Highly functionalised fused heterocycle synthesis from fluoropyridines

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A Thesis Entitled

Highly Functionalised Fused Heterocycle Synthesis from Fluoropyridines

Submitted by

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Acknowledgements

I would like to thank Dr. Graham Sandford for being a great supervisor and keeping me in check with all aspects of the work. Thanks to my industrial supervisor, Dr. John Christopher, for being so supportive and helping to make summer 2005, Stevenage, a truly great experience. Thanks also to Prof. Dick Chambers and Dr. David Miller (GSK) for their continued enthusiasm towards my work.

I'm most grateful to the analytical staff at Durham and GSK for their patient answers to my often inane questions. Also, Dr. Dima Yufit for his speedy analysis of my beloved crystals and Mr. Dave Hunter for his help with autoclave matters. Thanks also to all the staff in the department who help make the place tick.

Cheers to Takashi, Jelena, Mark, Aurelie, Rachel, Reza, Chris, Emma, Andrzej, Graham, Gemma, Laura and Nathalie for making lab life so much fun. Also, Ian, Tim, Ahmed, Nicholas, Ken and Helen from the High Throughput Chemistry department at GSK for being extremely helpful and friendly.

Finally, to my friends and family, all in the tea group and chemistry social club, and Meriel Avery for helping make life such a blast.

Memorandum

The work presented within this thesis was carried out at Durham University between October 2003 and September 2006. The thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

This work has been presented, in part, at:

- 6th Royal Society of Chemistry Fluorine Subject Group Meeting, Manchester, August 2006.
- 21st Royal Society of Chemistry Postgraduate Heterocyclic Symposium, Loughborough, September 2006.
- Durham University Chemistry Department Final Year Postgraduate Symposium, May 2006.
- 18th International Symposium on Fluorine Chemistry, Bremen, Germany, August 2006.

Abbreviations

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binapthyl
DBA	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-8-ene
DIPEA	Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
GCMS	Gas chromatography-mass spectrometry
LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
MDAP	Mass directed auto purification
MeCN	Acetonitrile
MW	Microwave
NMP	*N*-Methyl-2-pyrrolidone
nOe	Nuclear Overhauser effect
PFP	Pentafluoropyridine
PPSE	Polyphosphoric acid trimethylsilyl ester
SEM	2-(Trimethylsilylethoxy)methyl
TBDMS	Tert-butyldimethylsilyl
TDAE	Tetrakis(dimethylamino)ethane
TFA	Trifluoroacetic acid
TIC	Total ion content
TLC	Thin layer chromatography
TMAF	Tetramethylammonium fluoride

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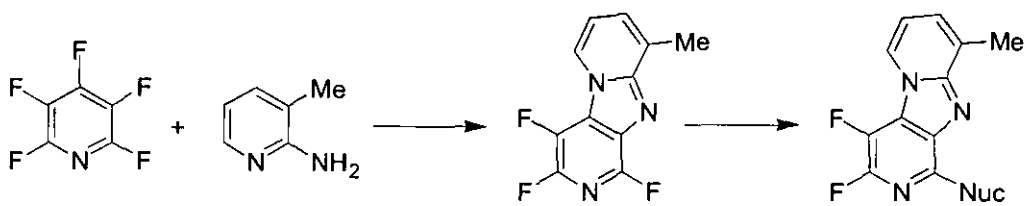
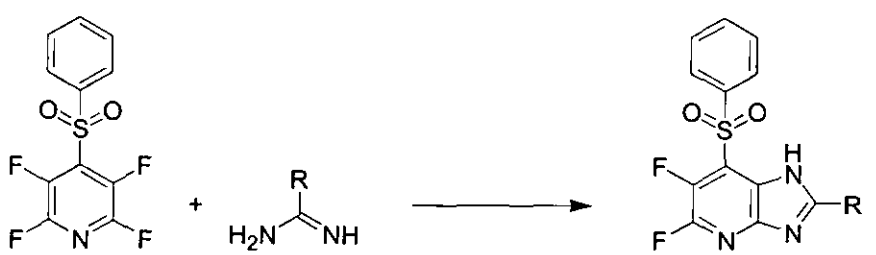
Abstract

Current approaches to drug discovery tends to involve the rapid analogue synthesis and testing of small, focused libraries of low molecular weight, structurally similar "drug-like" molecules, often based around heterocyclic core scaffolds. If some desired activity is shown by a compound, elaboration can give higher activity and more favourable pharmokinetic properties. As this "lead generation" stage of drug development has been identified as a major bottleneck in the drug pipeline process, there is a great demand for methodology detailing the synthesis of highly functionalised heterocyclic compounds.

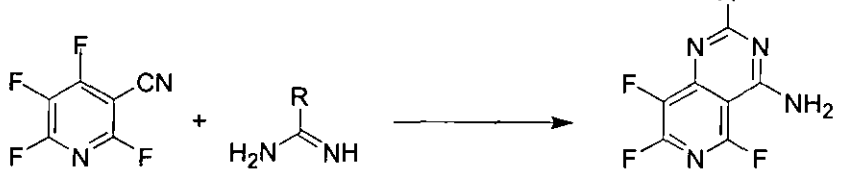
Our approach involves the sequential nucleophilic aromatic substitution of highly fluorinated pyridines, in an efficient and flexible manner, to furnish a range of novel, functionalised polycyclic systems.



Nuc = NEt_2, Ph, OMe, OH



R = Ph, Me



R = Ph, Me, H

Contents

Chapter 1

Introduction

1.1 The Pharmaceutical Industry

1.1.1 Development

The evolution of the pharmaceutical industry has been an interesting one. Emerging from the synthetic dye industry in Germany and following the watershed discovery and sale of aspirin, companies such as Bayer set about finding new drugs to market. The source of novel pharmaceuticals was generally through the extraction of natural products from plants and microorganisms and from the exploration of the chemicals making up coal tar,[1] which had previously yielded the collection of compounds constituting the first synthetic dye, mauve, discovered by the then teenage William Perkin. The chemical knowledge gleaned from this work, along with the drive to find drugs that could combat the serious health problems that had existed in mankind up until then, eventually led to the modern drug discovery process (and synthetic organic chemistry) that we know today.

1.1.2 Modern Drug Discovery

The approach to finding "lead compounds" by the systematic synthesis and testing of novel chemicals remained relatively unchanged until the development of combinatorial chemistry, that is, the science of creating and testing, *en masse*, large libraries of structurally diverse compounds with the aim of discovering lead compounds more quickly and inexpensively than previously possible.[2] However, since its inception in the 1980s, there has been an acknowledgement that this concept is not necessarily the most efficient way of generating lead compounds due to the fact that, through an attempt to maximise structural variation, a proportion of the structures making up a library will not be "drug-like" and hence are unlikely to have useful biological activity.[3, 4] As such, the current approach to lead generation and optimisation is to synthesise small, polar, "drug-like" molecules which, if shown to have some affinity against a selected target, can be elaborated in such way as to give improved activities and pharmokinetic

properties.[5] Concepts such as "privileged structures",[6] which describes the ability of a pharmacophore to exhibit varied biological activity through the judicious modification of the functional groups attached,[7] and Lipinski's "rules of 5",[8] which help to identify and improve favourable physico-chemical properties in potential lead compounds, have added weight to this approach. Given that this early stage of the drug discovery pipeline has been identified as a major bottleneck, it is largely down to chemists to provide new biologically relevant substances.[3, 9]

1.1.3 Heterocyclic Systems

The ability to vary the properties of heterocycles by manipulating their structures makes such systems highly amenable to drug discovery and accounts for the widespread occurrence of active compounds containing a heterocyclic core. However, the elaboration of heterocycles is often difficult due to their sometimes low reactivity and selectivity. There are various approaches that have been adopted, often in combination with one another, to circumvent these inherent disadvantages such as multi-component,[10] metal-catalysed coupling[11] and cycloaddition reactions, annulation of alkynes and their equivalents,[12, 13] and sequential nucleophilic aromatic substitution.[14, 15] It is this last approach that is the basis for the work submitted in this thesis, that is the perhalogenation of a suitable heterocycle followed by the sequential displacement of halide, in a selective fashion, to build in functionality around a parent scaffold.

1.1.4 [5,6] Fused Systems

The [5,6] fused-ring motif has been shown to be in the top eight most frequently occurring frameworks in drugs.[16] This is, of course, largely due to the relatively commonly employed pharmacophores indole, benzimidazole and purine. However, the ability to vary the heteroatoms present in these scaffolds gives systems with differing electronic properties and, potentially, improved activities. For example, in the development of vasorelaxants and using adenosine as a low affinity lead, scientists developed the following imidazopyridine based bioactive molecule (Figure 1.1).[17] As well as elaboration of the amino group, modification of the fused ring was also explored.

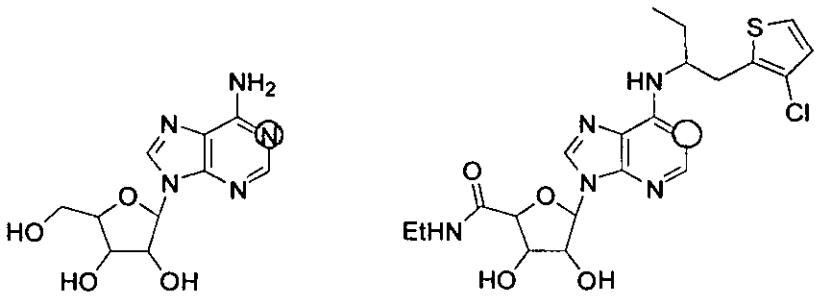


Figure 1.1 Adenosine (l) and imidazopyridine based vasorelaxant (r)

As a further example, conversion of indole **A**, a potentially novel antipsychotic agent, into pyrrolo-pyridine **B** resulted in a dramatic improvement in selectivity towards the desired dopamine D_4 receptor:[18]

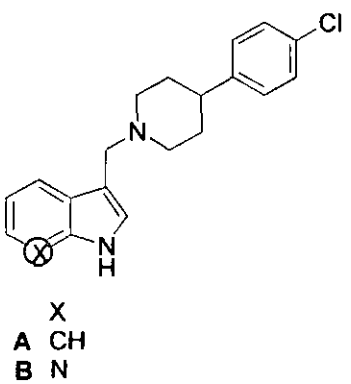


Figure 1.2 Indole and pyrrolo-pyridine based antipsychotic agents

1.1.5 [5,6] Pyridine Ring-Fused Synthesis

As can be seen from above, pyridine ring-fused heterocycles are potentially invaluable scaffolds for drug discovery. However, their synthesis is often non-trivial and can be convoluted because they are often derived from pyridine, a compound frequently difficult to functionalise in a selective and high yielding manner.[19, 20] This is no more true than in the case of the synthesis of [5,6] pyridine ring fused heterocycle synthesis of the type shown in Figure 1.3, where there exists a variety of approaches to access fused-compounds. In light of this thesis reporting new approaches to the synthesis of fused-ring systems, the following section will highlight the most common methods for

their synthesis, starting with imidazopyridines due to this motif's recurring nature in this thesis.

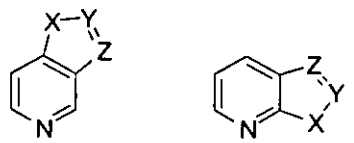


Figure 1.3 Possible pyridine ring-fused heterocycles

Imidazopyridines are most commonly synthesised by the reaction of an *ortho*-diaminopyridine precursor with a suitable electrophilic reagent,[21] as shown in the scheme below:

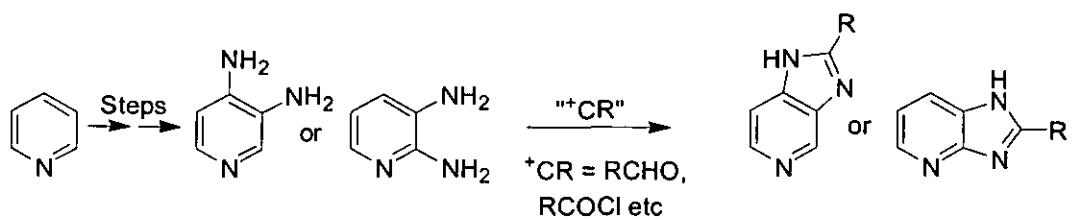


Figure 1.4 General approach to imidazopyridine synthesis

As well as the obvious challenges of forming the *ortho*-diaminopyridine intermediates, the annulation step often requires forcing conditions, such as high temperatures and the presence of an oxidising agent, as shown below in the following example, where imidazopyridine **C** was obtained via the condensation of 2,3-diamino-pyridine with benzaldehyde, in the presence of sulfur.[22]

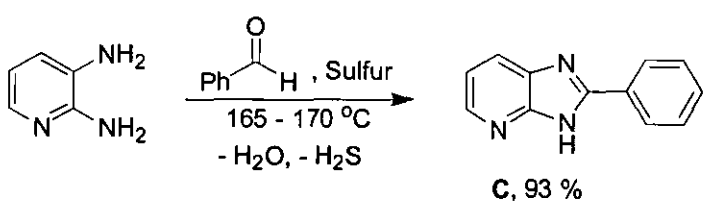


Figure 1.5 Phenyl-imidazopyridine synthesis via the condensation of pyridine-2,3-diamine with benzaldehyde

An interesting reaction reported, and one that illustrates the difficulty of synthesising [5,6] pyridine ring-fused structures, is the reaction of the following triamine with acetic anhydride:[23]

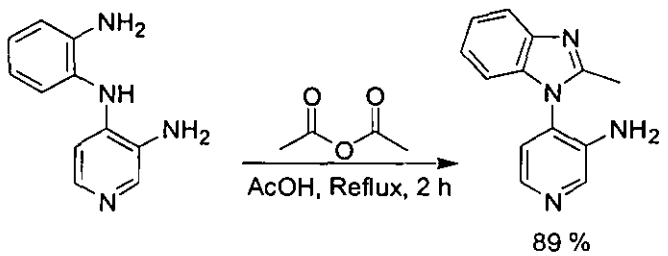


Figure 1.6

The formation of the benzimidazole fused ring, in excellent yield, rather than the pyridine ring-fused analogue, shows the ease of formation of the former compared with the latter.

A slightly different approach to imidazopyridine synthesis is shown in figure 1.7:[24, 25]

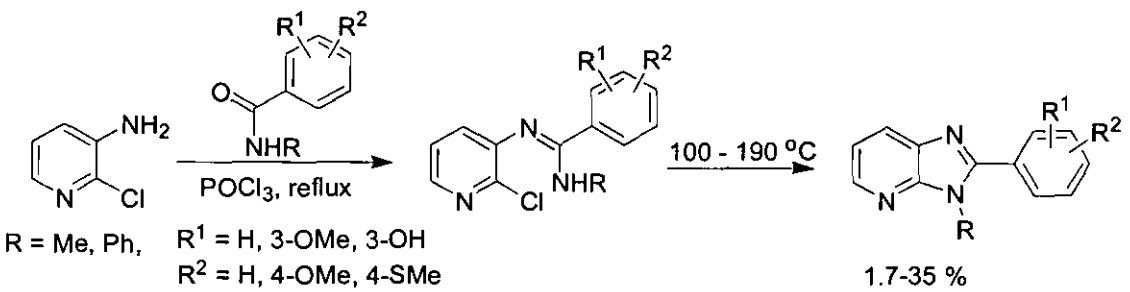


Figure 1.7

Reaction of 2-chloro-3-aminopyridine with a range of benzamides, in $POCl_3$, gave a series of tethered amidines, which in turn were cyclised by nucleophilic aromatic substitution of the carbon-chlorine bond to give the corresponding imidazopyridines, albeit in low yields.

2-Oxo (hydroxyl) and 2-thio (thioxy) substituted imidazopyridines are the most accessible compounds of this type and, like the majority of syntheses reported, proceed via an *ortho*-diaminopyridine precursor as discussed above:[21]

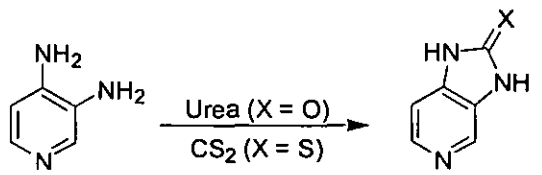


Figure 1.8 General approach to oxo- and thio-substituted imidazopyridines

Pyrazolopyridines have received interest due not only to their structural similarity to indoles and imidazopyridines but also due to their proven biological activity, as exemplified in the following two lead compounds:

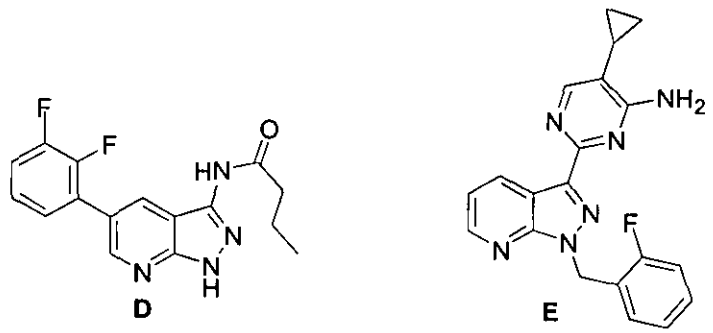


Figure 1.9 Pyrazolopyridine-based lead compounds

A series of pyridine ring-fused heterocycles, exemplified by compound **D**, were shown to be potent glycogen synthase kinase-3 inhibitors,[26] an enzyme thought to be involved in the regulation of several physiological processes, while compound **E** was shown to have a blood pressure lowering effect in rats.[27] The synthesis of pyrazolopyridines has been achieved through a range of synthetic strategies[28] including cycloaddition reactions,[29] the thermal decomposition of vinyl azides,[30] cyclisation of *N*-acyl-*N*-nitroso compounds,[31] and the reaction of an *ortho*-chloro-cyanopyridine with hydrazine (Figure 1.10).[32]

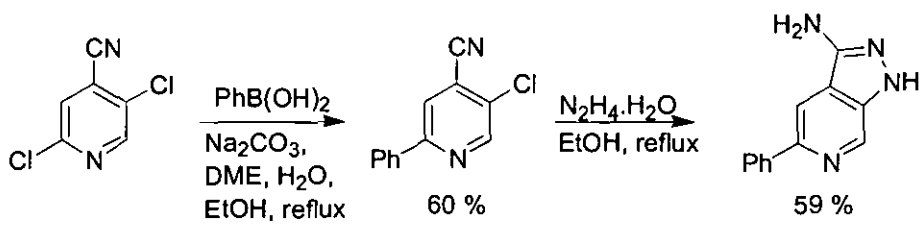


Figure 1.10

The synthesis of oxazolopyridines and thiazolopyridines can be achieved in an analogous manner to imidazopyridines, as shown below in the following examples of the formation of a bromo-substituted oxazolopyridine, an intermediate in the synthesis of a potential glycoprotein antagonist (Figure 1.11)[33] and the unsubstituted thiazolo[5,4-*c*]pyridine (Figure 1.12).[34]

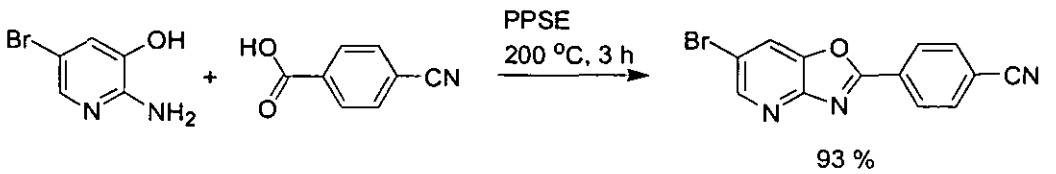


Figure 1.11

Reaction of 2-amino-5-bromo-pyridin-3-ol, obtained in 5 steps from furfural, with 4-cyano-benzoic acid and in the presence of polyphosphoric acid trimethylsilyl ester (PPSE), a dehydrating agent, gave the corresponding oxazolopyridine in excellent yield.

In the second example (Figure 1.12), once the desired heteroatoms have been positioned on the pyridine ring, cyclisation gave 2-methyl-thiazolo[5,4-c]pyridine, whilst subsequent hydrolysis and condensation with formic acid gave the parent heterocycle in poor yield.

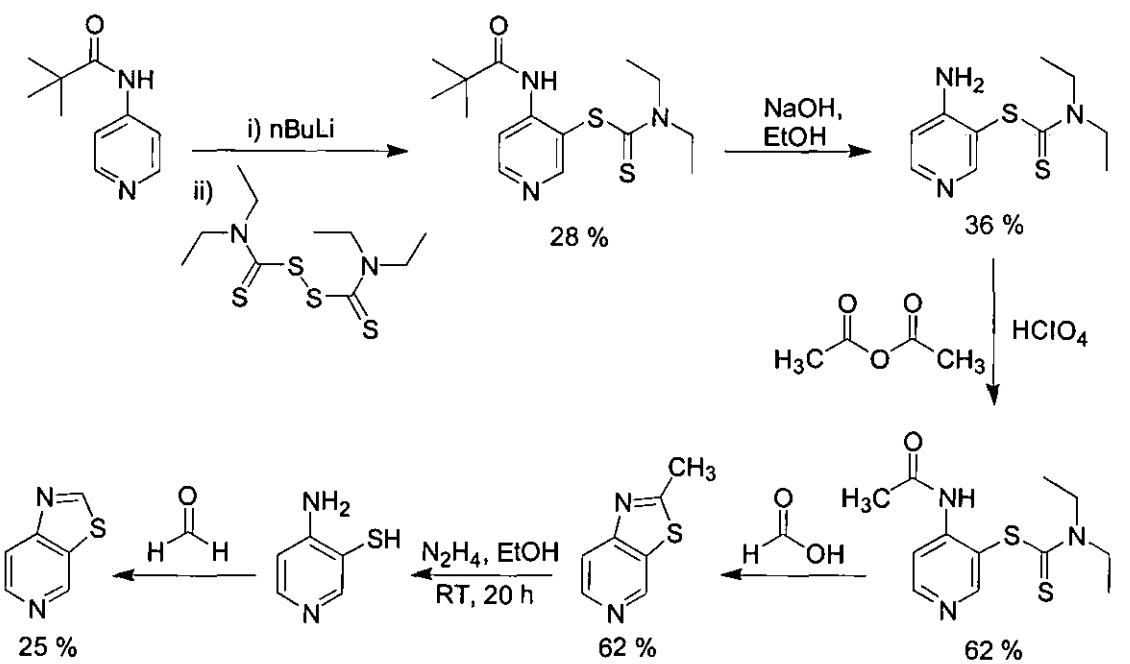


Figure 1.12 Synthesis of thiazolo[5,4-c]pyridine

The synthesis of triazolopyridines have been reviewed[35] and, as with the other pyridine-ring fused heterocycles involves various approaches, such as diazotization of *ortho*-diaminopyridines[36] and base induced pyridine annulation into a preformed triazole ring (Figure 1.13):[37]

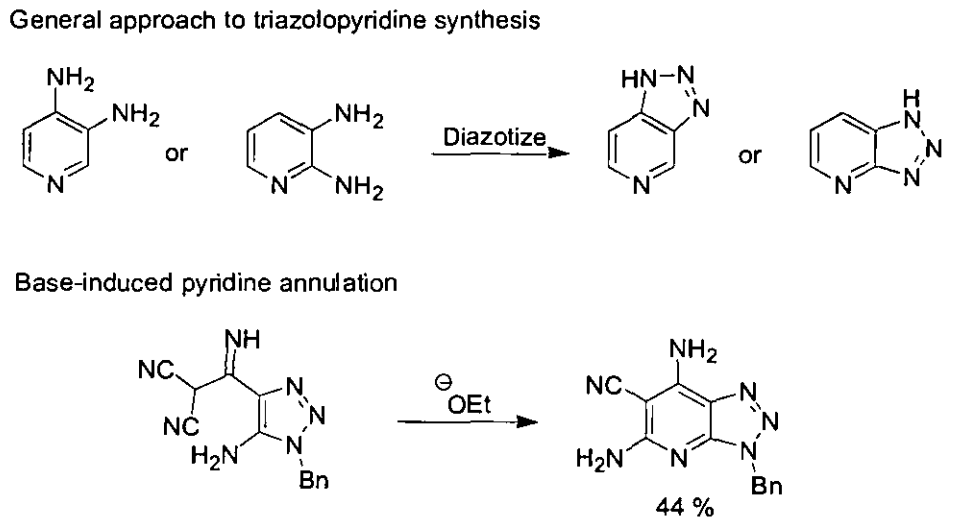
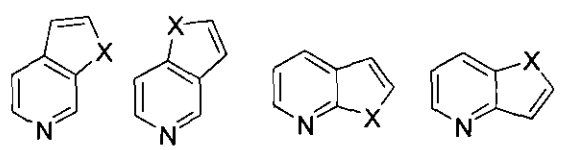


Figure 1.13 Examples of triazolopyridine synthesis

[C, X] centred [5,6] pyridine-ring fused heterocycles (where X = NH, NR, O, S) have been reported in the literature and the synthesis of these compounds will be briefly outlined below.



X = NH, NR, O, S

Figure 1.14

Pyrrolopyridines (X = NH, NR) are generally synthesised via the annulation of a suitable aminopyridine precursor to form the 5-membered pyrrole ring and are of interest as a potential bioisostere for indole.[38]

Furopyridines (X = O) are most frequently formed either by annulation onto a preformed pyridine or oxazole ring and have attracted interest from both medicinal chemists, due to their potentially useful biological activity and from theoretical

chemists, as a system containing both an electron deficient (pyridine) and rich (furan) ring.[39]

Thienopyridines (X = S) have been investigated as potential molecular switches and wires,[40] and as monomer units making up optoelectronic polymers.[41] In both cases, the fused rings have been derived from suitably substituted thiophenes.

1.1.6 Conclusions

As can be seen from the examples given, there is no general approach to the synthesis of [5,6] pyridine-fused rings and, furthermore, little functionality remains once the desired annulation is achieved, rendering further derivatisation difficult. The following section on fluorine chemistry, after outlining some basic principles, will show how highly fluorinated heterocycles can be excellent scaffolds for functionalised heterocycle synthesis.

1.2 Organofluorine Chemistry

In light of the central concept of the work submitted in this thesis, that is of using highly fluorinated pyridines as building blocks for the synthesis of functionalised pyridine ring-fused heterocycles, the following section will introduce the area of organofluorine chemistry. After a brief introduction, the review will focus on the effect fluorine has upon inclusion into molecules in general and, more specifically, drug-like molecules; the synthetic aspect of C-F bond formation will be reviewed, followed by the synthesis and reactivity of pentafluoropyridine, a key starting material for the research herein, and finally a comprehensive review of literature over the last decade that details chemistry involving this compound.

1.2.1 Background

Organofluorine chemistry has undergone a sporadic but continual growth since Henri Moisson's isolation of fluorine in 1886, resulting in its ubiquitous status in several areas of chemistry and materials science, from drug design and the development of anaesthetics, to polymer science and liquid crystal display technology.[42] The

incorporation of one or more fluorine atoms into an organic molecule can have a profound effect on properties such as reactivity, polarity and physical properties. This is due to the unique characteristics covalently bound fluorine exhibits:

- Fluorine is the most electronegative element (4.0 on the Pauling scale),[43] and is far more electron withdrawing than carbon (2.5). The consequence of this is that a C-F bond is highly polarised. Carbanions can be stabilised by this effect, and surrounding groups' electronic environments are different to those in the hydrocarbon equivalent.
- C-F bonds are the strongest single bonds to carbon. The consequence of this is the high thermal stability of some perfluorinated systems.
- Though the Van der Waals radius of fluorine is inbetween that for hydrogen and hydroxyl, its steric requirement is more akin the former, thus allowing a hydrogen atom to be replaced by a fluorine atom with the minimal of disruption to steric requirement.
- The electronic configuration:

Figure 1.15 Electronic configuration of hydrogen and fluorine

Fluorine will preferentially leave as F^-, as this completes the octet for the outer (second) shell. Hydrogen's preference is as H^+, though it can leave as H^- (hydride ion) as this has a full shell. Also, the existence of three tightly bound non bonding electron pairs makes for electron pair repulsions that do not exist in hydrocarbon systems.

Perfluorination, the replacement of all the hydrogens in a molecule by fluorine atoms, can have a pronounced effect on the physical and chemical properties that a molecule displays. Chemistry that is taken for granted in hydrocarbon systems is turned on its head when applied to the fluorocarbon equivalents, hence the regular use of the term

"mirror-image chemistry" to describe some of the chemistry of these man-made species (fluorinated compounds rarely exist in nature).[44] Take aromatic substitution, for example. Under standard reaction conditions, aromatic hydrocarbons readily undergo electrophilic substitution (figure 1.16) but not nucleophilic substitution whereas, in fluoroaromatic compounds, nucleophilic substitution tends to occur due to the presence of highly electronegative fluorine atoms (figure 1.17):

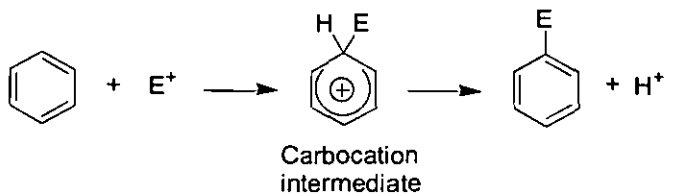


Figure 1.16 Electrophilic substitution of benzene

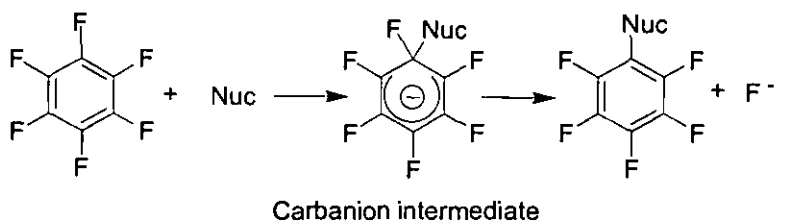
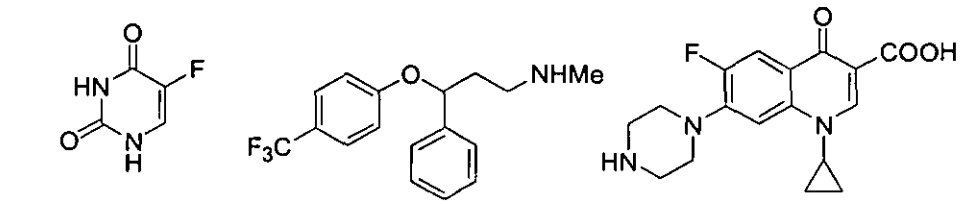


Figure 1.17 Nucleophilic aromatic substitution of hexafluorobenzene

1.2.2 Fluorine in Drugs

Although the effects of incorporating fluorine atoms into drug-like molecules / drugs was first investigated more than fifty years ago in the pioneering work by Fried,[45] it wasn't until the 1970s that this approach found a more common role in the drug discovery process. Indeed, nowadays, fluorinated molecules are often seen in research concerning the search for novel bioactive agents, whilst a recent review on the synthesis of fluorine-containing drug target molecules attests to their relevance and importance in the pharmaceutical industry.[46] In the United States of America in 2002, nine of the thirty-one drugs approved by the Food and Drug Administration (FDA) contained one or more fluorine,[47] while perusal of Forbes.com's list of the top ten selling drugs in America reveals four out of ten contain either one or more fluorine atoms or a trifluoromethyl group.[48] The exchange of a functional group (e.g. hydroxyl, methyl), or hydrogen, with a fluorine atom can not only have an effect on the chemical properties of

that molecule but it can limit its metabolism, increase biological activity against a desired target and increase cell penetration.[49, 50]



5-Fluorouracil (chemotherapy drug) | Prozac (Antidepressant) | Ciprofloxacin (Antibiotic)

Figure 1.18 Examples of Fluoine-containing drugs

In the case of ciprofloxacin (figure 1.18), the effect of the presence of fluorine in the C-6 position of the quinolone ring has been investigated,[51] and has been shown to increase binding affinity, reduce plasma protein binding leading to a higher bioavailability and increase cell penetration.

1.2.3 Fluorination Methods

Of course, to access these unnatural halogenated species, carbon-fluorine bonds must be made at some point in the synthetic strategy of a target molecule. The following section will outline some useful approaches to this.

There are two distinct types of fluorination; selective and perfluorination. Selective fluorination is the introduction of one or two fluorine atoms into a molecule e.g.

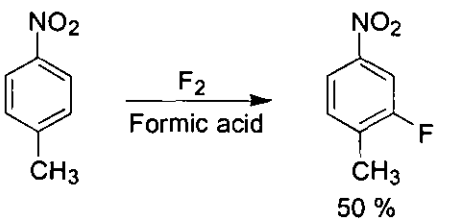


Figure 1.19

Fluorine gas, carried in a stream of inert nitrogen gas, is made susceptible to attack by a nucleophile through interaction with an acid and is hence an electrophilic fluorinating

agent. Nucleophilic fluorinating agents ("F⁻"), such as potassium fluoride[52] and tetramethylammonium fluoride (TMAF),[53] may be employed to displace either another halogen (Halex reaction) or a suitable leaving group, such as NO_2. Alternatively, a Balz-Schiemann reaction involving HBF_4 or pyridine-HF as a source of fluoride ion is possible:[54]

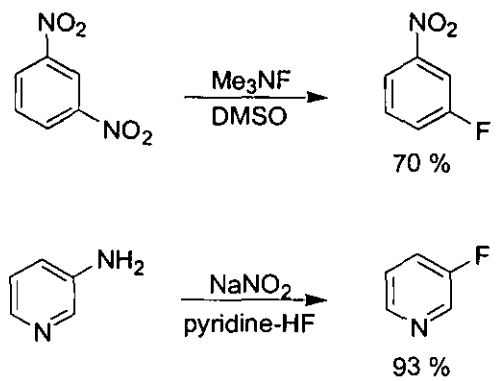


Figure 1.20 Fluorodenitration of 1,3-dinitrobenzene by TMAF (top) and pyridine-HF mediated Balz-Schiemann reaction (bottom)

The highly hygroscopic nature of fluoride, along with its low solubility and reactivity, limits this class of fluorination to reaction with highly reactive systems e.g. reaction of potassium fluoride with a perchlorinated ring, whilst the metal fluoride must be rigorously dry to maximise the nucleophilicity of fluoride ion.[55]

Alternatively, fluorine can be introduced to a molecule by reaction of a suitable precursor with a fluorinated building block, for example in the following formation of a pyrimidine intermediate in the synthesis of a novel fluoroquinolone:[56]

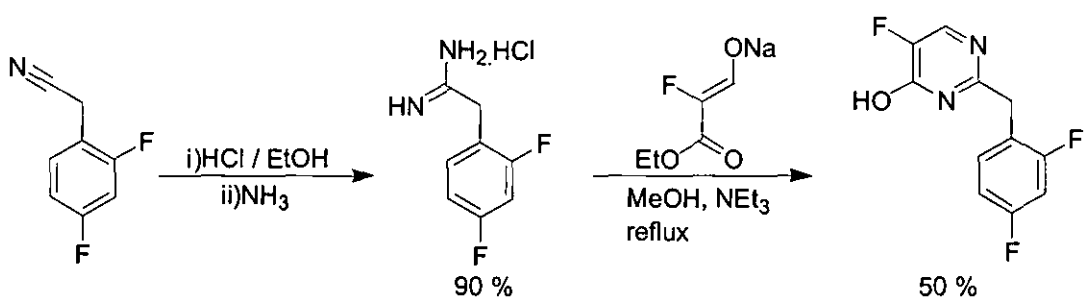


Figure 1.21

Amidination of the benzyl nitrile gave a difluorinated system, which was condensed with the sodium salt of an α, β unsaturated ester to give the desired trifluorinated pyrimidine.

Perfluorination is the replacement of all the hydrogen atoms in a molecule with fluorine atoms, and will be focused on in this review, as the molecules resulting from this process are the ones that are of relevance to this thesis. Perfluorination using cobalt trifluoride is a process run at plant scale.[57] The reagent is generated by passing fluorine over cobalt difluoride in a reactor vessel and reacted with a hydrocarbon species at high temperatures to give fluorination as indicated below:

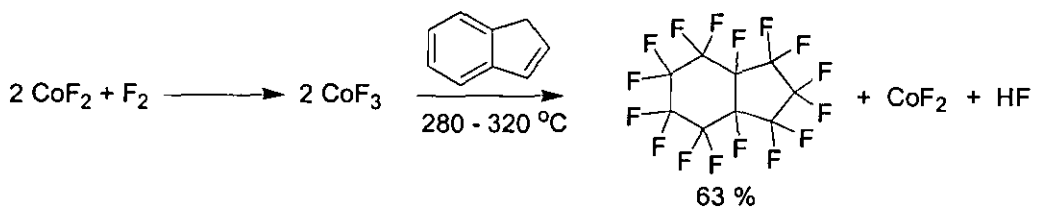


Figure 1.22

The drawback to this method is that unsaturated systems become saturated, though in the case of aromatic compounds, defluorination can restore unsaturation,[58] e.g.

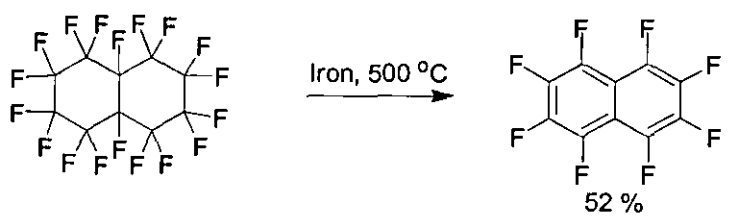


Figure 1.23

Passage of the vaporised fluorocarbon, in a stream of nitrogen, over iron gauze brings aromaticity to the fluorocarbon, whilst oxidising the iron to iron fluoride. Subsequent passage of hydrogen gas reduces the metal fluoride back to elemental iron.

Another common perfluorination technique is the reaction of a perchlorinated ring with potassium fluoride via the so called "Halex reaction", as shown in the following

fluorinations of the monocyclic heterocycles tetrachloro-pyrazine and -pyrimidine,[59] and perchloroquinoline:[60]

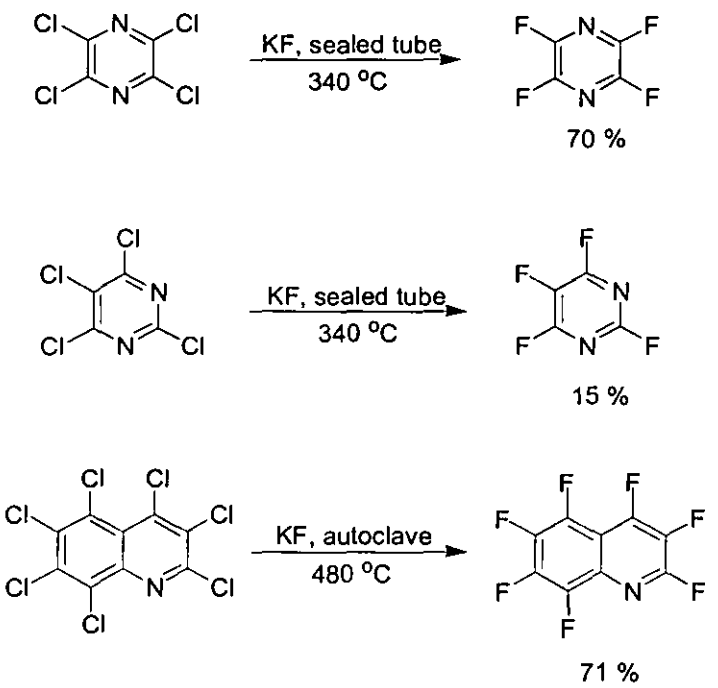


Figure 1.24 Representative reactions of perchloroheterocycles with potassium fluoride to give the corresponding perfluorinated systems

1.3 Pentafluoropyridine

In light of its central importance to this thesis, the following section will detail the synthesis, properties and reactivities of pentafluoropyridine.

1.3.1 Synthesis

Pentafluoropyridine was first prepared in low overall yield by electrochemical fluorination of pyridine, followed by defluorination.[61, 62]

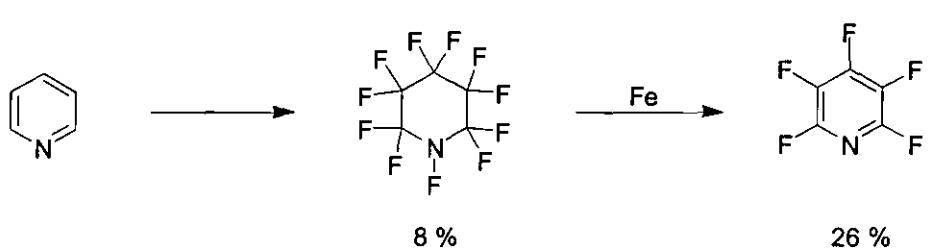


Figure 1.25

A subsequent synthesis, involving the reaction of pentachloropyridine with potassium fluoride, in an autoclave at high temperature, improved the above yield and provided a more convenient route for the synthesis of pentafluoropyridine.[63]

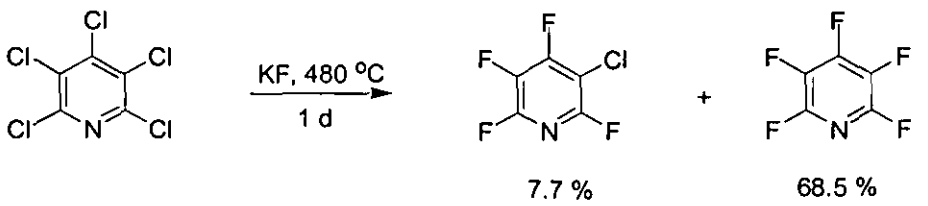


Figure 1.26

1.3.2 Reactivity

Pyridine is not very reactive towards electrophilic aromatic substitution, but will readily undergo nucleophilic aromatic substitution. In the perfluorinated analogue, the electron-withdrawing effect of the fluorine atoms makes attack by an electrophile even more unlikely. However, it readily undergoes nucleophilic substitution *para* to the ring nitrogen as can be seen clearly in the following reaction with hydrazine hydrate giving clean conversion to the corresponding 4-substituted-tetrafluoropyridine:[64]

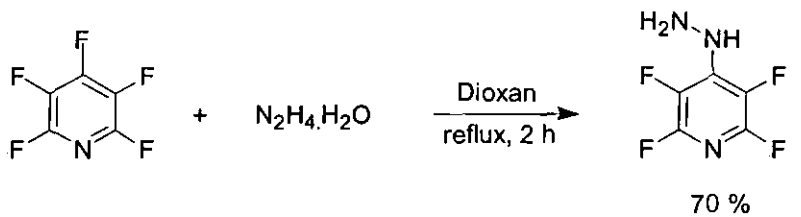


Figure 1.27

This remarkable reactivity and selectivity can be explained in terms of whether or not the negative charge developed in the Meisenheimer complex can be delocalised over the electronegative pyridine nitrogen.

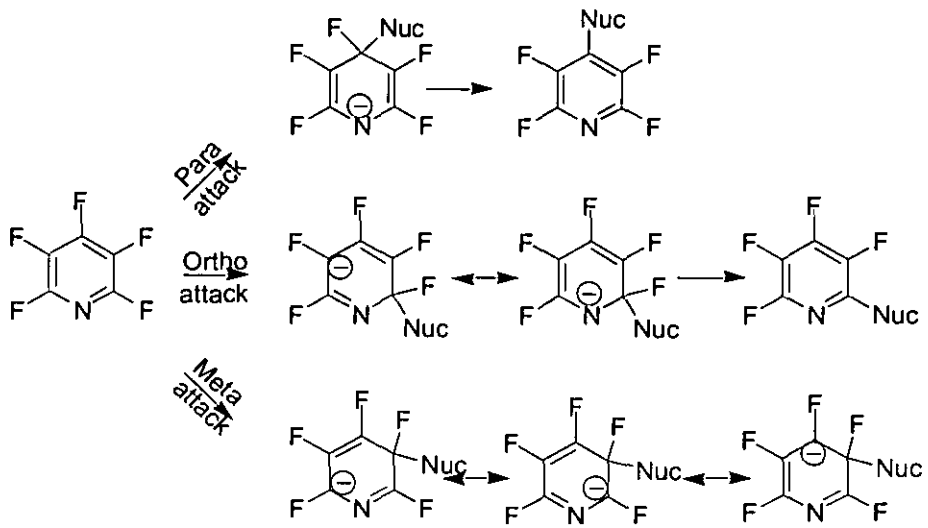


Figure 1.28

The activating influence of the nitrogen in pentafluoropyridine has been determined and found to activate the positions in the order; *para* ($2.3x10^5$), *ortho* ($6.2x10^4$), and *meta* ($8.5x10^2$),[65] and is the main factor in dictating the site of attack by a nucleophile. *Para* attack gives a carbanion intermediate with the negative charge localised on the electronegative nitrogen. This intermediate is also free of I_π repulsions, and is thus highly favoured. *Ortho* attack gives an intermediate with the negative charge localised on C-3, and thus I_π repulsion is experienced. Although resonance gives a structure with the charge on the nitrogen, the initial electron pair repulsion makes attack at this position less energetically favourable. *Meta* attack gives an intermediate that cannot resonate to give a structure that has the negative charge delocalised on the nitrogen, thus attack at this position is heavily deactivated.

Initial state effects can further explain the orientation of attack. The order of the activating effect of fluorine is:

$$F_{ortho} > F_{meta} >> F_{para}$$

A fluorine *para* to the site of attack is actually slightly deactivating since, although it is withdrawing electron density through induction, it is donating electron density back into the ring by resonance. The electronegative nitrogen atom also activates the ring to

attack. Combining these effects, it can be seen that the carbon *para* to the ring nitrogen, C-4, is most susceptible to attack followed by the 2- and 6-positions:

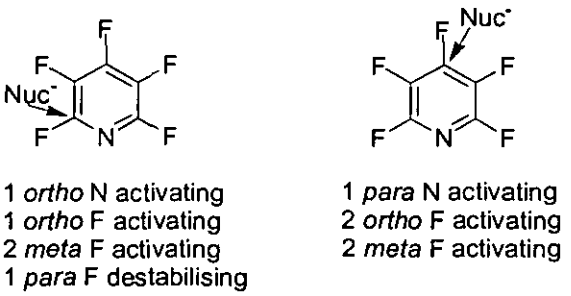
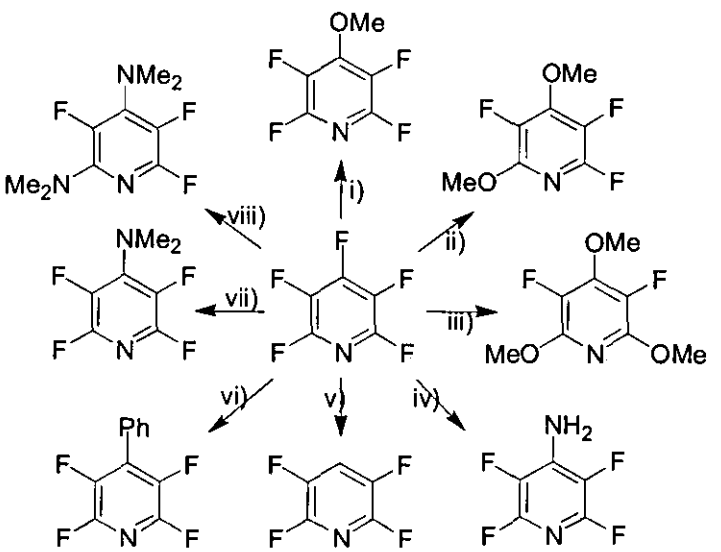


Figure 1.29 Initial state effects dictating site of attack

Early examples of reactions of pentafluoropyridine to give substituted perfluoropyridines include the following mono- di- and tri-substituted systems.[64, 66]



Reagents and conditions: i) NaOMe, MeOH, reflux, 3 h, 57 %; ii) 2.2 eq NaOMe, MeOH; iii) excess NaOMe, MeOH, reflux, 6 h, 74 %; iv) NH_3, ethanol, heat, 8 h, 81 %; v) $AlLiH_4$, reflux, 4 h, 74 %; vi) PhLi, RT, 1 h, 26 %; vii) aq Me_2NH, RT, 51 %; viii) xs aq Me_2NH, ethanol, heat, 20 h.

Figure 1.30 Early examples of reactions of pentafluoropyridine with nucleophiles

The orientation of monosubstituted perfluoropyridines was established by examination of the ^{19}F NMR spectra, which showed that the system had two-fold symmetry,

meaning the substituent must be in the 4-position. Substitution by a second equivalent of nucleophile was found to be possible under more forcing conditions, occurring exclusively at the 2-position, and resulted in three peaks in the ^{19}F NMR, whilst the trisubstituted 3,5-difluoro-2,4,6-trimethoxypyridine was accessed through refluxing pentafluoropyridine with an excess of methanolic sodium methoxide.

A large amount of work involving substitution in pentafluoropyridine has subsequently been undertaken in light of this excellent reactivity and selectivity and because of the ability to access compounds difficult to synthesise by other means.[67, 68]

1.4 Pentafluoropyridine: Its Uses in Synthetic Organic Chemistry Over the Last Ten Years

The following section will highlight research carried out involving the chemistry of pentafluoropyridine, with particular relevance to work in this thesis, since it was last reviewed by Brooke.[67] Advances in C-F activation in pentafluoropyridine by metal complexes[69, 70] and reactions of 2,4,6-tribromo-3-5-difluoropyridine[71] are outside the scope of this review and will not be discussed here. Reactions with mononucleophiles will be discussed first, followed by binucleophiles. Finally, there will be a section detailing the synthesis of partially fluorinated pyridines from pentafluoropyridine and other halogenated heterocycles as it could be argued that many of the nucleophilic displacement reactions discussed in this thesis could be adapted to reaction with tetra-, tri-, and difluorinated pyridines to give partially fluorinated derivatives. This could provide a useful technique in probing the effects of having fluorine atoms around the pyridine motif on physical properties and biological activities.

1.4.1 Reactions with Mononucleophiles

Scaffolds for Drug Discovery

There are few examples of the employment of pentafluoropyridine as a scaffold for drug discovery. The factors VIIa / TF complex and Xa are proteins known to be involved in the blood coagulation cascade[72] and as such are validated targets in the search for novel antithrombotic drugs.[73, 74] Having established a series of 2,6-diphenoxypyridines,

including several 3,5-difluoro,4-methyl-diaryloxypyridines derived from 4-methyl-tetrafluoropyridine, to be modest inhibitors of factor Xa, medicinal chemists synthesised a selection of 3,5-difluoro-triaryloxypyridines from pentafluoropyridine.[75] The 2,4,6-substitution pattern was obtained through sequential nucleophilic substitution by substituted phenols in typically high yields, whilst multiple additions could often be accomplished in a single reaction vessel.

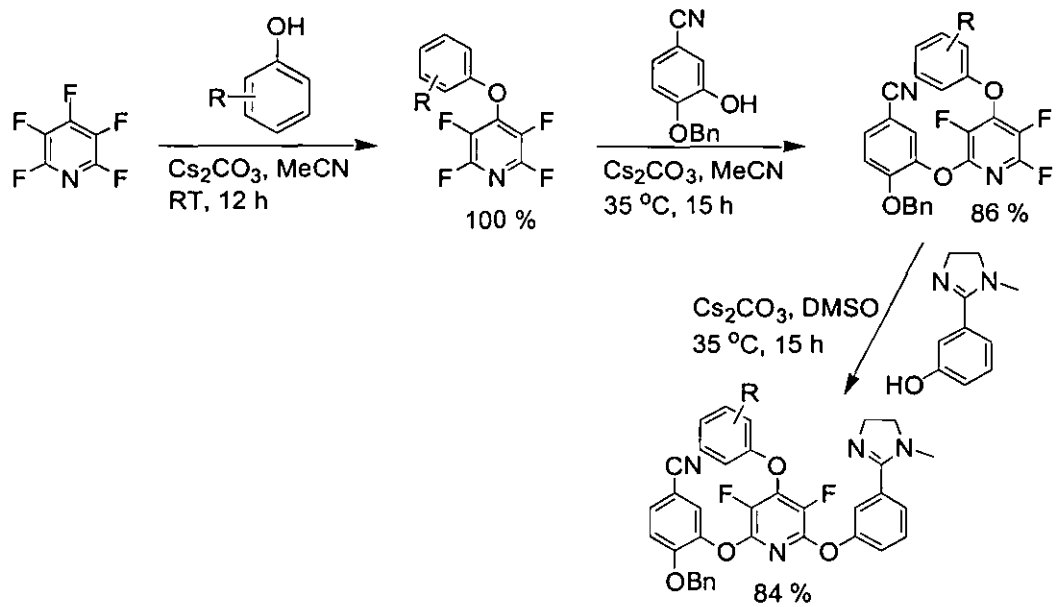


Figure 1.31 Synthesis of 3,5-difluorotriaryloxypyridines from pentafluoropyridine (yields given for R = 2-OMe, 4-CO_2Et)

Surprisingly high reactivity is shown by the fluoropyridine at each stage of substitution, despite the relatively poor nucleophilicities of the corresponding phenols.

In a similar vein and using compounds from the series of 2,6-diphenoxypyridines mentioned above as the basis for creating a more potent inhibitor, chemists synthesised a series of 4-amino-3,5-difluoro-2,6-diphenoxypyridines, again from pentafluoropyridine.[76] Derivatisation of the hydroxybenzoic acid side chain, to give compound **G,** led to an increase in potency whilst limited optimisation of substituents located at the 4-position of the core pyridine led to the potent FVIIa/TF inhibitor, **H**.

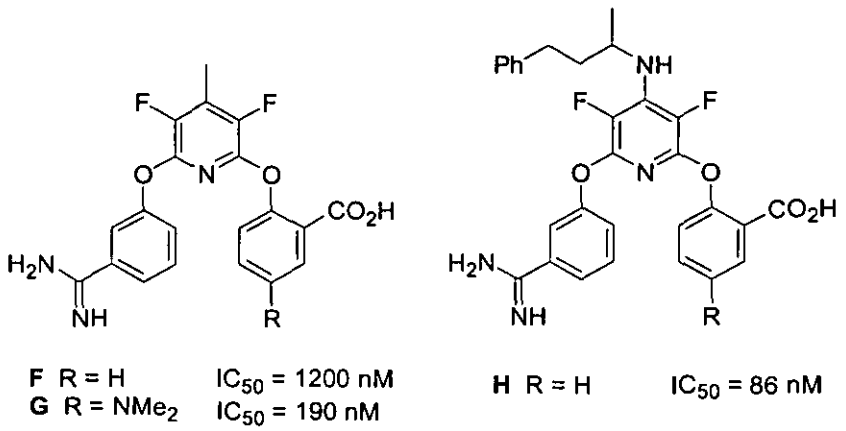


Figure 1.32 Lead inhibitors of FIIa /TF

To enhance the binding affinity of this series of compounds, a small library based on **H** (14 compounds, R = Me, ^{i}Pr, ^{t}Bu, Ph, NR^1R^2, OR) was synthesised:

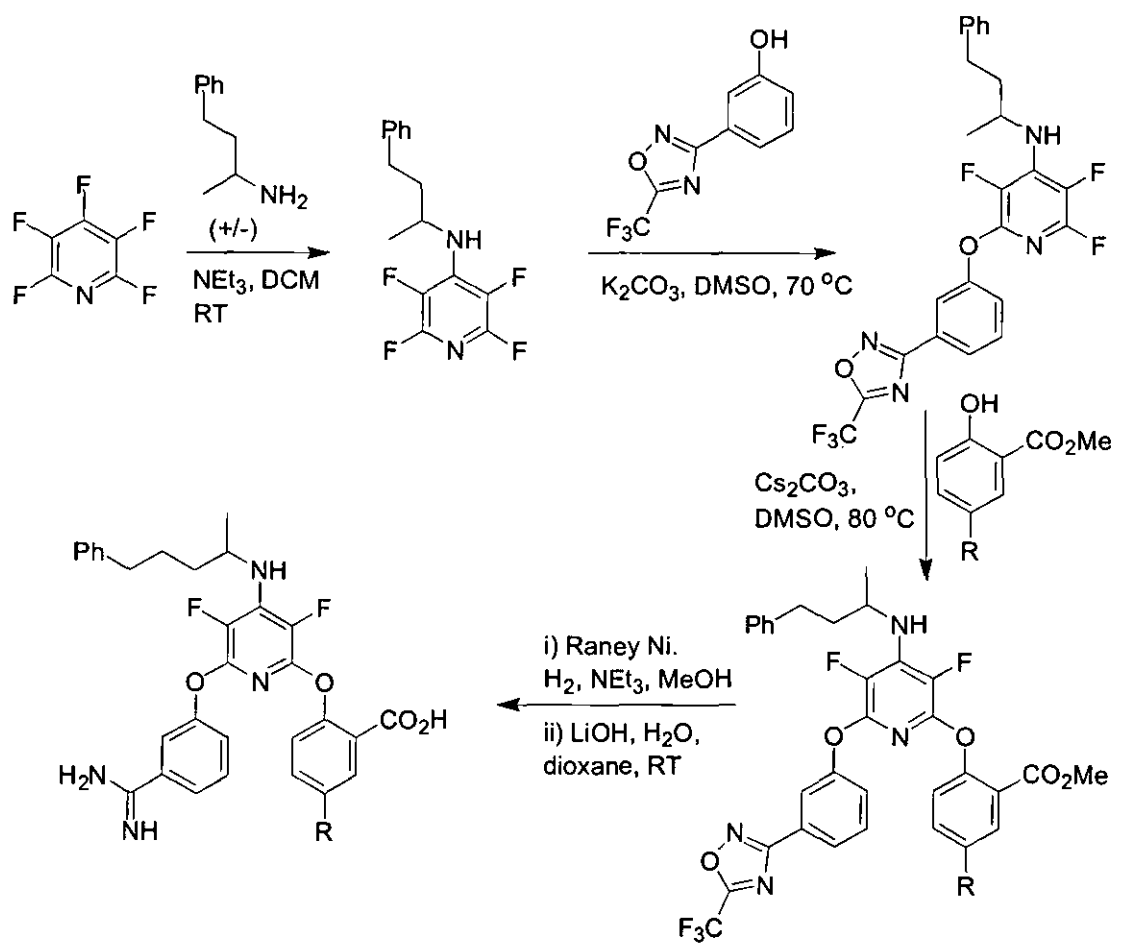


Figure 1.33 Synthesis of 3,5-difluoro-4-amino-2,6-diaryloxypyridines from pentafluoropyridine

Compounds containing mono- or dialkylated amino groups at the 5-position (R = NR^1R^2) gave the most improved potency, with 2- to 5-fold increases over lead compound **H**.

The same group of workers undertook a similar investigation in which a $N(^iPr)_2$ group was located at the 4-position of the pyridine.[77]

It is thought that inhibition of the p38 kinase protein could treat the underlying cause of chronic inflammatory diseases and stop its progression and it is in this context that chemists in Switzerland identified the motif shown in Figure 1.34 to give potentially high affinity binding to the active site.[78]

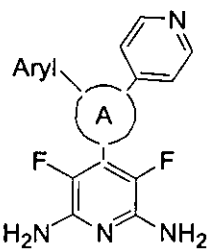


Figure 1.34 Pyridine motif identified as potetntial kinase inhibitor

A synthesis starting from pentafluoropyridine was developed that allowed variation of ring A:

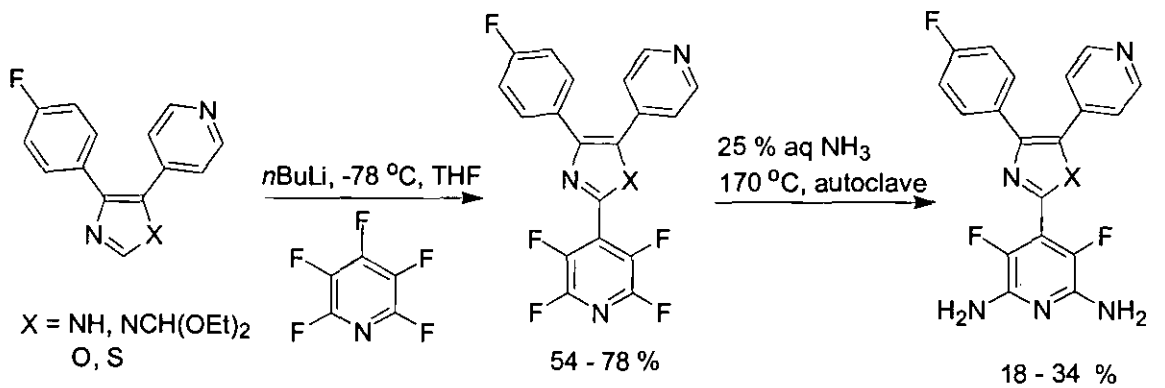
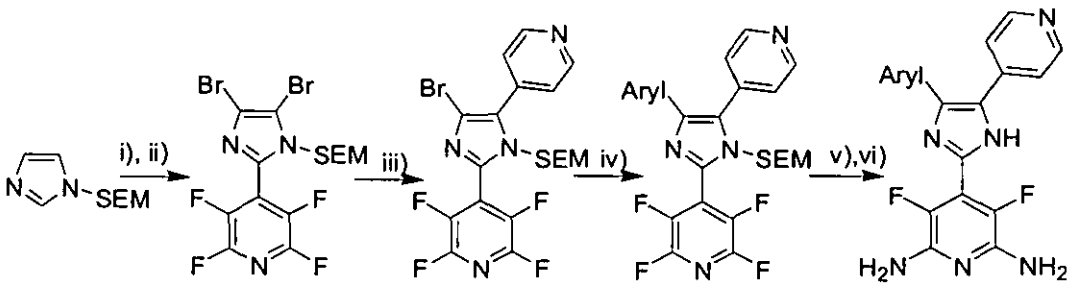


Figure 1.35 Difluoropyridine synthesis via autoclave reaction

Methodology for the preparation of a diverse set of aryl substituted pyridinylimidazoles was also developed:



Reagents and conditions: i) *n*BuLi, THF, -40 °C, 10 min, pentafluoropyridine, 74 %; ii) Br_2, AcOH, AcONa, 15 min, RT, 86 %; iii) 4-trimethylstannylpyridine, $PdCl_2(PPh_3)_2$, toluene, reflux, 12 h, 46 %; iv) Stille or Suzuki coupling; v) EtOH/conc HCl, RT, 1h, 78 – 85 %; vi) 25 % aq NH_3, 170 °C, autoclave, 12 h, 30 – 36 %

Figure 1.36

Deprotonation at the 2-position of the SEM-protected imidazole gave an anion which reacted with pentafluoropyridine to give the expected 4-substituted pyridine. Bromination at the 4- and 5-positions of the imidazole was followed by regioselective Stille reaction to yield a pyridinylimidazole whilst subsequent Suzuki or Stille coupling at the remaining carbon-bromine bond was followed by deprotection of the imidazole. Finally, diamination at the 2- and 6- position of the tetrafluoropyridine gave the desired 3,5-difluoropyridine.

