Polyfunctional heteroaromatic fused ring systems

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A Thesis Entitled

Polyfunctional Heteroaromatic Fused Ring Systems

Submitted by

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MEMORANDUM

The work presented within this thesis was carried out at the University of Durham between October 2002 and July 2005. The thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

Part of this work has been the subject of the following:

- Graham Sandford, Rachel Slater, Dmitrii S Yufit, Judith A K Howard, Antonio Vong, *J. Org. Chem*, 2005, **70(18)**, 7208.
- Aurelie Baron, Graham Sandford, Rachel Slater, Dmitrii S Yufit, Judith A K Howard, Antonio Vong, 2005, **70(23)**, 9377, *J. Org. Chem.*

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- Royal Society of Chemistry Fluorine Chemistry Group Postgraduate Symposium, Durham 2004
- American Chemical Society Winter Fluorine Chemistry Symposium, Florida 2005
- Durham University Chemistry Department Final Year Postgraduate Symposium, Durham 2005
- Royal Society of Chemistry Fluorine Chemistry Postgraduate Symposium, Oxford 2005

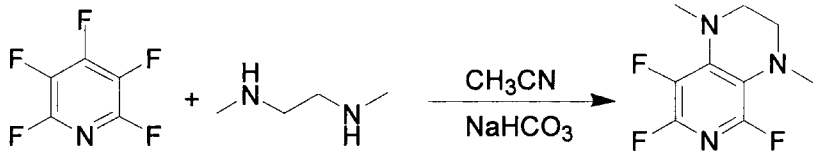
ABBREVIATIONS

DMF	Dimethylformamide
THF	Tetrahydrofuran
DIAD	Diisopropyl Azodicarboxylate
DME	Dimethoxyethane
DEAD	Diethylazodicarboxylate
PTFE	Poly(tetrafluoroethylene)
PFP	Pentafluoropyridine
NMR	Nuclear Magnetic Resonance
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Occupied Molecular Orbital
TMEDA	*N,N,N',N'*-Tetramethylethane-1,2-diamine
DMSO	Dimethylsulfoxide
HPLC	High Pressure Liquid Chromatography
nOe	nuclear Overhauser effect
DCM	Dichloromethane
LDA	Lithium Diisopropylamide
TLC	Thin Layer Chromatography
MOM	Methoxymethyl

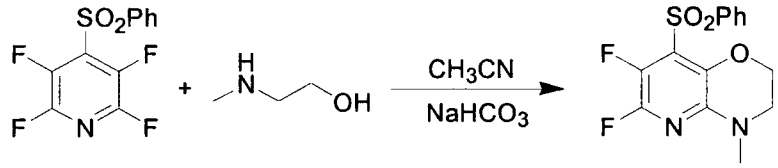
ABSTRACT

Many current therapeutic agents are based on a core structure consisting of a fused ring heteroaromatic polycyclic system. Methodology for the synthesis of a range of these structurally diverse heteroaromatic derivatives is therefore highly desirable and short, high yielding, regioselective and flexible routes to such systems is very important.

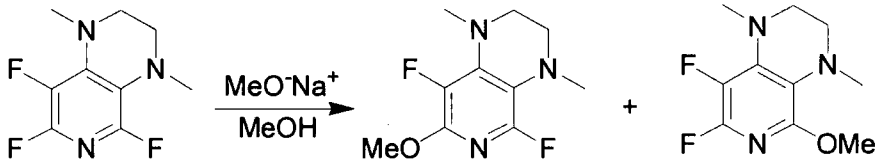
Our methodology utilises nucleophilic substitution reactions between pentafluoropyridine (PFP) and its derivatives, and various binucleophiles, e.g.



The methodology has also been extended to 4-substituted tetrafluoropyridine derivatives and different binucleophiles, resulting in the successful synthesis of, among others, the system shown below.



These fused systems are also reactive to further nucleophilic substitutions



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INTRODUCTION

The research presented in this thesis is concerned with the development of novel methodology for the synthesis of bicyclic [6,6] fused ring heteroaromatic systems which are of significant interest to the pharmaceutical and life science industries.[1, 2] Our methodology utilises highly fluorinated aromatic starting materials such as pentafluoropyridine and relies upon reactions of such compounds with suitable binucleophiles. This introductory chapter is designed to provide a review of the current existing methods for the synthesis of appropriate fused ring systems before moving on to review the chemistry of highly fluorinated systems, their reactions with binucleophiles and how this chemistry can be applied to the synthesis of bicyclic [6,6] heteroaromatic systems.

1.1) SYNTHESIS OF BICYCLIC [6,6] FUSED RING SYSTEMS

It is estimated that approximately 70% of all pharmaceutical products are based upon heterocyclic structures due to a favourable combination of drug-like properties.[3-5] Lipinski has suggested that molecules are most likely to possess drug-like physiochemical properties if they obey the empirical 'rules of 5'.[6] These rules are

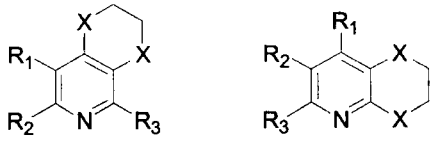
- The molecular weight is below 500
- The calculated log of the octanol/water partition coefficient is less than 5
- There are less than 5 hydrogen bonding donor atoms
- The sum of N and O atoms is less than 10

Many small heterocyclic compounds fall within these parameters. It is therefore desirable to develop effective methodology for the synthesis of such low molecular weight,

functional heterocycles bearing appropriate pharmacophoric features.[7] Advances in parallel,[8] combinatorial,[9-11] rapid analogue,[12] privileged structure[13-17] and diversity oriented[18-21] synthesis techniques require methodology for the generation of maximum structural diversity from readily available core scaffolds. It is also necessary for methodology to be regio- and stereo-selective, versatile, short and high yielding to allow the rapid synthesis of many analogues for bioassay.

However, the analogue synthesis of many poly-functionalised heterocyclic systems is hampered by the low reactivity and regioselectivity of such systems;[22] for example, the synthesis of highly substituted pyridine derivatives from pyridine itself in a regioselective manner is difficult, and syntheses giving access to polysubstituted pyridines for use as building blocks are highly desirable.[23-31]

Bicyclic [6,6] fused ring systems of the type shown in Fig. 1.1a can be found as the core structural unit in a wide range of biologically active molecules.[1, 2, 32] For this reason the synthesis of such compounds has been the focus of a number of publications over recent decades.



X = NH, NR, O, S
R_1 - R_3 = Cl, Br, F, NR_2, OR, SR, alkyl etc.

Fig. 1.1a bicyclic [6,6] fused ring core scaffolds of many biologically active molecules

This section provides a brief review to illustrate methods most often used to synthesise compounds of this type.

Most conventional syntheses of bicyclic [6,6] fused ring systems are concerned with either the reaction of a 1,2-dielectrophile with an aromatic 1,2-dinucleophile (Fig. 1.1b),

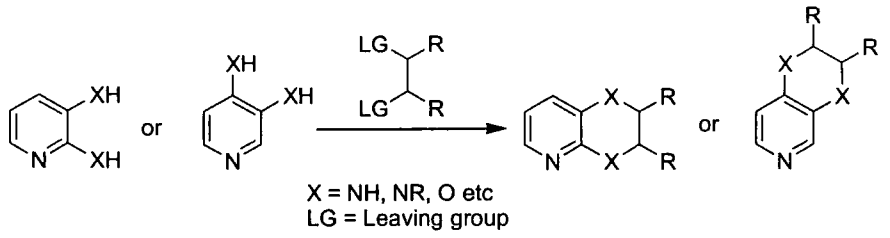


Fig. 1.1b Ring forming reaction of 1,2-dielectrophile with aromatic 1,2-dinucleophile

the reaction of an aromatic 1,2-dielectrophile with a 1,2-dinucleophile (Fig. 1.1c),

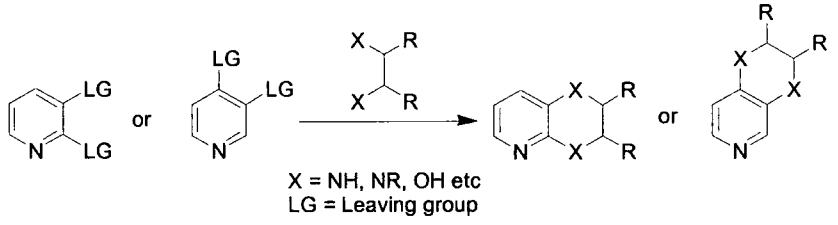


Fig. 1.1c Ring forming reaction of aromatic 1,2-dielectrophile with 1,2-dinucleophile

or the reaction of an aromatic component with a second compound, each containing a nucleophilic and electrophilic group (Fig. 1.1d).

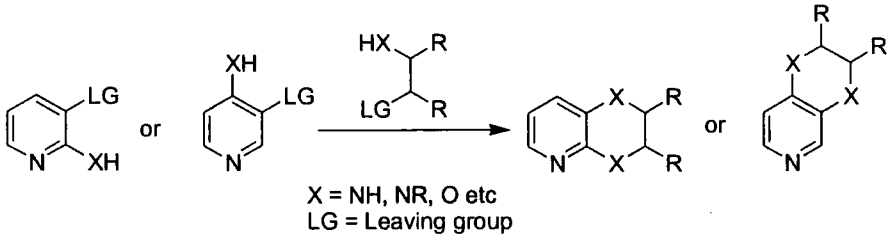


Fig. 1.1d Ring forming reactions of bifunctional aromatic and aliphatic components

1.1.1) Ring Forming Reactions of 1,2-Dielectrophiles with Aromatic 1,2-Dinucleophiles

There are many reports of ring forming reactions involving aromatic 1,2-dinucleophiles, with a selection shown here to illustrate the principles involved. Table 1.1.1a shows a representative set of reactions.

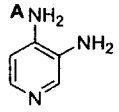
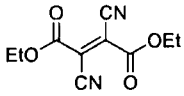
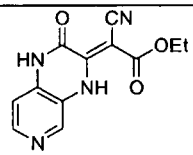
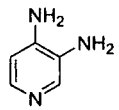
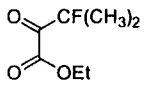
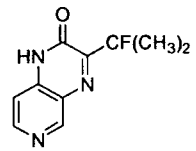
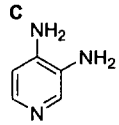
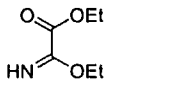
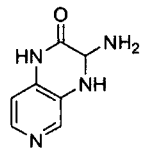
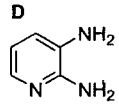
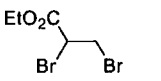
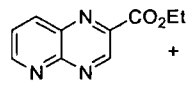
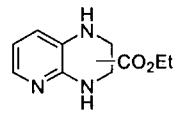
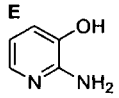
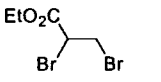
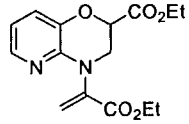
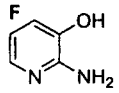
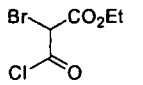
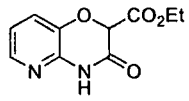
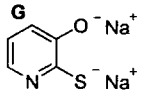
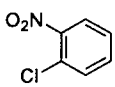
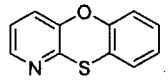
1,2-Dinucleophile	1,2-Dielectrophile	Conditions	Product(s)
A 		CH_3CN	
B 		Ethanol	
C 		Ethanol	
D 		K_2CO_3, DMF	 +  2-CO_2Et (trace) 3-CO_2Et (10%)
E 		K_2CO_3, DMF	
F 		1) Et_3N, THF 2) K_2CO_3, acetone	
G 		DMF reflux	

Table 1.1.1a Ring forming reactions of aromatic 1,2-dinucleophiles with 1,2-dielectrophiles[2, 32-36]

It can be seen from the table that a range of different dinucleophiles can be used both with symmetrical and unsymmetrical dielectrophiles to provide access to numerous [6,6] fused ring systems possessing known or potential biological activity. Reactions A, B and C can also be carried out using 2,3-diaminopyridine as the aromatic starting material. When unsymmetrical dielectrophiles are used (for example reactions C, F and G) reactions can be highly or completely chemospecific provided the two electron rich centres differ sufficiently in nucleophilicity.

1.1.2) Ring Forming Reactions of Aromatic 1,2-Dielectrophiles with 1,2-Dinucleophiles

Again there are many reports of ring forming reactions involving aromatic 1,2-dielectrophiles, and only a selection are shown in Table 1.1.2a.

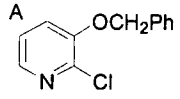
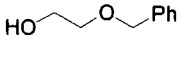
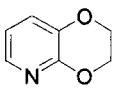
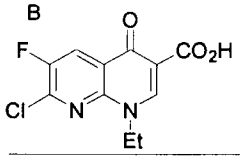
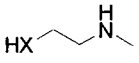
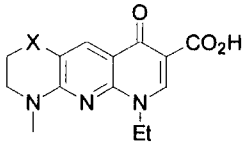
1,2-Dielectrophile	1,2-Dinucleophile	Conditions	Product(s)
A 		1) NaH, DMF 2) 10% Pd/C, H_2, MeOH 3) DIAD, PPh_3, THF	
B 	 X = NMe, O	DMF 100°C	

Table 1.1.2a Ring forming reactions of aromatic 1,2-dielectrophiles with 1,2-dinucleophiles[37, 38]

Reaction A gave the desired product in an overall yield of 69% with the utilisation of a Mitsunobu reaction for the cyclisation step and piperazine substituents were added to the product according to Fig. 1.1.2a to give a range of substituted compounds.

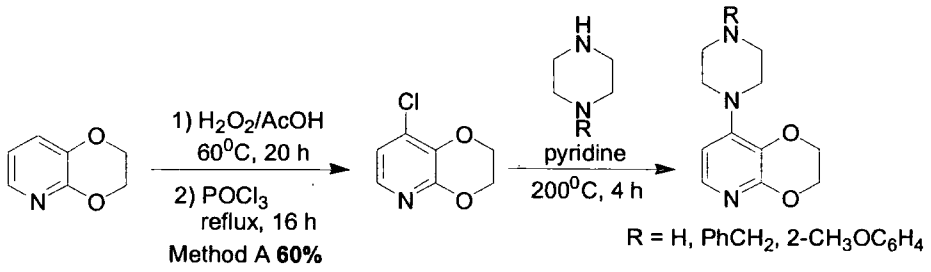


Fig. 1.1.2a Addition of piperazine substituents to 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine

Ring forming reactions of highly fluorinated aromatic compounds with binucleophiles can also be discussed in this section, however, as this topic is directly relevant to the research detailed in this thesis a thorough review of the material can be found in Section 1.5.

1.1.3) Ring Forming Reactions of Bifunctional Aromatic and Aliphatic Components

Examples of reactions of this type are less widespread with three examples outlined here. Several aza analogues of the 2,3-dihydro-1,4-benzodioxin core substituted with a bromomethyl group in the 1,4-dioxane ring, required for a drug discovery program at Johnson & Johnson, were synthesised according to the following reaction schemes (Fig. 1.1.3a).[39]

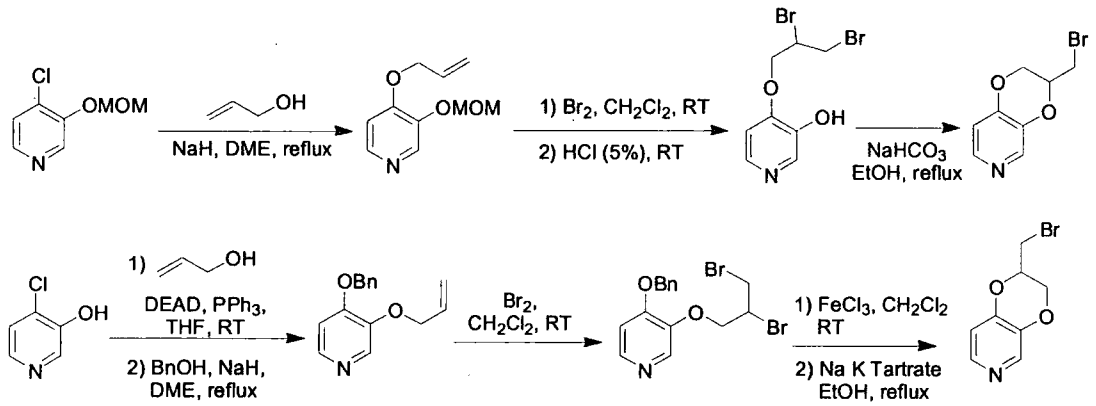


Fig. 1.1.3a Synthesis of aza analogues of 2,3-dihydro-1,4-benzodioxin core

The cyclisation step in the above reactions was carried out in the presence of a weak base, and analogues containing two nitrogen atoms in the aromatic ring were subsequently prepared.

Related compounds have been synthesised by Guillaumet *et al.*[40] (Fig. 1.1.3b).

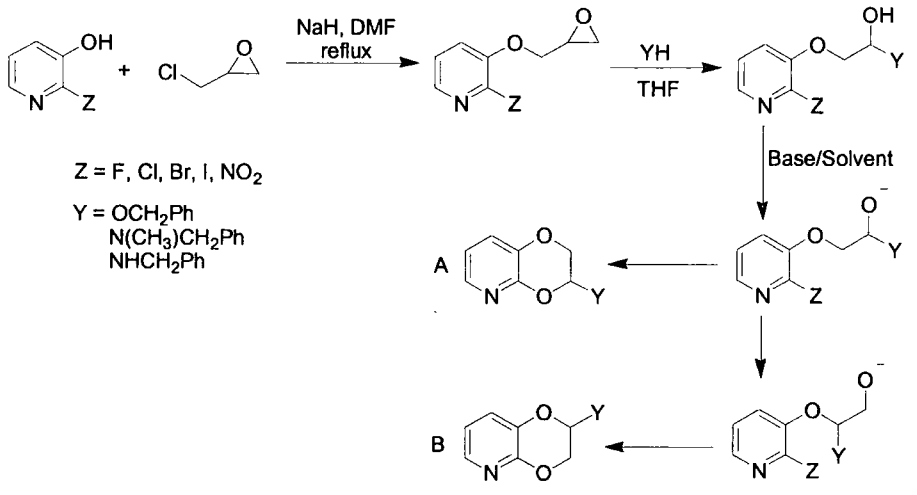


Fig. 1.1.3b Synthesis of functionalised 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine

The formation of isomer B is attributed to a Smiles rearrangement which is facilitated by electron withdrawing groups attached to the aromatic ring, and when Z was a nitro group, increased yields of the rearranged product B were observed. The choice of base and solvent also affects the ratio of isomers A to B, less of the rearranged product B was observed when sodium hydride and dimethoxyethane were used compared with potassium *tert*-butoxide in butanol.

Pyrido[4,3-*b*][1,4]thiazinones can also be synthesised using bifunctional aromatic and aliphatic components (Fig. 1.1.3c).[41]

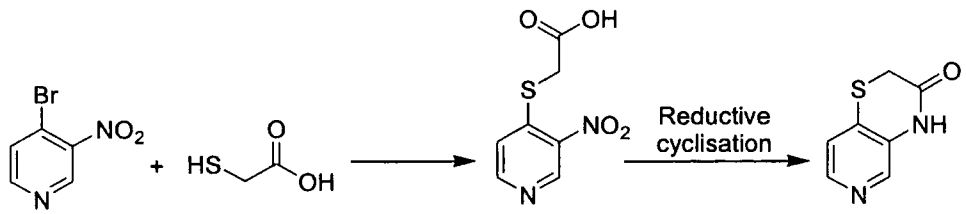


Fig. 1.1.3c Synthesis of pyrido[4,3-*b*][1,4]thiazines from 4-bromo-3-nitropyridine

1.2) APPLICATIONS OF BICYCLIC [6,6] FUSED RING SYSTEMS

Pharmaceuticals based upon bicyclic [6,6] fused ring systems are widely reported in the literature. Such compounds have been used for the treatment of dyspepsia[42] and as folic acid antagonists which may act as potential anti-cancer drugs.[43]

1.2.1) Folic Acid Antagonists

Two potential folic acid antagonists which are based upon a bicyclic [6,6] fused ring system are shown in Fig. 1.2.1a.

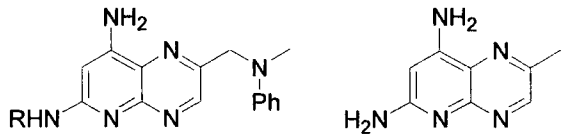


Fig. 1.2.1a Potential folic acid antagonists

Folic acid is a B-vitamin which the body uses to build cells. However, in cancer patients it can stimulate tumour growth. It is thought that molecules such as those shown above would bind to enzymes involved in this pathway of tumour growth and thus slow down the process.

1.2.2) Anti-Tumour Agents

It is known that polycyclic nitrogen containing heteroaromatics form the basis of numerous DNA intercalating drugs,[44] and specifically, the molecules such as those shown below in Fig. 1.2.2a have exhibited *in vitro* evidence of inhibition of cancerous cell growth which is promising for future anti-tumour agents.

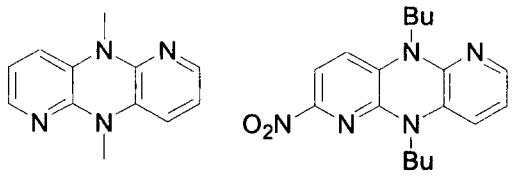


Fig. 1.2.2a Future anti-tumour agents?

Similarly, a separate class of polycyclic nitrogen containing heteroaromatics has been shown to cause regression in cancerous tumours (Fig. 1.2.2b)[45] whilst related molecules have also shown activity against certain strains of tuberculosis.[46]

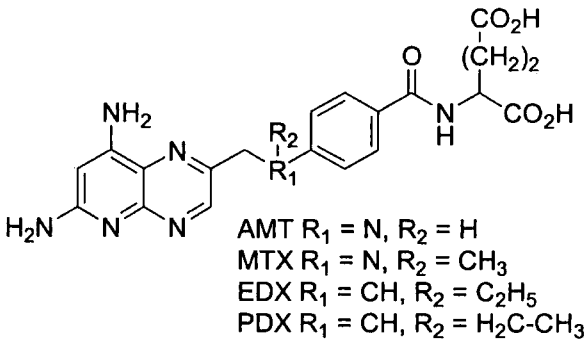


Fig. 1.2.2b Analogues of 10-deazaaminopterin exhibiting curative effects against human tumour xenografts

Polycyclic nitrogen containing heteroaromatics have been reported to act against diseases such as epilepsy, strokes and Alzheimer's disease,[47] and are proving attractive as potential antimalarial agents.[48]

1.2.3) Selective Glycine Antagonists and Antimalarial Agents

Two pyrido[2,3-*b*]pyrazine molecules that act as selective antagonists for glycine are shown in Fig. 1.2.3a. Glycine is known to stimulate the N-methyl-D-aspartate (NMDA) receptor in the brain and overactivation of this receptor has been implicated in such neurodegenerative diseases as epilepsy, stroke and Alzheimer's. Consequently, if the glycine site is targeted by an antagonist, then overactivation may be avoided.

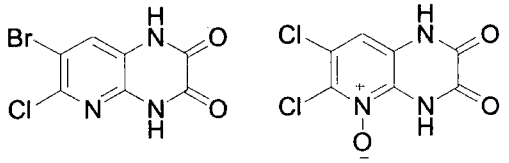


Fig. 1.2.3a Analogues of pyrido[2,3-*b*]pyrazine and pyrido[2,3-*b*]pyrazine-N-oxide as selective glycine antagonists

The synthesis of these analogues is shown in Fig. 1.2.3b.[47]

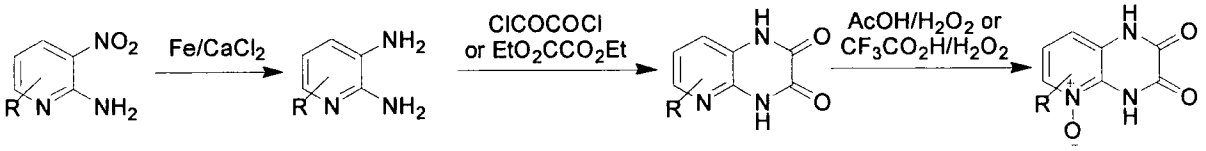


Fig. 1.2.3b Synthesis of selective glycine antagonists

Fig. 1.2.3c shows a particular compound that may be an effective antimalarial agent.[48]

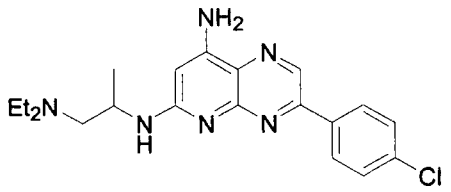


Fig. 1.2.3c 8-amino-3-(*p*-chlorophenyl)-6-[[4-diethylamino)-1-methylbutyl]amino]pyrido[2,3-*b*]pyrazine as a potential antimalarial agent

1.2.4) Anti-depressants

One class of compounds that has undergone significant investigation for anti-depressant activity is shown in Fig. 1.2.4a. They are known to act as antagonists for the production of a hormone which is secreted during times of stress.[49] If a molecule can act as an antagonist for the production of this hormone then it could be used as an anti-depressant.

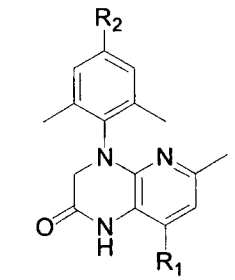


Fig. 1.2.4a Core structure of molecules investigated as anti-depressants

1.2.5) Treatment of Inflammation and Autoimmune Diseases

Autoimmune diseases such as rheumatism, asthma and psoriasis can be treated by drugs based on the following core structure (Fig. 1.2.5a).[50]

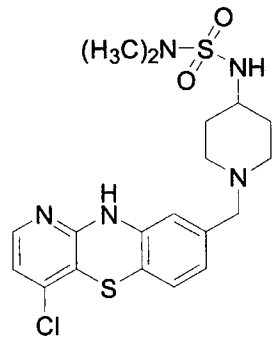


Fig. 1.2.5a Pyrido-thiazine analogue for the treatment of auto-immune diseases

1.2.6) Pharmaceuticals based on a 10H-Benzo[*b*]pyrido[2,3-e][1,4]thiazine Core

Several commercial pharmaceuticals which are related to a 10H-benzo[*b*]pyrido[2,3-e][1,4]thiazine exist, some of which are shown in Fig. 1.2.6a.

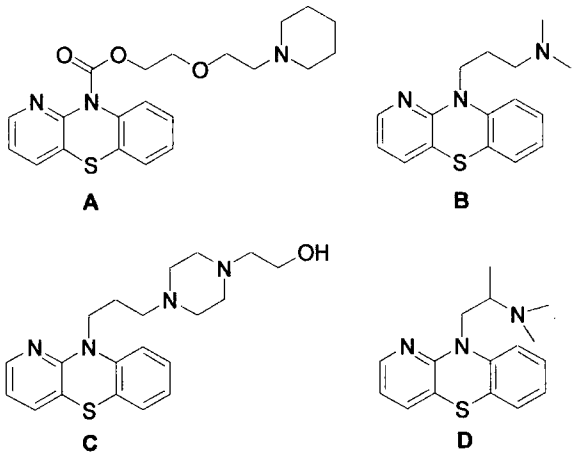


Fig. 1.2.6a Commercial pharmaceuticals based on a 10H-benzo[*b*]pyrido[2,3-e][1,4]thiazine core

Compound **A** is used as an antitussive agent which prevents or relieves coughing,[51] **B** is an antipsychotic,[52] **C** is an antiemetic agent which prevents or relieves nausea or vomiting[53] and **D** is an antihistamine.[52] The syntheses of compounds **B** and **D** are shown in Fig. 1.2.6b.

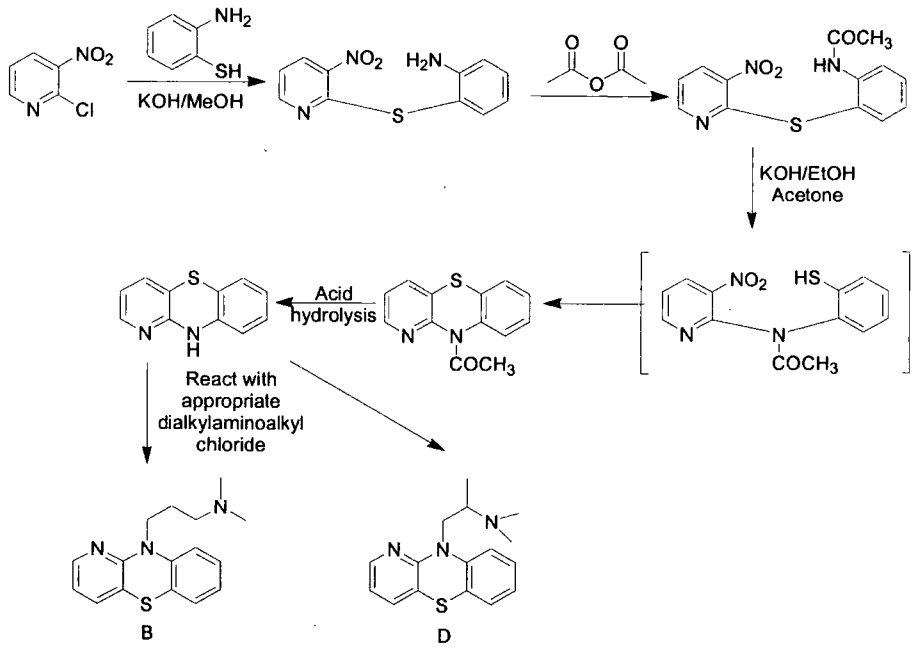


Fig. 1.2.6b Reaction scheme to show the formation of compounds **B** and **D**

1.3) ORGANOFLUORINE CHEMISTRY

Before we move on to discuss the ring forming reactions of highly fluorinated aromatic compounds it is necessary to introduce some general organofluorine chemistry along with a discussion of the synthesis and reactivity of such compounds.

Organic molecules found in nature are composed mainly of carbon, hydrogen, nitrogen and oxygen atoms, with very few examples of naturally occurring molecules that contain fluorine. In fact, the existence of molecules containing carbon-fluorine bonds is almost entirely due to human efforts, driven by the fact that the replacement of one or more C-H bonds by a C-F bond can dramatically change the physical, chemical and biological properties of a compound. For example, acetic acid is household vinegar but the

introduction of one fluorine atom gives fluoro-acetic acid which is highly toxic. The presence of fluorine can also impart different bioactivity or reactivity to a molecule,[54] and it is the unique characteristics of fluorine and its bonds to carbon that are responsible for these changes. The most important properties of fluorine atoms are listed below.

1) Fluorine is the most electronegative element,[55] which means that it can attract electrons present in a chemical bond towards itself, thereby completely changing the electronic environment and affecting the chemical reactivity of an organic molecule. For example, pentafluoropyridine is extremely non-basic and requires super acids for protonation of the ring nitrogen to occur[56] compared to pyridine which is a relatively strong base.

2) A carbon-fluorine bond is the strongest single bond to carbon that exists, so some highly fluorinated systems can be chemically inert and thermally stable, for example tetrafluoromethane only decomposes at temperatures greater than 2000°C.[57]

3) A fluorine atom possesses three pairs of negatively charged non-bonding electrons in its outer shell. This cloud of non-bonding electrons surrounding each fluorine atom can, in highly fluorinated systems such as poly(tetrafluoroethylene) (PTFE), be regarded as a protective sheath shielding the carbon backbone from chemical attack, providing many highly fluorinated systems with high thermal and chemical stability.[58]

4) Fluorine and hydrogen have van der Waals radii of 1.47 Å and 1.20 Å respectively,[59] and this means that fluorine can take the place of hydrogen in virtually every kind of organic molecule, thereby altering the chemical properties of the molecule without greatly changing

the geometry of the system.[60] There is also evidence to suggest that fluorine can act as a hydroxyl group mimic.[61, 62]

Today, many fluorinated products have found a wide range of uses in society; from pharmaceuticals (e.g. Prozac®), agrochemicals, anaesthetics and refrigerants; to non-stick coatings (e.g. Teflon®) and materials for the aerospace industry.[58]

1.4) SYNTHESIS OF HIGHLY FLUORINATED AROMATIC AND HETEROAROMATIC COMPOUNDS

The following sections are concerned with the synthesis and subsequent chemistry of highly fluorinated aromatic and heteroaromatic systems, with particular emphasis on pentafluoropyridine (PFP), the reactions of which form the basis of the experimental parts of this thesis. The first serious study of the chemistry of hexafluorobenzene began in 1956[63] and was the start of an exploration of a new area of chemistry, with fluorine as the predominant substituent in many types of aromatic and heteroaromatic systems.

The most important methods for the synthesis of highly fluorinated aromatic and heteroaromatic compounds are;

- Saturation-rearomatisation by defluorination
- Direct replacement of hydrogen by fluorine
- Direct replacement of chlorine by fluorine

The final method, direct replacement of chlorine by fluorine, produces far superior yields than the other two methods.

1.4.1.) Saturation-rearomatisation by Defluorination

Pentafluoropyridine was obtained for the first time by the electrochemical fluorination of pyridine followed by defluorination of perfluoropiperidine over iron (Fig. 1.4.1.a).[64, 65]

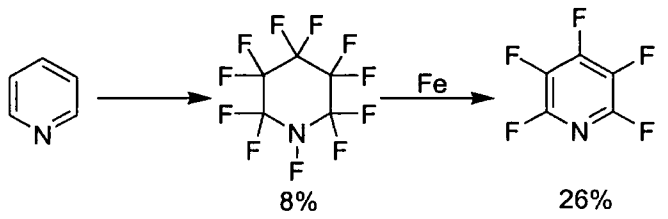


Fig. 1.4.1a Reaction scheme for the synthesis of PFP via saturation-rearomatisation by defluorination

1.4.2) Direct Replacement of Hydrogen by Fluorine

Direct replacement of all the hydrogen atoms in pyridine by fluorine atoms was achieved by the reaction of pyridine with $CsCoF_4$ at 350°C, again in low yield (15%).[66] Other products formed were undecafluoropiperidine, partially fluorinated pyridines and some acyclic fluorocarbons. The proposed mechanism for the reaction is outlined in Fig. 1.4.2a.

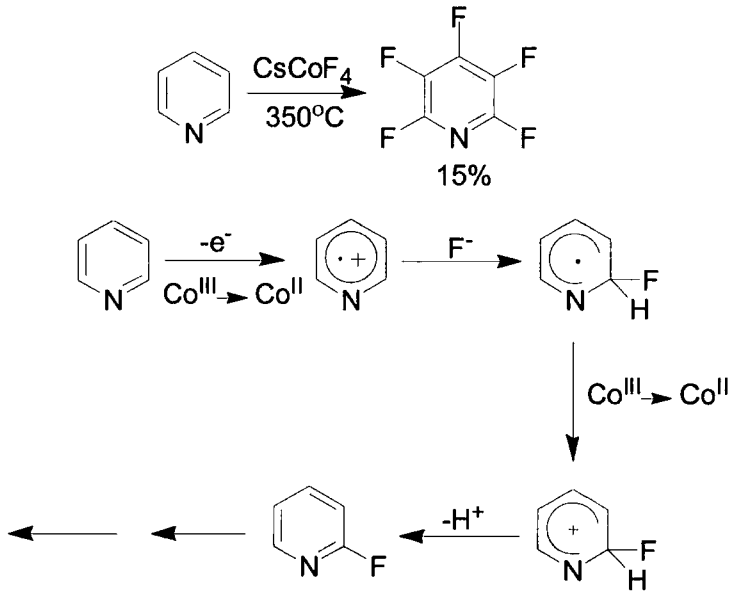


Fig. 1.4.2a Proposed mechanism for the perfluorination of pyridine

1.4.3) Direct Replacement of Chlorine by Fluorine

The third method to be discussed is the standard method by which perfluorinated nitrogen containing heterocycles and other aromatics are synthesised today. It was previously reported that chlorine in polychlorobenzenes could be replaced by fluorine using potassium fluoride via a nucleophilic aromatic substitution process in polar solvents like sulfolane.[67] However, it was found that without solvent, at higher temperatures, better yields of PFP could be produced, again using potassium fluoride as the source of fluoride ion. This method gives the best yields of PFP which are in the region of 68%[68] (Fig. 1.4.3a).

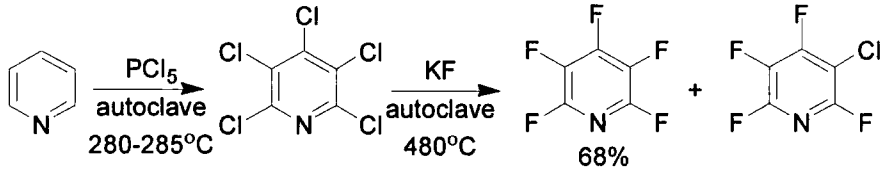


Fig. 1.4.3a Reaction scheme for the synthesis of PFP from pyridine via perchloropyridine

This halogen exchange process has also shown some success for perfluorinating nitrogen heterocycles containing functional groups, for example, 2-cyanotetrafluoropyridine can be reacted with potassium fluoride to give 2-cyanotetrafluoropyridine in a 75% yield.[69]

1.5) REACTIVITY OF HIGHLY FLUORINATED AROMATIC COMPOUNDS

When experiments began to assess the reactivity of hexafluorobenzene, it was found that the compound was relatively unreactive towards electrophiles which, is of course, the opposite trend to that observed for hydrocarbon benzenoid compounds. It was soon discovered that perfluoroaromatic compounds readily underwent nucleophilic substitution reactions due to the presence of the fluorine atoms withdrawing electron density from the

ring and leaving it susceptible to attack by nucleophiles. Consequently, the term 'mirror-image' chemistry was applied to the reactions of such perfluoroaromatic species.

1.5.1) Nucleophilic Aromatic Substitution in Highly Fluorinated Aromatic Compounds

The displacement of fluoride ion from a highly fluorinated system proceeds through a two step mechanism in which the first step is rate limiting (Fig. 1.5.1a).[70]

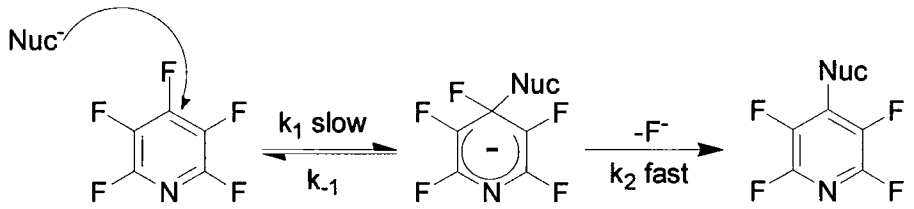


Fig. 1.5.1a Mechanism for nucleophilic aromatic substitution of PFP

A nucleophile attacks the aromatic ring to form a negatively charged Meisenheimer complex which then loses fluoride ion to give the substituted product. Evidence for the formation of such a Meisenheimer complex comes from the reaction of trifluoro-*s*-triazine with cesium fluoride in tetraglyme (Fig. 1.5.1b). The Meisenheimer complex formed in this case is stable at room temperature and can be observed by ^{19}F NMR.[71]

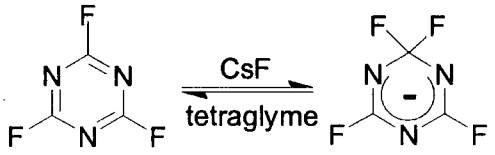
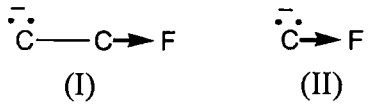


Fig. 1.5.1b Reaction of trifluoro-*s*-triazine with cesium fluoride to form a room temperature stable Meisenheimer complex

Kinetic studies of nucleophilic substitution reactions of various polyfluorobenzene derivatives have shown that fluorine atoms *ortho* and *meta* to the site of nucleophilic attack

are activating when compared to a hydrogen atom at the same position, whereas fluorine atoms *para* to the site of nucleophilic attack are deactivating.[72, 73] To explain these results it is necessary to consider the effects of fluorine on carbanion stability. In situation (I) shown in Fig. 1.5.1c, fluorine is strongly carbanion stabilising due to the withdrawal of electron density from the carbanion centre through the σ bonds, Iσ effects. However, in situation (II) there are two opposing effects to consider,



(I) (II)

Fig. 1.5.1c Representation of fluorine ortho to and directly bonded to a carbanion site

the Iσ effects mentioned above, and Iπ effects which arise from the repulsion between the non-bonding electron pairs at fluorine and the carbanion centre. Which effect dominates is determined by the geometry of the system, and it is found that Iπ effects are greater for a planar sp^2 hybridised carbanion than for a tetrahedral sp^3 hybridised carbanion (Fig. 1.5.1d).

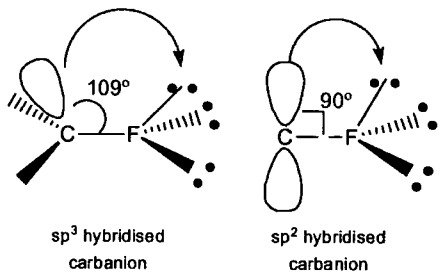


Fig. 1.5.1d Representation of the interactions between sp^3 and sp^2 hybridised carbanions and an adjacent fluorine atom

Overall, when fluorine is adjacent to an sp^3 hybridised carbanion it is stabilising, but when it is adjacent to an sp^2 hybridised carbanion it is destabilising.

So, in the case when a fluorine atom is *para* to the site of nucleophilic aromatic substitution, delocalisation of charge in the Meisenheimer transition state to this position would be destabilising (Fig. 1.5.1e), hence *para* fluorine atoms are deactivating.

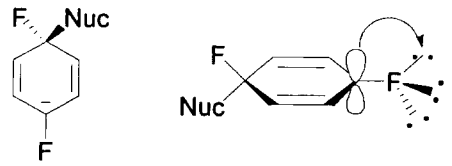


Fig. 1.5.1e Destabilising influence of fluorine atom *para* to site of nucleophilic attack

It would be expected that this would also be the case for a fluorine atom *ortho* to the site of nucleophilic attack, however, this is not the case due to the large activating effect of *ortho* fluorines in the initial state of the reaction. *Ortho* fluorine atoms can withdraw electron density from the adjacent C-F bond under attack making it more reactive towards nucleophiles, and this effect outweighs any Iπ repulsion observed in the transition state. Some studies suggest that the resonance canonical where the negative charge is delocalised onto the *para* site is more important than the canonical in which charge is delocalised to the *ortho* position meaning that the destabilising influence of *para* fluorine atoms is slightly enhanced.[74, 75] It is easy to see why *meta* fluorine atoms will be stabilising by considering the Meisenheimer complex formed in the reaction; the negative charge is delocalised to sites adjacent to a C-F bond which is stabilising due to Iσ effects (Fig. 1.5.1f).

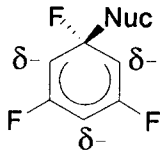


Fig. 1.5.1f Stabilising effect of fluorine atoms *meta* to the site of attack in nucleophilic aromatic substitution reactions

Based on the above arguments, it can be seen that the orientation of substitution in polyfluorobenzene derivatives is governed by the necessity to have a maximum number of activating fluorine atoms (*ortho* and *meta*) and a minimum number of *para* fluorines.

1.5.2) Nucleophilic Aromatic Substitution in Pentafluoropyridine

The presence of the ring nitrogen in pentafluoropyridine has the effect of lowering the LUMO energy of the molecule making it approximately 10^3 times more reactive towards nucleophilic aromatic substitution than hexafluorobenzene.[76] Nucleophilic aromatic substitution is highly selective, with the order of activation towards attack being:

$$4 > 2 > 3$$

with few exceptions.[77, 78] The selective replacement of fluorine atoms in PFP follows from arguments discussed in the previous section along with the added influence of the ring nitrogen. The 4- and the 2-positions are most activated towards nucleophilic attack due to the stabilising influence of the ring nitrogen in the transition state (Fig. 1.5.2a).

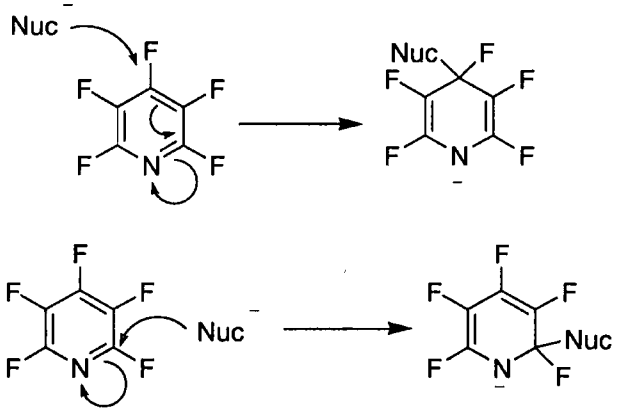


Fig. 1.5.2a Most stable resonance forms of Meisenheimer complexes formed by nucleophilic attack at the 4- and 2-positions

The 4-position has two *ortho*, two *meta* and no *para* fluorines compared with the 2-position which has one *ortho*, two *meta* and one *para* fluorine. Based on the arguments discussed in Section 1.5.1 this explains why the 4-position is favoured over the 2-position.

Many nucleophilic aromatic substitution reactions of pentafluoropyridine have been investigated and a comprehensive review by Brooke[79] is a good source of reference. Fig. 1.5.2b highlights a small number of molecules that can be synthesised by reaction of PFP with nucleophiles.

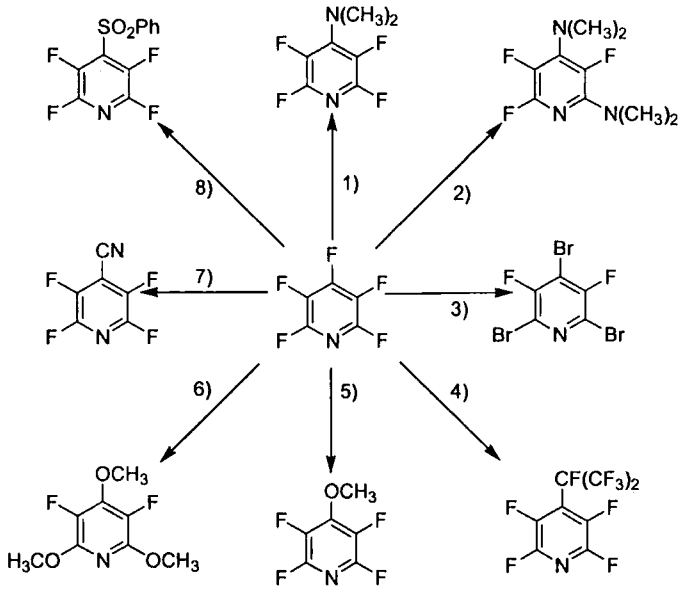


Fig 1.5.2b Nucleophilic substitutions of PFP, reagents: 1) 1 eq $NH(CH_3)_2$,[80] 2) 2 eq $NH(CH_3)_2$,[80] 3) $AlBr_3$, HBr, autoclave,[81] 4) KF, CF_2=$CFCF_3$, sulfolane,[65] 5) 1 eq NaOMe,[80] 6) 3 eq NaOMe,[80] 7) NaCN, DMF,[82] 8) $PhSO_2Na$, DMF.[83]

It can be seen that substitution at more than one position on the PFP ring can be achieved depending on the number of equivalents of nucleophile used in a reaction, and in this

manner highly functionalised PFP derivatives can be obtained such as those outlined in Fig. 1.5.2c.[84-86]

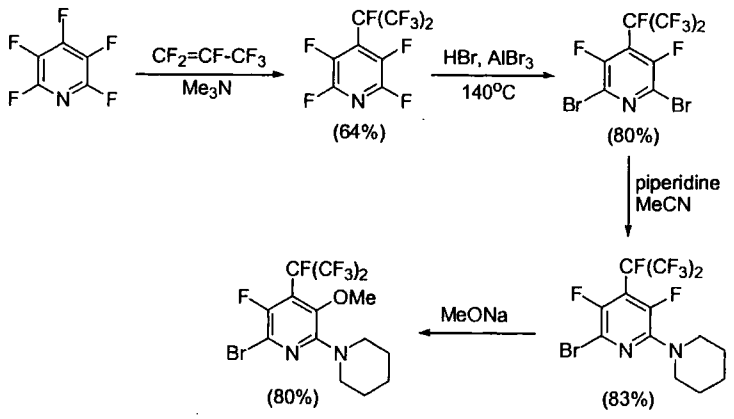


Fig. 1.5.2c Reaction scheme to show the formation of 6'-Bromo-5'-fluoro-3'-methoxy-4'-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl from PFP

1.6) REACTIONS OF PERHALOGENATED PYRIDINE DERIVATIVES WITH BINUCLEOPHILES

The previous section covered material relating to the reactions of highly fluorinated aromatic systems with nucleophiles and we now move on to discuss reactions of perfluoroaromatic systems with binucleophiles. There has been relatively little investigation into the reactions of binucleophiles with polyfluoroaromatic systems, and there are a limited number of reactions of PFP and hexafluorobenzene with binucleophiles reported in the literature.[87] Reports of the formation of fused ring systems by the reaction of perchloropyridine and 2,3,5,6-tetrachloropyridine derivatives with binucleophiles are also worth noting.[88, 89] This section is concerned with such reactions.

1.6.1) Reactions of Perchloropyridine and 2,3,5,6-Tetrachloropyridine Derivatives with Binucleophiles to Form [6,6] Fused Ring Systems

Dainter *et al.*[89] have shown that it is possible to form fused ring systems by the reaction of 2,3,5,6-tetrachloro-isonicotinonitrile with benzene-1,2-diol, 1,2-phenylenediamine and *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA), Fig. 1.6.1a.

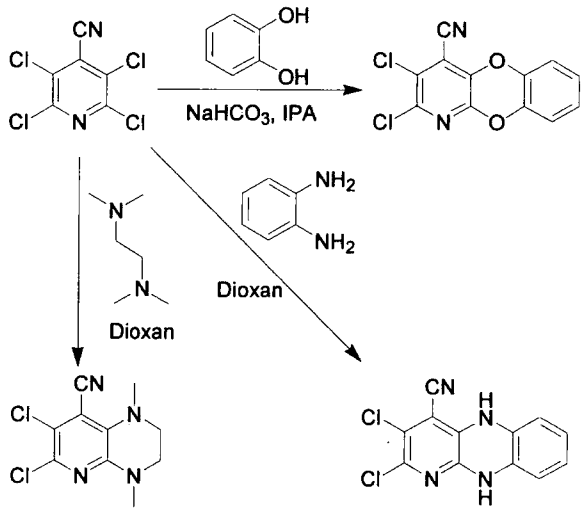


Fig. 1.6.1a Reaction of 2,3,5,6-tetrachloro-isonicotinonitrile with benzene-1,2-diol, 1,2-phenylenediamine and TMEDA

In all of the reactions shown in Fig. 1.6.1a, no uncyclised intermediate was observed making it unclear whether initial attack of the binucleophile was at the 2- or the 3-position. The preparation of fused ring heterocyclic compounds was attempted using perchloropyridine and aliphatic primary diamines as starting materials but no desired cyclised product was obtained.[88] Reactions were also attempted in dimethylformamide, dimethylaniline and in the absence of solvent without success. Fig. 1.6.1b shows the products formed by the reactions of perchloropyridine and 2,3,5,6-tetrachloropyridine with TMEDA and *N,N'*-dimethylethylenediamine.

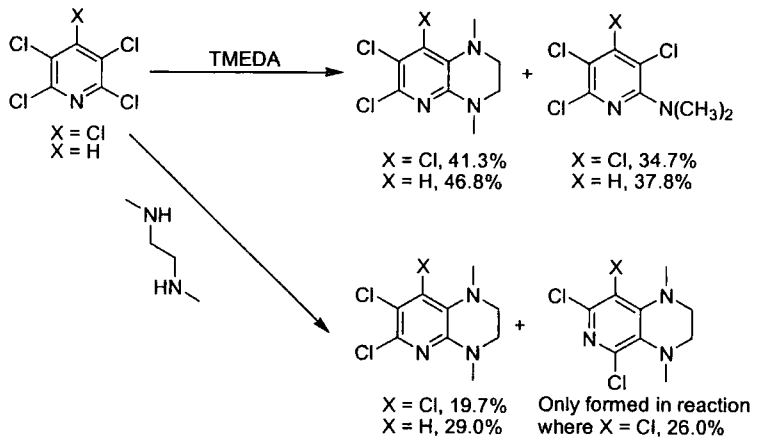


Fig. 1.6.1b Reaction of perchloropyridine and 2,3,5,6-tetrachloropyridine with TMEDA and *N,N'*-dimethylethylenediamine

When pentachloropyridine is reacted with *N,N'*-dimethylethylenediamine, initial attack occurs at the 2- and 4-positions followed by attack at the 3-position to yield a mixture of isomers. In the case of the reaction with TMEDA, it is only the less hindered 2-chlorine that is replaced to give one isomer. For the reaction of 2,3,5,6-tetrachloropyridine with both diamines, initial attack occurs at the 2-position followed by cyclisation at the 3-position. Further support for this mechanism is provided by the formation of the α-dimethylaminopyridines as by-products from the reaction of TMEDA with both pyridines. It is thought that these by-products are formed according to the following mechanism (Fig. 1.6.1c).

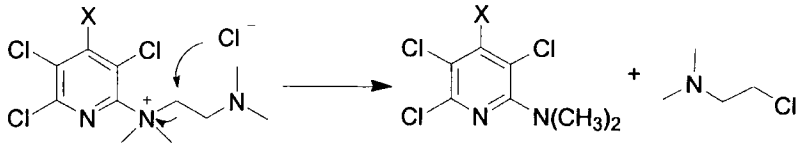


Fig. 1.6.1c Mechanism for the formation of the α-dimethylaminopyridine by-products

One point worth noting when discussing the reactions of perchloroaromatic systems is that it is difficult to prove the position of substitution on a perchloroaromatic ring. This is because ^{35}Cl and ^{37}Cl have spin quantum numbers of 3/2 which makes them less suitable for NMR than nuclei with spin quantum numbers of 1/2. ^{13}C NMR is also inadequate at providing sufficient structural information as the ring carbon atoms in perchloroaromatic compounds are in very similar environments and so the only way to categorically determine the regiochemistry of a reaction is to obtain an X-ray crystal structure of the product. This, and the mixture of products obtained,[90] has precluded the development of perchloroaromatic chemistry.

1.6.2) Reactions of Pentafluoropyridine and Perfluoro-4-isopropylpyridine with Binucleophiles to Form Macrocycles

In 1975 Wielgat and Domagala produced a paper in which PFP was reacted with several binucleophiles (Fig. 1.6.2a),[91] although the aim of their study was not to obtain cyclised products.

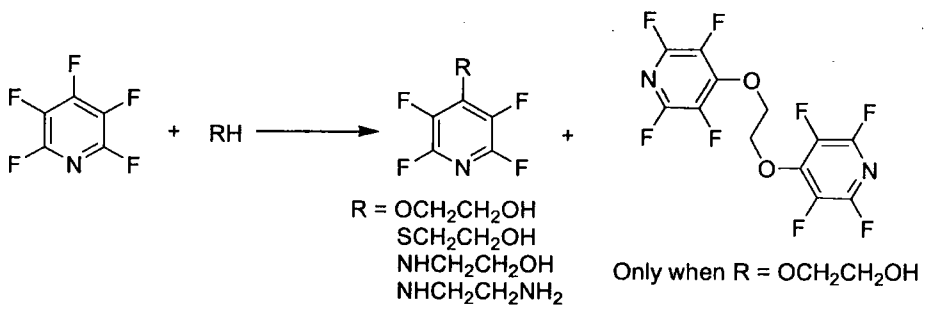


Fig 1.6.2a Reactions of PFP with selected binucleophiles

Similar work has been carried out to investigate the reactions of PFP with binucleophiles to form pyridine bridged systems which can then be reacted with other binucleophiles to form macrocycles.[92] This preliminary work has been expanded upon, and reactions of the type

shown in Fig. 1.6.2b have been carried out with a range of binucleophiles such as *N,N'*-dimethylethylenediamine and *N*-methylaminoethanol.[93-95]

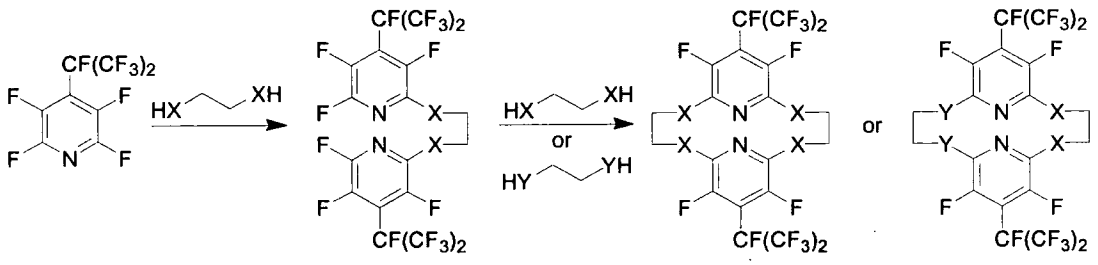


Fig. 1.6.2b Synthesis of macrocycles using perfluoro-4-isopropylpyridine and binucleophiles as starting materials

1.6.3) Reactions of Polyfluorobenzenes and Pentafluoropyridine with Binucleophiles to Form [6,6] Fused Ring Systems

As there is only a small amount of published work relating to ring forming reactions of pentafluoropyridine with binucleophiles, we can try and draw some comparisons from reactions of hexafluorobenzene with binucleophiles. Some work was carried out in this area in 1964 by Burdon *et al.*;[87] hexafluorobenzene was treated with ethylene glycol/sodium hydroxide, 2-aminoethanol, ethylenediamine and 2-mercaptoethanol to give the products shown in Fig. 1.6.3a.

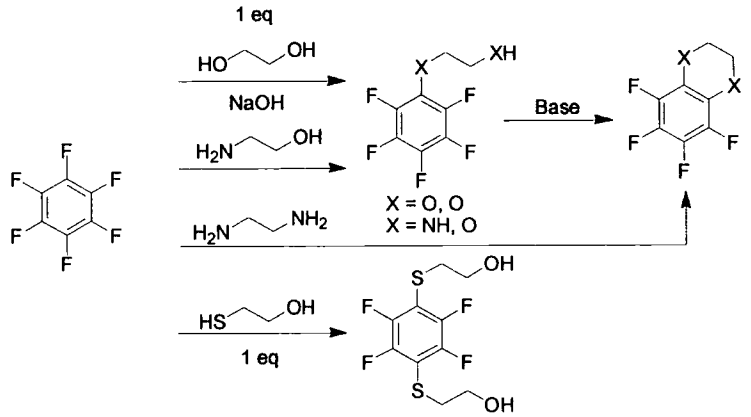


Fig. 1.6.3a Reactions of hexafluorobenzene with ethylene glycol, 2-aminoethanol, ethylenediamine and 2-mercapto-ethanol

It can be seen that it is possible to form fused ring systems in either one or two steps by reacting hexafluorobenzene with binucleophiles. In the case when the binucleophile used was 2-mercapto-ethanol (1 eq), the disubstituted product was formed exclusively indicating that the presence of the 2-hydroxyethylthio-group activates the pentafluorophenyl ring to further nucleophilic attack. When excess ethylene glycol was used the analogous disubstituted product was also formed.

Similarly, Yakobson *et al.*[96] have obtained fused ring systems utilising the initial reaction of potassium pentafluorophenoxide with 1-fluoro-2-nitrobenzene (Fig. 1.6.3b).

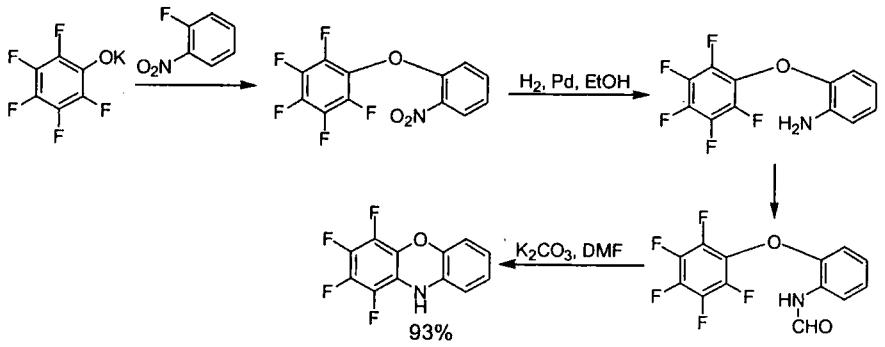


Fig. 1.6.3b Synthesis of 1,2,3,4-tetrafluorophenoxazine from potassium pentafluorophenoxide and 1-fluoro-2-nitrobenzene

When cyclisation of the *o*-(pentafluorophenoxy)aniline was attempted in the presence of potassium carbonate, a complex mixture of products was obtained so cyclisation of the formyl derivative was attempted and gave the desired fused ring product in high yield (93%).

Related reactions have also been carried out with substituted pentafluorobenzenes, and such cyclisations are thought to proceed via a Smiles' rearrangement (Fig. 1.6.3c).[97, 98] A Smiles' rearrangement can be described as an intramolecular displacement at an aromatic ring initiated by a nucleophilic centre located two or three atoms distant from the functional group which is displaced.[99]

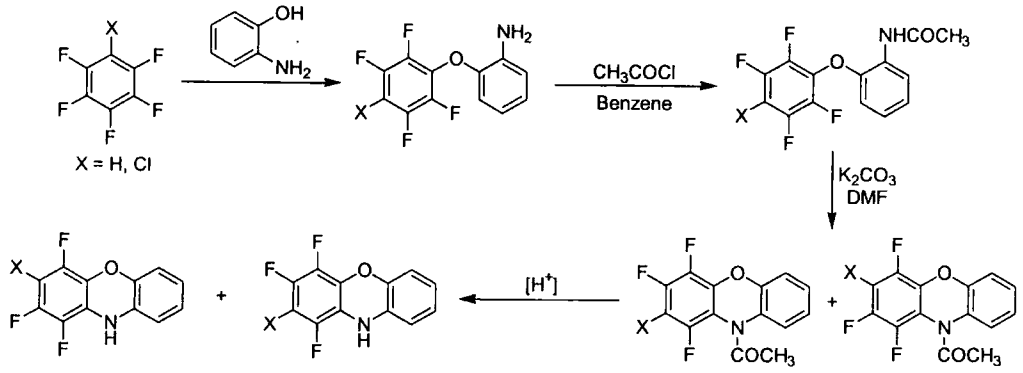


Fig. 1.6.3c Reactions of mono-substituted pentafluorobenzene derivatives with 2-aminophenol

The formation of the ether (step 1) is assisted by base, and the cyclisation step to form the phenoxazine (using K_2CO_3, DMF) is preceded by a Smiles' rearrangement, causing the change in the relative positions of the OAr and X substituents. The mechanism for this Smiles' rearrangement is shown in Fig. 1.6.3d. A sufficient degree of activation of the migrating aromatic ring is believed to be necessary for a Smiles' rearrangement to occur and the electron withdrawing fluorine atoms provide the activation in this case.[100, 101]

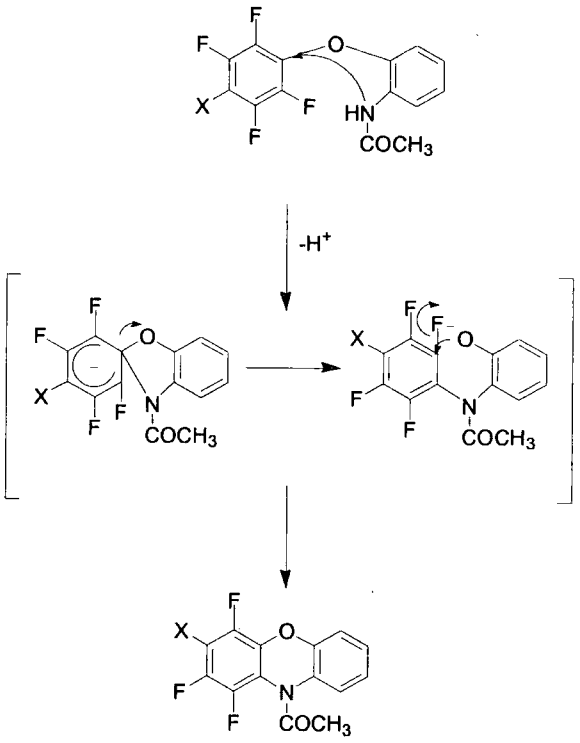


Fig. 1.6.3d Mechanism for Smiles' rearrangement

A separate study showed that the rate of cyclisation to form such phenoxazines increased with the nucleophilicity of the amino group[102] and, when cyclisation was more rapid, the rate at which the Smiles' rearrangement took place was slower. Consequently, there was a lower proportion of the phenoxazine isomer formed as a result of Smiles' rearrangement. Fig. 1.6.3e outlines the formation of the two possible isomeric products and it was found that when Y = Ac only isomer A was formed but when Y = H a mixture of isomers A and B were formed with B predominating, and when Y = CH_3 a large excess of B was obtained.

