upon reaction with hydrochloric acid. It seems reasonable to assume that the transformation also occurs through the 1,4-dicarbonyl compound.

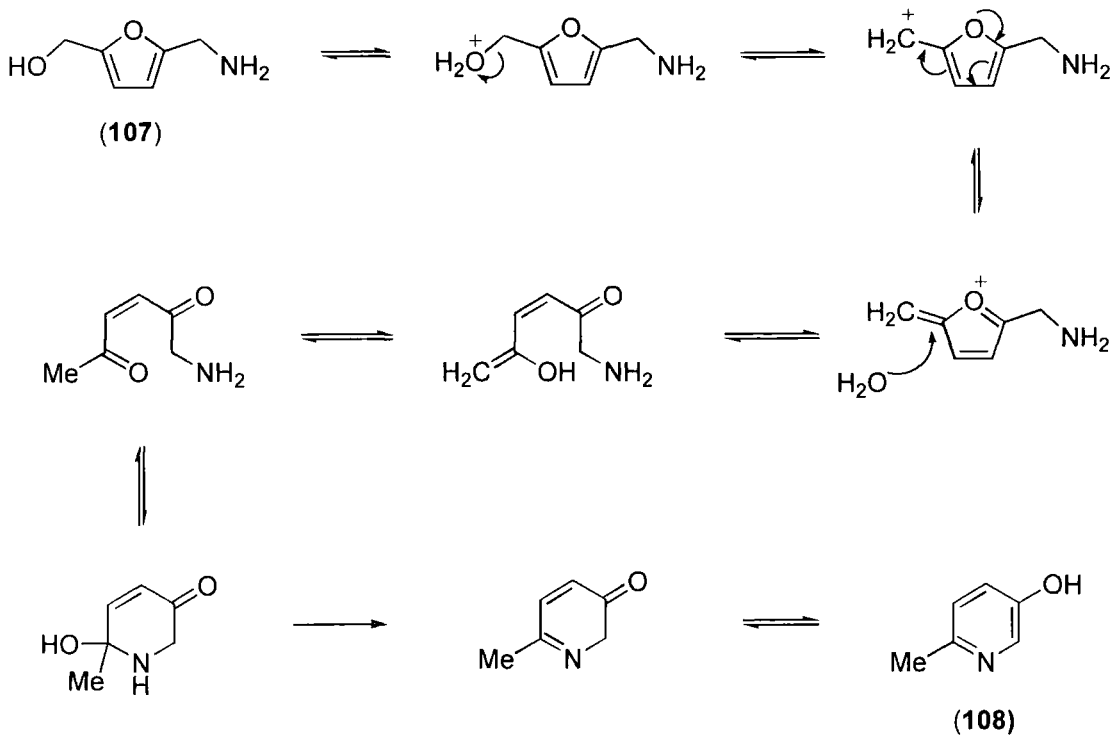


(**107**) (**108**)

Scheme 1.41 *Reagents and Conditions: i) HCl, H_2O*

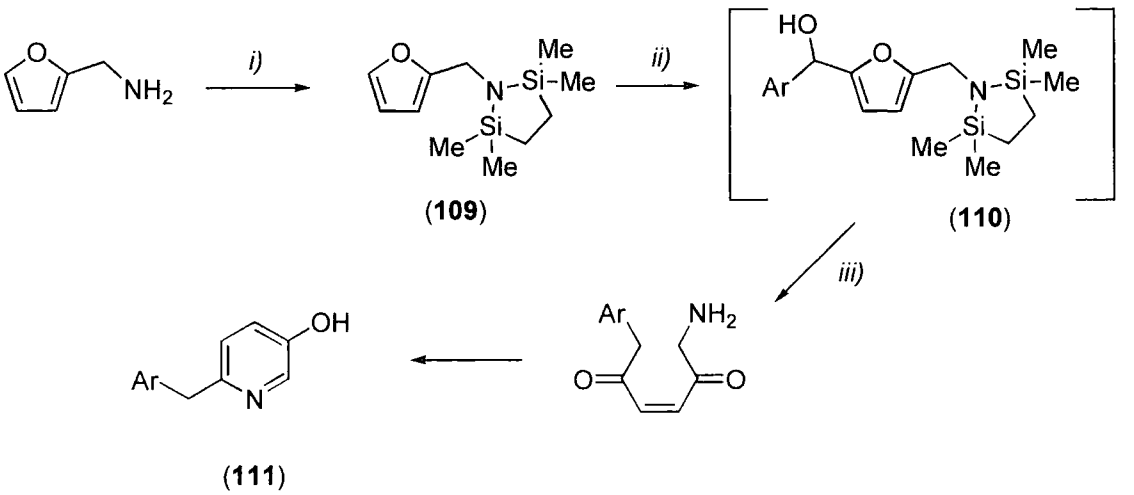
A plausible mechanism for the reaction involves protonation of the hydroxyl group of (**107**), then loss of water to give a carbocation, which through resonance can be stabilised by the positive charge moving onto the oxygen of the furan. Reattack by water leads to ring opening and the pyridine ring is produced through nitrogen lone

pair attack at the resulting carbonyl centre. Loss of water and tautomerism of the ketone gives the 3-hydroxypyridine (**108**).



Scheme 1.42

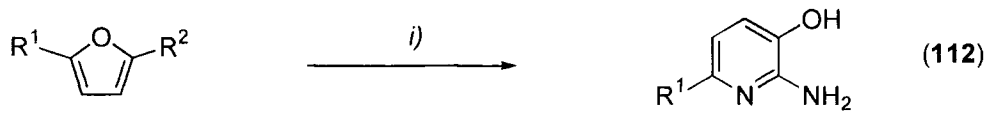
Barrett[81] reported a simple procedure for converting 2-aminomethylfuran into the corresponding pyridine derivative by C-5 lithiation. The 2-aminomethylfuran was firstly treated with 1,2-*bis*(chlorodimethylsilyl)ethane and triethylamine in anhydrous dichloromethane to give the protected amine (**109**). This group is stable to lithiation at the C-5 position with *tert*-butyllithium in tetrahydrofuran. Reaction of the lithio species with aryl aldehydes gave the alcohol (**110**). This was not isolated but reacted *in situ* with hydrochloric acid, which firstly removes the protecting group and then protonates the hydroxyl group and through the mechanism (**Scheme 1.42**) gives 6-arylmethyl-3-hydroxypyridine (**111**) (Ar=Phenyl, 37% yield).



Scheme 1.43 *Reagents and Conditions: i)1,2-bis(chlorodimethylsilyl)ethane, DCM, NEt_3, 0°C; ii) t-Butyllithium, THF, -78°C, then ArCHO, r.t.; iii) 1M HCl, reflux, 18h*

1.3.2.6.5 Furoic Acid Derivatives

2-Amino-3-hydroxypyridine has been used in the synthesis of highly active insecticides of low mammalian toxicity. The usual procedure for preparing (**112**) is from furfural following the work by Clauson-Kaas.[76] An alternative route[82] involves the reaction of furoic acid derivatives with ammonia at high temperatures and pressures. Reaction of 2-furamide, which is an oxidation product of furfural already containing one nitrogen atom, with ammonia gave 2-amino-3-hydroxypyridine (**112**) in 55% yield. Other derivatives were reacted in the same way with the yield being highly dependent on the choice of solvent, catalyst and reaction time; the highest yields are obtained by using amidic or related solvents. The best solvent is hexamethylphosphoric triamide (HMPT) though formamide, dimethylformamide or acetonitrile give good yields. The catalytic activity decreases in the order: ammonium iodide > ammonium bromide > ammonium chloride > ammonium fluoride ≈ diammonium hydrogen phosphate ≈ ammonium sulfate >> ammonium acetate. A temperature of 200-250°C was found to be optimal with the reaction time ranging from 0.5 to 15 h.



(112)

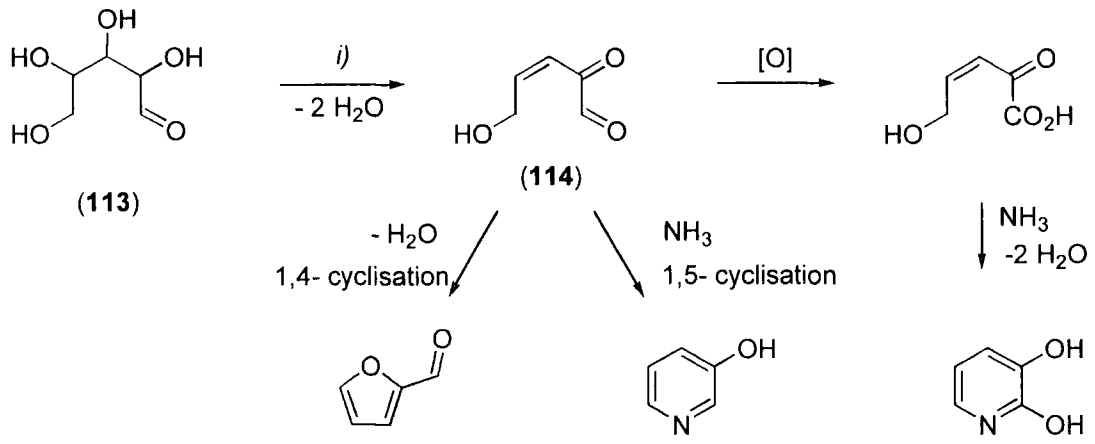
Scheme 1.44 *Reagents and Conditions: i) HMPT, NH_4OH, 200-250°C*

R^1	R^2	Temperature (°C)	Time (h)	Yield (%)
H	$CONH_2$	240	5	55
H	$COOC_2H_5$	240	8	50
H	COOH	240	11	45
H	$CONHCH_2C_6H_5$	240	10	20
H	CN	220	5	35
H	$C_2H_5OC=NH_2^+ Cl^-$	200	5	35
H	HC=NOH	220	10	1-5
CH_3	$COOCH_3$	240	10	30
CH_3	CN	240	8	25

Table 1.1[82]

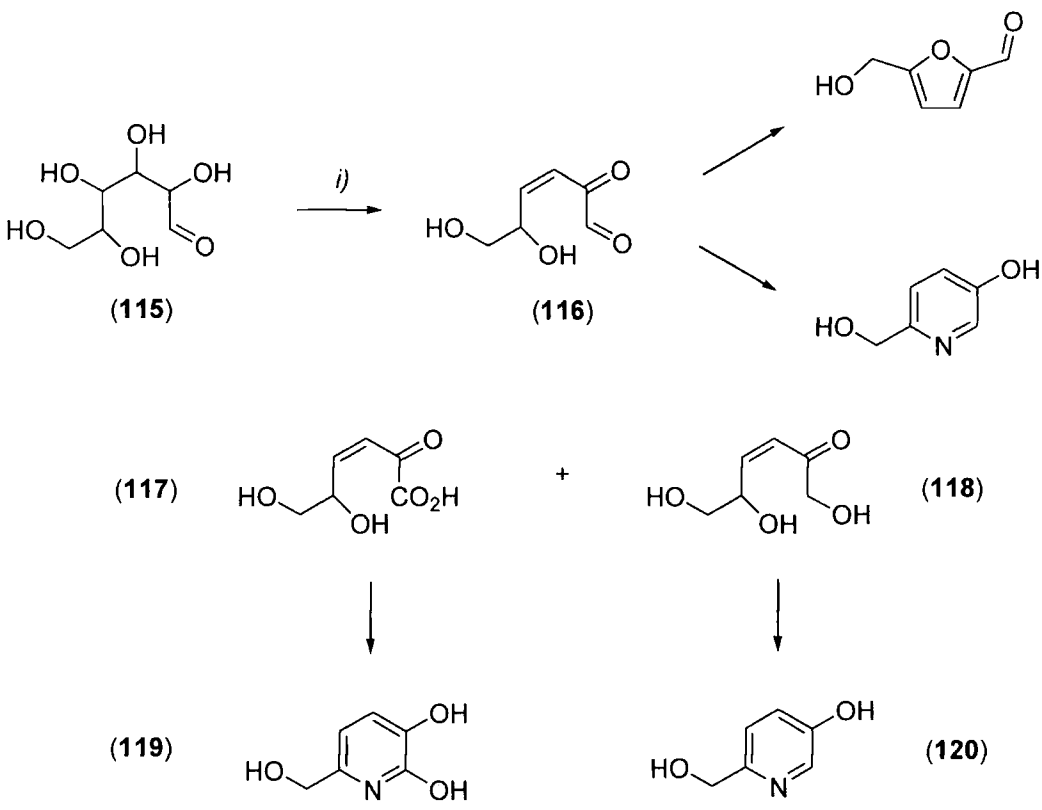
1.3.2.6.6 Carbohydrates

Formation of 3-hydroxypyridines by action of ammonium salts on carbohydrates at 160°C, does not proceed through a furan derivative. However, it is likely that the carbohydrate is converted to a common intermediate which gives either the furan or the pyridine. Thus, xylose (**113**) which has been converted to furfural in 89% yield,[83] also gives 3-hydroxypyridine and 2,3-dihydroxypyridine. The suggested intermediate for the reaction is (**114**).



Scheme 1.45 *Reagents and Conditions: i) $(NH_4)_2SO_4$, 155°C, 2h*

Similarly hexose (**115**)[84], which gives 5-hydroxymethylfurfural, also gives three other pyidine derivatives through the intermediate (**116**). The isolation of (**119**) and (**120**) indicates that some of the hexose or (**116**) undergoes a Cannizzaro reaction[85] to give the acid (**117**) or alcohol (**118**), before each cyclises to give (**119**) and (**120**), respectively.



Scheme 1.46 *Reagents and Conditions: i) $(NH_4)_2SO_4$, 155°C, 2h*

1.4 Reactions of 3-Hydroxypyridines

The phenolic structure for 3-hydroxypyridine was supported by Specker and Gawrosch[86] who found that the UV spectra of 3-hydroxypyridine and its methyl ether were identical in neutral or acidic methanolic solution. 3-Hydroxypyridine does exist in equilibrium with a corresponding zwitterionic tautomer, the exact ratio depending on the solvent (Figure 1.2).

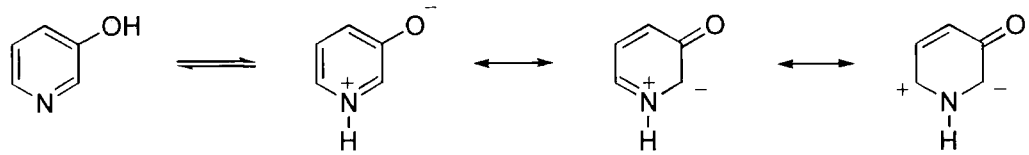
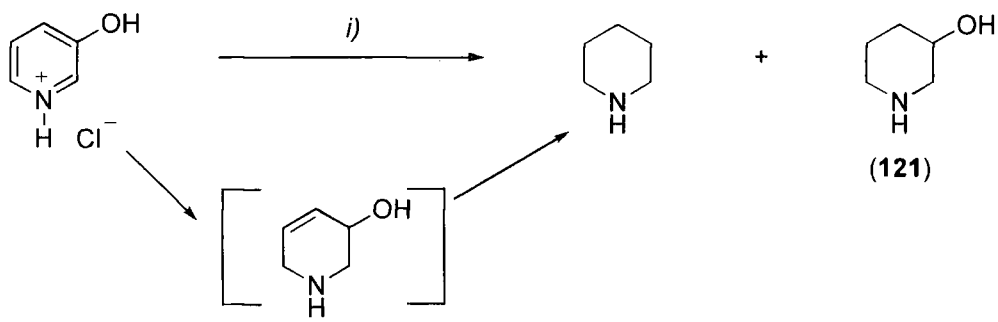


Fig. 1.2

1.4.1 Reduction

Catalytic reduction of 3-hydroxypyridine hydrochloride gives a mixture of 3-hydroxypiperidine (**121**) and piperidine. Since (**121**) resists further reduction, the piperidine is accounted for by formation of an intermediate allylic alcohol which undergoes hydrogenolysis.[87]



Scheme 1.47 *Reagents and Conditions: i) PbO_2, EtOH, H_2 (60 lb pressure)*

1.4.2 Deoxygenation

3-Hydroxypyridine undergoes replacement of the hydroxy group with hydrogen when dry distilled with zinc dust in a hydrogen atmosphere,[88] giving a poor yield. Replacement is usually achieved using a two step approach, *via* the hydroxy- and then the chloro- derivatives.

1.4.3 Alkylation

Most alkylations preferentially take place at the ring nitrogen to give *N*-quarternary pyridinium compounds.[89] However, the potassium salt of 3-hydroxypyridine with ethyl bromide gives 3-ethoxypyridine. The methyl ether has been reported[90] by creating the sodium salt (made by dissolving the pyridine in a methanolic solution with an equimolar amount of sodium methoxide), then adding dimethylsulfoxide. Removal of the methanol by distillation, and addition of iodomethane gives the product. Meyer[91] reported the reaction of diazomethane with 3-hydroxypyridine to give the methyl ether.

1.4.4 *O*- And *N*-Acylation or Aroylation

Reaction with acetic anhydride gives 3-acetoxypyridine[92] in 95% yield. Acylation also occurs with benzoyl chloride[93] (81%) and diphenylacetyl chloride[87] (96%). 2-Iodo-3-hydroxypyridine is benzoylated by benzoyl chloride in benzene with triethylamine as the base.[94]

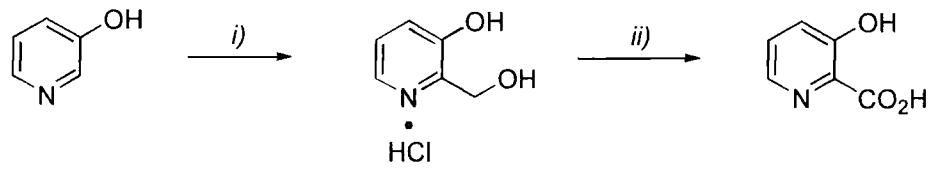
Substituted carbamates and their *N*-alkyl derivatives were found to inhibit cholinesterase and some derivatives are active against the influenza virus.[95] Preparation is achieved by action of a carbamoyl chloride on 3-hydroxypyridines in the presence of triethylamine[96] or pyridine.[97]

1.4.5 Electrophilic Substitution

Electrophilic substitution of 3-hydroxypyridine, which occurs more readliy than with pyridine itself, occurs at the 2-position. Bromination is usually achieved either with an equimolar amount of bromine in pyridine[98] or bromine in 60% sodium hydroxide.[99] Iodine and sodium carbonate give the 2-iodo product (90%). The 2-chloro derivative is made by reaction with a mixture of hydrochloric acid and hydrogen peroxide (51%).[100]

1.4.6 Base Catalysed Substitution

Base converts 3-hydroxypyridine into the resonating anion, which has a partial negative charge distributed on the ring carbons *ortho* and *para* to the hydroxy group. These can form covalent bonds with electron deficient carbons. 3-Hydroxypyridine undergoes the Mannich reaction,[101] by analogy with phenol,[102] with an alkaline aqueous solution of formaldehyde in 51% yield[103] and the 2-hydroxymethyl-3-hydroxypyridine hydrochloride is oxidised to the acid (**122**) in 58% yield using sodium permanganate .[104]



(**122**)

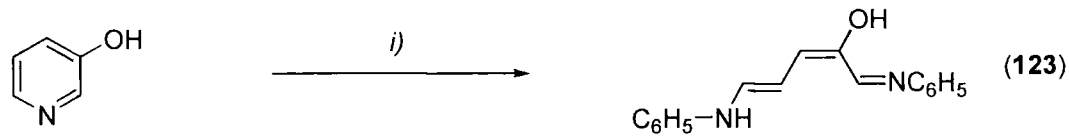
Scheme 1.48 *Reagents and Conditions: i) NaOH, 36% CH_2O, reflux then HCl; ii) Na_2CO_3, $NaMnO_4$*

1.4.7 *N*-Oxides

3-Hydroxypyridine, like other tertiary amines, is converted to the *N*-oxide by reaction with percarboxylic acids or hydrogen peroxide.[105] The *N*-oxide is more susceptible to electrophilc nitration than the free amine.

1.4.8 Ring Opening

There are few examples of ring opening of 3-hydroxypyridines, *e.g.* the reaction with cyanogen bromide and aniline, gives (**123**).[106]

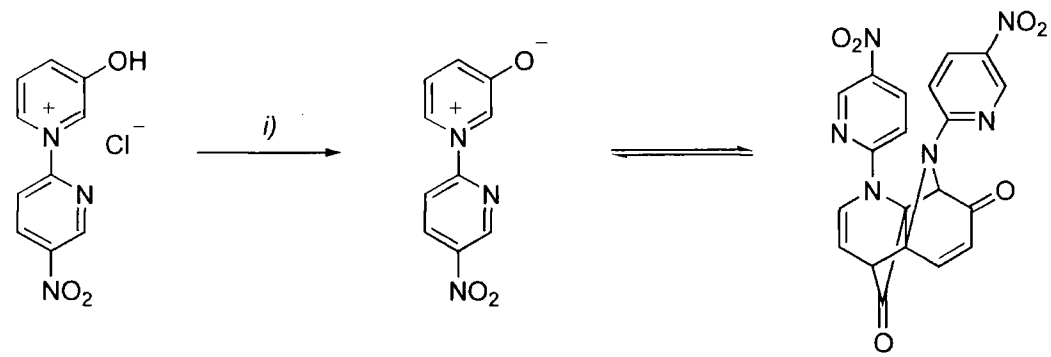


(**123**)

Scheme 1.49 *Reagents and Conditions: i) CNBr, 2 eq. $PhNH_2$*

1.4.9 3-Oxidopyridinium Betaines

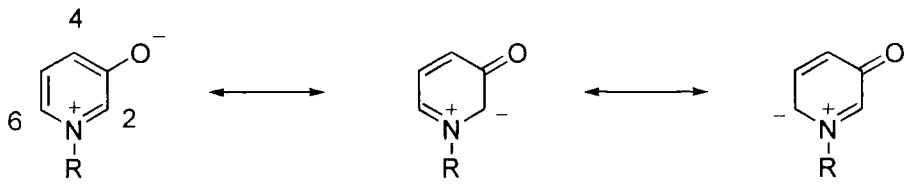
3-Hydroxypyridinium salts, mainly the *N*-methyl derivatives, are known for a large number of ring substituents. Many of these compounds have been made by nucleophilic displacement, heating the 3-hydroxypyridines and a suitable halogen compound.[107] These salts can be easily converted to the 3-oxidopyridinium betaines with bases such as sodium hydroxide, triethylamine or by ion-exchange resins. In some cases, usually when the *N*-substituent is strongly electron withdrawing, the betaine (**124**) tends to dimerise at ambient temperatures.[108] However, the equilibrium between monomer and dimer (**125**) can be shifted to give considerable amounts of the monomer at higher temperatures.



(**124**) (**125**)

Scheme 1.50 *Reagents and Conditions: i) Ion-exchange resin*

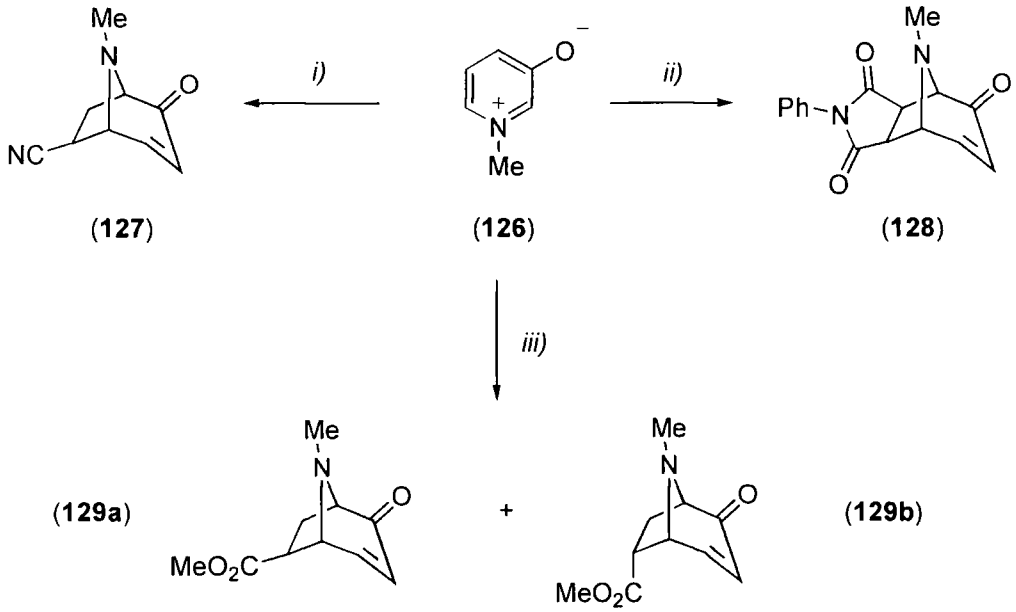
3-Oxidopyridinium betaines undergo cycloaddition reactions. They can act as 4π electron 1,3-dipoles across the 2,6- termini, as 6π electron 1,5-dipoles across the 2,4-termini, or as 8π electron 1,7-dipoles across the O and C-2 or O and C-4 positions.



Scheme 1.51

1.4.9.1 Addition Across the 2- and 6-Positions

Katritzky first observed a 1,3 dipolar addition in 1970,[109,110,111] by taking 1-methyl-3-oxidopyridinium betaine (**126**), obtained from the 3-hydroxy-1-methylpyridinium iodide and ion-exchange resin, and heating with the dienophiles acrylonitrile, *N*-phenyl maleimide or methyl acrylate gave the adducts (**127**), (**128**) and (**129a,b**) respectively. Since this initial work a large variety of *N*-substituted betaines have been reacted with dipolarophiles, giving the appropriate adducts.

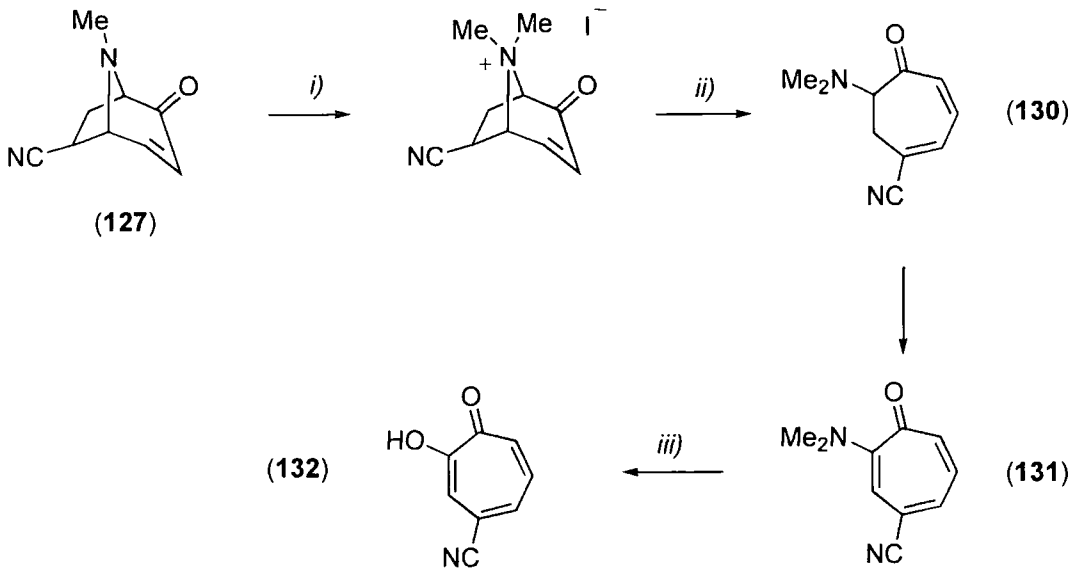


Scheme 1.52 Reagents and Conditions: i) Acrylonitrile; ii) N-Phenylmaleimide; iii) Methyl acrylate

These reactions can be rationalised by using FMO theory. According to these rules additions of an olefin is allowed across the 2- and 6- positions where the orbitals align correctly (Fig. 1.3).

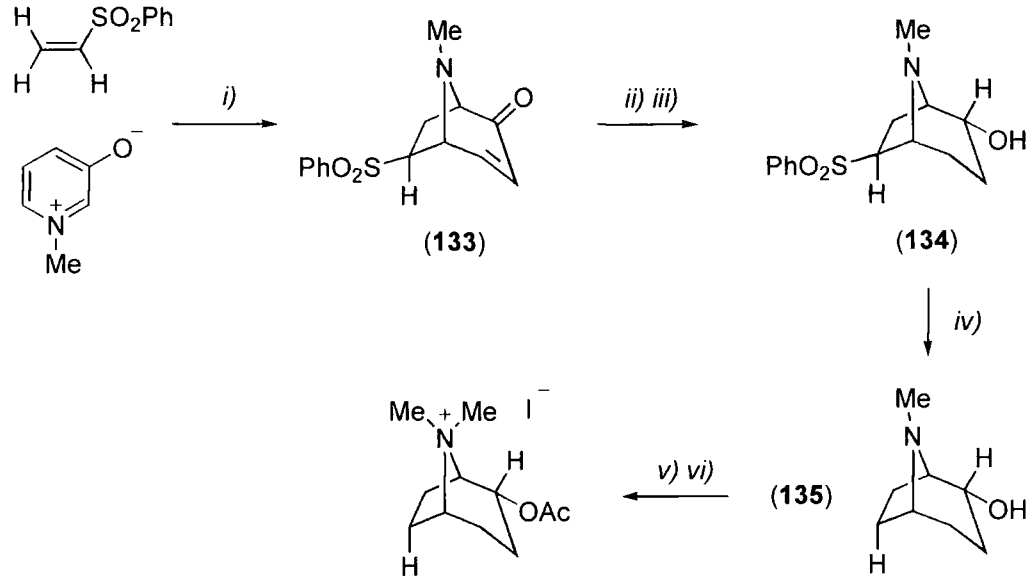
Fig 1.3

One of the first applications was in the synthesis of tropanes and tropalones.[112,113] Katritzky showed that Hoffmann degradation[114] of the quaternary salt of (**127**) led to formation of (dimethylamino)tropane (**131**) *via* the intermediate (**130**). Hydrolysis of (**131**) with sodium hydrogen carbonate gave the desired tropalone (**132**).



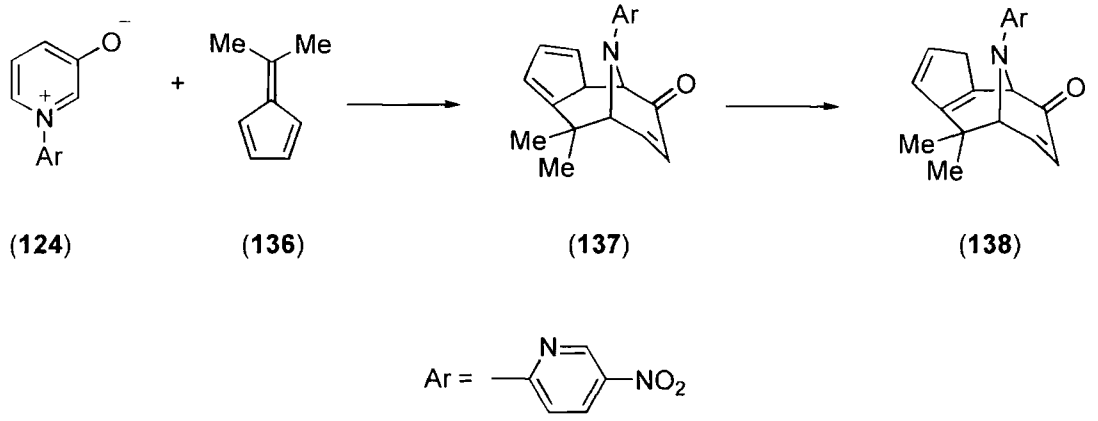
Scheme 1.53 *Reagents and Conditions: i) MeI; ii) Ag_2O, H_2O; iii) $NaHCO_3$*

The first published synthesis of a tropane alkaloid using this approach was by Koizumi in 1989.[115] Reaction of 1-methylpyridinium betaine with a number of vinylsulfones gave the initial 6-substituted or 6,6-disubstituted adducts. Reduction of the ketone (**133**) and hydrogenation gave a compound (**134**), which readily loses the phenyl sulfone group to give the 2-tropanol (**135**).



Scheme 1.54 *Reagents and Conditions: i) THF, 90°C; ii) $NaBH_4$, EtOH, r.t; iii) H_2, Pd-C, MeOH, 3 atm; iv) Na, EtOH/THF, 0°C; v) Ac_2O, reflux; vi) MeI, CH_3CN, 50-70°C*

Fulvenes react readily with (**124**) where the betaine contains a strong electron-withdrawing group on the nitrogen.[116] Hence, 6,6-dimethylfulvene (**136**) reacted with (**124**) afforded (**138**), *via* isomerisation of the intermediate (**137**).



Scheme 1.55 *Reagents and Conditions: i) Et_2O, 20°C, 2h*

This reaction is the addition of a 6π electron addend across the 2- and 6- positions of the betaine, and represents another symmetry allowed cycloaddition.

1.4.9.2 Addition Across the 2-and 4-Positions

This reaction can be considered either as a [4π+6π] or [4π+2π] process in which the betaine provides six or two electrons respectively, and the reaction occurs across the 2- and 4- positions of the betaine with a diene.

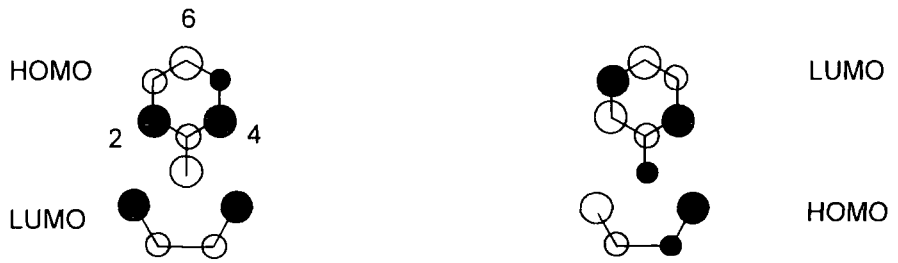
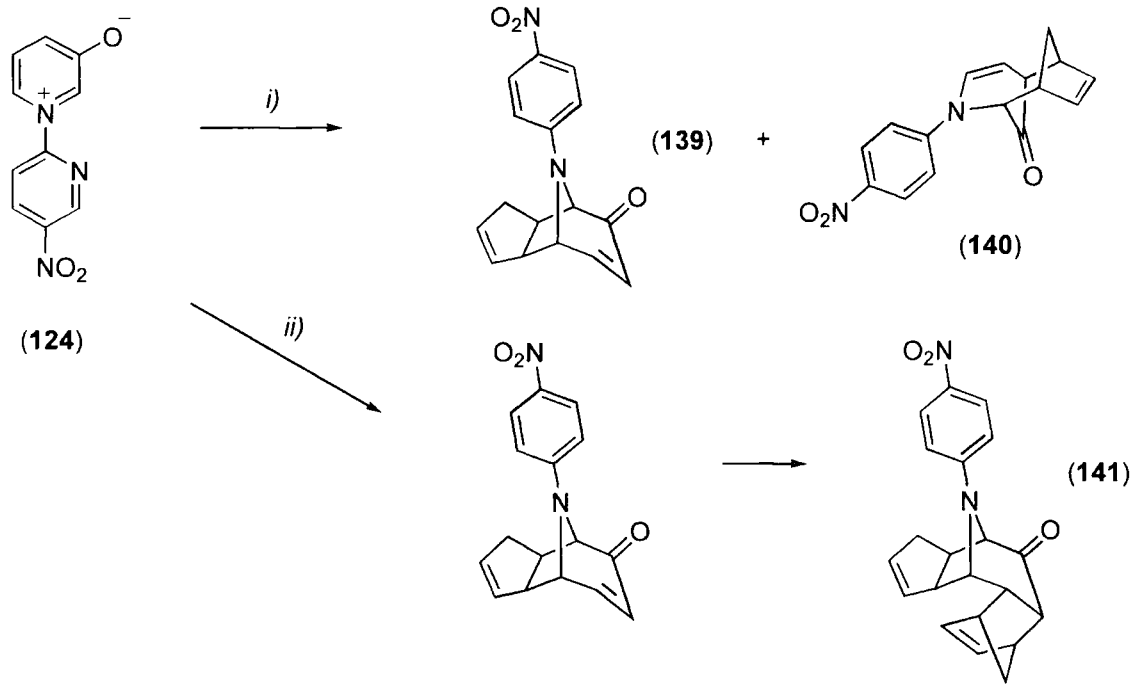


Fig 1.4

A mixture of products is obtained due to some reaction of the 2,6- positions with a double bond of the diene. The dimer (**125**) on heating dissociates to the monomer; heating of (**124**) with cyclopentadiene at 20°C leads to the formation of two distinct products.[116] Reaction with one double bond gives (**139**) (45%) whereas reaction with the diene gives (**140**) (37%).



Scheme 1.56 *Reagents and Conditions: i) Cyclopentadiene, 20°C; ii) Cyclopentadiene, 100°C*

Heating of the monomer and the diene at 100°C gave firstly the [4π+2π] adduct then further reaction of the diene in a Diels-Alder reaction gave the 2:1 adduct (**141**).

1.4.9.3 Addition Across the O and C-2 or O and C-4 Positions

These cycloadditions[117,118] are the result of an interaction between the HOMO of the betaine and the LUMO of an α-haloketene. The large coefficient of the ketene, residing on the carbonyl carbon atom[119], interacts with the large coefficient located on the betaine oxygen;[120] the other bond can then be formed between the 2- or 4-positions depending on the substituents R^1 and R^2.

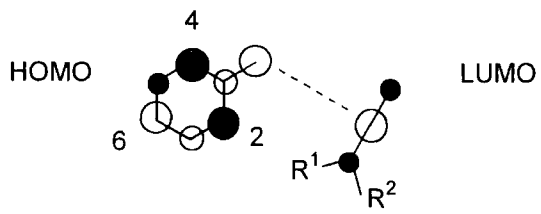
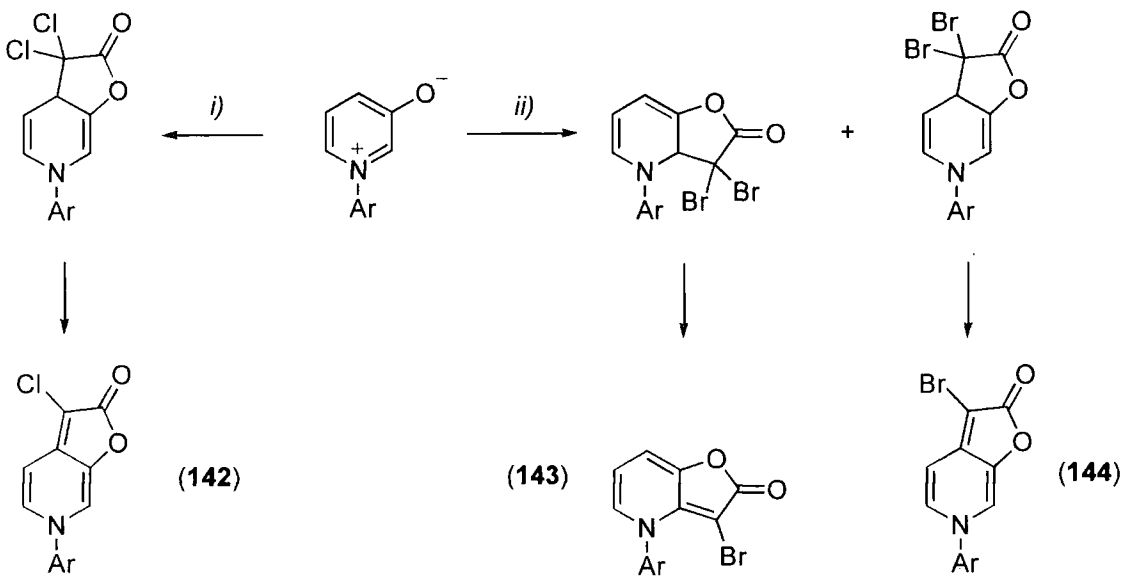


Fig 1.5

Dichloroketene, generated *in situ* form dichloroacetyl chloride,[121] or chloral,[122] adds across the O and C-4 positions. The intermediate, which cannot be isolated due to its instability, loses hydrochloric acid to give (**142**), which is consistent with an [8π+2π] addition.



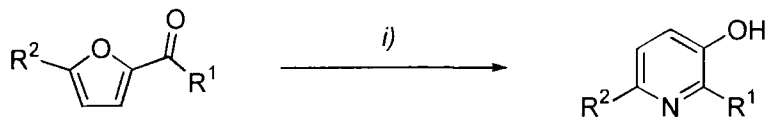
Scheme 1.57 *Reagents and Conditions: i) Dichloroketene; ii) Dibromoketene*

Dichloro, difluoro and α-chlorohaloketenes all add across the O and C-4 positions, however, dibromoketene gives a mixture of products due to some addition across the O and C-2 positions.[123] The ratio of isomers depends on the bulkiness of the *N*-substituent. The aroylvinyl substituent (Ar = *p*-ClC_6H_4COCH=CH) gives only the isomer arising from C-2 addition, in 61% yield, whereas phenyl (Ar = C_6H_5) gives a 1:1 mixture of products, (**143**) and (**144**) (**Scheme 1.57**).

CHAPTER 2

2-Furyl ketones

Chapter 1 has introduced the general chemistry of 3-hydroxypyridines and principally the various reactions of furan derivatives in generating this system. The project aimed to explore the reaction of 2-acylfurans with sources of ammonia following the precedents of Gruber[60] and Leditscke[61] (**Scheme 2.1**). This chapter looks into the various methodologies incorporated into the synthesis of 2-acylfurans.



