Polyfunctionalised pyrimidines and pyrazines from perhalogenated precursors

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A Thesis Entitled

Polyfunctionalised Pyrimidines and Pyrazines from Perhalogenated Precursors

Submitted by

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Memorandum

The work presented within this thesis was carried out at Durham University between October 2004 and December 2007. 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.

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Statement of Copyright

Abbreviations

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binapthyl
DBA	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-8-ene
DCM	Dichloromethane
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

Abstract

Chapter 1 introduces the modern pharmaceutical industry in terms of the drug discovery process leading into a discussion of the relevance of heterocyclic compounds with particular focus on the synthesis of multifunctional pyrimidines and pyrazines. An introduction into organofluorine chemistry is included followed by a review of the literature on 5-chloro-trifluoropyrimidine, tetrafluoropyrimidine and tetrafluoropyrazine.

Chapter 2 describes a study of the reactivity of 5-chlorotrifluoropyrimidine with mono- and difunctional-nucleophiles. This research demonstrates the former are not selective and in the latter the 5-position chlorine atom is inert to nucleophilic aromatic substitution and cross-coupling methodologies.

Chapter 3 explores the reactivity of tetrafluoropyrimidine with nitrogen, sulphur and oxygen containing nucleophiles and describes the development of a methodology for the synthesis of multisubstituted pyrimidines by establishing the regioselectivities of such processes.

Chapter 4 investigates the reactivity of tetrafluoropyrimidine with difunctional nucleophiles. This study indicated it was not possible to synthesise [5,6]-ring fused systems and that in some cases dimers were formed owing to the 5-position fluorine atom being inactive substitution.

Chapter 5 discusses the use of tetrafluoropyrazine in the syntheses of [5,6] ring-fused systems. The reactivity of the system towards *N,N*-dinucleophiles and C,O-dinucleophiles was investigated. Further functionalisations by nucleophilic aromatic substitution of the remaining fluorine atoms with nitrogen and oxygen nucleophiles are also discussed.

Chapter 6 contains the experimental data for Chapters 2 to 5.

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Chapter 1

Introduction

1.1 The Pharmaceutical Industry – A Brief History

Tracing the historical roots of the modern pharmaceutical industry leads to precedents established in the 19th century as a consequence of the development of synthetic dyestuffs. The earliest dye to be commercially successful was mauveine synthesised by William Perkin who, in 1865, serendipitously discovered that oxidising allyltoluidine with potassium dichromate produced a purple dye.[1] Further research in this field led to numerous synthetic compounds for dying fabrics, including dyes based on aniline, toluidine and quinoline. Companies including F. Bayer & Company and Farbenfabriken Hoeschst recognised that dyes and aromatics could have pharmaceutical applications as proven by the discovery of Aspirin in 1897. In the 21st century, the challenge remains to produce new and improved pharmaceuticals to advance the treatment of diseases and drug discovery remains as relevant today as in previous centuries.

1.1.1 The Modern Pharmaceutical Industry – The Drug Discovery Process

The process required to develop drugs for the market is highly complex and commercially risky because thousands of compounds screened for biological activity prove to be unsuccessful. To overcome these problems a number of strategies are employed in the early stages of drug discovery using targeted programs in an attempt to discover commercially viable candidates. In the late 1980s and early 1990s the major focus for drug discovery involved developing high throughput strategies (HTS) and combinatorial methods to supply many thousands of compounds that could be screened *in vitro* to deliver lead compounds possessing desired pharmacokinetic properties.[2-6]

In fact it is now widely accepted that creating vast libraries of compounds by this process has not resulted in the expected rise of lead compounds and in creating libraries of diverse compounds, many molecules possess undesirable properties, low diversity or few functional groups and consequently were not 'drug-like' in nature.[7-9] Attempts to understand and develop a systematic way of screening compounds have shown that molecules that are most likely to become lead compounds have to possess the right physicochemical (e.g. solubility, stability) and biological properties (e.g. absorption, distribution, metabolism, elimination and toxicity; ADME-Tox).[10] Thus library design had to change to become more oriented towards designing compounds with drug-like or lead-like properties.

In 1997 Lipinski published work outlining his "rules of five" (RO5) which gives a series of defined physiochemical relationships for medicinal chemists to use when developing compounds that have an increased likelihood of passing through successive screening campaigns as orally taken medicines, which are outlined below.[11, 12]

Rule of 5.[13]

- Molecular Weight ≤ 500
- The calculated log of the octanol/water partition coefficient, ClogP ≤ 5
- Hydrogen-bond donors ≤ 5
- Hydrogen-bond accepters (sum of N and O atoms) ≤ 10

Extensions.[14]

- The Polar surface area ≤ 140 Å^2 or sum of hydrogen-bond donors and acceptors ≤ 12
- Rotatable bonds ≤ 10

The RO5 is a useful set of physiochemical filters and if a compound fails to match the outlined criteria it is highly probable there will be issues with, for example, solubility and permeability. It must also be noted that structural features which make compounds 'drug-like' are not fully understood[15] as exemplified by some of the exceptions[11] e.g. antibiotics, antifungals, vitamins, and cardiac glycosides. Also, RO5 compliant molecules may not

possess the correct efficacy even though the rules have been met. Nevertheless, the RO5 is a useful criteria for analysing and categorising drug-like entity libraries and there has been a recent paradigm shift of thinking for medicinal chemists to encompass such ideas.[12]

The RO5 is useful in terms of defining physicochemical properties to improve lead-like compounds but do not guide the medicinal chemist on which types of structures need to be synthesised. Other approaches that have been undertaken involve increasing the structural diversity of molecules through modification of functional groups in an effort to provide a versatile mode of binding the pharmacophore, which is termed a 'privileged structure'. [16, 17]

Privileged structures

- Physiochemically active (obeys "rules of five" particularly $MW \leq 500$)[18]
- Present in a large amount of natural products with various biological activities
- Contains one or more rigid ring systems and easily chemically modified to produce a diverse library range.

Consequently numerous libraries of compounds have been synthesised[18] but the challenge still remains to develop candidates that will be effective against a biological target and possess excellent efficacy.

1.1.2 Heterocyclic Compounds

Heterocyclic compounds are very important in drug discovery as emphasised by the fact that 70% of all drug-like entities are based around a heterocyclic sub-structure and are often found in biologically important systems.[19] However, synthesising functionalised heterocycles - especially analogues for drug discovery - is challenging owing to, in general, a low reactivity towards nucleophiles and electrophiles as well as difficulties in obtaining defined regiochemistries.[20, 21] It therefore becomes imperative to design and implement synthetic strategies to synthesise functionalised heterocycles in a flexible and straightforward manner to provide compounds for lead identification.

To overcome such synthetic challenges many methodologies have been employed including parallel, combinatorial, diversity orientated and rapid analogue synthesis.[22] As this thesis is concerned with the synthesis of multifunctional diazine systems the following section provides an overview of methodology for the synthesis of relevant diazine systems as an introduction to the field.

1.1.3 Multifunctional Diazines – Pyrimidines and Pyrazines

Diazines such as pyrimidine and pyrazine are heterocycles that contain two nitrogen atoms with either a 1,3 or a 1,4 nitrogen pattern as shown in Figure 1.1.

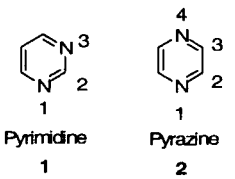


Figure 1.1

Heterocyclic compounds containing a pyrimidine or pyrazine ring are targets for medicinal application due to their observed pharmacological activity which can be shown from the extensive range of commercially available drugs containing these motifs, examples of which are shown in Figure 1.2.[23]

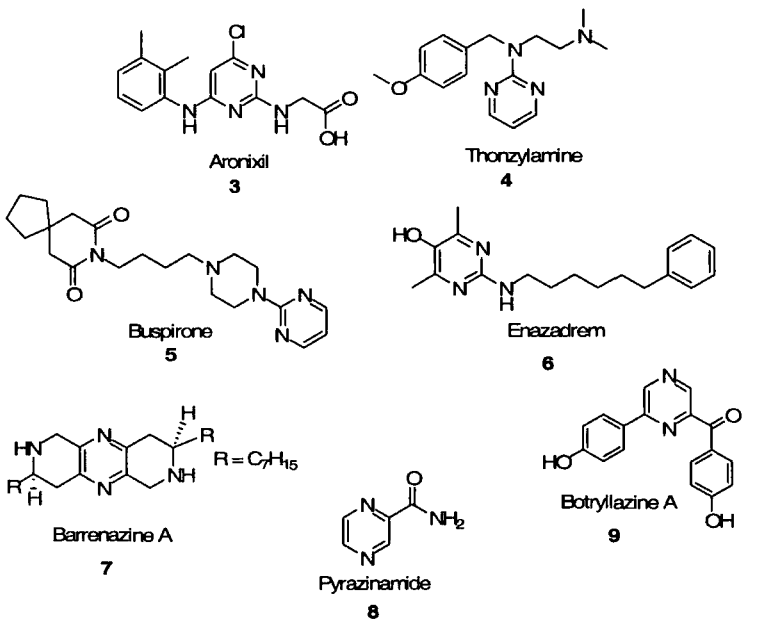


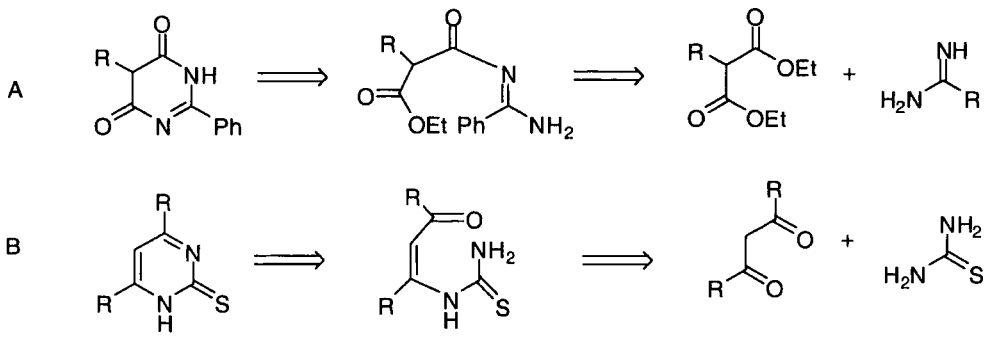
Figure 1.2

1.1.4 The General Syntheses of Multifunctional Diazines –Pyrimidines and Pyrazines

Comprehensive reviews within the literature show there are numerous routes to synthesise pyrimidines and pyrazines.[24-28] The following sections will briefly review the most common methods to construct multifunctional systems from aliphatic, carbon- and heterocyclic synthons as these motifs will appear frequently within this thesis.

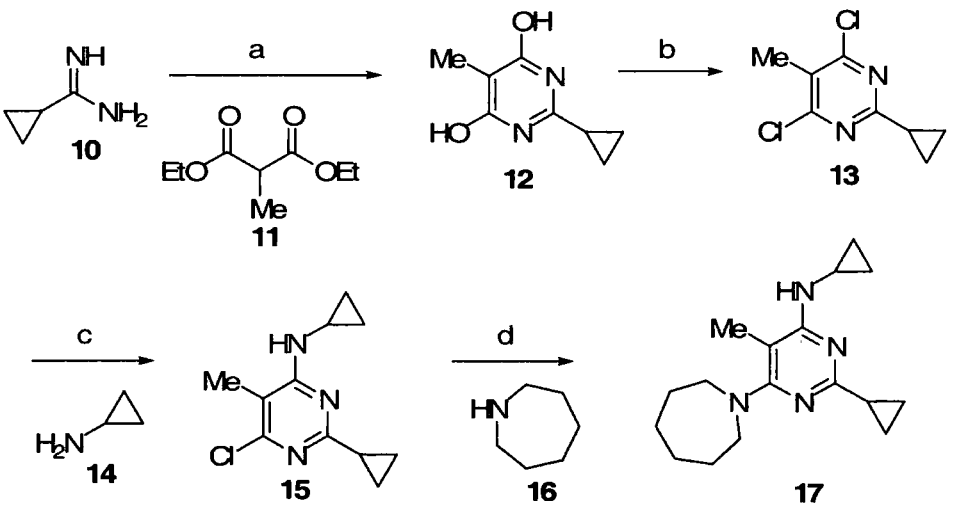
1.1.5 Multifunctional Pyrimidines and Pyrazines from Aliphatic Precursors

Synthesis of the pyrimidine core most commonly involves cyclocondensation by the reaction of amidines, guanidine or thiourea (N-C-N reagents) with 1,3-diketones, or 1,3-diesters (C-C-C reagents).[29]



Scheme 1.1

For example, pathway A (scheme 1.1) has recently been utilised in the creation of a library of compounds as M_3 antagonists and PDE4 inhibitors used for treating bronchodilating and anti-inflammatory ailments.

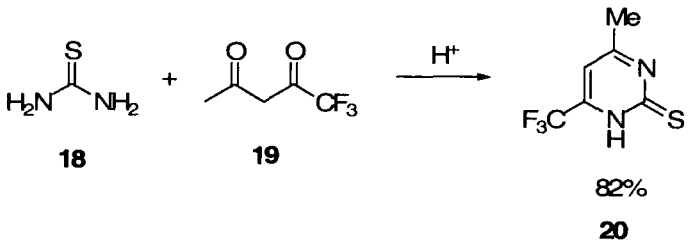


a) NaOEt, EtOH, 60 °C; b) $POCl_3$, *N,N*-diethylaniline, 100 °C; c) neat **14**, 45 °C; d) neat **16**, 100–120 °C;

Scheme 1.2

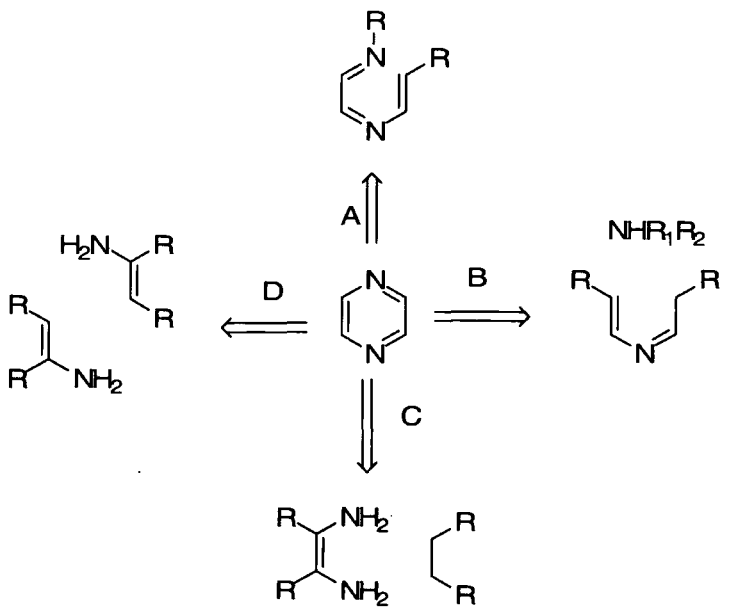
Compound **17** is synthesised through the reaction of compounds **10** and **11** in the presence of base to give the dihydroxypyrimidine, **12**, that is subsequently chlorinated with phosphorus oxychloride. Pyrimidine **13** is then subjected to reaction with primary and secondary amines **14** and **16** to displace the chlorine atoms, with compound **17** exhibiting the most potent physiochemical properties.[30]

Pathway B was also used in the synthesis of pyrimidine derivatives from the cyclisation of a 1,1,1-trifluoropentane-2,4-dione, **19**, with thiourea, **18**, to yield a functionalised pyrimidine, **20**.[31]



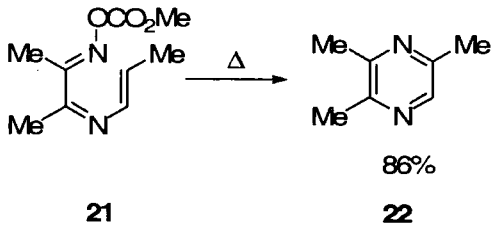
Scheme 1.3

Similarly, functionalised pyrazines can be synthesised through various methods of cyclocondensation as outlined in the general retrosynthetic treatment below, although it must be noted this is not an exhaustive list.



Scheme 1.4

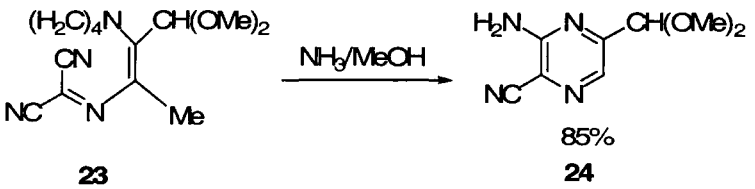
Retrosynthetic path **A** illustrates the synthon is N-C-C-N-C-C with the pyrazine formed through the cyclisation of intermediates such as when compound **21** is cyclised to 2,3,5-trimethylpyrazine, **22**, by brief thermolysis at 300 °C in toluene as shown in Scheme 1.5.



21 **22**

Scheme 1.5

Use of a one-atom and a five-atom synthon approach (Path C) is exemplified when ammonia is reacted with compound **23** as shown in Scheme 1.6.

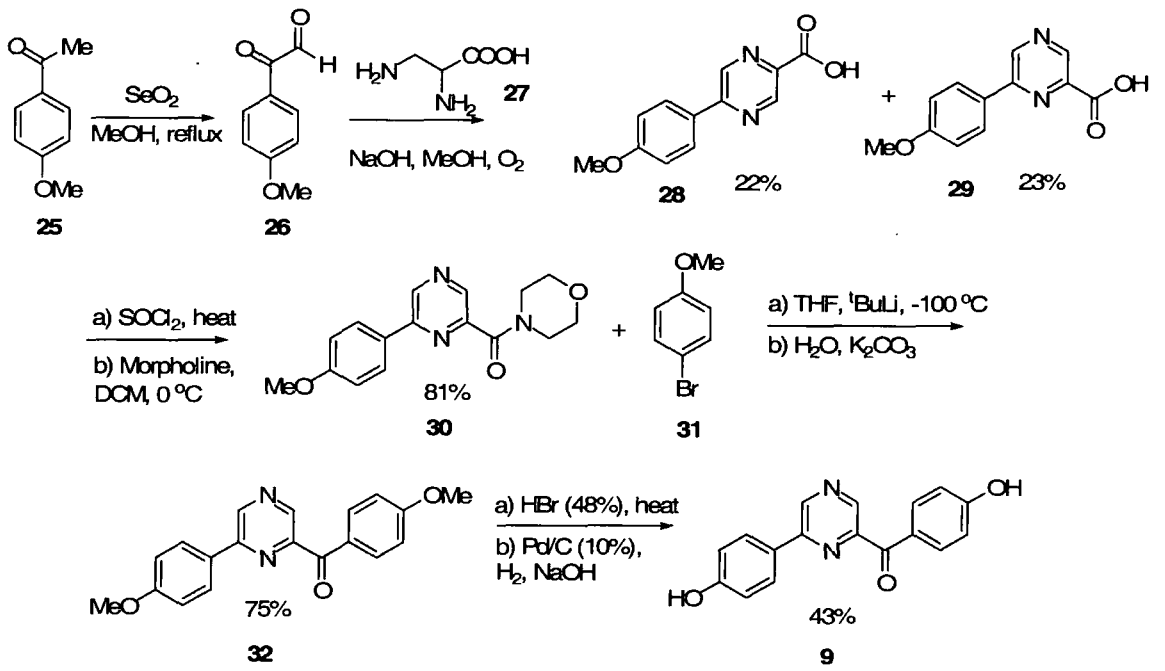


23 **24**

Scheme 1.6

Path **D** shows a two-atom and four-atom synthon approach which has been used to synthesise biologically relevant compounds as shown in Scheme 1.7.

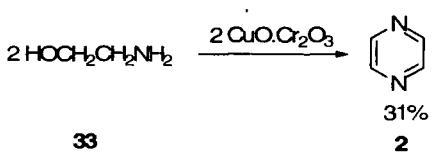
The pyrazine botryllus, **9**, has been shown to exhibit tumour inhibiting properties and is extracted from the red ascidian *Botryllus Leachi*.[32, 33]



Scheme 1.7

Synthesis was achieved through the oxidation of acetophenone, **25**, by SeO_2 with subsequent ring closure by reaction of the racemic 2,3-diaminopropionic acid, **27**, in methanolic NaOH solution. The isomers **28** and **29** were separated and the required isomer, **29**, was reacted with morpholine after conversion to the acid chloride and subsequent reaction with 4-methoxyphenyllithium. Two-fold demethylation using hydrobromic acid gave compound **9**.

Two three-atom building blocks can be employed (path **E**) and in the following example pyrazine was formed from the condensation of 2-aminoethanol: an N-C-C building block.[27]



Scheme 1.8

1.1.6 Conclusion

The previous section has demonstrated that it is possible to synthesise a selection of functionalised diazines by cyclocondensation processes but, in many syntheses, there remains difficulty in further derivatisation procedures. The following section will discuss how functionalised pyrimidines and pyrazines can be synthesised from halogenated precursors in order to furnish a range of functionalised pyrimidines and pyrazines.

1.1.7 Functionalised Pyrimidines and Pyrazines from Halogenated Precursors

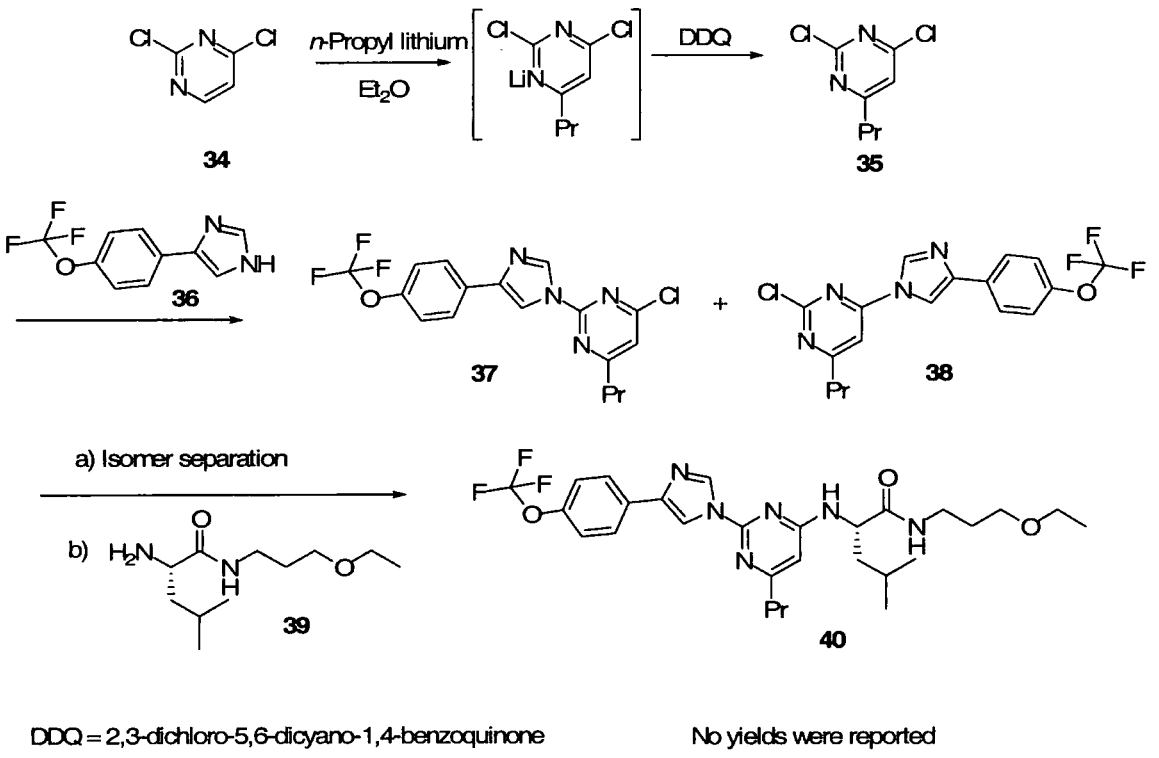
As outlined above, multifunctional pyrimidines and pyrazines are highly desired due to the numerous natural products and synthetic pharmacophores that contain these central heterocyclic cores.[27, 34, 35] Section 1.1.5 demonstrated that routes to synthesise heterocycles containing pyrimidine and pyrazine can be achieved though cyclocondensation reactions and yet such methodologies can suffer from a lack of regio-control as was shown in Scheme 1.7, and there is an added difficulty of synthesising multiple structurally related analogues. In attempts to provide syntheses to a range of structurally related heterocyclic analogues polyhalogenated heterocycles are frequently used as starting materials in drug discovery programmes. Many of the halogenated pyrimidine and pyrazine precursors utilised contain chlorine atoms that can be subjected to nucleophilic aromatic substitution (S_NAr) to produce diverse libraries of compounds and as such are relevant to the research discussed in this thesis.[24, 36] It must be noted at this point that S_NAr is not the only method to introduce functionality into heterocycles as palladium catalysed cross-coupling is commonly used for the functionalisation of heteroaromatic rings. Such methodologies will not be outlined in detail in this thesis but there are a number of reviews that cover this subject area.[36, 37]

Pyrimidines are electron-deficient in nature and, when halogenated, become very amenable to nucleophilic aromatic substitution. There are numerous chloro-pyrimidines that are commercially available and there are various routes to create pyrimidine-based libraries from these cores.[27, 34] Similarly chloro-pyrazines are used in the preparation of functionalised pyrazines as they are readily available from commercial sources.[24, 38]

Nucleophilic aromatic substitution methodologies can be employed for the synthesis of carbon-nitrogen and carbon-oxygen bonds which are very useful in creating numerous hetereoaromatic compounds which have been utilised for drug discovery programmes.[39] The next section 1.1.8 will involve discussing the syntheses of functionalised pyrimidines and pyrazines starting from chlorinated precursors.

1.1.8 Syntheses of Functionalised Pyrimidines

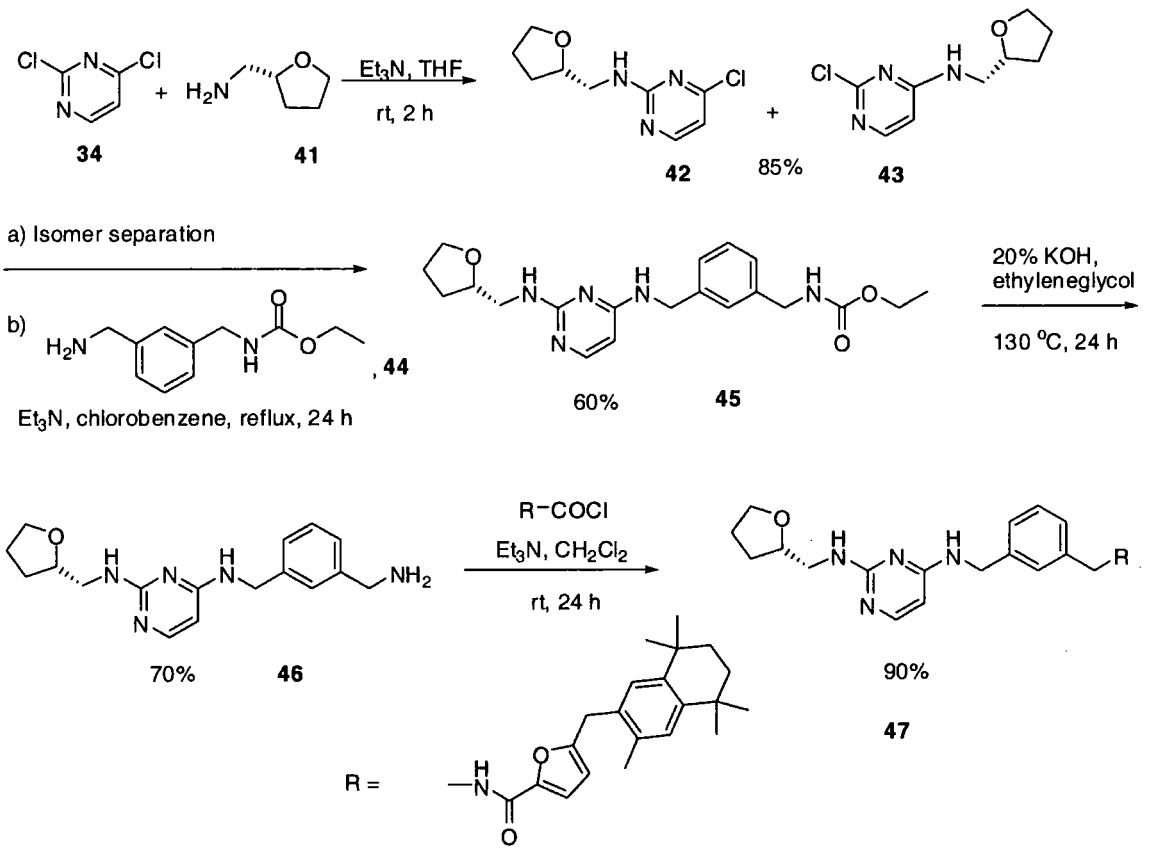
One of these commonly used compounds is 2,4-dichloropyrimidine which has been extensively utilised to synthesise libraries of functionalised pyrimidines. This is exemplified by the development of the imidazolylpyrimidine-based CXCR2 chemokine receptor antagonists that can be used to treat inflammatory diseases. Compound **40** has been synthesised from compound **34** and has been shown to have good potency (K_i < 50 nM) and oral availability (> 20%) in rats.



Scheme 1.9

One of the key steps in the synthesis is the substitution reaction of the 4-trifluoromethoxyphenylimidazole with compound **35** which leads to a product with increased potency against the biological target. Unfortunately, the reaction of compound **35** with the imidazole nucleophile, **36**, gives two isomers by substitution of the chlorine atom at the 2- or 4- position which have to be separated by column chromatography.[40]

In a second example, compound **47** was shown to exhibit behaviour as a novel and potent non peptide gonadotropin releasing hormone (GnRH) receptor antagonist and is also synthesised from compound **34**.