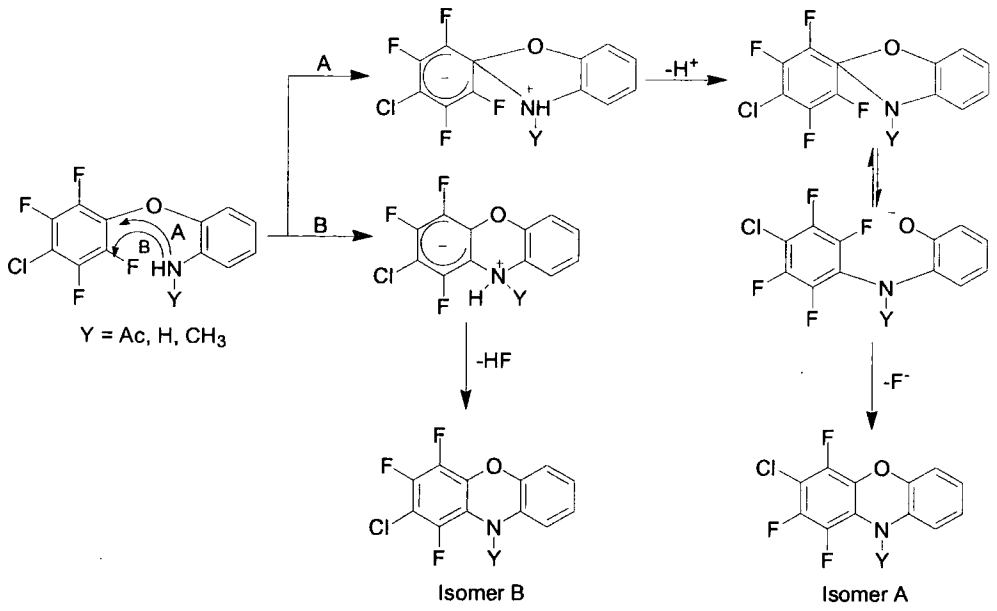


Fig. 1.6.3e Mechanism for the formation of phenoxazine compounds from intermediate ether

These results can be explained on the basis of the nucleophilicity of the NY groups. The nucleophilicity of the nitrogen atom in the NAc group is lowered due to the presence of the acyl group and therefore the cyclisation step is relatively slow, and rearrangement occurs to give exclusively isomer A. NH is more nucleophilic than NAc so the cyclisation step is more rapid, allowing for less rearrangement to occur and subsequent formation of both isomers, whilst NCH_3 is more nucleophilic still, allowing even less time for rearrangement and resulting in the formation of a greater amount of isomer B.

Similar phenoxazines have also been synthesised from pentafluoropyridine (Fig. 1.6.3f).[103-105]

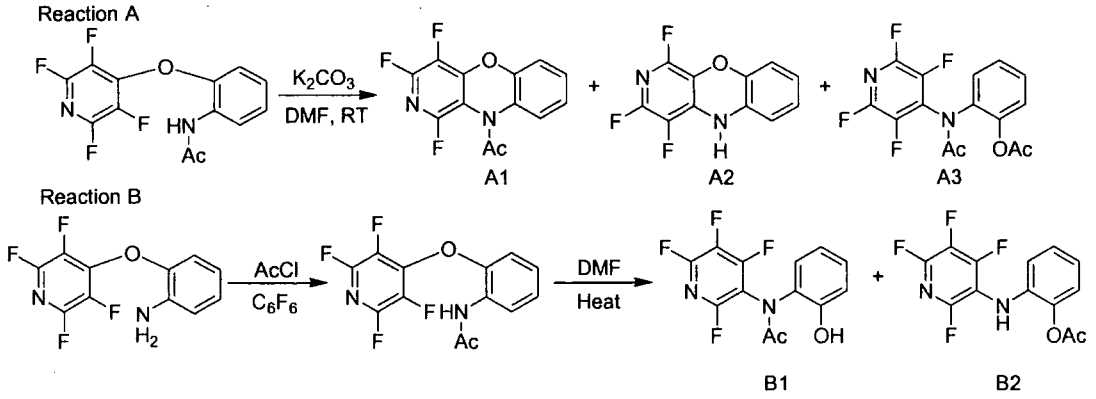


Fig. 1.6.3f Attempted cyclisation reactions of pentafluoropyridine

The initial ethers were formed by the reaction of pentafluoropyridine with the appropriate 1,2-disubstituted aminophenol in the presence of sodium hydroxide. In Reaction A, the cyclisation process is aided by potassium carbonate and the three products are formed in a ratio of roughly 1:1:1. The formation of the diacetyl derivative (A3) results from the acetylation of the intermediate 2-hydroxydiarylamine (B1) which is formed via a Smiles' rearrangement.

Reaction B does not result in the formation of any phenoxazine as there is no base present in the reaction mixture. However, the formation of the hydroxyl substituted diarylamine B1 does provide evidence for the Smiles' rearrangement which precedes cyclisation. The formation of B2 also shows that rearrangement is accompanied by migration of the acetyl group from the nitrogen to the oxygen atom, and it is assumed that this migration takes place through a cyclic structure of the type shown in Fig. 1.6.3g.

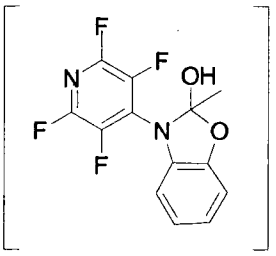
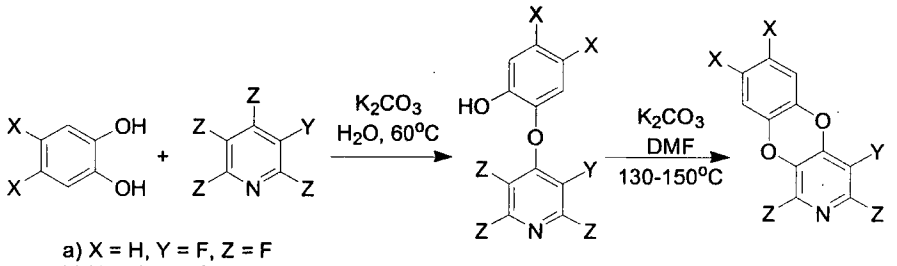


Fig. 1.6.3g Cyclic intermediate formed during the migration of an acetyl group from the diaryl amine group to the hydroxyl group of a 2-hydroxy-*N*-acetyldiarylamine

In 2001, reactions of pentafluoropyridine and their substituted derivatives with oxygen binucleophiles were investigated.[106, 107] The first study by Litvak *et al.* synthesised the following dioxins (Fig. 1.6.3h).



a) X = H, Y = F, Z = F
b) X = H, Y = Cl, Z = F
c) X = H, Y = Cl, Z = F
d) X = Cl, Y = F, Z = F
e) X = Cl, Y = Cl, Z = F
f) X = Cl, Y = Cl, Z = Cl
g) X = Br, Y = Cl, Z = F

Fig. 1.6.3h Synthesis of dioxins from pentafluoropyridine and catechol derivatives

The first step of the above reaction also resulted in the formation of appreciable amounts of pyridine bridged derivative. For this reason the reaction was carried out in two steps to remove unwanted products. To avoid unwanted side products in the second step, the substituted pentafluoropyridine derivatives were added slowly to a large volume of aprotic solvent containing anhydrous potassium carbonate.

Reactions of these tricyclic [6,6] fused ring systems were then investigated with nucleophiles (Fig. 1.6.3i).

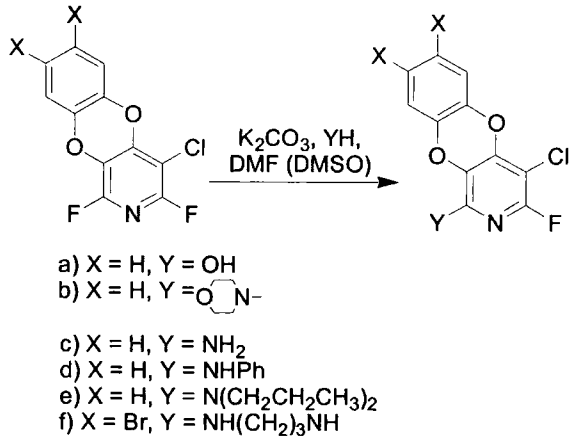


Fig. 1.6.3i Reaction of tricyclic [6,6] fused ring systems with nucleophiles

Substitution occurs at the most activated position *para* to the chlorine atom. Yields of the reactions are claimed to be between 50-95%.

Chambers *et al.* carried out similar reactions using catechols and 2,4,6-tribromo-3,5-difluoropyridine (Fig. 1.6.3j).

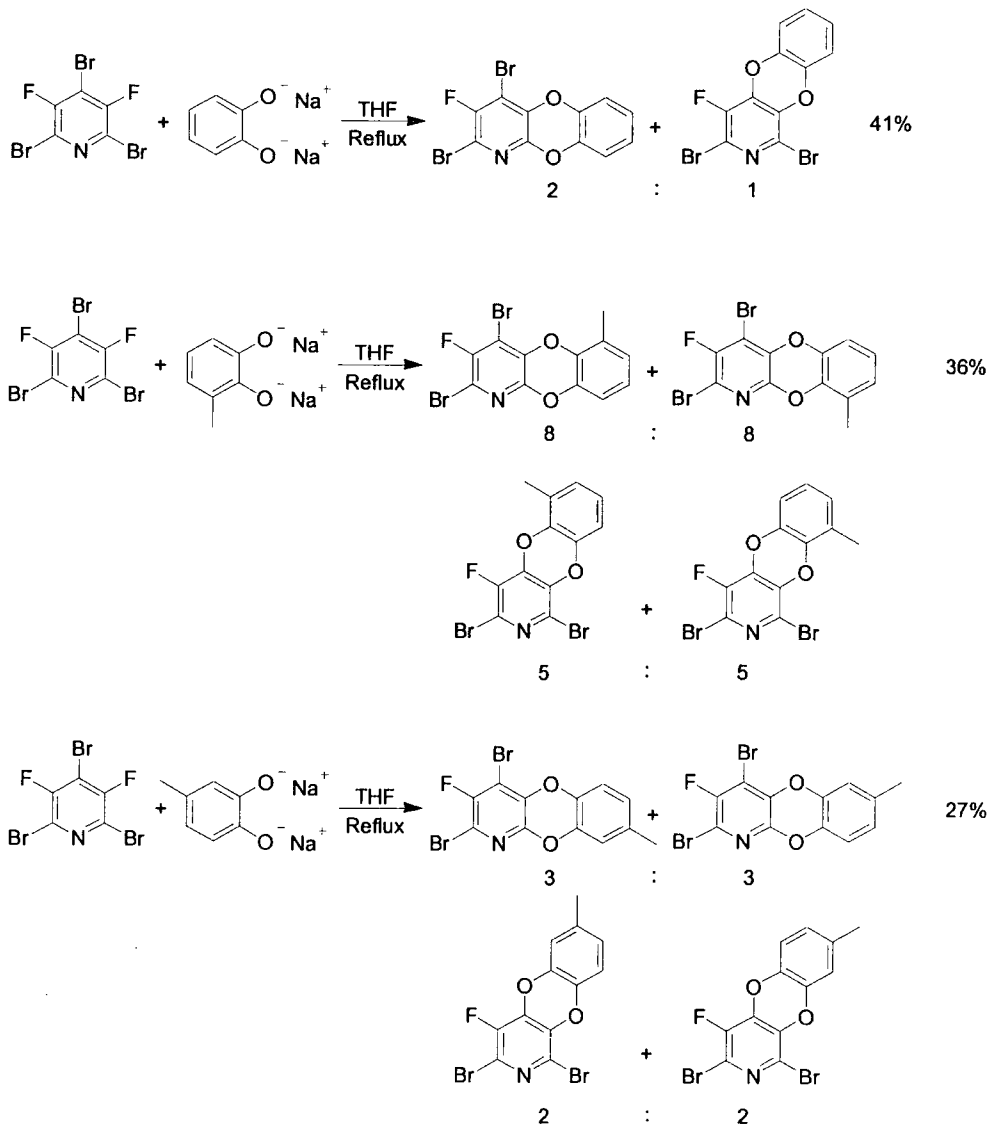


Fig. 1.6.3j Synthesis of dioxins from catechols and 2,3,6-tribromo-3,5-difluoropyridine

The binucleophile used in the above reactions contains two 'hard' oxygen atoms so it is assumed that reaction first occurs at the 3-position, displacing the 'hard' fluoride ion. It is then thought that intramolecular displacement of bromine occurs which competes favourably with intermolecular displacement of fluorine from another molecule of 2,4,6-tribromo-3,5-difluoropyridine, however, some formation of polymer probably occurs as an intractable material was also formed along with the desired product.

Intramolecular displacement of bromine at the 2-position is slightly favoured to the 4-position and it could be argued that this reflects a less crowded site at the 2-position as the directing effect of the nitrogen atom would normally favour the 4-position.

1.6.4) Formation of [5,6] Fused Ring Systems from Polyfluorobenzenes and Pentafluoropyridine

Examples of these types of reactions can be found in a review by Brooke[79] and only a few illustrative examples are discussed in this section. In 1979 Herkes reacted pentafluorophenylamine with a range of binucleophiles to give the [5,6] fused ring system shown below (Fig 1.6.4a).[108]

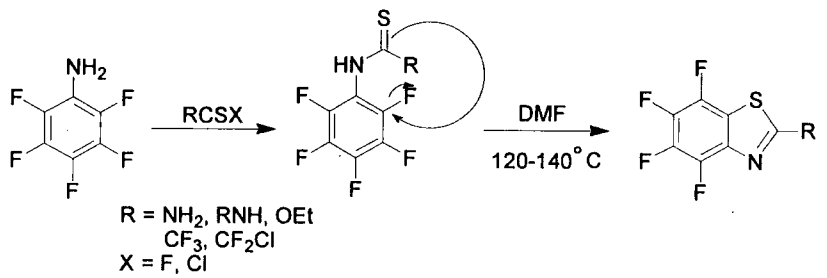


Fig. 1.6.4a Preparation of polyfluorobenzothiazoles via cyclisation of polyfluorothioanilides

Wakselman and Blazejewski have also utilised the condensation of enamines with various perfluoroarenes to give [5,6] fused ring systems (Fig. 1.6.4b).[109]

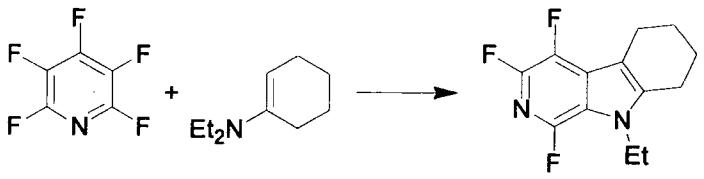


Fig. 1.6.4b Reaction of pentafluoropyridine with cyclohex-1-enyl-diethyl-amine

The reaction shown above occurred at room temperature in the absence of solvent and the same reaction failed for the perchloropyridine derivative.

This introductory chapter has focussed upon the existing methods available for the synthesis of [6,6] fused ring heteroaromatic systems and how highly halogenated starting materials have been utilised for this purpose. These fused ring systems are highly sought after as they have many applications in the pharmaceutical and life science industries. The following chapters are concerned with developing the methodology available for the synthesis of such systems by the reaction of pentafluoropyridine and related compounds with binucleophiles.

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TETRAHYDROPYRIDO[3,4-*b*]PYRAZINE SCAFFOLDS FROM PENTAFLUOROPYRIDINE

2.1) INTRODUCTION

As mentioned previously, the synthesis of highly substituted pyridine derivatives from pyridine itself in a regioselective manner is difficult, and strategies giving access to polysubstituted pyridines for use as building blocks are highly desirable.[1-9]

In contrast, perfluorinated heteroaromatic systems (e.g. PFP) are potentially excellent scaffolds[10, 11] as they are highly reactive towards nucleophilic attack and the order of monosubstitution is well established (see Section 1.5). In this chapter, we describe the use of pentafluoropyridine as a scaffold for the synthesis of a variety of [6,6] ring fused systems by utilising its reactivity towards nucleophilic substitution.

2.2) AIMS AND APPROACHES

The reaction of PFP with bifunctional nucleophiles, as outlined in Chapter 1, can provide access to fused ring systems which are otherwise difficult to synthesise. It has been demonstrated that a binucleophile will first attack the 4-position of pentafluoropyridine and cyclisation will then occur at the 3-position. The research presented in this thesis is based around the development of methodology for the synthesis of [6,6] fused ring heteroaromatic systems using a general approach which is shown in Fig. 2.2a.

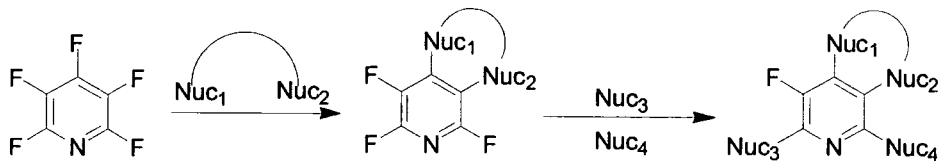


Fig. 2.2a General approach to the synthesis of fused ring heteroaromatic systems from pentafluoropyridine

The fused ring systems that can be accessed via reactions of pentafluoropyridine with binucleophiles also possess further sites, particularly those adjacent to ring nitrogen (C-2 and C-6), which are activated towards nucleophilic attack, and, as there are a huge number of bifunctional nucleophiles that could be involved in such an annelation procedure and an almost unlimited number of nucleophiles which could be used for further reaction with the fused ring core scaffold, this methodology could potentially provide access to a vast number of functionalised ring-fused heteroaromatic systems. By selecting the appropriate binucleophiles, a range of [6,6] fused ring systems could in principle be synthesised, but, equally, ring fused systems containing 5- or 7-membered rings could also be accessed by analogous strategies.

This chapter is concerned with the reactions of pentafluoropyridine with various 1,2-bifunctional nitrogen nucleophiles for the synthesis of several polyfunctional tetrahydropyrido[3,4-*b*]pyrazine scaffolds. General methodology for the synthesis of functionalised derivatives of the [6,6] fused ring system tetrahydropyrido[3,4-*b*]pyrazine remains undeveloped with only a limited number having been synthesised in low yields by multistep procedures. These syntheses have relied upon diaminopyridine[12] or chloro-aminopyridine[13] precursors, or the reduction of pyrido[3,4-*b*]pyrazine derivatives by metal hydrides.[14] An example of one such synthesis is shown in Fig. 2.2b,[12] however the starting

materials for syntheses of this nature and, particularly their functionalised derivatives, can also be difficult to obtain.

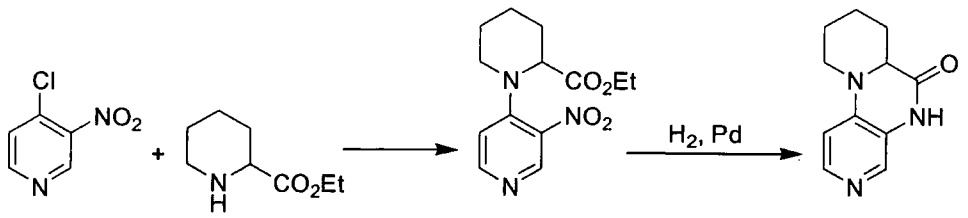


Fig. 2.2b Synthesis of pyridopyrazine derivative

This chapter also briefly describes reactions of PFP with 1,2-bifunctional nucleophiles containing nitrogen/oxygen and nitrogen/sulphur atoms.

2.3) SYNTHESIS OF TRIFLUOROPYRIDO[3,4-*b*]PYRAZINE SYSTEMS

Cyclisation reactions involving pentafluoropyridine **1** and bifunctional secondary diamines **2** were initially studied due to the relatively high nucleophilicity of these species (Table 2.3a). When **1** was reacted with *N,N'*dimethylethylenediamine **2a** in a concentrated reaction mixture, significant amounts of the pyridine bridged product **4** shown in Fig. 2.3a were formed, and, consequently, all cyclisation reactions were carried out in dilute acetonitrile solution to minimise intermolecular reactions. Reactions were also carried out in the presence of sodium hydrogen carbonate as base.

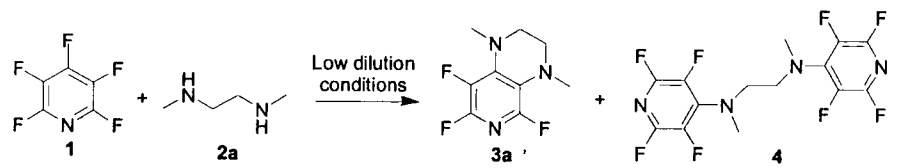


Fig. 2.3a Formation of pyridine bridged side product in concentrated reaction mixtures

The reaction of **1** and **2a** under such conditions gave the desired pyridopyrazine **3a** in excellent yield after purification of the crude product by recrystallisation from *n*-hexane. The reaction was monitored by ^{19}F NMR; the disappearance of signals attributed to the fluorine atoms at the 4- and 3-positions of **1** (-134.1 and -162.0 ppm respectively), and the appearance of signals attributed to the fluorine atoms located at the 5- 7- and 8-positions of pyridopyrazine **3a** (-85.0, -99.3, -162.6 ppm respectively) allowed the progress of the reaction to be followed easily.

It is known that microwave heating can dramatically reduce the reaction times for nucleophilic substitution reactions,[15] and the above cyclisation process could also be induced by microwave heating with a similar yield of **3a** achieved from **1** and **2a** in a much shorter reaction time.

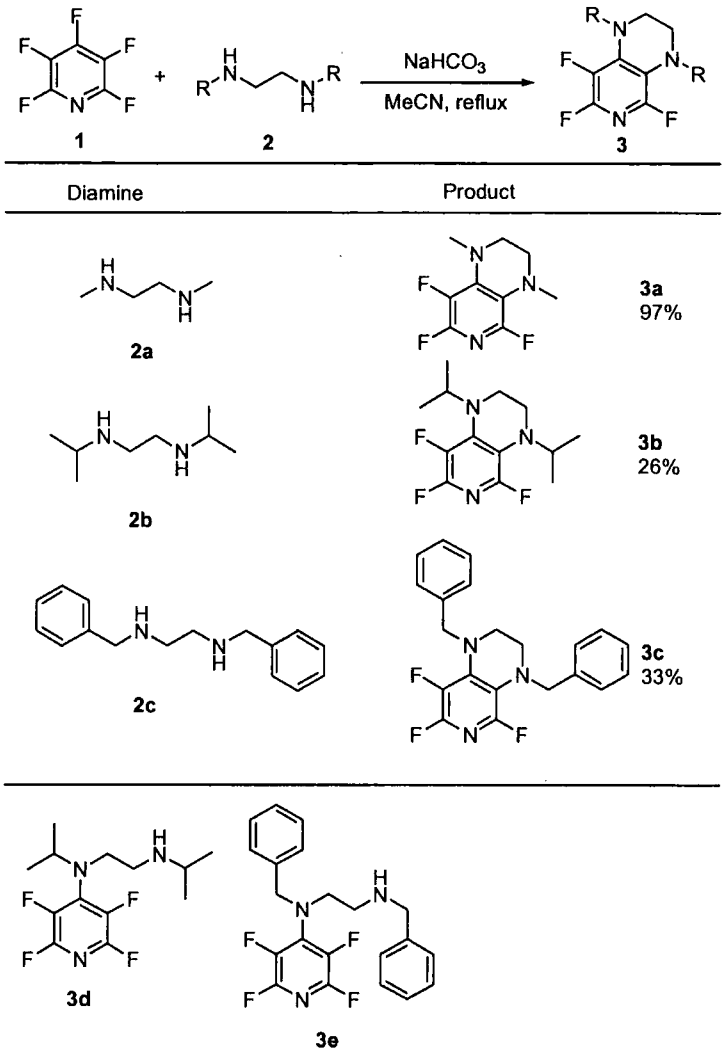


Table 2.3a Synthesis of trifluoropyrido[3,4-*b*]pyrazine systems **3**

Once it was established that this methodology was successful for the formation of the tetrahydropyrido[3,4-*b*]pyrazine system **3a**, investigations moved onto the use of alternative bifunctional secondary diamines (Table 2.3a). The related di-*iso*propyl- and dibenzyl-diamines **2b** and **2c** gave analogous cyclised products **3b** and **3c** by similar procedures, dibenzyl-diamine **2c** having been synthesised from ethylenediamine following literature procedures.[16] It was envisaged that a number of different substituents could be placed upon the phenyl rings of **2c** thus adding functionality to the core scaffolds in the same step as the cyclisation reaction. There is much greater steric hindrance around the

nucleophilic nitrogen atoms in **2b** and **2c**, and, consequently, cyclisation to give **3b** and **3c** is far slower than the corresponding synthesis of **3a**. ^{19}F NMR analysis of the reaction mixtures indicated the presence of the uncyclised intermediates **3d** and **3e** even after prolonged heating. After 5 d at reflux temperature the reactions were terminated despite the low conversions to cyclised products, but **3b** and **3c** were isolated by column chromatography, although **3d** and **3e** were not isolated. The low reported yields of **3b** and **3c** are therefore an indication of the low conversion of the cyclisation step rather than the formation of a complex mixture of products. The structures of **3a** and **3c** were confirmed by X-ray crystallography (Fig 2.3b & 2.3c).

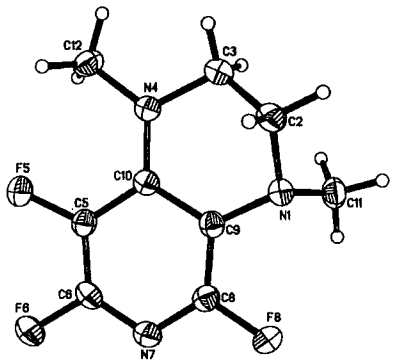


Fig. 2.3b X-Ray Molecular Structure of **3a**

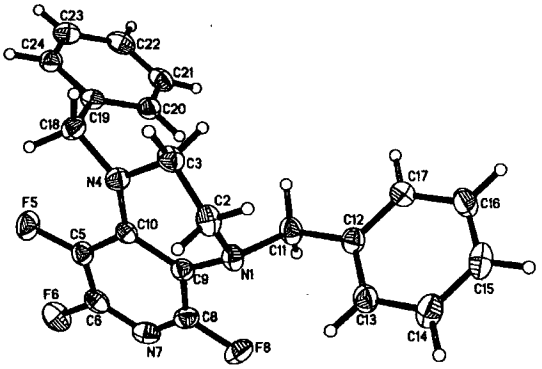


Fig. 2.3c X-Ray Molecular Structure of **3c**

Reactions were then attempted using primary amine binucleophiles, and readily available ethylenediamine **2d** was the obvious choice. The reaction of **1** with **2d,** gave no fused ring product, instead, uncyclised product **3f** was isolated, arising from substitution at the 4-position only, despite prolonged heating (Fig. 2.3d). Attempts to cyclise **3f** by reactions involving the use of stronger organic bases such as LDA and butyl lithium failed.

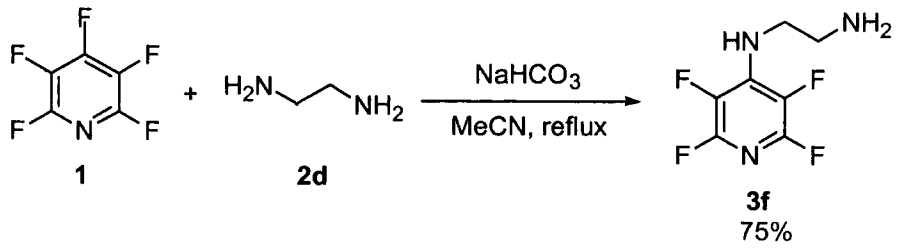


Fig. 2.3d Reaction of ethylenediamine **2d** with **1**

This result reflects the lower nucleophilicity of primary amine sites compared to secondary amines. Also, the relatively acidic proton attached to the nitrogen atom of the 4-substituent in **3f** may interact with the base present, deactivating the pyridine ring towards further nucleophilic attack. Similar results were obtained when 1,2-phenylenediamine was investigated and the structure of the product was confirmed by X-ray crystallography (Fig. 2.3e).

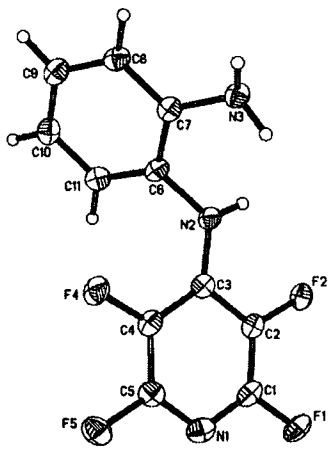


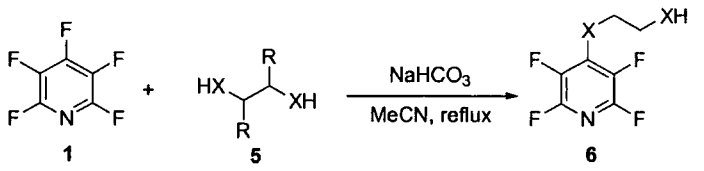
Fig. 2.3e X-Ray Molecular Structure of *N*-(2,3,5,6-Tetrafluoropyridin-4-yl)benzene-1,2-diamine

Formation of pyridine 'bridged systems' corresponding to **4** (Fig. 2.3a) as by-products were observed in the reactions of **1** with ethylenediamine and 1,2-phenylenediamine even under high dilution conditions, their presence identified by mass spectral data. The formation of

these by-products indicates the much higher reactivity of the 4-position over the 3-position in PFP.

2.4) REACTION OF PENTAFLUOROPYRIDINE WITH UNSYMMETRICAL BINUCLEOPHILES

In order to expand the scope of the fused systems that could be accessed by this methodology, reactions of **1** with unsymmetrical nitrogen/oxygen and nitrogen/sulfur binucleophiles were carried out (Table 2.4a).



1 **5** **6**

Binucleophile	Product	
5a	**6a**	85%
5b	**6b**	50%

Table 2.4a Reactions of **1** with unsymmetrical binucleophiles

In all of the cases shown in Table 2.4a it was not possible to obtain fused ring systems and products obtained are the result of substitution at the 4-position only. In the case of the binucleophile **5a**, the most nucleophilic nitrogen atom attacks in preference to oxygen to give **6a** as would be expected, and the oxygen atom is not sufficiently nucleophilic to attack

the 3-position which is deactivated towards nucleophilic attack by the electron donating nitrogen atom at the 4-position. Attempts to cyclise **6a** using sodium hydride to deprotonate the hydroxyl group also failed.

The structure of **6b** was confirmed by X-ray crystallography (Fig. 2.4a) and again it is assumed that the primary amine group is not sufficiently nucleophilic to attack the 3-position.

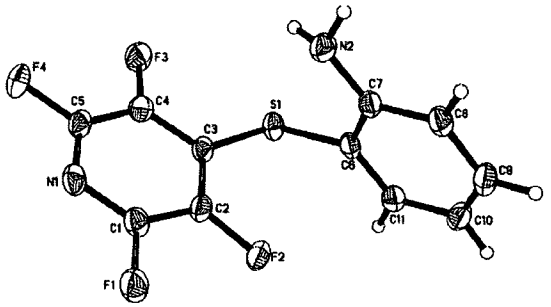


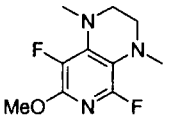
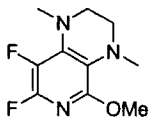
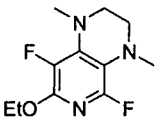
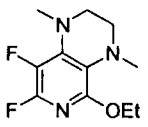
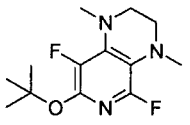
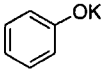
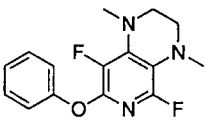
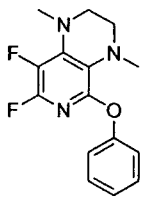
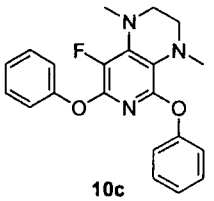
Fig. 2.4a X-Ray Molecular Structure of **6b**

2.5) NUCLEOPHILIC SUBSTITUTION REACTIONS OF 5,7,8-TRIFLUORO-1,4-DIMETHYL-1,2,3,4-TETRAHYDROPYRIDO[3,4-*b*]PYRAZINE 3a

We have shown that the methodology outlined in Fig. 2.2a does allow the synthesis of fused ring core scaffolds by the reaction of pentafluoropyridine with binucleophiles. So far, several tetrahydropyrido[3,4-*b*]pyrazine scaffolds have been synthesised in this manner and these systems possess several sites which are activated towards further nucleophilic substitution. This section is concerned with the investigation of the reactivity of these new core scaffolds.

Reactions of **3a** with a series of nucleophiles were carried out (Table 2.5a & 2.5b). Compound **3a** was chosen as the representative core scaffold as it could be most easily synthesised in higher yields than either **3b** or **3c**. Reactions with a range of both aliphatic and aromatic oxygen centred nucleophiles were carried out under the various conditions outlined in Table 2.5a.

3a + Nucleophile —Conditions→ Products

Nucleophile	Conditions	Product(s)*
MeONa	MeONa, MeOH reflux, 2 d	 **7a** 76%, 10 :1  **7b**
EtONa	EtONa, EtOH microwaves, 1.25 h	 **8a** 57%, 8:1  **8b**
t-BuOK	THF, reflux	 **9**, 66%
	Microwaves THF, 150°C, 1 h	 **10a**  **10b**  **10c** 65%, 4.9 : 1:1.2

*Minor products **7b** and **8b** were identified by ^{19}F nmr and gcms analysis but could not be isolated. Products **10a,b,c** were not separated but identified by spectroscopic analysis of enriched samples.

Table 2.5a Nucleophilic substitution reactions of **3a** with oxygen nucleophiles

The major product **7a** of the reaction of **3a** with sodium methoxide arises from substitution of fluorine at the 7-position with some minor isomer **7b**, arising from substitution of fluorine at the 5-position also formed. Similar results were obtained when microwave heating was used to induce this reaction. Isomers **7a** and **7b** were formed in the ratio 10:1 respectively as shown by ^{19}F NMR and GCMS analysis and, again the progress of the reaction was followed by ^{19}F NMR which indicated clean conversion of **3a** to **7a/b**. Compound **7a** was isolated by column chromatography and, inevitably some handling losses resulted from the purification stage which accounts for the low isolated yield. Similarly, sodium ethoxide gave a mixture of isomers **8a** and **8b** in a ratio of 8:1 after microwave heating, although reaction of **3a** with potassium *tert*-butoxide gave essentially only **9**, with minor traces of other products observed in the crude reaction mixture by ^{19}F NMR, reflecting the increased steric requirements of the *tert*-butoxy group. Products **10a,b** and **c**, formed by reaction of **3a** with potassium phenoxide, could not be separated but enriched samples (>80% purity) obtained by column chromatography allowed identification by NMR and mass spectrometry.

The structures of **7a** and **8a** were confirmed by X-ray crystallography and, therefore, the orientation of nucleophilic substitution, was unambiguously determined (Fig. 2.5a & 2.5b). The position of nucleophilic attack in all other products was confirmed by comparison to the ^{19}F and ^{13}C NMR data of **7a** whereas structures of isomeric products which were isolated in only trace quantities were assigned using ^{19}F NMR.

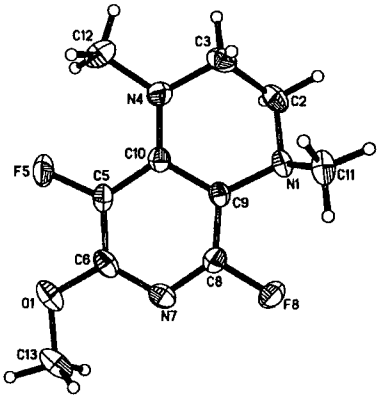


Fig. 2.5a X-Ray Molecular Structure of **7a**

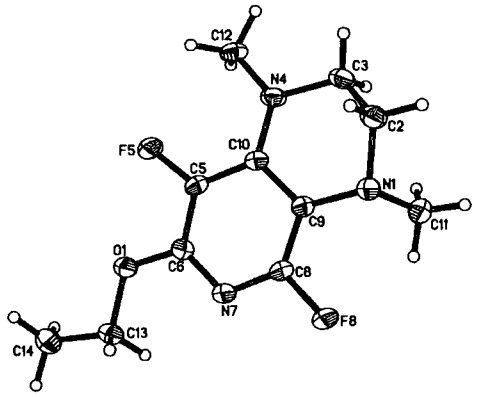


Fig.2.5b X-Ray Molecular Structure of **8a**

To explain the regioselectivity of nucleophilic substitution of **3a** it is necessary to consider the activating influences of the ring nitrogen and fluorine substituents attached to the pyridine ring based on well established arguments discussed in Section 1.5. It is known that the pyridine nitrogen atom significantly activates *ortho* and *para* sites, i.e. the 5- and 7-positions. The 7-position is attacked preferentially due to added activation by fluorine atoms *ortho* and *meta* to the site of attack whereas the 5-position is activated by only one *meta* fluorine and significantly deactivated by a *para* fluorine atom (Fig. 2.5c).

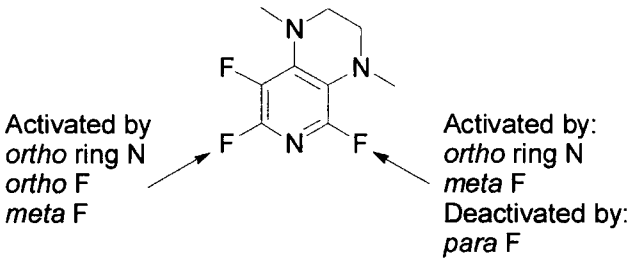


Fig. 2.5c Activating influences on **3a** for nucleophilic aromatic substitution processes

With bulky nucleophiles such as potassium *tert*-butoxide, reaction essentially occurs exclusively at the 7-position, possibly due to steric hindrance at the 5-position disfavouring the approach of a bulky nucleophile to this position.

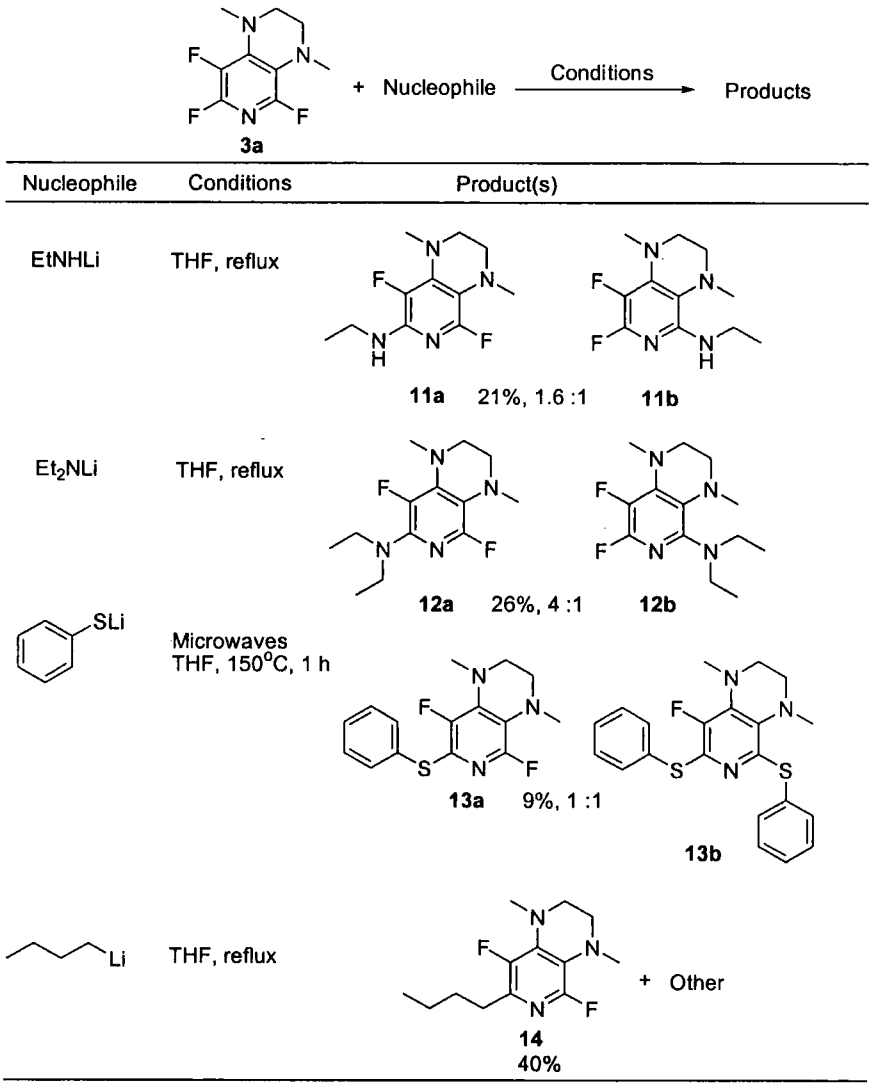


Table 2.5b Nucleophilic substitution reactions of **3a** with model N, S and C nucleophiles

Since we established that **3a** could be further functionalised by the attack of oxygen nucleophiles, various nitrogen, sulfur and carbon nucleophiles were investigated in order to demonstrate the possibility for further molecular diversity that could be accessed from this

core scaffold, and the results can be found in Table 2.5b. Again it was observed that nucleophilic substitution occurs preferentially at the 7-position, with some competing substitution at the 5-position. The low isolated yields of **11a** and **12a** were due to the loss of material during column chromatography. Reaction of lithium thiophenoxide proceeds slowly and it was necessary to add a large excess of nucleophile to obtain significant conversion even under microwave conditions, and, furthermore, isolation of the products **13** was complicated by the formation of phenyl disulfide as a by-product.

As it is known that fluorinated pyridine derivatives can be alkylated at the 2-position using alkyl lithium reagents,[17, 18] this was the method of choice for the formation of **14**, the product having been isolated by mass directed automated preparative HPLC followed by preparative thin layer chromatography. A high molecular weight system that could not be identified fully was also present in the crude product mixture.

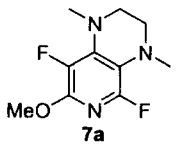
2.6) NUCLEOPHILIC SUBSTITUTION REACTIONS OF 5,8-DIFLUORO-7-METHOXY-1,4-DIMETHYL-1,2,3,4-TETRAHYDROPYRIDO[3,4-*b*]PYRAZINE 7a

The results of reactions between **3a** and a range of nucleophiles (Table 2.5a & 2.5b) demonstrate that the pyridopyrazine scaffold can indeed be further functionalised following the general strategy outlined in Fig. 2.2a. The question in hand was now whether further functionalisation could be performed in a stepwise manner using the core fused ring structure. Consequently, further nucleophilic substitution reactions of **7a**, the most readily accessible system derived from **3a**, were explored. A range of representative nucleophiles (oxygen, nitrogen and carbon) were studied (Table 2.6a) and several polysubstituted pyridopyrazine derivatives were isolated, again following the strategy outlined in Fig. 2.2a.

The decision to exclude further reaction using a sulfur nucleophile was based on the problematic reaction of lithium thiophenoxide with **3a** as outlined in Section 2.5.

Reaction of **7a** with the nucleophiles sodium ethoxide and *n*-butyl lithium gave single products **15** and **17** respectively, arising from substitution of the most activated fluorine atom located at C-7 *ortho* to the pyridine ring nitrogen atom. Products could be identified by ^{19}F NMR which showed one peak at approximately -160 ppm, attributed to the presence of fluorine located at C-8 *meta* to nitrogen. An nOe experiment carried out on **17** was also consistent with the regiochemistry of substitution; the resonance attributed to the methylene group attached directly to the pyridine ring was irradiated leading to an enhancement of an N-CH_3 signal, confirming the presence of the butyl group at the 5-position of the ring.

Reaction of **7a** with lithium diethylamide gave products **16a** and **16b**. The disubstituted product **16b** was not isolated but could be identified by ^{19}F NMR of the reaction mixture which showed two peaks between -150 and -160 ppm corresponding to different products. Product **16b** was subsequently removed from the crude product mixture by an aqueous wash and mass spectral data of the aqueous layer again confirmed the presence of **16b**.



7a

+ Nucleophile —Conditions→ Product

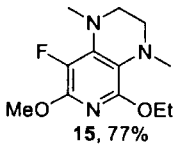
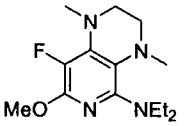
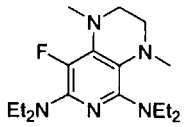
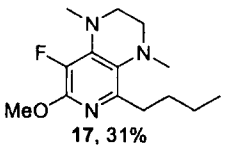
Nucleophile	Conditions	Product(s)
EtONa	EtOH, reflux	 **15**, 77%
Et_2NLi	THF, reflux	 **16a**, 64% 2:1  **16b**
BuLi	THF, reflux	 **17**, 31%

Table 2.6a Nucleophilic substitution reactions of **7a**

It has not been possible to replace the final fluorine atom located at the 8-position by a nucleophile due to the now less activated nature of the highly substituted pyridine ring. However, this may actually be an advantage as the presence of fluorine in numerous compounds has been known to confer favourable biological activity and metabolic stability which are useful in pharmaceutical and agrochemical products.[19-23]

2.7) CONCLUSION

It has been demonstrated that pentafluoropyridine **1** can be used as a substrate for the synthesis of polysubstituted pyridopyrazine derivatives by reaction with various diamines, and these pyridopyrazine derivatives can act as functional core scaffolds upon further reaction with nucleophiles to give products arising from substitution at sites *ortho* to the

pyridine ring nitrogen. The regioselectivity of nucleophilic substitution can be explained by a consideration of the activating effects of the ring fluorine and pyridine nitrogen atoms. Therefore, the approach of using perfluorinated heterocycles for the synthesis of otherwise relatively inaccessible polysubstituted [6,6] fused ring heteroaromatic systems is possible (Fig. 2.7a).

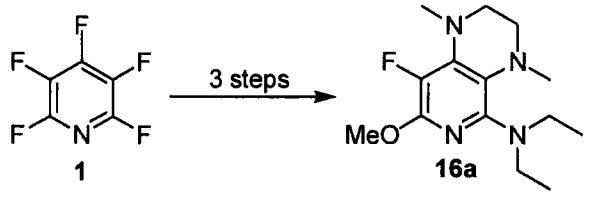


Fig. 2.7a Formation of **16a** from **1**

Minor drawbacks include the sometimes difficult separation of the major products from small quantities of minor products and the possible lability of the methoxy substituent in subsequent nucleophilic aromatic substitution reactions. Many polysubstituted pyridopyrazine derivatives could be synthesised from the vast number of nucleophilic species available following the general principles outlined in this chapter, and in subsequent chapters further applications of this annelation/functionalisation strategy will be investigated for the synthesis of other fused ring systems.

2.8) REFERENCES

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TETRAHYDROPYRIDO[2,3-*b*]PYRAZINE SCAFFOLDS FROM 4-SUBSTITUTED TETRAFLUOROPYRIDINE DERIVATIVES

3.1) INTRODUCTION

In the previous chapter a general approach for the synthesis of polyfunctional, heterocyclic fused ring systems was outlined and the successful synthesis of various model tetrahydropyrido[3,4-*b*]pyrazines from pentafluoropyridine was demonstrated. In order to increase the molecular diversity of the scaffolds that can be accessed by this approach, we sought to adapt the strategy outlined in Chapter 2 to obtain polyfunctional tetrahydropyrido[2,3-*b*]pyrazine scaffolds. This can be done, in principle, if the most active 4-position of PFP is first 'blocked' by reaction with a mononucleophile, and then reaction with a binucleophile may proceed at the 2- and 3-positions to give **19** as shown in Fig. 3.1a. **19** can then, potentially, be further functionalised to give derivatives of the type **20**.

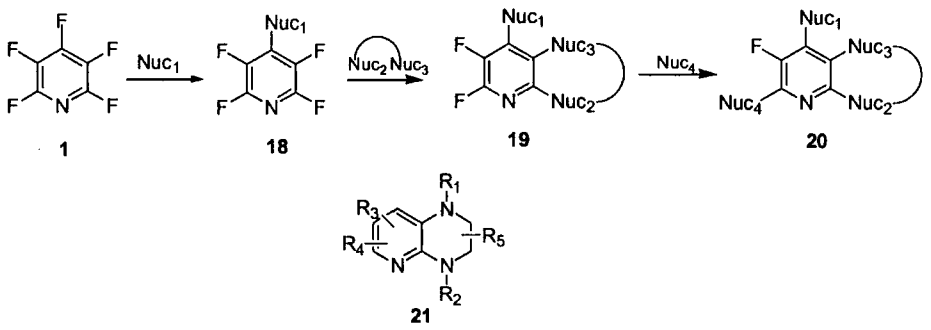


Fig. 3.1a Strategy for polysubstituted tetrahydropyrido[2,3-*b*]pyrazine synthesis

Polyfunctional pyrido[2,3-*b*]pyrazine derivatives **21** are difficult to synthesise by conventional methodology and have previously been prepared by reactions of 2,3-diamino pyridines with dicarbonyl systems[1-3] (Hinsberg reaction), cyclisations involving appropriate

chloro-aminopyridine derivatives[4, 5] or reduction[6, 7] of polycyclic heteroaromatic precursors as previously discussed. In general, all of these reported synthetic procedures require multi-step sequences, where the synthesis of the appropriate functionalised pyridine precursors can be very difficult indeed (Fig. 3.1b).

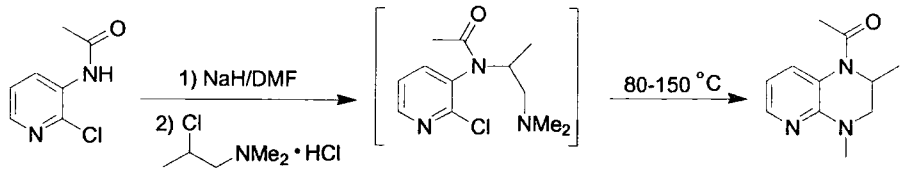


Fig. 3.1b Synthesis of pyrido[2,3-*b*]pyrazine derivative

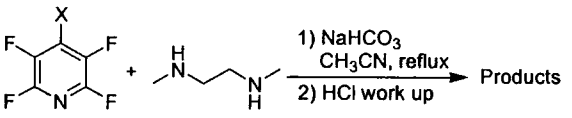
In this chapter the synthesis of several tetrahydropyrido[2,3-*b*]pyrazine systems by the reaction of 4-substituted tetrafluoropyridine derivatives bearing a range of electron donating and electron withdrawing substituents at the 4-position with N,N'-dimethylethylenediamine **2a** is outlined. It was envisaged that, if successful, this strategy would be complimentary to that outlined in Chapter 2 for the synthesis of tetrahydropyrido[3,4-*b*]pyrazines. To fully investigate the synthetic potential of this strategy it was necessary to investigate a number of tetrafluoropyridine derivatives containing both electron donating and electron withdrawing groups in order to establish the effects of these groups upon the annelation procedure.

3.2) TETRAFLUOROPYRIDINE DERIVATIVES BEARING ELECTRON DONATING SUBSTITUENTS AT THE 4-POSITION

The first set of 4-substituted tetrafluoropyridine derivatives that were investigated as starting materials for ring forming reactions possessed an electron donating group at the 4-

position, and the results of the reactions of these compounds with *N,N'*-dimethylethylenediamine **2a** are shown in Table 3.2a. **2a** was the binucleophile of choice as it was known to react well with **1** to give fused ring systems.

Compounds **18a**, **18b** and **18c** were synthesised by reaction of PFP with the appropriate nucleophile and **18d** can be obtained by the reaction of PFP with lithium aluminium hydride[8] or zinc in aqueous ammonia.[9] All reactions with *N,N'*-dimethylethylenediamine were carried out in dilute acetonitrile solution to minimise the formation of side products such as pyridine bridged systems, and in the presence of sodium hydrogen carbonate as base. All reactions were monitored by ^{19}F NMR and we observed that the only fused ring system **25** that is formed resulted from the reaction between 2,3,5,6-tetrafluoropyridine **18d** and **2a**.



18 **2a**

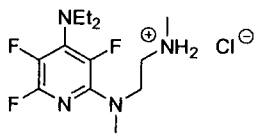
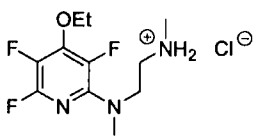
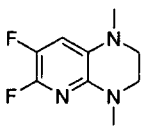
X	Product(s) (yield)
NEt_2 **18a**	 **22**, 15%
OMe **18b**	 **23**,72%
OEt **18c**	 **24**, 23%
H **18d**	 **25**, 66%

Table 3.2a Reactions of 4-substituted tetrafluoropyridine derivatives containing electron donating substituents

The reaction of diethyl-(2,3,5,6-tetrafluoro-pyridin-4-yl)-amine **18a** and 4-ethoxy-2,3,5,6-tetrafluoropyridine **18c** with **2a** gave the corresponding products **22** and **24** as a result of substitution by the binucleophile at the 2-position only. The structure of **22** isolated as the hydrochloride salt after acidic work up was confirmed by X-ray crystallography (Fig. 3.2a).

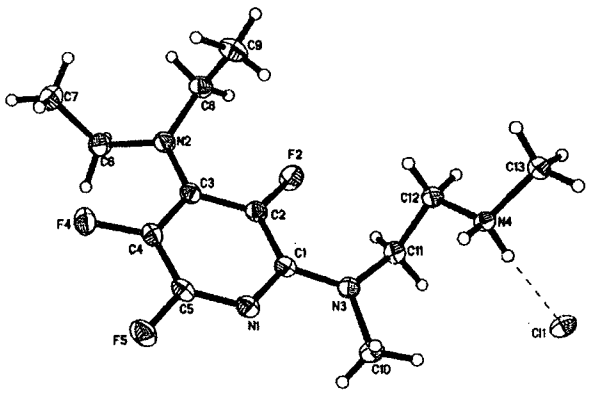
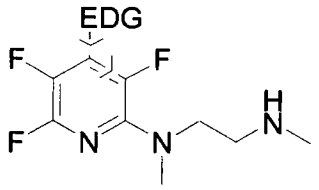


Fig. 3.2a X-Ray Molecular Structure of **22**

The electron donating groups at the 4-position of **18a** and **18c** enhance the electron density at the 3-position deactivating this position towards nucleophilic attack and thus retarding the cyclisation process (Fig. 3.2b).



Electron density pushed towards the 3-position causing deactivation towards nucleophilic aromatic substitution

Fig. 3.2b Schematic representation of the deactivation of the 3-position towards nucleophilic aromatic substitution by electron donating substituents

The reaction of 4-methoxy-2,3,5,6-tetrafluoropyridine **18b** with *N,N'*-dimethylethylenediamine **2a** gives the unusual product **23** which is thought to be formed by the following nucleophilic substitution procedure in which the pyridine ring acts as a good leaving group (Fig. 3.2c). Product **23** was fully characterised and the data was consistent with literature values.[10]

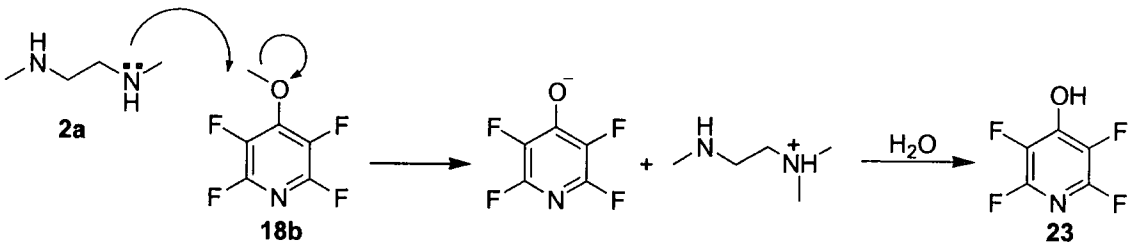


Fig. 3.2c Formation of **23** from **18b** and **2a**

Diamine **2a** initially attacks the methyl group and the electron withdrawing pyridine ring acts as a good leaving group in this S_N2 type reaction. The formation of **23** occurs for the reaction of the methoxy substituted derivative **18b** but not for the ethoxy substituted derivative **18c** and this can be explained on the basis of kinetic data relating to the reaction of nucleophiles with alkyl halides (Fig. 3.2d).[11] Methyl halides undergo nucleophilic substitution reactions at a significantly faster rate than ethyl halides, and so here, nucleophilic attack occurs at the methyl site whereas for ethyl, ring substitution competes very effectively.

Nuc^-	+	Me—X	Et —X	^iPr —X
$k_{SN2, rel}$	=	30	1	0.025

Fig. 3.2d Kinetic data for reactions of nucleophiles with alkyl halides

The formation of **25** is thought to proceed via reaction of **2a** at the 2-position of **18d** followed by cyclisation at the 3-position which is supported by the formation of **26** from the reaction of **18d** with diethylamine (Fig. 3.2e). The hydrogen atom present at the 4-position in **18d** is not sufficiently electron donating to completely inhibit the cyclisation process and the desired fused ring system is formed at a slow rate.

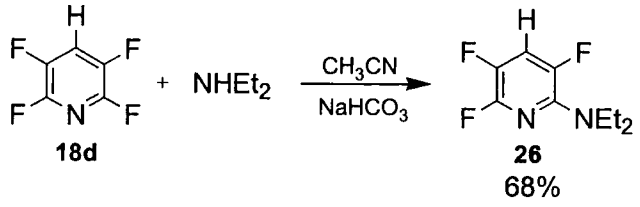


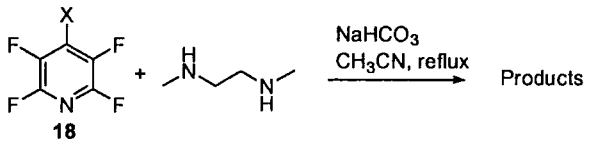
Fig. 3.2e Formation of **26** by reaction of **18d** with diethylamine

The reactions outlined in Table 3.2a have shown that at present it is not possible to form tetrahydropyrido[2,3-*b*]pyrazines by the reaction of tetrafluoropyridine derivatives bearing an electron donating group at the 4-position with binucleophiles. Consequently, studies moved on to investigate reactions of pyridine systems with electron withdrawing groups at the 4-position.

3.3) TETRAFLUOROPYRIDINE DERIVATIVES BEARING ELECTRON WITHDRAWING SUBSTITUENTS AT THE 4-POSITION

Various tetrafluoropyridine derivatives containing electron withdrawing substituents at the 4-position (e.g. bromo, perfluoroisopropyl, phenylsulfonyl, nitro and cyano) were reacted with *N,N'*-dimethylethylenediamine **2a** and the results are shown in Table 3.3a. Pyridine derivatives bearing bromo and cyano substituents at the 4-position are commercially

available whereas those bearing perfluoroisopropyl, phenylsulfonyl and nitro groups were synthesised following literature procedures.[12-14] In all cases the desired tetrahydropyrido[2,3-*b*]pyrazines were formed in good yields. The slightly low yield of **27** was due to handling losses at the purification stage. The electron withdrawing groups present at the 4-positions of the aromatic ring provide sufficient activation for nucleophilic aromatic substitution and hence cyclisation to occur at the 3-position while themselves avoiding displacement by the binucleophile, all apart from **18i** where the nitro group is displaced by the nucleophile.



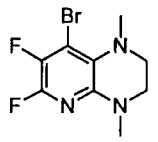
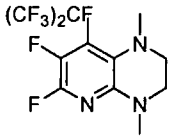
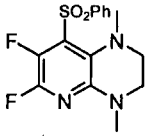
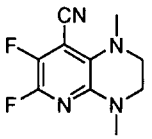
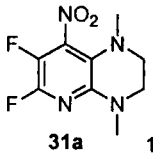
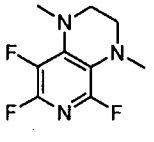
X	Product(s) (yield)
Br **18e**	 **27**, 20%
$CF(CF_3)_2$ **18f**	 **28**, 40%
SO_2Ph **18g**	 **29**, 65%
CN **18h**	 **30**, 90%
NO_2 **18i**	 **31a** 70% 1.2:1  **3a**

Table 3.3a Reactions of 4-substituted tetrafluoropyridine derivatives containing electron withdrawing substituents

A rough guide to the order of activation of an aromatic ring towards nucleophilic aromatic substitution by different groups is outlined in Fig. 3.3a along with the relative mobilities of different substituents.[15]

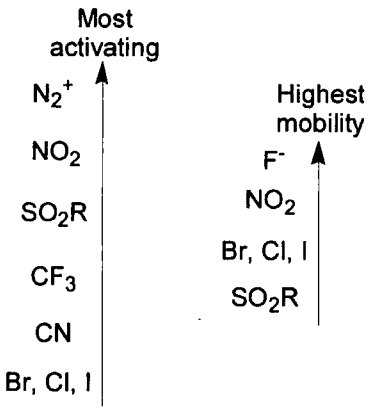


Fig. 3.3a Activating effects and mobilities of substituents in nucleophilic aromatic substitution reactions

The structures of **27**, **28**, **29** and **30** were confirmed by X-ray crystallography (Fig. 3.3b-3.3e).

