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A Thesis Entitled

Polyfunctional Heteroaromatic Fused Ring Systems

Submitted by

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(St Aidans College)

Department of Chemistry

A Candidate for the Degree of Doctor of Philosophy 2005

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I would like to thank my academic supervisor Dr Graham Sandford and my industrial supervisor Dr Antonio Vong for their invaluable help and support throughout this project. Thanks also go to the EPSRC and GlaxoSmithKline for funding, and to Professor Richard D Chambers and the other members of the research group past and present, namely: Miss Aurelie Baron, Mr Matthew Cartwright, Miss Gemma Clarke, Mr Christopher Hargreaves, Dr Darren Holling, Dr Christopher Murray, Dr Takashi Nakano, Miss Emma Parks, Mr Graham Pattison, Mr Andrzej Tadeusiak, Dr Jelena Trsćić and Dr Ian Wilson.

This research would not have been possible without the help of the technical staff, namely: Dr Alan Kenwright, Mr Ian McKeag and Mrs Catherine Heffernan (NMR); Dr Mike Jones and Miss Lara Turner (mass Spectrometry); Mrs Jarika Dostal (elemental analysis); Dr Dmitrii Yufit (X-ray crystallography), Mr Lenny Lauchlan (chromatography), Mr Malcolm Richardson and Mr Peter Coyne (glassblowing), Mr Barry Barker, Mr Kevin Appleby (electromechanical and electronics workshop); Mr Jim Hodgson and Mr Neil Holmes (mechanical workshop); Mr Dave Hunter (high pressure operations); Mr Tony Baxter and Mrs Elizabeth Wood (stores) and all the other people who worked and studied in the chemistry department and at GlaxoSmithKline who have not been mentioned.

I would also like to thank all my friends and family from Durham and around the world, especially my mum and dad for all their support throughout my time at university and the girls of 2 Highwood View, namely: Miss Lucy Wheatley, Miss Amy Thompson and Miss Rachel Roberts for providing endless entertainment, support and friendship.
MEMORANDUM

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


and has been presented at:

- XIVth European Symposium on Fluorine Chemistry, Poznan, Poland 2004
- 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

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

\[
\text{PFP} + \text{binucleophile} \rightarrow \text{product}
\]

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. 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. Lipinski has suggested that molecules are most likely to possess drug-like physiochemical properties if they obey the empirical 'rules of 5'. 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. Advances in parallel, combinatorial, rapid analogue, privileged structure and diversity oriented 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; 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.

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. For this reason the synthesis of such compounds has been the focus of a number of publications over recent decades.

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

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](image)

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](image)

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](image)
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.

<table>
<thead>
<tr>
<th>1,2-Dinucleophile</th>
<th>1,2-Dielectrophile</th>
<th>Conditions</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ClCN</td>
<td>CH₃CN</td>
<td>OCN</td>
</tr>
<tr>
<td>B</td>
<td>CF(CH₃)₂</td>
<td>Ethanol</td>
<td>OCF(CH₃)₂</td>
</tr>
<tr>
<td>C</td>
<td>OEt</td>
<td>Ethanol</td>
<td>OEt</td>
</tr>
<tr>
<td>D</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>2-CO₂Et (trace)</td>
</tr>
<tr>
<td>E</td>
<td>1) Et₃N, THF</td>
<td>2) K₂CO₃, acetone</td>
<td>3-CO₂Et (10%)</td>
</tr>
<tr>
<td>F</td>
<td>ClCO₂Et</td>
<td>DMF reflux</td>
<td>CO₂Et</td>
</tr>
<tr>
<td>G</td>
<td>Na⁺O⁻</td>
<td>DMF reflux</td>
<td>O⁻Na⁺</td>
</tr>
</tbody>
</table>

Table 1.1.1a Ring forming reactions of aromatic 1,2-dinucleophiles with 1,2-
dielectrophiles², 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.

<table>
<thead>
<tr>
<th>1,2-Dielectrophile</th>
<th>1,2-Dinucleophile</th>
<th>Conditions</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ( \text{N}^\text{N} \text{O} \text{H} \text{Ph} )</td>
<td>( \text{O}^\text{Ph} \text{O} \text{Ph} )</td>
<td>1) NaH, DMF 2) 10% Pd/C, H(_2), MeOH 3) DIAD, PPh(_3), THF</td>
<td>![Product Image]</td>
</tr>
<tr>
<td>B ( \text{Cl} \text{N} \text{Cl} \text{Et} )</td>
<td>( \text{X} ) X = NMe, O</td>
<td>DMF 100°C</td>
<td>![Product Image]</td>
</tr>
</tbody>
</table>

Table 1.1.2a Ring forming reactions of aromatic 1,2-dielectrophiles with 1,2-dinucleophiles

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.
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
Chapter 1

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. (Fig. 1.1.3b).

![Synthesis of functionalised 2,3-dihydro[1,4]dioxino[2,3-b]pyridine](image)

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).
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\textsuperscript{42} and as folic acid antagonists which may act as potential anti-cancer drugs.\textsuperscript{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.

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,\(^4^4\) and specifically, the molecules such as those shown below in Fig. 1.2.2a have exhibited \textit{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?](image)

Similarly, a separate class of polycyclic nitrogen containing heteroaromatics has been shown to cause regression in cancerous tumours (Fig. 1.2.2b)\(^4^5\) whilst related molecules have also shown activity against certain strains of tuberculosis.\(^4^6\)

![Fig. 1.2.2b Analogues of 10-deazaaminopterin exhibiting curative effects against human tumour xenografts](image)
Polycyclic nitrogen containing heteroaromatics have been reported to act against diseases such as epilepsy, strokes and Alzheimer's disease, and are proving attractive as potential antimalarial agents.

1.2.3) Selective Glycine Antagonists and Antimalarial Agents

Two pyrido[2,3-\textit{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-\textit{b}]pyrazine and pyrido[2,3-\textit{b}]pyrazine-N-oxide as selective glycine antagonists](image)

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

![Fig. 1.2.3b Synthesis of selective glycine antagonists](image)

Fig. 1.2.3c shows a particular compound that may be an effective 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. If a molecule can act as an antagonist for the production of this hormone then it could be used as an anti-depressant.

![Core structure of molecules investigated as anti-depressants](image)

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).
1.2.6) Pharmaceuticals based on a 10H-Benzop[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.

![Chemical structures](image)

**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.
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
Chapter 1

An 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, 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, 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 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.

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.

4) Fluorine and hydrogen have van der Waals radii of 1.47 Å and 1.20 Å respectively, 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.\textsuperscript{60} There is also evidence to suggest that fluorine can act as a hydroxyl group mimic.\textsuperscript{61,62}

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

\[ \text{Co}^{III} \rightarrow \text{Co}^{II} \]

![Fig. 1.4.1a Reaction scheme for the synthesis of PFP via saturation-rearomatisation by defluorination](image)

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%). 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](image)
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.\(^6^7\)

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\(^\%\)^\(^6^8\) (Fig. 1.4.3a).

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\(^\%\)^\(^6^9\) yield.

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). 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-5-triazine with cesium fluoride in tetrarglyme (Fig. 1.5.1b). The Meisenheimer complex formed in this case is stable at room temperature and can be observed by $^{19}$F NMR.

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-5-triazine with cesium fluoride in tetrarglyme (Fig. 1.5.1b). The Meisenheimer complex formed in this case is stable at room temperature and can be observed by $^{19}$F NMR.

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 \textit{para} to the site of nucleophilic attack are deactivating.\textsuperscript{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 \( \sigma \) bonds, \( \sigma \) effects. However, in situation (II) there are two opposing effects to consider,

\[
\begin{align*}
\text{(I)} & \quad \text{C} \quad \text{C} \rightarrow \text{F} \\
\text{(II)} & \quad \text{C} \rightarrow \text{F}
\end{align*}
\]

\textbf{Fig. 1.5.1c} Representation of fluorine ortho to and directly bonded to a carbanion site

the \( \sigma \) effects mentioned above, and \( \pi \) 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 \( \pi \) effects are greater for a planar \( \text{sp}^2 \) hybridised carbanion than for a tetrahedral \( \text{sp}^3 \) hybridised carbanion (Fig. 1.5.1d).

\textbf{Fig. 1.5.1d} Representation of the interactions between \( \text{sp}^3 \) and \( \text{sp}^2 \) hybridised carbanions and an adjacent fluorine atom

Overall, when fluorine is adjacent to an \( \text{sp}^3 \) hybridised carbanion it is stabilising, but when it is adjacent to an \( \text{sp}^2 \) hybridised carbanion it is destabilising.
So, in the case when a fluorine atom is \textit{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 \textit{para} fluorine atoms are deactivating.

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (a) at (0,0) {F};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (b) at (1,0) {Nuc};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (c) at (2,0) {F};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (d) at (2,1) {Nuc};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (e) at (2,2) {F};

  \draw (a) -- (b);  
  \draw (b) -- (c);  
  \draw (c) -- (d);  
  \draw (d) -- (e);
\end{tikzpicture}
\end{center}

\textbf{Fig. 1.5.1e} Destabilising influence of fluorine atom \textit{para} to site of nucleophilic attack

It would be expected that this would also be the case for a fluorine atom \textit{ortho} to the site of nucleophilic attack, however, this is not the case due to the large activating effect of \textit{ortho} fluorines in the initial state of the reaction. \textit{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 $\Pi$ repulsion observed in the transition state. Some studies suggest that the resonance canonical where the negative charge is delocalised onto the \textit{para} site is more important than the canonical in which charge is delocalised to the \textit{ortho} position meaning that the destabilising influence of \textit{para} fluorine atoms is slightly enhanced.\textsuperscript{74,75} It is easy to see why \textit{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 $\Pi$ effects (Fig. 1.5.1f).

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (a) at (0,0) {F};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (b) at (1,0) {Nuc};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (c) at (2,0) {F};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (d) at (2,1) {Nuc};
  \node[draw,shape=circle,outer sep=0pt,inner sep=1pt] (e) at (2,2) {F};

  \draw (a) -- (b);  
  \draw (b) -- (c);  
  \draw (c) -- (d);  
  \draw (d) -- (e);
\end{tikzpicture}
\end{center}

\textbf{Fig. 1.5.1f} Stabilising effect of fluorine atoms \textit{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.\textsuperscript{76} Nucleophilic aromatic substitution is highly selective, with the order of activation towards attack being:

$$4 > 2 > 3$$

with few exceptions.\textsuperscript{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
Chapter 1

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\textsuperscript{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.

![Diagram showing nucleophilic substitutions of PFP]

**Fig 1.5.2b** Nucleophilic substitutions of PFP, reagents: 1) 1 eq NH(CH\(_3\))\(_2\),\textsuperscript{80} 2) 2 eq NH(CH\(_3\))\(_2\),\textsuperscript{80} 3) AlBr\(_3\), HBr, autoclave,\textsuperscript{81} 4) KF, CF\(_2\)=CFCF\(_3\), sulfolane,\textsuperscript{65} 5) 1 eq NaOMe,\textsuperscript{80} 6) 3 eq NaOMe,\textsuperscript{80} 7) NaCN, DMF,\textsuperscript{82} 8) PhSO\(_2\)Na, DMF.\textsuperscript{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.\textsuperscript{84-86}

![Reaction scheme](image)

**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

![Reaction of 2,3,5,6-tetrachloro-isonicotinonitrile with benzene-1,2-diol, 1,2-phenylenediamine and TMEDA](image)

**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.\textsuperscript{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 $N,N'$-dimethylethlenediamine.
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, 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), although the aim of their study was not to obtain cyclised products.

![Fig 1.6.2a Reactions of PFP with selected binucleophiles](image)

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. 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 \(N,N'\)
dimethylethlenediamine 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, ethlenediamine 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,
ethlenediamine and 2-mercapto-ethanol

27
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-mercaptop-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.\textsuperscript{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](image)

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). 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.

![Diagram of reactions](image)

**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$_2$CO$_3$, 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.
A separate study showed that the rate of cyclisation to form such phenoxazines increased with the nucleophilicity of the amino group\textsuperscript{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 $Y = \text{Ac}$ only isomer A was formed but when $Y = \text{H}$ a mixture of isomers A and B were formed with B predominating, and when $Y = \text{CH}_3$ a large excess of B was obtained.
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 NCH₃ 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).
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.
In 2001, reactions of pentafluoropyridine and their substituted derivatives with oxygen binucleophiles were investigated. The first study by Litvak et al. synthesised the following dioxins (Fig. 1.6.3h).

![Diagram of dioxin synthesis](image)

**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-acetyl diarylamine

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).

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 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).\textsuperscript{108}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\includegraphics[width=\textwidth]{figure1.6.4a.png}};
  \node [below=1cm] at (A) {\textbf{Fig. 1.6.4a} Preparation of polyfluorobenzothiazoles via cyclisation of polyfluorothioanilides};
\end{tikzpicture}
\end{center}

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

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\includegraphics[width=\textwidth]{figure1.6.4b.png}};
  \node [below=1cm] at (A) {\textbf{Fig. 1.6.4b} Reaction of pentafluoropyridine with cyclohex-1-enyl-diethyl-amine};
\end{tikzpicture}
\end{center}
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.

1.7) REFERENCES


G. Sandford, Phil. Trans. R. Soc. Lond. A, 2000, 358, 455.


Chapter 1


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.\textsuperscript{1-9}

In contrast, perfluorinated heteroaromatic systems (e.g. PFP) are potentially excellent scaffolds\textsuperscript{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-è]pyrazine scaffolds. General methodology for the synthesis of functionalised derivatives of the [6,6] fused ring system tetrahydropyrido[3,4-è]pyrazine remains undeveloped with only a limited number having been synthesised in low yields by multistep procedures. These syntheses have relied upon diaminopyridine\(^\text{12}\) or chloroaminopyridine\(^\text{13}\) precursors, or the reduction of pyrido[3,4-è]pyrazine derivatives by metal hydrides.\(^\text{14}\) An example of one such synthesis is shown in Fig. 2.2b,\(^\text{12}\) however the starting
materials for syntheses of this nature and, particularly their functionalised derivatives, can also be difficult to obtain.

\[
\begin{align*}
\text{Cl} & \quad \text{NO}_2 \\
\text{N} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

**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 \(N,N^\prime\)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.

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{N} & \quad \text{N} \\
\text{F} & \quad \text{F}
\end{align*}
\]

**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, 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.
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-isopropyl- 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. 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).

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

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).

<table>
<thead>
<tr>
<th>Binucleophile</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NH}_2\text{OH} )</td>
<td>( \text{5a} )</td>
<td>85%</td>
</tr>
<tr>
<td>( \text{NH}_2\text{SH} )</td>
<td>( \text{5b} )</td>
<td>50%</td>
</tr>
</tbody>
</table>

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](image)

2.5) NUCLEOPHILIC SUBSTITUTION REACTIONS OF 5,7,8-TRIFLUORO-1,4-DIMETHYL-1,2,3,4-TETRAHYDROPYRIDO[3,4-ô]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.

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

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeONa</td>
<td>MeONa, MeOH reflux, 2 d</td>
<td>7a 76%, 10:1 7b</td>
</tr>
<tr>
<td>EtONa</td>
<td>EtONa, EtOH microwaves, 1.25 h</td>
<td>8a 57%, 8:1 8b</td>
</tr>
<tr>
<td>i-BuOK</td>
<td>THF, reflux</td>
<td>9, 66%</td>
</tr>
<tr>
<td>OK</td>
<td>Microwaves THF, 150°C, 1 h</td>
<td>10a 65%, 4.9 : 1:1.2 10b</td>
</tr>
</tbody>
</table>

*Minor products 7b and 8b were identified by 19F nmr and gcms analysis but could not be isolated. Products 10a,b,c were not separated but identified by spectroscopic analysis of enriched samples.
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.
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. 2.5a X-Ray Molecular Structure of 7a        Fig.2.5b X-Ray Molecular Structure of 8a

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.

![Chemical structure](attachment:structure.png)

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtNHLi</td>
<td>THF, reflux</td>
<td><img src="" alt="Product" /> 11a 21%, 1.6:1 11b</td>
</tr>
<tr>
<td>Et₂NLi</td>
<td>THF, reflux</td>
<td><img src="" alt="Product" /> 12a 26%, 4:1 12b</td>
</tr>
<tr>
<td>Sl</td>
<td>Microwaves THF, 150°C, 1 h</td>
<td><img src="" alt="Product" /> 13a 9%, 1:1 13b</td>
</tr>
<tr>
<td>Li</td>
<td>THF, reflux</td>
<td><img src="" alt="Product" /> 14 + Other 40%</td>
</tr>
</tbody>
</table>

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,\textsuperscript{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.
Chapter 2

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.
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. \cite{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


Chapter 3

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](image)

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\textsuperscript{4-5} or reduction\textsuperscript{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).

\[
\begin{align*}
\text{NH} & \quad 1) \text{NaH/DMF} \\
\text{Cl} & \quad 2) \text{Cl} \quad \text{NMe}_2 \cdot \text{HCl} \\
& \quad 80-150^\circ \text{C}
\end{align*}
\]

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'-dimethylethlenediamine 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 \( N,N' \)-dimethylethlenediamine \( 2a \) 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 \( N,N' \)-dimethylethlenediamine 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 \( 2a \).

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>( X )</th>
<th>Product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NET}_2 )</td>
<td>( 18a )</td>
</tr>
<tr>
<td>( \text{OMe} )</td>
<td>( 18b )</td>
</tr>
<tr>
<td>( \text{OEt} )</td>
<td>( 18c )</td>
</tr>
<tr>
<td>( H )</td>
<td>( 18d )</td>
</tr>
</tbody>
</table>

\( ^{19}F\) 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 \( 2a \).

**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).

![X-Ray Molecular Structure of 22](image)

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).

![Schematic representation](image)

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](image)

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.

\[
\begin{align*}
\text{Nuc}^- + \text{Me-X} & \rightarrow \text{Et-X} \quad \text{Pr-X} \\
k_{SN2, rel} & = 30 \quad 1 \quad 0.025
\end{align*}
\]

![Fig. 3.2d Kinetic data for reactions of nucleophiles with alkyl halides](image)
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.

![Diagram](image)

**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. 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.

![Reaction Scheme]

<table>
<thead>
<tr>
<th>X</th>
<th>Product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>27, 20%</td>
</tr>
<tr>
<td>CF(CF₃)₂</td>
<td>28, 40%</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>29, 65%</td>
</tr>
<tr>
<td>CN</td>
<td>30, 90%</td>
</tr>
<tr>
<td>NO₂</td>
<td>31a, 70% + 3a, 1.2:1</td>
</tr>
</tbody>
</table>

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.\textsuperscript{15}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3_3a.png}
\caption{Activating effects and mobilities of substituents in nucleophilic aromatic substitution reactions}
\end{figure}

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

\begin{figure}[h]
\centering
\includegraphics[width=0.4\textwidth]{fig3_3b.png} \hspace{1cm} \includegraphics[width=0.4\textwidth]{fig3_3c.png}
\caption{X-Ray Molecular Structure of 27 \hspace{1cm} X-Ray Molecular Structure of 28}
\end{figure}
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).

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.
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.$^{16}$

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-\textit{b}]pyrazine systems by reaction with \textit{N},\textit{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.

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


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'-dimethylethlenediamine 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.
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).$^1$

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.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHEt₂</td>
<td>NaHCO₃/CH₃CN</td>
<td>35a 35b 35c (16:1:8)</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>NaHCO₃/CH₃CN</td>
<td>NHPh 36a 36b Others 1:1</td>
</tr>
<tr>
<td>EtONa</td>
<td>EtOH</td>
<td>37a* 37b 37c (8.8:1:1.3) 44%</td>
</tr>
<tr>
<td>PhOH</td>
<td>NaHCO₃/CH₃CN</td>
<td>OPPh 38a 38b Others 7:3:1 37%</td>
</tr>
<tr>
<td>EtSH</td>
<td>NaHCO₃/CH₃CN</td>
<td>ŠEt 39a 39b* Others 26:1 11%</td>
</tr>
</tbody>
</table>

Products 36a 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 ¹⁹F 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](image)

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.