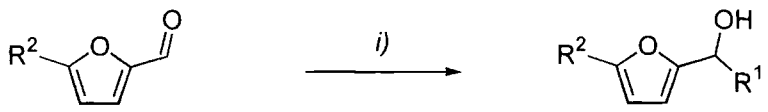
Scheme 2.1 *Reagents and Conditions: i) NH_3, 150°C, 10h*

2.1 Furylalcohols

All the simple carbinols are colourless liquids when pure. They change to a reddish brown on prolonged exposure to light or air, giving a viscous liquid which eventually solidifies on standing. They are slightly soluble in water, their density decreasing with increasing molecular weight. They exhibit typical behaviour of secondary alcohols, and can be converted into the normal functional derivatives. However, reactions carried out in acidic media are complicated by involvement of the reactive nucleus and this accounts for the widespread use of basic solvents (e.g. pyridine) in reactions which require acidic reagents or give acidic products. Also, the presence of water enhances the activity of the acid to promote resinification and this is made all the more difficult since the initial reaction leading to resin formation gives water as a by-product. The furylalcohols can easily be oxidised to the furylketones required for ring expansion using standard oxidising agents.

2.1.1 Grignard Reagents

Pawlinoff and Wagner[124] were the first to prepare a furyl alcohol by reaction of furfural with diethylzinc to give the ethylfuryl alcohol. Grignard[125] in 1901 was the first to obtain a furyl alcohol, *iso*-amylfuryl alcohol, by the reaction of furfural and *iso*-amylmagnesium chloride (**Scheme 2.2**).



Scheme 2.2 *Reagents and Conditions: i) R^1MgX, Et_2O, 0°C*

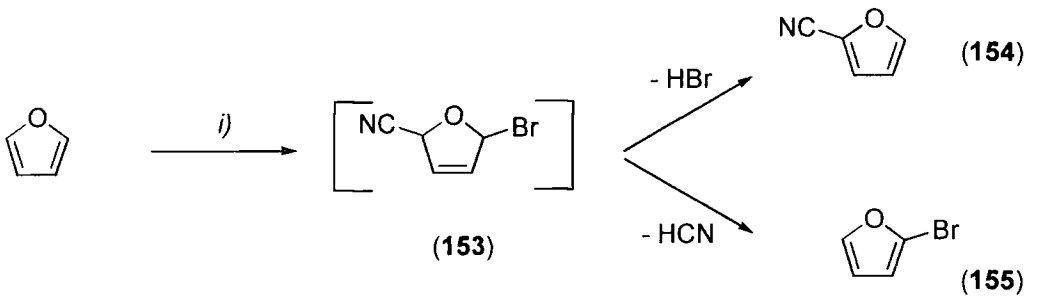
The reaction of the Grignard reagent at 0°C leads to high yields of the product alcohols. The two enantiomers were not separated due to the need to oxidise the alcohol fuctionality in the next step of the sequence. The reaction of Grignard reagents with various aldehydes is shown in **Table 2.1** below:

Alcohols	R^1 / R^2	Yield (%)
145[126]	R^1=*iso*-propyl, R^2=H	78
146[127]	R^1=*sec*-butyl, R^2=H	47
147[126]	R^1=phenyl, R^2=H	94
148	R^1=*p*-tolyl, R^2=H	98
149[128]	R^1=*iso*-propyl, R^2=Me	73
150	R^1=*sec*-butyl, R^2=Me	87
151[129]	R^1=phenyl, R^2=Me	97
152[129]	R^1=*p*-tolyl, R^2=Me	85

Table 2.1

The alcohols were purified by distillation at reduced temperatures using a Kugelrohr apparatus. However, the alcohols (**148**) and (**152**) decomposed during the distillation process and were, therefore, purified by column chromatography on silica.

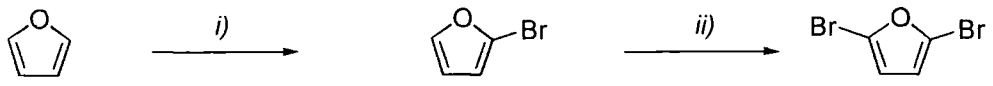
We chose to use the reaction of furfural and a Grignard reagent to synthesise the required alcohols, due to the difficulty involved in making 2-furylmagnesium halides. Ordinary or activated magnesium fails to give the Grignard reagent with 2-bromofuran; indeed a highly activated magnesium-copper alloy must be employed to give the product.[130] Difficulties in making the Grignard reagent must also lie in the synthesis of 2-bromofuran. Klopp and Wright[131] isolated small quantities of both 2-bromofuran and 2-furonitrile by the action of cyanogen bromide on furan. As pointed out by these investigators, this suggests the formation of a 1,4-addition compound (**153**), which through an elimination step, loses either hydrogen cyanide or hydrogen bromide, giving the two products (**154**) and (**155**) (**Scheme 2.3**). However, if the reaction is carried out in dioxane only the 2-bromofuran (**155**) is formed. No trace of the 2-furonitrile (**154**) could be detected.



Scheme 2.3 *Reagents and Conditions: i) CNBr*

2-Bromofuran can be synthesised from bromine and an ethereal solution of 2-lithiofuran; however, the separation of the product from diethyl ether is time consuming. An improvement comprises performing the bromination in dimethylformamide[132] between 20 and 40°C, giving a 70% yield. Performing the reaction at 20-30°C gives 2-bromofuran, but heating to between 30-40°C gives 2,5-dibromofuran (**156**), meaning the temperature of the reaction is highly important and difficult to control (**Scheme 2.4**).

The successful bromination of furan in dioxane at 0°C (~90% yield), has the major drawback of using vast quantities of dioxane. This is due to the bromine-dioxane complex having only a moderate solubility in the solvent.



(155) **(156)**

Scheme 2.4 *Reagents and Conditions: i) Br_2, dimethylformamide, 20-30°C; ii) Br_2, dimethylformamide, 30-40°C*

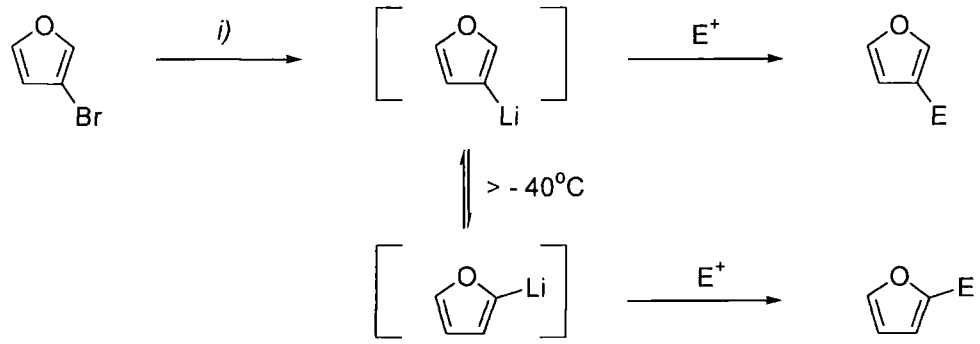
2.1.2 Lithiofuran Species

Furan and its homologues do not react with sodium or potassium, although they do with a liquid sodium-potassium amalgam. Furan has been metallated with other compounds; indeed, Gilman and Breur[133] showed that reaction with dibenzylmercury gave a 58% yield of 2-furoic acid. Carboxylation of the products of furan, sodium sand and *n*-amylchloride gave 2-5-difuroic acid (7%) and furoic acid (27%), suggesting either some of the dianion is formed or a stepwise dilithiation.

The use of lithio species has been well documented in the literature; for example, metallation of furan with phenyllithium gave 40% of 2-furoic acid after carboxylation, however, using methyllithium gave only an 8% yield of product. An interesting reaction involves the lithiation of 3-bromofuran with *n*BuLi in tetrahydrofuran. If the reaction is carried out at –78°C the 3-lithio species is formed as expected, but at temperatures > –40°C the 3-lithio rearranges to the 2-lithio isomer (**Scheme 2.5**).

The reaction of furan with *n*BuLi has been widely studied using different temperatures, solvents and equivalents of reactants. The first study was the reaction of furan and *n*BuLi at -78°C in diethyl ether, *i.e.* standard conditions for many lithiations. However, a test using the addition of phenaldehyde to lithiofuran gave none of the expected alcohol. Indeed we have found that while the literature holds many such reactions, we could consistently get only two procedures to work well. The first was the use of only 0.9 equivalents of *n*BuLi in diethyl ether at 0°C, the

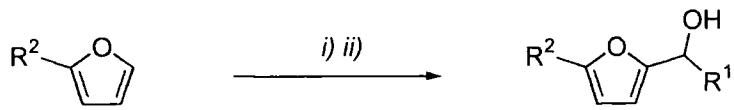
reaction then being heated at reflux for 3-4 h to form a yellow suspension which was then cooled to –78°C and the electrophile added.[134] The second, which also gave a high yield with methylfuran, involved lithiation with *n*BuLi in tetrahydrofuran at 0°C for 4 h, addition of the electrophile, then stirring at 0°C for another 3-4 h.[135] Both reactions gave similar yields, the second having advantages that it was performed at a more convenient temperature (0°C compared to –78°C) and used equimolar quantities of the starting materials.



Scheme 2.5 *Reagents and Conditions: i) nBuLi, THF, -78°C*

2.1.2.1 Pyridyl Alcohols

Of special interest to us was the reaction of the 2-furyllithium species with pyridine aldehydes. The product alcohols would lead, on oxidation, to the ketone, which upon ring expansion, would give bipyridyl systems. The lithiation of furan and 2-methylfuran was carried out using *n*BuLi (1.1 equivalent) in tetrahydrofuran at 0°C. The alcohols (**157-162**) which were formed (**Scheme 2.6**) were found to be relatively unstable to heat. Indeed, first attempts to isolate the products *via* distillation at reduced pressure caused resinification of the product, leading to a low yield (<1%). Any source of acid caused the solution to darken, hence, column chromatography on silica or using dichloromethane as the eluent caused the product to degrade. The alcohols (**157-162**) were purified using an alumina column with a 1:1 mix of ethyl acetate and hexane as the eluent. Hitherto, only alcohols (**158**) and (**159**) were known compounds. Due to the instability of the compounds, which have a shelf-life of only *ca* 48h at 20°C before resinification occurs, (**157-162**) were used immediately in the next step.



Scheme 2.6 *Reagents and Conditions: i) nBuLi, THF, 0°C; ii) R'CHO, 0°C*

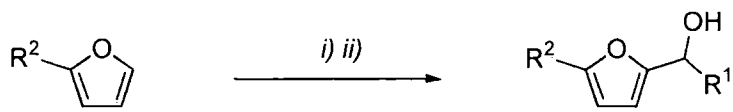
Product	R^1 / R^2	Yield (%)
157	R^1=2-pyridyl, R^2=H	45
158[136]	R^1=3-pyridyl, R^2=H	60
159[137]	R^1=4-pyridyl, R^2=H	56
160	R^1=2-pyridyl, R^2=Me	47
161	R^1=3-pyridyl, R^2=Me	48
162	R^1=4-pyridyl, R^2=Me	55

Table 2.2

Most of the alcohols were solids except (**157**), however, the melting points increased in the sequence 2-, 3-, 4-pyridyl. The 4-pyridyl compounds were also the most stable and easiest to isolate from the reaction.

2.1.2.2 Other Aromatic Alcohols

We also explored the synthesis of other aromatic furylalcohols, by reaction of the lithiofuran and an aldehyde. The results are shown in **Table 2.3**



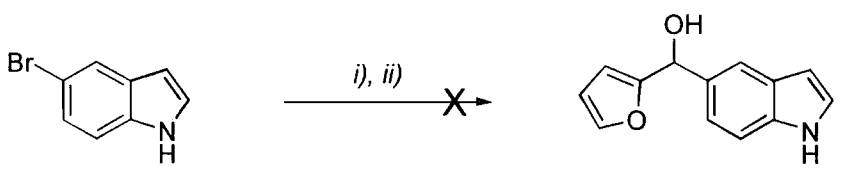
Scheme 2.7 *Reagents and Conditions: i) nBuLi, THF, 0°C; ii) R'CHO, 0°C*

Compound	R^1 / R^2	Yield (%)
163[138]	R^1=2-furyl, R^2=H	36
164	R^1=2-furyl, R^2=Me	18
165[139]	R^1=2-thienyl, R^2=H	28
166	R^1=2-thienyl, R^2=Me	22
167	R^1=3-quinolyl, R^2=H	48
168	R^1=3-quinolyl, R^2=Me	49
169	R^1=2-naphthyl, R^2=H	58
170	R^1=2-naphthyl, R^2=Me	42
171	R^1=ferrocenyl, R^2=H	48

Table 2.3

The lower molecular weight compounds (**163-166**) were isolated as yellow viscous oils, whereas the larger quinolyl, naphthyl and ferrocenyl alcohols (**167-171**) were solids. We also performed the comparable reaction by lithiation of 3-bromoquinoline and reaction with 2-furaldehyde giving (**167**). This method gave a slightly higher yield (58%) but this was not a vast improvement on the result (48%) in **Table 2.3**.

An attempt was also undertaken to prepare the indole derivative (**173**). 5-Bromoindole (**172**) when lithiated under normal lithiation procedures (e.g *n*BuLi at –78°C) does not give the 5-lithio species, but the *N*-lithio compound instead.[140]



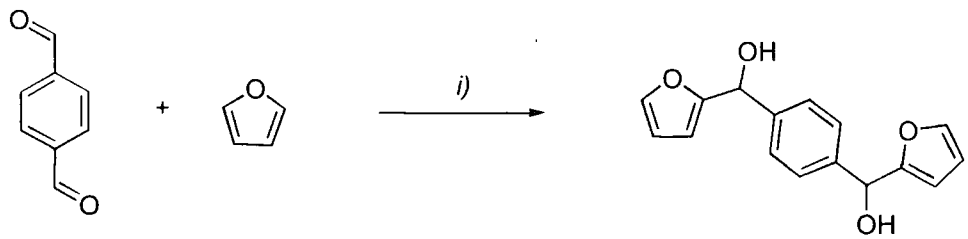
(**172**) (**173**)

Scheme 2.8 *Reagents and Conditions: i) tert-BuLi, THF, KH; ii) 2-furaldehyde*

However, we followed the work of Yang *et al*[141] which involved the use of potassium hydride and *tert*-BuLi. The potassium hydride is used to give the potassium salt of the 5-bromoindole whereby the lithiating agent cannot remove the amino hydrogen but instead substitutes with the bromine to give the lithiated species. 2-Furaldehyde was then added to the reaction and after stirring for 10h, ammonium chloride solution was added and the reaction worked up as usual. The alcohol (**173**) was not isolated from the reaction. Indeed, it seems the formation of the 5-lithio species did not occur. Other methods of making the ketone (**221**) derivative *via* reaction of 5-cyanoindole will be discussed below. (**Section 2.4.2**)

2.1.2.3 Reaction of Dialdehydes

The reaction of terephthaldicarboxaldehyde with two equivalents of the lithiofuran species gave the expected diol product (**175**) in 62% yield (**Scheme 2.9**). Terephthaldicarboxaldehyde (**174**) was chosen to minimize the steric hindrance that would occur during the subsequent two steps, *viz.* the oxidation to the diketone and the ring expansion. The insolubility of (**174**) in diethyl ether meant that the reaction was carried out in tetrahydrofuran.

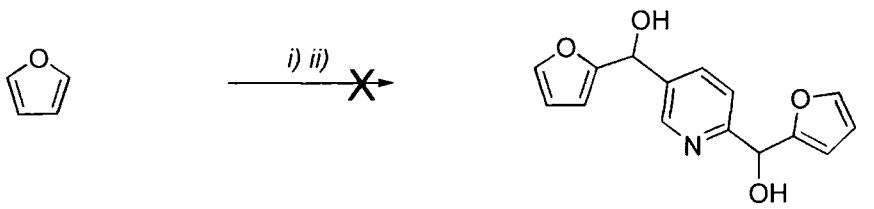


(**174**) (**175**)

Scheme 2.9 *Reagents and Conditions: i) nBuLi, THF, 0°C*

Significantly, diol (**175**) was purified by column chromatography on alumina using dichloromethane as the eluent, showing that in contrast to other furylalcohols the acidity of the dichloromethane does not cause the diol to resinify. Compound (**175**) was also stable in light and air without darkening, another characteristic which shows the increased stability of this diol.

After the success with terephthaldicarboxaldehyde (**174**) we turned our attention to the synthesis of the pyridine analogue (**177**). 2,5-Pyridindicarboxaldehyde (**176**) (prepared in 44% yield, from oxidation of 2,5-pyridinedimethanol with manganese dioxide[142]) was added to a solution of lithiofuran in tetrahydrofuran. However, we found that the dialdehyde was insoluble in either tetrahydrofuran or diethyl ether. Thus the starting materials were recovered, and the reaction yielded none of the



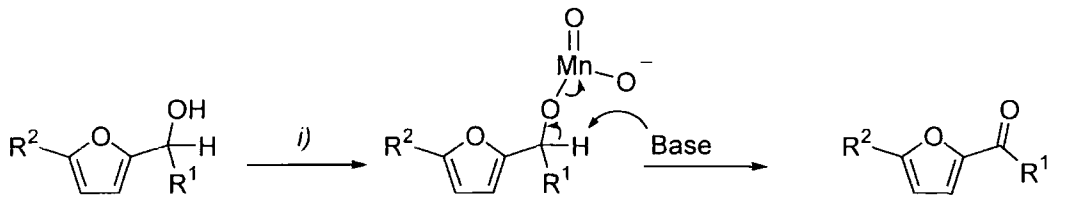
(**177**)

desired product.

Scheme 2.10 *Reagents and Conditions: i) nBuLi, THF, 0°C; ii) 2,5-pyridinedicarboxaldehyde (**176**), 0°C*

2.2 Oxidation of Furylalcohols

Furylalcohols have been oxidised to the corresponding ketones using various methodologies, *e.g.* the use of pyridinium chlorochromate (PCC) on alumina[143] or molecular sieves,[144] use of dimethyl sulfoxide,[145] pyridinium dichromate (PDC)[146] and manganese dioxide.[147] Our systems incorporate a secondary alcohol which on oxidation will give only a ketone. We found PCC and PDC to be too mild to oxidise the alcohol (**145**), indeed after a few days very little of the product had been formed. DMSO itself needs to be activated for the oxidation and this is usually done by the addition of a little acetic anhydride,[148] although pyridinium-sulfur trioxide[149] and *p*-toluenesulfonyl chloride[150] have also been used. This gives an acidic solution which may cause resinification of the furan; also, acetic anhydride has the abililty of reacting with the furan itself in a Friedel-Crafts acylation so these routes were not explored.

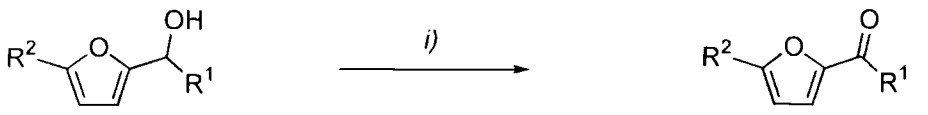


Scheme 2.11 Reagents and Conditions: i) MnO_2, DCM, 20°C

We chose to adapt the work of Miyakoshi,[151] who used manganese dioxide in benzene, but we used dichloromethane as the solvent. This oxidation has several good advantages over other oxidation reagents. The separation of the product from the managense dioxide is easily accomplished by filtration through a Celite plug, the filtrate then only contains the starting alcohol (if present) and the ketone product. Also, although the solution is acidic, we have seen little or no resinification of the furans even after several days of stirring. However, a drawback to this route is the length of time the reaction takes to go to completion.

2.2.1 Oxidation of Furlyalcohols (145-152)

Table 2.4 shows the oxidation of alcohols (**145-152**), synthesised as shown in **Table 2.1**.



178,R^1=*i*-Pr, R^2=H
179, R^1=*s*-But, R^2=H
180, R^1=Ph, R^2=H
181, R^1=*p*-Tolyl, R^2=H
182, R^1=*i*-Pr, R^2=Me
183, R^1=Ph, R^2=Me
184, R^1=*p*-Tolyl, R^2=Me

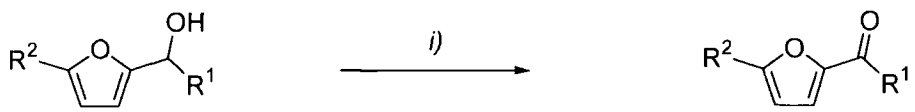
Scheme 2.12 Reagents and Conditions: i) MnO_2, DCM, 20°C

Table 2.4 clearly shows that the 5-methylfuran derivatives (**149-152**) take longer to oxidise than the 5-hydro derivatives (**145-148**). This is probably a steric factor due to the bulky size of the methyl group. The ketones, except (**184**), were purified by distillation at reduced pressure. Compound (**184**) did not distil due to its high boiling point, so was column chromatographed. The aromatic substituents (**147**), (**148**), (**151**) and (**152**) gave a higher yield of product than the aliphatic derivatives.

Alcohol	Ketone	Yield (%)	Reaction time (days)	Purification method and properties
145	**178**[12]	49	4	bp 40-42°C (0.2mmHg)
146	**179**[12]	54	5	bp 125-126°C (0.3mmHg)
147	**180**[152]	77	4	bp 50-52°C (0.3mmHg)
148	**181**[153]	86	4	bp 122-123°C (0.3mmHg) mp 30-32°C
149	**182**[154a]	43	7	bp 80-82°C (0.3mmHg)
151	**183**	58	10	bp 150-152°C (0.3mmHg)
152	**184**[154b]	80	4	Column SiO_2/CH_2Cl_2

Table 2.4

2.2.2 Oxidation of Pyridyl Alcohols



185,R^1=2-Py, R^2=H
186, R^1=3-Py, R^2=H
187, R^1=4-Py, R^2=H

188, R^1=2-Py, R^2=Me
189, R^1=3-Py, R^2=Me
190, R^1=4-Py, R^2=Me

Scheme 2.13 *Reagents and Conditions: i) MnO_2, DCM*

Alcohols (**157-162**) were all oxidised in good yields to give the corresponding ketones (**185-190**). The 2-pyridyl alcohols (**157**) and (**160**) are the least stable of the starting materials and this is shown in the lower yields compared to the 3- or 4-pyridyl compounds.

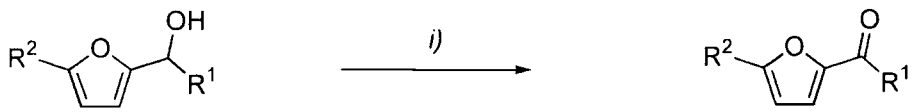
Alcohol	Ketone	Yield (%)[a]	Reaction time (days)
157	**185**[67]	74	3
158	**186**[136]	82	4
159	**187**[155]	77	3
160	**188**	75	4
161	**189**	79	4
162	**190**	84	4

[a] after purification by an alumina column, eluent EtOAc/hexane (1:1 $^{v}/_{v}$)

Table 2.5

2.2.3 Oxidation of Other Aromatic Alcohols

Alcohols from **Table 2.3** were oxidised using the same conditions of manganese dioxide in dichloromethane. The results of the oxidations are shown in **Table 2.6** below.



191,R^1=2-furyl, R^2=H **192**, R^1=2-furyl, R^2=Me
193, R^1=2-thienyl, R^2=H **194**, R^1=2-thienyl, R^2=Me
195, R^1=3-quinolyl, R^2=H **196**, R^1=3-quinolyl, R^2=Me
197, R^1=2-naphthyl, R^2=H **198**, R^1=2-naphthyl, R^2=Me
199, R^1=ferrocenyl, R^2=H

Scheme 2.14 *Reagents and Conditions: i) MnO_2, DCM, 20°C*

Alcohol	Ketone	Yield (%)	Reaction time (days)
163	**191**[156]	42[a]	3
164	**192**	36[a]	4
165	**193**[157a]	0	4
166	**194**	0	4
167	**195**	87[a]	4
168	**196**	77[a]	4
169	**197**	77[a]	4
170	**198**	89[a]	4
171	**199**[157b]	94[b]	1

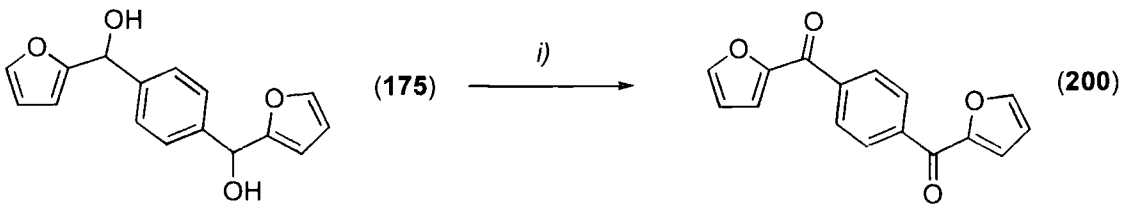
[a] after purification by an alumina column, eluent EtOAc/hexane (1:1 $^{v}/_{v}$); [b] after purification by an alumina column; eluent EtOAc.

Table 2.6

Oxidation of the thienyl alcohols (**165**) and (**166**) afforded no isolable product, and the starting material could not be recovered. Due to the reactivity of the starting alcohols, which must be reacted within a day of their synthesis or the solution turns dark, we think that the acidic solution caused the furan ring to open. The oxidation of the other alcohols affords the ketones, with the yield from the furan alcohols (**163**) and (**164**) being low. This is probably due to the same ring opening that occurs in the thiophene case but shows the former to be less susceptible to acid. (**191**) and (**192**) proved to be dark yellow oils, whereas the naphthyl and quinolyl ketones were pale yellow solids.

2.2.4 Oxidation of Diol, 175

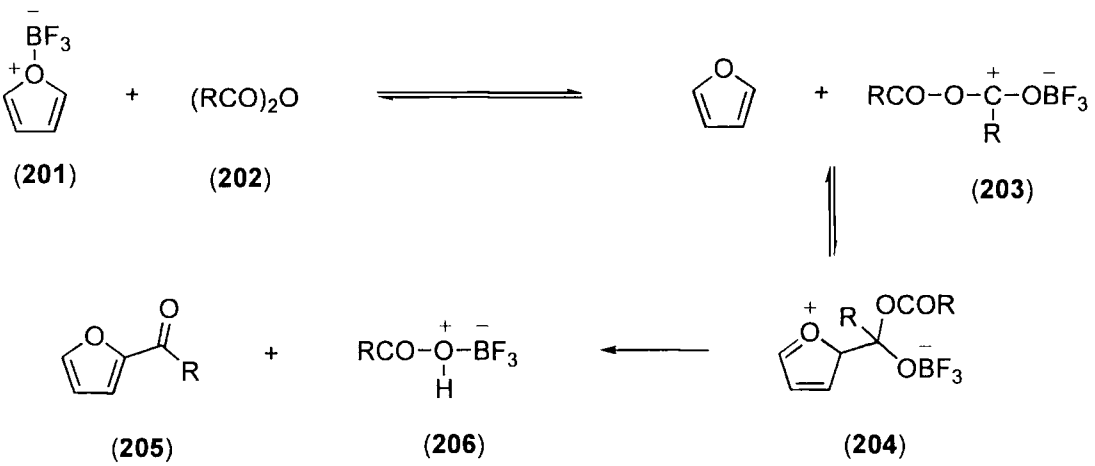
Similarly, diol (**175**) gave the ketone (**200**) in 76% yield showing it is stable to acid, with no need for purification by chromatography prior to recrystallisation from hexane.



Scheme 2.15 Reagents and Conditions: i) MnO_2, DCM, 20°C

2.3 Friedel-Crafts Acylation of Furan

There are reports that furylketones can be obtained by Friedel-Crafts acylation of furan, with both acid anhydrides and acid chlorides being employed, although the former gives better results. It is beneficial to minimise the contact time of the furan and condensing agent, either by careful addition of the furan or use of an ample amount of solvent. Elevated temperatures are detrimental to the yield, thus condensation of furan and acetic anhydride with zinc chloride at 0-20°C gave a 66% yield of 2-furylmethyl ketone, whereas raising the temperature to 30-60°C gave only a 40% yield.[158] The catalyst used for the reaction also leads to resinification of the furan, which depending on the reaction conditions may involve formation of a coating on the surface of the condensing agent or may prevent any products being isolated. According to Calloway[159] the efficiency of metal chloride catalysts decreases in the order: $SnCl_4$, $FeCl_3$, $AlCl_3$, $TiCl_4$.

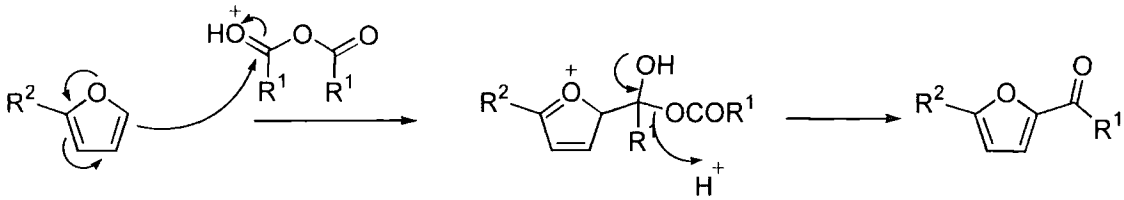


Scheme 2.16

A mention should be made of the work by Heid and Levine[160] on the effectiveness of catalytic amounts of boron trifluoride complexes in the acylation of furan and its derivatives with acid anhydrides. The etherate (**201**) reacts with the acid anhydride (**202**) to give the new complex (**203**), which then condenses with furan to give (**204**). Decomposition of (**204**) produces the ketone (**205**). It was also postulated that (**206**) being continuously recycled was the actual condensing agent, hence the catalytic nature of the reaction (**Scheme 2.16**).

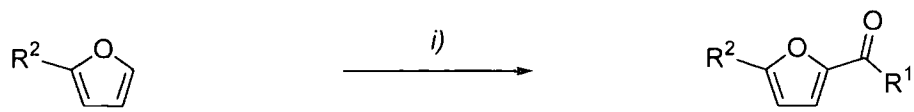
2.3.1 Acylation of Substituted Furans

As an alternative route to 2-acylfurans we decided to follow the work by Hartough *et al.*[158] which involves the reaction of strong inorganic oxyacids, such as orthophosphoric acid and acid anhydrides, with no diketone being formed. A mechanism is shown in **Scheme 2.17**.



Scheme 2.17

We have shown that many different acid anhydrides can be used ranging from simple alkyl derivatives in high yields, to aromatic derivatives in low yields (**Scheme 2.18**). The furan ring itself can contain other substituents although, of course, the 2-position must be free. Results are given in **Table 2.7**



Scheme 2.18: *Reagents and Conditions: i) $R^1COOCOR^1$, Phosphoric acid, 60°C*

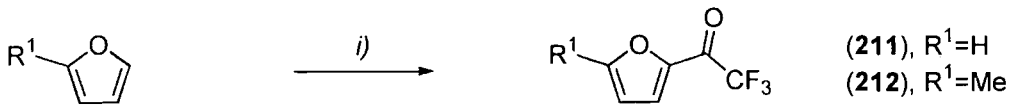
Ketone	R^1 / R^2	Yield (%)	Distillation
145[126]	R^1=*iso*-Pr, R^2=H	90	bp 40-42°C (0.2 mmHg)
149[128]	R^1=*iso*-Pr, R^2=Me	78	bp 80-81°C (0.3 mmHg)
207	R^1=*iso*-Pr, R^2=Et	41	bp 85-87°C (0.3 mmHg)
147[126]	R^1=Phenyl, R^2=H	10	None
208[159]	R^1=Et, R^2=H	76	bp 95-100°C (0.3 mmHg)
209	R^1=Et, R^2=Me	47	bp 102-105°C (0.2 mmHg)
210[160]	R^1=Me, R^2=Et	46	bp 120-122°C (0.3 mmHg)

Table 2.7

The reactions were carried out by warming a solution of the acid anhydride and the furan to 40°C. The heat was then removed, the inorganic acid added, and the solution heated at 60°C for 2 h. The furan ring is inherently unstable to acids and under these conditions some ring opening occurs. The yield decreases with increasing size of the alkyl group at the 5-position, as shown by the trend in compounds (**145**), (**149**) and (**207**). In the case of (**208**) there is no group on the ring so the acid anhydride can react at either α-position of furan to give the same product, but the reaction of 2-methylfuran and propionic anhydride giving (**209**) must take place at the 5 position of the ring, the bulky methyl group may cause some steric hindrance.

2.3.2 Synthesis of Trifluoromethylketones

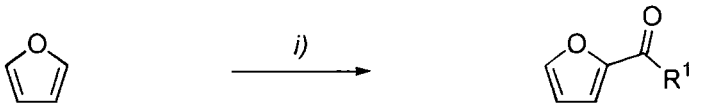
Compounds (**211**)[161] and (**212**)[162] were identified as potential precursors to novel trifluoromethyl pyridinols. The attempted synthesis of (**211**) *via* the reaction of furan, trifluoroacetic anhydride and phosphoric acid appeared to give no reaction. However, (**211**) was synthesised by the reaction of trifluoroacetic anhydride and furan in pyridine at 10°C albeit in only 23% yield. The 5-methyl derivative of (**212**) was prepared similarly in 23% yield (**Scheme 2.19**).



Scheme 2.19 *Reagents and Conditions: i) trifluoroacetic anhydride, pyridine, 10°C*

2.3.3 Synthesis of Aromatic Ketones Using $SnCl_4$

While the use of acid anhydrides gives good yields for simple alkyl groups (**Table 2.7**) only a low yield (10%) was obtained for R^1=Phenyl. We chose to look into the synthesis of diheteroyl monoketones by the direct Friedel-Crafts acylation of furan. Reaction of furan, the appropriate acid chloride and tin chloride at 0°C in dichloromethane gave the corresponding ketones (**180**), (**191**), (**193**) and (**197**) (**Scheme 2.20**). The low yields arise due to the acidity of the reaction conditions, which causes the furan ring to open to give succinaldehyde. The reaction of furan with acid chlorides has been studied previously; however, the use of heteroyl acid chlorides has not been studied so comprehensively. Reaction of 2-methylfuran in these Friedel-Crafts reactions has only been shown to occur with 5-nitrothiazole-2-carbonyl chloride[163] or 2-methylbutyryl chloride[164] with $AlCl_3$ as the catalyst and 1,2-dichloroethane as the solvent, giving low yields.



Scheme 2.20 *Reagents and Conditions: i) R^1COCl, $SnCl_4$, DCM, 20°C*

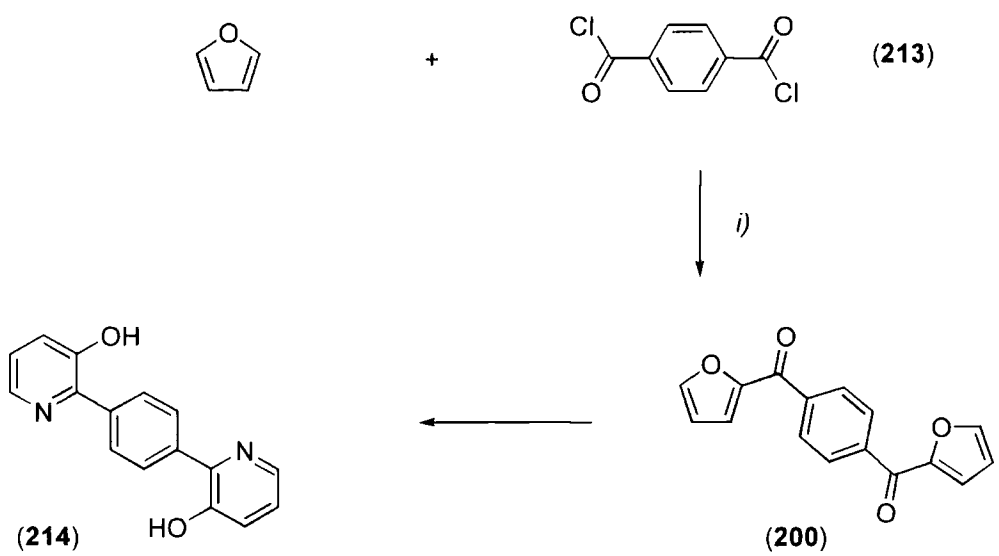
Compound	R^1	Yield (%)
180[152]	Phenyl	37
191[156]	2-furyl	44
193[157]	2-thienyl	24
197	3-naphthyl	21

Table 2.8

We have found that the similar reaction of 2-methylfuran with 2-furoylchloride or 2-thienylchloride in dichloromethane with tin chloride at 0°C did not give the corresponding ketone. The reactions polymerise to a much greater extent than with furan and none of the desired product was isolated.

2.3.3.1 Reaction of *Bis*-Acid Chlorides

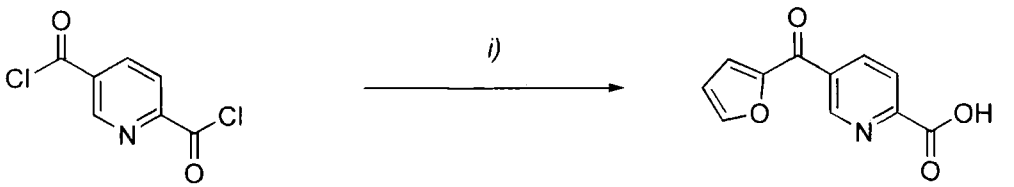
Due to the reaction proceeding with simple acid chlorides we examined the reaction of furan with a *bis*-acid chloride. Hence the reaction of terephthaloyl chloride (**213**) with furan should give the *bis*-ketone (**200**), which on reaction with ammonia could give the tricyclic system (**214**) (**Scheme 2.21**).



Scheme 2.21 *Reagents and Conditions: i) $SnCl_4$, DCM, 20°C*

We found that the insolubility of (**213**) in dichloromethane was a problem: all the other suitable solvents tried including, 1,2-dichloroethane and carbon disulfide failed to give sufficient solubility of the acid chloride. A different synthesis of (**200**) was achieved *via* reaction of lithiofuran with terephthalaldehyde, and oxidation of the product (**175**) to the ketone.

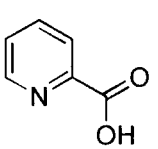
The reaction of 2,5-pyridinedicarbonyl dichloride (**215**), synthesised from the reaction of the 2,5-pyridinedicarboxylic acid and thionyl chloride, gave the mono-ketone (**216**) in 27% yield (**Scheme 2.22**). The structure of (**216**) has been assigned by comparison of its ^{13}C NMR spectrum with those of 2-, 3-, and 2,5-pyridinecarboxylic acids.



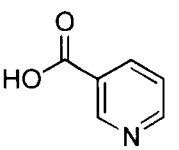
(**215**) (**216**)

Scheme 2.22 *Reagents and Conditions: i) furan, $SnCl_4$, DCM, 20°C*

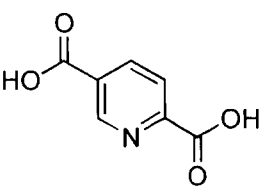
The C-2 carbon of (**216**, δ 152) shows a similar chemical shift to the C-2 carbons of (**217**, δ 148) and (**219**, δ 151), whereas the C-5 of (**216**, δ 138) has shifted downfield compared to (**218**, δ 127) and (**219**, δ 129). Clearly this suggests that the acid chloride group at the 5-position of (**215**) is more reactive than the 2-position. Indeed, even increasing the molar ratio of furan and tin chloride to > 10 equivalents failed to get the acid chloride at C-2 to react. Product (**216**) was always the only isolated product.



(**217**)



(**218**)

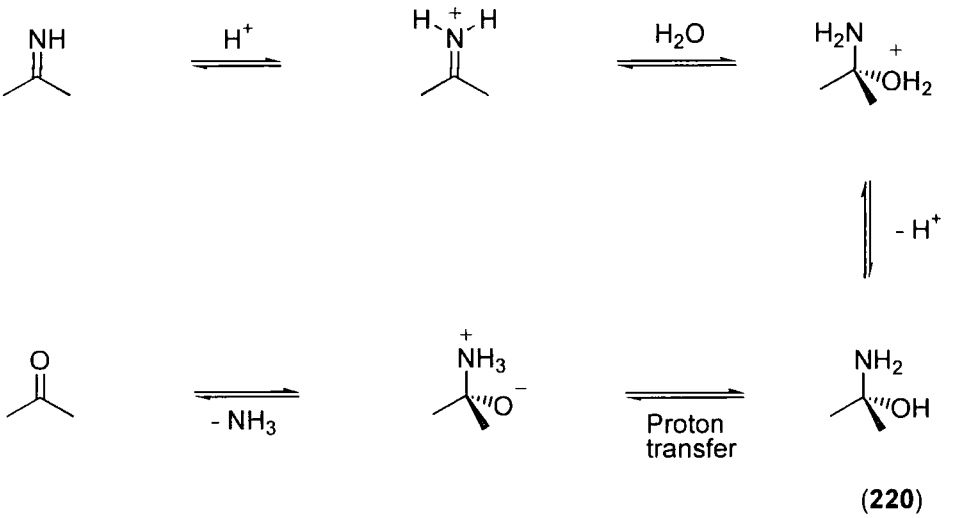


(**219**)

2.4 Reaction of Nitriles

Nitriles share many similarities to the chemistry of carbonyl compounds, notably the presence of electrophilic carbon atoms. Thus nitriles are attacked by nucleophiles to yield sp^2-hybridized intermediate imine anions in a reaction analogous to the formation of an sp^3-hybridized intermediate by nucleophilic addition to a carbonyl group.

The reaction of nitriles with lithio agents gives a ketimine intermediate, which can be hydrolysed to give the ketone (**Scheme 2.23**). Garcia *et al*[165] in their study of 2-furyllithium thus synthesised 2-benzoylfuran using benzonitrile in 89% yield.