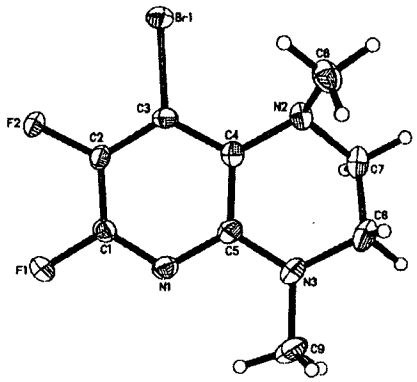


Fig. 3.3b X-Ray Molecular Structure of **27**

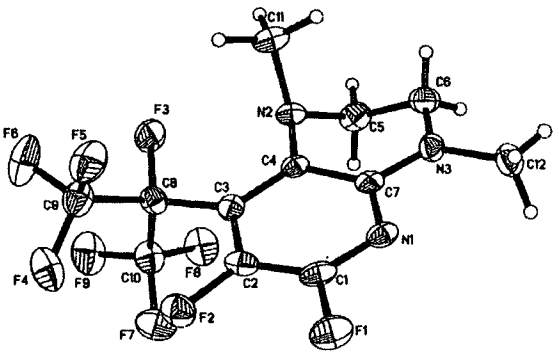


Fig. 3.3c X-Ray Molecular Structure of **28**

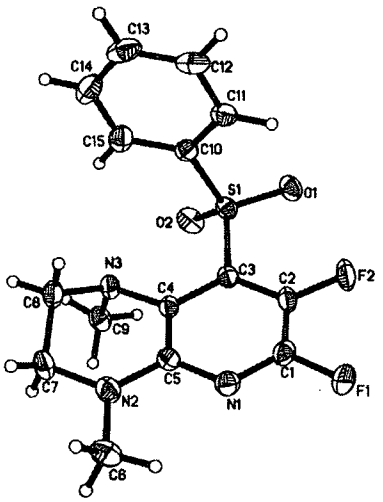


Fig. 3.3d X-Ray Molecular Structure of **29**

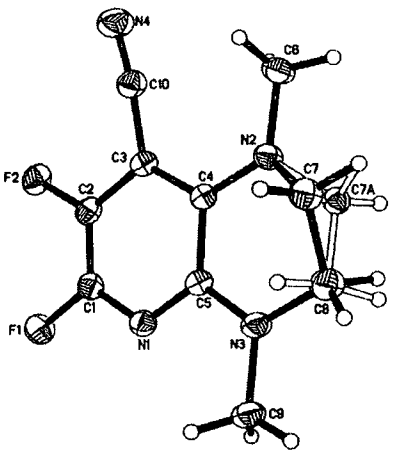


Fig. 3.3e X-Ray Molecular Structure of **30**

The formation of **27** is thought to occur by the initial attack of the binucleophile at the 2-position, analogous to the reaction of **18e** with diethylamine (Fig. 3.3f).

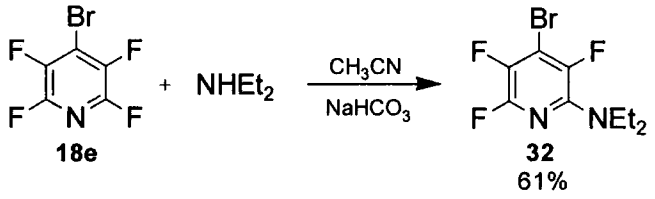
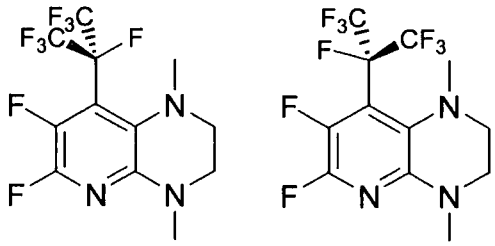


Fig. 3.3f Formation of **32** by reaction of **18e** with diethylamine

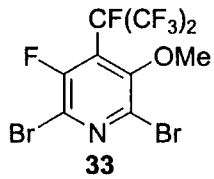
Fused ring system **28** exists as two conformers A and B shown in Fig. 3.3g which can be distinguished by ^{19}F NMR. The fused ring system exists mainly in the form of conformer A as there is no steric repulsion between the trifluoromethyl group and the 1-methyl group that exists in conformer B.



Conformer A Conformer B

Fig. 3.3g The two conformers of **28**

The ^{19}F NMR data for **28** reveals a $^{4}J_{FF}$ coupling of 89 Hz between F-7 and the fluorine atom of the perfluoroisopropyl group that is in close proximity for conformer B. This coupling is not observed for conformer A. A similar result has been reported for **33** shown in Fig. 3.3h, this compound also exists as two conformers that can be distinguished by ^{19}F NMR data.[16]



33

Fig. 3.3h Structure of 2,6-dibromo-3-fluoro-5-methoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine **33**

Two products **31a** and **3a** are formed by the reaction of **18i** with **2a**; **31a** is formed by the displacement of two fluorine atoms at the 2- and 3-positions, and **3a** is formed by displacement of the nitro group at the 4-position and the fluorine atom at the 3-position. **3a** is formed as a result of the nitro group acting as a good leaving group in nucleophilic substitution reactions[17] as shown in Fig 3.3a.

3.4) CONCLUSION

We have demonstrated that tetrafluoropyridine derivatives that are substituted at the 4-position by activating electron withdrawing groups can be used as substrates for the synthesis of tetrahydropyrido[2,3-*b*]pyrazine systems by reaction with *N,N'*-dimethylethylenediamine **2a** (Fig. 3.4a). Derivatives containing electron donating groups at the 4-position do not provide sufficient activation of the aromatic ring for cyclisation to occur via nucleophilic aromatic substitution.

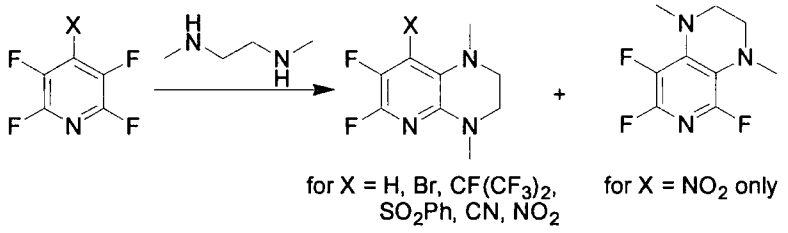


Fig. 3.4a Synthesis of tetrahydropyrido[2,3-*b*]pyrazines from 4-substituted tetrafluoropyridine derivatives

Now that it has been established that the blocking/ring annelation strategy outlined in Fig. 3.1a is feasible for the synthesis of fused ring systems from tetrafluoropyridine derivatives, reactions of these systems with alternative binucleophiles and further functionalisation strategies can be investigated. The results of these studies are presented in the following chapters.

3.5) REFERENCES

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RING FORMING REACTIONS OF 4-NITRO-2,3,5,6-TETRAFLUOROPYRIDINE AND 2,3,5,6-TETRAFLUORO-4-(PHENYLSULFONYL)PYRIDINE

4.1) INTRODUCTION

Work in the previous chapter was concerned with synthesising tetrahydropyrido[2,3-*b*]pyrazines from 4-substituted tetrafluoropyridine derivatives and 1,2-diamines. This chapter expands upon the work begun in Chapter 3 and focuses upon the use of 4-nitro-2,3,5,6-tetrafluoropyridine **18i** as a substrate for ring forming reactions by nucleophilic aromatic substitution reactions, moving onto the use of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **18g**. Work reported in Chapter 3 shows that it is possible to form fused ring systems by the reaction of **18i** and **18g** with *N,N'*-dimethylethylenediamine **2a**, and therefore the next step in the development of this ring forming methodology was to attempt reactions with alternative binucleophiles in order to potentially broaden the scope of this strategy.

It was noted in Chapter 3 that some reactions of 4-substituted tetrafluoropyridine derivatives with **2a** did not give straightforward results, e.g. the reaction of 4-methoxy-2,3,5,6-tetrafluoropyridine **18b**, therefore, before attempting reactions of **18i** and **18g** with binucleophiles, it was thought necessary to carry out a series of model reactions of these derivatives with mononucleophiles to establish the effects of the 4-nitro and 4-phenylsulfonyl substituents upon the reactivity of the pyridine system towards nucleophilic substitution reactions. There are three possible products that could be formed by the reaction of a 4-substituted tetrafluoropyridine molecule with a mononucleophile as shown in Fig. 4.1a.

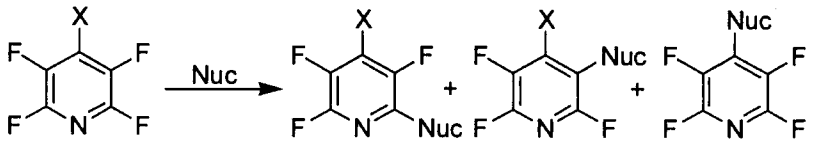


Fig. 4.1a Possible products formed as a result of the reaction of 4-substituted tetrafluoropyridine derivatives with mononucleophiles

The nucleophile could in principle attack at three positions; the 2- or the 3-position by displacement of a fluorine atom, or the 4-position by displacement of the substituent X. The following sections report the results of the reactions of **18i** and **18g** with both mono and binucleophiles.

4.2) REACTIONS OF 4-NITRO-2,3,5,6-TETRAFLUOROPYRIDINE 18i WITH MONONUCLEOPHILES

4-Nitro-2,3,5,6-tetrafluoropyridine **18i** was synthesised from pentafluoropyridine **1** via 2,3,5,6-tetrafluoropyridin-4-ylamine **34** (Fig. 4.2a).[1]

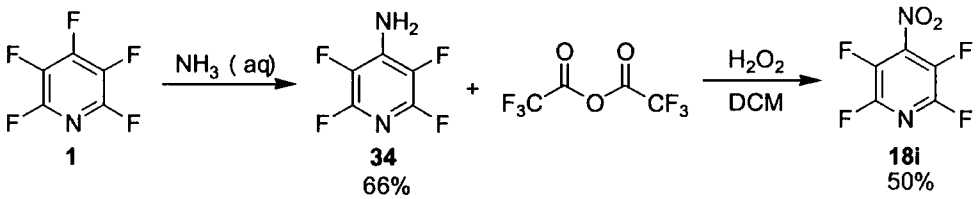
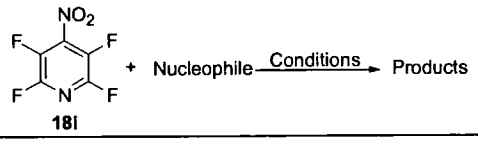


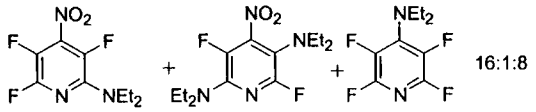
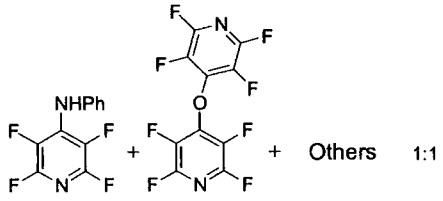
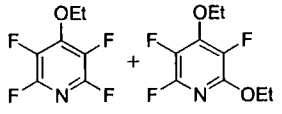
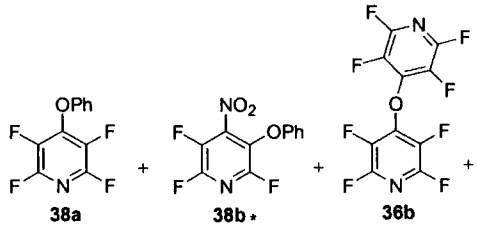
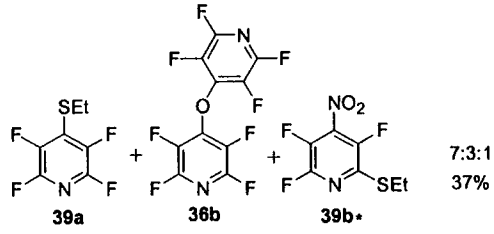
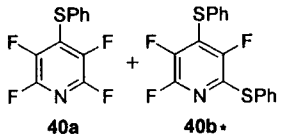
Fig. 4.2a Synthesis of **18i**

Table 4.2a shows the results of a series of reactions of **18i** with representative nucleophiles. Nitrogen, oxygen and sulfur nucleophiles were investigated, containing aromatic and

aliphatic groups to mimic a range of choices of binucleophiles that could in future be used for ring forming reactions.



18i

Nucleophile	Conditions	Product(s) (yield)
$NHEt_2$	$NaHCO_3/CH_3CN$	 **35a** 35% **35b** * **35c** * 16:1:8
$PhNH_2$	$NaHCO_3/CH_3CN$	 **36a** 12% **36b*** + Others 1:1
EtONa	EtOH	 **37a** * **37b** 37% + Others 1.4:1
PhOH	$NaHCO_3/CH_3CN$	 **38a** **38b** * **36b** + Others 8.8:1:1.3 44%
EtSH	$NaHCO_3/CH_3CN$	 **39a** **36b** **39b*** 7:3:1 37%
PhSH	$NaHCO_3/CH_3CN$	 **40a** 11% **40b*** 26:1

Products **38a** and **36b** were isolated as a mixture of compounds in the ratio 6.4:1 respectively, and products **39a** and **36b** were also isolated as a mixture in the ratio 7:3.

* Products not isolated but presence confirmed by ^{19}F NMR and mass spectral data.

Others specifies products resulting from multiple substitutions

Table 4.2a Reactions of **18i** with nucleophiles

Reaction conditions were kept constant (sodium hydrogen carbonate/acetonitrile) except for the reaction of **18i** with sodium ethoxide. No reaction occurred when attempts were made using ethanol and sodium hydrogen carbonate in acetonitrile so the more reactive sodium ethoxide nucleophile was used with ethanol as the solvent of choice. In the majority of cases shown in Table 4.2a it was possible to isolate the main component from the crude reaction mixture and the side products were identified by a combination of ^{19}F NMR and mass spectral data.

In all of the reactions attempted, a significant proportion of the product formed resulted from the displacement of the nitro group at the 4-position. These results may be explained by the fact that the nitro group is almost as easily displaced as fluorine in nucleophilic aromatic substitution reactions[2-7] and is located at the most activated position in the pyridine ring, for reasons discussed previously (Section 1.5).

The location of the dialkylamino substituents at the 2- and the 5-positions of **35b** were confirmed by a consideration of ^{19}F NMR shifts; two resonances appear at -71 and -152 ppm whereas the alternate isomer with the dialkylamino substituents located at the 2- and 6-positions would be expected to show only one resonance in the region of -150 ppm. It is assumed that the first position of nucleophilic attack is at the 2-position analogous to the formation of **35a**, and then a second nucleophilic attack occurs at the 5-position *para* to this dialkylamino substituent. The 5-position is activated by both an *ortho* fluorine atom and an *ortho* nitro group and it is not deactivated by the presence of a *para* fluorine favouring nucleophilic attack at this position.

Product **36b**, formed in the reaction of **18i** with aniline, phenol and ethanethiol, is slightly unusual and the structure was confirmed by ^{19}F NMR and mass spectral data. A mechanism for the formation of this product is tentatively suggested, arising from attack by water present in the system (Fig. 4.2b).

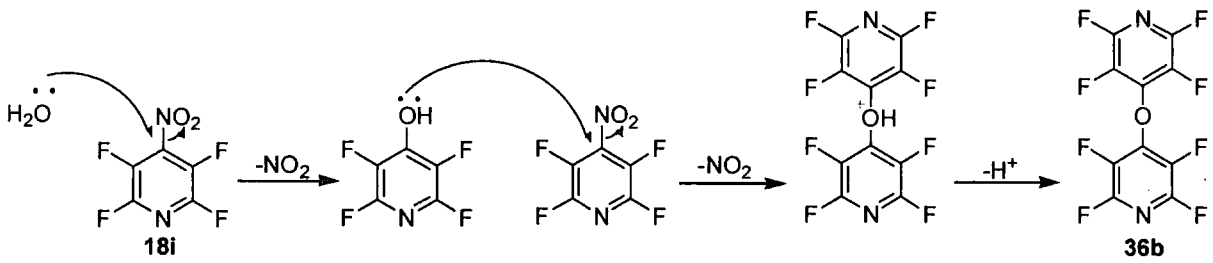


Fig. 4.2b Mechanism for the formation of **36b**

The presence of the phenoxy substituent at the 3-position of **38b** was again confirmed by a consideration of ^{19}F NMR data and indicates that the nitro group is very effective at activating the position *ortho* to it, so much so that it competes with the activating effect of the pyridine nitrogen atom which directs attack towards the 2- and 6-positions.[3, 8, 9]

In summary, the reactions outlined in Table 4.2a show that nucleophilic substitution of **18i** is not regioselective and can be difficult to control with reactions often resulting in polysubstitution. The table also shows that the nitro group is easily displaced by all of the nucleophiles investigated due to the lability of this substituent.

4.3) REACTIONS OF 4-NITRO-2,3,5,6-TETRAFLUOROPYRIDINE 18i WITH BINUCLEOPHILES

Once the effect of the nitro substituent on the reactivity of **18i** was established, studies moved on to investigate the formation of fused ring systems by the reaction of **18i** with binucleophiles. The reactions outlined in Section 4.2 indicate that the nitro group would probably not be a good 'blocking substituent' for the formation of fused ring systems at the 2- and 3-positions. However, as described in the previous chapter, the reaction of **18i** with N,N'-dimethylethylenediamine **2a** was attempted, and an almost 1:1 mixture of products was formed (Fig. 4.3a). This result is consistent with the reaction of **18i** with diethylamine and allows the synthesis of preparatively useful amounts of **31a** for further study.

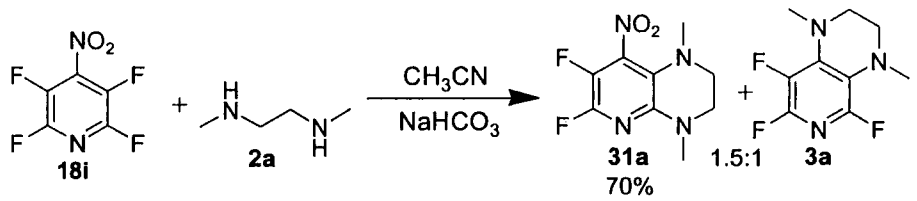


Fig. 4.3a Formation of products **31a** and **3a**

Displacement of the nitro substituent also occurred when the reaction of **18i** with 2-aminobenzenethiol **5b** was attempted (Fig. 4.3b) and the structure of **6b** was confirmed by X-ray crystallography (Fig. 4.3c).

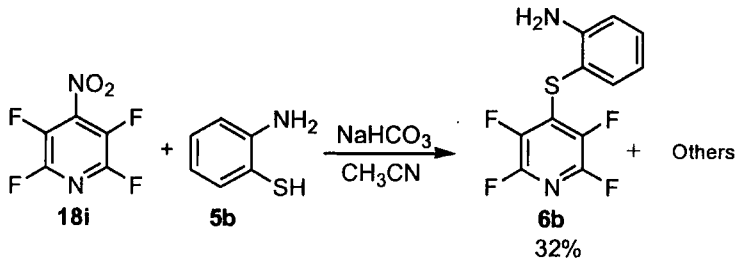


Fig. 4.3b Reaction of **18i** with **5b**

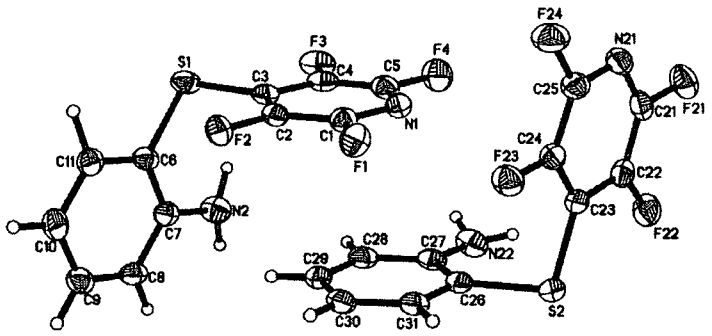


Fig. 4.3c X-Ray Molecular Structure of **6b**

The product formed in the above reaction again resulted from displacement of the nitro group which compares well with the relevant model reaction of benzenethiol with **18i**, where the first position of attack was *para* to the pyridine ring nitrogen.

Both attempted reactions of **18i** with binucleophiles demonstrate that the nitro group is not the most appropriate 'blocking group' for the 4-position, although some [6,6] fused ring systems can be obtained, and indeed ring forming reactions by the replacement of a nitro substituent attached to an aromatic ring have been reported and are termed 'aromatic nucleophilic denitrocyclisation reactions'.[10]

Based on these results it is therefore necessary to investigate tetrafluoropyridine systems with substituents at the 4-position that are less mobile than fluorine and nitro in nucleophilic aromatic substitution reactions, but will still activate the aromatic ring towards attack by nucleophiles. For this reason studies moved onto the use of the phenylsulfonyl group as a blocking substituent. Sulfonyl groups can also be desirable pharmacophoric features to include in the design of new libraries of drug molecules.[11, 12]

4.4) REACTIONS OF 2,3,5,6-TETRAFLUORO-4-(PHENYLSULFONYL)PYRIDINE 18g WITH MONONUCLEOPHILES

2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** was prepared by the reaction of pentafluoropyridine **1** with sodium phenylsulfinate in DMF (Fig. 4.4a) and purification by recrystallisation from ethanol gave excellent yields of the desired product.[13]

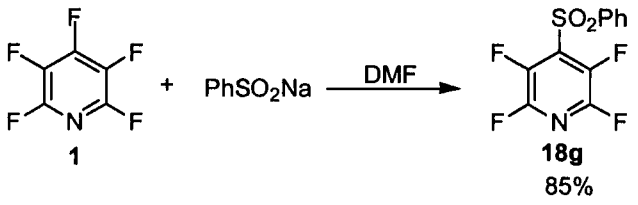
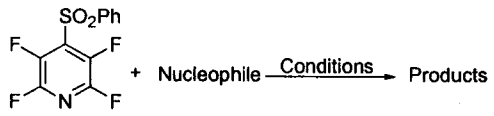
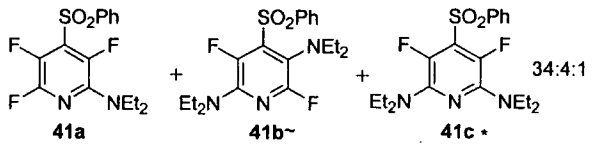
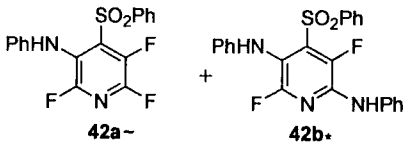
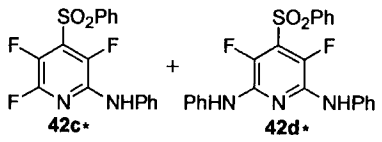
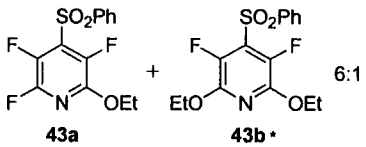
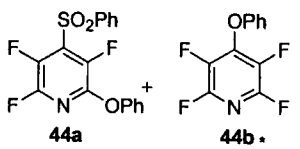
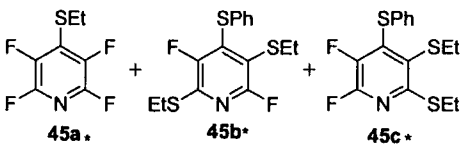
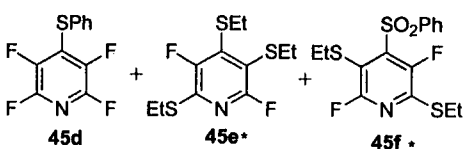


Fig. 4.4a Synthesis of **18g**

Again, an initial study of the reactions of **18g** with mononucleophiles was carried out to establish the effects of the 4-phenylsulfonyl substituent upon the reactivity of the pyridine system. The results of a series of reactions of **18g** with representative nucleophiles are shown in Table 4.4a and are the same as those used for model reactions of 4-nitro-2,3,5,6-tetrafluoropyridine **18i** so a direct comparison can be made.



18g

Nucleophile	Conditions	Product(s) (yield)
$NHEt_2$	$NaHCO_3/CH_3CN$	 **41a** 15% + **41b~** + **41c *** 34:4:1
$PhNH_2$	$NaHCO_3/CH_3CN$	 **42a~** + **42b*** 9.5:2:3.5:1
		 **42c*** + **42d***
EtONa	EtOH	 **43a** 76% + **43b*** 6:1
PhOH	$NaHCO_3/CH_3CN$	 **44a** 52% + **44b*** 3:2
EtSH	$NaHCO_3/CH_3CN$	 **45a*** + **45b*** + **45c***
		 **45d** 34% + **45e*** + Others + **45f *** 46:1:1:18:3.1:12.5
PhSH	$NaHCO_3/CH_3CN$	 **46** 29% + Others

* Products not isolated but presence confirmed by ^{19}F NMR and mass spectral data.
~ Products not isolated but presence confirmed by ^{19}F, ^{1}H, ^{13}C NMR and mass spectral data

Table 4.4a Reactions of **18g** with nucleophiles

It can be seen that reactions of **18g** with 'harder' nucleophiles (sodium ethoxide and diethylamine) gave products with the phenylsulfonyl substituent intact and reaction occurs at the 'harder' C-F bonds rather than the 'softer' C-S bond. Product **42a** is formed as a result of the phenylsulfonyl substituent significantly activating the positions *ortho* to itself.[14] When discussing the 'hardness' and 'softness' of nucleophiles, factors other than simply the nucleophile under discussion come into play, such as the solvent that the reaction is carried out in. All of the reactions of **18g** with mononucleophiles are carried out in acetonitrile except for the reaction with sodium ethoxide which was carried out in ethanol due to difficulties with the reaction of ethanol in acetonitrile mentioned previously. Ethanol is a polar protic solvent whereas acetonitrile is a polar aprotic solvent so it may not be possible to directly compare the reaction of sodium ethoxide with the reactions of the other nucleophiles in this case.

Reaction of pyridine **18g** with 'softer' nucleophiles (ethanethiol and benzenethiol) gave products that were mainly a result of reaction at the 'softest' site i.e. the C-S bond with displacement of the phenylsulfonyl group and, indeed, it is known that the phenylsulfonyl substituent can be a good leaving group in nucleophilic aromatic substitution processes.[15] The reaction with ethanethiol gave a complex mixture of products and it is thought that the product **45d** may possibly be formed by reduction of **18g** with ethanethiol as the source of electrons. It is known that elemental sulfur can reduce aryl sulfones to sulfides[16] and that ethanethiol and similar reagents can participate in single electron transfer reactions,[17] consequently, it is not unreasonable to suggest a similar reduction process is occurring in this case.

Nucleophiles such as phenol and aniline which cannot be classed as 'very hard' or 'very soft' in this case give **42a-42d, 44a** and **44b**. **42a-42d** are formed by aniline attacking the 'harder' C-F bonds of **18g, 44a** is formed by phenol attacking the 'harder' C-F bond of **18g** and **44b** is formed by phenol attacking the 'softer' C-S bond.

From these results, it is very difficult to predict how different nucleophiles will react under different conditions and the results shown in Table 4.4a should only be used as a rough guide. The most useful information that can be extracted from these reactions is that 'very hard' nucleophiles (e.g. ethoxide) should attack the 'harder' C-F sites and 'very soft' nucleophiles (e.g. phenylsulfanyl) should attack the 'softer' C-S site whereas mixtures are obtained when intermediate nucleophiles are used (Fig. 4.4b). The explanation of the 'hardness' and 'softness' of nucleophiles determining the position of attack in polyfluorinated pyridines bearing other substituents has been suggested previously by Chambers *et al.*[18]

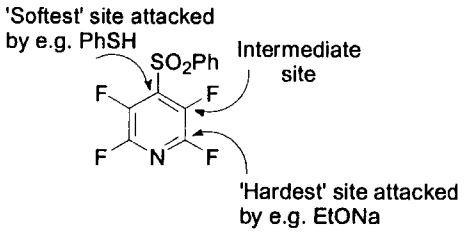


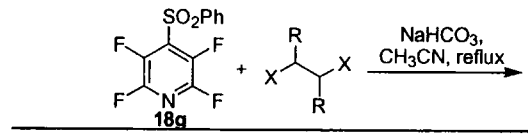
Fig. 4.4b Representation of 'hard' and 'soft' sites of **18g**

The model reactions outlined in this section suggest that it may be possible to use oxygen and nitrogen binucleophiles for the formation of fused ring systems but that the use of sulfur binucleophiles may be problematic. These reactions can also provide preparatively

useful amounts of certain compounds, namely **41a**, **43a** and **44a**, but can be unpredictable due to competition effects.

4.5) REACTIONS OF 2,3,5,6-TETRAFLUORO-4-(PHENYLSULFONYL)PYRIDINE 18g WITH BINUCLEOPHILES

The results of the reactions of **18g** with the mononucleophiles shown in Table 4.4a demonstrate that the phenylsulfonyl group is a better 'blocking substituent' than the nitro group upon reaction with oxygen and nitrogen nucleophiles, and therefore ring forming reactions of **18g** were attempted using oxygen and nitrogen binucleophiles (Table 4.5a).



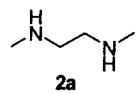
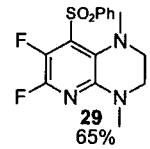
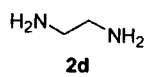
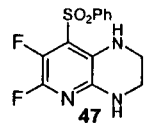
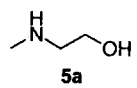
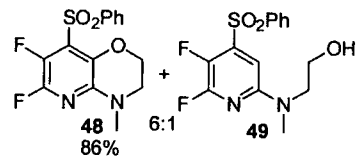
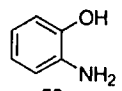
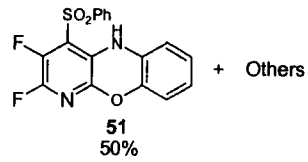
Binucleophile	Product(s)
 **2a**	 **29** 65% (See Chapter 3)
 **2d**	 **47** 71%
 **5a**	 **48** 86% : **49** 6:1
 **50**	 **51** 50% + Others

Table 4.5a Reactions of **18g** with binucleophiles

Again, reactions were conducted under high dilution conditions to minimise the formation of pyridine bridged products and the first binucleophile investigated was **2a**, reaction with **18g** gave **29** (see Chapter 3).

As it is known that the phenylsulfonyl group activates adjacent C-F bonds towards attack by nucleophiles,[14] reaction of **18g** with **2d** was attempted to investigate whether it is possible to carry out annelation reactions with primary amine binucleophiles, and **47** was isolated in a 71% yield after recrystallisation from dichloromethane.

Following model studies where oxygen and nitrogen nucleophiles reacted to give predominantly one product, reactions of oxygen/nitrogen binucleophiles were investigated to expand the range of core scaffolds that can be synthesised. The reaction of **5a** with **18g** gave two products; the desired fused ring system **48** and the uncyclised intermediate **49,** which could be separated by column chromatography followed by recrystallisation from dichloromethane. Conversion of the remaining uncyclised intermediate **49** could possibly be achieved with longer reflux times. The structure of **48** was confirmed by X-ray crystallography (Fig 4.5a) and it is assumed that the most nucleophilic secondary amine attacks the 2-position, in agreement with model studies using diethylamine, followed by attack of the oxygen at the 3-position.

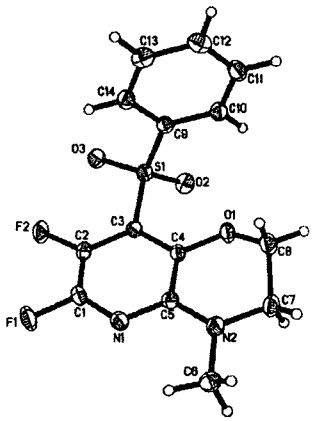


Fig. 4.5a X-Ray Molecular Structure of **48**

Reaction of the related binucleophile **50** with **18g** gives product **51**. The structure of **51** was confirmed by X-ray crystallography (Fig. 4.5b) which shows the relative positions of the nitrogen and oxygen atoms in the central ring.

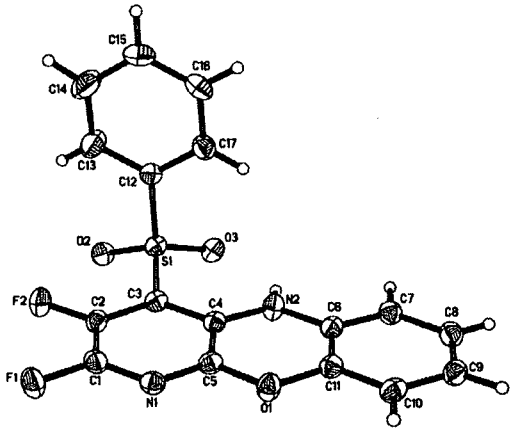


Fig. 4.5b X-Ray Molecular Structure of **51**

It is envisaged that there are two ways in which **51** could be formed; the nitrogen atom in **50** is more nucleophilic than the oxygen atom so the nitrogen atom could first attack the 3-position, in agreement with model studies using aniline, and then attack of the oxygen atom could occur at the 2-position to give **51**, or, the nitrogen atom could first attack the 2-

position, which is activated by the pyridine ring nitrogen, followed by a Smiles' rearrangement and cyclisation at the 3-position to give **51** (Fig. 4.5c).[19, 20] However, ^{19}F NMR data of the reaction mixture does not support this Smiles' rearrangement process.

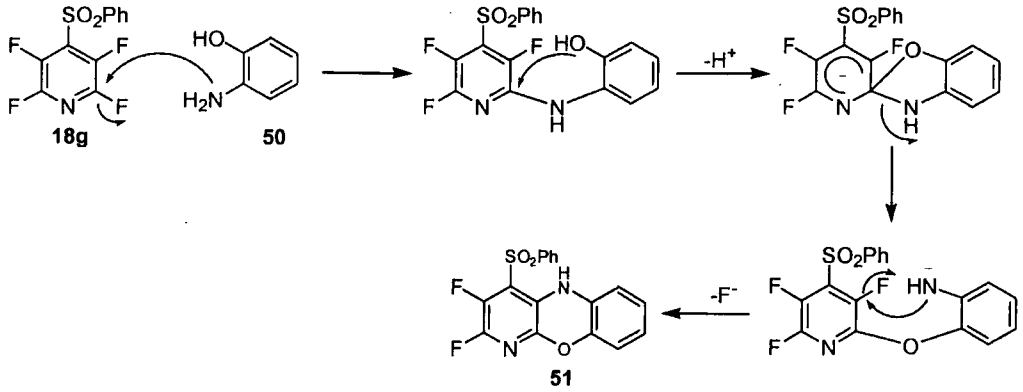


Fig. 4.5c Possible mechanism for the formation of **51**

The work presented in this chapter has demonstrated that it is possible to form [6,6] fused ring systems at the 2- and 3-positions of pyridine rings by the reaction of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **18g** with N,N and N,O binucleophiles, adding to the diversity of core scaffolds that may be accessed by this strategy. The next step in the development of this methodology was to investigate the further functionalisation of such core scaffolds as described in the next section.

4.6) FUNCTIONALISATION OF CORE SCAFFOLDS DERIVED FROM 2,3,5,6-TETRAFLUORO-4-(PHENYLSULFONYL)PYRIDINE

To establish whether the remaining fluorine atoms in fused ring systems such as those synthesised from **18g** are still activated towards nucleophilic attack, reactions of **29** with nitrogen and oxygen nucleophiles were investigated (Fig. 4.6a).

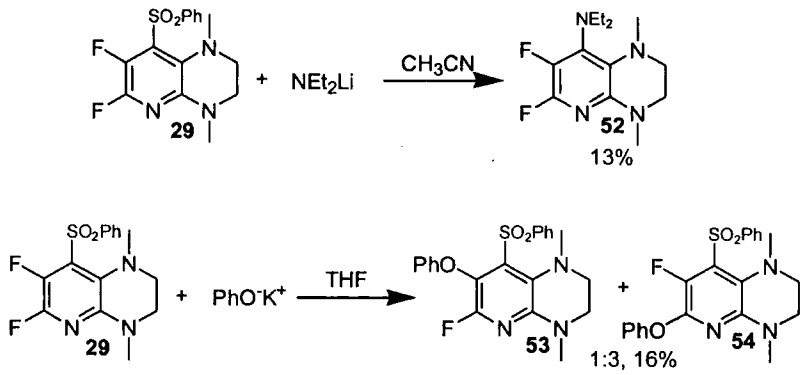


Fig. 4.6a Reactions of **29** with nitrogen and oxygen nucleophiles

Initially, reaction of **29** with diethylamine was attempted but no reaction was observed so the reactivity of the nucleophile was increased by using lithium diethylamide. The formation of **52** is slightly unexpected as lithium diethylamide is a 'hard' nucleophile which seems to have attacked at the 'softer' position, however, the phenylsulfonyl substituent is still located at the most activated position of the pyridine ring and the presence of the extra deactivating nitrogen substituents on the ring could force attack to occur at this most activated position.

Reaction of **29** with potassium phenoxide gave products **53** and **54**. The position of attack was again determined by a consideration of ^{19}F NMR shifts. Products **53** and **54** could not be separated, and the low yield results from attempts to separate the isomers by column chromatography. Fused ring system **53** was formed as a result of attack at C-7 *ortho* to the phenylsulfonyl group and **54** was formed by attack at C-6 *ortho* to the pyridine ring nitrogen, no replacement of the phenylsulfonyl group was observed in this case.

As the reactions of **29** with nucleophiles that are outlined above give mixtures of products which can sometimes be difficult to separate, an alternative strategy for functionalisation was attempted (Fig. 4.6b).

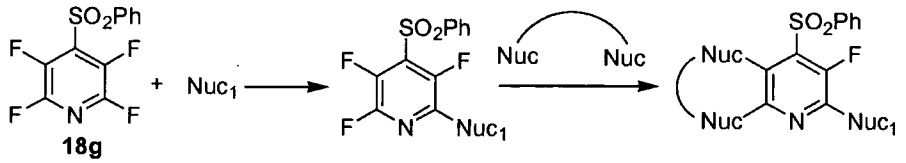


Fig. 4.6b Strategy for functionalisation of fused ring systems

If **18g** is first reacted with a nucleophile at the 2-position, subsequent attack of the product with a binucleophile may lead to a fused ring product and the first reaction of this type that was investigated produced a surprising result (Fig. 4.6c).

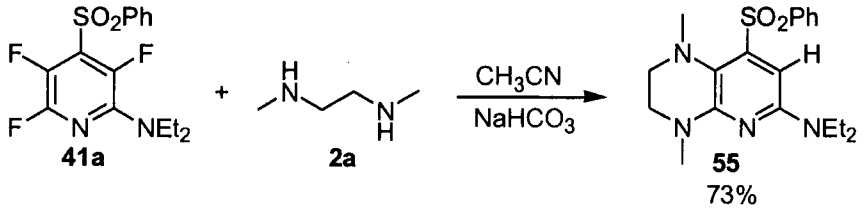


Fig. 4.6c Formation of **55**

When **41a** was reacted with *N,N'*-dimethylethylenediamine **2a** in acetonitrile in the presence of sodium hydrogen carbonate as base, **55**, which contains no fluorine atoms, was the only product, with structural confirmation by X-ray crystallography (Fig. 4.6d).

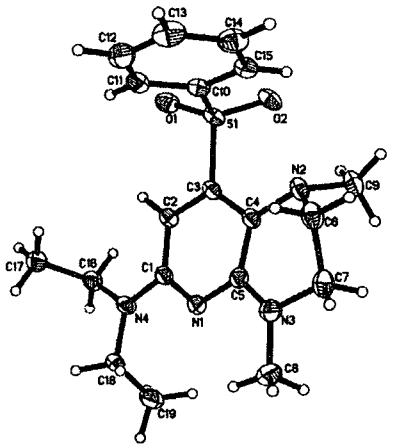


Fig. 4.6d X-Ray Molecular Structure of **55**

The formation of **55** could occur via a single electron transfer process such as that shown in Fig. 4.6e.

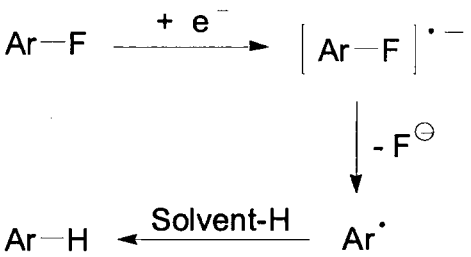


Fig. 4.6e Possible mechanism for the formation of **55**

The fused ring system could accept an electron from the electron rich binucleophile to form a radical anion which then loses a fluoride ion. It may then be possible for the resulting radical to abstract a proton from the solvent to give **55**.

Similar reactions were attempted as discussed below, and this replacement of fluorine by hydrogen is only observed for this particular substituent/binucleophile combination i.e. only when N,N'-diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine **41a** is reacted

with *N,N'*-dimethylethylenediamine **2a**. This may be due to the unique electronic properties, the electron affinity, of this ring system which allows the acceptance of an electron necessary for the process outlined in Fig. 4.6e to begin. Little is understood about the process behind the formation of **55** and further study into this area is required before a concrete mechanism can be proposed.

The reaction of **44a** with **2a** was also attempted in order to investigate this functionalisation strategy further (Fig. 4.6f).

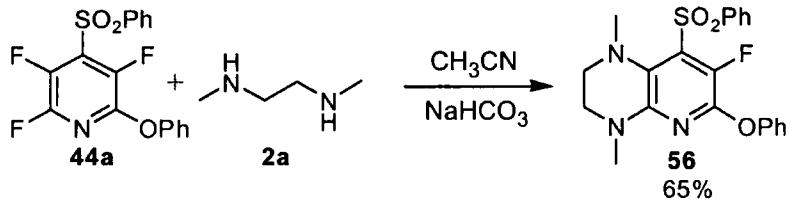


Fig. 4.6f Formation of **56**

It can be seen that the desired fused ring system **56** was successfully obtained in a 65% yield and no replacement of fluorine by hydrogen was observed, however, when reaction of **41a** with the unsymmetrical binucleophile **5a** was attempted, no fused ring system was obtained, and instead the uncyclised product **57** was isolated in a 58% yield after 6 d at reflux (Fig. 4.6g).

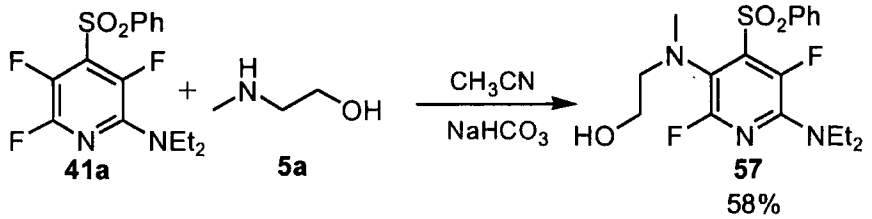


Fig. 4.6g Formation of **57**

It would appear that the diethylamine group in **41a** is sufficiently electron donating to deactivate the aromatic ring towards nucleophilic attack and stop cyclisation occurring completely when a less reactive binucleophile is used. The position of attack by **5a** was determined by ^{19}F NMR data (two resonances at -73.3 and -134.3 ppm were observed) and it can be seen that the nitrogen atom of **5a** is attached to the pyridine ring as coupling between the ring fluorine atom and the methyl group at the nitrogen centre can be observed. Attack of **5a** *ortho* to the phenylsulfonyl group occurs analogous to the formation of disubstituted **41b**, and this position of attack is not deactivated by the presence of a *para* fluorine atom.

After exploring reactions of the fluorinated ring of **29**, a complementary process would be the modification of the non-aromatic ring in some way. This strategy is demonstrated by the reaction of **47** with acetic anhydride in acetic acid (Fig. 4.6h)

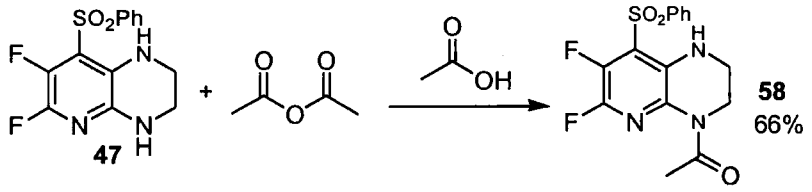


Fig. 4.6h Reaction of **47** with acetic anhydride

The nitrogen atom which is located at the 4-position of the pyrazine ring in **47** is acetylated exclusively. This could be due to steric factors, i.e. the phenylsulfonyl group is hindering the approach of electrophiles to the nitrogen atom at the 1-position, or it could be that the phenylsulfonyl group is withdrawing electron density from this nitrogen rendering this site less nucleophilic. It could be envisaged that the nitrogen atom at the 4-position of the

pyrazine ring could react with many different electrophiles which could add further diversity elements to core scaffolds synthesised using this methodology.

4.7) CONCLUSION

Nucleophilic substitution reactions of 4-nitro-2,3,5,6-tetrafluoropyridine **18i** have been carried out and it was found that all nucleophiles investigated result in some displacement of the nitro group from the 4-position, however, it is possible to form a fused ring system by the reaction of this tetrafluoropyridine derivative with N,N-dimethylethylenediamine **2a**.

Reactions of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **18g** with nucleophiles gave a range of products depending on the 'hardness' or 'softness' of the nucleophile, with 'soft' nucleophiles (e.g. sulfur nucleophiles) resulting in the displacement of the phenylsulfonyl substituent. It is possible to synthesise a variety of [6,6] fused ring systems by the reaction of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine with nitrogen and oxygen binucleophiles, and, in principle, many more than the few shown in this chapter are possible. It is also possible to add diversity elements to these core scaffolds by reaction with nucleophiles or electrophiles, however, occasionally the separation of isomers can be tricky. It is also possible to remove all of the fluorine atoms from one particular fused ring system in what is considered to be a radical mechanism, although more investigation into this reaction is required before it can be exploited synthetically.

4.8) REFERENCES

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RING FORMING REACTIONS OF 2,3,5,6-TETRAFLUORO-4-PYRIDINECARBONITRILE

5.1) INTRODUCTION

The work contained in this chapter further expands upon the work presented in Chapters 3 and 4 which is based upon ring forming reactions of binucleophiles with tetrafluoropyridine derivatives. This chapter focuses upon the use of 2,3,5,6-tetrafluoropyridine-4-carbonitrile **18h** in annelation reactions of this sort. It is known that the cyano group strongly activates an aromatic ring towards nucleophilic aromatic substitution and in addition is a poor leaving group in such reactions, so could suitably 'block' the 4-position of polyfluorinated pyridine derivatives towards attack by binucleophiles in contrast to nitro and phenylsulfonyl systems discussed previously.[1] These properties of the cyano substituent are potentially ideal for promoting the desired ring forming reactions outlined in previous chapters (Fig. 5.1a).

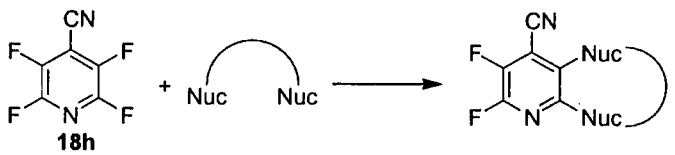


Fig. 5.1a Synthesis of fused ring systems from **18h**

The cyano group is also a versatile substituent that can be transformed into many different functional groups, for example, carboxylic acids, ketones and amines. The initial focus of this chapter concerns the use of **18h** as a starting material for the familiar ring forming

reactions that are discussed in previous chapters and shown in Fig. 5.1a, and then the focus shifts to the utilisation of this substrate in a further type of annelation procedure.

5.2) REACTIONS OF 2,3,5,6-TETRAFLUORO-4-PYRIDINECARBONITRILE 18h WITH MONOFUNCTIONAL NUCLEOPHILES

2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** can be prepared in one of two ways; either by the low yielding reaction of pentafluoropyridine with sodium cyanide which is difficult to control, or by the reaction of 2,3,5,6-tetrachloro-4-pyridinecarbonitrile and potassium fluoride (Fig. 5.2a).[2]

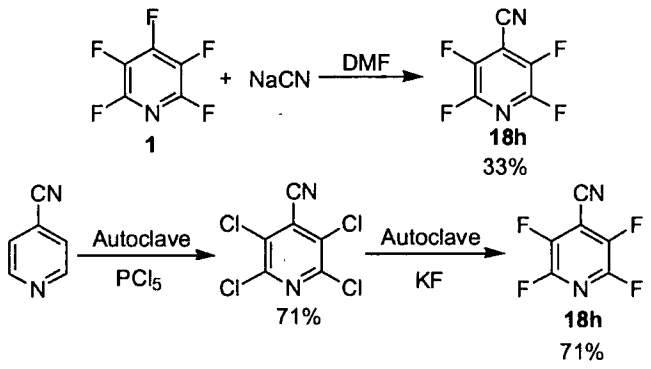
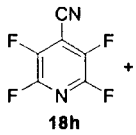
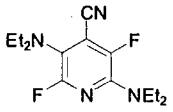
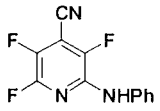
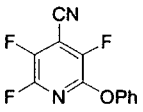
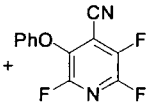
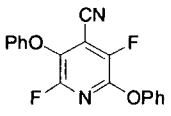
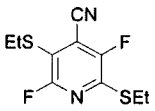
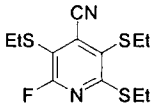
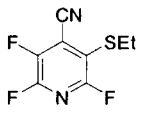
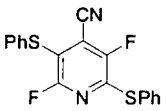


Fig. 5.2a Synthesis of **18h**

We decided to establish the effects of the cyano substituent upon the reactivity of the pyridine ring of **18h** by reaction with various nucleophiles, analogous to work previously described involving reactions of 4-nitro-2,3,5,6-tetrafluoropyridine and 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine. The results of these reactions are shown in Table 5.2a.



18h + Nucleophile —Conditions→ Products

Nucleophile	Conditions	Product(s) (yield)
$NHEt_2$	$NaHCO_3/CH_3CN$	 **59a** 17% +  **59b** 50% 1:68
$PhNH_2$	$NaHCO_3/CH_3CN$	 **60** 93%
EtONa	CH_3CN	 **61a** +  **61b** 3:1, 87%
PhOH	$NaHCO_3/CH_3CN$	 **62a** * +  **62b** 20% +  **62c** * 1:2.7:1.6
EtSH 2 eq	$NaHCO_3/CH_3CN$	 **63a** +  **63b** +  **63c** * + Others 9:3:1 10%
PhSH 2 eq	$NaHCO_3/CH_3CN$	 **64** 63%

Products **61a** and **61b** were isolated as a mixture of compounds in the ratio 94:1 respectively, and products **63a** and **63b** were also isolated as a mixture in the ratio 32:1.

* Products not isolated but presence confirmed by ^{19}F NMR and mass spectral data.

Others specifies unidentifiable products

Table 5.2a Reactions of **18h** with nucleophiles

In all of the reactions shown in Table 5.2a, the cyano substituent remains attached to the aromatic ring indicating that it is a very good 'blocking group' for the 4-position of the pyridine ring for reasons discussed previously. It can also be seen that the strongly electron

withdrawing cyano group significantly activates the aromatic ring, especially at the adjacent 3- and 5-positions, to give products resulting from multiple substitutions,[3] and in some cases this effect competes significantly with activation of the 2- and 6-positions by the pyridine ring nitrogen. Of course this is advantageous in ring forming reactions where less reactive binucleophiles are used and activation of the 3-position is required for cyclisation to occur. The position of attack of the nucleophiles was determined by a consideration of ^{19}F NMR data and, in particular, the structure of **60** was confirmed by X-ray crystallography (Fig. 5.2b).

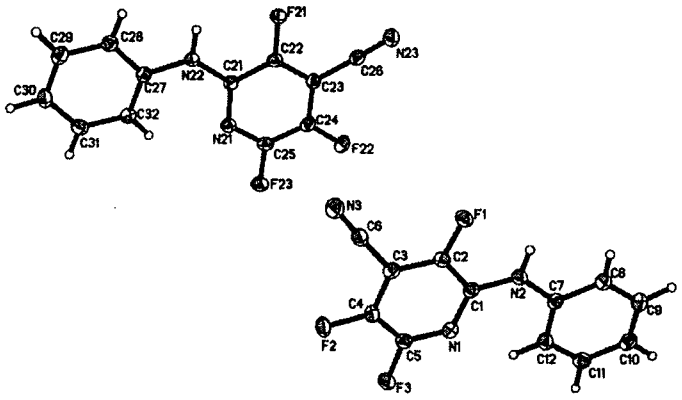


Fig 5.2b X-Ray Molecular Structure of **60**

Two equivalents of ethanethiol and benzenethiol were required in order to obtain significant conversion of starting material and in both these cases it can be seen that the products obtained, **63a-63c** and **64**, are the result of multiple substitutions by the nucleophile. The reactions of **18h** outlined in Table 5.2 have shown that secondary amine nucleophiles attack the aromatic ring selectively and therefore analogous binucleophiles such as N,N-dimethylethylenediamine should react favourably to form the desired fused ring systems. It can also be seen that sulfur and oxygen nucleophiles do not attack the aromatic ring in a selective manner and therefore, based on these findings, symmetrical

oxygen and sulfur binucleophiles may be required for successful annelation reactions. In light of these results, investigations moved onto the reactions of **18h** with binucleophiles, and the results are outlined in the following section.

5.3) REACTIONS OF 2,3,5,6-TETRAFLUORO-4-PYRIDINECARBONITRILE 18h WITH BIFUNCTIONAL NUCLEOPHILES

Reactions of **18h** with various binucleophiles were carried out and the results are presented in Table 5.3a. All reactions were conducted under high dilution conditions to avoid the formation of pyridine bridged products and in the presence of sodium hydrogen carbonate as base. Reactions were monitored by ^{19}F NMR and the disappearance of signals attributed to the fluorine atoms at the 2- and 3-positions of **18h** (-85.4 and -133.1 ppm respectively) and the appearance of signals attributed to the fluorine atoms at the 6- and 7-positions of the fused ring systems (approximately -100 and -150 ppm respectively) were observed.

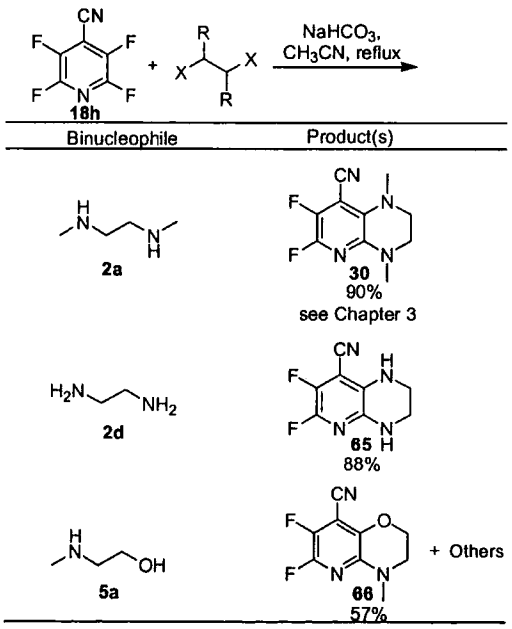


Table 5.3a Reactions of **18h** with binucleophiles

Initially **18h** was reacted with *N,N'*-dimethylethylenediamine **2a** as described in Chapter 3. The reaction of **18h** was then attempted with the primary amine binucleophile **2d** as it was hoped the cyano group would strongly activate adjacent 3- and 5-positions, encouraging cyclisation of this less reactive binucleophile to occur. Indeed, the desired fused ring product **65** was formed in good yield. In contrast, reaction with the unsymmetrical binucleophile **5a** gave the desired fused ring system **66** along with small amounts of other products which were thought to be a result of multiple substitutions by **5a**. The structure of **66** was confirmed by X-ray crystallography (Fig. 5.3a), and it is assumed that the more nucleophilic nitrogen of **5a** attacks first at the 2-position in agreement with the reaction of diethylamine and **18h** in which initial attack occurs exclusively at this position.

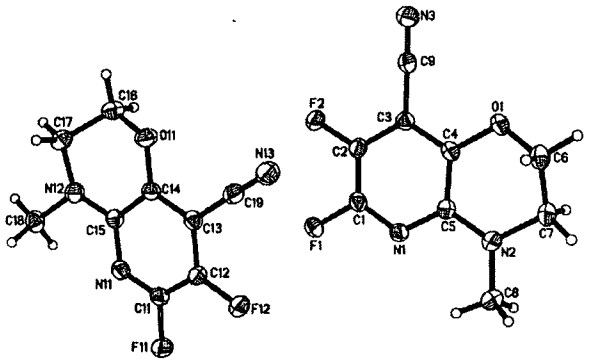


Fig. 5.3a X-Ray Molecular Structure of **66**

In Chapter 4 it was established that it is possible to further functionalise both rings of [6,6] fused ring structures obtained by the methodology outlined in this thesis, an alternative functionalisation strategy would be to vary the substituent *para* to the pyridine ring nitrogen after fusion of the second ring. Reaction of phenyl lithium led to transformation of the cyano group of **30** into a ketone rather than substitution at the pyridine ring (Fig. 5.3b).

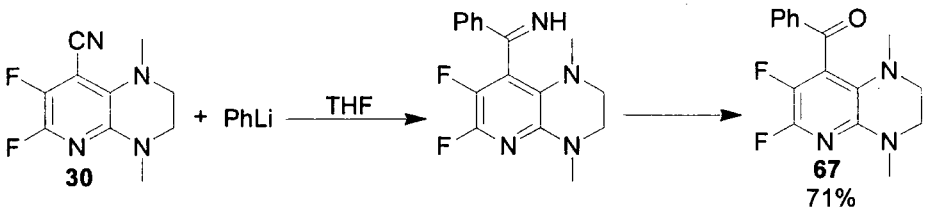


Fig. 5.3b Synthesis of **67**

Reaction of **18h** with the carbon/oxygen binucleophile ethyl acetoacetate shown in Fig. 5.3c led to a surprising result.

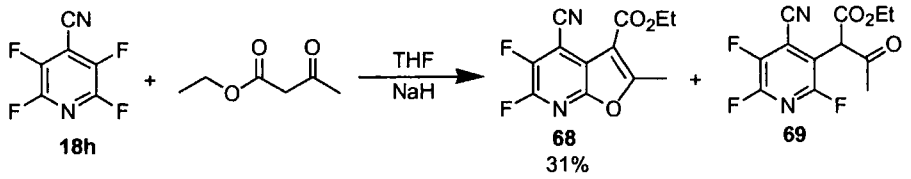


Fig. 5.3c Synthesis of **68** and **69**

Ethyl acetoacetate initially attacked *ortho* to the cyano group, and cyclisation occurred at the 2-position *ortho* to the pyridine ring nitrogen to form a 5-membered ring which is kinetically favoured over attack at the cyano group to give a 6-membered ring. The structure of **68** was confirmed by X-ray crystallography (Fig. 5.3d). Compound **69** was also isolated in an 18% yield and gives **68** in the presence of sodium hydride. If the initial reaction was refluxed for longer it would be possible to convert all of the isolated intermediate **69** through to **68** in one step. Facile routes to functionalised furo[2,3-*b*]pyridines like **68** are highly sought after as such compounds are useful in the search for pharmacologically active substances and are also parent systems for naturally occurring products such as furoquinolines and pterocarpans.[4]

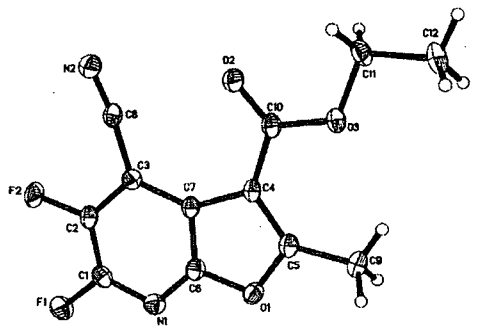
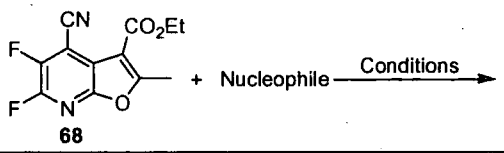


Fig. 5.3d X-Ray Molecular Structure of **68**

Fused ring system **68** was then reacted with oxygen, sulfur and nitrogen nucleophiles in order to establish if this type of [5,6] fused ring system is activated towards attack by nucleophiles in an analogous manner to [6,6] fused ring systems. The results are shown in Table 5.3b.



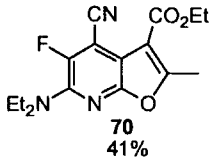
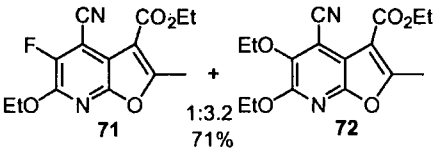
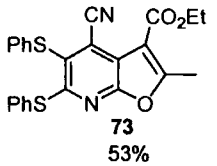
Nucleophile	Conditions	Product(s)
NEt_2Li	THF	 **70** 41%
EtONa excess	EtOH	 **71** + 1:3.2 **72** 71%
PhSLi 2 eq	THF	 **73** 53%

Table 5.3b Reactions of **68** with nucleophiles

Again it can be seen that when **68** is reacted with the nucleophiles shown in Table 5.3b, the cyano group is not affected and the fused ring system is activated towards this process. Reaction with sodium ethoxide and lithium thiophenoxide required an excess of nucleophile in order to obtain significant conversion and the products obtained are a result of multiple substitutions, and even the replacement of all the fluorine atoms in the system. Reaction with lithium diethylamide gives **70**, the position of attack determined by a consideration of ^{19}F NMR data, in which one resonance was observed at -131.4 ppm.

As the reaction of **18h** with ethyl acetoacetate successfully gave the [5,6] fused ring system **68**, the analogous reaction was carried out with 3-oxo-3-phenyl-propionic acid ethyl ester (Fig. 5.3e).

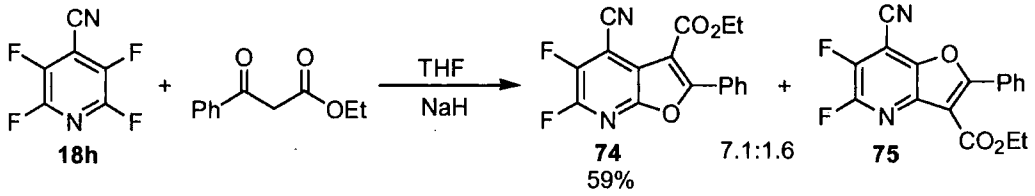


Fig. 5.3e Formation of **74**

The reaction mixture was heated at reflux for 6 d and no uncyclised intermediate remained. Two isomeric [5,6] fused ring systems **74** and **75** were formed as a result of the initial attack of the binucleophile at both the 2- and 3-positions, and **74** was isolated in a 59% yield. The structure of **74** was assigned by a comparison with ^{19}F and ^{13}C NMR data for **68**. It is unclear as to why two isomeric fused ring systems are formed when 3-oxo-3-phenyl-propionic acid ethyl ester is used as the binucleophile and only one fused ring system is

formed when ethyl acetoacetate is used, and more investigations need to be completed in order to establish the underlying reasons behind the formation of these products.

5.4) FUSED RING SYSTEM FORMATION BY INTRAMOLECULAR CYCLISATION REACTIONS INVOLVING THE CYANO GROUP

In order to investigate if it is possible to utilise the cyano group of **18h** in ring forming reactions the literature procedure shown in Fig. 5.4a was applied to polyfluorinated pyridine derivative **18h**.

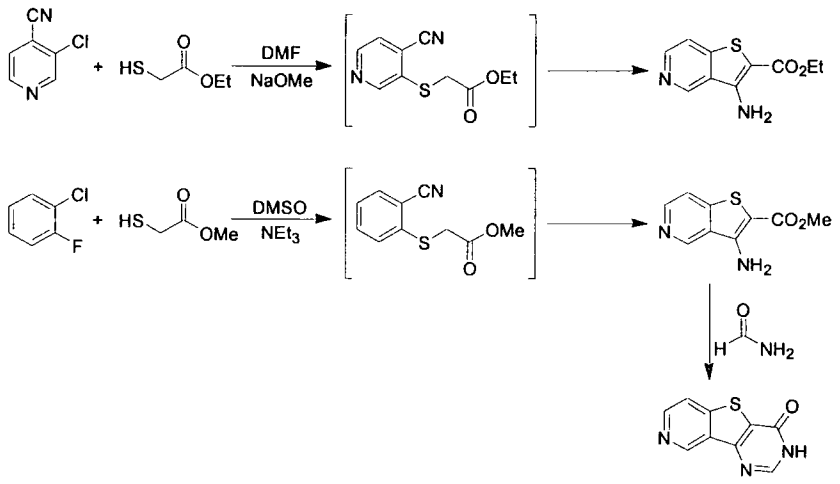


Fig. 5.4a Reaction of 3-chloroisonicotinonitrile[5] and 2-fluoro-benzonitrile[6] with mercapto-acetic acid ethyl ester and mercapto-acetic acid methyl ester

In the first procedure shown in Fig. 5.4a, 3-chloroisonicotinonitrile is reacted with mercapto-acetic acid ethyl ester to give a [5,6] fused ring system. Fig. 5.4b shows the application of this procedure to the reaction of **18h**. The second procedure shown in Fig. 5.4a is tolerant of many different functional groups around the aromatic ring so it is

envisaged that functionalised 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile derivatives could be used as starting materials for this sort of process.