Of all the antibacterial agents, the fluoroquinolones have proven to be the most successful class both economically and clinically[79] and, as such, 2-pyridones, as bioisosteres of quinolones, are a valuable source of potential new therapeutic agents. The following tricyclic 2-pyridone was synthesised using pentafluoropyridine as a template and displacing all but one fluorine:[80]

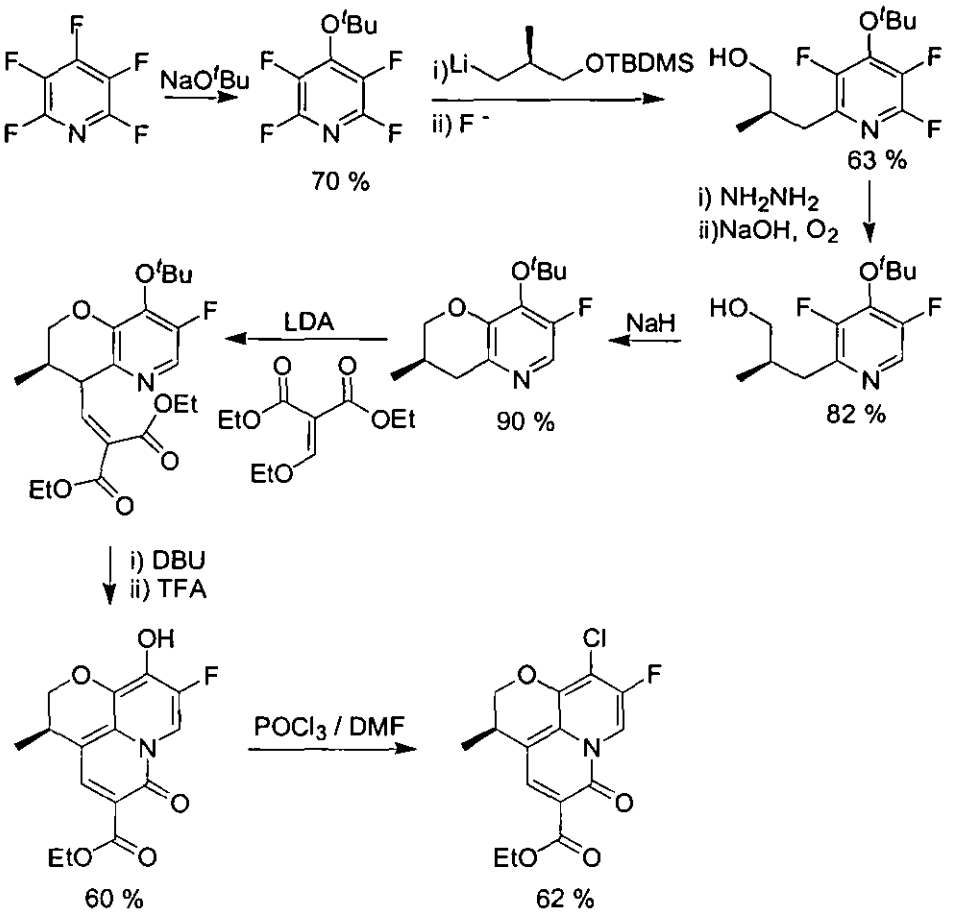


Figure 1.37 2-Pyridone synthesis

The high reactivity and selectivity of pentafluoropyridine is used to great effect here with tetrasubstitution (4-, 2-, 6-, and 3- respectively) proceeding in high yields.

Formation of Glycosyl Donors

The electron deficient nature of pentafluoropyridine has seen its use as a leaving group in the development of glycosylation strategies.[81]

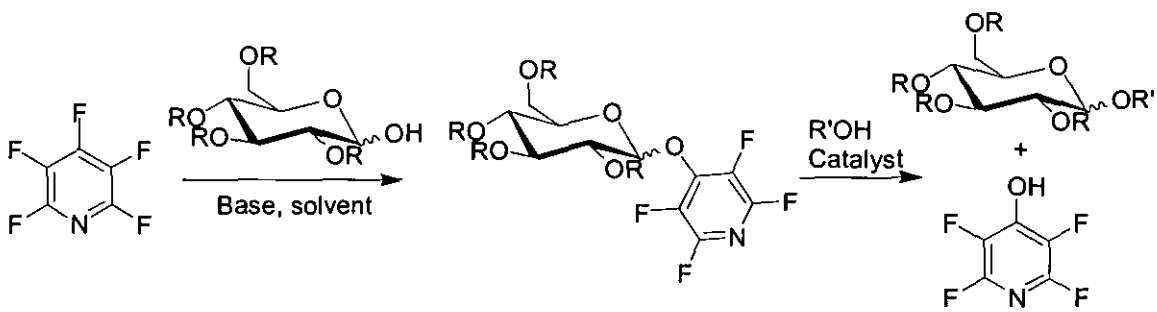


Figure 1.38 Glycosylation via fluoropyridine-based glycosyl donor strategy

Nucleophilic substitution at the 4-position of pentafluoropyridine with a protected sugar gives the glycosyl donor intermediate. Reaction of this species with an alcohol (i.e. another protected sugar), in the presence of a Lewis acid, gives the coupled product (disaccharide) and 2,3,5,6-tetrafluoro-pyridin-4-ol.

This concept has been developed through the employment of derivatised fluoropyridines, with the aim of introducing variation into the ability of the leaving group:[82]

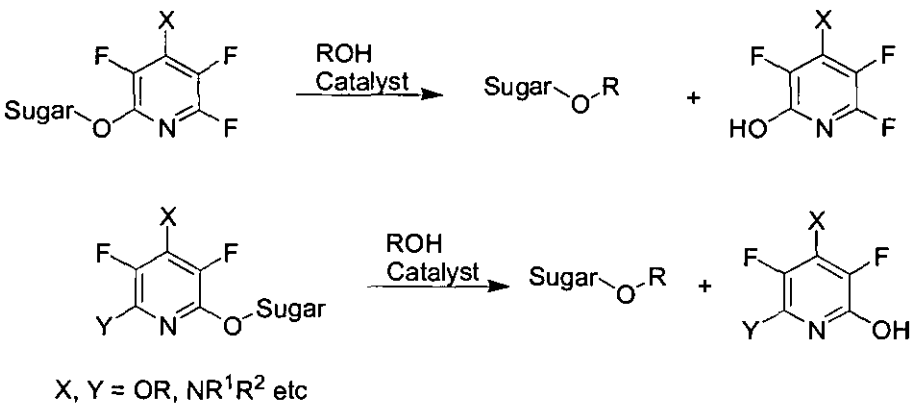
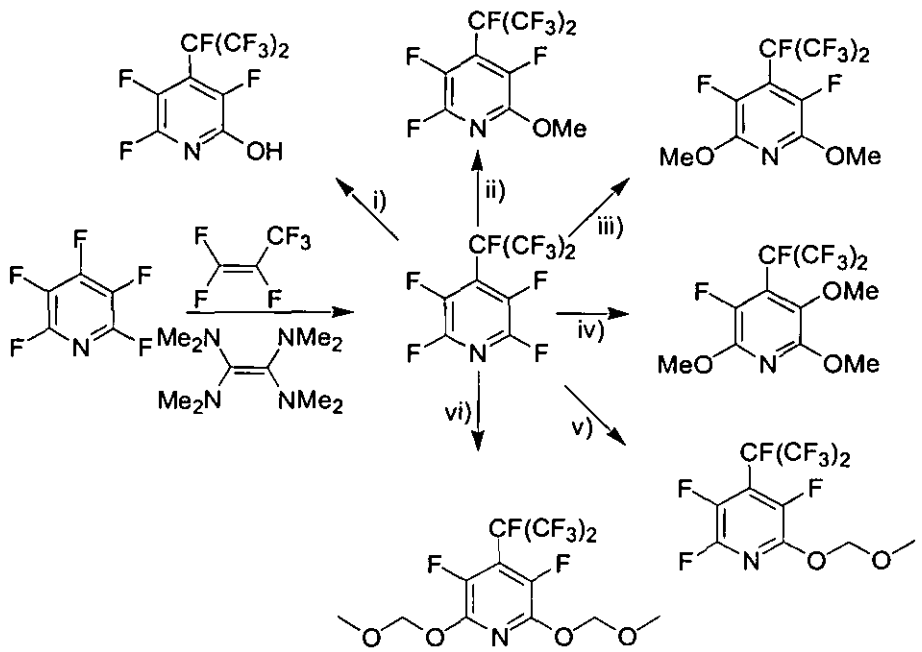


Figure 1.39

The normally electron-rich nature of nucleophilic species means that the introduction of groups X and Y will lead to a less electron-deficient pyridine ring hence requiring, in principle, a stronger Lewis acid to achieve the desired coupled product in the glycosylation step.

Functionalised, Fluorinated Pyridine Synthesis

The synthesis,[83] and some representative nucleophilic aromatic substitutions,[84] of perfluoro-(4-isopropylpyridine), a compound that has proven to be highly reactive and regioselective to nucleophilic aromatic substitution,[84-89] are shown in Figure 1.40:



Reagents and conditions: i) 1 eq KOH, ^{t}BuOH, reflux, 24 h, 61 %; ii) 1 eq NaOMe, MeOH, reflux, 24 h, 69 %; iii) 2.4 eq NaOMe, MeOH, reflux, 24 h, 66 %; iv) 11 eq NaOMe, MeOH, reflux, 24 h, 75 %; v) 1 eq CH_3OCH_2ONa, THF, reflux, 24 h, 38 %; 4 eq CH_3OCH_2ONa, THF, reflux, 24 h, 76 %.

Figure 1.40 Synthesis and reactions of perfluoro-(4-isopropylpyridine)

Reaction of TDAE, a very strong electron donor, with CF_2=$CFCF_3$ gives a fluoride salt, $F^-(TDAE)^+$-CF=$CFCF_3$, which in turn reacts with a second equivalent of the fluoroalkene to give $(CF_3)_2CF^-$. This can then attack the electron-deficient fluoropyridine ring to give perfluoro-4-isopropylpyridine along with fluoride ion, which can propagate carbanion formation and hence the formation of the 4-substituted pyridine. As can be seen from the diagram, nucleophilic aromatic substitution of this perfluorinated heterocycle proceeds regioselectively, and in the order 2-, 6- then finally, due to the highly electron-withdrawing 4-substituent, at the usually inaccessible 3-position of the fluoropyridine.

Research into the synthesis of high energy compounds has involved the strategic placement of electron withdrawing NO_2 groups onto the pyridine ring in order to activate to nucleophilic aromatic substitution, as shown in Figure 1.41. Reduction of pentafluoropyridine to 3,5-difluoropyridine, followed by formation of the *N*-oxide and

then trinitration should give a pyridine highly reactive to nucleophilic attack in the 3- and 5-positions by, for example amines, to give heterocycles high in nitrogen content and hence potential explosives:

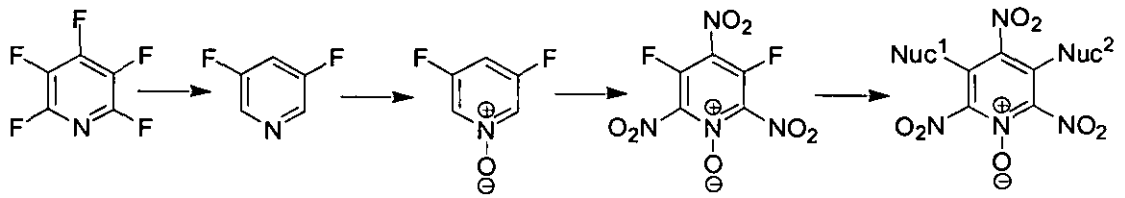


Figure 1.41 Approach to the synthesis of high energy pyridines

Formation of the difluoropyridine was achieved through bromination with HBr and $AlBr_3$ followed by hydrogenation:

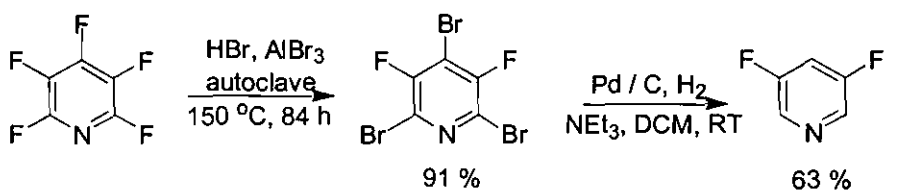


Figure 1.42 Synthesis of 3,5-difluoropyridine

Formation of the *N*-oxide was achieved with ethaneperoxoic acid and, whilst reaction with a mixture of fuming sulphuric and nitric acids only yielded a mixture of mononitrated pyridines, their reactivity towards nucleophilic attack was shown by reaction with ammonia to give the mixture of products shown in Figure 1.43:

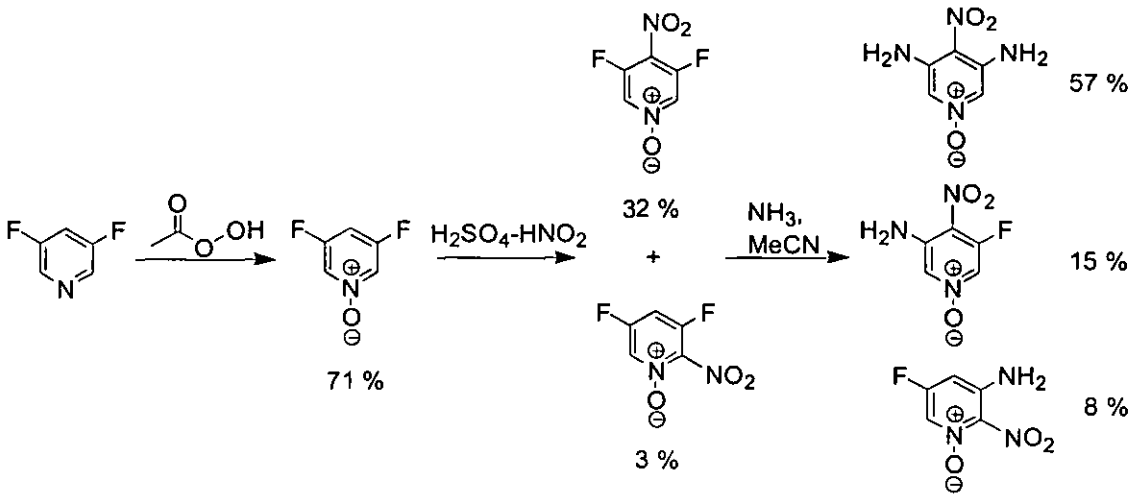


Figure 1.43 Derivatisation of 3,5-difluoropyridine

1.4.2 Reaction with Binucleophiles

Pyridine-Fused Ring Synthesis

Recent work has focused on the reaction of pentafluoropyridine with binucleophilic species to give fluoropyridine fused-ring systems. Once formed, these structures should still be reactive to further nucleophilic attack, hence making further elaboration of the fluoropyridine possible. This approach is illustrated conceptually in Figure 1.44:

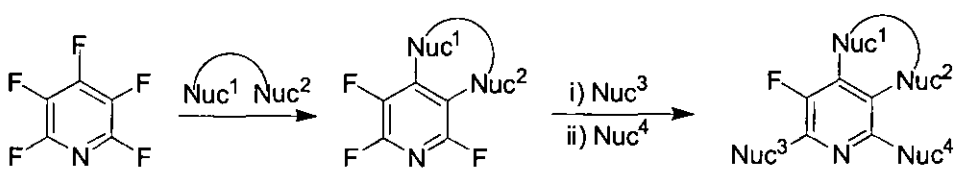


Figure 1.44 Approach to pyridine ring-fused heterocycle synthesis from pentafluoropyridine

[6,6] Pyridine-Fused Ring Formation

Reaction with a selection of diamine nucleophiles gave a series of tetrahydropyrido[3,4-b]pyrazines. Further displacement of fluorine from these scaffolds was shown to be possible:[14]

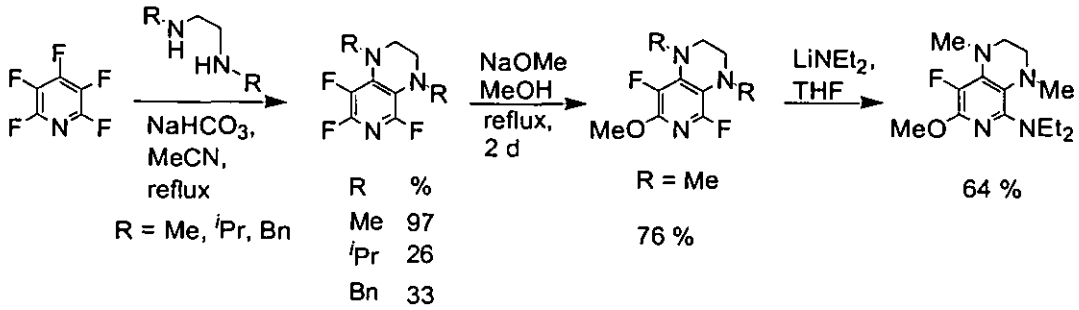


Figure 1.45

An alternative strategy is to functionalise pentafluoropyridine first at the 4-position and then form a fused ring at the 2- and 3-position:

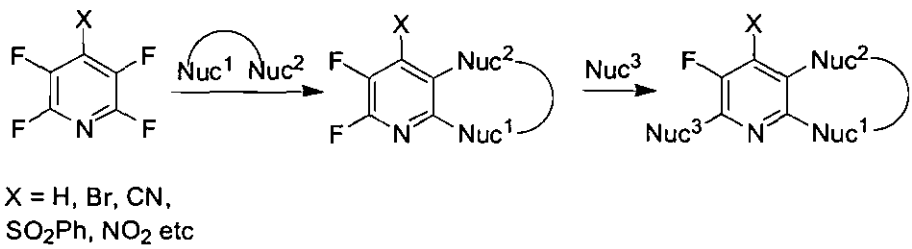


Figure 1.46

This strategy has proven effective where X = H, Br, CN, NO_2,[90] $CF(CF_3)_2$[87] and SO_2Ph[91]. In this last case, pentafluoropyridine was reacted with the sodium salt of phenylsulfinic acid to give the 4-substituted pyridine whilst subsequent reaction with a range of diamines led to a series of tetrahydropyrido-[2,3-*b*]-pyrazine scaffolds.

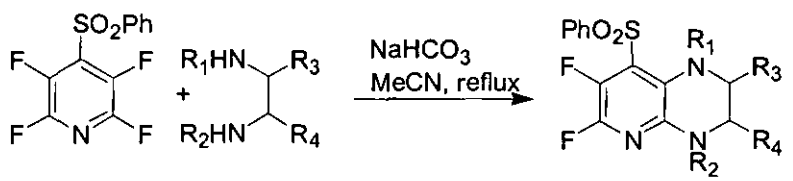


Figure 1.47

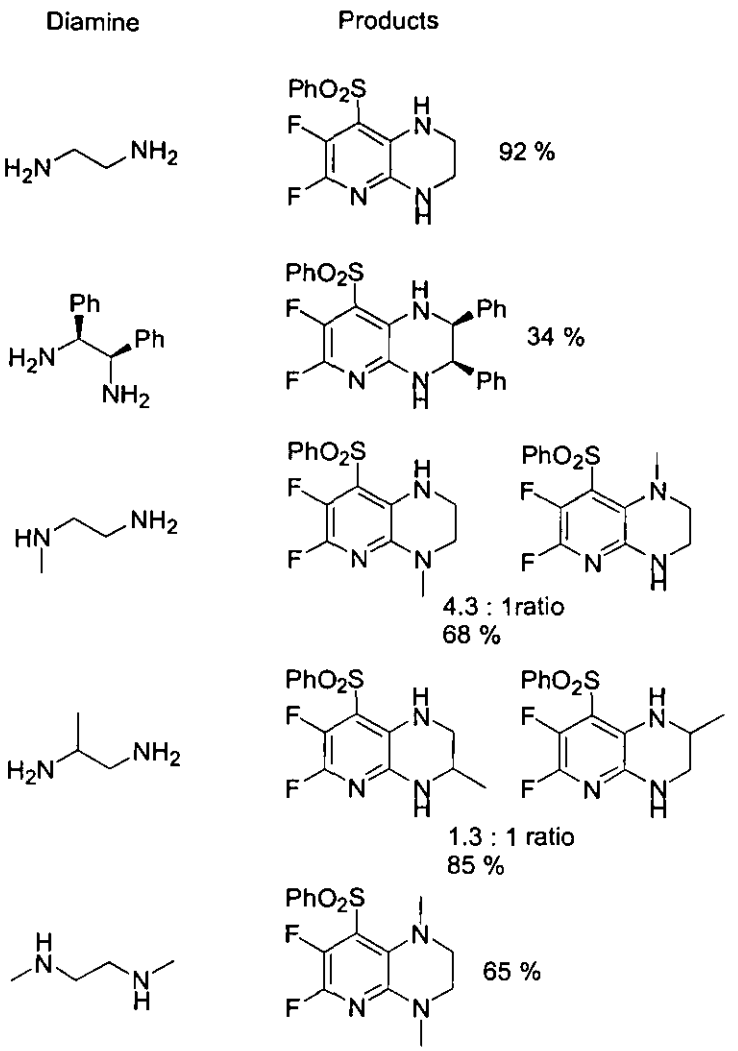


Figure 1.48

The 4-SO_2Ph group is electron-withdrawing to such an extent that a percentage of initial attack on the pyridine occurs at the 3-position, which gives rise to the mixture of products observed when reacted with unsymmetrical binucleophiles.

Further nucleophilic aromatic substitution of these scaffolds (R_1 and R_2 = H, Me) with representative oxygen, nitrogen and sulfur centred nucleophiles gave differing results. Hard nucleophiles (NaOMe, KOPh) gave inseparable mixtures arising from substitution of 4-SO_2Ph and 3-F whereas reaction with softer nucleophiles ($LiNEt_2$, NaSPh) gave substitution of the 4-SO_2Ph group.

The synthesis of the tricyclic 2-pyridone[80] discussed in Section 1.4.1 includes the interesting annulation to give a pyran ring at the 2- and 3-position of the fluoropyridine template through the formation and subsequent nucleophilic aromatic substitution of a tethered alkoxide ion.

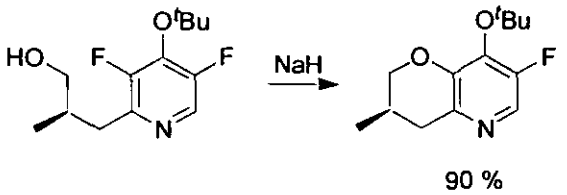


Figure 1.49 [6,6] pyridine fused-ring annulation

Despite the relatively electron-rich nature of the uncyclised pyridine (1 *ortho* O^{t}Bu, 1 *meta* fluorine to site of attack) the cyclisation proceeds in excellent yield. The removal of the slightly deactivating fluorine *para* to the site of attack probably has some bearing on the effectiveness of this ring formation.

[5,6] Pyridine Ring-Fused Formation

In light of research showing improved biological activity upon the replacement of a ring nitrogen in ribavirin, a broard spectrum antiviral agent, with a CF group,[92] Paul Coe *et al* investigated extending this idea to replacing a pyrimidine nitrogen of purine, probably the most ubiquitous of all biologically active molecules, to give a fluoro-imidazopyridine. After initial failed attempts focused around forming a suitable *ortho*-diaminopyridine from 3-chlorotetrafluoropyridine with which the imidazole ring could then be formed,[93] the Birmingham group reacted pentafluoropyridine with the binucleophilic species guanidine, urea and thiourea in an attempt to create a [5,6] pyridine ring-fused bicycle which could then yield the desired fluoro deazapurine.[94] Figure 1.50 shows this approach schematically:

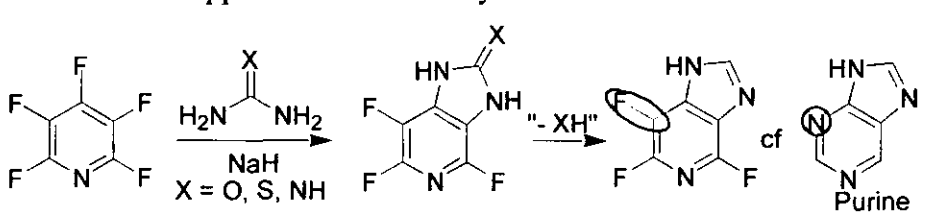


Figure 1.50 Approach to fluoroimidazopyridine synthesis

However, in practice only monosubstitution at the 4-position of pentafluoropyridine was achieved in the reaction with guanidine, whilst the reactions with urea and thiourea yielded bis-pyridyl compounds:

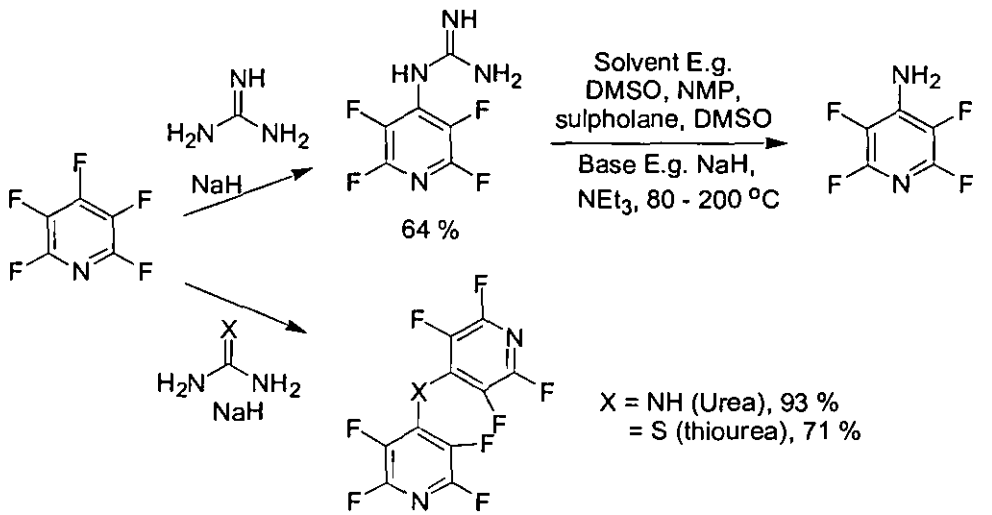


Figure 1.51

Attempts to cyclise the 4-pyridyl guanidine through the use of polar solvents, base and high temperatures only gave 4-amino-tetrafluoropyridine. Formation of the unexpected bis-pyridyl compounds was explained through the following base-induced mechanism:

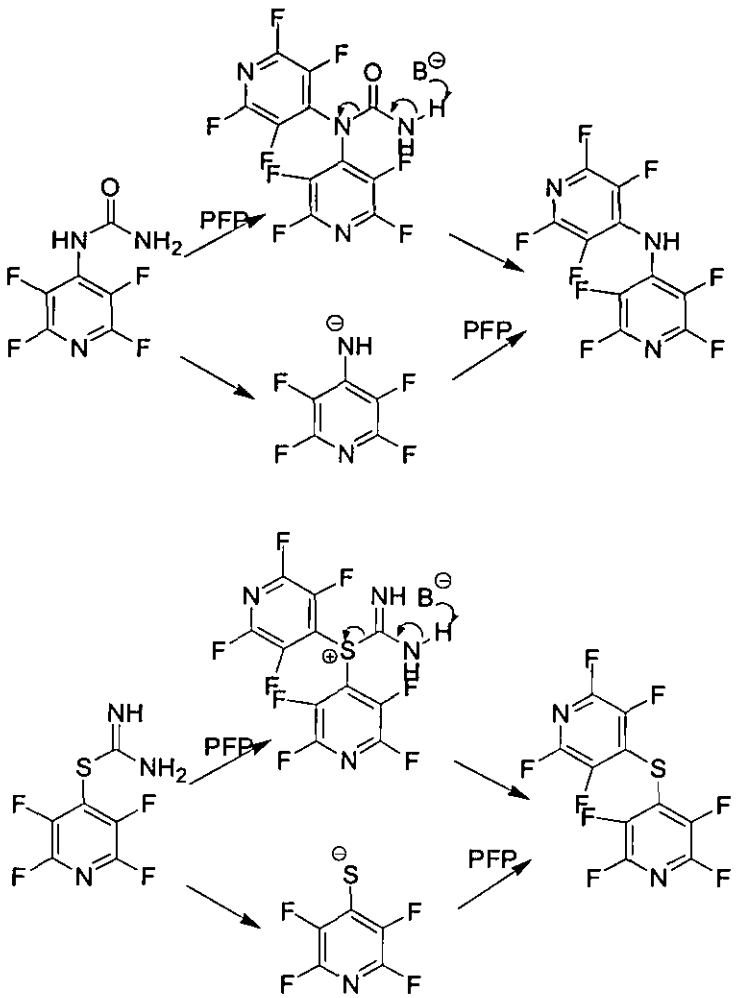


Figure 1.52 Base-induced decomposition pathway

Interestingly, the fluoro-imidazopyridine target molecule was reported independently in the same year.[95] Also in pursuit of novel antiviral agents, a seven step synthetic route was taken, starting from 3-chlorotetrafluoropyridine via the formation and subsequent condensation of 3,4-diamino-2,5,6-trifluoropyridine with diethoxymethyl acetate to give the pyridine-fused heterocycle in a 24 % overall yield.

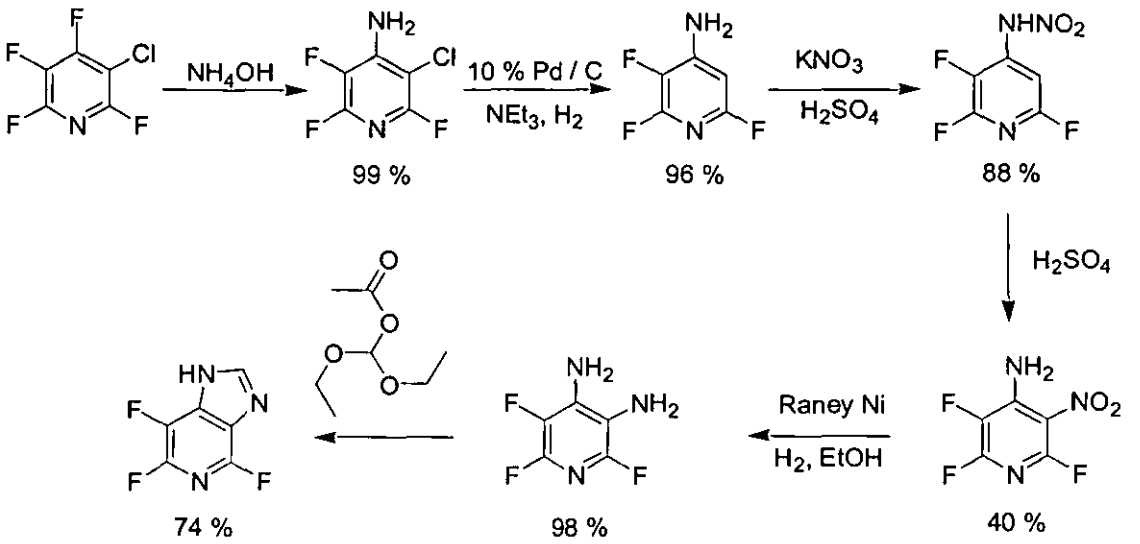
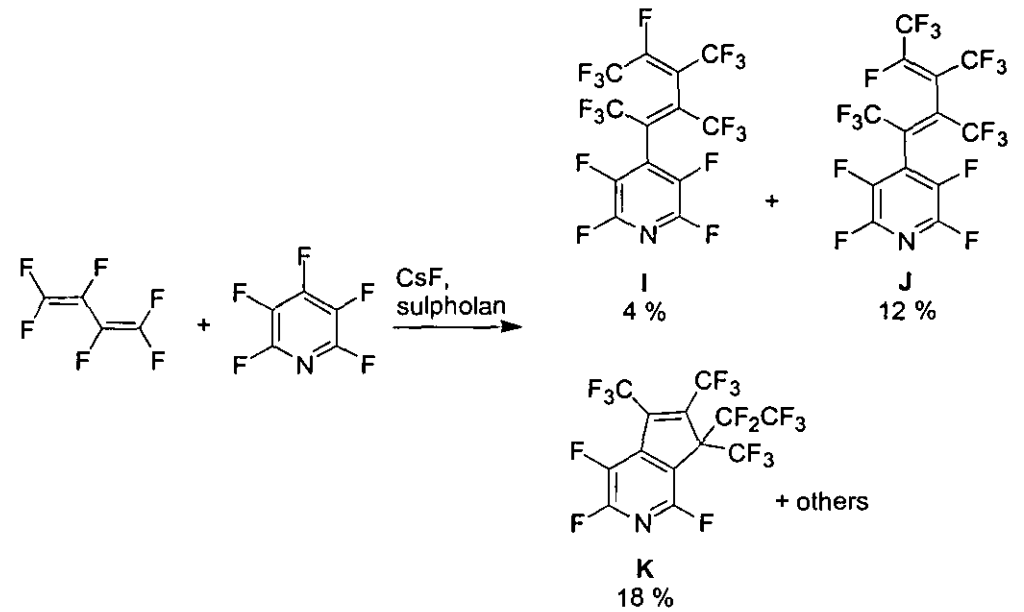


Figure 1.53 Synthesis of 4,6,7-trifluoro-imidazo[4,5-c]pyridine from 3-chloro-tetrafluoropyridine

Chambers et al, through the study of fluoride ion induced polymerisation of perfluoro-alkenes and –alkynes, reported the formation of the following fluorinated [5,6] ring-fused pyridine:[96]



Cyclopentadiene Ring Formation Mechanism:

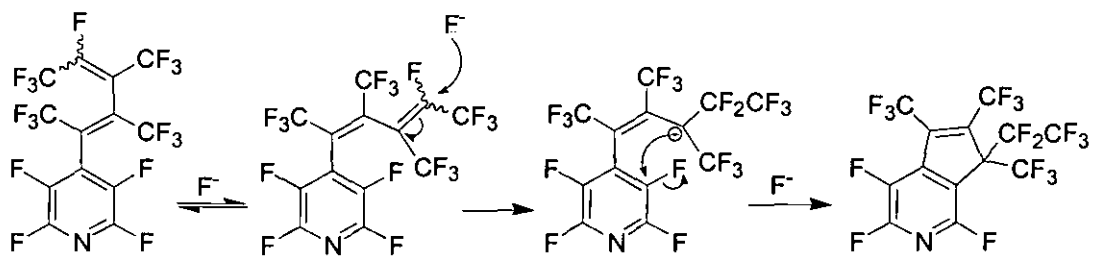


Figure 1.54

CsF-induced oligomerisation of hexafluorobutadiene gives a series of carbanions which were trapped by pentafluoropyridine to give a number of simple products along with hydrogen terminated oligomer. Formation of **K** proceeds via the fluoride induced cyclisation of **I** and **J**.

Macrocycle Synthesis

Appropriate use of 4-substituted polyfluoropyridine derivatives have been shown to react with binucleophilic compounds to form various novel macrocycles.[89, 97, 98] The general approach to their synthesis and an example is given below:

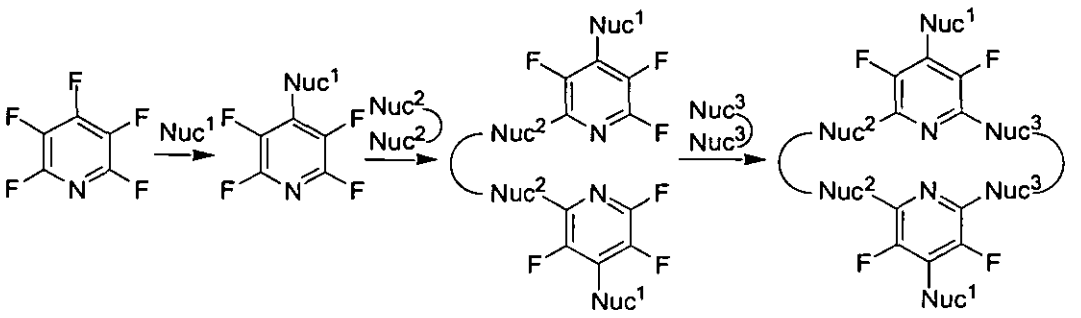
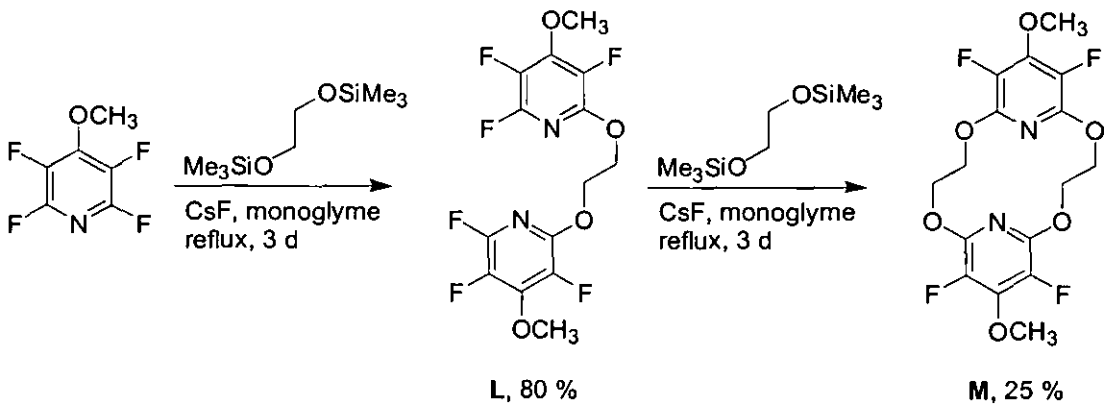


Figure 1.55 Approach to macrocycle synthesis



L, 80 %

M, 25 %

Figure 1.56

Desilylation of the ethane-diol by caesium fluoride gives the activated binucleophile which then attacks two equivalents of the tetrafluoropyridine, at the most activated 2-position, to give dimer **L**. The reason why the tethered nucleophile does not attack at the 3-position (in both steps) to form a 6-membered ring is also due to the deactivated nature of this site to nucleophilic attack and the high dilution conditions employed.

1.4.3 Synthesis of Partially Halogenated Pyridines

Although the following research carried out involved perhalogenated pyridines other than pentafluoropyridine (though it is employed), it is worth incorporating due to the possibility of these partially fluorinated pyridines themselves being of use as scaffolds for functionalised pyridine synthesis.

Schlosser and co-workers have set about synthesising all three tetrafluoropyridines , all six trifluoropyridines and five non-commercially available difluoropyridines through a combination of site-selective defluorinations and fluorinations.[99] Loss of fluorine was achieved by reduction with metals or complex hydrides;

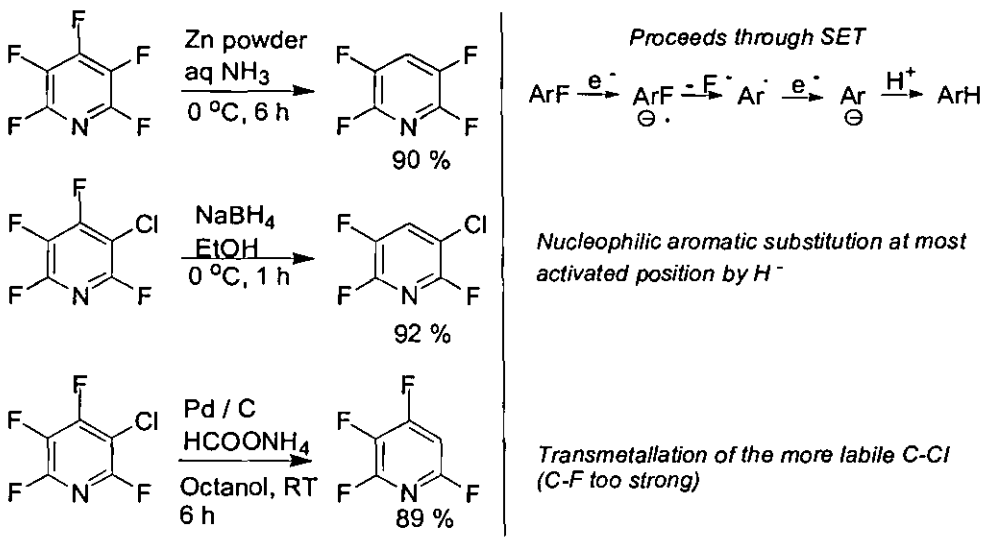


Figure 1.57 Defluorination Strategies

Alternatively, displacement of fluoride by hydrazine, followed by dehydrogenation-dediazotation when treated with cupric sulphate, or dehydrochlorination-dediazotation when heated with sodium hydroxide solution, gave access to 3-chloro-2,5-difluoropyridine and 2,5-difluoropyridine respectively:

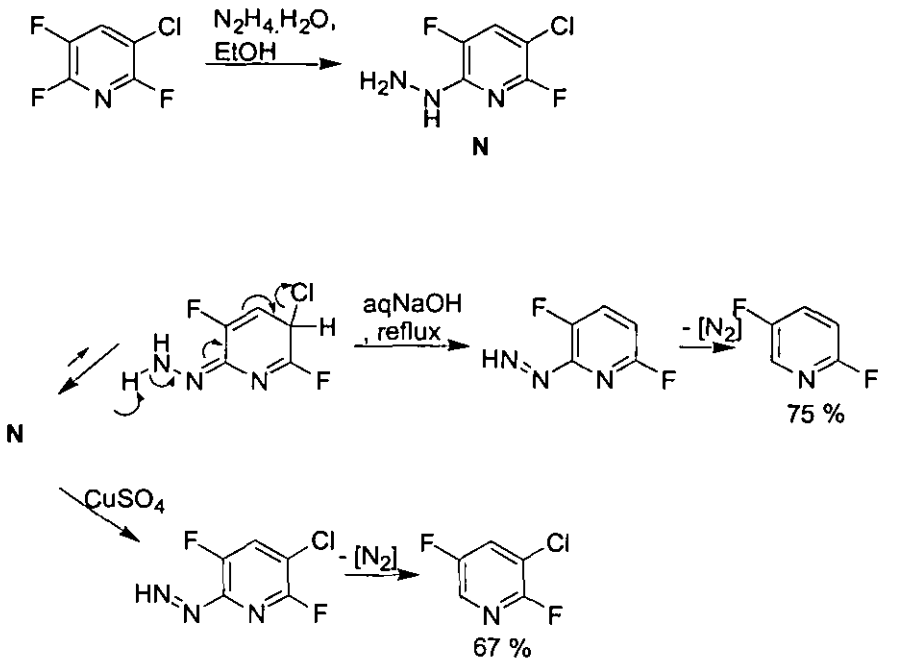


Figure 1.58

Introduction of fluorine into the pyridine ring was accomplished by insertion of a chlorine or bromine, followed by a Halex reaction.

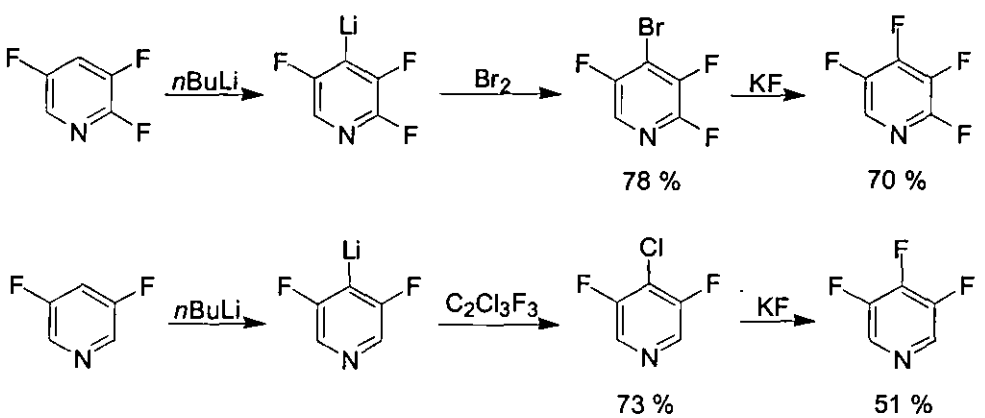


Figure 1.59

These reactions also illustrate the potential for tuning functionalised fluoropyridines e.g. a suitable perhalogenated pyridine may be reacted with nucleophiles and then dehalogenated in various positions to give a series of products.

1.5 Conclusions

It has been shown that the modern approach to "lead" generation in the drug discovery is often via relatively small, focused libraries of compounds often based around a heterocyclic core. Halogenated heterocycles, in particular perfluorinated systems, can be excellent scaffolds for the synthesis of functionalised heterocycles in short, efficient routes.

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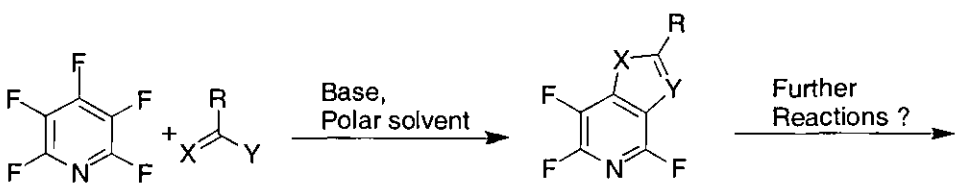
Chapter 2

[5,6] Pyridine Ring-Fused Heterocycle Synthesis from Pentafluoropyridine

2.1 Introduction

As discussed in Chapter 1, pyridine ring-fused heterocycles are an important source of biologically relevant compounds and have been made through various methods, often involving building the fused ring by attaching functionality around pyridine, a compound that is difficult to derivatise in a quick and flexible manner. Our approach to the synthesis of functionalised heteroaromatic systems is through the sequential nucleophilic substitution of highly fluorinated pyridines with suitable nucleophilic or binucleophilic species (see Section 1.4.2) and this has been shown to be successful for the synthesis of several [6,6] and [6,7] pyridine-fused heterocycles. This chapter will detail the reaction of pentafluoropyridine with various binucleophiles, with the aim of synthesising analogous [5,6] systems by a short, simple and flexible strategy. The resulting heterocycle should still be reactive to further nucleophilic aromatic substitution, due to the presence of three remaining fluorine atoms, thus opening up the possibility for further elaboration of the fluoropyridine core scaffold. A general scheme outlining this approach is shown below:



X = Y = N (amidines)
X = O, S; Y = N (amides / thioamides)
X = O; Y = C (1,3 dicarbonyls)

Figure 2.1 Approach to pyridine-fused heterocycle synthesis

We anticipated that the reactions should occur under basic conditions, to activate the binucleophile and quench the hydrogen fluoride byproduct and in a polar solvent to

stabilise the charged transition state, whilst high dilution would be employed to minimise intermolecular attack of a tethered binucleophile, though the desired intramolecular condensation is entropically favoured.

Reaction of pentafluoropyridine with a 1,3 binucleophile to give a [5,6] pyridine-fused ring is limited to only the two following examples, namely Chambers' *et al.'s* fluoride induced ring closure (See Section 1.4.2), though this was only formed as a very minor product, and the following single example of a condensation of a fluorinated heterocycle with a cyclic enamine to give the following tetrahydrocarboline in moderate yield:[1]

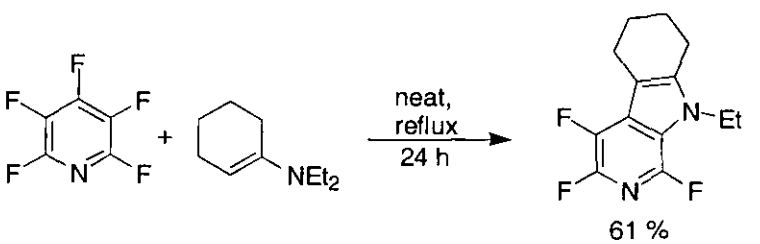


Figure 2.2

Coe *et al.'s* attempted condensation of pentafluoropyridine with guanidine, urea and thiourea (see Section 1.4.2) is probably the most relevant point of reference to the work carried out within this thesis on fused ring synthesis from pentafluoropyridine. Although each binucleophile was reactive enough to attack the 4-position of pentafluoropyridine, the resulting compounds either remained inert to cyclisation attempts or followed an undesired decomposition pathway.

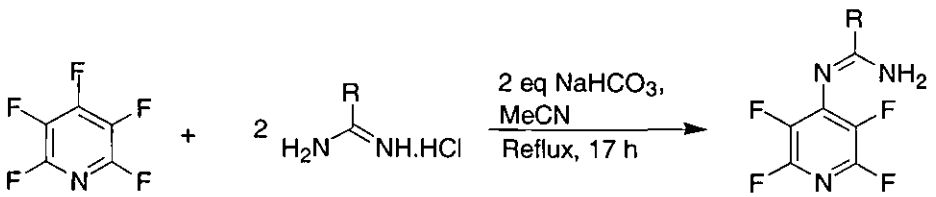
Formally replacing an amino group of guanidine with either a methyl or aryl group (making the system more nucleophilic) allowed a study of condensation reactions between pentafluoropyridine and a range of amidines.

2.2 Reaction of Pentafluoropyridine with *N, N*-Unsubstituted Amidines

Commercially available benzamidine hydrochloride (R = Ph) and acetamidine hydrochloride (R = Me) were chosen as suitable *N, N*-centred 1,3 binucleophiles for reaction with pentafluoropyridine. DMF was initially employed as the polar solvent to

dissolve the relatively insoluble amidine salts whilst an excess of inorganic base was added to neutralise any acidic byproducts.

Accordingly, stirring at room temperature gave two major new resonances by ^{19}F NMR of the reaction mixture after 20 h, indicative of the formation of symmetrical 4-substituted pyridines. Extraction followed by recrystallisation of the organic product from hexane gave the desired 4-aminido-tetrafluoropyridines in moderate yields (R = Ph, 61 %; Me, 56 %). A better synthesis was devised utilising acetonitrile as the reaction solvent and resulted in such a clean reaction as to negate the need for recrystallisation and giving excellent yields.



	R	%
1	Ph	96
2	Me	88

Figure 2.3

Many attempts were made to cyclise these two compounds, including using sodium hydride, refluxing aqueous potassium hydroxide, and heating at high temperature in polar solvents. It was found that the tethered amidine appeared to be somewhat fragile to these harsh conditions (strong bases, high temperatures etc) and often resulted in decomposition to give 4-amino-tetrafluoropyridine, presumably similar to Coe's base-induced mechanism (see Section 1.4.2).

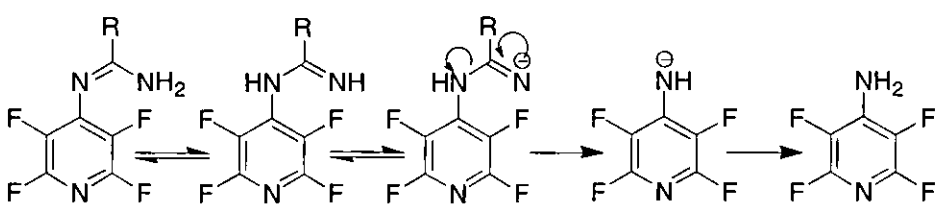


Figure 2.4 Decomposition of 4-amidino-tetrafluoropyridines

Bearing this in mind, a reaction was devised that would limit the temperature of the reaction attained and employ a strong base that should formally deprotonate the amidine moiety and allow the entropically favoured intramolecular attack at the 3-position to

occur. Thus, LDA was added to a stirring solution of **1** in dry THF at -78 °C, left for 2 h and gradually allowed to warm to room temperature. ^{19}F NMR of the reaction mixture after one day showed there to be no starting material remaining, only one new compound that gave three resonances by ^{19}F NMR spectroscopy. An aqueous acid work up followed by recrystallisation from acetonitrile yielded imidazopyridine **3** in excellent yield. Full NMR characterisation, mass spectrometry and elemental analysis confirmed the structure of the desired heterocycle.

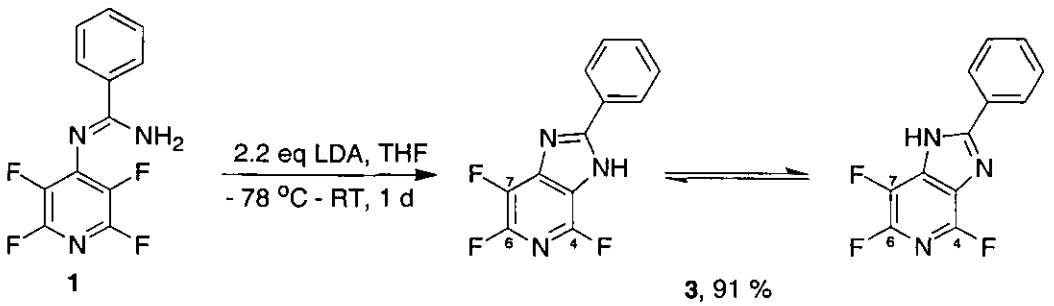


Figure 2.5

The heterocycle exists as a rapidly interconverting mixture of tautomers, which causes the broadening of the resonances observed in ^{19}F NMR and can even give rise to two sets of resonances (Figure 2.6); as such, for clarity, only one tautomer will be drawn (and named) from hence forth.

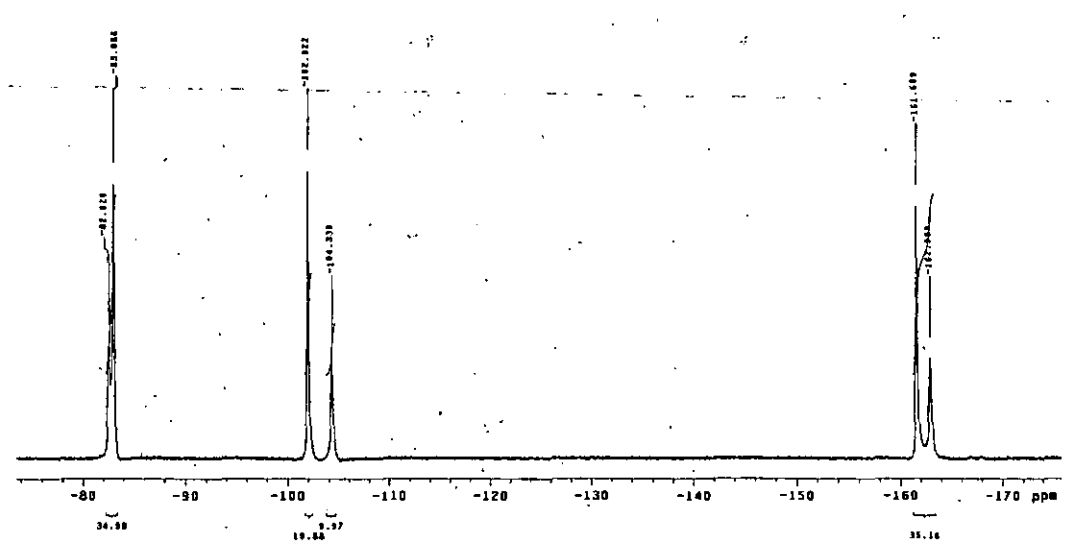


Figure 2.6 ^{19}F NMR spectrum of **3**; δ_F (DMSO-d_6) major tautomer (67 % by ^{19}F NMR) -83.08 (1F, br s, F-6), -102.02 (1F, br s, F-4), -161.60 (1F, br s, F-7); minor tautomer (33 %) -82.60 (1F, br s, F-6), -104.33 (1F, br s, F-4), -163.00 (1F, br s, F-7)

It is worth pointing out that the pH of the aqueous layer during extraction of the product is extremely important. Basic work up (resulting from the excess of LDA solution employed) only leads to a small amount of black tarry substance being extracted. This is presumably because the imidazole hydrogen atom is reasonably acidic, giving the formation of a water soluble lithium amine salt.

Thus, in two steps, pentafluoropyridine can be converted into a highly desirable fluorinated imidazopyridine. Furthermore, the cyclisation step has been carried out several times on various scales with consistently high yields.

Adopting these conditions to attempt cyclisation of 4-acetamidino-tetrafluoropyridine **2**, however, resulted again in the decomposition product **4** and, unfortunately, more sterically hindered amine bases, potassium and sodium hexamethyldisilazane, gave the same result.

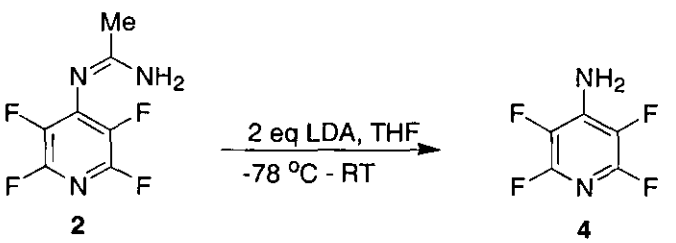


Figure 2.7

From this we can suggest that the phenyl group resists the base induced elimination of 4-amino-tetrafluoropyridine **4**, either through its steric bulk or electronically through resonance stabilisation:

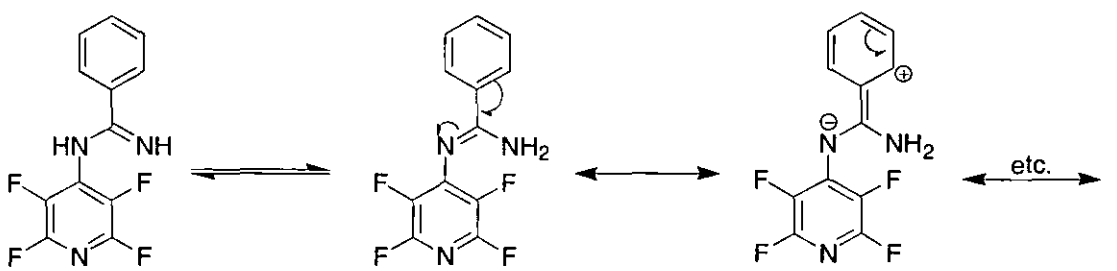


Figure 2.8

To extend the series of condensations with amidines, pentafluoropyridine was reacted with formamidine hydrochloride (R = H). In this case, refluxing the reaction mixture gave 4-amino-tetrafluoropyridine **4** as a byproduct (implying even less stability) along with the desired 4-substituted fluoropyridine. Repeating the experiment at room temperature gave improved conversion to the target molecule, whilst reaction with LDA gave the decomposition product.

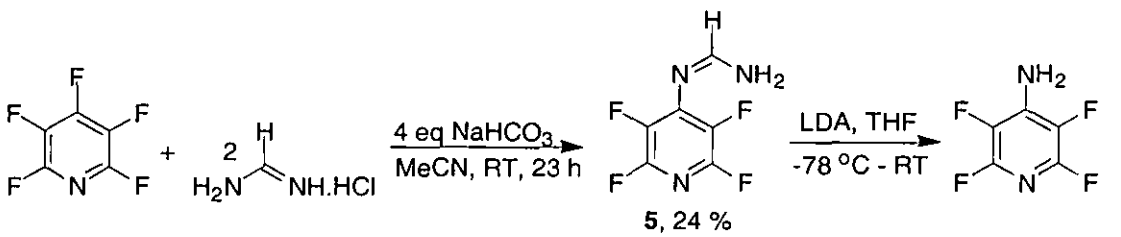


Figure 2.9

2.3 Reaction of Pentafluoropyridine with *N*-Substituted Amidines

Although the three amidines (R = Ph, Me, H) exhibit sufficient nucleophilicity to attack pentafluoropyridine, the tethered amidines are not sufficiently nucleophilic to achieve ring closure apart from under the specific conditions discussed. It was hypothesised that the employment of an *N*-substituted amidines, e.g. *N*-alkyl, should give a more nucleophilic species and, hence, increase the likelihood of imidazopyridine synthesis when reacted with pentafluoropyridine.