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).
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.\textsuperscript{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.\textsuperscript{13}

\[ \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{N} \quad \text{F} \quad \text{F} \quad + \quad \text{PhSO}_2\text{Na} \quad \xrightarrow{\text{DMF}} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{SO}_2\text{Ph} \quad \text{N} \quad \text{F} \quad \text{F} \quad \text{18g} \quad 85\% \]

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.
### Table 4.4a Reactions of 18g with nucleophiles

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHEt₂</td>
<td>NaHCO₂CH₂CN</td>
<td>41a : 34:4:1, 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41b⁻, 41c⁻</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>NaHCO₂CH₂CN</td>
<td>42a⁻, 42b⁻, 9:5:2:3:5:1</td>
</tr>
<tr>
<td>EtONa</td>
<td>EtOH</td>
<td>43a : 34:2:6:1, 76%</td>
</tr>
<tr>
<td>PhOH</td>
<td>NaHCO₂CH₂CN</td>
<td>44a : 44b⁻, 52%</td>
</tr>
<tr>
<td>EtSH</td>
<td>NaHCO₂CH₂CN</td>
<td>45a⁻, 45b⁻, 45c⁻, 46:1:1:8:3:1:12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45d⁻, 45e⁻, 45f⁻, Others</td>
</tr>
<tr>
<td>PhSH</td>
<td>NaHCO₂CH₂CN</td>
<td>46⁻, 29%</td>
</tr>
</tbody>
</table>

* Products not isolated but presence confirmed by ¹⁹F NMR and mass spectral data.
- Products not isolated but presence confirmed by ¹⁹F, ¹H, ¹³C NMR and mass spectral data.
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 sulfides16 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](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).

![Diagram](image_url)

<table>
<thead>
<tr>
<th>Binucleophile</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>![Image]</td>
</tr>
<tr>
<td>2d</td>
<td>![Image]</td>
</tr>
<tr>
<td>5a</td>
<td>![Image]</td>
</tr>
<tr>
<td>50</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

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,\textsuperscript{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.
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.

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). 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](image)

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).
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](image)

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](image)

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

\[
\begin{align*}
\text{Ar—F} + e^- & \rightarrow [\text{Ar—F}]^- \\
\text{Ar—H} & \rightarrow \text{Solvent—H} \quad \text{Ar}^+
\end{align*}
\]

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](image)

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](image)
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 $^{19}\text{F}$ 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)

![Reaction of 47 with acetic anhydride](image)

**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


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. 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](image)

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).\(^2\)

![Synthesis of 18h](image)

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.
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, 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 $^{19}\text{F NMR}$ data and, in particular, the structure of 60 was confirmed by X-ray crystallography (Fig. 5.2b).

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-dimethylethlenediamine 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 \(^{19}\text{F} \) 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 $18_{h}$ was reacted with $N,N'$-dimethylethylenediamine $2_{a}$ as described in Chapter 3. The reaction of $18_{h}$ was then attempted with the primary amine binucleophile $2_{d}$ 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 $6_{5}$ was formed in good yield. In contrast, reaction with the unsymmetrical binucleophile $5_{a}$ gave the desired fused ring system $6_{6}$ along with small amounts of other products which were thought to be a result of multiple substitutions by $5_{a}$. The structure of $6_{6}$ was confirmed by X-ray crystallography (Fig. 5.3a), and it is assumed that the more nucleophilic nitrogen of $5_{a}$ attacks first at the 2-position in agreement with the reaction of diethylamine and $18_{h}$ in which initial attack occurs exclusively at this position.

![Fig. 5.3a X-Ray Molecular Structure of 66](image)

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 $3_{0}$ into a ketone rather than substitution at the pyridine ring (Fig. 5.3b).
Reaction of 18h with the carbon/oxygen binucleophile ethyl acetoacetate shown in Fig. 5.3c led to a surprising result.

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.
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.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEt₂Li</td>
<td>THF</td>
<td><img src="image" alt="Product 70" /> 41%</td>
</tr>
<tr>
<td>EtONa</td>
<td>EtOH</td>
<td><img src="image" alt="Product 71" /> <img src="image" alt="Product 72" /> 71%</td>
</tr>
<tr>
<td>PhSLi</td>
<td>THF</td>
<td><img src="image" alt="Product 73" /> 53%</td>
</tr>
</tbody>
</table>

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).

![Reaction Scheme](image)

**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 18Һ in ring forming reactions the literature procedure shown in Fig. 5.4a was applied to polyfluorinated pyridine derivative 18Һ.

Fig. 5.4a Reaction of 3-chloroisonicotinonitrile\textsuperscript{5} and 2-fluoro-benzonitrile\textsuperscript{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 18Һ. The second procedure shown in Fig. 5.4a is tolerant of many different functional groups around the aromatic ring so it is
envisioned that functionalised 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile derivatives could be used as starting materials for this sort of process.

![Chemical structure]

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).

![X-ray molecular structure]

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.

![Chemical Structure](image)

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

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

![Chemical Structure](image)

**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-\textit{n}-butyl-amine was used as the nucleophile (Fig. 6.2.1a).⁵
Chapter 6

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.\(^14\)

![Fig. 6.2.1b Reactions of tetrafluoropyrimidine with nucleophiles](image)

1) \(\text{H}_2\text{O}/\text{THF, RT}\); 2) \(\text{CH}_3\text{N}_2/\text{ether, 20°C}\); 3) \(\text{MeOH}/\text{Na}_2\text{CO}_3, \text{RT}\); 4) \(\text{MeOH}/\text{MeONa, 0°C}\); 5) \(\text{MeOH}/\text{MeONa, reflux}\); 6) \(\text{NH}_3 (\text{aq}, \text{RT})\); 7) \(\text{NH}_3 (\text{aq, 60°C})\); 8) \(\text{PhNH}_2/\text{Na}_2\text{CO}_3/\text{THF, -15°C}\); 9) \(\text{PhNH}_2/\text{THF, reflux}\); 10) \(\text{MeNH}_2 (\text{aq, 0-20°C})\); 11) \(\text{MeNH}_2 (\text{aq, 0-20°C})/\text{DMF}\); 12) \(\text{Me}_2\text{NH (aq, 0-20°C)}\); 13) \(\text{Me}_2\text{NH (aq, DMF, 60°C)}\)

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.\(^15\),\(^16\)
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 \textit{para} to the nitrogen atom.\textsuperscript{17} Tetrafluoropyrazine is therefore of special interest as it possesses no fluorine atoms in this \textit{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.\textsuperscript{18}
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.\textsuperscript{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).
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).

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).

\[
\begin{align*}
\text{F}_2N\text{F} & \quad + \quad \text{CH}_3\text{CN} \\
\text{F} & \quad + \quad \text{NaHCO}_3 \\
\text{F}_2N & \quad \rightarrow \\
\text{N} & \quad \text{N} \\
\text{F} & \quad \text{F}
\end{align*}
\]

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.

![Figure 6.3.2c](image)

**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.

![Figure 6.3.3a](image)

**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).

\[
\begin{align*}
\text{reaction} & : \quad \text{F} \quad \text{N} \quad \text{F} \\
\text{79} + \text{N} \quad \text{OH} & \xrightarrow{\text{CH}_3\text{CN, NaHCO}_3} \quad \text{F} \quad \text{N} \quad \text{F} \\
\text{5} & \xrightarrow{\text{OH}} \quad \text{F} \quad \text{N} \quad \text{O} \\
\text{84} & \quad \text{85}
\end{align*}
\]

*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).

![Reaction of 79 with 5b](image)

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

![X-Ray Molecular Structure of 87](image)

**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).

![Reaction of 79 with ethyl acetoacetate](image)

**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](image)

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](image)
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\(^1\) 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).\(^2\)

![Fig. 6.5a Synthesis of 93](image)

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

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).
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 cyclised 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 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.

6.7) REFERENCES


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. \(N,N'-\)dimethylethlyenediamine 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.
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 ($\lambda$Mo$\alpha$, $\omega$-scan, 0.3$^\circ$/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

\[
\text{N,N'-Dimethylethylenediamine 2a (1.76 g, 20 mmol) and sodium hydrogen carbonate (3.36 g, 40 mmol) were added to acetonitrile (400 ml) under argon. Pentfluoropyridine 1 (1.69 g, 10 mmol) was added dropwise and the resulting solution was refluxed for 5 d after which time }^{19}\text{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_{9}H_{10}N_{3}F_{3} requires: C, 49.8; H, 4.6; N, 19.4%); }^{19}\text{F NMR: } \delta_{F} \text{-85.00 (1 F, m, F-5), -99.30 (1 F, m, F-7), -162.64 (1 F, t, }^{3}\text{J}_{CF} 22.2,^{5}\text{J}_{HF} 4.5, \text{F-8); }^{1}\text{H NMR: } \delta_{H} 3.28 (3H, d, ^{5}\text{J}_{HF} 4.8, 1-NCH_{3}), 3.23 (2H, t, ^{3}\text{J}_{HH} 4.8, \text{CH}_{2}), 3.04 (2H, t, ^{3}\text{J}_{HH} 5.2, \text{CH}_{2}), 2.73 (3H, s, 4-NCH_{3}); \delta_{C} 148.4 (d, ^{1}\text{J}_{CF} 233.3, ^{3}\text{J}_{CF} 16.3, \text{C-5}), 145.1 (d, ^{1}\text{J}_{CF} 230.4, ^{2}\text{J}_{CF} 17.6, \text{C-7}), 140.0 (m, \text{C-8a}), 131.8 (d, ^{1}\text{J}_{CF} 244.6, ^{2}\text{J}_{CF} 30.5, ^{4}\text{J}_{CF} 4.8, \text{C-8), 116.6 (d, }^{2}\text{J}_{CF} 29.1, ^{3}\text{J}_{CF} 4.3, \text{C-4a), 48.5 (s, CH}_{2}), 46.0 (s, \text{CH}_{2}), 43.6 (d, ^{4}\text{J}_{CF} 5.3, 4-NCH}_{3}), 41.6 (d, ^{4}\text{J}_{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_{4}H_{9}N]^+ 28).}
Preparation of 5,7,8-Trifluoro-1,4-diisopropyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine 3b

\[
\begin{array}{c}
\text{F} & \text{N} & \text{F} \\
\text{F} & \text{N} & \text{F} \\
1 & \text{CH}_3CN & \text{NaHCO}_3 \\
2b & \text{3b} & \text{26%}
\end{array}
\]

\(N,N'\)-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 \(^{19}\text{F}\) 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\(_3\)F\(_3\) requires [M+H]\(^+\) 274.1526); \(\delta\)F -82.67 (1F, t, \(^3\)J\(\text{FF}\) 20.3, F-5), -100.13 (1F, t, \(^3\)J\(\text{FF}\) 15.8, F-7), -161.45 (1F, t, \(^3\)J\(\text{FF}\) 22.3, F-8); \(\delta\)H 4.50 (1H, septet of doublets, \(^3\)J\(\text{HH}\) 6.5, \(^5\)J\(\text{HF}\) 3.0, 1-NCH(CH\(_3\))\(_2\)), 3.56 (1H, septet, \(^3\)J\(\text{HH}\) 7.0, 4-NCH(CH\(_3\))\(_2\)), 3.16 (2H, t, \(^3\)J\(\text{HH}\) 5.5, NCH\(_2\)), 3.04 (2H, t, \(^3\)J\(\text{HH}\) 5.0, NCH\(_2\)), 1.21 (6H, dd, \(^3\)J\(\text{HH}\) 7.0, \(^5\)J\(\text{HH}\) 1.5, NCH(CH\(_3\))\(_2\)), 1.11 (6H, dd, \(^3\)J\(\text{HH}\) 6.5, \(^5\)J\(\text{HF}\) 0.5, NCH(CH\(_3\))\(_2\)); \(\delta\)C 148.4 (dd, \(^1\)J\(_{\text{CF}}\) 232.3, \(^3\)J\(_{\text{CF}}\) 15.6, C-5), 144.8 (dt, \(^1\)J\(_{\text{CF}}\) 229.9, \(^2\)J\(_{\text{CF}}\) 19.1, C-7), 139.3 (quintet, \(^2\)J\(_{\text{CF}}\) 4.3, C-8\(_a\)), 132.1 (ddd, \(^1\)J\(_{\text{CF}}\) 243.8, \(^2\)J\(_{\text{CF}}\) 29.6, \(^4\)J\(_{\text{CF}}\) 4.8, C-8), 116.0 (dd, \(^2\)J\(_{\text{CF}}\) 27.8, \(^3\)J\(_{\text{CF}}\) 4.4, C-4\(_a\)), 53.2 (d, \(^4\)J\(_{\text{CF}}\) 6.1, 4-NCH(CH\(_3\))\(_2\)), 51.2 (d, \(^4\)J\(_{\text{CF}}\) 15.8, 1-
Chapter 8

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-CH$_3$]$^+$, 100), 230 ([M-CH(CH$_3$)$_2$]$^+$, 27), 216 ([M-CH$_2$CH(CH$_3$)$_2$]$^+$, 92), 202 ([M-(CH$_2$)$_2$CH(CH$_3$)$_2$]$^+$, 16).

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

![Reaction Diagram]

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; $\delta_H$ 7.34 (10H, m, Ar H), 3.80 (4H, s, CH$_2$), 2.79 (4H, s, CH$_2$); $\delta_C$ 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$_2$).
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Preparation of 1,4-Dibenzyl-5,7,8-trifluoro-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine 3c

\[
\begin{align*}
\text{F} & \quad \text{N} & \quad \text{F} \\
\text{F} & \quad \text{N} & \quad \text{F} \\
\text{F} & \quad \text{N} & \quad \text{F} \\
\text{N} & \quad \text{N} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{NH} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{CN} & \quad \text{NaHCO}_3 & \quad \text{3c} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{N} & \quad \text{Ph} \\
\text{Ph} & \quad \text{NH} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{N} & \quad \text{F} \\
\text{F} & \quad \text{N} & \quad \text{F} \\
\text{F} & \quad \text{N} & \quad \text{F} \\
\text{N} & \quad \text{N} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{NH} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{CN} & \quad \text{NaHCO}_3 & \quad \text{3c} \\
\end{align*}
\]

\[3c \quad 33\%
\]

\[
\begin{align*}
\text{N,N'}-\text{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 \ \textsuperscript{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 \times \ 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 \ \textit{n}-hexane/ethyl acetate) \ gave \ \textit{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^\circ C; \ ([\text{M+H}]^+ \ 370.1526, \ C_{21}H_{18}N_3F_3 \ requires \ [\text{M+H}]^+ \ 370.1529); \ \delta_F \ 83.54 \ (1F, \ dd, \ \textit{J}_{FF} \ 22.6, \ \textit{J}_{FF} \ 13.5, \ F-5), \ -98.78 \ (1F, \ dd, \ \textit{J}_{FF} \ 22.6, \ \textit{J}_{FF} \ 13.5, \ F-8), \ -161.23 \ (1F, \ t, \ \textit{J}_{FF} \ 22.6, \ F-7); \ \delta_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, \ \textit{J}_{HH} \ 5.1, \ \textit{NCH}_2CH_2), \ 2.80 \ (2H, \ t, \ \textit{J}_{HH} \ 5.1, \ \textit{NCH}_2CH_2); \ \delta_C \ 148.9 \ (dd, \ \textit{J}_{CF} \ 233.7, \ \textit{J}_{CF} \ 16, \ C-5), \ 145.1 \ (dt, \ \textit{J}_{CF} \ 230.3, \ \textit{J}_{CF} \ 19.1, \ C-7), \ 139.4 \ (m, \ C-4b), \ 138.0 \ (s, \ Ar \ C), \ 137.5 \ (s, \ Ar \ C), \ 132.1 \ (ddd, \ \textit{J}_{CF} \ 244.8, \ \textit{J}_{CF} \ 30.1, \ \textit{J}_{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, \ \textit{J}_{CF} \ 28.2, \ \textit{J}_{CF} \ 4.2, \ C-3b), \ (s, \ Ar \ CH), \ 59.5 \ (d, \ \textit{J}_{CF} \ 3.8, \ CH_2), \ 57.3
\]

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d, $^4$JC 12.6, CH$_2$), 43.9 (s, CH$_2$), 43.4 (s, CH$_2$); m/z (EI$^+$) 369 ([M]$^+$, 54), 278 ([M-CH$_2$C$_6$H$_5$]$^+$, 49), 91 ([CH$_2$C$_6$H$_5$]$^+$, 100).

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

![Reaction Scheme]

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$_7$H$_7$N$_3$F$_4$ requires: C, 40.2; H, 3.4; N, 20.1%); $^6$$^1$F($d_6$-Acetone) -98.42 (2F, t, $^3$J$_{FF}$ 18.8, F-2,6), -166.28 (2F, t, $^3$J$_{FF}$ 18.8, F-3,5); $^6$$^1$H($d_6$-Acetone) 3.75 (2H, $^3$J$_{HH}$ 8.4, NHCH$_2$), 3.46 (2H, t, $^3$J$_{HH}$ 6.4, CH$_2$NH$_2$); $^6$$^1$C($d_6$-Acetone) 144.1 (dm, $^1$JC 230.0, C-2,6), 138.4 (m, C-4), 131.1 (ddm, $^1$JC 245.4, $^2$JC 35.9, C-3,5), 50.8 (s, CH$_2$NH$_2$), 44.8 (t, $^4$JC 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

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{CH}_3\text{CN} & \quad \text{NaHCO}_3 \\
\text{NH} & \quad \text{NH}
\end{align*}
\]

1,2-Phenylenediamine (2.16 g, 20 mmol) and sodium hydrogen carbonate (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 \(^{19}\text{F}\) 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%); \(\delta\text{f}(d_0\text{-Acetone}) -96.22 \text{ (2F, m, F-2,6), -160.59 (2F, m, F-3,5); } \delta\text{h}(d_0\text{-Acetone}) 7.80 \text{ (3H, br s, NH & NH}_2\text{), 6.5-7.3 (4H, m, Ar H); } \delta\text{c}(d_0\text{-Acetone}) 144.4 \text{ (dm, } ^1\text{J_\text{CF} 237.5, C-2,6), 142.1 (s, C-1), 136.1 (m, C-4), 132.3 (dm, } ^1\text{J_\text{CF} 250.8, C-3,5), 128.3 (s, C-2), 125.6 (t, } ^5\text{J_\text{CF} 1.9, C-6), 124.9 (s, C-3), 119.2 (s, C-5), 116.6 (s, C-4); m/z (EI\text{)} 257 ([M]^+, 70), 237 ([M-HF]^+, 100).
Preparation of 2-[Methyl-(2,3,5,6-tetrafluoropyridin-4-yl)amino]ethanol 6a

\[
\begin{align*}
\text{1} & \quad \text{+} \quad \text{CH}_3\text{CN} \quad \text{NaHCO}_3 \\
\text{5a} & \quad \longrightarrow \\
\text{6a} & \quad 85\%
\end{align*}
\]

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$_8$H$_8$N$_2$F$_4$O requires: C, 42.9; H, 3.6; N, 12.5%); $\delta$F -94.46 (2 F, m, F-2,6), -155.24 (2F, m, F-3,5); $\delta$H 3.84 (2H, t, $^3$J$_{HH}$ 5.7, CH$_2$), 3.53 (2H, t, $^3$J$_{HH}$ 5.4, CH$_2$), 3.18 (3H, t, $^5$J$_{HF}$ 3.3, CH$_3$); $\delta$C 144.9 (dtm, $^1$J$_{CF}$ 237.5, $^2$J$_{CF}$ 18.1, C-2,6), 140.6 (m, C-4), 134.4 (ddm, $^1$J$_{CF}$ 249.9, $^2$J$_{CF}$ 23.9, C-3,5), 60.3 (t, $^4$J$_{CF}$ 1.5, CH$_3$), 56.5 (t, $^4$J$_{CF}$ 4.8, CH$_2$), 40.9 (t, $^5$J$_{CF}$ 5.8, CH$_2$); m/z (EI$^+$) 224 ([M$^+$], 18), 193 ([M-CH$_2$OH]$^+$, 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, 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, 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$_6$N$_2$F$_4$S requires: C, 48.2; H, 2.2; N, 10.2%); $\delta_F$ -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); $\delta$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$_2$); $\delta_C$ 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 $^{19}\text{F}$ 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$_3$F$_2$O requires: C, 52.4; H, 5.7; N, 18.3%); $\delta_F$ - 86.81 (1F, d, $^5J_{HF}$ 22.6, F-5), -161.91 (1F, m, F-8); $\delta_H$ 3.88 (3H, s, OCH$_3$), 3.20 (3H, d, $^3J_{HF}$ 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$_3$); $\delta_C$ 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-8a), 133.6 (dd, $^1J_{CF}$ 236, $^4J_{CF}$ 5.0, C-8), 113.2 (d, $^2J_{CF}$ 30.5, C-4a), 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,
7,8-difluoro-5-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine 7b as a colourless oil; δF -100.31 (1F, d, JF 24.8, F-7), -166.63 (1F, dd, JF 24.8, JHF 4.5, F-8); δH 3.94 (3H, s, OCH3), 3.16 (3H, d, JHF 3.9, NCH3), 3.15 (2H, t, JHH 6.3, NCH2), 3.02 (2H, t, JHH 5.1, NCH2), 2.64 (3H, s, 4-NCH3); m/z (EI+) 229 ([M]+, 100), 214 ([M-CН3]+, 66), 199 ([M-C2H5]+, 14); and a trace amount of 7,8-difluoro-5-methoxy-1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine 7a as a yellow oil; δF -100.31 (1F, d, JF 24.8, F-7), -166.63 (1F, dd, JF 24.8, JHF 4.5, F-8); δH 3.94 (3H, s, OCH3), 3.16 (3H, d, JHF 3.9, NCH3), 3.15 (2H, t, JHH 6.3, NCH2), 3.02 (2H, t, JHH 5.1, NCH2), 2.64 (3H, s, 4-NCH3); m/z (EI+) 229 ([M]+, 100), 214 ([M-CН3]+, 66), 199 ([M-C2H5]+, 14).