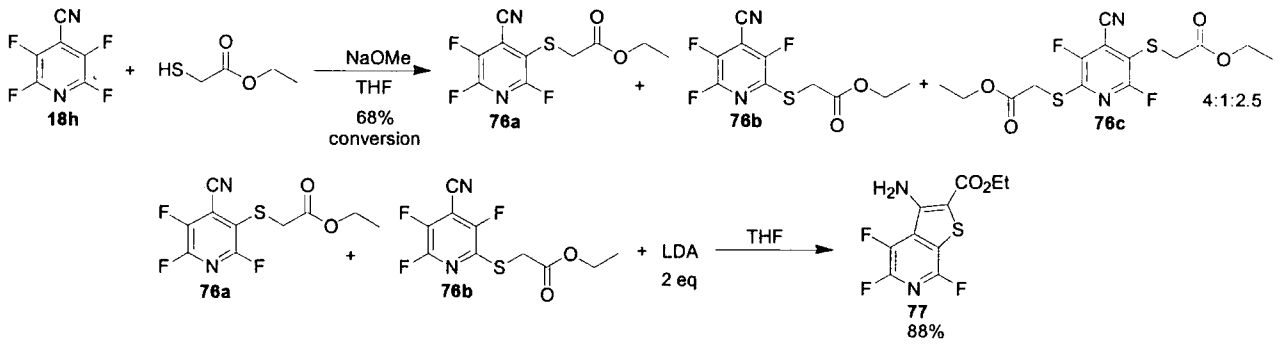


Fig. 5.4b Synthesis of **77**

It can be seen that reaction of **18h** with mercapto-acetic acid ethyl ester in the presence of sodium methoxide as base gave the three uncyclised products **76a-c**. Although it was possible to separate **76a** and **76b** from **76c** it was not possible to isolate **76a** alone. Reaction of the mixture of **76a** and **76b** with LDA in THF gave **77**, the structure confirmed by X-ray crystallography (Fig. 5.4c).

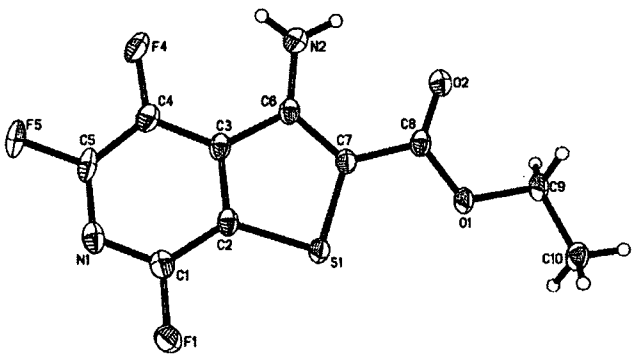


Fig. 5.4c X-Ray Molecular Structure of **77**

Disubstituted product **76c** can also be reacted with LDA to give the cyclised system **78** (Fig. 5.4d). This reaction is useful as it gives access to a fused ring system containing added functionality that can be exploited in further reactions.

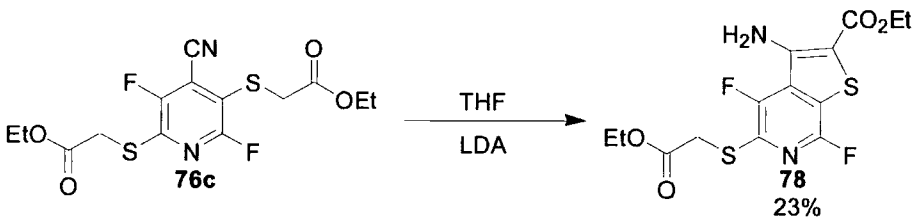


Fig. 5.4d Synthesis of **78**

5.5) CONCLUSION

In this chapter it has been shown that [6,6] fused ring systems can be synthesised from 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile **18h** by reaction with 1,2-binucleophiles containing nitrogen and oxygen atoms. [5,6] fused ring systems can also be synthesised by reaction of **18h** with ethyl acetoacetate and other dicarbonyl compounds which can be reacted further with nucleophiles to give highly functionalised fused ring derivatives. The cyano substituent of **18h** can also be used in ring forming reactions itself in an intramolecular cyclisation reaction to give [5,6] fused ring systems that could in principle be reacted further. This and previous chapters have demonstrated that a vast number of fused ring systems can be synthesised from pentafluoropyridine and 4-substituted tetrafluoropyridine derivatives by reaction with binucleophiles. The next chapter moves on to apply this type of methodology to other pyridine and diazine derivatives.

5.6) REFERENCES

1 C. Paradisi, 'Comprehensive Organic Synthesis', Vol. 4, Chap. 2.1, Pergamon Press, 1991.

2 R. E. Banks, R. N. Haszeldine, and I. M. Young, *J. Chem. Soc. (C)*, 1967, **20**, 2089.

3 C. J. Drayton, W. T. Flowers, and R. N. Haszeldine, *J. Chem. Soc., Perkin Trans. 1*, 1975, **11**, 1029.

4 W. Friedrichsen, 'Comprehensive Heterocyclic Chemistry', ed. A. R. Katritzky, Vol. 3, Chap. 3.17, Pergamon Press, 1984.

5 W. W. Mederski, D. Kux, M. Knoth, and M. J. Schwarzkopf-Hormann, *Heterocycles*, 2003, **60**, 925.

6 A. J. Bridges and H. Zhou, *J. Heterocycl. Chem.*, 1997, **34**, 1163.

RING FORMING REACTIONS OF 2,4,6-TRIBROMO-3,5-DIFLUOROPYRIDINE AND HIGHLY FLUORINATED DIAZINES

6.1) INTRODUCTION

The final discussion chapter of this thesis focuses upon the use of the ring forming fluorine displacement methodology that has been developed in previous chapters for highly fluorinated pyridine derivatives and applies it to structurally related starting materials. For example, our strategy has been extended to investigate the use of perhalogenated diazines, e.g. tetrafluoropyrimidine, which is approximately 10^4 times more reactive than pentafluoropyridine in nucleophilic aromatic substitution reactions as a result of the extra nitrogen atom which lowers the energy of the LUMO level.[1] As well as investigations into the use of perfluoro-diazines in ring forming reactions, this chapter also examines reactions of polyfunctional pyridine 2,4,6-tribromo-3,5-difluoropyridine. This heteroaromatic is interesting as it could potentially provide access to fused ring systems containing a mixture of fluorine and bromine substituents which could act as very effective scaffolds. Before discussing the ring forming reactions of tetrafluoropyrimidine and tetrafluoropyrazine, it is necessary to briefly review the existing, although relatively limited, literature concerned with the synthesis and reactions of such systems, and this is the topic of the following section.

6.2) SYNTHESIS AND REACTIONS OF PERHALOGENATED DIAZINES

Perfluorinated diazines can be synthesised in much the same way as pentafluoropyridine, i.e. by halogen exchange reactions using either potassium fluoride or silver fluoride (Fig. 6.2a).[2-4]

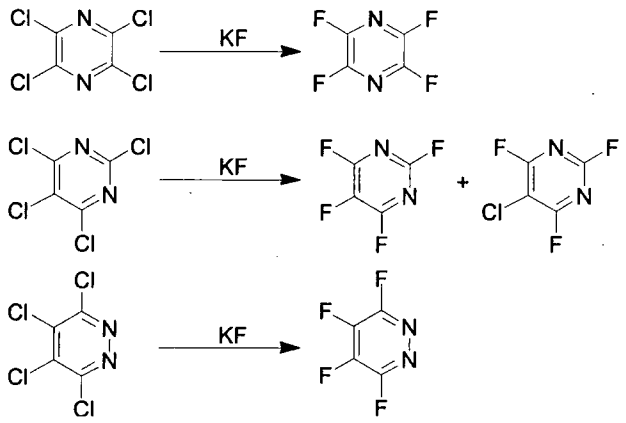


Fig. 6.2a Synthesis of perfluorinated diazines

All of the perfluorinated diazines shown in Fig. 6.2a readily undergo nucleophilic substitution and the following sections are concerned with such reactions.

6.2.1) Reactions of Tetrafluoropyrimidine and 5-Chloro-2,4,6-trifluoropyrimidine with Nucleophiles

Tetrafluoropyrimidine readily undergoes nucleophilic displacement of fluorine from the 4-position under mild conditions. More forcing conditions can cause displacement of fluorine from position 6 and subsequently position 2, although the fluorine at the 5-position resists displacement and replacement of all fluorine atoms has only been reported when di-*n*-butyl-amine was used as the nucleophile (Fig. 6.2.1a).[5]

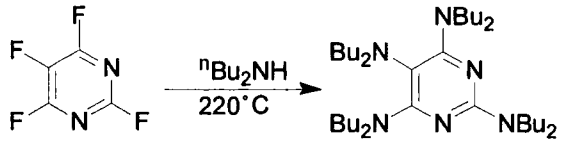
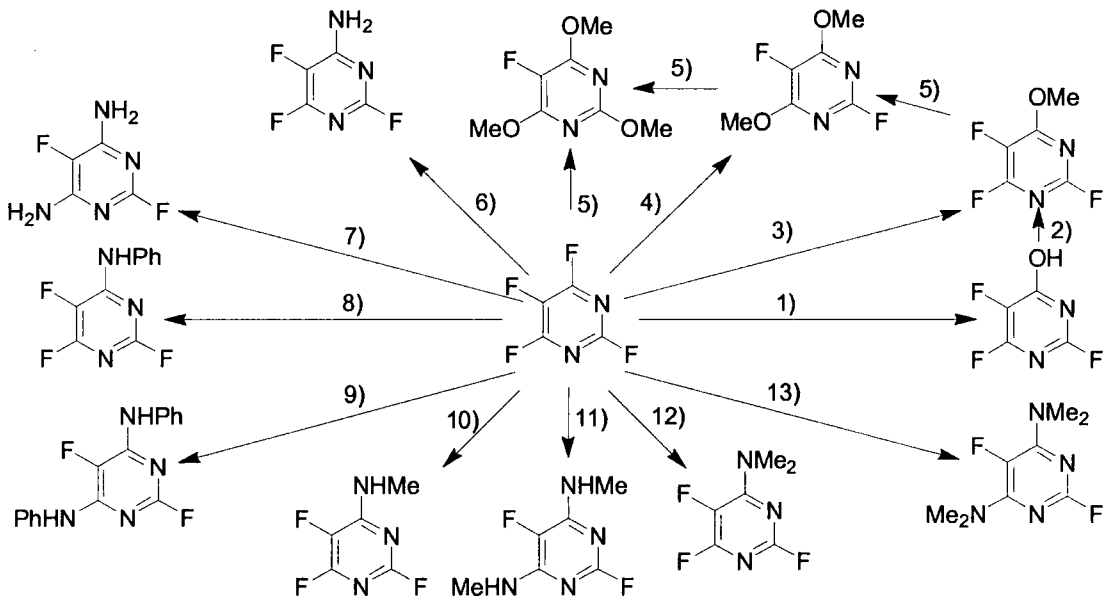


Fig. 6.2.1a Reaction of tetrafluoropyrimidine with di-*n*-butyl-amine

The orientation of nucleophilic attack in tetrafluoropyrimidine can be explained using similar arguments to those applied to pentafluoropyridine which are discussed in the introduction. A short series of reactions of tetrafluoropyrimidine with nucleophiles have been carried out[6-13] and the results of some of these reactions are shown in Fig. 6.2.1b.[14]



1) H_2O/THF, RT; 2) CH_2N_2/ether, 20°C; 3) MeOH/Na_2CO_3, RT; 4) MeOH/MeONa, 0°C; 5) MeOH/MeONa, reflux; 6) NH_3 (aq), RT; 7) NH_3 (aq), 60°C; 8) $PhNH_2$/Na_2CO_3/THF, -15°C; 9) $PhNH_2$/THF, reflux; 10) $MeNH_2$ (aq), 0-20°C; 11) $MeNH_2$ (aq)/DMF; 12) Me_2NH (aq), 0-20°C; 13) Me_2NH (aq)/DMF, 60°C

Fig. 6.2.1b Reactions of tetrafluoropyrimidine with nucleophiles

5-Chloro-2,4,6-trifluoropyrimidine, which is the by-product of the formation of tetrafluoropyrimidine, is also susceptible to attack by nucleophiles and a selected number of examples of this type of reaction are shown in Fig. 6.2.1c.[15, 16]

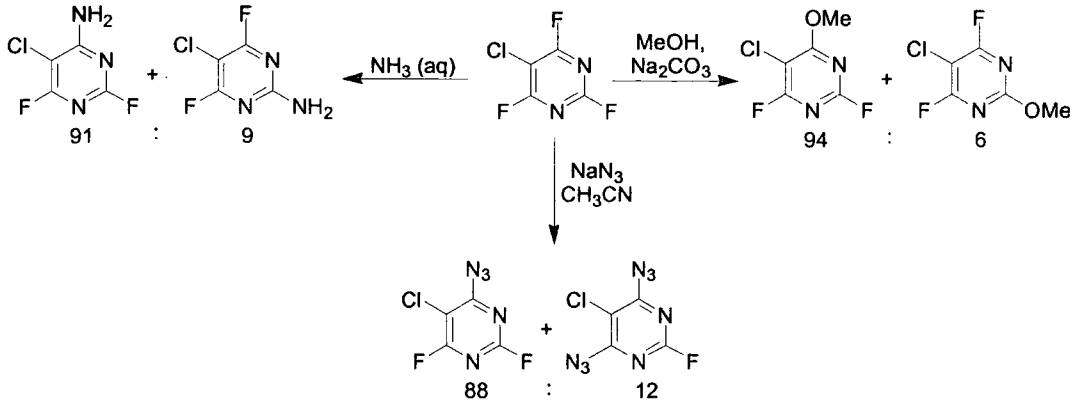


Fig. 6.2.1c Reactions of 5-chloro-2,4,6-trifluoropyrimidine with nucleophiles

6.2.2 Reactions of Tetrafluoropyrazine with Nucleophiles

It is known that nucleophilic aromatic substitution of monocyclic nitrogen containing perfluoroheteroaromatic systems occurs almost exclusively at positions *para* to the nitrogen atom.[17] Tetrafluoropyrazine is therefore of special interest as it possesses no fluorine atoms in this *para* position, and all of the fluorine atoms are equivalent in their orientation with respect to the ring nitrogen atoms. This means that the position of attack of a second nucleophile is controlled by the first, in competition with the effect of the remaining fluorine atoms. Again, only a limited number of reactions of tetrafluoropyrazine with nucleophiles have been carried out and a selection of these are shown in Fig. 6.2.2a.[18]

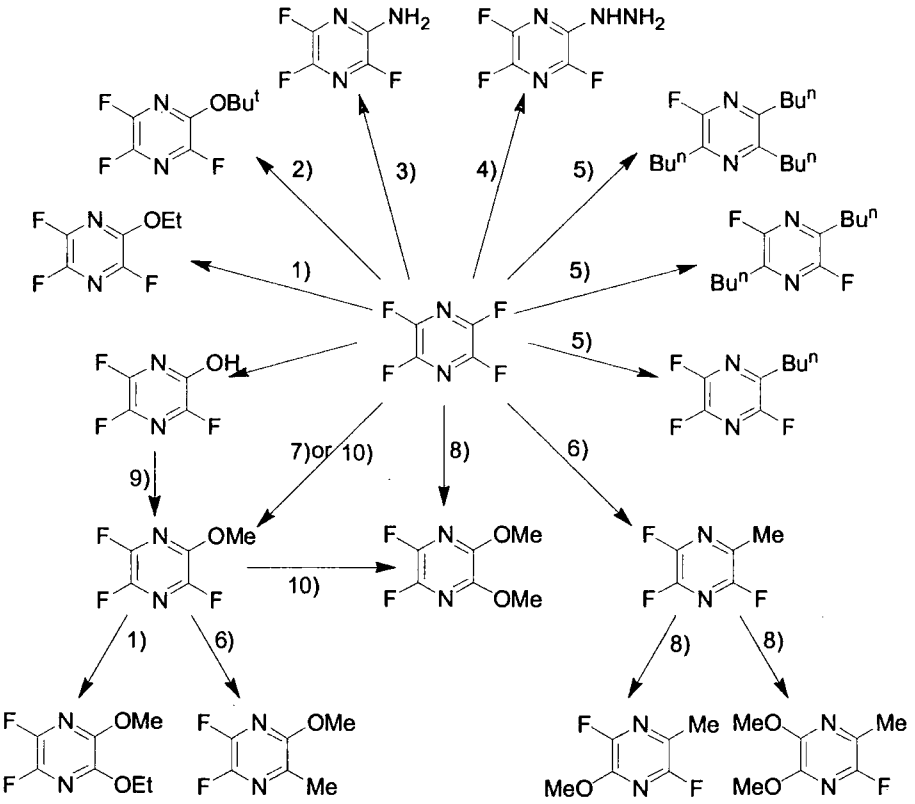


Fig. 6.2.2a Reactions of tetrafluoropyrazine with nucleophiles

The above scheme shows that the orientation of disubstitution in tetrafluoropyrazine depends on the initial substituent; alkoxy groups direct *ortho* while other groups shown direct *para*. Some examples of *meta* direction are known and are shown in Fig. 6.2.2b.[19, 20]

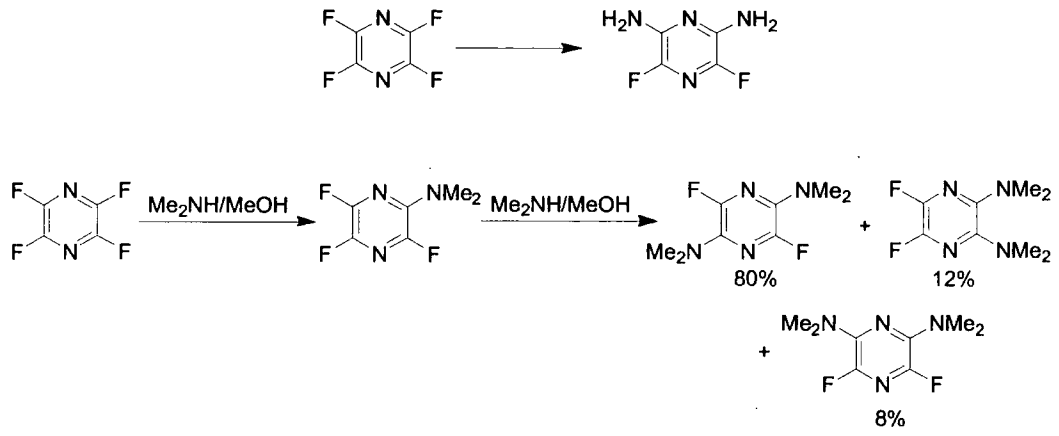


Fig. 6.2.2b Reaction of tetrafluoropyrazine with ammonia and Dimethylamine

It is not unexpected that alkyl groups direct a second nucleophilic substitution to the *para* position as it is known that *para* fluorine atoms are deactivating towards nucleophilic aromatic substitution (see Section 1.5.1). Methoxy and amino groups are strongly deactivating and it was thought that these groups would control the orientation of further substitution and direct attack towards the *meta* positions. However, further nucleophilic attack on 2,3,5-trifluoro-6-methoxy-pyrazine led to *ortho* attack (Fig. 6.2.2a), and further attack on dimethyl-(3,5,6-trifluoro-pyrazin-2-yl)-amine led principally to *para* attack (Fig. 6.2.2b).

These results indicate that the pattern of further substitution in the fluorinated pyrazine derivatives discussed above cannot be explained by the orienting influence of either the fluorine atoms or the other substituents (methoxy and dimethylamino). One alternative explanation for these results is outlined below. In the transition state of a nucleophilic aromatic substitution reaction, a nitrogen atom *ortho* to the position of attack will have a high electron density (Fig. 6.2.2c).

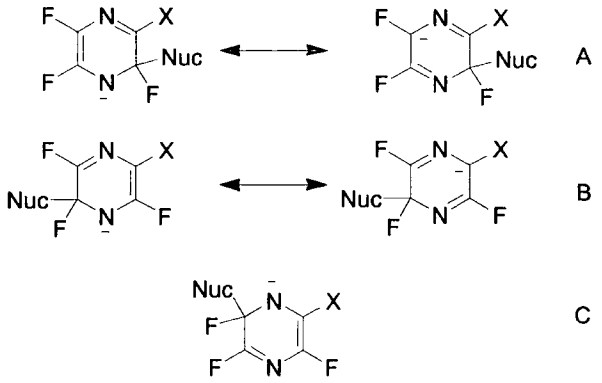


Fig. 6.2.2c Transition states for nucleophilic substitution reactions of tetrafluoropyrazine

For reasons previously discussed (see Section 1.5.1) a fluorine atom attached to a carbon adjacent to a negatively charged centre is strongly stabilising, and in situations A and B in Fig. 6.2.2c this is indeed the case. Situation C has a substituent (methoxy or dimethylamino) in the adjacent position and therefore should be much less stable. The preference for A over B is less clear but may be due to the presence of charge on the *para* positions therefore the resonance form of A on the right hand side of Fig. 6.2.2c may be more stable than the corresponding resonance form of B depending on the substituent X.

The reaction of tetrafluoropyrazine with the binucleophile ethylene glycol has been reported to give a polymer (Fig. 6.2.2d).[18]

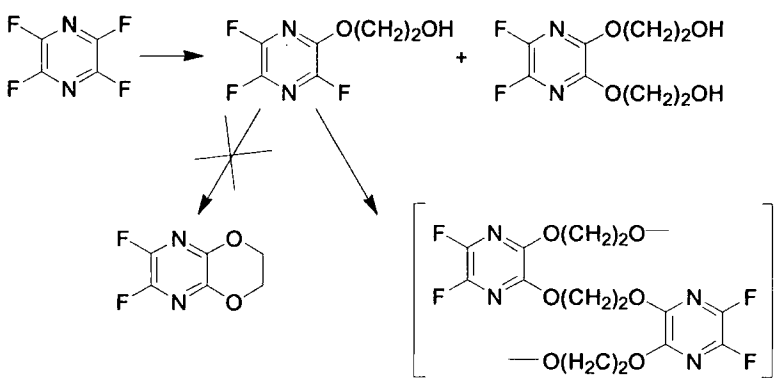


Fig. 6.2.2d Reaction of tetrafluoropyrazine with ethylene glycol

This concludes the brief review of the literature concerning the synthesis and reactions of perhalogenated diazines and the following sections are concerned with a discussion of the work which has been completed on such systems as part of this thesis.

6.3) REACTIONS OF TETRAFLUOROPYRAZINE

6.3.1) Reactions of Tetrafluoropyrazine with mononucleophiles

Tetrafluoropyrazine **79** was synthesised in the manner discussed above and reactions were initially carried out with the mononucleophiles lithium diethylamide and lithium thiophenoxide in order to assess the reactivity of the ring system (Fig. 6.3.1a).

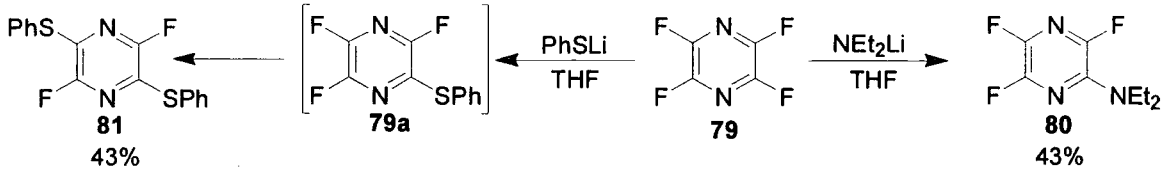


Fig. 6.3.1a Reactions of **79** with lithium diethylamide and lithium thiophenoxide

As with all previous reactions of this type, conversion of starting material was monitored by ^{19}F NMR with a single resonance for **79** appearing at -95.7 ppm. Reaction with lithium diethylamide occurred at room temperature and reaction with lithium thiophenoxide gave polysubstituted products even when a deficiency (0.9 eq) was used. It is reasonably assumed that the phenylsulfanyl substituent of **79a** directs the second substitution to the *para* position, thus maximising the number of activating *ortho* and *meta* fluorine atoms and avoiding a deactivating *para* fluorine.

6.3.2) Reactions of Tetrafluoropyrazine with Symmetrical Binucleophiles

As it was shown in the previous section that it is possible to add a diethylamine substituent to **79** at room temperature, the related reaction of pyrazine **79** with binucleophile N,N'-dimethylethylenediamine **2a** was attempted (Fig. 6.3.2a).

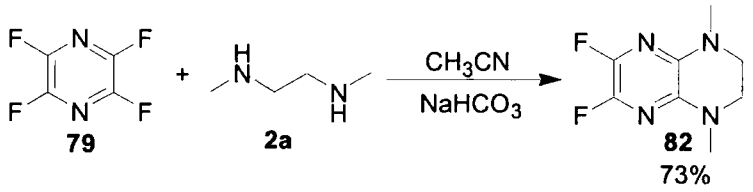


Fig. 6.3.2a Reaction of **79** with **2a**

The reaction occurred readily at room temperature under high dilution conditions and **82** was isolated in good yield after purification by recrystallisation from dichloromethane. The structure was confirmed by X-ray crystallography (Fig. 6.3.2b). Again the progress of the reaction was monitored by ^{19}F NMR with a new peak, at -118.6 ppm, attributed to the two identical fluorine atoms of **82**.

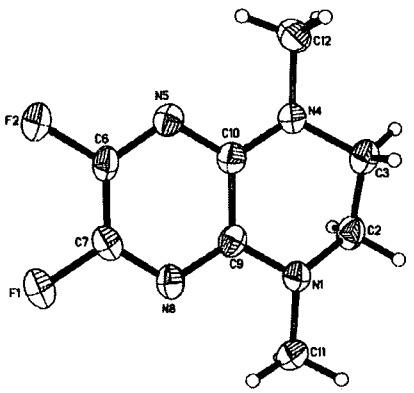


Fig. 6.3.2b X-Ray Molecular Structure of **82**

Reaction with the less nucleophilic primary amine binucleophile **2d** required reflux conditions in order to achieve cyclisation (Fig. 6.3.2c) and it was possible to isolate the desired fused ring product **83** in average yield. Fused ring system **83** is an extremely insoluble solid in both aqueous and organic solvents and the lower yield obtained is a result of difficulties in purification of the crude product.

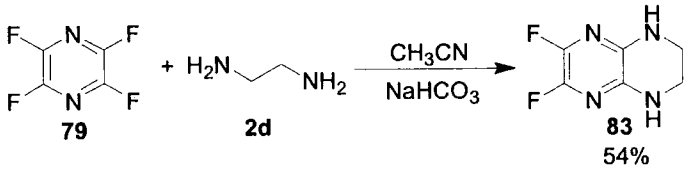


Fig. 6.3.2c Reaction of pyrazine **79** with **2d**

6.3.3) Reaction of Tetrafluoropyrazine with Unsymmetrical Binucleophiles

The previous section showed that it is possible to form symmetrical [6,6] fused ring systems by the reaction of tetrafluoropyrazine with certain binucleophiles. However, the reaction of pyrazine **79** with the unsymmetrical binucleophile 2-methylaminoethanol **5a** proved not to be so straightforward. Initially the reaction was carried out under high dilution conditions using 2 equivalents of **5a** and the results are shown in Fig. 6.3.3a.

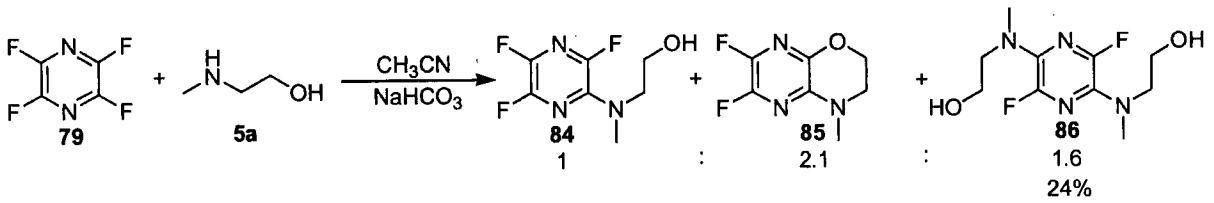


Fig. 6.3.3a Reaction of **79** with 2 equivalents of **5a**

Three products are formed, the monosubstituted compounds **84** and **85** along with the disubstituted product **86** isolated in 24% yield. Products **84** and **85** could only be identified

by a combination of ^{19}F NMR and mass spectral data. It was not possible to obtain a crystal structure of pyrazine **86** so that the relative positions of the two amino substituents could be unambiguously determined. It is reasonable to assume that the nitrogen atoms are bonded to the heteroaromatic ring as they are more nucleophilic than the alternative oxygen atoms, and, based on the reaction of tetrafluoropyrazine with dimethylamine forming predominantly the *para* isomer, the *para* orientation of the two substituents in pyrazine **86** is assumed. The reaction was repeated using only one equivalent of binucleophile **5a** in order to minimise the formation of disubstituted product **86** and effect the isolation of product **85** (Fig. 6.3.3b).

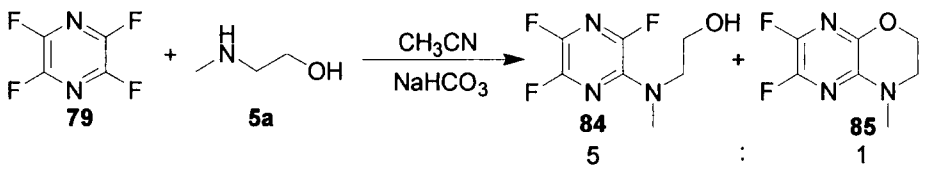


Fig. 6.3.3b Reaction of **79** with 1 equivalent of **5a**

This strategy was successful in suppressing the formation of pyrazine **86**, however, despite attempts at purification by column chromatography, it was still not possible to separate products **84** and **85**. The mixture of **84** and **85** was then reacted with sodium hydride in an attempt to convert **84** into **85**, but no further cyclisation of **84** was observed.

Reaction with 1 equivalent of **5b** was attempted to investigate the possibility of forming an unsymmetrical fused ring system using a nitrogen/sulfur binucleophile, however, the disubstituted system **87** was isolated (Fig. 6.3.3c) and the structure confirmed by X-ray crystallography (Fig. 6.3.3d). The structural confirmation of **87** supports the previous

assumption that the phenylsulfanyl groups of the related disubstituted product **81** are also *para* to one another (Fig. 6.3.1a).

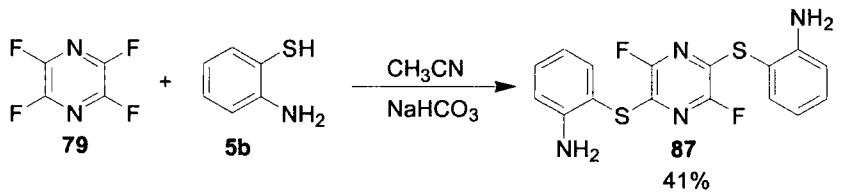


Fig. 6.3.3c Reaction of **79** with **5b**

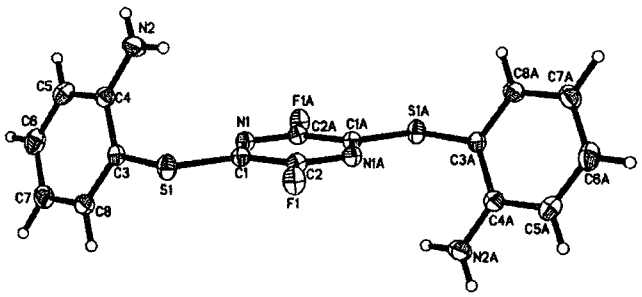


Fig. 6.3.3d X-Ray Molecular Structure of **87**

The possibility of forming unsymmetrical [5,6] fused ring systems using tetrafluoropyrazine **79** as a starting material in reaction with ethyl acetoacetate was then investigated (Fig. 6.3.3e).

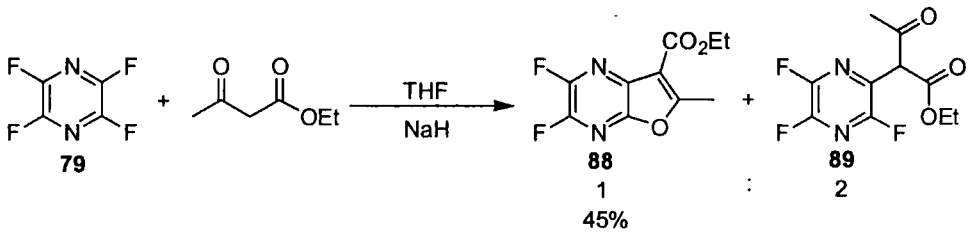


Fig. 6.3.3e Reaction of **79** with ethyl acetoacetate

The reaction occurred at room temperature to give two products; the uncyclised intermediate **89**, identified by ^{19}F NMR and mass spectral data, and the desired fused ring system **88** which could be isolated.

6.4) REACTIONS OF 5-CHLORO-2,4,6-TRIFLUOROPYRIMIDINE WITH BINUCLEOPHILES

5-Chloro-2,4,6-trifluoropyrimidine **90** is readily available, and a brief investigation into the use of this compound as a starting material for the synthesis of fused ring systems is discussed. Initially pyrimidine **90** was reacted with **2a** with the hope of obtaining the desired product **91** (Fig. 6.4a).

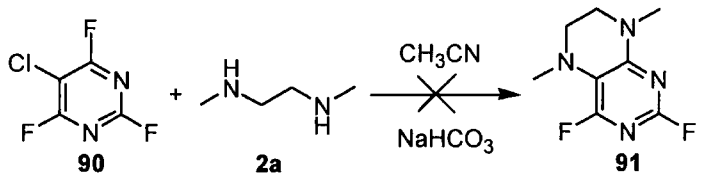


Fig. 6.4a Proposed synthesis of **91**

However, the formation of fused ring system **91** was not observed and instead an intractable mixture of dimers and polymers was formed, from which no pure compound could be isolated. The reaction of **90** with **5b** was also attempted, and in this case the uncyclised product **92** was isolated (Fig. 6.4b).

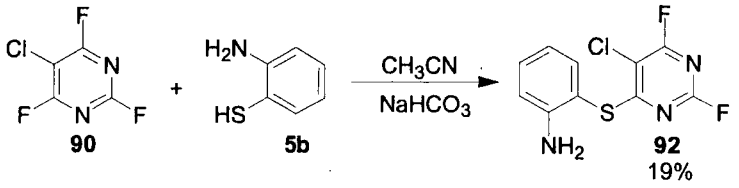
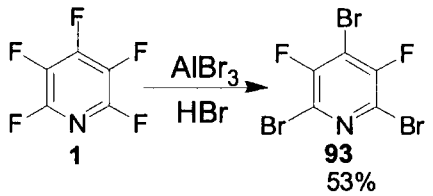


Fig. 6.4b Reaction of **90** with **5b**

Attempts to cyclise **92** by reaction with LDA were unsuccessful because the 5-chloro substituent is very resistant to displacement by nucleophiles. It is known that the 5-position of tetrafluoropyrimidine is relatively unreactive and as a chloro substituent is less activating towards nucleophilic attack than a fluorine atom, the 5-position of 5-chloro-2,4,6-trifluoropyrimidine will be even more unreactive.

6.5) REACTIONS OF 2,4,6-TRIBROMO-3,5-DIFLUOROPYRIDINE WITH BINUCLEOPHILES

Some studies on the reactions of 2,4,6-tribromo-3,5-difluoropyridine **93** have been carried out[21] and it is thought that 'hard' nucleophiles will attack the 'harder' C-F bonds and 'soft' nucleophiles will attack the 'softer' C-Br bonds. The substituted pyridine **93** was synthesised by the reaction of pentafluoropyridine **1** with aluminium bromide and hydrogen bromide in an autoclave following literature procedures (Fig. 6.5a).[21]



1 **93** 53%

Fig. 6.5a Synthesis of **93**

Purification by recrystallisation from dichloromethane gave **93** as a crystalline solid. Reaction of **93** with *N,N'*-dimethylethylenediamine **2a** gave two products, as shown in Fig. 6.5b and it was possible to isolate both systems.

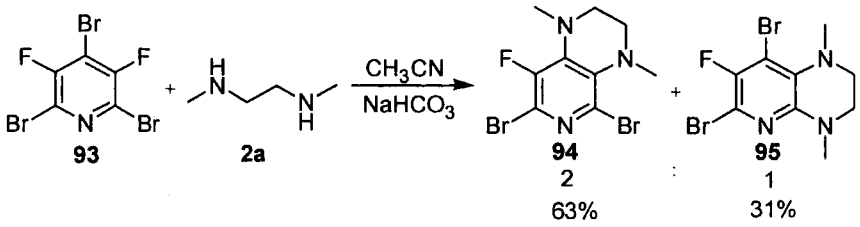


Fig. 6.5b Reaction of **93** with **2a**

The structure of **94** and **95** were confirmed by X-ray crystallography (Fig. 6.5c and 6.5d).

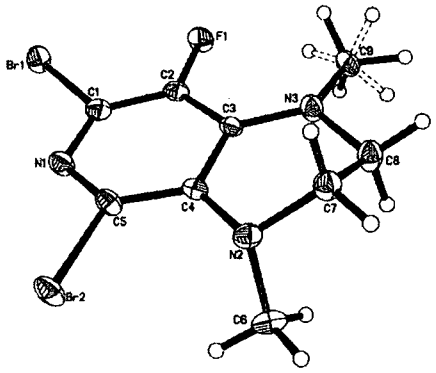


Fig. 6.5c X-Ray Molecular Structure of **94**

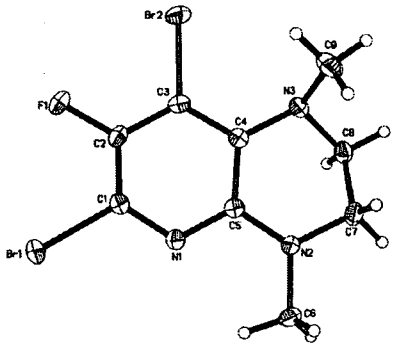


Fig. 6.5d X-Ray Molecular Structure of **95**

An amine nucleophile could be classed as relatively 'hard' so in theory would be expected to attack the C-F bond at the 3-position and cyclise to the 2- and 4-positions to give isomers **94** and **95**. However, attack at the C-Br bond at either the 2- or 4-position with cyclisation to the 3-position would also give the same two products. In this case it is assumed that the first position of attack is at the C-Br bonds at the 2- and the 4-positions, with cyclisation at the 3-position based on the results of the following reaction (Fig. 6.5e).

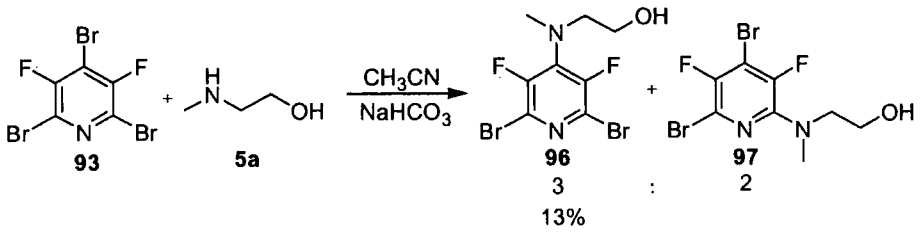


Fig. 6.5e Reaction of **93** with **5a**

Pyridine system **93** was reacted with the unsymmetrical binucleophile **5a** with the aim of synthesising a fused ring system. However, the two products isolated were the uncyclised isomers **96** and **97**, and ^{19}F NMR shows that attack occurred at the 2- and the 4-positions. It would seem that in this reaction the bromine atoms do not provide enough activation of the aromatic ring to encourage the less nucleophilic oxygen atom to cyclise at the 3-position.

As a mixture of two products are obtained when **93** is reacted with binucleophiles this may limit the use of this starting material for the formation of core scaffolds for library synthesis. However, it is possible to form both pyrido[3,4-*b*] and pyrido[2,3-*b*]pyrazines from one starting material which is potentially useful if the two regioisomers are desired. It could also be envisaged that the remaining bromine atoms in the fused ring systems could be further reacted in, for example, palladium catalysed cross coupling reactions or replaced by hydrogen atoms to add diversity to the core scaffolds.

6.6) CONCLUSION

This chapter has demonstrated that it is possible to extend the ring forming fluorine displacement methodology developed in previous chapters to perfluorinated diazines and

other halogenated compounds. The use of 2,4,6-tribromo-3,5-difluoropyridine **93** may be limited by the formation of mixtures of products although it is possible to synthesise the desired [6,6] fused ring systems. Preliminary work on the use of perfluorinated diazines demonstrated that it is possible to form [6,6] fused ring systems and this work will form the basis of a further PhD thesis.

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CONCLUSION

The aim of this piece of research work was to develop effective methodology for the synthesis of fused ring heterocyclic compounds utilising reactions of pentafluoropyridine and various tetrafluoropyridine derivatives with suitable bifunctional nucleophiles. As discussed in the introduction, it can be difficult to obtain fused bicyclic ring compounds using existing methods, and therefore new, efficient and high yielding routes were established. Modification of these fused ring systems in a selective manner gave polyfunctional core scaffolds. The general approach successfully utilised for the synthesis and diversification of fused ring systems using fluoride displacement methodology is outlined in Fig. 7a.

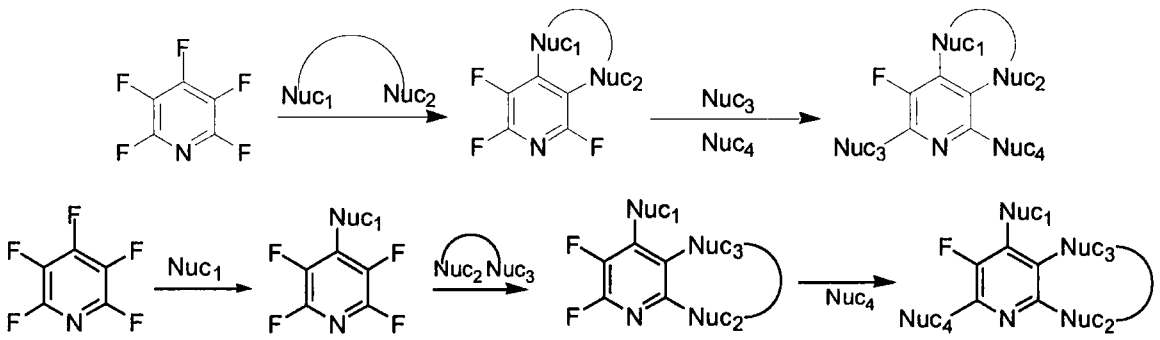


Fig. 7a General approach to the synthesis of fused ring systems by the reaction of pentafluoropyridine and tetrafluoropyridine derivatives with binucleophiles

The work described in the previous chapters demonstrated that it is now possible to synthesise [6,6] fused ring systems by the reaction of pentafluoropyridine and tetrafluoropyridine derivatives such as 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile, 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine and 4-nitro-2,3,5,6-tetrafluoropyridine with suitable binucleophiles e.g. *N,N'*-dimethylethylenediamine and 2-methylaminoethanol among

others. We have also demonstrated that such fused ring systems are activated towards further nucleophilic attack at the remaining fluorinated ring positions, allowing the addition of a number of substituents to the pyridine ring system. There is a vast range of compounds that can be synthesised by the fluoride displacement methodology developed within this thesis and several of the systems successfully synthesised are shown in Fig. 7b.

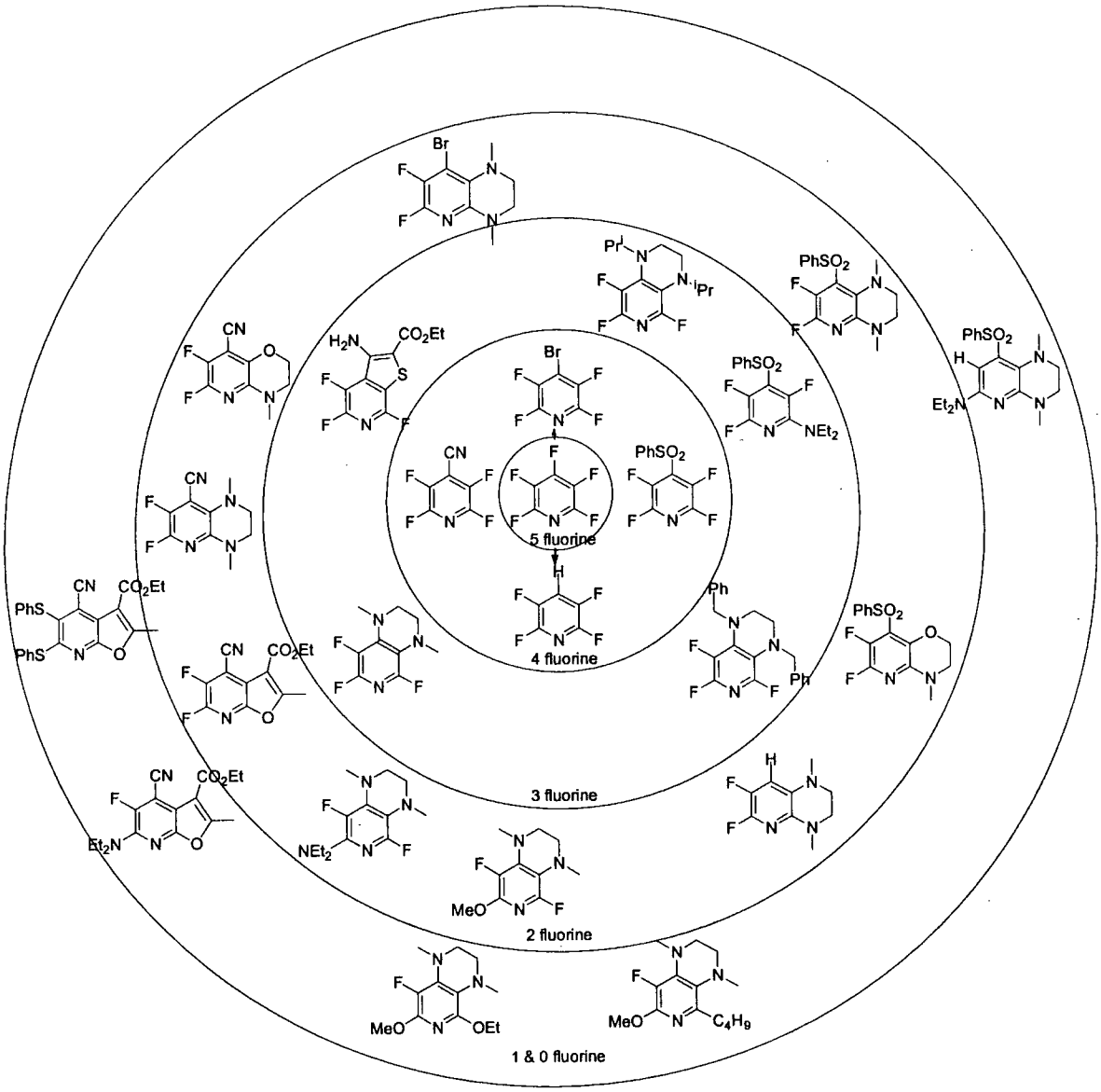


Fig. 7b Polyfunctional fused ring heteroaromatic systems synthesised from PFP

Fig. 7b shows that it is possible to start from a perfluorinated compound containing five fluorine atoms such as pentafluoropyridine and successively replace the fluorine atoms by nucleophiles to obtain compounds possessing a variety of pendant functionality.

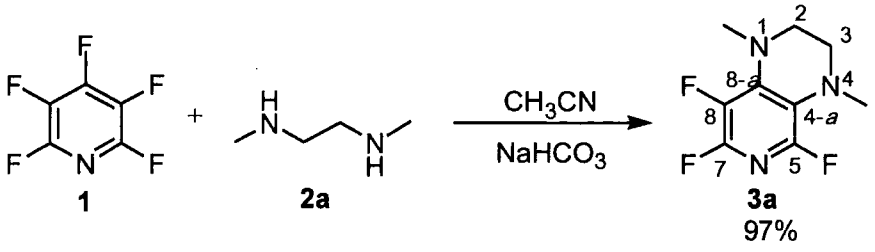
The research work contained in this thesis also explored the application of fluoride displacement methodology to the synthesis of fused ring systems derived from perfluorinated diazines, for example, tetrafluoropyrazine and 5-chloro-2,4,6-trifluoropyrimidine, with some success. This work forms the basis of a separate PhD thesis in which these reactions will be fully explored. Related work in progress also includes a study of the synthesis of [5,6] fused ring systems from pentafluoropyridine and tetrafluoropyridine derivatives.

In conclusion, we have shown that previously unexplored fluoride displacement methodology can be used for the synthesis of a number of polyfunctional fused ring heteroaromatic systems that are extremely difficult or impossible to synthesise. The methodology developed over the course of this work may find wide use in the drug discovery arena and work in this area is currently progressing at GlaxoSmithKline.

EXPERIMENTAL TO CHAPTER 2

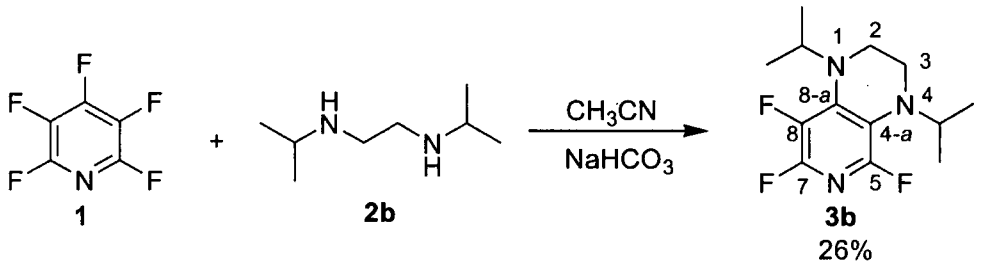
All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem). All solvents were dried using literature procedures. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040-0.063mm) or using the Biotage Horizon Flash Chromatography System and TLC analysis was performed on silica gel TLC plates (Merck). Mass Directed Automated Preparative HPLC was carried out using Supelco LCABZ++ column and MicroMass MassLynx v4.0 software. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 500S NMR spectrometer operating at 500 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 125 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl -silicone) column. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions were monitored by either ^{19}F NMR or gas-chromatography on an Shimadzu GC8A system using an SE30 column. Distillation was performed using a Fischer Spaltrohr MS220 microdistillation apparatus. All crystallographic data were collected at T = 120(1)K on a Bruker SMART-CCD 6000 diffractometer (λMoKα, ω-scan, 0.3°/frame). The structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically.

Preparation of 5,7,8-Trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 3a



N,N'-Dimethylethylenediamine **2a** (1.76 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Pentafluoropyridine **1** (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 5 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature and poured onto 1.0 M hydrochloric acid (150 ml), extracted with dichloromethane (2 x 100 ml), dried over magnesium sulfate and the solvent was evaporated to dryness to yield the crude product as a brown solid (2.12 g) consisting of one major component. Purification by recrystallisation from *n*-hexane gave *5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **3a** (2.1 g, 97%) as needle-like white crystals; mp 54.3-54.9°C; (Found: C, 49.7; H, 4.7; N, 19.3. $C_9H_{10}N_3F_3$ requires: C, 49.8; H, 4.6; N, 19.4%); δ_F -85.00 (1 F, m, F-5), -99.30 (1F, m, F-7), -162.64 (1F, tq, $^3J_{FF}$ 22.2, $^5J_{HF}$ 4.5, F-8); δ_H 3.28 (3H, d, $^5J_{HF}$ 4.8, 1-NCH_3), 3.23 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.04 (2H, t, $^3J_{HH}$ 5.2, CH_2), 2.73 (3H, s, 4-NCH_3); δ_C 148.4 (dd, $^1J_{CF}$ 233.3, $^3J_{CF}$ 16.3, C-5), 145.1 (dt, $^1J_{CF}$ 230.4, $^2J_{CF}$ 17.6, C-7), 140.0 (m, C-8*a*), 131.8 (ddd, $^1J_{CF}$ 244.6, $^2J_{CF}$ 30.5, $^4J_{CF}$ 4.8, C-8), 116.6 (dd, $^2J_{CF}$ 29.1, $^3J_{CF}$ 4.3, C-4*a*), 48.5 (s, CH_2), 46.0 (s, CH_2), 43.6 (d, $^4J_{CF}$ 5.3, 4-NCH_3), 41.6 (d, $^4J_{CF}$ 12.9, 1-NCH_3); *m/z* (EI$^+$) 218 ($[M+H]^+$, 6), 217 ($[M]^+$, 100), 202 ($[M-CH_3]^+$, 42), 187 ($[M-2CH_3]^+$, 36), 146 ($[M-C_4H_9N]^+$ 28).

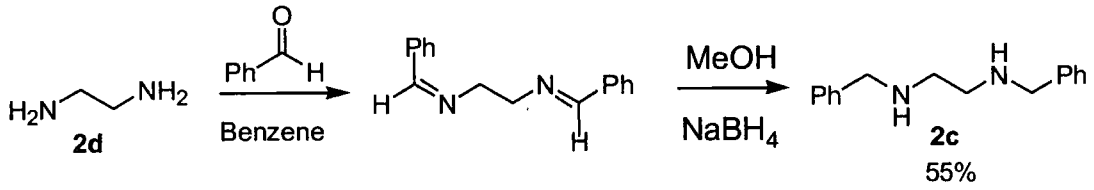
Preparation of 5,7,8-Trifluoro-1,4-diisopropyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 3b



N,N'-Diisopropylethylenediamine **2b** (2.88 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Pentafluoropyridine **1** (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 5 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown solid (3.47 g) consisting of one major component. Purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) gave *5,7,8-trifluoro-1,4-diisopropyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **3b** (0.71 g, 26%) as an orange solid; mp 50.7-53.5°C; ($[M+H]^+$ 274.1525, $C_{13}H_{18}N_3F_3$ requires $[M+H]^+$ 274.1526); δ_F -82.67 (1F, t, $^4J_{FF}$ 20.3, F-5), -100.13 (1F, t, $^3J_{FF}$ 15.8, F-7), -161.45 (1F, t, $^3J_{FF}$ 22.3, F-8); δ_H 4.50 (1H, septet of doublets, $^3J_{HH}$ 6.5, $^5J_{HF}$ 3.0, 1-NC*H*$(CH_3)_2$), 3.56 (1H, septet, $^3J_{HH}$ 7.0, 4-NC*H*$(CH_3)_2$), 3.16 (2H, t, $^3J_{HH}$ 5.5, NCH_2), 3.04 (2H, t, $^3J_{HH}$ 5.0, NCH_2), 1.21 (6H, dd, $^3J_{HH}$ 7.0, $^5J_{HH}$ 1.5, NCH$(CH_3)_2$), 1.11 (6H, dd, $^3J_{HH}$ 6.5, $^5J_{HF}$ 0.5, NCH$(CH_3)_2$); δ_C 148.4 (dd, $^1J_{CF}$ 232.3, $^3J_{CF}$ 15.6, C-5), 144.8 (dt, $^1J_{CF}$ 229.9, $^2J_{CF}$ 19.1, C-7), 139.3 (quintet, $^2J_{CF}$ 4.3, C-8*a*), 132.1 (ddd, $^1J_{CF}$ 243.8, $^2J_{CF}$ 29.6, $^4J_{CF}$ 4.8, C-8), 116.0 (dd, $^2J_{CF}$ 27.8, $^3J_{CF}$ 4.4, C-4*a*), 53.2 (d, $^4J_{CF}$ 6.1, 4-NCH$(CH_3)_2$), 51.2 (d, $^4J_{CF}$ 15.8, 1-

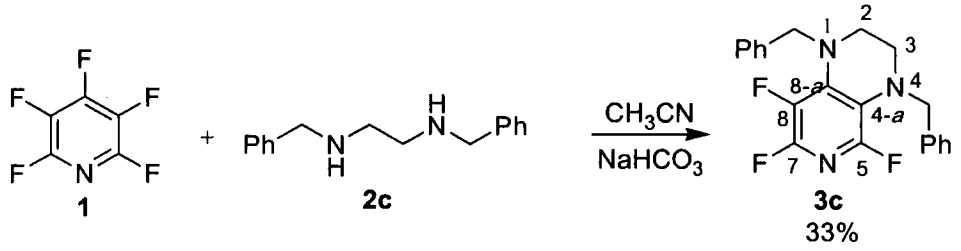
$NCH(CH_3)_2$), 40.9 (s, NCH_2), 39.1 (s, NCH_2), 20.8 (s, $NCH(CH_3)_2$), 20.3 (s, $NCH(CH_3)_2$); *m/z* (EI)$^+$ 273 ($[M]^+$, 84), 258 ($[M\text{-}CH_3]^+$, 100), 230 ($[M\text{-}CH(CH_3)_2]^+$, 27), 216 ($[M\text{-}CH_2CH(CH_3)_2]^+$, 92), 202 ($[M\text{-}(CH_2)_2CH(CH_3)_2]^+$, 16).

Preparation of *N,N'*-Dibenzylethane-1,2-diamine 2c



Activated molecular sieves were added to a solution of ethylenediamine **2d** (0.89 g, 14.8 mmol) and benzaldehyde (3.45 g, 32.5 mmol) in anhydrous benzene (7.5 ml) under argon. The solution was stirred gently for 7 h after which time the reaction mixture was filtered, the sieves washed with benzene and the solvent evaporated to yield the crude imine as an orange oily solid. To a stirred solution of the crude imine (2.32 g, 9.8 mmol) in dry methanol (25 ml) under argon, sodium borohydride (0.74 g, 19.6 mmol) was added in portions at 0°C. The solution was further stirred at 0°C for 3.5 h after which time the solvent was removed and the remaining residue was dissolved in diethyl ether (30 ml), washed with water (40 ml) and brine (40 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield *N,N'-dibenzylethane-1,2-diamine* **2c** (1.95 g, 55%) as a brown oil. The diamine was used in subsequent reactions without further purification; δ_H 7.34 (10H, m, Ar H), 3.80 (4H, s, CH_2), 2.79 (4H, s, CH_2); δ_C 140.8 (s, Ar CN), 128.6 (s, Ar C), 128.3 (s, Ar C), 127.1 (s, Ar C), 54.2 (s, CH_2), 49.1 (s, CH_2).[1]

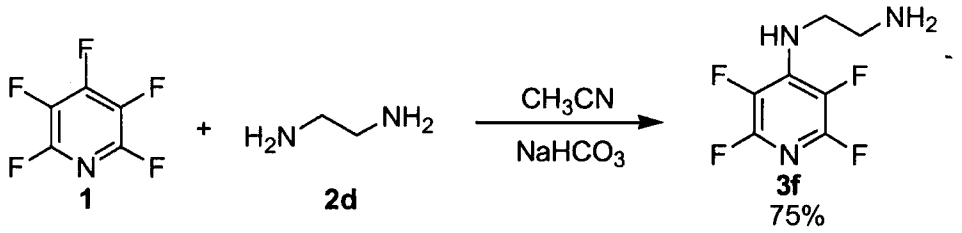
Preparation of 1,4-Dibenzyl-5,7,8-trifluoro-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 3c



N,N'-Dibenzylethane-1,2-diamine **2c** (2.4 g, 10 mmol) and sodium hydrogencarbonate (1.68 g, 20 mmol) were added to acetonitrile (175 ml) under argon. Pentafluoropyridine **1** (0.85 g, 5 mmol) was added and the resulting solution was refluxed for 5 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (2.68 g) consisting of one major component. Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *1,4-dibenzyl-5,7,8-trifluoro-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **3c** (0.61 g, 33%) as beige crystals; mp 97.5-98.5°C; ($[M+H]^+$ 370.1526, $C_{21}H_{18}N_3F_3$ requires $[M+H]^+$ 370.1529); δ_F -83.54 (1F, dd, $^4J_{FF}$ 22.6, $^5J_{FF}$ 13.5, F-5), -98.78 (1F, dd, $^3J_{FF}$ 22.6, $^5J_{FF}$ 13.5, F-8), -161.23 (1F, t, $^3J_{FF}$ 22.6, F-7); δ_H 7.00 – 7.80 (10H, m, Ar H), 4.67 (2H, s, CH_2Ph), 3.95 (2H, s, CH_2Ph), 3.08 (2H, t, $^3J_{HH}$ 5.1, NCH_2CH_2), 2.80 (2H, t, $^3J_{HH}$ 5.1, NCH_2CH_2); δ_C 148.9 (dd, $^1J_{CF}$ 233.7, $^3J_{CF}$ 16, C-5), 145.1 (dt, $^1J_{CF}$ 230.3, $^2J_{CF}$ 19.1, C-7), 139.4 (m, C-4*b*), 138.0 (s, Ar C), 137.5 (s, Ar C), 132.1 (ddd, $^1J_{CF}$ 244.8, $^2J_{CF}$ 30.1, $^4J_{CF}$ 4.6, C-8), 129.1 (s, Ar CH), 129.0 (s, Ar CH), 128.9 (s, Ar CH), 128.0 (s, Ar CH), 127.9 (s, Ar CH), 127.3, 116.6 (dd, $^2J_{CF}$ 28.2, $^3J_{CF}$ 4.2, C-3*b*), (s, Ar CH), 59.5 (d, $^5J_{CF}$ 3.8, CH_2), 57.3

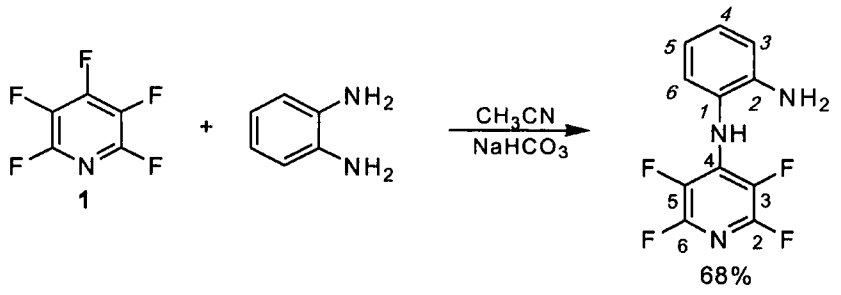
(d, $^4J_{CF}$ 12.6, CH_2), 43.9 (s, CH_2), 43.4 (s, CH_2); *m/z* (EI^+) 369 ($[M]^+$, 54), 278 ($[M-CH_2C_6H_5]^+$, 49), 91 ($[CH_2C_6H_5]^+$, 100).