A sample of *N*-methyl-benzamidine hydrochloride was reacted with pentafluoropyridine under basic conditions and microwave heating. LCMS of the resulting reaction mixture indicated two compounds to be present; the first at 3.1 minutes and representing 24 % of the total ion content (TIC) trace, with $[M^+ + H^+]$ 264.1 and the second at 3.3 minutes and representing 76 % of the TIC trace, with $[M^+ + H^+]$ 284.0. Mass directed auto purification (MDAP) of this crude material yielded these products as two white solids. ^{19}F NMR of the first sample (shown in Figure 2.10) revealed 3 major (-81.33, -100.31, -169.52 ppm) and three minor resonances (-86.72, -102.39, -162.03 ppm) whilst the other isolated solid consisted of two very broad resonances (-91.30, -152.58 ppm). From this data, we can deduce the two sets of isomers shown in Figure 2.11

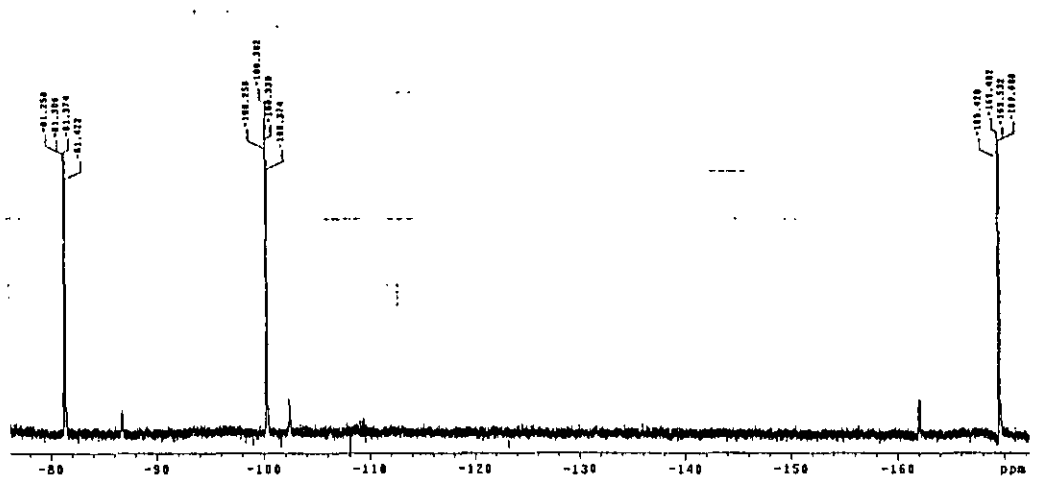


Figure 2.10; ^{19}F NMR spectrum of **6** and **7**; δ_F Major isomer -81.33 (J_{FF} 32.6, J_{FF} 12.7), -100.31 (J_{FF} 20.3, J_{FF} 12.8), -169.52 (J_{FF} 32.7, J_{FF} 20.7); Minor isomer -86.72 (1F, m), -102.39, -162.03 (dd, J_{FF} 32.5, J_{FF} 19.2,)

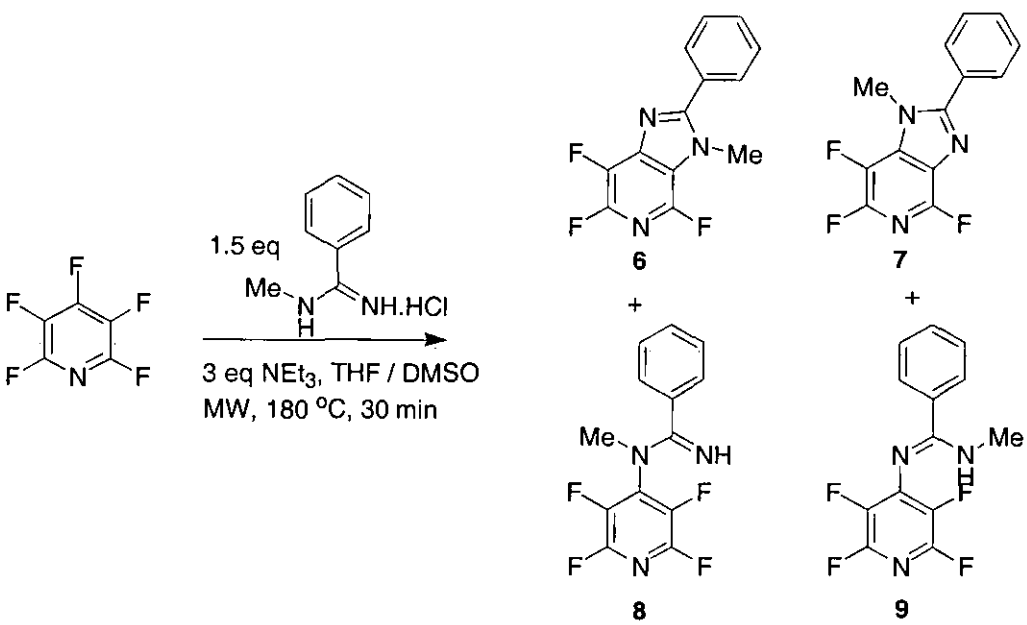


Figure 2.11

The characteristic pattern observed in the ^{19}F NMR of the first sample, along with the single [$M^+ + H^+$] peak observed by LCMS, indicates the desired [5,6] pyridine-fused heterocycles **6** and **7**, though which isomer predominates is unclear. It also follows that the other solid isolated must be the respective 4-substituted intermediates **8** and **9**. This

assignment was corroborated through the optimisation of the reaction by employing five equivalents of the slightly less volatile base DIPEA and microwave heating at 200 °C for 30 min. LCMS of the resulting mixture showed clean conversion again to the same compounds, this time in a ratio of 37 : 63 % (cyclised : uncyclised respectively) by TIC trace, implying a higher conversion to the disubstituted, fused heterocycle due to the more forcing reaction conditions.

The commercially available *N*-phenyl-benzamidine was also explored as a potentially useful binucleophile. Reaction with pentafluoropyridine gave the following products:

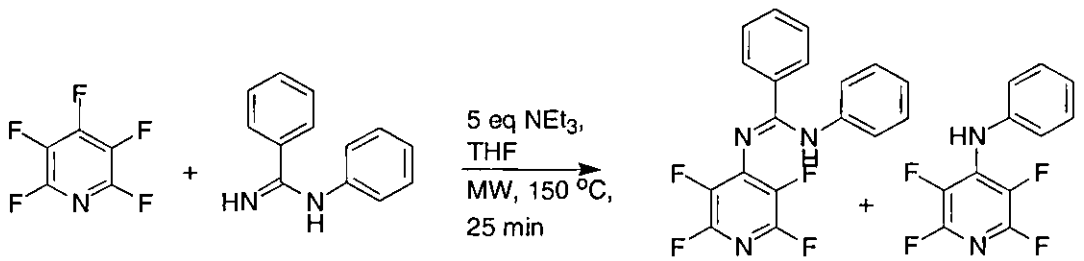


Figure 2.12

Along with the desired 4-aminido substituted pyridine **10**, a 4-substituted byproduct was observed, presumably through the decomposition, in an analogous manner to the unsubstituted amidine examples previously discussed, of an unstable species resulting from the initial attack of pentafluoropyridine by the *N*-phenyl nitrogen. It is for this reason that structure **10** has been assigned as the other possible isomer. Attempts to cyclise **10** with LDA resulted only in a 2-, 4- disubstituted trifluoropyridine, most probably through nucleophilic attack of $^{-}N^{i}Pr_2$ at the most active position *ortho* to the pyridine ring nitrogen. This is logical as, although LDA is supposedly a non-nucleophilic base, it has been shown to readily attack polyhaloaromatic compounds.[2]

The condensation of pentafluoropyridine with 2-imino-piperidine gave the most successful result in this series of reactions, forming tricycle **11** in a one pot process and, after optimisation of the reaction conditions, in moderate yield.

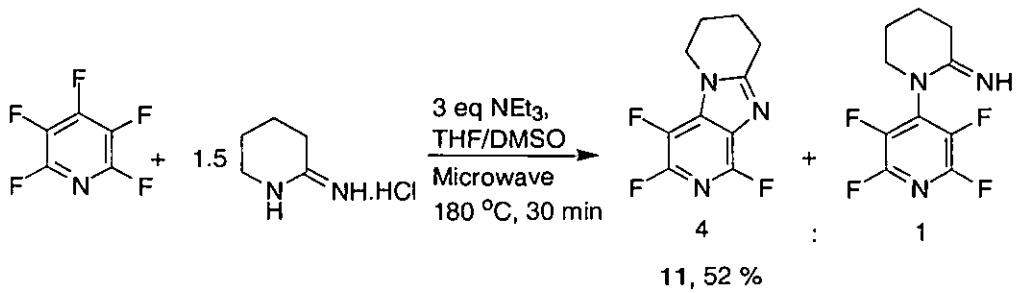
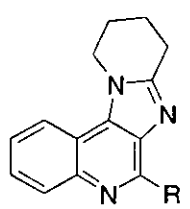


Figure 2.13 Reaction of pentafluoropyridine with 2-imino-piperidine hydrochloride

Initial attack of the binucleophile through the piperidine ring nitrogen, which, therefore must be the more nucleophilic site, is followed by attack of the tethered imine at an adjacent C-F bond to give ring annulation. A byproduct was also observed by LCMS of the reaction mixture and appeared to be the uncyclised intermediate.

A substructure search for this nitrogen-containing heterocyclic core reveals only one reference and involves the synthesis of the non-fluorinated analogue of tricycle **11** by the pyrolitic cyclisation of pyridine azide.[3] The only other similar structure to arise from the literature search is the following tetrahydro-pyridoimidazoquinoline motif that appears in three separate patents detailing immune response modifiers ($R = NH_2$)[4, 5] and as a compound useful for inducing interferon biosynthesis ($R = NH_2$, $N(Bz)_2$).[6]



$R = NH_2, N(Bz)_2$

Figure 2.14

2.4 Further Reactions of Trifluoropyridine Ring-Fused Heterocycles

Inspection of heterocycle **3** reveals several potential sites for further elaboration to give polyfunctional systems: derivatisation of the phenyl ring (or use of functionalised aryl amidines) as mentioned in the previous section, reaction of the imidazole ring nitrogens and nucleophilic substitution at one or more C-F bonds. The next stage of research

investigates these latter two reactions, establishing reactivities and selectivities of these processes, in order to expand the developing pyridine-fused ring synthetic methodology.

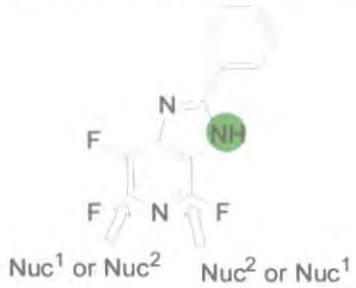


Figure 2.15 Potential sites for functionalisation of imidazopyridine **3**

2.4.1 NH Functionalisation of Imidazopyridine 3

The functionalisation of imidazole amine moieties via reaction with a suitable alkyl halide is a common method for their derivatisation and, as such, there are various procedures for their synthesis. Reaction between **3** and methyl iodide, in the presence of sodium bicarbonate and in acetonitrile, proceeded slowly, emphasising the deactivating effect the electron-deficient nature of the fused fluoropyridine ring has on the imidazole moiety. Changing the base to *n*-butyl-lithium resulted in a far more rapid reaction, forming the two expected and previously observed (see Section 2.3) isomers in essentially equal amounts (52 : 48 % by ^{19}F NMR) and excellent yield:

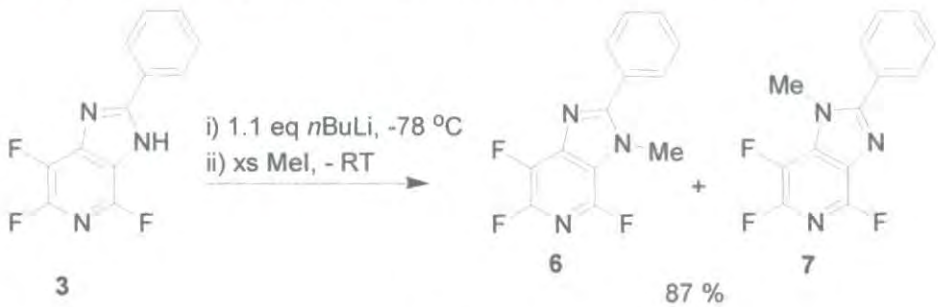


Figure 2.16

2.4.2 Nucleophilic Substitution of Imidazopyridine 3 by Amine Nucleophiles

To further develop the synthetic potential of these scaffolds, reactions of bicycle **3** with nucleophiles were explored. Early experiments involved refluxing with an excess of a very strong nucleophile such as the lithium salt of diethylamine, or hydrazine, in the

knowledge that the presence of the two nitrogen substituents on the fluoropyridine ring could have a deactivating effect to nucleophilic substitution. Though these reactions proceeded accordingly slowly, taking several days to achieve moderate conversion, they encouragingly showed the formation of only one product (by ^{19}F NMR of the resulting mixture) containing two fluorine atoms, implying the desired displacement of fluoride ion by the nucleophile. However, due to the small scale of the reactions and the forcing conditions, which gave a somewhat complex crude material, isolation of these products proved difficult.

Microwave heating of chemical reactions has become a reliable way of improving reaction times and yields, and is an especially useful technique in cases, such as above, where thermal decomposition of the reactants and products occurs due to prolonged heating. The ability to optimise reaction conditions quickly and efficiently, through automatically run arrays, on a small scale, are further advantages to this approach. Adopting this technology to the reactions of some of the deactivated fluoropyridines reported herein yielded suitably impressive results.

The optimised reaction conditions for the reaction of bicycle **3** with *N*-methyl-benzylamine are shown in Figure 2.17. It was found that an excess of the amine (to act as a base as well as nucleophile), along with heating at 180 °C for 30 min gave quantitative conversion to one compound with *m/z* (ES^+) 351.1 ($M^+ + H^+$) and ^{19}F NMR (2 doublet peaks; -100.09 and -174.97 ppm) corresponding to the desired substitution of a fluorine atom. A small quantity of DMSO was employed to help absorb microwave energy as THF alone was insufficiently polar to achieve the desired temperature. Single crystal X-ray analysis of a suitably prepared sample showed the product to have arisen from substitution at the 4-position of the imidazopyridine core scaffold.

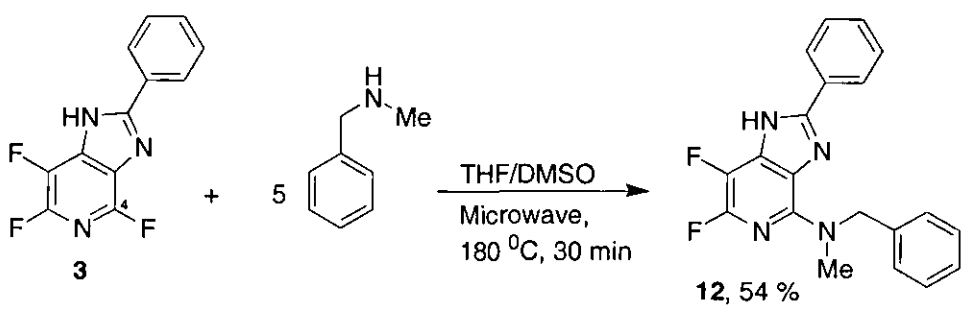


Figure 2.17

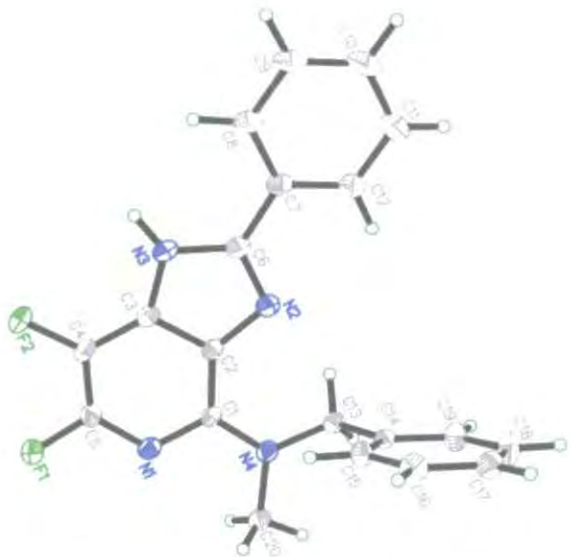


Figure 2.18 X-ray structure of **12**

This result is surprising for the following two reasons. Firstly, studying the initial state effects on the reactivity of the two potential C-F sites of attack (the third C-F site would be deactivated to attack relative to the sites *ortho* to the pyridine nitrogen and thus will not be considered) of the starting material, one would expect attack to occur at the other C-F site:

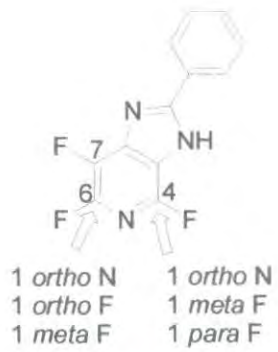


Figure 2.19

The 6 C-F position is activated by one *ortho* and one *meta* fluorine atoms, both activating this site to attack by a nucleophile whereas the 4 C-F position is only activated by one *meta* fluorine atom. As stated in Chapter 1, a *para* fluorine atom is actually slightly electron donating by resonance and hence will have a deactivating effect. Therefore, the selectivity obtained in practise appears to go against these

established reactivity rules developed for monocyclic perfluorinated heteroaromatic systems.

Secondly, this result is also in contrast to work reported on analogous [6,6] pyridine ring-fused heterocycles in which nucleophilic substitution follows the case expected if only the activating effects of fluorine are taken into account (see Section 1.4.2).

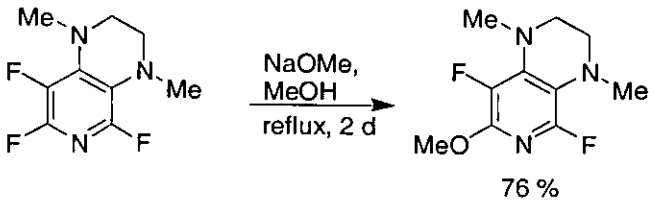


Figure 2.20

The influencing effects of the nitrogen substituents also fail to justify this observation. For example, the imine substituent, as drawn in Figure 2.17, would be expected to withdraw electron density by resonance *ortho* and *para* to itself, i.e. the 4- and the 6-position, leading to a mixture of the two substituted products. As this is not the case, it can only be deduced that there must be some sort of neighbouring group effect exerted by the 4c-C substituent on the site of nucleophilic attack. As detailed in Chapter 1, displacement of halogen from an electron deficient aromatic ring tends to proceed via a two-step addition elimination reaction, whereby the initial addition is the rate determining step. In the example of this reaction of fused heterocycle **3**, it is the formation of the following intermediate:

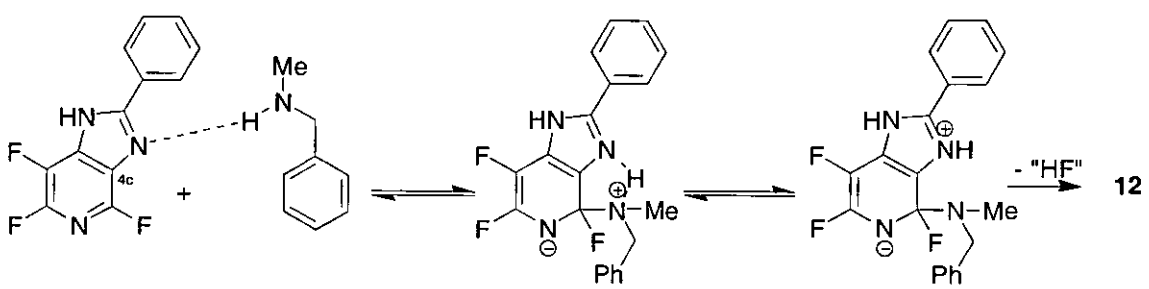


Figure 2.21

Hence the lone electron pair of the imine nitrogen can interact with the incoming nucleophile, "guiding" it in to displace fluoride ion. More importantly, intramolecular deprotonation can occur, which presumably lowers the energy of activation for this rate limiting step thus favouring attack at this site over the other activated C-F bond.

A similar phenomenon has been witnessed in the reactions of a range of fluorobenzene derivatives of the formula C_6F_5X with nucleophiles, whereby substitution *ortho* to the X group occurred as opposed to the expected *para*-fluoride displacement.[7] As an example, the reaction of nitropentafluorobenzene with methylamine is shown below:[8]

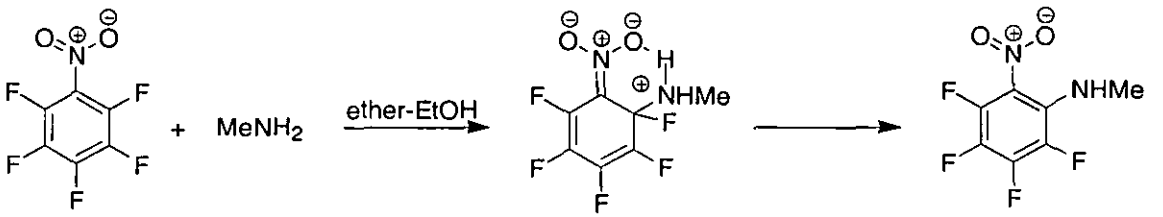


Figure 2.22

An interesting experiment, but one that was not carried out due to limited time and material, would be the reaction of the inseparable mixture of isomeric *N*-methyl imidazopyridines **6** and **7** with a nucleophilic species. If the neighbouring group participation hypothesis is correct, one would expect **7** to react in an analogous manner to **3**, that is react at the unexpected 4C-F site *ortho* to the imino group of the fused imidazole ring. On the other hand, it could be predicted that **6** would react in a manner akin to the example shown in Figure 2.20 and react in accordance with the established initial state effects i.e. displace fluoride ion from the 6-C position. As well as following by ^{19}F NMR of the reaction mixture, separation of the products could prove possible.

The reaction of **3** with diethylamine in a similar manner gave rise to the analogous diethylamino heterocycle **13** along with a small amount of inseparable impurity (~ 5 %; $[M^+ + H^+]$ 363.1; δ_F -99, -181 ppm) which at first was assumed to be from attack at the alternative C-F site. However this was not consistent with results obtained thus far so the reaction was optimised to try and increase conversion in an attempt to find out more about the structure. More forcing conditions gave accordingly higher conversion to the byproduct. Purification by mass directed auto purification gave a red solid whose structure was deduced to be compound **14**:

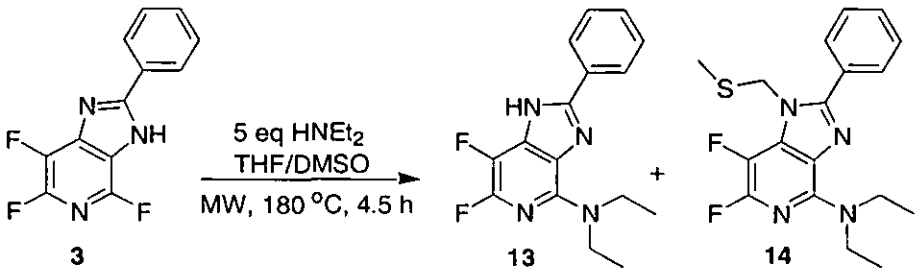


Figure 2.23

^{1}H NMR clearly showed there to be 2 resonances (5.37 and 2.00 ppm) not present in the spectrum of **13** and were indicative of a CH_2 and CH_3 group. Computer analysis of an accurate mass value suggested an empirical formula of SC_2H_5 surplus to **13**. Finally, a heteronuclear nOe NMR experiment was devised, whereby running a ^{1}H NMR experiment whilst irradiating the sample, with a frequency corresponding to the fluorine atom at -181 ppm, revealed any protons in close proximity (< 4 Å) to this fluorine atom. As can be seen from the corresponding spectrum in Figure 2.24, the unknown resonances at 5.37 and 2.00 ppm both gave strong positive peaks in the upper section of the spectrum, implying strong nOe couplings. From this data, structure **14** was suggested, whereby selective alkylation of the *1H*-imidazole nitrogen has occurred.

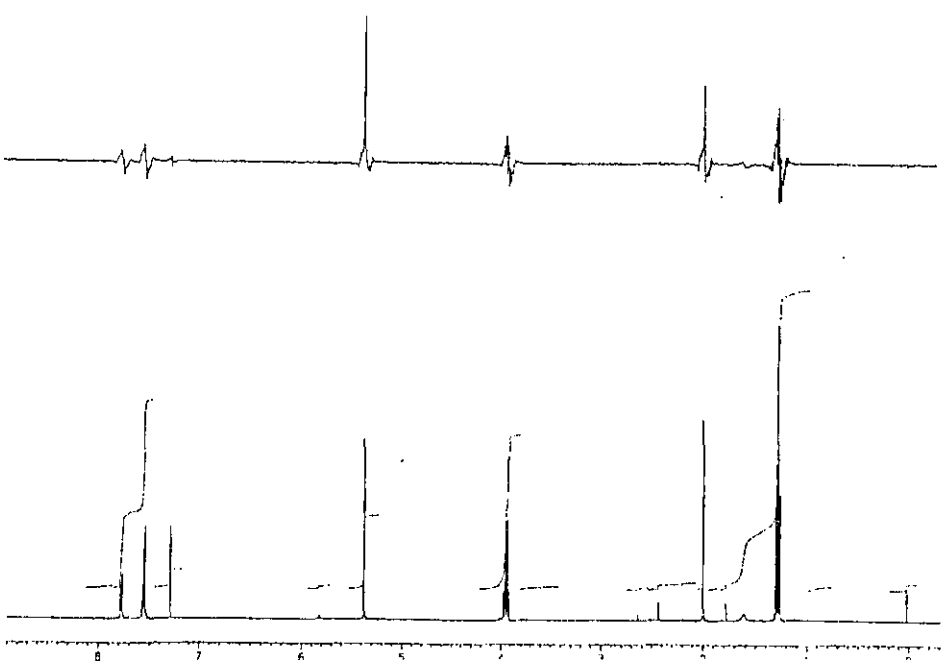


Figure 2.24 heteronuclear nOe NMR of **14**

The following mechanism, involving an electrophile derived from dimethyl sulfoxide reacting with the nucleophilic imidazole nitrogen, is proposed to explain this result. Selectivity towards this site for electrophilic substitution presumably occurs because of steric hindrance at the other (3*H*) imidazole nitrogen by the *ortho* dialkylated amino functionality.

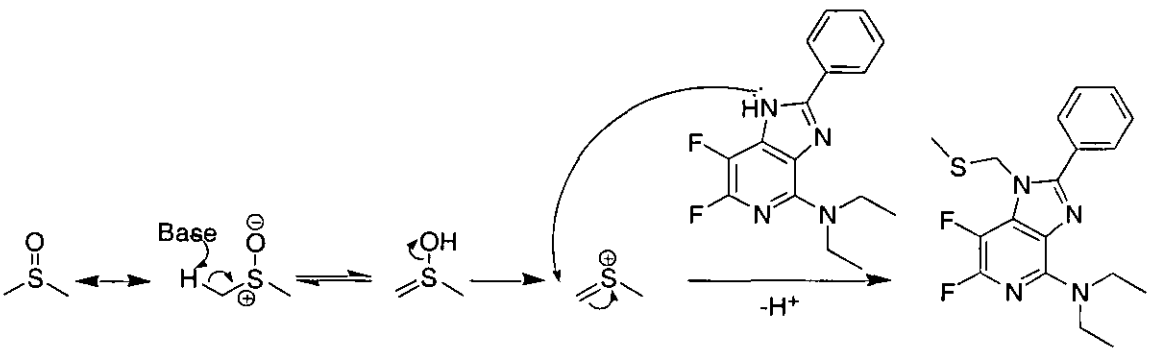


Figure 2.25

Why this is not the case in the reaction of bicycle **3** with *N*-methyl-benzylamine is uncertain. This byproduct formation could easily be circumvented by switching the dopant to another polar solvent, such as NMP.

2.4.3 Nucleophilic Substitution of Imidazopyridine 3 by Oxygen and Sulfur Nucleophiles

Reaction of scaffold **3** with sodium methoxide in dry methanol failed to provide the desired difluoro-imidazopyridine, despite the highly nucleophilic nature of NaOMe and the employment of microwave heating. It is suggested that instead of acting as a nucleophile, the methoxide ion is acting as a base and deprotonating **3** to give a relatively electron rich, inactive system.

Reflux of **3** with an excess of lithium thiophenoxide proceeded slowly but selectively to give one new product by ^{19}F NMR of the reaction mixture (see Figure 2.27) consisting of two doublet resonances at -107.65 and -164.43 ppm, presumably to give the regioisomer shown in Figure 2.26, in line with previous results. The low conversion (~ 15 % by integration) precluded purification of this small scale reaction.

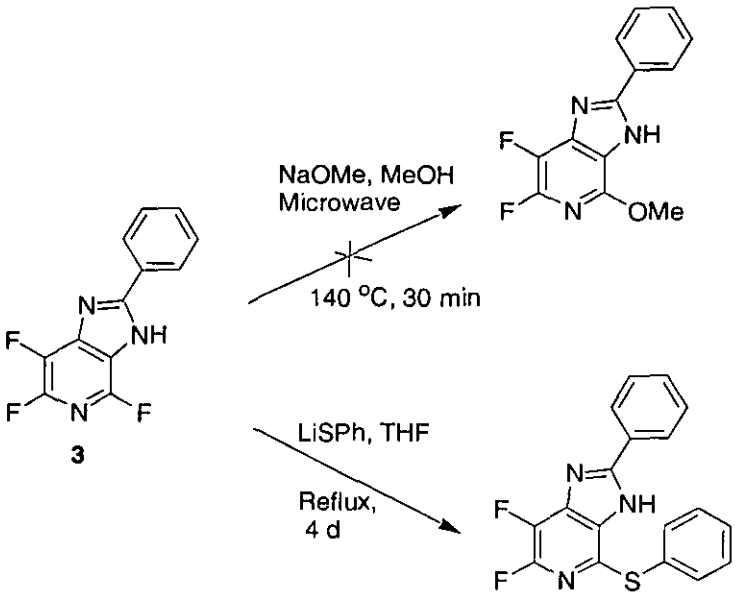


Figure 2.26

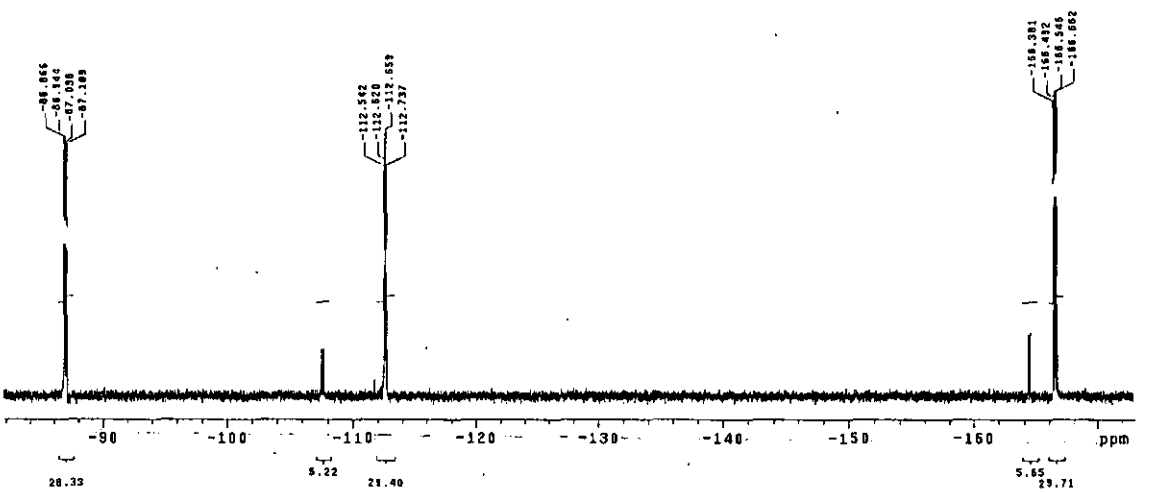


Figure 2.27 Reaction of imidazopyridine **3** with LiSPh (^{19}F NMR of reaction mixture)

One way of obtaining these difluorinated systems could be to *N*-protect the imidazopyridine before attempting nucleophilic substitution, thus preventing the deprotonation that presumably reduces the reactivity of this system to attack by a nucleophile

2.4.4 Nucleophilic Substitution of Imidazopyridine 11

The following reaction was carried out on a small scale to demonstrate that tricycle **11** was also reactive to further nucleophilic substitution and to ascertain as to whether the regioselectivity of displacement was as high as with the reactions of bicycle **3** with nitrogen nucleophiles. The protected nature of the imidazole moiety (I.e. N-R as opposed to NH) led to the employment of milder reaction conditions (160 °C and hence no need for DMSO) however the reaction proceeded sluggishly, taking 5 h to achieve around 80 % conversion, albeit with the same high selectivity observed in the analogous reactions with imidazopyridine **3**. In light of this high selectivity, the same reasoning as described in Section 2.4.2 is used, hence the regiochemistry of the product, **15**.

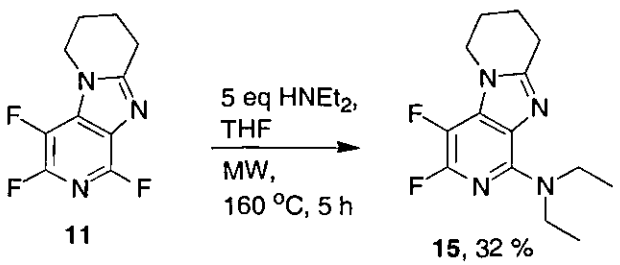


Figure 2.28

It is worth noting that optimisation of this reaction could be achieved quickly through carrying out a small screen of reactions and changing variables such as temperature and concentration of reactants in order to give a more satisfactory reaction and conversion.

2.5 A Complimentary Strategy to Difluoro-imidazopyridine Synthesis

As shown in Sections 2.4.2 and 2.4.4, trifluoropyridine-fused heterocycles derived from pentafluoropyridine appear to be highly regioselective and moderately reactive towards nucleophilic attack. In the case of bicycle **3**, whose synthesis necessitates a two step reaction from pentafluoropyridine, it was hypothesised that the 4-substituted uncyclised intermediate could be reacted with a mononucleophile to give a 2-, 4-disubstituted trifluoropyridine, treatment of which with LDA should affect ring closure at the most electron deficient *para* position to the newly introduced 2-substituent. This concept is shown in Figure 2.29:

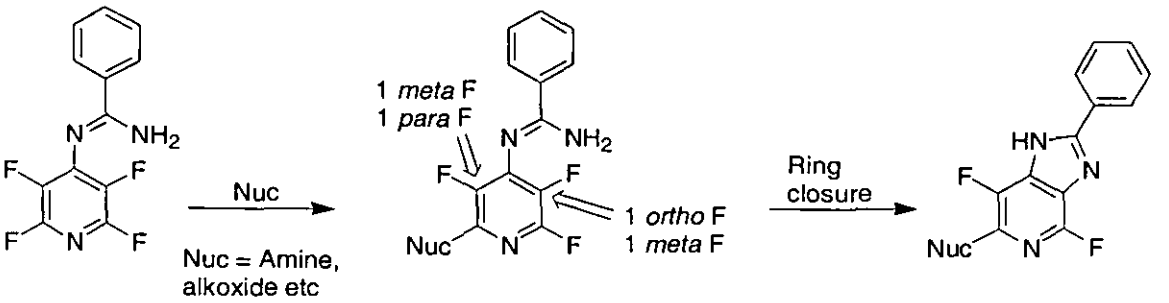


Figure 2.29

In light of the synthesis of the isolation of difluoro-imidazopyridine **12**, **1** was reacted with an excess of *N*-methyl-benzylamine to obtain the desired trifluorinated pyridine **16**. Reaction of this with LDA gave two new resonances only by ^{19}F NMR of the reaction mixture whilst purification by mass directed auto purification gave a white solid with different resonances, to those observed previously for isomer **12**, in the ^{1}H and ^{19}F NMR spectra. From this we can conclude that the desired regioisomer **17** was indeed successfully synthesised.

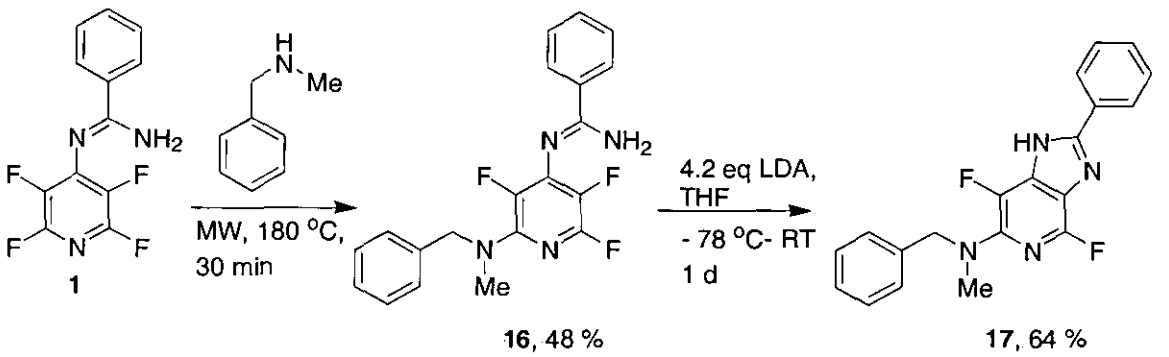


Figure 2.30

The microwave synthesiser also proved vital in this synthesis, providing a quick and clean route to **16**. Previous attempts by conventional heating took several days and resulted in such an extent of decomposition that purification was unreasonable.

2.6 Comparison of Reactivity between Uncyclised and Cyclised Systems to S_NAr

As part of this work, reactions of tetrafluoropyridine **1** and its trifluorinated imidazopyridine derivative **3** were screened for reactivity towards diethylamine under identical reaction conditions to one another while varying the temperature of the samples (Figure 2.31). Reaction times were kept constant at 30 min whilst conversions were obtained from the TIC trace from LCMS analysis of the reaction mixtures. Interestingly, the less fluorinated, and hence expected to be less reactive, imidazopyridine **3** showed far greater conversion under various conditions than **1** (Figure 2.32).

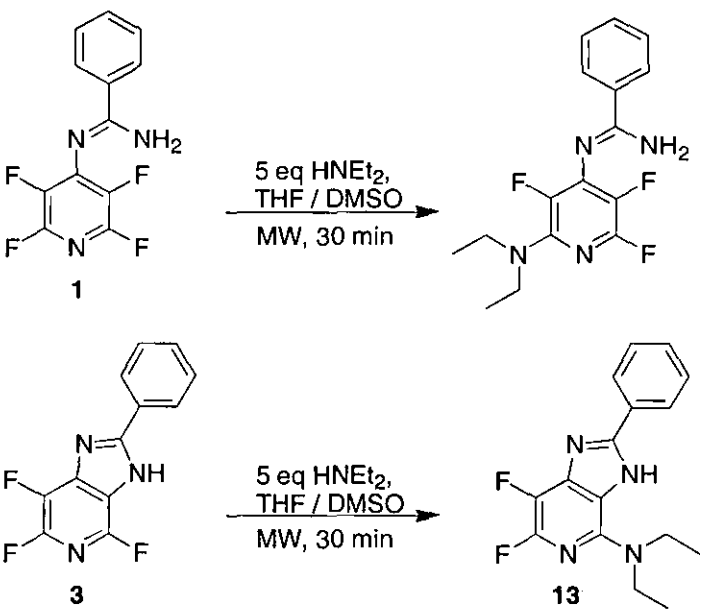


Figure 2.31

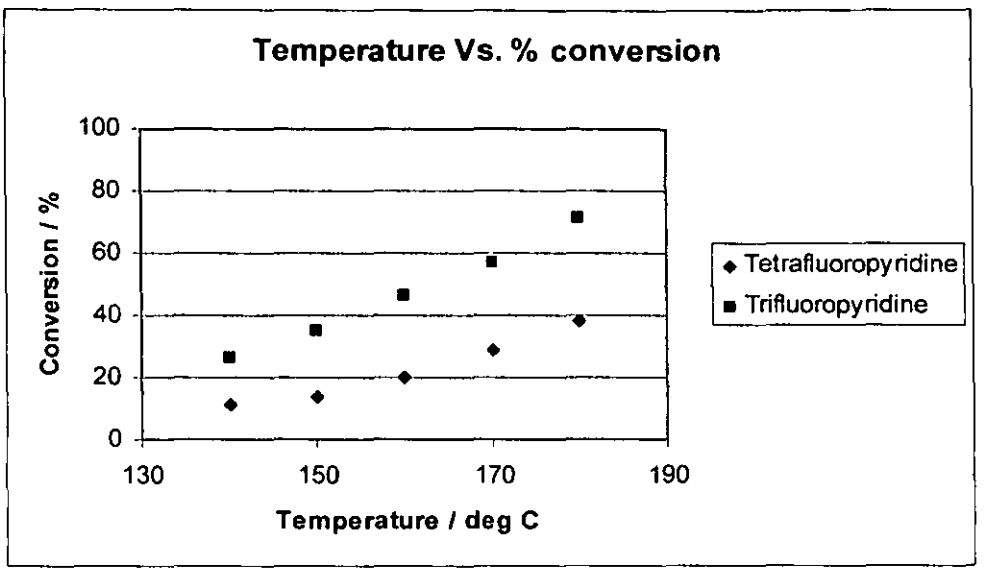


Figure 2.32 Conversion of **1** and **3** to respective products under varying reaction temperatures

The special activating and directing effect of the 4c-C imine functionality present in bicycle **3** presumably gives this surprising observation.

2.7 Reaction of Pentafluoropyridine with Other Binucleophiles

So far this chapter has dealt with the formation of imidazopyridine scaffolds via the reaction of pentafluoropyridine with suitable *N,N* binucleophiles. The following section will detail research carried out exploring various other binucleophiles.

2.7.1 Reaction with Guanidine

Following the breakthrough of employing LDA to form bicycle **3**, the reaction conditions were adapted to the cyclisation of **18**, attempted previously in other laboratories (See Section 1.4.2). Synthesis of tetrafluoropyridine **18** proceeded smoothly under identical conditions used to synthesise the 4-amidino-tetrafluoropyridines (see Section 2.2) and yielded the target molecule as a pale yellow solid. Attempts to cyclise with LDA, however, failed to yield the desired annulated product, and only succeeded in forming 4-amino-tetrafluoropyridine (observed in the reaction mixture by ^{19}F NMR; δ_F -102 and -164 ppm), as observed in the literature example.

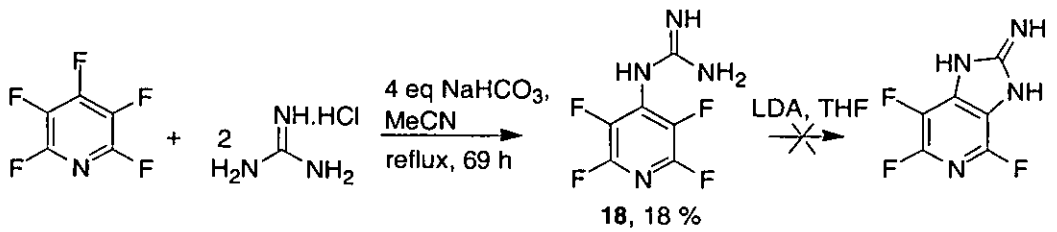


Figure 2.33

This is in keeping with the amidine work reported in this chapter whereby an aryl group is required on the binucleophile to give the desired annulation reaction as opposed to the unwanted elimination process.

2.7.2 Screen for Potential Cyclic Binucleophiles

As already mentioned, microwave technology is highly amenable to array chemistry, both in terms of being able to quickly optimise a specific reaction, but also to test reagents for suitable reactivity. The following screen was carried out in order to access the reactivity of three potentially binucleophilic heterocycles with pentafluoropyridine. The conditions shown in Figure 2.34 were chosen; forcing enough to permit reaction if sufficiently reactive whilst mild enough to prevent decomposition.

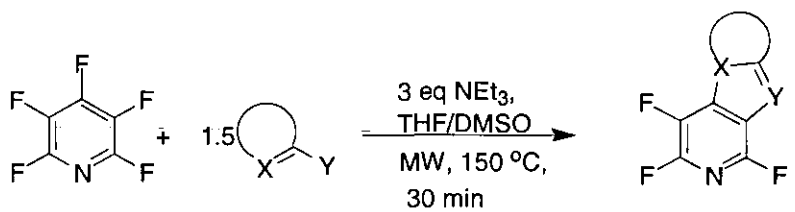


Figure 2.34

Automated LCMS analysis of the reaction mixtures was chosen, for its ease and quick results, as the method for deducing whether or not each reaction had worked. The following substrates were studied:

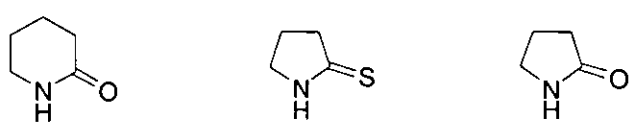


Figure 2.35

No desired product was observed in any of the reactions. In each case, the respective heteroatoms must withdraw electron density away from the ring nitrogen atoms to such an extent that they are insufficiently nucleophilic to attack pentafluoropyridine.

2.7.3 Reaction with 1,3 Dicarbonyl Compounds

The 1,3-dicarbonyl ethyl acetoacetate was reacted with pentafluoropyridine in an attempt to form a desirable furopyridine fused heterocycle and in an analogous manner to the following literature example involving tetrachloropyrazine:[9]

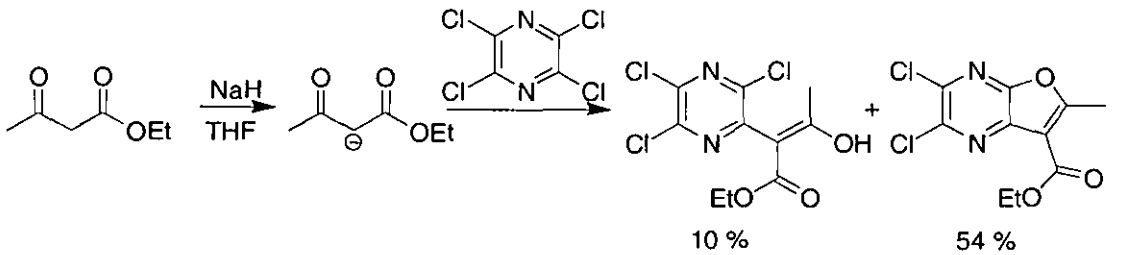


Figure 2.36

Adapting these conditions to the reaction with pentafluoropyridine gave only the 4-substituted product, **19**. Repeating this reaction with additions of excess base (such as LDA) failed to force cyclisation to occur.

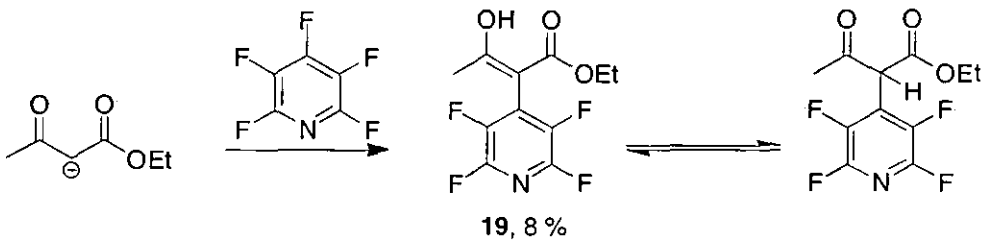


Figure 2.37

^{1}H NMR clearly shows us the configuration this pyridine derivative adopts:

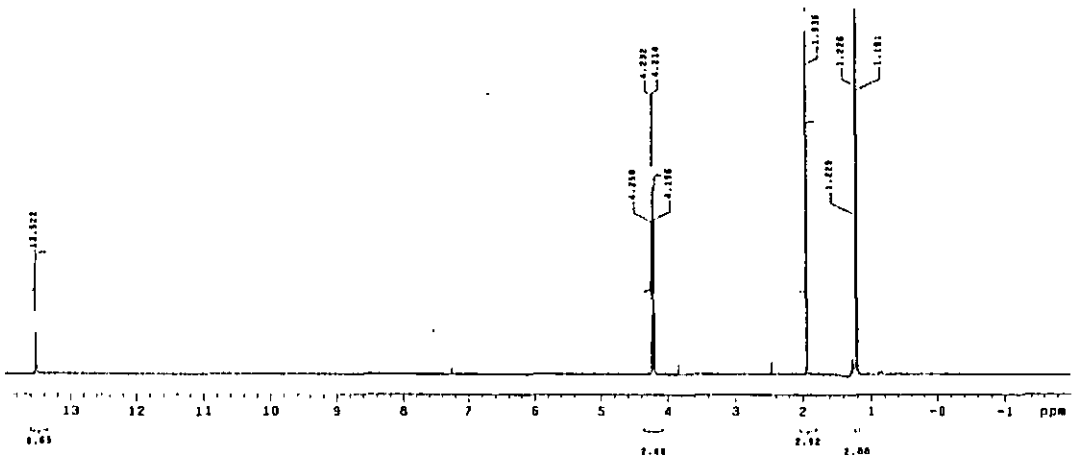


Figure 2.38; ^{1}H NMR spectrum of **19**; δ_H 13.52 (1H, s, OH), 4.22 (2H, q, $^{3}J_{HH}$ 7.1, CH_2CH_3), 1.94 (3H, t, $^{6}J_{HF}$ 0.9, $COCH_3$), 1.21 (3H, t, $^{3}J_{HH}$ 7.0, CH_2CH_3)

Apart from the alkyl protons at 4.2, 1.9 and 1.2 ppm, the only other resonance occurs at 13.5 and is indicative of a hydroxyl proton. As there is no sign of a methine resonance, it can be concluded that the 4-substituted group exists solely in the enol configuration.

The lack of cyclisation presumably stems from an insufficiently electron deficient 3C-F site. It is worth noting that the following reaction has successfully been carried out at Durham, between ethyl acetoacetate and 4-cyano-tetrafluoropyridine, to give the furopyridine shown below and its uncyclised isomer.[10]

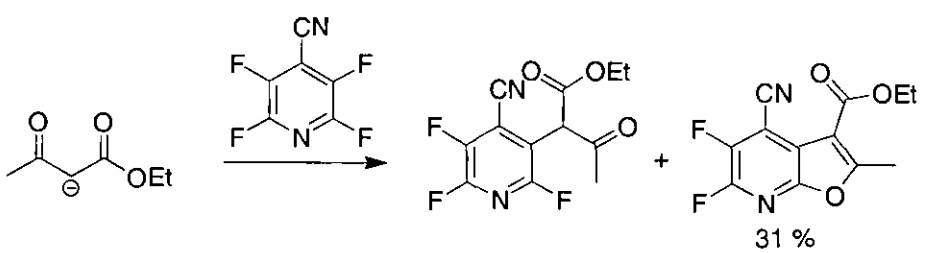


Figure 2.39 Furopyridine formation from pentafluoropyridine

2.8 Conclusions

A series of highly desirable fluorinated imidazopyridine fused heterocycles have been synthesised and, in the case of bicycle **3** and tricycle **11**, shown to be excellent scaffolds for further embellishment.

Although the reaction of pentafluoropyridine with *N*, *N*-unsubstituted amidines is limited to benzamidine-based systems in this work, it is possible to envisage the following type of aryl-substituted structures, which could contain further sites for functionalisation e.g. metal-catalysed coupling reactions (R = halogen).

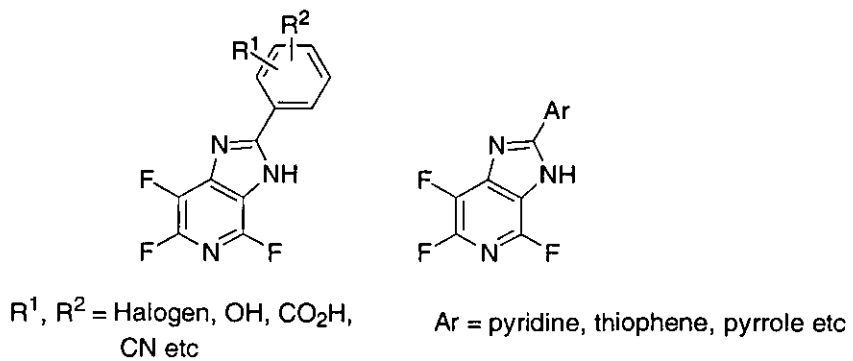


Figure 2.40

The one-pot synthesis of heterocycle **11** also provides an extremely interesting opportunity for the creation of a series of novel heterocycles, while a search for commercially available iminopiperidines reveals a range of chemicals available, including enantiomerically pure samples e.g.

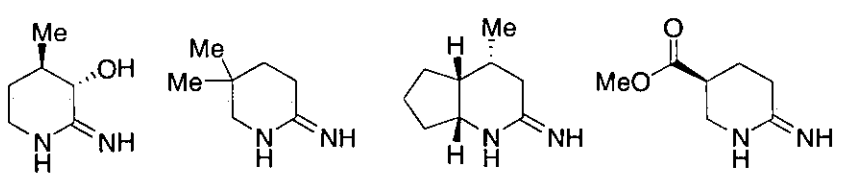


Figure 2.41 Examples of commercially available iminopiperidine derivatives

Hence a range of unusual and potentially biologically interesting fluorinated tricyclic tetrahydro-dipyrido-imidazole analogues could be synthesised in single and efficient steps.

The ability to synthesise these highly novel imidazopyridine scaffolds, in conjunction with the ability to introduce selectively a nucleophile in the *ortho* position of the

fluoropyridine scaffold, opens the possibility to make libraries of drug-like molecules in short, efficient syntheses, given sufficient time and resources.

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Chapter 3

Pyridine Ring-Fused Tricycle Synthesis from Pentafluoropyridine

3.1 Introduction

As shown in Chapter 2, pentafluoropyridine reacts with the *N, N*-unsubstituted benzamidine hydrochloride, in two steps, to furnish highly functionalised pyridine ring-fused heterocycle **3** in excellent overall yield. The analogous reactions with acetamidine and formamidine hydrochloride, however, failed to yield the desired imidazopyridine heterocycles. It was hypothesised that through fixing the amidine motif in a ring the binucleophile would possibly be more stable and, indeed, this was found to be the case when pentafluoropyridine was reacted with 2-imino-piperidine hydrochloride to yield the highly novel tricycle **11**. Furthermore, the condensation proceeded in one step, illustrating an improved reactivity of the *N*-alkyl amidine species over the unsubstituted phenyl amidine. In the knowledge that the ring nitrogen of pyridine can act as a nucleophile, the study was extended to ascertain whether aromatic diamino species, such as 2-aminopyridine, could act as suitable binucleophiles for fused pyridine synthesis (Figure 3.1).

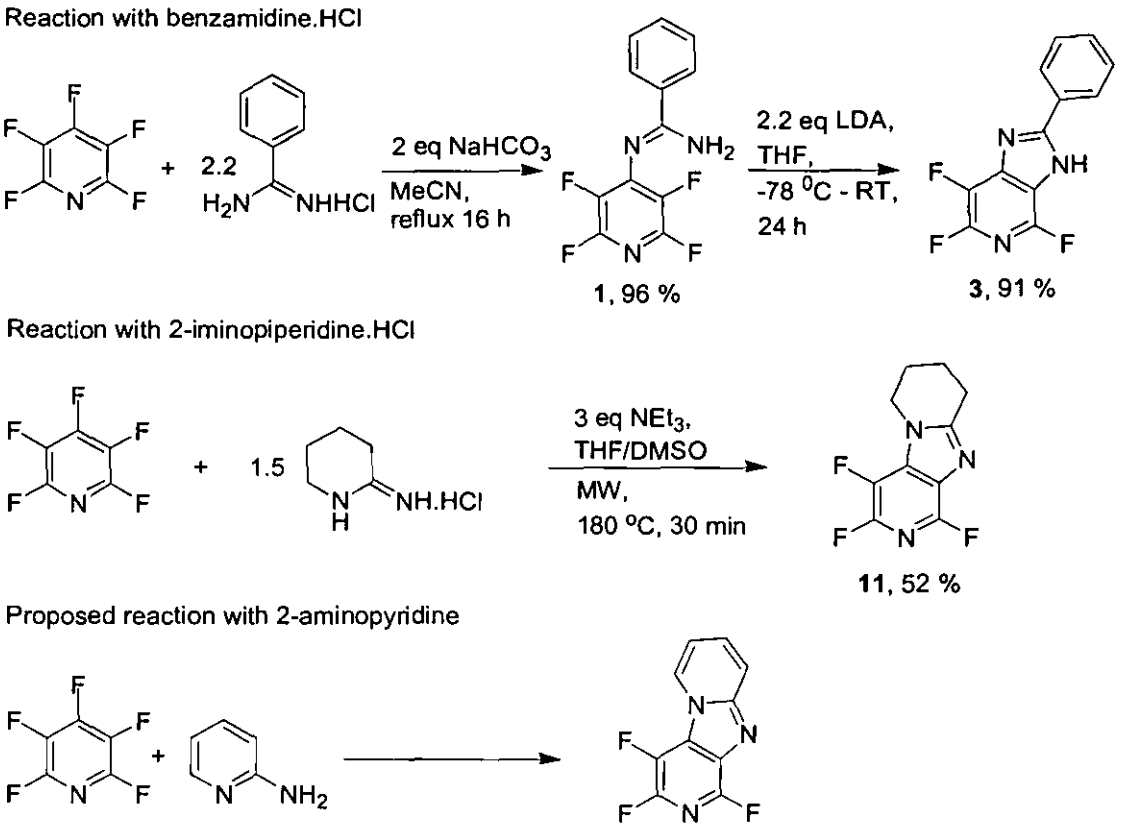


Figure 3.1

3.2 Background

If the condensation between pentafluoropyridine and 2-aminopyridine proved successful, it would provide access to a highly novel tricyclic heterocycic system. Indeed, there are very few examples of this motif in the scientific literature. [1-3] One of the more efficient procedures is given below:[2]

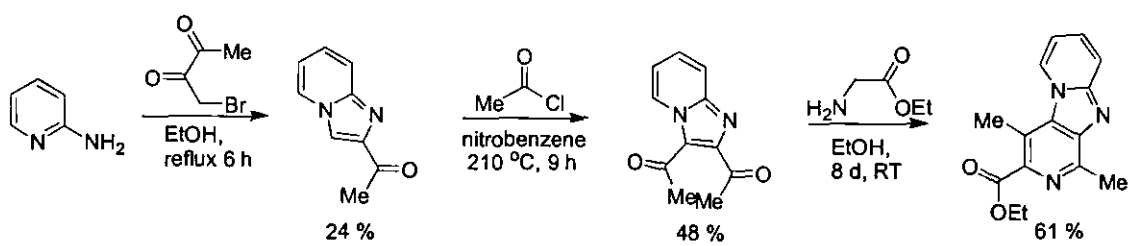
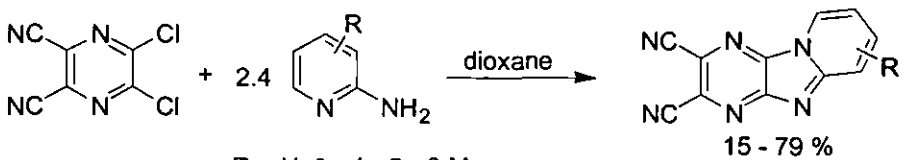


Figure 3.2

In this case, 2-aminopyridine is reacted with 1-bromo-butane-2,3-dione to give an imidazo[1,2-a]pyridine, which is then acylated and reacted with amino-acetic acid ethyl ester to yield the desired dipyridoimidazole in a 7 % overall yield.

Searching the literature for the reaction of an aminopyridine with a halogenated heterocyclic species also reveals a lack of work reported in this area.[4-6] In the following example, chemists reacted the highly electron deficient 2,3-dichloro-5,6-dicyanopyrazine with a selection of substituted 2-aminopyridines to give a series of pyridine ring-fused heterocycles.[4]



R = H, 3-, 4-, 5-, 6-Me, 4,6-Me_2, 3-OBz, 5-Cl, 5-Br

Figure 3.3

Electron-rich pyridines, such as the methyl-substituted systems, were sufficiently reactive to allow cyclisation at room temperature, while electron-deficient 5-chloro and -bromo analogues required reflux in dioxane. Dihalo- and nitro-aminopyridines failed to show any reaction and this is attributed to the more electron-rich pyridine systems being stronger nucleophiles than the electron-poor systems.

The following metal-catalysed coupling reactions have also been reported very recently between a dihalopyridine and a range of amino-substituted nitrogen heterocycles (six compounds) to give a series of tricyclic and tetracyclic systems, which are predicted to have potential antitumour properties:

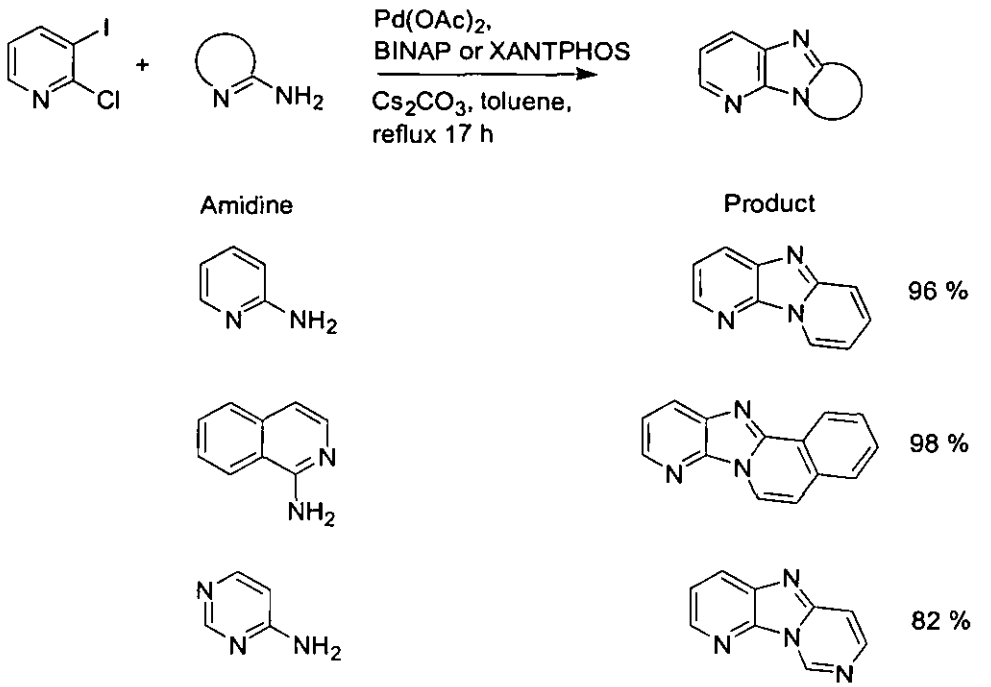


Figure 3.4 Representative examples of polycyclic rings formed by the metal-catalysed coupling of 2-chloro, 3-iodopyridine with diamino species

The one-pot double Buchwald-Hartwig amination of 2-chloro-3-iodopyridine with a selection of amino-azines and -diazines proceeds selectively and in high yields, going via an uncyclised intermediate resulting from the intermolecular C-N bond formation between the amino substituent of the binucleophilic species and the 3C-I site of the dihalopyridine.[5]

Altering the dihalogenated-species to 2,3-dibromopyridine gave only uncyclised material, resulting from intermolecular bond formation between the amino functionality on the binucleophile and the 2C-Br site of the dibromopyridine, but not the subsequent intramolecular bond formation desired.[6]

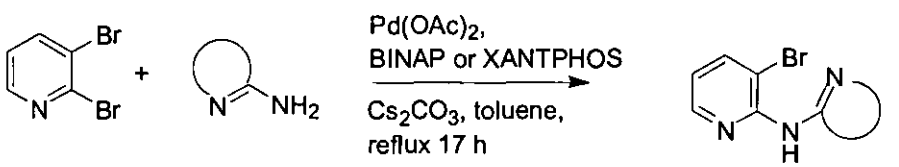


Figure 3.5

Employing the following orthogonal tandem palladium and copper-catalysed amination strategy was found to affect the desired annulation reaction.