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

\[
\begin{align*}
3a + \text{MeO}^- \text{Na}^+ & \rightarrow \text{MeOH} \\
\text{7a} & \text{945%} \\
\text{7b} & \text{1}
\end{align*}
\]

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 19F 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; δF -100.18 (1F, dm, $^3$JFF 29.0, F-7), -166.83 (1F, dm, $^3$JFF 24.6, F-8); δH 3.71 (2H, q, $^3$JHH 7.0, OCH$_2$CH$_3$), 3.20 (3H, d, $^5$JHF 4.2, 1-NCH$_3$), 3.17 (2H, t, $^3$JHH 5.2, NCH$_2$), 3.04 (2H, t, $^3$JHH 5.2, NCH$_2$), 2.67 (3H, s, 4-NCH$_3$), 1.23 (3H, t, $^3$JHH 7.0, OCH$_2$CH$_3$); 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; \( \text{C}_{11}\text{H}_{15}\text{N}_{3}\text{F}_{2}\text{O} \) requires: C, 54.3; H, 6.2; N, 17.3%); \( \delta_{\text{F}} \) -86.67 (1F, d, \( \delta_{\text{FF}} \) 22.6, F-5), -161.44 (1F, dm, \( \delta_{\text{FF}} \) 24.5, F-8); \( \delta_{\text{H}} \) 4.31 (2H, q, \( \delta_{\text{JHH}} \) 7.2, OCH\(_2\)CH\(_3\)), 3.21 (3H, d, \( \delta_{\text{HF}} \) 4.5, 1-NCH\(_3\)), 3.18 (2H, t, \( \delta_{\text{JHH}} \) 5.1, NCH\(_2\)), 3.04 (2H, t, \( \delta_{\text{JHH}} \) 5.4, NCH\(_2\)), 2.70 (3H, s, 4-NCH\(_3\)), 1.38 (3H, t, \( \delta_{\text{JHH}} \) 7.2, OCH\(_2\)CH\(_3\)); \( \delta_{\text{C}} \) 149.7 (d, \( \delta_{\text{CF}} \) 228.4, C-5), 146.1 (m, C-7), 139.04 (m, C-8a), 133.6 (dd, \( \delta_{\text{CF}} \) 241, \( \delta_{\text{CF}} \) 5, C-8), 112.8 (d, \( \delta_{\text{CF}} \) 30.1, C-4a), 62.6 (s, OCH\(_2\)CH\(_3\)), 48.8 (s, CH\(_2\)), 45.6 (s, CH\(_2\)), 43.6 (d, \( \delta_{\text{CF}} \) 4.6, 4-NCH\(_3\)), 41.5 (d, \( \delta_{\text{CF}} \) 13.3, 1-NCH\(_3\)), 14.9 (s, OCH\(_2\)CH\(_3\)); \( \text{m/z} \) (El\(^+\)) 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**

\[ \begin{align*}
3a + \text{EtO}^- \text{Na}^+ + \text{EtOH} & \rightarrow 8a \\
8a & \rightarrow 8b
\end{align*} \]

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 \(^{19}\text{F} \) 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_{3}O_{2} requires: C, 57.6; H, 7.0; N, 15.5%); δF -84.22 (1F, d, J_{FF} 26.3, F-5), -155.20 (1F, m, F-8); δH 3.14 (5H, overlapping d & t, 1-NCH₃ & CH₂), 2.99 (2H, t, J_{HH} 4.4, CH₂), 2.68 (3H, s, 4-NCH₃), 1.48 (9H, s, (CH₃)₃); δC 148.7 (dd, J_{CF} 229.1, J_{CF} 142.
1.5, C-5), 145.1 (dd, $^2$JCF 18.9, $^3$JCF 13.4, C-7), 138.7 (dd, $^2$JCF 8.3, $^3$JCF 6.6, C-8a), 136.4 (dd, $^1$JCF 243.3, $^4$JCF 5.3, C-8), 114.0 (d, $^2$JCF 31.5, C-4a), 81.2 (s, OC(CH$_3$)$_3$), 48.4 (s, NCH$_2$), 45.7 (s, NCH$_2$), 43.4 (d, $^4$JCF 5.1, 4-NCH$_3$), 41.5 (d, $^4$JCF 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$_2$), 65%.

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3.04 (2H, t, $^3J_{HH}$ 5.2, CH$_2$), 2.73 (3H, s, 4-NCH$_3$); $\delta_C$ 155.0 (s, Ar C), 149.3 (d, $^1J_{CF}$ 230.2, C-5), 143.0 (m, C-7), 139.3 (m, C-8a), 135.5 (dd, $^1J_{CF}$ 244.5, $^4J_{CF}$ 4.8, C-8), 129.4 (s, Ar CH), 123.8 (s, Ar CH), 119.2 (s, Ar CH), 115.6 (d, $^2J_{CF}$ 30.4, C-4a), 48.3 (s, CH$_2$), 45.8 (s, CH$_2$), 43.3 (d, $^4J_{CF}$ 5.5, 4-NCH$_3$), 41.4 (d, $^4J_{CF}$ 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; $\delta_F$ -96.71 (d, $^3J_{PF}$ 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-diphenoxo-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-diphenoxo-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine 10c also isolated in a trace amount; $\delta_F$ -156.49 (1F, m, F-8); $\delta_H$ 7.21 (4H, m, Ar CH), 7.00 (6H, m, Ar CH), 3.25 (3H, d, $^5J_{HF}$ 4.4, 1-NCH$_3$), 3.24 (2H, t, $^3J_{HH}$ 5.2, CH$_2$), 3.08 (2H, t, $^3J_{HH}$ 4.8, CH$_2$), 2.79 (3H, s, 4-NCH$_3$); $\delta_C$ 155.4 (s, Ar C), 154.8 (s, Ar C), 148.4 (s, C-5), 143.6 (d, $^2J_{CF}$ 13.9, C-7), 139.0 (d, $^2J_{CF}$ 5.3, C-8a), 135.0 (d, $^1J_{CF}$ 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-4a), 48.5 (s, NCH$_2$), 45.3 (s, NCH$_2$), 43.0 (s, 4-NCH$_3$), 41.6 (d, $^4J_{CF}$ 13.3, 1-NCH$_3$); $m/z$ (EI)$^+$ 366 ([M+H]$^+$, 100), 351 ([MH-CH$_3]^+$, 46).
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; $\delta_F$ -98.16 (1F, d, $^3J_{FF}$ 26.3, F-7), -172.07 (1F, q, $^3J_{FF}$ 22.6, F-8); $\delta_H$ 4.69 (1H, br s, NH), 3.36 (2H, q, $^3J_{HH}$ 7.2, NHCH$_2$CH$_3$), 3.23 (2H, t, $^3J_{HH}$ 4.8, NCH$_2$CH$_2$), 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$_3$); $\delta_C$ 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-8a), 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-4a), 48.1 (s, NCH$_2$CH$_2$), 44.3 (s, 145
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. \( \text{C}_{11}\text{H}_{16}\text{F}_{2}\text{N}_{4} \) requires: C, 54.6; H, 6.6; N, 23.1%); \( \delta_{\text{F}} \) -86.00 (1F, d, \( \text{J}_{\text{FF}} \) 22.6, F-5), -162.08 (1F, q, \( \text{J}_{\text{FF}} \) 22.6, F-8); \( \delta_{\text{H}} \) 4.13 (1H, br s, NH), 3.38 (2H, q, \( \text{J}_{\text{HH}} \) 6.8, NHCH\(_2\)CH\(_3\)), 3.17 (5H, overlapping d & t, 1-NCH\(_3\) & NCH\(_2\)CH\(_3\)), 3.03 (2H, q, \( \text{J}_{\text{HH}} \) 4.8, NCH\(_2\)CH\(_2\)), 2.66 (3H, s, 4-NCH\(_3\)), 1.21 (3H, t, \( \text{J}_{\text{HH}} \) 7.2, NHCH\(_2\)CH\(_3\)); \( \delta_{\text{C}} \) 151.6 (d, \( \text{J}_{\text{CF}} \) 224.2, C-5), 141.8 (m, C-7), 137.3 (m, C-8\( \alpha \)), 133.0 (dd, \( \text{J}_{\text{CF}} \) 234.1, \( \text{J}_{\text{CF}} \) 4.0, C-8), 109.0 (d, \( \text{J}_{\text{CF}} \) 32.1, C-4\( \alpha \)), 48.8 (s, NCH\(_2\)CH\(_2\)), 45.0 (s, NCH\(_2\)CH\(_2\)), 43.4 (d, \( \text{J}_{\text{CF}} \) 3.8, 4-NCH\(_3\)), 41.2 (d, \( \text{J}_{\text{CF}} \) 13.2, 1-NCH\(_3\)), 36.0 (s, NHCH\(_2\)CH\(_3\)), 15.4 (NHCH\(_2\)CH\(_3\)); \( m/z \) (EI\(^+\)) 242 ([M\(^+\), 100), 227 ([M-CH\(_3\)]\(^+\), 90), 213 ([M-CH\(_2\)CH\(_3\)]\(^+\), 14).

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

\[
\begin{align*}
\text{F} & \quad \text{Et}_2\text{N}\text{Li} \\
\text{F} & \quad \text{THF} \\
\text{12a} & \quad \text{12b} \\
\end{align*}
\]

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; $\delta_F$ -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-CH$_3$]$^+$, 69), 241 ([M-
CH$_3$CH$_2$]$^+$, 89), 225 ([M-(CH$_3$)$_3$]$^+$, 88), 211 ([M-(CH$_3$)$_2$CH$_2$]$^+$, 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$_4$F$_2$ requires [M+H]$^+$ 270.1656); $\delta_F$ -83.92 (1F, d, $^5J_{FF}$ 24.0, F-5), -150.42 (1F, d, $^5J_{FF}$ 25.3, F-8); $\delta_H$ 3.29 (4H, q, $^3J_{HH}$ 6.8, N(CH$_2$CH$_3$)$_2$),
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$_2$CH$_3$)$_2$); $\delta_C$ 150.4 (d, $^1J_{CF}$ 225.3, C-5),
141.9 (m, C-7), 139.3 (m, C-8a), 136.6 (dd, $^1J_{CF}$ 240.1, $^4J_{CF}$ 4.6, C-8), 111.7 (d, $^2J_{CF}$ 32.4,
C-4a), 48.7 (s, NCH$_2$), 46.0 (s, NCH$_2$), 44.6 (d, $^4J_{CF}$ 5.0, N(CH$_2$CH$_3$)$_2$), 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$_2$CH$_3$)$_2$); $m/z$ (EI$^+$) 270 ([M$^+$, 96), 255
([M-CH$_3$]$^+$, 100), 241 ([M-CH$_3$CH$_2$]$^+$, 70), 226 ([M-(CH$_3$)$_2$CH$_2$]$^+$, 79), 211 ([M-
(CH$_3$)$_3$CH$_2$]$^+$, 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; δF -135.91 (1F, q, 5JHF 3.8, F-8); δH 7.0-7.3 (10H, m, Ar H), 3.26 (2H, t, 3JHH 4.8, CH2), 3.21 (3H, d, 5JHF 1.6, 1-NCH3), 3.05 (2H, t, 3JHH 5.2, CH2), 2.76 (3H, s, 4-NCH3); 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_{2}N_{3} requires C, 58.6; H, 4.9; N, 13.7%; δ_F -78.41 (1F, d, ^3J_{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-NCH₃ & CH₂), 3.03 (2H, t, ^3J_{HH} 4.0, CH₂), 2.79 (3H, s, 4-NCH₃); 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-8α), 128.9 (s, Ar CH), 127.4 (s, Ar CH), 119.6 (dd, ^2J_{CF} 30.7, ^3J_{CF} 2.6, C-4α), 48.2, (s, NCH₂), 46.6 (s, NCH₂), 43.2 (d, ^4J_{CF} 7.2, 4-NCH₃), 41.9 (d, ^4J_{CF} 12.9, 1-NCH₃); m/z (EI)^+ 308 ([M+H]^+, 85), 277 ([M-(CH₃)₂]^+, 100), 233 ([M-(CH₃)₂NCH₂CH₂]^+, 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. ¹⁹F 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; δF -81.18 (1F, d, 5JFF 26.3, F-5), -142.91 (1F, q, 5JFF 22.6, F-8); δH 3.16 (5H, overlapping d & t, 1-NCH3 & NCH2), 3.03 (2H, t, 3JHH 4.4, NCH2), 2.77 (3H, d, 5JHF 1.2, 4-NCH3), 2.61 (2H, m, NCH2CH2CH2CH3), 1.64 (2H, m, NCH2CH2CH2CH3), 1.37 (2H, m, NCH2CH2CH2CH3), 0.93 (3H, t, 3JHH 7.6, NCH2CH2CH2CH3); δc 151.6 (d, 1JC 226.8, C-5), 145.4 (dd, 1JC 242.1, 4JC 3.7, C-8), 138.2 (m, C-7), 137.4 (m, C-8a), 128.1 (d, 2JC 31.5, C-4a), 48.2 (s, NCH2CH2N), 46.1 (s, NCH2CH2N), 43.3 (d, 4JC 6.1, 4-NCH3), 41.7 (d, 4JC 13.0, 1-NCH3), 30.7 (s, CH2CH2CH2CH3), 30.4 (s, CH2CH2CH2CH3), 29.7 (s, CH2CH2CH2CH3), 13.9 (s, CH2CH2CH2CH3); m/z (EI)⁺ 256 ([M+H]⁺, 81), 236 ([MH-HF]⁺, 5), 213 ([MH-CH2CH3]⁺, 7).

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

![Reaction Diagram]

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-б]pyrazine 7a (0.2 g, 0.8 mmol). The resulting solution was refluxed for 2 d after which time 19F 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_{3}F_{2} requires: C, 56.5; H, 7.1; N, 16.5%); δF -166.18 (1F, s, F-8); δH 4.38 (2H, q, 3J_{HH} 7.2, OCH_{2}CH_{3}), 3.90 (3H, s, OCH_{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}CH_{3}); δC 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-8a), 132.3 (d, 1J_{CF} 238.6, C-8), 113.6 (s, C-4a), 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}CH_{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; $\delta$F -164.87 (1F, d, $^5$JHF 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$_4$FO requires [M+H]$^+$ 283.1934); $\delta$F -158.19 (1F, d, $^5$JHF 3.8, F-8); $\delta$H 3.92 (3H, s, OCH$_3$), 3.61 (4H, $^3$JHH 7.2, N(CH$_2$CH$_3$)$_2$), 3.39 (2H, t, $^3$JHH 5.2, NCH$_2$CH$_2$), 3.30 (3H, d, $^5$JHF 4.8, 1-NCH$_3$), 3.05 (2H, t, $^3$JHH 5.2, NCH$_2$CH$_2$), 2.68 (3H, s, 4-NCH$_3$), 1.17 (6H, t, $^3$JHH 6.8, N(CH$_2$CH$_3$)$_2$); $\delta$C 150.5 (d, $^2$JCF 12.8, C-7), 137.9 (d, $^4$JCF 2.6, C-5), 136.2 (s, C-8a), 134.1 (d, $^1$JCF 249.8, C-8), 124.0 (s, C-4a), 53.7 (s, OCH$_3$), 51.7 (s, N(CH$_2$CH$_3$)$_2$), 48.0 (s, NCH$_2$), 44.4 (s, NCH$_2$), 43.7 (s, N(CH$_2$CH$_3$)$_2$), 40.8 (s, 4-NCH$_3$), 40.6 (d, $^4$JCF 12.5, 1-NCH$_3$); m/z (EI)$^+$ 283 ([M+H]$^+$, 100), 268 ([MH-CH$_3$]$^+$, 10), 254 ([MH-CH$_2$CH$_3$]$^+$, 80), 239 ([MH-CH$_2$CH$_3$CH$_3$]$^+$, 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\(_{14}H_{22}N_{3}F_{0}\) requires: C, 62.9; H, 8.2; N, 15.7%); δ\(_{F}\) -160.54 (1F, d, \(^{5}\)J\(_{HF}\) 4.1, F-8); δ\(_{H}\) 3.85 (3H, s, OCH\(_{3}\)), 3.13 (2H, t, \(^{3}\)J\(_{HH}\) 4.8, NCH\(_{2}\)), 3.09 (3H, d, \(^{5}\)J\(_{HF}\) 4.4, 1-NCH\(_{3}\)), 2.92 (2H, t, \(^{3}\)J\(_{HH}\) 5.2, NCH\(_{2}\)), 2.57 (2H, t, \(^{3}\)J\(_{HH}\) 8.0, CH\(_{2}\)CH\(_{2}\)CH\(_{2}\)CH\(_{3}\)), 2.48 (3H, s, 4-NCH\(_{3}\)), 1.63 (2H, quintet, \(^{3}\)J\(_{HH}\) 7.6, NCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)CH\(_{3}\)), 1.30 (2H, sextet, \(^{3}\)J\(_{HH}\) 7.6, NCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)CH\(_{3}\)), 0.86 (3H, t, \(^{3}\)J\(_{HH}\) 7.6, NCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)CH\(_{3}\)); δ\(_{C}\) 148.4 (d, \(^{2}\)J\(_{CF}\) 10.6, C-7), 145.8 (d, \(^{4}\)J\(_{CF}\) 4.6, C-5), 135.4 (d, \(^{2}\)J\(_{CF}\) 2.0, C-8α), 133.0 (d, \(^{1}\)J\(_{CF}\) 247.3, C-8), 126.1 (d, \(^{3}\)J\(_{CF}\) 1.0, C-4α), 52.0 (s, OCH\(_{3}\)), 47.6 (8, NCH\(_{2}\)), 43.4 (s, NCH\(_{2}\)), 42.4 (s, 4-NCH\(_{3}\)), 153
40.0 (d, $^4J_{CF}$ 13.0, 1-NCH$_3$), 30.4 (s, CH$_2$CH$_2$CH$_2$CH$_3$), 29.6 (s, CH$_2$CH$_2$CH$_2$CH$_3$), 21.8 (s, CH$_2$CH$_2$CH$_2$CH$_3$), 13.1 (s, CH$_2$CH$_2$CH$_2$CH$_3$); $m/z$ (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).