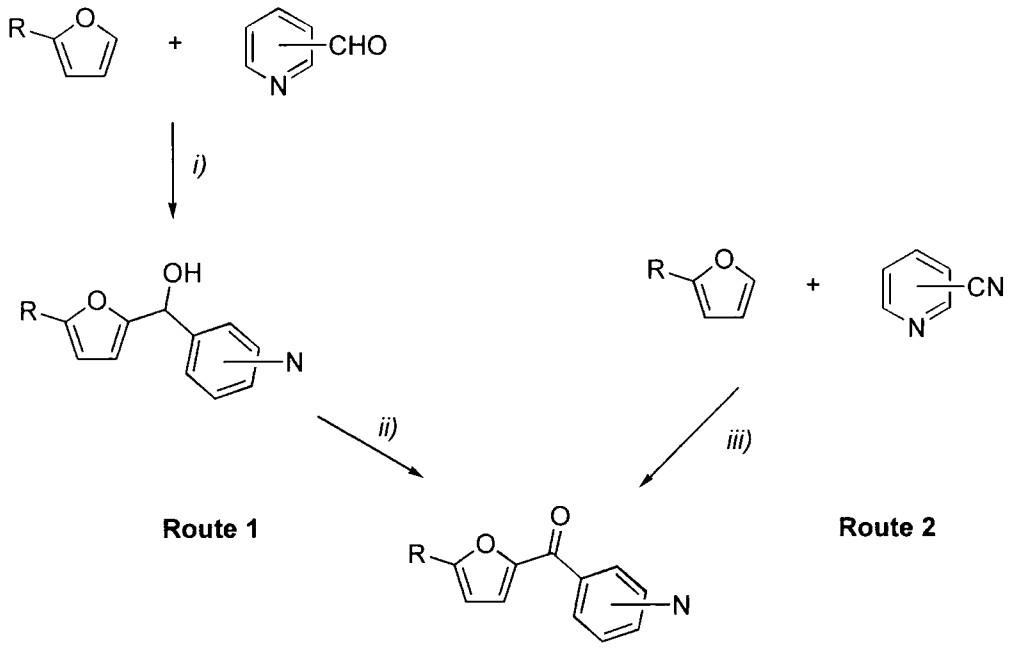


Scheme 2.23

The imine is hydrolysed by a reversible, acid-catalysed process. The nitrogen is first protonated, then nucleophilic attack by water and loss of a proton gives the carbinolamine intermediate (**220**), a neutral amino alcohol. Proton transfer leads to a molecule which loses ammonia, a good leaving group, to give the ketone.

2.4.1 Cyanopyridines

We chose to examine the synthesis of pyridine ketones (**185–190**) in one pot from cyanopyridines. Previously, these ketones have been made in modest overall yield by lithiation of the furan, reaction with a pyridine aldehyde and oxidation of the subsequent alcohol with manganese dioxide (**Schemes 2.6** and **2.13**).

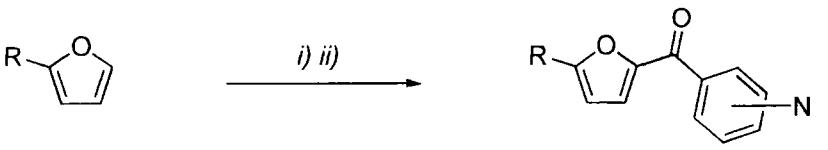


Scheme 2.24 *Reagents and Conditions: i) nBuLi, Et_2O, reflux; ii) MnO_2, DCM; iii) nBuLi, Et_2O, reflux; then 1M HCl, 60°C, 2h*

The lithiation of the furans was accomplished, as previously, by reaction with *n*BuLi (1.1 equivalents) in diethyl ether at 0°C. The cyanopyridine was added at -78°C and after 1 h the solution, which turned a dark brown, was quenched with water. The imine, thus formed, was not isolated. Hydrolysis with 1M HCl afforded the desired ketones (**185-190**) in good yields.

Lipinski *et al.*[66] quoted an 18 % yield for the synthesis of 4-pyridyl ketone (**187**) by the same reaction. However, although we followed their lithiation procedure, our subsequent procedure and yield of 69% is clearly a vast improvement over the literature method. The key difference is the pH of the solution during hydrolysis, ours

being a much lower pH, and our compound was not sublimed but column chromatographed instead. (**185**) has also been reported in the literature[67] but the other analogues have not.



185, R=H, 2-pyridyl
186, R=H, 3-pyridyl
187, R=H, 4-pyridyl
188, R=Me, 2-pyridyl
189, R=Me, 3-pyridyl
190, R=Me, 4-pyridyl

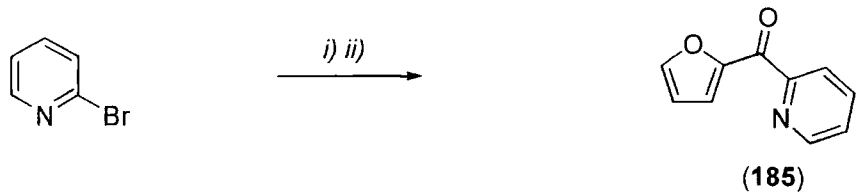
Scheme 2.25 *Reagents and Conditions: i) nBuLi, Et_2O, 0°C, then reflux 2h; ii) cyanopyridine, -78°C*

Table 2.9 below gives the yields for the synthesis of the six ketones from the reaction shown in **Scheme 2.25** (Route 2) along with the overall yields obtained from the other route used previously (Route 1, **Scheme 2.24**). Clearly route 2 (a one-pot process) is more efficient.

Ketone	Route 1 Yield (%)	Route 2 Yield (%)	M. P. (°C)
185[67]	33	65	Oil
186[136]	49	68	62-64
187[66]	43	69	79-81
188	31	65	64-66
189	36	74	64-66
190	42	76	79-80

Table 2.9

Synthesis of (**185**) has also been achieved by the reaction of 2-furonitrile with the lithiated pyridine species (**Scheme 2.26**). However, this gives a much lower yield of the product, for example for the ketone (**185**) the yield is only 38%, compared to synthesis *via* reaction of 2-furyllithium and 2-cynaopyridine (65% yield).

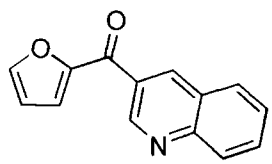


(**185**)

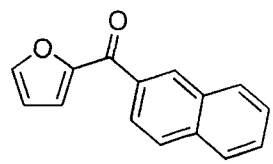
Scheme 2.26 *Reagents and Conditions: i) nBuLi, Et_2O, 0°C, then reflux 3-4h; ii) 2-furonitrile, -78°C*

2.4.2 Other Cyano Compounds

We have further studied the reactions of lithiated furan with other cyano arenes. For example, (**195**) was synthesised *via* route 1 in a 43% overall yield. We have found that this new route gives a yield of 56%, a slight improvement. Compound (**197**) has been prepared in the same way in 62% yield in comparison with 52% *via* route 1, and direct acylation of furan with 2-naphthoyl chloride gave only a 21% yield.

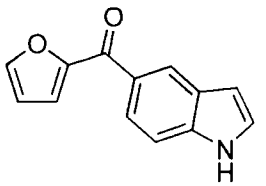


(**195**)

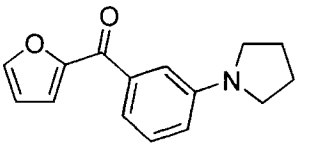


(**197**)

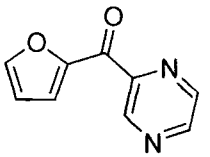
Route 2 has been applied to the formation of novel compounds (**221**, 62%), (**222**, 48%), (**223**, 53%) and (**224**, 42% yield).



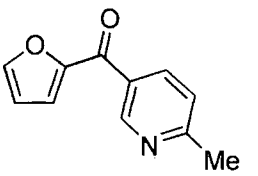
(**221**)



(**222**)



(**223**)

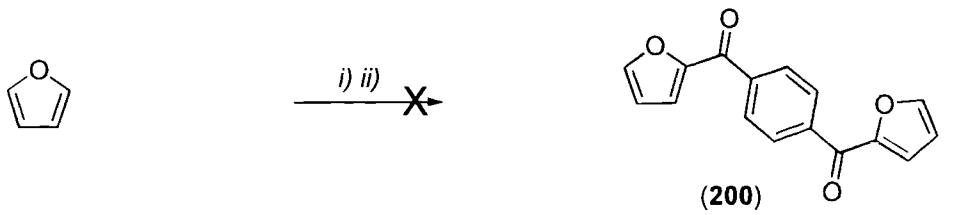


(**224**)

The pyrazine derivative (**223**) in particular would be difficult to make *via* other routes due to the instability of many pyrazine compounds. Metallations of pyrazine have not been widely reported because it readily undergoes nucleophilic addition. Pyrazine-2-carboxaldehyde is very unstable and rapidly decomposes.

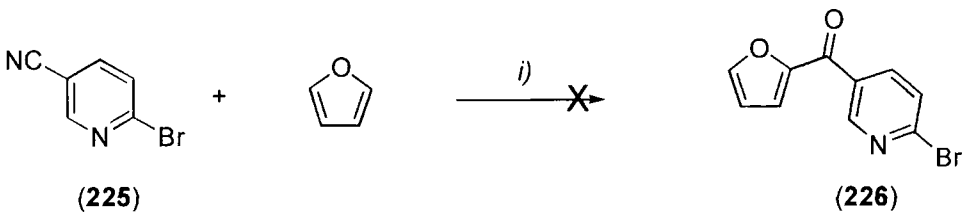
2.4.3 Reaction of Dicyano Compounds

While the reaction of cyano compounds with lithiated furans has been reported before, most notably by Siemanowski[67] there has been no mention of the use of dicyano compounds in this reaction to give *bis*-furyl ketones. Initially we attempted to use the method of Siemanowski and Witzel[67] to react 1,4-dicyanobenzene with two equivalents of 2-furyllithium with the hope of obtaining the *bis*-ketone, (**200**). However, on addition of 1,4-dicyanobenzene the solution turned a dark purple colour and on work-up none of the ketone could be isolated (**Scheme 2.27**).



Scheme 2.27 Reagents and Conditions: i) nBuLi, THF, 0°C; ii) 1,4-dicyanobenzene, 0°C

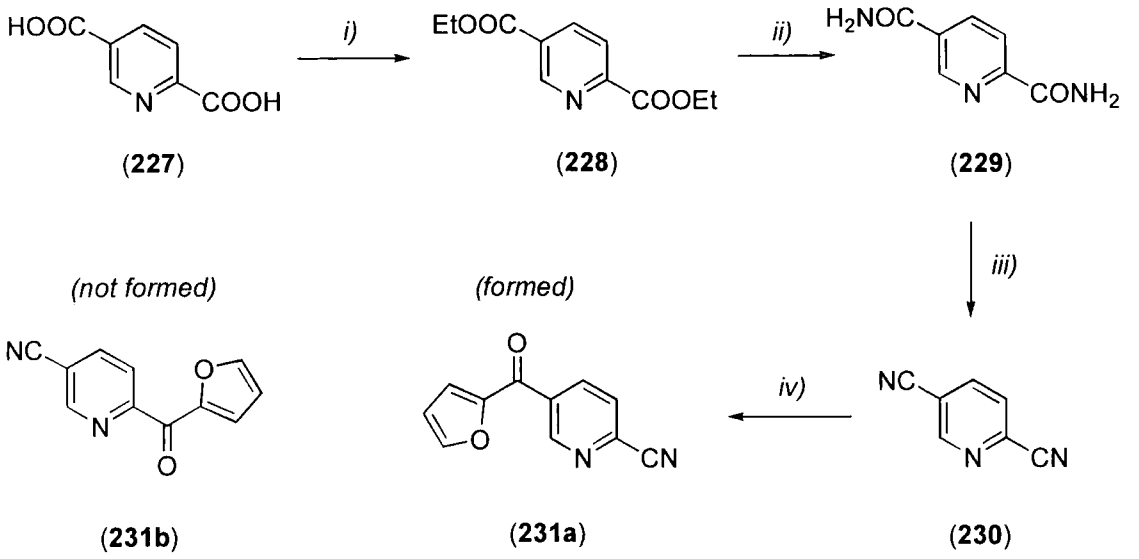
We considered that the presence of an electron-withdrawing group on the benzene ring may disfavour the reaction, and indeed we found that the similar reaction of 2-bromo-4-cyanobenzene (**225**) with 2-furyllithium did not produce the desired ketone, (**226**) (**Scheme 2.28**).



Scheme 2.28 Reagents and Conditions: i) nBuLi, Et_2O, 0°C

2.4.3.1 Synthesis of 2,5-Dicyanopyridine

We therefore turned to a similar reaction of a 2,5-disubstituted pyridine derivative, to see if either (or both) of the groups would react with 2-furyllithium. 2,5-Dicyanopyridine is not commercially available and was synthesised using **Scheme 2.29**. Stirring pyridine-2,5-dicarboxylic acid (**227**) in ethanol with a few drops of concentrated sulphuric acid, gave the diethyl ester (**228**). This was then reacted with ammonia solution giving the diamide, (**229**), which in turn was dehydrated using phosphorus oxychloride to give (**230**).

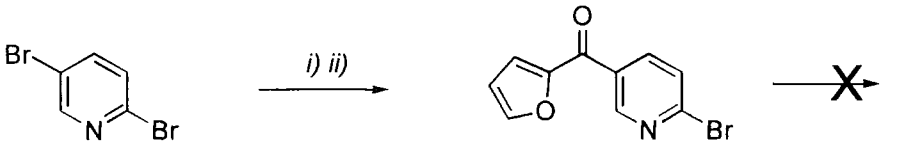


Scheme 2.29 *Reagents and Conditions: i) EtOH, H^+; ii) NH_4OH, reflux, iii) $POCl_3$, pyridine, iv) furan, nBuLi, Et_2O*

Compound (**230**) was then reacted with two equivalents of 2-furyllithium. The ^1H NMR spectrum of the isolated product suggested that only one of the cyano groups had reacted, and a single isomer had been formed in 28% yield. A comparison of the ^{13}C NMR spectra of 2,5-dicyanopyridine (C2 δ 139, C5 δ 116) with that of the product, showed that C2 (δ 142) of the product still had a cyano group attached to it, whereas the resonance from C5 (δ 131) had shifted in the spectrum due to substitution by the ketone group. Thus we established that the product is (**231a**) and not (**231b**).

2.4.4 Reaction of Dilithio Species

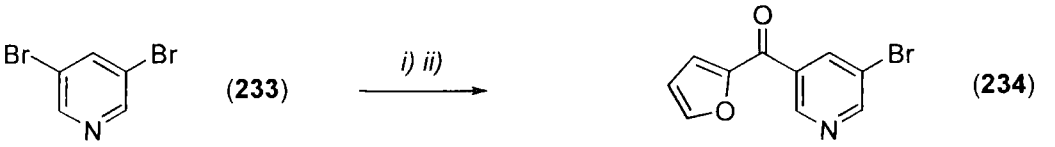
From work done earlier (**Section 2.4.1**) we have seen that the reaction can be inverted and a lithiated species reacted with 2-furonitrile to give a ketone, in a lower yield. Due to the failure of the reaction of dicyano compounds (**Section 2.4.3**) we sought to react a dilithio species with 2-furonitrile.



(232) (226)

Scheme 2.30 *Reagents and Conditions: i) nBuLi (1 eq), Et_2O, 0°C; ii) 2-furonitrile*

Work by Bolm *et al.*[166a] has shown that 2,5-dibromopyridine (**232**) can either be monolithiated with one equivalent of *n*BuLi or dilithiated with two equivalents. Bolm has shown that one equivalent of *n*BuLi removes the bromine at the C-5 position selectively. He also showed that a second equivalent of *n*BuLi in a stepwise process will remove the second bromine atom. Following this work, selective monolithiation of (**232**) and addition of 2-furonitrile, gives (**226**) in 30% yield, but further lithiation could not remove the second bromine atom (**Scheme 2.30**).

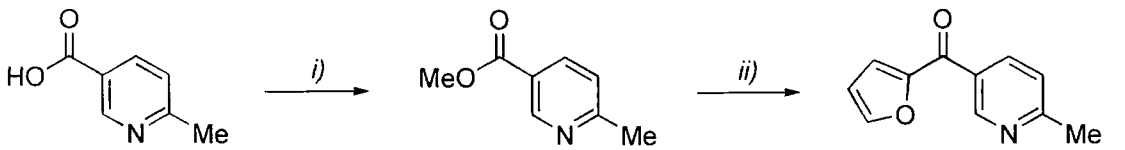


Scheme 2.31 *Reagents and Conditions: i) nBuLi (1 eq), Et_2O, 0°C; ii) 2-furonitrile*

We were also able to react 3,5-dibromopyridine (**233**) with one equivalent of 2-furyllithium to give (**234**) in 11% (**Scheme 2.31**).

2.5 Reaction of Esters

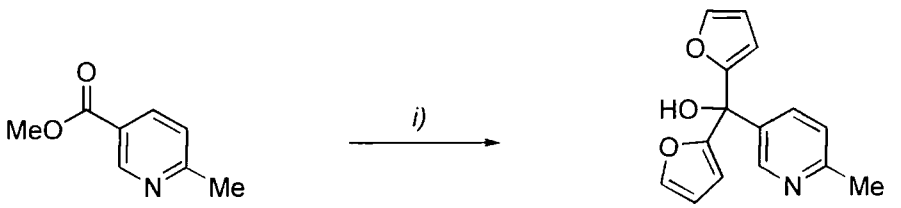
Due to problems involved with the cyano reactions, we chose to examine the reaction of pyridylesters with 2-furyllithium.



(235) (236) (224)

Scheme 2.32 Reagents and Conditions: i) methanol, H^+, reflux, 16h; ii) nBuLi, furan (1 eq), Et_2O, 0°C

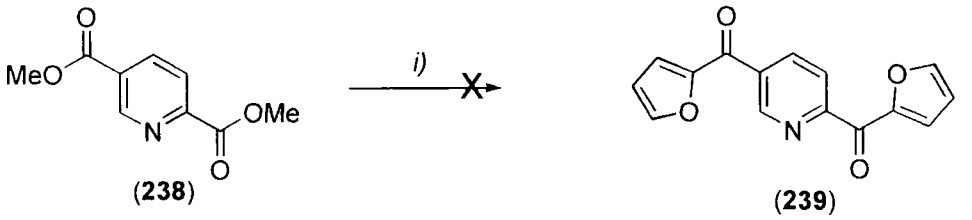
Ester (**236**), which was prepared heating to reflux 6-methylnicotinic acid (**235**) in methanol, with a few drops of sulphuric acid, was added to 2-lithiofuran and reacted in the usual way. The ketone (**224**) was isolated in 45% yield (**Scheme 2.34**). We found that two equivalents of the 2-furyllithium will react with the ester to give the novel alcohol (**237**) in 43% yield (**Scheme 2.33**).



(236) (237)

Scheme 2.33 Reagents and Conditions: i) nBuLi (2 eq), furan (2 eq), Et_2O, 0°C

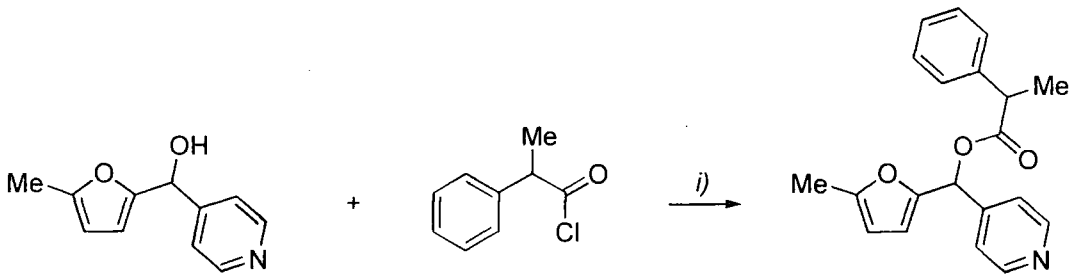
The success of reacting the esters with 2-furyllithium gave us hope for making the *bis*-ketone (**239**), from diester (**238**), which was synthesised in 43% yield from 2,5-pyridinedicarboxlyic acid. To a solution of 2-furyllithium in diethyl ether, 0.5 equivalents of (**238**) were added (**Scheme 2.34**), but tlc analysis of the reaction mixture showed that the esters had not reacted, and indeed only the starting ester was isolated. This contrasts with the observation that ester (**236**) had reacted to give the ketone (**224**), suggesting that having another ester group, at C-2, on the pyridine ring deactivates this ester to nucleophilic addition.



Scheme 2.34 Reagents and Conditions: i) nBuLi (2 eq), furan (2 eq), Et_2O, 0°C

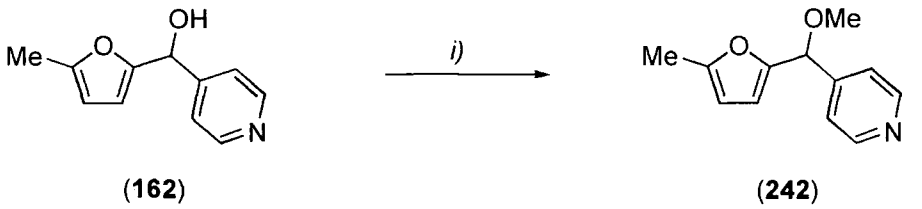
2.6 Reaction of Furan Alcohol, 162

As an aside we chose to look at the formation of the ester (**241**) from furan alcohol (**162**). Our first attempt at the synthesis involved reaction of (**162**) with phenyl propionic acid chloride (**240**) (made from phenyl propionic acid and thionyl chloride), but this gave no product. Using triethylamine as a base and addition also gave no reaction. The use of sodium hydride as a base gave (**241**) in 36% yield.



Scheme 2.35 Reagents and Conditions: i) NaH, THF

To show the reactivity of this alcohol the methyl ether (**242**) was formed by reaction with methyl iodide in tetrahydrofuran after the anion is formed by addition of sodium hydride. (**242**) was synthesised in 58% yield.



Scheme 2.36 Reagents and Conditions: i) NaH, MeI, THF

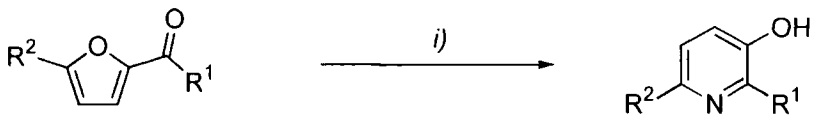
Chapter 3

3-Hydroxypyridines

The second chapter described the synthesis of 2-furyl ketones. This chapter concerns further reactions of these ketones with sources of ammonia to give substituted 3-hydroxypyridines, exploring the effects of temperature, time of reaction and solvents on the yield of the reactions. Later in the chapter we will describe some reactions of the 3-hydroxypyridines, namely the synthesis of benzyl ethers.

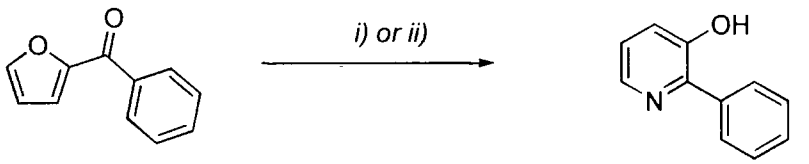
3.1 Formation of 3-Hydroxypyridines

A general method for the preparation of 3-hydroxy-2-alkylpyridines is the Hoffmann degradation of 2-alkylnicotinic acids.[166b,c] The preparation of higher alkylated 3-hydroxypyridines is harder due to difficulties in making the starting material and the side-chain. The first reported use of ammonia in the reaction of 2-furyl ketones to the 3-hydroxy-2-arylpyridines was reported by Leditschke[61] in 1952. He used either ammonium chloride and ammonia or ammonium acetate to facilitate the reaction. Gruber[60] studied simple 2-alkyl-3-hydroxypyridines and found that heating them with 2-3 moles of ammonia in an alcoholic solution in a sealed tube at 170°C for 15 h (**Scheme 3.1**) gave the best results. The ammonia solution was prepared by saturating absolute ethanol at 0°C. The reaction mixture was worked up by evaporating the alcohol under reduced pressure, distilling the residue *in vacuo*, and extracting a solution of the distillate in 2M sodium hydroxide with chloroform to remove the neutral contaminants. The alkaline solution was then neutralised and the hydroxypyridine extracted with chloroform.



Scheme 3.1 *Reagents and Conditions: i) aq. NH_3 or NH_3/EtOH, NH_4Cl at 170°C, 15h*

Gruber found that the reaction of 2-acetylfuran gave 3-hydroxypyridine in only 4.6% yield, while the yield increased rapidly with increasing size of R^1 and reached 74% for 3-hydroxy-2-propylpyridine. Equally satisfactory yields were obtained whether R^1 was a branched or straight chain. However, the rearrangement of 2-phenylfurylketone under the same conditions gave only a 5.4% yield of the pyridine product. The Leditschke method of heating the ketone in ammonium acetate, without the alcoholic solution, gives a much higher yield of 59% for the 2-phenylfuryl ketone (**Scheme 3.2**).



Scheme 3.2 *Reagents and Conditions: i) NH_3/EtOH, 175°C, 24h; ii) NH_4OAc,*

3.1.1 Rearrangement of Simple Alkyl and Aryl Ketones

We chose to examine the reaction of the simple ketones (**see Table 3.1**), using both the Gruber method of an alcoholic solution (NH_3/EtOH, NH_4Cl) and a variation of the Leditscke method (aq. NH_3), using 0.880 ammonia solution instead of ammonium acetate. The reactions were all heated to a temperature of 150°C for 15 h in a sealed Carius tube. Work-up involved removal of all the solvent under reduced pressure and distillation using a Kugelrohr apparatus to give the 3-hydroxypyridine derivative. The yields are compared in **Table 3.1**. 3-Hydroxypyridines (**243**) and (**247**) come from reaction of the commercially available ketones.

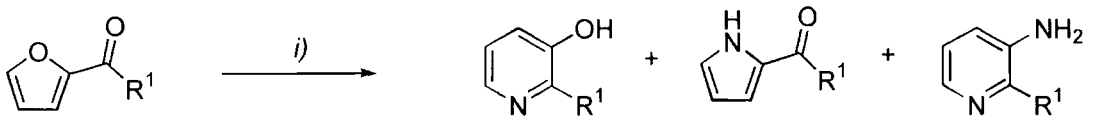
Pyridine	Ketone	R^1/R^2	aq. NH_3 Yield (%)	NH_3/EtOH Yield (%)	Melting point (°C)
243[167]	-	R^1=Me, R^2=H	23	2	168-169
244[60]	**145**	R^1=*i*-Pr, R^2=H	78	23	193-195
245[61]	**147**	R^1=Ph, R^2=H	21	9	202-204
246[61]	**148**	R^1=*p*-Tol, R^2=H	17	6	199-200
247[168]	-	R^1=Me, R^2=Me	30	45	210-213
248	**149**	R^1=*i*-Pr, R^2=Me	46	47	190-192
249	**151**	R^1=Ph, R^2=Me	20	22	230-232
250	**152**	R^1=*p*-Tol, R^2=Me	16	14	241-243
251[60]	**208**	R^1=Et, R^2=H	18	23	135-137
252[60]	**209**	R^1=Et, R^2=Me	24	53	171-173
253[169]	**210**	R^1=Me, R^2=Et	16	48	176-178

Table 3.1

Table 3.1 shows that the use of a non-alcoholic solution gives a higher yield when R^2=H, and R^1 is an alkyl or aryl group. The yield rises with increasing size of the alkyl chain, but decreases for aryl groups. Also, the size of R^2 affects the yield significantly, the increase in yield from 2% for (**243**) to 45 % for (**247**), occurs just with a change of hydrogen for a methyl group. Indeed, with an increase of the size of R^2 it is preferential to use an alcoholic solution, *i.e.* Gruber's method, of using and ethanolic ammonia solution.

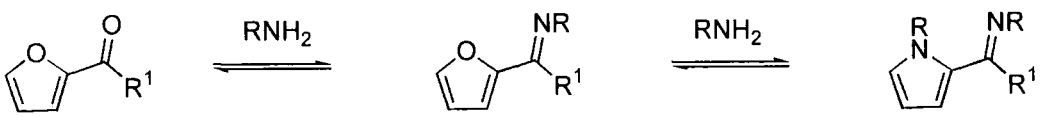
There is only a slight decrease in the yield by changing the aryl group from the phenyl (**245**), (**249**) to *p*-tolyl (**246**), (**250**) but this is unlikely to be due to the increased steric hindrance of the *p*-tolyl group. The ketones leading to compounds (**243**) and (**247**) were bought commercially. The ammonia must first react with the ketone to form an imine, and the large methyl group may affect this initial step to a slight extent.

All the yields are low compared to many other reactions, with the highest yield being just 53%. However, these have not been optimised; all the reactions were performed at the same temperature of 150°C and carried out for 15 h. It has been shown that lowering the temperature of the reaction to around 100°C and decreasing the time may improve the yield. The poor yield can be attributed to the other products produced from the reaction. These reactions can give a variety of products but the major products are the 3-hydroxypyridine, 3-aminopyridine, and 2-acylpyrrole, along with unreacted starting material (**Scheme 3.3**).



Scheme 3.3 *Reagents and Conditions: i) NH_3, 150°C, 15h*

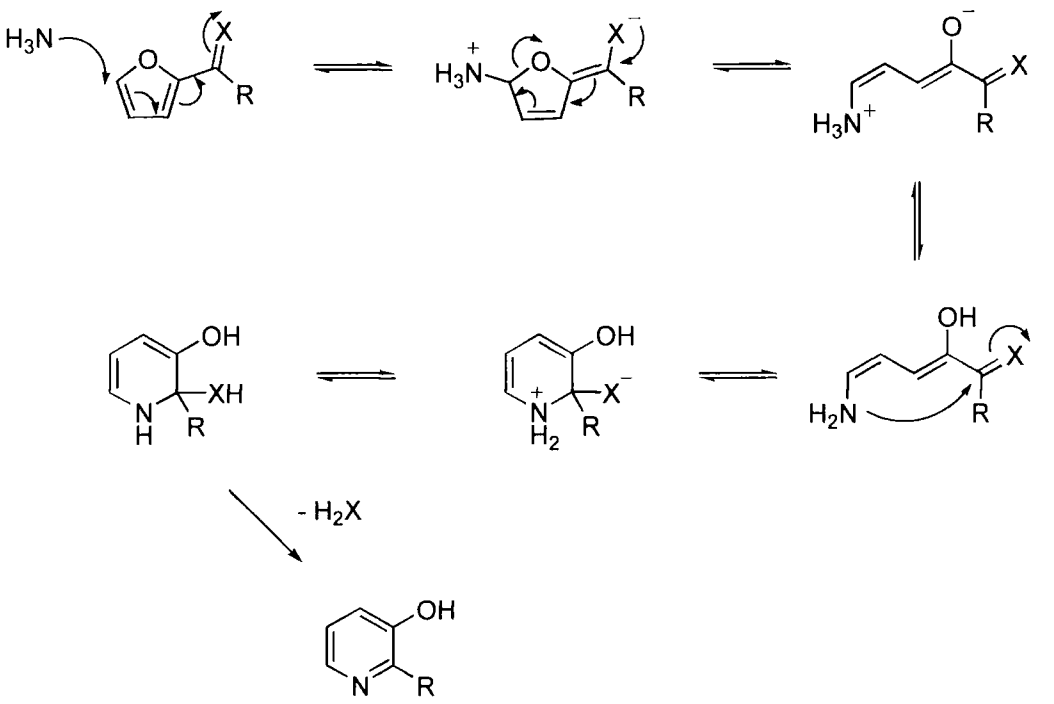
2-Acylpyrrole can be the major product according to Dunlop,[167] who found that the use of ethanol as the solvent gave the 3-hydroxypyridine as well as the 2-acylpyrrole. If a mixed alcohol-water medium, or water alone was used the competing hydroxypyridine reaction may proceed to the exclusion of the formation of the pyrrole. He found that no added solvent gave the best yield of pyrrole. One mole of the 2-acylfuran reacts with one mole of the nitrogen base to form a ketimine or "Schiff's base," and with an additional mole of the nitrogen base to form the pyrrole, with loss of two moles of water. The ketimine group is then easily hydrolysed to give the 2-acylpyrrole. Thus, two moles of the nitrogen base are required, (**Scheme 3.4**).



Scheme 3.4

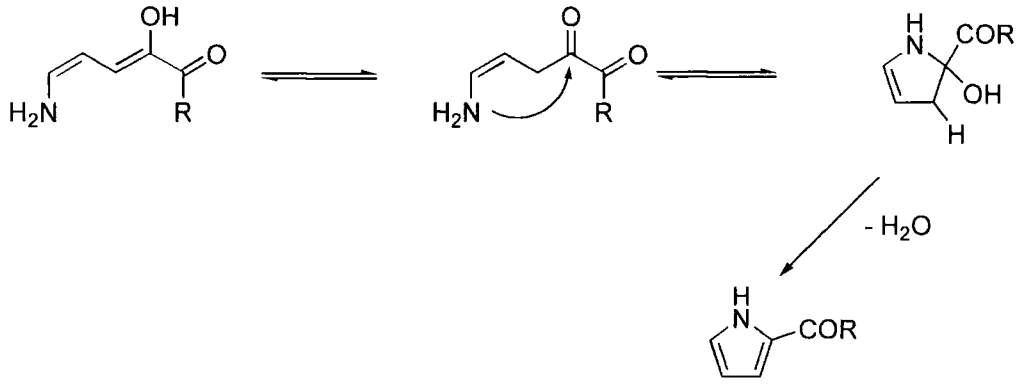
3.1.2 Mechanism

Aso's[58] suggested mechanism for the reaction, where X=O (**Scheme 3.5**) involves initial attack by the nitrogen lone pair at the 5-position of furan giving a furan enol, which then rearranges to ring open the furan. Reattack by the nitrogen at the carbonyl centre gives the six membered heterocycle: loss of water then gives the 3-hydroxypyridine.



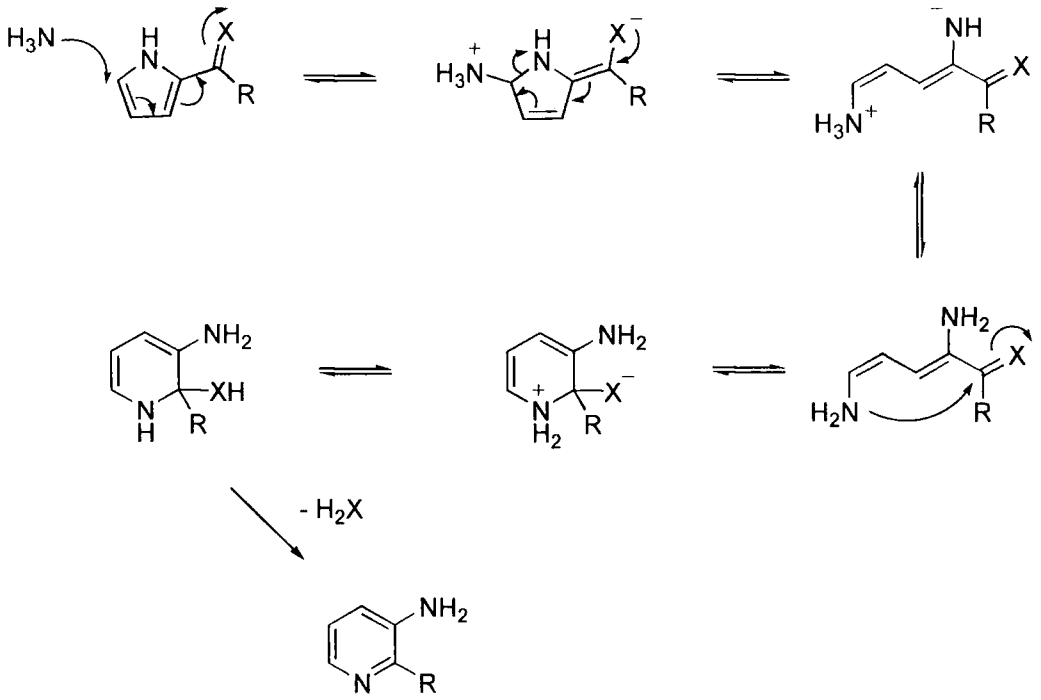
Scheme 3.5

Leditscke[61] suggested a slightly different mechanism, where X=NH. This firstly involves formation of a ketimine, by reaction of the starting ketone with ammonia, then attack of a second nitrogen source at the 5-position, as in Aso's mechanism. The aromatic system is produced by loss of ammonia in the final step. Both mechanisms are equally plausible with good leaving groups, *viz.* water and ammonia, in the final step. However, the ketimine would be less effective at stabilising the transition state than the carbonyl system.



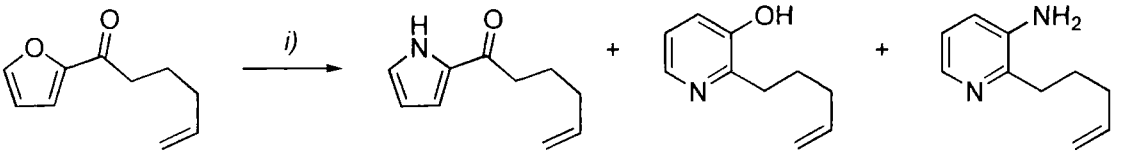
Scheme 3.6

The reaction does give a mixture of products. The mechanism offers an alternative ring closure leading to 2-acylpyrrole (**Scheme 3.6**). It has been shown that an aqueous medium favours formation of the 3-hydroxypyridine whereas an alcoholic solvent[167] favours the 2-acylpyrrole. Dunlop developed a reaction to form the 2-acylpyrrole as the major product (38%) compared to 2-methyl-3-hydroxypyridine 10%).



Scheme 3.7

The first indication[170] of a 3-amino by-product was found from the reaction of 1-(2-furyl)-5-hexen-1-one (**254**) and ammonia, which gave three easily separable products by column chromatography, namely the pyrrole (**255**), 3-hydroxpyridine (**256**) and the 3-aminopyridine (**257**). This presumably comes from the reaction of the 2-acylpyrrole with ammonia in much the same way as the 2-acylfuran (**Scheme 3.5**).



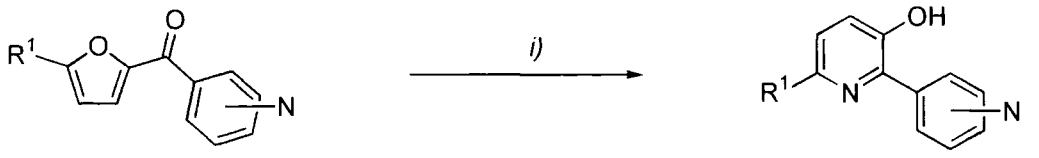
(**254**) (**255**) (**256**) (**257**)

Scheme 3.8 *Reagents and Conditions: i) aq. NH_3, 165°C, 20h*

By using an aqueous or alcoholic solvent, or a mixture of the two, the amount of the pyrrole by-product can be drastically reduced from a maximum amount of ~40% to almost nil. The 2-acylpyrrole is easily seen by thin layer chromatography as a dark red spot, and is a red oil.

3.1.3 Rearrangement of Ketones 185-190.

We have synthesised bipyridyl derivatives (**258-263**) from the corresponding pyridyl ketones (**185-190**). The reactions were carried out in an aqueous ammonia solution, and heating the sealed Carius tube to 150°C for 15 h.



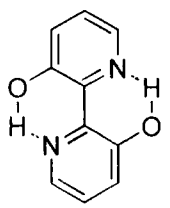
Scheme 3.9 *Reagents and Conditions: i) aq. NH_3, 150°C, 15h*

Ketone	3-Hydroxypyridine	R^1 / Py	Yields (%)	M.P. (°C)
185	**258**[67]	R^1=H, 2-Py	18	30-32
186	**259**	R^1=H, 3-Py	37	171-173
187	**260**[66]	R^1=H, 4-Py	35	234-236
188	**261**	R^1=Me, 2-Py	25	60-62
189	**262**	R^1=Me, 3-Py	27	195-196
190	**263**	R^1=Me, 4-Py	31	257-260

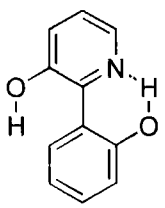
Table 3.2

Siemanowski[67] reacted (**185**) with ammonium acetate at 150°C for 2 h and sublimed the resulting 3-hydroxypyridine (**258**) in 62% yield. Lipinsk[66] reacted the ketone (**187**) with ammonium hydroxide in methanol at 155°C for 3 h to give (**260**) in 32% yield.

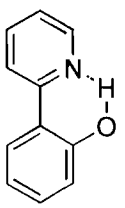
Derivatives of bipyridyls have been the subject of extensive studies due to their internal hydrogen bonding. The most important conclusions of several papers[171,172] are that symmetric, planar molecules with two equivalent internal hydrogen bonds like (2,2'-bipyridyl)-2,3'-diol [$BP(OH)_2$] (**264**) undergo an efficient excited state intramolecular double proton transfer accompanied by a strong Stokes shifted fluorescence. The absorption and fluorescence of (**258**) has been compared to (**264**), 2-(2-hydroxyphenyl)-pyridin-3-ol (HPP) (**265**) and 2-(2-pyridyl)phenol (PP) (**266**).



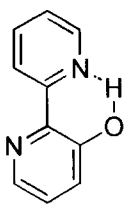
(**264**)



(**265**)



(**266**)



(**258**)

Scheme 3.10

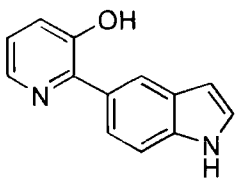
3.1.4 Rearrangement of Other Ketones

Table 3.3 lists the reaction of other ketones from chapter 2 with ammonia using the conditions in **Scheme 3.11**. One aim of the project was to look at which groups will withstand the reaction conditions and which ones will not. As seen in **Table 3.3** the thiophene ketone (**193**) does not give the desired product; instead gives non-aromatic products which were not isolated. Also, the ferrocene ketone (**199**) does not react, giving the starting material and some pyrolysed products.