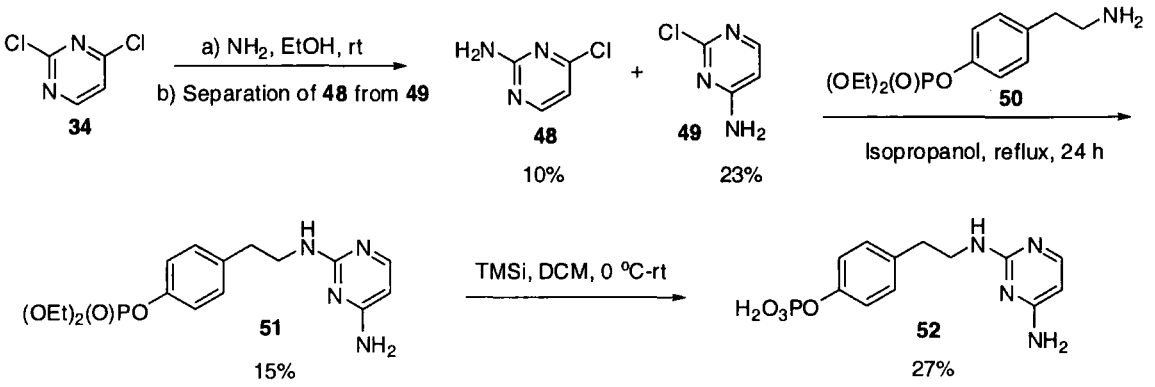


Scheme 1.10

In Scheme 1.9 it was demonstrated that separation of the isomers must be accomplished before further reaction can take place upon the scaffold. This is also true of the reaction shown in Scheme 1.10. Once this is achieved, further functionalisation is carried out by reaction of compound **42** with compound **44** to displace the chlorine atom at the 2-postion

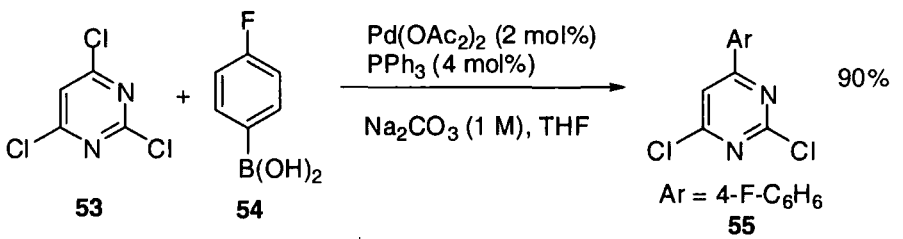
to give compound **45**. Compound **47** is obtained through deprotection of the masked amine in compound **45** and reaction with acyl chloride.[41]

In a third example, compound **52** has been shown to be a non-peptide antagonist of the SH2 domain of GRB2. This methodology, as shown in schemes 1.9 and 1.10, suffers from the formation of regioisomeric pyrimidines in the first step, leading to a low overall yield.[42]



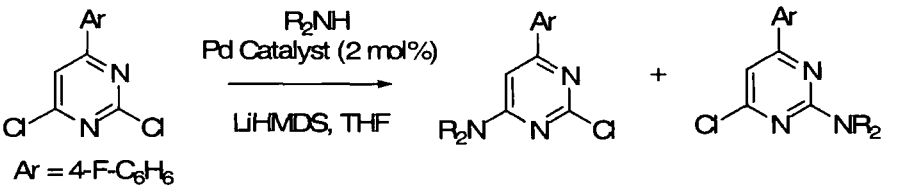
Scheme 1.11

The methodology demonstrated for the reaction of 2,4-dichloropyrimidine can be extended to the study of 2,4,6-trichloropyrimidine, which has the added advantage of an extra chlorine that is available for further functionalisation. Subsequently, compound **53** is coupled at the 4-position under Suzuki-Miyaura conditions with 4-fluorophenylboronic acid, **54,** leaving two chlorine atoms for further reaction.



Scheme 1.12

Palladium-catalysed amination of the 6-aryl derivative using aliphatic amines or anilines displaces the chlorine at the 4-position. Reaction with amines gives mixtures of 2- and 4-amino derivatives depending on the conditions that are used.



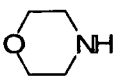
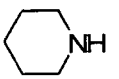
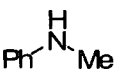
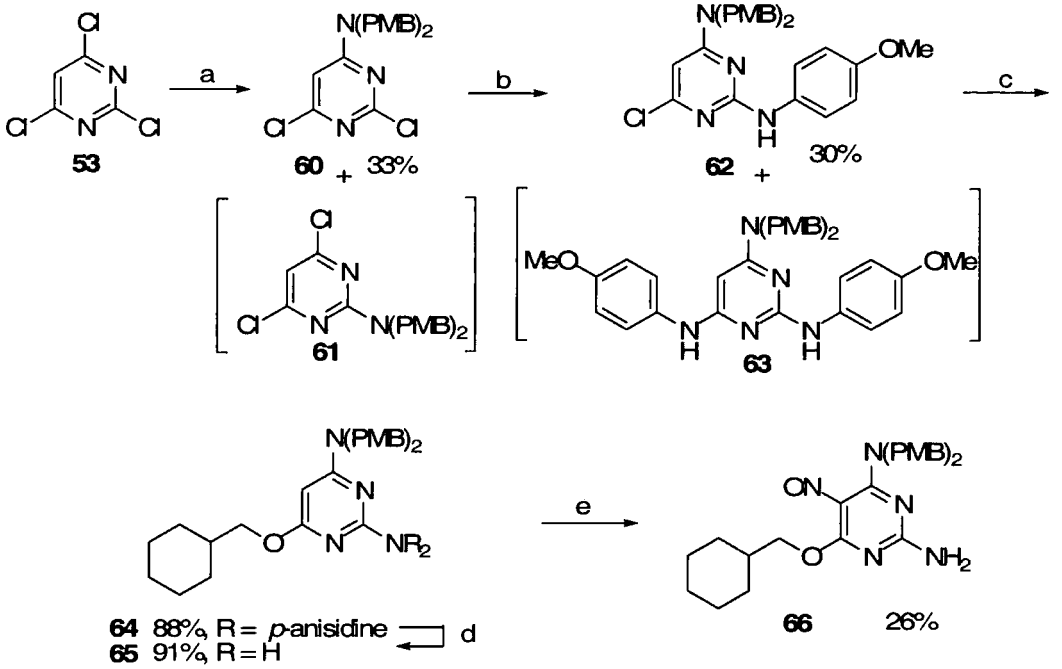
entry	amine	ratio 6:2 (% yield of 6)
56		> 99:1 (93%)
57		97:3 (92%)
58	$PhNH_2$	91:9 (89%)
59		97:3 (93%)

Table 1.1

One limitation is that only aliphatic secondary amines and anilines can be utilised because primary aliphatic amines give bis-aminated side products.[43]

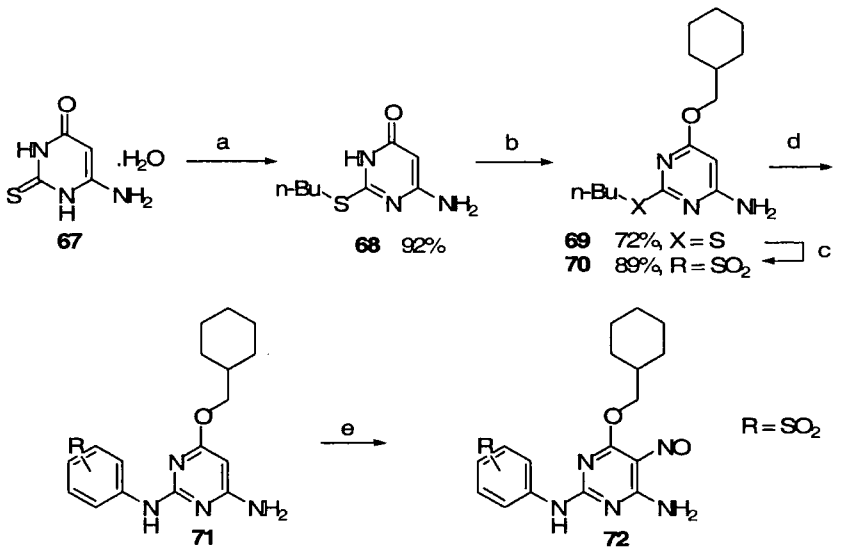
Recently an inhibitor of the cyclin-dependent kinase has been developed starting from compound **53**. However, as regioisomeric products were formed, separation was required as shown in the previous examples. Moreover, the addition of the aniline in the second step was only accomplished under forcing conditions leading to the formation of compounds **62** and **63** which also require a separation.



a) bis-(4-methoxybenzyl)amine, Et_3N, *n*-BuOH, 75 °C; b) *p*-anisidine, Et_3N, *n*-BuOH, DMSO, 95 °C; c) cyclohexylmethanol, Na, 170 °C; d) TFA, 60 °C; e) AcOH, H_2O, $NaNO_2$.

Scheme 1.13

Subsequently, development of a more efficient synthesis using 6-amino-2-mercaptopyrimidin-4-ol was undertaken to allow for reaction with a range of anilines followed by reaction with compound **67** to eliminate the regioselectivity problems found when starting from compound **53** but the yields obtained were moderate.[44]



a) EtOH, NaOH, *n*-BuBr; b) cyclohexylmethanol, PPh_3, DEAD, THF, 0 °C; c) *m*CPBA, DCM; d) R-aniline, TFE, TFA; e) AcOH, H_2O, $NaNO_2$.

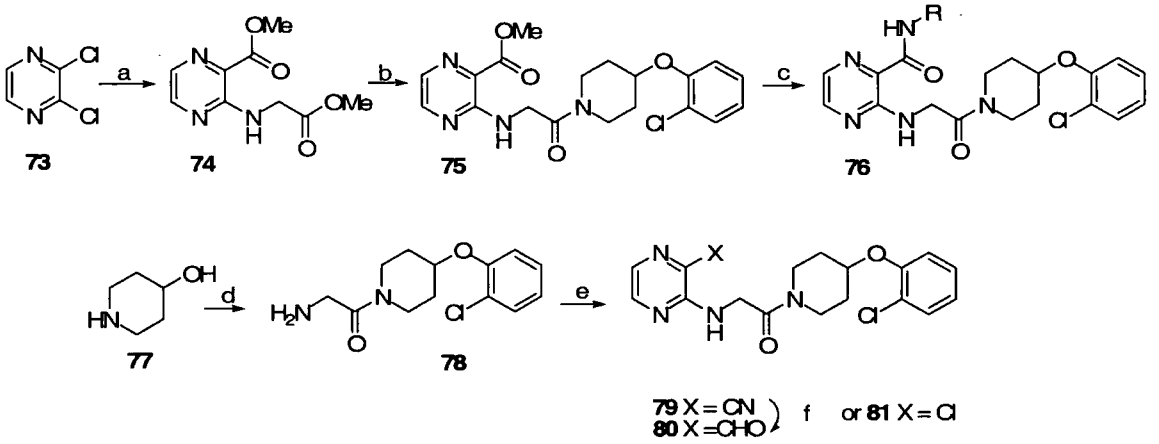
Scheme 1.14

Therefore a need remains for synthetic methodologies that allow for the synthesis of 2,4,6-polysubstituted pyrimidines that are regioselective in all steps and thus amenable for development of compounds of polyfunctional pyrimidine libraries. This is of particular importance within this thesis as a methodology for the sequential nucleophilic aromatic substitution of highly halogenated pyrimidines and pyrazines will be studied in detail.

1.1.9 Syntheses of Functionalised Pyrazines

The pyrazine moiety is not as common as pyrimidine moiety in commercially available drugs but they have been shown in recent studies to exhibit very useful pharmacological activity.

For example, compound **81** has been shown to act as a SCD1 inhibitor that could be used in the treatment of obesity.



a) (i) $NH_2CH_2CO_2$, $^tBu.HCl$, Et_3N, NMP, 150 °C, (ii) $PdCl_2(dppf)$-CH_2Cl_2, CO (60 psi), MeOH, 100 °C, (iii) HCl (4 N in dioxane); b) 4-(2-chlorophenoxy)piperidine hydrochloride, TBTU, Et_3N; c) (i) LiOH, (ii) amines, TBTU, Et_3N; d) (i) *N*-Boc-glycine, TBTU, Et_3N, (ii) 2-chlorophenol, Ph_3P, DEAD, (iii) HCl (4 N in dioxane); e) 2-chloro-3-cyano-pyrazine (for **79** and **80**) or **73** (for **81**), Et_3N, NMP, 140 °C; f) DIBAL-H

Scheme 1.15

Synthesis of compound **74** was achieved through palladium-catalysed carbonylation with the glycyl moiety added through nucleophilic aromatic substitution. Compound **81** showed the most potent activity of a series of analogues.[45]

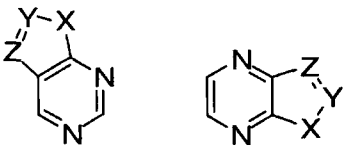
1.1.10 Conclusion

Both of the proceeding sections have demonstrated that although there are some strategies to synthesise functionalised heteroaromatic compounds by sequential S_NAr processes there is still further potential for a more effective methodology. This is particularly true in the case of pyrazine compounds were there are relatively few examples. The aim of this thesis is to utilise the inherent reactivity of perhalogenated pyrimidines and pyrazines towards nucleophilic aromatic substitution to develop a methodology for the synthesis of highly functionalised heterocycles (Chapters 2-5).

1.1.11 Syntheses of [5,6] Ring-Fused Diazines

In this section, discussion of the synthesis of [5,6] ring-fused diazines will be outlined as this area is the second major concern of this thesis.

Syntheses of [5,6] ring-fused systems are important because many of these systems exhibit biological activity and correspondingly are in the top eight most frequently occurring motifs in medicinal drugs. Synthesis of [5,6] ring-fused heteroaromatic compounds containing either a pyrimidine or pyrazine core can be accessed from a variety of routes to furnish a selection of compounds as shown in Figure 1.3.



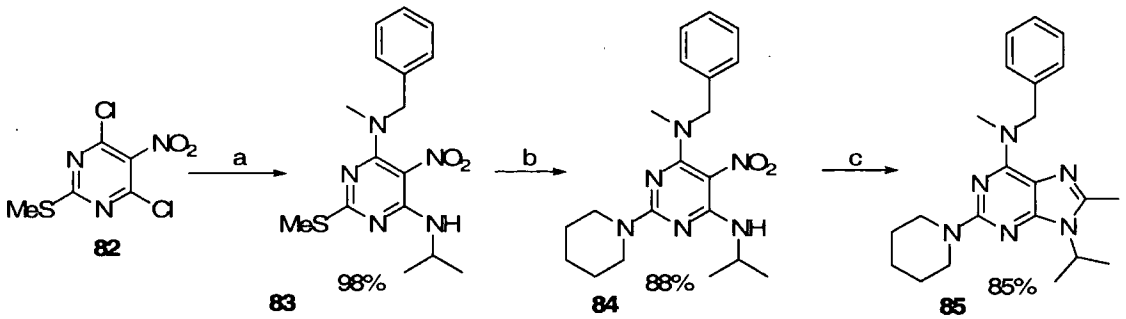
X, Y, Z = CH, NR, N, O

Figure 1.3

1.1.12 Syntheses of [5,6] Ring-Fused Pyrimidines

Ring-fused pyrimidines are import within the drug discovery arena as there are a wide range of drug compounds that contain the pyrimidine system. Novel purines have been shown to exhibit properties as inhibitors of various biological processes and the development of methodologies to synthesise these structures is of importance particularly as they are present in DNA and RNA[46, 47]. The following section will highlight the most common methods available to synthesise such compounds.

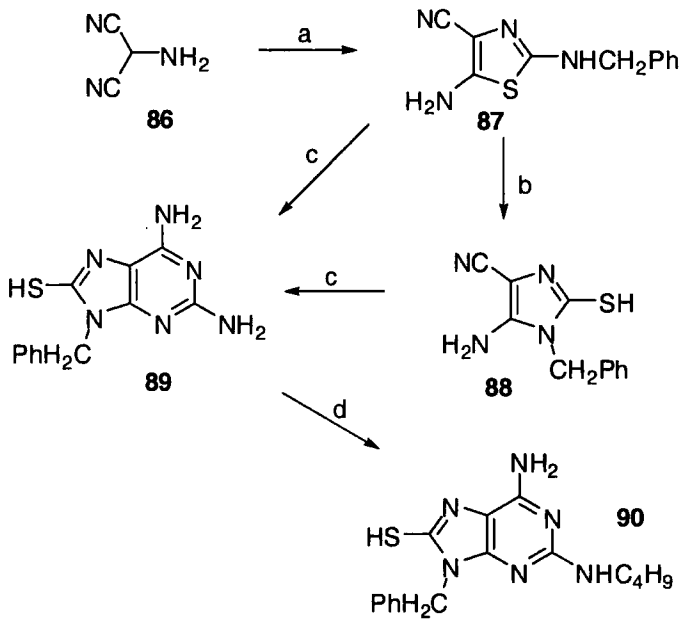
A library of purines starting from **82**, was synthesised with one example shown in figure 1.16 to exemplify the synthetic methodology utilised. Elaboration of 4,6-dichloro-2-(methylthio)-5-nitropyrimidine, **82**, starting with the nucleophilic displacement of chlorine at the 4-position with methylbenzylamine, followed by displacement of the chlorine at the 6-position by isopropylamine. Subsequently the methylthiol group can be oxidised to the sulfone which is then displaced by piperidine. The final step requires the reduction of the nitro group followed by acid catalysed cyclisation to afford purine **85**.[48]



a) Methylbenzylamine (1 eq), THF, DIPEA, 20 min, rt, then isopropylamine (3 eq); b) *m*CPBA, DCM, 16 h, rt, then piperidine; c) $CrCl_2$ (10 eq), 20:1 DMF:MeOH, 4 h, rt then $MeC(OCH_3)_3$, $MeSO_3H$ (cat.), 24 h, 100 °C

Scheme 1.16

Recently biological evaluation of 2,8-disubstituted 9-benzyladenine has shown that they are potent interferon (IFN) inhibitors which are important in the treatment the Hepatitis C virus.



a) $PhCH_2NCS$, THF, 40 °C; b) 5% Na_2CO_3, reflux; c) $H_2NC(NH)NH_2.HCl$, NaOEt, reflux; d) C_3H_7CHO, $NaBH_3CN$, MeOH, rt

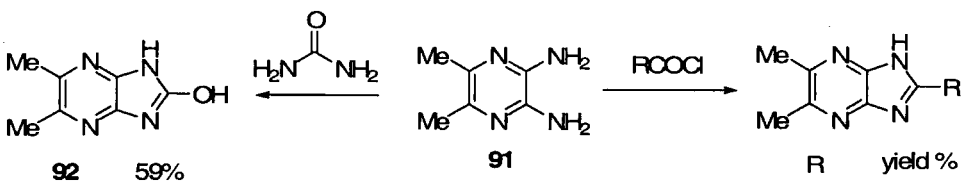
Scheme 1.17

An example of how an 2,8-disubstituted 9-benzyladenine is synthesised is shown in Scheme 1.17. The synthesis starts by reaction of aminomalonitrile, **86**, with benzyl isothiocyanate, followed by ring transformation of the resulting thiazole into an imidazole, **88**, under alkaline conditions. Formation of the [5,6] ring-fused system was achieved through reaction with guanidine to form 8-mercaptoadenine, **89**, which was alkylated at the 2-amino position to yield 9-benzyl-2-butylamino-8-mercatoadenine, **90**.[49]

This is by no means an exhaustive list but demonstrates the more commonly employed methods. More detailed reviews outlining the synthesis of purines and related compounds can be found in the literature but will not be discussed further in this thesis.[50-52]

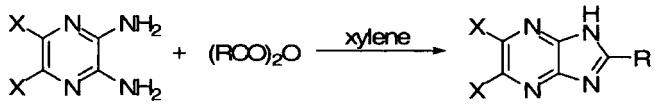
1.1.13 Syntheses of [5,6] Ring-Fused Pyrazines

The syntheses of imidazo[4,5-b]pyrazine ring systems as purine analogues are not as well represented in the literature as for the syntheses of pyrimidines but there are a few general methodologies that have been utilised.[53] One of the first syntheses of an imidazo[4,5-b]pyrazine involved the condensation of 2,3-diaminopyrazine, **91**, with an acid chloride or urea.[54]



Scheme 1.18

Alternatively, acylation of a selection of 2,3-diaminopyrazines followed by ring closure through heating in xylene has also been reported.[55]

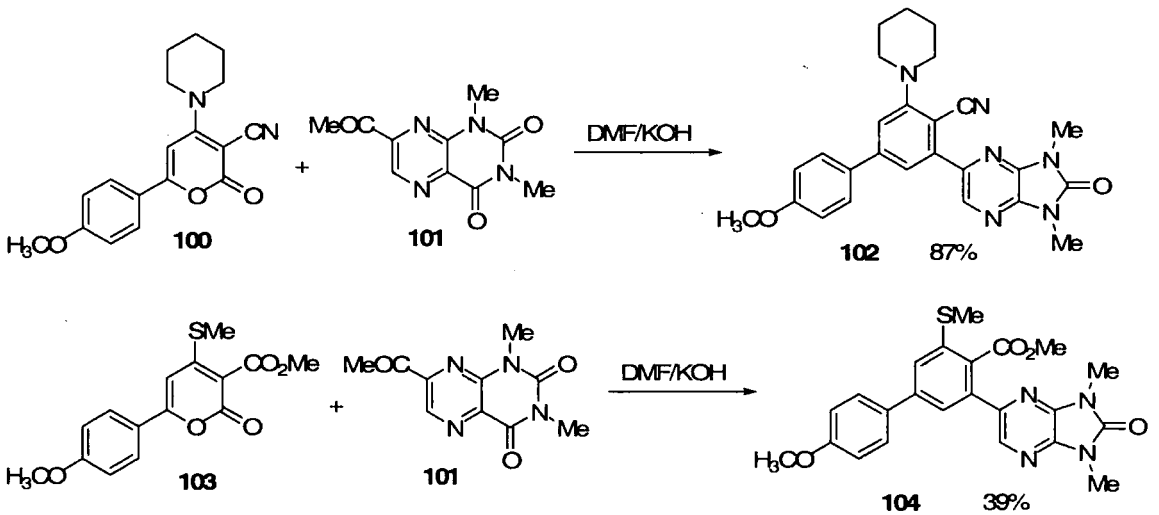


	X	R	yield %
96	Cl	CH_3	77%
97	H	CH_3	62%
98	Br	CF_3	37%
99	F	CF_3	60%

Scheme 1.19

The disadvantage to such an approach is the difficulty in synthesising the diamino compounds **96-99** and related precursors for functionalisation along with the fact that such a methodology lacks flexibility.

Recently a range of dimethylimidazo[4,5-b]pyrazine-2-ones have been synthesised utilising *in situ* ring construction and contraction from compounds **100** and **103**.[53]



Scheme 1.20

Such methodologies for library synthesis are limited in respect to the availability of start materials and as such alternatives for the synthesis of libraries of compounds, which is an important requirement in drug discovery, is required

1.1.14 Conclusion

This section shows that there is scope for new strategies for the synthesis of [5,6] pyrimidine and pyrazine fused-rings to complement those within the literature.

The following sections will outline some of the principles behind organofluorine chemistry and how they can be applied to the synthesis of highly functionalised hetereoaromatic derivatives. This will include how perfluorinated aromatic systems are synthesised, the general reactivity with both mono and di-nucleophiles including a discussion of the regiochemistries of multiple reactions. To conclude the section will be a short discussion on the relevance of this literature to the work outlined in the thesis.

1.2 An Introduction to Organofluorine Chemistry

As the major focus of this thesis concerns the synthesis of highly functionalised pyrimidine and pyrazines from polyfluorinated precursors it is prudent to introduce the subject area of fluorine chemistry by outlining how systems containing fluorine atoms are synthesised and how the introduction of fluorine atoms into molecules can have significant effects upon reactivity, physical, polarity and biological properties.

In general :-

- Fluorine is the most electronegative element[56] and is able to inductively move electrons towards itself to highly polarise C-F bonds, thereby changing both the electronic environment and the reactivity of molecules.
- The C-F bond is the strongest single bond to carbon and as such, many compounds that contain such bonds can be chemically stable and thermally inert as exemplified by Krytox® used in lubricating engine parts within high performance jet engines.
- A fluorine atom contains three tightly bound electron pairs in its outer shell which, in certain molecules such as PTFE, act as a protective shell around the carbon chain thereby making the molecule highly chemically stable and thermally resistant.[57]

- Fluorine has a van der Waals radius between that of a hydrogen atom and a hydroxyl group and can replace hydrogen with little disruption to the geometry of the system in which it is placed.
- Fluorine can be used as an bioisostere to replace atoms or functional groups without a significant change to the biological behaviour.[58]
- Lipophilicity (logD) can be significantly increased when a fluorine is substituted for a hydrogen which is important for the biological adsorption and distribution of drug molecules (although this is not true in all cases).[58]
- Fluorine in pharmaceuticals can lead to enhanced efficacy and selectivity due to the preferred orientation of the fluorine containing substituents towards the electropositive regions of the receptor sites.[58]

Organofluorine chemistry focuses upon the reaction and transformations of carbon-fluorine bonds. However, more recently the properties of fluorine have begun to be utilised in purification-orientated strategies through the use of what has been termed 'fluorous chemistry'.

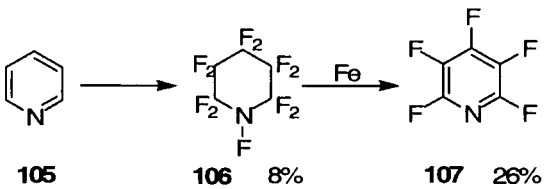
One of the strategies involves tagging the molecule with a highly fluorinated group so it dissolves into fluorocarbon solvents and thus is readily separated from the aqueous and organic phases into which it will not dissolve. This methodology also has environmental applications, as highly fluorinated catalysts can be recovered and re-used in other transformations.

Fluorous solid-phase extraction is a purification employed in the separation of fluorinated molecules with an added feature that lightly fluorinated molecules can be separated upon the use of this technology. This is especially useful in drug discovery for the synthesis of large numbers of molecules in the creation of a library amenable for screening purposes.[59]

1.2.1 General Synthesis of Perfluorinated Compounds

Incorporation of fluorine atoms into aromatic and heterocyclic compounds to furnish perfluorinated compounds can involve numerous methods, some of which are of relevance to this thesis and they are outlined below.

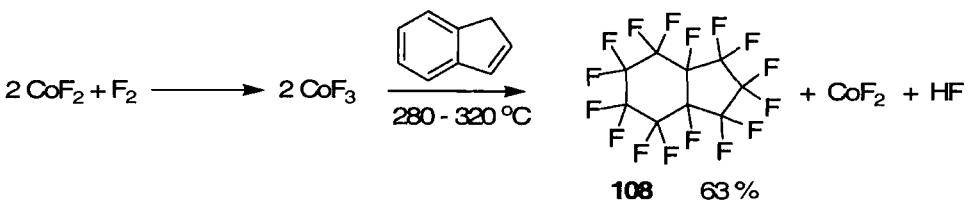
(i) saturation-rearomatisation by defluorination, involving electrochemical fluorination of the pyridine followed by defluorination over iron,[60, 61]



105 106 8% 107 26%

Scheme 1.21

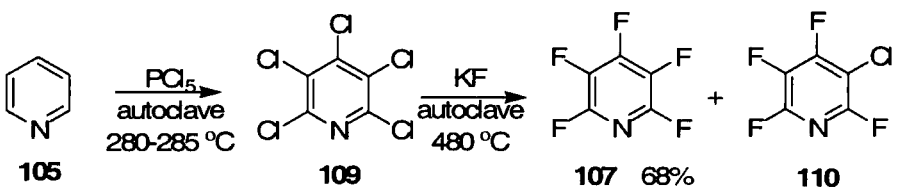
(ii) direct replacement of hydrogen by fluorine by passing fluorine over cobalt difluoride at high temperatures to give polyfluorination.[62]



108 63 %

Scheme 1.22

(iii) replacement of chlorine by fluorine, termed a halex reaction (which is most commonly used due to the associated high yields) and which will be discussed in more detail due to its relevance to this thesis.[63]



105 109 107 68% 110

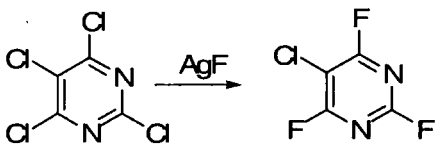
Scheme 1.23

1.2.2 General Synthesis of Perfluorinated Diazines – Pyrimidine and Pyrazines

The following section will start by outlining how perfluorinated diazines including 5-chlorotrifluoropyrimidine, tetrafluoropyrimidine are synthesised. All of these compounds are important as they are central to the work in this thesis and will be exploited to furnish highly functionalised hetereoaromatic derivatives.

Tetrachloropyrimidine has been extensively studied and its use is reviewed in a number of publications.[64-70] From tetrachloropyrimidine the synthesis of 5-chlorotrifluoropyrimidine, **112**, can be readily achieved and thus it is an inexpensive, commercially available compound.

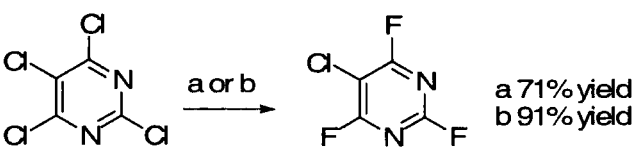
The first reported synthesis of 5-chlorotrifluoropyrimidine was achieved by the high yielding reaction of tetrachloropyrimidine with silver fluoride.[64]



111 **112** 84%

Scheme 1.24

Methodologies involve fluorinating tetrachloropyrimidine with potassium fluoride in the protic solvent sulfolone or in the presence of 18-crown-6 have provided the compound **112** in high yields.[71]

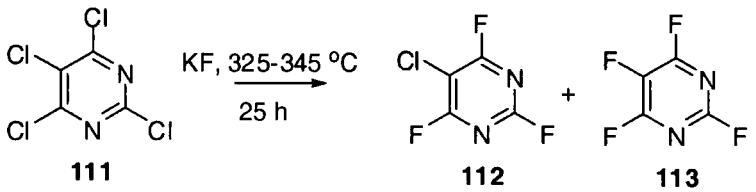


111 **112**

a KF, sulfolane
b KF, 18-crown-6, sulfolane

Scheme 1.25

The synthesis of compound **112** may also be achieved via the fluorination of tetrachloropyrimidine, **111**, with potassium fluoride in a sealed tube or an autoclave giving mixtures of **112** and **113**.[72, 73]



111 **112** **113**

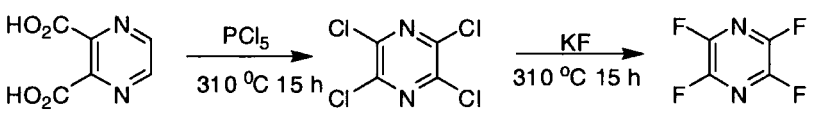
Scheme 1.26

Tetrafluoropyrimidine is most conveniently prepared by heating compound **112** in an autoclave with potassium fluoride due to the associated high yields.[72-74]

112 **113** 85%

Scheme 1.27

Tetrafluoropyrazine, **116**, is prepared by heating KF and tetrachloropyrazine in an autoclave at 310 °C. Compound **116** is synthesised from 2,3-dicarboxylic acid pyrazine by reaction with PCl_5 in an hastalloy autoclave at 310 °C.



114 **115** 70% **116** 90%

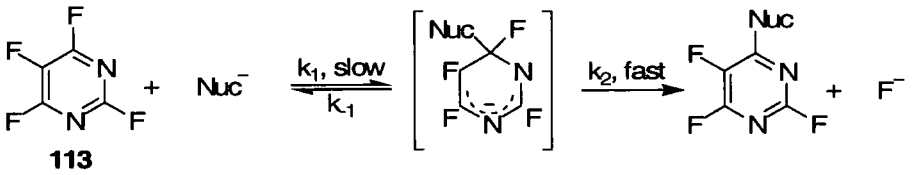
Scheme 1.28

Both tetrafluoropyrimidine and tetrafluoropyrazine are currently not commercially available and as such are synthesised at Durham using high pressure facilities.

1.3 Reactivity of Diazines – Pyrimidine and Pyrazines

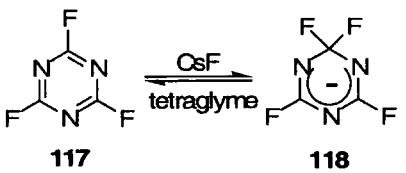
Perfluorinated –pyrimidine and –pyrazine are generally unreactive towards electrophiles due to the highly electron withdrawing nature of the fluorine atoms but they are very reactive towards nucleophiles for this very reason.