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

N,N'-dimethylethylenediamine 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-tetrafluoropyridin-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$_4$F$_3$Cl requires: C, 47.8; H, 6.7; N, 17.2%); δ$_F$(DMSO-d$_6$) -95.08 (1F, t, $^3$J$_{FF}$ 25.2, F-6), -145.03 (1F, d, $^4$J$_{FF}$ 23.4, F-3), -162.34 (1F, d, $^3$J$_{FF}$ 25.2, F-5); δ$_H$(DMSO-d$_6$) 9.78 (2H, br s, NH$_2$), 3.69 (2H, t, $^3$J$_{HH}$ 6.7, NCH$_2$CH$_2$NH$_2$), 3.35 (4H, q, $^3$J$_{HH}$ 7.0, N(CH$_2$CH$_3$)$_2$), 3.24 (2H, t, $^3$J$_{HH}$ 6.7, NCH$_2$CH$_2$NH$_2$), 3.08 (3H, d, $^3$J$_{HH}$ 4.3, NCH$_3$), 2.80 (3H, s, CH$_3$NH$_2$CH$_2$), 1.17 (6H, t, $^3$J$_{HH}$ 7.0, N(CH$_2$CH$_3$)$_2$); δ$_C$(DMSO-d$_6$)
145.9 (dd, $^1J_{CF} 225.2, ^2J_{CF} 15.0, C-6), 143.0 (m, C-4), 139.0 (dd, $^1J_{CF} 245.6, ^3J_{CF} 10.8, C-3), 138.3 (m, C-2), 132.0 (dd, $^1J_{CF} 244.5, ^2J_{CF} 31.2, C-5); m/z (EI$^+$) 270 ([M-HF]$^+$, 34), 246 ([M-CH$_2$NHCH$_3$]$^+$, 100), 179 ([M-(CH$_3$)$_2$CHN]$^+$, 82).

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

\[ \begin{align*}
\text{O} & \quad \text{Me} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{18b} & \\
\text{N'} & \\
\text{CH}_3\text{CN} & \quad \text{NaHCO}_3 \\
\text{2a} & \\
\text{CH}_3\text{CN} & \quad \text{NaHCO}_3 \\
\text{23} & 72\%
\end{align*} \]

$N,N'$-Dimethylethlenediamine 2a (1.94 g, 22 mmol) and sodium hydrogen carbonate (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$_5$HNOF$_4$ requires: C, 35.9; H, 0.6; N, 8.4%); $\delta_F$ -90.94 (2F, s, F-2,6), -163.66 (2F, m, F-3,5); $\delta_H$ 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

\[
\text{CH\textsubscript{3}CN} + \text{NaHCO\textsubscript{3}} \rightarrow \text{24} \quad \text{23%}
\]

\[\begin{array}{c}
\text{OEt} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{18c} \\
\text{N} \\
\text{N} \\
\text{2a} \\
\text{24} \\
\end{array} \]

\(N,N'-\text{Dimethylethylenediamine} \, 2a\) (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 \(^1\text{H}\text{NMR}\) 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\textsubscript{11}H\textsubscript{17}N\textsubscript{3}ClF\textsubscript{3}O requires: C, 44.1; H, 5.7; N, 14.0%); \(\delta_F\) -91.60 (1F, t, \(^3\text{J}_{\text{FF}}\) 25.5, F-6), -152.70 (1F, d, \(^3\text{J}_{\text{FF}}\) 29.4, F-5), -168.80 (1F, d, \(^4\text{J}_{\text{FF}}\) 24.6, F-3); \(\delta_H\) 9.67 (2H, br s, NH\textsubscript{2}), 4.42 (2H, q, \(^4\text{J}_{\text{HH}}\) 6.8, CH\textsubscript{2}CH\textsubscript{3}), 3.80 (2H, t, \(^3\text{J}_{\text{HH}}\) 6.8, NCH\textsubscript{2}), 3.22 (2H, t, \(^3\text{J}_{\text{HH}}\) 6.0, NCH\textsubscript{2}), 3.15 (3H, d, \(^3\text{J}_{\text{HH}}\) 4.0, NCH\textsubscript{3}), 2.77 (3H, t, \(^3\text{J}_{\text{HH}}\) 5.6, NH\textsubscript{2}CH\textsubscript{3}) 1.42 (3H, t, \(^3\text{J}_{\text{HH}}\) 7.2, CH\textsubscript{2}CH\textsubscript{3}); \(\delta_C\) 146.0 (m, C-2), 145.5 (dd, \(^1\text{J}_{\text{CF}}\) 232.6, \(^2\text{J}_{\text{CF}}\) 10.6, C-6), 141.7 (m, C-4), 138.0 (dd, \(^1\text{J}_{\text{CF}}\) 249.0, \(^3\text{J}_{\text{CF}}\) 5.7, C-3), 131.0 (dd, \(^1\text{J}_{\text{CF}}\) 249.7, \(^2\text{J}_{\text{CF}}\) 31.6, C-5), 70.4 (t, \(^4\text{J}_{\text{CF}}\) 3.4, NCH\textsubscript{2}), 48.3 (s, NCH\textsubscript{2}CH\textsubscript{2}NH\textsubscript{2}), 47.0 (s, OCH\textsubscript{2}), 39.2 (d, \(^4\text{J}_{\text{CF}}\) 9.6, NCH\textsubscript{3}), 33.3 (s, NH\textsubscript{2}CH\textsubscript{3}), 15.8 (s, CH\textsubscript{2}CH\textsubscript{3}); \(m/z\) (EI) 244 ([M-HFCl]+, 2), 219 ([M-CH\textsubscript{2}NH\textsubscript{2}CH\textsubscript{2}Cl]+, 43), 191 ([M-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}NH\textsubscript{2}CH\textsubscript{3}Cl]+, 88).
Preparation of 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine 25

\[
\begin{array}{c}
\text{F} & \text{H} & \text{F} \\
\text{18d} & & \\
\end{array} \quad \text{CH}_3\text{CN} \quad \text{NaNCO}_3 \\
\begin{array}{c}
\text{H} & \text{CH}_2 \text{CH}_2 \text{N} \text{H} \\
\text{2d} & & \\
\end{array} \quad \rightarrow \\
\begin{array}{c}
\text{F} & \text{H} & \text{N} & \text{N} \\
\text{6} & \text{1} & \text{2} & \text{3} & \text{4} \\
\end{array} \quad (66\%)
\]

\text{N,N'-Dimethylenediamine } 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 \(^{19}\text{F} \text{NMR} \) 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 \text{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; \([\text{M}+\text{H}]^+ 200.0994, \text{C}_9\text{H}_{11}\text{N}_3\text{F}_2 \) requires \([\text{M}+\text{H}]^+ 200.0994\); \(\deltaF_{-108.05} \) (1F, s, F-6), -160.50 (1F, s, F-7); \(\deltaH 6.42 \) (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\(_3\)); \(\deltaC 142.0 \) (dd, \(^1J_{\text{CF}} 220.4, ^2J_{\text{CF}} 15.2, \text{C-6}\)), 141.0 (d, \(^3J_{\text{CF}} 13.7, \text{C-4a}\)), 135.9 (dd, \(^1J_{\text{CF}} 238.6, ^2J_{\text{CF}} 28.6, \text{C-7}\)), 130.2 (s, C-8a), 107.8 (d, \(^2J_{\text{CF}} 21.8, \text{C-8}\)), 48.3 (s, CH\(_2\)), 48.2 (s, CH\(_2\)), 39.2 (s, CH\(_3\)), 36.7 (s, CH\(_3\)); \(m/z \text{(EI}^+) 199 ([\text{M}]^+, 100), 184 ([\text{M-CH}_3]^+, 56), 169 ([\text{M-(CH}_3)_2]^+, 16).
Preparation of \(N,N'-\text{Diethyl-3,5,6-Trifluoropyridin-2-amine 26}\)

\[
\begin{align*}
\text{F} & \quad \text{N} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\end{align*}
\]

\(\text{CH}_3\text{CN}
\]

\[
\begin{align*}
\text{NHEt}_2 & \quad \text{I} \\
\text{F} & \quad \text{N} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{N} \\
\end{align*}
\]

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 \(^{19}\text{F}\) 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 \(N,N'-\text{diethyl-3,5,6-trifluoropyridin-2-amine 26}\) (0.92 g, 68%) as a colourless oil; \([\text{M+H}]^+ 205.0947, \text{C}_9\text{H}_{11}\text{N}_2\text{F}_3\) requires \([\text{M+H}]^+ 205.0947\); \(\delta_\text{F} -93.44 (1\text{F}, t, ^{3}\text{J}_{\text{FF}} 31.6, \text{F-6}), -135.20 (1\text{F}, \text{dd}, ^{3}\text{J}_{\text{FF}} 31.6, ^{4}\text{J}_{\text{FF}} 11.3, \text{F-5}), -156.20 (1\text{F}, \text{dd}, ^{4}\text{J}_{\text{FF}} 24.8, ^{5}\text{J}_{\text{FF}} 6.8, \text{F-3}); \delta_\text{H} 7.17 (1\text{H}, \text{dt}, ^{3}\text{J}_{\text{HF}} 11.2, ^{3}\text{J}_{\text{HF}} 8.0, \text{4-H}), 3.44 (4\text{H}, \text{qd}, ^{3}\text{J}_{\text{HH}} 7.2, \text{CH}_2), 1.17 (6\text{H}, t, ^{3}\text{J}_{\text{HH}} 7.2, \text{CH}_3); \delta_\text{C} 144.5 (\text{dd}, ^{1}\text{J}_{\text{CF}} 229.1, ^{2}\text{J}_{\text{CF}} 14.1, \text{C-6}), 143.1 (\text{ddd}, ^{1}\text{J}_{\text{CF}} 251.2, ^{3}\text{J}_{\text{CF}} 5.3, ^{4}\text{J}_{\text{CF}} 1.9, \text{C-3}), 141.9 (\text{m}, \text{C-2}), 134.3 (\text{ddd}, ^{1}\text{J}_{\text{CF}} 248.2, ^{2}\text{J}_{\text{CF}} 32.4, ^{3}\text{J}_{\text{CF}} 5.4, \text{C-5}), 116.4 (\text{ddd}, ^{2}\text{J}_{\text{CF}} 25.2, ^{3}\text{J}_{\text{CF}} 19.8, ^{3}\text{J}_{\text{CF}} 3.8, \text{C-4}), 44.3 (\text{d}, ^{4}\text{J}_{\text{CF}} 5.8, \text{CH}_2), 13.8 (\text{s}, \text{CH}_3); m/z (\text{El}^+) 204 ([\text{M}]^+, 79), 189 ([\text{M}-\text{CH}_3]^+, 100), 175 ([\text{M-CH}_2\text{CH}_3]^+, 64), 161 ([\text{M-(CH}_2)_2\text{CH}_3]^+, 100).
Preparation of 8-Bromo-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine 27

\[
\begin{align*}
\text{Br} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
18e & \quad \text{H} \\
\text{N} & \quad \text{N} \\
2a & \quad \text{MeCN} \\
\text{NaHCO}_3 & \quad \text{27} \quad 20\% \\
\end{align*}
\]

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 \(^{19}\text{F NMR}\) 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\(_9\)H\(_{10}\)N\(_3\)BrF\(_2\) requires: C, 39.0; H, 3.6; N, 15.2%). \(\delta_F\) -94.67 (1F, d, \(^3\)J\(_{FF}\) 26.7, F-6), -152.39 (1F, d, \(^3\)J\(_{FF}\) 26.7, F-7); \(\delta_H\) 3.37 (2H, t, \(^3\)J\(_{HH}\) 5.0, CH\(_2\)), 3.12 (3H, s, CH\(_3\)), 3.06 (2H, t, \(^3\)J\(_{HH}\) 5.0, CH\(_2\)), 2.73 (3H, s, CH\(_3\)); \(\delta_C\) 145.9 (dd, \(^1\)J\(_{CF}\) 228.7, \(^2\)J\(_{CF}\) 15.6, C-6), 145.3 (dd, \(^3\)J\(_{CF}\) 15.6, \(^4\)J\(_{CF}\) 1.2, C-4a), 133.8 (dd, \(^1\)J\(_{CF}\) 241.6, \(^2\)J\(_{CF}\) 31.6, C-7), 126.4 (dd, \(^3\)J\(_{CF}\) 5.8, \(^4\)J\(_{CF}\) 2.2, C-8a), 117.8 (dd, \(^2\)J\(_{CF}\) 16.3, \(^3\)J\(_{CF}\) 5.0, C-8), 48.1 (s, CH\(_3\)), 43.3 (s, CH\(_2\)), 42.90 (s, CH\(_3\)), 36.6 (s, CH\(_2\)); \(m/z\) (El\(^+\)) 277 ([M]\(^+\), 96), 262 ([M-CH\(_3\)]\(^+\), 72), 183 ([M-CH\(_3\)Br]\(^+\), 26), 168 ([M-C\(_2\)H\(_6\)Br]\(^+\), 22).
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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'-Dimethylethylenediamine 2a (1.23 g, 14 mmol) and sodium hydrogen carbonate (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$_3$F$_9$ requires: C, 39.2; H, 2.7; N, 11.2%; $\delta_F$ -70.77 (2F, s, CF$_3$ of B), -74.88 (6F, br m, CF$_3$ of A), -92.47 (0.3F, d, $^3$J$_{FF}$ 33.0, F-6 of B), -94.44 (1F, d, $^3$J$_{FF}$ 27.6, F-6 of A), 155.65 (1F, sextet, $^3$J$_{FF}$ 27.6, F-7 of A), -156.80 (0.3F, d, $^4$J$_{FF}$ 44.5, F-7 of B), -168.43 (0.3F, d, $^4$J$_{FF}$ 88.8, (CF$_3$)$_2$CF of B), -179.66 (1F, s, (CF$_3$)$_2$CF of A); $\delta_H$ 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$_3$); $\delta_C$ 147.6 (dd, $^1$J$_{CF}$ 183.1, $^2$J$_{CF}$ 13.8, C-6), 147.2 (d, $^3$J$_{CF}$ 11.1, C-4a), 132.4 (dm, $^1$J$_{CF}$ 200.7, C-7), 128.5 (s, C-8a), 120.8 (qd, $^1$J$_{CF}$ 230.0, $^2$J$_{CF}$ 22.5, CF$_3$), 119.9
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(m, C-8), 92.0-96.0 (m, CF(CF3)2), 47.1 (s, CH2), 45.7 (d, 5JCF 5.7, 1-NCH3), 43.2 (s, CH2), 37.4 (s, 4-NCH3); m/z (EI⁺) 368 ([M+H]⁺, 34), 367 ([M⁺], 100), 352 ([M-CH3⁺], 90), 325 ([M-C2H4N]⁺, 49), 263 ([M-C4H9N3F]⁺, 89), 69 ([CF3]⁺, 32), 42 ([C2H4N]⁺, 53).

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

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad + \quad \text{NaHCO}_3 \\
\text{CH}_3\text{CN} & \quad \rightarrow \\
\text{Ph} & \quad \text{SO}_2
\end{align*}
\]

N,N'-Dimethylmethylenediamine 2a (0.58 g, 6.70 mmol) and sodium hydroygen carbonate (1.15 g, 13.75 mmol) were added to acetonitrile (200 ml) under argon. 4-Benzensulfonyl-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 19F 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, C15H15N3F2SO2 requires [M+H]⁺ 340.0926); δF -95.57 (1F, d, 3JFF 27, F-6), -157.04 (1F, d, 3JFF 27, F-7); δH 7.95 (2H, d, 3JHH 7.5, Arortho H), 7.60 (1H, m, Arpara H), 7.49 (2H, t, 3JHH 8.0, Armeta H), 3.35 (2H, t, 3JHH 5.2, CH2), 3.06 (3H, s, NCH3), 2.92 (3H, s, NCH3), 2.77 (2H, t, 3JHH 5.2, CH2); δC 146.3 (dd, 1JCF 231.0, 2JCF 16.7, C-6), 146.2 (d, 3JCF 13.7, C-4a), 142.2 (s, Ar C), 133.8 (s, Arortho CH), 132.1 (dd, 1JCF 253.1, 2JCF 31.7, C-7), 162
Preparation of 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-8-carbonitrile 30

\[
\begin{align*}
\text{CN} & \quad \text{CH}_3\text{CN} \\
\text{F} & \quad \text{NaHCO}_3 \\
\text{N} & \quad \text{2a} \\
\text{H} & \quad \text{30} \\
\end{align*}
\]

\(N,N'-\text{Dimethyl}n\text{ethylenediamine} \ 2a \ (0.67 \ g, \ 7.57 \ \text{mmol})\) 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 \(^{19}\text{F}\) 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; \(\text{C}_{10}\text{H}_{10}\text{N}_{4}\text{F}_{2}\) requires: C, 53.6; H, 4.5; N, 25.0\%); \(\delta\text{F} = -104.75 \ (d, \ 1\text{F}, \ ^{3}\text{J}\text{FF} \ 22.6, \ F-6), -156.79 \ (d, \ 1\text{F}, \ ^{3}\text{J}\text{FF} \ 22.9, \ F-7); \delta\text{H} = 3.40 \ (2\text{H}, \ m, \ \text{CH}_2), 3.39 \ (2\text{H}, \ m, \ \text{CH}_2), 3.30 \ (3\text{H}, \ s, \ \text{CH}_3), 3.05 \ (3\text{H}, \ s, \ \text{CH}_3); \delta\text{C} = 142.6 \ (dd, \ ^{3}\text{J}\text{CF} \ 15.5, \ ^{4}\text{J}\text{CF} \ 3.0, \ C-4\text{a}), 141.3 \ (dd, \ ^{1}\text{J}\text{CF} \ 223.6, \ ^{2}\text{J}\text{CF} \ 13.9, \ C-6), \)

163
134.7 (dd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 31.5, C-7), 133.5 (dd, $^3J_{CF}$ 4.4, $^4J_{CF}$ 2.4, C-8a), 113.4 (d, $^3J_{CF}$ 4.8, CN), 94.3 (dm, $^2J_{CF}$ 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**

$N,N'$-Dimethylethlenediamine 2a (0.58 g, 6.63 mmol) and sodium hydrogen carbonate (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$_9$H$_{10}$N$_4$F$_2$O$_2$ requires: C, 44.3; H, 4.1; N, 23.0%); $\delta_F$ -99.61 (1F, d, $^3J_{FF}$ 24.6, F-6), -170.43 (1F, d, $^3J_{FF}$ 23.7, F-7); $\delta_H$ 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\(_3\)); \(\delta_C 144.0\) (dd, \(^3J_{CF} 14.5\), \(^4J_{CF} 2.1\), C-4\(\alpha\)), 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\(\alpha\)), 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 hydrogen carbonate (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); \(\delta_F -90.45\) (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); \(\delta_H 3.45\) (4H, qd, \(^3J_{HH} 7.2\), \(^4J_{HF} 2.0\), CH\(_2\)), 1.19 (6H, t, \(^3J_{HH} 7.2\), CH\(_3\)); \(\delta_C 144.5\)
(ddd, \( ^1J_{CF} 231.0,^2J_{CF} 14.8,^4J_{CF} 2.3, C-6 \)), 141.6 (m, C-2), 141.2 (ddd, \( ^1J_{CF} 251.6,^3J_{CF} 6.1,^4J_{CF} 3.5, C-3 \)), 133.3 (ddd, \( ^1J_{CF} 248.2,^2J_{CF} 33.9,^3J_{CF} 1.6, C-5 \)), 111.7 (ddd, \( ^2J_{CF} 24.8,^2J_{CF} 19.4,^3J_{CF} 5.4, C-4 \)), 44.4 (d, \( ^4J_{CF} 6.1, CH_2 \)), 13.8 (s, CH_3); \( m/z \) (EI\(^+\)) 282 ([M]^+, 40), 267 ([M-CH_3]^+, 100).
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; C₅H₂N₂F₄ requires: C, 36.1; H, 1.2; N, 16.9%); δF -93.76 (2F, s, F-2,6), -164.63 (2F, m, F-3,5); δH 4.74 (2H, br s, NH₂); δC 143.7 (dt, ¹JC₁ 236.4, ²JC₁ 14.1, C-2,6), 137.2 (m, C-4), 131.2 (dd, ¹JC₁ 246.3, ²JC₁ 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$_2$O$_5$ (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; $\delta_F$ -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.