Preparation of N-(2,3,5,6-tetrafluoropyridin-4-yl)-ethane-1,2-diamine 3f



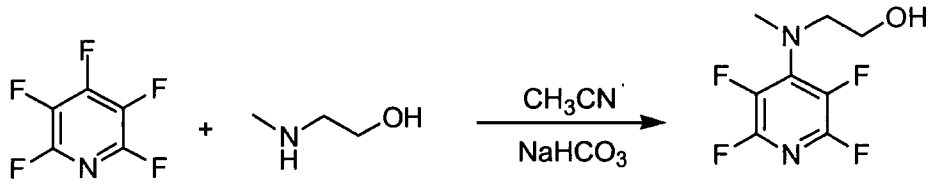
Ethylenediamine **2d** (1.20 g, 20 mmol) and sodium hydrogencarbonate (4.24 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Pentafluoropyridine **1** (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature and poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent was evaporated to dryness to yield the crude product as a white solid (3.13 g) consisting of one major component. Purification by recrystallisation from methanol gave *N-(2,3,5,6-tetrafluoropyridin-4-yl)ethane-1,2-diamine* **3f** (1.56 g, 75%) as a white solid; mp 114.0-116.5°C; (Found: C, 40.3; H, 3.4; N, 20.1. $C_7H_7N_3F_4$ requires: C, 40.2; H, 3.4; N, 20.1%); δ_F(d_6-Acetone) -98.42 (2F, t, $^3J_{FF}$ 18.8, F-2,6), -166.28 (2F, t, $^3J_{FF}$ 18.8, F-3,5); δ_H(d_6-Acetone) 3.75 (2H, t, $^3J_{HH}$ 8.4, NHCH_2), 3.46 (2H, t, $^3J_{HH}$ 6.4, CH_2NH$_2$); δ_C(d_6-Acetone) 144.1 (dm, $^1J_{CF}$ 230.0, C-2,6), 138.4 (m, C-4), 131.1 (ddm, $^1J_{CF}$ 245.4, $^2J_{CF}$ 35.9, C-3,5), 50.8 (s, CH_2NH_2), 44.8 (t, $^4J_{CF}$ 3.8, NHCH_2); *m/z* (EI^+) 210 ($[M+H]^+$, 95), 193 ($[M-NH_2]^+$, 100).

Preparation of *N*-(2,3,5,6-Tetrafluoropyridin-4-yl)benzene-1,2-diamine



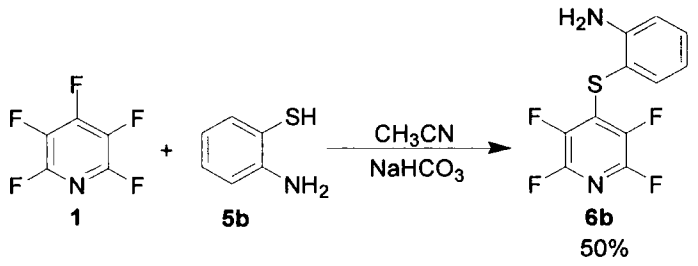
1,2-Phenylenediamine (2.16 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Pentafluoropyridine **1** (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 7 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue was redissolved in dichloromethane (75 ml). The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown solid (2.36 g) consisting of one major component. Purification by recrystallisation from *n*-hexane gave *N-(2,3,5,6-tetrafluoropyridin-4-yl)benzene-1,2-diamine* (1.75 g, 68%) as beige crystals; mp 147.5-148.0°C; (Found: C, 51.2; H, 2.7; N, 16.1. $C_{11}H_7N_3F_4$ requires: C, 51.4; H, 2.7; N, 16.3%); δ_F(d_6-Acetone) -96.22 (2F, m, F-2,6), -160.59 (2F, m, F-3,5); δ_H(d_6-Acetone) 7.80 (3H, br s, NH & NH_2), 6.5-7.3 (4H, m, Ar H); δ_C(d_6-Acetone) 144.4 (dm, $^1J_{CF}$ 237.5, C-2,6), 142.1 (s, C-*1*), 136.1 (m, C-4), 132.3 (dm, $^1J_{CF}$ 250.8, C-3,5), 128.3 (s, C-*2*), 125.6 (t, $^5J_{CF}$ 1.9, C-*6*), 124.9 (s, C-*3*), 119.2 (s, C-*5*), 116.6 (s, C-*4*); *m/z* (EI^+) 257 ($[M]^+$, 70), 237 ($[M-HF]^+$, 100).

Preparation of 2-[Methyl-(2,3,5,6-tetrafluoropyridin-4-yl)amino]ethanol 6a



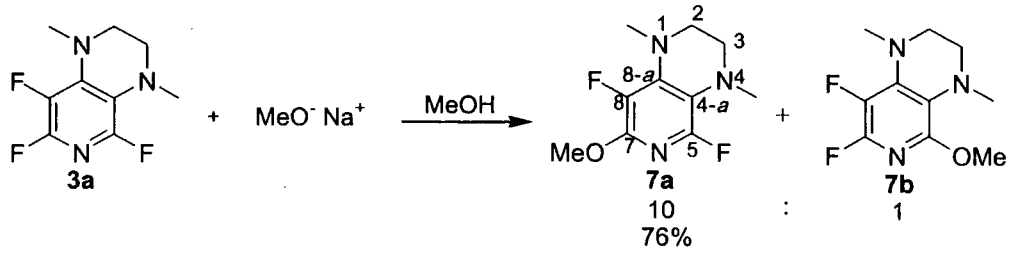
N-Methylaminoethanol **5a** (1.5 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Pentafluoropyridine **1** (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 19 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature and poured onto 1.0 M hydrochloric acid (150 ml), extracted with dichloromethane (2 x 100 ml), dried over magnesium sulfate and the solvent was evaporated to dryness to yield the crude product as a yellow/brown oil (2.12 g) consisting of one major component. Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) gave *2-[methyl-(2,3,5,6-tetrafluoropyridin-4-yl)amino]ethanol* **6a** (1.9 g, 85%) as a yellow oil; (Found: C, 42.6; H, 3.6; N, 12.5. $C_8H_8N_2F_4O$ requires: C, 42.9; H, 3.6; N, 12.5%); δ_F -94.46 (2 F, m, F-2,6), -155.24 (2F, m, F-3,5); δ_H 3.84 (2H, t, $^3J_{HH}$ 5.7, CH_2), 3.53 (2H, t, $^3J_{HH}$ 5.4, CH_2), 3.18 (3H, t, $^5J_{HF}$ 3.3, CH_3); δ_C 144.9 (dtm, $^1J_{CF}$ 237.5, $^2J_{CF}$ 18.1, C-2,6), 140.6 (m, C-4), 134.4 (ddm, $^1J_{CF}$ 249.9, $^2J_{CF}$ 23.9, C-3,5), 60.3 (t, $^4J_{CF}$ 1.5, CH_3), 56.5 (t, $^4J_{CF}$ 4.8, CH_2), 40.9 (t, $^5J_{CF}$ 5.8, CH_2); *m/z* (EI$^+$) 224 ($[M]^+$, 18), 193 ($[M\text{-}CH_2OH]^+$, 100).

Preparation of 2-(2,3,5,6-Tetrafluoro-pyridin-4-ylsulfanyl)-phenylamine 6b



2-Aminobenzenethiol **5b** (2.5 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40mmol) were added to acetonitrile (400 ml) under argon. Pentafluoropyridine **1** (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil/solid (2.0 g) consisting of one major component. Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) gave *2-(2,3,5,6-tetrafluoro-pyridin-4-ylsulfanyl)-phenylamine* **6b** (1.38 g, 50%) as an off-white solid; mp 67.8-70.4°C; (Found: C, 48.2; H, 2.2; N, 10.2. $C_{11}H_6N_2F_4S$ requires: C, 48.2; H, 2.2; N, 10.2%); δ_F -91.14 (2F, dt, $^3J_{FF}$ 38.4, $^4J_{FF}$ 13.5, F-2,6), -138.56 (2F, dt, $^3J_{FF}$ 38.4, $^4J_{FF}$ 13.5, F-3,5); δ_H 7.53 (1H, dm, $^3J_{HH}$ 7.6, Ar H), 7.24 (1H, m, Ar H), 6.74 (2H, tm, $^3J_{HH}$ 7.6, Ar H), 4.38 (2H, br s, NH_2); δ_C 149.3 (s, Ar CNH_2), 143.73 (dm, $^1J_{CF}$ 195.5, C-2,6), 141.22 (dm, $^1J_{CF}$ 234.0, C-3,5), 137.5 (s, Ar CS), 132.5 (s, Ar CH), 130.7 (tm, $^2J_{CF}$ 16.4, C-4), 119.2 (s, Ar CH), 115.9 (s, Ar CH), 110.2 (s, Ar CH); *m/z* $(EI)^+$ 274 ($[M]^+$, 60), 254 ($[M-HF]^+$, 34).

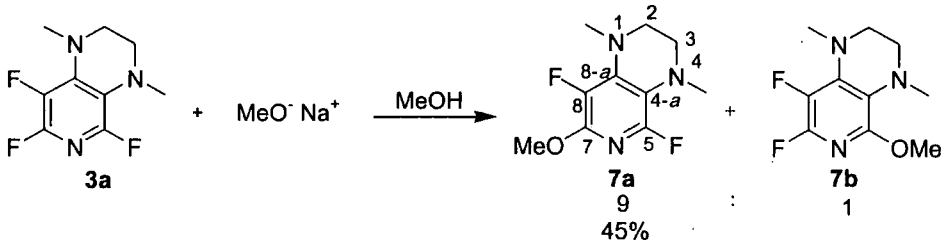
Preparation of 7-Methoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 7a Using Conventional Heating Methods



Sodium metal (0.7 g, 30.23 mmol) was added to anhydrous methanol (30 ml) under argon followed by the addition of 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.82 g, 3.78 mmol). The resulting solution was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 20 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow oil (0.7 g) consisting of two major components in the ratio 10:1 which were identified as *5,8-difluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **7a**; and *7,8-difluoro-5-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **7b**. Purification by column chromatography on silica gel (1:2 *n*-hexane/ethyl acetate) gave *5,8-difluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **7a** (0.66 g, 76%) as white crystals; mp 46.0-46.5°C; (Found: C, 52.4; H, 5.7; N, 18.3; $C_{10}H_{13}N_3F_2O$ requires: C, 52.4; H, 5.7; N, 18.3%); δ_F – 86.81 (1F, d, $^5J_{FF}$ 22.6, F-5), -161.91 (1F, m, F-8); δ_H 3.88 (3H, s, OCH_3), 3.20 (3H, d, $^5J_{HF}$ 3.6, 1-NCH_3), 3.18 (2H, t, $^3J_{HH}$ 5.1, CH_2), 3.02 (2H, t, $^3J_{HH}$ 5.1, CH_2), 2.68 (3H, s, 4-NCH_3); δ_C 149.7 (dd, $^1J_{CF}$ 228.7, $^4J_{CF}$ 1.1, C-5), 146.3 (dd, $^2J_{CF}$ 17.8, $^3J_{CF}$ 13.4, C-7), 139.0 (dd, $^2J_{CF}$ 8.0, $^3J_{CF}$ 4.9, C-8*a*), 133.6 (dd, $^1J_{CF}$ 236, $^4J_{CF}$ 5.0, C-8), 113.2 (d, $^2J_{CF}$ 30.5, C-4*a*), 54.0 (s, OCH_3), 48.7 (s, CH_2), 45.6 (s, CH_2), 43.6 (d, $^4J_{CF}$ 4.2, 4-NCH_3), 41.5 (d, $^4J_{CF}$ 13.3,

1-NCH_3); *m/z* (EI^+) 229 ($[M]^+$, 100), 214 ($[M-CH_3]^+$ 66), 199 ($[M-C_2H_6]^+$, 14); and a trace amount of *7,8-difluoro-5-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **7b** as a colourless oil; δ_F -100.31 (1F, d, $^3J_{FF}$ 24.8, F-7), -166.63 (1F, dd, $^3J_{FF}$ 24.8, $^5J_{HF}$ 4.5, F-8); δ_H 3.94 (3H, s, OCH_3), 3.16 (3H, d, $^5J_{HF}$ 3.9, 1-NCH_3), 3.15 (2H, t, $^3J_{HH}$ 6.3, NCH_2), 3.02 (2H, t, $^3J_{HH}$ 5.1, NCH_2), 2.64 (3H, s, 4-NCH_3); *m/z* (EI^+) 229 ($[M]^+$, 100, 214 ($[M-CH_3]^+$, 81), 199 ($[M-C_2H_6]^+$, 16).

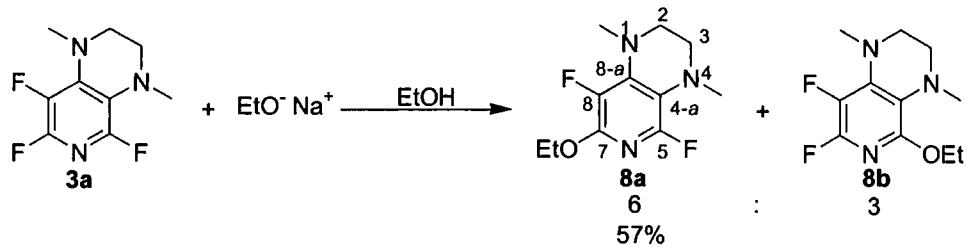
Preparation of 7-Methoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 7a Using Microwave Heating



Sodium methoxide (0.32 g, 6.0 mmol) and 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.65 g, 3.0 mmol) were added to a microwave vial which was then sealed and purged with argon. Methanol (15 ml) was added and the vial was irradiated with microwaves at 150°C for 1.25 h after which time ^{19}F NMR indicated 100% conversion of starting material. The above procedure was repeated and the two reaction mixtures cooled to room temperature and combined. The solvent was evaporated and the residue redissolved in dichloromethane, poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (100 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow oil (0.57 g) consisting of two major components in the ratio 9:1 which were identified as *7-methoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **7a**; and *7,8-difluoro-5-*

methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine **7b**; spectral data as above. Purification by mass directed automated preparative HPLC (30%-85% acetonitrile in formic acid) gave *7-methoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **7a** (0.31 g, 45%) as a white solid; spectral data as above.

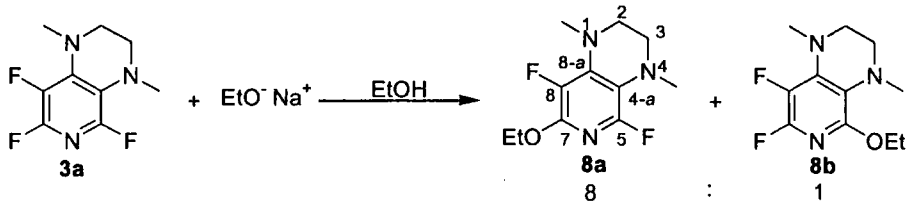
Preparation of 7-Ethoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 8a Using Conventional Heating Methods



Sodium metal (0.11 g, 4.6 mmol) was added to anhydrous ethanol (30 ml) under argon followed by the addition of 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (1.0 g, 4.6 mmol). The resulting solution was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 30 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow solid (1.37 g) consisting of two major components in the ratio 6:3 which were identified as *7-ethoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **8a**; and *5-ethoxy-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **8b**; δ_F -100.18 (1F, dm, $^3J_{FF}$ 29.0, F-7), -166.83 (1F, dm, $^3J_{FF}$ 24.6, F-8); δ_H 3.71 (2H, q, $^3J_{HH}$ 7.0, OCH_2CH_3), 3.20 (3H, d, $^5J_{HF}$ 4.2, 1-NCH_3), 3.17 (2H, t, $^3J_{HH}$ 5.2, NCH_2), 3.04 (2H, t, $^3J_{HH}$ 5.2, NCH_2), 2.67 (3H, s, 4-NCH_3), 1.23 (3H, t, $^3J_{HH}$ 7.0, OCH_2CH_3); *m/z* (EI^+) 243 ($[M]^+$, 100), 213 ($[M-(CH_3)_2]^+$, 80). Purification by

recrystallisation from *n*-hexane gave *7-ethoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **8a** (0.64 g, 57%) as off-white crystals; mp 71.3–72.2°C; (Found: C, 54.2; H, 6.2; N, 17.1; $C_{11}H_{15}N_3F_2O$ requires: C, 54.3; H, 6.2; N, 17.3%); δ_F -86.67 (1F, d, $^5J_{FF}$ 22.6, F-5), -161.44 (1F, dm, $^5J_{FF}$ 24.5, F-8); δ_H 4.31 (2H, q, $^3J_{HH}$ 7.2, OCH_2CH_3), 3.21 (3H, d, $^5J_{HF}$ 4.5, 1-NCH_3), 3.18 (2H, t, $^3J_{HH}$ 5.1, NCH_2), 3.04 (2H, t, $^3J_{HH}$ 5.4, NCH_2), 2.70 (3H, s, 4-NCH_3), 1.38 (3H, t, $^3J_{HH}$ 7.2, OCH_2CH_3); δ_C 149.7 (d, $^1J_{CF}$ 228.4, C-5), 146.1 (m, C-7), 139.04 (m, C-8*a*), 133.6 (dd, $^1J_{CF}$ 241, $^4J_{CF}$ 5, C-8), 112.8 (d, $^2J_{CF}$ 30.1, C-4*a*), 62.6 (s, OCH_2CH_3), 48.8 (s, CH_2), 45.6 (s, CH_2), 43.6 (d, $^4J_{CF}$ 4.6, 4-NCH_3), 41.5 (d, $^4J_{CF}$ 13.3, 1-NCH_3), 14.9 (s, OCH_2CH_3); *m/z* (EI^+) 243 ($[M]^+$, 100), 213 ($[M-(CH_3)_2]^+$, 88).

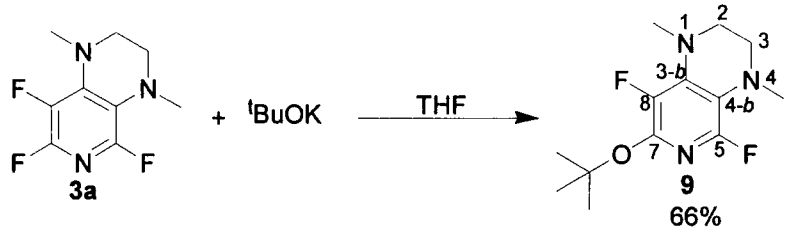
Procedure for the Preparation of 7-Ethoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 8a Using Microwave Heating



Sodium ethoxide 96% in mineral oil (0.07 g, 1.0 mmol) and 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.11 g, 0.5 mmol) were added to a microwave vial which was then sealed and purged with argon. Ethanol (15 ml) was added and the vial was irradiated with microwaves at 150°C for 1.25 h after which time ^{19}F NMR indicated 75% conversion of starting material. A solution of sodium ethoxide (0.07 g, 1.0 mmol) in ethanol (2 ml) was added to the reaction mixture and the vial was irradiated with microwaves at 150°C for a further 0.3 h. The reaction gave *7-ethoxy-5,8-difluoro-1,4-*

dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine **8a** and *5-ethoxy-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **8b** in the ratio 8:1 respectively, spectral data as above, work up and purification were not attempted.

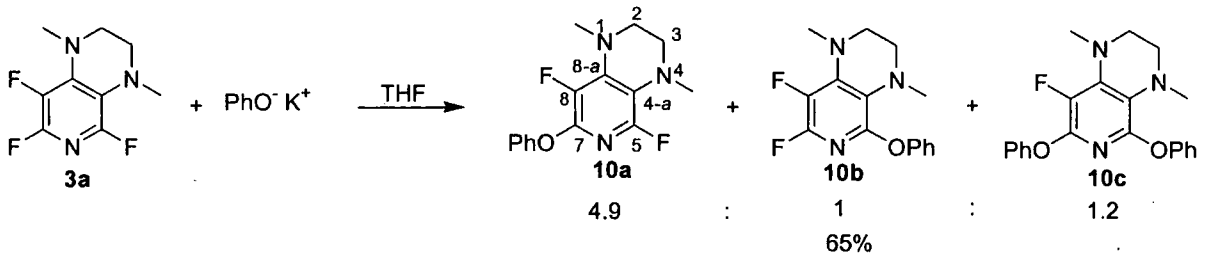
Preparation of 7-*Tert*-butoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 9



Potassium *tert*-butoxide (0.22 g, 2 mmol) and 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.22 g, 1 mmol) were added to dry tetrahydrofuran (15 ml) under argon and refluxed for 4 d after which time 2 extra equivalents of potassium *tert*-butoxide (0.22 g, 2 mmol) were added. Refluxing was continued for 18 h after which time HPLC indicated 97% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 0.5 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.19 g) consisting of one major component. Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane, 0%-100%) gave *7-tert-butoxy-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **9** (0.18 g, 66%) as a colourless oil; (Found: C, 57.6; H, 7.1; N, 15.5. $C_{13}H_{19}N_3OF_2$ requires: C, 57.6; H, 7.0; N, 15.5%); δ_F -84.22 (1F, d, $^5J_{FF}$ 26.3, F-5), -155.20 (1F, m, F-8); δ_H 3.14 (5H, overlapping d & t, 1-NCH_3 & CH_2), 2.99 (2H, t, $^3J_{HH}$ 4.4, CH_2), 2.68 (3H, s, 4-NCH_3), 1.48 (9H, s, $(CH_3)_3$); δ_C 148.7 (dd, $^1J_{CF}$ 229.1, $^4J_{CF}$

1.5, C-5), 145.1 (dd, $^{2}J_{CF}$ 18.9, $^{3}J_{CF}$ 13.4, C-7), 138.7 (dd, $^{2}J_{CF}$ 8.3, $^{3}J_{CF}$ 6.6, C-8*a*), 136.4 (dd, $^{1}J_{CF}$ 243.3, $^{4}J_{CF}$ 5.3, C-8), 114.0 (d, $^{2}J_{CF}$ 31.5, C-4*a*), 81.2 (s, $OC(CH_3)_3$), 48.4 (s, NCH_2), 45.7 (s, NCH_2), 43.4 (d, $^{4}J_{CF}$ 5.1, 4-NCH_3), 41.5 (d, $^{4}J_{CF}$ 13.4, 1-NCH_3), 28.9 (s, $C(CH_3)_3$); *m/z* (EI)$^{+}$ 272 ([M+H]$^{+}$, 38), 257 ([MH-CH_3]$^{+}$, 65).

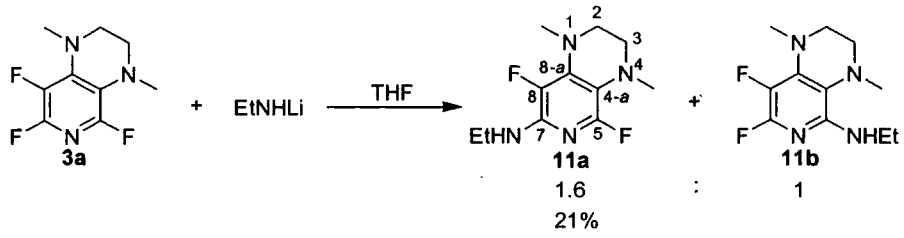
Preparation of 5,8-Difluoro-1,4-dimethyl-7-phenoxy-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 10a



Phenol (0.19 g, 2 mmol) and potassium metal (0.17 g, 3 mmol) were added to dry tetrahydrofuran (15 ml) and the reaction mixture was stirred until all the potassium had reacted. The resulting solution was transferred to a sealed microwave vial under argon containing 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.11 g, 0.5 mmol) and the vial was irradiated with microwaves at 150°C for 1 h, after which time HPLC indicated 89% conversion of starting material. The solvent was evaporated and the residue redissolved in dichloromethane, poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (100 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow oil (0.23 g) consisting of three major components in the ratio 4.9:1:1.2 which were identified as *5,8-difluoro-1,4-dimethyl-7-phenoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **10a**; δ_F -82.52 (1F, d, $^{5}J_{FF}$ 22.6, F-5), -156.02 (1F, m, F-8); δ_H 7.33 (2H, t, $^{3}J_{HH}$ 8.4, Ar H), 7.12 (1H, d, $^{3}J_{HH}$ 7.2, Ar H), 7.07 (2H, d, $^{3}J_{HH}$ 8.8, Ar H), 3.25 (3H, d, $^{5}J_{HF}$ 4.8, 1-NCH_3), 3.21 (2H, t, $^{3}J_{HH}$ 4.4, CH_2),

3.04 (2H, t, $^{3}J_{HH}$ 5.2, CH_2), 2.73 (3H, s, 4-NCH_3); δ_C 155.0 (s, Ar C), 149.3 (d, $^{1}J_{CF}$ 230.2, C-5), 143.0 (m, C-7), 139.3 (m, C-8*a*), 135.5 (dd, $^{1}J_{CF}$ 244.5, $^{4}J_{CF}$ 4.8, C-8), 129.4 (s, Ar CH), 123.8 (s, Ar CH), 119.2 (s, Ar CH), 115.6 (d, $^{2}J_{CF}$ 30.4, C-4*a*), 48.3 (s, CH_2), 45.8 (s, CH_2), 43.3 (d, $^{4}J_{CF}$ 5.5, 4-NCH_3), 41.4 (d, $^{4}J_{CF}$ 13.2, 1-NCH_3); *m/z* (EI)$^+$ 292 ([M+H]$^+$, 100), 277 ([MH-CH_3]$^+$, 52); *7,8-difluoro-1,4-dimethyl-5-phenoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **10b**; δ_F -96.71 (d, $^{3}J_{FF}$ 22.6, F-7), -163.39 (m, F-8); *m/z* (EI)$^+$ 292 ([M+H]$^+$, 100), 277 ([MH-CH_3]$^+$, 48); and *8-fluoro-1,4-dimethyl-5,7-diphenoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **10c**. Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane, 0%-70%) gave a mixture of *5,8-difluoro-1,4-dimethyl-7-phenoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **10a** and *7,8-difluoro-1,4-dimethyl-5-phenoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **10b** in the ratio 7.9:1 respectively (0.095 g, 65%) as a white solid, with *8-fluoro-1,4-dimethyl-5,7-diphenoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **10c** also isolated in a trace amount; δ_F -156.49 (1F, m, F-8); δ_H 7.21 (4H, m, Ar CH), 7.00 (6H, m, Ar CH), 3.25 (3H, d, $^{5}J_{HF}$ 4.4, 1-NCH_3), 3.24 (2H, t, $^{3}J_{HH}$ 5.2, CH_2), 3.08 (2H, t, $^{3}J_{HH}$ 4.8, CH_2), 2.79 (3H, s, 4-NCH_3); δ_C 155.4 (s, Ar C), 154.8 (s, Ar C), 148.4 (s, C-5), 143.6 (d, $^{2}J_{CF}$ 13.9, C-7), 139.0 (d, $^{2}J_{CF}$ 5.3, C-8*a*), 135.0 (d, $^{1}J_{CF}$ 246.6, C-8), 129.0 (s, Ar CH), 129.0 (s, Ar CH), 123.4 (s, Ar CH), 123.1 (s, Ar CH), 119.9 (s, Ar CH), 118.9 (s, Ar CH), 118.6 (s, C-4*a*), 48.5 (s, NCH_2), 45.3 (s, NCH_2), 43.0 (s, 4-NCH_3), 41.6 (d, $^{4}J_{CF}$ 13.3, 1-NCH_3); *m/z* (EI)$^+$ 366 ([M+H]$^+$, 100), 351 ([MH-CH_3]$^+$, 46).

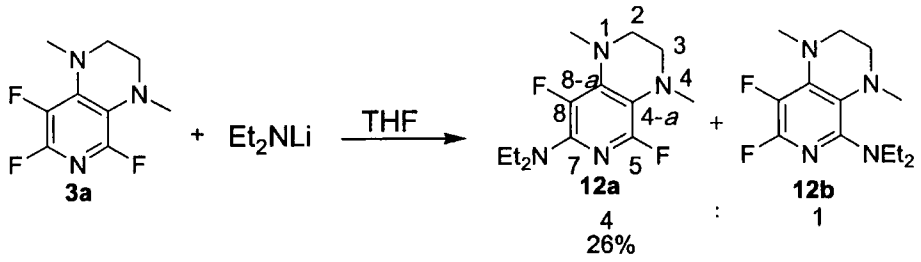
Preparation of *N*-Ethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-7-amine 11a



A 2.0 M solution of butyl lithium in tetrahydrofuran (1 ml, 2 mmol) was added to a solution of ethylamine (0.09 g, 2 mmol) in tetrahydrofuran (30 ml) at -78°C. The resulting solution was stirred at -78°C for 1 h before warming to room temperature and addition of 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.22 g, 1 mmol). The reaction mixture was refluxed for 5 d, and over the course of the reaction, 14 extra equivalents (28 mmol) of the lithium ethylamide salt were added following the procedure outlined above. HPLC indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (100 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.27 g) consisting of two major components in the ratio 1.6:1 which were identified as *N-ethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-7-amine* **11a**; and *N-ethyl-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-5-amine* **11b**; δ_F -98.16 (1F, d, $^3J_{FF}$ 26.3, F-7), -172.07 (1F, q, $^3J_{FF}$ 22.6, F-8); δ_H 4.69 (1H, br s, NH), 3.36 (2H, q, $^3J_{HH}$ 7.2, NHCH_2CH$_3$), 3.23 (2H, t, $^3J_{HH}$ 4.8, NCH_2CH$_2$), 3.19 (3H, d, $^5J_{HF}$ 4.0, 1-NCH$_3$), 2.97 (2H, t, $^3J_{HH}$ 5.2, NCH$_2$CH_2), 2.50 (3H, s, 4-NCH$_3$), 1.21 (3H, t, $^3J_{HH}$ 7.2, NHCH$_2$CH_3); δ_C 148.9 (dd, $^1J_{CF}$ 221.1, $^2J_{CF}$ 14.7, C-7), 146.8 (d, $^3J_{CF}$ 17.2, C-5), 138.0 (m, C-8*a*), 127.7 (dd, $^1J_{CF}$ 238.1, $^2J_{CF}$ 32.6, C-8), 112.9 (dd, $^3J_{CF}$ 3.7, $^4J_{CF}$ 1.1, C-4*a*), 48.1 (s, NCH$_2$CH$_2$), 44.3 (s,

NCH_2CH_2), 40.8 (d, $^4J_{CF}$ 13.2, 1-NCH_3), 40.7 (s, 4-NCH_3), 36.2 (s, $NHCH_2CH_3$), 15.4 (s, $NHCH_2CH_3$). Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane 0%-100%) gave *N-ethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-7-amine* **11a** (0.05 g, 21%) as an off white solid; mp 79.0-80.0°C; (Found: C, 54.5; H, 6.7; N, 22.8. $C_{11}H_{16}F_2N_4$ requires: C, 54.6; H, 6.6; N, 23.1%); δ_F -86.00 (1F, d, $^5J_{FF}$ 22.6, F-5), -162.08 (1F, q, $^5J_{FF}$ 22.6, F-8); δ_H 4.13 (1H, br s, NH), 3.38 (2H, q, $^3J_{HH}$ 6.8, $NHCH_2CH_3$), 3.17 (5H, overlapping d & t, 1-NCH_3 & NCH_2CH_2), 3.03 (2H, t, $^3J_{HH}$ 4.8, NCH_2CH_2), 2.66 (3H, s, 4-NCH_3), 1.21 (3H, t, $^3J_{HH}$ 7.2, $NHCH_2CH_3$); δ_C 151.6 (d, $^1J_{CF}$ 224.2, C-5), 141.8 (m, C-7), 137.3 (m, C-8*a*), 133.0 (dd, $^1J_{CF}$ 234.1, $^4J_{CF}$ 4.0, C-8), 109.0 (d, $^2J_{CF}$ 32.1, C-4*a*), 48.8 (s, NCH_2CH_2), 45.0 (s, NCH_2CH_2), 43.4 (d, $^4J_{CF}$ 3.8, 4-NCH_3), 41.2 (d, $^4J_{CF}$ 13.2, 1-NCH_3), 36.0 (s, $NHCH_2CH_3$), 15.4 ($NHCH_2CH_3$); *m/z* (EI)$^+$ 242 ([M]$^+$, 100), 227 ([M-CH_3]$^+$, 90), 213 ([M-CH_2CH_3]$^+$, 14).

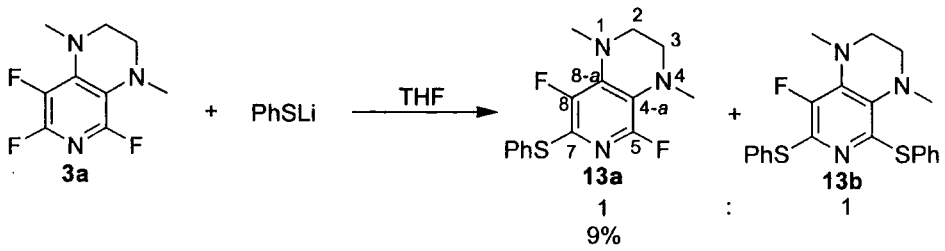
Preparation of *N,N*-Diethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-7-amine 12a



Butyl lithium 1.7 M in pentane (0.59 ml, 1 mmol) and diethylamine (0.073 g, 1 mmol) were added to dry tetrahydrofuran (5 ml) at -78°C and the solution was stirred for 1 h before warming to room temperature. The solution was added to 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.22 g, 1 mmol) in tetrahydrofuran (25 ml) and refluxed for 6 d and over the course of the reaction 6 extra equivalents of the lithium

diethylamide salt were added to the reaction mixture following the procedure outlined above. ^{19}F NMR indicated 100 % conversion of starting material so the reaction was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.57 g) consisting of two major components in the ratio 4:1 which were identified as *N,N-diethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-7-amine* **12a**; and *N,N-diethyl-7,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-5-amine* **12b**; δ_F -98.02 (1F, d, $^3J_{FF}$ 28.4, F-7), -166.21 (1F, d, $^3J_{FF}$ 29.3, F-8); *m/z* (EI^+) 270 ($[M]^+$, 100), 255 ($[M\text{-}CH_3]^+$, 69), 241 ($[M\text{-}CH_3CH_2]^+$, 89), 225 ($[M\text{-}(CH_3)_3]^+$, 88), 211 ($[M\text{-}(CH_3)_3CH_2]^+$, 96). Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *N,N-diethyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-7-amine* **12a** (0.38 g, 26 %) as a colourless oil; ($[M+H]^+$ 270.1668, $C_{13}H_{20}N_4F_2$ requires $[M+H]^+$ 270.1656); δ_F -83.92 (1F, d, $^5J_{FF}$ 24.0, F-5), -150.42 (1F, d, $^5J_{FF}$ 25.3, F-8); δ_H 3.29 (4H, q, $^3J_{HH}$ 6.8, $N(CH_2CH_3)_2$), 3.12 (2H, t, $^3J_{HH}$ 4.4, NCH_2), 3.10 (3H, d, $^5J_{HF}$ 4.4, 1-NCH_3), 2.98 (2H, t, $^3J_{HH}$ 4.8, NCH_2), 2.66 (3H, s, 4-NCH_3), 1.10 (6H, t, $^3J_{HH}$ 6.8, $N(CH_2CH_3)_2$); δ_C 150.4 (d, $^1J_{CF}$ 225.3, C-5), 141.9 (m, C-7), 139.3 (m, C-8*a*), 136.6 (dd, $^1J_{CF}$ 240.1, $^4J_{CF}$ 4.6, C-8), 111.7 (d, $^2J_{CF}$ 32.4, C-4*a*), 48.7 (s, NCH_2), 46.0 (s, NCH_2), 44.6 (d, $^4J_{CF}$ 5.0, $N(CH_2CH_3)_2$), 43.6 (d, $^4J_{CF}$ 4.6, 4-NCH_3), 42.1 (d, $^4J_{CF}$ 13.3, 1-NCH_3), 13.8 (s, $N(CH_2CH_3)_2$); *m/z* (EI^+) 270 ($[M]^+$, 96), 255 ($[M\text{-}CH_3]^+$, 100), 241 ($[M\text{-}CH_3CH_2]^+$, 70), 226 ($[M\text{-}(CH_3)_2CH_2]^+$, 79), 211 ($[M\text{-}(CH_3)_3CH_2]^+$, 35).

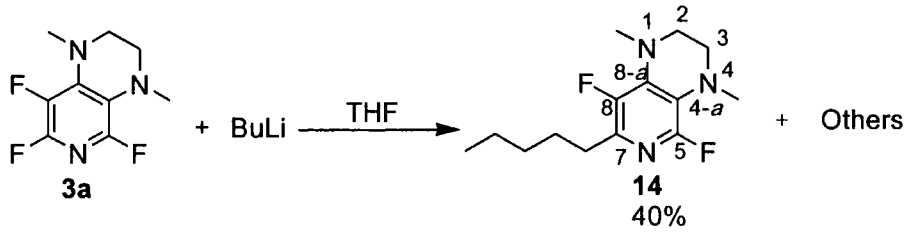
Preparation of 5,8-Difluoro-1,4-dimethyl-7-(phenylsulfanyl)-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 13a



Lithium thiophenoxide 1.0 M in tetrahydrofuran (16 ml, 16 mmol) was added to a sealed microwave vial under argon containing 5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.22 g, 1 mmol) and tetrahydrofuran (1 ml). The vial was irradiated with microwaves at 150°C for 1 h after which time HPLC indicated 98 % conversion of starting material. The above procedure was repeated three more times and the reaction mixtures were cooled to room temperature and combined. The solvent was evaporated and the residue redissolved in dichloromethane, poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), and dried over magnesium sulfate. The solvent was evaporated and the excess lithium thiophenoxide removed by passing through an SCX column to yield the crude product as a yellow oil (0.66 g) consisting of two major components in the ratio 1:1 which were identified as *5,8-difluoro-1,4-dimethyl-7-(phenylsulfanyl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **13a**; and *8-fluoro-1,4-dimethyl-5,7-bis(phenylsulfanyl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **13b**; δ_F -135.91 (1F, q, $^5J_{HF}$ 3.8, F-8); δ_H 7.0-7.3 (10H, m, Ar H), 3.26 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.21 (3H, d, $^5J_{HF}$ 1.6, 1-NCH_3), 3.05 (2H, t, $^3J_{HH}$ 5.2, CH_2), 2.76 (3H, s, 4-NCH_3); *m/z* $(EI)^+$ 398 ($[M+H]^+$, 100). Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane 0%-40%) followed by mass directed automated preparative HPLC (50%-99% acetonitrile in formic acid) gave *5,8-difluoro-1,4-dimethyl-7-(phenylsulfanyl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **13a** (0.33 g, 9%) as an amber oil; (Found: C, 58.7; H, 4.9;

N, 13.5; $C_{15}H_{15}F_2N_3S$ requires C, 58.6; H, 4.9; N, 13.7%); δ_F -78.41 (1F, d, $^5J_{FF}$ 23.2, F-5), -131.43 (1F, dq, $^5J_{FF}$ 23.2, $^5J_{HF}$ 4.1, F-8); δ_H 7.42 (2H, d, $^3J_{HH}$ 7.2, Ar H), 7.29 (2H, t, $^3J_{HH}$ 6.8, Ar H), 7.23 (1H, d, $^3J_{HH}$ 6.8, Ar H), 3.16 (5H, overlapping d & t, 1-NCH_3 & CH_2), 3.03 (2H, t, $^3J_{HH}$ 4.0, CH_2), 2.79 (3H, s, 4-NCH_3); δ_C 151.0 (d, $^1J_{CF}$ 232.0, C-5), 146.0 (dd, $^1J_{CF}$ 246.2, $^4J_{CF}$ 3.3, C-8), 137.2 (dd, $^2J_{CF}$ 9.8, $^3J_{CF}$ 8.2, C-7), 132.9 (s, Ar C), 131.7 (s, Ar CH), 130.5 (dd, $^2J_{CF}$ 23.7, $^3J_{CF}$ 18.2, C-8*a*), 128.9 (s, Ar CH), 127.4 (s, Ar CH), 119.6 (dd, $^2J_{CF}$ 30.7, $^3J_{CF}$ 2.6, C-4*a*), 48.2, (s, NCH_2), 46.6 (s, NCH_2), 43.2 (d, $^4J_{CF}$ 7.2, 4-NCH_3), 41.9 (d, $^4J_{CF}$ 12.9, 1-NCH_3); *m/z* (EI)$^+$ 308 ($[M+H]^+$, 85), 277 ($[MH-(CH_3)_2]^+$, 100), 233 ($[MH-(CH_3)_2NCH_2CH_2]^+$, 88).

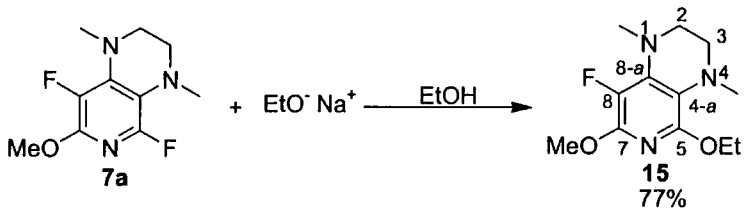
Preparation of 7-Butyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 14



5,7,8-Trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **3a** (0.22 g, 1 mmol) was added to tetrahydrofuran (15 ml) and cooled to -78°C. A 2.0 M solution of butyl lithium in tetrahydrofuran (1 ml, 2 mmol) was added and the reaction mixture was warmed to room temperature before refluxing for 4 d. Over the course of the reaction 4.3 extra equivalents of the 2.0 M butyl lithium solution (2.1 ml, 5.3 mmol) were added. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as

a brown oil (0.38 g) consisting of one major component. Purification by mass directed automated preparative HPLC (50%-99% acetonitrile in formic acid) followed by preparative thin layer chromatography (2:1 *n*-hexane/ethyl acetate) gave *7-butyl-5,8-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **14** (0.1 g, 40%) as a colourless oil; δ_F -81.18 (1F, d, $^5J_{FF}$ 26.3, F-5), -142.91 (1F, q, $^5J_{FF}$ 22.6, F-8); δ_H 3.16 (5H, overlapping d & t, 1-NCH_3 & NCH_2), 3.03 (2H, t, $^3J_{HH}$ 4.4, NCH_2), 2.77 (3H, d, $^5J_{HF}$ 1.2, 4-NCH_3), 2.61 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.64 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.37 (2H, m, $NCH_2CH_2CH_2CH_3$), 0.93 (3H, t, $^3J_{HH}$ 7.6, $NCH_2CH_2CH_2CH_3$); δ_C 151.6 (d, $^1J_{CF}$ 226.8, C-5), 145.4 (dd, $^1J_{CF}$ 242.1, $^4J_{CF}$ 3.7, C-8), 138.2 (m, C-7), 137.4 (m, C-8*a*), 128.1 (d, $^2J_{CF}$ 31.5, C-4*a*), 48.2 (s, NCH_2CH_2N), 46.1 (s, NCH_2CH_2N), 43.3 (d, $^4J_{CF}$ 6.1, 4-NCH_3), 41.7 (d, $^4J_{CF}$ 13.0, 1-NCH_3), 30.7 (s, $CH_2CH_2CH_2CH_3$), 30.4 (s, $CH_2CH_2CH_2CH_3$), 29.7 (s, $CH_2CH_2CH_2CH_3$), 13.9 (s, $CH_2CH_2CH_2CH_3$); *m/z* (EI)$^+$ 256 ($[M+H]^+$, 81), 236 ($[MH-HF]^+$, 5), 213 ($[MH-CH_2CH_2CH_3]^+$, 7).

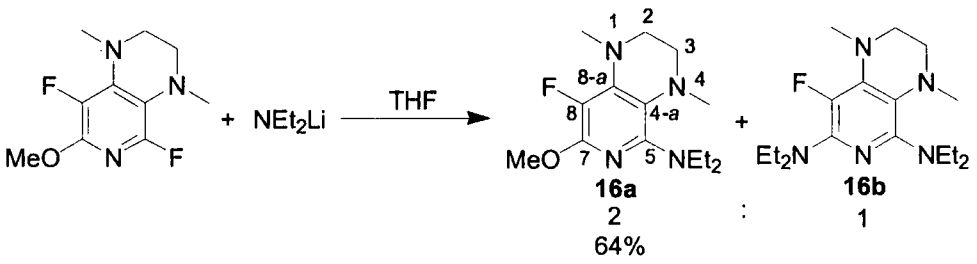
Preparation of 5-Ethoxy-8-fluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 15



Sodium metal (18.5 mg, 0.8 mmol) was added to anhydrous ethanol (30 ml) under argon followed by the addition of 5,8-difluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **7a** (0.2 g, 0.8 mmol). The resulting solution was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The

reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 20 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a brown oil (0.17 g) consisting of one major component. Purification by column chromatography on silica gel (1:3 *n*-hexane/ethyl acetate) gave *5-ethoxy-8-fluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **15** (0.17 g, 77 %) as a colourless oil; (Found: C, 56.8; H, 7.2; N, 16.2; $C_{12}H_{18}N_3FO_2$ requires: C, 56.5; H, 7.1; N, 16.5%); δ_F –166.18 (1F, s, F-8); δ_H 4.38 (2H, q, $^3J_{HH}$ 7.2, OC*H*$_2$CH$_3$), 3.90 (3H, s, OC*H*$_3$), 3.14 (3H, d, $^5J_{HF}$ 3.6, 1-NCH$_3$), 3.12 (2H, t, $^3J_{HH}$ 5.2, NCH$_2$), 3.02 (2H, t, $^3J_{HH}$ 5.2, NCH$_2$), 2.65 (3H, s, 4-NCH$_3$), 1.40 (3H, t, $^3J_{HH}$ 6.8, OCH$_2$C*H*$_3$); δ_C 150.0 (d, $^4J_{CF}$ 1.5, C-5), 146.2 (d, $^2J_{CF}$ 12.6, C-7), 138.3 (d, $^2J_{CF}$ 4.9, C-8*a*), 132.3 (d, $^1J_{CF}$ 238.6, C-8), 113.6 (s, C-4*a*), 61.7 (s, OCH$_2$), 53.4 (s, OCH$_3$), 48.9 (s, NCH$_2$), 45.1 (s, NCH$_2$), 42.6 (s, 4-NCH$_3$), 41.7 (d, $^4J_{CF}$ 13.4, 1-NCH$_3$), 15.2 (s, OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 255 ([M]$^+$, 100), 240 ([M-CH$_3$]$^+$, 15), 226 ([M-CH$_2$CH$_3$]$^+$ 92), 210 ([M-OCH$_2$CH$_3$]$^+$, 43).

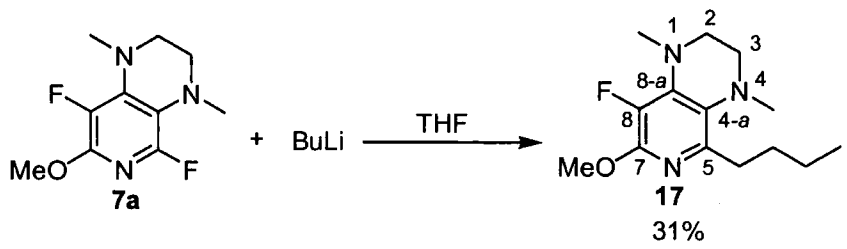
Preparation of *N,N'*-Diethyl-8-fluoro-7-methoxy-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-5-amine 16a



Butyl lithium 2.0 M in tetrahydrofuran (2 ml, 4 mmol) and diethylamine (0.29 g, 4 mmol) were added to tetrahydrofuran (20 ml) at -78°C and the solution was stirred for 1 h before warming to room temperature. 5,8-Difluoro-7-methoxy-1,4-dimethyl-1,2,3,4-

tetrahydropyrido[3,4-*b*]pyrazine **7a** (0.23 g, 1 mmol) was added and the reaction mixture refluxed for 5 d. Over the course of the reaction, 6 extra equivalents of the lithium diethylamide salt (24 mmol) were added to the reaction mixture following the procedure outlined above. ^{19}F NMR indicated 100% conversion so the reaction was cooled to room temperature, the solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.27 g) consisting of two major components in the ratio 2:1 which were identified as *N,N-diethyl-8-fluoro-7-methoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-5-amine* **16a**; and *N,N,N,N-tetraethyl-8-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine-5,7-diamine* **16b**; δ_F -164.87 (1F, d, $^5J_{HF}$ 3.8, F-8); *m/z* $(EI)^+$ 324 ($[M+H]^+$, 100). Purification by mass directed automated preparative HPLC (15%-55% acetonitrile in formic acid) gave *N,N-diethyl-8-fluoro-7-methoxy-1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-5-amine* **16a** (0.18 g, 64%) as an orange oil; ($[M+H]^+$ 283.1927, $C_{14}H_{23}N_4FO$ requires $[M+H]^+$ 283.1934); δ_F -158.19 (1F, d, $^5J_{HF}$ 3.8, F-8); δ_H 3.92 (3H, s, OCH_3), 3.61 (4H, $^3J_{HH}$ 7.2, $N(CH_2CH_3)_2$), 3.39 (2H, t, $^3J_{HH}$ 5.2, NCH_2CH_2), 3.30 (3H, d, $^5J_{HF}$ 4.8, 1-NCH_3), 3.05 (2H, t, $^3J_{HH}$ 5.2, NCH_2CH_2), 2.68 (3H, s, 4-NCH_3), 1.17 (6H, t, $^3J_{HH}$ 6.8, $N(CH_2CH_3)_2$); δ_C 150.5 (d, $^2J_{CF}$ 12.8, C-7), 137.9 (d, $^4J_{CF}$ 2.6, C-5), 136.2 (s, C-8*a*), 134.1 (d, $^1J_{CF}$ 249.8, C-8), 124.0 (s, C-4*a*), 53.7 (s, OCH_3), 51.7 (s, $N(CH_2CH_3)_2$), 48.0 (s, NCH_2), 44.4 (s, NCH_2), 43.7 (s, $N(CH_2CH_3)_2$), 40.8 (s, 4-NCH_3), 40.6 (d, $^4J_{CF}$ 12.5, 1-NCH_3); *m/z* $(EI)^+$ 283 ($[M+H]^+$, 100), 268 ($[MH-CH_3]^+$, 10), 254 ($[MH-CH_2CH_3]^+$, 80), 239 ($[MH-CH_2CH_3CH_3]^+$, 9).

Preparation of 5-Butyl-8-fluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 17



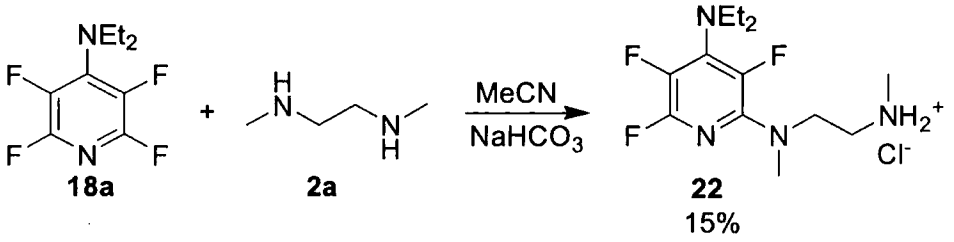
A 2.0 M solution of butyl lithium in tetrahydrofuran (1.4 ml, 2.71 mmol) was added to a solution of 5,8-difluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine **7a** (0.31 g, 1.35 mmol) in tetrahydrofuran (20 ml). The resulting solution was refluxed for 6 d, and over the course of the reaction 8 extra equivalents of the 2.0 M butyl lithium solution (5.6 ml, 10.84 mmol) were added. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, and the solvent was evaporated to dryness. The residue was redissolved in dichloromethane, poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a brown oil (0.39 g) consisting of one major component. Purification by column chromatography on silica gel (ethyl acetate in *n*-hexane, 0%-50%) gave *5-butyl-8-fluoro-7-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **17** (0.11 g, 31%) as a colourless oil; (Found: C, 62.8; H, 8.3; N, 15.4 %; $C_{14}H_{22}N_3FO$ requires: C, 62.9; H, 8.2; N, 15.7%); δ_F -160.54 (1F, d, $^5J_{HF}$ 4.1, F-8); δ_H 3.85 (3H, s, OCH_3), 3.13 (2H, t, $^3J_{HH}$ 4.8, NCH_2), 3.09 (3H, d, $^5J_{HF}$ 4.4, 1-NCH_3), 2.92 (2H, t, $^3J_{HH}$ 5.2, NCH_2), 2.57 (2H, t, $^3J_{HH}$ 8.0, $CH_2CH_2CH_2CH_3$), 2.48 (3H, s, 4-NCH_3), 1.63 (2H, quintet, $^3J_{HH}$ 7.6, $NCH_2CH_2CH_2CH_3$), 1.30 (2H, sextet, $^3J_{HH}$ 7.6, $NCH_2CH_2CH_2CH_3$), 0.86 (3H, t, $^3J_{HH}$ 7.6, $NCH_2CH_2CH_2CH_3$); δ_C 148.4 (d, $^2J_{CF}$ 10.6, C-7), 145.8 (d, $^4J_{CF}$ 4.6, C-5), 135.4 (d, $^2J_{CF}$ 2.0, C-8*a*), 133.0 (d, $^1J_{CF}$ 247.3, C-8), 126.1 (d, $^3J_{CF}$ 1.0, C-4*a*), 52.0 (s, OCH_3), 47.6 (s, NCH_2), 43.4 (s, NCH_2), 42.4 (s, 4-NCH_3),

40.0 (d, $^4J_{CF}$ 13.0, 1-NCH_3), 30.4 (s, $CH_2CH_2CH_2CH_3$), 29.6 (s, $CH_2CH_2CH_2CH_3$), 21.8 (s, $CH_2CH_2CH_2CH_3$), 13.1 (s, $CH_2CH_2CH_2CH_3$); *m/z* $(EI)^+$ 268 ($[M+H]^+$, 80), 253 ($[MH-CH_3]^+$, 17), 225 ($[MH-CH_3(CH_2)_2]^+$, 5), 211 ($[MH-CH_3(CH_2)_3]^+$, 7).

1 D. Bhuniya and V. K. Singh, *Synth. Commun.*, 1994, **24**, 375.

EXPERIMENTAL TO CHAPTER 3

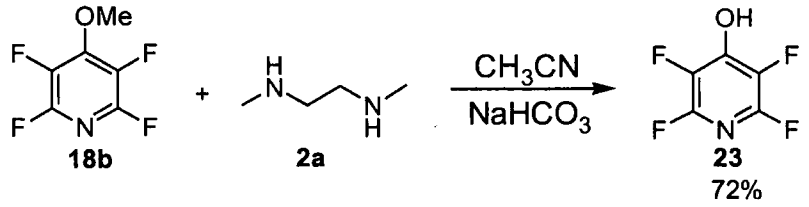
Preparation of 2-[[4-(Diethylamino)-3,5,6-trifluoropyridin-2-yl](methyl)amino]-*N*-methylethanaminium chloride 22



N,N'-dimethyleythylenediamine **2a** (1.44 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Diethyl-(2,3,5,6-tetrafluoro-pyridin-4-yl)-amine **18a** (2.22 g, 10 mmol) was added and the resulting solution refluxed for 4 d after which time ^{19}F NMR indicated 72 % conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (150 ml), extracted with dichloromethane (2 x 100 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.1 g) consisting of one major component. Purification by recrystallisation from ethyl acetate gave *2-[[4-(diethylamino)-3,5,6-trifluoropyridin-2-yl](methyl)amino]-N-methylethanaminium chloride* **22** (0.5 g, 15%) as beige crystals; mp 122.8-123.1°C; (Found: C, 47.6; H, 6.8; N, 17.0. $C_{13}H_{22}N_4F_3Cl$ requires: C, 47.8; H, 6.7; N, 17.2%); δ_F(DMSO-d_6) –95.08 (1F, t, $^3J_{FF}$ 25.2, F-6), -145.03 (1F, d, $^4J_{FF}$ 23.4, F-3), -162.34 (1F, d, $^3J_{FF}$ 25.2, F-5); δ_H(DMSO-d_6) 9.78 (2H, br s, NH_2), 3.69 (2H, t, $^3J_{HH}$ 6.7, $NCH_2CH_2NH_2$), 3.35 (4H, q, $^3J_{HH}$ 7.0, $N(CH_2CH_3)_2$), 3.24 (2H, t, $^3J_{HH}$ 6.7, $NCH_2CH_2NH_2$), 3.08 (3H, d, $^3J_{HH}$ 4.3, NCH_3), 2.80 (3H, s, $CH_3NH_2CH_2$), 1.17 (6H, t, $^3J_{HH}$ 7.0, $N(CH_2CH_3)_2$); δ_C(DMSO-d_6)

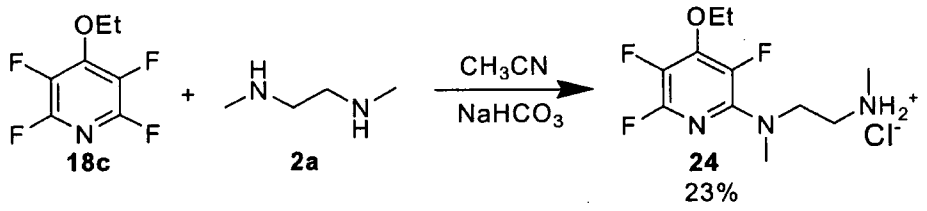
145.9 (dd, $^{1}J_{CF}$ 225.2, $^{2}J_{CF}$ 15.0, C-6), 143.0 (m,, C-4), 139.0 (dd, $^{1}J_{CF}$ 245.6, $^{3}J_{CF}$ 10.8, C-3), 138.3 (m, C-2), 132.0 (dd, $^{1}J_{CF}$ 244.5, $^{2}J_{CF}$ 31.2, C-5); *m/z* (EI^{+}) 270 ($[M\text{-}HF]^{+}$, 34), 246 ($[M\text{-}CH_2NHCH_3]^{+}$, 100), 179 ($[M\text{-}(CH_3)_2CH_2N]^{+}$, 82).

Preparation of 2,3,5,6-Tetrafluoropyridin-4-ol 23



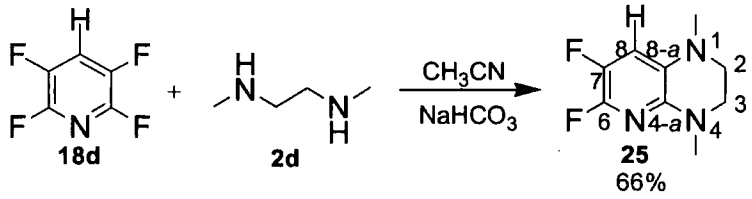
N,N'-Dimethylethylenediamine **2a** (1.94 g, 22 mmol) and sodium hydrogencarbonate (3.70 g, 44 mmol) were added to acetonitrile (400 ml) under argon. 2,3,5,6-Tetrafluoro-4-methoxypyridine **18b** (1.81 g, 10 mmol) was added and the resulting solution refluxed for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto 1.0 M hydrochloric acid (200 ml), extracted with dichloromethane (2 x 100 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (2.75 g) consisting of one major component. Purification by vacuum sublimation gave *2,3,5,6-tetrafluoropyridin-4-ol* **23** (1.2 g, 72%) as white crystals; mp 90.5-91.6°C; (Found: C, 35.6; H, 0.6; N, 8.6. C_5HNOF_4 requires: C, 35.9; H, 0.6; N, 8.4%); δ_F –90.94 (2F, s, F-2,6), -163.66 (2F, m, F-3,5); δ_H 6.82 (1H, br s, OH); *m/z* (EI^{+}) 168 ($[M+H]^{+}$, 6), 167 ($[M]^{+}$ 100), 119 (40), 74 (41), 31 (15).

Preparation of 2-[(4-ethoxy-3,5,6-trifluoropyridin-2-yl)(methyl)amino]-*N*-methylethanaminium chloride 24



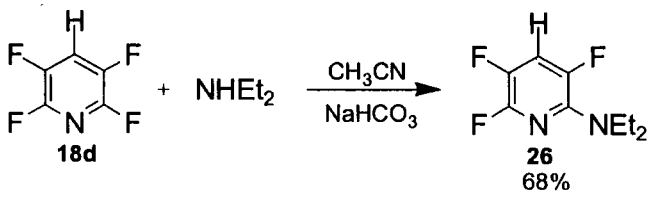
N,N'-Dimethyleythylenediamine **2a** (1.76 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. 4-Ethoxy-2,3,5,6-tetrafluoropyridine **18c** (1.95 g, 10 mmol) was added and the resulting solution refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto 1.0 M hydrochloric acid (100 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown/white solid (1.34 g) consisting of one major component. Purification by recrystallisation from dichloromethane gave *2-[(4-ethoxy-3,5,6-trifluoropyridin-2-yl)(methyl)amino]-N-methylethanaminium chloride* **24** (0.70 g, 23 %) as an off white solid; mp 139.0-141.2°C; (Found: C, 43.8; H, 5.7; N, 13.8. $C_{11}H_{17}N_3ClF_3O$ requires: C, 44.1; H, 5.7; N, 14.0%); δ_F -91.60 (1F, t, $^3J_{FF}$ 25.5, F-6), -152.70 (1F, d, $^3J_{FF}$ 29.4, F-5), -168.80 (1F, d, $^4J_{FF}$ 24.6, F-3); δ_H 9.67 (2H, br s, NH_2), 4.42 (2H, q, $^3J_{HH}$ 6.8, CH_2CH_3), 3.80 (2H, t, $^3J_{HH}$ 6.8, NCH_2), 3.22 (2H, t, $^3J_{HH}$ 6.0, NCH_2), 3.15 (3H, d, $^3J_{HH}$ 4.0, NCH_3), 2.77 (3H, t, $^3J_{HH}$ 5.6, NH_2CH_3) 1.42 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3); δ_C 146.0 (m, C-2), 145.5 (dd, $^1J_{CF}$ 232.6, $^2J_{CF}$ 10.6, C-6), 141.7 (m, C-4), 138.0 (dd, $^1J_{CF}$ 249.0, $^3J_{CF}$ 5.7, C-3), 131.0 (dd, $^1J_{CF}$ 249.7, $^2J_{CF}$ 31.6, C-5), 70.4 (t, $^4J_{CF}$ 3.4, NCH_2), 48.3 (s, $NCH_2CH_2NH_2$), 47.0 (s, OCH_2), 39.2 (d, $^4J_{CF}$ 9.6, NCH_3), 33.3 (s, NH_2CH_3), 15.8 (s, CH_2CH_3); *m/z* (EI^+) 244 ($[M\text{-}HFCl]^+$, 2), 219 ($[M\text{-}CH2NH_2CH_3Cl]^+$, 43), 191 ($[M\text{-}CH_2CH_2CH_2NH_2CH_3Cl]^+$, 88).

Preparation of 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 25



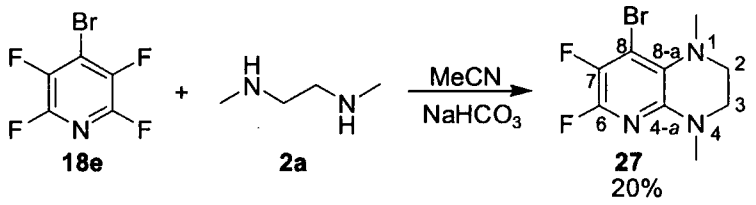
N,N'-Dimethylethylenediamine **2d** (1.17 g, 13.2 mmol) and sodium hydrogencarbonate (2.23 g, 26.5 mmol) were added to acetonitrile (175 ml) under argon. 2,3,5,6-Tetrafluoropyridine **18d** (1.0 g, 6.62 mmol) was then added and the resulting solution refluxed for 13 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a purple/black solid (1.23 g) consisting of one major component. Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **25** (0.87 g, 66%) as a red solid; mp 30.2-32.6°C; ($[M+H]^+$ 200.0994, $C_9H_{11}N_3F_2$ requires $[M+H]^+$ 200.0994); δ_F -108.05 (1F, s, F-6), -160.50 (1F, s, F-7); δ_H 6.42 (1H, m, H-8), 3.41 (2H, br s, CH_2), 3.17 (2H, br s, CH_2), 2.96 (3H, br s, CH_3), 2.73 (3H, br s, CH_3); δ_C 142.0 (dd, $^1J_{CF}$ 220.4, $^2J_{CF}$ 15.2, C-6), 141.0 (d, $^3J_{CF}$ 13.7, C-4*a*), 135.9 (dd, $^1J_{CF}$ 238.6, $^2J_{CF}$ 28.6, C-7), 130.2 (s, C-8*a*), 107.8 (d, $^2J_{CF}$ 21.8, C-8), 48.3 (s, CH_2), 48.2 (s, CH_2), 39.2 (s, CH_3), 36.7 (s, CH_3); *m/z* (EI^+) 199 ($[M]^+$, 100), 184 ($[M-CH_3]^+$, 56), 169 ($[M-(CH_3)_2]^+$, 16).