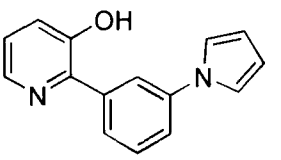
Scheme 3.11 *Reagents and Conditions: i) aq. NH_3, 150°C, 5h*

Ketone	Pyridine	R^1/R^2	Yield (%)	M.P. (°C)
191	**267**	R^1=2-furyl, R^2=H	17	210-212
193	-	R^1=2-thienyl, R^2=H	-	-
195	**268**	R^1=3-quinolyl, R^2=H	26	181-184
196	**269**	R^1=3-quinolyl, R^2=Me	30	214-216
197	**270**	R^1=2-naphthyl, R^2=H	24	156-159
198	**271**	R^1=2-naphthyl, R^2=Me	16	223-225
199	**272**	R^1=ferrocenyl, R^2=H	-	-
221	**273**	R^1=5-indole, R^2=H	12	141-143
222	**274**	R^1=3-(N-pyrrolyl)phenylphenyl, R^2=H	18	121-123
223	**275**	R^1=pyrazine, R^2=H	20	87-89
224	**276**	R^1=2-methylpyridyl, R^2=H	15	181-183
226	**277**	R^1=2-bromopyridyl, R^2=H	26	167-169

Table 3.3



(273)



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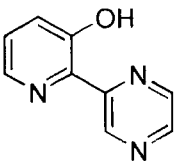

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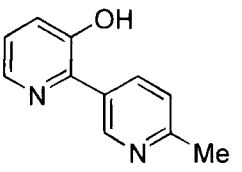
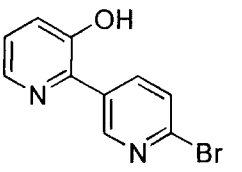
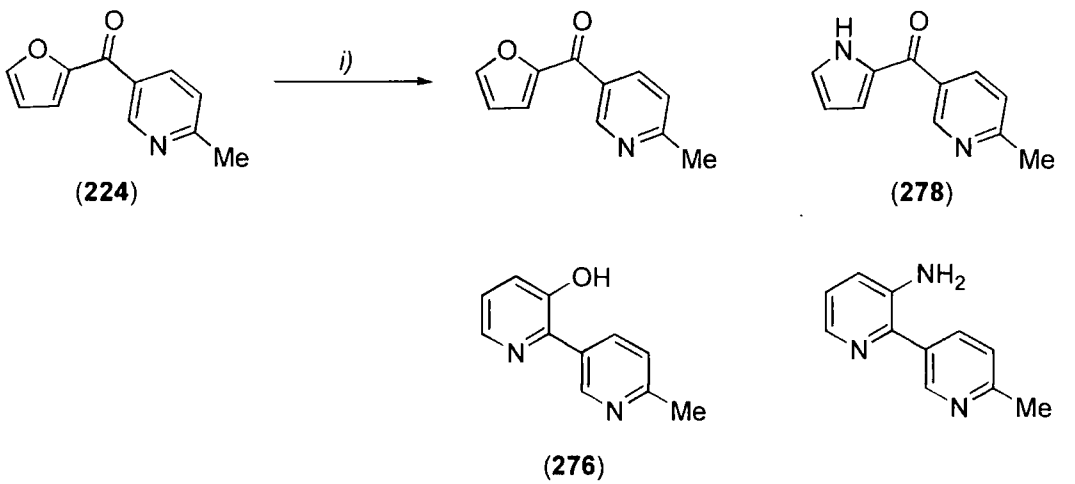
(276)





(277)

276 showed a low yield (17%) for the ring expansion under the normal conditions of 150°C for 5 h. However, as has been shown before the yield can be improved by a change in the temperature and length of the reaction. Therefore, (**224**) was heated with ammonia at 110°C for 12 h. This improved the yield to 27%. We also examined the other components of the reaction mixture and found 12% of the starting ketone (**224**) and 16% of the 2-acylpyrrole (**278**) (**Scheme 3.12**). We found none of the 3-aminopyridine product suggested by Brombridge.[170]



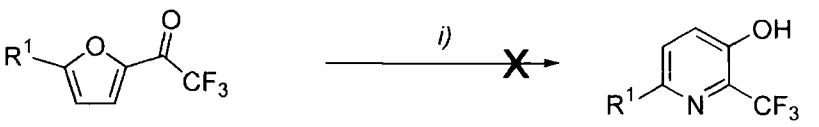
(224)

(278)

(276)

Scheme 3.12 *Reagents and Conditions: i) aq. NH_3, 110°C, 12h*

3.1.4.1 Trifluoromethyl Ketones 211 and 212



Scheme 3.13 Reagents and Conditions: i) aq. NH_3, 150°C, 12h

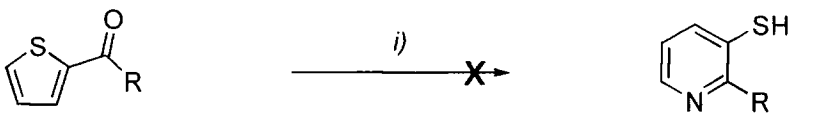
The reaction of the trifluoromethyl ketones (**211**) and (**212**) with ammonia in the carius tube at 150°C for 12 h did not give the 3-hydroxypyridine. The reaction produced a black polymer which was not soluble in any solvent.

3.2 Reaction of Other Systems

A look at the mechanism (**Scheme 3.5**) of the reaction of the 2-acylfurans shows that the furan oxygen becomes the oxygen on the 3-hydroxypyridine. Thus the oxygen atom has no real influence on the reaction. We therefore, hoped that other five membered rings would give similar pyridines.

3.2.1 2-Acylthiophene

We saw an opportunity to react 2-acylthiophenes in the same way to give 3-thiopyridines. A look through the literature turned up no mention of such a reaction.



(**279**) (**280**)

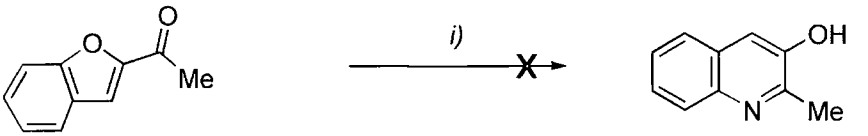
Scheme 3.14 Reagents and Conditions: i) NH_3/MeOH, NH_4Cl, 150°C, 15h

2-Acetylthiophene (**279**) was bought commercially and heated with ammonia in a sealed carius tube for 15 h at 150°C. From the reaction we could find no trace of the

3-thio derivative (**280**), the major products were dark tars and some 2-acetylthiophene was recovered. This may be due to the difficulty in ring opening the thiophene compared to furan, an essential requirement for the rearrangement to occur. Good evidence of this is the fact that thiophene is stable to all but very strong acids, whereas furan will ring open with concentrated sulphuric acid or Lewis acids such as aluminium chloride.

3.2.2 Benzofuran

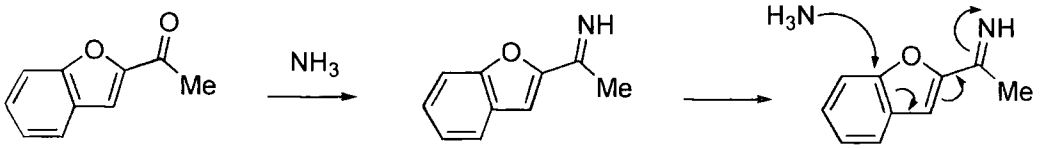
The mechanism for rearrangement of 2-acylfurans (**Scheme 3.5**) first involves formation of a ketimine and then nucleophilic attack of the 5-position by the nitrogen base. 2-Acetylbenzofuran if rearranged in a similar way would give 3-hydroxy-2-methylquinoline.



(**281**) (**282**)

Scheme 3.15 *Reagents and Conditions: i) NH_3/MeOH, NH_4Cl, 150°C, 15h*

The benzofuran-2-yl methyl ketone (**281**) was heated at 150°C for 15 h with ammonia. None of the quinoline (**282**) could be isolated, the benzofuran was recovered in 15% yield. A look at the mechanism (**Scheme 3.16**) of such a reaction would suggest why the benzofuran does not give the quinoline.



Scheme 3.16

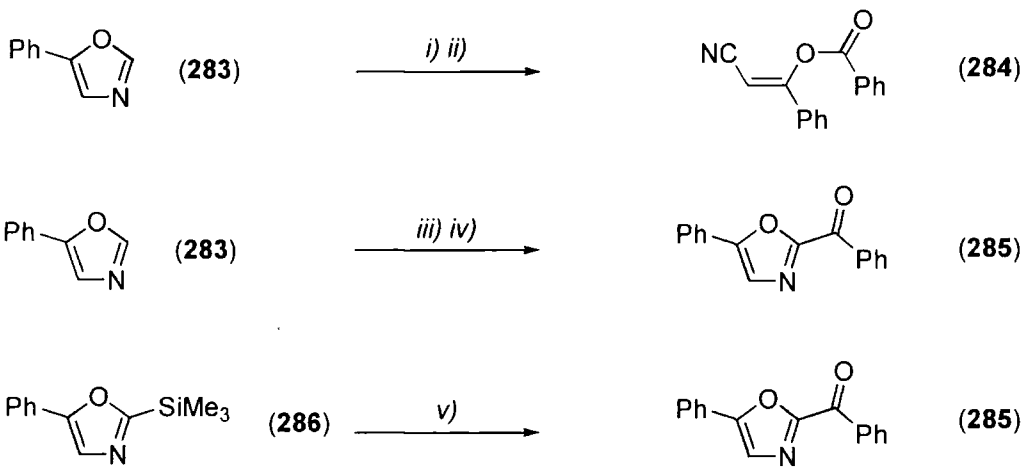
The ketone reacts with one mole of the ammonia to give the ketimine. However, the next step involves attack by another mole of ammonia at C-7a of imine. If this addition occurs then the benzofuran must lose aromaticity, this is a strongly disfavoured mechanism and this may be why none of the quinoline is isolated. Indeed, the only similar reaction in the literature is that by Langhals[68] who reacted 1,2-*bis*-benzofuran-2-yl-ethane-1,3-dione with ammonium chloride in methanol at 200°C (**Scheme 1.27**).

3.2.3 Oxazole

Oxazole is similar to furan except for a nitrogen in the ring. We chose to look at the reaction of a 2-acyl oxazole with ammonia, to determine if a product similar to 3-hydroxypyrdine is formed.

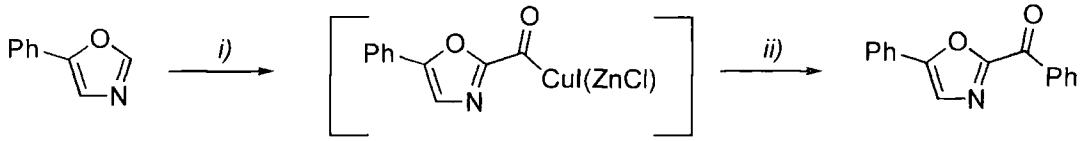
3.2.3.1 Preparation and Reaction of Phenyloxazole, 285

The literature has many ways of directly acylating the oxazole ring (**Scheme 3.17**). Reaction occurs at the C-2 carbon atom. Lithiation of 5-phenyloxazole (**283**) with nBuLi and addition of an acid chloride[173] leads to a ring opened product (**284**); lithiation and addition of amide[174] gives (**285**). Direct acylation can be achieved by reaction of the silane (**286**) with benzoyl chloride[175] to give (**285**).



Scheme 3.17 *Reagents and Conditions: i) nBuLi, ii) PhCOCl; iii) nBuLi, iv) PhCONMe; v) PhCOCl*

The disadvantage of these routes are the low yields. We followed the work by Harn *et al*[176] which involves the lithiation of 5-phenyloxazole (**283**) with nBuLi. Addition to the lithio species of zinc chloride and copper iodide gives the metal salt (**287**), which was reacted with benzoyl chloride to give the ketone (**285**) in 65% yield.



(**283**) (**287**) (**285**)

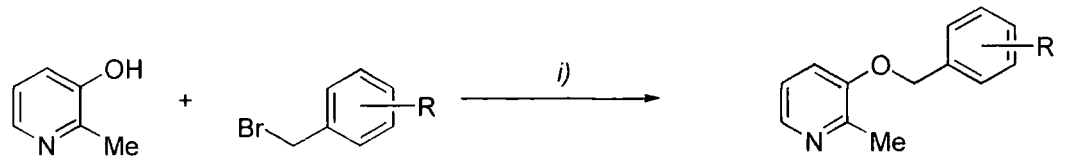
Scheme 3.18 *Reagents and Conditions: i) nBuLi, $ZnCl_2$, CuI; ii) PhCOCl*

The ketone (**285**) was reacted with ammonia at 150°C for 15 h. The reaction showed a mixture of non-aromatic products by ^{1}H NMR. We suggest that this is due to the oxazole ring system ring opening under the reaction conditions in a similar way to (**284**).

3.3 Reaction of 3-Hydroxypyridines

3.3.1 Reaction of 3-Hydroxy group

The hydroxy group and ring nitrogen are both nucleophilic, however, due to the tautomerism of 3-hydroxypyridines the former group is more nucleophilic. Addition of methyl iodide to pyridine causes an immediate exothermic reaction and the N-quartenary salt is formed. Methyl iodide or even methyl triflate do not react with 2-methyl-3-hydroxypyridine to form this salt or the methyl ether. The hydroxy group can be selectively reacted using the method reported by Bristol.[177] The benzyl ether (**288**) was made by reaction of 2-methyl-3-hydroxypyridine (**243**) with benzyl bromide in a vigorously stirring solution of 40% sodium hydroxide and dichloromethane. A catalytic amount of the phase transfer catalyst (PTC), cetyltrimethylammonium chloride, is required. **Table 3.4** shows the reaction of differing benzyl bromides with 2-methyl-3-hydroxypyridine.



(**243**)

(**288**), R=H (**291**), R=4-Br
(**289**), R=4-CN (**292**), R=2-Cl
(**290**), R=4-NO_2

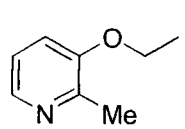
Scheme 3.19 *Reagents and Conditions: i) 40% NaOH, DCM, PTC*

Compound	Yield (%)	M.P. (°C)
288[178a]	65	Oil
289	53	102-104
290	62	106-108
291	43	58-60
292	61	62-65

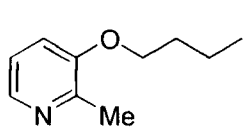
Table 3.4

We have shown the benzyl group to be a good protecting agent for these 3-hydroxypyridines. Hydrogenation of (**288**) is achieved using 40 atm hydrogen over a Pd/C catalyst to give 2-methyl-3-hydroxypyridine (**243**) in 86% yield.

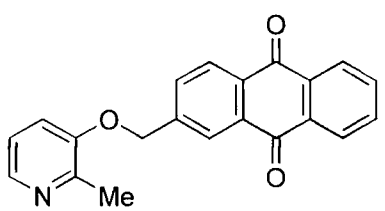
The same procedure was used for the formation of the ethers (**293**, 28%),[178b] (**294**, 21%) and (**295**, 33%). Synthesis of compound (**295**) was achieved by reaction of (**243**) with 2-bromomethylanthraquinone (synthesised[179] by reaction of 2-methylanthraquinone and NBS in CCl_4 in 42% yield).



(**293**)



(**294**)

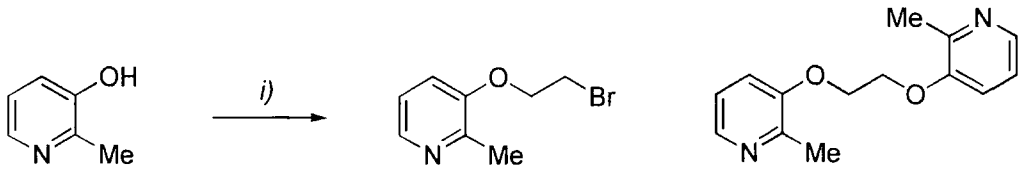


(**295**)

Scheme 3.20

3.3.1.1 Reaction With 1,2-Dibromoethane

It was envisaged that the use of a dibrominated alkane may couple two of the alcohols (**243**) together. We, therefore, chose to react 1,2-dibromoethane with (**243**); the product isolated after purification was the mono-substituted product (**296**, 21%).

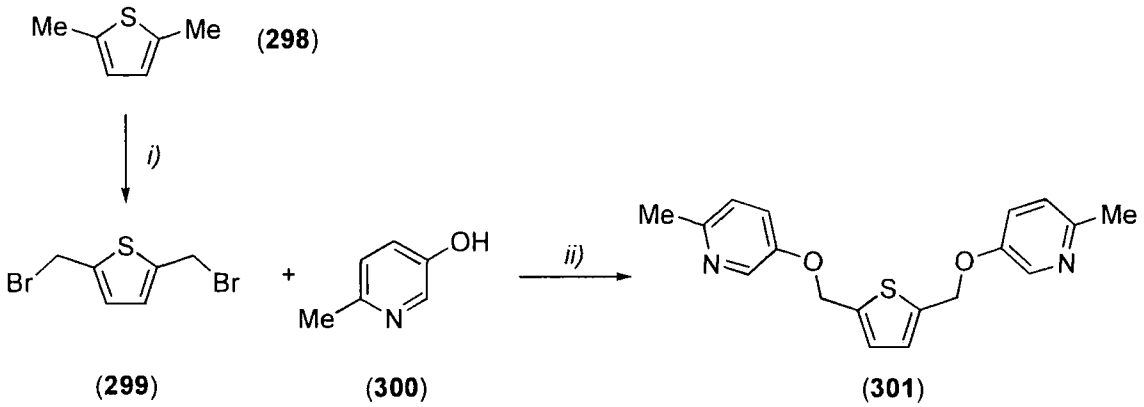


(**243**) (**296**) (**297**)

Scheme 3.21 *Reagents and Conditions: i) 40% NaOH, 1,2-dibromoethane, DCM, PTC*

3.3.1.2 Reaction With 2,5-Dibromomethylthiophene

2,5-Dimethylthiophene (**298**) was brominated by reaction with NBS in CCl_4 in 24% yield giving 2,5-dibromomethylthiophene[180] (**299**) in 20% yield. (**299**) was then reacted with two equivalents of (**300**) giving (**301**) in 57% yield.

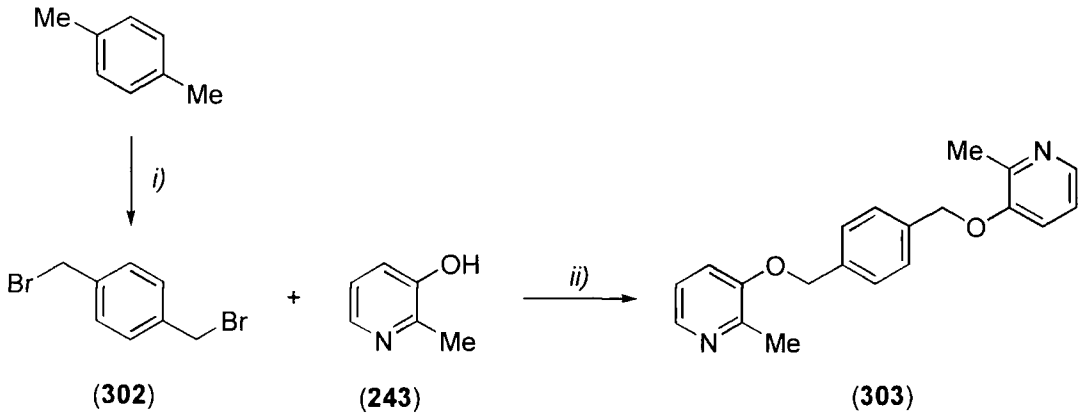


(**299**) (**300**) (**301**)

Scheme 3.22 *Reagents and Conditions: i) NBS, CCl_4; ii) 40% NaOH, DCM, PTC*

3.3.1.3 Reaction With *p*-Bromomethylxylene[181]

p-Xylene was brominated by reaction with NBS in CCl_4 in 45% yield giving *p*-bromomethylxylene[181] (**302**). This was then reacted with two equivalents of (**243**) giving (**303**) in 51% yield.

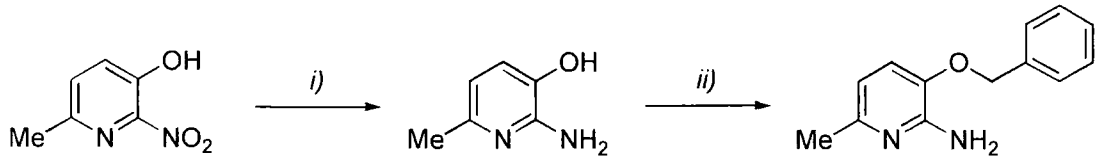


(**302**) (**243**) (**303**)

Scheme 3.23 *Reagents and Conditions: i) NBS, CCl_4; ii) 40% NaOH, DCM, PTC*

3.3.1.4 Reaction of 2-Amino-3-hydroxy-6-methylpyridine, 305

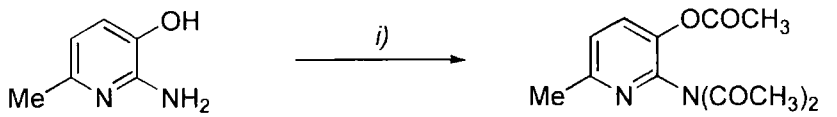
3-Hydroxy-6-methyl-2-nitropyridine (**304**) was hydrogented at 40atm in ethanol over Pd/C to give 2-amino-3-hydroxy-6-methylpyridine (**305**) in 94% yield. Reaction of (**305**) with one equivalent of benzyl bromide gave the product (**306**). Reaction had occurred at the hydroxy functionality instead of the amino group.



(**304**) (**305**) (**306**)

Scheme 3.24 *Reagents and Conditions: i) H_2 (40 atm.), EtOH, Pd/C; ii) benzyl bromide, 40% NaOH, DCM, PTC*

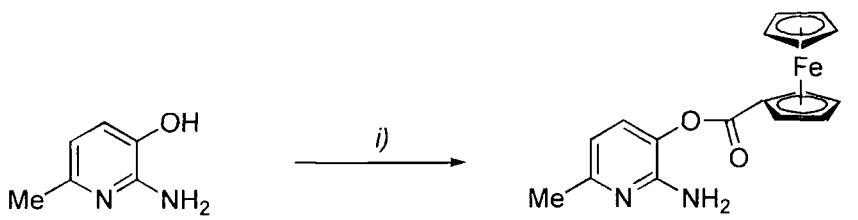
Reaction of (**305**) with a one equivalent of acetyl chloride gave the trisubstituted product (**307**) in 57% yield. The reaction of trifluoromethyl acetyl chloride under the same conditions did not give the corresponding fluorinated derivative. Indeed, ^{19}F NMR showed no incorporation of fluorine.



(**305**) (**307**)

Scheme 3.25 *Reagents and Conditions: i) acetyl chloride, DCM, 15h*

We turned to the more sterically demanding ferrocene acid chloride and reaction with (**305**) gave the product (**308**) in 51% yield (**Scheme 3.26**). Compared to the methyl group, ferrocene is too large to give the tri-substituted product. The fact that the ester (**308**) is made instead of the amide seems to suggest that the amino nitrogen may be slightly quaternised leaving the site less nucleophilic.



(**305**) (**308**)

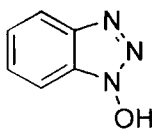
Scheme 3.26 *Reagents and Conditions: i) ferrocene acid chloride, DCM, pyridine, 15h*

Chapter 4

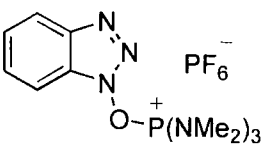
Azabenzotriazoles

4.1 Introduction

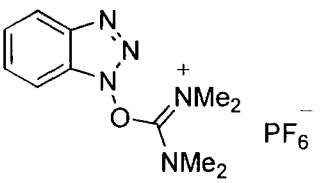
Chapter 3 looked into the synthesis of 3-hydroxypyridines by reaction of 2-acylfurans with sources of ammonia. This chapter explores the synthesis of azabenzotriazoles from 3-hydroxypyridines. The most common peptide coupling agent is 1-hydroxybenzotriazole (**309**) (HOBt)[182] which can be used either in combination with a carbodiimide or another coupling agent or is built into a stand alone reagent such as 1-benzotriazolyloxytris(dimethylamino)-phosphonium hexafluorophosphate (**310**) (BOP)[183] or an analagous uronium salt such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophophate (**311**) (HBTU).[184] These addititives have been shown to inhibit side reactions and reduce racemization (**Scheme 4.1**).



(**309**)



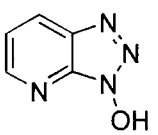
(**310**)



(**311**)

Scheme 4.1

Carpino[185] was the first to show that the aza analogue of HOBt, 1-hydroxy-7-azabenzotriazole **312**, is a more efficient additive which speeds up the coupling process, reduces the loss of chiral integrity and provides a visual indication (yellow to colourless) of the reaction endpoint.



(**312**)

(**313**)

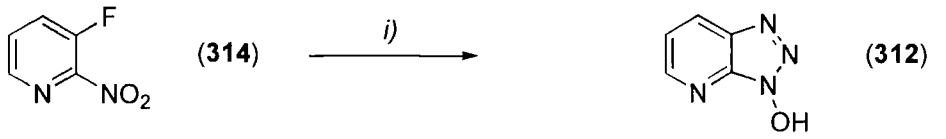
Scheme 4.2

1-Hydroxy-7-azabenzotriazole (HOAt) (**312**) incorporates both of the key elements of the 1:1 mixture of HOBt and a tertiary amine which is of greater effect than HOBt in

couplings involving active esters.[186] The increased efficiency of HOAt relative to HOBt is governed by the formation or reactivity of an active ester intermediate (**313**) (**Scheme 4.2**). It has been postulated that the neighbouring group effect depicted in (**313**) is a major factor in this increased efficiency.[187]

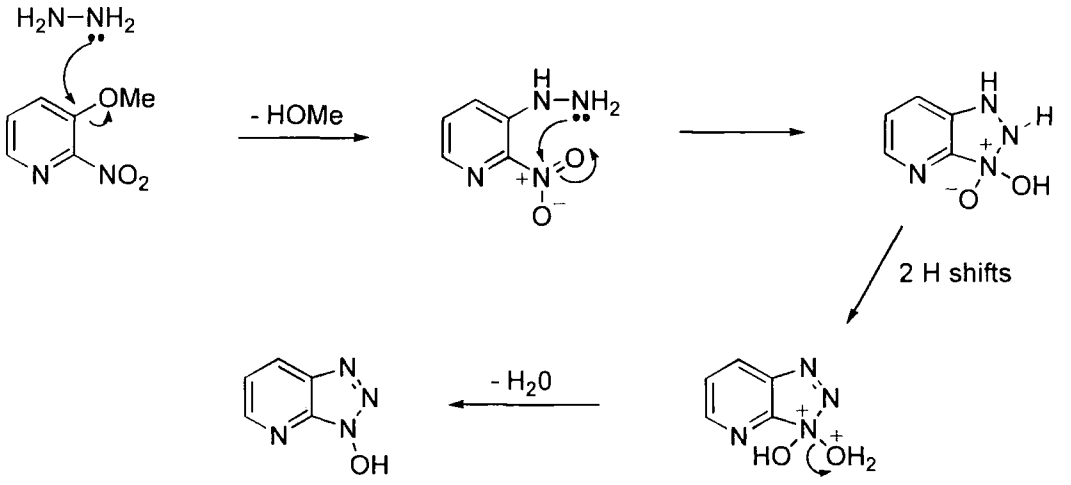
4.2 Synthesis of 5-Methyl-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol, 317

Originally 1-hydroxy-7-azabenzotriazole (**312**) was synthesised by reaction of 3-fluoro-2-nitropyridine (**314**) with hydrazine.[188]



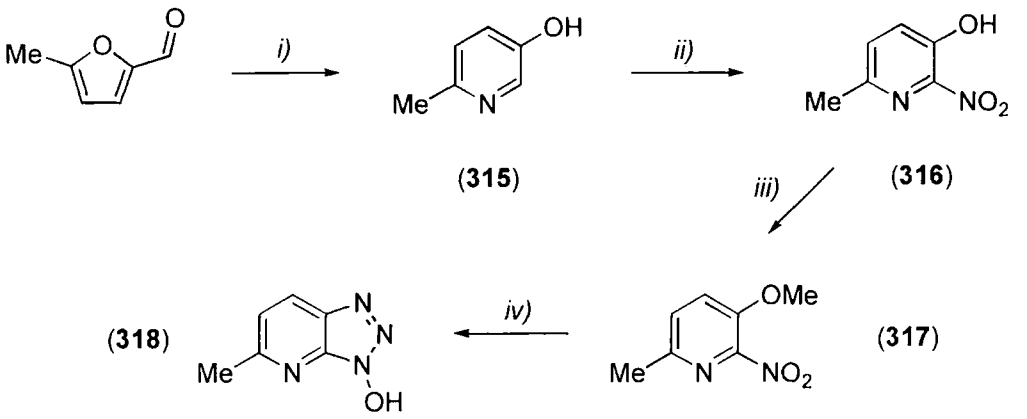
Scheme 4.3 *Reagents and Conditions: i) hydrazine hydrate, water, 60°C, 10 h*

This synthesis was simplified by Yutilov[189], who was able to methylate the hydroxy group of 3-hydroxy-2-nitropyridine with diazomethane in 80% yield. Then reaction of the methyl ether with hydrazine gave (**312**) in 65% yield. The mechanism of the final step is shown in **Scheme 4.4**.



Scheme 4.4

The first step in our synthesis (**Scheme 4.5**) was the reaction of 2-furaldehyde with ammonia in a sealed Carius tube at 110°C for 12 h. This gave 3-hydroxy-6-methylpyridine (**315**) in 32% yield. This compound was nitrated using a mixture of conc. HNO_3 and conc. H_2SO_4 to give the 2-nitro derivative (**316**) (35% yield). We have found that the hydroxy group of (**316**) can be deprotonated by stirring with potassium carbonate in dry acetone, giving a colour change from yellow to a bright orange. Methylation is achieved by refluxing this solution with an excess of methyl iodide for 24 h. The reaction is complete when the colour changes to a pale cream, giving (**317**) in 78% yield.

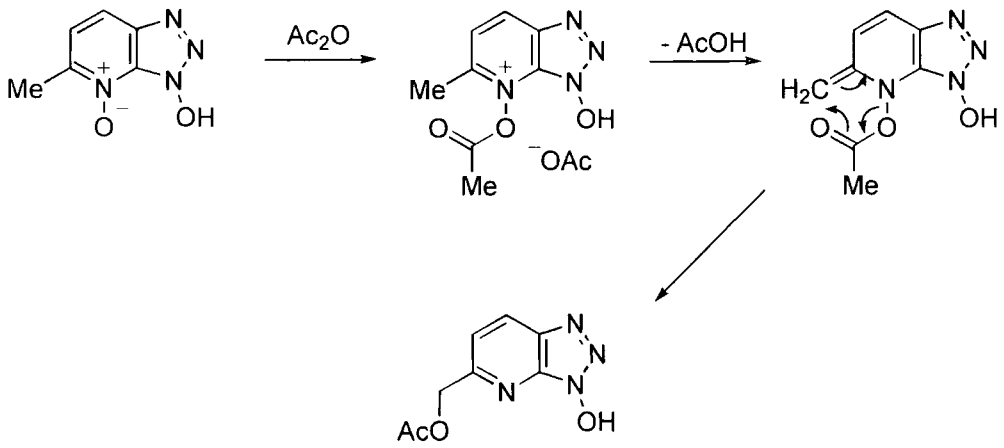


Scheme 4.5 *Reagents and Conditions: i) aq. NH_3, 110°C, 12h; ii) conc. HNO_3, conc. H_2SO_4, 40°C; iii) MeI, K_2CO_3, acetone, reflux 12h; iv) hydrazine hydrate, water, 85°C, 12h*

The original reaction of the methoxy ether (**317**) involves the use of dimethylformamide, water, hydrazine and heating to 60°C for a 5-6 h. However, we have found that the dimethylformamide is unnecessary for the reaction. (**317**) dissolves in water at over 80°C, and heating with hydrazine for 12 h, followed by cooling and acidification with conc. HCl to pH ca. 2-3 gave 5-methyl-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (**318**) in 67% yield.

Originally, we planned to develop the 6-methyl group of (**318**) into a reactive species with the possibility of attaching the system to a solid support, thereby easing recovery of the azabenzotriazole.

We planned to form the N-oxide of (**318**), and reaction with acetic acid at 100°C could rearrange the system to give an aceytoxymethyl group (**Scheme 4.6**). The original patent for HOAt[190] suggests that the N-oxide is formed using standard peroxide conditions. However, with our system the ring nitrogen is not oxidised by the use of hydrogen peroxide or *m*-chloroperbenzoic acid.



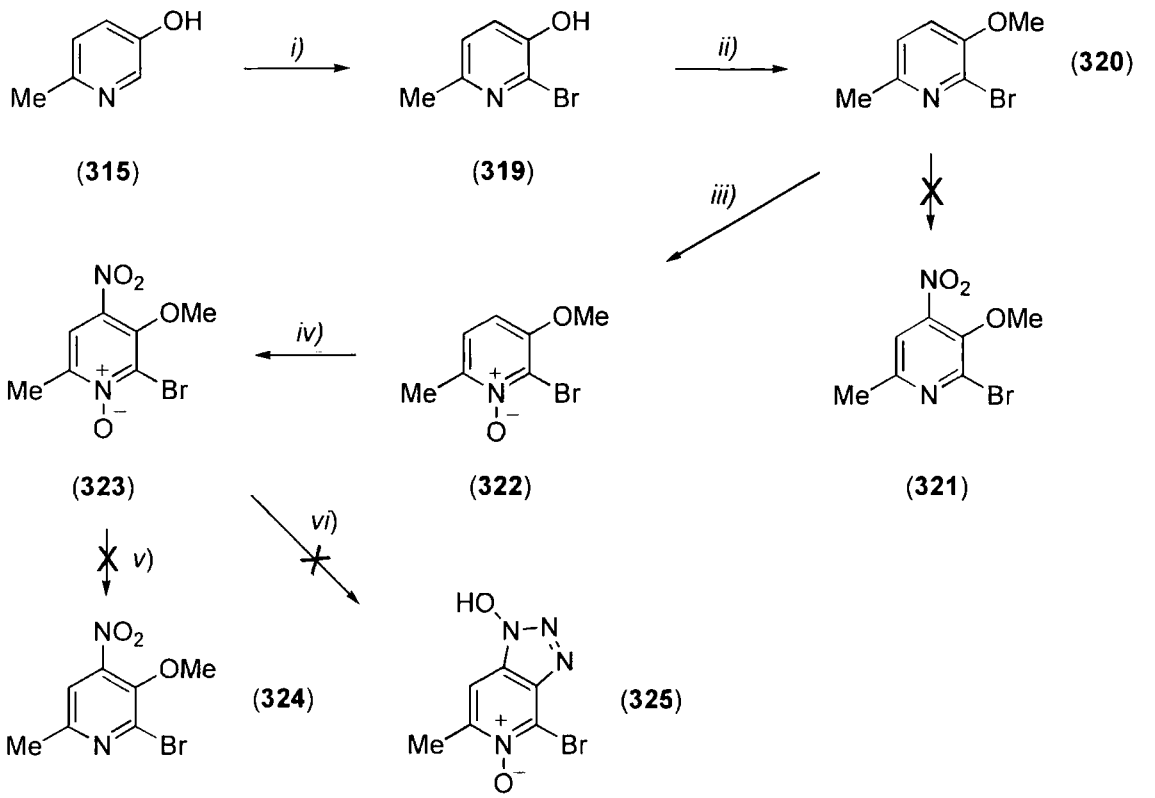
Scheme 4.6

The second way of developing the 6-methyl group was *via* oxidation to the carboxylic acid group. Aromatic methyl groups can be oxidised in this way using potassium permanganate in alkaline conditions. (**318**) was taken up in water, and heated to 85°C with $KMnO_4$ for 8h. However, after workup none of the acid had been formed, indeed ^1H NMR showed only starting material to be present.

4.3 4-Bromo-6-methyl-[1,2,3]triazolo[4,5-*c*]pyridin-1-ol

The 3-hydroxy can lead to (**318**) with the nitro group on C-2, but by blocking C-2 and introducing a nitro group into C-4 we envisaged the synthesis of the other isomeric form of this azabenzotriazole. We were able to take 3-hydroxy-6-methylpyridine (**315**), and brominate the C-2 position with bromine in 10% sodium hydroxide to give 2-bromo-3-hydroxy-6-methylpyridine (**319**) (30% yield). Methylation of (**319**) was achieved using potassium carbonate, methyl iodide and acetone, giving 2-bromo-3-methoxy-6-methylpyridine (**320**) (59% yield). Attempts to nitrate (**320**) with conc. HNO_3 and H_2SO_4, standard nitrating conditions, did not give (**321**) but starting material. The literature shows that the pyridine ring can be nitrated at C-4 by firstly

producing the N-oxide and secondly nitrating.[191] Reaction of (**320**) with *m*-chloroperbenzoic acid in chloroform gave 2-bromo-3-methoxy-6-methylpyridine-N-oxide (**322**) (62% yield). This was then easily nitrated with conc. HNO_3 and H_2SO_4 to give 2-bromo-3-methoxy-6-methyl-4-nitropyridine N-oxide (**323**) (45% yield).



Scheme 4.7 *Reagents and Conditions: 1) Br_2, 10% NaOH, 24h; ii) MeI, K_2CO_3, acetone, reflux 12h; iii) m-chloroperbenzoic acid, $CHCl_3$, rt 3h; iv) conc. HNO_3, conc. H_2SO_4, 40°C; v) PPh_3; vi) hydrazine hydrate, water, 85°C, 12h*

(**323**) was then subjected to the same conditions for formation of the azabenzotriazole, water, hydrazine, 85°C for 8 h. However, attempts to isolate the compound (**325**) from the water phase failed. (**318**) precipitates from solution at pH 2-3, but the azabenzotriazole (**325**) formed from (**323**) does not. We envisage that the N-oxide makes the compound too water soluble. Attempts to remove the N-oxide with triphenylphosphine[192] and $SOCl_2/NEt_3$[193] to give (**324**) were unsuccessful, and this approach was not pursued further.

CHAPTER 5

Experimental Section

5.1 General Experimental Methods

All reactions which required inert atmospheres were carried out under a blanket of argon which was dried by passing through a column of phosphorous pentoxide. Diethyl ether, toluene, and tetrahydrofuran were dried and distilled over sodium metal. Dichloromethane and acetone were dried and distilled over calcium hydride. Ethanol and methanol were dried and distilled over magnesium turnings. All other reagents were of commercial quality and used as supplied unless otherwise stated. All reactions were carried out at room temperature unless otherwise stated.

^{1}H and ^{13}C NMR spectra were obtained on Oxford 200, Varian Unity 300 and Varian VXR 400 spectrometers; chemical shifts are quoted in ppm, relative to tetramethylsilane (TMS) as an internal reference (0 ppm). Mass spectra (EI) were recorded on a Micromass Autospec spectrometer operating at 70eV. Infra-red spectra were recorded using a Paragon 1000 FTIR spectrometer operated from a Grams Analyst 1600; samples were embedded in KBr discs unless otherwise stated. Melting points were recorded on a Phillip Harris melting point apparatus and are uncorrected. Elemental analyse were obtained on a Carlo-Erba Strumentazione instrument.

Column chromatography was carried out using either Prolabo silica (70-230 mesh) or Merck alumina (activity I to II, 70-230 mesh); the latter was neutralised by pre-soaking in ethyl acetate for 24 h prior to use. Solvents were distilled prior to use for chromatography, with the exception of dichloromethane, and chloroform, which were used as supplied.

5.2 Experimental for Chapter 2

General Procedures

Procedure A: To a stirring solution of the aldehyde (18 mmol, 1 eq) in diethyl ether (80 ml) at 0°C was added the Grignard reagent (27 mmol, 1.5 eq) dropwise over 30 min. The solution was then allowed to warm to 20°C and stirred for 15 h. Ammonium chloride solution (50 ml) was added and the solution stirred for 30 min. The ethereal layer was decanted and the aqueous layer extracted with diethyl ether (3x30 ml). The ethereal layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The compound was then purified either by distillation at reduced pressure using a Kugelror apparatus or by column chromatography.

Procedure B: To *n*-butyllithium (1.6M solution in hexanes, 1.1 eq) at 0°C was added the furan (1 eq) as a solution in dry diethyl ether (30 ml). The reaction was refluxed for 3 h to give a light yellow suspension, cooled to -78°C and the electrophile (1.1 eq) added as a solution in diethyl ether (30 ml). The solution was stirred for 1 h at –78°C before being allowed to warm to room temperature and quenched with water (20 ml). 1M Hydrochloric acid (30 ml) was added and the aqueous layer separated, the ether layer was further washed with 1M hydrochloric acid (20 ml), the aqueous layers combined and allowed to stand for 1 h. The solution was then neutralised with sodium hydroxide and extracted with dichloromethane (3x30 ml). The combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The compound was then purified by column chromatography.

Procedure C: To a solution of the furan (1 eq) or 2-methylfuran (1 eq) in dry diethyl ether (40 ml) at -78°C was slowly added *n*-butyllithium (1.6M solution in hexanes, 0.9 eq). The reaction was stirred for 1 h, the nitrile (0.9 eq) was added as a solution in dry diethyl ether (30 ml), and the solution stirred for a further 2 h at -78°C. To this was added water (30 ml) and the solution was allowed to warm to room temperature. The reaction was acidified with conc. HCl and the aqueous phase separated and heated to 60°C for 2 h. The solution was then made basic with sodium hydroxide and extracted with diethyl ether (3x50 ml) and ethyl acetate (2x50 ml). The combined organic

layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The compound was then purified by column chromatography.

Procedure D: To the alcohol (1 eq) in dry dichloromethane (50 ml) was added activated manganese dioxide (5 eq). The reaction was stirred at room temperature until complete (t.l.c. monitoring), then filtered through celite, washed through with dichloromethane (3x30 ml) and the solvent removed *in vacuo*. The compound was then further purified (as stated below).

1-Furan-2-yl-2-methylpropan-1-ol, 145[126]

This was prepared by the general procedure **A** by the reaction of *iso*-propylmagnesium chloride with furfural. The product was distilled (84-87°C at 0.1 mmHg) giving a colourless oil in 78% yield.

^{1}H NMR ($CDCl_3$): δ = 7.46 (dd, 1H, J = 1, 2 Hz, Furan-5H), 6.42 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.32 (dd, 1H, J = 2, 4 Hz, Furan-4H), 4.47 (d, 1H, J = 7 Hz, C*H*OH), 2.29 (s, 1H, OH), 2.20 (septet, 1H, C*H*$(Me)_2$), 1.11 (d, 3H, J = 7 Hz, Me), 0.95 (d, 3H, J = 7 Hz, Me).