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-
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**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, ^J_{FF} 29.3, F-6), -151.91 (1F, d, ^J_{FF} 29.3, F-3); m/z (EI)^+ 302 ([M]^+, 80), 287 ([M-CH₃]^+, 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-CH₃]^+, 86), 179 ([M-(CH₂)₂CH₃]^+, 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, C₉H₁₀N₃F₃O₂ requires [M]^+ 249.0720); δ_F -85.35 (1F, m, F-6), -147.54 (1F, dd, ^J_{FF} 31.6, 4J_{FF} 13.5, F-5), -166.50 (1F, dd, ^J_{FF} 24.8, 5J_{FF} 11.3, F-3); δ_H 3.50 (4H, qd, 3J_{HH} 7.0, ^J_{HF} 2.0, CH₂), 1.21 (6H, t, 3J_{HH} 7.0, CH₃); 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, CH₂), 12.5 (s, CH₃); m/z (EI)^+ 249 ([M]^+, 66), 234 ([M-CH₃]^+, 100), 220 ([M-CH₂CH₃]^+, 8), 203 ([M-CH₂NO₂]^+, 77), 160 ([M-NO₂CH₂CH₂N]^+, 75).

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

\[
\begin{array}{c}
\text{F} & \text{F} & \text{N} \\
\text{F} & \text{N} & \text{F} \\
\text{F} & \text{F} & \text{F}
\end{array}
+ \text{PhNH₂} & \xrightarrow{\text{CH₃CN, NaHCO₃}} & \begin{array}{c}
\text{N} & \text{Ph} \\
\text{F} & \text{F} & \text{F} \\
\text{F} & \text{F} & \text{F}
\end{array} \\
\text{1} & \text{1} & \text{Others}
\]

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; δF -86.53 (4F, m, F-2,6), -156.22 (4F, m, F-3,5); δC 142.8 (dtm, $^1$JC 245.2, $^2$JC 14.5, C-2,6), 133.9 (ddm, $^1$JC 263.5, $^2$JC 28.2, C-3,5), 129.1 (d, $^2$JC 7.2, C-4); m/z (EI)$^+$ 316 ([M]$^+$, 100), 150 ([M-C$_3$F$_4$NO]$^+$, 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$_6$N$_2$F$_4$ requires [M+NH$_4$]$^+$ 260.0805); δF -92.87 (2F, t, $^3$JFF 15.8, F-2,6), -156.03 (2F, t, $^3$JFF 15.8, F-3,5); δH 7.29 (2H, t, $^3$JHH 7.6, Ar H), 7.14 (1H, t, $^3$JHH 7.6, Ar H), 7.03 (2H, d, $^3$JHH 6.8, Ar H), 6.28 (1H, br s, NH); δC 144.5 (dm, $^1$JC 234.0, C-2,6), 138.4 (s, Ar C), 134.4 (m, C-4), 132.7 (s, $^1$JC 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$_9$H$_8$]$^+$, 6). Data consistent with literature values.$^4$

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

\[
\begin{align*}
\text{18i} & \quad + \quad \text{EtO}^-\text{Na}^+ \quad \xrightarrow{\text{EtOH}} \quad \text{37a} & \quad + \quad \text{Others} \\
\text{37a} & \quad \xrightarrow{1.4} \quad \text{37b} & \quad + \quad \text{Others} \\
\end{align*}
\]
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 181 (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; $\delta_F$ -91.47 (2F, m, F-2,6), -159.87 (2F, m, F-3,5); m/z (EI)$^+$ 195 ([M]+, 66), 167 ([M-CH$_2$CH]+, 100), 29 ([M-C$_3$F$_4$O]+, 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$_9$H$_{10}$NO$_2$F$_3$ requires [M+H]$^+$ 222.0736); $\delta_F$ -94.62 (1F, t, $^3$J$_{FF}$ 24.8, F-6), -160.55 (1F, d, $^3$J$_{FF}$ 24.8, F-5), -167.86 (1F, d, $^4$J$_{FF}$ 22.6, F-3); $\delta_H$ 4.34 (2H, q, $^3$J$_{HH}$ 7.0, CH$_2$), 4.20 (2H, q, $^3$J$_{HH}$ 7.0, CH$_2$), 1.30 (3H, t, $^3$J$_{HH}$ 7.0, CH$_3$), 1.25 (3H, t, $^3$J$_{HH}$ 7.0, CH$_3$); $\delta_C$ 146.1 (m, C-2), 145.5 (m, C-4), 144.7 (ddd, $^1$J$_{CF}$ 231.8, $^2$J$_{CF}$ 13.9, $^4$J$_{CF}$ 3.4, C-6), 136.3 (dd, $^1$J$_{CF}$ 252.8, $^2$J$_{CF}$ 6.6, C-3), 132.1 (dd, $^1$J$_{CF}$ 249.9, $^2$J$_{CF}$ 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-CH$_3$]$^+$, 59), 193 ([M-CH$_3$CH]$^+$, 74), 178 ([M-(CH$_3$)$_2$CH]$^+$, 44), 165 ([M-(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. $^1$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; $\delta_F$ -89.16 (2F, m, F-2,6), -154.79 (2F, m, F-3,5); $\delta_H$ 7.32 (2H, t, $^3$J$_{HH}$ 7.8, Ar H), 7.15 (1H, m, Ar H), 6.99 (2H, d, $^3$J$_{HH}$ 8.1, Ar H); $\delta_C$ 154.8 (s, Ar C), 143.4 (m, C-4), 143.2 (dt, $^1$J$_{CF}$ 241.7, $^2$J$_{CF}$ 13.2, C-2,6), 135.2 (ddm, $^1$J$_{CF}$ 260.8, $^2$J$_{CF}$ 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-C$_3$F$_4$NO]$^+$, 100). Data consistent with literature values;$^5$ 2,3,6-trifluoro-4-nitro-5-phenoxypyridine 38b; $\delta_F$ -75.17 (1F, dd, $^3$J$_{FF}$ 30.1, $^4$J$_{FF}$ 12.8, F-2), -84.39 (1F, dd, $^4$J$_{FF}$ 21.1, $^5$J$_{FF}$ 12.8, F-6), 149.00 (1F, dd, $^3$J$_{FF}$ 30.1, $^5$J$_{FF}$ 20.9, F-3); m/z (EI$^+$) 270 ([M]$^+$, 79), 93 ([M-C$_5$N$_2$F$_3$O$_2$]$^+$, 98), 77 ([M-C$_5$N$_2$F$_3$O$_3$]$^+$, 100); and 4,4'-oxybis(tetrafluoropyridine) 36b; $\delta_F$ -86.49 (4F, m, F-2,6), -156.19 (4F, m, F-3,5); m/z (EI$^+$) 316 ([M]$^+$, 90), 150 ([M-C$_3$F$_4$NO]$^+$, 36), 93 ([M-C$_3$F$_4$N]$^+$, 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; $\delta_F$ -92.14 (2F, m, F-2,6), -139.35 (2F, m, F-3,5); $\delta_H$ 3.22 (2H, q, $^3J_{HH}$ 6.5, CH$_2$), 1.36 (3H, t, $^3J_{HH}$ 7.0, CH$_3$); $\delta_C$ 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-CH$_3$]$^+$, 40), 183 ([M-CH$_3$CH]$^+$, 100); 4,4'-oxybis(tetrafluoropyridine) 36b; and 2-(ethylsulfanyl)-3,5,6-trifluoro-4-nitropyridine 39b; m/z (EI)$^+$ 238 ([M]$^+$, 28), 210 ([M-CH$_3$CH]$^+$, 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 \(4,4'-\text{oxybis(tetrafluoropyridine)}\) \(36b\) (0.18 g, 35%) as a yellow oil, plus a trace amount of pure \(4,4'-\text{oxybis(tetrafluoropyridine)}\) \(36b\) as a yellow oil; \(\delta\text{F} -86.49 (4\text{F}, \text{s, F-2,6}), -156.20 (4\text{F}, \text{s, F-3,5}); \delta\text{C} 144.0 (\text{ddm, } ^1\text{J}_{\text{CF}} 248.1, ^2\text{J}_{\text{CF}} 14.4, \text{C-2,6}), 135.2 (\text{ddm, } ^1\text{J}_{\text{CF}} 264.6, ^2\text{J}_{\text{CF}} 38, \text{C-3,5}); m/z (\text{EI}^+) 316 ([M]^+, 58), 150 ([M-C_3\text{F}_4\text{NO}]^+, 24).

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

\[
\begin{align*}
\text{NO}_2 & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} \\
\text{N} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} \\
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{CH}_3\text{CN} & \quad \text{NaHCO}_3 & \quad \text{PhSH} & \quad \text{NaHCO}_3 & \quad \text{PhSH} \\
\end{align*}
\]

Benzenethiol (0.24 g, 2.14 mmol) and sodium hydrogen carbonate (0.36 g, 4.28 mmol) were added to acetonitrile (100 ml) under argon. 4-Nitro-2,3,5,6-tetrafluoropyridine \(18\) (0.42 g, 2.14 mmol) was added and the resulting solution was stirred at room temperature for 1 d after which time \(^{19}\text{F} \text{NMR indicated } 100\% \text{ 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 \(40b\); \(\delta\text{F} -65.55 (1\text{F}, \text{dd, } ^3\text{J}_{\text{FF}} 26.5, ^5\text{J}_{\text{FF}} 10.9, \text{F-2}), -86.77 (1\text{F}, \text{t, } ^5\text{J}_{\text{FF}} 10.9, \text{F-5}), -137.35 (1\text{F}, \text{d, } ^3\text{J}_{\text{FF}} 26.5, \text{F-3}); m/z (\text{EI}^+) 349 ([M]^+, 100), 240 ([M-SC_6\text{H}_5]^+, 56), 220 ([M-SC_6\text{H}_5\text{HF}]^+, 42), 77 ([M-C_11\text{H}_3\text{NF}_3\text{S}_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$_5$NF$_4$S requires [M+H]$^+$ 260.0152); $\delta$F -91.01 (2F, m, F-2,6), -136.92 (2F, m, F-3,5); $\delta$H 7.25-7.45 (5H, m, Ar H); $\delta$C 142.5 (dm, $^1$J$_{CF}$ 244.0, C-2,6), 140.0 (dm, $^1$J$_{CF}$ 257.3, C-3,5), 131.9 (s, Ar CH), 130.0 (tt, $^2$J$_{CF}$ 16.4, $^3$J$_{CF}$ 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$_2$NF$_4$S]$^+$, 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 hydrogen carbonate (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$_8$N$_2$F$_4$S requires: C, 48.2; H, 2.2; N, 10.2%);
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δF -91.25 (2F, m, F-2,6), -138.68 (2F, m, F-3,5); δH 7.53 (1H, d, 3JHH 7.5, Ar H), 7.25 (1H, td, 3JHH 7.0, 4JHH 1.5, Ar H), 6.76 (1H, dd, 3JHH 8.0, 4JHH 1.0, Ar H), 6.75 (1H, td, 3JHH 7.5, 4JHH 1.0, Ar H), 4.36 (2H, br s, NH2); δC 149.4 (s, ArCS), 143.6 (dtm, 1JCF 248.1, 2JCF 14.5, C-2,6), 141.4 (ddm, 1JCF 258.7, 2JCF 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 CNH2); m/z (EI+) 274 ([M]+, 100), 254 ([M-HF]+, 86), 165 ([M-C6H5SH]+, 10), 150 ([M-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 19F 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; (Found: C, 45.6; H, 1.8; N, 4.9; C11H5F4NSO2 requires: C, 45.4; H, 1.7; N, 4.8%); δF -86.19 (2F, m, F-2,6), -137.48 (2F, m, F-3,5); δH 8.12 (2H, d, 3JHH 7.2, Ar ortho H), 7.78 (1H, tt, 3JHH 7.2, 4JHH 1.2, Ar para H), 7.65 (2H, m, Ar meta H); δC 144.3 (dm, 1JCF 198.4, C-2,6), 139.4 (s, Ar C), 138.9 (dm, 1JCF 188.5, C-3,5), 136.0 (s, Ar ortho CH), 133.3 (t, 2JCF 10.7, C-4), 130.2 (s, Ar meta CH), 128.7 (s, Ar para CH); m/z (EI+) 291 ([M]+, 80), 141 ([M-C5F4N]+, 88), 77 ([M-C5F4NSO2]+, 100).
Preparation of \(N,N'-\text{Diethyl-3,5,6-trifluoro-4-}(\text{phenylsulfonyl})\text{pyridine-2-amine} \ 41\text{a}\)

\[
\begin{align*}
\text{F} & \quad \text{F} & \quad \text{F} & \quad \text{SO}_{2}\text{Ph} \\
\text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F}
\end{align*}
\]

Diethylamine (0.29 g, 4.0 mmol) and sodium hydrogen carbonate (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}\text{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 \(N,N'-\text{diethyl-3,5,6-trifluoro-4-}(\text{phenylsulfonyl})\text{pyridine-2-amine} \ 41\text{a}; 3,6\)-difluoro-\(N,N,N',N'-\text{tetraethyl-4-}(\text{phenylsulfonyl})\text{pyridine-2,5-diamine} \ 41\text{b}; \delta_r \text{F} -73.33 \text{ (IF, d, } J_{\text{FF}} 33.8, \text{ F-6), -134.99 (1F, d, } J_{\text{FF}} 31.3, \text{ F-3); } \delta_h \text{H} 7.95 \text{ (2H, d, } J_{\text{HH}} 7.5, \text{ Ar}_{\text{ortho}} \text{ H), 7.59 (1H, tm, } J_{\text{HH}} 7.5, \text{ Ar}_{\text{para}} \text{ H), 7.50 (2H, t, } J_{\text{HH}} 8.0, \text{ Ar}_{\text{meta}} \text{ H), 3.46 (4H, q, } J_{\text{HH}} 6.5, \text{ CH}_2), 2.81 (4H, m, CH2), 1.19 (6H, t, } J_{\text{HH}} 7.0, \text{ CH}_3), 0.59 (6H, t, } J_{\text{HH}} 7.5, \text{ CH}_3); \delta_c 156.3 \text{ (d, } J_{\text{CF}} 241.3, \text{ C-6), 145.3 (dd, } J_{\text{CF}} 16.8, \text{ C-2), 141.8 (dd, } J_{\text{CF}} 264.8, J_{\text{CF}} 5.3, \text{ C-3), 139.0 (t, } J_{\text{CF}} 7.3, \text{ C-4), 116.4 (d, } J_{\text{CF}} 33.3, \text{ C-5), 47.8 (d, } J_{\text{CF}} 3.4, \text{ CH}_2), 44.7 (d, } J_{\text{CF}} 6.3, \text{ CH}_2), 13.9 (s, CH3), 12.0 (s, CH3); m/z (El\textsuperscript{+}) 397 ([M\textsuperscript{+}], 70), 382 ([M-CH3\textsuperscript{+}], 100), 368 ([M-CH3CH2\textsuperscript{+}], 33), 77 ([M-C$_9$H$_{20}$N$_2$F$_2$SO$_2$\textsuperscript{+}], 30); and 3,5-difluoro-\(N,N',N'-\text{tetraethyl-4-}(\text{phenylsulfonyl})\text{pyridine-2,6-diamine} \ 41\text{c}; \delta_r \text{F} -152.61 \text{ (2F, s, F-3,5); m/z (El\textsuperscript{+}) 397 ([M\textsuperscript{+}], 28), 382 ([M-CH3\textsuperscript{+}], 40), 368 ([M-CH3CH2\textsuperscript{+}], 64), 77 ([M-C$_9$H$_{20}$N$_2$F$_2$SO$_2$\textsuperscript{+}], 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); \(\delta_F\) = -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); \(\delta_H\) 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\(_3\)); \(\delta_C\) 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\(_3\)CH\(_2\)NH\(^+\)], 76).

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

![Diagram](image)

Aniline (1.6 g, 17.2 mmol) and sodium hydrogen carbonate (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; δF -66.56 (1F, dd, JFF 31.6, JFF 13.2, F-5), -96.74 (1F, dd, 4JFF 23.7, 5JFF 13.2, F-2), -139.00 (1F, dd, 3JFF 31.6, 4JFF 23.7, F-6); δH 8.09 (1H, br s, NH), 7.97 (2H, dt, JHH 8.4, 4JHH 1.2, SO2Arortho H), 7.69 (1H, tt, 3JHH 7.6, 4JHH 1.2, SO2Arpara H), 7.54 (2H, tm, 3JHH 8.0, SO2Armeta H), 7.30 (2H, tm, 3JHH 7.6, NHArortho H), 7.11 (1H, tm, 3JHH 7.2, NHArpara H), 6.86 (2H, dm, 3JHH 7.6, NHArmeta H); δC 146.8 (dd, 1JCF 252.7, 3JCF 9.7, 4JCF 2.2, C-2), 142.0 (dd, 1JCF 223.4, 2JCF 12.2, C-6), 141.1 (d, 4JCF 2.3, NHAr C), 139.8 (s, SO2Ar C), 139.8 (dd, 1JCF 264.2, 2JCF 28.2, 4JCF 6.8, C-5), 130.6 (dd, 2JCF 11.9, 3JCF 3.3, C-4), 135.5 (s, SO2Arortho CH), 129.9 (s, SO2Arpara CH), 129.5 (s, NHArortho CH), 128.1 (s, SO2Armeta CH), 124.8 (dm, 2JCF 26.7, C-3), 124.0 (s, NHArpara CH), 119.4 (s, NHArmeta CH); m/z (EI)+ 364 ([M]+, 96), 77 ([M-C11H5N2F3SO2]+, 100); 3,6-difluoro-N,N-diphenyl-4-(phenylsulfonyl)pyridine-2,5-diamine 42b; δF -70.29 (1F, d, 5JFF 31.6, F-6), -138.20 (1F, d, 5JFF 31.6, F-3); m/z (EI)+ 437 ([M]+, 100), 77 ([M-C17H12N2F2SO2]+, 66); 3,5,6-trifluoro-N-phenyl-4-(phenylsulfonyl)pyridine-2-amine 42c; δF -88.62 (1F, dm, 3JFF 31.6, F-6), -138.47 (1F, dm, 3JFF 31.6, F-5), -153.34 (1F, dm, 4JFF 27.1, F-3); m/z (EI)+ 364 ([M]+, 84), 77 ([M-C11H5N2F3SO2]+, 100); and 3,5-difluoro-N,N-diphenyl-4-(phenylsulfonyl)pyridine-2,6-diamine 42d; δF -74.15 (2F, s, F-3,5); m/z (EI)+ 437 ([M]+, 100), 417 ([M-HF]+, 12), 77 ([M-C17H12N3F2SO2]+, 76). Purification by column chromatography on silica gel (2:1 n-hexane/ethyl acetate) was unsuccessful for the separation of the components.