Preparation of *N,N'*-Diethyl-3,5,6-Trifluoropyridin-2-amine 26



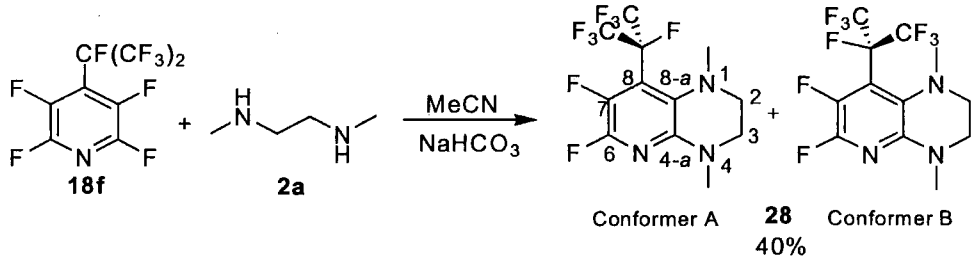
Diethylamine (0.48 g, 6.62 mmol) and sodium hydrogencarbonate (0.56 g, 6.62 mmol) were added to acetonitrile (20 ml) under argon. 2,3,5,6-Tetrafluoropyridine **18d** (1 g, 6.62 mmol) was added and the resulting solution refluxed for 7 d after which time ^{19}F NMR indicated 88% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.0 g) consisting of one major component. Purification by column chromatography on silica gel (10:1 *n*-hexane/ethyl acetate) gave *N,N-diethyl-3,5,6-trifluoropyridin-2-amine* **26** (0.92 g, 68%) as a colourless oil; ($[M+H]^+$ 205.0947, $C_9H_{11}N_2F_3$ requires $[M+H]^+$ 205.0947); δ_F -93.44 (1F, t, $^3J_{FF}$ 31.6, F-6), -135.20 (1F, dd, $^3J_{FF}$ 31.6, $^4J_{FF}$ 11.3, F-5), -156.20 (1F, dd, $^4J_{FF}$ 24.8, $^5J_{FF}$ 6.8, F-3); δ_H 7.17 (1H, dt, $^3J_{HF}$ 11.2, $^3J_{HF}$ 8.0, 4-H), 3.44 (4H, qd, $^3J_{HH}$ 7.2, CH_2), 1.17 (6H, t, $^3J_{HH}$ 7.2, CH_3); δ_C 144.5 (dd, $^1J_{CF}$ 229.1, $^2J_{CF}$ 14.1, C-6), 143.1 (ddd, $^1J_{CF}$ 251.2, $^3J_{CF}$ 5.3, $^4J_{CF}$ 1.9, C-3), 141.9 (m, C-2), 134.3 (ddd, $^1J_{CF}$ 248.2, $^2J_{CF}$ 32.4, $^3J_{CF}$ 5.4, C-5), 116.4 (ddd, $^2J_{CF}$ 25.2, $^2J_{CF}$ 19.8, $^3J_{CF}$ 3.8, C-4), 44.3 (d, $^4J_{CF}$ 5.8, CH_2), 13.8 (s, CH_3); *m/z* (EI^+) 204 ($[M]^+$, 79), 189 ($[M-CH_3]^+$, 100), 175 ($[M-CH_2CH_3]^+$, 64), 161 ($[M-(CH_2)_2CH_3]^+$, 100).

Preparation of 8-Bromo-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 27



N,N'-Dimethylethylenediamine **2a** (0.73 g, 8.73 mmol) and sodium hydrogencarbonate (1.47 g, 17.47 mmol) were added to acetonitrile (400 ml) under argon. 4-Bromo-2,3,5,6-tetrafluoropyridine **18e** (1.0 g, 4.37 mmol) was added and the resulting solution refluxed for 5 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown solid (0.48 g) consisting of one major component. Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) gave *8-bromo-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **27** (0.24 g, 20%) as yellow crystals; mp 76.2-77.0°C; (Found: C, 39.1; H, 3.7; N, 15.0; $C_9H_{10}N_3BrF_2$ requires: C, 39.0; H, 3.6; N, 15.2%); δ_F -94.67 (1F, d, $^3J_{FF}$ 26.7, F-6), -152.39 (1F, d, $^3J_{FF}$ 26.7, F-7); δ_H 3.37 (2H, t, $^3J_{HH}$ 5.0, CH_2), 3.12 (3H, s, CH_3), 3.06 (2H, t, $^3J_{HH}$ 5.0, CH_2), 2.73 (3H, s, CH_3); δ_C 145.9 (dd, $^1J_{CF}$ 228.7, $^2J_{CF}$ 15.6, C-6), 145.3 (dd, $^3J_{CF}$ 15.6, $^4J_{CF}$ 1.2, C-4*a*), 133.8 (dd, $^1J_{CF}$ 241.6, $^2J_{CF}$ 31.6, C-7), 126.4 (dd, $^3J_{CF}$ 5.8, $^4J_{CF}$ 2.2, C-8*a*), 117.8 (dd, $^2J_{CF}$ 16.3, $^3J_{CF}$ 5.0, C-8), 48.1 (s, CH_3), 43.3 (s, CH_2), 42.90 (s, CH_3), 36.6 (s, CH_2); *m/z* (EI^+) 277 ($[M]^+$, 96), 262 ($[M-CH_3]^+$, 72), 183 ($[M-CH_3Br]^+$, 26), 168 ($[M-C_2H_6Br]^+$, 22).

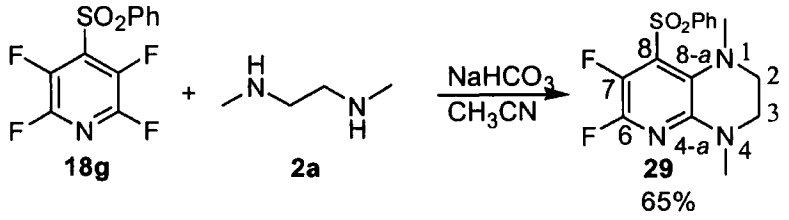
Preparation of 6,7-Difluoro-1,4-dimethyl-8-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 28



N,N'-Dimethyleythylenediamine **2a** (1.23 g, 14 mmol) and sodium hydrogencarbonate (1.24 g, 14.8 mmol) were added to acetonitrile (30 ml) under argon. 2,3,5,6-Tetrafluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine **18f** (2.02 g, 6.33 mmol) was added dropwise and the resulting solution refluxed for 21 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (2 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow/brown solid (1.2 g) consisting of one major component. Purification by recrystallisation from *n*-hexane gave *6,7-difluoro-1,4-dimethyl-8-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **28** (0.98 g, 40%) as light sensitive yellow needle-like crystals which turn black upon exposure; mp 57.9-58.5°C; (Found: C, 39.3; H, 2.7; N, 11.5. $C_{12}H_{10}N_3F_9$ requires: C, 39.2; H, 2.7; N, 11.2%; δ_F –70.77 (2.4F, s, CF_3 of B), -74.88 (6F, br m, CF_3 of A), -92.47 (0.3F, d, $^3J_{FF}$ 33.0, F-6 of B), -94.44 (1F, d, $^3J_{FF}$ 27.6, F-6 of A), 155.65 (1F, sextet, $^3J_{FF}$ 27.6, F-7 of A), -156.80 (0.3F, d, $^4J_{FF}$ 44.5, F-7 of B), -168.43 (0.3F, d, $^4J_{FF}$ 88.8, $(CF_3)_2CF$ of B), -179.66 (1F, s, $(CF_3)_2CF$ of A); δ_H 3.47 (2H, br s, CH_2), 3.13 (3H, s, CH_3), 2.97 (2H, br m, CH_2), 2.63 (3H, s, CH_3); δ_C 147.6 (dd, $^1J_{CF}$ 183.1, $^2J_{CF}$ 13.8, C-6), 147.2 (d, $^3J_{CF}$ 11.1, C-4*a*), 132.4 (dm, $^1J_{CF}$ 200.7, C-7), 128.5 (s, C-8*a*), 120.8 (qd, $^1J_{CF}$ 230.0, $^2J_{CF}$ 22.5, CF_3), 119.9

(m, C-8), 92.0-96.0 (m, $CF(CF_3)_2$), 47.1 (s, CH_2), 45.7 (d, $^5J_{CF}$ 5.7, 1-NCH_3), 43.2 (s, CH_2), 37.4 (s, 4-NCH_3); *m/z* (EI^+) 368 ($[M+H]^+$, 34), 367 ($[M]^+$, 100), 352 ($[M-CH_3]^+$, 90), 325 ($[M-C_2H_4N]^+$, 49), 263 ($[M-C_4H_9N_2F]^+$, 89), 69 ($[CF_3]^+$, 32), 42 ($[C_2H_4N]^+$, 53).

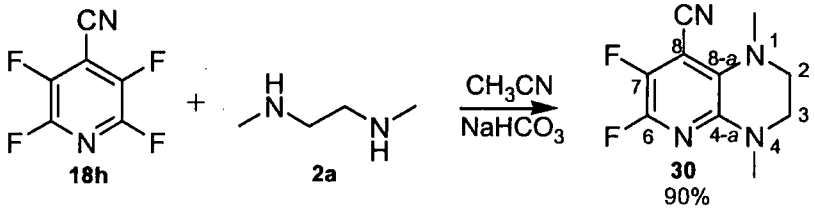
Preparation of Phenyl 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-sulfinate 29



N,N'-Dimethylethylenediamine **2a** (0.58 g, 6.70 mmol) and sodium hydrogencarbonate (1.15 g, 13.75 mmol) were added to acetonitrile (200 ml) under argon. 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **18g** (1.0 g, 3.44 mmol) was added and the resulting solution was refluxed for 16 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as an orange solid (1.7 g) consisting of one major component. Purification by recrystallisation from *n*-hexane gave *phenyl 6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-8-sulfinate* **29** (0.75 g, 65%) as yellow-orange light sensitive crystals; mp ~160°C (decomposes); ($[M+H]^+$ 340.0928, $C_{15}H_{15}N_3F_2SO_2$ requires $[M+H]^+$ 340.0926); δ_F -95.57 (1F, d, $^3J_{FF}$ 27, F-6), -157.04 (1F, d, $^3J_{FF}$ 27, F-7); δ_H 7.95 (2H, d, $^3J_{HH}$ 7.5, Ar_{ortho} H), 7.60 (1H, m, Ar_{para} H), 7.49 (2H, t, $^3J_{HH}$ 8.0, Ar_{meta} H), 3.35 (2H, t, $^3J_{HH}$ 5.2, CH_2), 3.06 (3H, s, NCH_3), 2.92 (3H, s, NCH_3), 2.77 (2H, t, $^3J_{HH}$ 5.2, CH_2); δ_C 146.3 (dd, $^1J_{CF}$ 231.0, $^2J_{CF}$ 16.7, C-6), 146.2 (d, $^3J_{CF}$ 13.7, C-4*a*), 142.2 (s, Ar C), 133.8 (s, Ar_{ortho} CH), 132.1 (dd, $^1J_{CF}$ 253.1, $^2J_{CF}$ 31.7, C-7),

131.1 (d, $^3J_{CF}$ 10.5, C-8*a*), 128.7 (s, Ar_{meta} CH), 127.9 (s, Ar_{para} CH), 126.9 (m, C-8), 47.1 (s, NCH_2), 47.0 (s, NCH_3), 43.4 (s, NCH_2), 37.0 (s, NCH_3); *m/z* (EI^+) 339 ($[M]^+$, 100), 198 ($[M-SO_2Ph]^+$, 16).

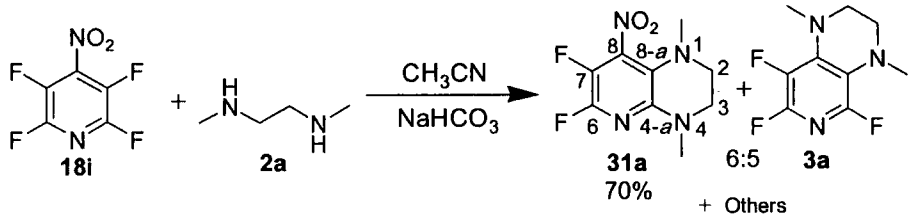
Preparation of 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-carbonitrile 30



N,N'-Dimethylethylenediamine **2a** (0.67 g, 7.57 mmol) and sodium hydrogencarbonate (1.27 g, 15.14 mmol) were added to acetonitrile (175 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (0.66 g, 3.79 mmol) was added and the resulting solution was refluxed for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane (50 ml). The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow/black solid (1.64 g) consisting of one major component. The solid was filtered through a silica plug and purification by recrystallisation from ethyl acetate/*n*-hexane gave *6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-8-carbonitrile* **30** (0.76 g, 90%) as bright yellow crystals; mp 128.0–128.8°C; (Found: C, 53.6; H, 4.5; N, 25.2; $C_{10}H_{10}N_4F_2$ requires: C, 53.6; H, 4.5; N, 25.0%); δ_F -104.75 (d, 1F, $^3J_{FF}$ 22.6, F-6), -156.79 (d, 1F, $^3J_{FF}$ 22.9, F-7); δ_H 3.40 (2H, m, CH_2), 3.39 (2H, m, CH_2), 3.30 (3H, s, CH_3), 3.05 (3H, s, CH_3); δ_C 142.6 (dd, $^3J_{CF}$ 15.5, $^4J_{CF}$ 3.0, C-4*a*), 141.3 (dd, $^1J_{CF}$ 223.6, $^2J_{CF}$ 13.9, C-6),

134.7 (dd, $^{1}J_{CF}$ 250.4, $^{2}J_{CF}$ 31.5, C-7), 133.5 (dd, $^{3}J_{CF}$ 4.4, $^{4}J_{CF}$ 2.4, C-8*a*), 113.4 (d, $^{3}J_{CF}$ 4.8, CN), 94.3 (dm, $^{2}J_{CF}$ 14.9, C-8), 49.7 (s, CH_2), 46.2 (s, CH_2), 42.8 (s, CH_3), 37.4 (s, CH_3); *m/z* (EI^+) 224 ($[M]^+$, 100), 209 ($[M-CH_3]^+$, 52), 194 ($[M-(CH_3)_2]^+$, 8).

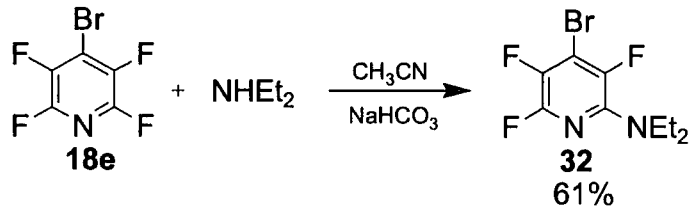
Preparation of 6,7-Difluoro-1,4-dimethyl-8-nitro-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 31a



N,N'-Dimethylethylenediamine **2a** (0.58 g, 6.63 mmol) and sodium hydrogencarbonate (1.11 g, 13.27 mmol) were added to acetonitrile (150 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.65 g, 3.32 mmol) was added and the resulting solution refluxed for 5 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a red oily solid (1.04 g) consisting of two major components in the ratio 6:5 which were identified as *6,7-difluoro-1,4-dimethyl-8-nitro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **31a**; and *5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **3a**, data as before. Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) gave *6,7-difluoro-1,4-dimethyl-8-nitro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **31a** (0.57 g, 70%) as red/black crystals; mp 79.4-80.9°C; (Found: C, 44.3; H, 4.1; N, 22.9; $C_9H_{10}N_4F_2O_2$ requires: C, 44.3; H, 4.1; N, 23.0%); δ_F -99.61 (1F, d, $^{3}J_{FF}$ 24.6, F-6), -170.43 (1F, d, $^{3}J_{FF}$ 23.7, F-7); δ_H 3.42

(2H, t, $^3J_{HH}$ 4.2, CH_2), 3.26 (2H, t, $^3J_{HH}$ 5.0, CH_2), 3.08 (3H, s, CH_3), 2.78 (3H, s, CH_3); δ_C 144.0 (dd, $^3J_{CF}$ 14.5, $^4J_{CF}$ 2.1, C-4*a*), 142.7 (dd, $^1J_{CF}$ 226.4, $^2J_{CF}$ 13.3, C-6), 136.5 (dm, $^2J_{CF}$ 12.5, C-8), 127.8 (dd, $^1J_{CF}$ 252.7, $^2J_{CF}$ 33.9, C-7), 122.1 (dd, $^3J_{CF}$ 5.3, $^4J_{CF}$ 3.1, C-8*a*), 49.3 (s, CH_2), 45.5 (s, CH_2), 42.0 (s, CH_3), 37.2 (s, CH_3); *m/z* (EI^+) 244 ($[M]^+$, 100), 214 ($[M-(CH_3)_2]^+$, 8), 198 ($[M-NO_2]^+$, 34).

Preparation of 4-Bromo-*N,N'*-diethyl-3,5,6-trifluoropyridin-2-amine 32

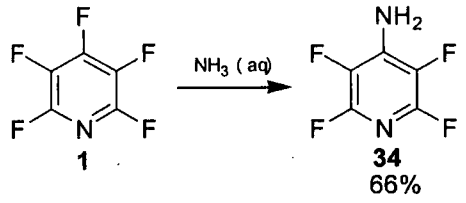


Diethylamine (0.21 g, 2.84 mmol) and sodium hydrogencarbonate (0.24 g, 2.84 mmol) were added to acetonitrile (20 ml) under argon. 4-Bromo-2,3,5,6-tetrafluoropyridine **18e** (0.65 g, 2.84 mmol) was added and the resulting solution refluxed for 1 d after which time ^{19}F NMR indicated 76% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.78 g) consisting of one major component. Purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave *4-bromo-N,N-diethyl-3,5,6-trifluoropyridin-2-amine* **32** (0.49 g, 61%) as a colourless oil; ($[M+H]^+$ 283.0050, $C_9H_{10}N_2F_3Br$ requires $[M+H]^+$ 283.0052); δ_F -90.45 (1F, t, $^3J_{FF}$ 27.1, F-6), -130.80 (1F, dd, $^3J_{FF}$ 29.3, $^4J_{FF}$ 9.0, F-5), 151.47 (1F, dd, $^4J_{FF}$ 24.8, $^5J_{FF}$ 6.8, F-3); δ_H 3.45 (4H, qd, $^3J_{HH}$ 7.2, $^4J_{HF}$ 2.0, CH_2), 1.19 (6H, t, $^3J_{HH}$ 7.2, CH_3); δ_C 144.5

(ddd, $^{1}J_{CF}$ 231.0, $^{2}J_{CF}$ 14.8, $^{4}J_{CF}$ 2.3, C-6), 141.6 (m, C-2), 141.2 (ddd, $^{1}J_{CF}$ 251.6, $^{3}J_{CF}$ 6.1, $^{4}J_{CF}$ 3.5, C-3), 133.3 (ddd, $^{1}J_{CF}$ 248.2, $^{2}J_{CF}$ 33.9, $^{3}J_{CF}$ 1.6, C-5), 111.7 (ddd, $^{2}J_{CF}$ 24.8, $^{2}J_{CF}$ 19.4, $^{3}J_{CF}$ 5.4, C-4), 44.4 (d, $^{4}J_{CF}$ 6.1, CH_2), 13.8 (s, CH_3); *m/z* (EI^+) 282 ($[M]^+$, 40), 267 ($[M\text{-}CH_3]^+$, 100).

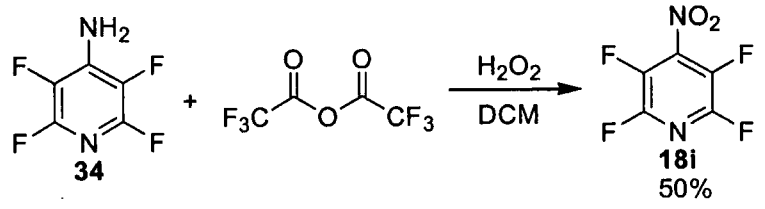
EXPERIMENTAL TO CHAPTER 4

Preparation of 4-Amino-2,3,5,6-tetrafluoropyridine 34



Pentafluoropyridine **1** (16.9 g, 0.1 mol) was added to 35% aqueous ammonia (100 ml) and stirred at room temperature for 16 h. The precipitated product was filtered, dissolved in dichloromethane, dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a white solid. Purification by recrystallisation from dichloromethane gave *4-amino-2,3,5,6-tetrafluoropyridine* **34** (11.0 g, 66%) as white crystals; mp 83.0-84.1°C; (Found: C, 35.9; H, 1.2; N, 16.9; $C_5H_2N_2F_4$ requires: C, 36.1; H, 1.2; N, 16.9%); δ_F -93.76 (2F, s, F-2,6), -164.63 (2F, m, F-3,5); δ_H 4.74 (2H, br s, NH_2); δ_C 143.7 (dt, $^1J_{CF}$ 236.4, $^2J_{CF}$ 14.1, C-2,6), 137.2 (m, C-4), 131.2 (dd, $^1J_{CF}$ 246.3, $^2J_{CF}$ 35.8, C-3,5); *m/z* (EI^+) 166 ($[M]^+$, 100). Data consistent with literature values.[1]

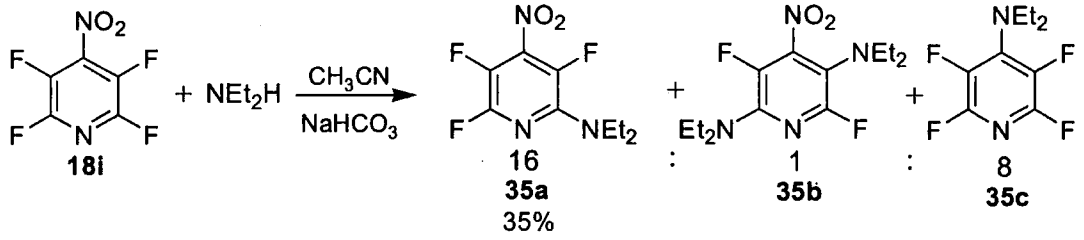
Preparation of 4-Nitro-2,3,5,6-tetrafluoropyridine 18i



50% Hydrogen peroxide (1.2 ml) was added very slowly to a solution of trifluoroacetic anhydride (8.96 g, 42.67 mmol) in dichloromethane (15 ml) and stirred at room temperature for 15 min. A solution of 4-amino-2,3,5,6-tetrafluoropyridine **34** (1.14 g, 6.87 mmol) in dichloromethane (5 ml) was added dropwise and the reaction mixture stirred for a further

30 min. A further addition of 50% hydrogen peroxide (0.6 ml) and trifluoroacetic anhydride (1.78 g, 8.50 mmol) was made and again after 3 h. The resulting solution was refluxed for 1 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml) and separated. The organic layer was washed with water (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as an orange/yellow oil (3.2 g). Purification by distillation over P_2O_5 (b. p. 152-154°C) gave *4-nitro-2,3,5,6-tetrafluoropyridine* **18i** (0.67 g, 50%) as a pale yellow liquid; bp 152-154°C; δ_F -83.09 (2F, t, $^3J_{FF}$ 15.8, F-2,6), -146.46 (2F, quintet, $^3J_{FF}$ 15.8, F-3,5); *m/z* (EI^+) 196 ($[M]^+$, 82), 150 ($[M-NO_2]^+$, 38). Data consistent with literature values.[2]

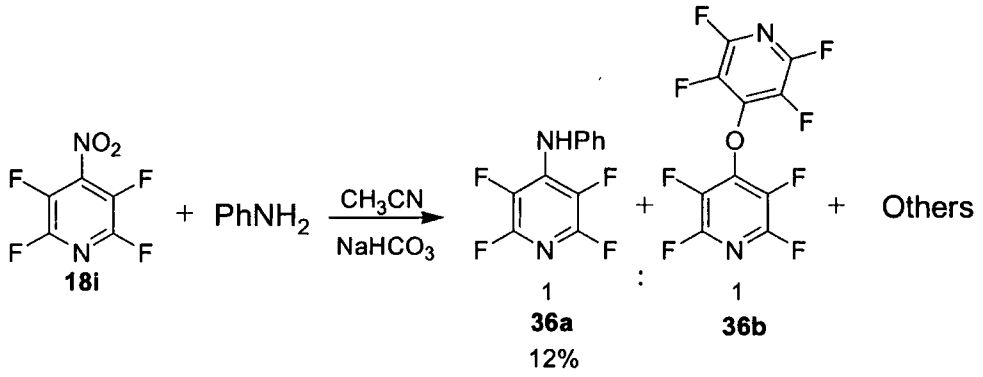
Preparation of N,N-Diethyl-3,5,6-trifluoro-4-nitropyridin-2-amine 35a



Diethylamine (0.19 g, 2.55 mmol) and sodium hydrogencarbonate (0.21 g, 2.55 mmol) were added to acetonitrile (175 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.5 g, 2.55 mmol) was added and the resulting solution stirred at room temperature for 16 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.55 g) consisting of three major components in the ratio 16:1:8 which were identified as *N,N-diethyl-3,5,6-*

trifluoro-4-nitropyridin-2-amine **35a**; *N,N,N',N'-tetraethyl-3,6-difluoro-4-nitropyridine-2,5-diamine* **35b**; δ_F -71.06 (1F, d, $^5J_{FF}$ 29.3, F-6), -151.91 (1F, d, $^5J_{FF}$ 29.3, F-3); *m/z* (EI)$^+$ 302 ([M]$^+$, 80), 287 ([M-CH_3]$^+$, 82); and *diethyl-(2,3,5,6-tetrafluoro-pyridin-4-yl)-amine* **35c**; δ_F -94.90 (2F, m, F-2,6), -156.64 (2F, m, F-3,5); *m/z* (EI)$^+$ 222 ([M]$^+$, 26), 207 ([M-CH_3]$^+$, 86), 179 ([M-$(CH_2)_2CH_3$]$^+$, 99); data consistent with literature values.[3] Purification by column chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) gave *N,N-diethyl-3,5,6-trifluoro-4-nitropyridin-2-amine* **35a** (0.22 g, 35%) as an orange oil; ([M]$^+$ 249.0718, $C_9H_{10}N_3F_3O_2$ requires [M]$^+$ 249.0720); δ_F -85.35 (1F, m, F-6), -147.54 (1F, dd, $^3J_{FF}$ 31.6, $^4J_{FF}$ 13.5, F-5), -166.50 (1F, dd, $^4J_{FF}$ 24.8, $^5J_{FF}$ 11.3, F-3); δ_H 3.50 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 2.0, CH_2), 1.21 (6H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 143.2 (ddd, $^1J_{CF}$ 233.6, $^2J_{CF}$ 12.9, $^4J_{CF}$ 1.9, C-6), 140.6 (m, C-2), 137.2 (m, C-4), 133.3 (dm, $^1J_{CF}$ 265.1, C-3), 124.7 (ddd, $^1J_{CF}$ 260.4, $^2J_{CF}$ 36.3, $^3J_{CF}$ 2.9, C-5), 43.4 (d, $^4J_{CF}$ 6.3, CH_2), 12.5 (s, CH_3); *m/z* (EI)$^+$ 249 ([M]$^+$, 66), 234 ([M-CH_3]$^+$, 100), 220 ([M-CH_2CH_3]$^+$, 8), 203 ([M-CH_3NO_2]$^+$, 77), 160 ([M-$NO_2CH_3CH_2N$]$^+$, 75).

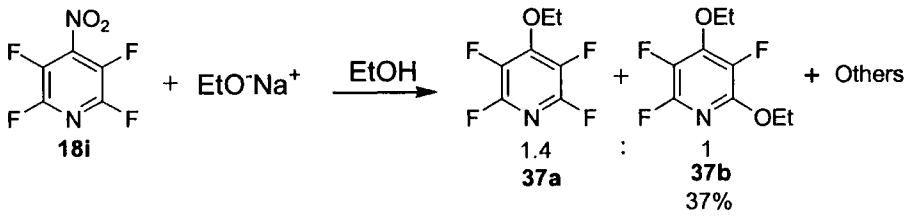
Preparation of 2,3,5,6-Tetrafluoro-N-phenylpyridin-4-amine 36a



Aniline (0.20 g, 2.14 mmol) and sodium hydrogencarbonate (0.36 g, 4.28 mmol) were added to acetonitrile (100 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.42 g, 2.14 mmol) was then added and the resulting solution stirred at room temperature for 1 d

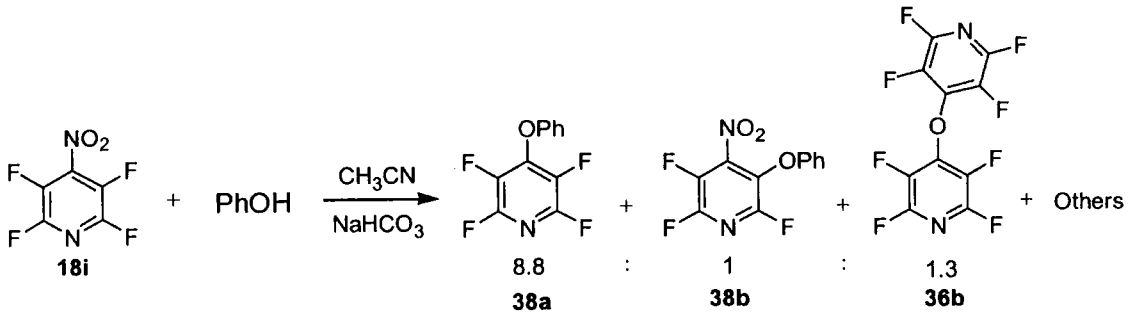
before refluxing at 90°C for 2 d. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.0 g) consisting of two major components in the ratio 1:1 which were identified as *2,3,5,6-tetrafluoro-N-phenylpyridin-4-amine* **36a** and *4,4'-oxybis(tetrafluoropyridine)* **36b**; δ_F -86.53 (4F, m, F-2,6), -156.22 (4F, m, F-3,5); δ_C 142.8 (dtm, $^1J_{CF}$ 245.2, $^2J_{CF}$ 14.5, C-2,6), 133.9 (ddm, $^1J_{CF}$ 263.5, $^2J_{CF}$ 28.2, C-3,5), 129.1 (d, $^2J_{CF}$ 7.2, C-4); *m/z* $(EI)^+$ 316 ($[M]^+$, 100), 150 ($[M-C_5F_4NO]^+$, 76). Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *2,3,5,6-tetrafluoro-N-phenylpyridin-4-amine* **36a** (0.06 g, 12%) as a red solid; mp 86.6-89.5°C; ($[M+NH_4]^+$ 260.0807, $C_{11}H_6N_2F_4$ requires $[M+NH_4]^+$ 260.0805); δ_F -92.87 (2F, t, $^3J_{FF}$ 15.8, F-2,6), -156.03 (2F, t, $^3J_{FF}$ 15.8, F-3,5); δ_H 7.29 (2H, t, $^3J_{HH}$ 7.6, Ar H), 7.14 (1H, t, $^3J_{HH}$ 7.6, Ar H), 7.03 (2H, d, $^3J_{HH}$ 6.8, Ar H), 6.28 (1H, br s, NH); δ_C 144.5 (dm, $^1J_{CF}$ 234.0, C-2,6), 138.4 (s, Ar C), 134.4 (m, C-4), 132.7 (s, $^1J_{CF}$ 251.6, C-3,5), 129.4 (s, Ar CH), 125.8 (s, Ar CH), 122.2 (s, Ar CH); *m/z* $(EI)^+$ 242 ($[M]^+$, 100), 222 ($[M-HF]^+$, 86), 150 ($[M-NHC_6H_5]^+$, 6). Data consistent with literature values.[4]

Preparation of 2,4-Diethoxy-3,5,6-trifluoropyridine 37b



Sodium metal (0.05 g, 2.14 mmol) was added to anhydrous ethanol (30 ml) under argon followed by the addition of 4-nitro-2,3,5,6-tetrafluoropyridine **18i** (0.42 g, 2.14 mmol). The resulting solution was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as an orange oil (0.34 g) consisting of two major components in the ratio 1.4:1 which were identified as *4-ethoxy-2,3,5,6-tetrafluoropyridine* **37a**; δ_F -91.47 (2F, m, F-2,6), -159.87 (2F, m, F-3,5); *m/z* $(EI)^+$ 195 ($[M]^+$, 66), 167 ($[M\text{-}CH_3CH]^+$, 100), 29 ($[M\text{-}C_5F_4O]^+$, 66); and *2,4-diethoxy-3,5,6-trifluoropyridine* **37b**. Purification by column chromatography on silica gel (7:1 *n*-hexane/ethyl acetate) gave *2,4-diethoxy-3,5,6-trifluoropyridine* **37b** (0.20 g, 37%) as a yellow oil; ($[M+H]^+$ 222.0738, $C_9H_{10}NO_2F_3$ requires $[M+H]^+$ 222.0736); δ_F -94.62 (1F, t, $^3J_{FF}$ 24.8, F-6), -160.55 (1F, d, $^3J_{FF}$ 24.8, F-5), -167.86 (1F, d, $^4J_{FF}$ 22.6, F-3); δ_H 4.34 (2H, q, $^3J_{HH}$ 7.0, CH_2), 4.20 (2H, q, $^3J_{HH}$ 7.0, CH_2), 1.30 (3H, t, $^3J_{HH}$ 7.0, CH_3), 1.25 (3H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 146.1 (m, C-2), 145.5 (m, C-4), 144.7 (ddd, $^1J_{CF}$ 231.8, $^2J_{CF}$ 13.9, $^4J_{CF}$ 3.4, C-6), 136.3 (dd, $^1J_{CF}$ 252.8, $^3J_{CF}$ 6.6, C-3), 132.1 (dd, $^1J_{CF}$ 249.9, $^2J_{CF}$ 30.5, C-5), 70.1 (m, CH_2), 63.2 (s, CH_2), 15.4 (s, CH_3), 14.4 (s, CH_3); *m/z* $(EI)^+$ 221 ($[M]^+$, 84), 206 ($[M\text{-}CH_3]^+$, 59), 193 ($[M\text{-}CH_3CH]^+$, 74), 178 ($[M\text{-}(CH_3)_2CH]^+$, 44), 165 ($[M\text{-}(CH_3)_2(CH)_2]^+$, 100).

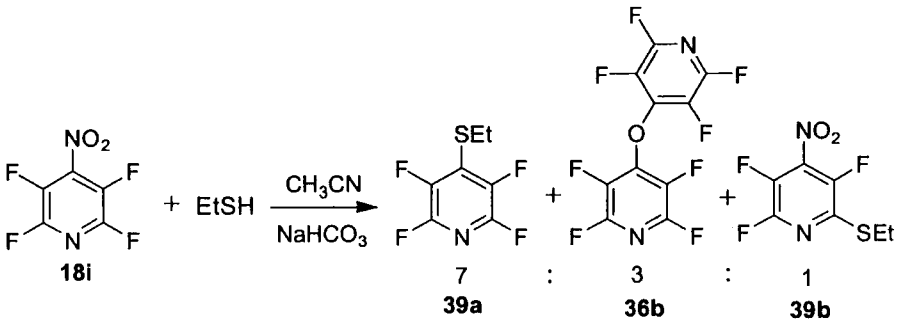
Preparation of 2,3,5,6-Tetrafluoro-4-phenoxypyridine 38a



Phenol (0.20 g, 2.14 mmol) and sodium hydrogencarbonate (0.18 g, 2.14 mmol) were added to acetonitrile (75 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.42 g, 2.14 mmol) was added and the resulting solution stirred at room temperature for 1 d before refluxing for 2 d. ^{19}F NMR indicated 61% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.80 g) consisting of three major components in the ratio 8.8:1:1.3 which were identified as *2,3,5,6-tetrafluoro-4-phenoxypyridine* **38a**; δ_F -89.16 (2F, m, F-2,6), -154.79 (2F, m, F-3,5); δ_H 7.32 (2H, t, $^3J_{HH}$ 7.8, Ar H), 7.15 (1H, m, Ar H), 6.99 (2H, d, $^3J_{HH}$ 8.1, Ar H); δ_C 154.8 (s, Ar C), 143.4 (m, C-4), 143.2 (dt, $^1J_{CF}$ 241.7, $^2J_{CF}$ 13.2, C-2,6), 135.2 (ddm, $^1J_{CF}$ 260.8, $^2J_{CF}$ 22.8, C-3,5), 129.0 (s, Ar CH), 124.1 (s, Ar CH), 115.6 (s, Ar CH); *m/z* (EI^+) 243 ($[M]^+$, 98), 77 ($[M\text{-}C_5F_4NO]^+$, 100). Data consistent with literature values;[5] *2,3,6-trifluoro-4-nitro-5-phenoxypyridine* **38b**; δ_F -75.17 (1F, dd, $^3J_{FF}$ 30.1, $^4J_{FF}$ 12.8, F-2), -84.39 (1F, dd, $^4J_{FF}$ 21.1, $^5J_{FF}$ 12.8, F-6), 149.00 (1F, dd, $^3J_{FF}$ 30.1, $^5J_{FF}$ 20.9, F-3); *m/z* (EI^+) 270 ($[M]^+$, 79), 93 ($[M\text{-}C_5N_2F_3O_2]^+$, 98), 77 ($[M\text{-}C_5N_2F_3O_3]^+$, 100); and *4,4'-oxybis(tetrafluoropyridine)* **36b**; δ_F -86.49 (4F, m, F-2,6), -156.19 (4F, m, F-3,5); *m/z* (EI^+) 316 ($[M]^+$, 90), 150 ($[M\text{-}C_5F_4NO]^+$, 36), 93 ($[M\text{-}C_5F_4N]^+$, 34). Partial purification by column chromatography on

silica gel (12:1 *n*-hexane/ethyl acetate) gave a mixture of *2,3,5,6-tetrafluoro-4-phenoxypyridine* **38a** and *4,4'-oxybis(tetrafluoropyridine)* **36b** in the ratio 6.4:1 respectively (0.28 g, 52%) as an orange oil.

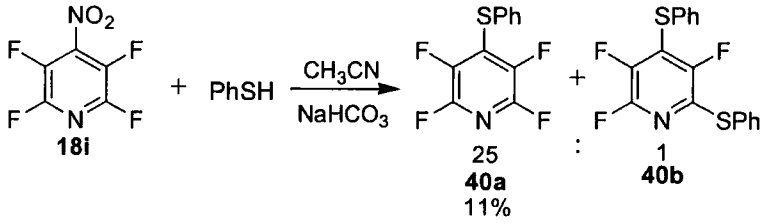
Preparation of 4-(Ethylsulfanyl)-2,3,5,6-tetrafluoropyridine 39a



Ethanethiol (0.13 g, 2.14 mmol) and sodium hydrogencarbonate (0.36 g, 4.28 mmol) were added to acetonitrile (75 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.42 g, 2.14 mmol) was added and the resulting solution was stirred at room temperature for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as an orange oil (0.59 g) consisting of three major components in the ratio 7:3:1 which were identified as *4-(ethylsulfanyl)-2,3,5,6-tetrafluoropyridine* **39a**; δ_F -92.14 (2F, m, F-2,6), -139.35 (2F, m, F-3,5); δ_H 3.22 (2H, q, $^3J_{HH}$ 6.5, CH_2), 1.36 (3H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 143.7 (dm, $^1J_{CF}$ 244.1, C-2,6), 141.1 (ddm, $^1J_{CF}$ 254.1, $^2J_{CF}$ 23.4, C-3,5), 131.7 (tt, $^2J_{CF}$ 17.3, $^3J_{CF}$ 3.0, C-4), 27.8 (t, $^4J_{CF}$ 5.3, CH_2), 15.3 (s, CH_3); *m/z* $(EI)^+$ 211 ($[M]^+$, 98), 196 ($[M\text{-}CH_3]^+$, 40), 183 ($[M\text{-}CH_3CH]^+$, 100); *4,4'-oxybis(tetrafluoropyridine)* **36b**; and *2-(ethylsulfanyl)-3,5,6-trifluoro-4-nitropyridine* **39b**; *m/z* $(EI)^+$ 238 ($[M]^+$, 28), 210 ($[M\text{-}CH_3CH]^+$, 24). Partial purification by

column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave a mixture of *4-(ethylsulfanyl)-2,3,5,6-tetrafluoropyridine* **39a** and *4,4'-oxybis(tetrafluoropyridine)* **36b** (0.18 g, 35%) as a yellow oil, plus a trace amount of pure *4,4'-oxybis(tetrafluoropyridine)* **36b** as a yellow oil; δ_F -86.49 (4F, s, F-2,6), -156.20 (4F, s, F-3,5); δ_C 144.0 (ddm, $^1J_{CF}$ 248.1, $^2J_{CF}$ 14.4, C-2,6), 135.2 (ddm, $^1J_{CF}$ 264.6, $^2J_{CF}$ 38, C-3,5); *m/z* (EI)$^+$ 316 ([M]$^+$, 58), 150 ([M-C_5F_4NO]$^+$, 24).

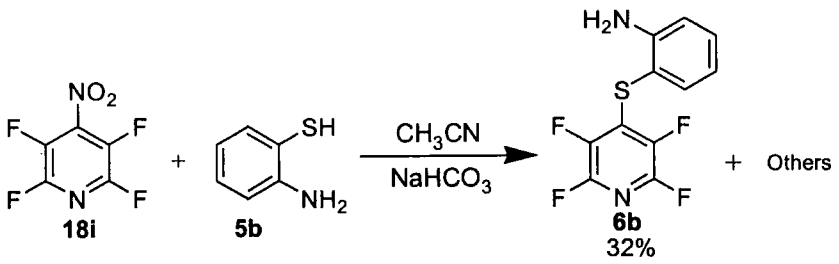
Preparation of 2,3,5,6-Tetrafluoro-4-(phenylsulfanyl)pyridine 40a



Benzenethiol (0.24 g, 2.14 mmol) and sodium hydrogencarbonate (0.36 g, 4.28 mmol) were added to acetonitrile (100 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.42 g, 2.14 mmol) was added and the resulting solution was stirred at room temperature for 1 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as an orange oil (0.59 g) consisting of two major components in the ratio 25:1 which were identified as *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **40a**; and *2,3,5,-trifluoro-4,6-bis(phenylsulfanyl)pyridine* **40b**; δ_F -65.55 (1F, dd, $^3J_{FF}$ 26.5, $^5J_{FF}$ 10.9, F-2), -86.77 (1F, t, $^5J_{FF}$ 10.9, F-5), -137.35 (1F, d, $^3J_{FF}$ 26.5, F-3); *m/z* (EI)$^+$ 349 ([M]$^+$, 100), 240 ([M-SC_6H_5]$^+$, 56), 220 ([M-SC_6H_5HF]$^+$, 42), 77 ([M-$C_{11}H_5NF_3S_2$]$^+$, 76). Purification by column chromatography on silica gel (*n*-hexane)

gave *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **40a** (0.06 g, 11%) as a colourless oil; ($[M+H]^+$ 260.0153, $C_{11}H_5NF_4S$ requires $[M+H]^+$ 260.0152); δ_F -91.01 (2F, m, F-2,6), -136.92 (2F, m, F-3,5); δ_H 7.25-7.45 (5H, m, Ar H); δ_C 142.5 (dm, $^1J_{CF}$ 244.0, C-2,6), 140.0 (dm, $^1J_{CF}$ 257.3, C-3,5), 131.9 (s, Ar CH), 130.0 (tt, $^2J_{CF}$ 16.4, $^3J_{CF}$ 3.0, C-4), 128.6 (s, Ar CH), 128.5 (s, Ar CH), 128.1 (s, Ar C); *m/z* $(EI)^+$ 259 ($[M]^+$, 100), 239 ($[M-HF]^+$, 96), 77 ($[M-C_5NF_4S]^+$, 94). Data consistent with literature values.[6]

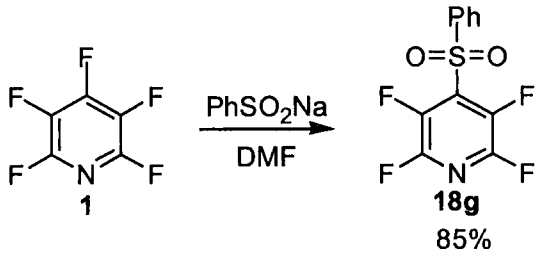
Preparation of 2-[(2,3,5,6-Tetrafluoropyridin-4-yl)amino]benzenethiol 6b



2-Aminothiophenol **5b** (0.83 g, 6.63 mmol) and sodium hydrogencarbonate (1.11 g, 13.27 mmol) were added to acetonitrile (150 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine **18i** (0.65 g, 3.32 mmol) was added and the resulting solution refluxed for 5 d, after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The reaction mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.15 g) which consisted of one major component. Purification by column chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) followed by recrystallisation from *n*-hexane gave *2-[(2,3,5,6-tetrafluoropyridin-4-yl)amino]benzenethiol* **6b** (0.29 g, 32%) as a yellow solid; mp 68.2-69.5°C; (Found: C, 48.2; H, 2.2; N, 10.3; $C_{11}H_6N_2F_4S$ requires: C, 48.2; H, 2.2; N, 10.2%);

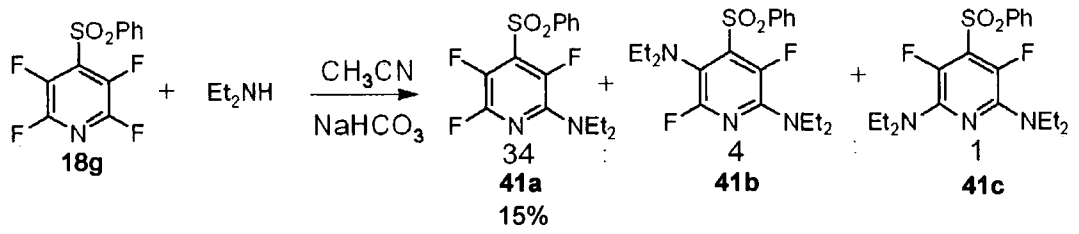
δ_F -91.25 (2F, m, F-2,6), -138.68 (2F, m, F-3,5); δ_H 7.53 (1H, d, $^3J_{HH}$ 7.5, Ar H), 7.25 (1H, td, $^3J_{HH}$ 7.0, $^4J_{HH}$ 1.5, Ar H), 6.76 (1H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.0, Ar H), 6.75 (1H, td, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.0, Ar H), 4.36 (2H, br s, NH_2); δ_C 149.4 (s, ArCS), 143.6 (dtm, $^1J_{CF}$ 248.1, $^2J_{CF}$ 14.5, C-2,6), 141.4 (ddm, $^1J_{CF}$ 258.7, $^2J_{CF}$ 21.0, C-3,5), 137.5 (s, Ar CH), 132.6 (s, Ar CH), 130.7 (m, C-4), 119.3 (s, Ar CH), 115.9 (s, Ar CH), 110.3 (Ar CNH_2); *m/z* (EI^+) 274 ($[M]^+$, 100), 254 ($[M\text{-}HF]^+$, 86), 165 ($[M\text{-}C_6H_5SH]^+$, 10), 150 ($[M\text{-}NHPhSH]^+$, 12).

Preparation of 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine 18g



Pentafluoropyridine 1 (5.34 g, 31.6 mmol) was added to a solution of phenylsulfinic acid sodium salt (4.99 g, 30.4 mmol) in dimethylformamide (25 ml) under argon. The reaction mixture was refluxed for 1 d, after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (250 ml) and the precipitated solid was filtered off and recrystallised from ethanol to give *2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine* **18g** (7.8 g, 85%) as beige crystals; mp 148.0-149.0°C;[6] (Found: C, 45.6; H, 1.8; N, 4.9; $C_{11}H_5NF_4O_2S$ requires: C, 45.4; H, 1.7; N, 4.8%); δ_F -86.19 (2F, m, F-2,6), -137.48 (2F, m, F-3,5); δ_H 8.12 (2H, d, $^3J_{HH}$ 7.2, Ar_{ortho} H), 7.78 (1H, tt, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.2, Ar_{para} H), 7.65 (2H, m, Ar_{meta} H); δ_C 144.3 (dm, $^1J_{CF}$ 198.4, C-2,6), 139.4 (s, Ar C), 138.9 (dm, $^1J_{CF}$ 188.5, C-3,5), 136.0 (s, Ar_{ortho} CH), 133.3 (t, $^2J_{CF}$ 10.7, C-4), 130.2 (s, Ar_{meta} CH), 128.7 (s, Ar_{para} CH); *m/z* (EI^+) 291 ($[M]^+$, 80), 141 ($[M\text{-}C_5F_4N]^+$, 88), 77 ($[M\text{-}C_5F_4NSO_2]^+$, 100).

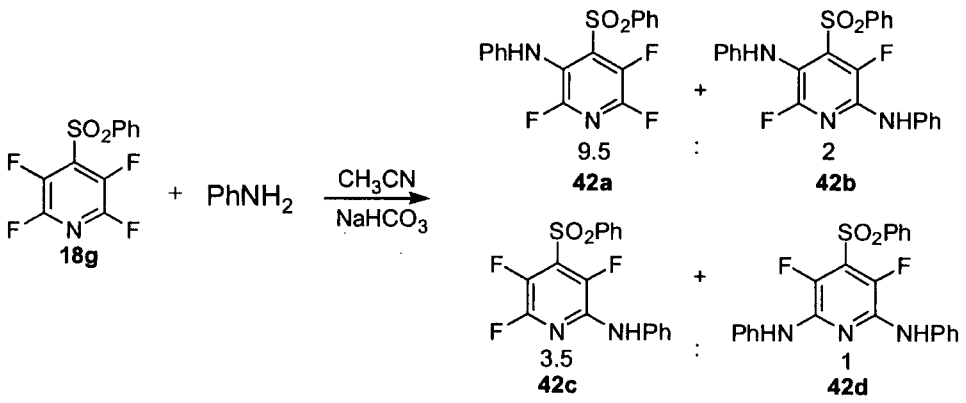
Preparation of *N,N'*-Diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine 41a



Diethylamine (0.29 g, 4.0 mmol) and sodium hydrogencarbonate (0.34 g, 4.0 mmol) were added to acetonitrile (150 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (1.16 g, 4.0 mmol) was then added and the resulting solution was refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, stirred with benzenesulfonic acid scavenger resin (200 mg) for 6 h, dried over magnesium sulfate, filtered and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.58 g) consisting of three major components in the ratio 34:4:1 which were identified as *N,N'-diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine* **41a**; *3,6-difluoro-N,N,N',N'-tetraethyl-4-(phenylsulfonyl)-pyridine-2,5-diamine* **41b**; δ_F -73.33 (1F, d, $^5J_{FF}$ 33.8, F-6), -134.99 (1F, d, $^5J_{FF}$ 31.3, F-3); δ_H 7.95 (2H, d, $^3J_{HH}$ 7.5, Ar_{ortho} H), 7.59 (1H, tm, $^3J_{HH}$ 7.5, Ar_{para} H), 7.50 (2H, t, $^3J_{HH}$ 8.0, Ar_{meta} H), 3.46 (4H, q, $^3J_{HH}$ 6.5, CH_2), 2.81 (4H, m, CH_2), 1.19 (6H, t, $^3J_{HH}$ 7.0, CH_3), 0.59 (6H, t, $^3J_{HH}$ 7.5, CH_3); δ_C 156.3 (d, $^1J_{CF}$ 241.3, C-6), 145.3 (dd, $^2J_{CF}$ 16.8, $^3J_{CF}$ 12.4, C-2), 141.8 (dd, $^1J_{CF}$ 264.8, $^4J_{CF}$ 5.3, C-3), 139.0 (t, $^2J_{CF}$ 7.3, C-4), 116.4 (d, $^2J_{CF}$ 33.3, C-5), 47.8 (d, $^4J_{CF}$ 3.4, CH_2), 44.7 (d, $^4J_{CF}$ 6.3, CH_2), 13.9 (s, CH_3), 12.0 (s, CH_3); *m/z* (EI$^+$) 397 ($[M]^+$, 70), 382 ($[M\text{-}CH_3]^+$, 100), 368 ($[M\text{-}CH_3CH_2]^+$, 33), 77 ($[M\text{-}C_9H_{20}N_3F_2SO_2]^+$, 30); and *3,5-difluoro-N,N,N',N'-tetraethyl-4-(phenylsulfonyl)-pyridine-2,6-diamine* **41c**; δ_F -152.61 (2F, s, F-3,5); *m/z* (EI$^+$) 397 ($[M]^+$, 28), 382 ($[M\text{-}CH_3]^+$, 40), 368 ($[M\text{-}CH_3CH_2]^+$, 64), 77 ($[M\text{-}C_9H_{20}N_3F_2SO_2]^+$, 54). Purification by column

chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) gave *N,N'-diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine* **41a** (0.2 g, 15%) as a yellow oil; ($[M+H]^+$ 345.0879, $C_{15}H_{15}N_2SO_2F_3$ requires $[M+H]^+$ 345.0885); δ_F -88.55 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 27.1, F-6), -134.06 (1F, dd, $^3J_{FF}$ 33.8, $^4J_{FF}$ 11.3, F-5), -156.72 (1F, dd, $^4J_{FF}$ 27.1, $^5J_{FF}$ 11.3, F-3); δ_H 8.06 (2H, d, $^3J_{HH}$ 7.2, Ar_{ortho} H), 7.69 (1H, tm, $^3J_{HH}$ 7.0, Ar_{para} H), 7.57 (2H, tm, $^3J_{HH}$ 7.0, Ar_{meta} H), 3.41 (4H, q, $^3J_{HH}$ 7.0, CH_2), 1.14 (6H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 145.4 (ddd, $^1J_{CF}$ 234.1, $^2J_{CF}$ 16.3, $^4J_{CF}$ 2.4, C-6), 142.8 (m, C-2), 140.78 (s, Ar C), 139.3 (dm, $^1J_{CF}$ 265.3, C-3), 134.9 (s, Ar_{ortho} CH), 129.5 (dd, $^1J_{CF}$ 259.38, $^2J_{CF}$ 33.9, C-5), 130.0 (m, C-4), 129.7 (s, Ar_{para} CH), 128.4 (s, Ar_{meta} CH), 44.8 (d, $^5J_{HF}$ 5.8, CH_2), 13.7 (s, CH_3); *m/z* (EI^+) 344 ($[M]^+$, 53), 329 ($[M-CH_3]^+$, 100), 301 ($[M-CH_3CH_2N]^+$, 76).

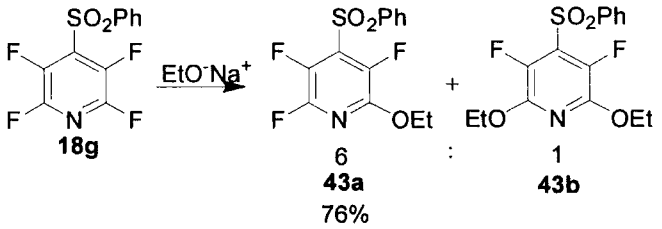
Preparation of 2,5,6-Trifluoro-*N*-phenyl-4-(phenylsulfonyl)pyridine-3-amine 42a



Aniline (1.6 g, 17.2 mmol) and sodium hydrogencarbonate (2.89 g, 34.4 mmol) were added to acetonitrile (100 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (1.0 g, 3.44 mmol) was then added and the resulting solution was refluxed for 13 d. Over the course of the reaction 7 extra equivalents of aniline (2.24 g, 24.08 mmol) were added. After this time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (20

ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (3.0 g) consisting of four major components in the ratio 9.5:2:3.5:1 which were identified as *2,5,6-trifluoro-N-phenyl-4-(phenylsulfonyl)pyridine-3-amine* **42a**; δ_F -66.56 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 13.2, F-5), -96.74 (1F, dd, $^4J_{FF}$ 23.7, $^5J_{FF}$ 13.2, F-2), -139.00 (1F, dd, $^3J_{FF}$ 31.6, $^4J_{FF}$ 23.7, F-6); δ_H 8.09 (1H, br s, NH), 7.97 (2H, dt, $^3J_{HH}$ 8.4, $^4J_{HH}$ 1.2, SO_2Ar_{ortho} H), 7.69 (1H, tt, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.2, SO_2Ar_{para} H), 7.54 (2H, tm, $^3J_{HH}$ 8.0, SO_2Ar_{meta} H), 7.30 (2H, tm, $^3J_{HH}$ 7.6, $NHAr_{ortho}$ H), 7.11 (1H, tm, $^3J_{HH}$ 7.2, $NHAr_{para}$ H), 6.86 (2H, dm, $^3J_{HH}$ 7.6, $NHAr_{meta}$ H); δ_C 146.8 (ddd, $^1J_{CF}$ 252.7, $^3J_{CF}$ 9.7, $^4J_{CF}$ 2.2, C-2), 142.0 (dd, $^1J_{CF}$ 223.4, $^2J_{CF}$ 12.2, C-6), 141.1 (d, $^4J_{CF}$ 2.3, NHAr C), 139.8 (s, SO_2Ar C), 139.8 (ddd, $^1J_{CF}$ 264.2, $^2J_{CF}$ 28.2, $^4J_{CF}$ 6.8, C-5), 130.6 (dd, $^2J_{CF}$ 11.9, $^3J_{CF}$ 3.3, C-4), 135.5 (s, SO_2Ar_{ortho} CH), 129.9 (s, SO_2Ar_{para} CH), 129.5 (s, $NHAr_{ortho}$ CH), 128.1 (s, SO_2Ar_{meta} CH), 124.8 (dm, $^2J_{CF}$ 26.7, C-3), 124.0 (s, $NHAr_{para}$ CH), 119.4 (s, $NHAr_{meta}$ CH); *m/z* (EI)$^+$ 364 ([M]$^+$, 96), 77 ([M-$C_{11}H_5N_2F_3SO_2$]$^+$, 100); *3,6-difluoro-N,N-diphenyl-4-(phenylsulfonyl)pyridine-2,5-diamine* **42b**; δ_F -70.29 (1F, d, $^5J_{FF}$ 31.6, F-6), -138.20 (1F, d, $^5J_{FF}$ 31.6, F-3); *m/z* (EI)$^+$ 437 ([M]$^+$, 100), 77 ([M-$C_{17}H_{12}N_3F_2SO_2$]$^+$, 66); *3,5,6-trifluoro-N-phenyl-4-(phenylsulfonyl)pyridine-2-amine* **42c**; δ_F -88.62 (1F, dm, $^3J_{FF}$ 31.6, F-6), -138.47 (1F, dm, $^3J_{FF}$ 31.6, F-5), -153.34 (1F, dm, $^4J_{FF}$ 27.1, F-3); *m/z* (EI)$^+$ 364 ([M]$^+$, 84), 77 ([M-$C_{11}H_5N_2F_3SO_2$]$^+$, 100); and *3,5-difluoro-N,N-diphenyl-4-(phenylsulfonyl)pyridine-2,6-diamine* **42d**; δ_F -74.15 (2F, s, F-3,5); *m/z* (EI)$^+$ 437 ([M]$^+$, 100), 417 ([M-HF]$^+$, 12), 77 ([M-$C_{17}H_{12}N_3F_2SO_2$]$^+$, 76). Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) was unsuccessful for the separation of the components.

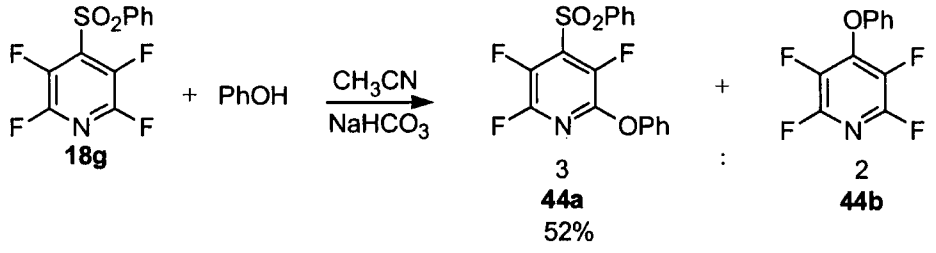
Preparation of 2-Ethoxy-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine 43a



Sodium metal (0.04 g, 1.72 mmol) was added to anhydrous ethanol (30 ml) under argon followed by the addition of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (0.5 g, 1.72 mmol). The resulting solution was refluxed for 6 h after which time ^{19}F NMR indicated 79% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow solid (0.48 g) consisting of two major components in the ratio 6:1 which were identified as *2-ethoxy-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine* **43a**; and *2,6-ethoxy-3,5-difluoro-4-(phenylsulfonyl)pyridine* **43b**; δ_F -137.43 (2F, m, F-3,5); *m/z* $(EI)^+$ 343 $([M]^+$, 14), 315 $([M\text{-}CH_3CH]^+$, 42), 287 $([M\text{-}(CH_3CH)_2]^+$, 100), 77 $([M\text{-}C_9H_{10}NF_2SO_4]^+$, 81). Purification by recrystallisation from *n*-hexane/ethyl acetate gave *2-ethoxy-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine* **43a** (0.41 g, 76%) as white crystals; mp 94.2-95.4°C; (Found: C, 49.4; H, 3.1; N, 4.5; $C_{13}H_{10}NSO_3F_3$ requires: C, 49.2; H, 3.2; N, 4.4%); δ_F -90.31 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 22.6, F-6), -136.67 (1F, dd, $^3J_{FF}$ 33.8, $^4J_{FF}$ 9.02, F-5), -150.03 (1F, dd, $^4J_{FF}$ 22.6, $^5J_{FF}$ 9.0, F-3); δ_H 8.10 (2H, d, $^3J_{HH}$ 7.5, Ar_{ortho} CH), 7.72 (1H, tm, $^3J_{HH}$ 7.5, Ar_{para} CH), 7.60 (2H, tm, $^3J_{HH}$ 7.8, Ar_{meta} CH), 4.39 (2H, q, $^3J_{HH}$ 7.2, CH_2), 1.40 (3H, t, $^3J_{HH}$ 6.9, CH_3); δ_C 147.1 (m, C-2), 144.8 (ddd, $^1J_{CF}$ 241.3, $^2J_{CF}$ 17.1, $^4J_{CF}$ 4.3, C-6), 140.2 (s, Ar C), 140.0 (ddd, $^1J_{CF}$ 269.4, $^3J_{CF}$ 6.8, $^4J_{CF}$ 2.4, C-3), 135.3 (s, Ar_{ortho} CH), 134.1 (ddd, $^1J_{CF}$ 262.8, $^2J_{CF}$ 31.0, $^3J_{CF}$ 2.0, C-5), 130.6 (m, C-4), 129.9 (s, Ar_{para} CH), 128.6

(s, Ar_{meta} CH), 64.7 (s, CH_2), 14.4 (s, CH_3); *m/z* (EI)$^+$ 317 ([M]$^+$, 64), 289 ([M-C_2H_4]$^+$, 76), 141 ([M-$C_7H_5NF_3O$]$^+$, 82), 77 ([M-$C_7H_5NF_3O_3S$]$^+$, 100).