1-Furan-2-yl-2-methylbutan-1-ol, 146[127]

This was prepared by the general procedure **A** by the reaction of *sec*-butylmagnesium chloride with furfural. The product was distilled (64-65°C at 0.3 mmHg) giving a colourless oil in 47% yield.

^{1}H NMR ($CDCl_3$): δ = 7.39 (dd, 1H, J = 1, 2 Hz, Furan-5H), 6.37 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.25 (d, 1H, J = 2, 4 Hz, Furan-4H), 4.51 (m, 1H, C*H*OH), 2.98 (s, 1H, OH), 2.00-1.60 (m, 9H).

Furan-2-yl-phenylmethanol, 147[126]

This was prepared by the general procedure **A** by the reaction of phenylmagnesium chloride with furfural. The product was distilled (130-132°C at 0.2 mmHg) giving a colourless oil in 94% yield.

^{1}H NMR ($CDCl_3$): δ = 7.60-7.30 (m, 6H, 5xPhenyl, Furan-5H), 6.30 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.13 (dd, 1H, J = 2, 4 Hz, Furan-4H), 5.82 (s, 1H, C*H*OH), 2.56 (s, 1H, OH).

Furan-2-yl-*p*-tolylmethanol, 148

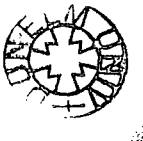
This was prepared by the general procedure **A** by the reaction of *p*-tolylmagnesium chloride with furfural. The product was purified by column chromatography on silica (dichloromethane), giving a yellow oil in 98% yield.
^{1}H NMR ($CDCl_3$): δ = 7.30-7.00 (m, 5H, 4xTolyl, Furan-5H), 6.17 (dd, 1H, J = 1, 4 Hz, Furan-3H), 5.98 (dd, 1H, J = 2, 4 Hz, Furan-4H), 5.60 (s, 1H, C*H*OH), 2.63 (s, 1H, OH), 2.23 (s, 3H, Me); ^{13}C NMR ($CDCl_3$): δ = 156.1, 142.3, 137.9, 129.0, 126.6, 111.5, 110.1, 107.1, 69.9, 21.1; ν_{max} (neat) 3386, 1514, 1011, 909, 733; m/z 188 (M^+); Accurate mass: 188.0845, $C_{12}H_{12}O_2$ requires 188.0837.

2-Methyl-1-(5-methylfuran-2-yl)propan-1-ol, 149[128]

This was prepared by the general procedure **A** by the reaction of *iso*-propylmagnesium chloride with 5-methylfurfural in 73% yield as a pale yellow oil.
^{1}H NMR ($CDCl_3$): δ = 6.16 (d, 1H, J = 3 Hz, Furan-3H), 5.97 (d, 1H, J = 3 Hz, Furan-4H), 4.35 (s, 1H, C*H*OH), 2.49 (s, 1H, OH), 2.35 (s, 3H, Furan-5Me), 2.18 (m, 1H, -C*H*(Me)$_2$), 1.10 (d, 3H, J = 7 Hz, Me), 0.94 (d, 3H, J = 7 Hz, Me).

2-Methyl-1-(5-methylfuran-2-yl)butan-1-ol, 150

This was prepared by the general procedure **A** by the reaction of *sec*-butylmagnesium chloride with 5-methylfurfural in 87% yield as a colourless oil.
^{1}H NMR ($CDCl_3$): δ = 6.32 (d, 1H, J = 3 Hz, Furan-3H), 5.87 (d, 1H, J = 3 Hz, Furan-4H), 4.32 (s, 1H, C*H*OH), 3.45 (s, 1H, OH), 2.36 (s, 3H, Furan-5Me), 2.19-1.65 (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 154.4, 151.2, 107.3, 105.8, 72.1, 39.5, 25.7, 15.0, 13.5, 11.5; ν_{max} (neat) 3405, 2962, 2923, 2876, 1565, 1019, 784cm^{-1}; m/z 168 (M^+); Accurate mass: 168.2337, $C_{10}H_{16}O_2$ requires 168.2328.



(5-Methylfuran-2-yl)phenylmethanol, 151[129]

This was prepared by the general procedure **A** by the reaction of phenylmagnesium chloride with 5-methylfurfural. The product was distilled (140-142°C at 0.3 mmHg) giving a yellow oil in 97% yield.

^{1}H NMR ($CDCl_3$): δ = 7.50-7.30 (m, 5H, 5xPhenyl), 5.95 (d, 1H, J = 3 Hz, Furan-3H), 5.90 (d, 1H, J = 3 Hz, Furan-4H), 5.77 (d, 1H, J = 4 Hz, C*H*OH), 2.45 (d, 1H, J = 4 Hz, OH), 2.28 (s, 3H, Furan-5Me).

(5-Methylfuran-2-yl)-*p*-tolylmethanol, 152[129]

This was prepared by the general procedure **A** by the reaction of *p*-tolylmagnesium chloride with 5-methylfurfural. The product was purified by column chromatography on silica (dichloromethane), giving **152** as a yellow oil in 85% yield.

^{1}H NMR ($CDCl_3$): δ =7.50-7.20 (m, 4H, 4xTolyl), 6.02 (d, 1H, J = 3 Hz, Furan-3H), 6.00 (d, 1H, J= 3 Hz, Furan-4H), 5.84 (s, 1H, C*H*OH), 3.32 (s, 1H, OH), 2.47 (s, 3H, Furan-5Me), 2.38 (s, 3H, Tolyl-Me).

Furan-2-yl-pyridin-2-ylmethanol, 157

Prepared by the general procedure **B** by reaction using *n*-butyllithium (9.2 ml, 15 mmol), furan (1.0 g, 15 mmol) and 2-pyridinecarboxaldehyde (1.6 g, 15 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **157** as a yellow oil (1.16 g, 45% yield).

^{1}H NMR ($CDCl_3$): δ = 8.51 (m, 1H, Py-6H), 7.72 (m, 1H, Py-4H), 7.43 (m, 1H, Furan-5H), 7.26-7.15 (m, 2H, 2xPy-3,5H), 6.19 (m, 1H, Furan-3H), 5.96 (m, 1H, Furan-4H), 5.70 (s, 1H, C*H*OH), 5.16 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 156.4, 153.9, 152.1, 146.9, 135.4, 122.7, 121.3, 108.3, 106.8, 71.3; ν_{max} (neat) 3410, 2960, 2915, 2765, 1567, 1123, 834; m/z 175 (M^+); Accurate mass: 175.0644, $C_{10}H_9NO_2$ requires 175.0633.

Furan-2-yl-pyridin-3-ylmethanol, 158[136]

Prepared by the general procedure **B** by reaction using *n*-butyllithium (9.2 ml, 15 mmol), furan (1.0 g, 15 mmol) and 3-pyridinecarboxaldehyde (1.6 g, 15 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **158** as a yellow solid (1.54 g, 60% yield). mp 34-35°C.

^{1}H NMR ($CDCl_3$): δ = 8.50 (m, 1H, Py-6H), 8.38 (m, 1H, Py-2H), 7.78 (m, 1H, Py-4H), 7.40-7.30 (m, 2H, Furan-5H, Py-5H), 6.28 (m, 1H, Furan-3H), 6.10 (m, 1H, Furan-4H), 5.80 (s, 1H, C*H*OH), 5.18 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 154.5, 148.4, 148.3, 142.3, 138.1, 136.6, 124.2, 111.4, 104.5, 73.4; ν_{max} (KBr) 3387, 3012, 2985, 1456, 1373, 870; m/z 175 (M^+); (Analysis found: C, 68.71, H, 5.32, N, 8.03%; $C_{10}H_9NO_2$ requires C, 68.56, H, 5.18, N, 8.00%).

Furan-2-yl-pyridin-4-ylmethanol, 159[137]

Prepared by the general procedure **B** by reaction using *n*-butyllithium (9.2 ml, 15 mmol), furan (1.0 g, 15 mmol) and 4-pyridinecarboxaldehyde (1.6 g, 15 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **159** as a yellow solid (1.44 g, 56% yield). mp 42-45°C.

^{1}H NMR ($CDCl_3$): δ = 8.54 (d, 2H, J = 6.3Hz, 2xPy-2,6H), 7.37 (d, 2H, J = 6.1Hz, 2xPy-3,5H), 7.11 (m, 1H, Furan-5H), 5.87 (m, 1H, Furan-3H), 5.84 (m, 1H, Furan-4H), 5.76 (s, 1H, C*H*OH), 4.41 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 154.3, 150.1, 142.3, 142.2, 122.4, 111.4, 111.4, 73.4; ν_{max} (KBr) 3365, 2987, 2945, 1789, 1287, 789; m/z 175 (M^+); (Analysis found: C, 68.57, H, 5.21, N, 8.11%; $C_{10}H_9NO_2$ requires C, 68.56, H, 5.18, N, 8.00%).

5-Methylfuran-2-yl-pyridin-2-ylmethanol, 160

Prepared by the general procedure **B** by reaction using *n*-butyllithium (6.9 ml, 11 mmol), 2-methylfuran (1.0 g, 10 mmol) and 2-pyridinecarboxaldehyde (1.2 g, 11 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **160** as a yellow solid (1.08 g, 47% yield). mp 84-86°C.

^{1}H NMR ($CDCl_3$): δ = 8.53 (m, 1H, Py-6H), 7.64 (m, 1H, Py-4H), 7.28-7.20 (m, 2H, 2xPy-3,5H), 6.08 (d, 1H, J = 3 Hz, Furan-3H), 5.87 (d, 1H, J = 3 Hz, Furan-4H), 5.72 (s, 1H, C*H*OH), 5.29 (bs, 1H, OH), 2.21 (s, 1H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 158.4, 153.3, 152.5, 147.9, 136.8, 122.7, 121.3, 108.7, 106.1, 68.8, 13.5; ν_{max} (KBr) 3412, 3123, 3011, 1675, 1480; m/z 189 (M^+); (Analysis found: C, 69.68, H, 5.99, N, 7.46%; $C_{11}H_{11}NO_2$ requires C, 69.83, H, 5.86, N, 7.40%).

5-Methylfuran-2-yl-pyridin-3-ylmethanol, 161

Prepared by the general procedure **B** by reaction using *n*-butyllithium (6.9 ml, 11 mmol), 2-methylfuran (1.0 g, 10 mmol) and 3-pyridinecarboxaldehyde (1.2 g, 11 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **161** as a yellow solid (1.11 g, 48% yield). mp 92-94°C.

^{1}H NMR ($CDCl_3$): δ = 8.65 (m, 1H, Py-2H), 8.50 (m, 1H, Py-6H), 7.82 (m, 1H, Py-4H), 7.35 (m, 1H, Py-5H), 6.04 (d, 1H, J = 3 Hz, Furan-3H), 5.94 (d, 1H, J = 3 Hz, Furan-4H), 5.81 (s, 1H, C*H*OH), 5.13 (bs, 1H, OH), 2.21 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 156.0, 152.8, 149.7, 149.5, 139.1, 135.0, 124.2, 108.8, 107.2, 68.4, 13.7; ν_{max} (KBr) 3378, 3067, 2987, 1652, 1456, 675; m/z 189 (M^+); (Analysis found: C, 69.72, H, 5.79, N, 7.21%; $C_{11}H_{11}NO_2$ requires C, 69.83, H, 5.86, N, 7.40%).

5-Methylfuran-2-yl-pyridin-4-ylmethanol, 162

Prepared by the general procedure **B** by reaction using *n*-butyllithium (6.9 ml, 11 mmol), 2-methylfuran (1.0 g, 10 mmol) and 4-pyridinecarboxaldehyde (1.3 g, 11 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **162** as a tan solid (1.27 g, 55% yield). mp 102-103°C.

^{1}H NMR ($CDCl_3$): δ = 8.47 (d, 2H, J = 6 Hz, 2xPy-2,6H), 7.37 (d, 2H, J = 6 Hz, 2xPy-3,5H), 5.98 (d, 1H, J = 3 Hz, Furan-3H), 5.88 (d, 1H, J = 3 Hz, Furan-4H), 5.75 (s, 1H, C*H*OH), 4.41 (bs, 1H, OH), 2.24 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 152.9, 152.8, 150.5, 149.3, 121.5, 108.9, 106.2, 68.4, 13.5; ν_{max} (KBr) 3356, 2987, 2875, 1567, 1432, 690; m/z 189 (M^+); (Analysis found: C, 69.94, H, 5.77, N, 7.31%; $C_{11}H_{11}NO_2$ requires C, 69.83, H, 5.86, N, 7.40%).

Bis(furan-2-yl)methanol, 163[138]

Prepared by the general procedure **B** by reaction using *n*-butyllithium (9.2 ml, 15 mmol), furan (1.0 g, 15 ml) and 2-furaldehyde (1.2 g, 15 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **163** as a red oil (087 g, 36% yield).

^{1}H NMR ($CDCl_3$): δ = 7.40 (m, 2H, 2xFuran-5H), 6.34 (m, 2H, 2xFuran-3H), 6.29 (m, 2H, 2xFuran-4H), 5.80 (s, 1H, C*H*OH), 3.18 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 150.8, 142.8, 111.3, 102.3, 69.5; m/z 164 (M^+).

Furan-2-yl-(5-methylfuran-2-yl)methanol, 164

Prepared by the general procedure **B** by reaction using *n*-butyllithium (8.4 ml, 13 mmol), 2-methylfuran (1.0 g, 12 ml) and 2-furaldehyde (1.1 g, 13 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **164** as a dark red oil (0.39 g, 18% yield).

^{1}H NMR ($CDCl_3$): δ = 7.38 (m, 1H, Furan-5H), 6.35-6.24 (m, 2H, 2xFuran-3,4H), 6.14 (d, 1H, J = 3 Hz, Furan-3H), 5.90 (d, 1H, J = 3 Hz, Furan-4H), 5.74 (s, 1H, C*H*OH), 1.72 (bs, 1H, OH), 1.16 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 153.4, 152.5, 151.4, 142.5, 110.3, 108.7, 107.5, 106.3, 64.1, 13.5; ν_{max} (neat) 3348, 3120, 1378, 1078, 820; m/z 178 (M^+); Accurate mass: 178.0638, $C_{10}H_{10}O_3$ requires 178.0630.

Furan-2-yl-thiophen-2-ylmethanol, 165[139]

Prepared by the general procedure **B** by reaction using *n*-butyllithium (9.2 ml, 15 mmol), furan (1.0 g, 15 ml) and 2-thiophenecarboxaldehyde (1.2 g, 15 mmol). Column chromatography on alumina (toluene:diethyl ether 4:1 $^{v}/_{v}$) afforded **165** as a red oil (0.74 g, 28% yield).

^{1}H NMR ($CDCl_3$): δ = 7.42 (m, 1H, Furan-5H), 7.30 (m, 1H, Thio-5H), 7.05-6.95 (m, 2H, 2xThio-3,4H), 6.35 (m, 1H, Furan-3H), 6.26 (m, 1H, Furan-4H), 6.06 (s, 1H, C*H*OH), 2.92 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 153.5, 145.7, 142.8, 128.9, 127.9, 123.1, 111.4, 106.8, 71.8; m/z 180 (M^+).

(5-Methylfuran-2-yl)-thiophen-2-ylmethanol, 166

Prepared by the general procedure **B** by reaction using *n*-butyllithium (10 ml, 16 mmol), 2-methylfuran (1.3 g, 16 mmol) and 2-thiophenecarboxaldehyde (1.8 g, 16 mmol). Column chromatography on alumina (toluene:diethyl ether 4:1 $^{v}/_{v}$) gave **166** as a yellow oil (0.52 g, 22% yield).

^{1}H NMR ($CDCl_3$): δ = 7.30 (m, 1H, Thio-5H), 7.03 (m, 1H, Thio-3H), 6.99 (m, 1H, Thio-4H), 6.15 (d, 1H, J = 3 Hz, Furan-3H), 6.02 (s, 1H, C*H*OH), 5.92 (d, 1H, J = 3 Hz, Furan-4H), 2.79 (bs, 1H, OH), 1.27 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 156.9, 152.7, 145.7, 128.8, 127.9, 122.7, 107.2, 106.1, 73.0, 14.0; ν_{max} (neat) 3354, 3388, 2921, 1563, 1218, 1008; m/z 194 (M^+); Accurate mass: 194.0411, $C_{10}H_{10}O_2S$ requires 194.0402.

Furan-2-yl-quinolin-3-ylmethanol, 167

Prepared by the general procedure **B** by the reaction using *n*-butyllithium (10.1 ml, 16 mmol), furan (1.0 g, 15 mmol) and 3-quinaldehyde (2.54 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **167** as a white solid (1.59 g, 48% yield). mp 100-102°C.

^{1}H NMR ($CDCl_3$): δ = 8.84 (m, 1H, Quin-2H), 8.24 (m, 1H, Quin-8H), 8.05-7.77 (m, 2H, Quin-4,6H), 7.66 (m, 1H, Quin-5H), 7.51 (m, 1H, Quin-7H), 7.35 (m, 1H, Furan-5H), 6.28 (m, 1H, Furan-3H), 6.14 (m, 1H, Furan-4H), 6.02 (s, 1H, C*H*OH), 3.75 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 155.2, 149.5, 147.3, 142.8, 134.0, 133.6, 129.6, 128.8, 128.0, 127.7, 126.9, 110.4, 107.9, 67.9; ν_{max} (KBr) 3420, 3056, 2967, 1621, 1453, 765; m/z 225 (M^+); (Analysis found: C, 74.60, H, 4.73, N, 6.34%; $C_{14}H_{11}NO_2$ requires C, 74.65, H, 4.92, N, 6.22%).

5-Methylfuran-2-yl-quinolin-3-ylmethanol, 168

Prepared by the general procedure **B** by the reaction using *n*-butyllithium (8.4 ml, 13 mmol), 2-methylfuran (1.0 g, 12 mmol) and 3-quinaldehyde (2.1 g, 13 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **167** as a white solid (1.43 g, 49% yield). mp 113-114°C.

^{1}H NMR ($CDCl_3$): δ = 8.60 (m, 1H, Quin-2H), 7.80 (m, 1H, Quin-8H), 7.68-7.63 (m, 2H, Quin-4,6H), 7.57 (m, 1H, Quin-5H), 7.45 (m, 1H, Quin-7H), 6.80 (s, 1H, C*H*OH), 6.08 (d, 1H, J = Hz, Furan-3H), 5.97 (d, 1H, J = Hz, Furan-4H), 5.69 (s, 1H, OH), 2.18 (s, 3H, Furan-5Me), ^{13}C NMR ($CDCl_3$): δ = 156.8, 153.7, 151.4, 146.4, 135.9, 132.4, 131.2, 128.9, 128.4, 127.8, 126.7, 197.3, 104.5, 73.7, 14.6; ν_{max} (KBr) 3412, 3010, 2867, 1546, 981; m/z 239 (M^+); (Analysis found: C, 75.36, H, 5.72, N, 5.67%; $C_{15}H_{13}NO_2$ requires C, 75.30, H, 5.48, N, 5.85%).

Furan-2-yl-naphthalen-2-ylmethanol, 169

Prepared by the general procedure **B** by the reaction using *n*-butyllithium (10.1 ml, 16 mmol), furan (1.0 g, 15 mmol) and 2-naphthaldehyde (2.5 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **168** as a white solid (1.91 g, 58% yield). mp 80-82°C.

^{1}H NMR ($CDCl_3$): δ = 8.45 (m, 1H, Nap-4H), 8.10-7.85 (m, 4H, 4xNap-1,3,5,8H), 7.65 (m, 1H, Furan-5H), 7.62-7.53 (m, 2H, 2xNap-6,7H), 6.60 (m, 1H, Furan-3H), 6.23 (m, 1H, Furan-4H), 6.11 (s, 1H, C*H*OH), 2.31 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 155.8, 142.3, 139.6, 136.1, 134.8, 128.2, 127.9, 127.4, 126.4, 126.1, 125.8, 125.6, 112.3, 106.8, 73.1; ν_{max} (KBr) 3367, 3109, 2965, 1235, 1015, 784; m/z 224 (M^+); (Analysis found: C, 80.55, H, 5.48%; $C_{15}H_{12}O_2$ requires C, 80.34, H, 5.39%).

5-Methylfuran-2-yl-naphthalen-2-ylmethanol, 170

Prepared by the general procedure **B** by the reaction using *n*-butyllithium (8.4 ml, 13 mmol), 2-methylfuran (1.0 g, 12 mmol) and 2-naphthaldeyde (2.0 g, 13 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **169** as a white solid (1.22 g, 42% yield). mp 95-95°C.

^{1}H NMR ($CDCl_3$): δ = 7.77 (m, 1H, Nap-4H), 7.66-7.63 (m, 2H, 2xNap-1,8H), 7.61 (m, 1H, Nap-5H), 7.50 (m, 1H, Nap-3H), 7.35 (m, 1H, Nap-7H), 7.30-7.25 (m, 1H, Nap-6H), 6.17 (s, 1H, C*H*OH), 6.01 (d, 1H, J = 3Hz, Furan-3H), 5.81 (d, 1H, J = 3Hz, Furan-4H), 5.66 (bs, 1H, OH), 2.18 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 156.6, 153.9, 139.6, 136.1, 134.5, 128.2, 127.2, 126.9, 126.7, 126.1, 125.8, 125.7,

107.3, 106.8, 73.1, 15.1; ν_{max} (KBr) 3367, 2989, 1478, 1013, 843; m/z 238 (M^+); (Analysis found: C, 80.87, H, 6.10%; $C_{15}H_{12}O_2$ requires C, 80.65, H, 5.92%).

Furan-2-yl-ferrocenylmethanol, 171

To a solution of *n*-butyllithium (1.5M in hexane, 25.6 ml, 41 mmol) in diethyl ether (60 ml) at 0°C was added furan (2.8 g, 41 mmol). The solution was refluxed for 3 h, then cooled to –78°C and a solution of ferrocene carboxaldehyde (8.0 g, 37 mmol) in diethyl ether (40 ml) and tetrahydrofuran (40 ml) was added slowly over 30 min. The reaction was allowed to warm to room temperature overnight, then ammonium chloride solution (50 ml) added. The organic phase was extracted with diethyl ether (3x30 ml) and ethyl acetate (3x30 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on alumina (ethyl actetate:hexane 1:1 $^v/_v$) afforded **171** as red solid (4.8 g, 42% yield). mp °C

^{1}H NMR ($CDCl_3$): δ = 7.43 (m, 1H, Furan-5H), 6.34 (m, 1H, Furan-3H), 6.23 (m, 1H, Furan-4H), 5.49 (s, 1H, C*H*OH), 4.87 (bs, 1H, CHO*H*), 4.27 (m, 1H, Fc), 4.20 (m, 1H, Fc), 4.11 (m, 2H, 2xFc), 4.03 (m, 5H, 5xFc); ^{13}C NMR ($CDCl_3$): δ = ; ν_{max} (neat) 3450-3350, 2922, 2853, 1460, 1376, 999; m/z 282; (Analysis found: C, H, %; $C_{15}H_{14}FeO_2$ requires C, 63.86, H, 5.00%).

Furan-2-yl-[4-(furan-2-yl-hydroxymethyl)phenyl]methanol, 175

To a solution of furan (2.0 g, 29 mmol) in tetrahydrofuan (60 ml) at 0°C was added *n*-butyllithium (20.2 ml, 32 mmol), the solution was stirred for 4 h, then terephthaldicarboxaldehyde (2.17 g, 16 mmol) was added as a solution in tetrahydrofuran (40 ml). The reaction was kept at 0°C for another 3 h, before being allowed to warm to room temperature. Ammonium chloride solution (40 ml) was added, and the organics extracted with diethyl ether (3x40 ml). The combined organic solutions were dried (MgSO4), filtered and the solvent removed *in vacuo*. Column chromatography on silica (dichloromethane) afforded **175** as a white solid (2.67 g, 62% yield). mp 95-97°C.

^{1}H NMR ($CDCl_3$): δ = 7.40 (s, 4H, 4xPhenyl), 7.37 (m, 2H, 2xFuran-5H), 6.30 (m, 2H, 2xFuran-3H), 6.11 (m, 2H, 2xFuran-4H), 5.80 (s, 2H, 2xC*H*OH), 2.61 (bs, 2H, 2xCHO*H*); ^{13}C NMR ($CDCl_3$): δ = 157.8, 142.6, 140.6, 126.7, 110.2, 107.5, 69.9;

ν_{max} (KBr) 3376, 3010, 2854, 1389, 1119, 923, 621; m/z 270 (M^+); (Analysis found: C, 71.07, H, 5.16%; $C_{16}H_{14}O_4$ requires C, 71.10, H, 5.22%).

1-Furan-2-yl-2-methylpropan-1-one, 178[12]

Prepared by the general procedure **D** using **145**. The product was distilled (40-42°C at 0.2 mmHg) giving **178** as a colourless oil in 49% yield.
^{1}H NMR ($CDCl_3$): δ = 7.64 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.24 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.59 (dd, 1H, J = 2, 4 Hz, Furan-4H), 3.39 (septet, 1H, C*H*(Me_2)), 1.26 (d, 6H, J = 7 Hz, 2xMe).

1-Furan-2-yl-2-methylbutan-1-one, 179[12]

Prepared by the general procedure **D** using **146**. The product was distilled (125-126°C at 0.3 mmHg) giving **179** as a pale yellow oil in 54% yield.
^{1}H NMR ($CDCl_3$): δ = 7.56 (m, 1H, Furan-5H), 7.10 (m, 1H, Furan-3H), 6.14 (m, 1H, Furan-4H), 3.27 (m, 1H), 2.34 (m, 3H), 1.80 (m, 6H).

Furan-2-yl-phenylmethanone, 180[152]

A stirring solution of furan (5.0 g, 80 mmol) and benzoic anhydride (36 g, 161 mmol), was warmed to 40°C. The heat was removed and phosphoric acid (1.65 g) added, the solution was then heated to 60°C for 2 hours. The solution was allowed to cool, water (100 ml) was added and stirred for 1 hour. Sodium bicarbonate was added to neutralise the reaction, the organic layer extracted with dichloromethane (3x30 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Product was purified by distillation (50-52°C at 0.3 mmHg), giving **180** as a yellow oil (1.26 g, 10% yield).
180 was also prepared in 77% yield by oxidation of **147** using the general procedure **D**.
^{1}H NMR ($CDCl_3$): δ = 7.98 (m, 1H, Phenyl), 7.96 (m, 1H, Phenyl), 7.71 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.60 (dd, 1H, J = 1, 3 Hz, Furan-3H), 7.50 (m, 2H, 2xPhenyl), 7.24 (m, 1H, Phenyl), 6.60 (dd, 1H, J = 2, 3 Hz, Furan-4H).

Furan-2-yl-*p*-tolylmethanone, 181[153]

This was prepared by oxidation of alcohol **148** using the general procedure **D**. Purified by column chromatography on silica (dichloromethane), giving a yellow solid in 86% yield. mp 30-32°C (Lit 41-42°C).

^{1}H NMR ($CDCl_3$): δ = 7.92 (m, 1H, Tolyl), 7.88 (m, 1H, Tolyl), 7.70 (m, 1H, Furan-5H), 7.32-7.29 (m, 2H., 2xTolyl), 7.28 (m, 1H, Furan-3H), 6.59 (m, 1H, Furan-4H), 2.44 (s, 3H, Tolyl-Me); ^{13}C NMR ($CDCl_3$): δ = 182.0, 152.1, 146.7, 143.3, 134.5, 129.4, 126.7, 120.0, 112.0, 21.6; ν_{max} (KBr) 1633, 1461, 1193, 1177, 1027, 790, 754, 626; m/z 186 (M^+); (Analysis found: C, 77.12, H, 5.53%; $C_{12}H_{10}O_2$ requires C, 77.40, H, 5.41%).

2-Methyl-1-(5-methylfuran-2-yl)propan-1-one, 182[154a]

A solution of 2-methylfuran (13.5 g, 160 mmol) and *iso*-butyric anhydride (52.2 g, 330 mmol) was warmed to 40°C. The heat was removed, phosphoric acid (3.3 g) added and then heated at 60°C for 2 h. The solution was allowed to cool, water (100 ml) added, and stirred for a further 1 h. The reaction was neutralised with sodium bicarbonate and stirred for 15 h. The organic layer was extracted with dichloromethane (3x30 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation (80-82°C at 0.3 mmHg) gave **182** as a yellow oil in (23.8 g, 78% yield).

182 was also prepared in 43% yield by oxidation of **149** using the general procedure **D**.

^{1}H NMR ($CDCl_3$): δ = 7.11 (d, 1H, J = 3 Hz, Furan-3H), 6.15 (d, 1H, J = 3 Hz, Furan-4H), 3.27 (septet, 1H, C*H*(Me)$_2$), 2.41 (s, 3H, Furan-5Me)1.18 (d, 6H, J = 7 Hz, 2xMe).

(5-Methylfuran-2-yl)phenylmethanone, 183

This was prepared by the general procedure **D** by oxidation of the alcohol **151**. The product was distilled (150-152°C at 0.3 mmHg) to give **183** as a yellow oil in 58% yield.

^{1}H NMR ($CDCl_3$): δ = 7.87 (m, 2H, 2xPhenyl), 7.60-7.30 (m, 3H, 3xPhenyl), 7.04 (d, 1H, J =3 Hz, Furan-3H), 6.14 (d, 1H, J = 3 Hz, Furan-4H), 2.37 (m, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 183.8, 159.7, 148.1, 144.2, 132.1, 129.4, 128.3, 120.4, 103.7, 13.6; ν_{max} (neat) 1654, 1432, 1123, 1067, 756; m/z 186 (M^+), Accurate mass: 186.0672, $C_{12}H_{10}O_2$ requires 186.0681.

(5-Methylfuran-2-yl)-*p*-tolylmethanone, 184[154b]

This was prepared by the general procedure **D** by oxidation of the alcohol **152**. The product was columned on silica (dichloromethane) to give **184** as a yellow solid in 80% yield. mp 39-40°C (Lit 41-42°C).

^{1}H NMR ($CDCl_3$): δ = 8.34 (d, 2H, J = 8Hz, 2xTolyl), 7.83 (d, 2H, J = 8 Hz, 2xTolyl), 7.12 (d, 1H, J = 3 Hz, Furan-3H), 6.50 (d, 1H, J = 3 Hz, Furan-4H), 2.69 (s, 3H, Furan-5Me), 2.32 (s, 3H, Tolyl-Me); ^{13}C NMR ($CDCl_3$): δ = 183.1, 160.2, 148.7, 144.0, 139.8, 129.3, 129.1, 120.7, 101.5, 21.6, 12.5; ν_{max} (neat) 1689. 1543, 1178, 1123, 1034, 824, 721; m/z 200 (M^+); (Analysis found: C, 80.12, H, 6.08%; $C_{13}H_{12}O_2$ requires C, 77.98, H, 6.04%).

Furan-2-yl-pyridin-2-ylmethanone, 185[67]

Prepared by the general procedure **B** by using furan (1.0 g, 15 mmol), *n*-butyllithium (10.1 ml, 16 mmol) and 2-cyanopyridine (1.7 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **185**, recrystallisation (hexane) gave a yellow solid (1.65 g, 65% yield).

185 was also prepared by the general procedure **D** by oxidation of the alcohol **157**, in 74% yield. mp 129-130°C (Lit 129°C).

^{1}H NMR ($CDCl_3$): δ = 8.72 (m, 1H, Py-6H), 8.41-7.98 (m, 2H, 2xPy-3,4H), 7.43-6.95 (m, 3H, Py-5H, 2xFuran-3,5H), 6.71-6.54 (dd, 1H, J = 2,4Hz, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 182.3, 151.2, 150.5, 149.6, 147.1, 138.7, 129.0, 125.4, 121.0, 111.7; m/z 173 (M^+); (Analysis found: C, 69.42, H, 4.31, N, 8.16%; $C_{10}H_7NO_2$ requires C, 69.36, H, 4.07, N, 8.09%).

Furan-2-yl-pyridin-3-ylmethanone, 186[136]

Prepared by the general procedure **B** by using furan (1.0 g, 15 mmol), *n*-butyllithium (10.1 ml, 16 mmol) and 3-cyanopyridine (1.7 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **186**, recrystallisation (hexane) gave as yellow solid (1.73 g, 68% yield).

186 was also prepared by the general procedure **D** by oxidation of the alcohol **158**, in 82% yield. mp 62-64°C (Lit 62-63°C).

^{1}H NMR ($CDCl_3$): δ = 9.21 (m, 1H, Py-2H), 8.80 (m, 1H, Py-6H), 8.27 (m, 1H, Py-4H), 7.74-7.44 (m, 2H, Py-5H, Furan-5H), 7.31 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.64 (dd, 1H, J = 2, 4 Hz, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 184.0, 154.7, 151.3, 149.6, 149.1, 139.9, 128.6, 123.3, 118.8, 109.2; m/z 173 (M^+); (Analysis found: C, 69.51, H, 4.22, N, 7.98%; $C_{10}H_7NO_2$ requires C, 69.36, H, 4.07, N, 8.09%).

Furan-2-yl-pyridin-4-ylmethanone, 187[155]

Prepared by the general procedure **B** by using furan (1.0 g, 15 mmol), *n*-butyllithium (10.1 ml, 16 mmol) and 3-cyanopyridine (1.7 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **187**, recrystallisation (hexane) gave a yellow solid (1.75 g, 69% yield). mp 79-80°C (Lit 79-81°C).

187 was also prepared by the general procedure **D** by oxidation of the alcohol **159**, in 77% yield.

^{1}H NMR ($CDCl_3$): δ = 8.81 (d, 2H, J = 6 Hz, 2xPy-2,6H), 7.77 (d, 2H, J= 6 Hz, 2xPy-3,5H), 7.56 (m, 1H, Furan-5H), 7.31 (m, 1H, Furan-3H), 6.64 (m, 1H, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 183.4, 151.8, 149.6, 149.0, 139.8, 125.9, 124.9, 109.2; m/z 173 (M^+); (Analysis found: C, 69.45, H, 4.15, N, 8.04%; $C_{10}H_7NO_2$ requires C, 69.36, H, 4.07, N, 8.09%).

5-Methylfuran-2-yl-pyridin-2-ylmethanone, 188

Prepared by the general procedure **C** by using 2-methylfuran (1.0 g, 12 mmol), *n*-butyllithium (6.9 ml, 11 mmol) and 2-cyanopyridine (1.2 g, 11 mmol). Column

chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **188**, recrystallisation (hexane) gave a yellow solid (1.48 g, 65% yield).

188 was also prepared by the general procedure **D** by oxidation of the alcohol **160**, 75% yield. mp 64-66°C.

^{1}H NMR ($CDCl_3$): δ = 8.70 (m, 1H, Py-6H), 8.14 (m, 1H, Py-4H), 7.95 (d, 1H, J = 3 Hz, Furan-3H), 7.83 (1H, m, Py-3H), 7.51 (m, 1H, Py-5H), 6.24 (d, 1H, J = 3 Hz, Furan-4H), 2.41 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 178.5, 159.3, 154.3, 150.1, 148.5, 136.9, 126.4, 126.3, 123.7, 109.5, 14.1; ν_{max} (KBr) 1656, 1223, 1189, 986, 823, 612; m/z 187 (M^+); (Analysis found: C, 70.39, H, 4.78, N, 7.43%; $C_{11}H_9NO_2$ requires C, 70.58, H, 4.85, N, 7.48%).

5-Methylfuran-2-yl-pyridin-3-ylmethanone, 189

Prepared by the general procedure **C** by using 2-methylfuran (1.0 g, 12 mmol), *n*-butyllithium (6.9 ml, 11 mmol) and 3-cyanopyridine (1.2 g, 11 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **189**, recrystallisation (hexane) gave a yellow solid (1.69 g, 74% yield).

189 was also prepared by the general procedure **D** by oxidation of the alcohol **161**, in 79% yield. mp 64-66°C.

^{1}H NMR ($CDCl_3$): δ = 9.13 (m, 1H, Py-2H), 8.76 (m, 1H, Py-6H), 8.19 (m, 1H, Py-4H), 7.43 (m, 1H, Py-5H), 7.17 (d, 1H, J = 3 Hz, Furan-3H), 6.24 (d, 1H, J = 3 Hz, Furan-4H), 2.44 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 179.9, 159.4, 152.7, 150.7, 150.0, 136.5, 133.2, 123.4, 123.2, 109.5, 14.2; ν_{max} (KBr) 1623, 1457, 1389, 1013, 783, 623; m/z 187 (M^+); (Analysis found: C, 70.51, H, 4.76, N, 7.13%; $C_{11}H_9NO_2$ requires C, 70.58, H, 4.85, N, 7.48%).

5-Methylfuran-2-yl-pyridin-4-ylmethanone, 190

Prepared by the general procedure **C** by using 2-methylfuran (1.0 g, 12 mmol), *n*-butyllithium (6.9 ml, 11 mmol) and 4-cyanopyridine (1.2 g, 11 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) afforded **190**, recrystallisation (hexane) gave a yellow solid (1.73 g, 76% yield).

190 was also prepared by the general procedure **D** by oxidation of the alcohol **162**, in 84% yield. mp 79-80°C.

^{1}H NMR ($CDCl_3$): δ = 8.77 (d, 2H, J = 6 Hz, 2xPy-2,6H), 7.70 (d, 2H, J = 6 Hz, 2xPy-3,5H), 7.16 (1H, d, J= 4 Hz, Furan-3H), 6.25 (1H, d, J = 4 Hz, Furan-4H), 2.45 (s, 3H. Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 180.5, 160.2, 150.6 (2H), 144.4, 124.2, 122.6, 109.6; ν_{max} (KBr) 1678, 1278, 1209, 1034, 865, 745; m/z 187 (M^+); (Analysis found: C, 70.30, H, 4.96, N, 7.57%; $C_{11}H_9NO_2$ requires C, 70.58, H, 4.85, N, 7.48%).

Bis(furan-2-yl) methanone, 191[156]

To a solution of furan (0.5 g, 7 mmol) and 2-furoyl chloride (0.9 g, 7 mmol) in dry dichloromethane at 0°C was added $SnCl_4$ and the mixture was stirred for 1 h at room temperature. The reaction was then quenched with water and the organic layer was extracted with dichloromethane (3x30 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on silica (dichloromethane) gave **191** as a yellow oil (0.52 g, 44% yield).

191 was also prepared by the general procedure **D** by oxidation of alcohol **163**. Column chromatography on silica (dichloromethane) gave **191** in 42% yield.

^{1}H NMR ($CDCl_3$): δ = 7.65 (dd, 2H, J = 1, 2 Hz, 2xFuran-5H), 6.97 (dd, 2H, J = 1, 3 Hz, 2xFuran-3H), 6.55 (dd, 2H, J = 2, 3 Hz, 2xFuran-4H); ^{13}C NMR ($CDCl_3$): δ = 180.2, 150.9, 144.5, 115.8, 110.8; m/z 162 (M^+).

Furan-2-yl-(5-methylfuran-2-yl)methanone, 192

192 was prepared by the general procedure **D** by oxidation of **164**. Column chromatography on silica (dichloromathane) gave **192** as a yellow oil in 36% yield.

^{1}H NMR ($CDCl_3$): δ = 7.49 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.08 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.68 (d, 1H, J = 3 Hz, Furan-3H), 6.46 (dd, 1H, J = 2, 4 Hz, Furan-4H), 6.01 (d, 1H, J = 3 Hz, Furan-4H), 2.56 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 175.7, 154.1, 151.0, 150.3, 143.6, 116.2, 115.2, 111.4, 104.7, 13.3; ν_{max} (neat) 1645, 1267, 1209, 1103, 956; m/z 176 (M^+); Accurate mass: 176.0481, $C_{10}H_8O_3$ requires 176.0473.

Furan-2-yl-thiophen-2-ylmethanone, 193[157a]

To a solution of furan (0.5 g, 7 mmol) and 2-thiophene carbonyl chloride (1.1 g, 7 mmol) in dry dichloromethane at 0°C was added $SnCl_4$ and the mixture was stirred for 1 h at room temperature. The reaction was then quenched with water and the organic layer was extracted with dichloromethane (3x30 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on silica (dichloromethane) gave **193** as a yellow oil (0.31 g, 24% yield).

^{1}H NMR ($CDCl_3$): δ = 8.15 (m, 1H, Furan-5H), 7.70-7.60 (m, 2H, 2xThio-3,5H), 7.38 (m, 1H, Thio-4H), 7.17 (m, 1H, Furan-3H), 6.57 (m, 1H, Furan-4H); m/z 178 (M^+).

Furan-2-yl-quinolin-3-ylmethanone, 195

Prepared by the general procedure **D** by oxidation of alcohol **167**. Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) gave **195** as white solid in 87% yield. mp 113-114°C.

Also prepared by the general procedure **B** using furan (1.0 g, 15 mmol), n-butyllithium (10.1 ml, 16 mmol) and 3-cyanoquinoline (2.7 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) gave **195** in 56% yield.

^{1}H NMR ($CDCl_3$): δ = 9.11 (d, 1H, J = 2 Hz, Quin-2H), 8.61 (m, 1H, Quin-4H), 8.17 (m, 1H, Quin-8H), 8.04-7.90 (m, 2H, Quin-5,6H), 7.60-7.50 (m, 2H, Quin-7H, Furan-5H), 7.14 (m, 1H, Furan-3H), 6.52 (m, 1H, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 180.4, 152.4, 149.8, 149.5, 147.4, 138.3, 131.9, 129.6, 129.5, 129.2, 127.5, 126.7, 120.7, 112.6; ν_{max} (KBr) 1654, 1256, 1178, 1054, 976, 812; m/z 223 (M^+); (Analysis found: C, 75.45, H, 4.05, N, 6.26%; $C_{14}H_9NO_2$ requires C, 75.33, H, 4.06, N, 6.27%).

(5-Methylfuran-2-yl)quinolin-3-ylmethanone, 196

Prepared by the general procedure **D** by oxidation of alcohol **168**. Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) gave **196** as a pale yellow solid in 77% yield. mp 133-136°C.