179
Preparation of 2-Ethoxy-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine 43a

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad \text{SO}_2\text{Ph} \\
\text{F} & \quad \text{F} \\
\text{N} & \quad \text{N} \\
18g & \quad 43a \\
\text{F} & \quad \text{OEt} \\
\text{EtO} & \quad \text{Na}^+ \\
\text{F} & \quad \text{F} \\
43b & \\
\text{OEt} & \\
6 & \quad 43a \\
76\% & \\
\end{align*}
\]

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 \(^{19}\text{F}\) 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; \(\delta_{\text{F}} -137.43\) (2F, m, F-3,5); \(m/z\) (EI)\(^+\) 343 ([M]\(^+\), 14), 315 ([M-CH\(_3\)CH]\(^+\), 42), 287 ([M-(CH\(_3\)CH\(_3\))]\(^+\), 100), 77 ([M-C\(_9\)H\(_{10}\)NF\(_2\)SO\(_4\)]\(^+\), 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\(_3\)F\(_3\) requires: C, 49.2; H, 3.2; N, 4.4%); \(\delta_{\text{F}} -90.31\) (1F, dd, \(^3\text{J}\_\text{FF} 31.6, \(^5\text{J}\_\text{FF} 22.6,\) F-6), -136.67 (1F, dd, \(^3\text{J}\_\text{FF} 33.8, \(^4\text{J}\_\text{FF} 9.0,\) F-5), -150.03 (1F, dd, \(^4\text{J}\_\text{FF} 22.6, \(^5\text{J}\_\text{FF} 9.0,\) F-3); \(\delta_{\text{H}} 8.10\) (2H, d, \(^3\text{J}\_\text{HH} 7.5,\) Ar\(_{\text{ortho}}\) CH), 7.72 (1H, tm, \(^3\text{J}\_\text{HH} 7.5,\) Ar\(_{\text{para}}\) CH), 7.60 (2H, tm, \(^3\text{J}\_\text{HH} 7.8,\) Ar\(_{\text{meta}}\) CH), 4.39 (2H, q, \(^3\text{J}\_\text{HH} 7.2,\) CH\(_2\)), 1.40 (3H, t, \(^3\text{J}\_\text{HH} 6.9,\) CH\(_3\)); \(\delta_{\text{C}} 147.1\) (m, C-2), 144.8 (ddd, \(^1\text{J}\_\text{CF} 241.3,\) \(^2\text{J}\_\text{CF} 17.1,\) \(^4\text{J}\_\text{CF} 4.3,\) C-6), 140.2 (s, Ar C), 140.0 (ddd, \(^1\text{J}\_\text{CF} 269.4,\) \(^3\text{J}\_\text{CF} 6.8,\) \(^4\text{J}\_\text{CF} 2.4,\) C-3), 135.3 (s, Ar\(_{\text{ortho}}\) CH), 134.1 (ddd, \(^1\text{J}\_\text{CF} 262.8,\) \(^2\text{J}\_\text{CF} 31.0,\) \(^3\text{J}\_\text{CF} 2.0,\) C-5), 130.6 (m, C-4), 129.9 (s, Ar\(_{\text{para}}\) CH), 128.6
Preparation of 2,3,5-Trifluoro-6-phenoxy-4-(phenylsulfonyl)-pyridine 44a

\[
\begin{align*}
\text{Phenol} & \quad \text{NaHCO}_3 \quad \text{PhOH} \\
\end{align*}
\]

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 \(^1^H\) 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; \(\delta H -87.77\) (2F, m, F-2), -135.34 (2F, dd, \(^3 J_{FF} 31.6, ^4 J_{FF} 9.0, F-3\)), -144.77 (1F, dd, \(^4 J_{FF} 22.6, ^5 J_{FF} 9.0, F-5\)); \(\delta H 8.15\)
(2H, d, $^3J_{HH} 8.0$, SO$_2$Ar$_{meta}$ H), 7.76 (1H, t, $^3J_{HH} 7.5$, SO$_2$Ar$_{para}$ H), 7.65 (2H, t, $^3J_{HH} 7.5$, SO$_2$Ar$_{ortho}$ 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); $\delta_C$ 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$_2$Ar C), 136.0 (dm, $^1J_{CF}$ 274.5, C-5), 135.6 (s, SO$_2$Ar$_{para}$ CH), 131.7 (m, C-6), 129.0 (m, C-4), 130.1 (s, OAr$_{meta}$ CH), 130.0 (s, SO$_2$Ar$_{meta}$ CH), 128.7 (s, SO$_2$Ar$_{ortho}$ CH), 126.3 (OAr$_{para}$ CH), 121.2 (OAr$_{ortho}$ CH); m/z (Et$^+$) 365 ([M]$^+$, 38), 345 ([M-HF]$^+$, 11), 224 ([M-SO$_2$Ph]$^+$, 9), 77 ([M-C$_5$F$_3$NSO$_3$Ph]$^+$, 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 46:1:18:3:12.5 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_2CH_2F]^+, 38); 2,5-bis(ethylsulfanyl)-3,6-difluoro-4-(phenylsulfanyl)pyridine 45b; δ_F -66.49 (1F, d, ^3J_FF 27.1, F-6), -123.57 (1F, d, ^3J_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, ^3J_FF 27.1, F-6), -124.03 (1F, d, ^3J_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, ^3J_FF 29.33, F-6), -114.33 (1F, d, ^3J_FF 31.6, F-3); m/z (EI)^+ 375 ([M]^+, 14), 282 ([M-C_8H_5O]^+, 96), 77 ([M-C_6H_20NF_2S_3O_2]^+, 100).

Purification by column chromatography on silica gel (6:1 n-hexane/ethyl acetate) followed by preparative 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.\(^6\)

183
Preparation of 2,3,5,6-Tetrafluoro-4-(phenylsulfanyl)pyridine 46

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad \text{CH}_3\text{CN} \\
\begin{array}{c}
\begin{array}{c}
\text{F} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{N} \\
\text{F}
\end{array}
\end{array} & \quad \text{PhSH} \quad \xrightarrow{\text{NaHCO}_3} \\
\begin{array}{c}
\begin{array}{c}
\text{F} \\
\text{F} \\
\text{SPh} \\
\text{F} \\
\text{N} \\
\text{F}
\end{array}
\end{array} & \quad \text{Others}
\end{align*}
\]

Benzenethiol (0.38 g, 3.44 mmol) and sodium hydrogen carbonate (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 $^{19}\text{F}$ 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$_5$NF$_4$S requires [M-H]$^+$ 257.9995); $\delta_F$ -91.05 (2F, m, F-2,6), -136.92 (2F, m, F-3,5); $\delta_H$ 7.15-7.45 (5H, m, Ar H); $\delta_C$ 143.7 (dtm, $^1J_C$F 245.0, $^2J_C$F 13.3, C-2,6), 141.2 (ddm, $^1J_C$F 223.2, $^2J_C$F 24.1, C-3,5), 133.2 (s, Ar C), 131.2 (tt, $^2J_C$F 16.9, $^3J_C$F 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$_5$NF$_4$S]$^+$, 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 hydrogen carbonate (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-difluoro-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$_2$F$_2$SO$_2$ requires 312.0613); $\delta$F -108.67 (1F, d, $^3$J$_{FF}$ 24.5, F-6), -157.57 (1F, d, $^3$J$_{FF}$ 24.8, F-7); $\delta$H 8.00 (2H, dm, $^3$J$_{HH}$ 5.7, Ar$_{ortho}$ H), 7.66 (1H, tm, $^3$J$_{HH}$ 7.2, Ar$_{para}$ H), 7.56 (2H, tm, $^3$J$_{HH}$ 7.8, Ar$_{meta}$ H), 3.49 (4H, s, CH$_2$); $\delta$C 141.6 (s, Ar C), 141.1 (dd, $^1$J$_{CF}$ 224.9, $^2$J$_{CF}$ 16.8, C-6), 140.7 (dd, $^2$J$_{CF}$ 14.8, $^3$J$_{CF}$ 3.8, C-8), 134.5 (s, Ar$_{ortho}$ CH), 132.4 (dd, $^1$J$_{CF}$ 248.2, $^2$J$_{CF}$ 29.7, C-7), 129.5 (s, Ar$_{meta}$ CH), 127.8 (d, $^3$J$_{CF}$ 2.6, C-4a), 127.5 (s, Ar$_{para}$ CH), 116.8 (d, $^3$J$_{CF}$ 13.3, C-8a), 39.3
Preparation of 6,7-Difluoro-3,4-dihydro-4-methyl-8-(phenylsulfonyl)-2H-pyrido[3,2-b][1,4]oxazine 48

2-Methylaminoethanol 5a (0.50 g, 6.67 mmol) and sodium hydrogen carbonate (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; $\delta_F$ -88.36 (1F, m, F-6), -131.58 (1F, d, $^3F_F$ 33.8, F-5), -154.46 (1F, dd, $^4F_F$ 27.1, $^5F_F$ 11.3, F-3); m/z (EI$^+$) 346 ([M]$^+$, 2), 326 ([M-HF]$^+$, 25), 315 ([M-CH$_2$OH]$^+$, 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_{2}F_{2}O_{3}S requires: C, 51.5; H, 3.7; N, 8.6%); δF -96.96 (1F, d, \( \beta^1 J_{FF} 27.1 \), F-6), -159.44 (1F, d, \( \beta^1 J_{FF} 24.5 \), F-7); δH 8.06 (2H, dm, \( \beta^1 J_{HH} 7.2 \), Ar\textsubscript{ortho} H), 7.65 (1H, tt, \( \beta^1 J_{HH} 7.5 \), \( \beta^1 J_{HH} 1.2 \), Ar\textsubscript{para} H), 7.54 (2H, tm, \( \beta^1 J_{HH} 6.9 \), Ar\textsubscript{meta} H), 4.18 (2H, t, \( \beta^1 J_{HH} 4.5 \), CH2), 3.44 (2H, t, \( \beta^1 J_{HH} 4.8 \), CH2), 3.03 (3H, s, NCH\textsubscript{3}); δC 144.7 (dd, \( \beta^1 J_{CF} 230.2 \), \( \beta^1 J_{CF} 16.8 \), C-6), 141.7 (dd, \( \beta^1 J_{CF} 14.9 \), \( \beta^1 J_{CF} 2.7 \), C-4a), 141.4 (s, Ar C), 134.4 (s, Ar\textsubscript{ortho} CH), 134.3 (m, C-8), 131.5 (dd, \( \beta^1 J_{CF} 255.1 \), \( \beta^1 J_{CF} 32.6 \), C-7), 129.2 (s, Ar\textsubscript{meta} CH), 128.3 (s, Ar\textsubscript{para} CH), 126.4 (d, \( \beta^1 J_{CF} 10.3 \), C-8a), 64.4 (s, NCH\textsubscript{2}), 47.0 (s, OCH\textsubscript{2}), 36.4 (s, CH\textsubscript{3}); m/z (EI\textsuperscript{+}) 326 ([M]\textsuperscript{+}, 100), 311 ([M-CH\textsubscript{3}]\textsuperscript{+}, 8), 185 ([M-SO\textsubscript{2}Ph]\textsuperscript{+}, 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 hydrgencarbonate (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 \(^{19}\text{F}\) 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; C17H10N2SO3F2 requires: C, 56.7; H, 2.8; N, 7.8%); δF -103.27 (d, JFF 22.2, F-2), -146.62 (d, JFF 22.9, F-3); δH 8.30 (1H, br s, NH), 8.03 (2H, dm, JHH 8.8, SO2Arortho H), 7.74 (1H, tt, JHH 7.6, JHH 1.2, SO2Arpara H), 7.62 (2H, tm, JHH 8.0, SO2Armeta H), 6.89 (1H, td, JHH 7.6, JHH 1.6, Ar H), 6.80 (1H, td, JHH 7.6, JHH 1.6, Ar H), 6.75 (1H, dd, JHH 8.0, JHH 1.6, Ar H), 6.59 (1H, dd, JHH 7.6, JHH 1.6, Ar H); δC 144.2 (d, JCF 3.9, C-4a), 142.1 (dd, JCF 234.8, JCF 17.5, C-2), 142.3 (s, Ar C), 140.3 (s, Ar C), 137.3 (dd, JCF 258.0, JCF 28.5, C-3), 135.3 (s, SO2Ar C), 128.8 (s, SO2Armeta CH), 127.9 (d, JCF 2.2, SO2Arortho CH), 127.2 (s, SO2Arpara CH), 126.8 (d, JCF 4.6, C-4), 125.7 (s, Ar CH), 123.9 (s, Ar CH), 119.8 (d, JCF 14.5, C-8a), 116.6 (s, Ar CH), 114.9 (s, Ar CH); m/z (EI+) 360 ([M]+, 100), 219 ([M-SO2Ph]+, 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 19F 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 \([M+H]^+ 271.1729\); \( \delta_H \) -99.24 (1F, d, \( ^3J_{HF} 27.4, F-6 \)), -168.29 (1F, d, \( ^3J_{HF} 27.3, F-7 \));
\( \delta_H \) 3.26 (4H,qd, \( ^3J_{HH} 7.0, ^5J_{HF} 1.5, N(\text{CH}_2\text{CH}_3)_2 \)), 3.17 (2H, t, \( ^3J_{HH} 4.5, \text{CH}_2 \)), 2.97 (3H, s,
\( \text{NCH}_3 \)), 2.96 (2H, t, \( ^3J_{HH} 4.5, \text{CH}_2 \)), 2.56 (3H, s, \( \text{NCH}_3 \)), 0.98 (6H, t, \( ^3J_{HH} 7.5,
\( \text{N(\text{CH}_2\text{CH}_3)_2} \)) ; \( \delta_C \) 145.7 (dd, \( ^1J_{CF} 224.6, ^2J_{CF} 15.3, \text{C-6} \)), 143.7 (d, \( ^3J_{CF} 16.8, \text{C-4a} \)), 139.6
(m, \( \text{C-8} \)), 132.6 (dd, \( ^1J_{CF} 240.0, ^2J_{CF} 29.1, \text{C-7} \)), 120.4 (d, \( ^3J_{CF} 4.8, \text{C-8a} \)), 47.5 (s, \( \text{NCH}_2 \)),
43.6 (d, \( ^4J_{CF} 4.8, \text{N(\text{CH}_2\text{CH}_3)_2} \)), 42.1 (s, \( \text{NCH}_2 \)), 40.5 (s, \( \text{NCH}_3 \)), 35.9 (s, \( \text{NCH}_3 \)), 12.3 (s,
\( \text{N(\text{CH}_2\text{CH}_3)_2} \)); \( m/z \) (EI)\(^+ 270 ([M]^+, 100), 255 ([M-\text{CH}_3]^+, 16), 241 ([M-\text{CH}_2\text{CH}_3]^+, 26), 226
([M-(\text{CH}_3)_2\text{CH}_2]^+, 52), 211 ([M-(\text{CH}_3)_3\text{CH}_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-CH₃]$^+$, 2), 257 ([M-C$_7$H$_8$SO₂]$^+$, 59), 77 ([M-C$_{15}$H$_{14}$N$_3$SO$_3$F]$^+$, 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, 3_J_HH 7.5, SO₂Arortho H), 7.51 (1H, t, 3_J_HH 7.5, SO₂Arpara H), 7.41 (2H, t, 3_J_HH 8.0, SO₂Armeta H), 7.23 (2H, t, 3_J_HH 7.5, OAr H), 7.03 (1H, t, 3_J_HH 7.5, OAr H), 6.96 (2H, d, 3_J_HH 8.0, OAr H), 3.22 (2H, t, 3_J_HH 5.0, CH₂), 2.85 (3H, s, CH₃), 2.77 (3H, s, CH₃), 2.72 (2H, t, 3_J_HH 5.0, CH₂); δ_C 153.5 (s, OAr C), 145.1 (d, $^1$JC 2.0, C-4a), 143.3 (d, $^2$JC 14.4, C-6), 141.5 (s, SO₂Ar C), 134.4 (d, $^1$JC 256.7, C-7), 132.3 (s, SO₂Arortho CH), 128.6 (d, $^2$JC 9.1, C-8), 128.1 (s, OAr CH), 127.4 (s, SO₂Armeta CH), 126.6 (s, SO₂Arpara CH), 123.7 (d, $^3$JC 2.4, C-8a), 122.8 (s, OAr CH), 118.8 (s, OAr CH), 46.4 (s, CH₂), 45.9 (s, CH₃), 42.1 (s, CH₂), 35.5 (s, CH₃); m/z (EI)$^+$ 413 ([M]$^+$, 90), 398 ([M-CH₃]$^+$, 4), 272 ([M-SO₂Ph]$^+$, 25), 77 ([M-C$_{15}$H$_{14}$N$_3$SO$_3$F]$^+$, 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 \(N,N'-\text{Diethyl-1,4-dimethyl-8-(phenylsulfonyl)}-1,2,3,4\)-tetrahydropyrido[2,3-\(b\)]pyrazin-6-amine 55

\(N,N'-\text{Dimethyl} \) ethylenediamine 2a (0.077 g, 0.88 mmol) and sodium hydrogencarbonate (0.13 g, 1.6 mmol) were added to acetonitrile (25 ml) under argon. \(N,N'-\text{Diethyl-3,5,6-trifluoro-4-(phenylsulfonyl)pyridine-2-amine} \) 41a (0.14 g, 0.45 mmol) was then added and the resulting solution was refluxed for 2 d after which time \(^{19}\text{F NMR} \) 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 \(N,N'-\text{diethyl-1,4-diimethyl-8-(phenylsulfonyl)}-1,2,3,4\)-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); \(\delta_H \) 7.95 (2H, d, \(^{3}J_{HH} 7.0, \text{SO}_2\text{Ar}_{ortho}\)), 7.50 (1H, t, \(^{3}J_{HH} 7.5, \text{SO}_2\text{Ar}_{para}\)), 7.40 (2H, t, \(^{3}J_{HH} 7.5, \text{SO}_2\text{Ar}_{meta}\)), 6.40 (1H, s, H-7), 3.48 (4H, q, \(^{3}J_{HH} 7.0, \text{N(CH}_2\text{CH}_3)_2\)), 3.31 (2H, t, \(^{3}J_{HH} 5.4, \text{CH}_2\)), 2.72 (3H, s, NCH\(_3\)), 2.39 (2H, t, \(^{3}J_{HH} 5.4, \text{CH}_2\)), 1.18 (6H, t, \(^{3}J_{HH} 7.0, \text{N(CH}_2\text{CH}_3)_2\)); \(\delta_C \) 152.3 (s, C-6), 150.8 (s, C-4\(\alpha\)), 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\(\alpha\)), 89.3 (s, C-7), 45.9 (s, CH\(_2\)), 43.6 (s, NCH\(_3\)), 41.8 (s, N(CH\(_2\text{CH}_3)_2\)), 41.7 (s, CH\(_2\)), 35.1 (s,
Preparation of 7-Fluoro-1,2,3,4-tetrahydro-1,4-dimethyl-6-phenoxy-8-(phenylsulfonyl)pyrido[2,3-b]pyrazine 56

$\text{N,N'}$-Dimethylethlenediamine 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 $^1$H 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$_3$O$_3$FS requires [M]$^+$ 413.1209); $\delta_H$ -151.88 (s, F-7); $\delta_H$ 7.96 (2H, d, $^3$J$_{HH}$ 7.5, SO$_2$Ar$_{ortho}$ H), 7.58 (1H, t, $^3$J$_{HH}$ 7.0, SO$_2$Ar$_{para}$ H), 7.48 (2H, t, $^3$J$_{HH}$ 8.0, SO$_2$Ar$_{meta}$H), 7.29 (2H, t, $^3$J$_{HH}$ 8.0, OAr H), 7.10 (1H, t, $^3$J$_{HH}$ 7.5, OAr H), 7.02 (2H, d, $^3$J$_{HH}$ 8.0, OAr H) 3.29 (2H, t, $^3$J$_{HH}$ 5.0, NCH$_2$), 2.92 (3H, s, NCH$_3$), 2.79 (2H, t, $^3$J$_{HH}$ 5.0, NCH$_2$); $\delta_C$ 153.7 (s, OAr C), 145.1 (d, $^4$J$_{CF}$ 2.0, C-4a), 143.3
Chapter 10

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

\[
\text{SO}_2\text{Ph} \quad \text{F} \quad \text{F} \\
\text{F} \quad \text{N} \quad \text{N} \quad \text{Et}_2 \\
\text{SO}_2\text{Ph} \quad \text{F} \quad \text{F} \\
\text{N} \quad \text{N} \quad \text{Et}_2
\]

\[
\text{CH}_2\text{CN} \quad \text{NaHCO}_3
\]

\[\text{57} \quad 58\%\]

2-Methylaminoethanol \(\text{5a}\) (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 \(\text{41a}\) (0.25 g, 0.79 mmol) was added and the resulting solution was refluxed for 6 d after which time \(^{19}\text{F}\) 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 \(\text{57}\) (0.17 g, 58%) as a yellow oil; ([M]^+ 399.1439, \(\text{C}_{18}\text{H}_{23}\text{N}_{3}\text{SO}_{3}\text{F}_{2}\) requires 399.1428); \(\delta_{\text{F}}\) -73.25 (1F, d, \(\text{J}_{\text{FF}}\) 31.6, F-2), -134.30 (1F, d, \(\text{J}_{\text{FF}}\) 33.8, F-5); \(\delta_{\text{H}}\) 8.01 (2H, dm, \(\text{J}_{\text{HH}}\) 8.0, \(\text{Ar}_{\text{ortho}}\) H), 7.64 (1H, tm,
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_{3}F_{2}SO_{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-4a), 130.7 (dd, 3J_{CF} 12.0, 4J_{CF} 5.0, C-8a), 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).