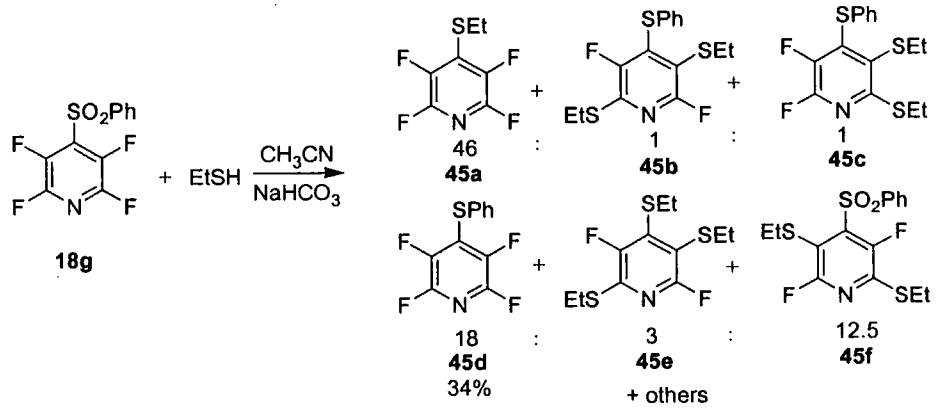
Preparation of 2,3,5-Trifluoro-6-phenoxy-4-(phenylsulfonyl)-pyridine 44a



Phenol (0.32 g, 3.44 mmol) and sodium hydrogencarbonate (0.29 g, 3.44 mmol) were added to acetonitrile (175 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (1.0 g, 3.44 mmol) was added and the resulting solution was refluxed for 3 d after which time ^{19}F NMR indicated 50% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid, extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.08 g) consisting of two major components in the ratio 3:2 which were identified as *2,3,5-trifluoro-6-phenoxy-4-(phenylsulfonyl)-pyridine* **44a**; and *2,3,5,6-tetrafluoro-4-phenoxypyridine* **44b**; δ_F -89.23 (2F, m, F-2,6), -154.81 (2F, m, F-3,5); *m/z* (EI$^+$) 243 ([M]$^+$, 70), 223 ([M-HF]$^+$, 54), 77 ([M-C_5F_4NO]$^+$, 100). Data consistent with literature values.[5] Purification by column chromatography on silica gel (3:1 *n*-hexane/ethyl acetate) gave *2,3,5-trifluoro-6-phenoxy-4-(phenylsulfonyl)-pyridine* **44a** (0.65 g, 52%) as a white solid which was further purified by recrystallisation from dichloromethane/*n*-hexane; mp 124.4–125.6°C; (Found: C, 55.6; H, 2.7; N, 3.8; $C_{17}H_{10}NF_3SO_3$ requires: C, 55.9; H, 2.7; N, 3.8%); δ_F -87.77 (1F, m, F-2), -135.34 (1F, dd, $^3J_{FF}$ 31.6, $^4J_{FF}$ 9.0, F-3), -144.77 (1F, dd, $^4J_{FF}$ 22.6, $^5J_{FF}$ 9.0, F-5); δ_H 8.15

(2H, d, $^3J_{HH}$ 8.0, SO_2Ar_{meta} H), 7.76 (1H, t, $^3J_{HH}$ 7.5, SO_2Ar_{para} H), 7.65 (2H, t, $^3J_{HH}$ 7.5, SO_2Ar_{ortho} H), 7.41 (2H, t, $^3J_{HH}$ 7.5, OAr_{meta} H), 7.26 (1H, t, $^3J_{HH}$ 7.5, OAr_{para} H), 7.10 (2H, d, $^3J_{HH}$ 9.0, OAr_{ortho} H); δ_C 152.4 (s OAr C), 144.8 (dm, $^1J_{CF}$ 244.1, C-2), 140.5 (dm, $^1J_{CF}$ 274.3, C-3), 140.0 (s, SO_2Ar C), 136.0 (dm, $^1J_{CF}$ 274.5, C-5), 135.6 (s, SO_2Ar_{para} CH), 131.7 (m, C-6), 129.0 (m, C-4), 130.1 (s, OAr_{meta} CH), 130.0 (s, SO_2Ar_{meta} CH), 128.7 (s, SO_2Ar_{ortho} CH), 126.3 (OAr_{para} CH), 121.2 (OAr_{ortho} CH); *m/z* (EI^+) 365 ($[M]^+$, 38), 345 ($[M\text{-}HF]^+$, 11), 224 ($[M\text{-}SO_2Ph]^+$, 9), 77 ($[M\text{-}C_5F_3NSO_3Ph]^+$, 100).

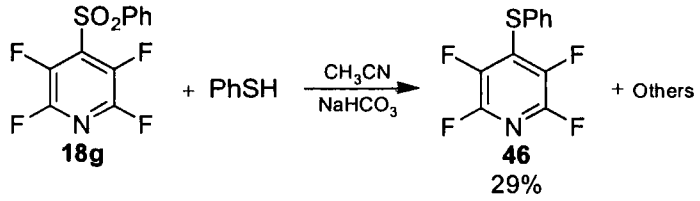
Preparation of 4-(Phenylsulfanyl)-2,3,5,6-tetrafluoropyridine 45d



Ethanethiol (0.21 g, 3.44 mmol) and sodium hydrogencarbonate (0.58 g, 6.88 mmol) were added to acetonitrile (75 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (1.0 g, 3.44 mmol) was then added and the resulting solution was stirred at room temperature for 1 d before refluxing for 22 h. 0.5 extra equivalents of ethanethiol (0.01 g, 1.72 mmol) were then added. Refluxing was continued for a further 18 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.2 g) consisting of six major

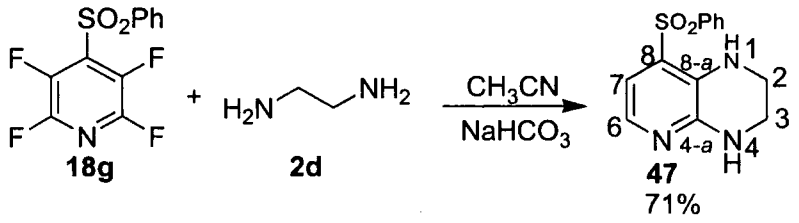
components in the ratio 46:1:1:18:3:12.5 which were identified as *4-(ethylsulfanyl)-2,3,5,6-tetrafluoropyridine* **45a**; δ_F -92.12 (2F, q, $^3J_{FF}$ 15.8, F-2,6), -139.34 (2F, q, $^3J_{FF}$ 15.7, F-3,5); *m/z* (EI)$^+$ 211 ([M]$^+$, 96), 183 ([M-CH_2CH_2]$^+$, 100), 163 ([M-CH_3CH_2F]$^+$, 38); *2,5-bis(ethylsulfanyl)-3,6-difluoro-4-(phenylsulfanyl)pyridine* **45b**; δ_F -66.49 (1F, d, $^5J_{FF}$ 27.1, F-6), -123.57 (1F, d, $^5J_{FF}$ 24.8, F-3); *m/z* (EI)$^+$ 343 ([M]$^+$, 80), 310 ([M-SH]$^+$, 100); *2,3-bis(ethylsulfanyl)-5,6-difluoro-4-(phenylsulfanyl)pyridine* **45c**; δ_F -66.21 (1F, d, $^3J_{FF}$ 27.1, F-6), -117.85 (1F, d, $^3J_{FF}$ 27.1, F-5); *m/z* (EI)$^+$ 343 ([M]$^+$, 72), 310 ([M-SH]$^+$, 100); *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **45d**; *2,4,5-tris(ethylsulfanyl)-3,6-difluoropyridine* **45e**; δ_F -67.45 (1F, d, $^5J_{FF}$ 27.1, F-6), -124.03 (1F, d, $^5J_{FF}$ 27.1, F-3); *m/z* (EI)$^+$ 295 ([M]$^+$, 88), 262 ([M-SH]$^+$, 100), 234 ([M-SCH_2CH_3]$^+$, 66); and *2,5-bis(ethylsulfanyl)-3,6-difluoro-4-(phenylsulfonyl)pyridine* **45f**; δ_F -77.41 (1F, d, $^5J_{FF}$ 29.33, F-6), -114.33 (1F, d, $^5J_{FF}$ 31.6, F-3); *m/z* (EI)$^+$ 375 ([M]$^+$, 14), 282 ([M-C_6H_5O]$^+$, 96), 77 ([M-$C_9H_{20}NF_2S_3O_2$]$^+$, 100). Purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) followed by preperative TLC (*n*-hexane) was unsuccessful for the separation of the components, and a mixture of *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **45d** and an unidentified component in the ratio 50:1 respectively was isolated (0.3 g, 34%) as a colourless oil; δ_F -90.97 (2F, quintet, $^3J_{FF}$ 13.5, F-2,6), -136.94 (2F, sextet, $^3J_{FF}$ 13.5, F-3,5); δ_H 7.33-7.53 (5H, m, Ar H); δ_C 143.8 (dm, $^1J_{CF}$ 244.7, C-2,6), 141.2 (dm, $^1J_{CF}$ 262.9, C-3,5), 133.2 (s, Ar C), 131.2 (m, C-4), 129.9 (s, Ar_{ortho} CH), 129.7 (s, Ar_{para} CH), 129.4 (s, Ar_{meta} CH); *m/z* (EI)$^+$ 259 ([M]$^+$, 100), 239 ([M-HF]$^+$, 92), 109 ([M-C_5F_4N]$^+$, 52), 77 ([M-C_5F_4NS]$^+$, 91). Data consistent with literature values.[6]

Preparation of 2,3,5,6-Tetrafluoro-4-(phenylsulfanyl)pyridine 46



Benzenethiol (0.38 g, 3.44 mmol) and sodium hydrogencarbonate (0.34 g, 4.0 mmol) were added to acetonitrile (150 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (1 g, 3.44 mmol) was then added and the resulting solution was refluxed for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (20 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow/brown solid (1.0 g) consisting of one major component. Purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) gave *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **46** (0.26 g, 29%) as a colourless oil; ($[M-H]^+$ 257.9997, $C_{11}H_5NF_4S$ requires $[M-H]^+$ 257.9995); δ_F -91.05 (2F, m, F-2,6), -136.92 (2F, m, F-3,5); δ_H 7.15-7.45 (5H, m, Ar H); δ_C 143.7 (dtm, $^1J_{CF}$ 245.0, $^2J_{CF}$ 13.3, C-2,6), 141.2 (ddm, $^1J_{CF}$ 223.2, $^2J_{CF}$ 24.1, C-3,5), 133.2 (s, Ar C), 131.2 (tt, $^2J_{CF}$ 16.9, $^3J_{CF}$ 2.8, C-4), 129.9 (s, Ar_{ortho} CH), 129.7 (s, Ar_{para} CH), 129.4 (s, Ar_{meta} CH); *m/z* $(EI)^+$ 259 ($[M]^+$, 83), 77 ($[M-C_5NF_4S]^+$, 100). Data consistent with literature values.[6]

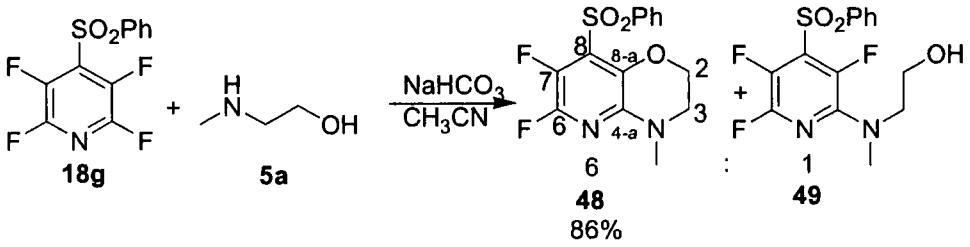
Preparation of 6,7-Difluoro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 47



Ethylenediamine **2d** (1.2 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (2.91 g, 10 mmol) was added and the resulting solution was refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The solution was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to give a brown/yellow solid. The solid was redissolved in dichloromethane and filtered through a silica plug to remove the brown colouration. The solvent was evaporated to dryness to yield the crude product as an orange/yellow solid (2.5 g). Purification by recrystallisation from dichloromethane gave *6,7-diflouro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **47** (2.2 g, 71%) as needle-like yellow crystals; mp 174.9-175.4°C; ($[M+H]^+$ 312.0613, $C_{13}H_{11}N_3F_2SO_2$ requires 312.0613); δ_F -108.67 (1F, d, $^3J_{FF}$ 24.5, F-6), -157.57 (1F, d, $^3J_{FF}$ 24.8, F-7); δ_H 8.00 (2H, dm, $^3J_{HH}$ 5.7, Ar_{ortho} H), 7.66 (1H, tm, $^3J_{HH}$ 7.2, Ar_{para} H), 7.56 (2H, tm, $^3J_{HH}$ 7.8, Ar_{meta} H), 3.49 (4H, s, CH_2); δ_C 141.6 (s, Ar C), 141.1 (dd, $^1J_{CF}$ 224.9, $^2J_{CF}$ 16.8, C-6), 140.7 (dd, $^2J_{CF}$ 14.8, $^3J_{CF}$ 3.8, C-8), 134.5 (s, Ar_{ortho} CH), 132.4 (dd, $^1J_{CF}$ 248.2, $^2J_{CF}$ 29.7, C-7), 129.5 (s, Ar_{meta} CH), 127.8 (d, $^3J_{CF}$ 2.6, C-4*a*), 127.5 (s, Ar_{para} CH), 116.8 (d, $^3J_{CF}$ 13.3, C-8*a*), 39.3

(s, CH_2), 39.2 (s, CH_2); *m/z* (EI^+) 311 ($[M]^+$, 100), 296 ($[M\text{-}NH]^+$, 7), 168 ($[M\text{-}H_2SO_2Ph]^+$, 44).

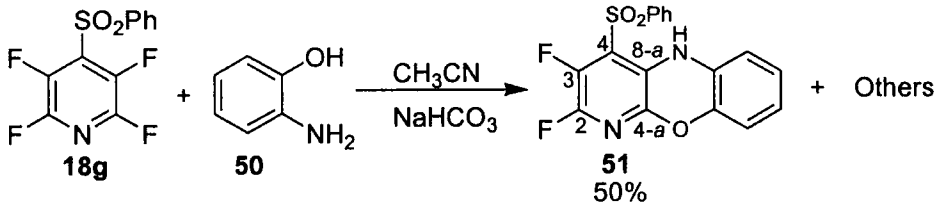
Preparation of 6,7-Difluoro-3,4-dihydro-4-methyl-8-(phenylsulfonyl)-2*H*-pyrido[3,2-*b*][1,4]oxazine 48



2-Methylaminoethanol **5a** (0.50 g, 6.67 mmol) and sodium hydrogencarbonate (1.12 g, 13.3 mmol) were added to acetonitrile (200 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (0.97 g, 3.33 mmol) was then added and the resulting solution was refluxed for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent was evaporated to dryness to yield the crude product as a brown oil (1.1 g) consisting of two major components in the ratio 6:1 which were identified as *6,7-difluoro-3,4-dihydro-4-methyl-8-(phenylsulfonyl)-2H-pyrido[3,2-b][1,4]oxazine* **48**; and *2-(N-(3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-yl)-N-methylamino)ethanol* **49**; δ_F -88.36 (1F, m, F-6), -131.58 (1F, d, $^3J_{FF}$ 33.8, F-5), -154.46 (1F, dd, $^4J_{FF}$ 27.1, $^5J_{FF}$ 11.3, F-3); *m/z* (EI^+) 346 ($[M]^+$, 2), 326 ($[M\text{-}HF]^+$, 25), 315 ($[M\text{-}CH_2OH]^+$, 100). Purification by column chromatography on silica gel (1:3 *n*-hexane/ethyl acetate) followed by several recrystallisations from dichloromethane gave *6,7-difluoro-3,4-*

dihydro-4-methyl-8-(phenylsulfonyl)-2H-pyrido[3,2-b][1,4]oxazine **48** (0.94 g, 86%) as yellow crystals, mp 177.2-178.5°C; (Found: C, 51.4; H, 3.7; N, 8.9; $C_{14}H_{12}N_2F_2O_3S$ requires: C, 51.5; H, 3.7; N, 8.6%); δ_F -96.96 (1F, d, $^3J_{FF}$ 27.1, F-6), -159.44 (1F, d, $^3J_{FF}$ 24.5, F-7); δ_H 8.06 (2H, dm, $^3J_{HH}$ 7.2, Ar_{ortho} H), 7.65 (1H, tt, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.2, Ar_{para} H), 7.54 (2H, tm, $^3J_{HH}$ 6.9, Ar_{meta} H), 4.18 (2H, t, $^3J_{HH}$ 4.5, CH_2), 3.44 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.03 (3H, s, NCH_3); δ_C 144.7 (dd, $^1J_{CF}$ 230.2, $^2J_{CF}$ 16.8, C-6), 141.7 (dd, $^3J_{CF}$ 14.9, $^4J_{CF}$ 2.7, C-4*a*), 141.4 (s, Ar C), 134.4 (s, Ar_{ortho} CH), 134.3 (m, C-8), 131.5 (dd, $^1J_{CF}$ 255.1, $^2J_{CF}$ 32.6, C-7), 129.2 (s, Ar_{meta} CH), 128.3 (s, Ar_{para} CH), 126.4 (d, $^3J_{CF}$ 10.3, C-8*a*), 64.4 (s, NCH_2), 47.0 (s, OCH_2), 36.4 (s, CH_3); *m/z* (EI^+) 326 ($[M]^+$, 100), 311 ($[M-CH_3]^+$, 8), 185 ($[M-SO_2Ph]^+$, 18).

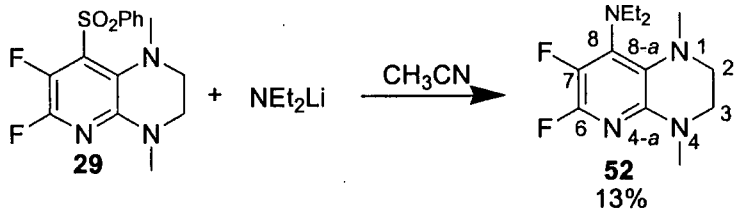
Preparation of 2,3-Difluoro-4-(phenylsulfonyl)-5H-pyrido[2,3-*b*][1,4]benzoxazine 51



2-Aminophenol **50** (0.75 g, 6.87 mmol) and sodium hydrogencarbonate (1.15 g, 13.7 mmol) were added to acetonitrile (200 ml) under argon. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **18g** (1.0 g, 3.44 mmol) was then added and the reaction mixture was refluxed for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a red/brown oil (1.23 g) consisting of one major component. Purification by column

chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *2,3-difluoro-4-(phenylsulfonyl)-5H-pyrido[2,3-b][1,4]benzoxazine* **51** (0.62 g, 50%) as orange crystals; mp ~222°C (decomposes); (Found: C, 56.7; H, 2.8; N, 7.7; $C_{17}H_{10}N_2SO_3F_2$ requires: C, 56.7; H, 2.8; N, 7.8%); δ_F -103.27 (d, $^3J_{FF}$ 22.2, F-2), -146.62 (d, $^3J_{FF}$ 22.9, F-3); δ_H 8.30 (1H, br s, NH), 8.03 (2H, dm, $^3J_{HH}$ 8.8, SO_2Ar_{ortho} H), 7.74 (1H, tt, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.2, SO_2Ar_{para} H), 7.62 (2H, tm, $^3J_{HH}$ 8.0, SO_2Ar_{meta} H), 6.89 (1H, td, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, Ar H), 6.80 (1H, td, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, Ar H), 6.75 (1H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.6, Ar H), 6.59 (1H, dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, Ar H); δ_C 144.2 (d, $^3J_{CF}$ 3.9, C-4*a*), 142.1 (dd, $^1J_{CF}$ 234.8, $^2J_{CF}$ 17.5, C-2), 142.3 (s, Ar C), 140.3 (s, Ar C), 137.3 (dd, $^1J_{CF}$ 258.0, $^2J_{CF}$ 28.5, C-3), 135.3 (s, SO_2Ar C), 128.8 (s, SO_2Ar_{meta} CH), 127.9 (d, $^5J_{CF}$ 2.2, SO_2Ar_{ortho} CH), 127.2 (s, SO_2Ar_{para} CH), 126.8 (d, $^2J_{CF}$ 4.6, C-4), 125.7 (s, Ar CH), 123.9 (s, Ar CH), 119.8 (d, $^3J_{CF}$ 14.5, C-8*a*), 116.6 (s, Ar CH), 114.9 (s, Ar CH); *m/z* (EI^+) 360 ($[M]^+$, 100), 219 ($[M\text{-}SO_2Ph]^+$, 80).

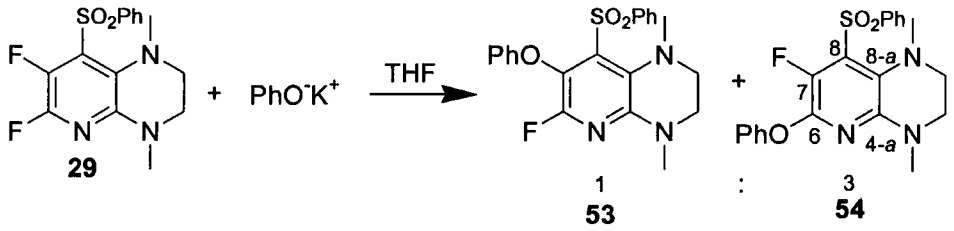
Preparation of *N, N'*-Diethyl-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-8-amine 52



A 2.5 M solution of butyl lithium in tetrahydrofuran (0.47 ml, 1.18 mmol) was added to a solution of diethylamine (0.086 g, 1.18 mmol) in tetrahydrofuran (25 ml) at -78°C. The resulting solution was stirred at -78°C for 1 h before warming to room temperature and addition of phenyl 6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-sulfinate **29** (0.20 g, 0.59 mmol). The reaction mixture was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was

cooled to room temperature, the solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (100 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown/yellow oil (0.87 g) consisting of one major component. Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *N, N'-diethyl-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-8-amine* **52** (0.02 g, 13%) as a yellow oil; ($[M+H]^+$ 271.1728, $C_{13}H_{20}N_4F_2$ requires $[M+H]^+$ 271.1729); δ_F -99.24 (1F, d, $^3J_{FF}$ 27.4, F-6), -168.29 (1F, d, $^3J_{FF}$ 27.3, F-7); δ_H 3.26 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, $N(CH_2CH_3)_2$), 3.17 (2H, t, $^3J_{HH}$ 4.5, CH_2), 2.97 (3H, s, NCH_3), 2.96 (2H, t, $^3J_{HH}$ 4.5, CH_2), 2.56 (3H, s, NCH_3), 0.98 (6H, t, $^3J_{HH}$ 7.5, $N(CH_2CH_3)_2$); δ_C 145.7 (dd, $^1J_{CF}$ 224.6, $^2J_{CF}$ 15.3, C-6), 143.7 (d, $^3J_{CF}$ 16.8, C-4*a*), 139.6 (m, C-8), 132.6 (dd, $^1J_{CF}$ 240.0, $^2J_{CF}$ 29.1, C-7), 120.4 (d, $^3J_{CF}$ 4.8, C-8*a*), 47.5 (s, NCH_2), 43.6 (d, $^4J_{CF}$ 4.8, $N(CH_2CH_3)_2$), 42.1 (s, NCH_2), 40.5 (s, NCH_3), 35.9 (s, NCH_3), 12.3 (s, $N(CH_2CH_3)_2$); *m/z* (EI)$^+$ 270 ($[M]^+$, 100), 255 ($[M-CH_3]^+$, 16), 241 ($[M-CH_2CH_3]^+$, 26), 226 ($[M-(CH_3)_2CH_2]^+$, 52), 211 ($[M-(CH_3)_3CH_2]^+$, 70).

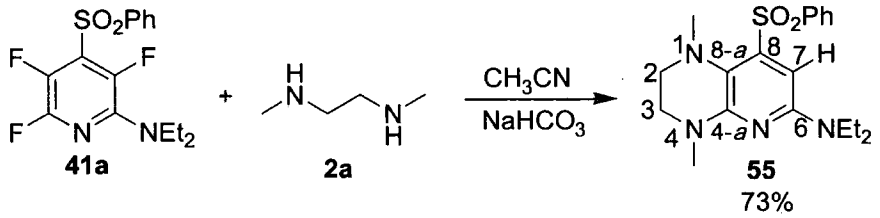
Preparation of 7-Fluoro-1,4-dimethyl-6-phenoxy-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 54



Phenol (0.11 g, 1.2 mmol) and potassium metal (0.02 g, 0.51 mmol) were added to dry tetrahydrofuran (20 ml) under argon and the reaction mixture was stirred until all the potassium had reacted before the addition of phenyl 6,7-difluoro-1,4-dimethyl-1,2,3,4-

tetrahydropyrido[2,3-*b*]pyrazine-8-sulfinate **29** (0.2 g, 0.59 mmol). The resulting solution was refluxed for 4 d after which time ^{19}F indicated 98% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.38 g) consisting of two major components in the ratio 1:3 which were identified as *6-fluoro-1,4-dimethyl-7-phenoxy-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **53**; δ_F -86.79 (1F, s, F-6); *m/z* (EI)$^+$ 413 ([M]$^+$, 100), 398 ([M-CH_3]$^+$, 2), 257 ([M-$C_7H_8SO_2$]$^+$, 59), 77 ([M-$C_{15}H_{15}N_3SO_3F$]$^+$, 62); and *7-fluoro-1,4-dimethyl-6-phenoxy-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **54**; δ_F -151.85 (1F, s, F-7); δ_H 7.90 (2H, d, $^3J_{HH}$ 7.5, SO_2Ar_{ortho} H), 7.51 (1H, t, $^3J_{HH}$ 7.5, SO_2Ar_{para} H), 7.41 (2H, t, $^3J_{HH}$ 8.0, SO_2Ar_{meta} H), 7.23 (2H, t, $^3J_{HH}$ 7.5, OAr H), 7.03 (1H, t, $^3J_{HH}$ 7.5, OAr H), 6.96 (2H, d, $^3J_{HH}$ 8.0, OAr H), 3.22 (2H, t, $^3J_{HH}$ 5.0, CH_2), 2.85 (3H, s, CH_3), 2.77 (3H, s, CH_3), 2.72 (2H, t, $^3J_{HH}$ 5.0, CH_2); δ_C 153.5 (s, OAr C), 145.1 (d, $^4J_{CF}$ 2.0, C-4*a*), 143.3 (d, $^2J_{CF}$ 14.4, C-6), 141.5 (s, SO_2Ar C), 134.4 (d, $^1J_{CF}$ 256.7, C-7), 132.3 (s, SO_2Ar_{ortho} CH), 128.6 (d, $^2J_{CF}$ 9.1, C-8), 128.1 (s, OAr CH), 127.4 (s, SO_2Ar_{meta} CH), 126.6 (s, SO_2Ar_{para} CH), 123.7 (d, $^3J_{CF}$ 2.4, C-8*a*), 122.8 (s, OAr CH), 118.8 (s, OAr CH), 46.4 (s, CH_2), 45.9 (s, CH_3), 42.1 (s, CH_2), 35.5 (s, CH_3); *m/z* (EI)$^+$ 413 ([M]$^+$, 90), 398 ([M-CH_3]$^+$, 4), 272 ([M-SO_2Ph]$^+$, 25), 77 ([M-$C_{15}H_{15}N_3SO_3F$]$^+$, 100). Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) gave a mixture of *6-fluoro-1,4-dimethyl-7-phenoxy-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **53** and *7-fluoro-1,4-dimethyl-6-phenoxy-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **54** in the ratio 0.2:99.8 respectively (40 mg, 16%) as a yellow oil.

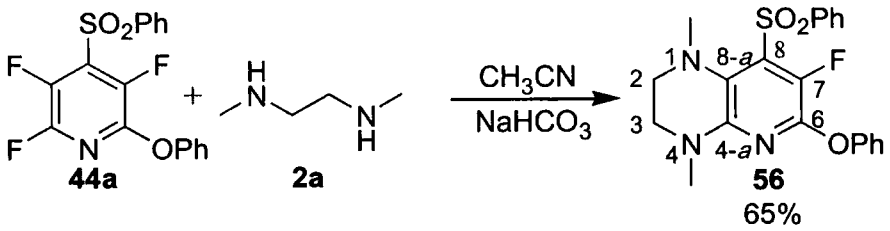
Preparation of *N,N'*-Diethyl-1,4-dimethyl-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-6-amine 55



N,N'-Dimethylethylenediamine **2a** (0.077 g, 0.88 mmol) and sodium hydrogencarbonate (0.13 g, 1.6 mmol) were added to acetonitrile (25 ml) under argon. N,N'-Diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine **41a** (0.14 g, 0.45 mmol) was then added and the resulting solution was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.56 g) consisting of one major component. Purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave *N,N-diethyl-1,4-diimethyl-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-6-amine* **55** (0.12 g, 78%) as yellow crystals; mp 139.3-141.1°C; ($[M+H]^+$ 375.1850, $C_{19}H_{26}N_4SO_2$ requires $[M+H]^+$ 375.1849); δ_H 7.95 (2H, d, $^3J_{HH}$ 7.0, SO_2Ar_{ortho}), 7.50 (1H, t, $^3J_{HH}$ 7.5, SO_2Ar_{para}), 7.40 (2H, t, $^3J_{HH}$ 7.5, SO_2Ar_{meta}), 6.40 (1H, s, H-7), 3.48 (4H, q, $^3J_{HH}$ 7.0, $N(CH_2CH_3)_2$), 3.31 (2H, t, $^3J_{HH}$ 5.4, CH_2), 3.07 (3H, s, NCH_3), 2.72 (3H, s, NCH_3), 2.39 (2H, t, $^3J_{HH}$ 5.4, CH_2), 1.18 (6H, t, $^3J_{HH}$ 7.0, $N(CH_2CH_3)_2$); δ_C 152.3 (s, C-6), 150.8 (s, C-4*a*), 142.6 (s, Ar C), 140.6 (s, C-8), 131.5 (s, Ar_{ortho} CH), 127.1 (s, Ar_{meta} CH), 126.8 (s, Ar_{para} CH), 114.3 (s, C-8*a*), 89.3 (s, C-7), 45.9 (s, CH_2), 43.6 (s, NCH_3), 41.8 (s, $N(CH_2CH_3)_2$), 41.7 (s, CH_2), 35.1 (s,

NCH_3), 12.1 (s, $N(CH_2CH_3)_2$); *m/z* (EI)$^+$ 374 ([M]$^+$, 100), 359 ([M-CH_3]$^+$, 92), 330 ([M-$(CH_3)_2CH_2$]$^+$, 14), 233 ([M-SO_2Ph]$^+$, 28).

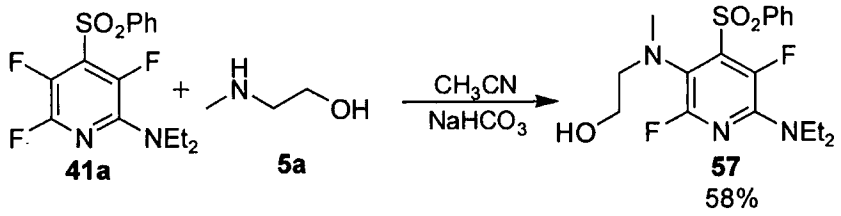
Preparation of 7-Fluoro-1,2,3,4-tetrahydro-1,4-dimethyl-6-phenoxy-8-(phenylsulfonyl)pyrido[2,3-*b*]pyrazine 56



N,N'-Dimethylethylenediamine **2a** (0.019 g, 0.22 mmol) and sodium hydrogencarbonate (0.037 g, 0.44 mmol) were added to acetonitrile (25 ml) under argon. 2,3,5-Trifluoro-6-phenoxy-4-(phenylsulfonyl)-pyridine **44a** (0.04 g, 0.11 mmol) was added and the resulting solution was refluxed for 1 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was then poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.04 g) consisting of one major component. Purification by preparative TLC on silica gel (2:1 *n*-hexane/ethyl acetate) gave *7-fluoro-1,2,3,4-tetrahydro-1,4-dimethyl-6-phenoxy-8-(phenylsulfonyl)pyrido[2,3-b]pyrazine* **56** (0.03 g, 65%) as a yellow solid; mp 137.3-139.4°C; ([M]$^+$ 413.1197, $C_{21}H_{20}N_3O_3FS$ requires [M]$^+$ 413.1209); δ_F -151.88 (s, F-7); δ_H 7.96 (2H, d, $^3J_{HH}$ 7.5, SO_2Ar_{ortho} H), 7.58 (1H, t, $^3J_{HH}$ 7.0, SO_2Ar_{para} H), 7.48 (2H, t, $^3J_{HH}$ 8.0, SO_2Ar_{meta}H), 7.29 (2H, t, $^3J_{HH}$ 8.0, OAr H), 7.10 (1H, t, $^3J_{HH}$ 7.5, OAr H), 7.02 (2H, d, $^3J_{HH}$ 8.0, OAr H) 3.29 (2H, t, $^3J_{HH}$ 5.0, NCH_2), 2.92 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 2.79 (2H, t, $^3J_{HH}$ 5.0, NCH_2); δ_C 153.7 (s, OAr C), 145.1 (d, $^4J_{CF}$ 2.0, C-4*a*), 143.3

(d, $^{2}J_{CF}$ 14.3, C-6), 141.5 (s, SO_2Ar C), 134.4 (d, $^{1}J_{CF}$ 254.6, C-7), 132.3 (s, SO_2Ar_{ortho} CH), 128.7 (d, $^{2}J_{CF}$ 9.1, C-8), 128.1 (s, OAr CH), 127.4 (s, SO_2Ar_{meta} CH), 126.7 (s, SO_2Ar_{para} CH), 123.8 (d, $^{3}J_{CF}$ 2.0, C-8*a*), 122.9 (s, OAr CH), 118.8 (s, OAr CH), 46.4 (s, CH_2), 45.9 (s, CH_3), 42.2 (s, CH_2), 35.5 (s, CH_3); *m/z* (EI)$^{+}$ 413 ([M]$^{+}$, 100), 398 ([M-CH_3]$^{+}$, 6), 272 ([M-SO_2Ph]$^{+}$, 28), 77 ([M-$C_{15}H_{15}N_3SO_3F$]$^{+}$, 100).

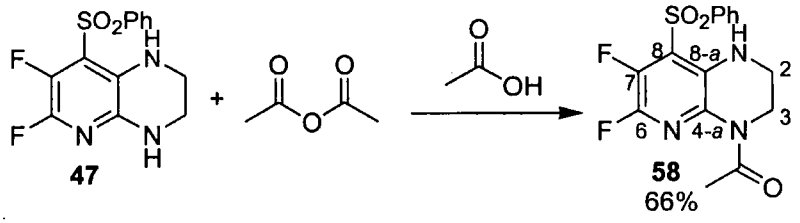
Preparation of 2-(*N*-(6-(Diethylamino)-2,5-difluoro-4-(phenylsulfonyl)pyridine-3-yl)-*N*-methylamino)ethanol 57



2-Methylaminoethanol **5a** (0.12 g, 1.58 mmol) and sodium hydrogencarbonate (0.27 g, 3.16 mmol) were added to acetonitrile (50 ml) under argon. *N,N'*-Diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine **41a** (0.25 g, 0.79 mmol) was added and the resulting solution was refluxed for 6 d after which time ^{19}F NMR indicated 91% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.23 g) consisting of one major component. Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *2-(N-(6-(diethylamino)-2,5-difluoro-4-(phenylsulfonyl)pyridine-3-yl)-N-methylamino)ethanol* **57** (0.17 g, 58%) as a yellow oil; ([M]$^{+}$ 399.1439, $C_{18}H_{23}N_3SO_3F_2$ requires 399.1428); δ_F -73.25 (1F, d, $^{5}J_{FF}$ 31.6, F-2), -134.30 (1F, d, $^{5}J_{FF}$ 33.8, F-5); δ_H 8.01 (2H, dm, $^{3}J_{HH}$ 8.0, Ar_{ortho} H), 7.64 (1H, tm,

$^{3}J_{HH}$ 7.6, Ar_{para} H), 7.56 (2H, tm, $^{3}J_{HH}$ 7.2, Ar_{meta} H), 3.73 (1H, m, NCH_aH$_b$), 3.55 (1H, dt, $^{1}J_{HH}$ 12.0, $^{3}J_{HH}$ 4.0, NCH$_a$$H_b$), 3.44 (4H, q, $^{3}J_{HH}$ 6.8, N(CH_2CH$_3$)$_2$), 3.10 (3H, m, NCH$_a$H$_b$CH_2), 2.17 (3H, s, NCH$_3$), 1.17 (6H, t, $^{3}J_{HH}$ 6.8, N(CH$_2$CH_3)$_2$); δ_C 156.4 (d, $^{1}J_{CF}$ 242.4, C-2), 145.4 (m, C-6), 142.1 (s, Ar C), 139.1 (d, $^{1}J_{CF}$ 263.8, C-5), 137.7 (m, C-4), 134.1 (s, Ar_{ortho} CH), 129.3 (s, Ar_{meta} CH), 128.2 (s, Ar_{para} CH), 118.1 (d, $^{2}J_{CF}$ 32.8, C-3), 59.6 (s, NCH$_a$H$_b$CH_2), 59.4 (d, $^{4}J_{CF}$ 3.4, NCH$_a$H$_b$CH$_2$), 44.8 (d, $^{4}J_{CF}$ 6.5, N(CH_2CH$_3$)$_2$), 41.1 (d, $^{4}J_{CF}$ 2.2, NCH$_3$), 13.8 (s, N(CH$_2$CH_3)$_2$); *m/z* (EI)$^{+}$ 399 ([M]$^{+}$, 42), 368 ([M-CH$_2$OH]$^{+}$, 100), 77 ([M-C$_{12}$H$_{18}$N$_3$SO$_3$F$_2$]$^{+}$, 42).

Preparation of 4-Acetyl-6,7-difluoro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 58



Acetic anhydride (0.06 g, 0.60 mmol) was added to a solution of 6,7-difluoro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine **47** (0.09 g, 0.30 mmol) in acetic anhydride and the reaction mixture was stirred at room temperature for 5 h before refluxing for 1 d after which time ^{19}F NMR indicated 80% conversion of starting material. The reaction mixture was cooled to room temperature, poured onto water (30 ml), extracted with dichloromethane (100 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.12 g) consisting of one major component. Purification by mass directed automated preparative HPLC (30%-85% acetonitrile in formic acid) gave *4-acetyl-6,7-difluoro-8-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **58** (0.07 g, 68%) as a yellow oil; ([M+H]$^{+}$ 354.0718,

$C_{15}H_{13}N_3F_2SO_3$ requires $[M+H]^+$ 354.0718); δ_F -104.66 (1F, d, $^3J_{FF}$ 26.3, F-6), -140.85 (1F, dd, $^3J_{FF}$ 26.3, F-7); δ_H 8.04 (2H, dm, $^3J_{HH}$ 8.4, Ar_{ortho} H), 7.72 (1H, tt, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.2, Ar_{para} H), 7.60 (2H, tm, $^3J_{HH}$ 8.4, Ar_{meta} H), 7.42 (1H, br s, NH), 3.95 (2H, t, $^3J_{HH}$ 4.8, 2-CH_2), 3.52 (2H, m, 3-CH_2), 2.42 (3H, s, $COCH_3$); δ_C 169.7 (s, C=O), 140.7 (s, Ar C), 139.0 (dd, $^1J_{CF}$ 230.7, $^2J_{CF}$ 17.5, C-6), 138.9 (dd, $^1J_{CF}$ 263.0, $^2J_{CF}$ 30.4, C-7), 134.8 (s, Ar_{para} CH), 131.2 (dd, $^3J_{CF}$ 4.2, $^4J_{CF}$ 1.2, C-4*a*), 130.7 (dd, $^3J_{CF}$ 12.0, $^4J_{CF}$ 5.0, C-8*a*), 129.5 (s, Ar_{meta} CH), 127.5 (s, Ar_{ortho} CH), 119.3 (d, $^2J_{CF}$ 12.0, C-8), 41.0 (s, C-2), 36.7 (s, C-3), 24.5 (s, CH_3); *m/z* (EI^+) 352 ($[M]^+$, 100), 309 ($[M-COCH_3]^+$, 92).

1 G. A. Selivanova, T. V. Chuikova, A. A. Shtark, and V. D. Shteingarts, *Zh. Org. Khim.*, 1989, **24**, 2513.

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5 W. Dmowski and A. Haas, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2119.

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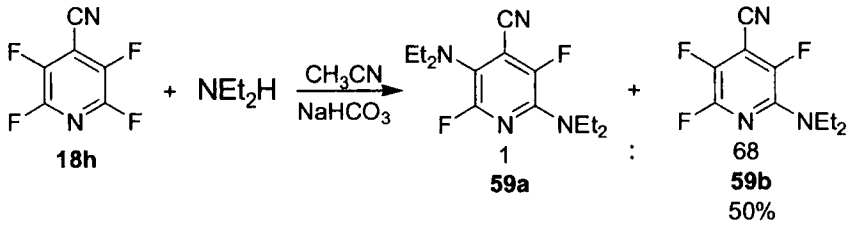
EXPERIMENTAL TO CHAPTER 5

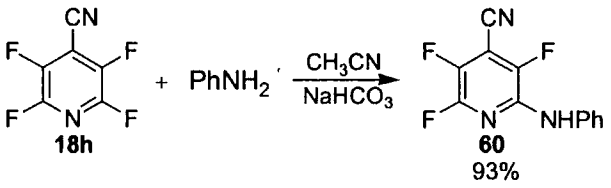
Preparation of 2-(Diethylamino)-3,5,6-trifluoroisonicotinonitrile 59b



Diethylamine (0.41 g, 5.68 mmol) and sodium hydrogencarbonate (0.48 g, 5.68 mmol) were added to acetonitrile (175 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (1.0 g, 5.68 mmol) was added and the resulting solution was stirred at room temperature for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.87 g) consisting of two major components in the ratio 1:68 which were identified as *2,5-(bisdiethylamino)-3,6-difluoroisonicotinonitrile* **59a**; and *2-(diethylamino)-3,5,6-trifluoroisonicotinonitrile* **59b**. Purification by column chromatography on silica gel (1:1 *n*-hexane/dichloromethane) gave *2-(diethylamino)-3,5,6-trifluoroisonicotinonitrile* **59b** (0.65 g, 50 %) as a yellow oil; ($[M+H]^+$ 230.0901, $C_{10}H_{10}N_3F_3$ requires $[M+H]^+$ 230.0900); δ_F -88.14 (1F, m, F-6), -130.48 (1F, dd, $^3J_{FF}$ 33.8, $^4J_{FF}$ 11.3, F-5), -153.41 (1F, dd, $^4J_{FF}$ 24.8, $^5J_{FF}$ 9.0, F-3); δ_H 3.49 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 2.0, CH_2), 1.21 (6H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 143.2 (dd, $^1J_{CF}$ 216.5, $^2J_{CF}$ 12.4, C-6), 142.7 (m, C-3), 140.5 (m, C-2), 131.6 (dd, $^1J_{CF}$ 260.0, $^2J_{CF}$ 33.9, C-5), 107.0 (s, CN), 102.5 (m, C-4), 43.4 (d, $^4J_{CF}$ 5.8, CH_2), 12.5 (s, CH_3); *m/z* (EI^+) 229 ($[M]^+$, 19), 214 ($[M-CH_3]^+$, 82), 186 ($[M-NCH_2CH_3]^+$, 100); and *2,5-(bisdiethylamino)-3,6-difluoroisonicotinonitrile* **59a** (0.27 g, 17

%) also as a yellow oil; ($[M+H]^+$ 283.1730, $C_{14}H_{20}N_4F_2$ requires $[M+H]^+$ 283.1729); δ_F -74.68 (1F, d, $^5J_{FF}$ 31.6, F-6), -132.58 (1F, d, $^5J_{FF}$ 31.6, F-3); δ_H 3.49 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, CH_2), 3.06 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.0, CH_2), 1.21 (6H, t, $^3J_{HH}$ 7.0, CH_3), 1.02 (6H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 153.6 (d, $^1J_{CF}$ 240.0, C-6), 143.0 (d, $^1J_{CF}$ 232.3, C-3), 141.9 (m, C-2), 118.1 (d, $^2J_{CF}$ 34.4, C-5), 114.2 (m, C-4), 110.7 (m, CN), 47.4 (d, $^4J_{CF}$ 2.4, CH_2), 43.1 (d, $^4J_{CF}$ 5.8, CH_2), 12.7 (s, CH_3), 12.6 (s, CH_3); *m/z* (EI^+) 282 ($[M]^+$, 71), 267 ($[M-CH_3]^+$, 100), 253 ($[M-CH_2CH_3]^+$, 10), 239 ($[M-CH_2CH_2CH_3]^+$, 53).

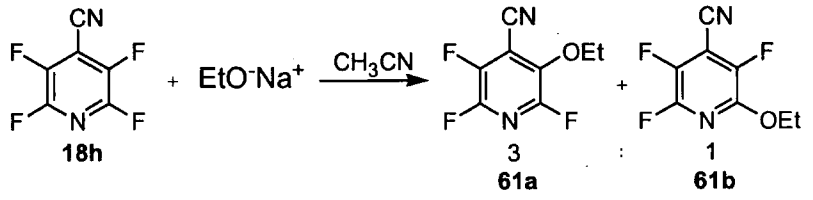
Preparation of 2-Anilino-3,5,6-trifluoroisonicotinonitrile 60



Aniline (0.26 g, 2.84 mmol) and sodium hydrogencarbonate (0.48 g, 5.68 mmol) were added to acetonitrile (100 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (0.5 g, 2.84 mmol) was added and the resulting solution was stirred at room temperature for 1 d before refluxing for 13 d. Over the course of the reaction 12 extra equivalents of aniline (3.17 g, 34 mmol) were added. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.32 g) consisting of one major component. Purification by column chromatography on silica gel (3:1 *n*-hexane/ethyl acetate) followed by recrystallisation from ethyl acetate gave *2-anilino-3,5,6-trifluoroisonicotinonitrile* **60** (0.66 g, 93%) as

orange crystals; mp 204.5-205.5°C; (Found: C, 57.7; H, 2.4; N, 17.0; $C_{12}H_6N_3F_3$ requires: C, 57.8; H, 2.4; N, 16.9%); δ_F(d_6-Acetone) -87.96 (1F, dd, $^3J_{FF}$ 32.0, $^4J_{FF}$ 22.0, F-5), -134.61 (1F, dd, $^3J_{FF}$ 31.0, $^5J_{FF}$ 9.0, F-6), -148.75 (1F, dd, $^4J_{FF}$ 22.0, $^5J_{FF}$ 9.2, F-3); δ_H(d_6-Acetone) 7.55 (2H, d, $^3J_{HH}$ 7.6, Ar_{ortho} H), 7.39 (2H, t, $^3J_{HH}$ 7.6, Ar_{meta} H), 7.16 (1H, t, $^3J_{HH}$ 7.0, Ar_{para} H), 6.69 (1H, br s, NH); δ_C(d_6-Acetone) 144.5 (ddm, $^1J_{CF}$ 229.9, $^2J_{CF}$ 13.2, C-5), 143.9 (dm, $^1J_{CF}$ 270.5, C-3), 139.6 (m, C-4), 139.0 (s, Ar C), 134.4 (dd, $^1J_{CF}$ 258.5, $^2J_{CF}$ 34.3, C-6), 129.1 (s, Ar_{meta} CH), 123.8 (s, Ar_{para} CH), 120.2 (s, Ar_{ortho} CH), 107.8 (d, $^3J_{CF}$ 4.2, CN), 102.4 (m, C-2); *m/z* (EI^+) 248 ($[M-H]^+$, 100), 77 ($[M-C_6HN_3F_3]^+$, 94).

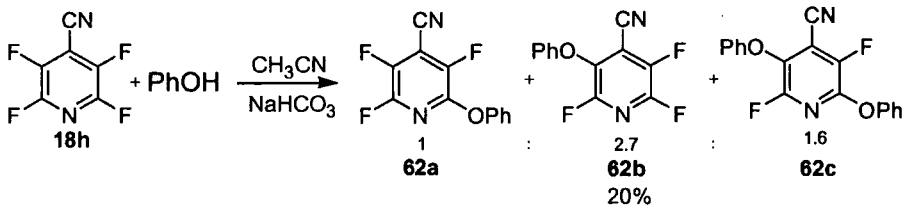
Preparation of 2,3,6-Trifluoro-5-ethoxyisonicotinonitrile 61a



Dry ethanol (0.13 g, 2.84 mmol) and sodium (0.07 g, 2.84 mmol) were added to tetrahydrofuran (3 ml) under argon and stirred for 2 h. The tetrahydrofuran was evaporated and the residue redissolved in acetonitrile (20 ml). This solution was added dropwise to 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile **18h** (0.5 g, 2.84 mmol) in acetonitrile (20 ml) and the resulting reaction mixture was stirred at room temperature for 1 d before refluxing for 6 d. Over the course of the reaction three further equivalents of sodium ethoxide (0.57 g, 8.52 mmol) were added. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent was evaporated to dryness to yield the crude product as a brown oil (0.9 g)

consisting of two major components in the ratio 3:1 which were identified as *2,3,6-trifluoro-5-ethoxyisonicotinonitrile* **61a**; δ_F(d_6-Acetone) -87.44 (1F, dd, $^3J_{FF}$ 29.3, $^4J_{FF}$ 13.5, F-2), -99.46 (1F, t, $^4J_{FF}$ 15.8, F-6), -139.32 (1F, dd, $^3J_{FF}$ 29.3, $^5J_{FF}$ 20.3, F-3); δ_C(d_6-Acetone) 144.2 (ddd, $^1J_{CF}$ 238.9, $^2J_{CF}$ 11.0, $^3J_{CF}$ 2.9, C-2), 142.8 (ddd, $^1J_{CF}$ 262.8, $^3J_{CF}$ 30.1, $^4J_{CF}$ 6.6, C-6), 141.2 (dd, $^2J_{CF}$ 34.4, $^3J_{CF}$ 6.3, C-5), 139.7 (dm, $^1J_{CF}$ 234.6, C-3), 108.8 (t, $^2J_{CF}$ 3.8, C-4), 104.6 (m, CN), 54.31 (s, CH_2), 30.0 (s, CH_3); *m/z* (EI^+) 202 ($[M]^+$, 21), 187 ($[M-CH_3]^+$, 4), 174 ($[M-CH_3CH]^+$, 100); and *2,3,5-trifluoro-6-ethoxyisonicotinonitrile* **61b**; δ_F(d_6-Acetone) -90.96 (1F, t, $^3J_{FF}$ 22.6, F-2), -134.94 (1F, dd, $^3J_{FF}$ 29.3, $^4J_{FF}$ 6.8, F-3), -146.87 (1F, dd, $^4J_{FF}$ 22.6, $^5J_{FF}$ 9.0, F-5); *m/z* (EI^+) 202 ($[M]^+$, 5), 187 ($[M-CH_3]^+$, 2), 174 ($[M-CH_3CH]^+$, 100). Partial purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) followed by recrystallisation from chloroform gave a mixture of *2,3,6-trifluoro-5-ethoxyisonicotinonitrile* **61a** and *2,3,5-trifluoro-6-ethoxyisonicotinonitrile* **61b** in the ratio 94:1 respectively (0.5, 87%).

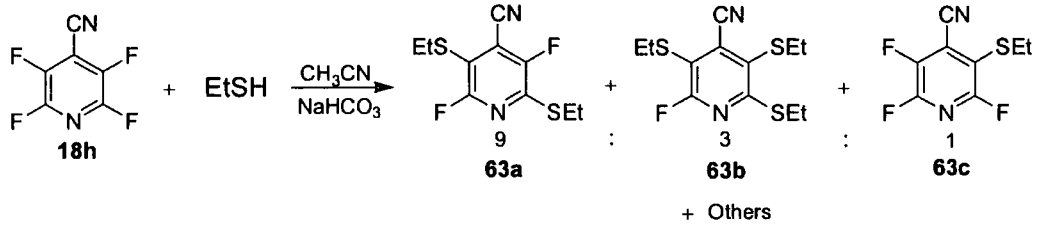
Preparation of 2,3,6-Trifluoro-5-phenoxyisonicotinonitrile 62b



Phenol (0.27 g, 2.84 mmol) and sodium hydrogencarbonate (0.24 g, 2.84 mmol) were added to acetonitrile (50 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (0.5 g, 2.84 mmol) was added and the solution stirred at room temperature for 20 h before refluxing for 4 d. ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30

ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent was evaporated to dryness to yield the crude product as a brown solid (1.03 g) consisting of three major components in the ratio 1:2.7:1.6 which were identified as *2,3,5-trifluoro-6-phenoxyisonicotinonitrile* **62a**; δ_F -87.31 (1F, dd, $^3J_{FF}$ 31.0, $^5J_{FF}$ 21.1, F-2), -131.33 (1F, dd, $^3J_{FF}$ 31.0, $^4J_{FF}$ 7.3, F-3), -140.67 (1F, dd, $^4J_{FF}$ 20.1, $^5J_{FF}$ 7.3, F-5); *m/z* (EI^+) 250 ($[M]^+$, 94), 77 ($[M-C_6N_2OF_3]^+$, 100); *2,3,6-trifluoro-5-phenoxyisonicotinonitrile* **62b**; and 2,5-*difluoro-3,6-phenoxyisonicotinonitrile* **62c**; δ_F -85.43 (1F, m, F-2), 133.11 (1F, m, F-5); *m/z* (EI^+) 324 ($[M]^+$, 77), 77 ($[M-C_{12}H_5N_2O_2F_2]^+$, 100). Purification by recrystallisation from *n*-hexane gave *2,3,6-trifluoro-5-phenoxyisonicotinonitrile* **62b** (0.14 g, 20%) as a white solid; mp 90.1-91.5°C; (Found: C, 57.4; H, 2.0; N, 11.2; $C_{12}H_5N_2OF_3$ requires: C, 57.6; H, 2.0; N, 11.2%); δ_F -77.92 (1F, dd, $^3J_{FF}$ 32.0, $^4J_{FF}$ 12.8, F-2), -87.21 (1F, dd, $^4J_{FF}$ 20.1, $^5J_{FF}$ 12.8, F-6), -134.53 (1F, dd, $^3J_{FF}$ 31.0, $^5J_{FF}$ 20.1, F-3); δ_H 7.32 (2H, tm, $^3J_{HH}$ 7.6, OAr_{ortho} H), 7.15 (1H, tm, $^3J_{HH}$ 7.2, OAr_{para} H), 6.92 (2H, dm, $^3J_{HH}$ 8.4, OAr_{meta} H); δ_C 156.5 (s, OAr C), 147.8 (ddd, $^1J_{CF}$ 250.8, $^3J_{CF}$ 11.0, $^4J_{CF}$ 3.4, C-6), 144.2 (dd, $^1J_{CF}$ 246.5, $^2J_{CF}$ 12.4, C-3), 142.9 (ddd, $^1J_{CF}$ 271.8, $^2J_{CF}$ 30.0, $^3J_{CF}$ 6.6, C-2), 137.3 (m, C-5), 130.4 (s, OAr_{ortho} CH), 125.4 (s, OAr_{para} CH), 116.7 (s, OAr_{meta} CH), 111.3 (m, C-4), 107.7 (t, $^3J_{CF}$ 3.8, CN); *m/z* (EI^+) 250 ($[M]^+$, 74), 77 ($[M-C_6N_2OF_3]^+$, 100).

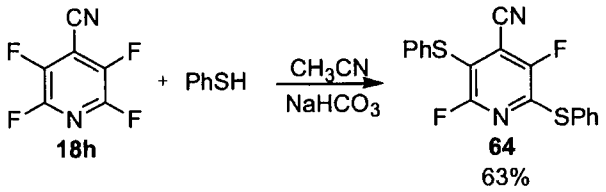
Preparation of 2,5-Bis(ethylsulfanyl)-3,6-difluoroisonicotinonitrile 63a



Ethanethiol (0.18 g, 2.84 mmol) and sodium hydrogencarbonate (0.48 g, 5.68 mmol) were added to acetonitrile (100 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h**

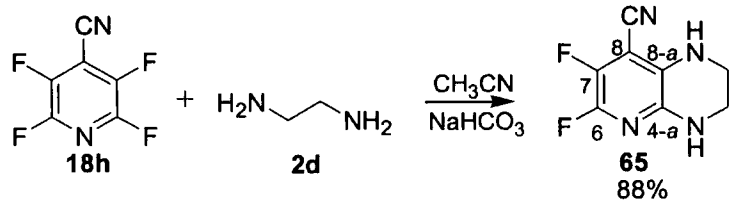
(0.5 g, 2.84 mmol) was then added and the resulting solution was stirred at room temperature for 1 d before refluxing for 8 d. Over the course of the reaction an extra equivalent of ethanethiol (0.18 g, 2.84 mmol) was added. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.86 g) consisting of three major components in the ratio 9:3:1 which were identified as *2,5-bis(ethylsulfanyl)-3,6-difluoroisonicotinonitrile* **63a**; δ_F -64.89 (1F, d, $^5J_{FF}$ 29.3, F-6), -119.01 (1F, d, $^5J_{FF}$ 27.1, F-3); δ_H 3.19 (2H, q, $^3J_{HH}$ 7.5, CH_2), 3.01 (2H, q, $^3J_{HH}$ 7.5, CH_2), 1.39 (3H, t, $^3J_{HH}$ 7.5, CH_3), 1.29 (3H, t, $^3J_{HH}$ 7.5, CH_3); δ_C 158.5 (dd, $^1J_{CF}$ 237.5, $^4J_{CF}$ 2.4, C-6), 153.7 (dd, $^1J_{CF}$ 265.6, $^4J_{CF}$ 5.3, C-3), 148.7 (dd, $^2J_{CF}$ 20.1, $^3J_{CF}$ 15.3, C-2), 116.3 (dd, $^2J_{CF}$ 13.3, $^3J_{CF}$ 5.1, C-4), 114.2 (dd, $^2J_{CF}$ 41.5, $^3J_{CF}$ 3.4, C-5), 110.4 (d, $^3J_{CF}$ 4.3, CN), 29.9 (d, $^4J_{CF}$ 3.8, SCH_2), 24.5 (d, $^4J_{CF}$ 1.5, SCH_2), 15.2 (s, CH_3), 14.4 (s, CH_3); *m/z* (EI^+) 260 ($[M]^+$, 90), 199 ($[M\text{-}SCH_2CH_3]^+$, 100); *2,3,5-tris(ethylsulfanyl)-6-fluoroisonicotinonitrile* **63b**; δ_F -60.47 (1F, s, F-6); *m/z* (EI^+) 302 ($[M]^+$, 76), 273 ($[M\text{-}Et]^+$, 100); and *3-(ethylsulfanyl)-2,5,6-trifluoroisonicotinonitrile* **63c**; δ_F -63.42 (1F, dd, $^3J_{FF}$ 30.1, $^4J_{FF}$ 11.8, F-6), -84.05 (1F, dd, $^4J_{FF}$ 20.1, $^5J_{FF}$ 10.0, F-2), -136.11 (1F, dd, $^3J_{FF}$ 29.3, $^5J_{FF}$ 21.1, F-5); *m/z* (EI^+) 218 ($[M]^+$, 57), 190 ($[M\text{-}CH_2CH_2]^+$, 100). Partial purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave a mixture of *2,5-bis(ethylsulfanyl)-3,6-difluoroisonicotinonitrile* **63a** and *2,3,5-tris(ethylsulfanyl)-6-fluoroisonicotinonitrile* **63b** in the ratio 32:1 respectively (0.08 g, 10%) as a yellow oil.

Preparation of 2,5-Difluoro-3,6-bis(phenylsulfanyl)isonicotinonitrile 64



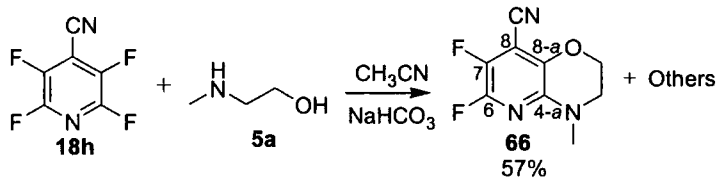
Benzenethiol (0.31 g, 2.84 mmol) and sodium hydrogencarbonate (0.48 g, 5.68 mmol) were added to acetonitrile (100 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (0.5 g, 2.84 mmol) was added and the resulting solution was stirred at room temperature for 12 d. Over the course of the reaction an extra equivalent of benzenethiol (0.31 g, 2.84 mmol) was added. ^{19}F NMR indicated 100% conversion of starting material so the solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.07 g) consisting of one major component. Purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) gave *2,5-difluoro-3,6-bis(phenylsulfanyl)isonicotinonitrile* **64** (0.63 g, 63%) as a yellow solid; mp 84.2-85.0°C; (Found: C, 60.6; H, 2.9; N, 7.8; $C_{18}H_{10}N_2S_2F_2$ requires: C, 60.8; H, 2.8; N, 7.9%); δ_F -62.61 (1F, d, $^5J_{FF}$ 27.1, F-2), -117.95 (1F, d, $^5J_{FF}$ 29.3, F-5); δ_H 7.55 (2H, m, Ar H), 7.45 (5H, m, Ar H), 7.32 (3H, m, Ar H); δ_C 158.0 (dd, $^1J_{CF}$ 240.4, $^4J_{CF}$ 1.9, C-2), 153.2 (dd, $^1J_{CF}$ 267.5, $^4J_{CF}$ 4.8, C-5), 148.9 (m, C-4), 135.9 (s, Ar CH), 132.2 (s, Ar CH), 130.5 (s, Ar CH), 129.9 (s, Ar CH), 129.1 (s, Ar CH), 125.7 (d, $^4J_{CF}$ 2.0, Ar C), 116.7 (dd, $^2J_{CF}$ 14.4, $^3J_{CF}$ 3.8, C-6), 116.2 (dd, $^2J_{CF}$ 40.5, $^3J_{CF}$ 3.4, C-3); *m/z* (EI^+) 356 ($[M]^+$, 97), 109 ($[M\text{-}C_{12}H_5N_2F_2S]^+$, 76), 77 ($[M\text{-}C_{12}H_5N_2F_2S_2]^+$, 100).

Preparation of 6,7-Difluoro-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-carbonitrile 65



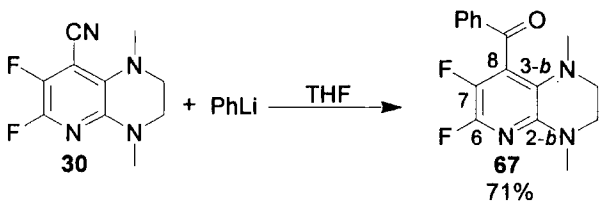
Ethylenediamine **2d** (1.2 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (1.76 g, 10 mmol) was added and the resulting solution was refluxed for 5 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane (50 ml). The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow solid (1.35 g) consisting of one major component. Purification by mass directed automated preparative HPLC (30%-85% acetonitrile in formic acid) gave *6,7-difluoro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-8-carbonitrile* **65** (1.19 g, 61%) as an orange solid; mp 280.3-281.7°C; (Found: C, 48.7; H, 3.1; N, 28.5; $C_8H_6N_4F_2$ requires: C, 49.0; H, 3.1; N, 28.6%); δ_F -104.78 (1F, d, $^3J_{FF}$ 22.6, F-6), -156.14 (1F, d, $^3J_{FF}$ 22.6, F-7); δ_H 7.30 (1H, br s, NH), 7.00 (1H, br s, NH), 3.28 (2H, m, CH_2), 3.28 (2H, m, CH_2); δ_C 140.7 (dd, $^3J_{CF}$ 17.0, $^4J_{CF}$ 2.6, C-4*a*), 138.7 (dd, $^1J_{CF}$ 217.5, $^2J_{CF}$ 13.5, C-6), 132.5 (dd, $^3J_{CF}$ 3.5, $^4J_{CF}$ 1.3, C-8*a*), 132.0 (dd, $^1J_{CF}$ 246.2, $^2J_{CF}$ 31.7, C-7), 112.0 (dd, $^3J_{CF}$ 4.6, $^4J_{CF}$ 1.3, CN), 88.2 (dd, $^2J_{CF}$ 16.6, $^3J_{CF}$ 3.3, C-8), 38.7 (s, CH_2), 38.3 (s, CH_2); *m/z* (EI)$^+$ 197 ([M+H]$^+$, 100), 177 ([MH-HF]$^+$, 3).