Perfluorinated pyrimidines react with nucleophiles due to their electron-deficient nature in reactions proceeding via a two-step S_NAr mechanism with the addition of the nucleophile being the rate determining step.[74, 75]



Scheme 1.29

The intermediate formed is called a Mesienheimer complex with evidence for the intermediate provided from the reaction of trifluoro-*s*-triazine with cesium fluoride in tetraglyme by observation of two distinct resonances in ^{19}F NMR.[76]



Scheme 1.30

Initial attack on compound **113** occurs at the 4/6- position because it is most activated due to the stabilisation of the resulting negative charge in the Meisenheimer intermediate on the *para* nitrogen and is the main factor dictating the first position of attack.[74] Attack at the 2-position is less favoured owing to the presence of a fluorine *para* to this site which is destabilising. Attack at the 5-position is highly disfavoured due to the *para* fluorine at the 2-position and due to the lack of stabilisation of the negative charge in the Meisenheimer complex onto either a *para* or *ortho* ring nitrogen (see figure 1.4).

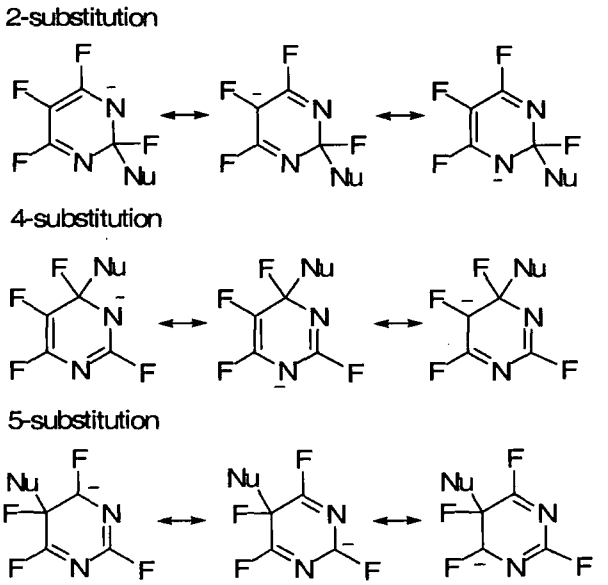


Figure 1.4

A *para* fluorine is destabilising due to donation back into the ring through resonance even though it withdraws electron density through induction, although this depends on geometry.

12

Strongly activating/stabilising

13

Inductive electron withdrawal offset by electron-pair repulsions

Figure 1.5

Initial state effects also influence the position of nucleophilic attack in terms of regioselectively depending upon whether there is a fluorine *ortho*, *meta* or *para* to the site of nucleophilic attack. Kinetic studies have shown that an *ortho* fluorine is more activating than a *meta* fluorine which in turn is significantly more activating than a *para* fluorine.

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

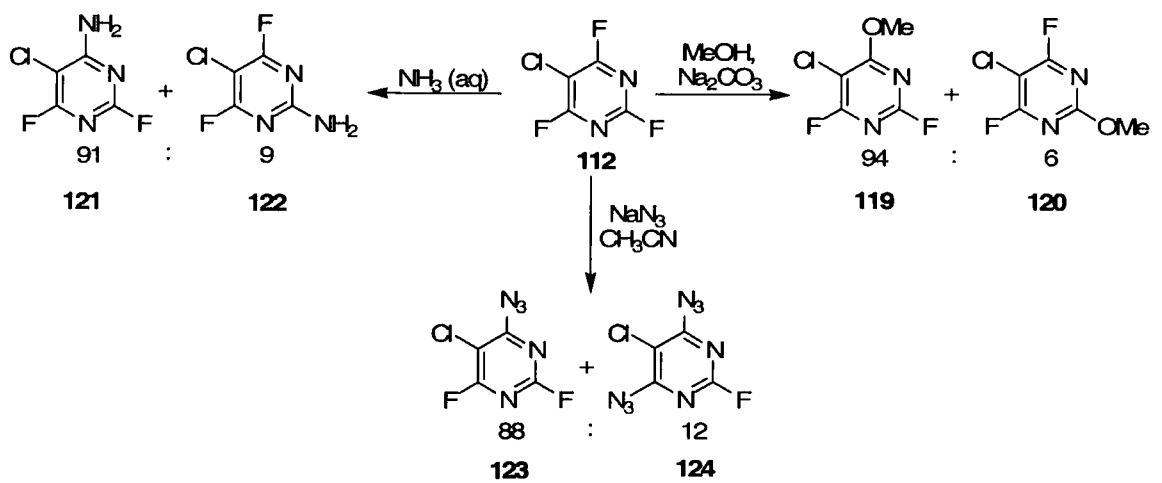
The 5-position has two *ortho* fluorines but also a *para* fluorine and most importantly there is no stabilisation of the negative charge on to a *para* nitrogen in the Mesienheimer

complex which is a dominating effect. Thus the 4- position contains one *ortho* fluorine, two *meta* fluorines and no *para* fluorines whereas the 2- position has two *meta* fluorines but a destabilising *para* fluorine and so 4- is substituted rather then 2-.

Tetrafluoropyrazine differs in reactivity with nucleophiles due to the lack of a *para* ring nitrogen which contributes to a significant drop in the rate of reactivity in comparison to that of tetrafluoropyrimidine.[72, 74] As all the fluorine atoms are equivalent there are no problems encountered in regioselectivity in the first step.

1.3.1 Reactivity of 5-Chlorotrifluoropyrimidine with Nucleophiles

In the literature it has been demonstrated that compound **112** reacts with ammonia, sodium methoxide, or sodium azide leading to the 4-substitued derivatives as the major products (see section 1.3 for rationale) with the minor product arising from substitution at the 2-position.[73, 77]



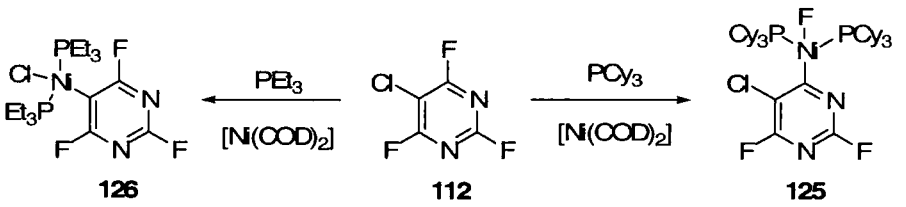
Scheme 1.31

It must be noted from this review that there is very little work within the literature documenting the reaction of compound **112** with nucleophiles and that orientation of nucleophilic substitution with a range of nucleophiles has yet to be fully established.

The use of compound **112** as a fibre reactive dye has been well discussed and many patents issued, charting this subject.[78]

1.3.2 Palladium-Catalysed Substitution Processes Involving 5-Chlorotrifluoropyrimidine

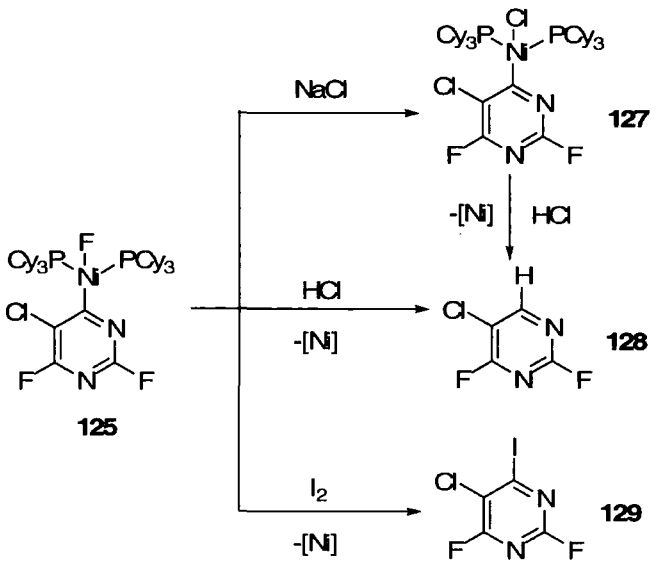
As shown in previous examples, nucleophilic aromatic substitution of compound **112** can be accomplished although this has not been adequately exploited. Although C-F bond activation is not a direct concern of this thesis it is important to note that systems incorporating compound **112** are able to undergo such reactions and in doing so new functionalised pyrimidines can be developed and exploited.



126 **112** **125**

Scheme 1.32

Braun has shown that compound **112** can be reacted with various nickel catalysts to insert into either the C-F bond or the C-Cl bond depending upon the size of the attached phosphine moiety as shown in Scheme 1.32.

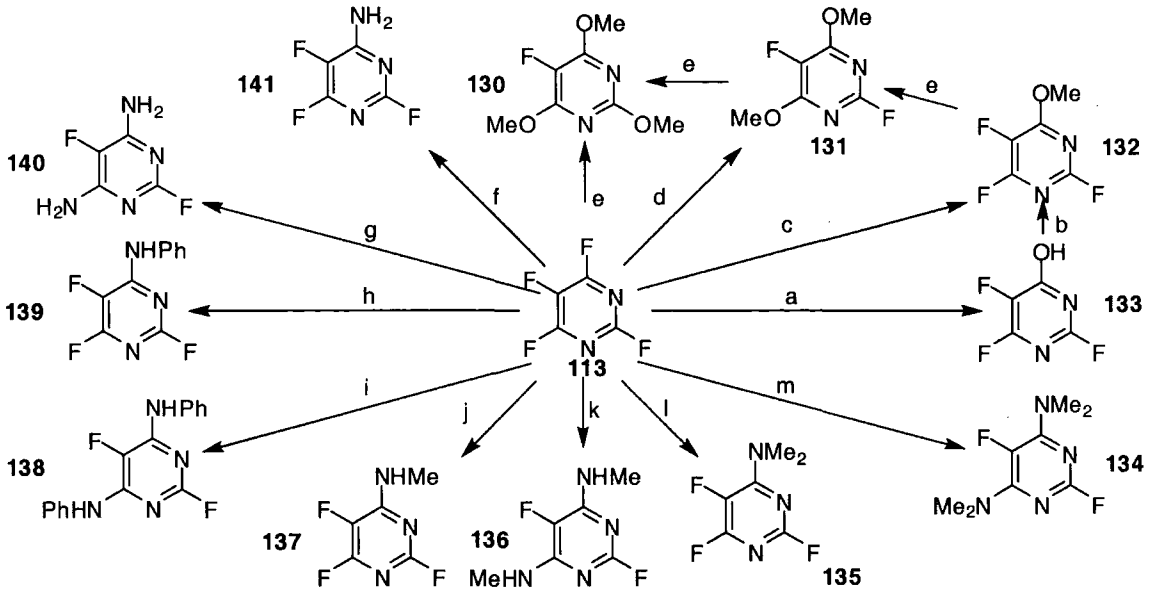


Scheme 1.33

Additionally the nickel catalyst can be removed through treatment with excess HCl or iodine as shown in Scheme 1.33 to leave hydro- or iodo pyrimidine derivatives respectively.[79]

1.3.3 Reactivity of Tetrafluoropyrimidine with Nucleophiles

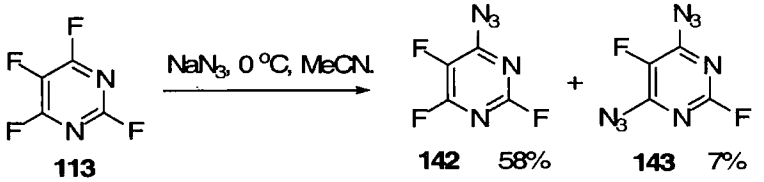
Reaction of **113** with a series of nitrogen- and oxygen-containing nucleophiles under basic conditions, as shown in Scheme 1.34, results in nucleophilic attack at the 4-position. More forcing conditions result in the replacement of further fluorine atoms attached to the ring and in the case of methoxide these reactions are believed to proceed in a regioselective manner with the following order; 4- < 6- < 2-.[73, 74, 80] It should be noted that at this point this is the only example of regioselective replacement of several fluorine atoms starting from tetrafluoropyrimidine and that further research is required to elaborate the subject area.



a) H_2O/THF, RT; b) CH_2N_2/ether, 20 °C; c) MeOH/Na_2CO_3, RT; d) MeOH/MeONa, 0 °C; e) MeOH/MeONa, reflux; f) NH_3 (aq), rt; g) NH_3 (aq), 60 °C; h) $PhNH_2$/Na_2CO_3/THF, 15 °C; i) $PhNH_2$/THF, reflux; j) $MeNH_2$ (aq), 0-20 °C; k) $MeNH_2$ (aq)/DMF; l) Me_2NH (aq), 0-20 °C; m) Me_2NH (aq)/DMF, 60 °C

Scheme 1.34

Reaction of compound **113** with sodium azide provides mainly the 4-substituted pyrimidine with some formation of the bis-compound which is readily isolated by distillation.



Scheme 1.35

The azide functionality may be further reacted to give a selection of unique compounds.[77]

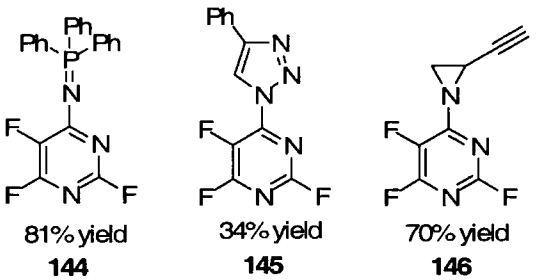
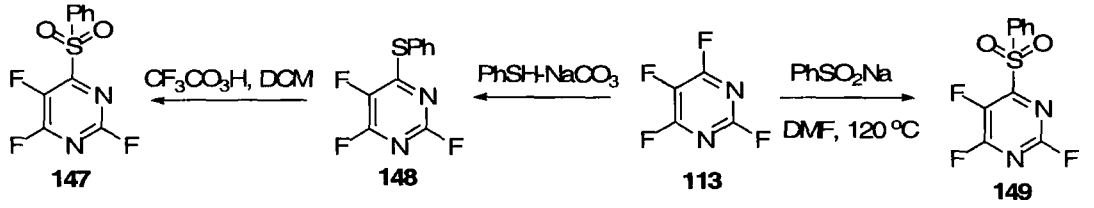


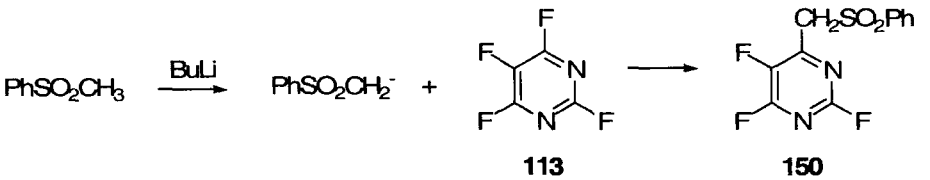
Figure 1.6

Addition of a sulfur-containing group such as a sulfone at the 4-position can be achieved via two different routes; either directly by reaction with sodium benzenesulfinate or reaction with benzenethiol and subsequent oxidation to the sulfone.[77]



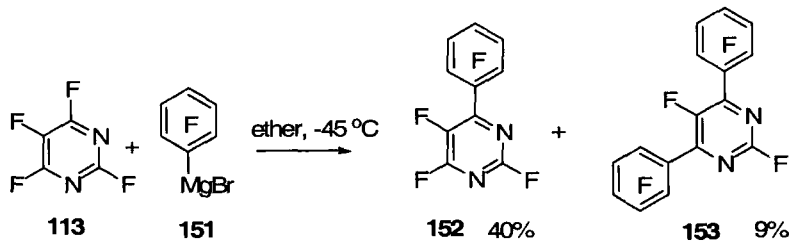
Scheme 1.36

Reaction of compound **113** with carbon nucleophiles is feasible in the presence of butyllithium as formation of the mono 4- substituted pyrimidine is seen exclusively.[81]



Scheme 1.37

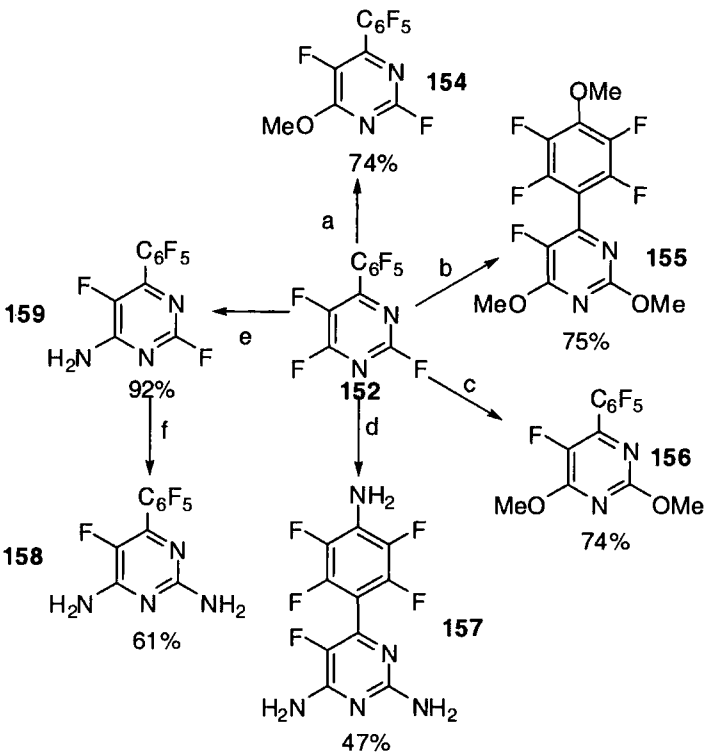
Other carbon nucleophiles such as pentafluorophenylmagnesium bromide result in replacement of the fluorine atom at the 4-position to form compound **152** as the major product. However, in this example a small percentage of the bis-substituted compound **153** is formed.



Scheme 1.38

The remaining fluorine atoms are still labile to nucleophilic aromatic substitution and this is shown when compound **152** is reacted with ammonia and methoxide nucleophiles as replacement of the fluorine atom at the 6-position is observed. Moreover, reaction of

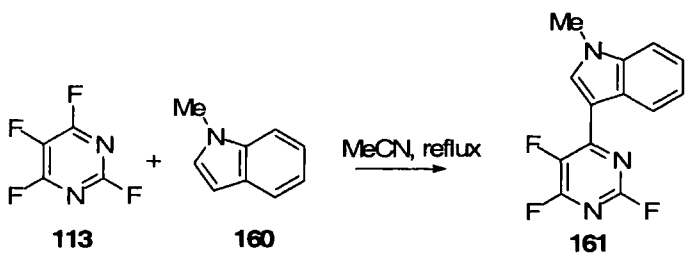
compound **152** with an excess of methoxide and ammonia results in formation of a trisubstituted pyrimidine due to replacement of the fluorine on the attached aryl group.[82]



a) MeOH-Na_2CO_3, -10-20 °C, b) 3 N NaOMe in MeOH, 0-20 °C, c) 2 N NaOMe in MeOH, -35-0 °C, d) xs. NH_3 aq. (d = 0.880), 100 °C, e) NH_3 aq. (d = 0.880), 70 °C, f) NH_3 aq. (d = 0.880), 60 °C,

Scheme 1.39

Reaction with carbon nucleophiles such as *N*-methylindole, also results in substitution of the fluorine atom at the 4- position.[83]



113 **160** **161**

Scheme 1.40

1.3.4 Polyfluoroalkylation of Tetrafluoropyrimidine

Polyfluoroalkylation of compound **113** occurs due to its ability to undergo nucleophilic attack by anions created via the reaction of fluoride ion (CsF), with polyfluoro-alkenes.

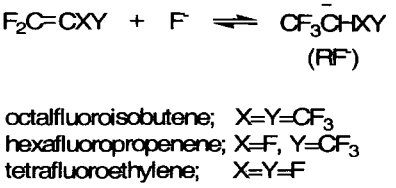
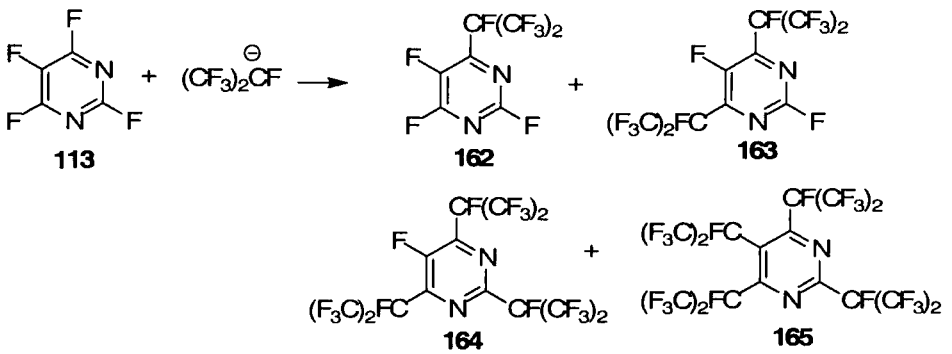


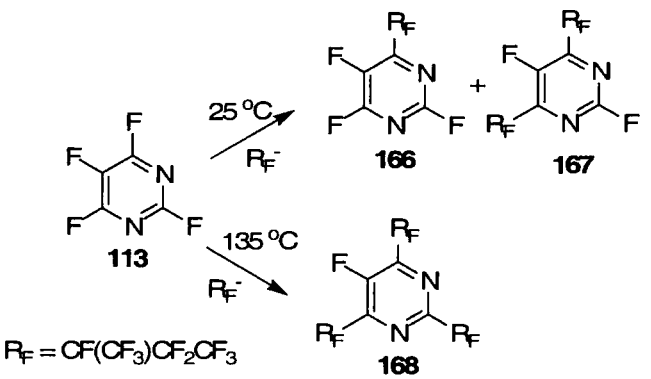
Figure 1.7

Reaction with heptafluoropropyl anions, results in the formation of perfluoro-(4-*iso*propylpyrimidine) and perfluoro-(4,6-di-*iso*propylpyrimidine) as shown in scheme 1.41.[84]



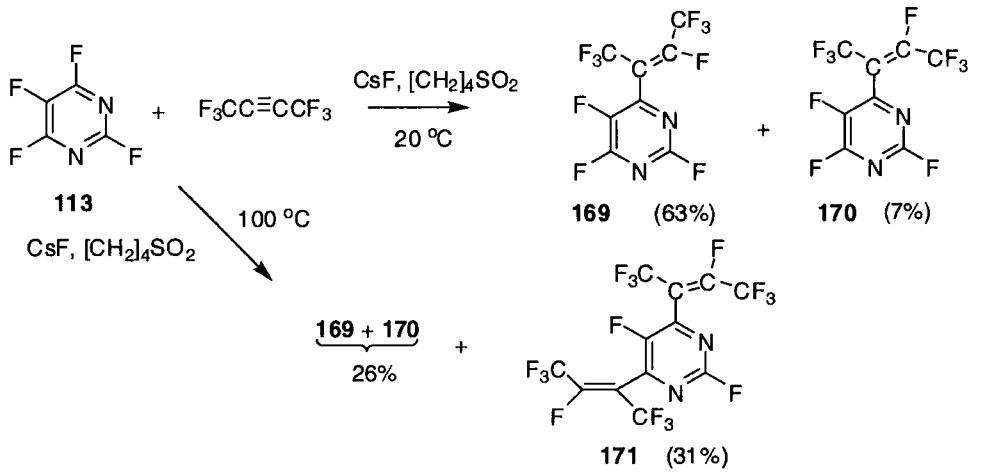
Scheme 1.41

Similarly reaction with nonanefluorobut-2-yl anion gives analogous results to hexafluoropropene, although no tetra-substituted product was formed[85].



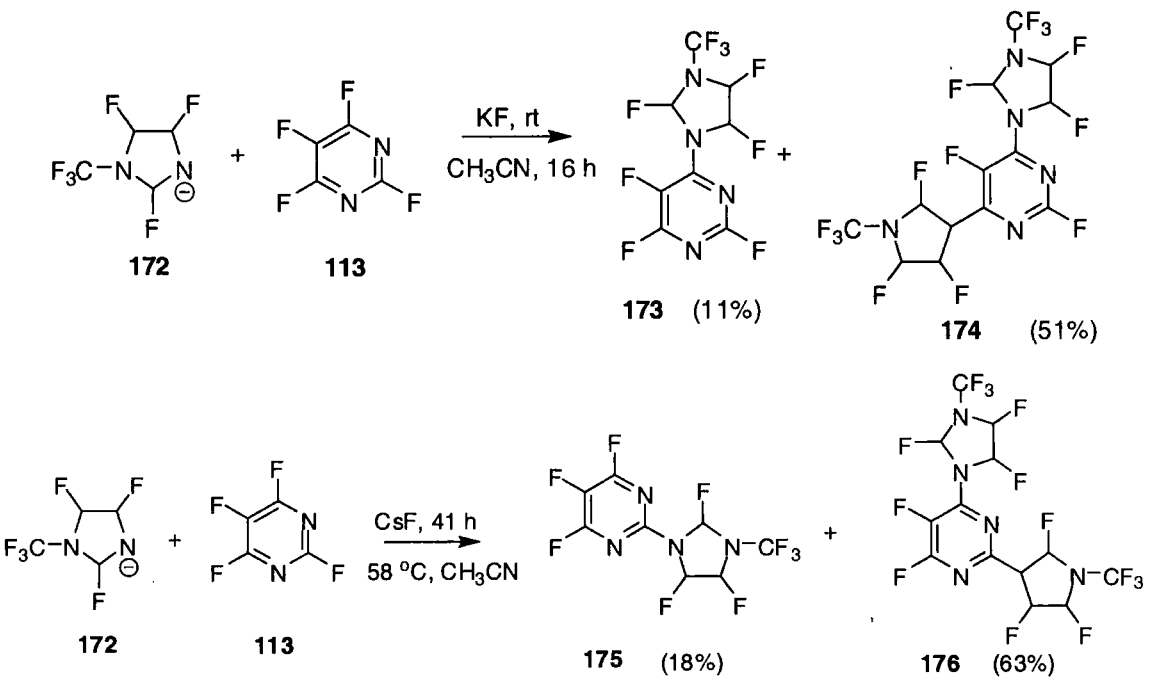
Scheme 1.42

Reaction with the perfluoroacetylene derived anion at 20 °C forms *cis*- and *trans*-perfluoro-4-(1-methylprop-1-enyl) pyrimidine and reaction at 100 °C yields the disubstituted product **171** as shown in scheme 1.43.[86]



Scheme 1.43

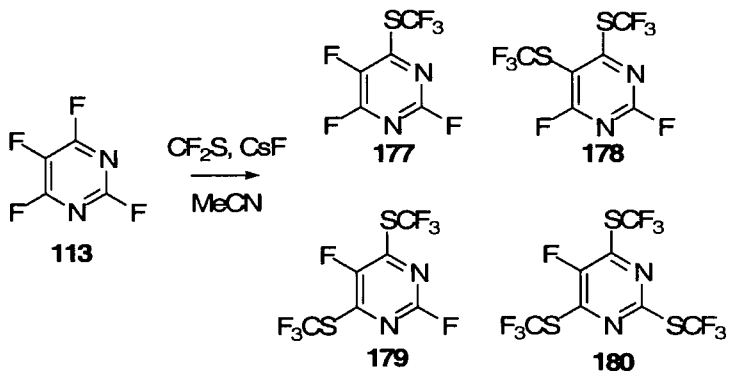
Compound **113** reacts readily with the nitrogen anion **172**, to generate the expected 4- and 4-,6- substituted pyrimidines as shown in Scheme 1.44.