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$_3$F$_3$ requires [M+H]$^+$ 230.0900); $\delta_F$ -88.14 (1F, m, F-6), -130.48 (1F, dd, $^3$J$_{FF}$ 33.8, $^4$J$_{FF}$ 11.3, F-5), -153.41 (1F, dd, $^4$J$_{FF}$ 24.8, $^5$J$_{FF}$ 9.0, F-3); $\delta_H$ 3.49 (4H, qd, $^3$J$_{HH}$ 7.0, $^4$J$_{HF}$ 2.0, CH$_2$), 1.21 (6H, t, $^3$J$_{HH}$ 7.0, CH$_3$); $\delta_C$ 143.2 (dd, $^1$J$_{CF}$ 216.5, $^2$J$_{CF}$ 12.4, C-6), 142.7 (m, C-3), 140.5 (m, C-2), 131.6 (dd, $^1$J$_{CF}$ 260.0, $^2$J$_{CF}$ 33.9, C-5), 107.0 (s, CN), 102.5 (m, C-4), 43.4 (d, $^4$J$_{CF}$ 5.8, CH$_2$), 12.5 (s, CH$_3$); m/z (EI$^+$) 229 ([M]$^+$, 19), 214 ([M-CH$_3$]$^+$, 82), 186 ([M-NCH$_2$CH$_3$]$^+$, 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_{4}F_{2} requires [M+H]^+ 283.1729); δF - 74.68 (1F, d, ^5J_{FF} 31.6, F-6), -132.58 (1F, d, ^5J_{FF} 31.6, F-3); δH 3.49 (4H, qd, ^3J_{HH} 7.0, ^5J_{HF} 1.5, CH2), 3.06 (4H, qd, ^3J_{HH} 7.0, ^5J_{HF} 1.0, CH2), 1.21 (6H, t, ^3J_{HH} 7.0, CH3), 1.02 (6H, t, ^3J_{HH} 7.0, CH3); δC 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, CH2), 43.1 (d, ^4J_{CF} 5.8, CH2), 12.7 (s, CH3), 12.6 (s, CH3); m/z (EI') 282 ([M]^+, 71), 267 ([M-CH3]^+, 100), 253 ([M-CH2CH3]^+, 10), 239 ([M-CH2CH2CH3]^+, 53).

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

\[
\begin{align*}
\text{CN} & \quad \text{F} \\
\text{F} & \quad \text{N} \\
\text{18h} & \quad \text{PhNH}_2 + \text{CH}_3\text{CN} \xrightarrow{\text{NaHCO}_3} \text{CN} & \quad \text{F} \\
\text{F} & \quad \text{N} \\
\text{60} & \quad \text{NHPh} \\
\end{align*}
\]

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. ^19F 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\textsubscript{12}H\textsubscript{6}N\textsubscript{3}F\textsubscript{3} requires: C, 57.8; H, 2.4; N, 16.9%); \( \delta \text{f(d\textsubscript{6}-Acetone)} -87.96 \) (1F, dd, \( ^3J \text{FF} 32.0, ^4J \text{FF} 22.0, \text{F-5} \)), -134.61 (1F, dd, \( ^3J \text{FF} 31.0, ^5J \text{FF} 9.0, \text{F-6} \)), -148.75 (1F, dd, \( ^4J \text{FF} 22.0, ^5J \text{FF} 9.2, \text{F-3} \)); \( \delta \text{h(d\textsubscript{6}}-\text{Acetone) 7.55 (2H, d, } ^1J \text{HH 7.6, Ar\textsubscript{ortho} H), 7.39 (2H, t, } ^3J \text{HH 7.6, Ar\textsubscript{meta} H), 7.16 (1H, t, } ^3J \text{HH 7.0, Ar\textsubscript{para} H), 6.69 (1H, br s, NH); } \delta \text{c(d\textsubscript{6}-Acetone) 144.5 (ddm, } ^1J \text{CF 229.9, } ^2J \text{CF 13.2, C-5), 143.9 (dm, } ^1J \text{CF 270.5, C-3), 139.6 (m, C-4), 139.0 (s, Ar C), 134.4 (dd, } ^1J \text{CF 258.5, } ^2J \text{CF 34.3, C-6), 129.1 (s, Ar\textsubscript{meta} CH), 123.8 (s, Ar\textsubscript{para} CH), 120.2 (s, Ar\textsubscript{ortho} CH), 107.8 (d, } ^3J \text{CF 4.2, CN), 102.4 (m, C-2); m/z (EI\textsuperscript{+}) 248 ([M-H]\textsuperscript{+}, 100), 77 ([M-C\textsubscript{6}HN\textsubscript{3}F\textsubscript{3}]\textsuperscript{+}, 94).

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

\[
\begin{align*}
\text{CN} & \quad \text{F} & \quad \text{CN} & \quad \text{F} & \quad \text{EtO}^+ \quad \text{Na}^+ \\
\text{F} & \quad \text{N} & \quad \text{F} \quad & \quad \text{CN} & \quad \text{OEt} & \quad \text{F} & \quad \text{F} \\
18h & \quad & \quad 61a & \quad & \quad 61b \\
\end{align*}
\]

Dry ethanol (0.13 g, 2.84 mmol) and sodium (0.07 g, 2.84 mmol) were added to tetrahydrofurran (3 ml) under argon and stirred for 2 h. The tetrahydrofurran 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. \( ^19F \text{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, 3_J_F 29.3, 4_J_F 13.5, F-2), -99.46 (1F, t, 4_J_F 15.8, F-6), -139.32 (1F, dd, 3_J_F 29.3, 5_J_F 20.3, F-3); δ_C(d_6-Acetone) 144.2 (ddd, 1_J_CF 238.9, 2_J_CF 11.0, 3_J_CF 2.9, C-2), 142.8 (ddd, 1_J_CF 262.8, 3_J_CF 30.1, 4_J_CF 6.6, C-5), 141.2 (dd, 2_J_CF 34.4, 3_J_CF 6.3, C-5), 139.7 (dm, 1_J_CF 234.6, C-3), 108.8 (t, 2_J_CF 3.8, C-4), 104.6 (m, CH_2), 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, 3_J_F 22.6, F-2), -134.94 (1F, dd, 3_J_F 29.3, 4_J_F 6.8, F-3), -146.87 (1F, dd, 4_J_F 22.6, 5_J_F 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

![Reaction Scheme]

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 18b (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; δF -87.31 (1F, dd, 3JFF 31.0, 5JFF 21.1, F-2), -131.33 (1F, dd, 3JFF 31.0, 4JFF 7.3, F-3), -140.67 (1F, dd, 4JFF 20.1, 5JFF 7.3, F-5); m/z (EI) 250 ([M]+, 94), 77 ([M-C6N2O3]+, 100); 2,3,6-trifluoro-5-phenoxyisonicotinonitrile 62b; and 2,5-difluoro-3,6-phenoxyisonicotinonitrile 62c; δF -85.43 (1F, m, F-2), 133.11 (1F, m, F-5); m/z (EI) 324 ([M]+, 77), 77 (12H5N2O3F3)+, 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; C12H5N2O3F3 requires: C, 57.6; H, 2.0; N, 11.2%); δF -77.92 (1F, dd, 3JFF 32.0, 4JFF 12.8, F-2), -87.21 (1F, dd, 4JFF 20.1, 5JFF 12.8, F-6), -134.53 (1F, dd, 3JFF 31.0, 5JFF 20.1, F-3); δH 7.32 (2H, tm, 3JHH 7.6, OArortho H), 7.15 (1H, tm, 3JHH 7.2, OArpara H), 6.92 (2H, dm, 3JHH 8.4, OArmeta H); δC 156.5 (s, OAr C), 147.8 (ddd, 1JCF 250.8, 3JCF 11.0, 4JCF 3.4, C-6), 144.2 (dd, 1JCF 246.5, 2JCF 12.4, C-3), 142.9 (ddd, 1JCF 271.8, 2JCF 30.0, 3JCF 6.6, C-2), 137.3 (m, C-5), 130.4 (s, OArortho CH), 125.4 (s, OArpara CH), 116.7 (s, OArmeta CH), 111.3 (m, C-4), 107.7 (t, 3JCF 3.8, CN); m/z (EI) 250 ([M]+, 74), 77 (12H5N2O3F3)+, 100).

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

![Chemical Structure](image)

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 200
(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, $^5$J$_{FF}$ 29.3, F-6), -119.01 (1F, d, $^5$J$_{FF}$ 27.1, F-3); δ$_H$ 3.19 (2H, q, $^3$J$_{HH}$ 7.5, CH$_2$), 3.01 (2H, q, $^3$J$_{HH}$ 7.5, CH$_2$), 1.39 (3H, t, $^3$J$_{HH}$ 7.5, CH$_3$), 1.29 (3H, t, $^3$J$_{HH}$ 7.5, CH$_3$); δ$_C$ 158.5 (dd, $^1$J$_{CF}$ 237.5, $^4$J$_{CF}$ 2.4, C-6), 153.7 (dd, $^1$J$_{CF}$ 265.6, $^4$J$_{CF}$ 5.3, C-3), 148.7 (dd, $^2$J$_{CF}$ 20.1, $^3$J$_{CF}$ 15.3, C-2), 116.3 (dd, $^2$J$_{CF}$ 13.3, $^3$J$_{CF}$ 5.1, C-4), 114.2 (dd, $^2$J$_{CF}$ 41.5, $^3$J$_{CF}$ 3.4, C-5), 110.4 (d, $^3$J$_{CF}$ 4.3, CN), 29.9 (d, $^4$J$_{CF}$ 3.8, SCH$_2$), 24.5 (d, $^4$J$_{CF}$ 1.5, SCH$_2$), 15.2 (s, CH$_3$), 14.4 (s, CH$_3$); m/z (EI$^+$) 260 ([M$^+$]), 199 ([M-SCH$_2$CH$_3$]$^+$, 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-Et]$^+$, 100); and 3-(ethylsulfanyl)-2,5,6-trifluoroisonicotinonitrile 63c; δ$_F$ -63.42 (1F, dd, $^3$J$_{FF}$ 30.1, $^4$J$_{FF}$ 11.8, F-6), -84.05 (1F, dd, $^4$J$_{FF}$ 20.1, $^5$J$_{FF}$ 10.0, F-2), -136.11 (1F, dd, $^3$J$_{FF}$ 29.3, $^5$J$_{FF}$ 21.1, F-5); m/z (EI$^+$) 218 ([M$^+$]), 57), 190 ([M-CH$_2$CH$_3$]$^+$, 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

\[
\begin{align*}
&\text{CN} & \text{CN} \\
&\text{F} & \text{F} \\
&\text{N} & \text{Ph} \\
&\text{F} & \text{F} \\
&\text{18h} & \text{PhSH} \\
\end{align*}
\]

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; \(\text{C}_{18}\text{H}_{10}\text{N}_{2}\text{S}_{2}\text{F}_{2}\) requires: C, 60.8; H, 2.8; N, 7.9%; \(\delta_{\text{CF}}\) -62.61 (1F, d, \(^{5}\)J\(_{\text{FF}}\) 27.1, F-2), -117.95 (1F, d, \(^{5}\)J\(_{\text{FF}}\) 29.3, F-5); \(\delta_{\text{H}}\) 7.55 (2H, m, Ar H), 7.45 (5H, m, Ar H), 7.32 (3H, m, Ar H); \(\delta_{\text{C}}\) 158.0 (dd, \(^{1}\)J\(_{\text{CF}}\) 240.4, \(^{4}\)J\(_{\text{CF}}\) 1.9, C-2), 153.2 (dd, \(^{1}\)J\(_{\text{CF}}\) 267.5, \(^{4}\)J\(_{\text{CF}}\) 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, \(^{4}\)J\(_{\text{CF}}\) 2.0, Ar C), 116.7 (dd, \(^{2}\)J\(_{\text{CF}}\) 14.4, \(^{3}\)J\(_{\text{CF}}\) 3.8, C-6), 116.2 (dd, \(^{2}\)J\(_{\text{CF}}\) 40.5, \(^{3}\)J\(_{\text{CF}}\) 3.4, C-3); \(m/z\) (EI\(^{+}\)) 356 ([M\(^{+}\)], 97), 109 ([M-C\(_{12}\text{H}_{3}\text{N}_{2}\text{F}_{2}\text{S}])^{+}, 76), 77 ([M-C\(_{12}\text{H}_{3}\text{N}_{2}\text{F}_{2}\text{S}])^{+}, 100).
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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 hydrogen carbonate (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$_8$H$_6$N$_4$F$_2$ requires: C, 49.0; H, 3.1; N, 28.6%); $\delta_F$ -104.78 (1F, d, $^3$J$_{FF}$ 22.6, F-6), -156.14 (1F, d, $^3$J$_{FF}$ 22.6, F-7); $\delta_H$ 7.30 (1H, br s, NH), 7.00 (1H, br s, NH), 3.28 (2H, m, CH$_2$), 3.28 (2H, m, CH$_2$); $\delta_C$ 140.7 (dd, $^3$J$_{CF}$ 17.0, $^4$J$_{CF}$ 2.6, C-4a), 138.7 (dd, $^1$J$_{CF}$ 217.5, $^2$J$_{CF}$ 13.5, C-6), 132.5 (dd, $^3$J$_{CF}$ 3.5, $^4$J$_{CF}$ 1.3, C-8a), 132.0 (dd, $^1$J$_{CF}$ 246.2, $^2$J$_{CF}$ 31.7, C-7), 112.0 (dd, $^3$J$_{CF}$ 4.6, $^4$J$_{CF}$ 1.3, CN), 88.2 (dd, $^2$J$_{CF}$ 16.6, $^3$J$_{CF}$ 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-2H-pyrido[3,2-b][1,4]oxazine-8-carbonitrile 66

2-Methylaminoethanol 5a (0.85 g, 11.36 mmol) and sodium hydrogen carbonate (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$_9$H$_7$N$_3$F$_2$O requires: C, 51.2; H, 3.3; N, 19.9%); $\delta$F -97.60 (1F, d, $^3$J$_{FF}$ 22.9, F-6), -155.35 (1F, d, $^3$J$_{FF}$ 22.9, F-7); $\delta$H 4.39 (2H, t, $^3$J$_{HH}$ 4.6, CH$_2$), 3.49 (2H, t, $^3$J$_{HH}$ 4.8, CH$_2$), 3.08 (3H, s, CH$_3$); $\delta$C 143.5 (dd, $^1$J$_{CF}$ 215.3, $^2$J$_{CF}$ 13.4, C-6), 141.4 (dd, $^3$J$_{CF}$ 15.3, $^4$J$_{CF}$ 2.3, C-4a), 139.2 (dd, $^3$J$_{CF}$ 5.4, $^4$J$_{CF}$ 1.5, C-8a), 134.0 (dd, $^1$J$_{CF}$ 255.8, $^2$J$_{CF}$ 32.4, C-7), 109.9 (d, $^3$J$_{CF}$ 4.2, CN), 99.5 (dd, $^2$J$_{CF}$ 15.2, $^3$J$_{CF}$ 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$_3$N]$^+$, 60), 156 ([M-CH$_3$NCN]$^+$, 37), 128 ([M-CH$_3$NCH$_2$CH$_2$CN]$^+$, 50).
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Preparation of (6-pyrazolyl)(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]pyrazine-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$_3$F$_2$O requires [M+H]$^+$ 304.1261; δ$_F$ -99.56 (1F, d, $^3$J$_{FF}$ 26.3, F-6), -162.43 (1F, d, $^3$J$_{FF}$ 26.3, F-7); δ$_H$ 7.89 (2H, dm, $^3$J$_{HH}$ 7.2, Ar H), 7.62 (1H, tm, $^3$J$_{HH}$ 8.0, Ar H), 7.48 (2H, tm, $^3$J$_{HH}$ 7.2, Ar H), 3.37 (2H, t, $^3$J$_{HH}$ 4.8, CH$_2$), 3.11 (3H, s, CH$_3$), 3.06 (2H, t, $^3$J$_{HH}$ 4.8, CH$_2$), 2.59 (3H, s, CH$_3$); δ$_C$ 192.2 (m, C=O), 144.1 (dm, $^3$J$_{CF}$ 11.7, C-4a), 144.0 (dd, $^1$J$_{CF}$ 227.7, $^2$J$_{CF}$ 15.0, C-6), 136.4 (s, Ar C), 134.2 (s, Ar CH), 132.3 (dd, $^1$J$_{CF}$ 242.1, $^2$J$_{CF}$ 31.0, C-7), 129.6 (s, Ar CH), 128.8 (s, Ar CH), 128.1 (m, C-8a), 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

![Chemical Structure]

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$_8$N$_2$F$_2$O$_3$ requires: C, 54.1; H, 3.0; N, 10.5%); $\delta$F -89.51 (1F, d, $^3$J$_{FF}$ 20.9, F-7), -138.36 (1F, d, $^3$J$_{FF}$ 21.1, F-6); $\delta$H 4.52 (2H, q, $^3$J$_{HH}$ 7.0, CH$_2$), 2.86 (3H, s, 3-CH$_3$), 1.46 (3H, t, $^3$J$_{HH}$ 7.5, CH$_2$CH$_3$); $\delta$C 167.2 (d, $^5$J$_{CF}$ 4.4, C-3), 161.8 (s, C=O), 151.6 (dd, $^3$J$_{CF}$ 15.0, $^4$J$_{CF}$ 3.4, C-1a), 148.0 (dd, $^1$J$_{CF}$ 247.5, $^2$J$_{CF}$ 17.3, C-7), 146.0 (dd, $^1$J$_{CF}$ 266.4,
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$^2$J_{CF} 28.9, C-6), 116.1 (dd, $^3$J_{CF} 3.9, $^4$J_{CF} 1.4, C-4a), 110.2 (d, $^3$J_{CF} 4.8, CN), 109.9 (s, C-4), 106.0 (dd, $^2$J_{CF} 14.9, $^3$J_{CF} 3.8, C-5), 61.6 (s, CH$_2$CH$_3$), 15.0 (s, CH$_2$CH$_3$), 14.6 (s, 3-CH$_3$); m/z (EI$^+$) 266 ([M]$^+$, 36), 193 ([M-CO$_2$CH$_2$CH$_3$]$^+$, 30), 138 ([M-C$_6$H$_8$O$_3$]$^+$, 26); and ethyl 2-(4-cyano-2,5,6-trifluoropyridin-3-yl)-3-oxobutanoate 69 (0.30 g, 18%) as a yellow oil; $\delta_F$ - 68.44 (1F, dd, $^4$J$_FF$ 20.9, $^5$J$_FF$ 10.9, F-2), -68.42 (1F, dd, $^3$J$_FF$ 28.4, $^4$J$_FF$ 11.1, F-6), -137.81 (1F, overlapping dd, $^3$J$_FF$ 28.4, F-5); m/z (EI$^+$) 286 ([M]$^+$, 36), 198 ([M-C$_3$H$_5$O$_3$]$^+$, 100).

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

![Chemical Structure]

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-ß]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$_3$O$_3$F requires [M+H]$^+$ 320.1405; $\delta_F$ -131.43 (1F, s, F-5); $\delta_H$ 4.40 (2H,
q, $^3$J$_{HH}$ 7.0, OCH$_2$CH$_3$), 3.50 (4H, qd, $^3$J$_{HH}$ 7.0, $^5$J$_{HF}$ 2.0, N(CH$_2$CH$_3$)$_2$), 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$_3$)$_2$); $\delta_C$ 163.0 (s, C=O), 161.8 (d, $^4$J$_{CF}$ 1.9, C-2), 155.0 (d, $^4$J$_{CF}$ 2.4, C-7a), 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-3a), 105.3 (s, CN), 105.5 (d, $^2$J$_{CF}$ 19.2, C-4), 61.0 (s, OCH$_2$CH$_3$), 44.9 (d, $^4$J$_{CF}$ 6.3, N(CH$_2$CH$_3$)$_2$), 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$_2$CH$_3$]$^+$, 30).