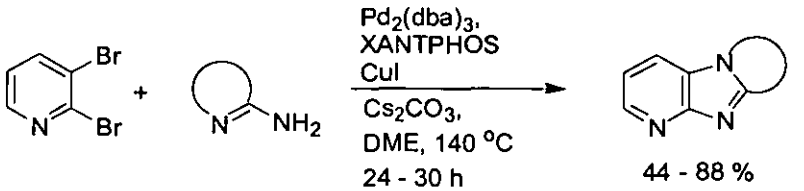


Figure 3.6

However, in the process of exploring these more forcing DME-mediated reaction conditions, it was found that the following ring annulations occurred without the presence of a metal catalyst and under basic conditions i.e. implying that, in these cases, reaction proceeds via nucleophilic aromatic substitution of bromide by the aminopyridine ring nitrogen.

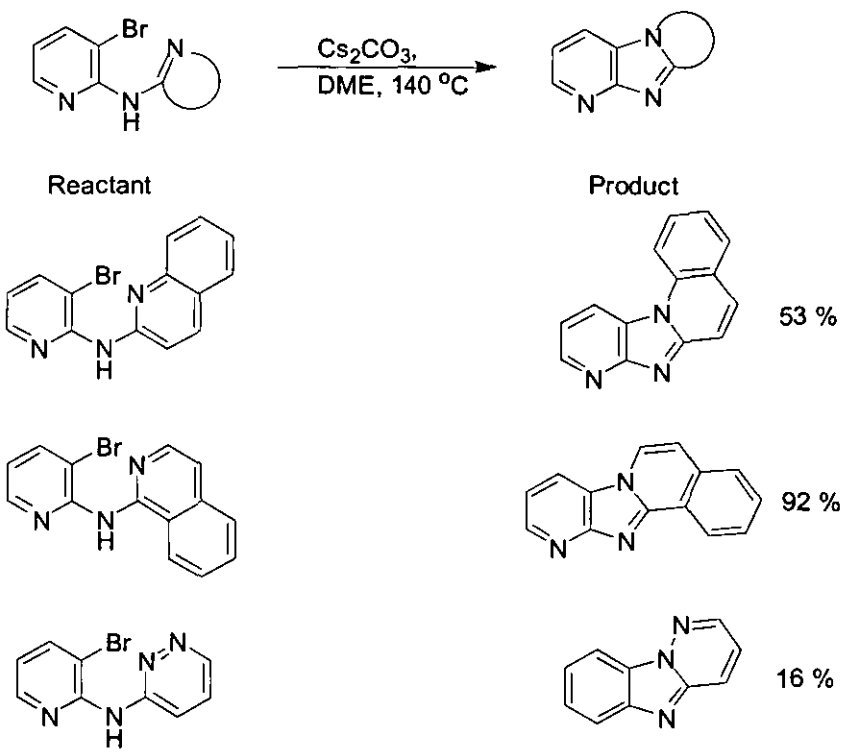
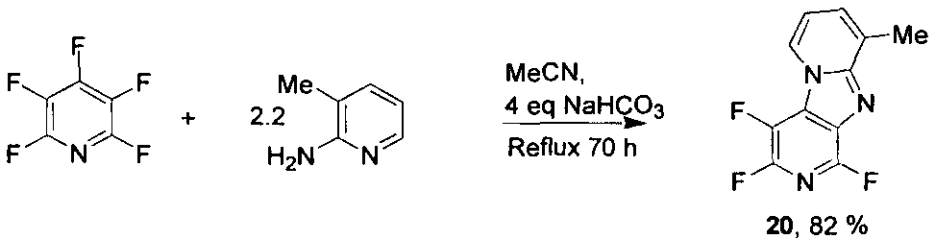


Figure 3.7

3.3 Reaction of Pentafluoropyridine with 2-Aminopyridine Binucleophiles

To extend the study of the reactions of suitable diamino derivatives with pentafluoropyridine and also to ascertain the reactivities of aminopyridines with

fluorinated electrophilic pyridines, pentafluoropyridine was reacted accordingly with the electron rich (to increase the nucleophilicity of the diamino species) 2-amino-3-picoline, under basic conditions. ^{19}F NMR of the reaction mixture after three days at reflux showed there to be no starting material remaining and one product displaying three resonances (-82, -105 and -164 ppm), implying the formation of a [3,4]-fused fluoropyridine ring system. Regular work up and recrystallisation of this product gave a white solid whilst X-ray crystallography confirmed the structure of the product.



20, 82 %

Figure 3.8 Reaction of pentafluoropyridine with 2-amino-3-picoline

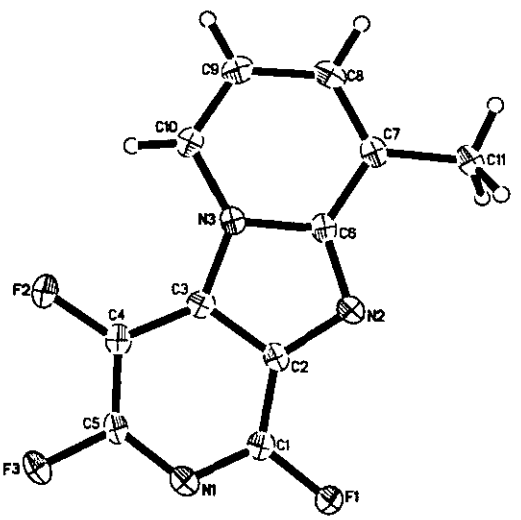


Figure 3.9 X-ray structure of **20**

Initial attack of pentafluoropyridine through the ring nitrogen of 2-amino-3-picoline gives the highly reactive pyridinium salt shown in fig 3.10. The highly electron-withdrawing nature of this quaternary amino substituent affects ring annulation at the adjacent C-F site by the tethered amino nucleophile, indeed, this uncyclised

intermediate must be short-lived as it is not observed by ^{19}F NMR of the reaction mixture at any point.

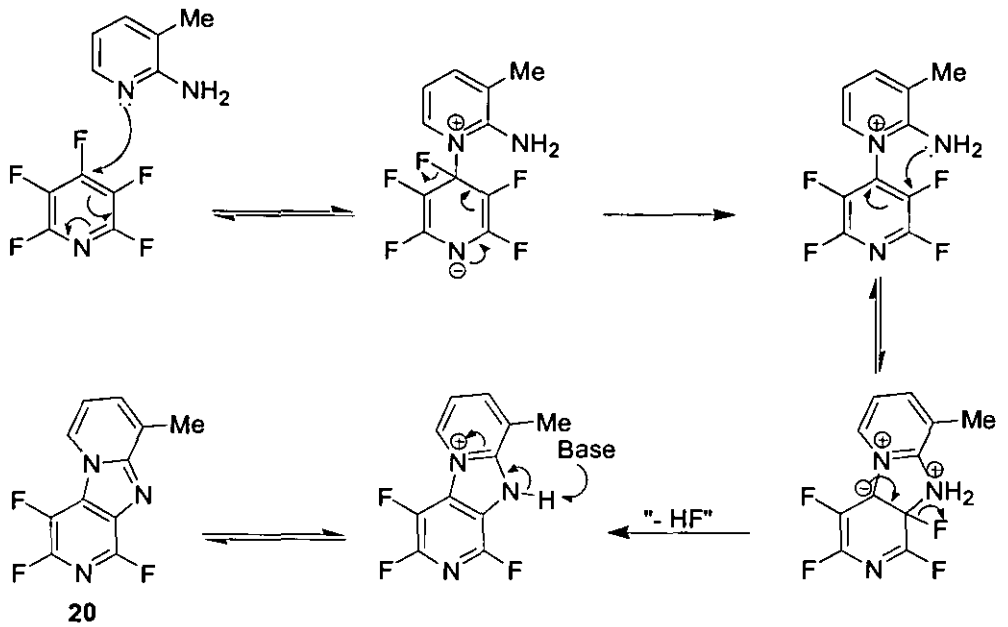


Figure 3.10 Mechanism for the formation of tricycle **20**

Despite the high reactivity of the intermediate pyridinium salt, the reaction proceeded slowly overall and this can be attributed to the relatively poor nucleophilicity of the picoline. Microwave heating, to provide a greater amount of energy to aid conversion and reduce reaction time, proved ideal in this case, with 100 % clean conversion to **20** being obtained after heating at 160 °C for 15 minutes only.

With this result in hand, the reaction of pentafluoropyridine with 2-aminopyridine was carried out. The reaction proceeded even more sluggishly and less cleanly, giving a correspondingly lower isolated yield of 25 %. This is attributed to the lower nucleophilicity of the binucleophile, compared to the previous example, leading to slower conversion and, also, the formation of byproducts.

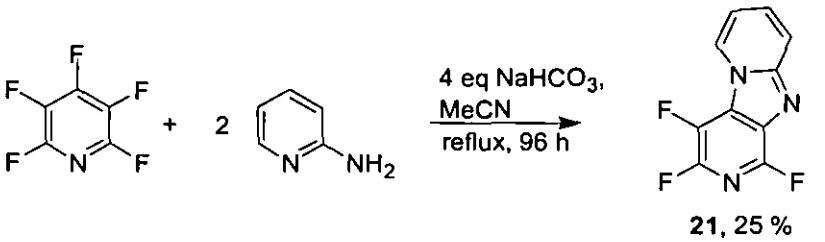


Figure 3.11 Reaction of pentafluoropyridine with 2-aminopyridine

These subtle electronic effects were also observed in the reaction with 2-amino-5-bromo-3-picoline, which was employed in an attempt to add further functionalisation to the tricyclic scaffold. Although the presence of a methyl group on the nucleophilic species would no doubt aid the nucleophilicity of the reagent, the bromine atom would be expected to deactivate accordingly. After optimisation, tricycle **22** was obtained in low yield, illustrating the significant deactivating effect the bromine atom exerts. In this example, microwave irradiation proved paramount, as regular heating showed no conversion whatsoever, even after prolonged refluxing of the reaction.

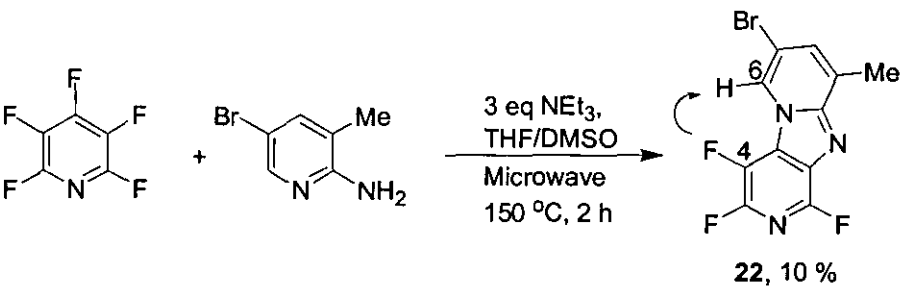


Figure 3.12

In the case of this heterocycle, the structure was confirmed by a heteronuclear nOe NMR experiment, which revealed a strong interaction between F-4 and H-6 (8.7 ppm), implying the two atoms to be in close proximity through space and hence structure **22**.

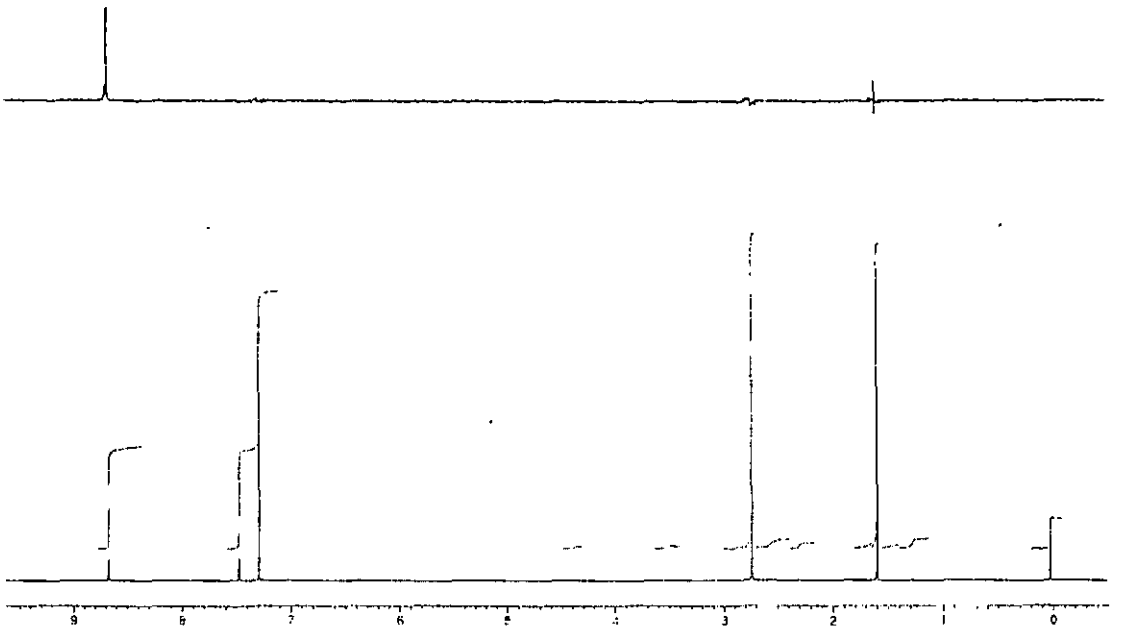
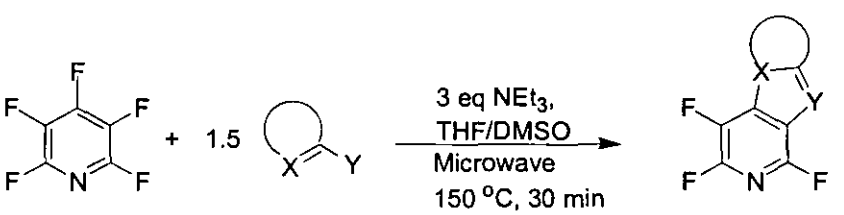


Figure 3.13 heteronuclear nOe NMR of **22** (F-4 irradiated)

3.4 Reaction of Pentafluoropyridine with other Aromatic Species

To extend the range of pyridine-fused heterocycles obtainable via the condensation of pentafluoropyridine with a suitable binucleophilic species, a small selection of commercially available *N, N* and *N, X*-centred heterocycles (X = O, S) were chosen and tested for suitable reactivity, under identical microwave conditions.



Substrates screened:

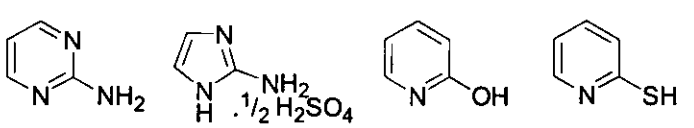


Figure 3.14

In each experiment, no desired annulation product or uncyclised intermediate was identified by LCMS analysis of the crude reaction mixtures. In the case of the *N, N* centred systems 2-aminopyrimidine and 2-aminoimidazole, the presence of a further electronegative ring nitrogen clearly reduces the nucleophilicity of the species to an extent whereby they are unreactive towards pentafluoropyridine. The same can be said for pyridine-2-ol, where the electronegative (relative to nitrogen) oxygen substituent effectively renders the ring nitrogen non-nucleophilic towards displacement of fluoride ion from the fluoropyridine reactant. The lack of reactivity shown by pyridine-2-thiol is somewhat harder to explain due the fact that sulfur is less electronegative than nitrogen and should therefore not greatly affect the nucleophilicity of the ring nitrogen. It can be argued, however, that the pyridine-thiol is in equilibrium with its thioamide tautomer, and this intramolecular electron delocalisation is favourable to the desired intermolecular nucleophilic attack.

Figure 3.15 Tautomerisation of pyridine-2-thiol

3.5 Further Functionalisation of Tricycle 20

Given that the dipyridoimidazoles obtained have three fluorine atoms remaining, study into their reactivity towards further nucleophilic aromatic substitution was carried out. Tricycle **20** was chosen as the substrate for the following reactions due to its quick and high yielding synthesis.

3.5.1 Reaction with Nitrogen Nucleophiles

Compound **20** proved to be an excellent reagent for nucleophilic aromatic substitution by nitrogen nucleophiles, reacting smoothly and under both microwave and conventional heating with benzylamine, *N*-benzylamine and diethylamine, in each case giving one product, observable by ^{19}F NMR of the reaction mixtures, with two resonances. Regular work-up of the reactions and recrystallisation of the crude solids gave the corresponding products in good to excellent yields.

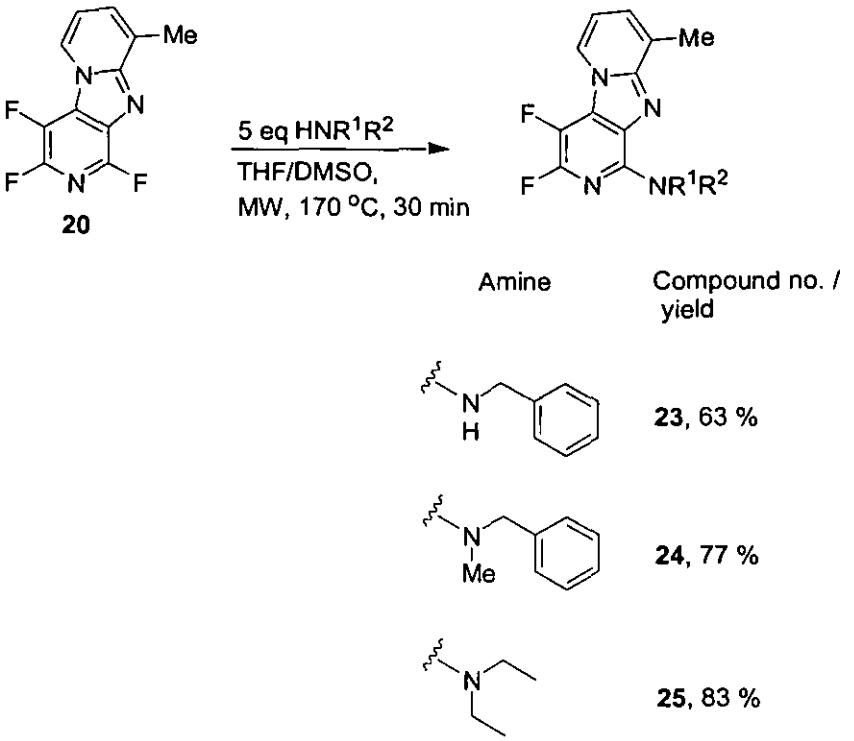


Figure 3.16 Microwave-mediated reaction of **20** with amine nucleophiles

In the reaction with the primary amine benzylamine, X-ray crystallography of a suitable grown sample led to confirmation of the site of attack by the nucleophile.

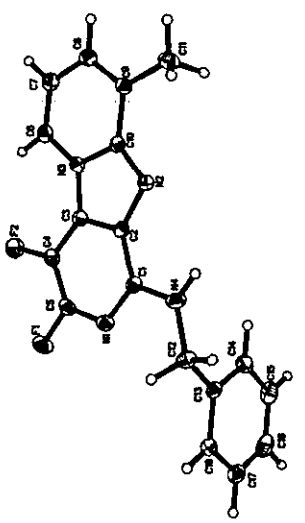


Figure 3.17 X-ray structure of **23**

As discussed in Section 2.4.2, this selectivity contradicts the predictions from the initial state activation effects of the three fluorines and must therefore be due to a neighbouring group participation effect by the N=C group *ortho* to the site of attack.

The reaction of **20** with the less nucleophilic aniline *p*-anisidine was also investigated and, after optimisation, yielded compound **26** in low yield.

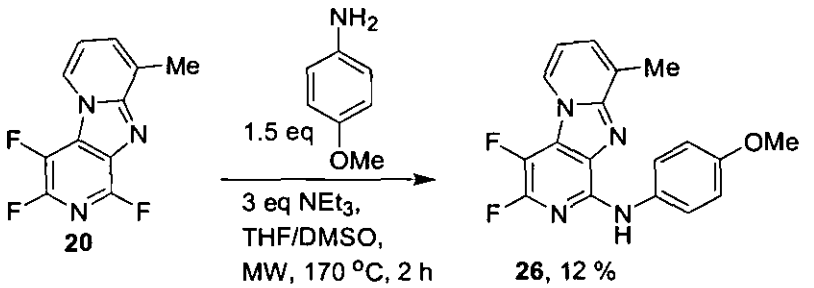


Figure 3.18

Even under these forcing conditions the reaction failed to achieve high conversion to the difluorinated product (45 % by LCMS reaction mixture analysis). This is in keeping with the poor nucleophilic nature of anilines due to the donation of electron density, by resonance, of the nitrogen electron lone pairs into the benzene ring, thus making them less accessible for attacking, intermolecularly, the trifluorinated core scaffold.

3.5.2 Reaction with Oxygen Nucleophiles

In light of the excellent reactivity shown by **20** towards nucleophilic aromatic substitution by nitrogen nucleophiles, the study was extended to reactions with oxygen nucleophiles. Sodium methoxide was chosen as a simple, reactive alkoxide ion and was reacted with the fluorotricycle in dry methanol and under microwave heating. Complete, clean conversion was observed by ^{19}F NMR and, as such, simply evaporating the reaction mixture to dryness and washing the resulting solid with water to remove unreacted NaOMe and KF yielded the product as a white solid.

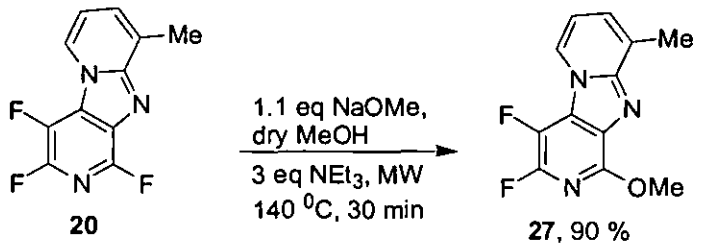


Figure 3.19

Extending the methodology to reacting **20** with KOH was seen as important due to potential for *N*-alkylation or derivatisation to brominated systems amenable to metal-catalysed coupling reactions (Figure 3.20).

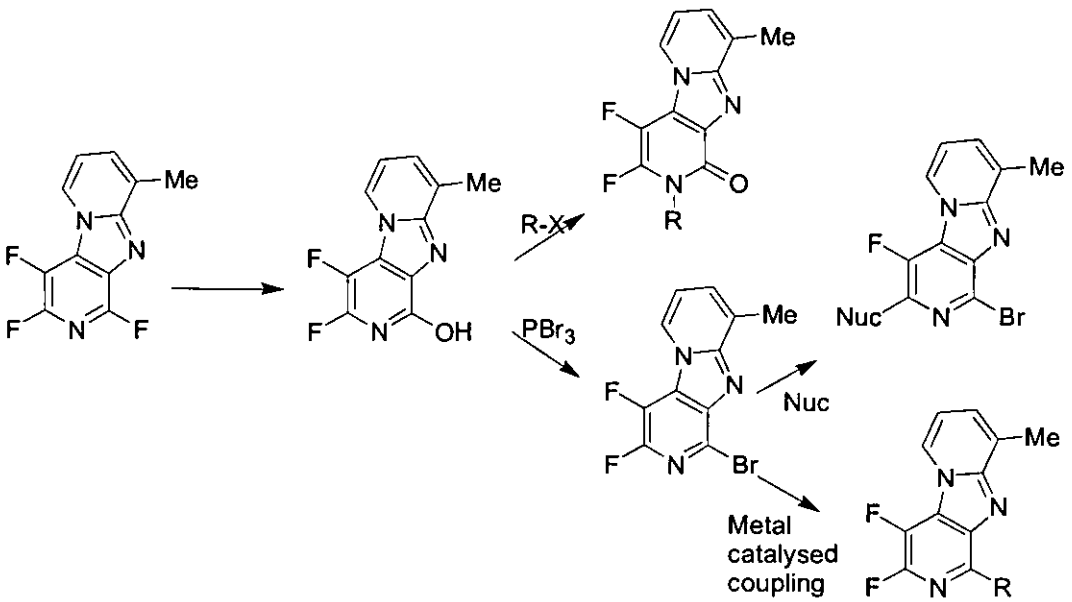


Figure 3.20

The reaction was first attempted by reaction with KOH in refluxing ^{t}butanol and although this did show some desired reactivity, it was not deemed to be a viable route due to low conversion. Although another strategy considered was via the demethylation of **27** by refluxing in HI solution, the eventual successful procedure was inspired by literature examples involving refluxing fluorinated heterocycles in aqueous KOH solution to give the desired substitution reaction (Figure 3.21).[7,8]

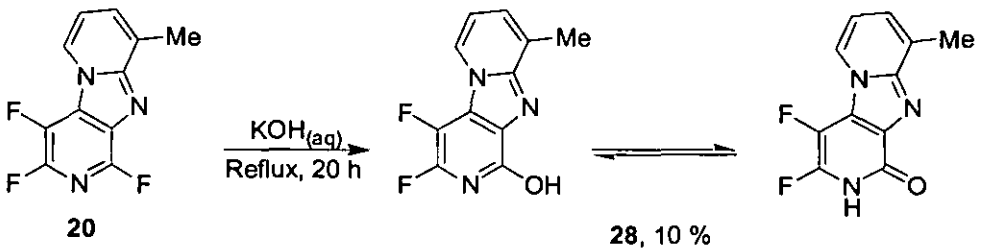


Figure 3.21

Despite the starting material appearing insoluble in the boiling aqueous solution, a suitably prepared (reaction mixture plus a small amount of acetone to aid dissolution) ^{19}F NMR sample taken after one day at reflux showed 100 % conversion to one product with two resonances. The low isolated yield is thus attributed to loss of material during work up. Scale up and improvement of the work up could yield a synthetically useful intermediate obtainable in two short efficient steps from pentafluoropyridine.

3.5.3 Reaction with a Carbon Nucleophile

To widen the scope for functionalisation of these novel fluorinated dipyridoimidazoles, **20** was reacted with a representative carbon nucleophile, phenyl magnesium bromide, to give difluorinated system **29**. The site of attack is assumed the same as the analogous nitrogen-substituted systems discussed previously and, again, can be justified through neighbouring group participation of the –N=C group, possibly helping to disrupt the electrostatic charges between the charged nucleophilic species and hence facilitating attack (figure 3.23).

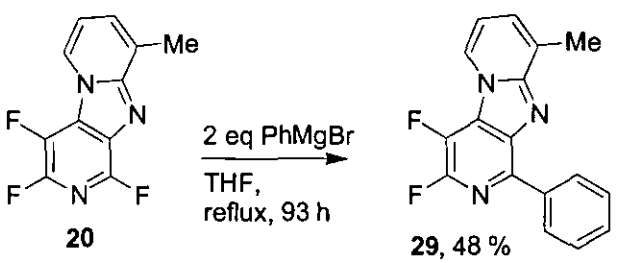


Figure 3.22

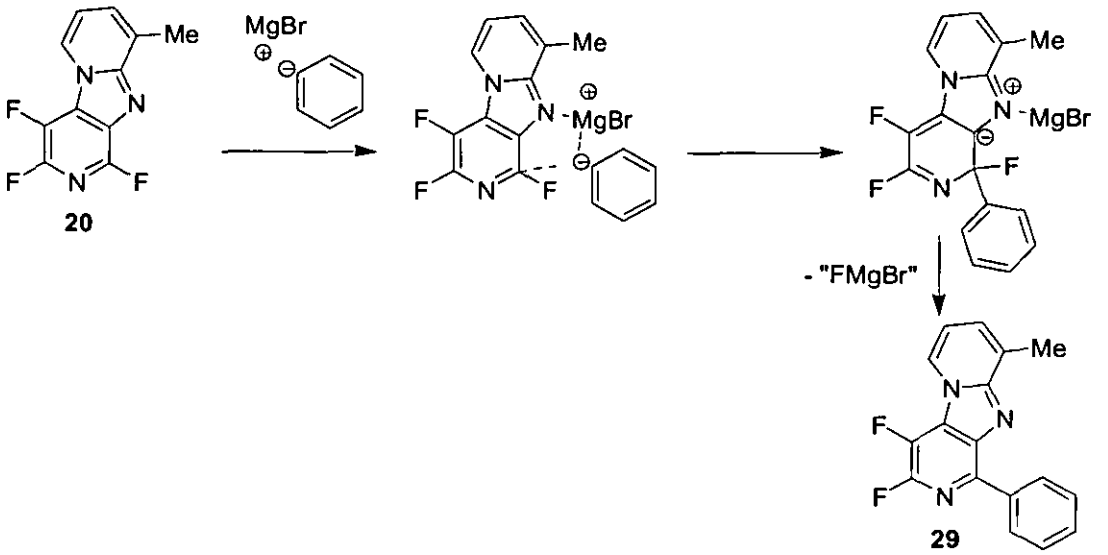


Figure 3.23

The reaction proceeded cleanly and, although no other reactions with carbon centred nucleophiles were carried out, the assembly of a large series of carbon-substituted heterocycles, such as **29**, could be envisaged due to there being a plethora of commercially available functionalised phenyl and aryl Grignard reagents.

3.5.4 Reaction with a Sulfur Nucleophile

Expanding the methodology further still to encompass sulfur nucleophiles brought the only anomaly to the series of nucleophilic displacement reactions of **20**, whereby reaction with two equivalents of lithium thiophenoxide gave 100 % clean conversion to one compound, with only one resonance, by ^{19}F NMR of the reaction mixture. Full analysis of this product (NMR, mass spectrometry, elemental analysis) confirmed that two fluorine atoms had been displaced by the sulfur reagent to give a monofluorinated tricyclic species.

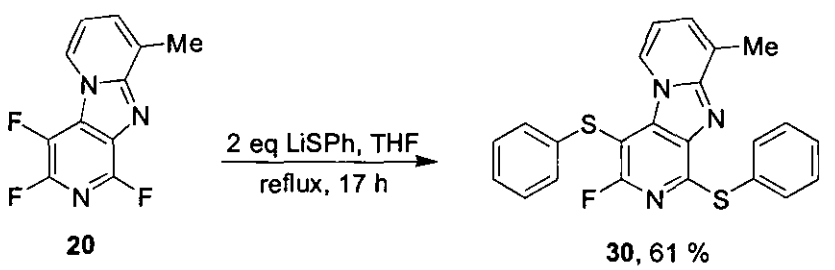


Figure 3.24

The reaction was repeated accordingly using one equivalent of the nucleophilic reagent. However, as can be seen from a ^{19}F NMR spectrum of the reaction mixture, this also resulted in the formation of a monofluorinated system (singlet peak at -76 ppm), with only a small amount of the desired difluoro pyridine remaining (weak doublet resonances at -102 and -167 ppm).

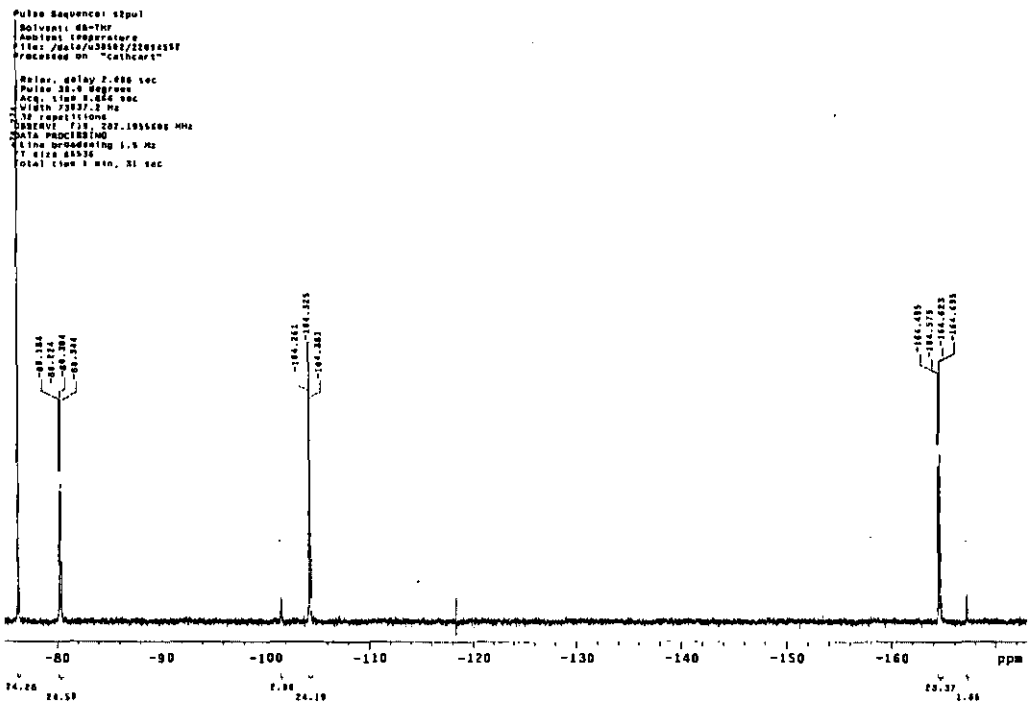


Figure 3.25

Assuming initial attack of **20** by the nucleophile occurs, as before, at the C-F site *ortho* to the activating imine group, this would give the difluorinated intermediate shown in Figure 3.26. A second equivalent of lithium thiophenoxide then attacks the fluoropyridine core scaffold *para* to the first sulfur group to give the monofluorinated derivative, **30**. Mechanistically, this is logical due to the stabilisation effect resulting from the ability to delocalise negative charge, developed in the Meisenheimer complex, over the first sulfur substituted carbon. This could not be possible if attack occurred at the other remaining C-F site as the negative charge could not develop over the C-SPh site. In terms of deducing this structure by physical characterisation, the only possible indicator as to the regiochemistry of the displacement reactions is by ^{19}F NMR; in this

case, the singlet resonance occurs at -75 ppm which, in fluoropyridine-based systems, is indicative of a fluorine atom situated *ortho* to the ring nitrogen of pyridine.

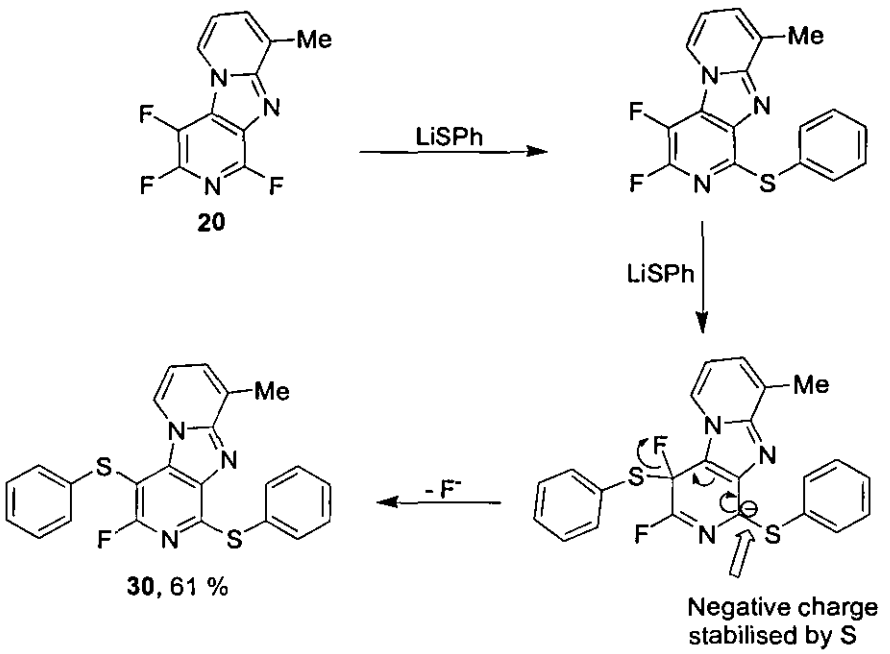
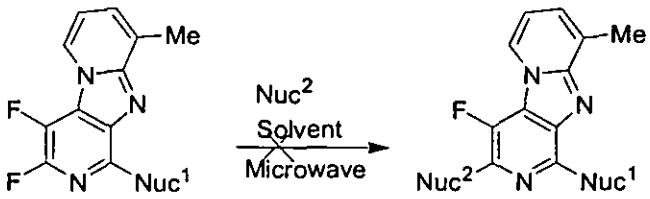


Figure 3.26

3.6 Penultimate Fluoride Displacement

As shown in Section 3.5, the trifluorinated tricycle **20** readily reacts with a range of nucleophiles in a regioselective fashion and under relatively mild reaction conditions. In light of this surprisingly high reactivity it was hoped that a further nucleophilic aromatic displacement of the resulting difluorinated derivatives be possible.

The diethylamino-substituted heterocycle **25** was studied first and reacted with benzylamine. No conversion was observed, even when the experiment was run with at high temperature and a large excess of the nitrogen nucleophile (Figure 3.27, entry 1). This was also found to be the case when **25** was reacted with NaOMe. A similar lack of reactivity was found when methoxy-substituted tricycle **27** was reacted with benzylamine and diethylamine (Figure 3.27, entries 3 and 4).



Nuc^1	Nuc^2 / equivalents	Solvent	Temperature / °C	Reaction Time / min
NEt_2	10 Benzylamine	THF/DMSO	220	30
NEt_2	1.5 NaOMe	MeOH / NEt_3	140	30
OMe	5 Benzylamine	THF / DMSO	180	30
OMe	5 diethylamine	THF / DMSO	180	30

Figure 3.27 Attempted reactions of heterocycles **25** and **27** with nucleophiles

The reaction of **27** with NaOMe did show some reactivity, however, to the desired monofluorinated product, with 66 % clean conversion by LCMS reaction mixture analysis to a product with an m/z (ES^+) value corresponding to the expected monofluorinated heterocycle ($[M^+ + H^+]$ 262.1). Mass directed auto purification yielded two fractions corresponding to the following isomeric products (ratio calculated from masses obtained):

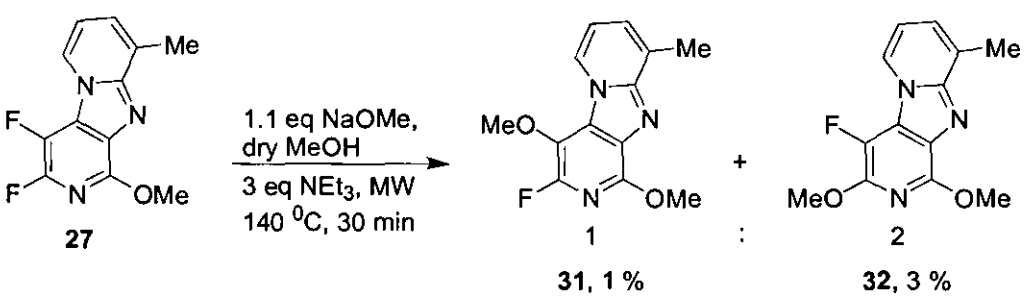


Figure 3.28

Clearly the methoxy substituent is slightly less deactivating than the comparative amino-functionalised systems tested, as the analogous reaction carried out on diethylamino-substituted heterocycle **25** gave no conversion (Figure 3.27, entry 2), while the strongly nucleophilic alkoxide reagent is needed to affect reaction, as **27**

showed no desired reactivity when heated with nitrogen nucleophiles (Figure 3.27, entries 3 and 4).

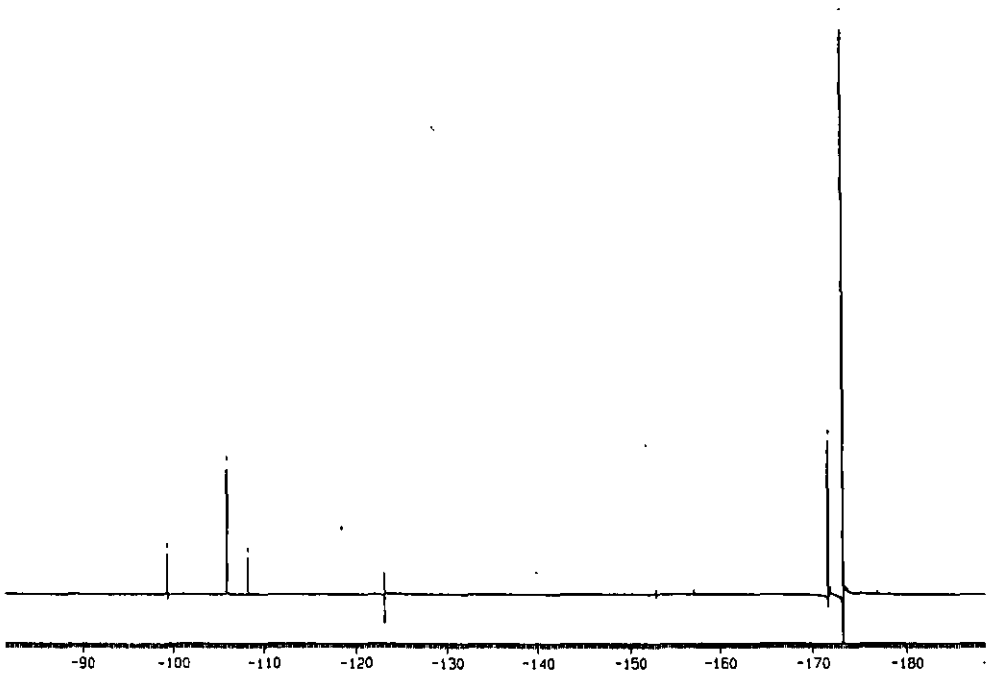
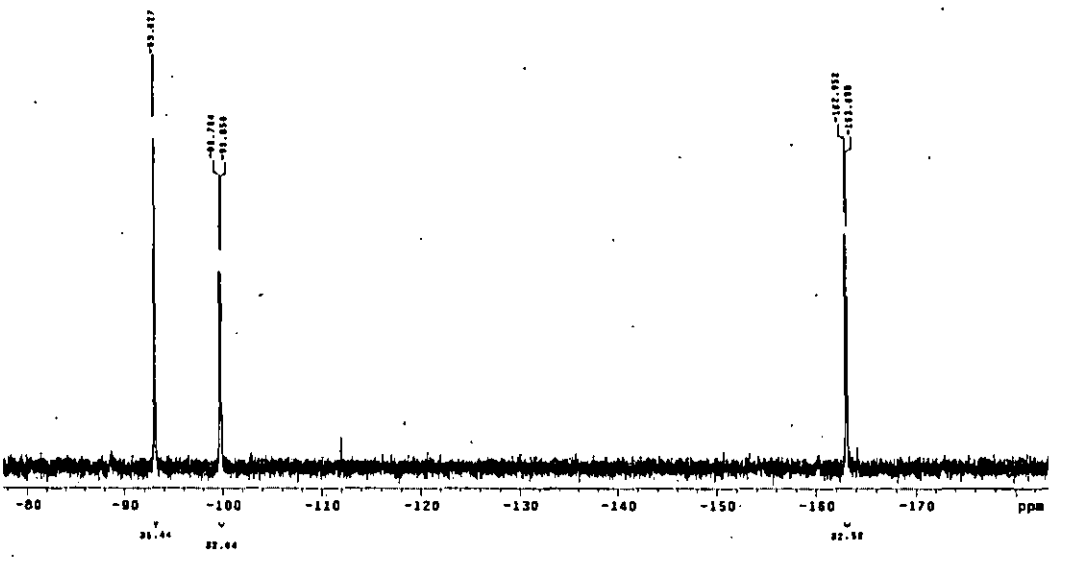
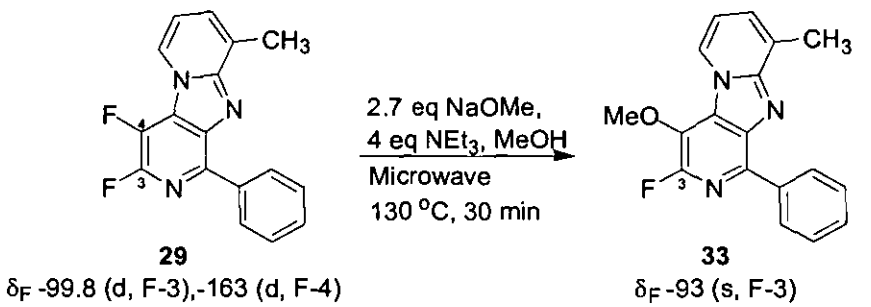


Figure 3.29 ^{19}F NMR of the reaction mixture resulting from microwave irradiation of **27** (-106, -172 ppm) with NaOMe to give **31** (-98 ppm) and **32** (-174 ppm)

Though poorly phased, this spectrum illustrates the prominence of isomer **32** as a major product (singlet peak at -174 ppm).

Repeating this reaction with phenyl substituted derivative **29** gave one product by ^{19}F NMR of the resulting mixture. Though the reaction was carried out on a small scale, work up yielded a yellow solid, which was shown by LCMS analysis to have a mass corresponding to the desired monofluorinated product. Furthermore, the singlet resonance observed by ^{19}F NMR (52 % conversion by integration) at -93 ppm suggested the product to be highly functionalised dipyridoimidazole derivative **33** (Figure 3.30).





29
δ_F -99.8 (d, F-3),-163 (d, F-4)

33
δ_F -93 (s, F-3)

Figure 3.30 ^{19}F NMR of the crude obtained from the reaction of **29** with NaOMe (top); suggested product from this reaction (bottom)

The phenyl substituent activates and directs the site of attack by the oxygen nucleophile due to its ability to stabilise the negative charge developed in the course of the reaction (Figure 3.31). This would evidently not be the case if attack occurred at the other C-F site.

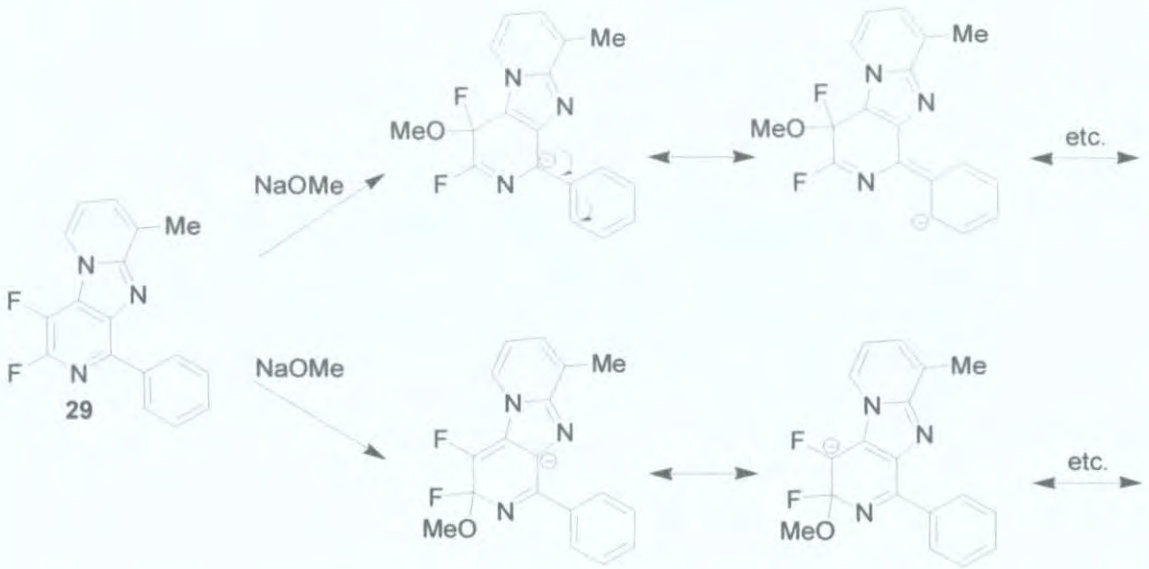


Figure 3.31

3.7 Fluorescence Studies

Virtually all the tricyclic compounds discussed in this Chapter proved to be highly fluorescent when exposed to long wave UV light. As this is an area of interest to material scientists, in particular electron deficient heterocycles,[9] emission spectroscopy was undertaken on tricycle **20** to establish the characteristics of this emitted light.

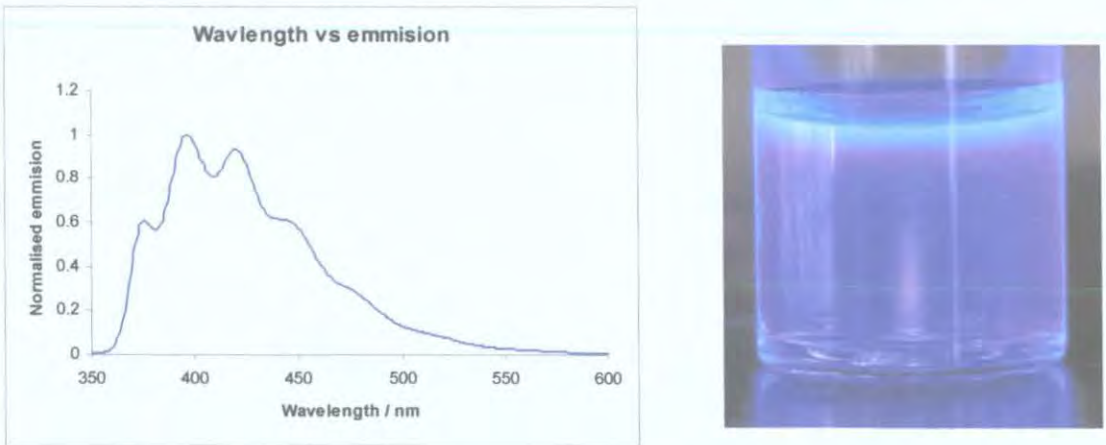


Figure 3.32 Emission spectrum and sample, under UV light, of **20**

Excitation at 325 nm gave the above spectrum and, while the observed photoluminescence with λ_{max} 397 nm is in the violet region of the electromagnetic

spectrum, the sample appears blue violet due to the shoulder of the emission trace extending well into the blue region.

3.8 Conclusions

To summarise, the synthesis of three partially fluorinated and highly novel tricyclic dipyridoimidazoles have been developed in facile one pot processes from the commercially available pentafluoropyridine. In particular, the methyl-substituted heterocycle **20** has proven to be an excellent scaffold for further nucleophilic aromatic substitution, reacting regioselectively and under relatively mild conditions to yield a series of nitrogen, oxygen, carbon and sulfur-substituted heterocycles. Further substitution has been proven possible with the formation of dibenzenethiol-, dimethoxy- and phenyl-methoxy-substituted monofluoro heterocycles. Using this methodology, a wide range of highly functionalised compounds, built around a novel core scaffold, can be envisaged and would be of interest to organic chemists in both the life sciences and materials arenas.

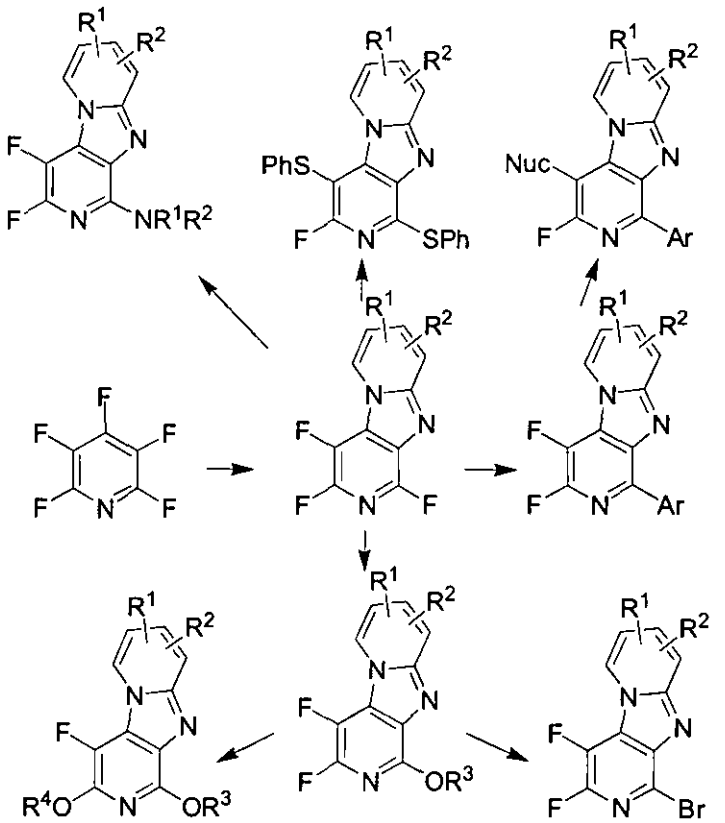


Figure 3.33

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Chapter 4

3-Chloro-2,4,5,6-tetrafluoropyridine as a Scaffold for Pyridine Ring-Fused Heterocycle Synthesis

4.1 Introduction

As shown in Chapters two and three, pentafluoropyridine reacts with suitable *N, N*-centred binucleophilic species, in one or two steps, to give novel trifluorinated pyridine ring-fused heterocycles in mainly very good to excellent yields. Furthermore, a selection of the core scaffolds were shown to be reactive to further nucleophilic displacement, hence providing scope for library synthesis based upon such drug-like motifs.

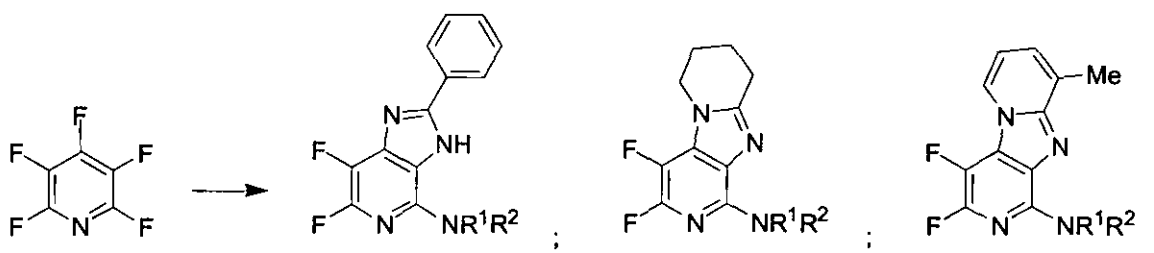


Figure 4.1 Possible [5,6] systems from pentafluoropyridine

In light of its close structural similarity to pentafluoropyridine, 3-chloro-2,4,5,6-tetrafluoropyridine was hypothesised to undergo reaction with the aforementioned binucleophiles in a closely analogous manner. The planned reaction with benzamidine is given as an example to illustrate this (Figure 4.2):

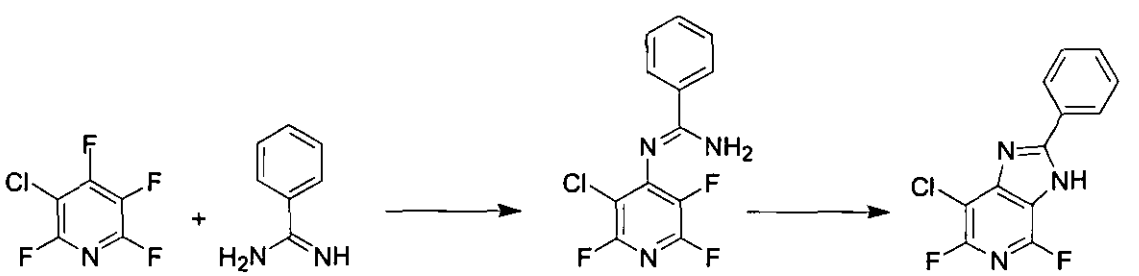


Figure 4.2 Predicted reaction of 3-chloro-2,4,5,6-tetrafluoropyridine with benzamidine

The resulting chlorinated heterocycles could possibly undergo reaction at the C-Cl site, such as metal-catalysed coupling reactions or reduction to C-H, giving rise to other functionalised ring-fused systems and expanding considerably the range of products available.

4.2 Background

3-Chloro-2,4,5,6-tetrafluoropyridine is a byproduct from the large scale synthesis of pentafluoropyridine and, as such, is a cheap and commercially available perhalogenated starting material.[1]

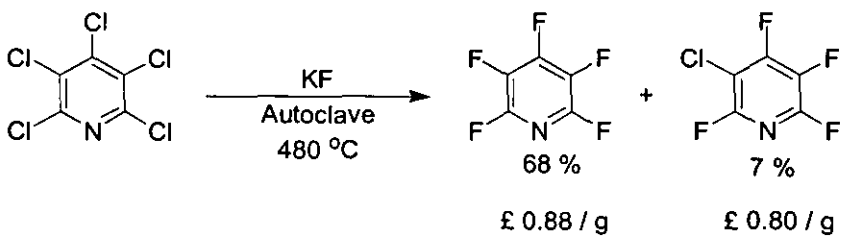


Figure 4.3 Fluorination of pentafluoropyridine to give pentafluoropyridine and 3-chloro-tetrafluoropyridine

Although the majority of early work in perhalogenated heteroaromatic chemistry focused on the reactions of pentafluoropyridine, a kinetic study carried out on a range of perhalogenated heterocycles showed that, as well as reacting with ammonia to give exclusively 4-substituted product, 3-chloro-2,4,5,6-tetrafluoropyridine actually reacted more rapidly than its perfluoro counterpart.[2]

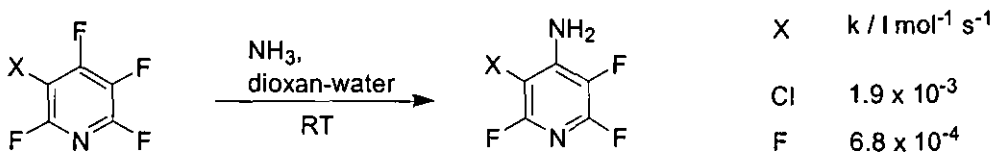


Figure 4.4 Rate constants for reactions of pentafluoropyridine and 3-chloro-2,4,5,6-tetrafluoropyridine with ammonia

It is argued that the higher reactivity shown by the chlorine-containing ring towards nucleophilic attack cannot be explained by comparing the intermediate Meisenheimer

complexes of the two reactions, rather, the initial state effects must be studied (Figure 4.5).

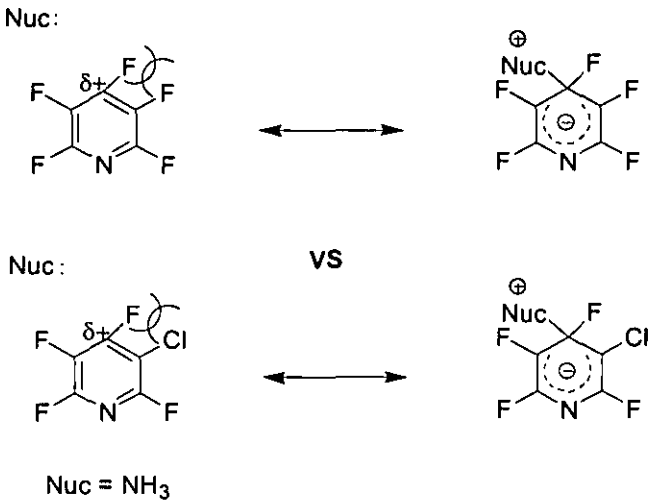


Figure 4.5 Initial states (l) and Meiseheimer complexes (r) between perhalogenated pyridines and nucleophile

It is suggested that in the case of pentafluoropyridine, a strong repulsion would be expected between the two highly polarised and electron dense fluorine atoms, whereas, in the chloro-system, the more diffuse chlorine would provide less of a destabilising effect.

This trend is reversed, however, when the study was carried out with the more sterically demanding nucleophile, diethylamine. Not only did the reaction proceed more slowly in the chlorine containing system but a proportion of the 6-substituted product also formed, reflecting the more crowded nature of the 4-position by the relatively bulky chlorine atom.

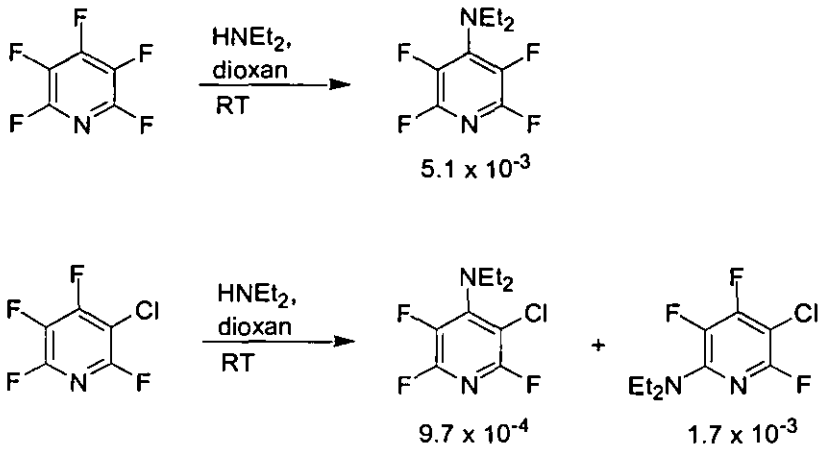


Figure 4.6 Rate constants (k / l mol^{-1} s^{-1}) for reactions of pentafluoropyridine and 3-chloro-2,4,5,6-tetrafluoropyridine with ammonia

More recently, 3-chloro-2,4,5,6-tetrafluoropyridine has been used as a scaffold for the synthesis of novel fluorinated pyridones[3] and nucleoside analogues by multistep strategies as shown in Section 1.4.2 and the following example:[4]

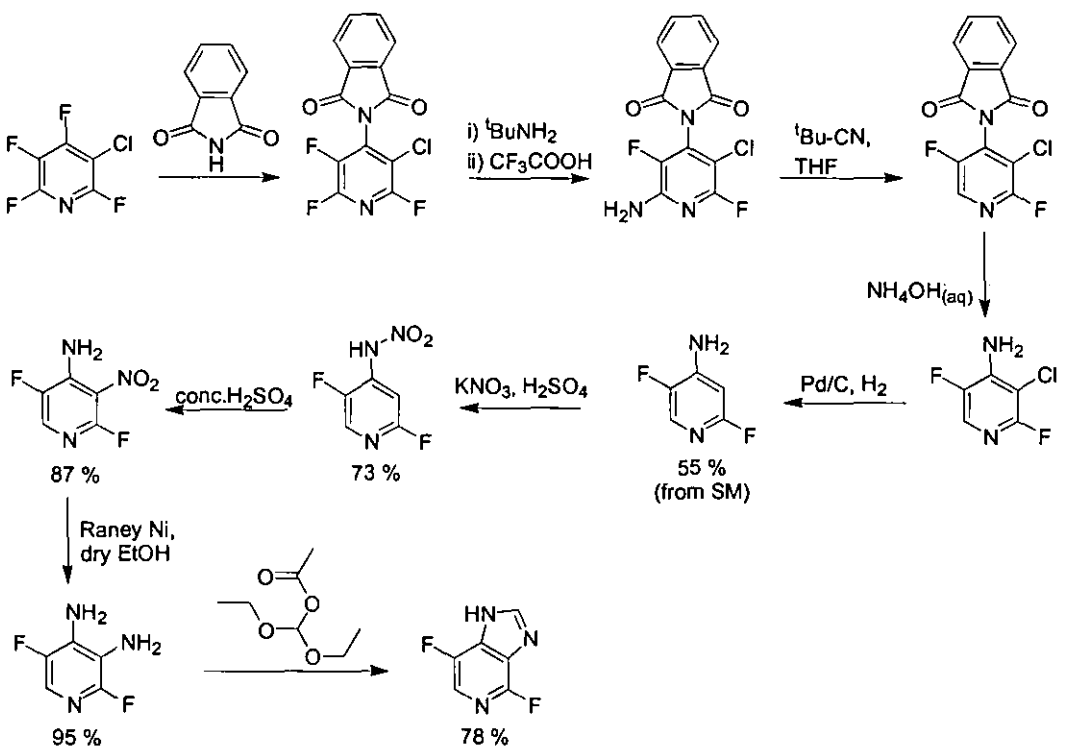


Figure 4.7

Reaction of 3-chloro-tetrafluoropyridine with phthalimide gave the 4-substituted system, which was then substituted at the 6-position by *tert*-butylamine. Reduction and subsequent removal of this group gave the desired difuoropyridine core scaffold, which was then reacted appropriately to give 4,7-difluoro-imidazo[4,5-c]pyridine via an *ortho*-diamine annulation strategy.