Scheme 1.44

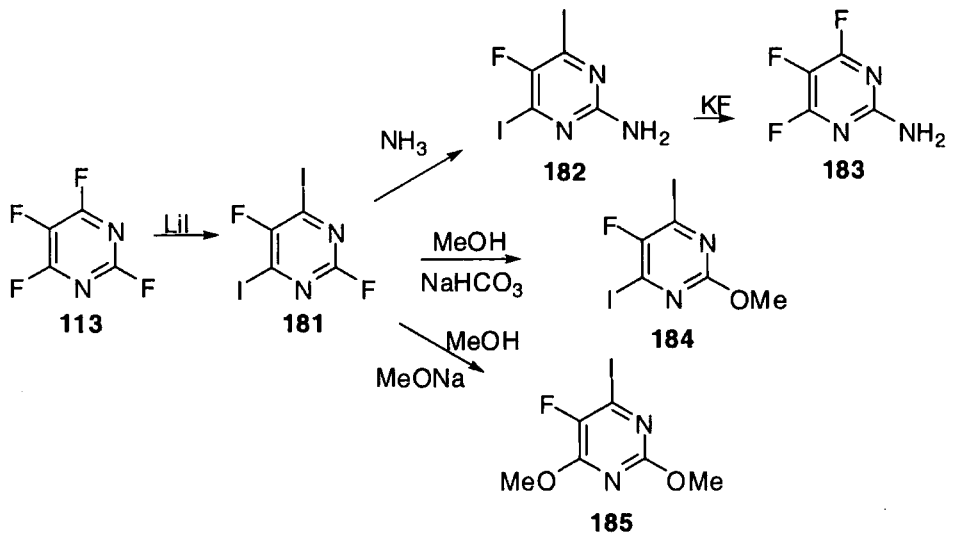
Conversely, when cesium fluoride was used the 2- and 2-,4- substituted products were formed.[87]

Reaction with the trifluoromethanethiolate ion results in the substitution of the fluorine at the 4-position (compound **177**) and other minor byproducts. Varying the reactant ratios gives compound **177**, **178** and **179** in a 1.1:1.8:1 ratio when compound **113** and CF_2S were mixed in a 1:4 ratio in the presence of the fluoride ion.[88]



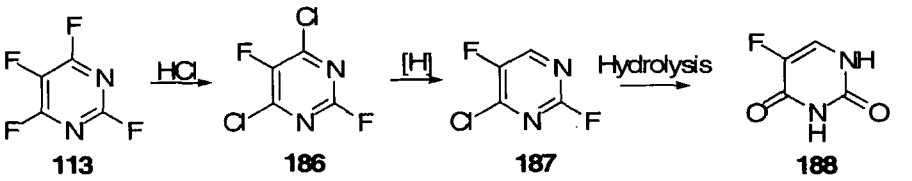
Scheme 1.45

When compound **113** is reacted with excess lithium iodide, substitution of the fluorine atoms at the 4- and 6-position occurs. Further reaction with ammonia and methoxide nucleophiles replaces the fluorine at the 2-postion. In addition the iodine atoms can be re-exchanged for fluorine atoms under halex conditions to furnish compound **183**.[82]



Scheme 1.46

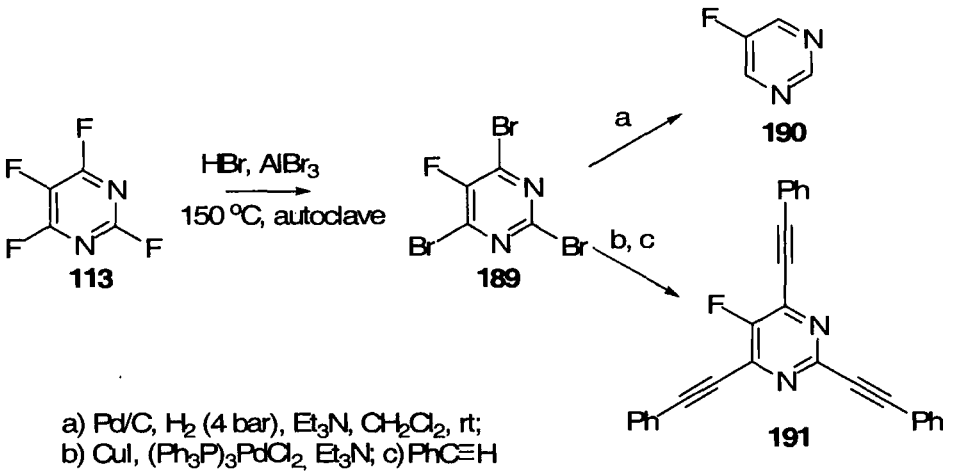
Similarly replacement of two fluorine atoms can be utilised in the synthesis of 5-fluorouracil, a chemotherapeutic agent, from tetrafluoropyrimidine by reaction with HCl, hydrogenation and subsequent hydrolysis.[89]



113 186 187 188

Scheme 1.47

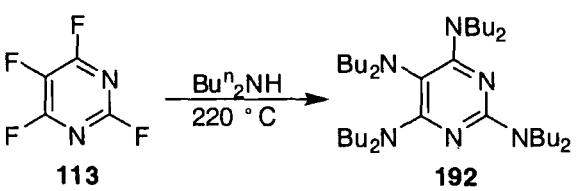
Substitution of three fluorine atoms can be achieved through the use of an autoclave and reacting compound **113** with an excess of HBr which replaces the fluorine atoms at the 2-, 4- and 6- positions. Hydrogenation or reaction utilising cross-coupling conditions result in replacement of all three bromine atoms with either hydrogen atoms or various alkynyl groups as shown in scheme 1.48.[90]



113 189 190 191

Scheme 1.48

Replacement of all four fluorine atoms may be achieved by reaction of compound **113** with di-*n*-butyl-amine as shown in Scheme 1.49.[91]



113 192

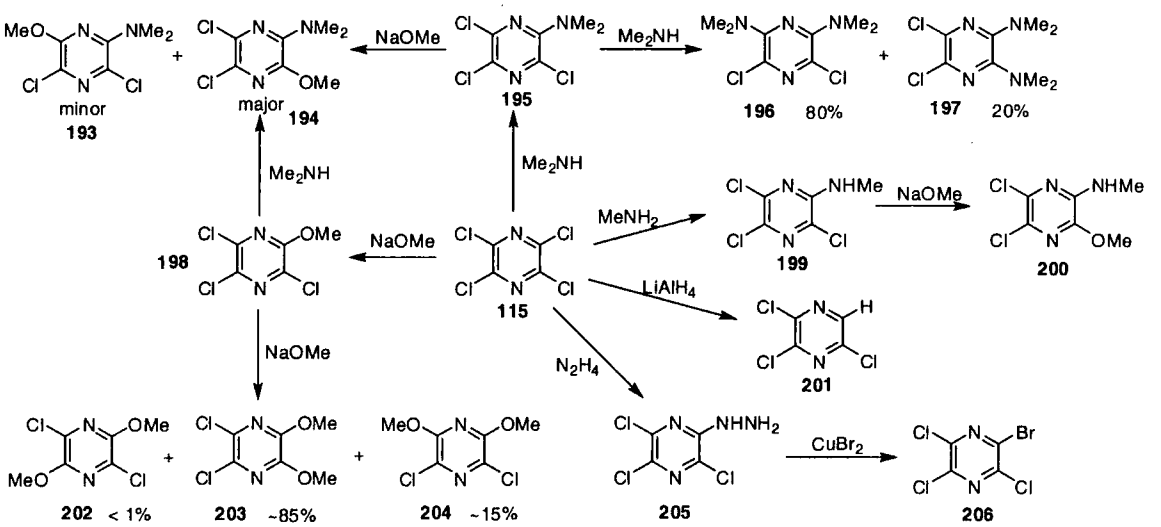
Scheme 1.49

This section has shown that only a small amount of literature exists on the reactions of compound **113**. Further investigation is required to screen other nucleophiles and to define the regiochemistry of attack after replacement of the fluorine atom at the 4-position. Both these points are a major concern of this thesis and will be outlined in subsequent chapters.

1.3.5 Reactivity of Tetrachloropyrazine with Nucleophiles

The following section will highlight research carried out involving the chemistry of tetrachloropyrazine when reacted with a range of nucleophiles via nucleophilic aromatic substitution with nucleophiles being discussed first, followed by dinucleophiles. This section will lead through to a discussion of the reactions of tetrafluoropyrazine, **116**.

Reactions of compound **115** with nucleophiles to replace one or more chlorine atoms on the ring can be achieved as shown in Scheme 1.50.[92]



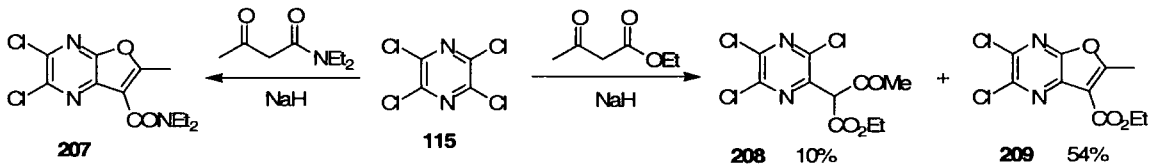
Scheme 1.50

Reactions of the mono-substituted trichloropyrazines (compounds **198**, and **199**) with methoxide and dimethylamine leads to replacement of a second chlorine atom at the *ortho* position to give the major product. However, compound **195** gives predominantly the *meta* product due to the steric influence of the dimethylamine preventing attack at the *ortho* position.

1.3.6 Reactions of Tetrachloropyrazine with Dinucelophiles

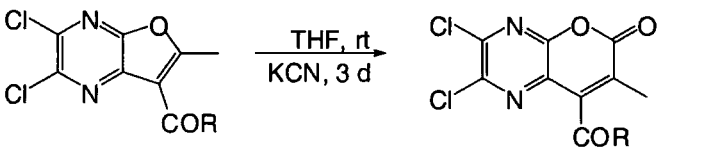
Tetrachloropyrazine has also been reacted with a selection of dinucleophiles to furnish a range of novel ring-fused compounds, although this methodology has not been comprehensively developed.

For example, formation of [5,6] ring-fused systems are possible by reaction of tetrachloropyrazine with dinucleophiles such as ethylacetoacetate and *N,N*-diethylacetoacetamide anions.[55]



Scheme 1.51

Furthermore it has been shown that these systems can undergo ring expansion by reaction with cyanide ions to give [6,6] ring-fused systems albeit in low yields.[93]

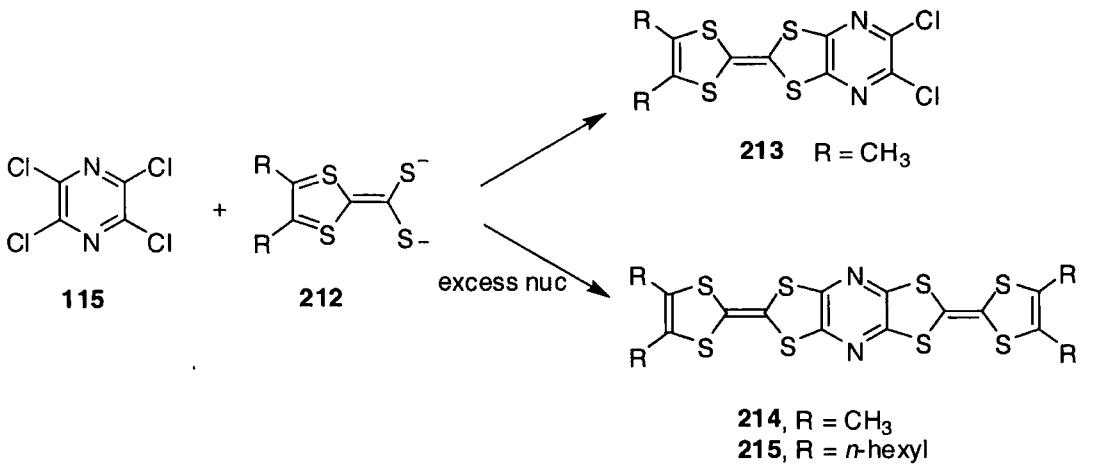


207, R = OEt
209, R = NEt

210, R= OEt, yield = 33%
211, R = NEt_2, yield = 30%

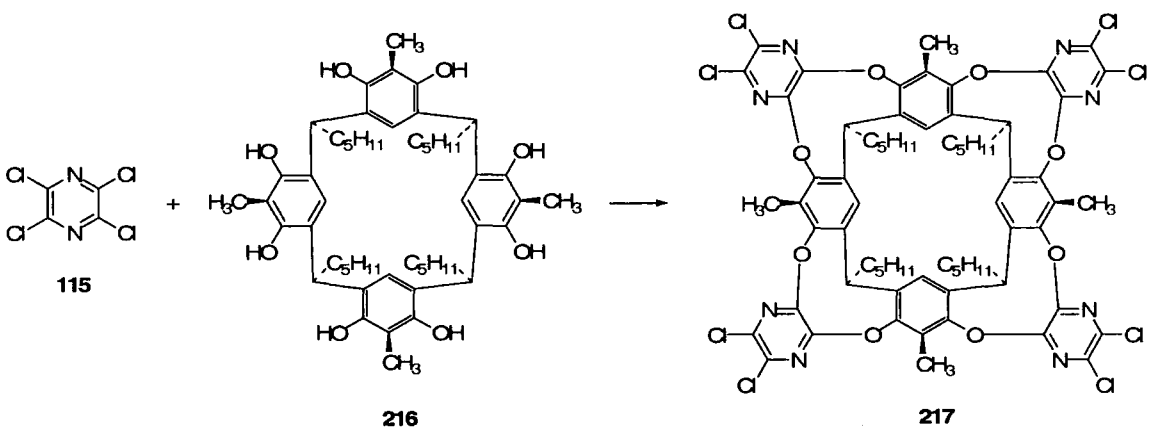
Scheme 1.52

Other [5,6] ring-fused systems can be synthesised including pyrazine-fused bistetrathiafulvalenes using a bidentate sulfur nucleophile to give either the unsymmetrically substituted pyrazine-TTF or the pyrazine-fused bis-TTF which may have applications as molecular wires.[94]



Scheme 1.53

Large macrocycles including velcraplexes and cavitands may be synthesised from tetrachloropyrazine due to the pair of vicinal chlorines which are able to undergo nucleophilic substitution with octol **216**, to form nine membered rings.[95, 96]



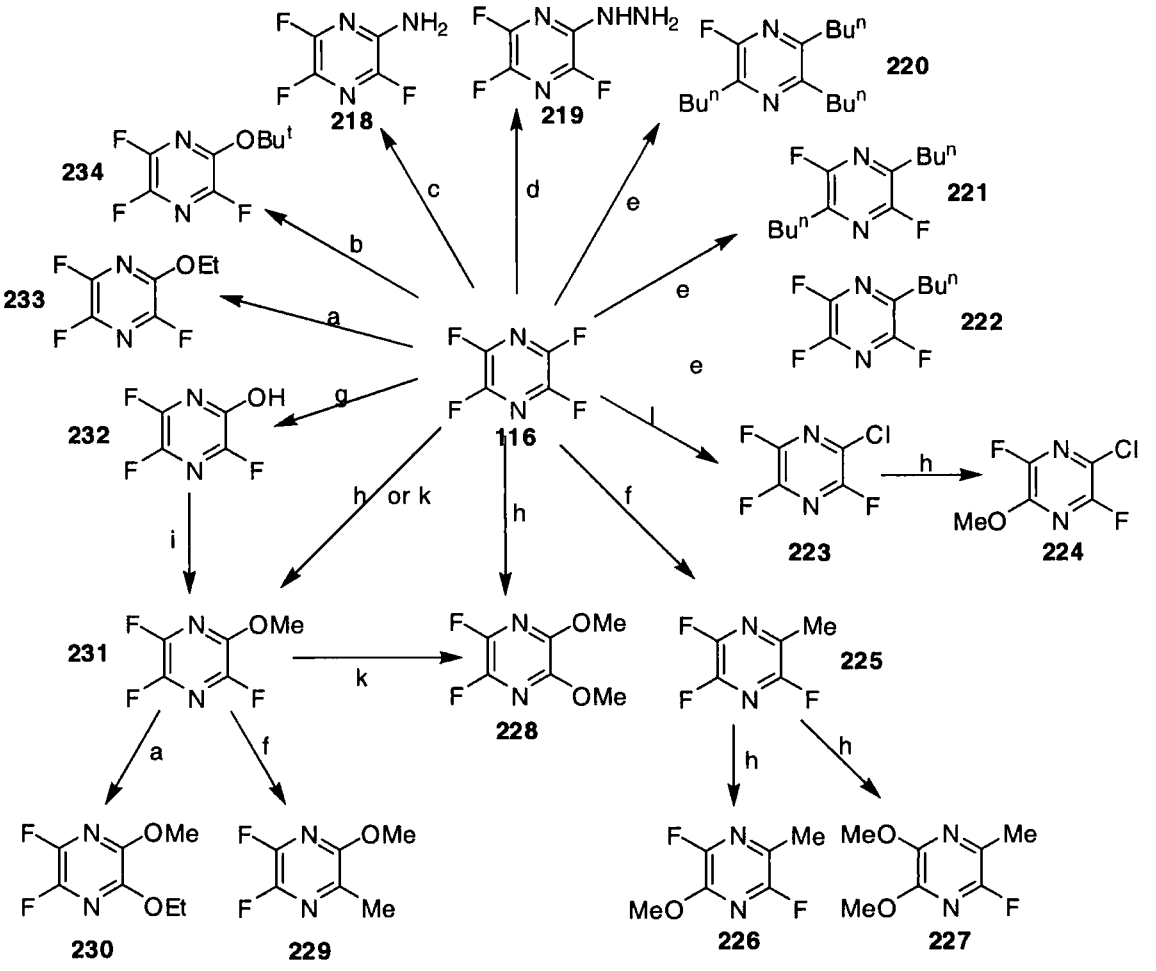
Scheme 1.54

As noted there is little in terms of literature precedent for the reactivity of compound **115** with dinucleophiles and as such there remains the possibility for methodology development in this area by screening more candidates to expand upon this area.

1.3.7 Reactivity of Tetrafluoropyrazine with Nucleophiles

The following section will outline the research present within the literature on the reactivity of tetrafluoropyrazine, **116** with a selection of nucleophiles followed by a review of the few methods available for synthesising fused ring systems

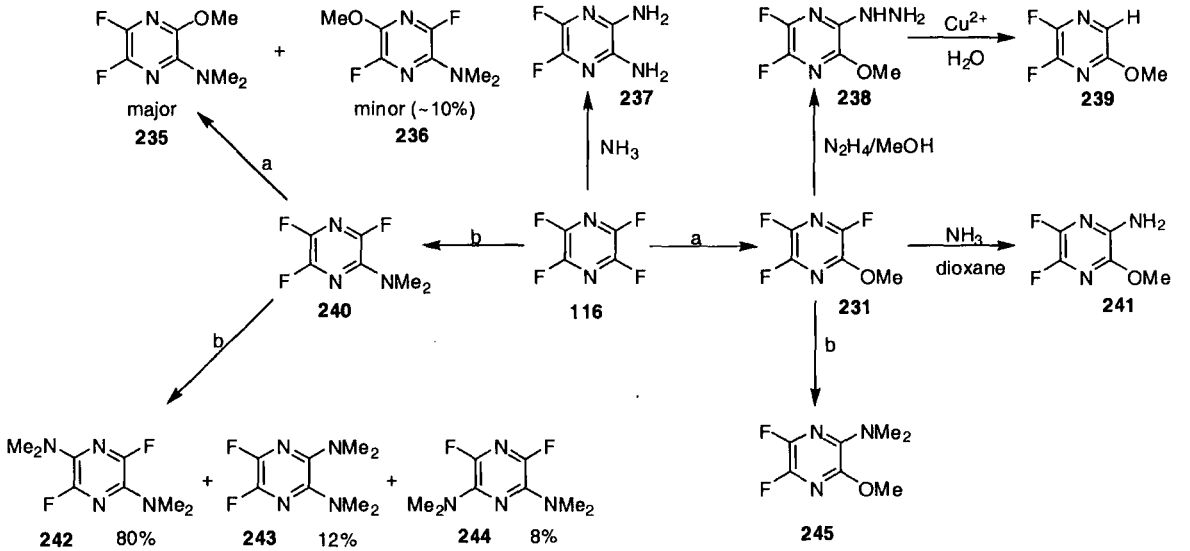
In section 1.3.3 it was shown that reaction of tetrafluoropyrimidine with nucleophiles results in nucleophilic attack *para* to that of the ring nitrogen unlike tetrafluoropyrazine, which is reflected in the reduced reactivity[72] of the system towards nucleophilic attack compared to tetrafluoropyrimidine.[74] Scheme 1.55 outlines substitution reactions of compound **116** with nucleophiles.[97]



Reagents: a) NaOEt/EtOH; b) $KOBu^t/Bu^tOH/Et_2O$; c) NH_3 (aq); d) N_2H_4, H_2O/EtOH; e) $^nBuLi/Et_2O$ f) $MeLi/Et_2O$; g) $KOH/^tBuOH$; h) NaOMe/MeOH; i) CH_2N_2/Et_2O; j) $MeOH/H_2SO_4$; k) N_2H_4,H_2O/ETOH, then CuX_2-HX aq.

Scheme 1.55

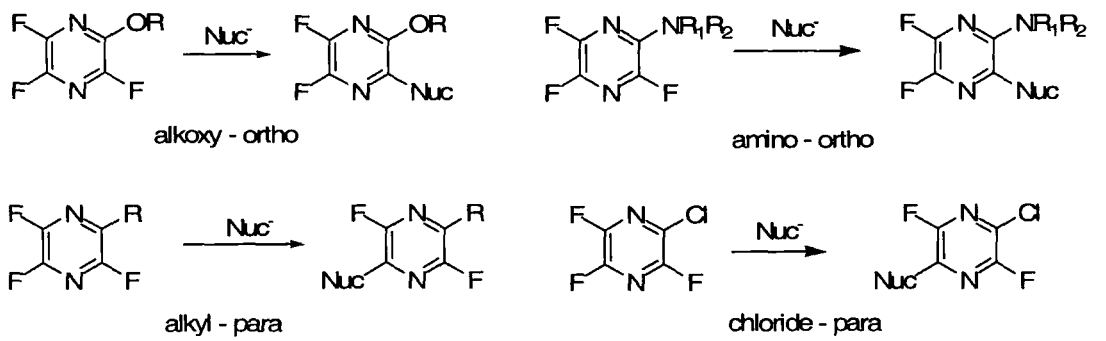
The position attacked by the second nucleophile is reliant upon the character of the initial group in which alkoxy and amino groups direct *ortho* (unless sterically hindered) and alkyl and Cl groups direct *para* as shown in Scheme 1.56 and Scheme 1.57.



Reagents: a) NaOMe/MeOH; b) Me_2NH/MeOH

Scheme 1.56

The alkoxy and amino groups are electron withdrawing and so would be expected to direct incoming nucleophiles to the *meta* position relative to the first substituent, however, incoming nucleophiles are directed *ortho* and this is attributed to transition state influences.



Scheme 1.57

In the case of situation A, B and C the nitrogen atom that is *ortho* to the incoming nucleophile has high electron density. In A and B the transition states have a fluorine atom adjacent to the negatively charged nitrogen atom which is a stabilising influence whereas situation C has a alkoxy or amino substituent which is less stabilising. Although it is not clear why A is favoured over that of B it is postulated that *Iπ* repulsion that would occur between that of the nitrogen or oxygen *para* to the position of attack is similar or greater to the situation found in the case of when a fluorine is *para*.[97,98]

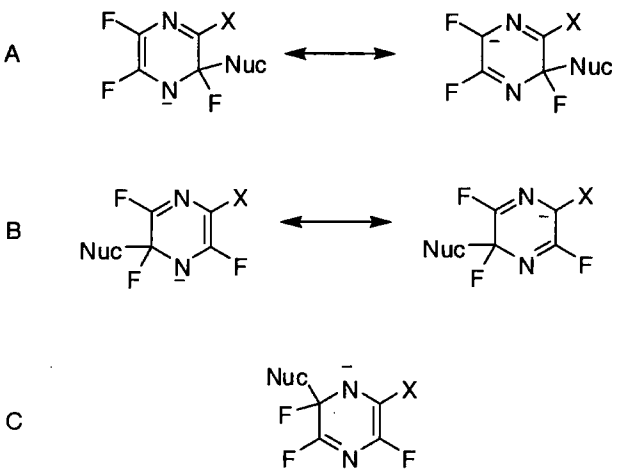
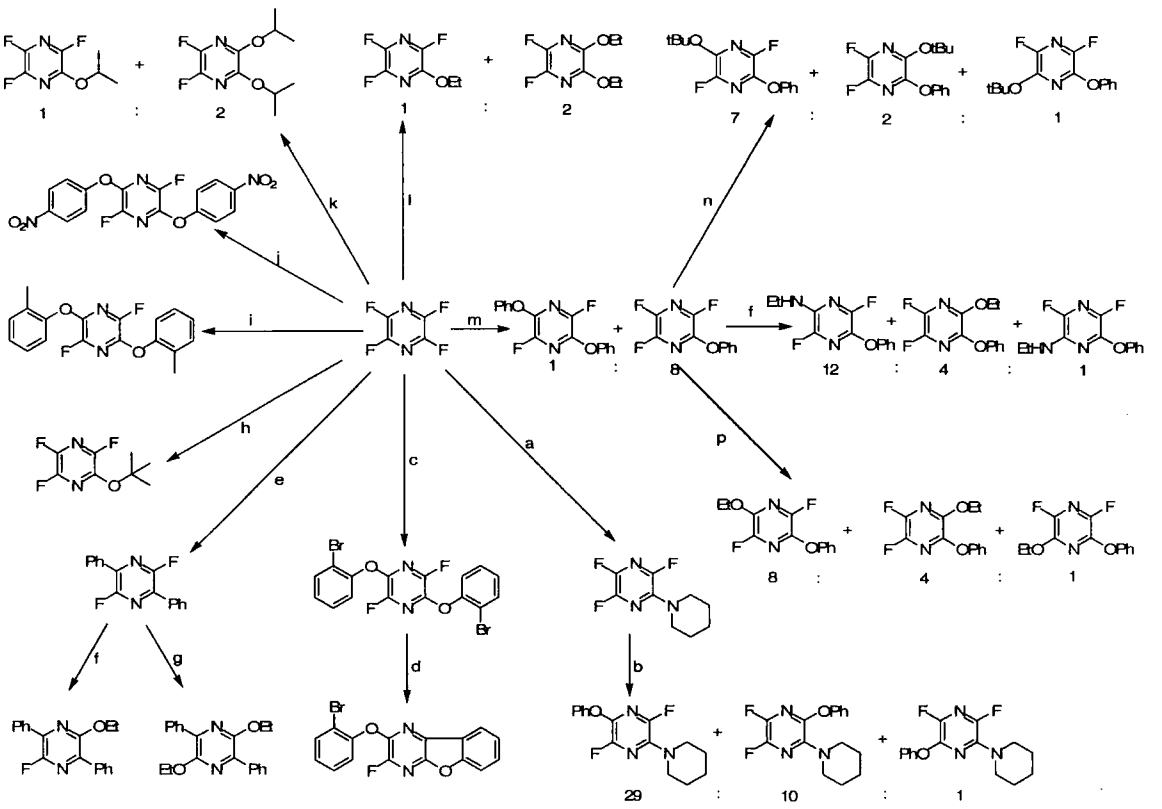


Figure 1.8

More recently the Durham group has further developed this methodology (see Scheme 1.56 and 1.57) by studying the nucleophilic aromatic substitution of tetrafluoropyrazine with mono- nucleophiles to form poly-substituted pyrazine systems.

Scheme 1.58 demonstrates that phenoxy substituents direct *para* which differs from the early research in that alkoxy- substituents direct *ortho* to themselves. Other phenoxide nucleophiles with pendent groups containing either electron donating or electron withdrawing substituents are consistent with this observation. Reactions of mono-substituted phenoxy pyrazine with nucleophiles varying in electronic and steric character show a lack of regio-control attributed to the steric hindrance of the *ortho* site.



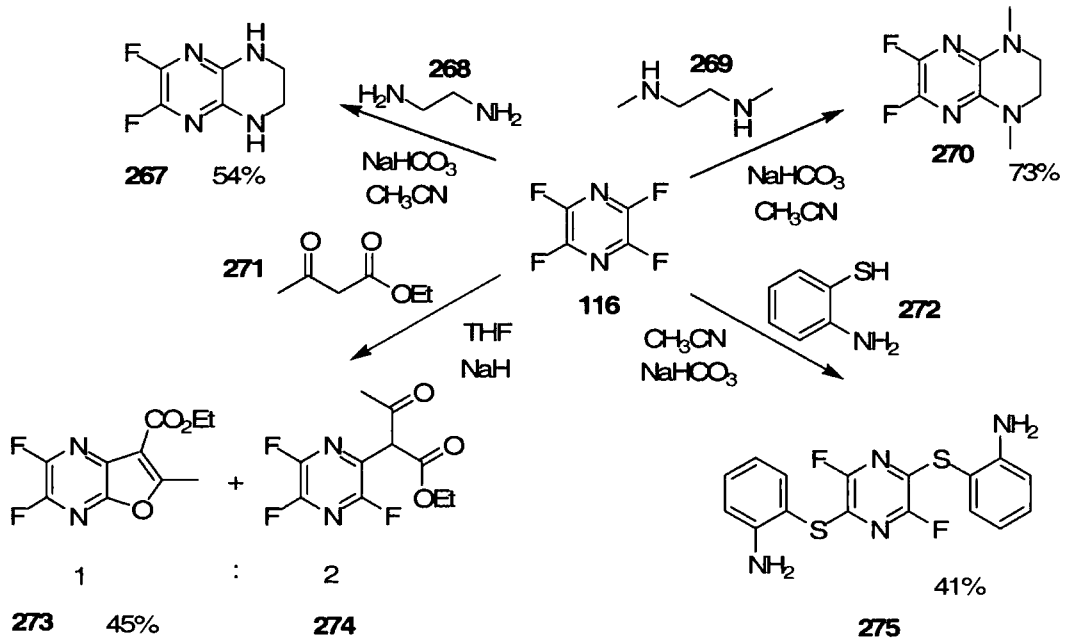
Reagents: a, C5H11N/THF/DIPEA; b, PhONa/THF; c, 2C6H5BrO/THF/NaH; d, n-BuLi/THF;-780C; e, PhMgBr/THF; f, NaOEt/THF; g, ex. NaOEt/THF; h; tBuONa/Et2O; i, 2C3H8O/NaH/THF; j, 2C6H4NNaO3/EtOH; k, C3H8OH/THF/NaH; l, NaOEt/THF; m, NaOPh/THF; n, tBuONa/Et2O; o, 2EtNH2/THF; p, NaOEt/THF.

Scheme 1.58

Reactions with neutral nitrogen nucleophiles and *tert*-butoxide gave mono-substituted products exclusively. Subsequent reaction after piperidine was attached led to mixtures of products due to a lack of regio-control attributed to the steric hindrance of the *ortho* site as observed for the phenoxy compounds. Tri- and tetra- substituted pyrazine systems have been synthesised to form multi-substituted systems. Reaction with phenylmagnesium bromide gave the disubstituted compound a result that fits in with the observation that alkyl groups direct to the *para* position to avoid destabilising Iπ repulsion from fluorine atoms.[99]

1.3.8 Reactions of Tetrafluoropyrazine with Dinucleophiles

In initial work, the Durham group has also studied the reaction of compound **116** with a short series of dinucleophiles, synthesising a selection of novel [6,5] and [6,6] ring-fused compounds[100].



Scheme 1.59

Reactions of **116**, with various dinucleophiles, including the symmetrical compounds **268** and **269**, resulted in the formation of the desired [6,6] systems in moderate to good yields. Reactions with unsymmetrical dinucleophiles such as ethylacetoacetate gave two compounds with the main product being the acyclic compound **274**. On the other hand reaction with a nitrogen/sulfur dinucleophile results in the disubstituted product with no observed cyclisation.[100]

Similar velcraplexes can be formed from tetrafluoropyrazines as shown in the example where tetrachloropyrazine was utilised.[95]

This review demonstrates how tetrafluoropyrazine may be used to form a series of polysubstituted compounds but there is further scope for the development of the

methodology of reacting tetrafluoropyrazine with dinucleophiles, which is a major concern of this thesis.

1.3.9 Conclusion

The literature outlined in this Chapter has summarised the importance of drug discovery with particular focus on the syntheses of heterocyclic compounds such as pyrimidines and pyrazines and how such systems can be accessed through various methodologies. The main focus of the thesis will concern the reaction of perfluoro –pyrimidines and –pyrazines and how functionalised heterocycles can be prepared from these start materials.

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Chapter 2

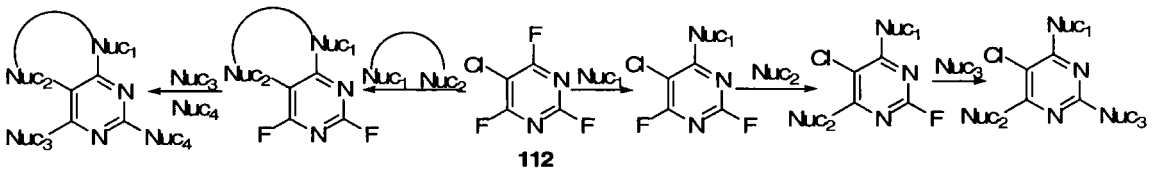
Novel Multisubstituted Heterocyclic Synthesis from 5-Chloro-trifluoropyrimidine

2 Introduction

As outlined in Chapter 1 this work concerns the formation of highly functionalised heteroaromatic derivatives which are important for drug discovery. Various methodologies to synthesise a range of polyfunctionalised pyrimidines and related ring-fused pyrimidines are available and because such functionalised pyrimidines are of great importance within the life-science industries many drug discovery programs have been implemented in an attempt to realise new compounds for commercial application. Consequently pyrimidine core scaffolds, which may be transformed into diverse ranges of functionalised derivatives through efficient and regioselective reactions, are very important. However, as was discussed in Chapter 1 it can be difficult to synthesise di- and trisubstituted pyrimidines in a regioselective manner. This Chapter will show how our methodology, starting from highly fluorinated precursors, attempts to overcome such problems for the synthesis of polyfunctionalised pyrimidines and related ring-fused pyrimidines.

2.1 Aims and Approach

Our approach towards the syntheses of functionalised heteroaromatic derivatives is to start from highly fluorinated heterocyclic precursors and replace fluorine atoms by sequential nucleophilic aromatic substitution as shown in Scheme 2.1.



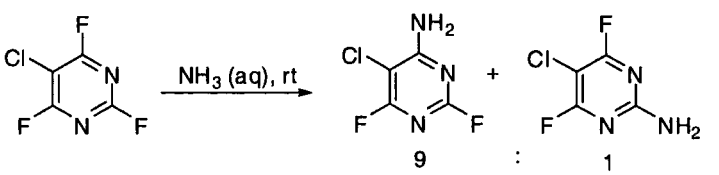
Nuc_1, Nuc_2, Nuc_3, Nuc_4 = N, O and S centred nucleophiles

Scheme 2.1

This study will firstly involve the reaction of compound **112** with nucleophiles to form carbon-nitrogen bonds which is a highly desirable process but one that has been reported to be difficult to achieve in practice.[1] Methodologies that can be used to create carbon-nitrogen bonds can either involve cross-couplings such as the Buchwald-Hartwig reaction or nucleophilic aromatic substitution by reaction of nucleophiles with sufficiently electron deficient haloaromatic compounds.[2, 3] The latter is the preferred choice for compound **112** due to the precedent within the literature (see section 1.3.1) and it was hoped to fit well within the parameters of being an efficient and regioselective reaction which is desirable for library synthesis.