^{1}H NMR ($CDCl_3$): δ = 9.09 (d, 1H, J = 2 Hz, Quin-2H), 8.55 (m, 1H, Quin-4H), 8.17 (m, 1H, Quin-8H), 8.04-7.90 (m, 2H, Quin-5,6H), 7.53 (m, 1H, Quin-7H), 6.69 (d, 1H, J = 3Hz, Furan-3H), 6.11 (d, 1H, J = 3Hz, Furan-4H), 2.31 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 183.8, 162.2, 160.1, 149.5, 148.1, 133.8, 133.2, 132.3, 130.0, 127.9, 126.9, 126.8, 118.8, 103.7, 14.0; ν_{max} (KBr) 1689 1234, 1210, 1068, 1011, 892, 765; m/z 237 (M^+); (Analysis found: C, 76.24, H, 4.76, N, 5.64%; $C_{15}H_{11}NO_2$ requires C, 75.94, H, 4.67, N, 5.90%).

Furan-2-yl-naphthalen-2-ylmethanone, 197

To a solution of furan (1.0 g, 15 mmol) and 2-naphthoyl chloride (2.66 g, 14 mmol) in dry dichloromethane at 0°C was added $SnCl_4$ and the mixture was stirred for 1 h at room temperature. The reaction was then quenched with water and the organic layer was extracted with dichloromethane (3x30 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) gave **197** as a white solid (0.69 g, 21% yield). mp 96-98°C.

197 was also prepared by the general procedure **D** by oxidation of alcohol **169**. Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) gave **195** as white solid in 77% yield.

Also prepared by the general procedure **B** using furan (1.0 g, 15 mmol), *n*-butyllithium (10.1 ml, 16 mmol) and 2-cyanonaphthalene (0.7 g, 16 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) gave **197** (2.02 g, 62% yield).

^{1}H NMR ($CDCl_3$): δ = 8.54 (m, 1H, Nap-1H), 8.10-7.82 (m, 4H, 4xNap-3,4,5,8H), 7.74 (m, 1H, Furan-5H), 7.62-7.30 (m, 2H, 2xNap-6,7H), 7.30 (m, 1H, Furan-3H), 6.62 (m, 1H, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 182.5, 152.5, 147.1, 135.3, 134.5, 132.4, 130.8, 129.4, 128.3, 128.3, 127.8, 126.8, 125.2, 120.6, 112.3; ν_{max} (KBr) 1636,

1458, 1391, 1310, 1018; m/z 222 (M^+); (Analysis found: C, 79.97, H, 4.60%; $C_{15}H_{10}O_2$ requires C, 81.07, H, 4.54%).

5-Methylfuran-2-yl-naphthalen-2-ylmethanone, 198

Prepared by the general procedure **D** by oxidation of alcohol **170**. Column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) gave **198** as an off-white solid in 89% yield. mp 125-127°C.

^{1}H NMR ($CDCl_3$): δ = 8.52 (m, 1H, Nap-1H), 8.15 (m, 1H, Nap-4H), 8.08-7.90 (m, 3H, 3xNap-3,5,8H), 7.70 (m, 1H, Nap-7H), 7.35 (m, 1H, Nap-6H), 6.51 (d, 1H, J = 3Hz, Furan-3H), 6.02 (d, 1H, J = 3Hz, Furan-4H), 2.48 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 183.1, 159.7, 148.6, 147.1, 133.1, 131.9, 131.8, 131.6, 128.8, 128.3, 128.0, 127.8, 127.6, 121.1, 103.7, 13.6; ν_{max} (KBr) 1623, 1435, 1387, 1301, 1016, 896, 675; m/z 236 (M^+); (Analysis found: C, 81.07, H, 5.23%; $C_{16}H_{12}O_2$ requires C, 81.34, H, 5.12%).

Furan-2-yl-ferrocenylmethanone, 199[157b]

Prepared by the general procedure **D** by oxidation of **171**. Column chromatography on alumina (ethyl acetate) gave **199** in 96% yield as a red solid. mp °C.

^{1}H NMR ($CDCl_3$): δ = 7.62 (m, 1H, Furan-5H), 7.32 (m, 1H, Furan-3H), 6.56 (m, 1H, Furan-4H), 5.16 (m, 2H, 2xFc), 4.58 (m, 2H, 2xFc), 4.17 (s, 5H, 5xFc); ^{13}C NMR ($CDCl_3$): δ = 184.7, 153.7, 145.2, 116.6, 112.0, 77.76, 72.45, 70.78, 70.12.

[4-Furan-2-carbonyl)phenyl]furan-2-ylmethanone, 200

Prepared by the general procedure **D** by the oxidation of furan-2-yl-benzene-1,4-ylmethanol **175**. There was no need to further purify the product, giving **200** as a white solid in 76% yield. mp 162-163°C.

^{1}H NMR ($CDCl_3$): δ = 8.10 (s, 4H, 4xPhenyl), 7.76 (dd, 2H, J = 1, 2 Hz, 2xFuran-5H), 7.31 (dd, 2H, J = 1, 3 Hz, 2xFuran-3H), 6.65 (dd, 2H, J = 2, 3 Hz, 2xFuran-4H); ^{13}C NMR ($CDCl_3$): δ = 181.7, 152.0, 147.5, 140.3, 129.2, 121.1, 112.5; ν_{max} (KBr)

2836, 1656, 1334, 1278, 1103, 895; m/z 266 (M^+); (Analysis found: C, 71.99, H, 3.77%; $C_{16}H_{10}O_4$ requires C, 72.18, H, 3.79%).

Furan-2-ylpropan-1-one, 208[159]

A stirring solution of furan (8.0 g, 120 mmol) with propionic anhydride (30.6 g, 240 mmol) was heated at 40°C. The heat was removed, phosphoric acid (2.5 g) added and the solution heated to 60°C for 2 h. The reaction was allowed to cool to 25°C, water (100 ml) added and stirred for a further 1 h. The solution was neutralised with $NaHCO_3$ and the organic layer extracted with dichloromethane (3x30 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation (95-100°C at 0.3 mmHg) afforded **208** (11.10 g, 76% yield).

^{1}H NMR ($CDCl_3$): δ = 7.48 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.07 (dd, 1H, J = 1, 3 Hz, Furan-3H), 6.42 (dd, 1H, J = 2, 3 Hz, Furan-4H), 2.73 (q, 2H, J = 15 Hz, CH_2), 1.07 (t, 3H, J = 7 Hz, CH_3).

1-(5-Methylfuran-2-yl)propan-1-one, 209

A solution of 2-methylfuran (13.5 g, 160 mmol) and propionic anhydride (41.6 g, 320 mmol) was heated to 40°C. The heat was removed, phosphoric acid (3.3 g) added and the solution heated to 60°C for 2 h. The reaction was allowed to cool to 25°C, water (100 ml) added and stirred for a further 1 h. The solution was neutralised with $NaHCO_3$ and the organic layer extracted with dichloromethane (3x30 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation (102-105°C at 0.2 mmHg) gave **209** as a pale yellow oil (10.7 g, 47% yield).

^{1}H NMR ($CDCl_3$): δ = 7.01 (d, 1H, J = 3 Hz, Furan-3H), 6.07 (d, 1H, J = 3 Hz, Furan-4H), 2.71 (q, 2H, J = 15 Hz, CH_2CH_3), 2.30 (s, 3H, Furan-5Me), 1.11 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ =187.8, 156.0, 149.8, 117.2, 107.2, 29.8, 12.5, 6.9; ν_{max} (KBr) 1669, 1513, 1206, 1015, 903, 790; m/z 138 (M^+); Accurate mass: 138.0685, $C_8H_{10}O_2$ requires 138.0681.

1-(5-Ethylfuran-2-yl)methanone, 210[160]

A solution of 2-ethylfuran (2.0 g, 21 mmol) and acetic anhydride (2.4 g, 40 mmol) was heated to 40°C. The heat was removed, phosphoric acid (1.1 g) added and the solution heated to 60°C for 2 h. The reaction was allowed to cool to 25°C, water (100 ml) added and stirred for a further 1 h. The solution was neutralised with $NaHCO_3$ and the organic layer extracted with dichloromethane (3x30 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation (120-122°C at 0.3 mmHg) gave **210** as a colourless oil (1.21 g, 46% yield).

^{1}H NMR ($CDCl_3$): δ = 7.09 (d, 1H, J = 3 Hz, Furan-3H), 6.13 (d, 1H, J = 3 Hz, Furan-4H), 2,68 (q, 2H, J = 8 Hz, CH_2CH_3), 2.38 (s, 3H, $COCH_3$), 1.23 (t, 3H, J = 8 Hz, CH_2CH_3).

2,2,2-Trifluoro-1-furan-2-ylethanone, 211[161]

To a stirring solution of furan (10.0 g, 147 mmol) and pyridine (12.5 ml, 150 mmol) under argon at 10°C was added trifluoroacetic anhydride (16.9 ml, 120 mmol) over 1 h, the solution was the stirred for 16 h. Dichloromethane (60 ml) and 10% hydrochloric acid (60 ml) were added, the organic layer separated, washed sequentially with water (60 ml) and 10% sodium hydroxide (60 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation (70-72°C at 0.2 mmHg) gave **211** as a colourless oil in (5.55 g, 23% yield).

^{1}H NMR ($CDCl_3$): δ = 7.85 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.52 (dd, 1H, J = 1, 4 Hz, Furan-3H), 6.70 (dd, 1H, J = 2, 4 Hz, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 168.6, 150.5, 147.0, 124.5, 116.4 (q, J = 230 Hz), 113.4; ^{19}F NMR ($CDCl_3$): δ = 74.1; ν_{max} (neat) 1696, 1459, 1142, 966, 761, 733; m/z 164 (M^+).

2,2,2-Trifluoro-1-(5-methylfuran-2-yl)ethanone, 212[162]

To a stirring solution of 2-methylfuran (5.0 g, 60 mmol) and pyridine (6.1 ml, 75 mmol) under argon at 10°C was added trifluoroacetic anhydride (8.5 ml, 60 mmol) over 1 h, the solution was the stirred for 16 h. Dichloromethane (60 ml) and 10% hydrochloric acid (60 ml) were added, the organic layer separated, washed

sequentially with water (60 ml) and 10% sodium hydroxide (60 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation (80-82°C at 0.08 mmHg) gave **212** as a colourless oil (2.50 g, 23% yield).

^1H NMR ($CDCl_3$): δ = 7.36 (d, 1H, J = 3 Hz, Furan-3H), 6.26 (d, 1H, J = 3 Hz, Furan-4H), 2.37 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ = 168.4, 162.9, 145.8, 126.6, 116.6 (q, J = 242 Hz), 110.6, 14.0; ^{19}F NMR ($CDCl_3$): δ = 74.2; ν_{max} (neat) 1697, 1509, 1245, 1209, 1195, 1041, 736; m/z 178 (M^+).

5-(Furan-2-carbonyl)pyridine-2-carboxylic acid, 216

To a stirring solution of furan (0.15 g, 2.2 mmol) in dry dichloromethane (30 ml) was added 2,5-bis-pyridoyl chloride (0.22 g, 1.1 mmol) (prepared by refluxing 2,5-pyridoic acid with thionyl chloride). The solution was cooled to 0°C, $SnCl_4$ (0.6 g, 0.3 ml) added and stirred for 1 h. The reaction was quenched with water (50 ml) and the organic layer extracted with dichloromethane (3x40 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on silica (ethyl acetate:methanol 1:1 $^v/_v$) afforded a yellow solid (0.13 g, 27% yield). mp 71-73°C.

^1H NMR ($CDCl_3$): δ = 9.92 (dd, 1H, J = 1, 2 Hz, Py-6H), 8.5 (dd, 1H, J = 2, 8 Hz, Py-4H), 8.48 (dd, 1H, J = 1, 8 Hz, Py-3H), 7.56 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.16 (dd, 1H, J = 1, 3 Hz, Furan-3H), 6.98 (bs, 1H, CO_2H), 6.52 (dd, 1H, J = 2, 3 Hz, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 183.3, 165.5, 155.3, 152.3, 149.6, 148.9, 137.7, 130.0, 125.9, 118.9, 109.1; ν_{max} (KBr) 1678, 1456, 1234, 1210. 1078, 942; m/z 217 (M^+); (Analysis found: C, 60.64, H, 3.12, N, 6.31%; $C_{11}H_7NO_4$ requires C, 60.83, H, 3.25, N, 6.45%).

Furan-2-yl-(*1*H-indol-5-yl)methanone, 221

Prepared by the general procedure **C** by using *n*-butyllithium (8.3 ml, 13 mmol), furan (1.0 g, 15 mmol) and 5-cyanoindole (1.9 g, 13 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) gave **221** as a white solid (1.92 g, 62% yield). mp 109-111°C.

^{1}H NMR ($CDCl_3$): δ = 8.81 (bs, 1H, NH), 8.17 (m, 1H, Ind-4H), 7.87 (m, 1H, Ind-6H), 7.70-7.60 (m, 1H, Ind-7H), 7.47 (dd, 1H, J = 1, 2 Hz, Furan-5H), 7.10-6.90 (m, 2H, Ind-2H, Furan-3H), 6.45 (dd, 1H, J = 2, 4 Hz, Furan-4H), 5.34 (m, 1H, Ind-3H); ^{13}C NMR ($CDCl_3$): δ = 180.7, 149.6, 149.1, 141.3, 134.1, 126.3, 125.4, 124.9, 123.8, 119.9, 113.4, 111.1, 109.6; ν_{max} (KBr) 1665, 1435, 1289, 1164, 1102, 978, 764; m/z 211 (M^+); (Analysis found: C, 74.05, H, 4.56, N, 6.89%; $C_{13}H_9NO_2$ requires C, 73.92, H, 4.29, N, 6.63%).

Furan-2-yl-(3-pyrrol-1-yl-phenyl)methanone, 222

Prepared by general procedure **C** by reaction using *n*-butyllithium (13 mmol), furan (1.0 g, 15 mmol) and *N*-(3-cyanophenyl)pyrrole (2.12 g, 13 mmol). Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) afforded **222** as a white solid (1.67 g, 48% yield). mp 56-59°C

^{1}H NMR ($CDCl_3$): δ = 7.88 (m, 1H, Phenyl-2H), 7.73 (m, 1H, Phenyl-4H), 7.16 (m, 1H, Phenyl-5H), 7.51-7.40 (m, 2H, Furan-5H, Phenyl-6H), 7.18 (m, 1H, Furan-3H), 7.05 (m, 2H, 2xPyrrole-2,5H), 6.50 (m, 1H, Furan-4H), 6.27 (m, 2H, 2xPyrrole-3,4H); ^{13}C NMR ($CDCl_3$): δ = 181.4, 151.9, 147.3, 140.7, 138.4, 129.6, 126.2, 124.0, 120.8, 120.7, 119.1, 112.3, 110.9; ν_{max} (KBr) 1635, 1278, 1176, 1013, 875; m/z 237 (M^+); (Analysis found: C, 75.68, H, 4.61, N, 5.88%; $C_{15}H_{11}NO_2$ requires C, 75.94, H, 4.67, N, 5.90%).

Furan-2-yl-pyrazin-2-ylmethanone, 223

Prepared by the general procedure **C** by using furan (1.0 g, 15 mmol), *n*-butyllithium (8.3 ml, 13 mmol) and 2-cyanopyrazine (1.4 g, 13 mmol). Column chromatography on alumina (ethyl actetate:hexane 1:1 $^v/_v$) afforded **223**, recrystallisation (hexane) gave yellow needles (1.36 g, 53% yield). mp 87-89°C.

^{1}H NMR ($CDCl_3$): δ = 9.36 (m, 1H, Pyraz-3H), 8.77 (m, 1H, Pyraz-6H), 8.68 (m, 1H, Pyraz-5H), 8.02 (m, 1H, Furan-5H), 7.78 (m, 1H, Furan-3H), 6.65 (m, 1H, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 177.5, 150.4, 148.3, 148.2, 147.2, 145.3, 142.9, 124.4, 112.5; ν_{max} (KBr) 1659, 1510, 1209, 1105, 1067, 921, 834, 657; m/z 174 (M^+); (Analysis

found: C, 61.97, H, 3.50, N, 15.97%; $C_9H_6N_2O_2$ requires C, 62.07, H, 3.47, N, 16.09%).

Furan-2-yl-(6-methylpyridin-3-yl)methanone, 224

Prepared by the general procedure **C** using furan (1.2 g, 18 mmol), *n*-butyllithium (10.1 ml, 16 mmol) and 6-methylnicotinonitrile (1.3 g, 10.8 mmol). Purification by column chromatography on alumina (ethyl acetate) and recrystallisation (heaxane:ethanol 1:1 $^{v}/_{v}$) to give **224** as a tan solid in 42% yield.

Prepared by the general procedure **B** using furan (1.0 g, 15 mmol), *n*-butyllithium (10.1 ml, 16 mmol) and methyl 6-methylnicotinoate (2.2 g, 16 mmol) to give **224** (1.49 g, 45% yield). mp 75-78°C.

^{1}H NMR ($CDCl_3$): δ = 9.11 (dd, 1H, J = 1, 2 Hz, Py-2), 8.24 (dd, 1H, J = 2, 8 Hz, Py-4H), 7.69 (m, 1H, Furan-5H), 7.21 (m, 2H, Py-5H, Furan-3H), 6.62 (m, 1H, Furan-4H), 2.68 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 206.3, 162.3, 152.0, 149.7, 147.6, 137.7, 123.0, 112.1, 30.8, 24.7; ν_{max} (KBr) 1632, 1436, 1410, 1289, 1106, 1045, 1002, 956, 781; m/z 187 (M^+); (Analysis found: C, 70.65, H, 4.79, N, 7.49%; $C_{11}H_9NO_2$ requires C, 70.58, H, 4.85, N, 7.48%).

(6-Bromopyridin-3-yl)furan-2-ylmethanone, 226

To a solution of 2,5-dibromopyridine (1.5 g, 6.4 mmol) in dry diethyl ether (40 ml) at -78°C was added 1.6 M *n*-butyllithium (3.9 ml, 6.4 mmol). After stirring for 1 h, 2-furonitrile (0.83 ml, 9.5 mmol) and the reaction stirred for 2 h. To this was added water (30 ml) and the solution allowed to warm to room temperature. The reaction was acidified with conc. HCl and the aqueous phase separated and heated to 60°C for 2 h. The solution was then made basic with sodium hydroxide and extracted with diethyl ether (3x50 ml) and ethyl acetate (2x50 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography on alumina (ethyl acetate:hexane 1:1 $^{v}/_{v}$) to give a yellow solid. This was recrystallised (hexane) to give pale yellow needles (0.48 g, 30% yield). mp 45-48°C.

^{1}H NMR ($CDCl_3$): δ = 8.93 (dd, 1H, J = 1, 2 Hz, Py-2H), 8.14 (dd, 1H, J = 2, 8 Hz, Py-4H), 7.77 (dd, 1H, J = 1, 8 Hz, Py-5H), 7.12 (dd, 1H, J = 1, 2 Hz, Furan-5H), 6.81 (dd, 1H, J = 1, 3 Hz, Furan-3H), 6.53 (dd, 1H, J = 2, 3 Hz, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 184.6, 149.8, 149.5, 149.0, 148.8, 138.1, 130.5, 128.7, 119.9, 105.3; ν_{max} (KBr) 1657, 1390, 1271, 1134, 1003, 834; m/z 251 (M^+); (Analysis found: C, 47.60, H, 2.58, N, 5.87%; $C_{10}H_6BrNO_2$ requires C, 47.65, H, 2.40, N, 5.56%).

Pyridine-2,5-dicarboxlic acid diethyl ester, 228[194]

A solution of 2,5-pyridine carboxylic acid (20.3 g, 121.2mml), dry ethanol (100 ml) and conc. H_2SO_4 (95%, 5 ml) was refluxed for 24 h. The solution was allowed to cool and the solvent removed *in vacuo*. The residue was taken up in water (30 ml), neutralised (K_2CO_3), and the organic phase extracted with diethyl ether (3x30 ml). The organic layers were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* giving **228** as a yellow solid (18.1 g, 67% yield). This was used without further purification.

^{1}H NMR ($CDCl_3$): δ = 9.31 (m, 1H, Py-6H), 8.46 (m, 1H, Py-4H), 8.17 (m, 1H, Py-3H), 4.39 (q, 4H, J = 6Hz, 2x$CH_2$$CH_3$), 1.25 (t, 6H, J = 6Hz, 2x$CH_2$$CH_3$).

Pyridine-2,5-dicarboxylic acid diamide, 229[195]

Pyridine-2,5-dicarboxlic acid diethyl ester, 228 (18.1 g, 81.1 mmol) was suspended in ammonia solution (.880, 200 ml) and water (100 ml) and refluxed for 15 h. The mixture was filtered to give **229** as a pale cream powder (6.69 g, 50% yield).

^{1}H NMR (DMSO-$δ_6$): δ = 9.03 (m, 1H, Py-6H), 8.37 (m, 1H, Py-4H), 8.25 (bs, 2H, NH_2), 8.19 (m, 1H, Py-3H), 7.74 (bs, 2H, NH_2).

2,5-Dicyanopyridine, 230[196]

Phosphorous oxychloride (7.94 ml, 85.2 mmol) was added to a solution of pyridine-2,5-dicarboxylic acid diamide, **229**, (6.7 g, 40.6 mmol) in dry pyridine (40 ml). The solution was refluxed for 3 h and then poured onto ice. The organic phase was extracted with dichloromethane (3x30 ml), dried ($MgSO_4$), filtered and the solvent

removed *in vacuo*. The crude product was recrystallised (isopropyl alcohol) to give **230** as an orange solid (4.83 g, 44% yield).

^{1}H NMR ($CDCl_3$): δ = 8.99 (m, 1H, Py-6H), 8.16 (m, 1H, Py-4H), 7.86 (m, 1H, py-3H).

5-(Furan-2-carbonyl)pyridin-2-carbonitrile, 231a

Prepared by the general procedure **B** with furan (1.0 g, 15 mmol), *n*-butyllithium (10.1 ml, 15 mmol) and 2,5-dicyanopyridine **230** (1.37 g, 8.8 mmol). The product was purified by column chromatography on silica (ethyl acetate) to give **231a** as a tan solid (0.82 g, 28% yield). mp 71-73°C.

^{1}H NMR ($CDCl_3$): δ = 9.14 (dd, 1H, J = 1, 2 Hz, Py-6H), 8.3 (dd, 1H, J = 2, 8 Hz, Py-4H), 8.07 (dd, 1H, J = 1, 8 Hz, Py-3H), 7.77 (m, 1H, Furan-5H), 6.64 (m, 1H, Furan-3H), 6.36 (m, 1H, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 181.6, 151.8, 149.5, 149.3, 142.5, 139.3, 131.2, 129.3, 117.7, 116.4, 105.7; ν_{max} (KBr); m/z 198 (M^+); (Analysis found: C, 66.56, H, 2.88, N, 14.32%; $C_{11}H_6N_2O_2$ requires C, 66.67, H, 3.05, N, 14.14%).

(5-Bromopyridin-3-yl)furan-2-ylmethanone, 234

To a solution of 3,5-dibromopyridine (2.8 g, 12.0 mmol) in diethyl ether (40 ml) at -78°C was added 1.6 M *n*-butyllithium (7.5 ml, 12.0 mmol). After stirring for 1 h, 2-furonitrile (1.57 ml, 18.0 mmol) and the reaction stirred for 2 h. To this was added water (30 ml) and the solution allowed to warm to room temperature. The reaction was acidified with conc. hydrochloric acid and the aqueous phase separated and heated to 60°C for 2 h. The solution was then made basic with sodium hydroxide and extracted with diethyl ether (3x50 ml) and ethyl acetate (2x50 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) to give a pale brown solid. This was recrystallised (hexane) to give **234** as a yellow solid (0.33 g, 11% yield). mp 50-53°C.

^{1}H NMR ($CDCl_3$): δ = 9.13 (t, 1H, J = 2 Hz, Py-2H), 8.86 (t, 1H, J = 2 Hz, Py-6H), 8.41 (t, 1H, J = 2 Hz, Py-4H), 7.74 (m, 1H, Furan-5H), 7.36 (m, 1H, Furan-3H), 6.65

(m, 1H, Furan-4H); ^{13}C NMR ($CDCl_3$): δ = 183.7, 152.3, 149.6, 149.0, 148.6, 142.8, 129.4 125.4, 117.1, 109.2; ν_{max} (KBr); m/z 251 (M^+); (Analysis found: C, 47.86, H, 2.45, N, 5.61%; $C_{10}H_6BrNO_2$ requires C, 47.65, H, 2.40, N, 5.56%).

Di-furan-2-yl-(6-methylpyridin-3-yl)methanol, 237

To a solution of furan (2.0 g, 29 mmol) in dry tetrahydrofuran (50 ml) at 0°C was added *n*-butyllithium (20.3 ml of 1.6M solution in hexanes, 32 mmol). After 4 h methyl 6-methylnicotinate (2.44g, 16 mmol) as a solution in tetrahydrofuran (30 ml) was added and the stirring continued for 3 h, before addition of saturated ammonium chloride solution (30 ml). The mixture was extracted with diethyl ether (3x30 ml), the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on alumina (ethyl acetate:hexane 1:1 $^v/_v$) gave **237** as a white solid (3.26 g, 43% yield). mp 125-126°C.

^1H NMR ($CDCl_3$): δ = 8.42 (dd, 1H, J = 1, 2 Hz, Py-2H), 7.66 (dd, 1H, J = 2, 8 Hz, Py-4H), 7.39 (m, 2H, Furan-5H), 7.12 (dd, 1H, J = 1, 8 Hz, Py-5H), 6.32 (m, 2H, Furan-3H), 6.08 (m, 2H, Furan-4H), 4.50 (bs, 1H, OH), 2.53 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 157.7, 155.3, 147.5, 142.8, 134.8, 122.5, 111.9, 110.2, 108.9, 72.5, 23.8; ν_{max} (KBr) 3419, 3110, 1523, 1325, 1289, 1103, 1078, 1041, 974, 623; m/z 255 (M^+); (Analysis found: C, 70.23, H, 5.29, N, 5.45%; $C_{15}H_{13}NO_3$ requires C, 70.48, H, 5.13, N, 5.49%).

2-Phenylpropionic acid-(5-methylfuran2-yl)pyridin-4-ylmethyl ester, 241

A solution of 2-phenylpropionic acid (0.6 g, 3.9 mmol) and thionyl chloride (15 ml) was refluxed for 2 h. The excess thionyl chloride was removed *in vacuo*. The resulting acid chloride was taken up in diethyl ether (40 ml). Then to a solution of 5-methylfuran-2-yl-pyridin-4-yl-methanol (**162**) (1.0 g, 5.2 mmol) in tetrahydrofuran (50 ml) at 0°C was slowly added dry sodium hydride (0.14 g, 5.9 mmol). The solution was stirred for 1 h before addition of 2-phenylpropionoyl chloride solution. The reaction was stirred for 2 h before addition of water (30 ml). The organic phase was extracted with diethyl ether (3x30 ml), dried over ($MgSO_4$), filtered and the

solvent removed *in vacuo*. Column chromatography on alumina (dichloromethane) afforded **241** as a yellow solid (0.60 g, 36% yield). mp 78-80°C.

^{1}H NMR ($CDCl_3$): δ = 8.39 (m, 2H, 2xPy-2,6H), 7.25-7.10 (m, 5H, 2xPy-3,5H, 3xPhenyl), 6.95 (m, 2H, 2xPhenyl), 6.64 (m, 1H, C*H*OH), 6.20 (m, 1H, Furan-3H), 6.03 (m, 1H, Furan-4H), 3.68 (m, 1H, C*H*Me), 2.18 (s, 3H, Furan-5Me), 1.45 (d, 3H, J = 7.0Hz, CH*Me*); ^{13}C NMR ($CDCl_3$): δ = 172.5, 150.2, 150.1, 141.3, 140.7, 138.0, 130.5, 130.1, 129.0, 121.4, 113.3, 108.8, 77.5, 45.4, 18.7, 13.8; ν_{max} (neat); m/z 321 (M^+); (Analysis found: C, 74.79, H, 6.12, N 4.23%; $C_{20}H_{19}NO_3$ requires C, 74.75, H, 5.96, N, 4.36%).

4-[Methoxy-(5-methylfuran-2-yl)methyl]pyridine, 242

To a solution of 5-methylfuran-2-yl-pyridin-4-ylmethanol (**162**) (0.5 g, 2.6 mmol) in tetrahydrofuran (40 ml) at 0°C was added slowly dry sodium hydride (0.07 g, 2.9 mmol). The solution was stirred for 1 h before addition of methyl iodide (0.9 ml, 3.1 mmol). Stirring was continued for 2 h before addition of water (30 ml). The organic phase was extracted with diethyl ether (3x30 ml), then dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on alumina (dichloromethane) afforded **242** as a yellow solid (0.31 g, 58% yield).

^{1}H NMR ($CDCl_3$): δ = 8.54 (d, 2H, J = 5 Hz, 2xPy-2,6H), 7.26 (d, 2H, J = 5 Hz, 2xPy-3,5H), 6.02 (d, 1H, J = 3 Hz, Furan-4H), 5.84 (d, 1H, J = 3 Hz, Furan-3H), 5.13 (s, 1H, OH), 3.33 (s, 3H, OMe), 2.18 (s, 3H, Furan-5Me); ^{13}C NMR ($CDCl_3$): δ =; ν_{max} (neat); m/z 203 (M^+); Accurate mass: 203.0939, $C_{12}H_{13}NO_2$ requires 203.0946.

5.3 Experimental for Chapter 3

Procedure E: To a solution of 40% sodium hydroxide (30 ml) and dichloromethane (30 ml) was added cetyltrimethylammonium bromide (0.1 eq), the alcohol (1 eq) and the bromomethyl compound (1.1 eq), the reaction stirred vigorously for 16 h. The dichloromethane layer was separated, the aqueous phase diluted with water (150 ml) and the extracted with dichloromethane (3x30 ml). The combined organic phases

were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The compound was purified by column chromatography.

2-Methylpyridin-3-ol, 243[167]

2-Acetylfuran (0.5 g, 4.5 mmol) was reacted with ammonia solution (.880, 2 ml) in a sealed vessel at 150°C for 15 h. The solvent was removed and distillation (123°C at 0.3 mmHg) gave **243** as a white solid (0.11 g, 23% yield). mp 168-169°C (Lit 170-171°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 2% yield.

^{1}H NMR (DMSO-d_6): δ = 9.33 (bs, 1H, OH), 8.38 (t, 1H, J = 3 Hz, Py-6H), 7.55 (dd, 1H, J = 3, 8 Hz, Py-5H), 7.03 (dd, 1H, J = 3, 8 Hz, Py-4H), 2.35 (s, 3H, Py-2Me), ^{13}C NMR (DMSO-d_6): δ = 161.6 (C), 148.7 (C), 132.0 (CH), 127.1 (CH), 124.5 (CH), 18.9 (CH_3); m/z 109 (M^+).

2-*iso*-Propylpyridin-3-ol, 244[60]

1-Furan-2-yl-2-methylpropan-1-one, **178** (0.4 g, 2.9 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (158-161°C at 0.3 mmHg) gave **244** as a yellow solid (0.11 g, 28% yield). mp 193-195°C (Lit 191-193°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 23% yield.

^{1}H NMR (DMSO-d_6): δ = 10.12 (bs, 1H, OH), 8.24 (t, 1H, J = 3Hz, Py-6H), 7.05 (dd, 1H, J = 3,8Hz, Py-5H), 6.94 (dd, 1H, J = 3,8Hz, Py-4H), 3.30 (septet, 1H, C*H*(Me_2), 1.00 (d, 6H, J = 8.2Hz, 2xMe); ^{13}C NMR (DMSO-d_6): δ = 154.8 (C), 130.9 (C), 125.0 (CH), 116.2 (CH), 110.4 (CH), 36.6 (CH), 19.6 (2xCH_3); m/z 137 (M^+).

2-Phenylpyridin-3-ol, 245[61]

Furan-2-yl-phenylmethanone, **180** (0.5 g, 2.9 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (176-179°C at 0.3 mmHg) gave **245** as a white solid (0.10 g, 21% yield).

mp 202-204°C (Lit 206-207°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 9% yield.

^{1}H NMR (DMSO-d_6): δ = 9.67 (bs, 1H, OH), 8.29 (m, 1H, Py-6H), 7.91 (m, 2H, 2xPhenyl), 7.60-7.45 (m, 3H, 3xPhenyl), 7.16 (m, 1H, Py-5H), 6.89 (m, 1H, Py-4H), ^{13}C NMR (DMSO-d_6): δ = 162.6 (C), 156.1 (C), 149.8 (CH), 134.5 (C), 141.1 (2xCH), 130.0 (2xCH), 129.1 (CH), 125.5 (CH), 128.4 (CH); m/z 171 (M^+).

2-*p*-Tolylpyridin-3-ol, 246[61]

Furan-2-yl-*p*-tolylmethanone, **181** (0.8 g, 4.3 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and column chromatography on alumina (ethyl acetate) gave **246** as a white solid (0.14 g, 17% yield). mp 198-199°C (Lit 199-200°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 6% yield.

^{1}H NMR (DMSO-d_6): δ = 9.56 (bs, 1H, OH), 8.28 (m, 1H, Py-6H), 7.51 (m, 2H, 2xTolyl), 7.20 (m, 3H, 2xTolyl, Py-5H), 7.00 (m, 1H, Py-4H), 2.39 (s, 3H, Tolyl-Me); ^{13}C NMR (DMSO-d_6): δ = 163.2 (C), 148.9 (C), 142.7 (CH), 136.9 (C), 130.2 (C), 128.6 (2xCH), 127.2 (2xCH), 125.2 (CH), 123.6 (CH), 20.9 (CH_3); m/z 185 (M^+).

2,6-Dimethylpyridin-3-ol, 247[168]

2-Acetyl-5-methylfuran (0.5 g, 4.0 mmol) was reacted with ammonia solution (.880, 2 ml) in a sealed vessel at 150°C for 15 h. The solvent was removed and distillation (110-115°C at 0.3 mmHg) gave **247** as a yellow solid (0.15 g, 30% yield). mp 210-213°C (Lit 211-212°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 45% yield.

^{1}H NMR (DMSO-d_6): δ = 10.57 (bs, 1H, OH), 6.82 (d, 1H, J = 8Hz, Py-5H), 5.95 (d, 1H, J = 8Hz, Py-4H), 2.38 (s, 3H, Py-2Me), 2.31 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 187.1 (C), 122.5 (C), 121.4 (C), 118.6 (CH), 109.2 (CH), 24.9 (CH_3), 23.6 (CH_3); m/z 123 (M^+).

6-Methyl-2-*iso*-propylpyridin-3-ol, 248

2-Methyl-1-(5-methylfuran-2-yl)propan-1-one, **182** (0.5 g, 3.3 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (173-176°C at 0.3 mmHg) gave **248** as a white solid (0.23 g, 46% yield). mp 190-192°C. Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 47% yield.

^{1}H NMR (DMSO-d_6): δ = 10.15 (bs, 1H, OH), 6.85 (d, 1H, J = 8Hz, Py-5H), 6.41 (d, 1H, J = 8Hz, Py-4H), 3.32 (1H, septet, $CH(Me)_2$), 2.43 (s, 3H, Py-6Me), 1.12 (d, 6H, J = 7Hz, $CH(Me)_2$); ^{13}C NMR (DMSO-d_6): δ = 195.4 (C), 130.9 (C), 125.0 (C), 116.2 (CH), 110.4 (CH), 35.6 (CH), 19.6 (CH_3), 19.5 ($2xCH_3$); ν_{max} (KBr) 2900-2500, 1609, 1567, 1423, 1410, 1290, 905, 855; m/z 151 (M^+); (Analysis found: C, 71.67, H, 8.89, N, 9.03%; $C_9H_{13}NO$ requires C, 71.49, H, 8.67, N, 9.26%).

6-Methyl-2-phenylpyridin-3-ol, 249

(5-Methylfuran-2-yl)phenylmethanone, **183** (0.5 g, 2.7 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (184-186°C at 0.3 mmHg) gave **249** as a tan solid (0.10 g, 20% yield). mp 230-232°C. Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 22% yield.

^{1}H NMR (DMSO-d_6): δ = 9.81 (bs, 1H, OH), 7.68 (m, 2H, 2xPhenyl), 7.50-7.40 (m, 3H, 3xPhenyl), 6.78 (d, 1H, J = 7Hz, Py-5H), 6.39 (d, 1H, J = 7Hz, Py-4H), 2.39 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 161.7 (C), 155.3 (C), 149.1 (C), 135.8 (2xCH), 129.3 (C), 128.9 (2xCH), 125.3 (CH), 123.6 (CH), 123.1 (CH), 24.1 (CH_3); ν_{max} (KBr) 2850-2600, 1489, 1435, 1267, 1209, 1034, 965, 858; m/z 185 (M^+); (Analysis found: C, 77.95, H, 6.12, N, 7.59%; $C_{12}H_{11}NO$ requires C, 77.81, H, 5.99, N, 7.56).

6-Methyl-2-*p*-tolylpyridin-3-ol, 250

(5-Methylfuran-2-yl)-*p*-tolylmethanone, **184** (0.5 g, 2.5 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and column chromatography on alumina (ethyl acetate) gave **250** as a tan solid (0.08 g, 16% yield). mp 241-243°C. Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 14% yield.

^{1}H NMR (DMSO-d_6): δ = 9.18 (bs, 1H, OH), 7.63 (m, 2H, 2xTolyl), 7.20 (m, 2H, 2xTolyl), 6.95 (d, 1H, J = 7Hz, Py-5H), 6.45 (d, 1H, J = 7Hz, Py-4H), 2.56 (s, 3H, Tolyl-Me), 2.34 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 162.7 (C), 155.3 (C), 149.9 (C), 136.9 (C), 129.1 (C), 128.9 (2xCH), 127.6 (2xCH), 125.4 (CH), 123.1 (CH), 24.7 (CH_3), 20.1 (CH_3); ν_{max} (KBr) 2950-2600, 1503, 1439, 1410, 1399, 1234, 1178, 1055, 834; m/z 199 (M^+); (Analysis found: C, 78.50, H, 6.66, N, 6.96%; $C_{13}H_{13}NO$ requires C, 78.36, H, 6.58, N, 7.03).

6-Ethylpyridin-3-ol, 251[60]

Furan-2-ylpropan-1-one, **208** (1.0 g, 8.0 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (135-136°C at 0.3 mmHg) gave **251** as a white solid (0.18 g, 18% yield). mp 133-136°C (Lit 134-135°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 23% yield.

^{1}H NMR (DMSO-d_6): δ = 9.65 (bs, 1H, OH), 8.10 (m, 1H, Py-6H), 7.01 (m, 1H, Py-5H), 6.80 (m, 1H, Py-4H), 2.90 (q, 2H, J = 8Hz, CH_2CH_3), 1.29 (t, 3H, J = 8Hz, CH_2CH_3); ^{13}C NMR (DMSO-d_6): δ = 161.0 (C), 148.2 (C), 141.1 (CH), 123.6 (CH), 123.2 (CH), 25.3 (CH_2), 14.4 (CH_3); m/z 123 (M^+).

2-Ethyl-6-methylpyridin-3-ol, 252[60]

1-(5-Methylfuran-2-yl)propan-1-one, **209** (0.5 g, 3.6 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (143-146°C at 0.3 mmHg) gave **249** as a tan solid (0.12 g,

24% yield). mp 171-173°C (Lit 171-172°C). Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 53% yield.

^{1}H NMR (DMSO-d_6): δ = 9.46 (bs, 1H, OH), 6.84 (d, 1H, J = 7hz, Py-5H), 6.23 (d, 1H, J = 7Hz, Py-4H), 2.64 (q, 2H, J = 15Hz, C*H*$_2$CH$_3$), 2.25 (s, 3H, Py-6Me), 1.04 (t, 3H, J = 7Hz, CH$_2$C*H*$_3$); ^{13}C NMR (DMSO-d_6): δ = 160.4 (C), 146.8 (C), 142.5 (C), 127.9 (CH), 124.4 (CH), 29.8 (CH_2), 12.5 (CH_3), 6.9 (CH_3); m/z 137 (M^+).

6-Ethyl-2-methylpyridin-3-ol, 253[169]

1-(5-Ethylfuran-2-yl)methanone, **210** (0.5 g, 3.6 mmol) was heated in a sealed vessel with ammonia solution (.880, 2 ml) at 150°C for 15 h. The solvent was removed and distillation (146-148°C at 0.3 mmHg) gave **253** as a white solid (0.08 g, 16% yield). mp 176-178°C. Heating with sat. ammonia in ethanol (2 ml) and ammonium chloride (0.05 g) gave a 48% yield.

^{1}H NMR (DMSO-d_6): δ = 9.87 (bs, 1H, OH), 6.76 (d, 1H, J = 7Hz, Py-5H), 6.29 (d, 1H, J = 7Hz, Py-4H), 2.62 (q, 2H, J = 14Hz, C*H*$_2$CH$_3$), 2.18 (s, 3H, Py-2Me), 0.98 (t, 3H, J = 7Hz, CH$_2$C*H*$_3$); ^{13}C NMR (DMSO-d_6): δ = 159.9 (C), 146.6 (C), 141.9 (C), 127.8 (CH), 124.5 (CH), 28.1 (CH_2), 12.4 (CH_3), 6.6 (CH_3); m/z 137 (M^+).

[2,2']Bipyridin-3-ol, 258[67]

Furan-2-yl-pyridin-2-ylmethanone **185** (1.0 g, 5.7 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 15 h. The vessel was washed out with water and methanol, and solvent removed *in vacuo*. Trituration with acetone gave a brown solid which was recrystallised (ethanol) to give **258** (0.18 g, 1.0 mmol) as a tan solid (0.18 g, 18% yield). mp 91-93°C (Lit. 91-92°C).