With the methodology developed in Chapters two and three in hand, 3-chloro-2,4,5,6-tetrafluoropyridine was concisely explored as a scaffold for [5,6] heterocycle synthesis, starting with the reaction with the *N, N*-unsubstituted binucleophile, benzamidine hydrochloride.

4.3 Reaction with Benzamidine

Nucleophilic substitution of benzamidine occurred under the same conditions as employed in the analogous reaction with pentafluoropyridine and also more rapidly, going to completion in only three hours, consistent with kinetic studies carried out on these systems as discussed above. While attack by the sterically relatively undemanding amidino-species occurred exclusively at the 4-position, by ^{19}F NMR, recrystallisation was necessary to provide a pure sample, hence a lower yield was obtained than in the equivalent reaction with pentafluoropyridine.

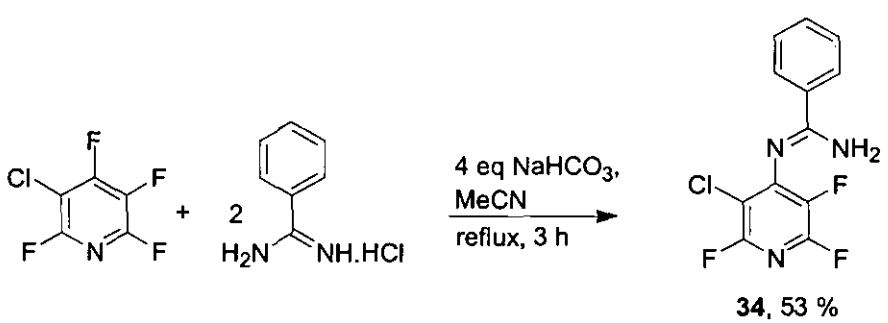


Figure 4.8

A sample of this 4-amidino-substituted pyridine was reacted with LDA and resulted in the successful formation of imidazopyridine **35**, in an unoptimised yield of 34 %, with no attack at the C-Cl site being observed.

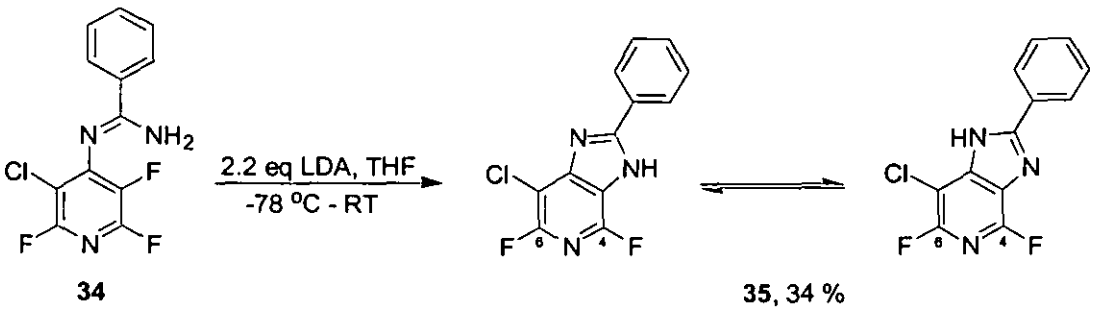


Figure 4.9

X-ray crystallography confirmed the bicyclic structure, whilst two sets of fluorine resonances were observed by ^{19}F NMR of the isolated solid, consistent with trifluorinated analogue **3** (Figure 4.10).

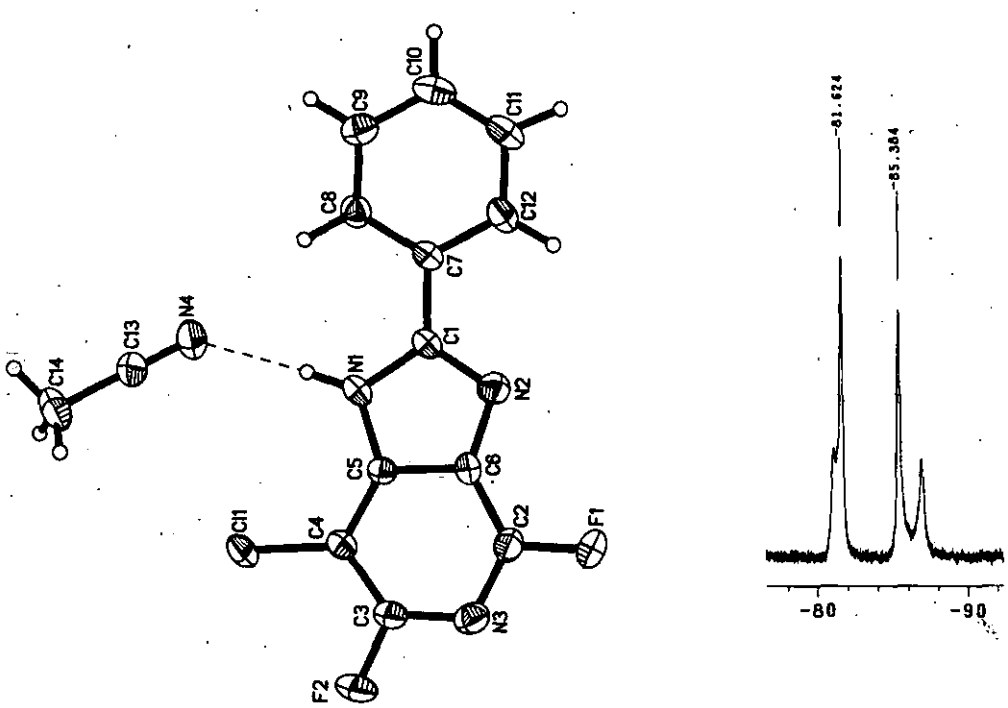


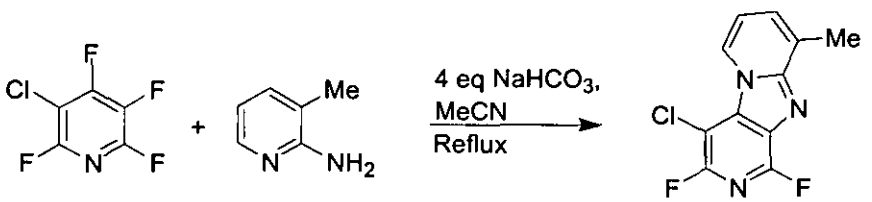
Figure 4.10 Crystal structure and ^{19}F NMR of **35**; δ_F (DMSO-d_6) major tautomer -81.62 (1F, br s, F-6), -85.38 (1F, br s, F-4); minor tautomer -81.10 (1F, br s, F-6), -86.88 (1F, br s, F-4)

Co-crystallisation of the heterocycle with acetonitrile illustrates the acidic nature of the NH group, which coordinates to the basic nitrogen of the acetonitrile solvent.

Although chloride ion is a weaker base and thus a better leaving group than fluoride, the rate determining step of nucleophilic aromatic substitutions, in general, is the initial attack of nucleophilic species on the pyridine ring. Hence in this case, attack by the tethered amidine occurs at the C-F site due to this being more electron deficient than C-Cl.

4.4 Reaction with 2-amino-3-picoline

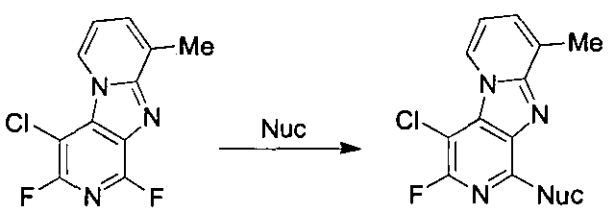
The reaction of 3-chloro-2,4,5,6-tetrafluoropyridine with 2-amino-3-picoline reacted accordingly to give tricycle **36** in good yield.



36, 69 %

Figure 4.11

Subsequently, with multigram quantities at disposal, this core scaffold was reacted with a small selection of nucleophiles to give a series of monofluorinated derivatives in work carried out by L. Convery (M.Chem student, 2006).

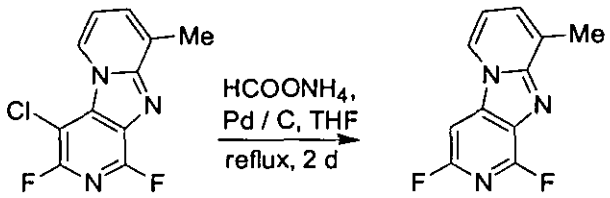


Nuc	% yield
NHBu	97
NEt_2	71
OMe	32

Figure 4.12

In each case, ^{19}F NMR of the reaction mixture indicated substitution was occurring regioselectively at the same site as in the pentafluoropyridine derived system. This is due to the close similarity of the two heterocycles.[5]

Furthermore, reduction of the C-Cl bond was achieved using conditions employed by Schlosser *et al* on halogenated pyridines[6] to yield difluoro compound **37** in an unoptimised yield of 40 %.



37, 40 %

Figure 4.13

Insertion of the metal catalyst occurs at this position, as opposed to a fluorinated site, due to the weaker bond strength of the C-Cl bond relative to C-F. Indeed, reduction of a C-F bond would not be possible at all under these reaction conditions.

4.5 Conclusions

Though relatively few reactions are reported in this chapter we have demonstrated that partially fluorinated analogues of the pentafluoropyridine-derived compounds discussed in Chapters two and three can be readily synthesised from 3-chloro-2,4,5,6-tetrafluoropyridine. This is especially important in the context of probing the effects of fluorine on physical properties and also biological activities. Figure 4.14 shows an example of how this could be implemented. Further to providing data on the change in physical properties depending on the positioning of fluorine on the pyridine ring, by employing a range of nucleophiles a large number of compounds could be created in short and high yielding syntheses.

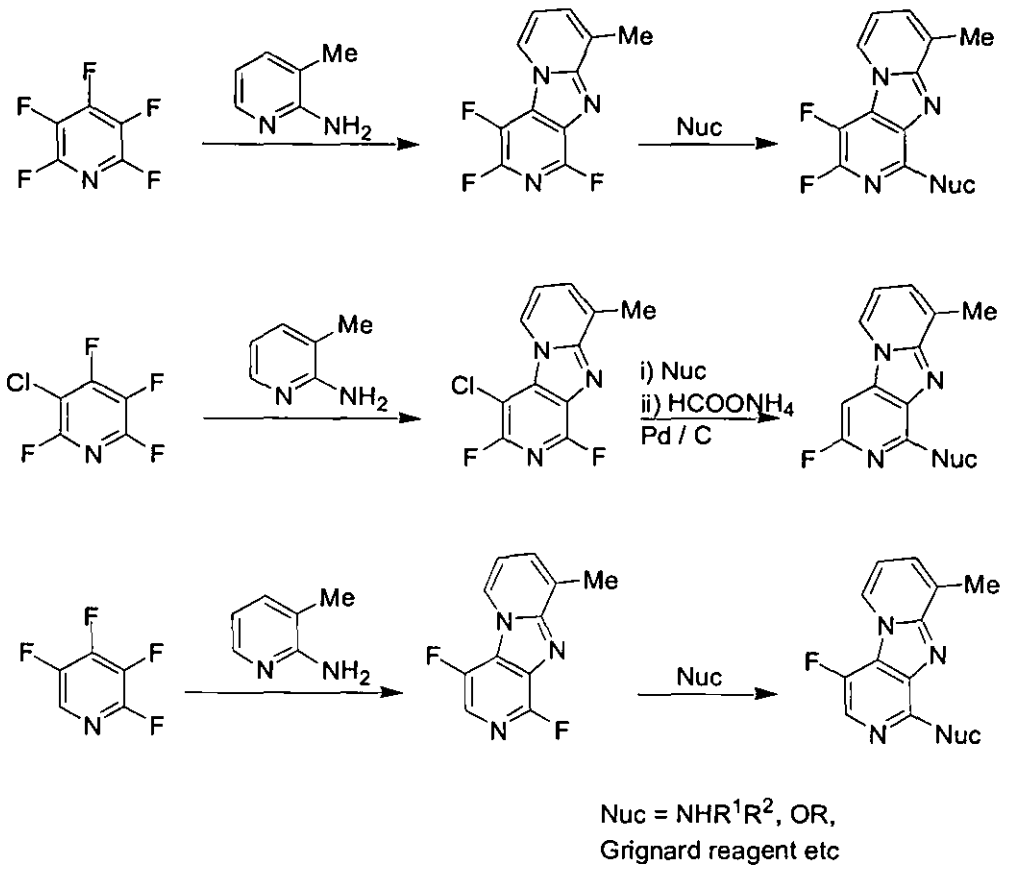


Figure 4.14

References

1 Calculated from prices stated for 100 g bottles from Apollo Scientific Ltd. 2005-2006

2 R. D. Chambers, D. Close, W. K. R. Musgrave, J. S. Waterhouse, and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1774.

3 Q. Li et al, *J. Med. Chem.*, 1996, **39**, 3070.

4 K. Sakthivel and P. D. Cook, *Tetrahedron Lett.*, 2005, **46**, 3883.

5 L. J. Convery, Durham University, M.Chem thesis, 2006.

6 M. Schlosser, C. Bobbio, and T. Rausis, *Chem. Eur. J.*, 2005, **11**, 1903.

Chapter 5

4-Substituted Tetrafluoropyridines as Scaffolds for [5,6] Pyridine Ring-Fused Heterocycle Synthesis

5.1 Introduction

As shown in Chapter 1, pentafluoropyridine, since it was first synthesised in the 1960s, has proven a most reactive and selective species towards nucleophilic substitution by mononucleophiles, as shown in the following example of a 4-amino-3,5-difluoro-2,6-diphenoxypyridine synthesis:[1]

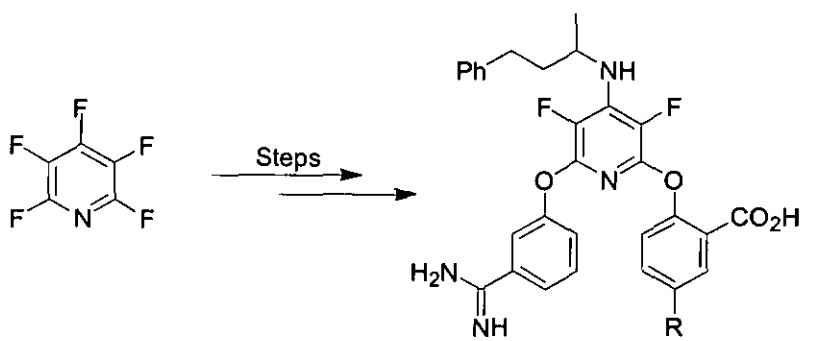
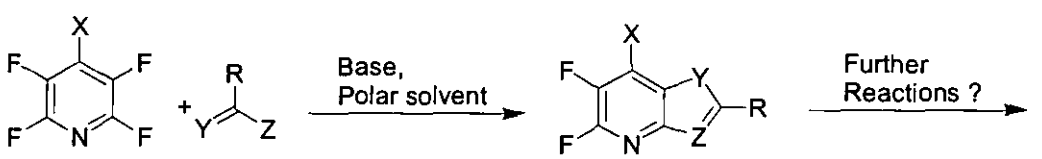


Figure 5.1

It has also been shown in chapters 2 and 3 that pentafluoropyridine reacts with suitable binucleophiles to give highly novel pyridine ring-fused heterocycles. Thus it was reasoned that reaction of 4-substituted tetrafluoropyridines, obtained either through commercial sources or synthesised from pentafluoropyridine, with binucleophiles should, potentially, give access to a range of [2,3]-pyridine-fused core scaffolds. This strategy is illustrated schematically in Figure 5.2



Y = Z = N (amidines)
Y = O, S; Z = N (amides / thioamides)
Y = O; Z = C (1,3 dicarbonyls)

Figure 5.2

As shown in Section 1.4.2, this approach has proven to be effective for [6,6] ring-fused synthesis when 4-benzenesulfonyl-tetrafluoropyridine was reacted with a series of ethylene-diamino species:[2]

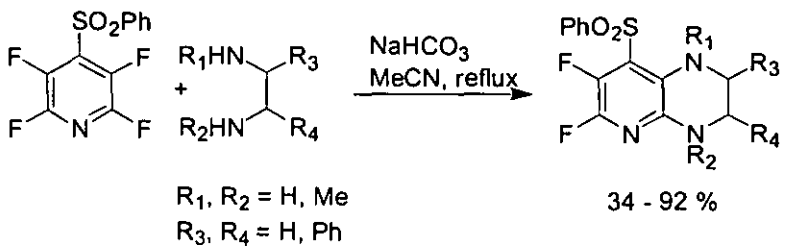


Figure 5.3

As well as giving access to [2, 3]-pyridine ring-fused heterocycles, this strategy could yield compounds bearing useful functional groups, such as a bromine atom for further derivatisation. Furthermore, if a strongly electron withdrawing group were employed, it should aid nucleophilic attack at the usually least activated 3-position of the pyridine scaffold, e.g. in a similar manner to the perfluoroisopropyl activating effect as shown in Section 1.4.1:

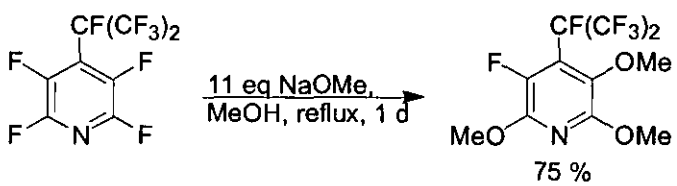
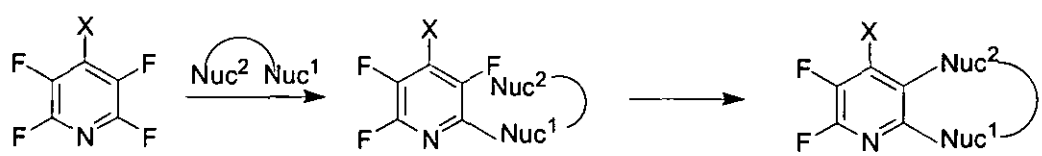


Figure 5.4

As such, the following section will detail the reaction of a small selection of 4-substituted tetrafluoropyridines with *N, N* –centred binucleophilic species with the aim of achieving a range of novel heterocyclic scaffolds. A range of fluoropyridine derivatives were tried in order to assess functional group compatibility of this process (Figure 5.5).



X = H, Br, SO_2Ph, CN

Figure 5.5 Desired reaction between 4-substituted tetrafluoropyridines and binucleophilic species

5.2 Reaction of 2,3,5,6-Tetrafluoropyridine and 4-Bromo-2,3,5,6-tetrafluoropyridine with Benzamidine

Reaction of the commercially available 2,3,5,6-tetrafluoropyridine with benzamidine hydrochloride proceeded extremely slowly, taking eleven days at reflux to achieve 90 % conversion. As expected, attack occurred exclusively at the 2-position, whilst a yield of 34 % was obtained:

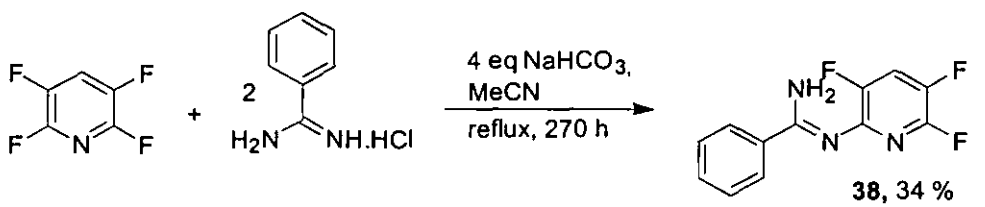


Figure 5.6

Attempts to cyclise this tethered amidino-substituted system using the strong organic base LDA failed and this can be attributed to the lower electrophilicity of the pyridine ring. As such, this fluoropyridine derivative is unsuitable for imidazopyridine synthesis via the developed methodology.

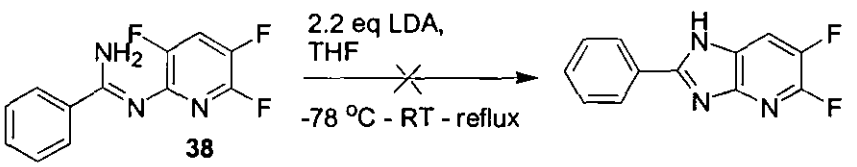


Figure 5.7

Reaction of 4-bromotetrafluoropyridine with benzamidine gave the uncyclised system **39** after prolonged refluxing in acetonitrile, with attack by the hard nucleophilic species occuring at the hard 2C-F position rather than the softer C-Br site.

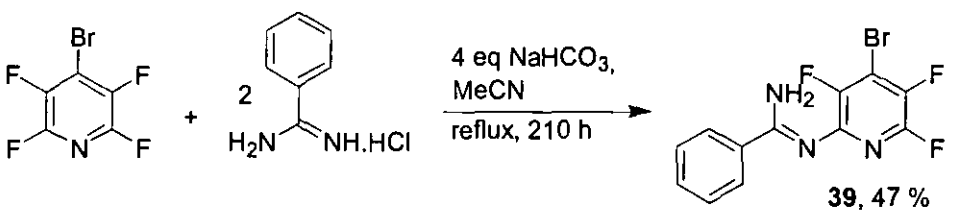


Figure 5.8

However, even the presence of a bromine atom in the 4-position failed to affect cyclisation, when **39** was reacted with LDA, in an attempt to reach the imidazopyridine target molecule.

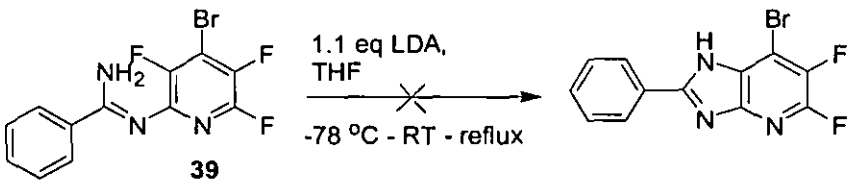


Figure 5.9

From these systems we can deduce that a more electron deficient pyridine is required, not only to aid cyclisation but also so that the binucleophilic species can be initially tethered under reasonable reaction conditions. Thus, our study led us to explore the reactions of 4-benzenesulfonyl-2,3,5,6-tetrafluoropyridine (X = SO_2Ph) and 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile (X = CN), as highly electron-deficient pyridine systems, with suitable binucleophilic species. 4-Nitro-2,3,5,6-tetrafluoropyridine (X = NO_2) was not included as this has been shown previously to be a poor scaffold for derivatisation, with nucleophilic substitution of the nitro group competing significantly.[3]

5.3 Reaction of 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine with Binucleophilic Species

5.3.1 Reaction with Amidines

Synthesis of 4-benzenesulfonyl-2,3,5,6-tetrafluoropyridine **40** was achieved according to literature procedure,[4] giving a 62 % yield after recrystallisation.

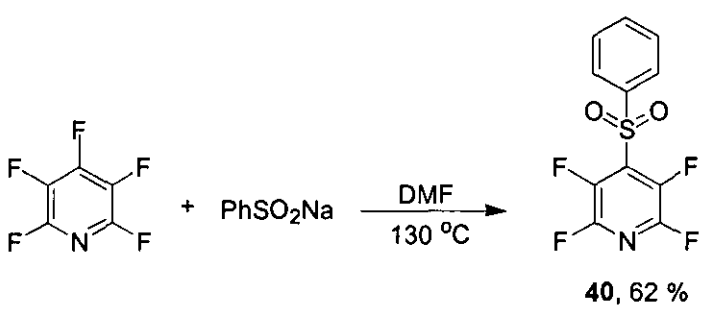


Figure 5.10

Reflux of **40** with benzamidine hydrochloride was followed by ^{19}F NMR of the reaction mixture and, although proceeding slowly, a major product containing two fluorine atoms by ^{19}F NMR could be seen to form. Work up and recrystallisation of this experiment yielded a yellow solid, which proved to be the desired [2,3]-pyridine annulated system by NMR and MS characterisation. Analogous reaction of the sulfonyl derivative with acetamidine hydrochloride gave similar results and X-ray spectroscopy gave definitive proof as to the ring formation (Figure 5.12).

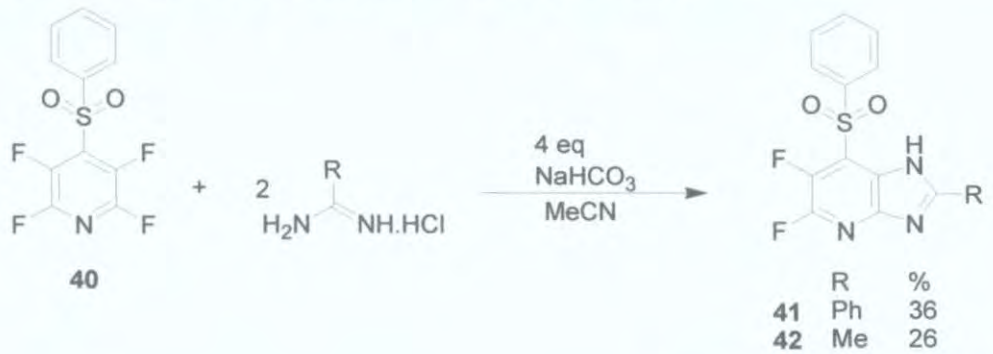


Figure 5.11 Reaction of **40** with benzamidine and acetamidine hydrochloride

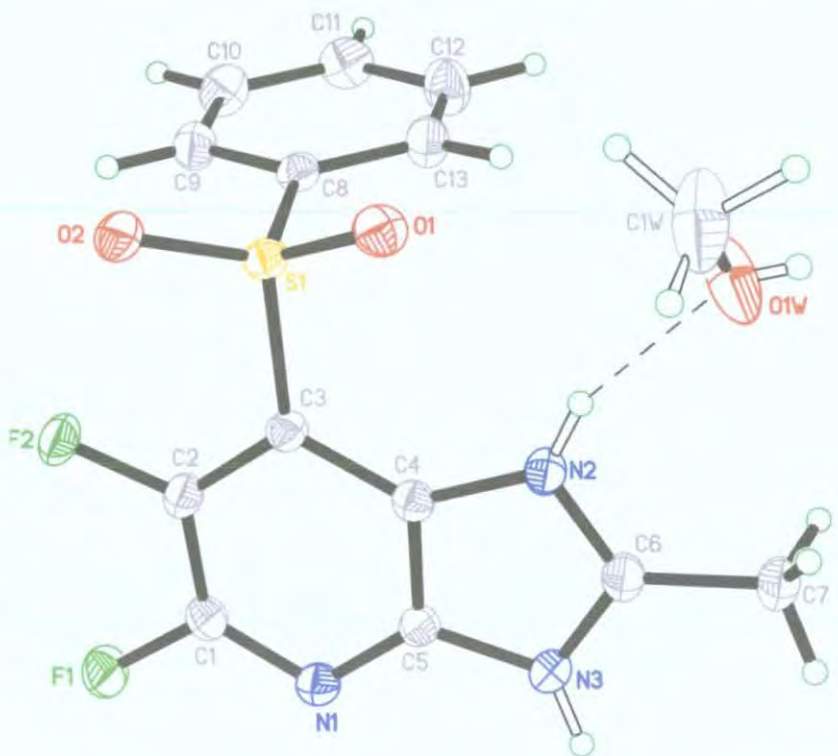


Figure 5.12 X-ray structure of **42**

Although both initial attack and ring annulation was achieved in a one-pot process, the yields are moderate to low. This is due, in part, to prolonged heating of the reactions, leading to thermal decomposition of the materials. Another probable factor in this case is the undesired displacement of the 4-substituent by the nucleophilic species, with 4-substituted byproducts clearly observed by ^{19}F NMR of the reaction mixture.

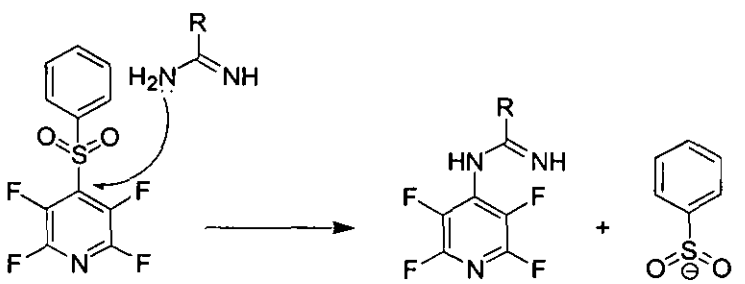


Figure 5.13

Consistent with previous chemistry carried out on this compound that showed a similar displacement of the sulfonyl group by lithium diethylamide to occur,[2] it can be reasoned that the highly electron withdrawing nature of the benzenesulfonyl group makes the carbon to which it is attached liable to attack as well as the desired 2C-F site.

Elaboration of these core scaffolds was studied briefly through the reaction with oxygen nucleophiles. Refluxing **41** with sodium ethoxide gave 86 % conversion to several products (by ^{19}F NMR of the reaction mixture), whilst this observation was corroborated through NMR and GCMS analysis obtained from the mixture resulting from the reaction between **42** and sodium methoxide.

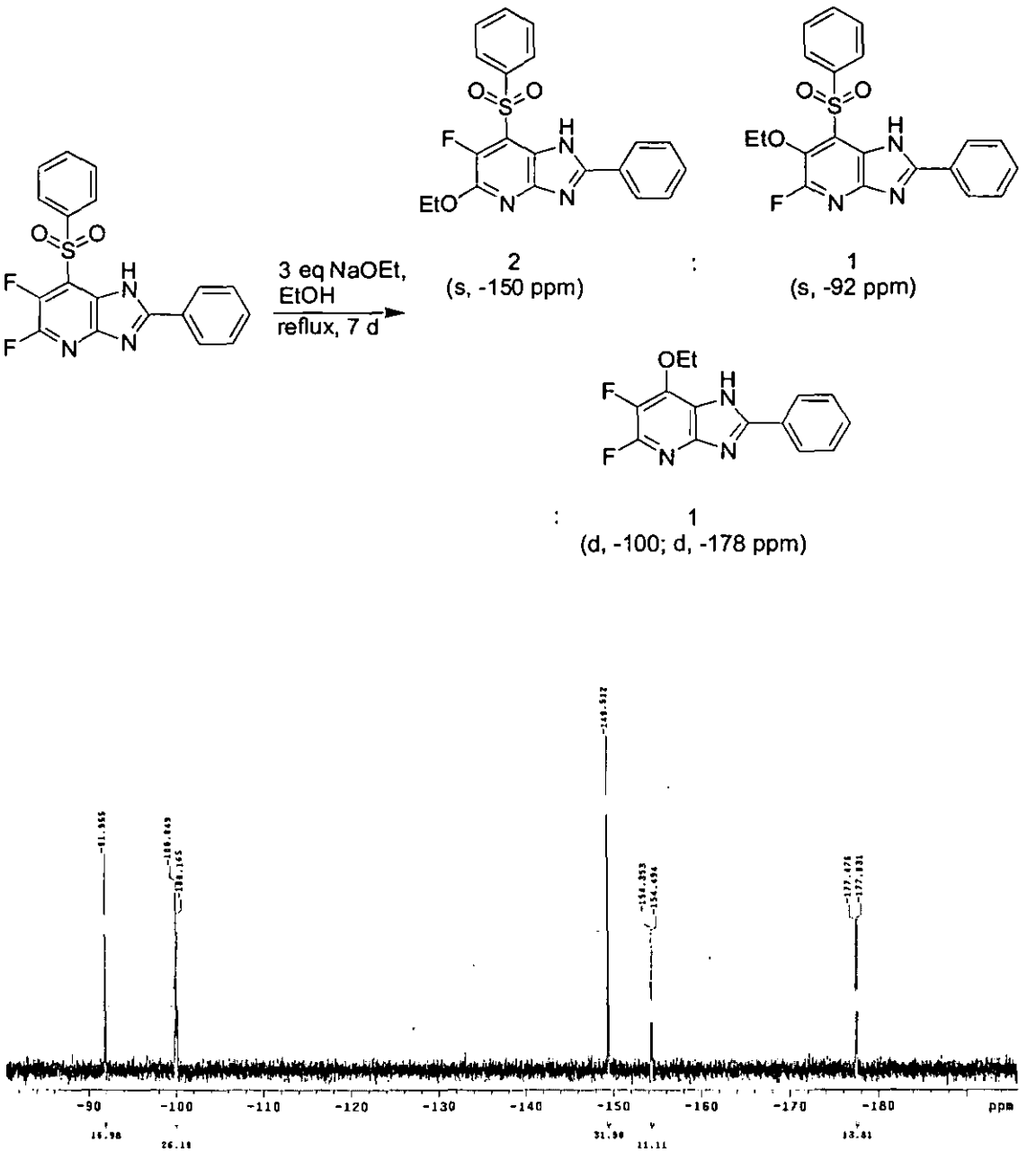


Figure 5.14 Products formed from the reaction of **41** with NaOEt and their appearance by ^{19}F NMR of the reaction mixture

This result is logical as, although one would expect the C-F site *ortho* to the pyridine nitrogen to be the most activated site to nucleophilic substitution, the benzenesulfonyl group has such an electron-withdrawing effect that displacement of the fluorine located

adjacent to the C-SO_2Ph site occurs. Again, displacement of the benzenesulfonyl group is also a competing process. Purification of products proved to be too difficult to achieve.

5.3.2 Reaction with 2-Amino-3-picoline

Reaction with the cyclic binucleophile 2-amino-3-picoline proceeded slowly in keeping with its low initial reactivity, giving roughly 50 % conversion after one week at reflux and resulting in a complicated ^{19}F NMR of the reaction mixture. Work up and purification, along with the knowledge that the benzenesulfonyl group is also labile in these nucleophilic displacement reactions, led to the assignment of the following three compounds as the main products.

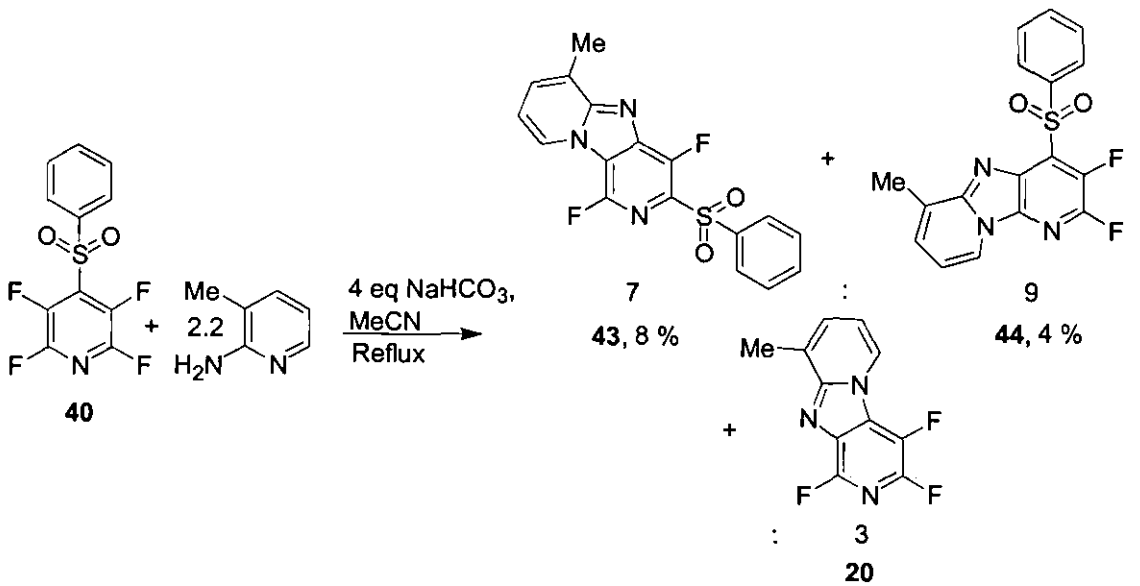


Figure 5.15

Marginally the major isomer, **44** was the desired compound in that initial attack at the 2-position of the fluoropyridine and subsequent cyclisation was expected, whilst X-ray crystallography confirmed the structure of this product:

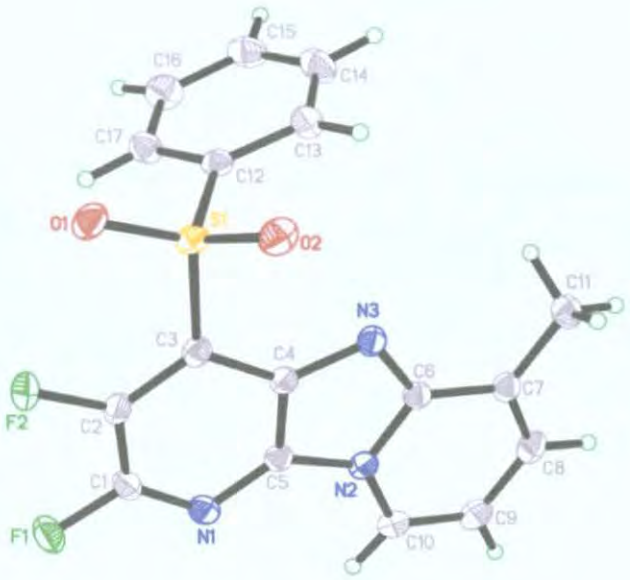


Figure 5.16 X-ray structure of **44**

X-ray crystallography of the other major product revealed the surprising isomeric structure **43**:

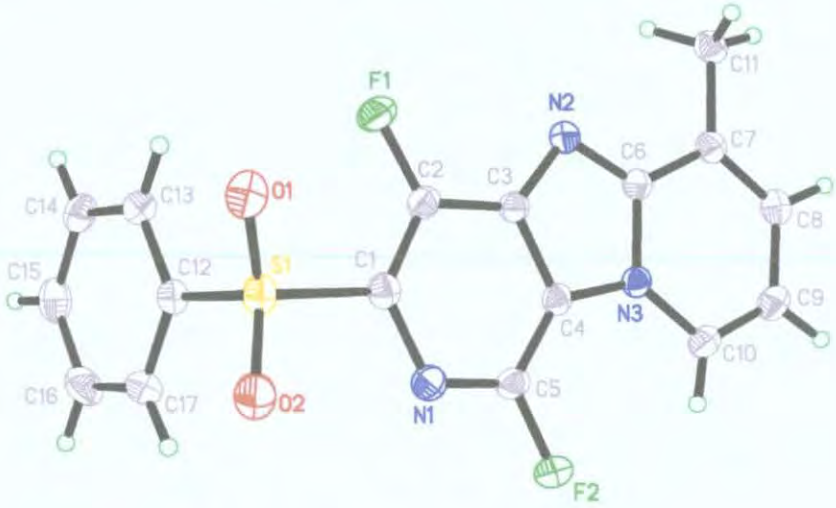


Figure 5.17 X-ray structure of **43**

This unexpected product presumably arises from initial attack of the picoline at the 3-position of the fluoropyridine followed by ring closure at the most activated 4-position, via the displacement of the benzenesulfonyl group. The newly displaced sulfonyl group being anionic and hence nucleophilic, then attacks the fluoropyridine at the 6-position to give tricycle **43**. As the third major product, the [3, 4]-pyridine-fused tricycle **20** could

clearly be observed by ^{19}F NMR of the reaction mixture. Overall, attack occurs at C-2 and C-3 in roughly equal quantities. This is not in keeping with previous studies, where attack by amine nucleophiles occurred at C-2, and is attributed to the *ortho*-directing effect of the benzenesulfonyl group towards the binucleophilic species.

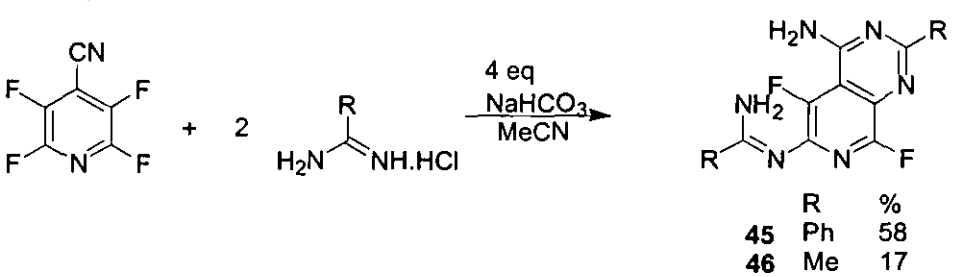
As well as forming two functionalised and highly novel heterocycles, this reaction illustrates the selectivity of this fluoropyridine to nucleophilic attack. It goes without saying that these new tricyclic species were both highly fluorescent.

5.4 Reaction of 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile with Binucleophilic Species

To further the scope of this chemistry, the commercially available 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile was deemed a potentially excellent core for fused ring synthesis, having been used previously to make [6,6] systems upon reaction with ethylene diamino binucleophilic species.[3]

5.4.1 Reaction with Amidine Nucleophiles

Reaction with two equivalents of benzamidine hydrochloride led to two major resonances by ^{19}F NMR after seven days at reflux, while work up and recrystallisation gave a yellow solid in good yield. Analysis of this compound clearly showed that this was not the expected [2, 3]-pyridine ring-fused structure but a [2, 5]-substituted system. X-ray analysis of a suitable crystalline sample showed the product to be the [6,6] fused-pyridopyrimidine **45** (Figure 5.19). A similar result was obtained in the reaction with acetamidine hydrochloride.



	R	%
45	Ph	58
46	Me	17

Figure 5.18

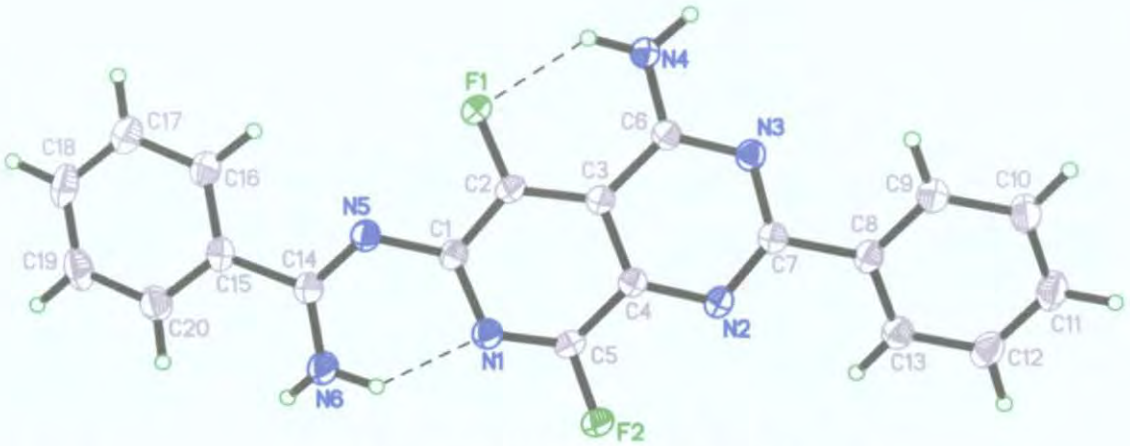
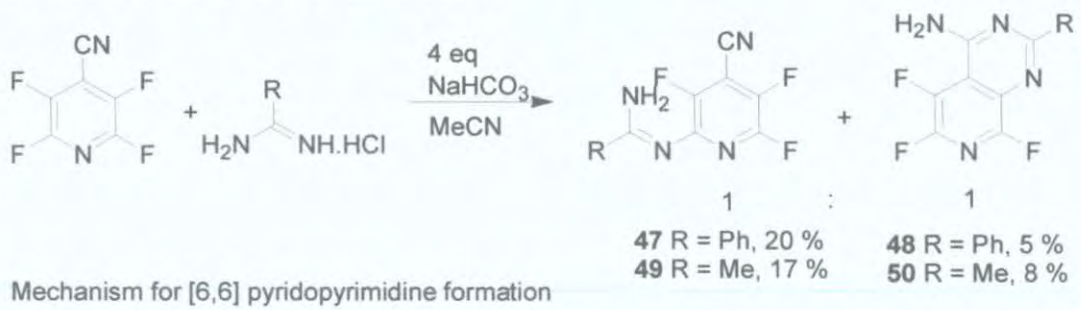


Figure 5.19 X-ray structure of **45**

The reactions were repeated with one equivalent of the binucleophile to see whether the fused rings could be obtained without the addition of a second amidine moiety to the fluoropyridine (I.e. **48** and **50**) and, although this was found to be the case, the uncyclised isomers **47** and **49** were also formed to give a roughly 1 : 1 mixture of the isomeric structures shown in Figure 5.20:



Mechanism for [6,6] pyridopyrimidine formation

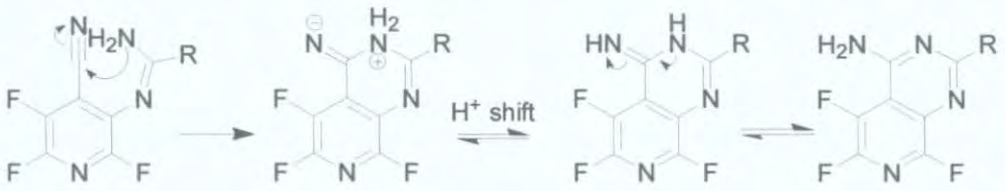


Figure 5.20

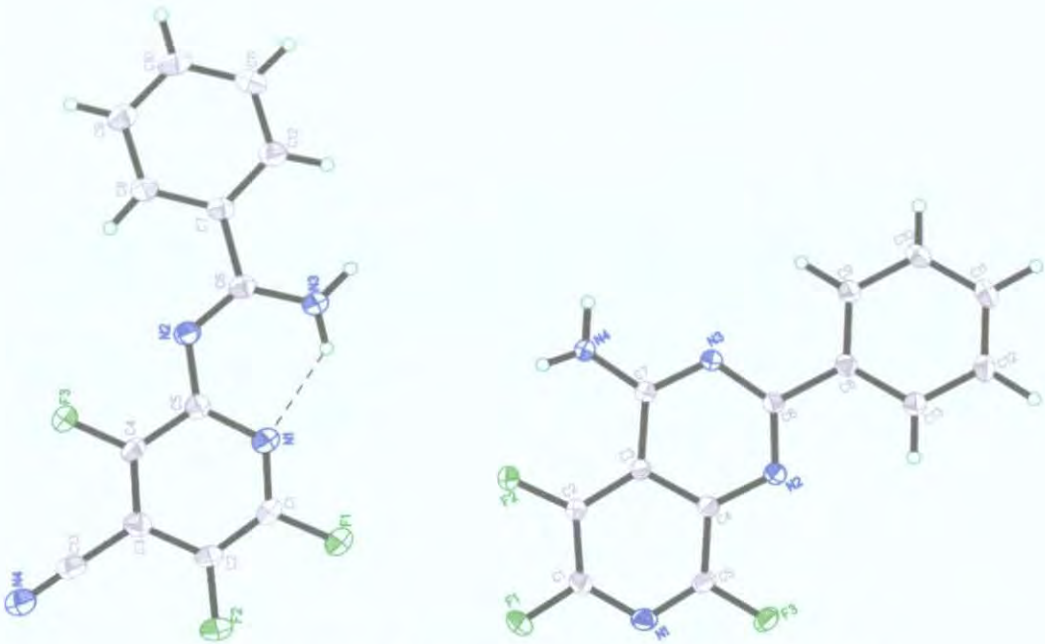


Figure 5.21 X-ray structures of **47** (l) and **48** (r)

From these isomeric products we can deduce that, in the case of the formation of **45** and **46**, the first equivalent of amidine attacks both the 2- and 3-position of 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile at roughly equal rates to give the uncyclised intermediate and the pyridopyrimidine respectively while the second equivalent attacks *para* to the site of initial attack, in both cases (Figure 5.22). This is somewhat surprising in the case of pathway II, where one might expect attack to occur *ortho* to the first equivalent, in light of the neighbouring group effect –N=C showed in the imidazopyridine systems. This is presumably down to differing electronic properties between the imidazo- and pyrimido- fused rings.

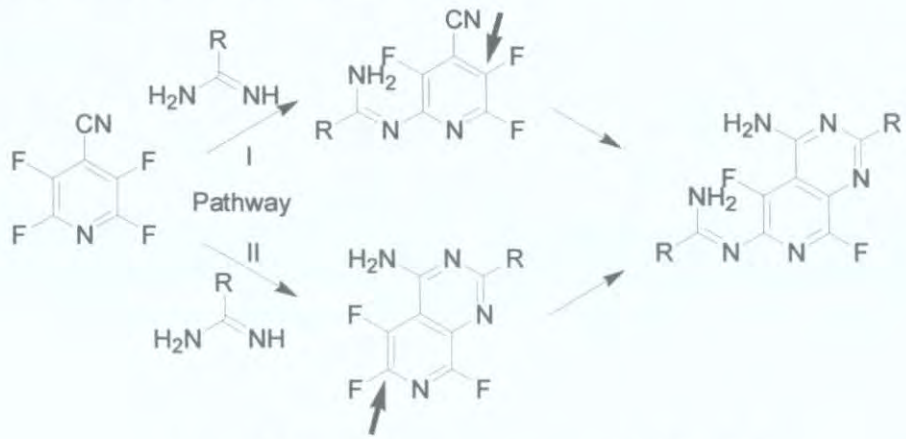


Figure 5.22 Two routes to compounds **45** and **46**

5.4.2 Reaction with 2-Amino-3-picoline

Although reacting slowly, reaching 70 % conversion after two weeks, owing to the low nucleophilicity of the picoline and despite the electron deficient nature of the fluoropyridine, ^{19}F NMR of the reaction mixture showed one major product consisting of two doublet resonances. The reaction was worked up and the crude subjected to column chromatography to yield the main product as a yellow solid. Whilst characterisation of this compound indicated that two fluorine atoms had been displaced by a single picoline species the structure of this pyridine-fused ring could not be established. Thus, it has been assumed that initial attack through the ring nitrogen of 2-amino-3-picoline occurred at the least sterically hindered 2-position of the fluoropyridine core scaffold, leading to the formation of tricycle **51.**

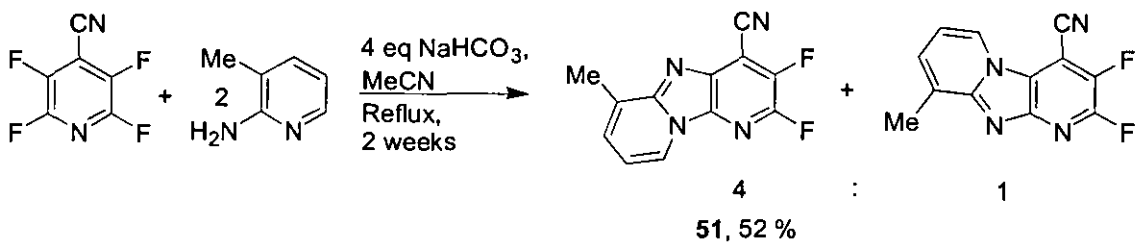


Figure 5.23

This reaction is surprisingly selective given the mixture obtained from the analogous reaction on the 4-SO_2Ph substituted tetrafluropyridine and illustrates how these condensation reactions are very dependent on both the nature of the binucleophilic species and the fluoro-core scaffold.

This compound was shown to be a useful scaffold for functionalisation through the reaction with diethylamine, under relatively mild reaction conditions, to give monofluorinated tricycle **52** (Figure 5.24). Although an unoptimised yield of only 17 % was obtained, ^{19}F NMR and LCMS of the crude showed this to be a surprisingly selective reaction, both techniques clearly showing this to be the predominant product.

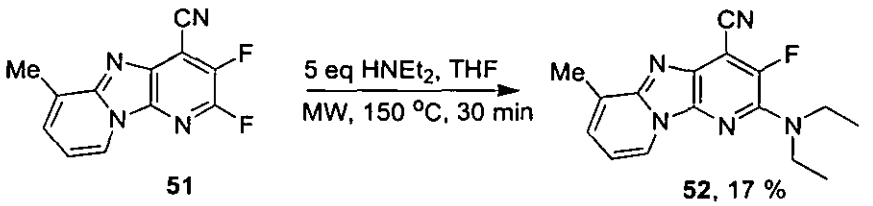
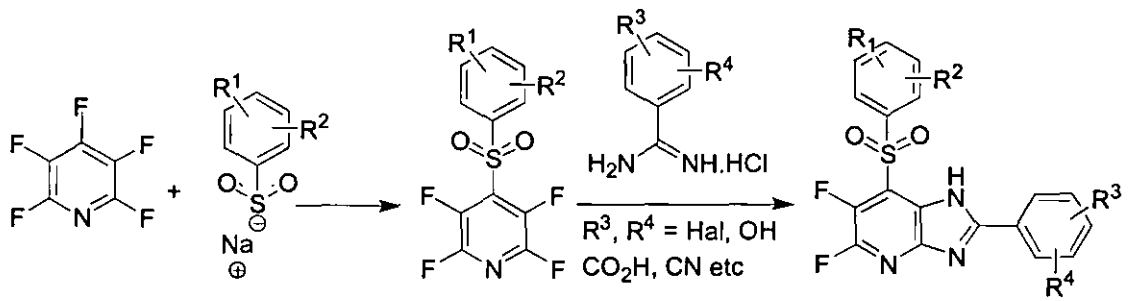


Figure 5.24

5.5 Conclusions

To summarise, 4-substituted tetrafluoropyridines can be effective reagents for the synthesis of [5,6] and [6,6] pyridine ring-fused heterocycles as long as a strongly electron withdrawing group activates the heterocyclic ring and hence favour this process. In the case of the benzenesulfonyl substituted rings, a small library could be envisaged through the employment of substituted benzamidines and also the use of commercially available benzenesulfonyl anionic species:



R^1 = 4-Me, R^2 = 2-Cl
R^1 = 4-F, Cl or Br, R^2 = H
R^1 = 4-OMe, R^2 = 2-NHAc
R^1 = 3-CF_3, R^2 = H
R^1 = 4-CH=CH_2

Figure 5.25

Reaction with the 4-cyano substituted fluoropyridine with the acyclic amidines benzamidine and acetamidine, rather than forming an imidazopyridine fused ring, gave the intriguing [6,6] aza quinoline motif.

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Chapter 6

Perhalogenated Cyanopyridines as Scaffolds for Pyridine Ring-Fused Heterocycle Synthesis

6.1 Introduction

The discovery that the presence of a nitrile functionality on the fluoropyridine core, as well as activating to nucleophilic attack, could itself act as a site for reaction, gave access to a small number of pyrido-pyrimidine heterocycles. A lack of initial selectivity of nucleophilic attack, however, led to moderate yields at best of these [6,6] fused ring systems for example as shown by the reaction of 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile with one equivalent of benzamidine:

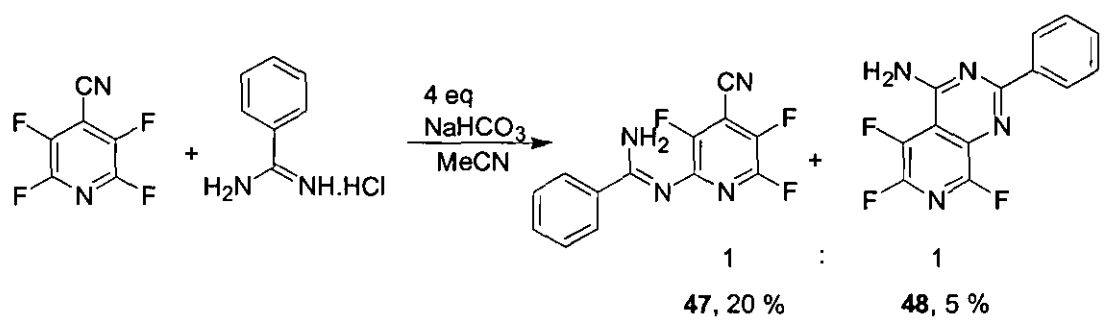

Figure 6.1 Reaction of 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile with one equivalent of benzamidine hydrochloride

Exploring this condensation between an *N,N*-centred binucleophile and pyridine systems containing an *ortho*-fluorine-nitrile moiety was thus considered appropriate both in terms of accessing further pyridine ring-fused heterocycles of this type and also to improve upon yields obtained on the 4-cyano-fluoropyridine based systems.

Both the isomeric 2- and 3-cyano tetrafluoropyridines have been reported in the literature and were considered as substrates for reaction with suitable binucleophilic species. A consideration of the initial state effects of the electron withdrawing substituents resulted in the following predictions as to the site of attack if each ring were attacked by a mononucleophile.

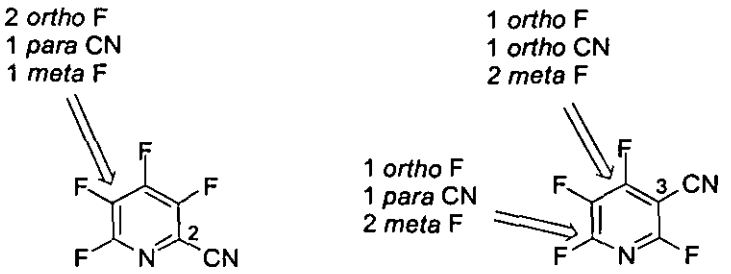

Figure 6.2 Predicted initial state reactivities of 2- and 3-cyano tetrafluoropyridine towards nucleophilic attack

In the case of 3,4,5,6-tetrafluoropyridine-2-carbonitrile, one would expect attack to occur *para* to the cyano substituent, due to the activating effects of two *ortho* and one *meta* fluorine atoms, while the negative charge developed in the course of the reaction could be delocalised onto the *para* nitrile functionality:

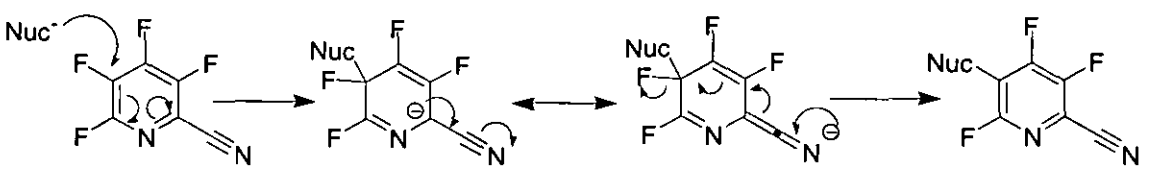

Figure 6.3

Studying the initial state effects in 2,4,5,6-tetrafluoro-nicotinonitrile, towards attack by a nucleophilic species, leads to two potential sites of attack, *para* and *ortho* to the cyano group. Given that we wish to bring about attack of an amidines binucleophile at a C-F site *ortho* to a cyano functionality, this compound was chosen as the most appropriate reagent for exploration.

As well as reacting with amidines to give [6,6] scaffolds, the reaction with suitable reagents, such as hydrazine, could give highly novel and interesting [5,6] pyridine-fused heterocycles:

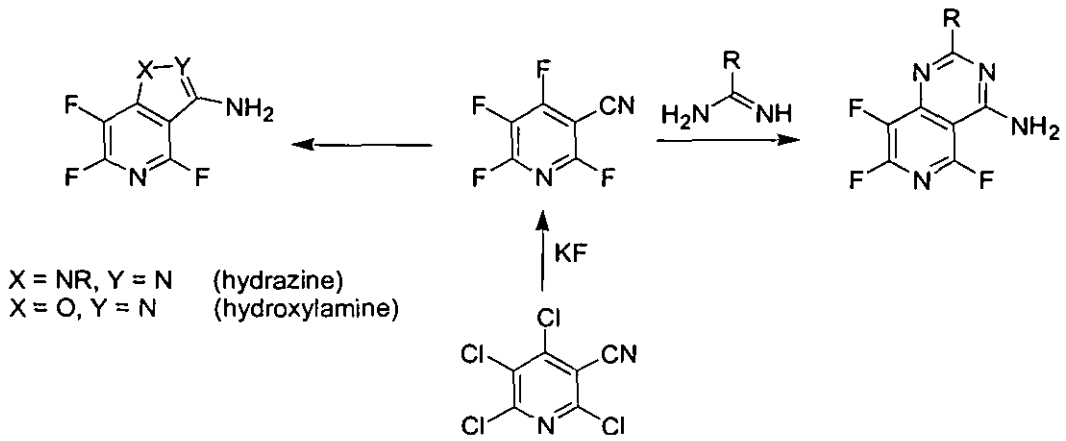

Figure 6.4 Synthesis and potential reactions of 2,4,5,6-tetrafluoro-nicotinonitrile

As well as the studying the reactions of 2,4,5,6-tetrafluoro-nicotinonitrile, the reactivity of its perchlorinated precursor, through reaction with nucleophilic species, could be studied to ascertain whether this precursor could be a useful core scaffold.