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

![Chemical structure](image)

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; $\delta_F$ -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; $\delta_H$ 4.47 (4H, q, $^3$J$_{HH}$ 7.2, OCH$_2$CH$_3$), 4.26 (2H, q, $^3$J$_{HH}$ 6.8, CO$_2$CH$_2$CH$_3$), 2.76 (3H, s, 2-CH$_3$), 1.46 (9H, 2
overlapping t, OCH\textsubscript{2}CH\textsubscript{3} & CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}; m/z (El\textsuperscript{+}) 318 ([M]\textsuperscript{+}, 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 \textsuperscript{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]\textsuperscript{+} 446.0754, C\textsubscript{24}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}S\textsubscript{2} requires [M]\textsuperscript{+} 446.0753); \textsuperscript{1}H 7.15-7.50 (10H, m, Ar CH), 4.39 (2H, q, \textsuperscript{3}J\textsubscript{HH} 7.2, CH\textsubscript{2}), 2.65 (3H, s, 2-CH\textsubscript{3}), 1.34 (3H, t, \textsuperscript{3}J\textsubscript{HH} 7.2, CH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C 164.8 (s, C-2), 162.3 (s, C-7a), 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-3a), 109.5 (s, CN), 61.4 (s, CH₂),
14.7 (s, CH₃), 14.6 (s, CH₃); m/z (EI⁺) 446 ([M]⁺, 100), 417 ([M-CH₂CH₃]⁺, 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. ¹⁹F 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; δF -84.26 (IF, d, ³JFF 23.7, F-5), -136.68 (IF, d, ³JFF 23.7, F-6); m/z (EI⁺) 328 ([M]⁺, 50), 283 ([M-OCH₂CH₃]⁺, 82), 256 ([MH-CO₂CH₂CH₃]⁺, 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_{2}F_{2}O_{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-7a), 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-3a), 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**

![Chemical structure](image)

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. ^19F 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
Chapter 11

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; δF -63.03 (1F, dd, 3JFF 29.3, 4JFF 11.3, F-6), -81.75 (1F, dd, 4JFF 22.6, 5JFF 11.3, F-2), -135.46 (1F, dd, 3JFF 27.1, 5JFF 20.3, F-5); m/z (EI+) 276 ([M]+, 66), 203 ([M-CO2CH2CH3]+, 100); ethyl[(4-cyano-3,5,6-trifluoropyridin-2-yl)sulfanyl]acetate 76b; δF -85.95 (1F, dd, 3JFF 31.6, 5JFF 22.6, F-6), -116.45 (1F, dd, 3JFF 31.6, 4JFF 4.5, F-5), -137.61 (1F, dd, 4JFF 22.6, 5JFF 4.5, F-3); m/z (EI+) 276 ([M]+, 4), 203 ([M-CO2CH2CH3]+, 16); and ethyl[(4-cyano-6-ethoxycarbonylmethylsulfanyl-2,5-difluoropyridin-3-yl)sulfanyl]-acetic acid ethyl ester 76c; δF -64.35 (1F, d, 5JFF 29.1, F-2), -118.85 (1F, d, 5JFF 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-trifluorothienc[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

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room temperature and stirred for 2 d, after which time $^{19}\text{F} \text{NMR}$ 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-trifluorothieno[2,3-c]pyridine-2-carboxylate 77 (0.07 g, 88%) as a yellow solid; mp 104.1-105.6°C; $\delta_F$ -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); $\delta_H$ 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$_3$); $\delta_C$ 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 (dd, $^2J_{CF}$ 12.1, $^3J_{CF}$ 7.2, $^4J_{CF}$ 2.4, C-3a), 117.9 (dd, $^2J_{CF}$ 39.3, $^3J_{CF}$ 4.3, C-7a), 103.6 (s, C-2), 60.4 (s, CH$_2$), 13.3 (s, CH$_3$); $m/z$ (EI) 276 ([M]$^+$, 50), 230 ([M-CH$_3$CH$_2$OH]$^+$, 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
$^{19}\text{F} \text{ NMR indicated 100\% conversion of starting material. The reaction mixture was concentrated, poured onto water (30 ml), extracted with dichloromethane (3 x 50 ml) and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the crude product as a yellow oil (0.28 g) consisting of one major component. Purification by column chromatography on silica gel (4:1 n-hexane/ethyl acetate) followed by recrystallisation from ethyl acetate gave 3-amino-5-ethoxycarbonylmethylsulfanyl-4,7-difluoro-thieno[2,3-c]pyridine-2-carboxylic acid ethyl ether 78 (50 mg, 23\%) as a yellow solid; mp 110.2-111.5°C; ([M+H]$^+$ 377.0435, C$_{14}$H$_{14}$N$_2$O$_4$F$_2$S$_2$ requires [M+H]$^+$ 377.0436); δ$_F$ -71.35 (1F, d, $^5$$J_{FF}$ 31.6, F-7), -137.26 (1F, d, $^5$$J_{FF}$ 31.6, F-4); δ$_H$ 6.20 (2H, br s, NH$_2$), 4.37 (2H, q, $^3$$J_{HH}$ 7.2, CH$_2$CH$_3$), 4.22 (2H, q, $^3$$J_{HH}$ 7.2, CH$_2$CH$_3$), 3.95 (2H, s, SCH$_2$), 1.39 (3H, t, $^3$$J_{HH}$ 6.8, CH$_2$CH$_3$), 1.28 (3H, t, $^3$$J_{HH}$ 7.2, CH$_2$CH$_3$); δ$_C$ 169.2 (s, C=O), 164.7 (s, C=O), 152.5 (d, $^1$$J_{CF}$ 238.0, C-7), 150.2 (dd, $^1$$J_{CF}$ 251.9, $^4$$J_{CF}$ 5.6, C-4), 145.6 (s, C-2), 134.2 (dd, $^2$$J_{CF}$ 22.5, $^3$$J_{CF}$ 13.4, C-5), 131.1 (s, C-3), 130.5 (dd, $^2$$J_{CF}$ 14.3, $^3$$J_{CF}$ 7.1, C-7α), 118.9 (d, $^2$$J_{CF}$ 41.4, C-3α), 62.1 (s, CH$_2$CH$_3$), 61.5 (s, CH$_2$CH$_3$), 32.7 (s, SCH$_2$), 14.6 (s, CH$_2$CH$_3$), 14.3 (s, CH$_2$CH$_3$); m/z (EI$^+$) 376 ([M$^+$, 58), 331 ([M-CH$_3$CH$_2$O]$^+$, 16), 303 ([M-CO$_2$CH$_2$CH$_3$]$^+$, 100), 257 ([M-SCH$_2$CO$_2$CH$_2$CH$_3$]$^+$, 42).
Preparation of \(N,N'-\text{Diethyl-3,5,6-trifluoropyrazin-2-amine} \) 80

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\text{N} \\
\text{F} \\
\text{F} \\
\text{N} \\
\text{F} \\
\text{79}
\end{array}
\begin{array}{c}
\text{NEt}_2\text{Li} \\
\text{THF} \\
\text{80}
\end{array}
\begin{array}{c}
\text{F} \\
\text{N} \\
\text{Et}_2
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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 \(^{19}\text{F} \text{NMR}\) 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 \(N,N'-\text{diethyl-3,5,6-trifluoropyrazin-2-amine} \) 80 (0.58 g, 43%) as a colourless oil; ([M]° 205.0818, \(C_8H_{10}N_3F_3\) requires [M]° 205.0821); \(\delta_F\) -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); \(\delta_H\) 3.44 (4H, qd, \(^3J_{HH}\) 7.0, \(^5J_{HH}\) 1.5, CH2), 1.14 (6H, \(^3J_{HH}\) 7.5, CH3); \(\delta_C\) 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, CH2), 13.7 (s, CH3); \(m/z\) (El⁺) 205 ([M]⁺, 41), 190 ([M-CH3]⁺, 100), 162 ([M-NCH2CH3]⁺, 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$_2$F$_2$S$_2$ 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, $^1$J$_{CF}$ 251.2, $^4$J$_{CF}$ 9.1, C-2,5), 135.9 (t, $^2$J$_{CF}$ 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$_{16}$H$_{15}$N$_2$F$_2$S$_2$]$^+$, 100).

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

$N,N'$-Dimethylethlenediamine 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; C₈H₁₀N₄F₂ requires: C, 48.0; H, 5.0; N, 28.0%); δF -118.60 (2F, s, F-6,7); δH 3.43 (4H, s, CH₂), 3.01 (6H, s, CH₃); δC 138.5 (t, 3JC₅ 5.3, C-4a,8a), 136.7 (d, 1JC₅ 229.1, C-6), 136.3 (d, 1JC₅ 229.1, C-7), 46.9 (s, CH₂), 36.7 (s, CH₃); m/z (EI⁺) 200 ([M⁺], 100), 185 ([M-CH₃]⁺, 90), 171 ([M-CH₂CH₃]⁺, 64).

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

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\text{N} & \quad \text{N} \\
\text{F} & \quad \text{F}
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Ethylenediamine 2d (1.13 g, 18.8 mmol) and sodium hydrogen carbonate (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. ¹⁹F 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, C₆H₈N₄F₂ requires [M+H]⁺ 173.0633); δF(DMSO-d₆) -118.2 (2F, s, F-6,-7); δH(DMSO-d₆) 7.12 (2H,
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 hydrogen carbonate (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; $\delta_F$ -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-CH$_2$OH]$^+$, 100); 6,7-difluoro-4-methyl-3,5-dihydro-2H-pyraino[2,3-b]/[1,4]oxazine 85; $\delta_F$ -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, C10H18N4F2O2 requires [M]+ 262.1236); δF -88.17 (2F, s, F-3,6); δH 3.72 (4H, t, 3JHH 5.5, CH2), 3.42 (4H, t, 3JHH 5.0, CH2), 2.96 (6H, s, CH3), 2.50 (2H, br s, OH); δC 142.2 (dd, 1JCF 252.6, 4JCF 13.8, C-3,6), 132.4 (t, 2JCF 18.1, C-3,5), 59.3 (s, CH2), 53.4 (s, CH2), 37.3 (s, CH3); m/z (EI+) 262 ([M]+, 76), 231 ([M-CH2OH]+, 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 hydrogen carbonate (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 19F 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; δF -90.01 (1F, dd, 3JFF 49.6, 5JFF 11.3, F-6), -99.57 (1F, dd, 3JFF 47.4, 4JFF 18.0, F-5), -113.79 (1F, dd, 4JFF 15.8, 5JFF 11.3, F-3); δH 3.87 (2H, t, 3JHH 5.5, CH2), 3.69 (2H, t, 3JHH 5.0, CH2), 3.22 (3H, d, 5JHF 3.0, CH3), 1.92 (1H, br s, OH); δC 141.3 (ddd, 1JCF 243.2, 2JCF 28.7, 4JCF 3.8, C-6), 140.5 (ddd, 2JCF 24.1, 3JCF 8.6, 4JCF 2.8, C-2), 139.1 (dt, 1JCF 255.3, 3JCF 3.4, C-3), 132.9 (ddd, 1JCF 246.6, 3JCF 26.0, 3JCF 6.2, C-5), 60.8 (s, CH2), 54.1 (d, 4JCF 5.3, CH2), 38.8 (d, 219
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$^4\text{J}_{\text{CF}}$ 6.7, CH$_3$; $m/z$ (El$^+$) 207 ([M]$^+$, 60), 176 ([M-CH$_2$OH]$^+$, 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)disulfanediyldianiline 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)disulfanediyldianiline 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$_{13}$NaF$_2$S$_2$ requires: C, 53.0; H, 3.3; N, 15.5\%); $\delta_{\text{F}}$(DMSO-d$_6$) -82.10 (2F, s, F-3,6); $\delta_{\text{H}}$(DMSO-d$_6$) 7.24 (2H, dd, $^3\text{J}_{\text{HH}}$ 7.5, $^4\text{J}_{\text{HH}}$ 1.5, Ar CH), 7.18 (2H, td, $^3\text{J}_{\text{HH}}$ 6.9, $^4\text{J}_{\text{HH}}$ 1.5, Ar CH), 6.76 (2H, dd, $^3\text{J}_{\text{HH}}$ 8.1, $^4\text{J}_{\text{HH}}$ 1.2, Ar CH), 6.55 (2H, td, $^3\text{J}_{\text{HH}}$ 7.2,
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$^4$JHH 1.2, (Ar CH), 5.45 (4H, br s, NH$_2$); $^4$JC$_F$ 252.0, $^4$JC$_F$ 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, ArC NH$_2$); 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; $^5$F -79.96 (1F, dd, $^3$J$_{FF}$ 43.8, $^5$J$_{FF}$ 9.0, F-6), -91.39 (1F, dd, $^3$J$_{FF}$ 20.1, $^5$J$_{FF}$ 8.1, F-3), -94.86 (1F, dd, $^3$J$_{FF}$ 42.9, $^4$J$_{FF}$ 19.9, F-5); m/z (EI$^+$) 262 ([M]$^+$, 41), 174 ([M-(CH$_3$)$_2$CH$_2$CO$_2$]$^+$, 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\textsubscript{10}H\textsubscript{8}N\textsubscript{2}F\textsubscript{2}O\textsubscript{3} requires: C, 49.6; H, 3.3; N, 11.6\%); δ\textsubscript{F} -93.26 (1F, d, \textsuperscript{3}J\textsubscript{FF} 22.0, F-2), -95.61 (1F, d, \textsuperscript{3}J\textsubscript{FF} 22.0, F-3); δ\textsubscript{H} 4.43 (2H, q, \textsuperscript{3}J\textsubscript{HH} 7.2, CH\textsubscript{2}), 2.86 (3H, s, 6-CH\textsubscript{3}), 1.42 (3H, t, \textsuperscript{3}J\textsubscript{HH} 7.2, CH\textsubscript{2}CH\textsubscript{3}); δ\textsubscript{C} 168.5 (d, \textsuperscript{3}J\textsubscript{CF} 5.4, C-6), 161.9 (s, C=O), 147.3 (dd, \textsuperscript{3}J\textsubscript{CF} 8.0, \textsuperscript{4}J\textsubscript{CF} 1.9, C-4\textsubscript{a}), 146.5 (dd, \textsuperscript{1}J\textsubscript{CF} 245.9, \textsuperscript{2}J\textsubscript{CF} 28.2, C-2), 143.5 (dd, \textsuperscript{1}J\textsubscript{CF} 257.0, \textsuperscript{2}J\textsubscript{CF} 34.0, C-3), 131.6 (dd, \textsuperscript{3}J\textsubscript{CF} 11.8, \textsuperscript{4}J\textsubscript{CF} 5.3, C-7\textsubscript{a}), 109.7 (s, C-7), 61.5 (s, CH\textsubscript{2}), 15.4 (s, CH\textsubscript{3}), 14.5 (s, CH\textsubscript{2}CH\textsubscript{3}); m/z (EI\textsuperscript{+}) 242 ([M\textsuperscript{+}]\textsuperscript{+}, 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 \textsuperscript{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; δ\textsubscript{F}(CD\textsubscript{3}CN) -46.67 (1F, s, F-2), -65.34 (1F, s, F-6); δ\textsubscript{H}(CD\textsubscript{3}CN) 7.31 (2H, m, Ar H), 6.88 (1H, dm, \textsuperscript{3}J\textsubscript{HH} 8.0, Ar H), 6.74 (1H, tm, \textsuperscript{3}J\textsubscript{HH} 7.5, Ar H), 4.67 (2H, br s, NH\textsubscript{2}); δ\textsubscript{C}(CD\textsubscript{3}CN)
175.1 \text{(dd, } ^{2}J_{CF} 14.4, ^{4}J_{CF} 2.8, C-5\text{)}, 165.4 \text{(dd, } ^{1}J_{CF} 250.9, ^{3}J_{CF} 16.6, C-2\text{)}, 158.2 \text{(dd, } ^{1}J_{CF} 219.4, ^{4}J_{CF} 19.0, C-6\text{)}, 150.9 \text{(s, Ar C), 137.4 \text{(s, Ar CH), 132.8 \text{(s, Ar CH), 115.7 \text{(s, Ar CH), 109.1 \text{(dd, } ^{3}J_{CF} 28.4, ^{3}J_{CF} 8.2, C-4\text{), 107.2 \text{(s, Ar C); m/z (EI\textsuperscript{+}) 273.5 ([M\textsuperscript{+}], 67).}}}})

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

![Chemical structure](image)

A hastalloy autoclave (equipped with a teflon gasket and an inconel bursting disc) was charged with aluminium bromide \(50.0 \text{ g, 0.187 mol}\), pentafluoropyridine \(1 \text{ (20.0 g, 0.118 mol)}\) and hydrogen bromide \(25.0 \text{ g, 0.31 mol}\). 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 \(21.8 \text{ g, 53\%) as white crystals; mp 107.8-109.4°C; (Found: C, 17.0; N, 4.3; C\textsubscript{5}NBr\textsubscript{3}F\textsubscript{2} requires: C, 17.2; N, 4.0\%); \delta_{F} -103.64 (2F, s, F-3,5); \delta_{C} 153.9 \text{(dd, } ^{1}J_{CF} 262.2, ^{3}J_{CF} 0.8, C-3,5\text{), 122.8 \text{(dt, } ^{2}J_{CF} 20.6, ^{4}J_{CF} 6.1, C-2,6\text{), 110.4 \text{(t, } ^{2}J_{CF} 24.0, C-4\text{); m/z (EI\textsuperscript{+}) 349 ([M\textsuperscript{+}], 100), 270 ([M-Br]\textsuperscript{+}, 82), 191 ([M-Br\textsubscript{2}]\textsuperscript{+}, 88), 112 ([M-Br\textsubscript{3}]\textsuperscript{+}, 84).}}\)
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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

\[
\text{\[93\] + 2a} \xrightarrow{\text{CH₃CN, NaHCO₃}} \text{\[94\] (63%) + \[95\] (31%)}
\]

\(N,N'\)-dimethylethylenediamine 2a (1.76 g, 20 mmol) and sodium hydrogen carbonate (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 \(^{19}\text{F} \) 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. \(C_{9}H_{10}N_{3}Br_{2}F\) requires: C, 32.0; H, 3.0; N, 12.5%); \(\delta_{F} -128.29\) (1F, d, \(^{5}\text{J}_{HF} 4.5, \text{F-8}\)); \(\delta_{H} 3.30\) (2H, t, \(^{3}\text{J}_{HH} 4.8, \text{CH}_{2}\)), 3.28 (3H, d, \(^{5}\text{J}_{HF} 5.4, \text{CH}_{3}\)), 3.04 (2H, t, \(^{3}\text{J}_{HH} 5.1, \text{CH}_{2}\)), 2.75 (3H, s, \text{CH}_{3}); \(\delta_{C} 144.4\) (d, \(^{1}\text{J}_{CF}\))

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200.7, C-8), 138.4 (d, 2J_CF 5.4, C-8a), 132.3 (d, 3J_CF 1.5, C-4a), 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,
11-NCH_3); m/z (EI') 339 ([M]^+, 100), 324 ([M-CH_3]^+, 25), 309 ([M-(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_10N_2Br_2F requires: C, 32.0; H, 3.0; N, 12.5%); δF -123.02 (IF, r, F-7); δH 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); δC 148.2
(s, C-4a), 146.4 (s, C-8a), 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

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 19F 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 hydrocholic 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; δF -123.8 (1F, d, 4J_F 3.6, F-5), -120.7 (1F, t, 4J_F 3.8, F-3); m/z (EI⁺) 346 ([M]+, 24), 315 ([M-CH₃OH]+, 100), 234 ([M-CH₂OHBr]+, 19), 155 ([M-CH₂OHBr₂]+, 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. C₈H₈N₂Br₂F₂O requires: C, 27.9; H, 2.3; N, 8.1%); δF -120.75 (2F, s, F-3,5); δH 3.86 (2H, t, 3J_HH 5.4, NCH₂), 3.50 (2H, t, 3J_HH 5.4, CH₂O), 3.14 (3H, t, 5J_HF 3.3, CH₃), 1.62 (1H, br s, OH); δC 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, CH₂OH), 56.8 (t, 4J_CF 4.4, NCH₂), 41.1 (t, 4J_CF 5.3, NCH₃); m/z (EI⁺) 344 ([M]+, 15), 313 ([M-CH₂OH]+, 100).