The next stage of the experimental investigation involved screening a selection of dinucleophiles, including benzamidine and 2-aminopicoline by a short, simple and flexible strategy to synthesise [5,6] systems as purine analogues.

Previous research has demonstrated the reaction of compound **112** with a few nitrogen nucleophiles such as ammonia resulted predominantly in the substitution of the fluorine atom at the 4-position with some replacement of the fluorine at the 2-position being observed as shown in Scheme 2.2.



112 **121** **122**

Scheme 2.2

2.2 5-Chloro-2,4,6-trifluoropyrimidine as a Scaffold

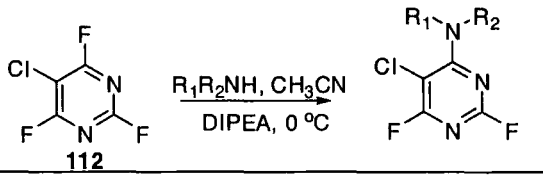
As only a few examples of the reactions of compound **112** with nitrogen nucleophiles are reported in the literature[4, 5] it was decided that a small study was required to screen the reactivity of compound **112** with various primary and secondary nucleophiles. The aim of this study was to assess the utility of compound **112** as a scaffold for library synthesis by establishing methodology that could be used to make numerous analogues with differing pendent amino groups amenable for biological screening.

2.2.1 Reactions of Compound 112 with Monofunctional Amine Nucleophiles

A series of reactions between compound **112** and a range of primary and secondary amines was carried out and the results are collated in Table 2.1.

As this was a model study the reaction conditions of using acetonitrile as the solvent and DIPEA as the base to neutralise any acidic by-products were kept constant. All of the reactions were monitored via ^{19}F NMR and the isomer ratios were measured by ^{19}F NMR spectroscopy integration from samples taken directly from the reaction mixture.

It was found that the reaction of compound **112** with ammonia results in two isomers shown by ^{19}F NMR analysis with two distinctive peaks (-48.18 and -69.47 ppm) for the 4-substituted isomer and one peak (-65.44 ppm) for the 2-isomer in a 9:1 ratio, the chemical shifts being consistent with those from previous studies.[6] Similarly, reaction with ethylamine yielded two distinct isomers in an 8:1 ratio by ^{19}F NMR by reaction at the 4- and 2- position shown by two fluorine signals (-47.48 and -70.83 ppm) and one signal (-63.59 ppm), respectively. Distillation afforded the 4-isomer in good yield. Other reactions gave a mixture of products which were identified by ^{19}F NMR as described above. In all cases, the major product could be isolated by either recrystallisation or column chromatography.



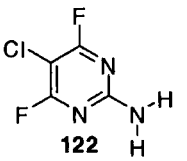
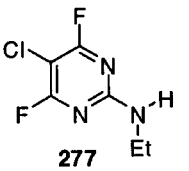
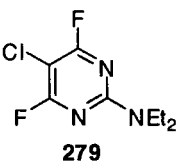
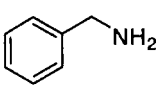
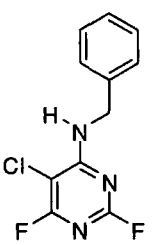
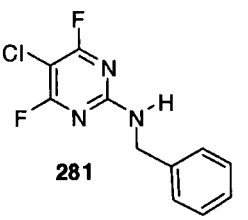
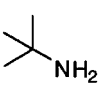
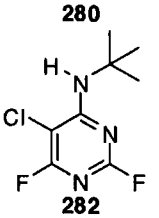
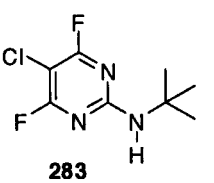
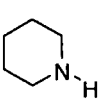
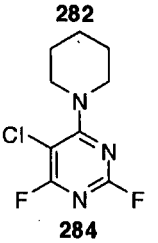
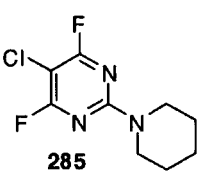
R_1R_2NH	Products		ratio	yield %
NH_3	 **121**	 **122**	9:1	57%
$EtNH_2$	 **276**	 **277**	8:1	43%
Et_2NH	 **278**	 **279**	5:1	54%
	 **280**	 **281**	5:1	41%
	 **282**	 **283**	3:1	49%
	 **284**	 **285**	3:1	25%

Table 2.1 The reactions of compound **112** with nitrogen nucleophiles.

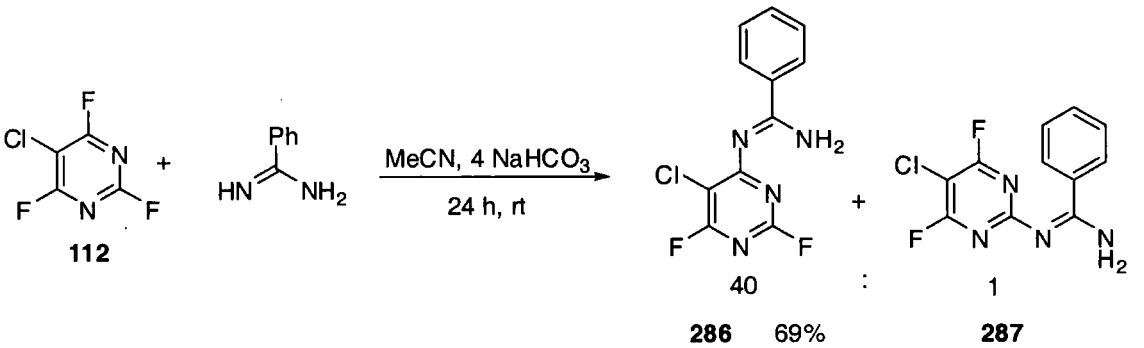
Thus, reactions of compound **112** with various amine nucleophiles resulted in attack predominately at the 4-position which is the most activated site due to the *para* ring nitrogen. This is consistent with previous observations for these types of perfluorinated heterocycles (see section 1.3). However, as the steric bulk of the nucleophile increases there was a larger ratio of the 2-substituted regioisomer and this reflects the steric hindrance to nucleophilic attack on the chlorine atom located at the 5-position.

It therefore becomes clear that this system is not ideal for analogue synthesis or for multiple substitution processes because before further reaction can take place, purification must be performed to remove the 2-substituted regioisomer from the mixture. In some cases, particularly for piperidine derivatives, this involves extensive purification and thus fails to meet either synthetic requirement for the reaction to be regioselective or efficient.

2.2.2 Reactions of Compound 112 with Difunctional Nucleophiles

Following on from the model studies with monofunctional nitrogen nucleophiles, compound **112** was reacted with benzamidine in an attempt to synthesise a purine analogue via a ring-fusion process which has been shown in Chapter 1 to be highly desirable.

Reflux of compound **112** with benzamidine, which can essentially be considered to be a primary nitrogen nucleophile, in the presence of sodium bicarbonate predominantly reacts at the 4-position rather than giving a mixture of isomers, consistent with the above findings. Indeed, when compound **112** is reacted with benzamidine at room temperature it results in nucleophilic substitution of the fluorine at the 4- and the 2- position in a 40:1 ratio shown by ^{19}F NMR with two peaks corresponding to compound **286** (-47.48 and -66.05 ppm) and one peak for compound **287** (-60.70 ppm). Isomer **286** easily isolated by recrystallisation from acetonitrile.



Scheme 2.3.

Single crystal x-ray analysis provided further proof of this structure.

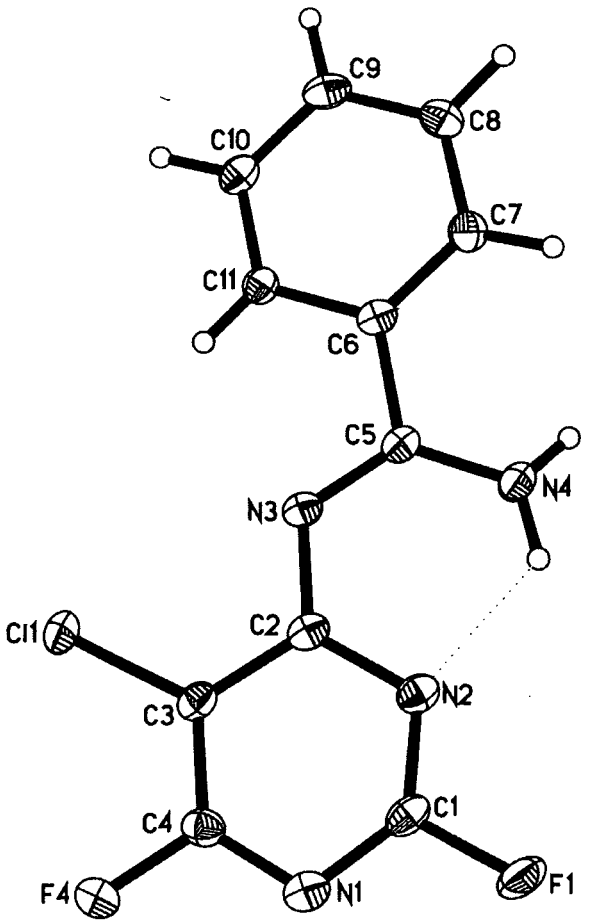
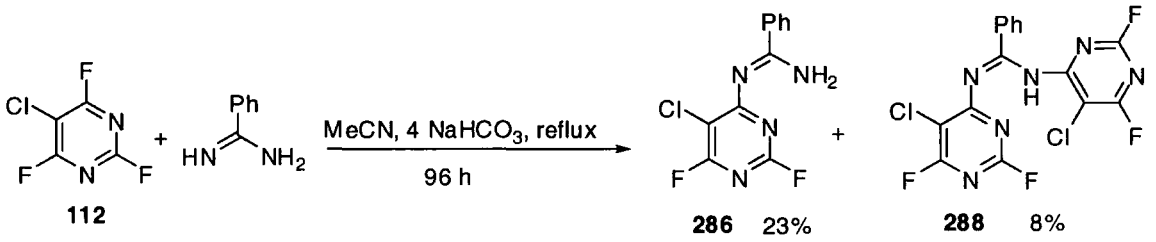


Figure 2.1 The X-ray crystallography structure of compound **286**.

Attempts to synthesise a [5,6]-fused ring system through prolonged heating of the reaction mixture results in the formation of compound **286** as the major product and compound **288** as the minor by-product. Proof of the synthesis of compound **288** was shown from ^{19}F NMR because the shifts of **288**, -47.99 ppm (1F, s, C-6) and -64.39 ppm (1F, s, C-2)) differ from those of compound **286**, and the compound **288**, has an *m/z* of 416 (M^+, 2%). This indicates the intermolecular reaction occurs faster then than intramolecular cyclisation onto the least activated 5-position.

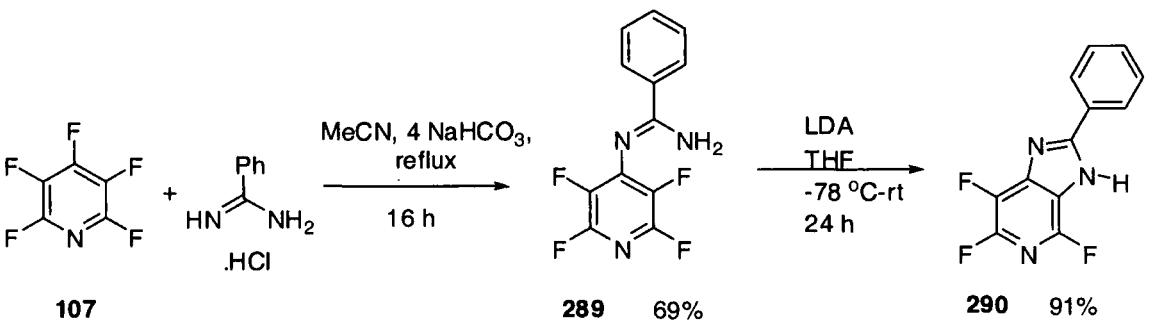


112 **286** 23% **288** 8%

Scheme 2.4

As neither experiment resulted in any annulation the next step was to attempt to form the cyclised compound **291** through the use of strong bases such as LDA or *n*-BuLi.

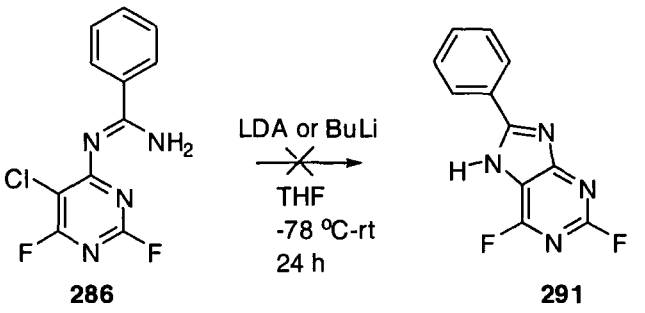
The precedent for this methodology has been shown via the reaction of pentafluoropyridine with benzamidine which proceeds via substitution of the fluorine atom at the 4-position of the pyridine ring with annulation achieved through addition of LDA to yield compound **290**.[7]



107 **289** 69% **290** 91%

Scheme 2.5

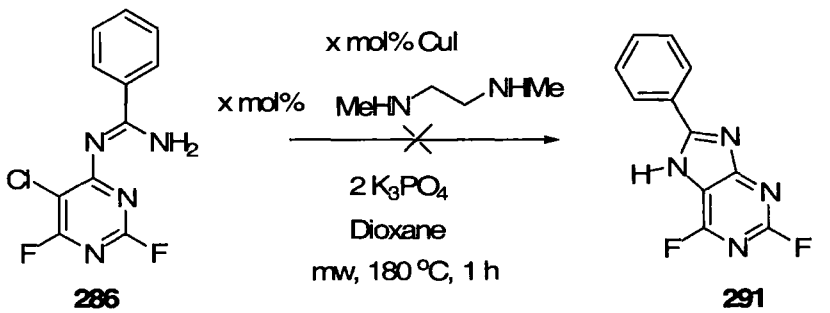
This methodology was applied firstly using LDA which results in no conversion as shown through both ^{19}F NMR and LCMS studies and secondly with *n*-BuLi which also gives no cyclised product. In both cases the starting material was recovered.



Scheme 2.6

As both the nucleophilic aromatic substitution and the base induced cyclisations had failed the next step was to take attempt the annulation process through a copper-catalysed cross-coupling such as the Buchwald-Hartwig C-N bond forming reaction. Such methodologies have been extensively utilised to provide a wide range of compounds and there are a number of comprehensive reviews of this subject area.[8-11]

Copper I Iodide was chosen initially due to the fact that experimentally it is easy to use and is amenable to microwave synthesis.



Scheme 2.7

Coupling onto a C-Cl bond is generally quite difficult to achieve and all of the reactions that were tried, including different loadings of catalyst (5%, 10% and 20%), failed to yield any cyclised products and resulted in mixtures of oligomers. At this point, this study was abandoned and no further attempts were undertaken.

2.3 Conclusion

The conclusion that can be drawn is that reactions of compound **112** with nitrogen nucleophiles are not selective and the chlorine at the 5-position is not reactive towards either nucleophilic aromatic substitution or cross-coupling methodologies for fused-ring synthesis. Consequently, alternative fluorinated pyrimidine scaffolds will be used as precursors for polyfunctional ring-fused systems.

2.4 References

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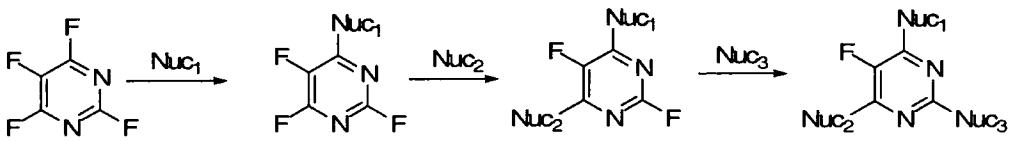
Chapter 3

Multisubstituted Pyrimidine Derivatives From Tetrafluoropyrimidine

3 Introduction

In Chapter 2 it was detailed how 5-chlorotrifluoropyrimidine, **112**, reacts with nitrogen nucleophiles to undergo nucleophilic aromatic substitution to create carbon-nitrogen bonds. However, as the steric bulk of the nitrogen nucleophile increases the amount of 2- isomer was amplified leading to more protracted purification. This meant the methodology was neither suitably efficient or regioselective enough to meet the requirements required for rapid analogue synthesis.

In order to overcome this limitation it was considered that replacement of chlorine by the less sterically demanding fluorine would remove this problem and potentially lead to a series of mono substituted compounds which would be suitable for further derivatisation.



113

Nuc_1, Nuc_2, Nuc_3 = N, O and S centred nucleophiles

e.g. Aniline, Benzylamine, Ethylamine, Diethylamine, Morpholine, Phenoxide, Ethanethiolate, Benzenethiolate

Scheme 3.1

In Chapter 1 it was demonstrated that the reaction of tetrafluoropyrimidine, **113**, is represented within the literature but a comprehensive study has not been discussed. Furthermore, such methodology could be extended to the reaction of compound **113** with oxygen and sulfur nucleophiles to form carbon-oxygen and carbon-sulfur bonds. These

classes of compounds are important in the development of pharmacologically active compounds and in the development of the scope of the methodology for multisubstituted pyrimidine synthesis.

This chapter will discuss the reactivity of compound **113** with a range of nitrogen, oxygen and sulfur (both aromatic and aliphatic) centred nucleophiles with a view to synthesising trisubstituted pyrimidine systems. The importance of such derivatives was outlined in Chapter 1.

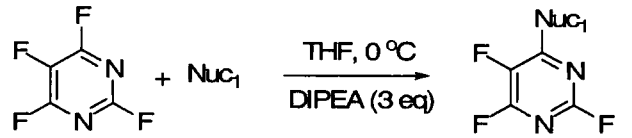
A single precedent for sequential poly-substitution reactions to regioselectively replace the fluorine atoms has been described and occurs through the step-wise reaction of compound **113** with sodium methoxide.[1] Development of this sequential methodology by reaction with nitrogen, oxygen and sulphur-centred nucleophiles to furnish highly functionalised heterocylic derivatives and establishing regioselectivity of such processes is the aim of this work.

Therefore, it may become a realistic possibility to develop routes to synthesise novel pyrimidines that are otherwise difficult to access and, thus, have the potential to be utilised by the pharmaceutical and life-science industries for drug discovery.

3.1 Reactions of Tetrafluoropyrimidine 113 with Nitrogen Nucleophiles

In Chapter 1 it was demonstrated that compound **113** undergoes nucleophilic aromatic substitution with various amine nucleophiles with replacement of the fluorine at the activated 4-position[1-4] and this was also the case when primary amines such as ethylamine, benzylamine and aniline were screened. Each of the reactions was performed in THF and under basic conditions with an excess of DIPEA as a base to neutralise any hydrogen fluoride by-products. Stirring the reaction mixture at 0 °C for 1-2 hours and monitoring by ^{19}F NMR results in the appearance of three distinct resonances (see Scheme 3.2 for values) due to the regiospecific displacement of the fluorine atom at the 4-position. Subsequent

work-up using standard methods and either simple recrystallisation or column chromatography gave the products in good yields and high purity.



113

Nuc_1	^{19}F NMR ppm	%	
NH_2Et	- 48.80, - 87.72, - 174.15	75	**292**
NH_2CH_2Ph	- 47.21, - 86.61, - 180.69	59	**293**
NH_2Ph	- 46.10, - 84.09, - 177.80	68	**139**

Scheme 3.2

With these results in hand, reactions of compound **113** with secondary amines were carried out under identical conditions with substitution of the fluorine atom occurring at the 4-position regiospecifically, as observed by ^{19}F NMR. Recrystallisation from either *n*-hexane or DCM gave compounds **294** and **295** in fair yield and purity.

113

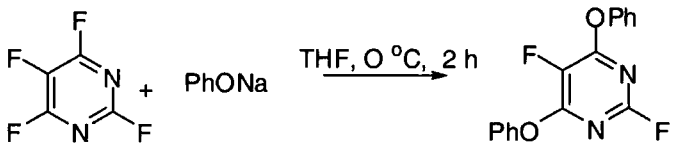
Nuc_1	^{19}F NMR ppm	%	
$NHEt_2$	- 47.61, - 86.76, - 177.38	26	**294**
Morpholine	- 47.90, - 84.66, - 172.39	84	**295**

Scheme 3.3

Each reaction was complete within a 1-2 hour period which was determined by ^{19}F NMR spectroscopy. After full conversion of the start material to product a rapid work-up and purification sequence was completed making the turn around time very short for the production of 4-substituted heterocycles. Moreover, with ethylamine, aniline and morpholine, scale-up is possible and products were obtained in batches of up to 10g with high yields, providing ample material for further reaction.

3.2 Reactions of Tetrafluoropyrimidine 113 with Oxygen Nucleophiles

As an extension to the study involving aliphatic alkoxides,[1] compound **113** was reacted with sodium phenoxide, an aromatic nucleophile, in THF at 0 °C, which resulted in the formation of a disubstituted compound **296** (even under high dilution conditions with only one equivalent of nucleophile) as shown via ^{19}F NMR with two peaks appearing at -45.9 and -174.2 ppm. A pure sample amenable for full analysis was obtained through recrystallisation from *n*-hexane.



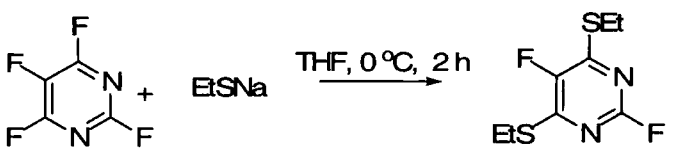
113 **296**, 43 %

Scheme 3.4

This reaction indicates that the mono-phenoxide system must be more reactive towards nucleophiles than the starting material and the reasons for this are not clear as we would expect that the electronegative fluorine atom to activate the ring more strongly with respect to a phenoxide substituent.

3.3 Reactions of Tetrafluoropyrimidine 113 with Sulfur Nucleophiles

There are few examples of reaction of compound **113** with sulfur nucleophiles within the literature and so the reaction with EtSNa was performed in an analogous manner to those discussed previously.



113 **297**, 54 %

Scheme 3.5

Monitoring the reaction by ^{19}F NMR showed the appearance of two peaks at -50.25 and -139.16 ppm with a *m/z* of 236 (M^+, 100%) corresponding to the formation of the di-substituted compound **297**. The formation of this compound is probably the result of the inherent reactivity of the sulfur nucleophile and also, as seen in the alkoxide case leads to the conclusion that the mono substituted product is more reactive than tetrafluoropyrimidine.

3.4 Conclusion

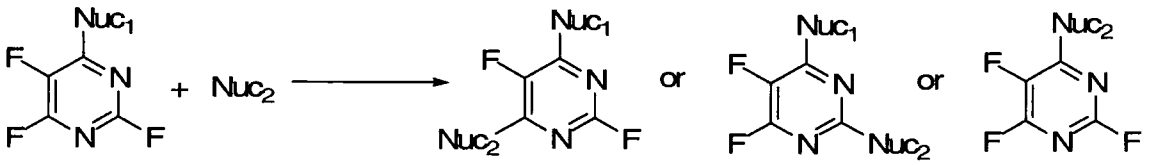
It has been outlined how nitrogen nucleophiles are ideal for the synthesis of mono substituted derivatives preferentially over that of the oxygen or sulfur nucleophiles. The latter led to disubstituted compounds preferentially.

This has concluded the study of compound **113** with mono nucleophiles and the next stage is to explore the reactivity of the mono substituted compounds with other representative nucleophiles which will be outlined in the subsequent sections.

Consequently, extending the research by screening a selection of new nitrogen nucleophiles proceeded in accordance with literature precedent and the study moved on to exploring the possibility of further derivatisation by the replacement of the remaining fluorine atoms attached to the heterocyclic ring.

3.5 Reactions of 4-Substituted Perfluoropyrimidines with Nucleophiles

Given that the 4-amine substituted pyrimidines have three fluorine atoms remaining a study into their reactivity towards further nucleophilic aromatic substitution was carried out with a selection of nucleophiles.

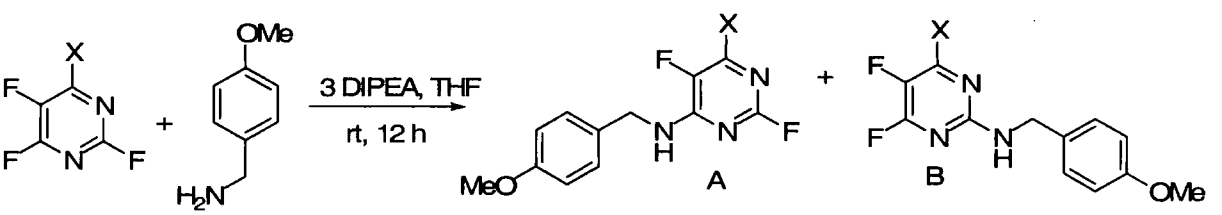


Scheme 3.6

In principle the nucleophile is most likely to attack at three positions when reacted with nucleophiles: the 6- or 2- positions involving displacement of the fluorine atom or the 4-position involving displacement of Nuc_1. The next section will outline the result of the reaction of compounds **292**, **295** and **139** with mono nucleophiles.

3.5.1 Reaction of 4-Substituted Trifluoropyrimidines with Nitrogen Nucleophiles

Primary and secondary aliphatic nitrogen nucleophiles were reacted with the mono substituted systems **292** and **295**. Reactions of 4-methoxybenzylamine with **292** and **295** in THF at room temperature gave two products with the major product being the 6-substituted isomer and minor quantities of the 2-substituted isomer in a 19:1 and 16:1 ratio respectively, which was determined by ^{19}F NMR of the reaction mixture. Extraction and simple recrystallisations from *n*-hexane gave the 6-subtituted isomers as a white solids in good yield and excellent purity.

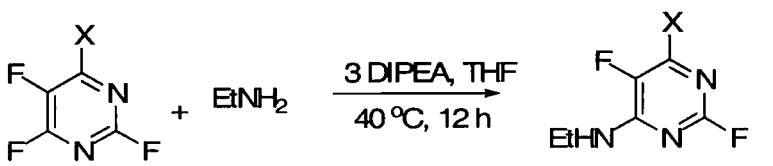


X	ratio A:B	^{19}F NMR ppm	% of isomer 6 isolated	
NHEt	19:1	-49.58, -186.07	61	**298**
Morpholine	16:1	-49.99, -175.45	66	**299**

Scheme 3.7

The formation of the 6-substitued isomer can be attributed to the 6-site being the most activated site due to the presence of a *para* nitrogen although competing 2-substitution can occur due to activation by two *ortho* nitrogens.

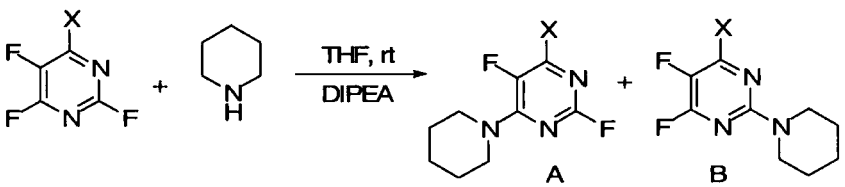
The reactivity of compounds **139** and **295** with the primary nitrogen nucleophile, ethylamine, resulted in attack at the 6-postion preferentially as seen by ^{19}F NMR, with the formation of two distinct resonances (see Scheme 3.8). Heating of the reaction mixture was required to give full conversion to the disubstituted system and reflects the lower reactivity of the heterocyclic ring.



X	^{19}F NMR ppm	%	
NHPH	-49.12, -149.23	72	**300**
Morpholine	-50.11 , -175.77	61	**301**

Scheme 3.8

The next nucleophiles screened were secondary amines such as piperidine which were reacted with compounds **295** and **293** and resulted in the formation of two regioisomers with displacement of the fluorines at the 6-position and the 2-position in a 1:1 ratio respectively.



X	ratio, A:B	% of isomer 6 isolated	
Morpholine	1:1	51	**302**
Benzylamine	1:1	36	**303**

Scheme 3.9

This result demonstrates the formation of the products is not dependent on the initial substituent but on other factors present within the system. A possible explanation of this reactivity may come from the fact that as the bulk of the nucleophile induces steric repulsion from the fluorine atom at the 5-position becomes more pronounced resulting in an increased amount of substitution of the fluorine at the 2-position.

Represented in Figure 3.1 is the x-ray structure of compound **303** which confirmed that reaction with secondary amines gives substitution of the fluorine atom at the 2-position.

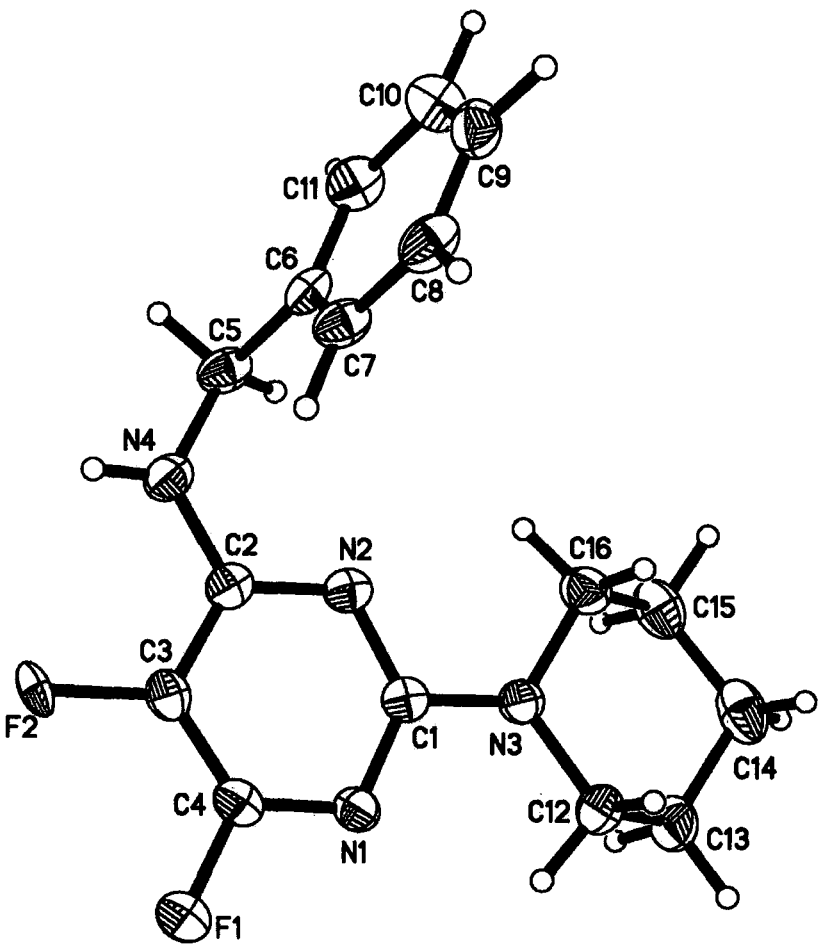
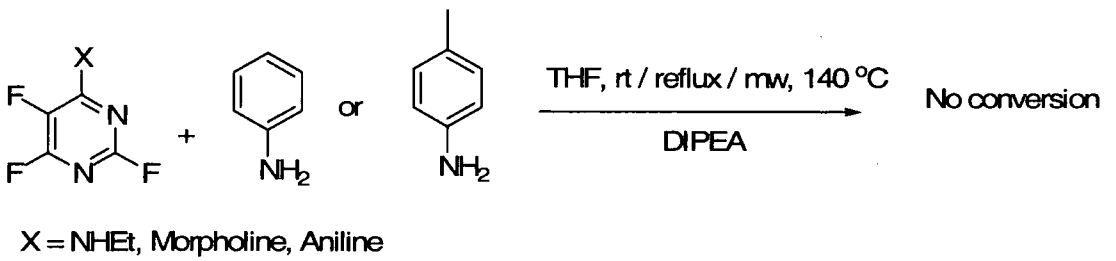


Figure 3.1 The x-ray crystallography structure of compound **303**

In contrast to the reactions above, all attempts to react tetrafluoropyrimidine with aniline resulted in no reaction and the starting material was reclaimed. Following on from this result, the more reactive 4-methyl aniline was employed, however, no reaction was observed and this in turn reflects the lower nucleophilicity of aniline and derivatives even under prolonged microwave heating.