6.2 Background

There has been relatively little reported on 2,4,5,6-tetrachloro-nicotinonitrile (40 'hits' on a Scifinder Scholar structure search). This literature can be split into articles concerning its synthesis and characterisation, the formation of 2,4,5,6-tetrafluoro-nicotinonitrile (Halex reaction) from 2,4,5,6-tetrachloro-nicotinonitrile, the oxidation of the cyano group to give tetrachloro-3-nicotinic acid and nucleophilic attack to give substituted chloro-cyano-pyridines.

Synthesis of 2,4,5,6-tetrachloro-nicotinonitrile revolves around reacting nicotinonitrile with chlorine gas at high temperatures with or without a catalyst.[1-4] In the following example, synthesis was achieved by passing nicotinonitrile and a slight excess of Cl_2 through a nickel coated U-tube containing an activated C catalyst impregnated with 27 % $BaCl_2$ at 370 °C.[1] Recrystallisation from CCl_4 gave the perchlorinated compound in 57 % yield.

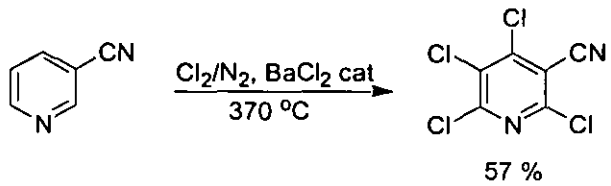

Figure 6.5

Large scale synthesis of the perfluorinated system has been accomplished by reaction of 2,4,5,6-tetrachloro-nicotinonitrile with KF in benzonitrile at elevated temperatures.[5, 6]

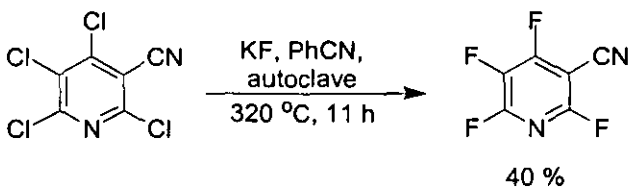

Figure 6.6

Though there is no literature concerning the reaction of the perfluorinated nicotinonitrile with nucleophiles, the synthesis of the following thio-substituted pyridines from 2,4,5,6-tetrachloro-nicotinonitrile has been reported (Figure 6.7).[7, 8]

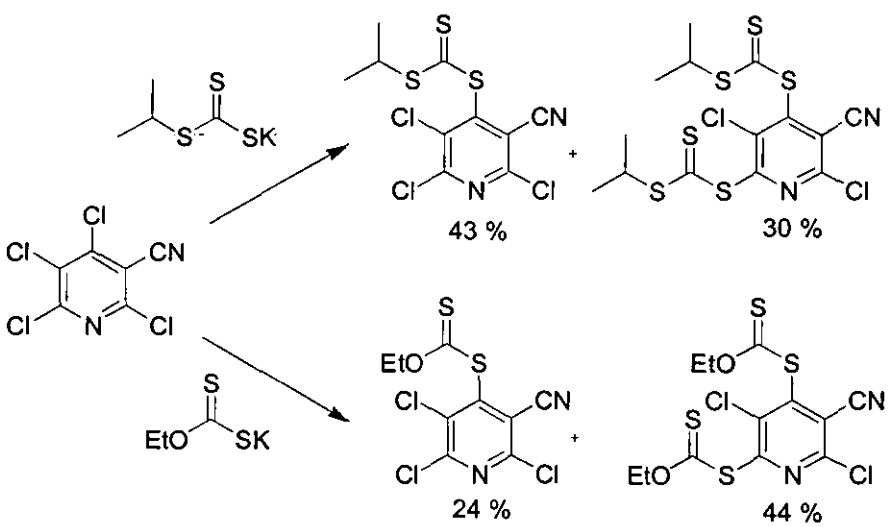

Figure 6.7

Reaction with the sulfur nucleophiles potassium *iso*-propyltrithiocarbonate and potassium ethylxanthate gave a mixture of 4- and 4, 6-substituted pyridines.

Synthesis of the following pyridine ring-fused heterocycles, through the reaction of 2,4,5,6-tetrachloro-nicotinonitrile with suitable binucleophilic species, has also been reported:[9]

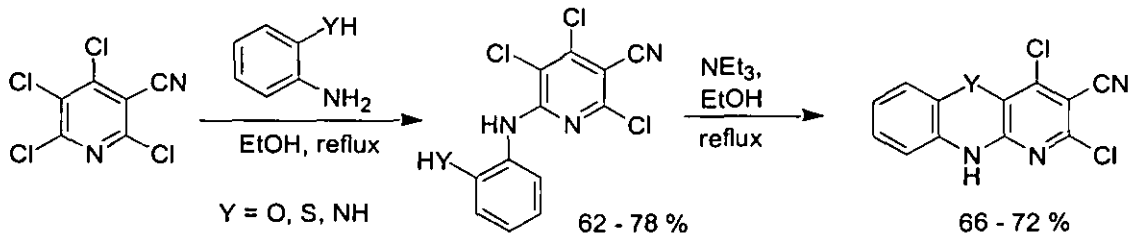

Figure 6.8

6.3 Reaction of 2,4,5,6-Tetrachloro-nicotinonitrile with Nucleophiles

2,4,5,6-Tetrachloro-nicotinonitrile was accordingly reacted with the sterically unhindered mononucleophile butylamine to confirm the assessment of regiochemistry of attack and gave two new products by tlc and no starting material after 4 h at reflux. Work up and purification by column chromatography gave a major fraction consisting of predominantly one compound (by ^{13}C NMR) which, after purification by recrystallisation, was shown by X-ray crystallography to be isomer **53** (Figure 6.10):

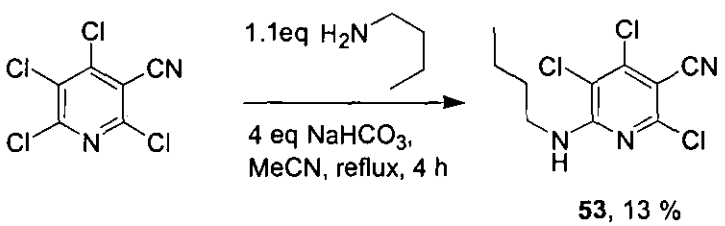

Figure 6.9

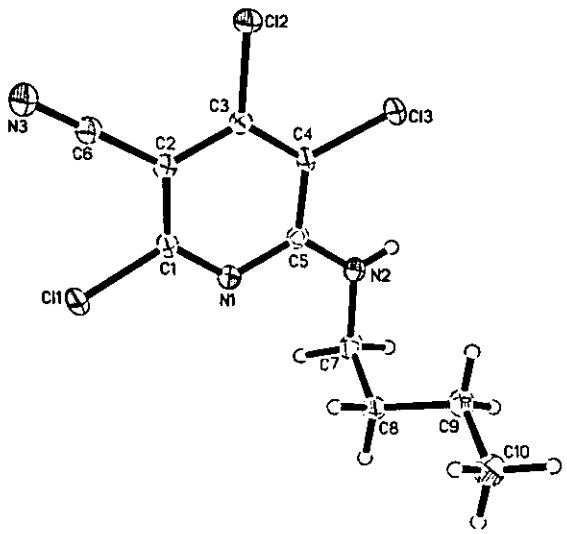

Figure 6.10 X-ray structure of **53**

Reaction with benzamidine hydrochloride also gave complete conversion to two compounds (by tlc), whilst the major product proved quite insoluble in DCM during work up, so was filtered to give **54** as a yellow solid.

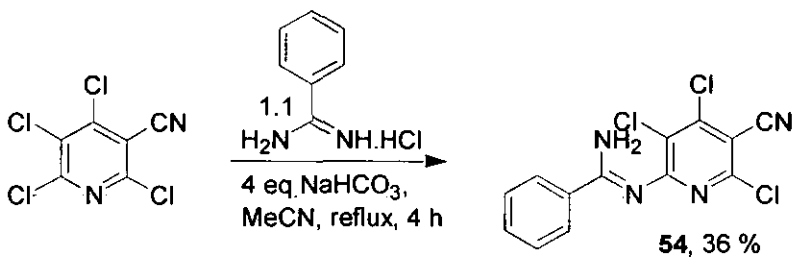

Figure 6.11

Attack at the 2-position rather than the electronically favoured 4-position is presumably due to the relatively large bulk of chlorine atoms thus making the 4-position of the pyridine quite sterically congested and making reaction at the more accessible 6-position the energetically lower pathway. Although this does give access to a range of novel trichlorinated pyridines, it doesn't provide any opportunity for the desired annulation at the cyano group in the reaction with the binucleophilic amidines and thus the focus of the work progressed to the fluorinated analogue.

6.4 2,4,5,6-Tetrafluoro-nicotinonitrile as a Scaffold for [6,6] Fused-Ring Synthesis

6.4.1 Synthesis

Synthesis of **55** was carried out under solventless conditions in line with the group's general approach to the synthesis of perfluorinated heterocycles. As such, a stainless steel autoclave was charged with 2,4,5,6-tetrachloro-nicotinonitrile and flame-dried potassium fluoride, sealed and heated at 320 °C for 22 h. The autoclave was allowed to cool to 200 °C, the gaseous fluorinated products removed under reduced pressure and condensed in a Young's tap-equipped vessel, ^{19}F NMR of which showed the products in Figure 6.12 to be present. The presence of a large amount of 5-chloro-2,4,6-trifluoro-nicotinonitrile is in keeping with the 5-position being the least activated to nucleophilic attack, in keeping with the general reactivities of fluorinated pyridines.

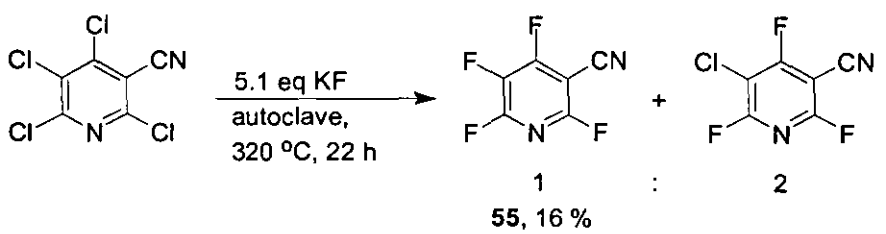

Figure 6.12

Distillation of this crude oil gave 2,4,5,6-tetrafluoro-nicotinonitrile (4.59 g, 16 %) in 92 % purity. The remaining crude, along with more 2,4,5,6-tetrachloro-nicotinonitrile, was reacted again in the autoclave, this time under more forcing conditions. A higher conversion to the desired product was obtained and distilled to furnish more perfluorinated pyridine. With several grams of this starting material in hand, a study to explore its reactivity and utility as a core scaffold for elaboration was undertaken.

6.4.2 Reaction with Butylamine

Reaction of **55** with butylamine gave two products, the presence of fluorine resonances in ^{19}F NMR enabling the assignment to be made and, as is often the case in these substitution reactions of perfluorinated pyridines, providing a useful probe for the selectivity of reaction. Purification of this reaction mixture was not carried out.

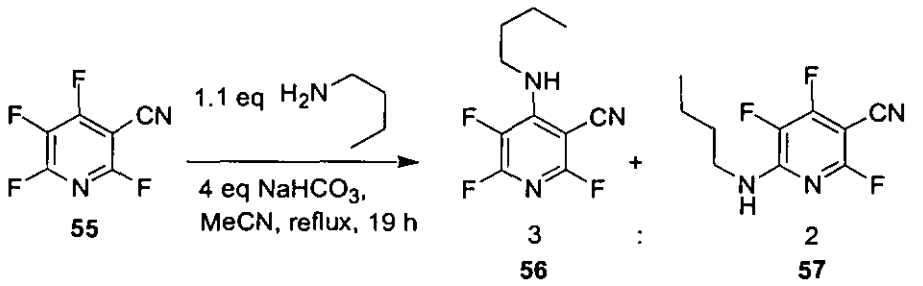

Figure 6.13 Reaction of **55** with butylamine (ratio calculated from ^{19}F NMR of crude)

The fact the major isomer is the 4-substituted pyridine reflects the sterically less demanding nature of fluorine atoms compared to chlorine atoms, with attack occurring at the *ortho* position to the cyano substituent as opposed to the *para* 6-position as observed in the reactions of the chlorinated analogues. That the major product resulted from attack adjacent to the -CN site meant the desired reaction with an amidine binucleophile be possible.

6.4.3 Reaction with Amidines

Reaction of **55** with benzamidine hydrochloride proceeded at room temperature to the two products shown in Figure 6.14, [6,6] pyridopyrimidine-fused heterocycle **58** being isolated by recrystallisation in good yield. The better selectivity towards attack at the 4-position compared to the reaction with butylamine presumably stems from interaction between the binucleophilic species and the nitrile group, providing a directing effect to this position.

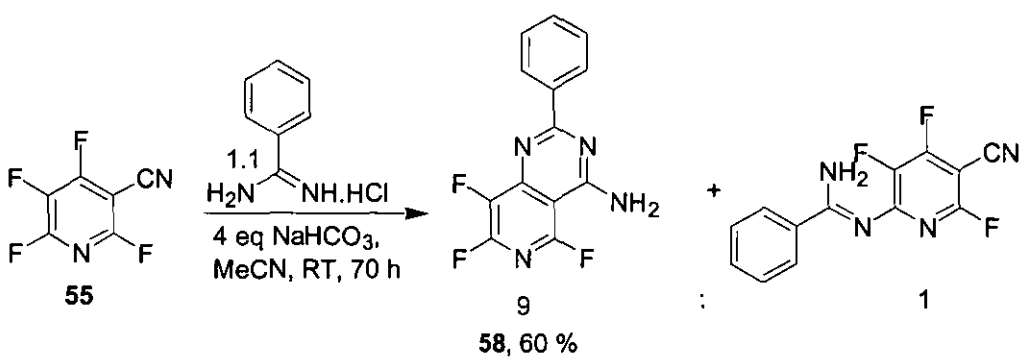

Figure 6.14 Reaction of **55** with benzamidine (ratio calculated from ^{19}F NMR of reaction mixture)

This experiment was repeated with acetamidine and formamidine hydrochloride to yield the 2-methyl **59** and -hydro **60** heterocycles respectively (Figure 6.15). The formation of the latter is interesting as this is the first and only example from the work reported herein of where formamidine has been used successfully to form a pyridine ring-fused heterocycle and this can be attributed to the mild reaction conditions (room temperature and weak base), which in turn is thanks to the highly reactive nature of the pyridine scaffold. In the case of the methyl-substituted system, a sample suitable for X-ray analysis was grown, leading to conformation of the annulated product (Figure 6.16).

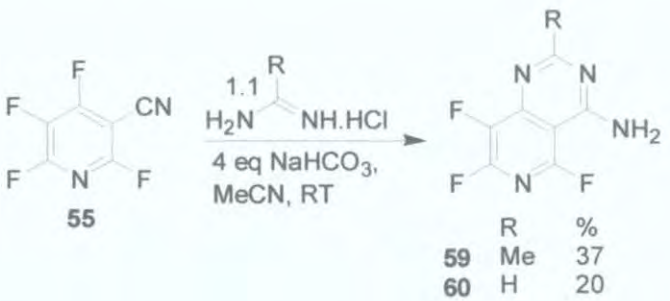

Figure 6.15 Reaction of **55** with acetamidine and formamidine

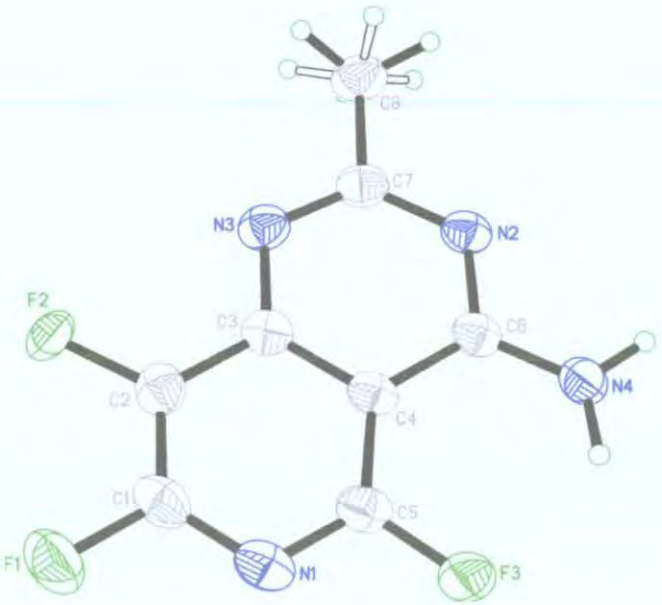

Figure 6.16 X-ray structure of **59**

Even without crystallographic evidence, cyclisation can be inferred by comparing the ^{13}C NMR shifts observed for the nitrile carbon in the starting material (106 ppm) and the respective products (159-160 ppm). This marked difference certainly shows that the nitrile group has changed.

It should be noted at this point that any trace of the 5-chloro intermediate from the synthesis of **55** results in its similar reaction to form a highly insoluble pyridine-fused ring. In some cases, even a small amount of this impurity precluded its removal via recrystallisation or column chromatography. Thus, **55** must be distilled to high purity to ensure minimal formation of byproduct.

6.5 2,4,5,6-Tetrafluoro-nicotinonitrile as a Scaffold for [5,6] Fused-Ring Synthesis

Having shown 2,4,5,6-tetrafluoro-nicotinonitrile to be an effective scaffold for [6,6] fused heterocycle synthesis via the reaction with amidine binucleophiles, the reaction with hydrazine hydrate was explored to ascertain whether [5,6] synthesis be possible using a similar strategy. Carrying out the experiment under the typically employed base and solvent choice of sodium bicarbonate and acetonitrile, no starting material was observed after 39 h at room temperature. The reaction was worked up to give an orange crude product, recrystallisation of which gave a yellow solid. Though ^{19}F NMR of this sample consisted three resonances (-65, -90 and -165 ppm), indicating the desired substitution had taken place, mass spectrometry clearly showed the product not to be the expected [5,6] fused ring. This product has been tentatively labelled as **61**, forming via the following mechanism:

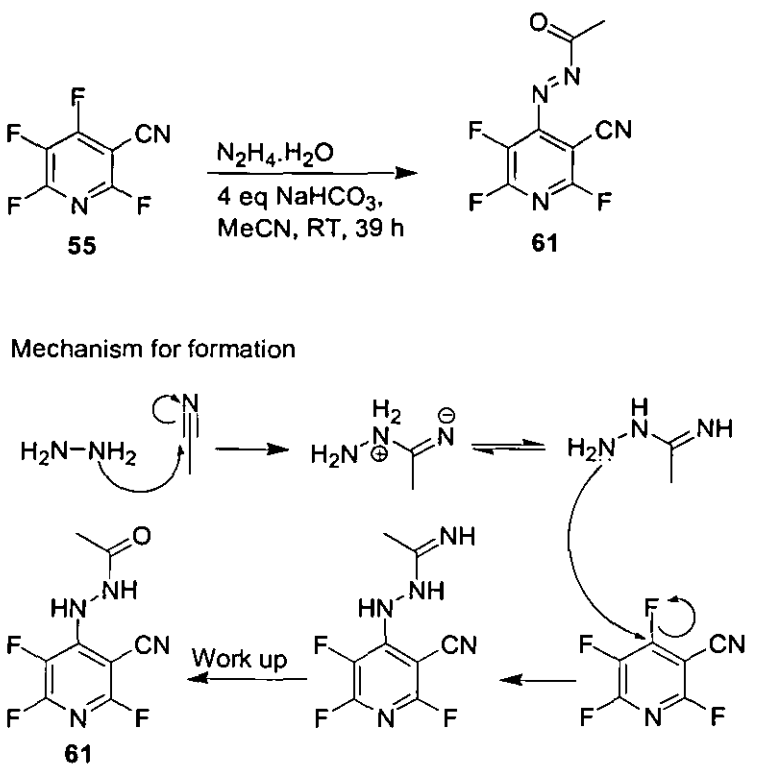

Figure 6.17

The reaction was repeated using ethanol as solvent, as in the condensation reaction between an *ortho*-chloro-nitrile species and hydrazine shown in Section 1.1.5. This time, analysis (NMR, MS, elemental analysis) of the resulting isolated product was consistent with the target molecule:

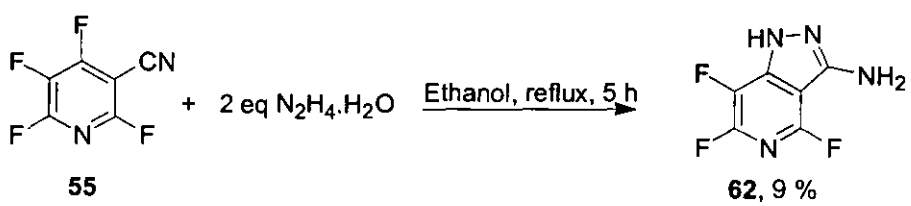

Figure 6.18 Formation of pyrazolopyridine **62**

Thus, in a single reaction, a highly functionalised and desirable pyrazolopyridine was obtained.

6.6 Conclusions

A small series of novel fused pyridopyridimidines have been synthesised in a short sequence from 2,4,5,6-tetrafluoro-nicotinonitrile, a compound never previously used as a core scaffold for derivatisation, by nucleophilic substitution. Exploration of this scaffold, through further nucleophilic substitution on the fluoropyridine core and derivatisation of the amino functionality, could yield a range of derivatised products.

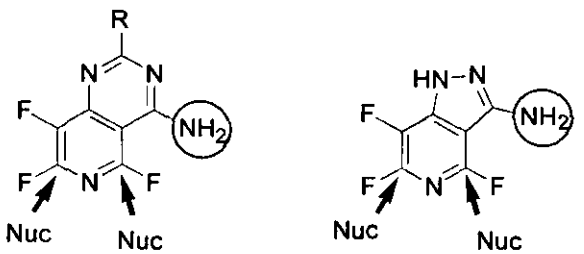

Figure 6.19

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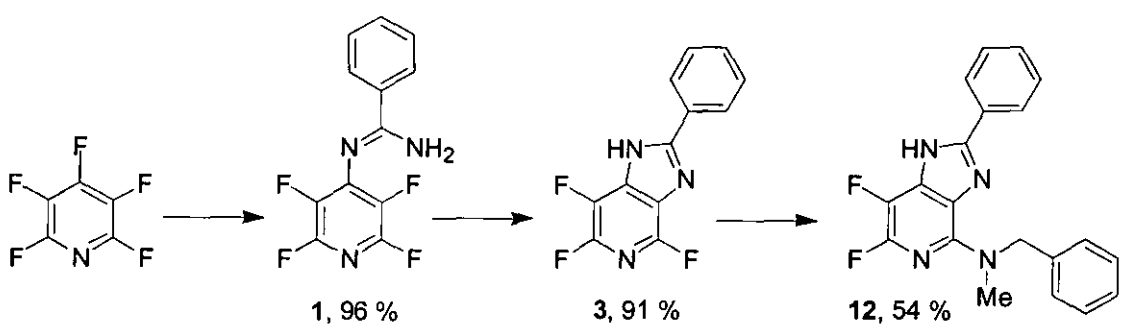
Chapter 7

Conclusions

The aim of this project was to develop methodology for the synthesis of highly functionalised fused-pyridines from fluorinated heterocycles via sequential nucleophilic substitution reactions. As stated in Chapter 1, there is a great demand for small, novel, "drug-like" heterocycles in the lead generation stage of drug discovery, and as such, the methodology developed herein could provide quick and efficient routes to library syntheses.

Pentafluoropyridine proved to be an excellent core scaffold when reacted with suitable binucleophilic species, giving access to highly interesting imidazopyridine and dipyridoimidazole (both fully and partially unsaturated) fused ring systems. Each core scaffold proved to undergo further nucleophilic substitution in a highly selective manner, giving further scope for rapid analogue synthesis. An example of the formation and derivatisation of imidazopyridine **3** is given below:



1, 96 % **3**, 91 % **12**, 54 %

Figure 7.1

Employment of 4-substituted tetrafluoropyridines also proved successful when a suitable electron withdrawing group (-SO_2Ph) was present on the ring and gave access to [2,3] imidazopyridine fused bicycles.

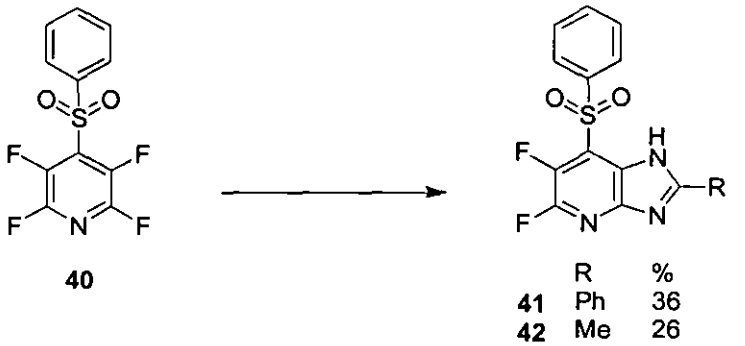


Figure 7.2

The presence of a cyano functionality on the core scaffold led to the surprising pyrimidine annulation rather than the expected 5-membered ring formation. This result widened the range of heterocycles obtainable and was exploited to give a small series of highly functionalised [5,6] and [6,6] heterocycles, in one pot processes, from a fluorinated heterocycle never previously studied as a substrate for nucleophilic attack.

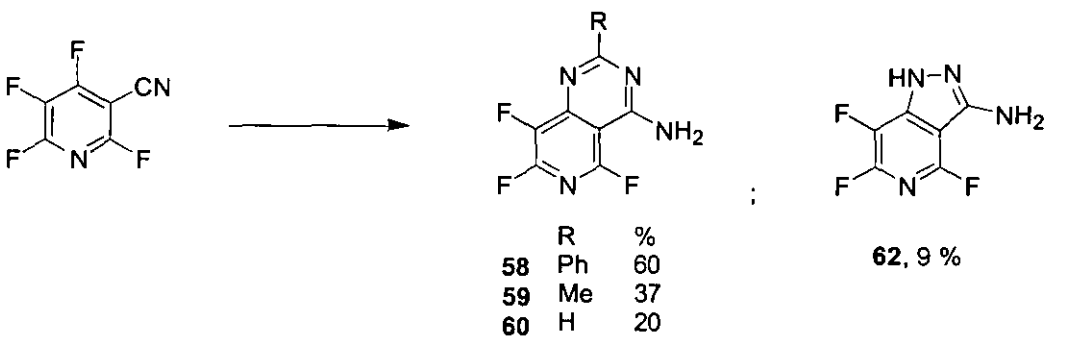


Figure 7.3

Overall, a range of polycyclic heterocycles were accessed bearing one, two or three fluorine atoms, from perfluoropyridine (five fluorine atoms) some of which are shown in Figure 7.4:

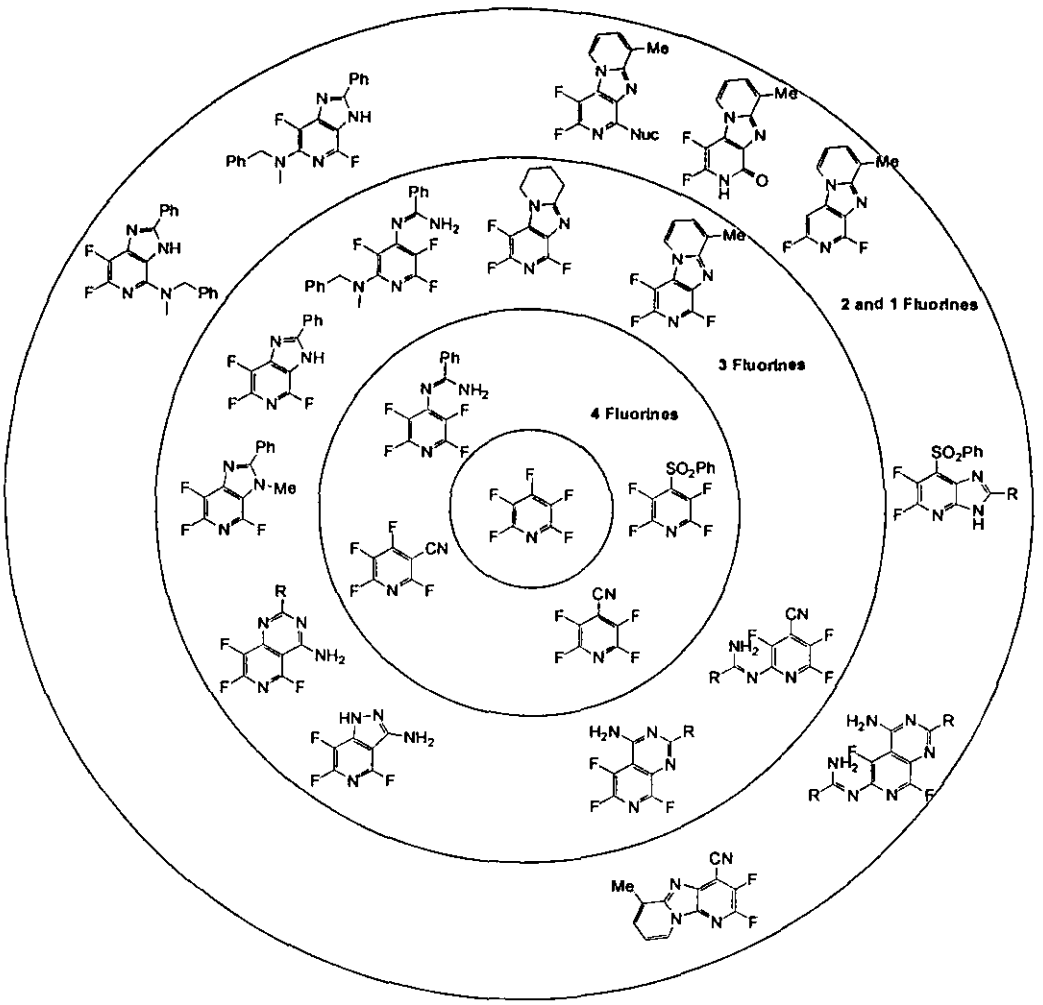


Figure 7.4

In the majority of the developed methodology, much scope remains for varying the functional groups upon the binucleophilic species employed for ring annulation as well as the nucleophilic species subsequently substituted onto the fused rings, in a parallel manner and as described in the Conclusions of Chapters two to five. This, along with the general amenability of the methodology to microwave synthesis, could provide access to a range of highly novel heterocycles in a quick and efficient manner.

To conclude, we have shown that a range of fused heterocycles of potential biological interest can be synthesised in a facile manner from pentafluoropyridine, or derivatives, using standard chemistry and mild reaction conditions. There exists considerable scope for library synthesis and, in this context, is of great interest to the pharmaceutical industry.

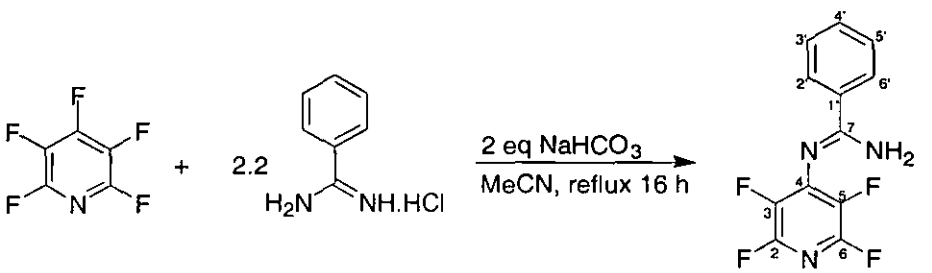
Chapter 8

Technical Detail

Ratios of products calculated from ^{19}F NMR of reaction mixture unless stated otherwise. All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem) or from GlaxoSmithKline's chemical stores, Stevenage. All solvents were dried using either literature procedures or via the Innovative Technology solvent purification system. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040-0.063 mm) or using the Biotage Horizon flash chromatography system and TLC analysis was performed on silica gel or aluminium oxide TLC plates. NMR spectra were recorded in deuteriocholoroform, 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 trichlorofluoromethane as an internal standard (^{19}F NMR). Mass spectra were recorded on a Thermo Finnigan TRACE GCMS system and a Waters Micromass LCT spectrometer. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless stated and are uncorrected. The progress of reactions were monitored by either ^{19}F NMR or LCMS analysis. All crystallographic data was collected at T = 120 K on a Bruker SMART-CCD 6000 diffractometer (λMoKα, ω-scan, 0.3 ^{o}/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.

Experimental to Chapter 2

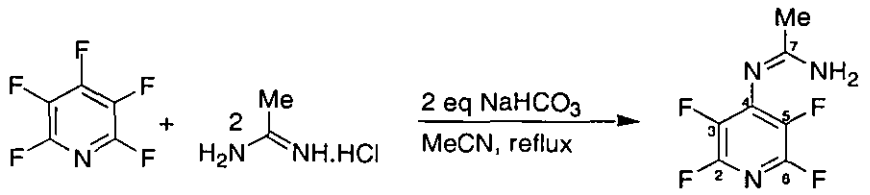
N-(2,3,5,6-tetrafluoro-pyridin-4-yl) benzamidine, **1**



1, 96 %

Pentafluoropyridine (6.76 g, 40.0 mmol), benzamidine hydrochloride (13.78 g, 88.0 mmol) and sodium hydrogen carbonate (6.72 g, 80.0 mmol) were stirred under an atmosphere of argon in MeCN (400 ml) for 16 h at reflux temperature. The reaction was poured onto water (50 ml) and extracted with DCM (3 x 40 ml). Drying ($MgSO_4$) and evaporation of the organic layer gave *N-(2,3,5,6-tetrafluoro-pyridin-4-yl) benzamidine* **1** (10.35 g, 96 %) as a white solid; mp 157-159 ^{0}C; (Found: C, 53.4; H, 2.6; N, 15.7. $C_{12}H_7N_3F_4$ requires: C, 53.4; H, 2.6; N, 15.6%); δ_F (Acetone-d_6) -94.90 (2F, m, F- 2), -153.88 (2F, m, F-3); δ_H 8.01 (2H, m, H- 2'), 7.56 (1H, m, H- 4'), 7.49 (2H, m, H- 3'), 7.02 (2H, s, NH_2); δ_C 159.44 (s, C-7), 144.73 (dm, $^1J_{CF}$ 236.6, C-2), 143.72 (m, C-4), 136.53 (dm, $^1J_{CF}$ 236.8, C-3), 134.94 (s, C-1'), 132.31 (s, C-4'), 129.32 (s, C-3'), 128.37 (s, C-2'); *m/z* (EI$^+$) 269 (M^+, 100 %), 253 (M^+ - NH_2, 72 %), 249.0 (M^+ - HF, 90 %,), 77.0 (C_6H_5, 94 %).

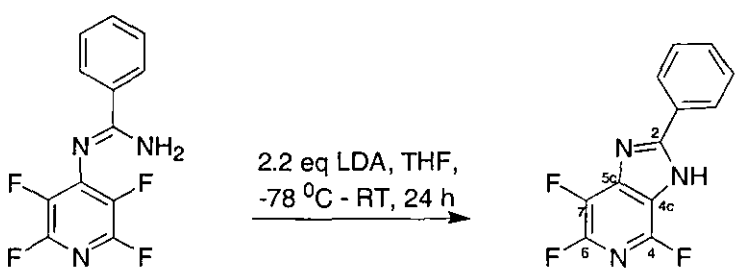
N-(2,3,5,6-tetrafluoro-pyridin-4-yl) acetamidine, **2**



2, 88 %

Pentafluoropyridine (3.38 g, 20.0 mmol), acetamidine hydrochloride (4.16 g, 44.0 mmol) and sodium hydrogen carbonate (3.36 g, 40.0 mmol) were stirred under argon in MeCN (200 mL) for 17 h at reflux temperature. The reaction solvent was evaporated and the remaining residue treated with water (50 ml). Extraction by DCM (3 x 40 ml), drying ($MgSO_4$) and evaporation of solvent gave *N-(2,3,5,6-tetrafluoro-pyridin-4-yl) acetamidine* **2** (3.64 g, 88 %) as an off-white solid; mp 142-145 °C; (Found: C, 40.6; H, 2.4; N, 20.2. $C_7H_5F_4N_3$ requires: C, 40.6; H, 2.4; N, 20.3 %); δ_F (DMSO-d_6) -94.96 (m, F-2), -154.09 (m, F-3); δ_H 7.42, 6.94 (2H, br s, NH_2), 1.97 (3H, s, CH_3); δ_C 161.15 (s, C-7), 143.34 (dm, $^1J_{CF}$ 237.3, C-2), 142.96 (m, C-4), 135.49 (dm, $^1J_{CF}$ 249.5, C-3), 20.65 (s, CH_3); *m/z* (EI^+) 207.0 (M^+, 100 %), 192.0 (M^+ - CH_3, 82 %).

4,6,7-trifluoro-2-phenyl-3H-imidazo[4,5-c] pyridine, **3**



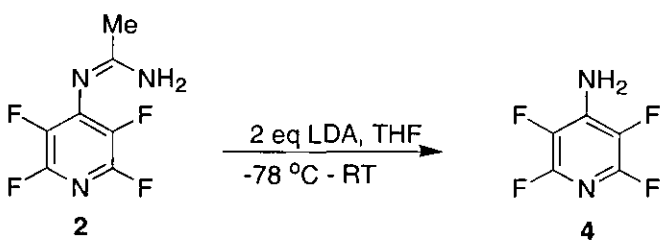
1

3, 91 %

LDA (17.19 mL 1.8 M solution in heptane/THF/ethylbenzene, 30.9 mmol) was added to a stirring solution of N-(2,3,5,6-tetrafluoro-pyridin-4-yl) benzamidine **1** (3.79 g, 14.1 mmol) in dry THF (250 mL) at -78 °C, under an atmosphere of dry argon. After warming to room temperature, the solution was stirred at room temperature for 24 h. The reaction mixture was evaporated and 50 mL 0.5 M HCl solution added. Extraction

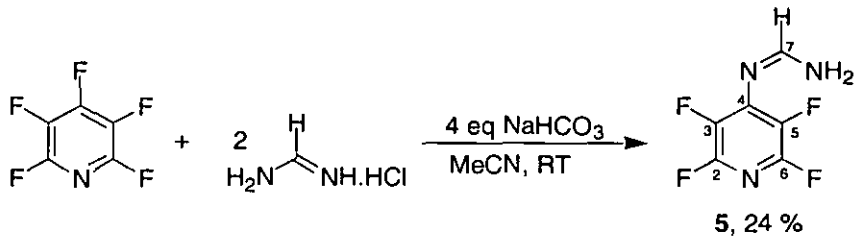
of the organic layer (DCM, 3 x 40 mL) followed by evaporation gave a brown crude solid. Recrystallisation from MeCN gave *4,6,7-trifluoro-2-phenyl-3H-imidazo[4,5-c] pyridine* **3** (3.20 g, 91 %) as an off-white solid and as a mixture of tautomers; mp 208-209 ^{0}C; (Found: C, 57.8; H, 2.4; N, 17.0. $C_{12}H_6N_3F_3$ requires: C, 57.8; H, 2.4; N,16.9 %); δ_F (DMSO-d_6) major tautomer (67 % by ^{19}F NMR) -83.08 (1F, br s, F-6), -102.02 (1F, br s, F-4), -161.60 (1F, br s, F-7); minor tautomer (33 %) -82.60 (1F, br s, F-6), -104.33 (1F, br s, F-4), -163.00 (1F, br s, F-7); δ_H 8.18 (2H, br m, H-2'), 7.56-7.52 (3H, br m, H-3',4'); δ_C 155.42 (br m, C-2), 143.80 (dm, RH peak obscured, C-4), 142.50 (dm, $^{1}J_{CF}$ 228.5, C-6), 135.20 (br m, C-5c), 131.25 (s, C-4'), 128.95 (s, C-3'), 128.07 (s, C-1'), 127.26 (s, C-2'); *m/z* (EI$^+$) 249.0 (M$^+$, 100 %).

Attempted Cyclisation of N-(2,3,5,6-tetrafluoro-pyridin-4-yl) acetamidine



LDA (1.11 mL 1.8 M solution in heptane/THF/ethylbenzene, 2.0 mmol) was added to a stirring solution of *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl) acetamidine **2** (0.21 g, 1.0 mmol) in dry THF (25 mL) at -78 ^{0}C, under an atmosphere of dry argon. After warming to room temperature, the solution was stirred at room temperature for 65 h. ^{19}F NMR of the reaction mixture showed 2 new peaks (-96, -165 ppm). GCMS of the worked up crude had a major peak (7.8 min); m/z (EI) 165.9 (M$^+$, 100 %). This data corresponds to 4-amino-tetrafluoropyridine **4**.

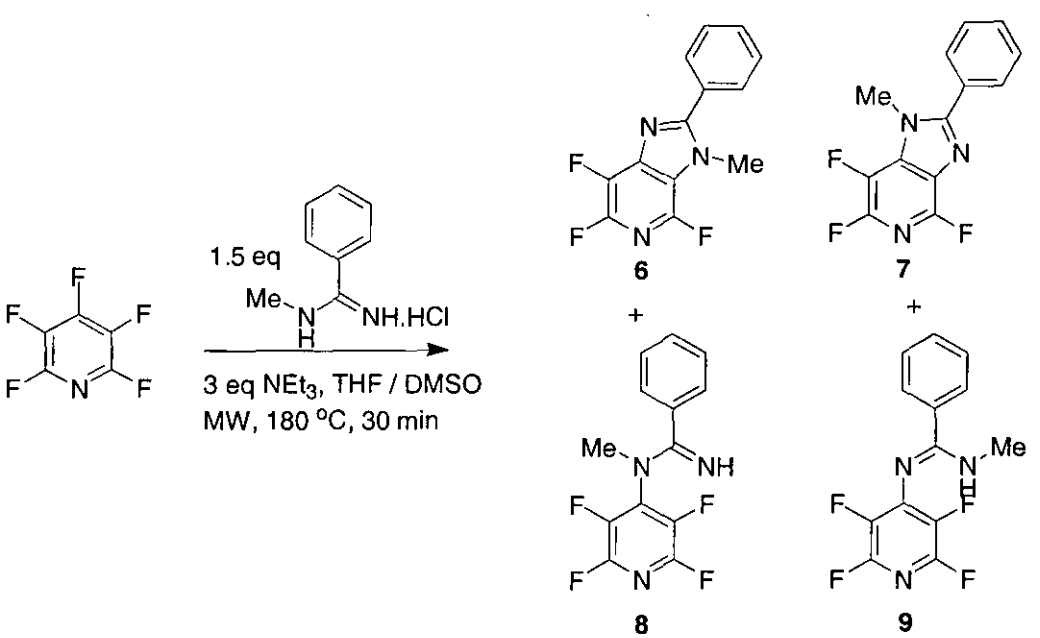
N-(2,3,5,6-tetrafluoro-pyridin-4-yl) formamidine, **5**



5, 24 %

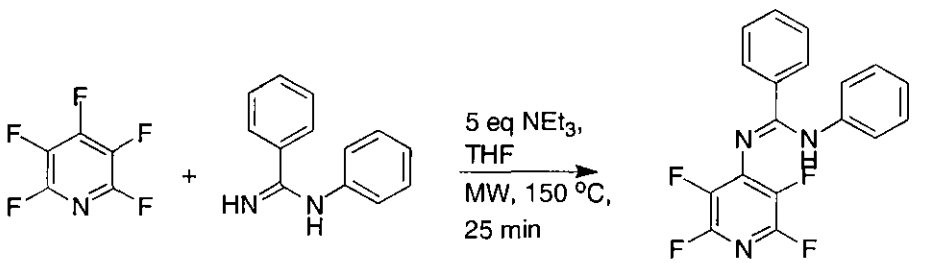
Pentafluoropyridine (1.69 g, 10.0 mmol), formamidine hydrochloride (1.61 g, 20.0 mmol) and sodium hydrogen carbonate (3.36 g, 40.0 mmol) were stirred under argon in MeCN for 23 h at room temperature. The reaction mixture was treated with water (50 ml) and the organic products extracted into DCM (3 x 40 ml). The organic phase was dried ($MgSO_4$) and the solvent evaporated to give a white crude. Recrystallisation from MeCN gave *N-(2,3,5,6-tetrafluoro-pyridin-4-yl) formamidine* **5** (0.47 g, 24 %) as a white crystalline solid; mp 168-170 °C; (Found: C, 37.2, H, 1.5, N, 21.8. $C_6H_3N_3F_4$ requires: C, 37.3; H, 1.6; N, 21.8 %); δ_F (DMSO-d_6) -95.17 (2F, m, F-2), -156.89 (2F, br m, F-3); δ_H 7.95 (3H, br m, NH_2, H-7); δ_C 157.66 (s, C-7), 143.73 (m, C-4), 143.38 (dm, $^1J_{CF}$ 236.5, C-2), 135.97 (dm, $^1J_{CF}$ 248.9, C-3); m/z (EI) 193.0 (M^+, 95 %).

Reaction of Pentafluoropyridine with N-methyl-benzamidine hydrochloride



Pentafluoropyridine (0.0200 g, 0.1183 mmol), *N*-methyl-benzamidine hydrochloride (0.0303 g, 0.1776 mmol) and triethylamine (0.0359 g, 0.3549 mmol) were stirred together, in a mixture of THF (0.75 mL) and DMSO (0.30 mL), in a sealed microwave vial at 180 °C for 30 min. LCMS of the reaction mixture consisted of two peaks; the first at 3.1 min (24 % by TIC trace) with $M^+ + H^+$ 264.1 and the second at 3.3 min (76 %) with $M^+ + H^+$ 284.0. MDAP of the crude yielded *4,6,7-trifluoro-3-methyl-2-phenyl-3H-imidazo[4,5-c]pyridine* **6** and *4,6,7-trifluoro-1-methyl-2-phenyl-1H-imidazo[4,5-c]pyridine* **7** as a white solid (0.0031 g, 10 %); δ_F Major isomer -81.33 (J_{FF} 32.6, J_{FF} 12.7), -100.31 (J_{FF} 20.3, J_{FF} 12.8), -169.52 (J_{FF} 32.7, J_{FF} 20.7); Minor isomer -86.72 (1F, m), -102.39, -162.03 (dd, J_{FF} 32.5, J_{FF} 19.2,). *N-Methyl-N'-(2,3,5,6-tetrafluoro-pyridin-4-yl)-benzamidine* **8** and *N-methyl-N-(2,3,5,6-tetrafluoro-pyridin-4-yl)-benzamidine* **9** were also isolated as a white solid (0.0039 g, 12 %); δ_F -91.30 (br m), -152.58 (br m).

N-phenyl-N'-(2,3,5,6-tetrafluoro-pyridin-4-yl)-benzamidine, **10**

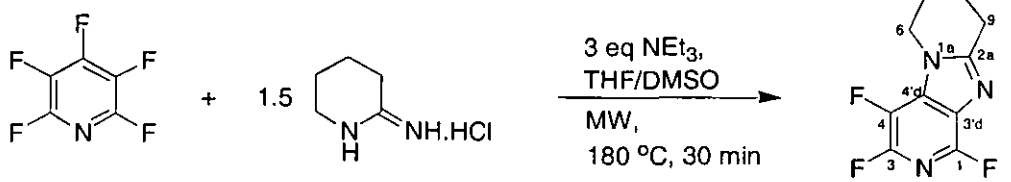


10, 32 %

Pentafluoropyridine (0.51 g, 3.0 mmol), *N*-phenyl-benzamidine (0.59 g, 3.0 mmol) and triethylamine (1.52 g, 15.0 mmol) were stirred together in THF (7.5 mL), in a sealed microwave vial, for 25 min at 150 °C. ^{19}F NMR showed starting material and 2 new products. The reaction mixture was evaporated, poured onto water (20 mL) and the organic products extracted into DCM (3 x 15 mL). Drying ($MgSO_4$) and evaporation of the combined extracts gave a yellow crude. Column chromatography (silica) yielded *N-phenyl-N'-(2,3,5,6-tetrafluoro-pyridin-4-yl)-benzamidine* **10** (0.33 g, 32 %) as a pale yellow solid; mp 155-156 °C; ([M + H^+] 346.0961. $C_{18}H_{12}N_3F_4$ requires [M + H^+] 346.0967); δ_F -93.85 (2F, m, F-2), -154.93 (2F, m, F-3); δ_H 7.61 (br m, NH), 7.50-7.35 (9H, Ar-H), 7.18 (1H, m, Ar-H), 7.03 (br s, NH); δ_C 159.05 (s, NCN), 143.79 (dm, $^1J_{CF}$

238.3, C-2), 142.50 (m, C-4), 138.36 (s, Ph-C), 134.86 (dm, $^{1}J_{CF}$ 252.8, C-3), 134.16 (s, Ph-C), 131.44 (s, Ph-CH), 129.30 (s, Ph-CH), 129.26 (s, Ph-CH), 127.15 (s, Ph-CH), 125.21 (s, Ph-CH), 121.20 (s, Ph-CH); m/z (EI) 345.0 (M^+, 30 %), 343.9 (M^+ - 1, 50 %), 254.1 (M^+ - PhN, 30 %), 252.8 (M^+ - PhNH, 80 %), 76.5 (Ph, 100 %).

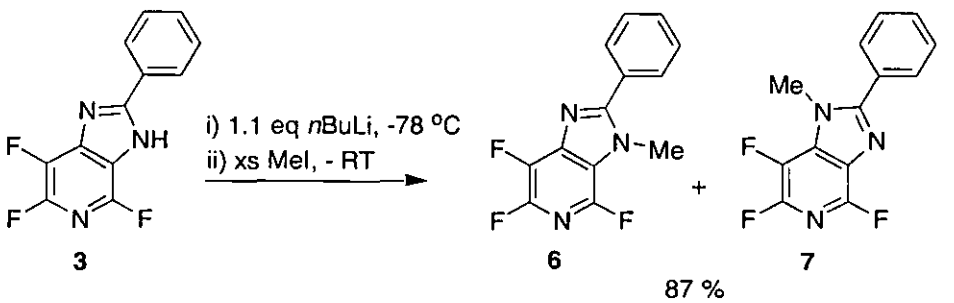
1,3,4-Trifluoro-6,7,8,9-tetrahydro-dipyrido[1,2-a; 3',4'-d]imidazole, **11**



11, 52 %

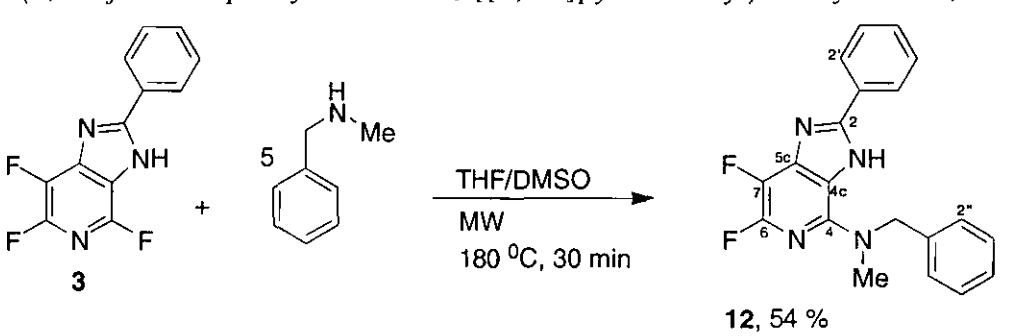
Pentafluoropyridine (0.30 g, 1.77 mmol), 2-iminopiperidine hydrochloride (0.36 g, 2.67 mmol) and triethylamine (0.54 g, 5.34 mmol) were stirred together in a mixture of THF (11.25 mL) and DMSO (4.50 mL), in a sealed 20 mL vial, under microwave heating, for 30 min at 180 °C. The reaction mixture was evaporated to dryness, heated in THF (50 mL) and filtered to remove excess starting material. The crude was absorbed onto silica and purified by column chromatography (120 g silica column, 40 – 80 % ethyl acetate in hexane over 30 min) to give *1,3,4-trifluoro-6,7,8,9-tetrahydro-dipyrido[1,2-a; 3',4'-d]imidazole* **11** (0.21 g, 52 %) as a white solid; mp 175-178 °C; (Found: C, 52.8; H, 3.4; N, 18.1. $C_{10}H_8N_3F_3$ requires: C, 52.9; H, 3.6; N, 18.5 %); δ_F (DMSO-d_6) -85.36 (dd, $^{3}J_{FF}$ 31.8, $^{4}J_{FF}$ 13.3, F-3), -104.36 (dd, $^{5}J_{FF}$ 22.0, $^{4}J_{FF}$ 13.4, F-1), -167.93 (m, F-4); δ_H 4.36 (2H, t, $^{3}J_{HH}$ 6.0, H-6), 3.01 (2H, t, $^{3}J_{HH}$ 6.0, H-9), 2.05 (2H, m, H-7), 1.93 (2H, m, H-8); δ_C 156.11 (q, $^{4}J_{CF}$ 1.3,C-2a), 143.06 (dd, $^{1}J_{CF}$ 244.5, $^{3}J_{CF}$ 14.2, C-1), 141.02 (ddd, $^{1}J_{CF}$ 227.7, $^{2}J_{CF}$ 15.2, $^{3}J_{CF}$ 15.0, C-3), 134.44 (ddd, $^{2}J_{CF}$ 11.7, $^{3}J_{CF}$ 7.7, $^{3}J_{CF}$ 5.8, C-4'd), 129.57 (ddd, $^{1}J_{CF}$ 253.71, $^{2}J_{CF}$ 32.0, $^{4}J_{CF}$ 7.8, C-4), 125.57 (dd, $^{2}J_{CF}$ 34.8, $^{3}J_{CF}$ 3.2, C-3'd), 44.91 (d, $^{4}J_{CF}$ 2.8, C-6), 24.97 (s, C-9), 21.65 (s, C-7), 19.17 (s, C-8); *m/z* (ES^+) 228.05 ($M^+ + H^+$, 100 %).

4,6,7-trifluoro-3-methyl-2-phenyl-3H-imidazo[4,5-c]pyridine, **6**, and *4,6,7-trifluoro-1-methyl-2-phenyl-1H-imidazo[4,5-c]pyridine*, **7**



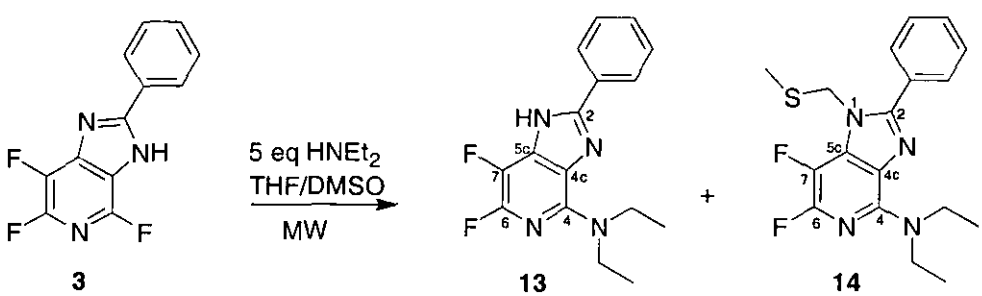
nBuli (1.4 mL, 1.6 M soln in hexanes) was syringed into a stirring solution of **3** (0.49 g, 2.0 mmol) in THF (40 mL), at -78 °C. After 1 h, methyl iodide (0.37 mL, 6.0 mmol) was syringed into the reaction mixture and the vessel allowed to warm to room temperature. After 18 h, the resulting mixture was poured onto water (50 mL) and extracted into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of solvent gave a pale yellow solid. Column chromatography on silica (ethyl acetate:hexane, 1:1) yielded *4,6,7-trifluoro-3-methyl-2-phenyl-3H-imidazo[4,5-c]pyridine* **6** and *4,6,7-trifluoro-1-methyl-2-phenyl-1H-imidazo[4,5-c]pyridine* **7** (0.46 g, 87 %) as an inseparable mixture of tautomers; m.p. 103-106 °C; (Found: C, 59.3; H, 3.0; N, 16.0. $C_{13}H_8F_3N_3$ requires: C, 59.3; H, 3.1; N, 16.0 %); δ_F major tautomer (52 % by ^{19}F NMR) -81.59 (dd, $^3J_{FF}$ 32.3, $^4J_{FF}$ 12.9, F-6), -100.51 (dd, $^5J_{FF}$ 20.6, $^4J_{FF}$ 13.1, F-4), -169.39 (dd, $^3J_{FF}$ 32.6, $^5J_{FF}$ 20.8, F-7); minor tautomer (48 %) -86.67 (dd, $^3J_{FF}$ 32.8, $^4J_{FF}$ 13.9, F-6), -102.59 (dd, $^5J_{FF}$ 18.8, $^4J_{FF}$ 14.2, F-4), -162.18 (dd, $^3J_{FF}$ 33.0, $^5J_{FF}$ 19.1, F-7); δ_H 7.77-7.52 (m, Ar-H), 4.05 (m, CH_3); δ_C 159.79-119.61, 34.09 (m, CH_3); m/z (EI) 263.0 (M^+, 60 %), 261.8 (100 %).

Benzyl-(6,7-difluoro-2-phenyl-3H-imidazo[[4,5-c]pyridine-4-yl)-methyl-amine, **12**



4,6,7-Trifluoro-2-phenyl-3H-imidazo[4,5-c] pyridine **3** (0.0555 g, 0.2227 mmol) and *N*-benzylmethylamine (0.1349 g, 1.1132 mmol) were stirred together in THF (2.25 mL) and DMSO (0.90 mL) at 180 °C (microwave) for 30 minutes. LCMS of the reaction mixture showed no starting material. The reaction solvents were evaporated and the orange crude dissolved in MeOH:DMSO (1:1 mixture, 2 mL). This mixture was subjected to mass directed auto purification (x2 injections). Evaporation under reduced pressure gave *benzyl-(6,7-difluoro-2-phenyl-3H-imidazo[4,5-c]pyridine-4-yl)-methyl-amine* **12** as a white solid (0.0424 g, 54 %); mp 79 – 83 ^{0}C; ([M + H$^+$] 351.1416. $C_{20}H_{16}F_2N_4$ requires [M + H$^+$] 351.1416); δ_F (DMSO-d_6) -100.09 (1F, d, $^3J_{FF}$ 27.1, F-6), -174.97 (1F, d, $^3J_{FF}$ 26.9, F-7); δ_H (DMSO-d_6) 10.05 (1H, br s, NH), 7.99-7.89 (2H, m, H-2'), 7.50-7.43 (3H, m, H-3', 4'), 7.37 (2H, d, $^3J_{HH}$ 7.6, H-2''), 7.33 (2H, t, $^3J_{HH}$ 7.6, H-3''), 7.27 (1H, t, $^3J_{HH}$ 7.6, H-4''), 5.34 (2H, CH_2), 3.35 (3H, s, CH_3); δ_C ($CDCl_3$) 149.12 (m, C-2), 144.92 (dd, $^1J_{CF}$ 222.1, $^2J_{CF}$ 11.4, C-6), 144.63 (m, C-4), 138.94 (m, C-1''), 130.22 (s, C-4'), 129.04 (s, C-3'), 128.46 (s, C-3''), 127.81 (s, C-2''), 127.05 (s, C-4''), 126.22 (s, C-2'), 54.58 (s, CH_2), 36.93 (s, CH_3); *m/z* (ES$^+$) 351.1 (M$^+$ + H$^+$, 100 %). Crystals suitable for X-ray analysis were grown from MeCN.

6,7-Difluoro-2-phenyl-1H-imidazo[4,5-c]pyridine-4-yl)-diethyl-amine, **13**, *and (6,7-difluoro-1-methylsulfanylmethyl-2-phenyl-1h-imidazo[4,5-c]pyridine-4-yl)-diethyl-amine*, **14**



13:

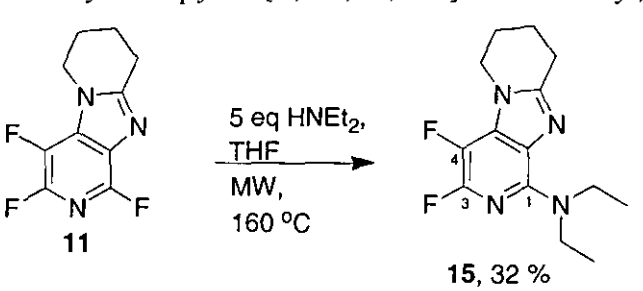
3 (0.0185 g, 0.0742 mmol) and diethylamine (0.0272 g, 0.3715 mmol) were stirred together in THF (0.75 mL) and DMSO (0.30 g), under microwave heating at 180 °C, for 30 min. LCMS of the reaction mixture indicated 71 % conversion to one product. The reaction mixture was evaporated to dryness and purified by reverse phase HPLC to give *6,7-Difluoro-2-phenyl-1H-imidazo[4,5-c]pyridine-4-yl)-diethyl-amine* **13** (0.0051 g, 23

%) as a yellow solid; δ_F (DMSO-d_6) -99.79 (1F, d, $^3J_{FF}$ 27.8, F-6), -176.21 (1F, d, $^3J_{FF}$ 27.9, F-7); δ_H 13.58 (1H, br s, NH), 8.14 (2H, m, H-2'), 7.57-7.47 (3H, m, H-3',4'), 3.89 (4H, q, $^3J_{HH}$ 6.9, CH_2), 1.21 (6H, t, $^3J_{HH}$ 6.9, CH_3); δ_C 149.83 (s, C-2), 143.96 (dd, $^1J_{CF}$ 216.7, $^2J_{CF}$ 11.4, C-6), 143.01 (d, $^3J_{CF}$ 14.0, C-4), 132.64 (dd, $^2J_{CF}$ 9.4, $^3J_{CF}$ 7.4, C-5c), 129.90 (s, C-4'), 129.28 (s, C-1'), 128.94 (s, C-3'), 126.99 (m, C-4c), 126.26 (s, C-2'), 122.52 (dd, $^1J_{CF}$ 244.3, $^2J_{CF}$ 36.2, C-7), 42.88 (s, CH_2), 13.50 (s, CH_3); *m/z* (ES^+) 303.08 ($M^+ + H^+$, 100 %).