Preparation of 6,7-Difluoro-4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-8-carbonitrile 66



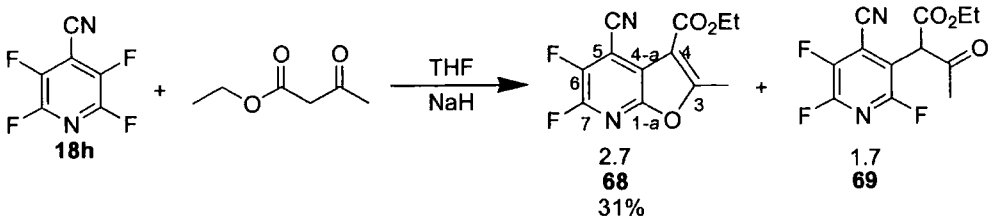
2-Methylaminoethanol **5a** (0.85 g, 11.36 mmol) and sodium hydrogencarbonate (1.91 g, 22.72 mmol) were added to acetonitrile (175 ml) under argon. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (1.0 g, 5.68 mmol) was added and the resulting solution was refluxed for 6 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The reaction mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (1.33 g) consisting of one major component. Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *6,7-difluoro-4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-8-carbonitrile* **66** (0.68 g, 57%) as yellow crystals; mp 79.1-80.7°C; (Found: C, 51.2; H, 3.4; N, 19.8; $C_9H_7N_3F_2O$ requires: C, 51.2; H, 3.3; N, 19.9%); δ_F -97.60 (1F, d, $^3J_{FF}$ 22.9, F-6), -155.35 (1F, d,$^3J_{FF}$ 22.9, F-7); δ_H 4.39 (2H, t, $^3J_{HH}$ 4.6, CH_2), 3.49 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.08 (3H, s, CH_3); δ_C 143.5 (dd, $^1J_{CF}$ 215.3, $^2J_{CF}$ 13.4, C-6), 141.4 (dd, $^3J_{CF}$ 15.3, $^4J_{CF}$ 2.3, C-4*a*), 139.2 (dd, $^3J_{CF}$ 5.4, $^4J_{CF}$ 1.5, C-8*a*), 134.0 (dd, $^1J_{CF}$ 255.8, $^2J_{CF}$ 32.4, C-7), 109.9 (d, $^3J_{CF}$ 4.2, CN), 99.5 (dd, $^2J_{CF}$ 15.2, $^3J_{CF}$ 4.2, C-8), 65.3 (s, CH_2), 47.1 (s, CH_2), 36.2 (s, CH_3); *m/z* (EI$^+$) 211 ([M]$^+$, 100), 196 ([M-CH_3]$^+$, 91), 182 ([M-CH_3N]$^+$, 60), 156 ([M-CH_3NCN]$^+$, 37), 128 ([M-$CH_3NCH_2CH_2CN$]$^+$, 50).

Preparation of (6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-8-yl)(phenyl)methanone 67



Phenyl lithium 1.8 M in tetrahydrofuran (0.49 ml, 0.88 mmol) was added to a solution of 6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-carbonitrile **30** (0.20 g, 0.88 mmol) in tetrahydrofuran (50 ml) so the reaction mixture was stirred at room temperature for 8 h before refluxing for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow solid (0.58 g) consisting of one major component. Purification by mass directed automated preparative HPLC (30%-85% acetonitrile in formic acid) gave *(6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-8-yl)(phenyl)methanone* **67** (0.19 g, 71%) as a yellow solid; mp 134.8-138.0°C; ($[M+H]^+$ 304.1255, $C_{16}H_{15}N_3F_2O$ requires $[M+H]^+$ 304.1261); δ_F -99.56 (1F, d, $^3J_{FF}$ 26.3, F-6), -162.43 (1F, d, $^3J_{FF}$ 26.3, F-7); δ_H 7.89 (2H, dm, $^3J_{HH}$ 7.2, Ar H), 7.62 (1H, tm, $^3J_{HH}$ 8.0, Ar H), 7.48 (2H, tm, $^3J_{HH}$ 7.2, Ar H), 3.37 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.11 (3H, s, CH_3), 3.06 (2H, t, $^3J_{HH}$ 4.8, CH_2), 2.59 (3H, s, CH_3); δ_C 192.2 (m, C=O), 144.1 (dm, $^3J_{CF}$ 11.7, C-4*a*), 144.0 (dd, $^1J_{CF}$ 227.7, $^2J_{CF}$ 15.0, C-6), 136.4 (s, Ar C), 134.2 (s, Ar CH), 132.3 (dd, $^1J_{CF}$ 242.1, $^2J_{CF}$ 31.0, C-7), 129.6 (s, Ar CH), 128.8 (s, Ar CH), 128.1 (m, C-8*a*), 126.1 (m, C-8), 53.9 (s, CH_2), 44.6 (s, CH_3), 44.4 (s, CH_2), 36.9 (s, CH_3); *m/z* (EI)$^+$ 304 ($[M+H]^+$, 100), 289 ($[MH-CH_3]^+$, 20).

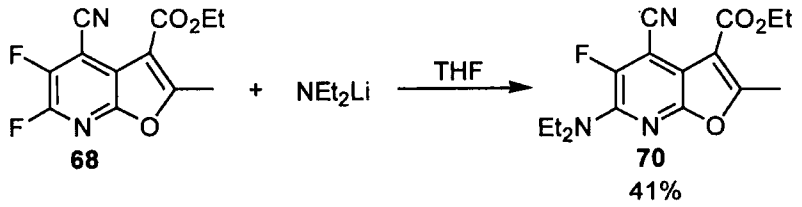
Preparation of Ethyl-5-cyano-6,7-difluoro-3-methyl-2H-pyrano[2,3-*b*]pyridine-4-carboxylate 68



Ethyl acetoacetate (0.74 g, 5.68 mmol) and sodium hydride 60% dispersion in mineral oil (0.27 g, 6.82 mmol) were added to dry tetrahydrofuran (50 ml) under argon and stirred at room temperature for 1 h. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (1.0 g, 5.68 mmol) was added and the reaction mixture stirred at room temperature for 4.5 h before refluxing for 16 h. ^{19}F NMR indicated 64% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown solid (0.94 g) consisting of two major components in the ratio 2.7:1.7 which were identified as *ethyl-5-cyano-6,7-difluoro-3-methyl-2H-pyrano[2,3-b]pyridine-4-carboxylate* **68**; and *ethyl 2-(4-cyano-2,5,6-trifluoropyridin-3-yl)-3-oxobutanoate* **69**. Purification by column chromatography on silica gel (3:1 *n*-hexane/ethyl acetate) gave *ethyl-5-cyano-6,7-difluoro-3-methyl-2H-pyrano[2,3-b]pyridine-4-carboxylate* **68** (0.47 g, 31%) as a white solid; mp 91.8-93.3°C; (Found: C, 54.1; H, 3.0; N, 10.6; $C_{12}H_8N_2F_2O_3$ requires: C, 54.1; H, 3.0; N, 10.5%); δ_F -89.51 (1F, d, $^3J_{FF}$ 20.9, F-7), -138.36 (1F, d, $^3J_{FF}$ 21.1, F-6); δ_H 4.52 (2H, q, $^3J_{HH}$ 7.0, CH_2), 2.86 (3H, s, 3-CH_3), 1.46 (3H, t, $^3J_{HH}$ 7.5, CH_2CH_3); δ_C 167.2 (d, $^5J_{CF}$ 4.4, C-3), 161.8 (s, C=O), 151.6 (dd, $^3J_{CF}$ 15.0, $^4J_{CF}$ 3.4, C-1*a*), 148.0 (dd, $^1J_{CF}$ 247.5, $^2J_{CF}$ 17.3, C-7), 146.0 (dd, $^1J_{CF}$ 266.4,

$^2J_{CF}$ 28.9, C-6), 116.1 (dd, $^3J_{CF}$ 3.9, $^4J_{CF}$ 1.4, C-4*a*), 110.2 (d, $^3J_{CF}$ 4.8, CN), 109.9 (s, C-4), 106.0 (dd, $^2J_{CF}$ 14.9, $^3J_{CF}$ 3.8, C-5), 61.6 (s, CH_2CH_3), 15.0 (s, CH_2CH_3), 14.6 (s, 3-CH_3); *m/z* (EI^+) 266 ($[M]^+$, 36), 193 ($[M-CO_2CH_2CH_3]^+$, 30), 138 ($[M-C_6H_8O_3]^+$, 26); and *ethyl 2-(4-cyano-2,5,6-trifluoropyridin-3-yl)-3-oxobutanoate* **69** (0.30 g, 18%) as a yellow oil; δ_F -68.44 (1F, dd, $^4J_{FF}$ 20.9, $^5J_{FF}$ 10.9, F-2), -68.42 (1F, dd, $^3J_{FF}$ 28.4, $^4J_{FF}$ 11.1, F-6), -137.81 (1F, overlapping dd, $^3J_{FF}$ 28.4, F-5); *m/z* (EI^+) 286 ($[M]^+$, 36), 198 ($[M-C_3H_8O_2]^+$, 100).

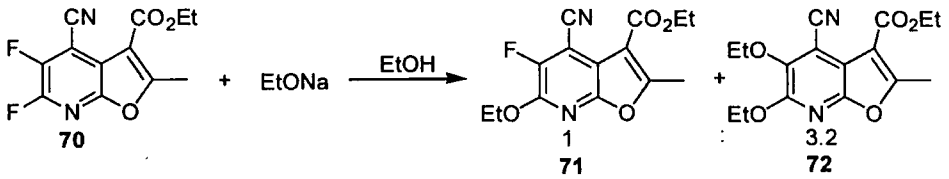
Preparation of 4-Cyano-6-diethylamino-5-fluoro-2-methyl-furo[2,3-*b*]pyridine-3-carboxylic acid ethyl ester 70



Butyl lithium 1.6 M in pentane (0.83 ml, 1.32 mmol) and diethylamine (0.096 g, 1.32 mmol) were added to dry tetrahydrofuran (5 ml) at -78°C and the solution was stirred for 1 h before warming to room temperature. The solution was added to ethyl-5-cyano-6,7-difluoro-3-methyl-2H-pyrano[2,3-*b*]pyridine-4-carboxylate **68** (0.35 g, 1.32 mmol) in tetrahydrofuran (45 ml) and stirred at room temperature for 2 d. ^{19}F NMR indicated 82% conversion of starting material so the reaction was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a red oil (0.57 g) consisting of one major product. Purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) gave *4-cyano-6-diethylamino-5-fluoro-2-methyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **70** (0.20 g, 48%) as a yellow oil; $[M+H]^+$ 320.1406, $C_{16}H_{18}N_3O_3F$ requires $[M+H]^+$ 320.1405); δ_F -131.43 (1F, s, F-5); δ_H 4.40 (2H,

q, $^{3}J_{HH}$ 7.0, OCH_2CH$_3$), 3.50 (4H, qd, $^{3}J_{HH}$ 7.0, $^{5}J_{HF}$ 2.0, N(CH_2CH$_3$)$_2$), 2.67 (3H, s, 2-CH$_3$), 1.37 (3H, t, $^{3}J_{HH}$ 7.5, OCH$_2$CH_3), 1.18 (6H, t, $^{3}J_{HH}$ 7.0, N(CH$_2$CH_3)$_2$); δ_C 163.0 (s, C=O), 161.8 (d, $^{5}J_{CF}$ 1.9, C-2), 155.0 (d, $^{4}J_{CF}$ 2.4, C-7*a*), 148.9 (d, $^{1}J_{CF}$ 262.0, C-5), 144.9 (d, $^{2}J_{CF}$ 9.6, C-6), 112.1 (d, $^{4}J_{CF}$ 1.9, C-3), 109.3 (d, $^{3}J_{CF}$ 1.4, C-3*a*), 105.3 (s, CN), 105.5 (d, $^{2}J_{CF}$ 19.2, C-4), 61.0 (s, OCH_2CH$_3$), 44.9 (d, $^{4}J_{CF}$ 6.3, N(CH_2CH$_3$)$_2$), 14.7 (s, OCH$_2$$CH_3$), 14.5 (s, 2-CH$_3$), 13.9 (d, $^{5}J_{CF}$ 0.9, N(CH$_2$$CH_3$)$_2$); *m/z* (EI$^+$) 319 ([M]$^+$, 78), 304 ([M-CH$_3$]$^+$, 100), 290 ([M-CH$_2CH_3$]$^+$, 30).

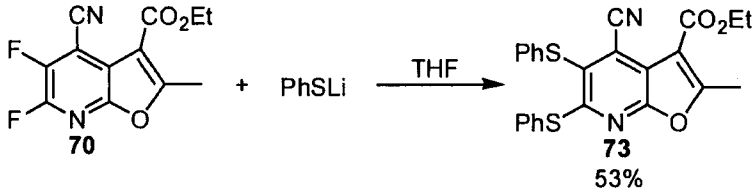
Preparation of 4-Cyano-6-ethoxy-5-fluoro-2-methyl-furo[2,3-*b*]pyridine-3-carboxylic acid ethyl ester 71



Sodium metal (0.01 g, 0.45 mmol) was added to anhydrous ethanol (30 ml) under argon followed by the addition of ethyl-5-cyano-6,7-difluoro-3-methyl-2H-pyrano[2,3-*b*]pyridine-4-carboxylate **70** (0.12 g, 0.45 mmol). The resulting solution was stirred at room temperature for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (30 ml), extracted with dichloromethane (3 x 30 ml), dried over magnesium sulfate and evaporated to dryness to yield the crude product as a yellow oil (0.18 g) consisting of two major components in the ratio 1:3.2 which were identified as *4-cyano-6-ethoxy-5-fluoro-2-methyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **71**; δ_F -136.13 (1F, s, F-5); *m/z* (EI$^+$) 292 ([M]$^+$, 55), 263 ([M-CH$_2$CH$_3$]$^+$, 36), 218 ([M-CH$_2$(CH$_3$)$_2$]$^+$, 100); and *4-cyano-5,6-diethoxy-2-methyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **72**; δ_H 4.47 (4H, q, $^{3}J_{HH}$ 7.2, OCH_2CH$_3$), 4.26 (2H, q, $^{3}J_{HH}$ 6.8, CO$_2$CH_2CH$_3$), 2.76 (3H, s, 2-CH$_3$), 1.46 (9H, 2

overlapping t, OCH_2CH_3 & $CO_2CH_2CH_3$); *m/z* (EI^+) 318 ($[M]^+$, 94). Purification by preparative TLC (3:1 *n*-hexane/ethyl acetate) was unsuccessful and gave a mixture of *4-cyano-6-ethoxy-5-fluoro-2-methyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **71** and *4-cyano-5,6-diethoxy-2-methyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **72** (0.1 g, 71%) in the ratio 1:2 respectively as a colourless oil.

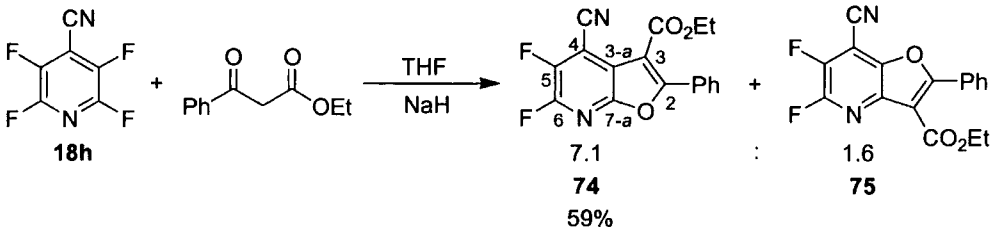
Preparation of 4-Cyano-2-methyl-5,6-bis-phenylsulfanyl-furo[2,3-*b*]pyridine-3-carboxylic acid ethyl ester 73



Ethyl-5-cyano-6,7-difluoro-3-methyl-2H-pyrano[2,3-*b*]pyridine-4-carboxylate **70** (0.1 g, 0.38 mmol) and lithium thiophenoxide 1.0 M in tetrahydrofuran (0.75 ml, 0.75 mmol) were added to tetrahydrofuran (30 ml) under argon and the resulting solution was refluxed at 80°C for 18 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown solid (0.22 g) consisting of one major component. Purification by preparative TLC (3:1 *n*-hexane/ethyl acetate) gave *4-cyano-2-methyl-5,6-bis-phenylsulfanyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **73** (0.09 g, 53%) as a yellow solid; mp 139.3-143.2°C; ($[M]^+$ 446.0754, $C_{24}H_{18}N_2O_3S_2$ requires $[M]^+$ 446.0753); δ_H 7.15-7.50 (10H, m, Ar CH), 4.39 (2H, q, $^3J_{HH}$ 7.2, CH_2), 2.65 (3H, s, 2-CH_3), 1.34 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3); δ_C 164.8 (s, C-2), 162.3 (s, C-7*a*), 160.3 (s,

C=O), 135.9 (s, Ar CH), 134.2 (s, C-5), 129.8 (s, C-6), 129.8 (Ar CH), 129.6 (s, Ar CH), 127.7 (s, Ar C), 121.4 (s, C-3), 115.8 (s, C-4), 114.3 (s, C-3*a*), 109.5 (s, CN), 61.4 (s, CH_2), 14.7 (s, CH_3), 14.6 (s, CH_3); *m/z* (EI^+) 446 ($[M]^+$, 100), 417 ($[M\text{-}CH_2CH_3]^+$, 20).

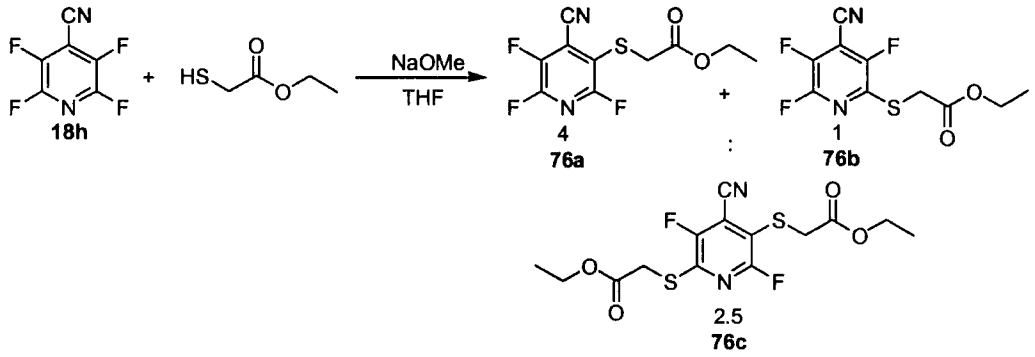
Preparation of 4-Cyano-5,6-difluoro-2-phenyl-furo[2,3-*b*]pyridine-3-carboxylic acid ethyl ester 74



3-Oxo-3-phenyl-propionic acid ethyl ester (1.09 g, 5.68 mmol) and sodium hydride 60% dispersion in mineral oil (0.27 g, 6.82 mmol) were added to dry tetrahydrofuran (50 ml) under argon and stirred at room temperature for 1 h. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **18h** (1.0 g, 5.68 mmol) was added and the reaction mixture refluxed for 6 d. ^{19}F NMR indicated 61% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (1.37 g) consisting of two major components in the ratio 7.1:1.6 which were identified as *4-cyano-5,6-difluoro-2-phenyl-furo[2,3-b]pyridine-3-carboxylic acid ethyl ester* **74**; and *7-cyano-5,6-difluoro-2-phenyl-furo[3,2-b]pyridine-3-carboxylic acid ethyl ester* **75**; δ_F -84.26 (1F, d, $^3J_{FF}$ 23.7, F-5), -136.68 (1F, d, $^3J_{FF}$ 23.7, F-6); *m/z* (EI^+) 328 ($[M]^+$, 50), 283 ($[M\text{-}OCH_2CH_3]^+$, 82), 256 ($[MH\text{-}CO_2CH_2CH_3]^+$, 100). Purification by column chromatography on silica gel (7:1 *n*-hexane/ethyl acetate) gave *4-cyano-5,6-difluoro-2-phenyl-furo[2,3-b]pyridine-3-carboxylic*

acid ethyl ester **74** (1.1 g, 59%) as a white solid; mp 118.4-120.3°C; (Found: C, 62.2; H, 3.1; N, 8.5; $C_{17}H_{10}N_2F_2O_3$ requires: C, 62.2; H, 3.0; N, 8.5%); δ_F -88.11 (1F, d, $^3J_{FF}$ 21.1, F-6), -137.90 (1F, d, $^3J_{FF}$ 21.1, F-5); δ_H 8.05 (2H, m, Ar H), 7.59-7.52 (3H, m, Ar H), 4.54 (2H, q, $^3J_{HH}$ 7.2, CH_2), 1.43 (3H, t, $^3J_{HH}$ 7.2, CH_3); δ_C 162.7 (d, $^5J_{CF}$ 4.6, C-2), 161.6 (s, C=O), 151.7 (dd, $^3J_{CF}$ 15.2, $^4J_{CF}$ 3.5, C-7*a*), 148.6 (dd, $^1J_{CF}$ 247.0, $^2J_{CF}$ 16.8, C-6), 146.2 (d, $^1J_{CF}$ 264.9, C-5), 132.2 (s, Ar CH), 129.8 (s, Ar CH), 128.9 (s, Ar CH), 127.4 (s, Ar C), 117.4 (d, $^3J_{CF}$ 5.3, C-3*a*), 110.1 (d, $^3J_{CF}$ 4.6, CN), 109.3 (s, C-3), 106.2 (dd, $^2J_{CF}$ 14.8, $^3J_{CF}$ 3.8, C-4), 62.1 (s, CH_2), 14.4 (s, CH_3); *m/z* (EI$^+$) 328 ([M]$^+$, 84), 283 ([M-OCH_2CH_3]$^+$, 100).

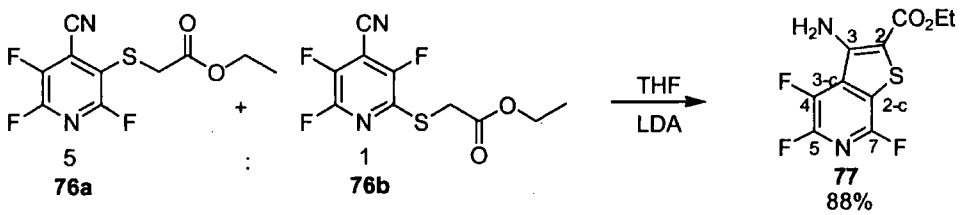
Preparation of Ethyl[(4-cyano-2,5,6-trifluoropyridin-3-yl)sulfanyl]acetate 76a and ethyl[(4-cyano-3,5,6-trifluoropyridin-2-yl)sulfanyl]acetate 76b



Sodium methoxide (0.61 g, 11.36 mmol) and mercapto-acetic acid ethyl ester (0.68 g, 5.68 mmol) were added to dry tetrahydrofuran (50 ml) and the resulting solution was stirred at room temperature for 1 h. 2,3,5,6-Tetrafluoropyridine-4-carbonitrile (1.0 g, 5.68 mmol) in tetrahydrofuran (50 ml) was added and the resulting solution was stirred at room temperature for 1 d before refluxing for 4 h. ^{19}F NMR indicated 84% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (40

ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (0.83 g) consisting of three major components in the ratio 4:1:2.5 which were identified as *ethyl[(4-cyano-2,5,6-trifluoropyridin-3-yl)sulfanyl]acetate* **76a**; δ_F -63.03 (1F, dd, $^3J_{FF}$ 29.3, $^4J_{FF}$ 11.3, F-6), -81.75 (1F, dd, $^4J_{FF}$ 22.6, $^5J_{FF}$ 11.3, F-2), -135.46 (1F, dd, $^3J_{FF}$ 27.1, $^5J_{FF}$ 20.3, F-5); *m/z* (EI^+) 276 ($[M]^+$, 66), 203 ($[M\text{-}CO_2CH_2CH_3]^+$, 100); *ethyl[(4-cyano-3,5,6-trifluoropyridin-2-yl)sulfanyl]acetate* **76b**; δ_F -85.95 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 22.6, F-6), -116.45 (1F, dd, $^3J_{FF}$ 31.6, $^4J_{FF}$ 4.5, F-5), -137.61 (1F, dd, $^4J_{FF}$ 22.6, $^5J_{FF}$ 4.5, F-3); *m/z* (EI^+) 276 ($[M]^+$, 4), 203 ($[M\text{-}CO_2CH_2CH_3]^+$, 16); and *(4-cyano-6-ethoxycarbonylmethylsulfanyl-2,5-difluoro-pyridin-3-ylsulfanyl)-acetic acid ethyl ester* **76c**; δ_F -64.35 (1F, d, $^5J_{FF}$ 29.3, F-2), -118.85 (1F, d, $^5J_{FF}$ 29.1, F-5). Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate followed by 4:1 *n*-hexane/ethyl acetate) gave a mixture of *ethyl[(4-cyano-2,5,6-trifluoropyridin-3-yl)sulfanyl]acetate* **76a** and *ethyl[(4-cyano-3,5,6-trifluoropyridin-2-yl)sulfanyl]acetate* **76b** in the ratio 5:1 respectively (0.55 g, 35%) as a yellow oil.

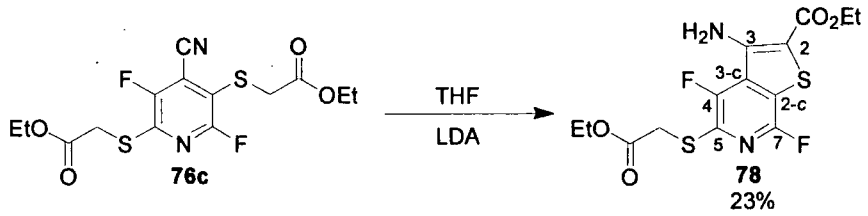
Preparation of Ethyl 3-Amino-4,5,7-trifluorothieneo[2,3-*c*]pyridine-2-carboxylate 77



A mixture of Ethyl[(4-cyano-2,5,6-trifluoropyridin-3-yl)sulfanyl]acetate **76a** and ethyl[(4-cyano-3,5,6-trifluoropyridin-2-yl)sulfanyl]acetate **76b** (0.08 g, 0.29 mmol) was added to a solution of 1.8 M lithium diisopropylamide (0.32, 0.58 mmol) in dry tetrahydrofuran (200 ml) at -78°C and stirred at this temperature for 2 h. The reaction mixture was warmed to

room temperature and stirred for 2 d, after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was concentrated, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a brown/yellow solid (0.12 g) consisting of one major component. Purification by preparative TLC on silica gel (4:1 *n*-hexane/ethyl acetate) gave *ethyl 3-amino-4,5,7-trifluorothieneo[2,3-c]pyridine-2-carboxylate* **77** (0.07 g, 88%) as a yellow solid; mp 104.1-105.6°C; δ_F -71.69 (1F, dd, $^3J_{FF}$ 29.3, $^4J_{FF}$ 11.3, F-5), -100.52 (1F, dd, $^4J_{FF}$ 20.3, $^5J_{FF}$ 13.5, F-7), -158.14 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 20.3, F-4); δ_H 6.13 (2H, br s, NH_2), 4.32 (2H, q, $^3J_{HH}$ 7.0, CH_2), 1.33 (3H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 163.2 (s, C=O), 147.9 (ddd, $^1J_{CF}$ 245.2, $^2J_{CF}$ 13.4, $^3J_{CF}$ 2.4, C-5), 144.6 (m, C-3), 143.4 (ddm, $^1J_{CF}$ 239.9, $^3J_{CF}$ 13.4, C-7), 137.5 (ddd, $^1J_{CF}$ 257.2, $^2J_{CF}$ 27.3, $^4J_{CF}$ 7.2, C-4), 131.7 (ddd, $^2J_{CF}$ 12.1, $^3J_{CF}$ 7.2, $^3J_{CF}$ 2.4, C-3*a*), 117.9 (dd, $^2J_{CF}$ 39.3, $^3J_{CF}$ 4.3, C-7*a*), 103.6 (s, C-2), 60.4 (s, CH_2), 13.3 (s, CH_3); *m/z* (EI^+) 276 ($[M]^+$, 50), 230 ($[M-CH_3CH_2OH]^+$, 100).

Preparation of 3-Amino-5-ethoxycarbonylmethylsulfanyl-4,7-difluoro-thieno[2,3-*c*]pyridine-2-carboxylic acid ethyl ether 78

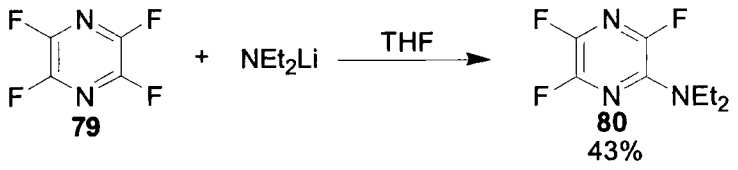


Diethyl 2,2'-[(4-cyano-3,6-difluoropyridine-2,5-diyl)disulfanediyl]diacetate **76c** (0.22 g, 0.59 mmol) and a 1.8 M solution of lithium diisopropylamide in *n*-hexane (1.3 ml, 2.34 mmol) were added to dry tetrahydrofuran under argon at -78°C. The reaction mixture was stirred for 1 h before warming to room temperature and stirring for 17 h, after which time

^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was concentrated, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow oil (0.28 g) consisting of one major component. Purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate) followed by recrystallisation from ethyl acetate gave *3-amino-5-ethoxycarbonylmethylsulfanyl-4,7-difluoro-thieno[2,3-c]pyridine-2-carboxylic acid ethyl ether* **78** (50 mg, 23%) as a yellow solid; mp 110.2-111.5°C; ($[M+H]^+$ 377.0435, $C_{14}H_{14}N_2O_4F_2S_2$ requires $[M+H]^+$ 377.0436); δ_F -71.35 (1F, d, $^5J_{FF}$ 31.6, F-7), -137.26 (1F, d, $^5J_{FF}$ 31.6, F-4); δ_H 6.20 (2H, br s, NH_2), 4.37 (2H, q, $^3J_{HH}$ 7.2, CH_2CH_3), 4.22 (2H, q, $^3J_{HH}$ 7.2, CH_2CH_3), 3.95 (2H, s, SCH_2), 1.39 (3H, t, $^3J_{HH}$ 6.8, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3); δ_C 169.2 (s, C=O), 164.7 (s, C=O), 152.5 (d, $^1J_{CF}$ 238.0, C-7), 150.2 (dd, $^1J_{CF}$ 251.9, $^4J_{CF}$ 5.6, C-4), 145.6 (s, C-2), 134.2 (dd, $^2J_{CF}$ 22.5, $^3J_{CF}$ 13.4, C-5), 131.1 (s, C-3), 130.5 (dd, $^2J_{CF}$ 14.3, $^3J_{CF}$ 7.1, C-7*a*), 118.9 (d, $^2J_{CF}$ 41.4, C-3*a*), 62.1 (s, CH_2CH_3), 61.5 (s, CH_2CH_3), 32.7 (s, SCH_2), 14.6 (s, CH_2CH_3), 14.3 (s, CH_2CH_3); *m/z* (EI^+) 376 ($[M]^+$, 58), 331 ($[M-CH_3CH_2O]^+$, 16), 303 ($[M-CO_2CH_2CH_3]^+$, 100), 257 ($[M-SCH_2CO_2CH_2CH_3]^+$, 42).

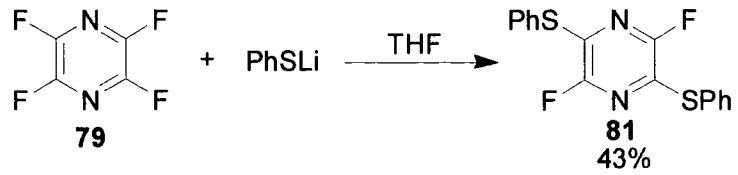
EXPERIMENTAL TO CHAPTER 6

Preparation of *N,N'*-Diethyl-3,5,6-trifluoropyrazin-2-amine 80



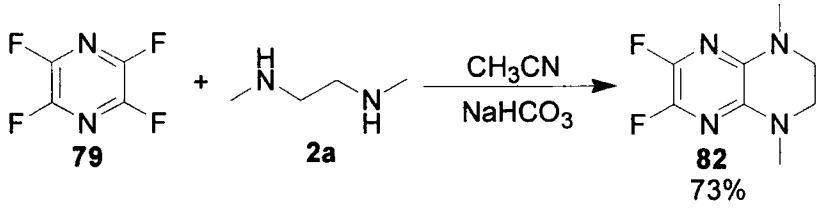
A 1.6 M solution of butyl lithium in tetrahydrofuran (3.75 ml, 6.0 mmol) was added to a solution of diethylamine (0.44 g, 6.0 mmol) in tetrahydrofuran (5 ml) at -78°C. The resulting solution was warmed to room temperature, 2,3,5,6-tetrafluoropyrazine **79** (1.0 g, 6.58 mmol) was added and the reaction mixture stirred for 19 h after which time ^{19}F NMR indicated 100% conversion of starting material. The solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil (0.62 g) consisting of one major component. Purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave *N,N'-diethyl-3,5,6-trifluoropyrazin-2-amine* **80** (0.58 g, 43%) as a colourless oil; ($[M]^+$ 205.0818, $C_8H_{10}N_3F_3$ requires $[M]^+$ 205.0821); δ_F -87.73 (1F, dd, $^3J_{FF}$ 49.3, $^5J_{FF}$ 10.9, F-6), -99.65 (1F, dd, $^3J_{FF}$ 49.3, $^4J_{FF}$ 17.3, F-5), -115.40 (1F, m, F-3); δ_H 3.44 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, CH_2), 1.14 (6H, $^3J_{HH}$ 7.5, CH_3); δ_C 141.5 (ddd, $^1J_{CF}$ 240.0, $^2J_{CF}$ 28.5, $^4J_{CF}$ 3.8, C-6), 139.5 (dd, $^2J_{CF}$ 23.4, $^3J_{CF}$ 9.5, C-2), 138.6 (dt, $^1J_{CF}$ 252.6, $^3J_{CF}$ 3.3, C-3), 132.2 (ddd, $^1J_{CF}$ 243.1, $^2J_{CF}$ 36.3, $^3J_{CF}$ 6.1, C-5), 44.7 (d, $^4J_{CF}$ 5.6, CH_2), 13.7 (s, CH_3); *m/z* (EI^+) 205 ($[M]^+$, 41), 190 ($[M\text{-}CH_3]^+$, 100), 162 ($[M\text{-}NCH_2CH_3]^+$, 92).

Preparation of 2,5-Difluoro-3,6-bis(phenylsulfanyl)pyrazine 81



1.0 M Lithium thiophenoxide (6.0 ml, 6.0 mmol) was added to 2,3,5,6-tetrafluoropyrazine **79** (1.0 g, 6.58 mmol) at 0°C, before refluxing for 18 h. ^{19}F NMR indicated 100% conversion of starting material so the reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), and the resulting precipitate was collected to give *2,5-difluoro-3,6-bis(phenylsulfanyl)pyrazine* **81** (0.9 g, 43%) as a yellow solid; mp >220°C; ($[M]^+$ 332.0247, $C_{16}H_{10}N_2F_2S_2$ requires $[M]^+$ 332.0248); δ_F (d_6-DMSO) -80.76 (2F, s, F-2,5); δ_H (d_6-DMSO) 7.20-7.60 (10H, m, Ar CH); δ_C (d_6-DMSO) 153.4 (dd, $^1J_{CF}$ 251.2, $^4J_{CF}$ 9.1, C-2,5), 135.9 (t, $^2J_{CF}$ 25.6, C-3,6), 134.6 (s, Ar CH), 130.4 (s, Ar CH), 130.3 (s, Ar CH), 127.9 (s, Ar C); *m/z* (EI^+) 332 ($[M]^+$, 8), 77 ($[M-C_{10}H_5N_2F_2S_2]^+$, 100).

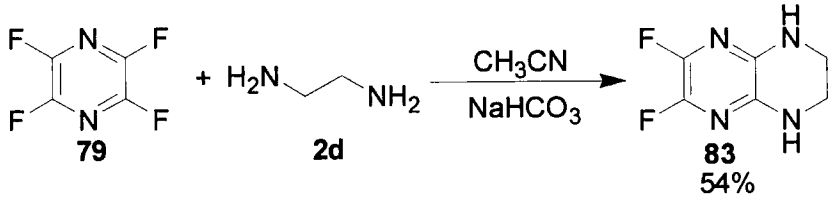
Preparation of 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydro-pyrazino[2,3-*b*]pyrazine 82



N,N'-Dimethylethylenediamine **2a** (1.45 g, 16.45 mmol) and sodium hydrogencarbonate (2.76 g, 32.9 mmol) were added to a solution of 2,3,5,6-tetrafluoropyrazine **79** (1.25 g, 8.22 mmol) in acetonitrile (300 ml). The reaction mixture was stirred at room temperature for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The solvent

was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as an orange solid (3.32 g) consisting of one major component. Purification by recrystallisation from dichloromethane gave *6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydro-pyrazino[2,3-b]pyrazine* **82** (1.19 g, 73%) as a yellow solid; mp 118.2-119.5°C; (Found: C, 47.9; H, 5.0; N, 27.7; $C_8H_{10}N_4F_2$ requires: C, 48.0; H, 5.0; N, 28.0%); δ_F -118.60 (2F, s, F-6,7); δ_H 3.43 (4H, s, CH_2), 3.01 (6H, s, CH_3); δ_C 138.5 (t, $^3J_{CF}$ 5.3, C-4*a*,8*a*), 136.7 (d, $^1J_{CF}$ 229.1, C-6), 136.3 (d, $^1J_{CF}$ 229.1, C-7), 46.9 (s, CH_2), 36.7 (s, CH_3); *m/z* (EI^+) 200 ($[M]^+$, 100), 185 ($[M-CH_3]^+$, 90), 171 ($[M-CH_2CH_3]^+$, 64).

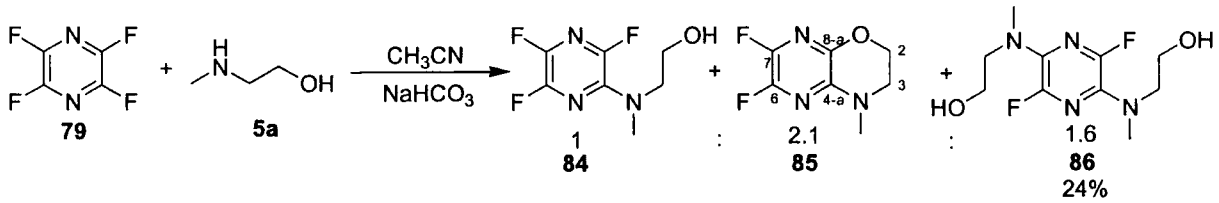
Preparation of 6,7-Difluoro-1,2,3,4-tetrahydro-pyrazino[2,3-*b*]pyrazine 83



Ethylenediamine **2d** (1.13 g, 18.8 mmol) and sodium hydrogencarbonate (3.16 g, 37.6 mmol) were added to a solution of 2,3,5,6-tetrafluoropyrazine **79** (1.43 g, 9.41 mmol) in acetonitrile (300 ml). The reaction mixture was stirred at room temperature for 3.5 h before refluxing for 2 d. ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), and the resulting precipitate was collected to give *6,7-difluoro-1,2,3,4-tetrahydro-pyrazino[2,3-b]pyrazine* **83** (0.86 g, 54%) as a yellow solid; mp >250°C; ($[M+H]^+$ 173.0637, $C_6H_6N_4F_2$ requires $[M+H]^+$ 173.0633); δ_F(DMSO-d_6) -118.2 (2F, s, F-6,-7); δ_H(DMSO-d_6) 7.12 (2H,

s, NH), 3.28 (4H, s, CH_2); δ_C(DMSO-d_6) 138.4 (t, $^3J_{CF}$ 6.1, C-4*a*,-8*a*), 135.9 (d, $^1J_{CF}$ 225.6, C-6), 135.6 (d, $^1J_{CF}$ 225.2, C-7), 39.3 (s, CH_2); *m/z* (EI^+) 172 ($[M]^+$, 24).

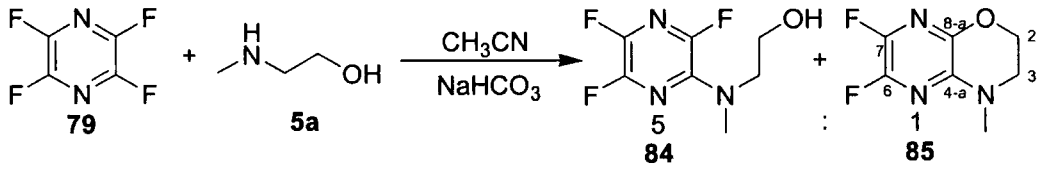
Preparation of 2-({3,6-Difluoro-5-[(2-hydroxy-ethyl)-methyl-amino]-pyrazin-2-yl}-methyl-amino)-ethanol 86



2-Methylaminoethanol **5a** (1.07 g, 14.2 mmol) and sodium hydrogencarbonate (2.39 g, 28.4 mmol) were added to a solution of 2,3,5,6-tetrafluoropyrazine **79** (1.08 g, 7.11 mmol) in acetonitrile (300 ml). The reaction mixture was refluxed for 2 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown oil/solid (1.33 g) consisting of three major components in the ratio 1:2.1:1.6 which were identified as *2-[methyl-(3,5,6-trifluoro-pyrazin-2-yl)-amino]-ethanol* **84**; δ_F -85.00 (1F, dd, $^3J_{FF}$ 49.6, $^5J_{FF}$ 11.3, F-6), -99.58 (1F, $^3J_{FF}$ 49.6, $^4J_{FF}$ 15.8, F-5), -113.84 (1F, t, $^4J_{FF}$ 11.3, F-3); *m/z* (EI^+) 207 ($[M]^+$, 56), 176 ($[M\text{-}CH_2OH]^+$, 100); *6,7-difluoro-4-methyl-3,5-dihydro-2H-pyrazino[2,3-b][1,4]oxazine* **85**; δ_F -107.16 (1F, d, $^3J_{FF}$ 18.0, F-6), -115.07 (1F, d, $^3J_{FF}$ 18.0, F-7); *m/z* (EI^+) 187 ($[M]^+$, 90); and *2-({3,6-difluoro-5-[(2-hydroxy-ethyl)-methyl-amino]-pyrazin-2-yl}-methyl-amino)-ethanol* **86**. Purification by column chromatography on silica gel (1:3 *n*-hexane/ethyl acetate) followed by preparative TLC (1:3 *n*-hexane/ethyl acetate) gave *2-({3,6-difluoro-5-[(2-hydroxy-ethyl)-methyl-amino]-*

pyrazin-2-yl}-methyl-amino)-ethanol **86** (0.45 g, 24%) as a yellow oil; ($[M]^+$ 262.1237, $C_{10}H_{16}N_4F_2O_2$ requires $[M]^+$ 262.1236); δ_F -88.17 (2F, s, F-3,6); δ_H 3.72 (4H, t, $^3J_{HH}$ 5.5, CH_2), 3.42 (4H, t, $^3J_{HH}$ 5.0, CH_2), 2.96 (6H, s, CH_3), 2.50 (2H, br s, OH); δ_C 142.2 (dd, $^1J_{CF}$ 252.6, $^4J_{CF}$ 13.8, C-3,6), 132.4 (t, $^2J_{CF}$ 18.1, C-3,5), 59.3 (s, CH_2), 53.4 (s, CH_2), 37.3 (s, CH_3); *m/z* (EI^+) 262 ($[M]^+$, 76), 231 ($[M\text{-}CH_2OH]^+$, 100).

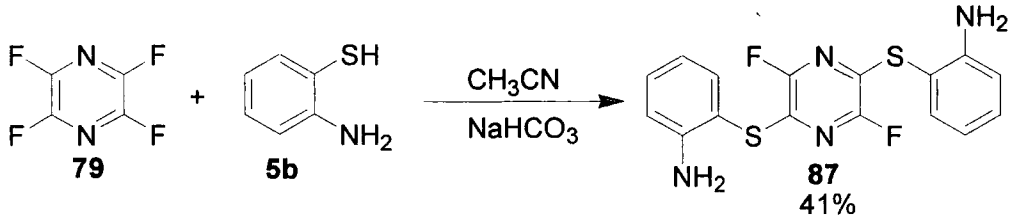
Preparation of 2-[Methyl-(3,5,6-trifluoro-pyrazin-2-yl)-amino]-ethanol 84



2-Methylaminoethanol **5a** (0.49 g, 6.58 mmol) and sodium hydrogencarbonate (1.11 g, 13.16 mmol) were added to a solution of 2,3,5,6-tetrafluoropyrazine **79** (1.0 g, 6.58 mmol) in acetonitrile (300 ml). The reaction mixture was refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (1.33 g) consisting of two major components in the ratio 5:1 which were identified as *2-[methyl-(3,5,6-trifluoro-pyrazin-2-yl)-amino]-ethanol* **84**; δ_F -90.01 (1F, dd, $^3J_{FF}$ 49.6, $^5J_{FF}$ 11.3, F-6), -99.57 (1F, dd, $^3J_{FF}$ 47.4, $^4J_{FF}$ 18.0, F-5), -113.79 (1F, dd, $^4J_{FF}$ 15.8, $^5J_{FF}$ 11.3, F-3); δ_H 3.87 (2H, t, $^3J_{HH}$ 5.5, CH_2), 3.69 (2H, t, $^3J_{HH}$ 5.0, CH_2), 3.22 (3H, d, $^5J_{HF}$ 3.0, CH_3), 1.92 (1H, br s, OH); δ_C 141.3 (ddd, $^1J_{CF}$ 243.2, $^2J_{CF}$ 28.7, $^4J_{CF}$ 3.8, C-6), 140.5 (ddd, $^2J_{CF}$ 24.1, $^3J_{CF}$ 8.6, $^4J_{CF}$ 2.8, C-2), 139.1 (dt, $^1J_{CF}$ 255.3, $^3J_{CF}$ 3.4, C-3), 132.9 (ddd, $^1J_{CF}$ 246.6, $^2J_{CF}$ 36.0, $^3J_{CF}$ 6.2, C-5), 60.8 (s, CH_2), 54.1 (d, $^4J_{CF}$ 5.3, CH_2), 38.8 (d,

$^4J_{CF}$ 6.7, CH_3); *m/z* (EI^+) 207 ($[M]^+$, 60), 176 ($[M-CH_2OH]^+$, 100); and *6,7-difluoro-4-methyl-3,5-dihydro-2H-pyrazino[2,3-b][1,4]oxazine* **85**; data as before. Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) was unsuccessful and gave a mixture of *2-[methyl-(3,5,6-trifluoro-pyrazin-2-yl)-amino]-ethanol* **84** and *6,7-difluoro-4-methyl-3,5-dihydro-2H-pyrazino[2,3-b][1,4]oxazine* **85** (1.09 g, 80%) in the ratio 5:1 respectively as a yellow oil

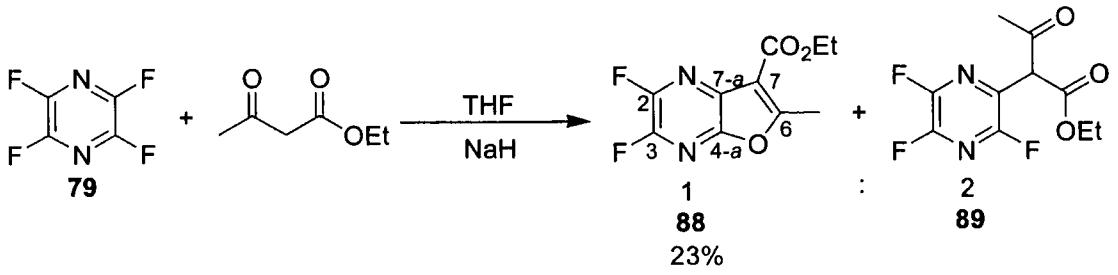
Preparation of 2,2'-[(3,6-Difluoropyrazine-2,5-diyl)disulfanediyl]dianiline 87



2-Amino-benzenethiol **5b** (0.59 g, 4.74 mmol) and sodium hydrogencarbonate (0.80 g, 9.47 mmol) were added to a solution of 2,3,5,6-tetrafluoropyrazine **79** (0.72 g, 4.74 mmol) in acetonitrile (300 ml). The reaction mixture was refluxed for 19 h after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow/brown solid (0.76 g) consisting of one major component. Purification by recrystallisation from acetone gave *2,2'-[(3,6-difluoropyrazine-2,5-diyl)disulfanediyl]dianiline* **87** (0.7 g, 41%) as a yellow solid; mp >220°C; (Found: C, 52.9; H, 3.3; N, 15.5; $C_{16}H_{12}N_4F_2S_2$ requires: C, 53.0; H, 3.3; N, 15.5%); δ_F(DMSO-d_6) -82.10 (2F, s, F-3,6); δ_H(DMSO-d_6) 7.24 (2H, dd, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.5, Ar CH), 7.18 (2H, td, $^3J_{HH}$ 6.9, $^4J_{HH}$ 1.5, Ar CH), 6.76 (2H, dd, $^3J_{HH}$ 8.1, $^4J_{HH}$ 1.2, Ar CH), 6.55 (2H, td, $^3J_{HH}$ 7.2,

$^4J_{HH}$ 1.2, Ar CH), 5.45 (4H, br s, NH_2); δ_C(DMSO-d_6) 153.6 (dd, $^1J_{CF}$ 252.0, $^4J_{CF}$ 9.3, C-3,6), 151.9 (s, Ar CS), 137.9 (s, Ar CH), 135.1 (m, C-2,5), 132.5 (s, Ar CH), 117.0 (s, Ar CH), 115.8 (s, Ar CH), 106.8 (s, $ArCNH_2$); *m/z* (EI^+) 363 ($[M+H]^+$, 100).

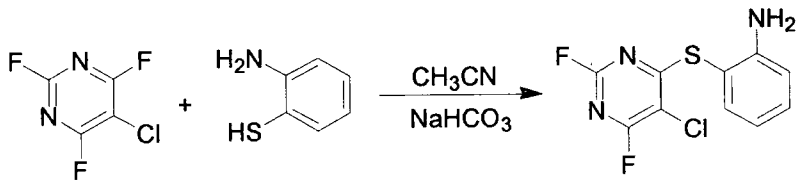
Preparation of Ethyl 2,3-Difluoro-6-methylfuro[2,3-*b*]pyrazine-7-carboxylate 88



Ethylacetoacetate (0.90 g, 6.91 mmol) and sodium hydride 60% in mineral oil (0.33 g, 8.29 mmol) were added to tetrahydrofuran (100 ml) and stirred for 15 min before the addition of 2,3,5,6-tetrafluoropyrazine **79** (1.05 g, 6.91 mmol). The reaction mixture was stirred at room temperature for 17.5 h, after which time ^{19}F NMR indicated 100% conversion of starting material. The solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as an orange oil (1.34 g) consisting of two major components in the ratio 1:2 which were identified as *ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate* **88**; and *3-oxo-2-(3,5,6-trifluoro-pyrazin-2-yl)-butyric acid ethyl ester* **89**; δ_F -79.96 (1F, dd, $^3J_{FF}$ 43.8, $^5J_{FF}$ 9.0, F-6), -91.39 (1F, dd, $^3J_{FF}$ 20.1, $^5J_{FF}$ 8.1, F-3), -94.86 (1F, dd, $^3J_{FF}$ 42.9, $^4J_{FF}$ 19.9, F-5); *m/z* (EI^+) 262 ($[M]^+$, 41), 174 ($[M-(CH_3)_2CH_2CO_2]^+$, 100). Purification by column chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) gave *ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate* **88** (0.45 g, 27%) as a white solid; mp 98.9-102.4°C; (Found: C, 49.7; H, 3.4; N, 11.4;

$C_{10}H_8N_2F_2O_3$ requires: C, 49.6; H, 3.3; N, 11.6%); δ_F -93.26 (1F, d, $^3J_{FF}$ 22.0, F-2), -95.61 (1F, d, $^3J_{FF}$ 22.0, F-3); δ_H 4.43 (2H, q, $^3J_{HH}$ 7.2, CH_2), 2.86 (3H, s, 6-CH_3), 1.42 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3); δ_C 168.5 (d, $^5J_{CF}$ 5.4, C-6), 161.9 (s, C=O), 147.3 (dd, $^3J_{CF}$ 8.0, $^4J_{CF}$ 1.9, C-4*a*), 146.5 (dd, $^1J_{CF}$ 245.9, $^2J_{CF}$ 28.2, C-2), 143.5 (dd, $^1J_{CF}$ 257.0, $^2J_{CF}$ 34.0, C-3), 131.6 (dd, $^3J_{CF}$ 11.8, $^4J_{CF}$ 5.3, C-7*a*), 109.7 (s, C-7), 61.5 (s, CH_2), 15.4 (s, CH_3), 14.5 (s, CH_2CH_3); *m/z* (EI^+) 242 ($[M]^+$, 44).

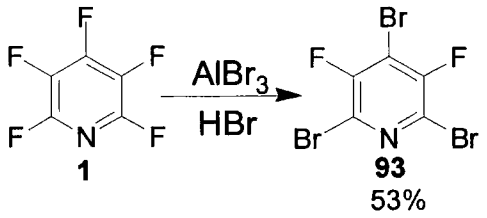
Preparation of 2-(5-Chloro-2,6-difluoro-pyrimidin-4-ylsulfanyl)-phenylamine 92



2-Amino-benzenethiol **5b** (0.31 g, 2.5 mmol) and sodium hydrogencarbonate (0.42 g, 5.0 mmol) were added to a solution of 5-chloro-2,4,6-trifluoropyrimidine **90** (0.42 g, 2.5 mmol) in acetonitrile (150 ml). The reaction mixture was refluxed for 1 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow/brown solid (0.76 g) consisting of one major component. Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave *2-(5-chloro-2,6-difluoro-pyrimidin-4-ylsulfanyl)-phenylamine* **92** (0.13 g, 19%) as a white solid; $\delta_F(CD_3CN)$ -46.67 (1F, s, F-2), -65.34 (1F, s, F-6); $\delta_H(CD_3CN)$ 7.31 (2H, m, Ar H), 6.88 (1H, dm, $^3J_{HH}$ 8.0, Ar H), 6.74 (1H, tm, $^3J_{HH}$ 7.5, Ar H), 4.67 (2H, br s, NH_2); $\delta_C(CD_3CN)$

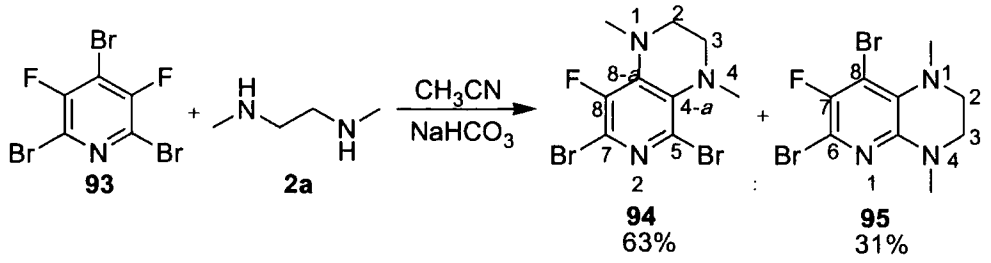
175.1 (dd, $^{2}J_{CF}$ 14.4, $^{4}J_{CF}$ 2.8, C-5), 165.4 (dd, $^{1}J_{CF}$ 250.9, $^{3}J_{CF}$ 16.6, C-2), 158.2 (dd, $^{1}J_{CF}$ 219.4, $^{4}J_{CF}$ 19.0, C-6), 150.9 (s, Ar C), 137.4 (s, Ar CH), 132.8 (s, Ar CH), 115.7 (s, Ar CH), 109.1 (dd, $^{3}J_{CF}$ 28.4, $^{3}J_{CF}$ 8.2, C-4), 107.2 (s, Ar C); *m/z* (EI^{+}) 273.5 ($[M]^{+}$, 67).

Preparation of 2,4,6-Tribromo-3,5-difluoropyridine 93



A hastalloy autoclave (equipped with a teflon gasket and an inconel bursting disc) was charged with aluminium bromide (50.0 g, 0.187 mol), pentafluoropyridine **1** (20.0 g, 0.118 mol) and hydrogen bromide (25.0 g, 0.31 mol). The autoclave was heated to 150°C for 3 d after which time the reaction mixture was cooled and excess gaseous hydrogen bromide was neutralised by release through a solution of aqueous sodium hydrogen carbonate. The autoclave was opened and ice water was added to the solid contents. The aqueous layer was then extracted with a large volume of dichloromethane, dried over magnesium sulfate, evaporated to dryness and purification by recrystallisation from dichloromethane gave *2,4,6-tribromo-3,5-difluoropyridine* **93** (21.8 g, 53%) as white crystals; mp 107.8-109.4°C; (Found: C, 17.0; N, 4.3; $C_5NBr_3F_2$ requires: C, 17.2; N, 4.0%); δ_F –103.64 (2F, s, F-3,5); δ_C 153.9 (dd, $^{1}J_{CF}$ 262.2, $^{3}J_{CF}$ 0.8, C-3,5), 122.8 (dt, $^{2}J_{CF}$ 20.6, $^{4}J_{CF}$ 6.1, C-2,6), 110.4 (t, $^{2}J_{CF}$ 24.0, C-4); *m/z* (EI^{+}) 349 ($[M]^{+}$, 100), 270 ($[M\text{-}Br]^{+}$, 82), 191 ($[M\text{-}Br_2]^{+}$, 88), 112 ($[M\text{-}Br_3]^{+}$, 84).

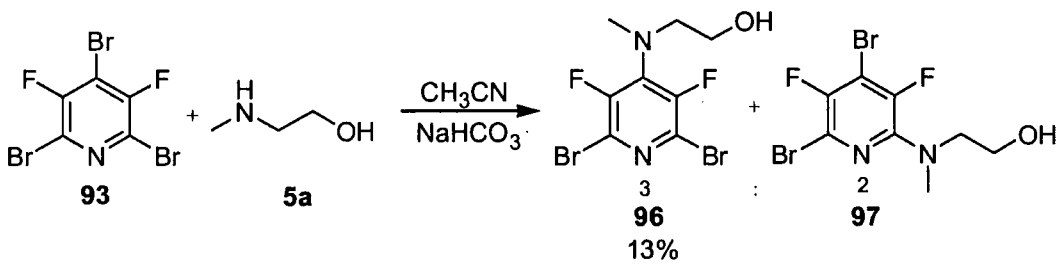
Preparation of 5,7-dibromo-8-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine 94 and 6,8-dibromo-7-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 95



N,N'-dimethylethylenediamine **2a** (1.76 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. 2,4,6-Tribromo-3,5-difluoropyridine **93** (3.49 g, 10 mmol) was added and the resulting solution was refluxed for 4 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a brown/yellow solid (3.18 g) consisting of two major components in the ratio 2:1 which were identified as *5,7-dibromo-8-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **94**; and *6,8-dibromo-7-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **95**. Purification by column chromatography on silica gel (3:2 *n*-hexane/ethyl acetate) gave *5,7-dibromo-8-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine* **94** (2.12 g, 63%) as needle-like white crystals; mp 98.4-100.1°C; (Found: C, 32.0; H, 3.0; N, 12.4. $C_9H_{10}N_3Br_2F$ requires: C, 32.0; H, 3.0; N, 12.5%); δ_F -128.29 (1F, d, $^5J_{HF}$ 4.5, F-8); δ_H 3.30 (2H, t, $^3J_{HH}$ 4.8, CH_2), 3.28 (3H, d, $^5J_{HF}$ 5.4, CH_3), 3.04 (2H, t, $^3J_{HH}$ 5.1, CH_2), 2.75 (3H, s, CH_3); δ_C 144.4 (d, $^1J_{CF}$

200.7, C-8), 138.4 (d, $^2J_{CF}$ 5.4, C-8*a*), 132.3 (d, $^3J_{CF}$ 1.5, C-4*a*), 131.7 (d, $^4J_{CF}$ 1.2, C-5), 122.9 (d, $^2J_{CF}$ 21.0, C-7), 47.8 (s, CH_2), 45.5 (s, CH_2), 43.1 (s, 4-NCH_3), 41.5 (d, $^4J_{CF}$ 10.7, 1-NCH_3); *m/z* (EI^+) 339 ($[M]^+$, 100), 324 ($[M\text{-}CH_3]^+$, 25), 309 ($[M\text{-}(CH_3)_2]^+$, 12); and *6,8-dibromo-7-fluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **95** (1.06 g, 31%) as needle-like yellow crystals; mp 94.8-95.9°C; (Found: C, 32.0; H, 3.0; N, 12.5. $C_9H_{10}N_3Br_2F$ requires: C, 32.0; H, 3.0; N, 12.5%); δ_F -123.02 (1F, s, F-7); δ_H 3.36 (2H, t, $^3J_{HH}$ 4.5, CH_2), 3.15 (3H, s, CH_3), 3.07 (2H, t, $^3J_{HH}$ 4.8, CH_2), 2.78 (3H, s, CH_3); δ_C 148.2 (s, C-4*a*), 146.4 (s, C-8*a*), 144.5 (s, C-6), 129.3 (s, C-8), 117.0 (dd, $^1J_{CF}$ 434, $^2J_{CF}$ 26.3, C-7), 48.3 (s, CH_3), 43.4 (s, CH_2), 43.2 (s, CH_3), 37.0 (s, CH_2); *m/z* (EI^+) 339 ($[M]^+$, 100), 324 ($[M\text{-}CH_3]^+$, 85), 309 ($[M\text{-}(CH_3)_2]^+$, 13).

Preparation of 2-[(2,6-dibromo-3,5-difluoropyridin-4-yl)(methyl)amino]ethanol 96



2-Methylaminoethanol **5a** (1.5 g, 20 mmol) and sodium hydrogencarbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. 2,4,6-Tribromo-3,5-difluoropyridine **93** (3.49 g, 10 mmol) was added and the resulting solution was refluxed for 3 d after which time ^{19}F NMR indicated 100% conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto 1.0 M hydrochloric acid (50 ml), extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and the solvent evaporated to dryness to yield the crude product as a yellow oil (3.14 g) consisting

of two major components in the ratio 3:2 which were identified as *2-[(2,6-dibromo-3,5-difluoropyridin-4-yl)(methyl)amino]ethanol* **96**; and *2-[(4,6-dibromo-3,5-difluoro-pyridin-2-yl)-methyl-amino]-ethanol* **97**; δ_F -123.8 (1F, d, $^4J_{FF}$ 3.6, F-5), -120.7 (1F, t, $^4J_{FF}$ 3.8, F-3); *m/z* (EI^+) 346 ($[M]^+$, 24), 315 ($[M\text{-}CH_2OH]^+$, 100), 234 ($[M\text{-}CH_2OHBr]^+$, 19), 155 ($[M\text{-}CH_2OHBr_2]^+$, 78). Purification by column chromatography on silica gel (1:2 *n*-hexane/ethyl acetate) gave *2-[(2,6-dibromo-3,5-difluoropyridin-4-yl)(methyl)amino]ethanol* **96** (0.44 g, 13%) as white crystals; mp 73.1-75.3°C; (Found: C, 27.7; H, 2.3; N, 8.1. $C_8H_8N_2Br_2F_2O$ requires: C, 27.9; H, 2.3; N, 8.1%); δ_F -120.75 (2F, s, F-3,5); δ_H 3.86 (2H, t, $^3J_{HH}$ 5.4, NCH_2), 3.50 (2H, t, $^3J_{HH}$ 5.4, CH_2O), 3.14 (3H, t, $^5J_{HF}$ 3.3, CH_3), 1.62 (1H, br s, OH); δ_C 148.4 (dd, $^1J_{CF}$ 256.1, $^3J_{CF}$ 3.8, C-3,5), 137.5 (t, $^2J_{CF}$ 11.5, C-4), 123.6 (dd, $^2J_{CF}$ 24.4, $^4J_{CF}$ 9.6, C-2,6), 60.5 (d, $^5J_{CF}$ 1.5, CH_2OH), 56.8 (t, $^4J_{CF}$ 4.4, NCH_2), 41.1 (t, $^4J_{CF}$ 5.3, NCH_3); *m/z* (EI^+) 344 ($[M]^+$, 15), 313 ($[M\text{-}CH_2OH]^+$, 100).