Scheme 3.10

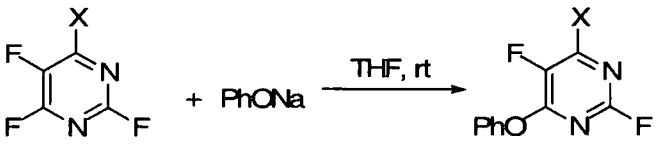
In summary, these results demonstrate novel polysubstituted pyrimidine systems can be synthesised by reaction of mono substituted perfluoropyrimidine compounds with aliphatic amines. In the case of primary amines there was selective replacement of the fluorine atom at the 6-position to yield a range of unique disubstituted systems whereas secondary amines led to a mixture of products that could be separated.

3.5.2 Reactions of 4-Substituted Perfluoropyrimidines with Oxygen Nucleophiles

In light of the excellent reactivity demonstrated towards nucleophilic aromatic substitution with primary amines, the study was extended to reaction of compounds **292**, **295** and **139** with oxygen nucleophiles in order to access a set of novel disubstituted pyrimidines by reaction with aliphatic and aromatic alkoxides.

Firstly compounds **292**, **295** and **139** were reacted with the sodium phenoxide in THF at room temperature which gave exclusive replacement of the fluorine atom at the 6-position. Monitoring the reaction via ^{19}F NMR showed the formation of two distinct resonances (see Scheme 3.11 for values) with the peak at around -80 ppm, corresponding to substitution of

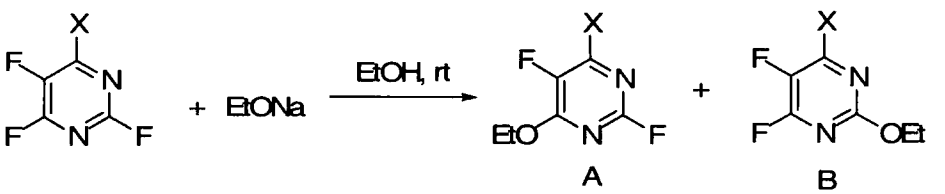
the fluorine at the 6-position, which decreased over the time, with complete conversion achieved over a 12-13 hour period.



X	^{19}F NMR ppm	%	
NHEt	-47.81, -180.23	63	**304**
NHPH	-49.97, -179.31	79	**305**
Morpholine	-49.59, -172.81	70	**306**

Scheme 3.11

THF which was used in previous reactions (see Schemes 3.7, 3.8 and 3.9) gave no conversion to any products. Consequently, due to the lack of solubility of the sodium ethoxide in solution ethanol was used in its place, see Scheme 3.12.



X	ratio A:B	^{19}F NMR ppm	% of isomer 6 isolated	
NHEt	6:1	-49.33 , -186.07	77	**307**
NHPH	5:1	-49.97, -179.31	64	**308**
Morpholine	6:1	-49.59 -172.81	71	**309**

Scheme 3.12

Unlike the reaction with sodium phenoxide, a mixture of isomers formed with the predominate formation of the 6-substituted isomer with a general ratio of 6:1. As sodium ethoxide is a harder nucleophile then phenoxide it would be expected that there would be some substitution of the fluorine atom at the 2-position as it is a hard site due to the two *ortho* nitrogens withdrawing electron density from the carbon. However due to the

stabilisation of the negative charge in the transition state onto the *para* nitrogen being the dominant effect the nucleophile is mainly orientated towards the 6-position.

Also, ethoxide in ethanol as a solvent makes the nucleophile 'bigger' due to solvation and as the 2-position is less sterically demanding and there is some substitution of the fluorine atom (this also agrees with what was observed for the reactivity with HNR_1R_2 nucleophiles).

It must also be noted that as ethanol is a polar protic solvent and THF is a polar aprotic solvent direct comparisons between this nucleophile's reactivity and others in this series can not be made.

Represented in Figure 3.2 is the x-ray structure of compound **308** which confirms the formation of this compound.

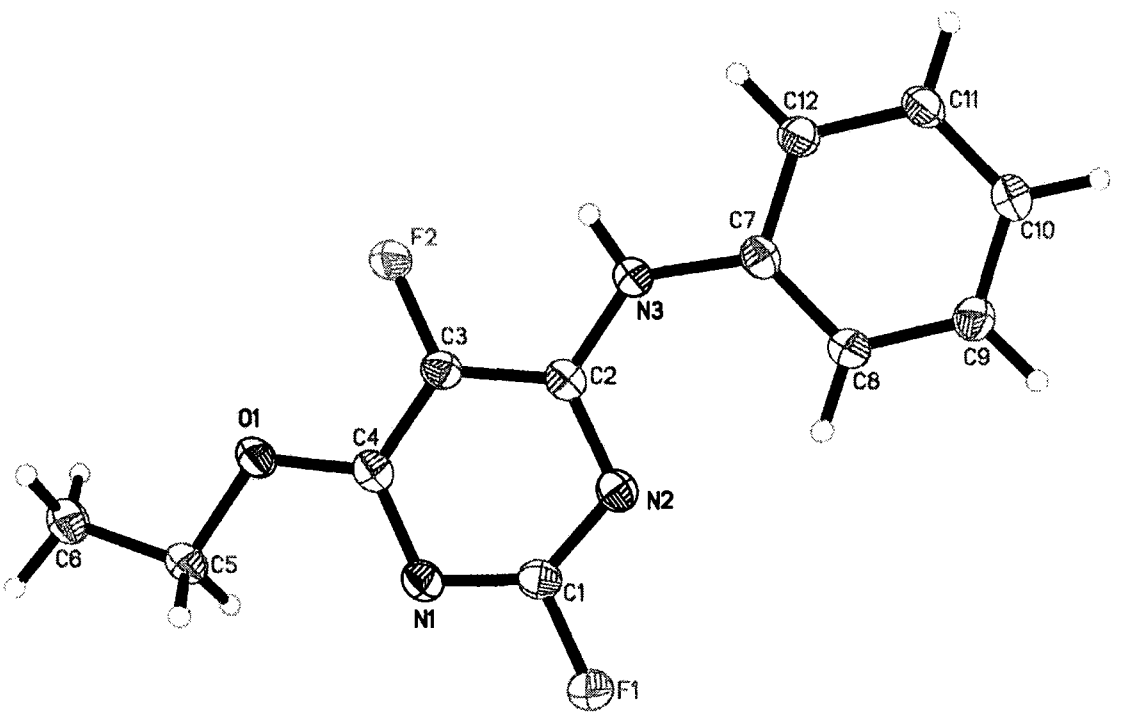
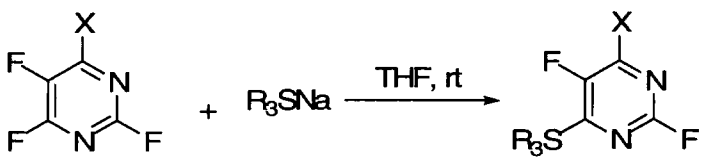


Figure 3.2 The x-ray crystallography structure of compound **308**

These results have demonstrated that it is possible to synthesise a selection of nitrogen and oxygen disubstituted pyrimidines and has significantly expanded the methodology of the second step which in terms of library synthesis is an ideal situation.

3.5.3 Reactions of 4-Substituted Perfluoropyrimidines with Sulfur Nucleophiles

The last part of this research was to study the reactions of compounds **292**, **295** and **139** with aliphatic and aromatic sulfur-containing nucleophiles. The site of attack is analogous to the oxygen-substituted systems as substitution of the fluorine at the 6-position is readily seen by the appearance of two distinct peaks in the ^{19}F NMR when the reaction is performed in THF at room temperature. There was no substitution of the fluorine at the less activated 2-positon.



X	R_3	^{19}F NMR ppm	%	
NHEt	Et	-56.67, -167.93	63	**310**
NHEt	Ph	-48.55 , -159.30	51	**311**
NHPh	Et	-48.50, -158.50	68	**312**
NHPh	Ph	-47.30, -157.10	71	**313**
Morpholine	Ph	-49.10, -149.21	88	**314**

Scheme 3.13

Furthermore, the regiochemistry of attack at the 6-position was confirmed by growing a single crystal of compound **312** from MeOH which was then subjected to x-ray analysis to confirm this structure.

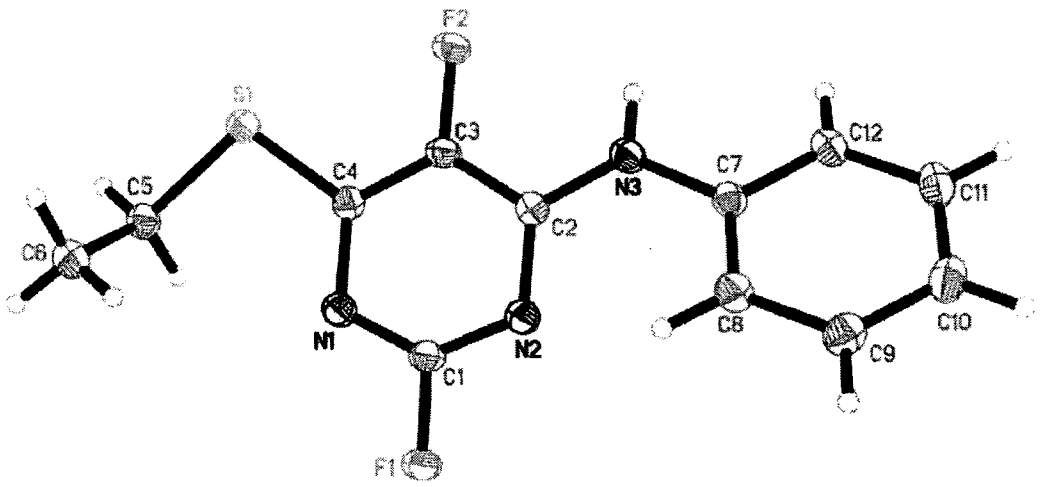


Figure 3.3 The x-ray crystallography structure of compound **312**

At the start of this section the question of what would happen if a series of mono substituted amine derivatives were reacted with a second nucleophile was raised. Through reaction with nitrogen, oxygen and sulfur-centred nucleophiles it has been demonstrated in most cases that primary amines and soft nucleophiles react at the 6-position exclusively.

Consequently, in two steps from tetrafluoropyrimidine, a sequential build up of functionality around the pyrimidine core was achieved to furnish a selection of novel disubstituted pyrimidine derivatives.

3.6 Reactions of *N*-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine 304 with Mono Nucleophiles

Following on from section 3.8 it was hoped that further nucleophilic aromatic displacement of the difluorinated derivatives to form a trisubstituted pyrimidine would be possible.

3.6.1 Reactions of *N*-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine 304 with Nitrogen Nucleophiles

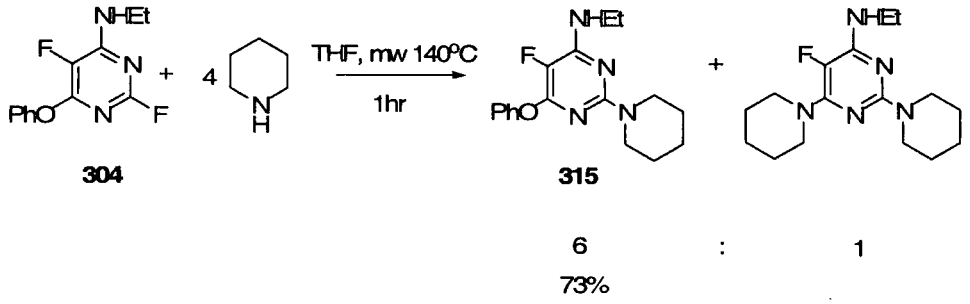
It must be noted that an exploration of the reactivity of disubstituted pyrimidines with nucleophiles was initially conducted by refluxing the components in THF but there was no conversion to any products even after varying the concentrations of the reactants and prolonged heating over several days. This lack of reactivity and the need for more forcing conditions to effect the substitution is due to the presence of the deactivating amine groups.

It was therefore decided to employ microwave techniques in an attempt to synthesise the desired compounds which is a very useful technique due to the ability to optimise reactions quickly through screening a number of reaction conditions. In recent years the use of microwaves for chemical synthesis has become increasingly popular and there are many papers and books outlining such research.[5] This proved very successful in synthesising a number of compounds as demonstrated in the proceeding sections.

The next few sections will detail the reactions of compound **304** with various nucleophiles and how in certain cases a selection of novel trisubstituted pyrimidines were synthesised.

The system chosen for the initial study was compound **304** as it was relatively easy to synthesise in large quantities. Firstly, compound **304** was reacted with an excess of piperidine under the reaction conditions shown below which resulted in substitution of the fluorine at the 2-position with a single peak at -191 ppm corresponding to compound **315**. However, a second peak was also observed at -182 ppm which showed that replacement of the phenoxide group at the 6-position had occurred. The ratio of compound **315**, to that of the bis-substituted compound was 6:1 (see Scheme 3.14).

^{19}F NMR and mass spectrometry analysis of the reaction mixture showed that fluorine was displaced by piperidine exclusively before substitution of the phenoxy group occurred which reflects the electrophilicity of the C-F site at the 2-position. The structure of compound **315** was confirmed by x-ray analysis.



Scheme 3.14

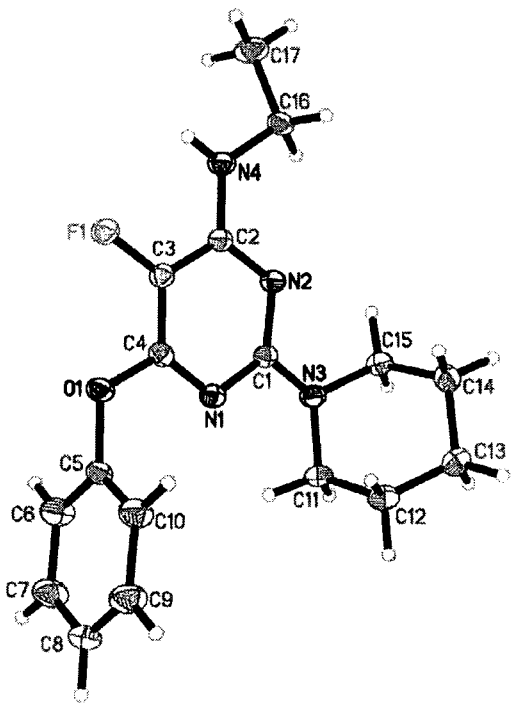
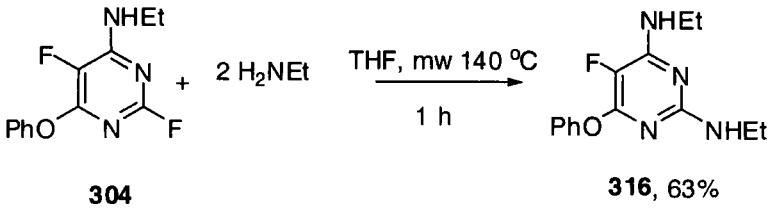


Figure 3.4 The x-ray crystallography structure of compound **315**

Reaction with an excess of ethylamine under the reaction conditions shown below resulted in substitution of the fluorine at the 2-position with a single peak observed at -190 ppm corresponding to compound **316**.



304 **316**, 63%

Scheme 3.15

The structure of compound **316** was confirmed by x-ray analysis.

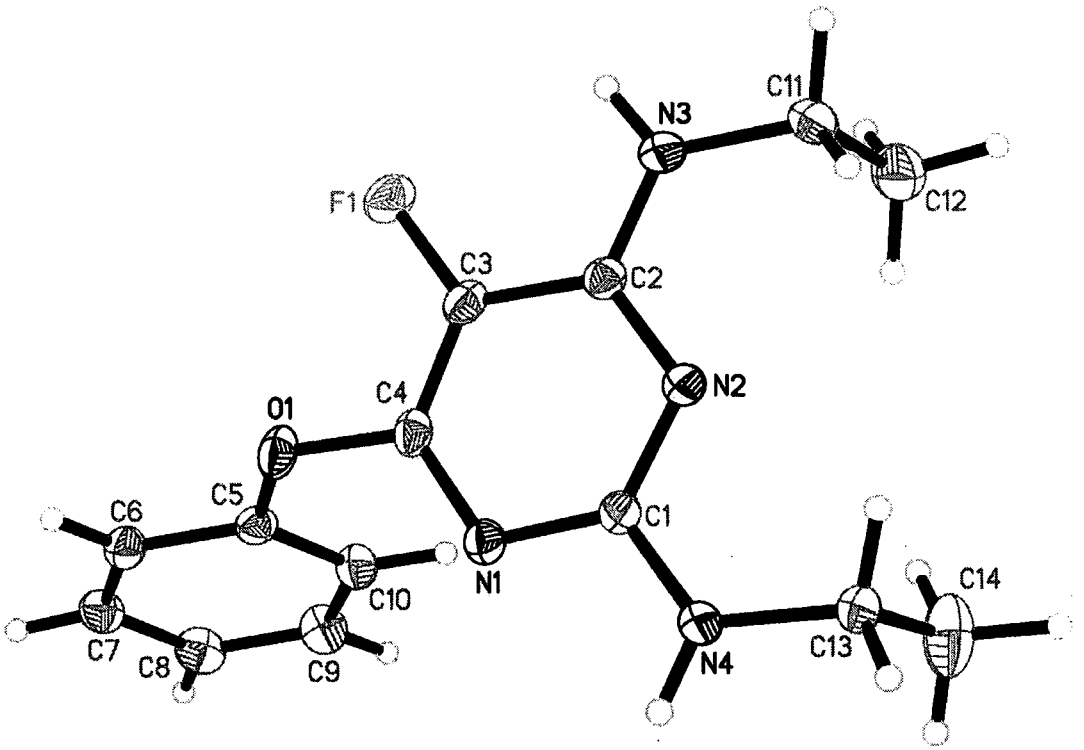
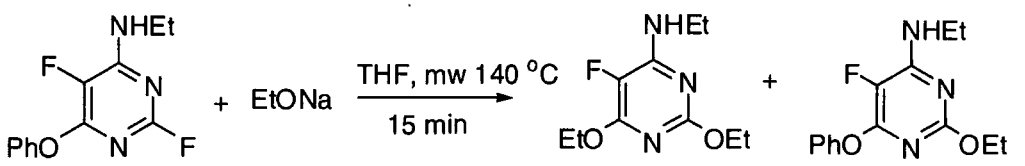


Figure 3.5 The x-ray crystallography structure of compound **316**

These results indicate the 6-position is still activated towards nucleophilic attack and, furthermore, phenoxide is a good leaving group. However, reducing the time of the reaction led exclusively to the mono substituted product in the case of the piperidine nucleophile.

3.6.2 Reactions of Compound *N*-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine 304 with Oxygen Nucleophiles

Reaction of compound **304** with sodium ethoxide resulted in the formation of two products in a 1.5:1 ratio with the major product **317** corresponding to replacement of both the 6-phenoxide group and the fluorine at the 2-position. The minor compound **318** resulted from replacement of the fluorine at the 2-position only.



1.5 : 1

304 **317**, 16% **318**, 13%

Scheme 3.16

All attempts to reduce the formation of the bis-substituted compound by screening multiple reaction conditions such as varying the reaction times, solvents and concentrations of the reagents gave the same result and it was not possible to form only compound **318**. However, purification of the two compounds was achieved through reverse phase chromatography allowing each compound to be characterised.

Furthermore, structures of both compounds **317** and **318** were confirmed by growing single crystals from MeOH and subjecting them to x-ray analysis

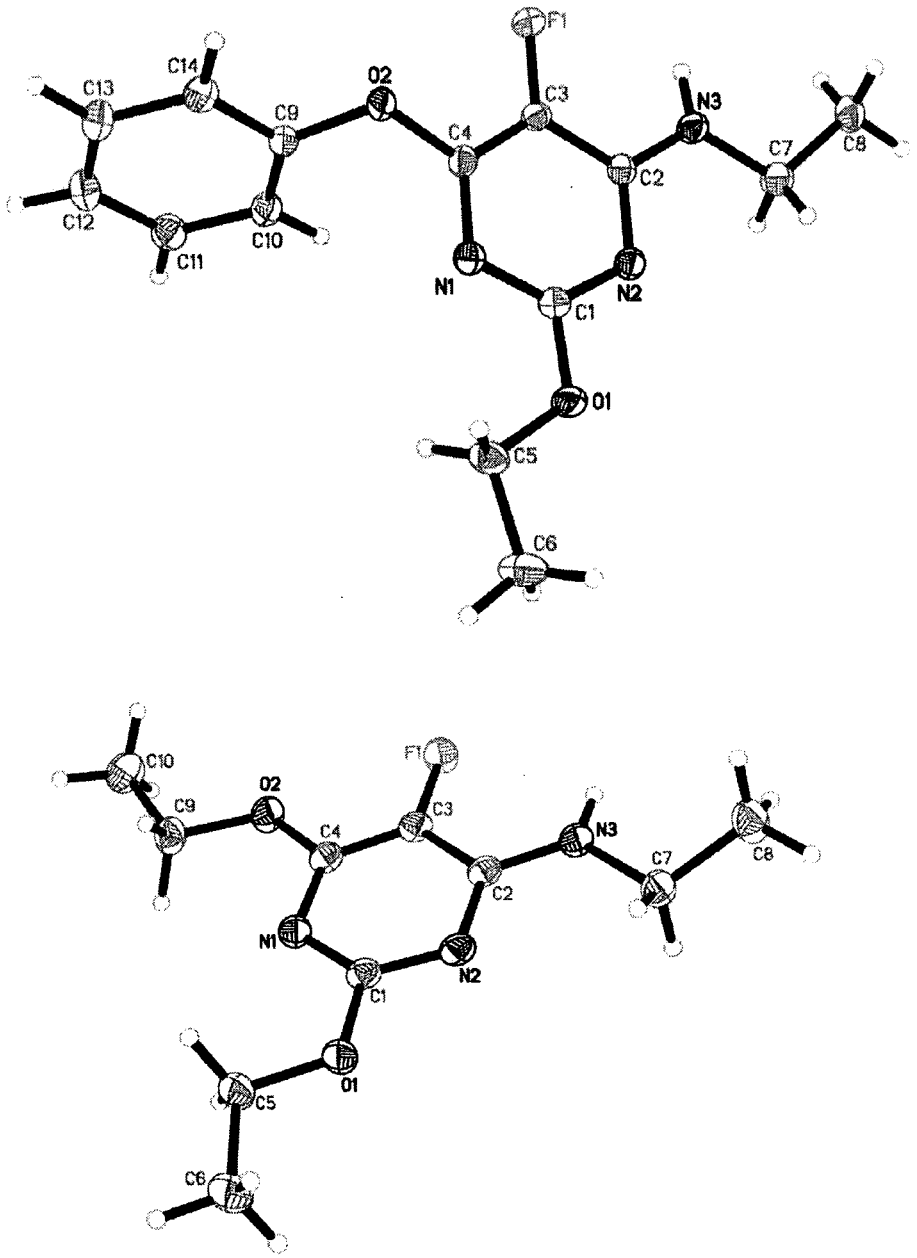
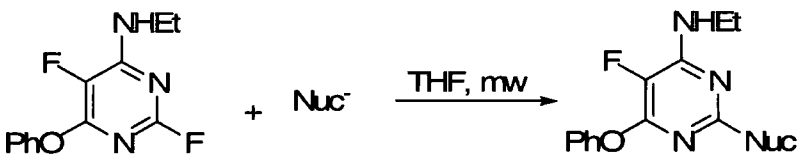


Figure 3.6 The x-ray crystallography structures of compounds **317** and **318**

This result reflects that the phenoxide is a good leaving group and, when attached to an activated site, can be displaced in competition with fluoride at the 2-position.

3.6.3 Conclusion

This research has demonstrated that the phenoxide group at the 6-positon is a good leaving group and can be displaced by reaction with nucleophiles. It has also shown that it is possible to functionalise the pyrimidine scaffold by reaction with a third nucleophile to give trifuctionalised pyrimidine systems.



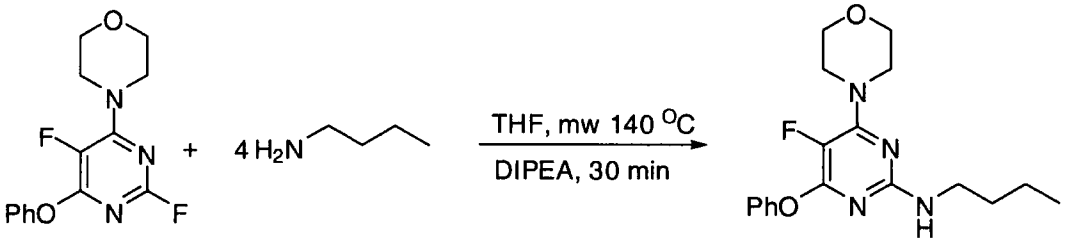
Scheme 3.17

3.7 Reactions of 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine 306 with Mono Nucleophiles

Following on from section 3.9 it was decided to explore the reactivity of the morpholine compound **306** with nitrogen, oxygen and sulfur nucleophiles to further extend the investigation of the methodology. This was to determine whether replacement of the phenoxide group would also occur.

3.7.1 Reactions of 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine with Nitrogen Nucleophiles

Compound **306** was firstly reacted with the primary amine butylamine in an analogous manner to the reaction conditions for compound **304** detailed in section 3.9 which resulted in the selective replacement of the fluorine atom at the 2-position to form compound **319** with a single peak observed at -179.4 ppm. Recrystallisation from *n*-hexane gave the compound in fair yield and purity which were then analysed using the standard analytical techniques (see Chapter 6).



306 319, 50%

Scheme 3.18

A single crystal was grown from MeOH and subjected to x-ray analysis which confirmed the structure of compound **319**.

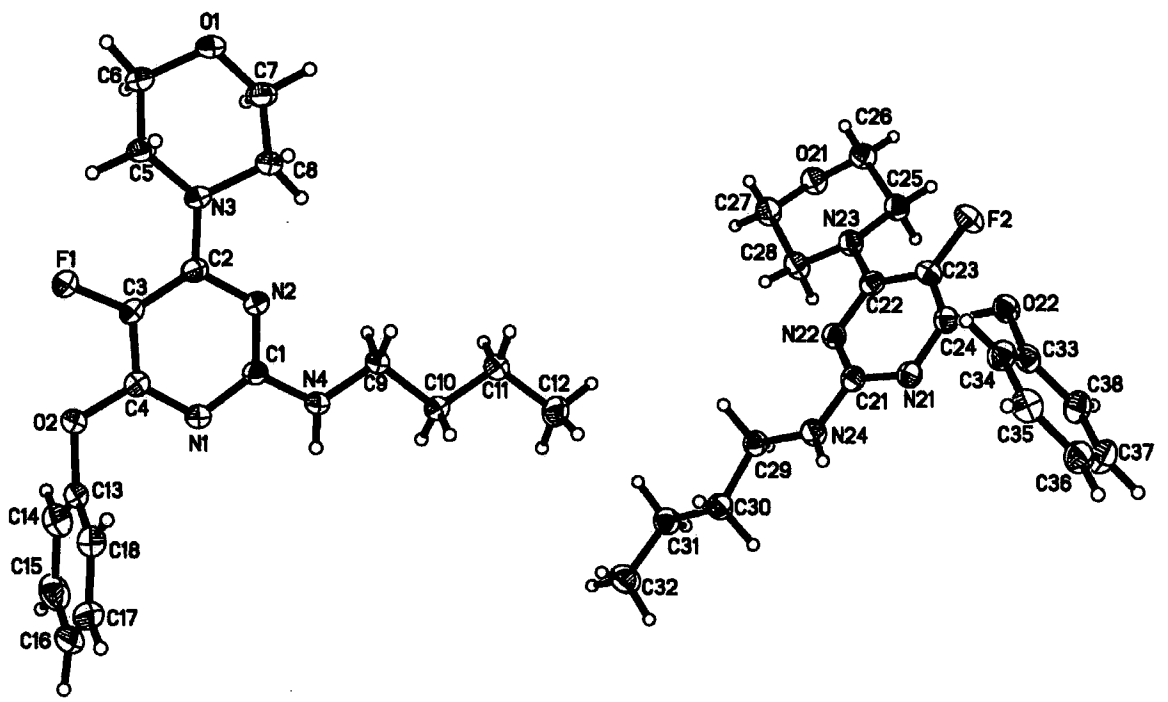
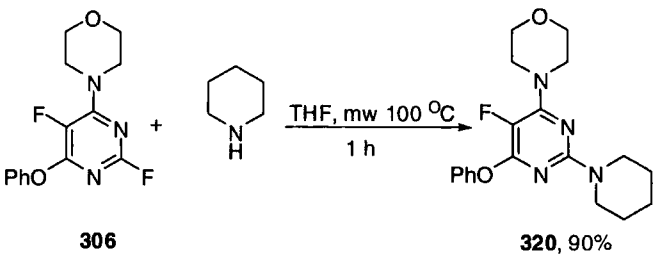


Figure 3.7 The x-ray crystallography structure of compound **319**

Compound **306** was then reacted with an excess of the secondary amine piperidine. This resulted in replacement of the fluorine at the 2-position with a single peak observed at -180.0 ppm corresponding to compound **320**.



Scheme 3.19

A single crystal was grown from MeOH and subjected to x-ray analysis. Although the structure was not fully resolved it gives clear evidence for the formation of the trisubstituted pyrimidine system of compound **320**.