14:

A mixture of **3** (0.0370 g, 0.1486 mmol) and diethylamine (0.0543 g, 0.7424 mmol) were stirred together in THF (0.3750 mL) and DMSO (0.1500 mL) for 4.5 h at 180 °C. The reaction solvents were evaporated and the crude dissolved in MeOH:DMSO (1:1, 1 mL). Mass directed auto purification of this sample gave *(6,7-difluoro-1-methylsulfanylmethyl-2-phenyl-1H-imidazo[4,5-c]pyridine-4-yl)-diethyl-amine* **14** (0.0060 g, 11 %) as a red solid; (Found: $M^+ + H^+$ 363.1445. $C_{18}H_{21}N_4F_2S$ requires: $M^+ + H^+$ 363.1455); δ_F -99.33 (1F, d, $^3J_{FF}$ 30.1, F-6), -181.14 (1F, d, $^3J_{FF}$ 30.1, F-7); δ_H 7.77 (2H, m, H-2'), 7.56 (3H, m, H-3', 4'), 5.37 (2H, s, SCH_2), 3.94 (4H, q, $^3J_{HH}$ 6.9, NCH_2), 2.00 (3H, s, SCH_3), 1.28 (6H, t, $^3J_{HH}$ 7.0, $NCH_2\mathbf{H_3}$); δ_C 151.11 (s, C-2), 145.57 (dd, $^1J_{CF}$ 220.5, $^2J_{CF}$ 12.6, C-6), 143.88 (d, $^3J_{CF}$ 17.6 C-4), 132.92 (m, C-5c) 129.95 (s, C-4'), 129.60 (s, C-2'), 129.51 (s, C-1'), 128.88 (s, C-3'), 125.90 (m, C-4c), 123.46 (dd, $^1J_{CF}$ 243.5, $^2J_{CF}$ 36.4, C-7), 48.91 (d, $^4J_{CF}$ 5.2, NCH_2S), 43.47 (s, NCH_2), 14.49 (d, $^6J_{CF}$ 2.0, SCH_3), 13.60 (s, $NCH_2\mathbf{C}H_3$); *m/z* (ES^+) 363.1 ($M^+ + H^+$, 100 %).

3,4-difluoro-6,7,8,9-tetrahydro-dipyrido[1,2-a; 3',4'-d]imidazol-1-yl)-diethyl-amine, **15**

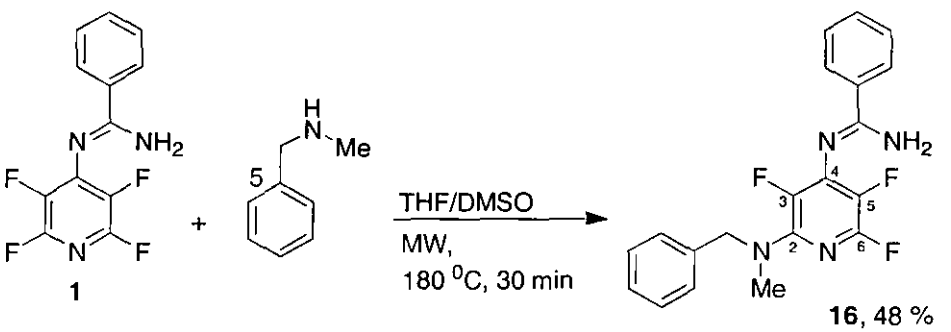


11 **15**, 32 %

A mixture of **11** (0.05 g, 0.22 mmol) and diethylamine (0.080 g, 1.10 mmol) were stirred together in THF (4 mL) for 5 h in a sealed microwave vial at 160 °C. ^{19}F NMR

indicated clean conversion (78 % by integration) to a compound with 2 fluorine resonances (-107 and -189 ppm). The reaction was evaporated and poured onto water (20 mL). Extraction of the products with DCM (3 x 15 mL), drying of the organic layer ($MgSO_4$) and evaporation gave a crude solid. Purification by HPLC gave *3,4-difluoro-6,7,8,9-tetrahydro-dipyrido[1,2-a; 3',4'-d]imidazol-1-yl)-diethyl-amine* **15** (0.02 g, 32 %) as a pale yellow solid; δ_F -107.78 (1F, br s, F-3), -183.97 (1F, d, $^3J_{FF}$ 27.5, F-4); δ_H 4.29 (2H, td, $^3J_{HH}$ 6.3, $^4J_{HH}$ 1.4, H-6), 3.86 (4H, q, J_{HH} 7.1, $C\mathbf{H}_2CH_3$), 3.02 (2H, t, $^3J_{HH}$ 6.5, H-9), 2.09 (2H, m, H-7), 1.98 (2H, m, H-8), 1.20 (6H, t, $^3J_{HH}$ 6.9, $CH_2C\mathbf{H}_3$); *m/z* (ES^+) 281.1 ($M^+ + H^+$, 100 %).

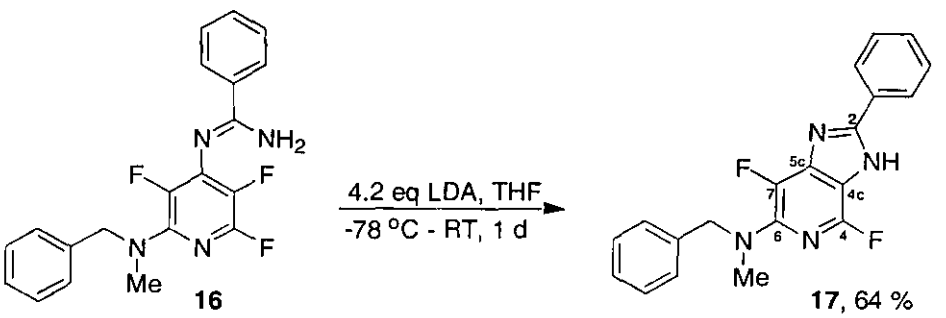
N-[2-(Benzyl-methyl-amino)-3,5,6-trifluoro-pyridin-4-yl]-benzamidine, **16**



N-(2,3,5,6-tetrafluoro-pyridin-4-yl) benzamidine **1** (0.40 g, 1.4859 mmol) and *N*-benzylmethylamine (0.9003 g, 7.4292 mmol) were stirred together in THF (7.50 mL) and DMSO (3.00 mL) in a 20 mL capped vial, at 180 °C (microwave) for 30 minutes. Evaporation of the reaction solvents gave a yellow crude product. Purification by HPLC gave *N-[2-(Benzyl-methyl-amino)-3,5,6-trifluoro-pyridin-4-yl]-benzamidine* **16** (0.26 g, 48 %) as a yellow solid; mp 106-110 °C; ([M + H^+] 371.1478. $C_{20}H_{17}F_3N_4$ requires [M + H^+] 371.1478); δ_F (DMSO-d_6) -93.73 (1F, t, J_{FF} 27.5, F-6), -144.51 (1F, d, $^3J_{FF}$ 26.7, F-5), -164.03 (1F, d, $^5J_{FF}$ 27.5 F-3); δ_H (DMSO-d_6) 7.93 (2H, m, Ar-H), 7.55-7.45 (3H, m, Ar-H), 7.37-7.24 (5H, m, Ar-H), 4.55 (2H, s, CH_2), 2.91 (3H, d, $^5J_{HF}$ 2.5, CH_3); δ_C ($CDCl_3$) 157.64 (s, $NCNH_2$), 144.67 (dd, $^1J_{CF}$ 226.4, $^2J_{CF}$ 13.1, C-6), 142.25 (dd, $^2J_{CF}$ 15.1, $^3J_{CF}$ 9.1, C-2), 140.20 (m, C-4), 138.76 (s, Ar-C), 137.63 (dm, $^1J_{CF}$ 245.5, C-3), 134.73 (s, Ar-C), 131.22 (s,Ar-CH), 130.29 (dd, $^1J_{CF}$ 243.5, $^2J_{CF}$ 32.2, C-5), 128.75 (s,

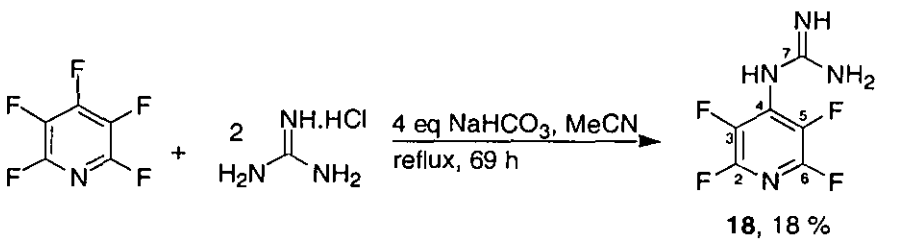
Ar-CH), 128.56 (s, Ar-CH), 127.74 (s, Ar-CH), 127.32 (s, Ar-CH), 55.15 (d, $^5J_{CF}$ 6.0, CH_2), 37 (d, $^5J_{CF}$ 5.0, CH_3); *m/z* (ES^+) 371.1 ($M^+ + H^+$, 100 %).

Benzyl-(4,7-difluoro-2-phenyl-3H-imidazo[4,5-c]pyridin-6-yl)-methyl-amine, **17**



LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.2 mL) was added to a stirring solution of *N*-[2-(benzyl-methyl-amino)-3,5,6-trifluoro-pyridin-4-yl]-benzamidine **16** (0.0351 g, 0.0948 mmol) in THF (5.0 mL) at -78 °C, under argon. After 1 h the reaction was warmed to room temperature and stirred for 4 h. The reaction was quenched with water (10 mL) and evaporated. Water (20 mL) was added to the crude mixture and HCl solution added to make acidic. Extraction of the organic products into DCM (3 x 20 mL) followed by drying ($MgSO_4$) yielded a brown crude product. Mass directed auto purification yielded *benzyl-(4,7-difluoro-2-phenyl-3H-imidazo[4,5-c]pyridine-6-yl)-methyl-amine* **17** (21.4 mg, 64 %) as a white solid; mp 121 °C (decomposed); (Found: C, 68.1; H, 4.6; N, 16.2. $C_{20}H_{16}F_2N_4$ requires: C, 68.6; H, 4.6; N, 16.0 %); δ_F (DMSO-d_6) -81.18 (1F, d, $^5J_{FF}$ 28.9, F- 4), -154.54 (1F, d, $^5J_{FF}$ 29.9, F-7); δ_H ($CDCl_3$) 8.03 (2H, m, Ar-H), 7.47 (3H, m, Ar-H), 7.31 (4H, m, Ar-H), 7.26 (1H, m, Ar-H), 4.65 (2H, s, CH_2), 3.04 (3H, d, $^5J_{HF}$ 2.6, CH_3); δ_C (DMSO-d_6) 141.08 (dd, $^2J_{CF}$ 15.0, $^3J_{CF}$ 6.6, C-6), 138.78 (s, Ar), 130.89 (s, Ar), 129.14 (s, Ar), 128.73 (s, Ar), 128.43 (s, Ar), 127.77 (s, Ar), 127.07 (s, Ar), 126.79 (s, Ar), 56.17 (d, $^4J_{CF}$ 5.2, CH_2), 37.78 (d, $^4J_{CF}$ 5.6, CH_3); *m/z* (ES^+) 351.1 ($M^+ + H^+$, 100 %).

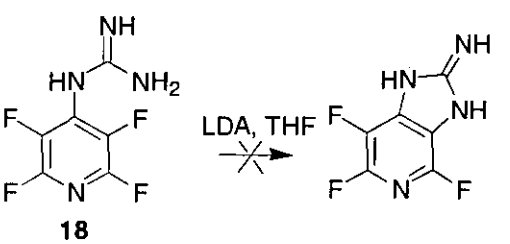
N-(2,3,5,6-Tetrafluoro-pyridin-4-yl)-guanidine, **18**



18, 18 %

Pentafluoropyridine (1.69 g, 10.0 mmol), guanidine hydrochloride (1.91 g, 20.0 mmol) and sodium hydrogencarbonate (3.36 g, 40.0 mmol) were refluxed together for 69 h. Evaporation of the reaction mixture followed by the addition of 50 mL water and extraction into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of the organic layer yielded an oil which solidified on standing to give *N-(2,3,5,6-tetrafluoro-pyridin-4-yl)-guanidine* **18** (0.38 g, 18 %) as a pale yellow solid; mp 132-135 °C; (Found: C, 34.7; H, 1.9; N, 27.0. $C_6H_4F_4N_4$ requires: C, 34.6; H, 1.9; N, 26.9 %); δ_F -97.01 (2F, m, F-2), -154.71 (2F, m, F-3); δ_H 6.17 (br s, NH); 156.39 (s, C-7), 143.59 (dm, $^1J_{CF}$ 234.1, C-2), 143.54 (m, C-4), 136.11 (dm, $^1J_{CF}$ 247.8, C-3); *m/z* (EI) 208.0 (M^+, 65 %), 43.1 ($NH{=}CNH_2$, 100 %)

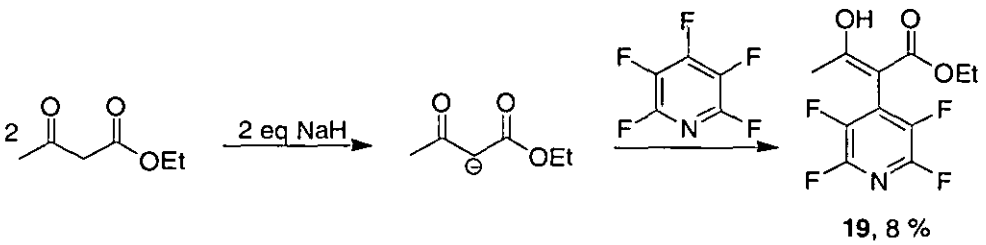
Attempted Cylisation of N-(2,3,5,6-tetrafluoro-pyridin-4-yl)-guanidine



18

LDA (0.61 mL, 1.8 M solution in heptane/THF/ethylbenzene, 1.10 mmol) was added to a stirring solution of (N-(2,3,5,6-tetrafluoro-pyridin-4-yl)-guanidine **18** (0.1041 g, 0.50 mmol) in THF (20 mL), at -78 °C. The solution was allowed to warm to room temperature after 2 h and stirred for a further 2 d, at which point ^{19}F NMR showed two new resonances (-102 and -164 ppm), corresponding to 2-amino-tetrafluoropyridine, and starting material only. Reflux of the solution for 2 h gave an identical ^{19}F NMR spectrum so the reaction was terminated.

3-Hydroxy-2-(2,3,5,6-tetrafluoro-pyridin-4-yl)-but-2-enoic acid ethyl ester, **19**



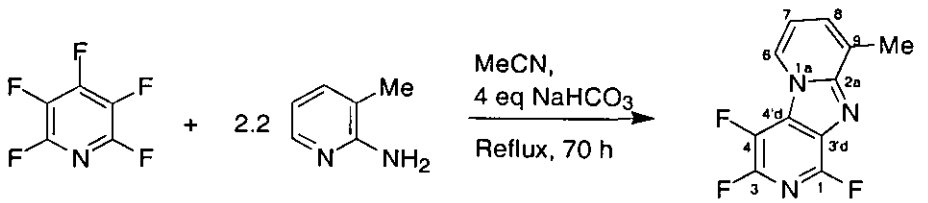
19, 8 %

Sodium hydride (1.20 g, 30.0 mmol 60 % suspension in mineral oil) was added to a stirring solution of pentafluoropyridine (2.56 g, 15.0 mmol) and ethyl acetoacetate (3.90 g, 30 mmol) in dry THF (50 ml). once the base had fully dissolved, the reaction mixture was refluxed at 65 ^{0}C for 70 h. ^{19}F NMR showed no starting material so the reaction was worked up. The reaction was poured onto water (50 ml) and the organic products extracted into dichloromethane (4 x 30 ml). Drying ($MgSO_4$) and evaporation of the solvent gave a colourless oil. Distillation under reduced pressure gave *3-hydroxy-2-(2,3,5,6-tetrafluoro-pyridin-4-yl)-but-2-enoic acid ethyl ester* **19** (0.33 g, 8 %) as a colourless oil; bp 32 °C, 0.50 mbar; (Found: C, 47.8; H, 3.4; N, 5.0. $C_{11}H_9F_4NO_3$ requires: C, 47.3; H, 3.3; N, 5.0 %); δ_F -91.70 (2F, m, F-2), -140.12 (2F, m, F-3); δ_H 13.52 (1H, s, OH), 4.22 (2H, q, $^3J_{HH}$ 7.1, $\mathbf{CH_2}CH_3$), 1.94 (3H, t, $^6J_{HF}$ 0.9, $COCH_3$), 1.21 (3H, t, $^3J_{HH}$ 7.0, $CH_2\mathbf{CH_3}$); δ_C 177.84 (s, $COOC_2H_5$), 170.05 ($\mathbf{C}OHCH_3$), 143.56 (dm, $^1J_{CF}$ 245.4, C-2), 140.41 (dm, $^1J_{CF}$ 257.3, C-3), 128.62 (m, C-4), 89.60 (d, $^3J_{CF}$ 2.3, C-7), 61.86 (s, $\mathbf{CH_2}CH_3$), 20.08 (s, $COH\mathbf{CH_3}$), 14.15 (s, $CH_2\mathbf{CH_3}$); m/z (EI) 278.9 (M^+, 78 %), 42.8 ($COCH_3$, 100 %).

Chapter 9

Experimental to Chapter 3

1,3,4-Trifluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole, **20**



20, 82 %

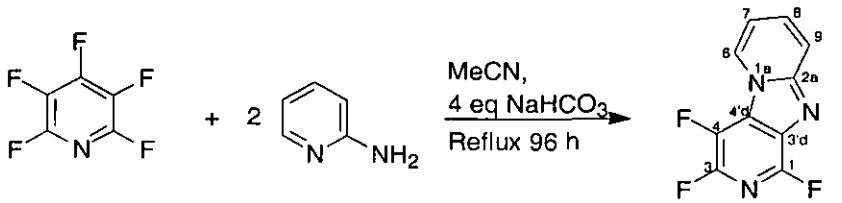
Pentafluoropyridine (1.69 g, 10.0 mmol), 2-amino-3-picoline (2.38 g, 22.0 mmol) and sodium hydrogen carbonate (3.36 g, 40.0 mmol) were stirred in dry MeCN (200 mL) at reflux temperature, under an atmosphere of argon, for 70 h. ^{19}F NMR of the reaction mixture showed no starting material remaining. Evaporation of the reaction and addition of water (50 mL) was followed by extraction into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of the solvent yielded a green solid. Recrystallisation from MeCN yielded *1,3,4-trifluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole* **20** (1.94 g, 82 %) as a white solid; mp 174-176 °C; (Found; C, 55.6; H, 2.5; N, 17.8. $C_{11}H_6F_3N_3$ requires; C, 55.5; H, 2.6; N, 17.7 %.); δ_F -79.01 (1F, dd, $^3J_{FF}$ 34.8, $^4J_{FF}$ 13.7, F-3), -102.43 (1F, dd, $^5J_{FF}$ 20.1, $^4J_{FF}$ 12.8, F-1), -164.73 (1F, dd, $^3J_{FF}$ 33.7, $^5J_{FF}$ 20.1, F-4); δ_H 8.49 (1H, d, $^3J_{HH}$ 7.1, H-6), 7.36 (1H, dm, $^3J_{HH}$ 6.9, H-8), 6.93 (1H, m, H-7), 2.67 (3H, s, CH_3); δ_C 151.07 (s, C-2a), 145.22 (dd, $^1J_{CF}$ 251.3, $^2J_{CF}$ 14.5, C-3), 140.94 (dm, $^1J_{CF}$ 233.9, C-1), 131.17 (ddd, $^1J_{CF}$ 257.1, $^2J_{CF}$ 32.8, $^4J_{CF}$ 8.7, C-4), 129.87 (s, C-8), 129.44 (S, C-9), 128.24 (m, C-3'd), 127.63 (dd, $^2J_{CF}$ 35.3, $^3J_{CF}$ 3.8, C-4'd), 124.93 (d, $^4J_{CF}$ 5.1, C-6), 113.20 (s, C-7), 17. 57 (s, CH_3); *m/z* (EI) 237.0 (M^+, 60 %). Crystals suitable for X-ray analysis were grown from MeCN.

Microwave Mediated Formation of **20**

Pentafluoropyridine (0.0200 g, 0.1183 mmol), 2-amino-3-picoline (0.0192 g, 0.1775 mmol) and triethylamine (0.0359 g, 0.3549 mmol) were stirred together in THF (0.75

mL) and DMSO (0.30 mL), under microwave heating, for 15 min at 160 °C. The reaction was evaporated to remove NEt_3 and the reaction solvents. ^1H NMR (DMSO-d) of the crude showed there to be 100 % clean conversion to **20**. No further work up or purification carried out at this point.

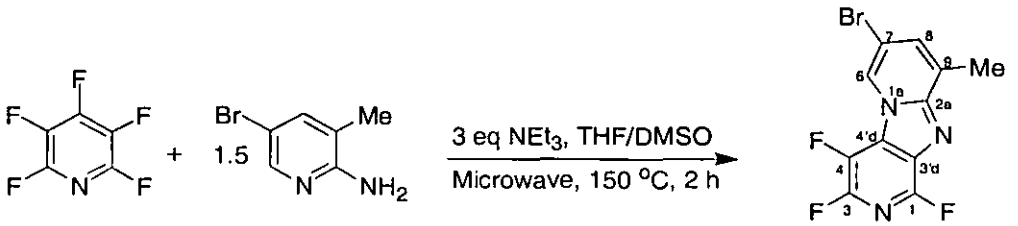
1,3,4-Trifluoro -dipyrido[1,2-a;3',4'-d]imidazole, **21**



21, 25 %

Pentafluoropyridine (1.69 g, 10.0 mmol), 2-amino-pyridine (1.88 g, 20.0 mmol) and sodium hydrogen carbonate (3.36 g, 40.0 mmol) were stirred together in dry MeCN (200 mL) at reflux temperature, under an atmosphere of argon, for 96 h. Evaporation of the reaction and addition of water (50 mL) was followed by extraction into DCM (4 x 40 mL). Evaporation of the solvent yielded a dark red solid. The crude was refluxed with charcoal in MeOH, filtered and dried to give a pale orange solid. Recrystallisation from MeCN gave *1,3,4-trifluoro-dipyrido[1,2-a;3',4'-d]imidazole* **21** (0.55 g, 25 %) as a pale orange solid; mp 197-198 °C; (Found; C, 53.8; H, 1.7; N, 18.9. $C_{10}H_4F_3N_3$ requires; C, 53.8; H, 1.8; N, 18.8 %); δ_F -79.05 (1F, dd, $^3J_{FF}$ 34.3, $^4J_{FF}$ 13.4, F-3), -102.07 (1F, dd, $^5J_{FF}$ 19.9, $^4J_{FF}$ 13.3, F-1), -164.36 (1F, dd, $^3J_{FF}$ 34.4, $^5J_{FF}$ 20.3, F-4); δ_H 8.64 (1H, dm, $^3J_{HH}$ 7.0, H-6), 7.77 (1H, m, H-9), 7.59 (1H, m, H-8), 7.03 (1H, m, H-7); δ_C 150.24 (s, C-2a), 145.07 (dm, $^1J_{CF}$ 250.7, C-3), 141.07 (dm, $^1J_{CF}$ 233.7, C-1), 131.95 (s, C-8), 131.22 (ddd, $^1J_{CF}$ 256.6, $^3J_{CF}$ 32.1, $^4J_{CF}$ 8.5, C-4), 128.00 (dd, $^2J_{CF}$ 35.4, $^3J_{CF}$ 3.8, C-4'd), 127.73 (hidden m, C-3'd), 127.44 (d, $^4J_{CF}$ 5.0, C-6), 119.30 (s, C-9), 113.08 (s, C-7); *m/z* (EI) 222.8 (M^+, 100 %).

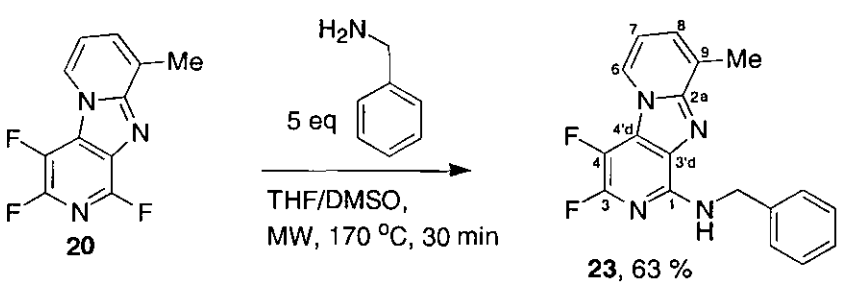
7-bromo-1,3,4-trifluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole **22**



22, 10 %

Pentafluoropyridine (0.30 g, 1.77 mmol), 2-amino-5-bromo-3-methylpyridine (0.50 g, 2.66 mmol) and triethylamine (0.54 g, 5.32 mmol) were stirred together in a mixture of THF (10.00 mL) and DMSO (4.00 mL), in a sealed 20 mL vial, under microwave heating for 2 h at 150 °C. The resulting mixture was evaporated to dryness and the yellow crude absorbed onto silica. Column chromatography of this material (on silica, DCM/MeOH/NH_3; 0.5 – 4 % MeOH gradient over 15 minutes) gave *7-bromo-1,3,4-trifluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole* **22** (0.06 g, 10 %) as a yellow solid; ($[M^+ + H^+]$ 315.9687. $C_{11}H_6N_3F_3Br$ requires $[M^+ + H^+]$ 315.9697); δ_F -77.80 (1F, dd, $^3J_{FF}$ 34.4, $^4J_{FF}$ 13.8, F-3), -100.90 (dd, $^5J_{FF}$ 20.1, $^4J_{FF}$ 13.2, F-1), -164.49 (dd, $^3J_{FF}$ 34.4, $^5J_{FF}$ 19.5, F-4); δ_H 8.65 (1H, s, C-6), 7.45 (1H, m, C-8), 2.72 (3H, s, CH_3); δ_C 149.27 (s, C-2a), 145.16 (dd, $^1J_{CF}$ 252.1, $^3J_{CF}$ 11.8, C-1), 141.29 (dm, $^1J_{CF}$ 236.0, C-3), 133.20 (s, C-8), 130.83 (ddd, $^1J_{CF}$ 257.0, $^2J_{CF}$ 32.0, $^4J_{CF}$ 8.6, C-4), 130.52 (s, C-9), 127.76 (m, C-4'd), 124.51 (d, $^4J_{CF}$ 5.2, C-6), 107.42 (s, C-7), 17.33 (s, CH_3); m/z (ES^+) 318.0 (M^+ + H^+, 100 %), 316.0 ($M^+ + H^+$, 100 %).

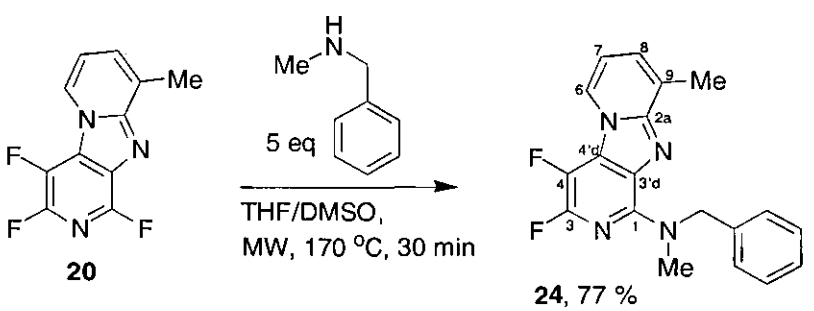
Benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazol-1-yl)-amine, **23**



23, 63 %

20 (0,50 g, 2.11 mmol) and benzylamine (1.13 g, 10.54 mmol) were stirred together in a mixture of THF (10 mL) and DSMO (2 mL) at 170 °C for 30 min (MW). LCMS of the resulting mixture consisted of 1 peak only. The reaction mixture was evaporated to dryness. 50 mL H_2O was added and the organic products extracted into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of the combined fractions gave an orange solid (0.78 g). Recrystallisation from MeCN gave *benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazol-1-yl)-amine* **23** (0.43 g, 63 %) as a yellow solid; mp 148 – 149 °C; (Found: C, 66.7; H, 4.3; N, 17.3. $C_{18}H_{14}F_2N_4$ requires: C, 66.7; H, 4.4; N, 17.3 %); δ_F -103.97 (1F, m, F-3), -179.55 (1F, d, $^3J_{FF}$ 23.7, F-4); δ_H 8.34 (1H, dm, $^3J_{HH}$ 6.8, H-6), 7.39 (2H, dm, $^3J_{HH}$ 7.6, H-2'), 7.29 (3H, m, H-3',4'), 7.14 (1H, dm, $^3J_{HH}$ 6.8, H-8), 6.75 (1H, m, H-7), 6.12 (1H, br s, NH), 4.75 (2H, d, $^4J_{HH}$ 5.6, CH_2), 2.57 (3H, s, CH_3); δ_C 148.30 (s, C-2a), 144.77 (dd, $^1J_{CF}$ 222.0, $^2J_{CF}$ 12.7, C-3), 144.40 (d, $^3J_{CF}$ 18.4, C-1), 139.03 (s, C-1'), 128.74, 128.66, 128.40 (obscured, C-3'd), 128.27, 127.54, 127.48, 125.65 (dd, $^1J_{CF}$ 246.2, $^2J_{CF}$ 35.3, C-4), 124.89 (d, $^4J_{CF}$ 4.6, C-6), 124.40 (dd, $^2J_{CF}$ 16.1, $^3J_{CF}$ 8.9, C-4'd), 112.31 (s, C-7), 45.60 (s, CH_2), 17.56 (s, CH_3); *m/z* (ES^+) 325.1 ($M^+ + H^+$, 100 %). Crystals suitable for X-ray analysis were grown from MeCN.

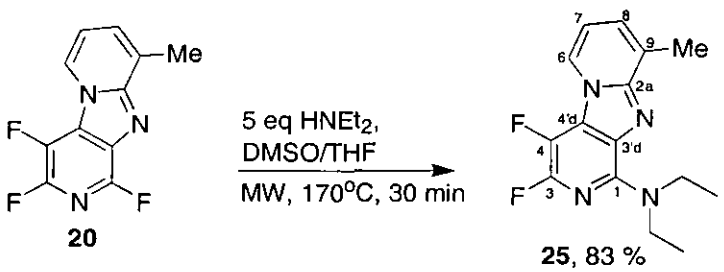
Benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazol-1-yl)-methyl-amine, **24**



20 (0,50 g, 2.11 mmol) and *N*-benzylmethylamine (1.28 g, 10.54 mmol) were stirred together in a mixture of THF (10 mL) and DSMO (2 mL) at 170 °C for 30 min (MW). LCMS of the resulting mixture consisted of 1 peak only. The reaction mixture was evaporated to dryness. 50 mL H_2O was added and the organic products extracted into DCM (5 x 40 mL). Drying ($MgSO_4$) and evaporation of the combined fractions gave an orange solid (0.73 g). Recrystallisation from MeCN gave *benzyl-(3,4-difluoro-9-methyl-*

dipyrido[1,2-a;3',4'-d]imidazol-1-yl)-methyl-amine **24** (0.55 g, 77 %) as a dark green solid; mp 111-113 °C; (Found: C, 67.7; H, 4.7; N, 16.8. $C_{19}H_{16}N_4F_2$ requires: C, 67.5; H, 4.8; N, 16.6 %); δ_F -102.56 (1F, d, $^3J_{FF}$ 26.3, F-3), -180.01 (1F, d, $^3J_{FF}$ 26.0, F-4); δ_H 8.31 (1H, d, $^3J_{HH}$ 7.1, H-6), 7.37 – 7.22 (5H, m, H-2', 3', 4'), 7.06 (1H, dm, $^3J_{HH}$ 6.7, H-8), 6.67 (1H, m, H-7), 5.46 (2H, s, CH_2), 3.37 (3H, s, NCH_3), 2.53 (3H, s, CH_3); δ_C 146.71 (br s, C-2a), 144.88 (d, $^3J_{CF}$ 16.6, C-1), 143.38 (dd, $^1J_{CF}$ 219.5, $^2J_{CF}$ 12.1, C-3), 139.09 (s, C-1'), 128.71 (s, C-9), 128.46, 128.12 (m, C-3'd), 127.99, 127.06, 126.50, 125.90 (dd, $^2J_{CF}$ 8.2, $^3J_{CF}$ 7.0, C-4'd), 124.98 (dd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 36.3, C-4), 124.28 (d, $^4J_{CF}$ 6.1, C-6), 111.79 (s, C-7), 54.57 (s, CH_2), 37.00 (s, NCH_3), 17.21 (s, CH_3); *m/z* (ES^+) 339.1 ($M^+ + H^+$, 100 %).

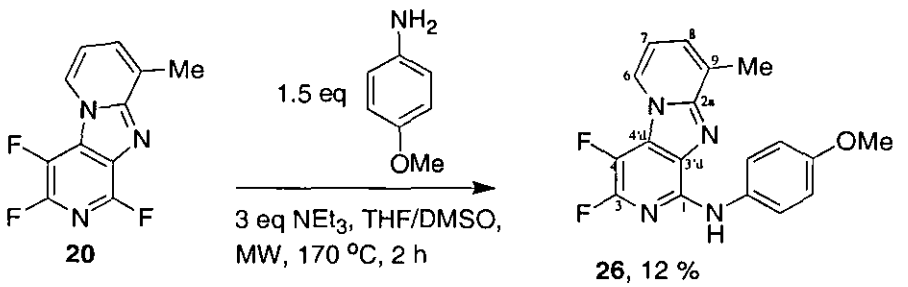
3,4-Difluoro-9-methyl-dipyrido[1,2-a,3',4'-d]imidazol-1-yl)-diethyl-amine, **25**



20 (0.50 g, 2.11 mmol) and diethylamine (0.77 g, 10.54 mmol) were stirred together in a mixture of DMSO (4.0 mL) and THF (20 mL) for 30 min at 170 °C (x2 reaction vials). LCMS of the crude showed no starting material remaining. The reaction mixture was evaporated to dryness and water (50 mL) added. Extraction of the organic products into DCM (3 x 40 mL) followed by drying ($MgSO_4$) and evaporation of the solvent gave a yellow crude. Recrystallisation from MeCN gave *3,4-Difluoro-9-methyl-dipyrido[1,2-a,3',4'-d]imidazol-1-yl)-diethyl-amine* **25** (0.51 g, 83 %) as a pale yellow solid; mp 91-93 °C; (Found: C, 61.8; H, 5.5; N, 19.2. $C_{15}H_{16}N_4F_2$ requires: C, 62.1; H, 5.6; N, 19.3 %); δ_F -102.42 (1F, d, $^3J_{FF}$ 27.0, F-3), -181.52 (1F, d, $^3J_{FF}$ 26.8, F-4); δ_H 8.42 (1H, d, $^3J_{HH}$ 6.9, H-6), 7.15 (1H, d, $^3J_{HH}$ 6.7, H-8), 6.77 (1H, m, H-7), 4.03 (4H, q, $^3J_{HH}$ 7.0, CH_2), 2.63 (3H, s, CH_3), 1.28 (6H, t, $^3J_{HH}$ 6.8, $-N(CH_2CH_3)_2$; δ_C 146.81 (s, C-2a), 144.28 (d, $^3J_{CF}$ 17.0, C-1), 143.68 (dd, $^1J_{CF}$ 218.0, $^2J_{CF}$ 12.1, C-3), 128.76 (s, C-9), 127.94 (m, C-

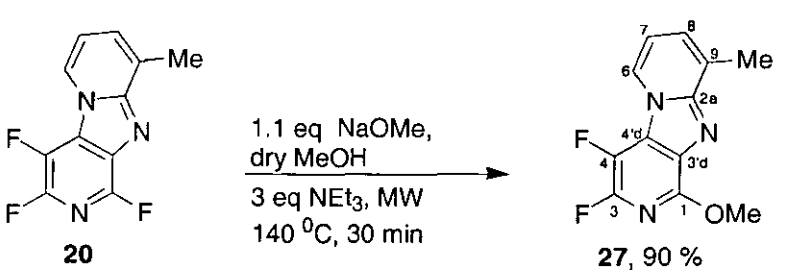
3'd), 126.16 (s, C-8), 126.00 (obscured m, C-4'd), 124.45 (dd, $^{1}J_{CF}$ 243.6, $^{2}J_{CF}$ 36.7, C-4), 124.42 (d, $^{4}J_{CF}$ 6.0, C-6), 111.66 (s, C-7), 43.73 (s, CH_2), 17.20 (s, CH_3), 13.79 (s, NCH_2CH_3); *m/z* (EI) 290.1 (M^+, 90 %), 275.1 (M^+ - 15, 100 %).

(3,4-Difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazol-1-yl)-(4-methoxy-phenyl)-amine, **26**



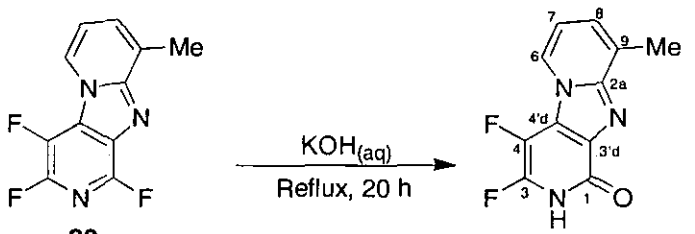
20 (0.10 g, 0.42 mmol), *p*-anisidine (0.08 g, 0.63 mmol) and triethylamine (0.13 g, 1.26 mmol) were stirred together in THF (1.0 mL) and DMSO (0.2 mL) at 170 °C for 2 h (MW). The reaction was evaporated and subjected to mass directed autopurification. Evaporation of the collected fractions yielded *(3,4-difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazol-1-yl)-(4-methoxy-phenyl)-amine* **26** (0.02 g, 12 %) as a yellow solid; mp 161 – 162 °C; ([$M^+ + H^+$] 341.1208. $C_{18}H_{15}N_4OF_2$ requires [$M^+ + H^+$] 341.1214); δ_F -102.91 (1F, d, $^{3}J_{FF}$ 24.3, F-3), -176.50 (1F, d, $^{3}J_{FF}$ 24.1, F-4); δ_H 8.42 (1H, d, $^{3}J_{HH}$ 6.9, H-6), 7.74 (2H, d, $^{3}J_{HH}$ 8.8, Ar-H), 7.63 (br s, NH), 7.21 (1H, dm, $^{3}J_{HH}$ 6.8, H-8), 6.93 (2H, d, $^{3}J_{HH}$ 9.0, Ar-H), 6.81 (1H, t, $^{3}J_{HH}$ 6.9, H-7), 3.82 (3H, s, OCH_3), 2.65 (3H, s, CH_3); *m/s* (ES^+) 341.1 ($M^+ + H^+$, 100%).

3,4-Difluoro-1-methoxy-9-methyl-dipyrido[1,2-a,3',4'-d]imidazole, **27**



20 (0.40 g, 1.69 mmol), NaOMe (0.10 g, 1.86 mmol) and NEt_3 (0.51 g, 5.08 mmol) were stirred together in anhydrous MeOH (4 x 10 mL) under microwave heating for 30 min at 140 ^{0}C. No starting material was observed by LCMS. The reaction mixtures were poured onto water (10 mL) to quench any excess NaOMe. Evaporation under reduced pressure gave a white crude which was triturated with water to give *3,4-difluoro-1-methoxy-9-methyl-dipyrido[1,2-a;3'4'-d]imidazole* **27** (0.38 g, 90 %) as a white solid; m.p 187-188 °C; (Found; C, 57.3; H, 3.5; N, 16.4. $C_{12}H_9F_2N_3O$ requires; C, 57.8; H, 3.6; N, 16.9 %.); δ_F -104.26 (1F, d, $^3J_{FF}$ 22.0, F-3), -172.77 (1F, d, $^3J_{FF}$ 21.9, F-4); δ_H 8.45 (1H, dd, $^3J_{HH}$ 7.0, $^4J_{HH}$ 0.6, H-6), 7.25 (1H, dm, $^3J_{HH}$ 6.8, H-8), 6.84 (1H, m, H-7), 4.16 (3H, s, OCH_3), 2.68 (3H, s, CH_3); δ_C 149.51 (s, C-2a), 148.55 (dd, $^3J_{CF}$ 13.8, $^4J_{CF}$ 1.2, C-1), 142.70 (dd, $^1J_{CF}$ 227.0, $^2J_{CF}$ 14.0, C-3), 129.35 (s, C-9), 128.71 (m, C-3'd), 128.49 (dd, $^1J_{CF}$ 251.5, $^2J_{CF}$ 33.7, C-4), 128.38 (s, C-8), 126.04 (m, C-4'd), 124.82 (d, $^4J_{CF}$ 5.2, C-6), 112.64 (s, C-7), 54.87 (s, OCH_3), 17.73 (s, CH_3); *m/z* (ES^+) 250.1 (M^+ + H^+, 100 %).

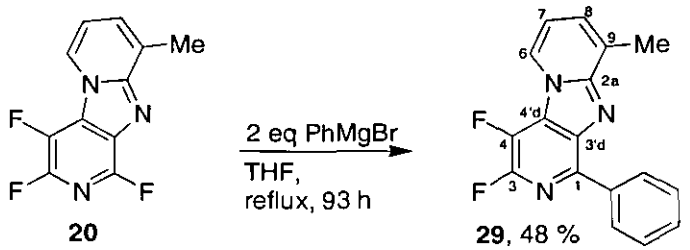
3,4-Difluoro-9-methyl-2H-dipyrido[1,2-a;3',4'-d]imidazol-1-one, **28**



20 (0.30 g, 1.26 mmol) was stirred in 0.36 M KOH solution (0.30 g KOH in 15 mL H_2O), under reflux, for 20 h. The reaction mixture was allowed to cool, acidified, and the organic products extracted into DCM by continuous extraction. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a pale green crude (0.22 g). Recrystallisation from MeCN gave *3,4-Difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazol-1-ol* **28** (0.03 g, 10 %); mp 229 °C (decomposed); (Found: C, 56.1; H, 2.9; N, 17.9. $C_{11}H_7N_3F_2O$ requires: C, 56.2; H, 3.0; N, 17.9 %); δ_F (DMSO-d_6) -104.56 (1F, br s, F-3), -172.30 (1F, d, $^3J_{FF}$ 22.1, F-4); δ_H 12.21 (br s, NH), 8.52 (1H, d,

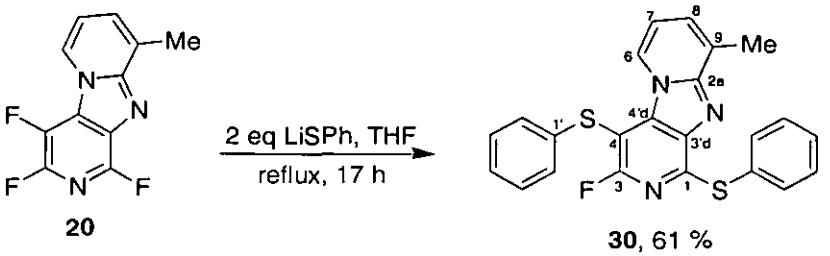
$^3J_{HH}$ 6.9, H-6), 7.37 (1H, dm, $^3J_{HH}$ 6.8, H-8), 6.93 (1H, m, H-7), 2.52 (3H, s, CH_3); δ_C 148.69 (d, $^3J_{CF}$ 16.2, C-1), 148.50 (s, C-2a), 141.37 (dd, $^1J_{CF}$ 221.3, $^2J_{CF}$ 13.4, C-3), 128.43 (s, C-8), 127.93 (m, C-3'd), 127.66 (s, C-9), 127.00 (d, $^1J_{CF}$ 249.6, C-4), 125.88 (m, C-4'd), 125.45 (d, $^4J_{CF}$ 4.8, C-6), 112.41 (s, C-7), 16.95 (s, CH_3); *m/z* (ES^+) 236.1 ($M^+ + H^+$, 100 %).

3,4-difluoro-9-methyl-1-phenyl-dipyrido[1,2-a;3',4'-d]imidazole, **29**



20 (0.41 g, 1.70 mmol) and PhMgBr (3.49 mL 1 M soln in THF, 3.50 mmol) were refluxed in THF (40 mL) for 93 h. The resulting mixture was poured onto 0.5 M HCl solution (50 mL) and extracted into DCM. Drying ($MgSO_4$) and evaporation of solvent gave a yellow crude. Recrystallisation from MeCN gave *3,4-difluoro-9-methyl-1-phenyl-dipyrido[1,2-a;3',4'-d]imidazole* **29** (0.25 g, 48 %) as a pale yellow solid; m.p 188-189 °C; (Found: C, 69.2; H, 3.7; N, 14.2. $C_{17}H_{11}F_2N_3$ requires: C, 69.2; H, 3.8; N, 14.2%); δ_F -99.81 (1F, d, $^3J_{FF}$ 28.2, F-3), -162.95 (1F, d, $^3J_{FF}$ 27.5, F-4); δ_H 8.79 (2H, dm, $^3J_{HH}$ 8.3, H-2'), 8.42 (1H, d, $^3J_{HH}$ 6.9, H-6), 7.52 (2H, m, H-3'), 7.44 (1H, m, H-4'), 7.24 (1H, dm, $^3J_{HH}$ 6.7, H-8), 6.78 (1H, m, H-7), 2.66 (3H, s, CH_3); δ_C 150.60 (s, C-2a), 144.03 (dd, $^1J_{CF}$ 223.7, $^2J_{CF}$ 11.9, C-3), 140.26 (dd, $^3J_{CF}$ 13.5, $^4J_{CF}$ 5.6, C-1), 139.35 (m, C-3'd), 136.19 (s, C-1'), 131.68 (dd, $^1J_{CF}$ 264.5, $^2J_{CF}$ 36.6, C-4), 129.52, 129.39, 129.20 (s, C-9), 129.10, 128.52, 125.84 (m, C-4'd), 125.19 (d, $^4J_{CF}$ 5.5, C-6), 112.29 (s, C-7), 17.49 (s, CH_3); m/z (EI) 295.1 (M^+, 100 %).

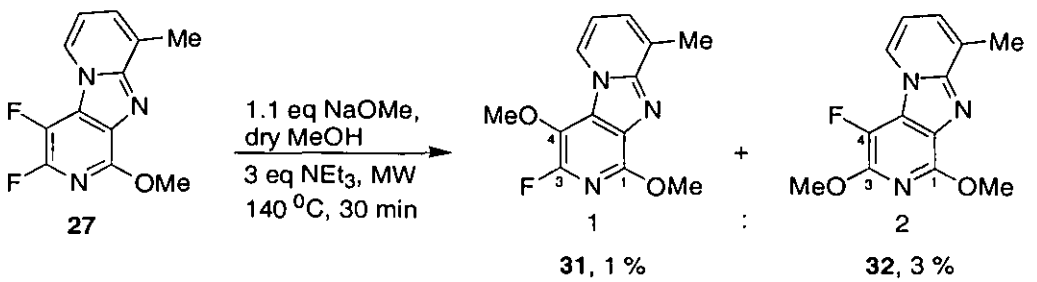
3-Fluoro-9-methyl-1,4-bis-phenylsulfanyl-dipyrido[1,2-a;3',4'-d]imidazole, **30**



20 **30**, 61 %

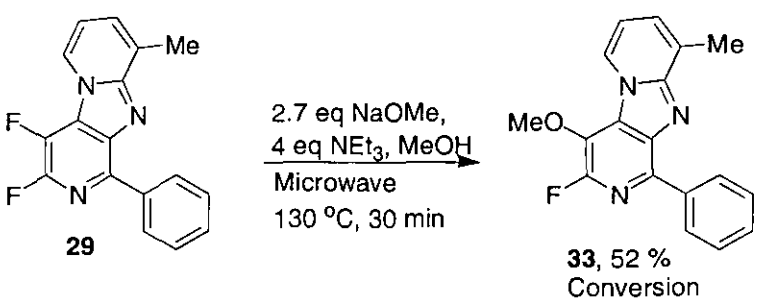
LiSPh (4.00 mL 1M solution in THF, 4.0 mmol) was added to a stirring solution of **20** (0.47 g, 2.0 mmol) in dry THF at room temperature, under dry argon. The solution was refluxed for 17 h, at which point ^{19}F NMR showed no starting material to be remaining. Evaporation of the solvent was followed by addition of 0.5 M HCl solution (50 mL). Extraction of the organic products into DCM (3 x 40 mL), drying ($MgSO_4$) and evaporation of DCM gave a yellow solid. Recrystallisation from MeCN yielded *3-fluoro-9-methyl-1,4-bis-phenylsulfanyl-dipyrido[1,2-a;3',4'-d]imidazole* **30** as a yellow solid (0.51 g, 61 %); mp 174 – 176 °C; (Found: C, 65.9; H, 3.8; N, 10.2. $C_{23}H_{16}N_3FS_2$ requires: C, 66.2; H, 3.9; N, 10.1 %); δ_F -75.62 (1F, s, F-3); δ_H 9.31 (1H, d, $^3J_{HH}$ 7.1, H-6), 7.75-7.72 (2H, m, Ar-H), 7.49-7.45 (3H, m, Ar-H), 7.24-7.17 (3H, m, H-9, Ar-H), 7.15-7.09 (3H, m, Ar-H), 6.71 (1H, m, H-7), 2.70 (3H, s, CH_3); δ_C 158.57 (d, $^1J_{CF}$ 230.6, C-3), 152.00 (d, $^3J_{CF}$ 17.7, C-1), 150.60 (d, $^5J_{CF}$ 1.8, C-2a), 136.74 (d, $^4J_{CF}$ 1.9, C-1'), 135.58 (s, Ar-CH), 135.25 (br s, C-3'd), 134.86 (d, $^3J_{CF}$ 5.9,C-4'd), 129.58 (s, Ar-CH), 129.51 (s, C-8), 129.36 (s, Ar-CH), 128.98 (s, Ar-C), 128.76 (s, Ar-CH), 127.99 (s, C-9), 127.11 (s, Ar-CH), 126.62 (s, Ar-CH), 125.26 (s, C-6), 112.06 (s, C-7), 93.13 (d, $^2J_{CF}$ 44.3, C-4), 17.71 (s, CH_3); *m/z* (ES^+) 418 ($M^+ + H^+$, 100 %).

Reaction of 3,4-Difluoro-1-methoxy-9-methyl-dipyrido[1,2-a,3',4'-d]imidazole with NaOMe



3,4-Difluoro-1-methoxy-9-methyl-dipyrido[1,2-a,3',4'-d]imidazole (0.0800 g, 0.32 mmol), NaOMe (0.0434 g, 0.80 mmol) and NEt_3 (0.0974 g, 0.96 mmol) were stirred together in dry MeOH (10 mL) for 30 min at 150 °C. LCMS of the resulting mixture showed there to be starting material (34 % by TIC trace) and 1 new peak (66 %) with *m/z* (ES^+) 262.1, corresponding to the desired monosubtituted product. The mixture was quenched (1 mL H_20), evaporated and the resulting yellow solid washed with water. Following a failed purification attempt by HPLC, mass directed auto purification of a crude sample gave 2 fractions both with $M^+ + H^+$ 262. Evaporation of the fractions gave white solids. ^{19}F NMR of the first fraction (0.0010 g, 1 %) showed there to be 1 fluorine present (-98.32 ppm), corresponding to *3-fluoro-1,4-dimethoxy-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole* **31**. ^{19}F NMR of the second fraction (0.0022 g, 3 %) showed there to be 1 fluorine present (-174.35 ppm), corresponding to *4-fluoro-1,3-dimethoxy-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole* **32**.

Reaction of 3,4-difluoro-9-methyl-1-phenyl-dipyrido[1,2-a;3',4'-d]imidazole with Sodium methoxide

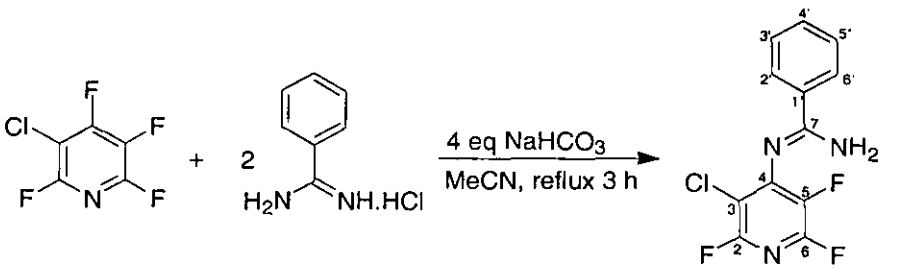


3,4-Difluoro-9-methyl-1-phenyl-dipyrido[1,2-a;3',4'-d]imidazole **29** (0.0150 g, 0.0508 mmol)), NaOMe (0.0074 g, 0.1372 mmol) and triethylamine (0.0206 g, 0.2032 mmol) were stirred together in dry MeOH (1 mL) for 30 min at 130 °C. The reaction mixture was evaporated, diluted with water (20 mL), the organic products extracted by DCM (3 x 15 mL) and subsequently evaporated to give a yellow solid (0.01 g). ^{19}F NMR of this crude showed starting material and *3-fluoro-4-methoxy-9-methyl-1-phenyl-dipyrido[1,2-a;3',4'-d]imidazole* **33** (52 % by integration) to be present; δ_F -93.03 (s, F-3); LCMS of this solid resulted in a TIC trace with two main peaks; 20.5 min (100 % relative abundance; *m/z* (ES^+) 308.1 (product $M^+ + H^+$, 100 %)) and 21.0 min (90 % relative abundance; *m/z* (ES^+) 296.1, starting material $M^+ + H^+$)).

Chapter 10

Experimental to Chapter 4

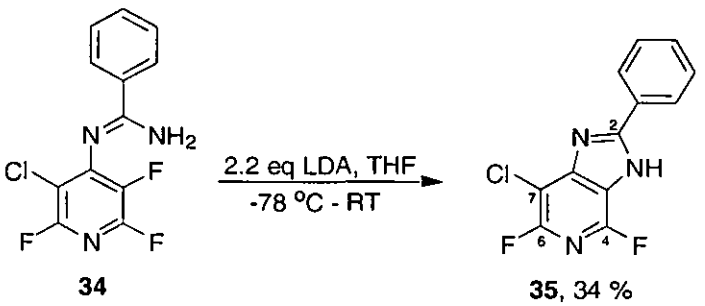
N-(3-Chloro-2,5,6-trifluoro-pyridin-4-yl)-benzamidine, **34**



34, 53 %

3-Chloro-2,4,5,6-tetrafluoropyridine (1.86 g, 10.0 mmol), benzamidine hydrochloride (3.13 g, 20.0 mmol) and $NaHCO_3$ (3.36 g, 40.0 mmol) were refluxed together in MeCN (200 mL) for 3 h. After evaporation of the reaction solvent, water (50 mL) was added and the organic products extracted into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of solvent gave a white solid. Recrystallisation from MeCN gave *N-(3-chloro-2,5,6-trifluoro-pyridin-4-yl)-benzamidine* **34** (1.50 g, 53 %) as a white solid; mp 206-208 °C; (Found: C, 50.4; H, 2.4; N, 14.8. $C_{12}H_7N_3F_3Cl$ requires: C, 50.5; H, 2.5; N, 14.7 %); δ_F -77.08 (1F, dd, $^3J_{FF}$ 23.6, $^4J_{FF}$ 13.5, F-6), -99.36 (1F, dd, $^5J_{FF}$ 22.9, $^4J_{FF}$ 13.7, F-2), -154.36 (1F, t, J_{FF} 23.5, F-5); δ_H 7.98 (2H, m, H-2'), 7.57 (1H, m, H-4'), 7.50 (2H, m, H-3'), 7.15 (br s, NH); δ_C 157.41 (s, C-7), 151.71 (dm, $^2J_{CF}$ 13.4, C-4), 150.82 (ddd, $^1J_{CF}$ 235.8, $^3J_{CF}$ 16.4, $^4J_{CF}$ 2.2, C-2), 146.92 (ddd, $^1J_{CF}$ 238.3, $^2J_{CF}$ 17.5, $^3J_{CF}$ 16.3, C-6), 135.41 (ddd, $^1J_{CF}$ 248.1, $^2J_{CF}$ 26.0, $^4J_{CF}$ 6.0, C-5), 133.77 (s, Ar-CH), 131.39 (s, Ar-C), 128.41 (s, Ar-CH), 127.62 (s, Ar-CH), 106.26 (dd, $^2J_{CF}$ 33.2, $^3J_{CF}$ 5.6, C-3); *m/z* (EI) 287.0 (M^+, 30 %, ^{37}Cl), 285.0 (M^+, 85 %, ^{35}Cl), 250.0 (M^+ - Cl, 70 %).

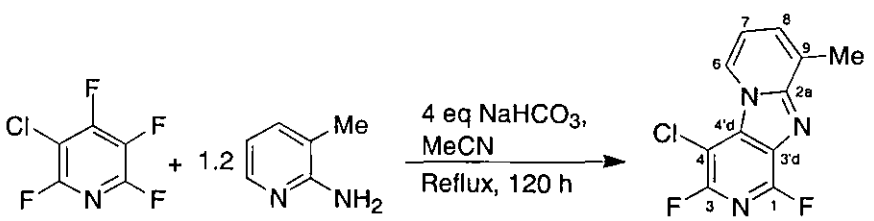
7-Chloro-4,6-difluoro-2-phenyl-3H-imidazo[4,5-c]pyridine, **35**



34 **35**, 34 %

LDA (1.22 mL 1.8 M soln in THF, 2.20 mmol) was syringed into a stirring solution of **34** (0.29 g, 1.0 mmol) in THF (30 mL) at -78 °C. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature. ^{19}F NMR after 20 h showed no starting material remaining. The reaction was evaporated and poured onto 50 mL 0.5 M HCl solution. The organic product was extracted into DCM (4 x 30 mL), dried ($MgSO_4$) and evaporated to give a yellow solid. Recrystallisation from MeCN gave *7-chloro-4,6-difluoro-2-phenyl-3H-imidazo[4,5-c]pyridine* **35** (0.09 g, 34 %) as an off-white solid; mp 216 – 218 °C; (Found: C, 53.9; H, 2.3; N, 15.7. $C_{12}H_5N_3F_2Cl$ requires: C, 54.3; H, 2.3; N, 15.6 %); δ_F (DMSO-d_6) major tautomer -81.62 (1F, br s, F-6), -85.38 (1F, br s, F-4); minor tautomer -81.10 (1F, br s, F-6), -86.88 (1F, br s, F-4); δ_H 8.26 (2H, m, H-2'), 7.59 (3H, m, H-3', 4'); δ_C 156.31 (br s, C-2), 149.84 (dd, $^1J_{CF}$ 230.1, $^3J_{CF}$ 15.6, C-6), 131.51 (s, C-4'), 129.12 (s, C-3'), 128.20 (s, C-1'), 127.58 (s, C-2'); *m/z* (EI) 267.0 (M^+, 30 %, ^{37}Cl), 265.0 (M^+, 30 %, ^{35}Cl). Crystals suitable for X-ray analysis were grown from MeCN.

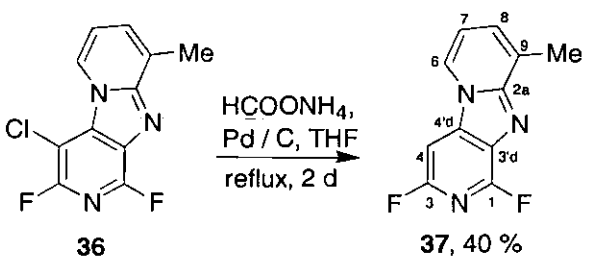
4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-a,3',4'-d]imidazole, **36**



36, 69 %

3-Chloro-2,4,5,6-tetrafluoropyridine (1.86 g, 10.0 mmol), 2-amino-3-picoline (1.30 g, 12.0 mmol) and $NaHCO_3$ (3.36 g, 40.0 mmol) were refluxed together in MeCN for 120 h. The reaction mixture was evaporated, 50 mL water added and the organic products extracted into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of these combined organic fractions gave a crude solid, recrystallisation of which gave *4-chloro-1,3-difluoro-9-methyl-dipyrido[1,2-a,3',4'-d]imidazole* **36** (1.74 g, 69 %) as a yellow solid; mp 193 - 194°C; (Found: C, 52.0; H, 2.3; N, 16.6. $C_{11}H_6N_3F_2Cl$ requires: C, 52.0; H, 2.3; N, 16.5 %); δ_F -77.84 (1F, d, $^4J_{FF}$ 12.8, F-3), -86.15 (1F, d, $^4J_{FF}$ 12.7, F-1); δ_H 9.04 (1H, dm, $^3J_{HH}$ 7.2, H-6), 7.34 (1H, dm, $^3J_{HH}$ 6.9, H-8), 6.90 (1H, t, $^3J_{HH}$ 7.1, H-7), 2.67 (3H, br s, CH_3); δ_C 151.37 (m, C-2a), 149.72 (dd, $^1J_{CF}$ 234.3, $^3J_{CF}$ 13.9, C-3), 149.46 (dd, $^1J_{CF}$ 253.5, $^3J_{CF}$ 14.9, C-1), 135.61 (dd, $^3J_{CF}$ 10.9, $^3J_{CF}$ 5.2, C-4'd), 129.66 (s, C-8), 129.43 (s, C-9), 127.19 (dd, $^2J_{CF}$ 33.9, $^4J_{CF}$ 3.9, C-3'd), 124.37 (s, C-6), 112.69 (s, C-7), 97.34 (dd, $^2J_{CF}$ 40.2, $^4J_{CF}$ 8.6, C-4), 17.58 (s, CH_3); *m/z* (EI) 254.9 (M^+, 10 %, ^{37}Cl), 252.9 (M^+, 25 %, ^{35}Cl).