^{1}H NMR (DMSO-d_6): δ = 9.89 (bs, 1H, OH), 8.67 (m, 1H, Py-6'H), 8.33 (t, 1H, J = 3Hz, Py-6H), 8.29 (m, 1H, Py-3'H), 7.69 (m, 1H, Py-4H), 7.20-7.10 (m, 2H, Py-5,5'H), 7.01 (dd, 1H, J = 3,8Hz, Py-4H) ; ^{13}C NMR (DMSO-d_6): δ = 163.2 (C), 155.0 (C), 150.9 (C), 150.6 (CH), 143.2 (CH), 138.2 (CH), 125.2 (CH), 123.6 (CH), 121.6 (CH), 118.1 (CH); ν_{max} (KBr) 2900-2500, 1612, 1587, 1423, 1401, 1265, 943, 675; m/z 172 (M^+); (Analysis found: C, 69.85, H, 4.81, N, 16.06%; $C_{10}H_8N_2O$ requires C, 69.76, H, 4.68, N, 16.27).

[2,3']Bipyridin-3-ol, 259

Furan-2-yl-pyridin-3-ylmethanone **186** (0.25 g, 1.5 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 15 h. The vessel was washed out with water and methanol, and then all solvents removed to dryness. Trituration with acetone gave a dark brown solid, which was purified by recystallistion (ethanol) to give **259** as a yellow solid (0.09 g, 37% yield). mp 171-173°C.

^{1}H NMR (DMSO-d_6): δ = 9.14 (bs, 1H, OH), 8.52 (m, 1H, Py-2'H), 8.32 (m, 1H, Py-6'H), 8.17 (m, 1H, Py-6H), 7.50-7.20 (m, 3H, 3xPy-4',5',5H), 6.98 (m, 1H, Py-4H); ^{13}C NMR (DMSO-d_6): δ = 152.9 (C), 150.4 (C), 149.4 (CH), 148.1 (CH), 141.5 (CH), 136.8 (CH), 134.4 (CH), 125.0 (CH), 124.6 (CH), 124.0 (C); ν_{max} (KBr) 2800-2550, 1578, 1472, 1413, 1298, 1210, 845 ; m/z 172 (M^+); (Analysis found: C, 69.58, H, 4.39, N, 16.30%; $C_{10}H_8N_2O$ requires C, 69.76, H, 4.68, N, 16.27%).

[2,4']Bipyridin-3-ol, 260[66]

Furan-2-yl-pyridin-4-ylmethanone **187** (0.40 g, 2.3 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 15 h. The vessel was washed out with water and methanol, and solvent removed *in vacuo*. Trituration with acetone gave a brown solid which was recrystallised (ethanol) to give **260** as a tan solid (0.13 g, 35% yield). mp 234-236°C (Lit 233-235°C).

^{1}H NMR (DMSO-d_6): δ = 10.17 (bs, 1H, OH), 8.70 (d, 2H, J = 5Hz, 2xPy-2'6'H), 8.35 (t, 1H, J = 3Hz, Py-6H), 7.98 (d, 2H, J = 5Hz, Py-3',5'H), 7.20 (dd, 1H, J = 3,8Hz, Py-5H), 7.05 (dd, 1H, J = 3,8Hz, Py-4H); ^{13}C NMR (DMSO-d_6): δ = 164.2 (C), 151.8 (2xCH), 149.5 (C), 143.4 (CH), 134.5 (C), 125.2 (CH), 124.3 (CH), 117.4 (2xCH); ν_{max} (KBr) 2750-2400, 1540, 1459, 1432, 1256, 1202; 902, 834 m/z 172 (M^+); (Analysis found: C, 69.71, H, 4.58, N, 16.33%; $C_{10}H_8N_2O$ requires C, 69.76, H, 4.68, N, 16.27%).

6-Methyl-[2,2']bipyridin-3-ol, 261

5-Methylfuran-2-yl-pyridin-2-ylmethanone **188** (0.30 g, 1.6 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 10 h. The vessel was

washed out with water and methanol, and solvent removed *in vacuo*. Column chromatography on alumina (ethyl acetate then methanol) gave **261** as a yellow solid (0.07 g, 25% yield). mp 100-112°C.

^{1}H NMR (DMSO-d_6): δ = 8.98 (bs, 1H, OH), 8.55 (m, 1H, Py-6'H), 8.39 (m, 1H, Py-3'H), 7.79 (m, 1H, Py-4'H), 7.19 (m, 1H, Py-5'H), 7.16 (d, 1H, J = 8Hz, Py-4H), 6.99 (d, 1H, J = 8Hz, Py-5H), 2.45 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 162.7 (C), 155.1 (C), 154.8 (C), 154.2 (C), 150.8 (CH), 138.5 (CH), 125.8 (CH), 123.5 (CH), 121.5 (CH), 118.4 (CH), 24.3 (CH_3); ν_{max} (KBr); 2919, 1597, 1561, 1478, 1278, 1235, 746; m/z 186 (M^+); (Analysis found: C, 80.12, H, 5.38, N, 15.23%; $C_{11}H_{10}N_2O$ requires C, 70.95, H, 5.41, N, 15.04%).

6-Methyl-[2,3']bipyridin-3-ol, 262

5-Methylfuran-2-yl-pyridin-2-ylmethanone **189** (0.26 g, 1.4 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 10 h. The vessel was washed out with water and methanol, and solvent removed *in vacuo*. Column chromatography on alumina (ethyl acetate then methanol) gave **262** (0.07 g, 0.3 mmol) as a yellow solid (0.07 g, 27% yield). mp 195-196°C.

^{1}H NMR (DMSO-d_6): δ = 9.67 (bs, 1H, OH), 9.15 (m, 1H, Py-2'H), 8.51 (m, 1H, Py-6'H), 8.33 (m, 1H, Py-5'H), 7.45 (m, 1H, Py-4'H), 7.25 (d, 1H, J = 8Hz, Py-4H), 7.10 (d, 1H, J = 8Hz, Py-5H), 2.45 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 163.1 (C), 155.7 (C), 149.3 (CH), 148.7 (C), 147.0 (CH), 136.2 (CH), 136.0 (CH), 127.1 (CH), 124.1 (CH), 121.4 (C), 24.1 (CH_3); ν_{max} (KBr) 2950-2500, 1534, 1378, 1289, 1267, 1210, 1167, 1054, 867; m/z 186 (M^+); (Analysis found: C, 70.87, H, 5.56, N, 15.06%; $C_{11}H_{10}N_2O$ requires C, 70.95, H, 5.41, N, 15.04%).

6-Methyl-[2,4']bipyridin-3-ol, 263

5-Methylfuran-2-yl-pyridin-4-ylmethanone **190** (0.3 g, 1.6 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 10 h. The vessel was washed out with water and methanol, and solvent removed *in vacuo*. Trituration with diethyl ether gave a brown solid which was filtered off. Recyrstallisation from (ethanol) gave **263** (0.09 g, 31% yield). mp 257-260°C.

^{1}H NMR (DMSO-d_6): δ = 10.26 (bs, 1H, OH), 8.61 (d, 2H, J = 6Hz, 2xPy-2',6'H), 8.00 (d, 2H, J = 6Hz, 2xPy-3',5'H), 7.26 (d, 1H, J = 8Hz, Py-4H), 7.14 (d, 1H, J = 8Hz, Py-5H), 2.41 (s, 3H, OH), 2.36 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 151.5 (C), 150.3 (C), 149.2 (2xCH), 145.9 (C), 140.4 (C), 125.9 (CH), 125.3 (CH), 123.8 (2xCH), 24.1 (CH_3); ν_{max} (KBr) 3000-2600, 1520, 1396, 1278, 1267, 1206, 1034, 784, 689; m/z 186 (M^+); (Analysis found: C, 70.91, H, 5.58, N, 14.97%; $C_{11}H_{10}N_2O$ requires C, 70.95, H,5.41, N, 15.04%).

2-Furan-2-ylpyridin-3-ol, 267

Di-furan-2-ylmethanone **191** (0.40 g, 2.5 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed out with water and methanol, and solvent removed *in vacuo*. Trituration with diethyl ether gave a brown solid which was recrystallised (ethanol) to afford **267** as a tan solid (0.07 g, 17% yield). mp 210-212°C.

^{1}H NMR (DMSO-d_6): δ = 9.32 (bs, 1H, OH), 8.32 (m, 1H, Py-6H), 7.39 (m, 1H, Furan-5H), 7.35 (m, 2H, 2xPy-4,5H), 7.07 (m, 1H, Furan-3H), 6.43 (m, 1H, Furan-4H); ^{13}C NMR (DMSO-d_6): δ = 156.2 (C), 149.7 (C), 148.8 (CH), 147.7 (CH), 141.9 (C), 126.9 (CH), 125.2 (CH), 120.0 (CH), 107.1 (CH); ν_{max} (KBr) 2900-2600, 1556, 1410, 1337, 1005, 973, 879; m/z 161 (M^+); (Analysis found: C, 59.89, H, 4.52, N, 8.83%; $C_9H_7NO_2$ requires C, 67.07, H, 4.38, N, 8.69%).

3-Quinolin-3-ylpyridin-3-ol, 268

Furan-2-yl-quinolin-3-ylmethanone **195** (0.31 g, 1.4 mmol) and ammonia solution (0.88, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (methanol) gave **268** as a white solid (0.08 g, 26% yield). mp 181-184°C.

^{1}H NMR (DMSO-d_6): δ = 10.50 (bs, 1H, OH), 9.50 (m, 1H, Quin-2H), 8.92 (m, 1H, Py-6H), 8.23 (m, 1H, Quin-4H), 8.04 (m, 2H, 2xQuin-6,8H), 7.77 (m, 1H, Quin-5H), 7.61 (m, 1H, Quin-7H), 7.39 (m, 1H, Py-5H), 7.27 (m, 1H, Py-4H); ^{13}C NMR (DMSO-d_6): δ = 161.9 (C), 150.8 (C), 147.6 (C), 145.0 (CH), 144.3 (CH), 129.9 (CH), 128.8 (CH), 128.3 (CH), 127.7 (CH), 127.2 (C), 126.5 (CH), 126.0 (CH), 125.2

(CH), 120.9 (C); ν_{max} (KBr) 2900-2500, 1578, 1510, 1268, 1231, 1185, 1073, 1018, 832, 754; m/z 222 (M^+); (Analysis found: C, 75.70, H, 4.53, N, 12.34%; $C_{14}H_{10}N_2O$ requires C, 75.66, H, 4.54, N, 12.60%).

6-Methyl-2-quinolin-3-ylpyridin-3-ol, 269

(5-Methylfuran-2-yl)quinolin-3-ylmethanone **196** (0.40 g, 1.7 mmol) and ammonia solution (0.88, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (methanol) gave **269** as a tan solid (0.12 g, 30% yield). mp 214-216°C.
^{1}H NMR (DMSO-d_6): δ = 10.12 (bs, 1H, OH), 9.18 (m, 1H, Quin-2H), 7.96 (m, 1H, Quin-4H), 7.90 (m, 1H, Quin-8H), 7.77 (m, 1H, Quin-6H), 7.60-7.40 (m, 2H, 2xQuin-5,7H), 7.06 (d, 1H, J = 8Hz, Py-4H), 6.98 (d, 1H, J = 8Hz, Py-5H), 2.39 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 161.6 (C), 155.2(C), 149.5(C), 148.9(C), 145.3 (CH), 130.2 (CH), 128.8 (CH), 128.3 (CH), 127.7 (CH), 127.5 (C), 126.5 (CH), 126.4 (CH), 124.8 (CH), 119.6 (C), 24.4 (CH_3); ν_{max} (KBr) 2950-2500, 1535, 1509, 1299, 1254, 1034, 985, 852, 634; m/z 236 (M^+); Analysis found: C, 76.45, H, 5.23, N, 11.99%; $C_{15}H_{12}N_2O$ requires C, 76.25, H, 5.12, N, 11.86%).

2-Naphthalen-2-ylpyridin-3-ol, 270

Furan-2-yl-naphthalen-2-ylmethanone **197** (0.50 g, 2.2 mmol) and ammonia solution (0.88, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (ethyl acetate then methanol) gave **270** as a white solid (0.12 g, 24% yield). mp 156-159°C.
^{1}H NMR (DMSO-d_6): δ = 9.13 (bs, 1H, OH), 8.40-8.20 (m, 2H, Py-6H, Nap-1H), 8.05 (m, 1H, Nap-4H), 7.78 (m, 1H, Nap-8H), 7.73-7.65 (m, 2H, Nap-3,5H), 7.44 (m, 1H, Nap-7H), 7.26 (m, 1H, Nap-6H), 7.18 (m, 1H, Py-4H), 6.98 (m, 1H, Py-5H); ^{13}C NMR (DMSO-d_6): δ = 163.8 (C), 149.2 (C), 142.9 (CH), 135.3 (C), 133.5 (C), 132.6 (C), 128.5 (CH), 128.1 (CH), 126.7 (CH), 126.2 (CH), 125.9 (CH), 125.4 (CH), 125.3 (CH), 125.1 (CH), 123.8 (CH); ν_{max} (KBr) 3000-2700, 1546, 1502, 1286, 1231, 1177,

1091, 856; m/z 221 (M^+); Analysis found: C, 81.15, H, 4.87, N, 6.40%; $C_{15}H_{11}NO$ requires C, 81.43, H, 5.01, N, 6.33%).

6-Methyl-2-naphthalen-2-ylpyridin-3-ol, 271

5-Methylfuran-2-yl-quinolin-2-ylmethanone **198** (0.40 g, 1.7 mmol) and ammonia solution (0.88, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (methanol) gave **271** as a yellow solid (0.06 g, 16% yield). mp 223-225°C.

^{1}H NMR (DMSO-d_6): δ = 9.54 (bs, 1H, OH), 8.24 (m, 1H, Nap-1H), 7.98 (m, 1H, Nap-4H), 7.80-7.60 (m, 3H, Nap-3,5,8H), 7.43 (m, 1H, Nap-7H), 7.25 (m, 1H, Nap-6H), 6.95 (d, 1H, J = 8Hz, Py-4H), 6.91 (d, 1H, J = 8Hz, Py-5H), 2.20 (s, 3H, Py-6Me); ^{13}C NMR (DMSO-d_6): δ = 163.3 (C), 154.3 (C), 150.1 (C), 135.3 (C), 132.6 (C), 132.4 (C), 128.9 (CH), 128.1 (CH), 126.7 (CH), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.6 (CH), 125.1 (CH), 123.5 (CH), 24.3 (CH_3); ν_{max} (KBr) 2900-2650, 1588, 1547, 1348, 1299, 1249, 1172, 1097, 821; m/z 235 (M^+); (Analysis found: C, 81.56, H, 5.65, N, 5.90%; $C_{16}H_{13}NO$ requires C, 81.68, H, 5.57, N, 5.95%).

2-(1*H*-Indol-5-yl)pyridin-3-ol, 273

Furan-2-yl-(1H-indol-5-yl)methanone **221** (0.50 g, 2.4 mmol) and ammonia solution (0.88, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (ethyl acetate then methanol) gave **273** as a white solid (0.06 g, 12% yield). mp 141-143°C.

^{1}H NMR (DMSO-d_6): δ = 9.23 (bs, 1H, OH), 8.43 (bs, 1H, NH), 8.28 (m, 1H, Py-6H), 7.86 (m, 1H, Ind-7H), 7.62 (m, 1H, Ind-4H), 7.40-7.20 (m, 3H, 2xInd-2,6H, Py-5H), 6.99 (m, 1H, Py-4H), 6.45 (m, 1H, Ind-3H); ^{13}C NMR (DMSO-d_6): δ = 164.5 (C), 149.6 (C), 142.4 (CH), 133.7 (C), 133.1 (C), 128.2 (C), 125.8 (CH), 125.4 (CH), 125.2 (CH), 123.3 (CH), 120.7 (CH), 118.8 (CH), 111.1 (CH); ν_{max} (KBr) 2900-2700, 1478, 1323, 1306, 1266, 1034, 891; m/z 210 (M^+); (Analysis found: C, 74.51, H, 4.69, N, 13.39%; $C_{13}H_{10}N_2O$ requires C, 74.27, H, 4.79, N, 13.33%).

2-(2-Pyrrol-1-yl-phenyl)pyridin-3-ol, 274

Furan-2-yl-(3-pyrrol-1-yl-phenyl)methanone, **222** (0.51 g, 2.2 mmol) and ammonia solution (0.88, 2 ml) was heated in a sealed vessel at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (ethyl acetate then methanol) gave **274** as a tan solid (0.09 g, 18% yield). mp 121-123°C.

^{1}H NMR (DMSO-d_6): δ = 9.67 (bs, 1H, OH), 8.27 (t, 1H, J = 3Hz, Py-6H), 7.70-7.50 (m, 3H, 3xPhenyl), 7.20-7.10 (m, 2H, Phenyl, Py-5H), 7.03 (t, 2H, J = 2Hz, 2xPyrrole-2,5H), 6.99 (dd, 1H, J = 3,8Hz, Py-4H), 5.90 (m, 2H, 2xPyrrole-3,4H); ^{13}C NMR (DMSO-d_6): δ = 163.1 (C), 152.3 (C), 150.9 (CH), 148.8 (C), 143.8 (C), 136.3 (CH), 132.7 (CH), 127.0 (CH), 125.3 (CH), 120.1 (2xCH), 119.4 (CH), 117.3 (2xCH), 112.1 (CH); ν_{max} (KBr) 2950-2600, 1478, 1452, 1408, 1221, 1189, 1023, 783, 631; m/z 236 (M^+); (Analysis found: C, 76.21, H, 4.97, N, 11.78%; $C_{15}H_{12}N_2O$ requires C, 76.25, H, 5.12, N, 11.86%).

2-Pyrazin-2-ylpyridin-3-ol, 275

Furan-2-yl-pyrazin-2-ylmethanone **223** (0.50 g, 2.8 mmol) and ammonia solution (0.88, 2 ml) was heated at 150°C for 5 h. The vessel was washed with water and methanol and evaporated to dryness. Column chromatography on alumina (methanol) gave **275** as a yellow solid (0.10 g, 20% yield). mp 87-89°C.

^{1}H NMR (DMSO-d_6) δ = 12.70 (bs, 1H, OH), 9.88 (m, 1H, Pyraz-3H), 8.67 (m, 1H, Pyraz-6H), 8.46 (m, 1H, Pyraz-5H), 8.27 (m, 1H, Py-6H), 7.41-7.28 (m, 2H, 2xPy-4,5H); ^{13}C NMR (DMSO-d_6): δ = 156.7 (C), 152.6 (C), 144.1 (C), 143.5 (CH), 140.7 (CH), 139.3 (CH), 135.2 (CH), 126.5 (CH), 125.8 (CH); ν_{max} (KBr) 2900-2600, 1503, 1477, 1469, 1434, 1209, 967, 642; m/z 173 (M^+); (Analysis found: C, 62.54, H, 4.13, N, 24.39%; $C_9H_7N_3O$ requires C, 62.42, H, 4.07, N, 24.27%).

6'-Methyl-[2,3']bipyridin-3-ol, 276

Furan-2-yl-(6-methylpyridin-3-yl)methanone **224** (0.31 g, 1.7 mmol) and ammonia solution (.880, 2 ml) was heated in sealed vessel for 12 h at 110°C. The vessel was

washed out with water and methanol and evaporated to dryness. Column chromatography on alumina (methanol) gave in order of elution **224** (0.04g, 12%), pyrrol-2-yl-(6-methylpyridin-3-yl)methanone **278** (0.05 g, 16%) as a red oil and **276** as a tan solid (0.08 g, 27% yield). mp 181-183°C.

Data for **276**: ^{1}H NMR (DMSO-d_6): δ = 10.40 (bs, 1H, OH), 9.05 (m, 1H, Py-2'H), 8.25 (m, 1H, Py-6H), 8.15 (m, 1H, Py-4'H), 7.40-7.18 (m, 3H, 3xPy-4,5,5'H), 2.49 (s, 3H, Py-6'Me); ^{13}C NMR (DMSO-d_6): δ = 157.8 (C), 152.7 (C), 149.8 (C), 142.4 (CH), 141.4 (CH), 137.0 (CH), 131.7 (CH), 124.7 (CH), 124.5 (CH), 123.2 (C), 24.7 (CH_3); ν_{max} (KBr) 2850-2600, 1567, 1523, 1434, 1410, 1378, 1205, 832 m/z 186 (M^+); (Analysis found: C, 70.87, H, 5.53, N, 14.89%; $C_{11}H_{10}N_2O$ requires C, 70.95, H, 5.41, N, 15.04%).

Data for **(6-Methyl-pyridin-3-yl)-(1*H*-pyrrol-2-yl)methanone, 278**:

^{1}H NMR (DMSO): δ = 10.02 (bs, 1H, NH), 8.97 (m, 1H, Py-2H), 8.16 (m, 1H, Py-4H), 7.33 (m, 2H, Pyrrole-3H, Py-5H), 6.77 (dd, 1H, J = 2,3Hz, Pyrrole-5H), 5.89 (dd, 1H, J = 3,4Hz, Pyrrole-4H), 2.56 (s, 3H, Py-6Me); ^{13}C NMR (DMSO): δ = 188.8 (C=O), 163.3 (C), 150.2 (CH), 140.5 (CH), 127.0 (C), 126.9 (C), 126.8 (CH), 126.6 (CH), 119.0 (CH), 108.9 (CH), 24.1 (CH_3); ν_{max} (KBr) 1654, 1521, 1447, 1439, 1356, 1258, 945, 731; m/z 186 (M^+); Accurate mass: 186.0803, $C_{11}H_{10}N_2O$ requires 186.0793.

6'-Bromo-[2,3']bipyridin-3-ol, 277

(6-Bromopyridin-3-yl)-furan-2-ylmethanone **226** (0.45 g, 1.8 mmol) and ammonia solution (.880, 2 ml) was heated in a sealed vessel for 5 h at 150°C. The vessel was washed out with water and methanol and the solvents removed. Trituration with diethyl ether gave a tan solid. Recrystallisation (ethyl acetate/ethanol) gave **277** as a tan solid (0.12 g, 26% yield). mp 167-169°C.

^{1}H NMR (DMSO-d_6): δ = 9.78 (bs, 1H, OH), 8.85 (dd, 1H, J = 1,2Hz, Py-2'H), 8.40 (t, 1H, J = 3Hz, Py-6H), 8.00 (dd, 1H, J = 1,8Hz, Py-5'H), 7.51 (dd, 1H, J = 2,8Hz, Py-4'H), 7.27 (dd, 1H, J = 3,8Hz, Py-5H), 7.10 (dd, 1H, J = 3,8Hz, Py-4H); ^{13}C NMR (DMSO-d_6): δ = 162.8 (C), 153.4 (C), 147.3 (CH), 144.0 (CH), 141.4 (C), 136.5 (CH), 128.1 (CH), 126.0 (CH), 124.9 (CH), 118.9 (C); ν_{max} (KBr) 3000-2600, 1589, 1534,

1491, 1467, 1223, 845; m/z 251 (M^+); (Analysis found: C, 47.90, H, 2.93, N, 11.34%; $C_{10}H_7N_2OBr$ requires C, 47.84, H, 2.81, N, 11.16%).

3-Benzyloxy-2-methylpyridine, 288[178a]

Prepared by General Procedure **E** by the reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and benzyl bromide (0.2 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **288** as a white solid (0.13 g, 65% yield).
^{1}H NMR ($CDCl_3$): δ = 8.12 (t, 1H, J = 3Hz, Py-6H), 7.20-7.05 (m, 6H, 5xPhenyl, Py-5H), 6.85 (dd, 1H, 3,8Hz, Py-4H), 4.89 (s, 2H, OC*H*$_2$), 2.37 (s, 3H, Py-2Me); m/z 199 (M^+).

3-(4-Cyanobenzyloxy)-2-methylpyridine, 289

Prepared by General Procedure **E** by the reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 4-cyanobenzyl bromide (0.21 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **289** as a white solid (0.12 g, 53% yield). mp 102-104°C.
^{1}H NMR ($CDCl_3$): δ = 7.59 (d, 2H, J = 8Hz, 2xPhenyl), 7.13 (d, 2H, J = 8Hz, 2xPhenyl), 7.04 (m, 1H, Py-6H), 6.95 (m, 1H, Py-5H), 6.26 (m, 1H, Py-4H), 5.58 (s, 2H, OC*H*$_2$), 2.41 (s, 3H, Py-2Me); ^{13}C NMR ($CDCl_3$): δ = 188.4 (C), 143.8 (C), 132.4 (C), 130.6 (CH), 121.3 (2xCH), 127.2 (2xCH), 120.7 (CH), 118.7 (CH), 111.2 (CN), 109.1 (C), 52.4 (CH_2), 27.2 (CH_3); ν_{max} (KBr) 1720, 1557, 1384, 1101, 1023, 1007; m/z 224 (M^+); (Analysis found: C, 74.75, H, 5.17, N, 12.32%; $C_{14}H_{12}N_2O$ requires: C, 74.98, H, 5.39, N, 12.49%).

3-(4-Nitrobenzyloxy)-2-methylpyridine, 290

Prepared by General procedure **E** by the reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 4-nitrobenzylbromide (0.24 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **290** (0.15 g) as a white solid in 62% yield. mp 106-108°C

^{1}H NMR ($CDCl_3$): δ = 8.09 (d, 2H, J = 8Hz, 2xPhenyl), 7.13 (d, 2H, J = 8Hz, 2xPhenyl), 6.98 (m, 1H, Py-6H), 6.89 (m, 1H, Py-5H), 6.65 (m, 1H, Py-4H), 5.58 (s, 2H, OCH_2), 2.33 (s, 3H, Py-2Me); ^{13}H NMR ($CDCl_3$): δ = 188.4 (C), 145.8 (C), 133.7 (C), 130.6 (CH), 129.1 (2xCH), 127.2 (2xCH), 123.8 (CH), 118.7 (CH), 109.1 (C), 52.2 (CH_2), 27.1 (CH_3); ν_{max} (KBr) 1634, 1509, 1399, 1340, 731; m/z 244 (M^+); (Analysis found: C, 63.67, H, 4.91, N, 11.24%; $C_{13}H_{12}N_2O_3$ requires C, 63.93, H, 4.95, N, 11.47%)

3-(4-Bromobenzyloxy)-2-methylpyridine, 291

Prepared by General procedure **E** by reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 4-bromobenzylbromide (0.28 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **291** as a yellow solid (0.12 g, 43% yield). mp 58-60°C.

^{1}H NMR ($CDCl_3$): δ = 7.50 (d, 2H, J = 8Hz, 2xPhenyl), 7.27 (d, 2H, J = 8Hz, 2xPhenyl), 7.04-7.00 (m, 2H, Py-5,6H), 6.56 (m, 1H, Py-4H), 4.99(s, 2H, OCH_2), 2.50 (s, 3H, Py-2Me); ^{13}C NMR ($CDCl_3$): δ = 152.8 (C), 149.3 (C), 141.0 (C), 135.7 (CH), 131.9 (2xCH), 129.0 (2xCH), 122.1 (CH), 121.8 (CH), 117.9 (C), 69.2 (CH_2), 19.8 (CH_3); ν_{max} (KBr) 1655, 1406, 1326, 733; m/z 278 (M^+); (Analysis found: C, 56.25, H, 4.44, N, 4.89%; $C_{13}H_{12}BrNO$ requires C, 56.14, H, 4.35, N, 5.04%).

3-(2-Chlorobenzyloxy)-2-methylpyridine, 292

Prepared by General procedure E by reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 2-chlorobenzylchloride (0.18 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **292** as a white solid (0.14 g, 61% yield). mp 62-65°C.

^{1}H NMR ($CDCl_3$): δ = 7.40-7.35 (m, 1H, Phenyl), 7.22-7.15 (m, 2H, 2xPhenyl), 7.05 (m, 1H, Py-6H), 6.90 (m, 1H, Phenyl), 6.64-6.58 (m, 1H, Py-5H), 6.22 (m, 1H, Py-4H), 5.68 (s, 2H, OCH_2), 2.43 (s, 3H, Py-2Me); ^{13}H NMR ($CDCl_3$): δ = 188.6 (C), 136.5 (C), 132.8 (CH), 130.8 (C), 129.6 (C), 128.8 (CH), 128.0 (CH), 127.4 (CH), 121.7 (CH), 120.3 (CH), 109.0 (CH), 50.6 (CH_2), 27.5 (CH_3); ν_{max} (KBr) 1645, 1396,

1330, 1086, 1038, 743; m/z 234 (M^+); (Analysis found: C, 66.78, H, 5.34, N, 5.87%; $C_{13}H_{12}ClNO$ requires C, 66.81, H, 5.18, N, 5.99%).

3-Ethoxy-2-methylpyridine, 293[178b]

Prepared by General procedure **E** by reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and bromoethane (0.11 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **293** as a yellow oil (0.4 g, 28% yield).

^1H NMR ($CDCl_3$): δ = 8.20 (t, 1H, J = 3Hz, Py-6H), 7.11 (dd, 1H, J = 3,8Hz, Py-5H), 6.89 (dd, 1H, J = 3,8Hz, Py-4H), 3.87 (q, 2H, J = 7Hz, CH_2CH_3), 2.38 (s, 3H, Py-2Me), 1.40 (t, 3H, J = 7Hz, CH_2CH_3); ν_{max} (KBr) 1647, 1378, 1330, 1109, 1056, 987, 659; m/z 137 (M^+).

3-Butoxy-2-methylpyridine, 294

Prepared with General procedure **E** by reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 1-bromobutane (0.15 g, 1.1 mmol). Column chromatography on silica (dichloromethane) afforded **294** as a brown oil (0.04 g, 21% yield).

^1H NMR ($CDCl_3$): δ = 6.95, (m, 1H, Py-6H), 6.80 (m, 1H, Py-5H), 6.12 (m, 1H, Py-4H), 5.40 (m, 2H, OCH_2), 4.31 (t, 2H, J = 7.2Hz, OCH_2CH_2), 2.43 (s, 3H, Py-2Me), 1.70 (tt, 2H, CH_2CH_3), 1.16 (3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ = 154.3 (C), 146.7 (C), 128.7 (CH), 118.8 (CH), 106.4 (CH), 48.2 (CH_2), 32.1 (CH_2), 26.0 (CH_2), 18.4 (CH_3), 12.4 (CH_3); ν_{max} (KBr) 1648, 1399, 1329, 738; m/z 165 (M^+); Accurate mass: 165.1148, $C_{10}H_{15}NO$ requires 165.1154.

3-Anthraquinone-2-methylpyridine, 295

Prepared by General procedure **E** by reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 2-bromomethylanthraquinone (0.33 g, 1.1 mmol). Column chromatography on silica (dichloromethane). Recrystallisation (ethanol) afforded **295** as a white solid (0.11 g, 33% yield). mp 150-151°C.

^1H NMR ($CDCl_3$): δ = 8.30-8.20 (m, 3H, 3xAnthraq), 7.96 (m, 1H, Anthraq), 7.79 (m, 2H, 2xAnthraq), 7.45 (m, 1H, Anthraq), 7.08 (m, 1H, Py-6H), 7.00 (m, 1H, Py-5H),

6.29 (m, 1H, Py-4H), 5.36 (s, 2H, OCH_2), 2.41 (s, 3H, Py-2Me); ^{13}C NMR ($CDCl_3$): δ = 188.4 (C=O), 183.0 (C=O), 182.7 (C), 145.3 (C), 134.1 (C), 134.0 (CH), 133.7 (CH), 133.5 (CH), 132.5 (C), 132.2 (CH), 128.6 (C), 128.2 (C), 127.8 (C), 127.2 (CH), 126.8 (CH), 126.5 (CH), 125.0 (CH), 123.7 (CH), 120.8 (CH), 52.5 (CH_2), 17.4 (CH_3); ν_{max} (KBr) 1634, 1402, 1367, 1354, 1067, 893; m/z 329 (M^+); (Analysis found: C, 76.67, H, 4.58, N, 4.19%; $C_{21}H_{15}NO_3$ requires C, 76.58, H, 4.59, N, 4.25%).

3-Bromoethoxy-2-methylpyridine, 296

Prepared by General procedure **E** by reaction of 2-methyl-pyridin-3-ol **243** (0.11 g, 1.0 mmol) and 1,2-dibromoethane (0.11 g, 0.6 mmol). Column chromatography on silica (dichloromethane) afforded **296** as a brown oil (0.05 g, 21% yield).

^{1}H NMR ($CDCl_3$): δ = 7.01 (m, 1H, Py-6H), 6.94 (m, 1H, Py-5H), 6.16 (m, 1H, Py-4H), 4.65 (m, 2H, OCH_2), 3.67 (m, 2H, CH_2Br), 2.44 (s, 3H, Py-2Me); ^{13}C NMR ($CDCl_3$): δ = 188.7 (C), 131.7 (C), 130.0 (CH), 121.3 (CH), 108.4 (CH), 51.6 (CH_2), 32.5 (CH_2), 27.4 (CH_3); ν_{max} (KBr) 1675, 1389, 1345, 1208, 1044, 895, 721; m/z 216 (M^+); Accurate mass: 215.0149, $C_8H_{10}BrNO$ requires 215.0146.

2,5-*bis*-Bromomethylthiophene, 299[180]

This was prepared following the literature route[180] using 2,5-dimethylthiophene (0.79 g, 7 mmol), N-bromosuccinimide (2.76 g, 15 mmol), AIBN (0.05 g) and CCl_4 (100 ml) in 20% yield.

^{1}H NMR ($CDCl_3$): δ = 6.98 (s, 2H, 2xThio), 4.56 (s, 4H, 2xCH_2Br).

Bis-thiophene-pyridine, 301

Prepared by General procedure **E** by reaction of 6-methyl-pyridin-3-ol (0.15 g, 13 mmol) and 2,5-*bis*-bromomethylthiophene **299** (0.18 g, 6.7 mmol). Column chromatography on silica (petroleum ether: ethyl acetate 1:1 $^v/_v$) afforded **301** as a yellow solid (0.11 g, 57% yield). mp 96-98°C.

^{1}H NMR ($CDCl_3$): δ = 8.25 (m, 2H, 2xPy-6H), 7.26 (m, 2H, 2xPy-5H), 7.16 (s, 2H, 2xThio), 7.00 (m, 2H, 2xPy-4H), 5.20 (s, 4H, 2xOCH_2), 2.49 (s, 6H, 2xPy-6Me); ^{13}C

NMR ($CDCl_3$): δ = 152.5 (2xC), 151.3 (2xC), 140.0 (2xC), 137.2 (2xCH), 127.0 (2xCH), 124.0 (2xCH), 123.0 (2xCH), 65.8 (2xCH_2), 23.6 (2xCH_3); ν_{max} (KBr) 1669, 1388, 1362, 1209, 1022, 938, 871; m/z 326 (M^+); (Analysis found: C, 65.97, H, 5.55, N, 8.38%; $C_{18}H_{18}N_2O_2S$ requires C, 66.23, H, 5.56, N, 8.58%).

1,4-*bis*-Bromomethylbenzene, 302[181]

To a solution of *p*-xylene (5.0 g, 47 mmol) in dry carbon tetrachloride (60 ml) was added N-bromosuccinimide (16.7g, 94 mmol) and benzoyl peroxide (3.4 g, 14 mmol), the solution was refluxed for 2 h, allowed to cool to room temperature and filtered through celite. The solution was allowed to stand overnight to evaporate, then filtered and washed with hexane to give **302** as a white solid (5.54 g, 45% yield). mp 144-145°C (Lit. 143-144°C).

^{1}H NMR ($CDCl_3$): δ = 6.53 (s, 4H, 4xPhenyl), 4.43 (s, 4H, 2xCH_2Br).

Benzyloxy-di-2-methylpyridine, 303

Prepared by General procedure **E** by reaction of 2-methyl-pyridin-3-ol (0.30 g, 28 mmol) and 1,4-bis-bromomethylbenzene **302** (0.74 g, 29 mmol). Column chromatography on silica (ethyl acetate) afforded **303** as a white solid (0.21 g, 51% yield). mp 124-125°C.

^{1}H NMR ($CDCl_3$): δ = 8.26 (m, 2H, 2xPy-6H), 7.44 (s, 4H, 4xPhenyl), 7.15-7.00 (m, 4H, 2xPy-4,5H), 5.01 (s, 4H, 2xOCH_2), 2.49 (s, 6H, 2xPy-2Me); ^{13}C NMR ($CDCl_3$): δ = 152.7 (2xC), 150.7 (2xC), 137.0 (2xCH), 136.4 (2xC), 127.7 (4xCH), 123.4 (2xCH), 122.5 (2xCH), 70.1 (2xCH_2), 23.4 (2xCH_3); ν_{max} (KBr) 1638, 1415, 1378, 1331, 1107, 989, 921, 634; m/z 320 (M^+); (Analysis found: C, 74.91, H, 6.34, N, 8.83%; $C_{20}H_{20}N_2O_2$ requires C, 74.98, H, 6.29, N, 8.74%).

2-Amino-3-benzyloxy-6-methylpyridine, 306

Prepared by General procedure **E** by reaction of 2-Amino-6-methylpyridin-3-ol (0.50 g, 4.0 mmol) and benzyl bromide (0.87 g, 5 mmol). Column chromatography on silica (ethyl acetate) afforded **306** as a yellow solid (0.37 g, 43% yield). mp 95-96°C

^{1}H NMR ($CDCl_3$): δ = 7.35-7.10 (m, 5H, 5xPhenyl), 7.12 (d, 1H, J = 8Hz, Py-5H), 6.84 (d, 1H, J = 8Hz, Py-4H), 5.34 (s, 2H, OCH_2), 4.13 (bs, 2H, NH_2), 1.56 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 186.5 (C), 133.2 (C), 131.5 (C), 127.4 (C), 123.6 (CH), 120.9 (2xCH), 118.5 (2xCH), 111.2 (CH), 110.7 (CH), 70.1 (CH_2), 21.4 (CH_3); m/z 214 (M^+); (Analysis found: C, 72.94, H, 6.65, N, 12.99%; $C_{13}H_{14}N_2O$ requires C, 72.87, H, 6.59, N, 13.07%).

2-(Diacetylamino)-3-pyridinol acetate, 307

To a solution of dry dichloromethane (40 ml) and acetyl chloride [prepared *in situ* from acetic acid (0.12 g, 2 mmol) and oxalyl chloride (0.25 g, 2 mmol)] was added pyridine (1 ml) and 2-amino-6-methyl-3-hydroxypyridine **305** (0.1 g, 0.4 mmol). The resulting solution was stirred for 15 h. The solvent was removed *in vacuo* and column chromatography on silica (ethyl acetate) afforded **307** as a yellow solid (0.08 g, 57% yield). mp 139-141°C.

^{1}H NMR ($CDCl_3$): δ = 7.51 (d, 1H, J = 8Hz, Py-4H), 7.15 (d, 1H, J = 8Hz, Py-5H), 2.55 (s, 3H, OCOCH_3), 2.27 (s, 6H, N(COCH_3)$_2$), 2.24 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 172.4 (2xC=O), 168.5 (C=O), 156.4 (C), 144.1 (C), 141.6 (C), 132.8 (CH), 125.2 (CH), 26.5 (2xCH_3), 23.9 (CH_3), 20.9 (CH_3); ν_{max} (KBr) 1716, 1630, 1481, 1276, 1170, 1113; m/z 336 (M^+); (Analysis found: C, 57.59, H, 5.71, N, 10.99%; $C_{12}H_{14}N_2O_4$ requires C, 57.59, H, 5.64, N, 11.19%).

3-(Oxycarbinol-ferrocenyl)-2-amino-6-methylpyridine, 308

To a solution of dry dichloromethane (40 ml) and ferrocene acid chloride [prepared in situ from ferrocene carboxylic acid (0.46 g, 20 mmol) and oxalyl chloride (0.25 g, 20 mmol)] was added dry pyridine (1 ml) and 2-amino-6-methyl-3-hydroxypyridine (0.25 g, 18 mmol). The resulting solution was stirred for 15 h. The solvent was removed *in vacuo* and column chromatography on silica (ethyl acetate) afforded **308** as a yellow solid (0.31 g, 51% yield). mp 139-141°C.

^{1}H NMR ($CDCl_3$): δ = 7.20 (d, 1H, J = 7Hz, Py-4H), 6.51 (d, 1H, J=7Hz, Py-5H), 4.89 (bs, 2H, NH_2), 4.46 (m, 4H, 4xFc), 4.23 (s, 5H, 5xFc), 2.34 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 169.9 (C=O), 153.9 (C), 150.7 (C), 131.3 (C), 130.3 (CH), 113.8

(CH), 72.4 (5xCH), 70.8 (C), 70.3 (2xCH), 69.6 (2xCH), 24.0 (CH_3); ν_{max} (KBr) 1716, 1630, 1481, 1276, 1170, 1113; m/z 336 (M^+); (Analysis found: C, 60.82, H, 4.79, N, 8.11%; $C_{17}H_{16}FeN_2O_2$ requires C, 60.74, H, 4.80, N, 8.33%).

5.4 Experimental for Chapter 4

6-Methyl-2-nitropyridin-3-ol, 316[197]

To 6-methylpyridin-3-ol **315** (1.0 g, 9 mmol) in an ice-bath was added conc. H_2SO_4 (8 ml). Then slowly over 20 min a solution of conc. H_2SO_4 (5 ml) and conc. HNO_3 (5 ml). The solution was stirred for 5 h, before neutralisation with NaOH. Extraction with dichloromethane (3x40 ml), dried ($MgSO_4$), filtered and solvent removed *in vacuo* gave **316** as a yellow solid (0.5 g, 35% yield). mp 175-178°C (Lit 176°C).
^{1}H NMR (DMSO-δ_6): δ = 8.45 (bs, 1H, OH), 7.18 (d, 1H, J = 8Hz, Py-5H), 6.89 (d, 1H, J = 8Hz, Py-4H), 2.20 (s, 3H, Py-6Me).

3-Methoxy-6-methyl-2-nitropyridine, 317[198]

6-Methyl-2-nitropyridin-3-ol **316** (0.4 g, 2.5 mmol) was taken up in dry acetone (60 ml) and potassium carbonate (0.42 g, 3 mmol) added. After 1 h a red solution is formed and to this was added methyl iodide (2.13 g, 15 mmol) and refluxed for 15 h or until the solution turns yellow. The acetone was removed *in vacuo* and water (40 ml) added. The organic phase was extracted with dichloromethane (3x40 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give **317** as a white solid (0.34 g, 78% yield). mp 213-214°C (Lit 212°C).
^{1}H NMR ($CDCl_3$): δ = 7.34 (d, 1H, J = 8Hz, Py-5H), 6.99 (d, 1H, J = 8Hz, Py-4H), 3.41 (s, 3H, OMe), 2.11 (s, 3H, Py-6Me).