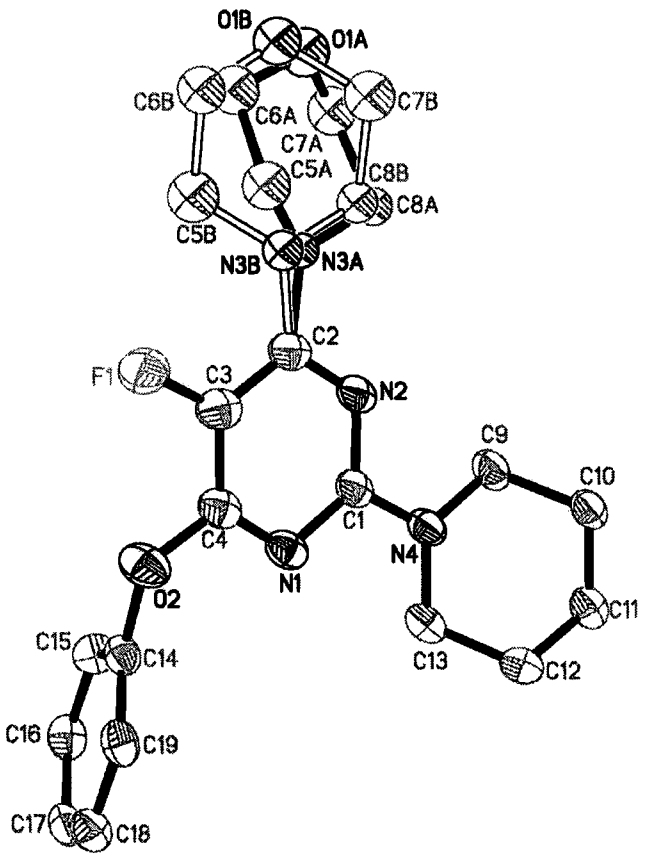
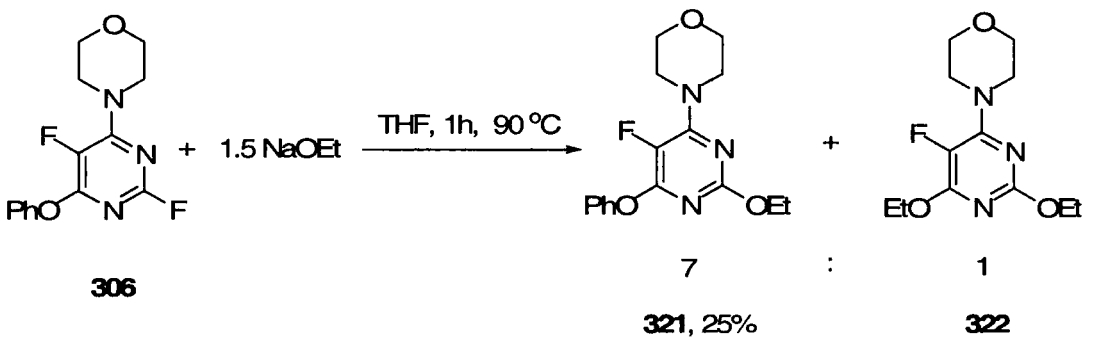


Figure 3.8 The x-ray crystallography structure of compound **320**

These reactions, when compared those of compound **304**, showed that the methodology can be replicated to give more examples of trifunctionalised pyrimidines analogues. Less reactive nitrogen nucleophiles give rise to products from displacement of the fluorine only whereas more reactive nitrogen nucleophiles can give mixtures under forcing conditions.

3.7.2 Reactions of 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine 306 with Oxygen Nucleophiles

Reaction of compound **306** with sodium ethoxide results in the formation of two products in a 7:1 ratio with the major product being that of compound **321,** and the minor product compound **322**, which is the result of 6-phenoxide group and the fluorine at the 2-position being replaced with the ethoxy group.



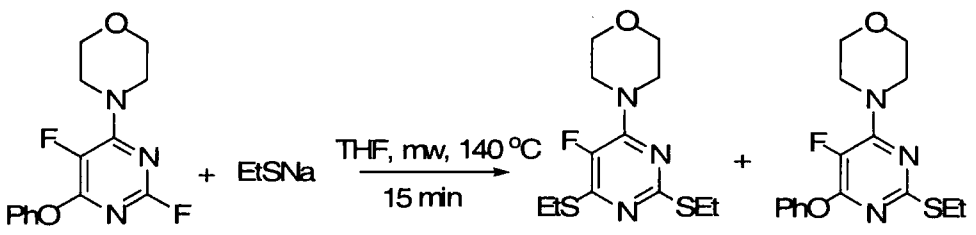
Scheme 3.20

Attempting to control the reaction to form only compound **321**, by suppressing the formation of the bis-substituted compound **322**, through screening reaction conditions such as varying the reaction times, solvents and concentrations failed to give the desired trifunctionalised pyrimidine as a single product and in all instances both compounds were observed.

3.7.3 Reaction of 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine 306 with Sulfur Nucleophiles

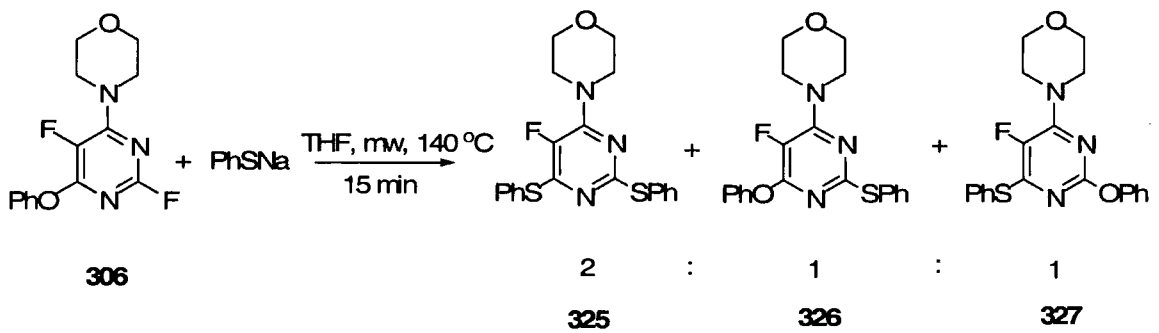
Subsequently, reaction of compound **306** with sulfur-centred nucleophiles was attempted and proved more problematic, in that a wide range of products were observed using either sodium ethanethiolate and benzene thiophenoxide.

Reaction of compound **306** with sodium ethanethiolate led to the formation of two compounds **323** and **324** which could be seen from the ^{19}F NMR with two peaks occurring at -171.8 and -173.5 ppm.



Scheme 3.21

Reaction with the sodium benzene thiolate ion gave three main products including compounds **325**, **326** and **327** which could be seen from the ^{19}F NMR with three peaks occurring at -170.9, -148.3 and -180.2 ppm.



Scheme 3.22

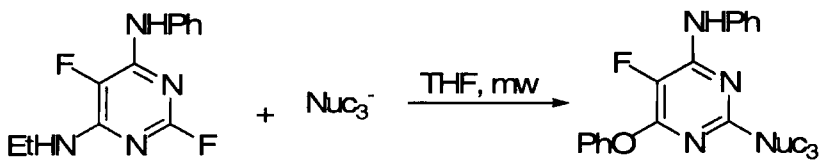
Isolation of compounds from the mixture was attempted but met with little success.

In conclusion, this result demonstrates again that if a sufficiently reactive nucleophile is used displacement of the phenoxide group at the 6-positon can occur similar to what was observed when compound **306** was reacted with the ethoxide nucleophile (see Scheme 3.2).

3.8 Reactions of N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine 300, with Mono Nucleophiles

In section 3.9 it was demonstrated that when compound **304** was reacted with a selection of nitrogen, and oxygen-centred nucleophiles, a range of trifunctionalised pyrimidines could be synthesised. When compound **306** is reacted with amine nucleophiles, functionalisation of the pyrimidine is achieved if the conditions are carefully controlled, whereas reaction with alkoxides and sulfur nucleophiles led to mixtures of compounds and the occurrence of which was explained in terms of the labile nature of the phenoxide group (see sections 3.7.2 and 3.7.3).

It was, therefore, envisioned that using amines in this second step would result in a less labile group attached to the 6-position and lead to a set of trifunctionalised pyrimidines that could be easily obtained and purified. The system chosen for this study was compound **300** which was readily synthesised in large quantities. It was anticipated that remaining fluorine atoms would be amenable for functionalisation by replacement with nitrogen, and oxygen-centred nucleophiles.



300

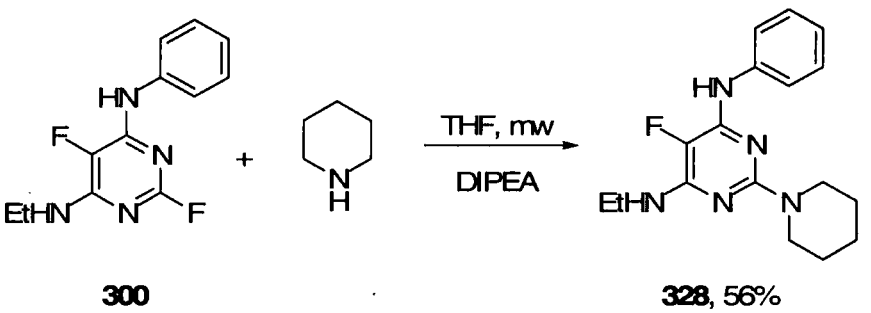
Nuc_3 = piperidine, NaOPh,

Scheme 3.23

3.8.1 Reaction of N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine 300 with Nitrogen Nucleophiles

Compound **300** was reacted with amines using similar reaction conditions to those described previously in section 3.6.1 for compound **304**.

Reaction with piperidine resulted in the formation of compound **328** with no replacement of either the ethylamine or aniline group. This is easily seen from the ^{19}F NMR peak at -191.96 ppm and *m/z* (ES^+) 316 ($[M + H]^+$). Purification was readily achieved by recrystallisation from DCM:*n*-hexane mixtures.

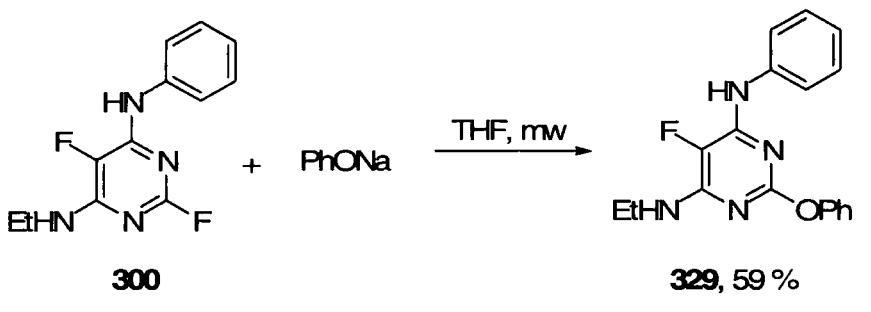


300 **328**, 56%

Scheme 3.24

3.8.2 Reaction of N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine 300 with Oxygen Nucleophiles

Reaction of compound **300** with sodium phenoxide resulted in replacement of the fluorine atom at the 2-position but no replacement of the either the aniline or ethylamine groups reflecting the less labile nature of the ethylamine to that of the phenoxy group.



300 **329**, 59 %

Scheme 3.25

3.9 Conclusion

The reaction of tetrafluoropyrimidine, **113** with mono nucleophiles demonstrates that nitrogen nucleophiles are ideal for the synthesis of mono substituted derivatives over that of reaction with oxygen or sulfur nucleophiles. The latter led to disubstituted compounds preferentially (see Figure 3.9 for the compounds that were synthesised).

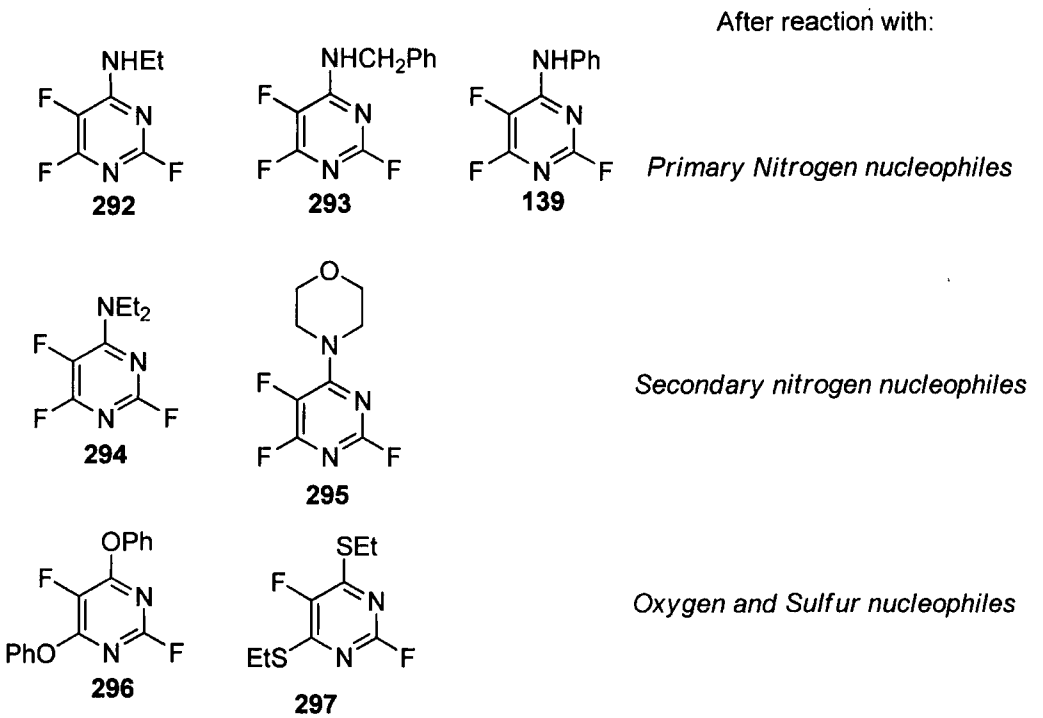


Figure 3.9. Monofunctionalised pyrimidines synthesised from tetrafluoropyrimidine, **113**.

However, this methodology does have several limitations in that during the second step reaction with secondary amines and ethoxide ions gives regioisomers by competing replacement of the fluorine atom at both the 6- and 2-position. This is not too problematic because isolation of the desired 6-substuted isomers is readily achieved.

Similarly, the third step has limitations in that reaction with nucleophiles can lead to replacement of a good leaving group such as the phenoxide group at the 6-position if forcing conditions or reactive nucleophiles are used. If a less labile group such as ethylamine is used this issue can be overcome and a number of compounds synthesised.

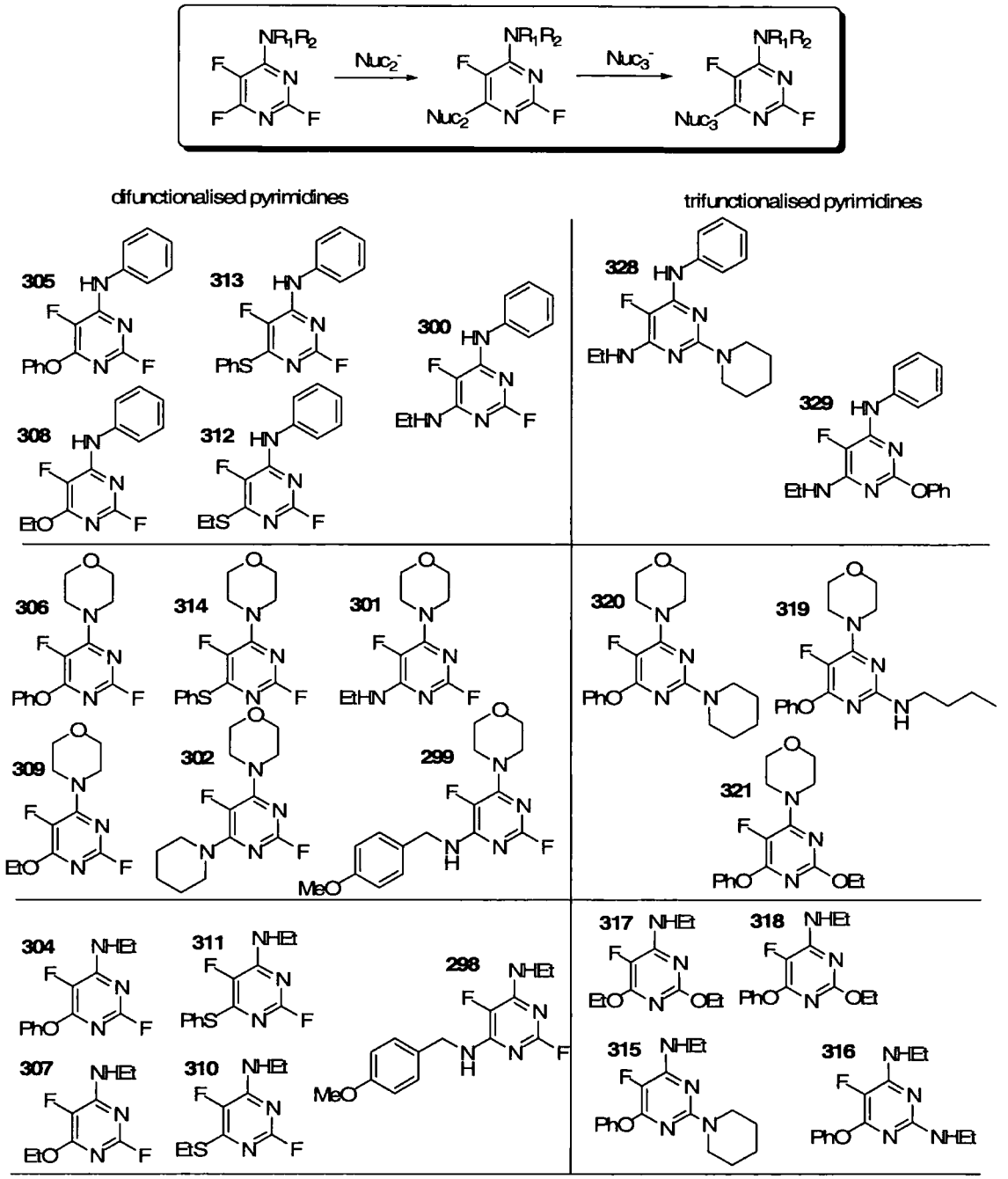


Figure 3.10. Difunctionalised and trifunctionalised pyrimidines synthesised from tetrafluoropyrimidine, **113**.

Overall this study has shown that it is possible to form a selection of highly functionalised pyrimidine scaffolds by a series of high-yielding nucleophilic aromatic substitution processes. The methodology has shown that mono-, di- and trisubstituted pyrimidines can

be synthesised with the orientation of nucleophilic attack shown to occur in the general order of 4- > 6- > 2- which is consistent with a previous study involving substitution using an excess of sodium methoxide (see Figure 3.10 for an outline of the scaffolds synthesised).

This research has demonstrated that a rapid and easily controlled methodology for the synthesis of mono-, di- and tri- substituted pyrimidines is readily achievable and that such a scheme may have applicability for designing libraries of compounds amenable for biological testing and thus drug discovery.

3.10 References

1 R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc. (C)*, 1967, 1822-1826.

2 R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc. (C)*, 1970, 1280-1285.

3 R. D. Chambers, M. J. Seabury, D. L. H. Williams, and N. Hughes, *J. Chem. Soc., Perkin Trans. 1*, 1988, 225-257.

4 R. E. Banks, A. Prakash, and N. D. Venayak, *J. Fluorine Chem.*, 1980, **16**, 325-338.

5 J. P. Tiernay and P. Lidstrom, 'Microwave assisted organic synthesis', Blackwell, 2005.

Chapter 4

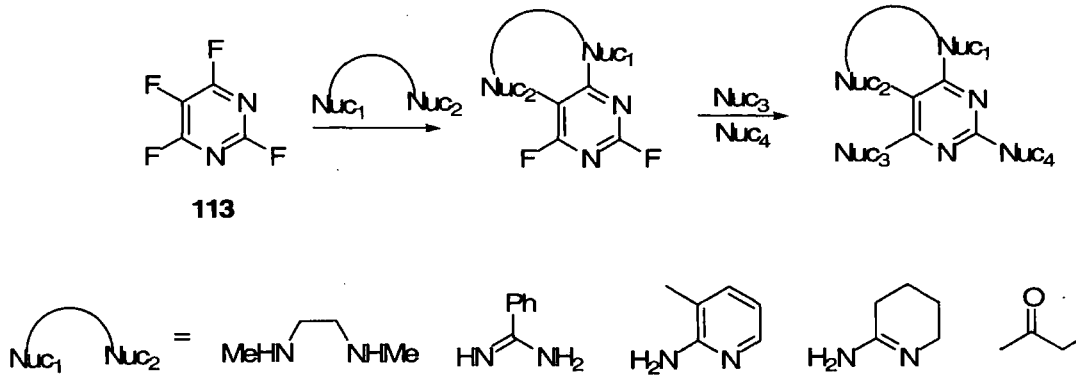
Attempted [5,6] Pyrimidine Ring-Fused Heterocycle Syntheses from Tetrafluoropyrimidine

4 Introduction

As demonstrated in Chapter 1, annulation processes to form pyrimidine ring-fused systems are important within the life-science industries which is demonstrated by the wide range of drug compounds that contain these systems. However, methodologies to achieve their syntheses can be difficult in practice. In Chapter 2 it was outlined how reaction of 5-chlorotrifluoropyrimidine with a selection of dinucleophiles resulted in no annulation products and was thought to be the result of the chlorine at the 5-position being unreactive to nucleophilic aromatic substitution processes and cross-coupling methodologies. Therefore, our next approach was to replace the chlorine with a fluorine to try to improve the reactivity of the system and thus develop a new methodology for the synthesis of a range of [6,6] and [5,6] ring-fused based pyrimidine heterocycles from tetrafluoropyrimidine.

4.1 Aims and Approach

Our approach was to react tetrafluoropyrimidine **113** with a selection of dinucleophiles with the aim of synthesising a selection of diverse heteroaromatic compounds through nucleophilic aromatic substitution annulation processes in a short and efficient manner. In turn the remaining fluorine atoms that are left on the pyrimidine ring have the potential for further reaction with other selections of nucleophiles to give novel classes of compounds as outlined in the general scheme below.



Nuc_3, Nuc_4 = N, O and S centred nucleophiles

Scheme 4.1

Precedent for this methodology has been extensively demonstrated using pentafluoropyridine in the Durham group (see Chapter 2).

4.2 Tetrafluoropyrimidine as a Scaffold

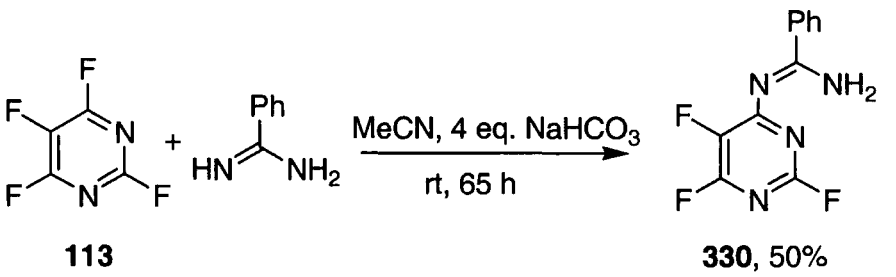
Within the literature there are no examples of the reaction of tetrafluoropyrimidine with dinucleophiles. Reactions of tetrafluoropyrimidine and dinucleophiles were performed in basic conditions to neutralise any acidic by-products and using a large volume of polar solvent to promote the intramolecular cyclisation rather than intermolecular reaction. All the reactions were monitored using ^{19}F NMR as a probe to follow the progress of the reactions.

4.2.1 Reaction of Tetrafluoropyrimidine with Difunctional Amine Nucleophiles

Benzamidine was reacted with compound **113** in an attempt to synthesise a purine analogue via a ring-fusion process which as discussed in Chapter 1, is a highly desirable target.

Reaction at room temperature in the presence of sodium bicarbonate over 65 hours gave substitution at the activated 4-position shown in ^{19}F NMR by way of three peaks corresponding to compound **330** (-48.6, -84.6 and, -166.7 ppm). There was no evidence for

the cyclised compounds either through NMR or mass spectrometry analysis. Compound **330** was isolated by recrystallisation from ethyl acetate and was fully characterised.



113 **330**, 50%

Scheme 4.2

Single crystal x-ray analysis confirmed the structure of compound **330** with partial co-crystallistion observed with water when the sample was recrystallised from ethyl acetate.

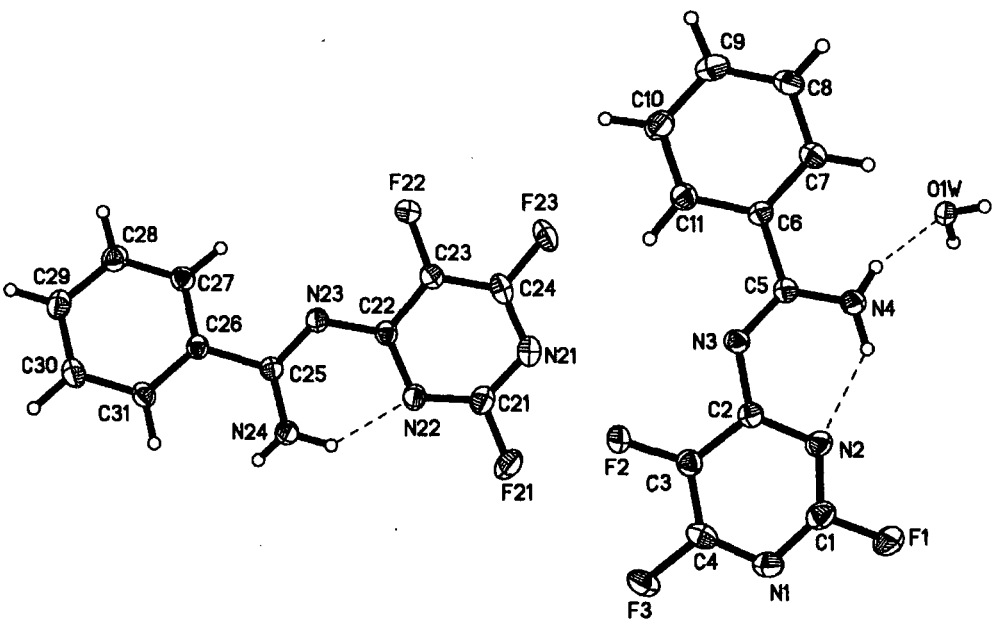
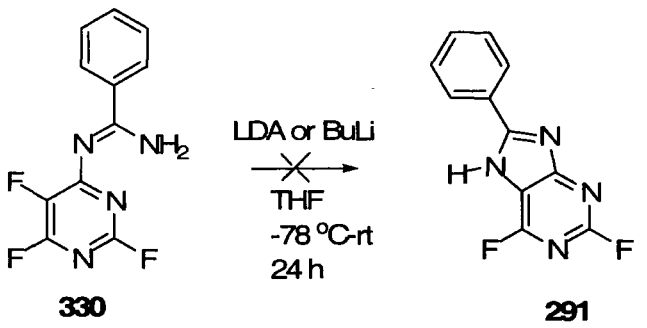


Figure 4.1 The x-ray crystallography structure of compound **330**

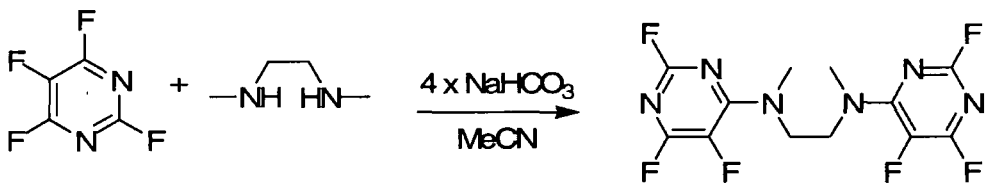
Numerous attempts to induce annulation failed even when using a selection of strong bases, including *n*-BuLi and LDA and starting material was recovered in all cases.



330 **291**

Scheme 4.3

The next dinucleophile to be screened was *N,N'*-dimethyl-ethylene-1,2-diamine with the aim to create a [6,6] fused-ring system. The reaction was performed at room temperature in the presence of sodium bicarbonate but the product that was formed was compound **331**, which was purified by recrystallisation from ethyl acetate. The reaction was monitored using ^{19}F NMR with three new resonances appearing at -48.80, -87.72 and -174.15 ppm and with a molecular ion observed at *m/z* 268.



113 **331**, 45%

Scheme 4.4

Subsequently a single crystal amenable for x-ray analysis was grown from MeOH which was used to confirm the structure of the dipyrimidine compound.

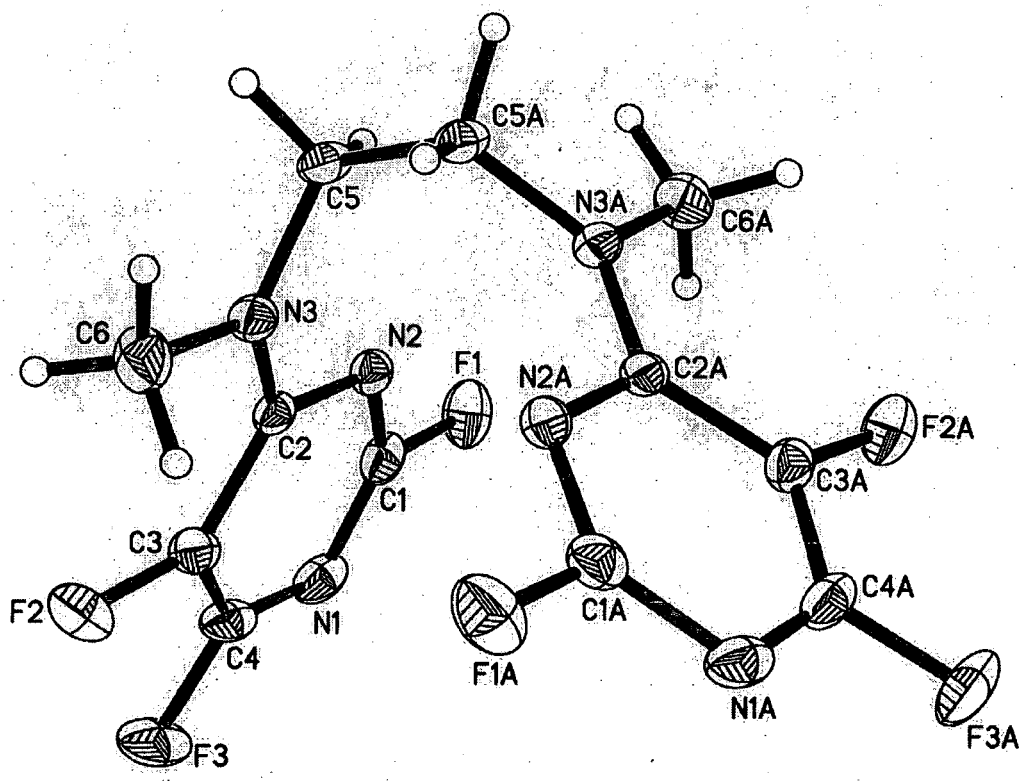
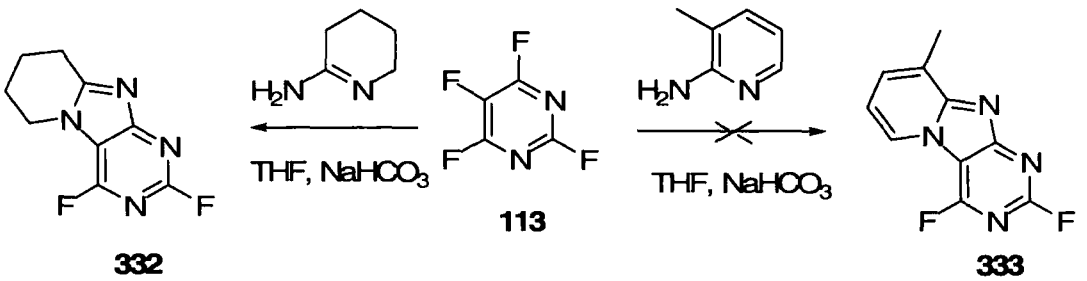


Figure 4.2 The x-ray crystallography structure of compound **331**

This result shows that even when high dilution is employed to minimise the intermolecular reaction the compound prefers to react at the activated 4-position rather then at the considerably less activated 5-position to give the annulated product. At no stage was any ring-fused product detected in either the reaction mixture or the isolated crude product.