1,3-Difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole, **37**



36 **37**, 40 %

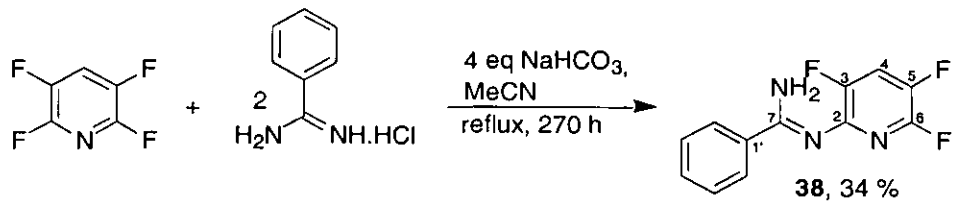
4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-a;3',4'-d]imidazole **36** (4.01g, 15.81 mmol), ammonium formate (1.00 g, 15.81 mmol) and 30% palladium on charcoal were stirred together and refluxed in THF (160ml) for 48 hours. ^{19}F NMR indicated 80% conversion of starting material to one product. The reaction mixture was filtered, poured onto water (100ml) and extracted with DCM (4 x 30ml). The resulting mixture was dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield a white crude, recrystallisation of which from methanol gave *1,3-difluoro-9-methyl-*

dipyrido[1,2-a;3',4'-d]imidazole **37** (1.38g, 40%) as a white solid; m.p. 234 - 235°C; (Found: C, 60.1; H, 3.3; N, 19.2. $C_{11}H_7N_3F_2$ requires: C 60.3; H 3.2; N 19.2 %); δ_F -74.92 (1F, d, $^4J_{FF}$ 13.1, CF), -79.47 (1F, d, $^4J_{FF}$ 12.9, CF); δ_H 8.20 (1H, d, $^3J_{HH}$ 7.0, H-6), 7.32 (1H, dm, $^3J_{HH}$ 6.8, H-8), 7.26 (1H, m, H-4), 6.89 (1H, t, $^3J_{HH}$ 6.9, H-7), 2.70 (3H, br s, CH_3); δ_C (DMSO-d_6) 152.99 (dd, $^1J_{CF}$ 230.5, $^3J_{CF}$ 13.6, CF), 150.61 (br s, C-2a), 149.88 (dd, $^1J_{CF}$ 248.1, $^3J_{CF}$ 17.2, CF), 140.83 (t, $^3J_{CF}$ 12.4, C-4'd), 130.22 (s, C-8), 127.63 (s, C-9), 125.10 (s, C-6), 124.82 (dd, $^2J_{CF}$ 32.5, $^4J_{CF}$ 3.8, C-3'd), 112.18 (s, C-7), 90.62 (dd, $^2J_{CF}$ 43.4, $^4J_{CF}$ 7.3, C-4), 16.69 (s, CH_3); m/z (EI) 219.0 (M^+, 100%).

Chapter 11

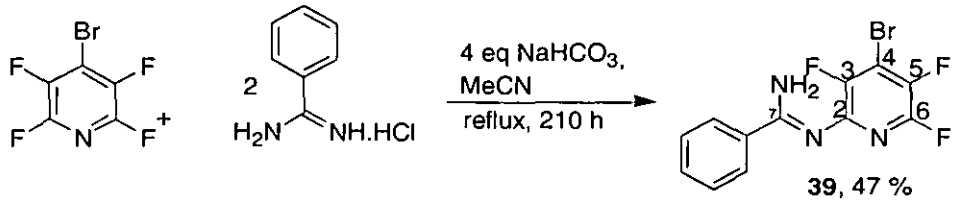
Experimental to Chapter 5

N-(3,5,6-Trifluoro-pyridin-2-yl)-benzamidine, **38**



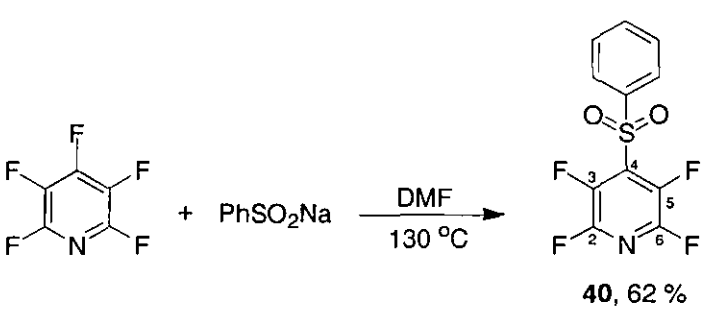
2,3,5,6-Tetrafluoropyridine (2.54 g, 16.8 mmol), benzamidine hydrochloride (5.26 g, 33.6 mmol), and sodium hydrogen carbonate (5.64 g, 67.1 mmol) were stirred together in dry MeCN at 80 ^{0}C, under dry argon for 11 d. The mixture was evaporated, 50 mL water was added and the organic products extracted into $CHCl_3$ (3 x 40 mL). Evaporation of the solvent gave an off-white crude. Recrystallisation from MeCN gave *N-(3,5,6-trifluoro-pyridin-2-yl)-benzamidine* **38** (1.45 g, 34 %) as a pale yellow solid; mp 137-139 ^{o}C; (Found: C, 57.4; H, 3.1; N, 16.8. $C_{12}H_8N_3F_3$ requires: C, 57.4; H, 3.2; N, 16.7 %); δ_F -93.28 (1F, m, F-6), -127.05 (1F, dd, $^3J_{FF}$ 28.7, $^4J_{FF}$ 8.4, F-5), -144.99 (1F, dd, $^5J_{FF}$ 24.3, $^4J_{FF}$ 8.4, F-3); δ_H 9.29, 6.16 (2H, br s, NH_2), 7.90 (2H, m, H-3'), 7.49-7.39 (4H, m, H-4, 2', 4'); δ_C 158.98 (s, C-7), 149.73 (ddd, $^1J_{CF}$ 259.6, $^2J_{CF}$ 5.6, $^4J_{CF}$ 2.2, C-6), 143.84 (m, C-2), 143.42 (ddd, $^1J_{CF}$ 236.9, $^2J_{CF}$ 15.9, $^4J_{CF}$ 3.4, C-5), 138.72 (ddd, $^1J_{CF}$ 256.5, $^3J_{CF}$ 30.4, $^4J_{CF}$ 5.8, C-3), 136.38 (s, C-1'), 131.36 (s, C-4'), 128.79 (s, C-3'), 127.15 (s, C-2'), 115.80 (ddd, $^2J_{CF}$ 28.0, $^2J_{CF}$ 19.2, $^3J_{CF}$ 3.9, C-4); m/z (EI) 251.1 (M^+, 100 %), 232.1 (M^+ - 19, 80 %)

N-(4-Bromo-3,5,6-trifluoro-pyridin-2-yl) benzamidine **39**



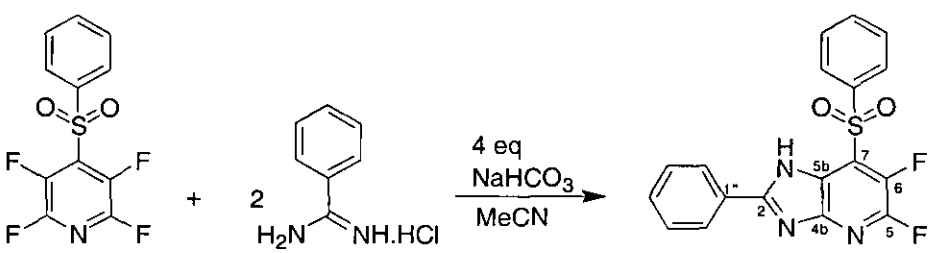
4-Bromo-2,3,5,6-tetrafluoropyridine (0.94 g, 4.1 mmol), benzamidine hydrochloride (1.26 g, 8.0 mmol), and sodium hydrogen carbonate (1.33 g, 15.9 mmol) were stirred together in dry acetonitrile at 80 ^{0}C, under dry argon. ^{19}F NMR after 210 h showed no starting material remaining. The mixture was evaporated, 50 mL water was added and the organic products extracted into $CHCl_3$ (3 x 40 mL). Evaporation of the solvent gave an light brown solid. Column chromatography (ethyl acetate:hexane, 1:1) on silica yielded *N-(4-bromo-3,5,6-trifluoro-pyridin-2-yl) benzamidine* **39** (0.64 g, 47 %) as an off white solid; mp 150-152 °C; (Found: C, 43.0; H, 2.3; N, 12.5. $C_{12}H_7N_3F_3Br$ requires: C, 43.7; H, 2.1; N, 12.7 %); δ_F (DMSO-d_6) -90.31 (1F, m, F-6), -124.04 (1F, dd, $^3J_{FF}$ 26.6, $^4J_{FF}$ 3.7, F-5), -142.85 (1F, dd, $^5J_{FF}$ 26.4, $^4J_{FF}$ 4.1, F-3); δ_H 8.19 (br s, NH_2), 8.00 (2H, m, H-2'), 7.55 (1H, m, H-4'), 7.50 (2H, m, H-3'); δ_C 159.43 (s, C-7), 147.22 (dm, $^1J_{CF}$ 253.0, C-6), 144.78 (m, C-2), 144.35 (dm, $^1J_{CF}$ 233.1, C-5), 137.29 (dd, $^1J_{CF}$ 251.8, $^2J_{CF}$ 33.0, C-3), 135.61 (s, C-1'), 131.86 (s, C-4'), 128.94 (s, C-3'), 128.18 (s, C-2'), 111.65 (m, C-4); m/z (EI) 330.97 (M^+, 58 %), 328.98 (M^+, 60 %), 312.0 (M^+ - F, 59 %), 310.0 (M^+ - F, 57 %).

4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **40**



Pentafluoropyridine (5.07 g, 30 mmol) was added to a solution of phenylsulfinic acid (4.96 g, 30 mmol) in DMF (25 ml) under argon. After stirring the mixture at 130 ^{0}C for 22 h the reaction mixture was left to cool and poured into water (250 ml). The solid which precipitated was filtered and the residue recrystallised from ethanol to yield 4-*benzenesulfonyl-2,3,5,6-tetrafluoropyridine* **40** (5.41 g, 62 %) as beige crystals; mp 145-147 $^{\circ}$C (Found: C, 45.3; H, 1.7; N, 4.8; $C_{11}H_5NF_4O_2S$ requires: C, 45.3; H, 1.7; N, 4.8 %); δ_F -86.19 (2F, m, F- 2), -137.47 (2F, m, F- 3); δ_H 8.12 (2H, m, H- 2'), 7.71 (1H, m, H- 4'), 7.65 (2H, m, H- 3'); δ_C 144.36 (dm, $^1J_{CF}$ 256.0, C- 2), 139.41 (s, C- 1'), 139.00 (dm, $^1J_{CF}$ 263.2, C- 3), 135.93 (s, C-4'), 133.34 (m, C-4), 130.16 (s, C-3'), 128.74 (s, C-2'); m/z (EI) 291.0 (M^+, 66 %), 140.9 (SO_2Ph, 80 %), 76.9 (C_6H_5, 100 %).

7-Benzenesulfonyl-5,6-difluoro-2-phenyl-1H-imidazo[4,5-b]pyridine **41**

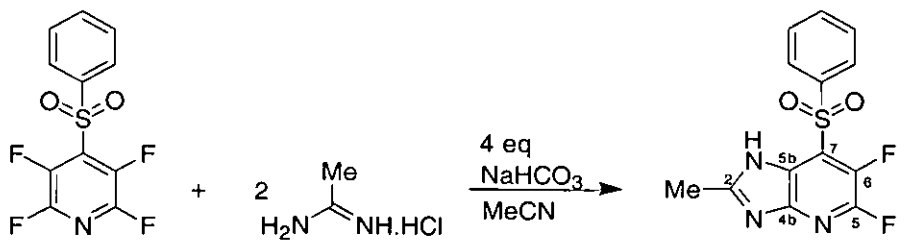


40 **41**, 36 %

4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **40** (2.33 g, 8.0 mmol), benzamidine hydrochloride (2.51 g, 16.0 mmol) and sodium hydrogen carbonate (2.69 g, 32.0 mmol) were stirred together under argon in MeCN (300 ml) for 120 h. The reaction was poured into water (50 ml) and extracted into dichloromethane (4 x 30 ml). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow solid. Recrystallisation from MeCN yielded *7-benzenesulfonyl-5,6-difluoro-2-phenyl-1H-imidazo[4,5-b]pyridine* **41** (1.1 g, 36 %) as a yellow powder; mp 241-245 ^{0}C; (Found: C, 58.3; H, 3.0; N, 11.6. $C_{18}H_{11}F_2N_3O_2S$ requires: C, 58.2; H, 3.0; N, 11.3 %); δ_F (DMSO-d_6) -91.33 (1F, d, $^3J_{FF}$ 27.9, F-5), -147.73 (1F, m, F-6); δ_H 8.25 (2H, m, C-2'), 8.22 (2H, m, C-2''), 7.80 (1H, m, C-4'), 7.70 (2H, m, C-3'), 7.61-7.58 (3H, m, C-3'', 4''); δ_C 156.42 (br m, C-2, C-4b), 147.92 (dd, $^1J_{CF}$ 236.1, $^2J_{CF}$ 18.0, C-5), 139.99 (s, C-1'), 138.06 (dd, $^1J_{CF}$ 259.6, $^2J_{CF}$ 31.1, C-6), 135.13 (s, C-4'), 131.43 (s, C-4''), 129.70 (s, C-3'), 129.08 (s, C-3''), 128.63 (s, C-2'),

128.34 (s, C-2''), 127.52 (br s, C-1'', C-7), 125.99 (br m, C-5b); *m/z* (EI^+) 371.0 (M^+, 100 %).

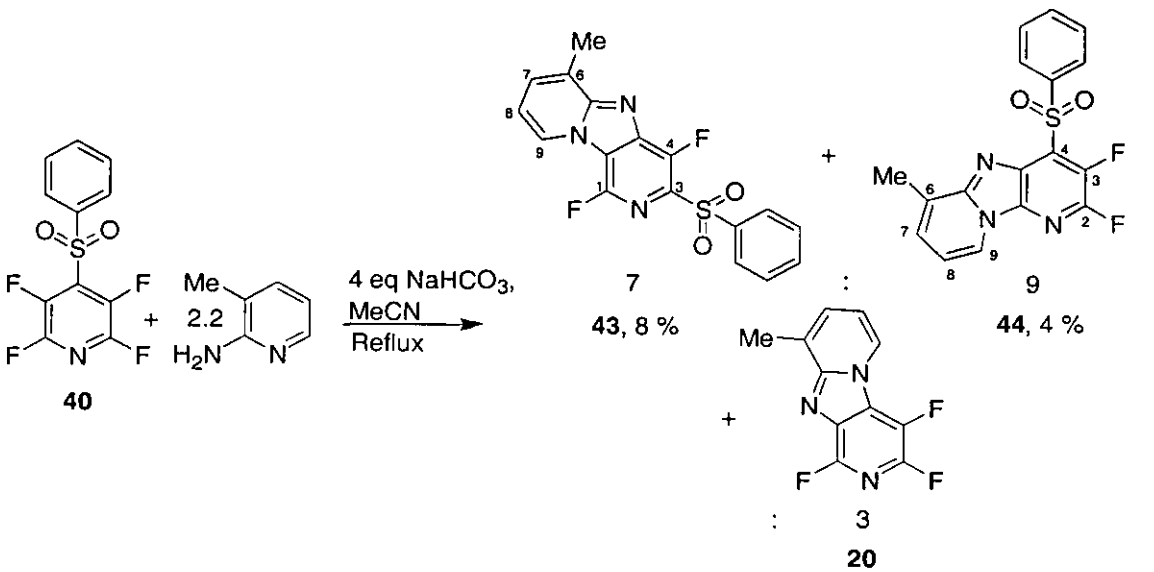
7-Benzenesulfonyl-5,6-difluoro-2-methyl-1H-imidazo[4,5-b]pyridine **42**



40 **42**, 26 %

4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **40** (1.46g, 5.0 mmol), acetamidine hydrochloride (0.95 g, 10.0 mmol) and sodium hydrogen carbonate (1.68 g, 20.0 mmol) were stirred together under argon in MeCN (200 ml) for 120 h. The reaction was poured onto water (50 ml) and extracted into dichloromethane (4 x 30 ml). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow solid. Recrystallisation from MeCN yielded *7-benzenesulfonyl-5,6-difluoro-2-methyl-1H-imidazo[4,5-b]pyridine* **42** (0.40 g, 26 %) as yellow crystals; mp 225-227 ^{0}C; (Found: C, 50.5; H, 3.0; N, 13.8. $C_{13}H_9F_2N_3O_2S$ requires: C, 50.5; H, 2.9; N, 13.6 %); δ_F (DMSO-d_6) -93.18 (1F, d, $^3J_{FF}$ 28.2, C-5), -148.80 (1F, d, $^3J_{FF}$ 27.5, C-6); δ_H 13.14 (1H, br s, NH), 8.11 (2H, m, H-2'), 7.77 (1H, m, H-4'), 7.68 (2H, m, H-3'); δ_C 159.44 (s, C-2), 147.80 (br m, C-4b), 147.05 (dd, $^1J_{CF}$ 232.0, $^2J_{CF}$ 17.3, C-5), 139.53 (s, C-1'), 136.94 (dd, $^1J_{CF}$ 257.7, $^2J_{CF}$ 32.5, C-6), 135.34 (s, C-4'), 130.05 (s, C-3'), 127.71 (s, C-2'), 122.91 (m, C-7), 121.55 (br m, C-5b), 15.31 (s, CH_3); m/z (EI) 309.0 (M^+, 80 %), 76.9 (C_6H_5, 100 %). Crystals suitable for X-ray analysis were grown from MeOH.

3-Benzenesulfonyl-1,4-difluoro-6-methyl-dipyrido[1,2-a;4',3'-d]imidazole, **43** *and 4-benzenesulfonyl-2,3-difluoro-6-methyl-dipyrido[1,2-a;3'2'-d]imidazole*, **44**

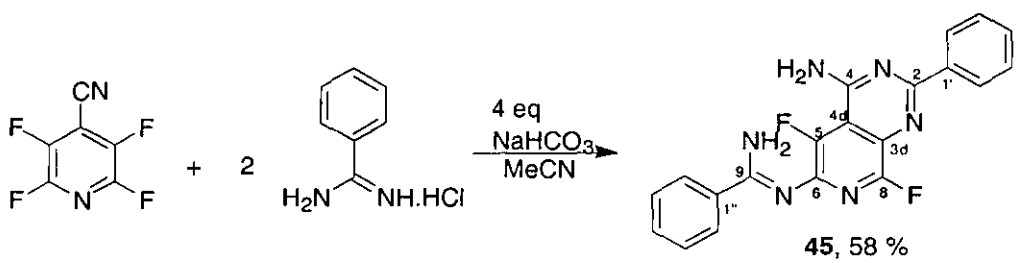


4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **40** (1.46 g, 5.0 mmol), 2-amino-3-picoline (1.19 g, 11.0 mmol) and sodium hydrogencarbonate (1.68 g, 20.0 mmol) were stirred together in dry MeCN (100 mL) at reflux temperature, under argon. After 1 week the reaction was evaporated to dryness, poured onto 1M HCl solution (50 mL) and extracted into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow crude. Recrystallisation from MeCN gave *3-benzenesulfonyl-1,4-difluoro-6-methyl-dipyrido[1,2-a;4',3'-d]imidazole* **43** (0.14 g, 8 %) as planar yellow crystals; mp 288-290 °C; (Found: C, 56.6; H, 3.0; N, 11.8. $C_{17}H_{11}F_2N_3O_2S$ requires: C, 56.8; H, 3.1; N, 11.7 %); δ_F -76.61 (1F, d, $^5J_{FF}$ 30.9, F-1), -132.08 (1F, d, $^5J_{FF}$ 31.6, F-4); δ_H 8.60 (1H, d, $^3J_{HH}$ 6.8, C-9), 8.15 (2H, m, C-2'), 7.62 (1H, m, C-7), 7.54 (3H, m, C-3', 4'), 7.11 (1H, m, C-8), 2.74 (3H, s, CH_3); *m/z* (ES^+) 360.1 ($M^+ + H^+$, 100 %). Crystals suitable for X-ray analysis were grown from MeCN.

Column chromatography (on silica, ethyl acetate: hexane, 2:1) of the remaining material followed by recrystallisation from MeCN yielded *4-benzenesulfonyl-2,3-difluoro-6-methyl-dipyrido[1,2-a;3'2'-d]imidazole* **44** (0.08 g, 4 %) as a yellow solid; mp 242-244 °C; (Found: C, 56.8; H, 3.1; N, 11.9. $C_{17}H_{11}F_2N_3O_2S$ requires: C, 56.8; H, 3.1; N, 11.7

%); δ_F -91.53 (1F, d, $^3J_{FF}$ 24.8, F-2), -140.24 (1F, d, $^3J_{FF}$ 24.6, F-3); δ_H 8.42 (3H, m, C-2', 4'), 7.64 (1H, m, C-9), 7.55 (2H, m, C-3'), 7.37 (1H, m, C-7), 6.93 (1H, m, C-8), 2.71 (3H, s, CH_3); δ_C 151.21 (s, C-2a), 147.21 (dd, $^1J_{CF}$ 243.9, $^2J_{CF}$ 19.8, C-2), 141.44 (dd, $^1J_{CF}$ 267.9, $^2J_{CF}$, C-3), 140.66 (s, C-2'd), 134.62 (s, C-9), 133.90 (dm, $^2J_{CF}$ 15.2, C-4), 131.29 (d, $^4J_{CF}$ 3.1, C-1'), 130.24 (s, C-7), 129.26 (s, C-2'), 129.14 (s, C-3'), 128.99 (s, C-6), 128.51 (m, C-3'd), 121.95 (s, C-4'), 112.87 (s, C-8), 17.02 (s, CH_3); *m/z* (ES^+) 360.0 ($M^+ + H^+$, 100 %). Crystals suitable for X-ray analysis were grown from $CDCl_3$.

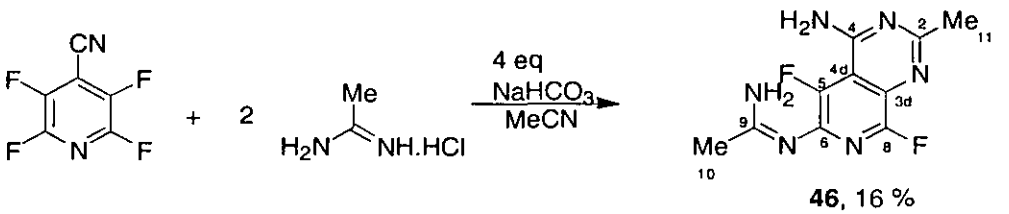
N-(-4-Amino-5,8-difluoro-2-phenyl-pyrido[3,4-d]pyrimidin-6-yl)-benzamidine, **45**



2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile (0.88 g, 5.0 mmol), benzamidine hydrochloride (1.57 g, 10.0 mmol) and sodium hydrogen carbonate (1.68 g, 20.0 mmol) were stirred together under argon in MeCN (200 ml) for 170 h at 80 ^{0}C. The reaction mixture was treated with water (50 ml) and the organic products extracted into DCM (3 x 40 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Recrystallisation from MeCN of the crude material yielded *N-(-4-amino-5,8-difluoro-2-phenyl-pyrido[3,4-d]pyrimidin-6-yl)-benzamidine* **45** (1.09 g, 58 %) as a yellow solid; mp 215-216 ^{0}C; ([M + H^+] 377.1320. $C_{20}H_{14}F_2N_6$ requires [M + H^+] 377.1321); δ_F (DMSO-d_6) -97.79 (d, $^5J_{FF}$ 28.0, F-8), -153.97 (d, $^5J_{FF}$ 29.3, F-5); δ_H 8.41 (2H, m, H-2'), 8.21, 7.76, 7.38 (4H, br s, NH_2), 8.11 (2H, m, H-2''), 7.55-7.47 (6H, m, H-3', 3'', 4', 4''); δ_C 159.59 (s, C-2), 159.35 (m, C-4), 157.80 (s, C-9), 154.90 (dd, $^2J_{CF}$ 12.8, $^3J_{CF}$ 3.7, C-6), 144.19 (dd, $^1J_{CF}$ 227.9, $^4J_{CF}$ 16.9, C-8), 140.25 (m, C-3d), 137.82 (s, C-1'), 135.64 (s, C-1''), 132.99 (dd, $^1J_{CF}$ 254.8, $^4J_{CF}$ 30.8, C-5), 130.87 (s, C-4''), 130.42 (s, C-4'), 128.35 (s, C- 3'), 128.31 (s, C-3''), 127.80 (s, C-2'), 127.65 (s, C-2''),

110.99 (dd, $^{2}J_{CF}$ 8.3, $^{3}J_{CF}$ 3.6, C-4d); *m/z* (ES^{+}) 377.1 (M^{+} + H^{+}, 100 %). Crystals suitable for X-ray analysis were grown from MeCN.

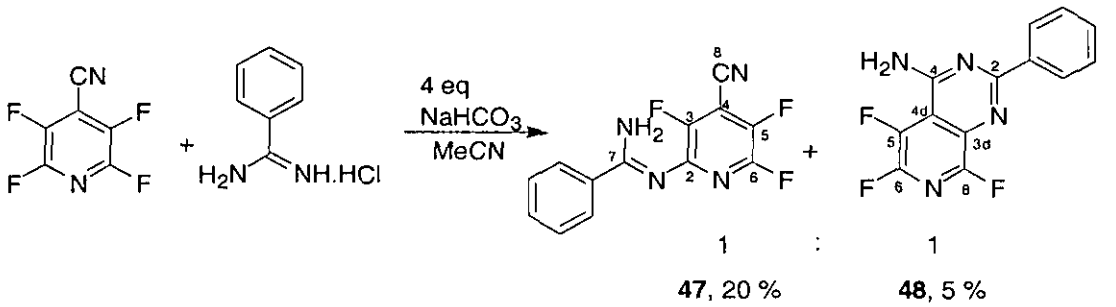
N-(-4-amino-5,8-difluoro-2-methyl-pyrido[3,4-d]pyrimidin-6-yl)-acetamidine, **46**



46, 16 %

2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile (0.44 g, 2.5 mmol), acetamidine hydrochloride (0.47 g, 5.0 mmol) and sodium hydrogen carbonate (0.84 g, 10.0 mmol) were stirred together under argon in MeCN (100 ml) for 72 h at 80 ^{0}C. The reaction mixture was treated with water (100 ml) and the organic products extracted into DCM (3 x 100 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting crude was recrystallised from MeCN to give *N-(-4-amino-5,8-difluoro-2-methyl-pyrido[3,4-d]pyrimidin-6-yl)-acetamidine* **46** (0.10 g, 16 %) as a yellow paper like solid; mp 224-228 ^{0}C; ([M + H^{+}] 253.1009. $C_{10}H_{10}F_2N_6$ requires [M + H^{+}] 153.1008); δ_F (DMSO-d_6) -98.58 (d, $^{5}J_{FF}$ 28.12, C-8), -155.18 (d, $^{5}J_{FF}$ 27.88, C-5); δ_H 8.02, 7.17 (4H, br s, NH_2), 2.41 (3H, s, C-10), 1.92 (3H, s, C-11); δ_C 163.69 (s, C-2), 160.61 (s, C-9), 158.92 (m, C-4), 154.29 (dd, $^{2}J_{CF}$ 12.9, $^{3}J_{CF}$ 3.0, C-6), 143.52 (dd, $^{1}J_{CF}$ 226.2, $^{4}J_{CF}$ 15.6, C-8), 140.05 (m, C-3d), 132.30 (dd, $^{1}J_{CF}$ 254.9, $^{4}J_{CF}$ 30.7, C-5), 110.06 (dd, $^{2}J_{CF}$ 8.2, $^{3}J_{CF}$ 3.2, C-4d), 25. 80 (s, C-11), 20.78 (s, C-10).

N-(-4-Cyano-3,5,6 trifluoro-pyridin-2yl-)-benzamidine, **47** *and 5,6,8-trifluoro-2-phenyl-pyrido[3,4-d]pyrimidin-4-ylamine*, **48**

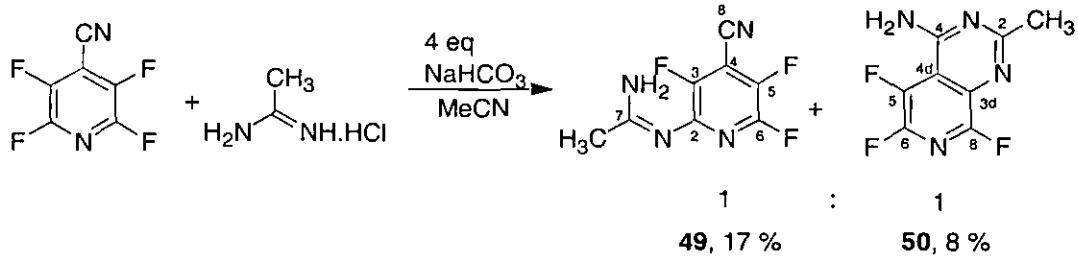


2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile (0.44 g, 2.5 mmol), benzamidine hydrochloride (0.39 g, 2.5 mmol) and sodium hydrogen carbonate (0.42 g, 5.0 mmol) were stirred together under argon in MeCN (100 ml) for 1 week at 80 ^{0}C. The reaction mixture was treated with water (50 ml) and extracted into dichloromethane (3 x 40 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give an orange/red crude solid. Column chromatography on alumina (DCM:hexane 3:2) gave *N-(-4-cyano-3,5,6 trifluoro-pyridin-2yl-)-benzamidine* **47** (0.14 g, 20 %) as a pale yellow solid; δ_F (DMSO-d_6) -88.90 (dd, $^3J_{FF}$ 30.0, $^5J_{FF}$ 25.2, F-6), -123.03 (dd, $^3J_{FF}$ 29.4, $^4J_{FF}$ 7.0, F-5), -144.10 (dd, $^5J_{FF}$ 25.0, $^4J_{FF}$ 6.5, F-3); δ_H 8.37 (2H, br s, NH_2), 8.02 (2H, m, H-2'), 7.58 (1H, m, H-4'), 7.51 (2H, m, H-3'); δ_C 159.44 (s, C-7), 148.53 (ddd, $^1J_{CF}$ 268.0, $^2J_{CF}$ 7.5, $^4J_{CF}$ 3.2, C-6), 145.01 (m, C-2), 143.39 (ddd, $^1J_{CF}$ 234.2, $^2J_{CF}$ 13.7, $^3J_{CF}$ 3.9, C-5), 136.88 (dd, $^1J_{CF}$ 264.6, $^3J_{CF}$ 34.1, C-3), 134.60 (s, C-1'), 131.51 (s, C-4'), 128.40 (s, C-3'), 127.75 (s, C-2'), 108.39 (m , C-8), 102.50 (m, C-4); *m/z* (EI$^+$) 276.0 (M^+, 78 %), 257.0 (M^+ - F, 100 %). Crystals suitable for X-ray analysis were grown from MeCN.

Recrystallisation of the remaining crude material from MeCN yielded *5,6,8-trifluoro-2-phenyl-pyrido[3,4-d]pyrimidin-4-ylamine* **48** (0.036 g, 5 %) as a yellow solid; mp 220-223 ^{0}C; (Found; C 56.1; H, 2.5; N, 20.4. $C_{13}H_7F_3N_4$ requires; C, 56.5; H, 2.6; N, 20.3 %); δ_F (DMSO-d_6) -76.92 (dd, $^3J_{FF}$ 34.9, $^4J_{FF}$ 14.0, F-6), -100.11 (dd, $^5J_{FF}$ 21.7, $^4J_{FF}$ 13.8, F-8), -145.26 (dd, $^3J_{FF}$ 35.3, $^5J_{FF}$ 22.0, F-5); δ_H 8.67 and 7.9 (2H, br s, NH_2), 8.40 (2H, m, H-2'), 7.54-7.48 (3H, m, H-3', 4'); δ_C 161.84 (s, C-2), 158.65 (d, $^3J_{CF}$ 3.4, C-4), 149.93 (ddd, $^1J_{CF}$ 253.8, $^3J_{CF}$ 10.7, $^4J_{CF}$ 2.0, C-8), 141.40 (ddd, $^1J_{CF}$ 236.5, $^2J_{CF}$ 18.6, $^3J_{CF}$

13.5, C-6), 136.87 (ddd, $^{1}J_{CF}$ 259.6, $^{2}J_{CF}$ 27.5, $^{4}J_{CF}$ 7.1, C-5) 136.81 (S, C-1'), 134.76 (dm, $^{2}J_{CF}$ 31.4, C-3d), 131.19 (s, C-4'), 128.52 (s, C-3'), 128.10 (s, C-2'), 113.41 (m, C-4d); *m/z* (EI^{+}) 276 (M^{+}, 100 %), 260 (M^{+}-NH_2, 49 %). Crystals suitable for X-ray analysis were grown from MeCN.

N-(4-Cyano-3,5,6-trifluoro-pyridin-2-yl)-acetamidine, **49** *and 5,6,8-trifluoro-2-methyl-pyrido[3,4-d]pyrimidin-4-ylamine*, **50**

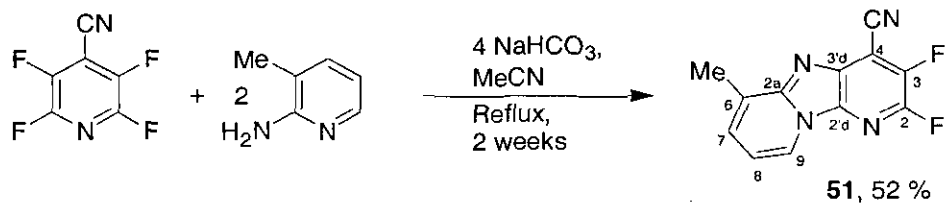


2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile (0.44 g, 2.5 mmol), acetamidine hydrochloride (0.24 g, 2.5 mmol) and sodium hydrogen carbonate (0.42 g, 5.0 mmol) were stirred together under argon in MeCN (100 ml) for 7 d. Evaporation under reduced pressure was followed by treatment with water (50 ml). Extraction of the organic products by DCM (3 x 40 ml), drying ($MgSO_4$), filtering and removal of solvent under reduced pressure gave a brown/black solid. Filtration of the crude material through alumina (DCM as eluant) yielded a yellow solid, *N-(4-cyano-3,5,6-trifluoro-pyridin-2-yl)-acetamidine* **49** (0.09 g, 17 %); ([M + H^{+}] 215.0540. $C_8H_6N_4F_3$ requires [M + H^{+}] 215.0539); δ_F ($DMSO-d_6$) -88.94 (dd, $^{3}J_{FF}$ 29.5, $^{5}J_{FF}$ 26.2, F-6), -124.26 (m, F-5), -145.02 (dd, $^{5}J_{FF}$ 23.2, $^{4}J_{FF}$ 6.9, F-3); δ_H 8.02-7.76 (2H, br m, NH_2), 2.04 (3H, s, CH_3); δ_C 163.35 (s, C-7), 147.91 (ddd, $^{1}J_{CF}$ 266.6, $^{2}J_{CF}$ 6.2, $^{4}J_{CF}$ 3.1, C-6), 144.61 (m , C-2), 143.38 (ddd, $^{1}J_{CF}$ 232.1, $^{2}J_{CF}$ 13.1, $^{3}J_{CF}$ 3.3, C-5), 136.55 (dd, $^{1}J_{CF}$ 263.2, $^{3}J_{CF}$ 34.6, C-3), 108.43 (m, C-8), 102.19 (m, C-4), 21.26 (s, CH_3); *m/z* (EI) 214.0 (M^{+}, 90 %), 197.0 (M^{+} - 17, 100 %).

Washing the alumina with methanol followed by recrystallisation of the residue from MeCN yielded *5,6,8-trifluoro-2-methyl-pyrido[3,4-d]pyrimidin-4-ylamine* **50** (0.04 g, 8

%) as an orange solid; ([M + H^+] 215.0541. $C_8H_6N_4F_3$ requires [M + H^+] 215.0545); δ_F (DMSO-d_6) -77.42 (dd, $^3J_{FF}$ 35.1, $^4J_{FF}$ 14.0, F-6), -100.78 (dd, $^5J_{FF}$ 22.1, $^4J_{FF}$ 14.0, F-8), -145.35 (dd, $^3J_{FF}$ 35.0, $^5J_{FF}$ 22.2, F-5); δ_H 8.56 (2H, br s, NH_2), 2.46 (3H, s, CH_3); δ_C 166.42 (s, C-2), 158.18 (d, $^3J_{CF}$ 3.4, C-4), 149.36 (ddd, $^1J_{CF}$ 252.4, $^2J_{CF}$ 11.0, $^3J_{CF}$ 2.2, C-6), 140.99 (ddd, $^1J_{CF}$ 234.4, $^3J_{CF}$ 18.3, $^4J_{CF}$ 13.3, C-8), 136.74 (ddd, $^1J_{CF}$ 258.6, $^2J_{CF}$ 27.0, $^4J_{CF}$ 7.1, C-5), 134.30 (dm, $^2J_{CF}$ 28.3, C-3d), 112.78 (m, C-4d), 25.80 (s, CH_3).

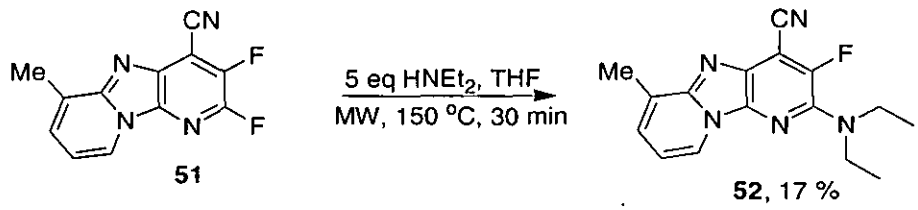
2,3-Difluoro-6-methyl-dipyrido[1,2-a,3',2'd]imidazole-4-carbonitrile, **51**



51, 52 %

2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile (0.88 g, 5.0 mmol), 2-amino-3-picoline (1.08 g, 10.0 mmol) and Sodium hydrogen carbonate (1.68 g, 20.0 mmol) were stirred together in MeCN at reflux temperature, under dry argon. After 2 weeks the reaction was cooled to room temperature and the solvent evaporated. The residue was redissolved in DCM and poured onto water (50 mL). Extraction of the organic products into DCM, followed by drying ($MgSO_4$) and evaporation of the solvent *in vacuo* left a brown crude. Column chromatography on silica (hexane: ethyl acetate, 1:1) yielded *2,3-difluoro-6-methyl-dipyrido[1,2-a,3',2'd]imidazole-4-carbonitrile* **51** (0.63 g, 52 %) as a yellow solid; mp 197-198 °C; (Found: C, 58.9; H, 2.4; N, 23.1. $C_{12}H_6N_4F_2$ requires: C, 59.2; H, 2.5; N, 22.9 %); δ_F -91.96 (1F, d, $^3J_{FF}$ 22.5, F-2), -135.23 (1F, d, $^3J_{FF}$ 23.1, F-3); δ_H 8.53 (1H, d, $^3J_{HH}$ 6.9, H-9), 7.45 (1H, dm, $^3J_{HH}$ 6.9, H-7), 7.02 (m, H-8), 2.73 (3H, br s, CH_3); δ_C 151.79 (s, C-2a), 146.35 (dd, $^1J_{CF}$ 245.5, $^2J_{CF}$ 17.3, C-2), 145.72 (dd, $^1J_{CF}$ 268.5, $^2J_{CF}$ 31.6, C-3), 134.72 (d, $^3J_{CF}$ 2.9, C-2'd), 133.50 (m, C-3'd), 131.03 (s, C-7), 128.94 (s, C-6), 122.31 (s, C-9), 113.28 (s, C-8), 109.91 (d, $^3J_{CF}$ 5,0, CN), 101.49 (dd, $^2J_{CF}$ 13.0, $^3J_{CF}$ 4.5, C-4), 17.03 (s, CH_3); *m/z* (EI) 243.8 (M^+, 100 %).

2-Diethylamino-3-fluoro-6-methyl-dipyrido[1,2-a;3',2'-d]imidazole-4-carbonitrile, **52**

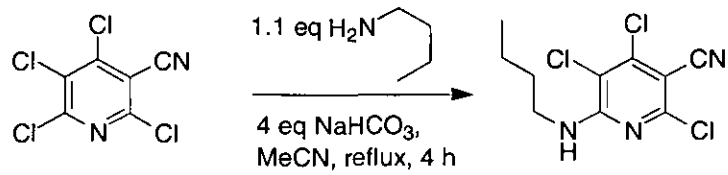


2,3-difluoro-6-methyl-dipyrido[1,2-a,3',2'd]imidazole-4-carbonitrile (0.05 g, 0.20 mmol) and diethylamine (0.07 g, 1.0 mmol) were stirred together in THF, under microwave heating, for 30 min at 150 °C. ^{19}F NMR of the reaction mixture showed no starting material remaining and one major new resonance. The reaction was worked up and the dark orange crude purified by preparative HPLC to give *2-diethylamino-3-fluoro-6-methyl-dipyrido[1,2-a;3',2'-d]imidazole-4-carbonitrile* **52** (0.01 g, 17 %) as a yellow solid; δ_F -125.47 (s, F-3); δ_H 8.40 (1H, d, $^3J_{HH}$ 6.8, H-9), 7.22 (1H, dm, $^3J_{HH}$ 6.7, H-7), 6.83 (1H, m, H-8), 3.61 (4H, qd, $^3J_{HH}$ 6.9, $^5J_{HF}$ 1.7, CH_2), 2.67 (3H, br s, CH_3), 1.28 (6H, t, $^3J_{HH}$ 6.9, $CH_2\mathbf{CH_3}$); *m/z* (ES^+) 298.1 ($M^+ + H^+$, 100 %).

Chapter 12

Experimental to Chapter 6

6-Butylamino-2,4,5-trichloro-nicotinonitrile, **53**

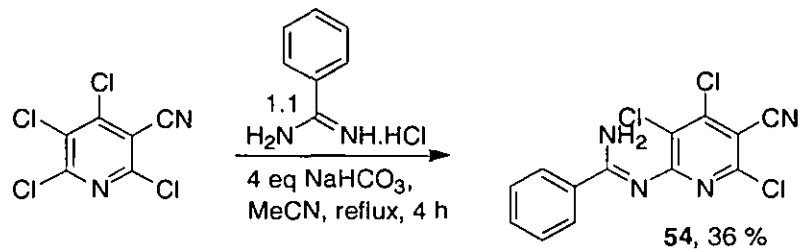


53, 13 %

A mixture of 2,4,5,6-tetrachloro-nicotinonitrile (1.21 g, 5.00 mmol), butylamine (0.40 g, 5.50 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) were refluxed together in MeCN (100 mL), under an atmosphere of dry argon, for 4 h. No starting material was observed by tlc. The reaction was evaporated and poured onto water (100 mL). Extraction of the organic products into DCM (4 x 30 mL), drying of the fractions ($MgSO_4$), and evaporation, gave an off-white solid. Column chromatography (silica, hexane: ethyl acetate, 10 : 1) gave 2 fractions. The major fraction (0.48 g, yellow solid) consisted of predominantly 1 compound (by ^{13}C NMR). Recrystallisation from MeCN yielded *6-Butylamino-2,4,5-trichloro-nicotinonitrile* **53** (0.18 g, 13 %) as an off-white solid; m.p. 137-141 °C; ([M + H^+] 278.0012. $C_{10}H_{11}N_3Cl_3$ requires [M + H^+] 278.0019); δ_H 5.77 (br s, NH), 3.53 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.41 (2H, m, CH_2), 0.96 (3H, t, $^3J_{HH}$ 7.4, CH_3); δ_C 155.07, 151.72, 143.67, 113.92, 112.10, 98.44, 42.09, 31.27, 20.10, 13.85; *m/z* (EI) 280.9 (M^+, 4 %; ^{37}Cl, ^{37}Cl, ^{35}Cl), 278.9 (M^+, 8 %; ^{37}Cl, ^{35}Cl, ^{35}Cl), 276.9 (M^+, 8 %; ^{35}Cl, ^{35}Cl, ^{35}Cl), 237.9 (M^+ - C_3H_7, 34 %; ^{37}Cl, ^{37}Cl, ^{35}Cl), 235.9 (M^+- C_3H_7, 100 %; ^{37}Cl, ^{35}Cl, ^{35}Cl), 233.9 (M^+ - C_3H_7, 100 %; ^{35}Cl, ^{35}Cl, ^{35}Cl). Crystals for X-ray analysis were grown from $CDCl_3$.

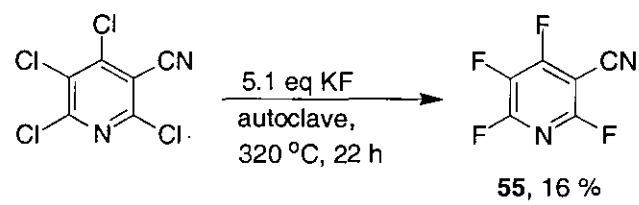
The minor fraction (0.17 g off-white solid), was also collected. NMR and MS data was consistent with the 4-substituted regioisomer of the major product.

N-(3,4,6-Trichloro-5-cyano-pyridin-2-yl)-benzamidine, **54**



A mixture of 2,4,5,6-tetrachloro-nicotinonitrile (1.21 g, 5.00 mmol), benzamidine hydrochloride (0.86 g, 5.50 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) were refluxed together in MeCN, under an atmosphere of dry argon, for 4 h. No starting material was observed by tlc. The reaction was evaporated and poured onto water (50 mL). The organic products were extracted into DCM (4 x 30 mL) and the fractions filtered to yield *N-(3,4,6-trichloro-5-cyano-pyridin-2-yl)-benzamidine* **54** (0.59 g, 36 %) as a yellow solid; m.p. 228-231 °C; (Found: C, 48.0; H, 2.1; N, 17.3. $C_{13}H_7Cl_3N_4$ requires: C, 48.0; H, 2.2; N, 17.2 %); δ_H 8.92, 8.71 (2H, br s, NH_2), 8.06 (2H, m, Ar-CH), 7.60 (1H, m, Ar-H), 7.53 (2H, m, Ar-CH); δ_C 160.85, 160.73, 148.59, 144.24, 134.00, 132.06, 128.49, 127.99, 122.60, 133.76, 101.70; *m/z* (EI) 327.9 (M^+, 30 %; ^{37}Cl, ^{37}Cl, ^{35}Cl), 325.9 (M^+, 80 %; ^{37}Cl, ^{35}Cl, ^{35}Cl), 323.9 (M^+, 85 %; ^{35}Cl, ^{35}Cl, ^{35}Cl), 104.0 (PhCHN, 100 %), 77.0 (Ph, 95 %).

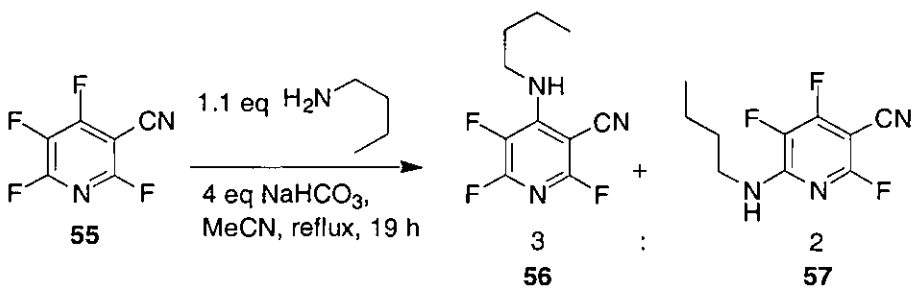
2,4,5,6-Tetrafluoro-nicotinonitrile, **55**



A stainless steel autoclave was charged with 2,4,5,6-tetrachloro-nicotinonitrile (40 g, 0.17 mol) and flame-dried potassium fluoride (50 g, 0.86 mol). The autoclave was sealed and heated at 320 °C for 22 h after which time the reaction mixture was allowed to cool to 200 °C. The gaseous fluorinated products were removed under reduced

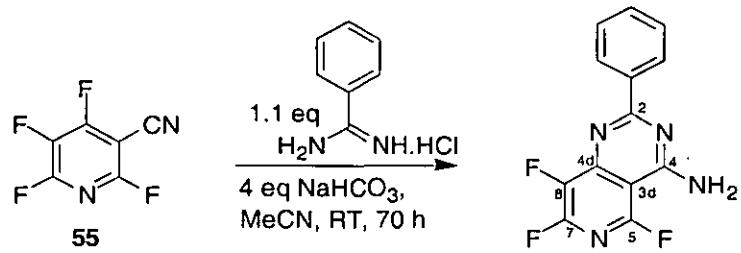
pressure and condensed in a Young's tap-equipped vessel. Distillation of this crude material yielded *2,4,5,6-tetrafluoro-nicotinonitrile* **55** (4.59 g, 16 %) as a colourless oil; b.p. 150 - 154 °C; (Found: C, 40.4; N, 15.9. $C_6F_4N_2$ requires: C, 40.9; N, 15.9 %); δ_F -60.24 (1F, m), -72.26 (1F, m), -106.12 (1F, ddd, $^3J_{FF}$ 24.3, $^4J_{FF}$ 18.8, $^4J_{FF}$ 7.4, F-4), -163.30 (1F, m, F-5); δ_C 160.58 (dm, $^1J_{CF}$ 277.8, CF), 155.70 (dm, $^1J_{CF}$ 254.3, CF), 152.79 (dm, $^1J_{CF}$ 255.1, C-4), 133.21 (dm, $^1J_{CF}$ 264.4, C-5), 106.22 (d, $^3J_{CF}$ 5.5, CN), 87.62 (dm, $^2J_{CF}$ 35.9, C-3); *m/z* (EI) 175.9 (M^+, 100 %).

Reaction with butylamine



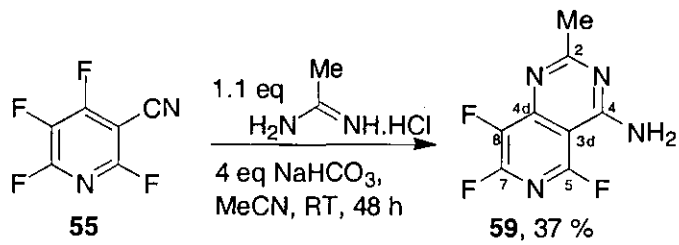
A mixture of 2,4,5,6-tetrafluoro-nicotinonitrile **55** (0.88 g, 5.00 mmol), butylamine (0.40 g, 5.50 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) were refluxed together in MeCN (100 mL), under an atmosphere of dry argon, for 19 h. No starting material was observed by ^{19}F NMR. The reaction was evaporated and poured onto water (50 mL). Extraction of the organic products into DCM (3 x 50 mL), drying of the fractions ($MgSO_4$), and evaporation, gave a yellow solid. ^{19}F NMR of the crude showed there to be two major products, *4-butylamino-2,5,6-trifluoro-nicotinonitrile* **56** (-73, -97 and -176 ppm) and *6-butylamino-2,4,5-trifluoro-nicotinonitrile* **57** (-70, -131, -177 ppm), in a 3:2 ratio. No further purification was carried out.

5,7,8-Trifluoro-2-phenyl-pyrido[4,3-d]pyrimidin-4-ylamine **58**



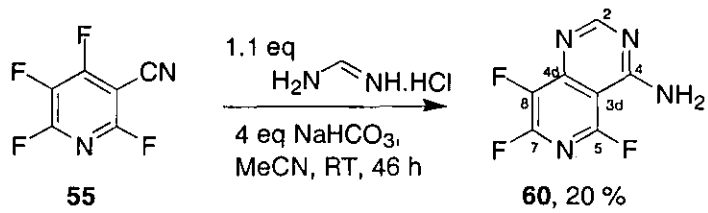
A mixture of **55** (0.88 g, 5.00 mmol), benzamidine hydrochloride (0.86 g, 5.50 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) were stirred together in MeCN, under an atmosphere of dry argon, for 70 h. No starting material was observed by ^{19}F NMR. The reaction was evaporated and poured onto water (50 mL). The organic products were extracted into DCM (3 x 50 mL) and the fractions filtered to remove a yellow solid. Recrystallisation from MeCN gave *5,7,8-trifluoro-2-phenyl-pyrido[4,3-d]pyrimidin-4-ylamine* **58** (0.84 g, 60 %) as a pale yellow solid; m.p. 195-198 °C; (Found: C, 56.4; H, 2.5; N, 20.3. $C_{13}H_7F_3N_4$ requires: C, 56.5; H, 2.6; N, 20.3 %); δ_F -59.19 (1F, dd, $^3J_{FF}$ 29.7, $^4J_{FF}$ 11.3, F-7), -91.54 (dd, $^5J_{FF}$ 19.1, $^4J_{FF}$ 12.2, F-5), -161.31 (dd, $^3J_{FF}$ 29.6, $^5J_{FF}$ 19.0, F-8); δ_H 8.82 (br s, NH), 8.42 (2H, m, H-2'), 7.92 (d, J_{HF} 6.0, NH), 7.56 (1H, m, H-4'), 7.52 (2H, m, H-3'); δ_C 164.74 (s, C-2), 159.67 (d, $^3J_{CF}$ 6.8, C-4), 152.02 (ddd, $^1J_{CF}$ 250.1, $^2J_{CF}$ 16.8, $^3J_{CF}$ 2.6, C-7), 151.73 (m, C-4d), 147.96 (ddd, $^1J_{CF}$ 238.8, $^3J_{CF}$ 19.0, $^4J_{CF}$ 15.2, C-5), 136.58 (s, Ar-C), 133.47 (ddd, $^1J_{CF}$ 253.8, $^2J_{CF}$ 23.0, $^4J_{CF}$ 8.1, C-8), 131.77 (s, Ar-CH), 128.69 (s, Ar-CH), 128.46 (s, Ar-CH), 97.15 (dd, $^2J_{CF}$ 27.4, $^3J_{CF}$ 3.7, C-3d); *m/z* (EI) 275.8 (M^+, 100 %).

5,7,8-Trifluoro-2-methyl-pyrido[4,3-d]pyrimidin-4-ylamine **59**



A mixture of **55** (0.88 g, 5.00 mmol), acetamidine hydrochloride (0.52 g, 5.50 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) were stirred together in MeCN, under an atmosphere of dry argon, for 48 h. The reaction was evaporated and poured onto water (50 mL). The organic products were extracted into DCM (3 x 40 mL), dried ($MgSO_4$) and evaporated to give a yellow solid (0.84 g). Recrystallisation from MeCN gave *5,7,8-trifluoro-2-methyl-pyrido[4,3-d]pyrimidin-4-ylamine* **59** (0.40 g, 37 %) as a pale yellow solid; m.p. 217-219 °C; (Found: C, 44.8; H, 2.3; N, 26.2. $C_8H_5F_3N_4$ requires: C, 44.9; H, 2.4; N, 26.2 %); δ_F -58.95 (1F, dd, $^3J_{FF}$ 30.2, $^4J_{FF}$ 10.4, F-7), -91.76 (dd, $^5J_{FF}$ 19.0, $^4J_{FF}$ 12.2, F-5), -161.79 (dd, $^3J_{FF}$ 29.7, $^5J_{FF}$ 19.2, F-8); δ_H 8.72 (1H, br s, NH), 7.82 (1H, br s, NH), 2.42 (3H, br s, CH_3); δ_C 170.32 (s, C-2), 159.81 (d, $^3J_{CF}$ 6.7, C-4), 152.57 (ddd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 16.8, $^3J_{CF}$ 2.6, C-7), 151.96 (m, C-4d), 148.33 (ddd, $^1J_{CF}$ 240.0, $^3J_{CF}$ 18.8, $^4J_{CF}$ 15.1, C-5), 135.53 (ddd, $^1J_{CF}$ 252.5, $^2J_{CF}$ 23.2, $^4J_{CF}$ 8.4, C-8), 97.11 (dd, $^2J_{CF}$ 27.5, $^3J_{CF}$ 3.6, C-3d), 26.22 (s, CH_3); *m/z* (EI) 213.9 (M^+, 100 %). Crystals suitable for X-ray analysis were grown from MeCN.

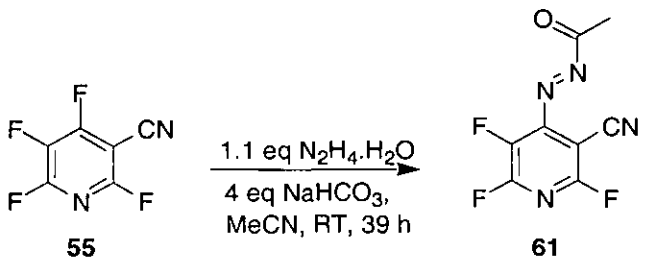
5,7,8-Trifluoro-pyrido[4,3-d]pyrimidin-4-ylamine **60**



A mixture of **55** (0.88 g, 5.00 mmol), formamidine hydrochloride (0.44 g, 5.50 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) were stirred together in MeCN, under an atmosphere of dry argon, for 46 h. The reaction was evaporated and poured onto water (50 mL). The organic products were extracted into DCM (3 x 40 mL), dried ($MgSO_4$) and evaporated to give an off-white solid (0.92 g). Recrystallisation from MeCN gave *5,7,8-trifluoro -pyrido[4,3-d]pyrimidin-4-ylamine* **60** (0.20 g, 20 %) as a white solid; m.p. 196-200 °C; (Found: C, 41.9; H, 1.4; N, 28.0. $C_7H_3F_3N_4$ requires: C, 42.0; H, 1.5; N, 28.0 %); δ_F (DMSO-d_6) -58.26 (1F, dm, $^3J_{FF}$ 30.3, F-7), -91.22 (1F, dd, $^5J_{FF}$ 18.8, $^4J_{FF}$ 12.1, F-5), -161.23 (1F, dd, $^3J_{FF}$ 30.3, $^5J_{FF}$ 18.8, F-8); δ_H 8.86, 7.99 (br s,

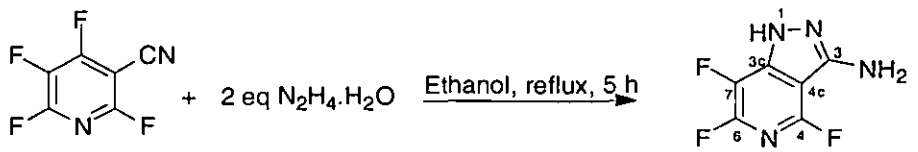
NH), 8.58 (s, H-2); δ_C 160.53 (s, C-2), 159.34 (d, $^3J_{CF}$ 6.6, C-4), 151.85 (ddd, $^1J_{CF}$ 250.9, $^2J_{CF}$ 16.1, $^3J_{CF}$ 2.9, C-7), 150.79 (m, C-4d), 147.65 (ddd, $^1J_{CF}$ 239.1, $^3J_{CF}$ 18.6, $^4J_{CF}$ 15.1, C-5), 135.32 (ddd, $^1J_{CF}$ 253.4, $^2J_{CF}$ 22.3, $^4J_{CF}$ 8.5, C-8), 98.40 (dd, $^2J_{CF}$ 27.6, $^3J_{CF}$ 3.8, C-3d); *m/z* (EI) 199.9 (M^+, 100 %).

Attempted Synthesis of *4,6,7-Trifluoro-1H-pyrazolo[4,3-c]pyridine-3-ylamine*



Hydrazine hydrate (0.28 g, 5.50 mmol) was syringed into a stirring solution of **55** (0.88 g, 5.00 mmol) and sodium hydrogen carbonate (1.68 g, 20.00 mmol) in MeCN (100 mL), under an atmosphere, at room temperature. ^{19}F NMR after 39 h showed three new major resonances. The reaction was evaporated and the crude poured onto water (50 mL). The pH was adjusted to 2 and the organic products extracted into DCM (3 x 40 mL). Drying ($MgSO_4$) and evaporation yielded a pale yellow solid (0.63 g). Recrystallisation from MeCN gave a yellow solid (0.58 g) corresponding to **61**; δ_F (DMSO-d_6) -65.41 (1F, dd, $^3J_{FF}$ 20.4), -89.77 (1F, dd, $^5J_{FF}$ 21.4, $^4J_{FF}$ 11.3), -164.66 (1F, m, F-7); δ_H 10.64 (br s, NH), 2.03; δ_C 160.20, 158.11 (ddd, J_{CF} 240.4, J_{CF} 18.8, J_{CF} 2.0), 149.47 (ddd, J_{CF} 238.0, J_{CF} 20.5, J_{CF} 13.6), 146.73 (dm, J_{CF} 10.6), 129.31 (ddd, J_{CF} 246.5, J_{CF} 28.1, J_{CF} 5.4), 112.15 (d, J_{CF} 5.2), 78.48 (ddd, J_{CF} 37.7, J_{CF} 3.3, J_{CF} 2.5), 24.09, 18.17; *m/z* (EI) 228.0 (M^+, 30 %), 187.1 (60 %), 144.9 (55 %), 55.9 (100 %)

4,6,7-Trifluoro-1H-pyrazolo[4,3-c]pyridine-3-ylamine, **62**



55 **62**, 9 %

55 (1.76 g, 10.00 mmol) and hydrazine hydrate (1.00 g, 20.00 mmol) were refluxed in ethanol (200 mL) for 5 h. ^{19}F NMR showed there to be 3 main peaks and no starting material to be remaining. Water (50 mL) was added and the ethanol evaporated. The organic products were extracted into DCM (3 x 30 mL). Drying ($MgSO_4$) and evaporation gave a dark red solid. Recrystallisation from MeCN yielded *4,6,7-Trifluoro-1H-pyrazolo[4,3-c]pyridine-3-ylamine* **62** (0.16 g, 9 %) as a pale red solid; m.p. 192 °C (decomposed); (Found: C, 38.5; H, 1.7; N, 29.8. $C_6H_3N_4F_3$ requires: C, 38.3; H, 1.6; N, 29.8 %); δ_F (DMSO-d_6) -72.11 (1F, dd, $^3J_{FF}$ 30.0, $^4J_{FF}$ 11.1, F-6), -104.37 (1F, dd, $^5J_{FF}$ 19.0, $^4J_{FF}$ 11.8, F-4), -170.25 (1F, dd, $^3J_{FF}$ 29.8, $^5J_{FF}$ 19.2, F-7); δ_H 13.00 (1H, s, NH), 5.88 (2H, s, NH_2); δ_C 148.68 (d, $^3J_{CF}$ 5.6, C-3), 147.24 (dd, $^1J_{CF}$ 244.4, $^2J_{CF}$ 17.6, C-6), 144.79 (ddd, $^1J_{CF}$ 229.5, $^3J_{CF}$ 16.9, $^4J_{CF}$ 14.5, C-4), 139.02 (m, C-3c), 127.52 (ddd, $^1J_{CF}$ 248.7, $^2J_{CF}$ 29.4, $^4J_{CF}$ 8.0, C-7), 100.22 (d, $^2J_{CF}$ 38.5, C-4c); *m/z* (EI) 188.0 (M^+, 100 %).