5-Methyl-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol, 318

To distilled water (50 ml) was added **317** (0.3 g, 1.8 mmol) and hydrazine hydrate (0.12 g, 3.6 mmol), this was heated to 85°C, so that all the solid dissolved, and stirred

for 12 hr. The solution was allowed to cool, and placed in an ice-bath. Conc. HCl was then added slowly, being careful not to warm the solution above 30°C, precipitating **318** as a white solid around pH 3. The product was purified by recrystallisation (water) to give **318** (0.18 g, 67% yield). mp 227°C dec.

^{1}H NMR (DMSO): δ = 7.67 (d, 1H, J = 8Hz, Py-5H), 7.32 (d, 1H, J = 8Hz, Py-4H), 2.00 (s, 3H, Py-6Me); ^{13}C NMR (DMSO): δ = 160.8, 139.3, 133.3, 128.6, 121.3, 24.5; ν_{max} (KBr) 1587, 1439, 1369, 1226, 1110, 836, 793, 769; m/z (Ammonia CI) 151 (57%, M^++1), 168 (18.4%, M^++NH_4^+); (Analysis found: C, 47.79, H, 4.00, N, 37.50%; $C_6H_6N_4O$ requires C, 48.00, H, 4.03, N, 37.31%).

2-Bromo-6-methylpyridin-3-ol, 319[199]

A solution of bromine (1 ml) in 10% sodium hydroxide (50 ml) was slowly added over 1 h to a stirred solution of 6-methylpyridin-3-ol **315** (1.0 g, 9 mmol) in 10% sodium hydroxide (30 ml). Stirring was continued for a further 15 h. The solution was neutralised with conc. HCl and the solid formed filtered off. Column chromatography on silica (chloroform:methanol, 95:5 $^v/_v$) gave **319** as a white solid (0.52 g, 30% yield). mp 175°C (Lit. 174-176°C).

^{1}H NMR (DMSO-δ_6): δ = 8.67 (bs, 1H, OH), 6.99 (d, 1H, J = 8Hz, Py-5H), 6.79 (d, 1H, J = 8Hz, Py-4H), 2.43 (s, 3H, Py-6Me).

2-Bromo-3-methoxy-6-methylpyridine, 320[199]

2-Bromo-6-methylpyridin-3-ol **319** (0.5 g, 2 mmol) was taken up in dry acetone (60 ml) and potassium carbonate (0.5 g, 4 mmol) added. After 1 hr to the red solution was added methyl iodide (2.4 g, 17 mmol) and refluxed for 15 hr or until yellow. The acetone was removed *in vacuo* and water (40 ml) added. The organic phase was extracted with dichloromethane (3x40 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give **320** as a white solid (0.32 g, 59% yield). mp 54°C (Lit. 52-54°C)

^{1}H NMR ($CDCl_3$): δ = 7.05 (d, 1H, J = 9Hz, Py-5H), 6.95 (d, 1H, J = 9Hz, Py-4H), 3.98 (s, 3H, OMe), 2.48 (s, 3H, Py-6Me).

Purified 3-chloroperoxybenzoic acid (*m*CPBA)[200]

Phospate buffer was prepared by dissolving potassium dihydrogen phosphate (1.0 g, 8 mmol) and sodium hydrogen phosphate (4.3 g, 30 mmol) in distilled water (1000 ml). Commercial 3-chloroperoxybenzoic acid (25 g) was washed with the phosphate buffer (500 ml), the mixture filtered and the process repeated. The washed 3-chloroperoxybenzoic acid was dissolved in dichloromethane (200 ml), the residual phosphate buffer separated and the organic layer dried ($MgSO_4$). The solvent was removed *in vacuo* to give white solid which was dried under vacuum for 24 h to yield essentially pure (~90%) 3-chloroperoxybenzoic acid (15 g).

2-Bromo-3-methoxy-6-methylpyridine-1-oxide, 321

A solution of 2-bromo-3-methoxy-6-methylpyridine **320** (0.3 g, 1.5 mmol) and *m*-chloroperbenzoic acid (0.5 g) in chloroform (30 ml) was stirred at room temperature for 3 h. The solvent was evaporated at room temperature under vacuum and the residue chromatographed on alumina (chloroform) to give 2-bromo-3-methoxy-6-methylpyridine-1-oxide, **321** (0.20 g, 62% yield). mp 198-200°C.

^{1}H NMR ($CDCl_3$): δ = 7.13 (d, 1H, J = 8Hz, Py-5H), 6.71 (d, 1H, J = 8Hz, Py-4H), 4.10 (s, 3H, OMe), 2.35 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 156.2, 130.2, 126.4, 125.4, 120.1, 58.1, 19.1; ν_{max} (KBr); m/z 218; (Analysis found: C, 38.64, H, 3.89, N, 6.23%; $C_7H_8BrNO_2$ requires C 38.56, H, 3.70, 6.42%).

2-Bromo-3-methoxy-6-methyl-4-nitropyridine-1-oxide, 322

To 2-bromo-3-methoxy-6-methylpyridine-1-oxide, **321** (0.2 g, 0.9 mmol) in an ice-bath was added conc. H_2SO_4 (8 ml). Then slowly over 20 min a solution of conc. H_2SO_4 (5 ml) and conc. HNO_3 (5 ml). The solution was stirred for 5 h, before neutralisation with NaOH. Extraction with dichloromethane (3x40 ml), dried ($MgSO_4$), filtered and solvent removed *in vacuo* gave **322** as a yellow solid (0.11 g, 45% yield). mp 236-238°C.

^{1}H NMR ($CDCl_3$): δ = 8.51 (s, 1H, Py-5H), 3.96 (s, 3H, OMe), 2.55 (s, 3H, Py-6Me); ^{13}C NMR ($CDCl_3$): δ = 145.0, 139.0, 131.7, 120.4, 118.9, 58.3, 20.1; ν_{max} (KBr); m/z

263 (M+); (Analysis found: C, 32.12, H, 2.87, N, 10.61%; $C_7H_7BrN_2O_4$ requires C, 31.96, H, 2.68, N, 10.65%).

Bibliography

[1] R. Anderson, *Trans. Roy. Soc. Edinburgh* **1849,** *16*, 123.

[2] E. Späth, E. Zajic, *Chem. Ber.* **1935**, *68*, 1667.

[3] E. Späth, E. Zajic, *Chem. Ber.* **1936**, *69*, 2448.

[4] K. E. Jackson, *Chem. Rev.* **1941**, *41*, 123.

[5] C. O'Driscoll, 'high hopes for cannabis', *Chemistry in Britain* **2000**, *36(4)*, 20.

[6] S. A. Harris, E. E. Harris, R. W. Burg, in 'Kirk-Othmer, Encyclopedia of chemical technology', interscience, New York **1968**, 2nd Edition, Vol 16, pp 806.

[7] G. Odham, E. Stenhegen, *Acc. Chem. Res.* **1971**, *4*, 121.

[8] P. György, *J. Am. Chem. Soc.* **1938**, *60*, 983.

[9] R. Kuhn, G. Wendt, *Chem. Ber.* **1938**, *71*, 780; R. Kuhn, G. Wendt, *Chem. Ber.* **1938**, *71*,1118; R. Kuhn, G. Wendt, *Chem. Ber.* **1938**, *71*,1534.

[10] R. L. Shriner, T. A. Turner, *J. Am. Chem. Soc.* **1930**, *60*, 1267.

[11] S. A. Harris, K. Folkers, *J. Am. Chem. Soc.* **1939**, *61*, 2145.

[12] M. Tiecco, M. Tingoli, L. Testaferri, D. Chainelli, E. Wenkert, *Tetrahedron* **1986**, *42*, 1475.

[13] W. Antkowiak, W. Gessner, *Tetrahedron Lett.* **1979**, *21*, 1931.

[14] T. Bailey, G. Goe, E. Scriven, 'Pyridine and its derivatives'. Wiley and Sons, New York, Part V, pp. 1-252.

[15] U. S. Patent 2,557,076, Chitwood to union carbide and carbon corp., **1951**; *Chem. Abs.* **1952**, *46*, 145.

[16] A. Cohen, J. W. Haworth, E. G. Hughes, *J. Chem. Soc.* **1952**, 4374.

[17] K. Heyns, G. Vogelsang, *Chem. Ber.* **1954**, *87*, 1440.

[18] R. J. C. Kleipool, J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas* **1947**, *66*, 24.

[19] R. J. C. Keipoll, J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1041.

[20] G. A. Garkusha, *J. Gen. Chem. U. S. S. R.* **1946**, *16*, 2025; *Chem. Abs.* **1948**, *42*, 566d.

[21] D. Kostermans, *Recl. Trav. Chim. Pays-Bas* **1947**, *66*, 93.

[22] R. J. C. Kleipool, J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas* **1947**, *66*, 459.

[23] H. Ost, *J. Prakt. Chem.* **1879**, *19*, 203; H. Ost, *J. Prakt. Chem.* **1881**, *23*, 441; H. Ost, *J. Prakt. Chem.* **1883**, *27*, 257.

[24] M. Ya. Karpeiskii, V. L. Florent, *Russ. Chem. Rev. (Engl. Transl.)* **1969**, *38*, 540.

[25] R. Lakhan, B. Ternai, *Adv. Heterocycl. Chem.* **1974**, *17*, 255.

[26] R. Grigg, J. L. Jackson, *J. Chem. Soc. (C)* **1970**, 552.

[27] H. Takagaki, N. Yasuda, M. Asaoka, H. Takei, *Chem. Lett.* **1979**, 183.

[28] French Patent 1,400,843, Takeda Chemical Industries Ltd. 1965; *Chem. Abs.* **1965**, *63*, 9922.

[29] J. A. Moore, *J. Am. Chem. Soc.* **1955**, *77*, 3417.

[30] H. C. Van der Plas, 'Ring transformations of heterocycles', Academic, London, Vol. 2, **1973**.

[31] M. G. Pleiss, J. A. Moore, *J. Am. Chem. Soc.* **1968**, *90*, 4378.

[32] T. Tezuka, O. Seshimoto, T. Mukai, *Tetrahedron Lett.* **1975**, 1067.

[33] J. Kurita, K. Iwata, T. Tsuchiya, *J. Chem. Soc. Chem. Commun.* **1986**, 1188.

[34] F. W. Fowler, *J. Org. Chem.* **1972**, *37*, 1321.

[35] W. Ried, F. Bütz, *Ann. Chem.* **1972**, *762*, 1.

[36] H. Morita, S. Shiotani, *J. Heterocycl. Chem.* **1987**, *24*, 373.

[37] H. Maier-Bode, *Chem. Ber.* **1936**, 1534.

[38] Patent US 2,028,065, *Dow Chem. Co.* **1933**.

[39] Weidel, Blau, *Monatsh* **1885**, *6*, 651.

[40] H. J. Den Hertog, A. W. M. Falter, A. van der Linde, *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 377.

[41] H. J. Den Hertog, M. van Ammers, S. Schukking, *private communication*; *Chem. Abs.* **1956**, *50*, 5656b.

[42] O. Wulff, US Patent 1,880,645 (Oct. 4, 1932), German 541,681 (1931), British 335,818 (1929); *Chem. Abs.* **1933**, *27*, 513[8].

[43] Weidel, Murmann, *Monatsh* **1895**, *16*, 749.

[44] G. R. Lappin, F. B. Slezak, *J. Am. Chem. Soc.* **1950**, *72*, 2806.

[45] M. Katada, *J. Pharm. Soc. Jpn.* **1947**, *67*, 41; *Chem. Abs.* **1951**, *45*, 9536.

[46] J. A. Berson, T. Cohen, *J. Am. Chem. Soc.* **1955**, *77*, 1281.

[47] K. Biemann, G. Büchi, B. H. Walker, *J. Am. Chem. Soc.* **1957**, *79*, 5558.

[48] M. Murakami, E. Matsumura, *J. Chem. Soc. Jpn., Pure Chem. Sec.* **1949**, *70*, 393. *Chem. Abs.* **1951**, *45*, 4698.

[49] E. Matsumura, *J. Chem. Soc. Jpn. Pure Chem. Sec.* **1953**, *74*, 547. *Chem. Abs.* **1954**, *48*, 13687.

[50] T. Zincke, G. Muhlhausen, *Chem. Ber.* **1905**, *38*, 3824.

[51] K. Aso, *Bull. Inst. Phys. Chem. Res. (Tokyo)*, **1939**, *18*, 182; *Chem. Abs.* **1940**, 3273[6].

[52] H. Sugisawa, K. Aso, *J. Agr. Chem. Soc. Jpn.* **1954**, *28*, 282; *Chem. Abs.* **1956**, *50*, 16, 767.

[53] K. Aso, *J. Agr. Chem. Soc. Jpn.* **1940**, *16*, 249; *Chem. Abs.* **1940**, *34*, 6278.

[54] J. Rombaut, G. Smets, *Bull. Soc. chim. Belges*, **1949**, *58*, 421; *Chem. Abs.* **1951**, *45*, 569.

[55] J. C. McGowan, *J. Chem. Soc.* **1954**, 4032.

[56] C. F. Koelsch, J. J. Carney, *J. Am. Chem. Soc.* **1950**, *72*, 1669.

[57] K. Aso, *Bull. Inst. Phys. Chem. Res. (Tokyo)*, **1937**, *18*, 177; *Chem. Abs.* **1940**, *34*, 3273[5].

[58] K. Aso, *J. Agr. Chem. Soc. Jpn.* **1940**, *16*, 253; *Chem. Abs.* **1940**, *34*, 6940.

[59] A. Sugisawa, *Tohoku J. Agric. Chem.* **1954**, *5*, 147; *Chem. Abs.* **1956**, 4941.

[60] W. Gruber, *Can. J. Chem.* **1953**, *31*, 564.

[61] H. Leditschke, *Chem. Ber.* **1952**, *85*, 202.

[62] W. Gruber, *Chem. Ber.* **1955**, *88*, 178; W. Gruber, *Chem. Ber.* **1955**, *88*, 185.

[63] H. Leditschke, *Chem. Ber.* **1953**, *86*, 612.

[64] L. A. Walter, C. K. Springer, J. Kenney, S. K. Galen, N. Spenber, *J. Med. Chem.* **1968**, *11*, 792.

[65] L. Kaczmarek, R. Balicki, J. Lipkowski, P. Borowicz, A. Grabowska, *J. Chem. Soc. Perkin Trans. 2* **1994**, *7*, 1603.

[66] C. A. Lipinski, J. L. LaMattina, P. J. Oates, *J. Med. Chem.* **1986**, *29*, 2154.

[67] W. Siemanowski, H. Witzel, *Liebigs Ann. Chem.* **1984**, *10*, 1731.

[68] H. Langhals, S. Pust, *Chem. Ber.* **1985**, *118*, 4674.

[69] V. Rapoport, *J. Am. Chem. Soc.* **1956**, *78*, 2451, 2454.

[70] B. R. Baker, F. J. McEvoy, *J. Org. Chem.* **1955**, *20*. 137.

[71] K. Alder, H. F. Rickert. *Chem. Ber.* **1937**, *70*, 1354.

[72] H. Williams, P. Kaufmann, H. S. Mosher, *J. Org. Chem.* **1955**, *20*, 1139.

[73] N. Clauson-Kaas, P. Nedenskov, *Acta Chem. Scand.* **1955**, *9*, 14.

[74] N. Clauson-Kaas, N. Elming, Z. Tyle, *Acta Chem. Scand.* **1955**, *9*, 1.

[75] N. Clauson-Kaas, Z. Tyle, *Acta Chem. Scand.* **1952**, *6*, 667.

[76] N. Clauson-Kaas, P. Nedenskov, *Acta Chem. Scand.* **1955**, *9*, 27.

[77] J. T. Nielsen, N. Elming, N. Clauson-Kaas, *Acta Chem. Scand.* **1955**, *9*, 9.

[78] L. S. Mourning, E. Roberts, *J. Org. Chem.* **1978**, *43*, 1911.

[79] L. Meier, H-D. Scharf, *Liebigs Ann. Chem.* **1986**, *4*, 731.

[80] N. Elming, N. Clauson-Kaas, *Acta Chem. Scand.* **1956**, *10*, 1603.

[81] A. G. M. Barrett, S. A. LeBold, *Tetrahedron Lett.* **1987**, *28*, 5791.

[82] H. Greuter, D. Bellus, *J. Heterocycl. Chem.* **1977**, *14*, 203.

[83] A. Nakama, E-H. Kim, K. Shinohara, H. Omura, *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1757.

[84] T. Ahmad, L. Kenne, K. Olsson, O. Theander, *Carbohydr. Res.* **1995**, *276*, 309.

[85] For a review, see Geismann, *Org. React.* **1944**, *2*, 94.

[86] H. Specker, H. Gawrosch, *Chem. Ber.* **1942**, *75*, 1338.

[87] J. H. Biel, H. L. Friedman, H. A. Leiser, E. P. Sprengler, *J. Am. Chem. Soc.* **1952**, *74*, 1485.

[88] O. Fischer, *Chem. Ber.* **1884**, *17*, 764.

[89] S. Leonard, *J. Am. Chem. Soc.* **1955**, *77*, 2855.

[90] T. Joergensen, H. C. Nielsen, N. Malhotra, J. Becher, M. Begtrup, *J. Heterocycl. Chem.* **1992**, *29*, 1841.

[91] H. Meyer, *Monatsh* **1905**, *26*, 1312.

[92] O. Fischer, *Chem. Ber.* **1884**, *17*, 1897.

[93] H. Cavallito, *J. Am. Chem. Soc.* **1944**, *66*, 1166.

[94] L. Baker, H. McEvoy, *J. Org. Chem.* **1955**, *20*, 118; L. Baker, H. McEvoy, *J. Org. Chem.* **1955**, *20*, 131.

[95] R. Woods, *J. Am. Chem. Soc.* **1942**, *64*, 2348.

[96] H. M.. Wuest, E. H. Saval, *J. Am. Chem. Soc.* **1951**, *73*, 1210.

[97] R. D. Haworth, A. H. Lamberton, D. Woodcock, *J. Chem. Soc.* **1947**, 182.

[98] H. J. Den Hertog, *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1281.

[99] G. J. Clark, L. W. Deady, *Aust. J. Chem.* **1981**, *34*, 927.

[100] D. Heinert, A. E. Martell, *Tetrahedron* **1958**, *3*, 49, 56.

[101] For review see: Tramontini, Angiolini, *Tetrahedron* **1990**, *46*, 1791.

[102] K. Auwers, *Chem. Ber.* **1907**, *40*, 2524.

[103] K. M. Dyumaev, L. D. Smirnov, *Russ. Chem. Rev. (Engl. Transl.)* **1975**, *44*, 823.

[104] T. Urbanski, *J. Chem. Soc.* **1946**, 1104.

[105] E. Shaw, *J. Am. Chem. Soc.* **1949**, *71*, 67.

[106] W. Dieckmann, L. Beck, *Chem. Ber.* **1905**, *38*, 4123.

[107] A. R. Katritzky, N. Dennis, *Chem. Rev.* **1989**, *89*, 827.

[108] N. Dennis, A. R. Katritzky, H. Wilde, *J. Chem. Soc. Perkin Trans. 1* **1976**, 2338.

[109] A. R. Katritzky, Y. Tekeuchi, *J. Chem. Soc. (C)* **1971**, 874.

[110] N. Dennis, H. A. Dowlatshahi, A. R. Katritzky, *J. Chem. Res.* **1978**, 1182.

[111] A. R. Katritzky, N. E. Grzeskowiak, *J. Chem. Res.* **1981**, 2345.

[112] A. R. Katritzky, Y. Tekeuchi, *J. Chem. Soc. (C)* **1971**, 878.

[113] A. R. Katritzky, J. Banerji, N. Dennis, J. Ellison, G. J. Sabongi, E. –U. Wurthwein, *J. Chem. Soc. Perkin Trans. 1* **1979**, 2528.

[114] A. W. Hoffmann, *Chem. Ber.* **1881**, *14*, 659.

[115] T. Takahashi, T. Hagi, K. Kitano, Y. Takwuchi, T. Koizumi, *Chem. Lett.* **1989**, 593.

[116] N. Dennis, B. Ibrahim, A. R. Katritzky, *J. Chem. Soc. Perkin Trans. 1* **1976**, 2307.

[117] N. Dennis, A. R. Katritzky, G. J. Sabounji, *Tetrahedron Lett.* **1976**, 2959.

[118] A. R. Katritzky, A. T. Cutler, N. Dennis, G. J. Sabongi, S. Rahimi-Rastgoo, G. W. Fischer, I. J. Fletcher, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1176.

[119] K. N. Houk, R. W. Strozier, J. A. Hall, *Tetrahedron Lett.* **1974**, 897.

[120] N. Dennis, B. Ibrahim, A. R. Katritzky, *J. Chem. Soc. Perkin Trans. 1* **1976**, 2296.

[121] H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, E. J. Gaughan, *J. Am. Chem. Soc.* **1975**, *87*, 5257.

[122] F. I. Luknitskii, *Chem. Rev.* **1975**, 261.

[123] A. R. Katritzky, A. T. Cutler, N. Dennis, G. J. Sabongi, S. Rahimi-Rastgoo, G. W. Fischer, I. J. Fletcher, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1176.

[124] A. Pawlinoff, G. Wagner, *Chem. Ber.* **1884**, *17*, 1967.

[125] V. Grignard, *Ann. Chim. Phys.* **1901**, *24*, 468.

[126] F. N. Peters Jr, R. Fischer, *J. Am. Chem. Soc.* **1930**, *52*, 2079.

[127] V. G. Bukharov, T. E. Pozdnyakova, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1960**, *6*, 1031; *Chem. Abs.* **1961**, *55*, 503.

[128] M. I. Ushakov, V. F. Kucherov, *J. Gen. Chem. USSR* **1944**, *14*, 1080; *Chem. Abs.* **1946**, *40*, 7185.

[129] G. Pianacatelli, A. Scettri, G. David, M. D'Auria, *Tetrahedron* **1978**, *34*, 2775.

[130] A. Takeda, K. Shinhama, S. Tsuboi, *J. Org. Chem.* **1980**, *45*, 3125.

[131] A. H. Klopp, G. F. Wright, *J. Org. Chem.* **1939**, *4*, 142; *Chem. Abs.* **1939**, *33*, 5844[8].

[132] A. P. Terent'ev, L. I. Belen'kii, L. A. Yanovskaya, *Zhur. Obschei Khim.* **1954**, *24*, 1265; *Chem. Abs.* **1955**, *49*, 12327.

[133] H. Gilman, F. Breur, *J. Am. Chem. Soc.* **1934**, *56*, 1123.

[134] V. Ramanathan, R. Levine, *J. Org. Chem.* **1962**, *27*, 1216.

[135] H. C. Ooi, H. Suschitzky, *J. Chem. Soc. Perkin Trans. 1* **1982**, 2871.

[136] F. Sauter, P. Stanetty, W. Sittenthaler, R. Waditschatka, *Monatsh* **1988**, *119*, 1427.

[137] N. Furukawa, T. Shibutani, K. Matsumura, H. Fujikara, *Tetrahedron Lett.* **1986**, *27*, 3899.

[138] B. Szechner, *Tetrahedron* **1981**, *37*, 949.

[139] M. D'Auria, *Heterocycles* **2000**, *52*, 185.

[140] R. M. Soll, J. A. Parks, T. J. Rimele, R. J. Heaslip, A. Wojdan, *Eur. J. Med. Chem. Chim. Ther.* **1990**, *25*, 2.

[141] Y. Yang, A. R. Martin, D. L. Nelson, J. Regan, *Heterocycles* **1992**, *34*, 1169.

[142] C. D. Hall, J. H. R. Tucker, S. Y. F. Chu, A. W. Parkins, S. C. Nyburg, *J. Chem. Soc. Chem. Commun.* **1993**, *19*, 1505.

[143] Y-S. Cheng, W-L. Liu, S-H, Chen, *Synthesis* **1980**, 223.

[144] J. Herscovici, K. Antonakis, *J. Chem. Soc. Chem. Commun.* **1980**, 561.

[145] D. A. Schwartz, P. Yates, *Can. J. Chem.* **1983**, *61*, 1126.

[146] E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, 399.

[147] M. Tsubuki, K. Kanai, T. Honda, *J. Chem. Soc. Chem. Commun.* **1992**, *22*, 1640.

[148] G. E. Keck, E. P. Boden, M. R. Wiley, *J. Org. Chem.* **1989**, *54*, 896.

[149] J. D. Godfrey Jr., E. M. Gordon, D. J. von Langen, *Tetrahedron Lett.* **1987**, *28*, 1603.

[150] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651.

[151] T. Miyakoshi, H. Togashi, *Synthesis* **1990**, 407.

[152] C. W. Picard, K. S. Sharples, F. S. Spring, *Chemistry & Industry* **1939**, *33*, 58; *Chem. Abs.* **1939**, 4234.

[153] M. Fiorenza, A. Ricci, G. Pirazzini, C. Eaborn, J. G. Stamper, *J. Chem. Soc. Perkin Trans. 2* **1978**, 1232.

[154] a) G. Carr, C. Dean, D. Whittaker, *J. Chem. Soc. Perkin Trans. 2* **1989**, 71; b) S. Yoshina, A. Tanaka, K. Katsumi, *Yakugaku Zasshi* **1968**, *88*, 997; *Chem. Abs.* **1969**, *70*, 47187.

[155] C. A. Lipinski, J. L. LaMattina, P. J. Oates, *J. Med. Chem.* **1986**, 2154.

[156] N. A. Bugamin, Y. V. Gulevich, I. P. Beletskaya, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1984**, *33*, 2600.

[157] a) H. Gilman, *Recl. Trav. Chim. Pays-Bas* **1933**, 395 ; b) H. Du, Q. Liu, S. Shi, S. Zhang, *J. Organometallic Chem.* **2001**, *627*, 127.

[158] H. D. Hartough, I. Kosak, *J. Am. Chem. Soc.* **1947**, *69*, 1012.

[159] H. Gilman, N. O. Calloway, *J. Am. Chem. Soc.* **1933**, *55*, 4197.

[160] J. V. Heid, R. Levine, *J. Org. Chem.* **1948**, 409.

[161] V. G. Glukhovtsev, Y. V. Ilin, A. V. Ignatenko, L. Y. Brezhnev, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1987**, *36*, 2631; *Izv. Akad. Nauk SSSR Ser. Khim.* **1987**, *12*, 2834.

[162] J. Bergman, L. Renstroem, B. Sjoeberg, *Tetrahedron* **1980**, *36*, 2505.

[163] P. Strehlke, *Eur. J. Med. Chem. Chim. Ther.* **1974**, *9*, 35.

[164] S. Scholz, H. Marschall-Weyerstahl, P. Weyerstahl, *Liebigs. Ann. Chem.* **1985**, *10*, 1935.

[165] H. Garcia, A. Gilbert, O. Griffiths, *J. Chem. Soc. Perkin Trans. 2* **1994**, 247.

[166] a) C. Bolm, M. Ewald, M. Felder, G. Schlingloff, *Chem. Ber.* **1992**, *125*, 1169; b) P. Baumgarten, A. Dornow, *Chem. Ber.* **1939**, *72*, 563; c) A. Dornow, *Chem. Ber.* **1940**, *73*, 78.

[167] P. Dunlop, US Patent 2,655,512, *Quaker Oats Co.* **1950**.

[168] US Patent 2636882, *Quaker Oats Co.* **1950**.

[169] Y-H. Kuo, K-S. Shih, *Chem. Pharm. Bull.* **1991**, *39*, 181.

[170] S. M. Brombridge, D. A. Archer, P. G. Sammes, *Synthesis*, **1992**, 645.

[171] L. Kaczmarek, R. Balicki, J. Lipkowski, P. Borowicz, A. Grabowska, *J. Chem. Soc. Perkin Trans. 2* **1994**, 1603.

[172] H. Bolska, *Chem. Phys. Lett.* **1983**, *98*, 398.

[173] B. Iddon, *Heterocycles* **1994**, *37*, 1321.

[174] C. N. Pridgen, S. C. Shilcrat, *Synthesis* **1984**, 1048.

[175] A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, *J. Org. Chem.* **1987**, *52*, 3413.

[176] N. K. Harn, C. J. Gramer, B. A. Anderson, *Tetrahedron Lett.* **1995**, *36*, 9453.

[177] J. A. Bristol, I. Gross, R. G. Lovey, *Synthesis* **1981**, 971.

[178] a) S. Hagishita, M. Yamada, K. Shirahase, T. Okada, Y. Murakami, *J. Med. Chem.* **1996**, *39*, 3636; b) I. Hagakawa, S. Norio, K. Suzuki, Y. Tanaka, *Chem. Pharm. Bull.* **1984**, *32*, 4914.

[179] R. L. Blankespoor, A. N. K. Lau, L. L. Miller, *J. Org. Chem.* **1984**, *49*, 4441.

[180] P. R. Ashton, J. A. Preece, J. F. Stoddard, M. S. Tolley, A. J. P. White, D. J. Williams, *Synthesis* **1994**, 1344.

[181] V. Paul, A. Sudalai, T. Daniel, K. V. Srinivasan, *Tetrahedron Lett.* **1994**, *35*, 7055.

[182] a) W. König, R. Greiger, *Ber. Dtsch. Chem. Ges.* **1970**, *103*, 788; b) W. König, R. Greiger, *Ber. Dtsch. Chem. Ges.* **1970**, *103*, 2024; W. König, R. Greiger, *Ber. Dtsch. Chem. Ges.* **1970**, *103*, 2034.

[183] Review: D. Le Nguyen, B. Castro, *Peptide Chemistry 1987, Proc. Jpn. Symp. Pept. Chem.* **1988**, 231.

[184] R. Knorr, A. Trzeciak, W. Bannworth, D. Gillessen, *Tetrahedron Lett.* **1989**, 1927.

[185] L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397.

[186] L. A. Carpino, H. G. Chao, M. Beyermann, M. Bienert, *J. Org. Chem.* **1991**, *56*, 2635.

[187] a) H. –D. Jakube, A. Voigt, *Chem. Ber.* **1966**, *99*, 2419; b) H. –D. Jakube, A. Voigt, S. Burkhardt, *Chem. Ber.* **1967**, *100*, 2367.

[188] Y. Azev, G. A. Mokrushina, I. Y. Postovoskii, Y. N. Sheinker, O. S. Anisimova, *Chem. Heterocycl. Compds.* **1976**, 1172.

[189] Y. M. Yutilov, A. G. Ignatenko, *Khim. Prom-st., Ser. Reakt. Osobo Chist. Veshchestva* **1981**, 27; *Chem. Abs.* **1982**, *96*, 68773s.

[190] L. A. Carpino, US Patent 5,580,981, *Research Corporation Technologies* **1996.**

[191] H. J. Den Hertog, M. van Ammers, Recl. Trav. *Chem. Pays-Bas*, **1955**, *74*, 1160.

[192] L. Xiyan, S. Junhui, T. Xiaochun, *Synthesis* **1982**, 185.

[193] M. L. Ash, R. G. Pews, *J. Heterocycl. Chem.* **1981**,*18*, 939.

[194] M. Kristiansen, J. Erikson, K. Jørgensen, J. Chem. Soc. Perkin Trans. 1 **1990**, 101.

[195] M. Häring, B. Prijis, H. Erlenmeyer, *Helv. Chim. Acta.* **1954**, *37*, 147.

[196] F. Bohlmann, M. Bohlmann, *Chem. Ber.* **1953**, *86*, 1419.

[197] R. K. Iho, *Bl. Inst. Phys. Chem. Res. Abstr. Tokyo*, **1939**, *12*, 10; *Chem. Abs.* **1940**, 3273.

[198] J. J. Kaminski, J. M. Hilbert, B. N. Pramanik, D. M. Solomon, D. J. Conn, etc. *J. Med. Chem.* **1987**, *30*, 2031.

[199] T. R. Kelly, F. Lang, *J. Org. Chem.* **1996**, *61*, 4623.

[200] L. A. White, "Heterocyclic *o*-Quinodimethanes", Ph. D. Thesis, University of Liverpool, 1995.

COMMUNICATION

Synthesis of 2-heteroaryl-3-hydroxypyridines by ring expansion reactions of 2-acylfurans with ammonia

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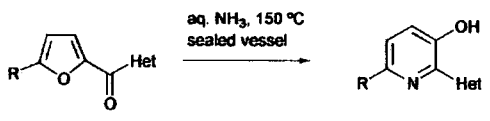
A straightforward and versatile synthesis of 2-heteroaryl-3-hydroxypyridine derivatives is described by the one-step reaction of 2-acylfurans with ammonia at 150 °C.

Heteroaryl-substituted pyridine derivatives, including bipyridyls, are a very important family of compounds in diverse areas of chemistry such as metal-coordination complexes,[1] supramolecular assemblies,[2] pharmaceutical agents,[3] natural products[4] and molecular electronic device materials.[5] The vast majority of syntheses of heteroaryl- (or aryl-) substituted pyridines involve metal-catalysed cross-coupling reactions of the Stille or Suzuki type.[6] A few non-coupling procedures have been developed, but they are generally applicable only to a limited range of ring systems and substituents. Examples are: (i) cyclisation of a substituent which is attached to the pyridine ring (*e.g.* thioamide → thiazole);[1a] (ii) reaction of a lithioheterocycle with a pyridinium cation;[7] (iii) oxidation of a 2-heteroaryl-5-(phenylseleno)-3,4,5,6-tetrahydropyridine derivative.[8]

In the context of non-coupling routes to biaryls we were attracted to the work of Leditschke who reported in 1952 that 2-benzoylfuran (**1**, Het = Ph; R = H) reacted with ammonia to give 2-phenyl-3-hydroxypyridine. The proposed mechanism involves initial attack of ammonia at C-5 of the furan, leading to a ring opening–ring closure sequence, and the furan oxygen becomes the hydroxy group in the product.[9] Gruber extended this route to substituted phenyl substituents.[10] However, this reaction is essentially unexplored as a route to bi(heteroaryl) systems, although it has been established that the reaction will proceed with Het = dibenzofuran[11] and 2- and 4-pyridyl substituents.[12] We now report that this methodology is considerably more versatile than has been realised hitherto, and it provides a general route to a range of 2-heteroaryl-3-hydroxypyridine derivatives **2a–l** (Scheme 1 and Table 1).



Scheme 1

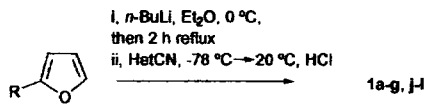
The precursor acylfuran derivatives **1a–l** were readily obtained as shown in Schemes 2–4. Lithiation of furan or 2-methylfuran **3**, followed by reaction with the appropriate cyano-substituted heterocycle, afforded compounds **1a–g,j–l** in 42–76% yields (Scheme 2). Compound **1h** was obtained (30% yield) by selective lithiation of 2,5-dibromopyridine **4** at C-5[13] and reaction with 2-cyanofuran (Scheme 3) and compound **1i** was prepared (42% yield) by the literature route from di-2-furylmethanol **5** (Scheme 4).[14]

Reaction of **1a–l** with aqueous ammonia at 150 °C in a sealed tube afforded products **2a–l** in the yields shown after purification in Table 1. Although these yields are only low or moderate, the reaction has many attractive and viable features from a synthetic viewpoint: (i) the starting furan derivatives **1a–l** are readily accessible from commercial reagents; (ii) it is usually straightforward to obtain analytically pure products **2** by a single recrystallisation of the crude product mixture (see Experimental below); (iii) the reaction proceeds with both electron-deficient (*e.g.* pyridyl, quinolyl, pyrazinyl) and electron-rich (*e.g.* furyl, indolyl) Het substituents; (iv) the products **2** carry a 3-hydroxy substituent which would not be tolerated by

Table 1 Compounds **2a–l** obtained by the route shown in Scheme 1

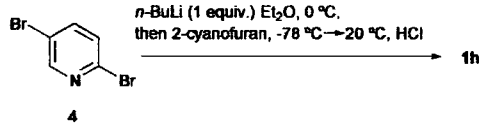
	Het	R	Yield (%)[a]	Mp/°C
a	2-Pyridyl	H	18	30–32
b	2-Pyridyl	Me	25	60–62
c	3-Pyridyl	H	37	171–173
d	3-Pyridyl	Me	27	195–196
e	4-Pyridyl	H	35	234–236
f	4-Pyridyl	Me	31	257–260
g	2-Me-5-pyridyl	H	15 (27)[b]	181–183
h	2-Br-5-pyridyl	H	26	167–169
i	2-Furyl	H	17	210–212
j	3-Quinolyl	H	26	181–184
k	5-Indolyl	H	12	141–143
l	Pyrazin-2-yl	H	20	87–89

[a] Yields refer to analytically pure product fully characterised by spectroscopic data after recrystallisation or column chromatography. [b] Yield obtained from reaction at 110 °C for 12 h.



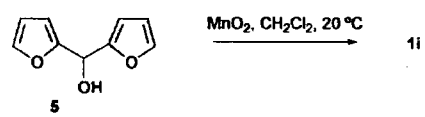
3 R = H or Me

Scheme 2



4

Scheme 3



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Scheme 4

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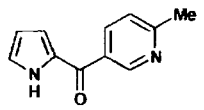
standard metal-catalysed cross-coupling routes, or other non-coupling routes without use of a protecting group.

We have found that the most widely applicable reaction conditions are 150 °C for 5 h. Although the yield of the pyridine products **2** can be raised by using a lower reaction temperature, this benefit is offset by the formation of more by-products which complicated the work-up procedure. For example, a detailed study of the conditions for **1g** established that reaction at 110 °C for 12 h gave **2g** in 27% yield along with the pyrrolyl pyridyl ketone derivative **6** (16% yield) which were separated chromatographically.



6

It is also significant that the presence of the 5-methyl substituent R in **1b**, **d** and **f** does not hinder the ring-expansion reaction. This augers well for the use of more highly functionalised furans as precursors to new 3-hydroxypyridine derivatives[15] with otherwise inaccessible substitution patterns.

Experimental

A mixture of compound **1** (2.5 mmol) and aqueous ammonia solution (0.880, 2 cm^3) was heated in a sealed thick-walled glass Carius tube at 150 °C for 5 h. The tube was cooled, water and methanol were added and the crude product mixture was evaporated *in vacuo* to yield a brown gum. Trituration with acetone or ether gave a brown solid which was recrystallised to afford product **2**, or chromatographed on an alumina column with ethyl acetate as eluent. Spectroscopic and analytical data are entirely consistent with their structures.

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References

1 (*a*) C. R. Rice, S. Wörl, J. C. Jeffrey, R. L. Paul and M. D. Ward, *J. Chem. Soc., Dalton Trans.*, 2001, 550; (*b*) S. S. Zhu, R. P. Kingsborough and T. M. Swager, *J. Mater. Chem.*, 1999, **9**, 2117; (*c*) P. Pickup, *J. Mater. Chem.*, 1999, **9**, 1641.

2 A. Ranganathan, V. R. Pedireddi, S. Chatterjee and C. N. R. Rao, *J. Mater. Chem.*, 1999, **9**, 2407.

3 (*a*) W. J. Thompson, J. H. Jones, P. A. Lyle and E. J. Thies, *J. Org. Chem.*, 1988, **53**, 2052; (*b*) M. Ishikura, M. Kamada and M. Terashima, *Synthesis*, 1984, 936.

4 M. Tiecco, M. Tingoli, L. Testaferri, D. Chainelli and E. Wenkert, *Tetrahedron*, 1986, **42**, 1475.

5 (*a*) U. Mitschke and P. Bäuerle, *J. Mater. Chem.*, 2000, **10**, 1471; (*b*) C. Wang, C.-Y. Jung, Y. Hua, C. Pearson, M. R. Bryce, M. C. Petty, A. S. Batsanov, A. E. Goeta and J. A. K. Howard, *Chem. Mater.*, 2001, **13**, 1167.

6 (*a*) Review: S. P. Stanforth, *Tetrahedron*, 1997, **54**, 263; (*b*) N. Zhang, L. Thomas and B. Wu, *J. Org. Chem.*, 2001, **66**, 1500; (*c*) M. Feuerstein, D. Laurenti, C. Bougeant, H. Doucet and M. Santelli, *Chem. Commun.*, 2001, 325; (*d*) J. J. Li and W. S. Yue, *Tetrahedron Lett.*, 1999, **40**, 4507.

7 M.-J. Shiao, L.-H. Shih, W.-L. Chia and T.-Y. Chan, *Heterocycles*, 1991, **32**, 2111.

8 M. Tingoli, M. Tiecco, L. Testaferri, R. Andrenacci and R. Balducci, *J. Org. Chem.*, 1993, **58**, 6097.

9 H. Leditschke, *Chem. Ber.*, 1952, **85**, 202.

10 (*a*) W. Gruber, *Chem. Ber.*, 1955, **88**, 178; (*b*) W. Gruber, *Chem. Ber.*, 1955, **88**, 185.

11 H. Leditschke, *Chem. Ber.*, 1953, **86**, 612.

12 C. A. Lipinski, J. L. LaMattina and P. J. Oates, *J. Med. Chem.*, 1986, **29**, 2154.

13 C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169.

14 N. A. Bugamin, Y. V. Gulevich and I. P. Beletskaya, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Trans.)*, 1984, **33**, 2600.

15 3-Hydroxypyridine derivatives have many important pharmacological properties: *e.g.* (*a*) nikkomyzin Z (antifungal): A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan, H. Gurzik and A. K. Ganguly, *Tetrahedron Lett.*, 1993, **34**, 3267; (*b*) cicletanine (antihypertensive): L. Kalinowski, I. T. Dobrucki and T. Malinski, *J. Cardiovasc. Pharmacol.*, 2001, **37**, 713; (*c*) pantoprazole (antiulcer): H. Terauchi, A. Tanitame, K. Tada, K. Nakamura, Y. Seto and Y. Nishikawa, *J. Med. Chem.*, 1997, **40**, 313.