The next stage involved screening 2-iminopiperidine hydrochloride and 2-amino-3-picoline with the aim to synthesise the associated annulated systems **332** and **333**, however in both cases a mixture of oligomers was formed under all reaction conditions such as varying the solvent, and concentrations of reactants. No products could be isolated from any of the reactions attempted.



332 333

Scheme 4.5

Reaction of compound **113** with amine dinucleophiles results only in nucleophilic aromatic substitution at the activated 4-position and indicates the intermolecular reaction is very strongly favoured over the desired intramolecular reaction.

4.3 Conclusion

The reactions outlined in this Chapter have shown that compound **113**, is a poor candidate for the construction of ring-fused systems by reaction with dinucleophiles. This probably arises owing to the 5-position being very unreactive towards nucleophilic aromatic substitution. This result is similar to that observed for the 5-chlorotrifluoropyrimidine system (Chapter 2) and demonstrates that both fluorine and chlorine and the 5-position are unlikely to undergo any nucleophilic aromatic substitution processes and that it is not possible to form annulated products from these precursors.

Chapter 5

Pyrazine Ring-Fused Heterocycle Synthesis from Tetrafluoropyrazine

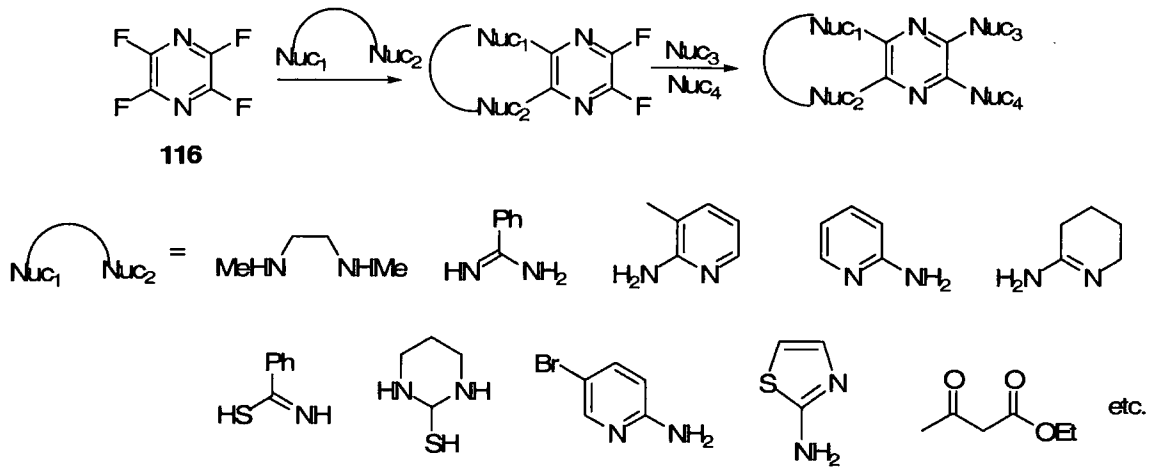
5.1 Introduction

In Chapter 1 it was outlined how ring-fused heterocyclic systems are important within the life-science industries but that applications to syntheses of libraries of compounds that are amenable for biological testing can be difficult. Methodologies that can overcome such problems are of great interest to drug discovery and there is a drive towards the development of novel methods for the construction of multifunctional ring-fused compounds.

In Chapter 1 it was demonstrated that heterocycles containing the pyrazine motif are important, however there is still a large requirement to create unique pyrazine derived ring-fused entities and the following study aims to approach this need through the utilisation of tetrafluoropyrazine as the starting material and achieve functionalisation by reaction with a selection of dinucleophiles and nucleophiles.

5.1.1 Aims and Approach

In Chapters 2 and 4 it was envisioned that purine analogues could be synthesised from perfluorinated pyrimidine precursors by reaction with suitable dinucleophiles. However, in practice, the chlorine and fluorine present in compounds **112** and **113** proved inert to nucleophilic aromatic substitution (as well as cross coupling methodologies for compound **112**). It was, therefore, decided to investigate the reactivity of compound **116** with dinucleophiles in an attempt to synthesise a set of novel ring-fused pyrazine compounds. In tetrafluoropyrazine, all the fluorine atoms are located *ortho* to ring nitrogens and therefore, should be susceptible towards nucleophilic attack.



Nuc_3, Nuc_4 = N, O and S centred nucleophiles

Scheme 5.1

As discussed in Chapter 3 the reactions were performed utilising basic conditions to neutralise any acidic by-products and using a large volume of polar solvent to stabilise the charged transition state and to promote the intramolecular cyclisation rather than intermolecular reaction.

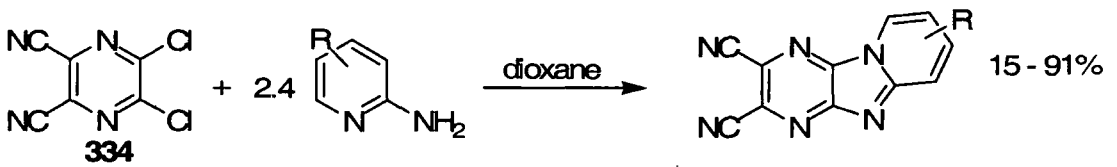
It was previously noted (Chapter 1, section 1.3.7) that tetrafluoropyrazine has no activating nitrogen *para* to a fluorine atom which can be seen clearly when its reactivity is compared to that of reactivity of tetrafluoropyrimidine and suggests longer reaction times are likely. Correspondingly, the resulting annulated products would have the possibility for further derivatisation through reaction with nucleophiles due to the remaining fluorine atoms and thus open up the possibility for libraries of novel pyrazines that have potential for further development amenable to screening purposes.

5.1.2 Background

As noted in Chapter 1, the development of functionalised pyrazines is important, but few methodologies for their syntheses exist within the literature. Some of these methodologies have been shown utilise either chloropyrazines or diamino precursors that are

functionalised through reaction with electrophiles (see Chapter 1, section 1.1.13).

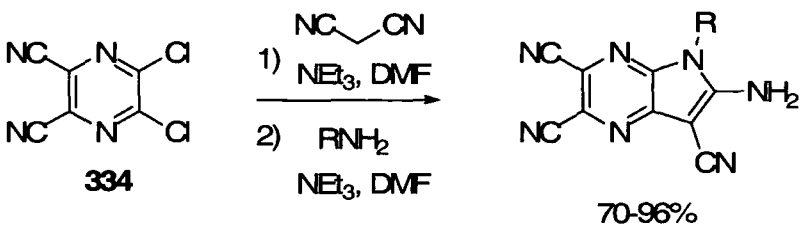
The synthesis of [5,6]-ring fused pyrazines is poorly represented within the literature with only a few methods, some of which are outlined below. In the following example a range of tricyclic pyrazines were synthesised from compound **334** upon reaction with a selection of substituted 2-amino pyridines which led to a set of unique fused-pyrazine compounds.[1]



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

Scheme 5.2

A selection of compounds have been synthesised from compound **334** and this again demonstrates the high reactivity of the electron deficient heterocycle with various nucleophiles.



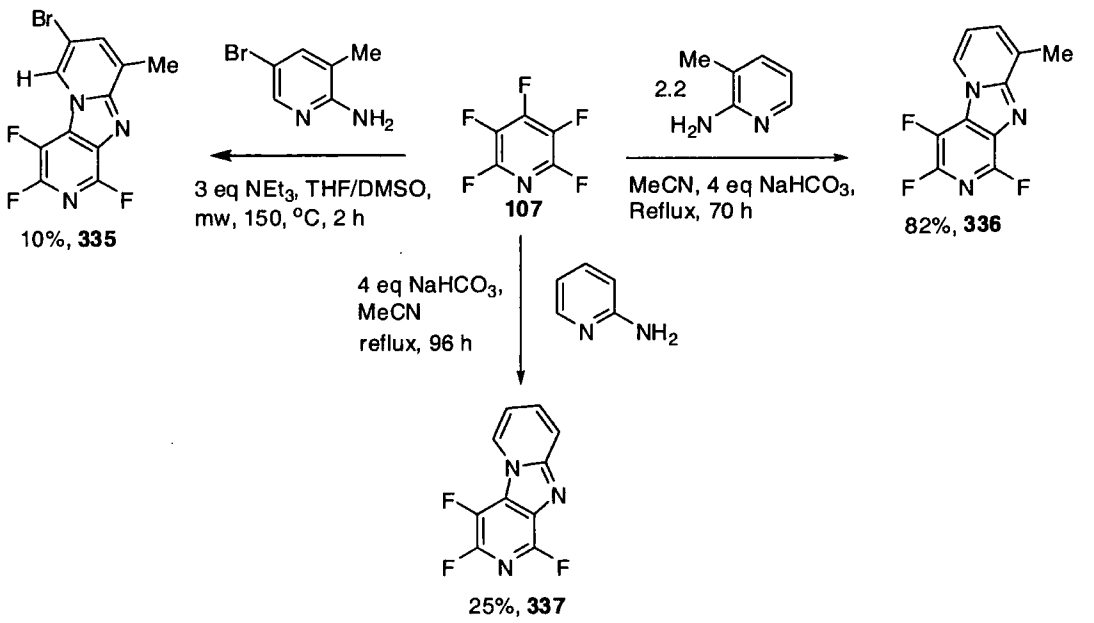
R = $PhCH_2$, $PhCH_2CH_2$, etc.

Scheme 5.3

The Durham group has studied the reactivity of compound **116** with a short series of dinucleophiles in order to synthesise novel [5,6] and [6,6] fused-ring compounds as shown in Chapter 1, section 1.3.8. Here we expand this work to other [5,6] fused-ring systems using *N,N* dinucleophiles.

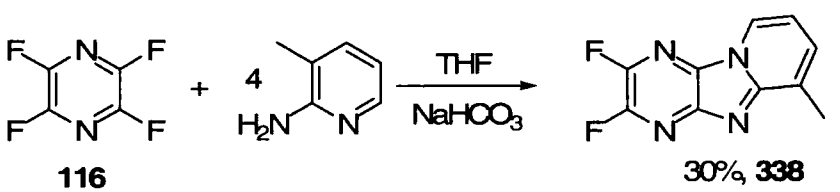
5.2 Reaction of Tetrafluoropyrazine with 2-Amino Pyridine Nucleophiles

Reaction of pentafluoropyridine with substituted 2-aminopyridines has been demonstrated by the Durham group to give a series of novel tricyclic dipyridoimidazoles **335**, **336**, and **337** (see Scheme 5.4).



Scheme 5.4

By a similar procedure, tetrafluoropyrazine, **116** was reacted with 2-aminopicoline resulting in the formation of compound, **338**. The progress of this reaction was followed with ^{19}F NMR and showed the formation of two new peaks at -89.52 and -98.62 ppm with 83% conversion after 5 days at reflux. Purification was achieved by successive recrystallisations from ethyl acetate to remove excess dinucleophile which contributed to the low isolated yield that was observed.



Scheme 5.5

Confirmation of the structure was shown through x-ray crystallography studies by growing a single crystal from MeOH.

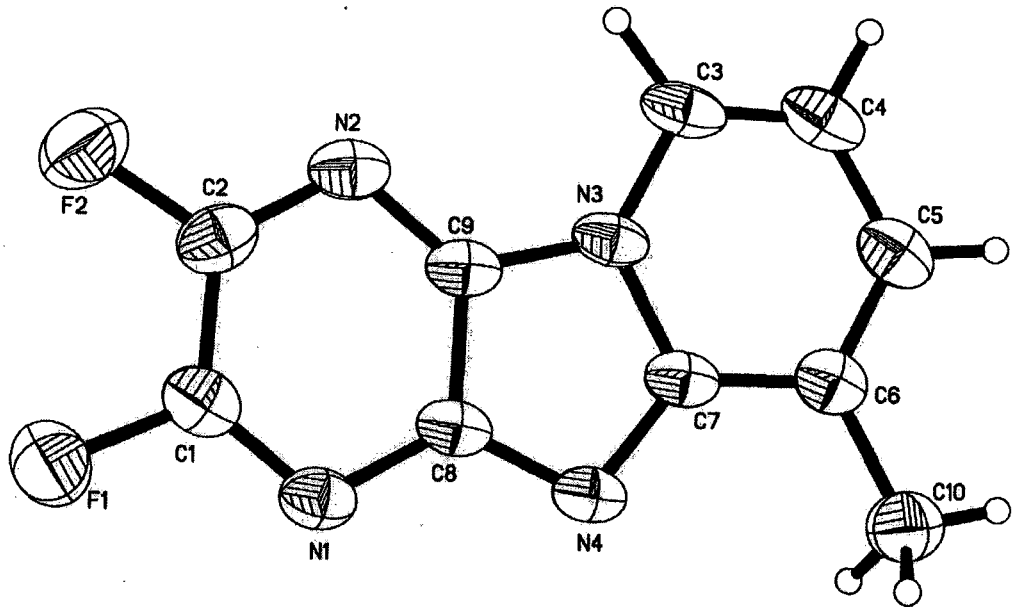
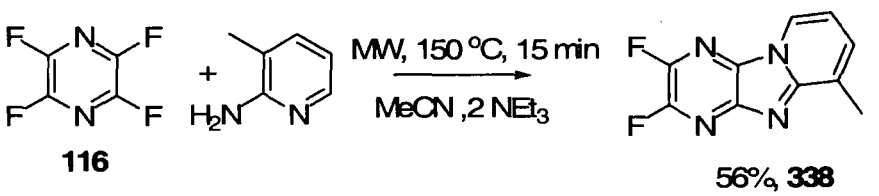


Figure 5.1 The x-ray crystallography structure of compound **338**

Repeating the reaction under microwave conditions for 15 minutes in MeCN at 150 °C gave an improved conversion of 87% and also led to a higher isolated yield when recrystallised from ethyl acetate.



Scheme 5.6

It was decided to react compound **116** with a range of aromatic dinucleophiles to assess the scope of this methodology.

The screening of potential dinucleophiles (Figure 5.2) under microwave conditions was useful to give an indication as to whether they are useful in synthesising unique scaffolds and allows for a significant saving of time compared conventional heating methods (see Chapter 3, Section 3.6.1).

Each reaction was performed under the same conditions by heating tetrafluoropyrazine with a dinucleophile in the microwave at 150 °C for 5 minutes in acetonitrile and monitored using ^{19}F NMR. In all cases no reaction was observed except for the case of 2-amino pyridine which gave conversion to the tricyclic product with two peaks in the ^{19}F NMR appearing at -89.5, and -99.2 ppm.

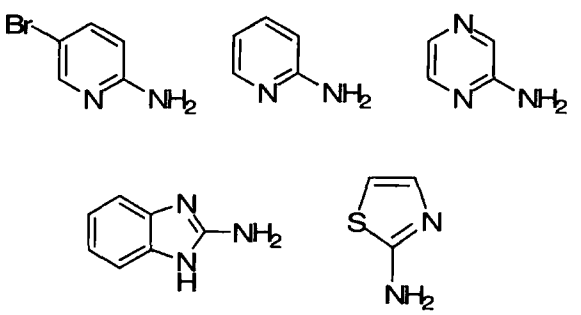
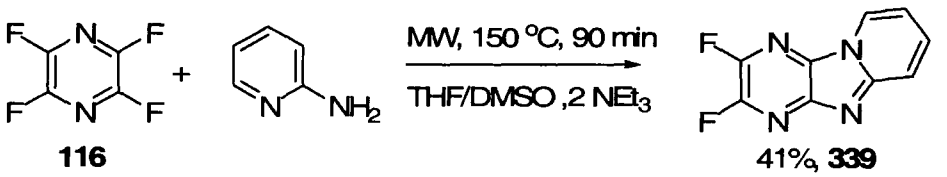


Figure 5.2.

Repeating the reaction on a larger scale and for a longer reactions time of 1.5 h resulted in nearly 100% conversion to product which was readily isolated through recrystallisation from ethyl acetate.

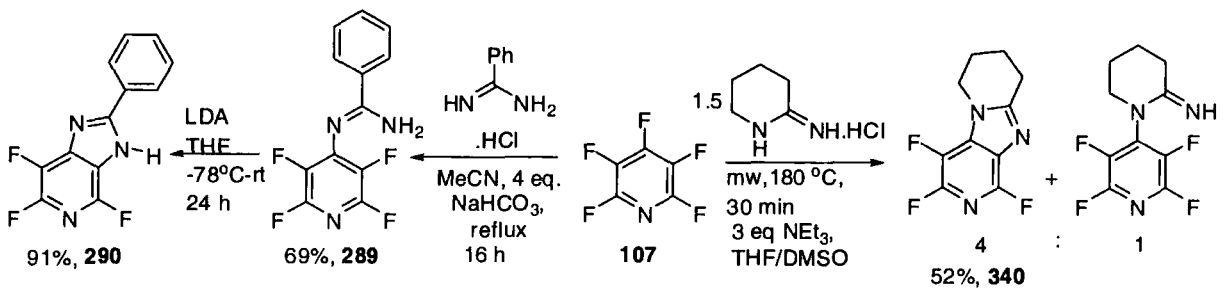


116 41%, **339**

Scheme 5.7

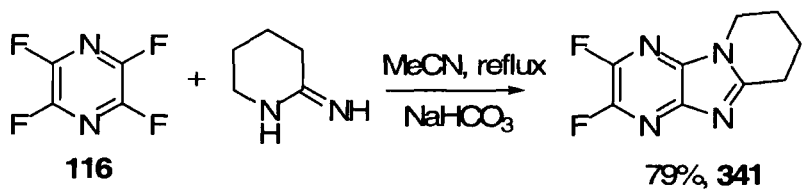
5.3 Reaction of Compound 116 with Amidine Nucleophiles

Pentafluoropyridine is reacted to give purine type analogues.[2]



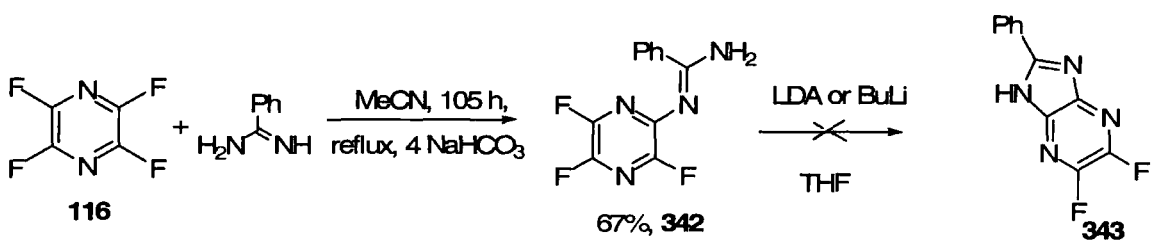
Scheme 5.8

With this in mind compound **116** was allowed to react with 2-iminopiperidine hydrochloride at reflux for 105 h. A ^{19}F NMR spectrum of the reaction mixture showed two peaks at -98.41 and -100.38 ppm that correspond to the annulated product. Purification was achieved through recrystallisation from DCM to give the product in good yield.



Scheme 5.9

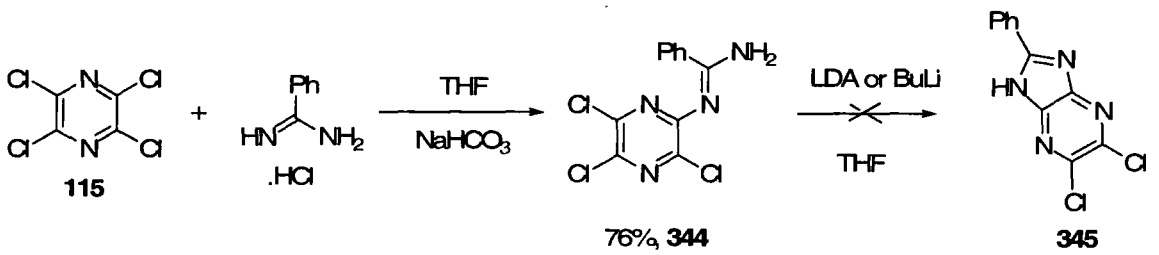
Following on from this reaction, compound **116** was reacted with benzamidine at reflux which showed nucleophilic substitution of one fluorine atom by ^{19}F NMR spectrum had the presence of three distinct peaks at -87.29, -97.78, and -105.02 ppm. No cyclised product was observed by ^{19}F NMR and mass spectrometry studies.



Scheme 5.10

This compound was then subjected to the same reaction conditions as for pentafluoropyridine:[2] where LDA was used to induce the cyclisation process . However, all attempts to induce cyclisation of compound **342** did not succeed as observed by LCMS or ^{19}F NMR analysis.

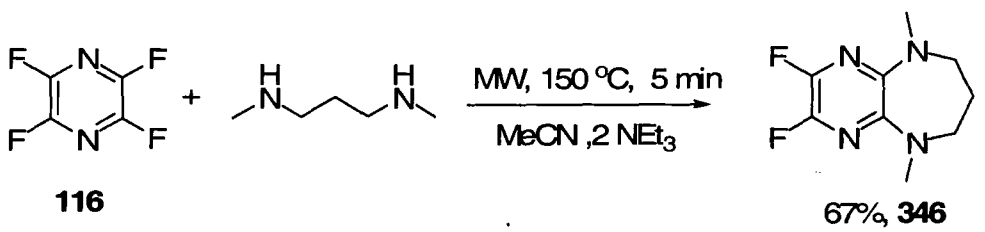
We observed a similar result when the same reaction was undertaken with the tetrachloropyrazine derivative in that initial reaction with benzamidine led to the mono substituted product but when cyclisation was attempted with a selection of strong bases there was no resulting annulated product.



Scheme 5.11

5.4 Reaction of Compound 116 with an *N,N*-Dinucleophile.

We decided to take compound **116** and allow it to react with N^1,N^2-dimethylethane-1,2-diamine to synthesise a seven-membered ring to form a novel [6,7] ring-fused pyrazine. Reaction with the diamine performed under microwave conditions led to high conversions with ^{19}F NMR showing the presence of a single fluorine peak at -115.73 ppm (C-2). Subsequently the compound was purified by passing the mixture through silica gel which yielded the compound as a low melting orange solid.

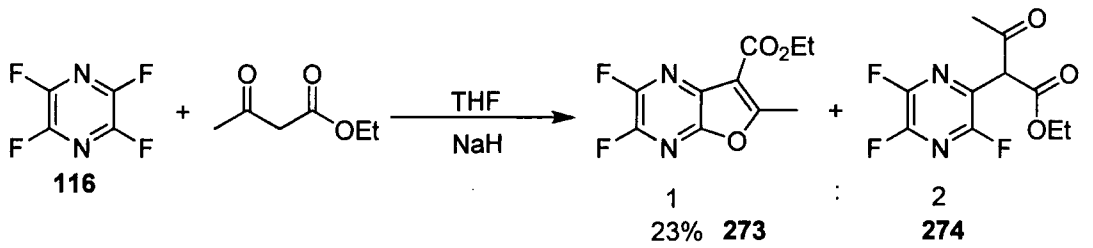


Scheme 5.13

Thus, from the analytical data it has been shown that reaction of compound **112** with *N,N*-dinucleophiles allows the synthesis of [6,7]-fused ring systems.

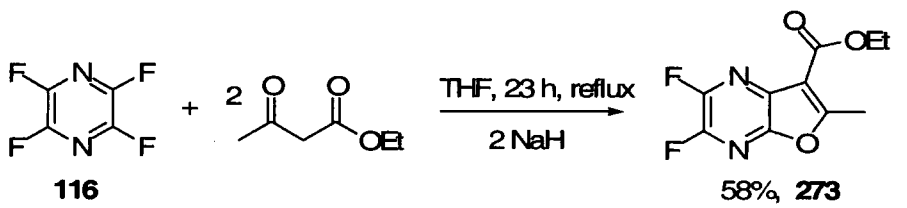
5.5 Reaction of Tetrafluoropyrazine with C,O Dinucleophiles

Previously the Durham group has also investigated the reaction of compound **112** with the ethylacetoacetate which resulted in the formation of two products with the uncyclised product being the major product.[3]



Scheme 5.14

Repeating the reaction with a longer reaction time gave only compound **273** which was easily purified by column chromatography to provide the cyclised product in moderate yield.



Scheme 5.15

A single crystal of the compound was grown from MeOH and subjected to x-ray analysis to confirm the structure.

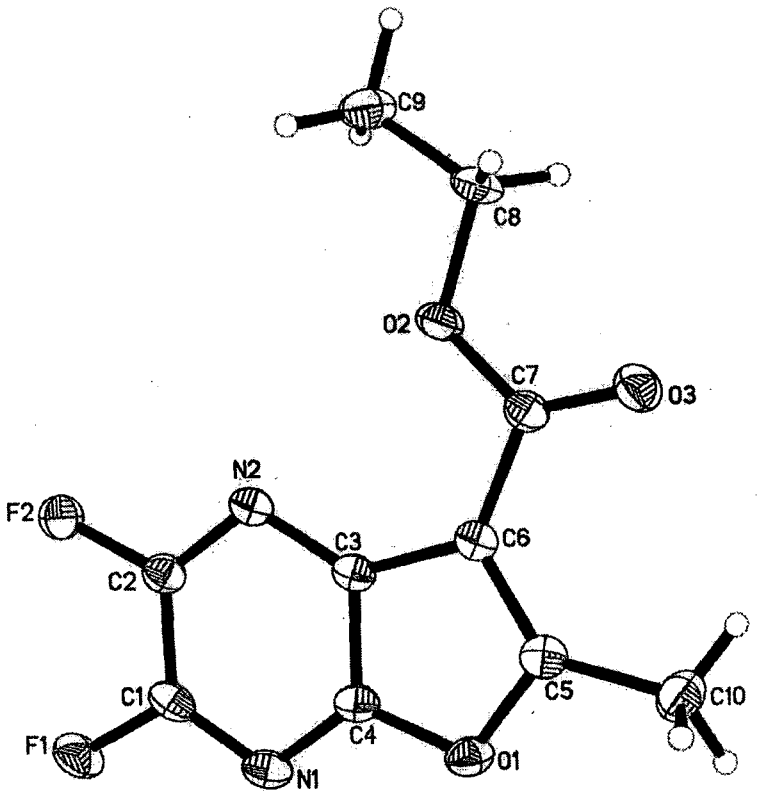
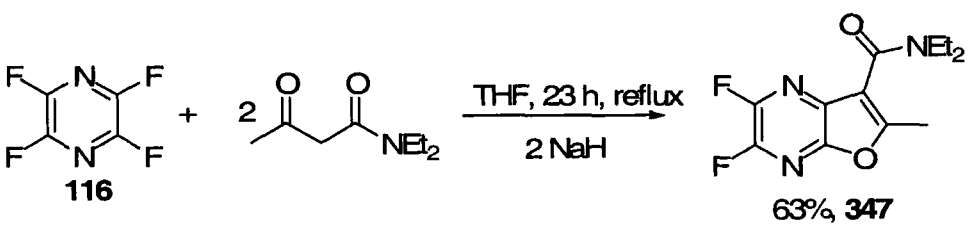


Figure 5.3 The x-ray crystallography structure of compound **273**

Subsequently, a 1,3-dicarbonyl derivative bearing an amide group was reacted with compound **116** and led to the formation of a single compound by ^{19}F NMR with a single peak appearing at -91.90 ppm. Purification was achieved by column chromatography to give the product in moderate yield.



Scheme 5.16

A single crystal was also grown from MeOH and subjected to x-ray analysis which confirmed the structure.

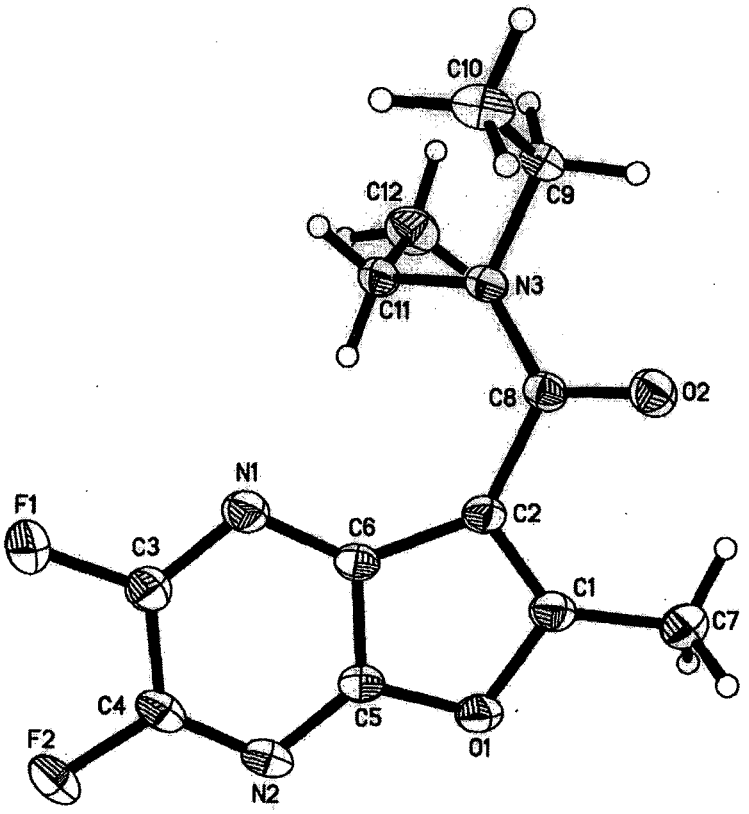


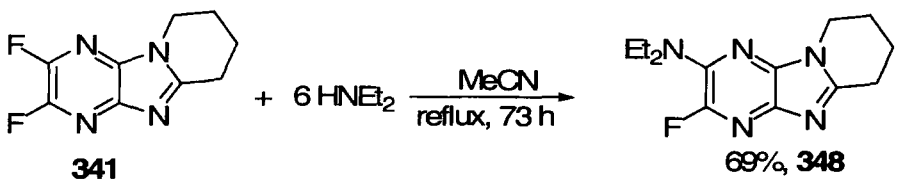
Figure 5.4 The x-ray crystallography structure of compound **347**

5.6 Further Functionalisation of Heterocyclic Cores

Further functionalisation of the imidazo[4,5-*b*]pyrazine is a desirable aim as it will help to determine fundamental chemical principles pertaining to the selectivity of nucleophilic attack on the system.

5.6.1 Reactions of Imidazo[4,5-*b*]pyrazines with Nitrogen Mono Nucleophiles

Thus, compound **341** was reacted with diethylamine which led to the selective substitution of the fluorine atom *para* to the N=C in high yield and 100% conversion with a single peak in the ^{19}F NMR at -84.4 ppm.



Scheme 5.19

Confirmation of this structure was determined by x-ray crystallography by growing a single crystal from MeOH.

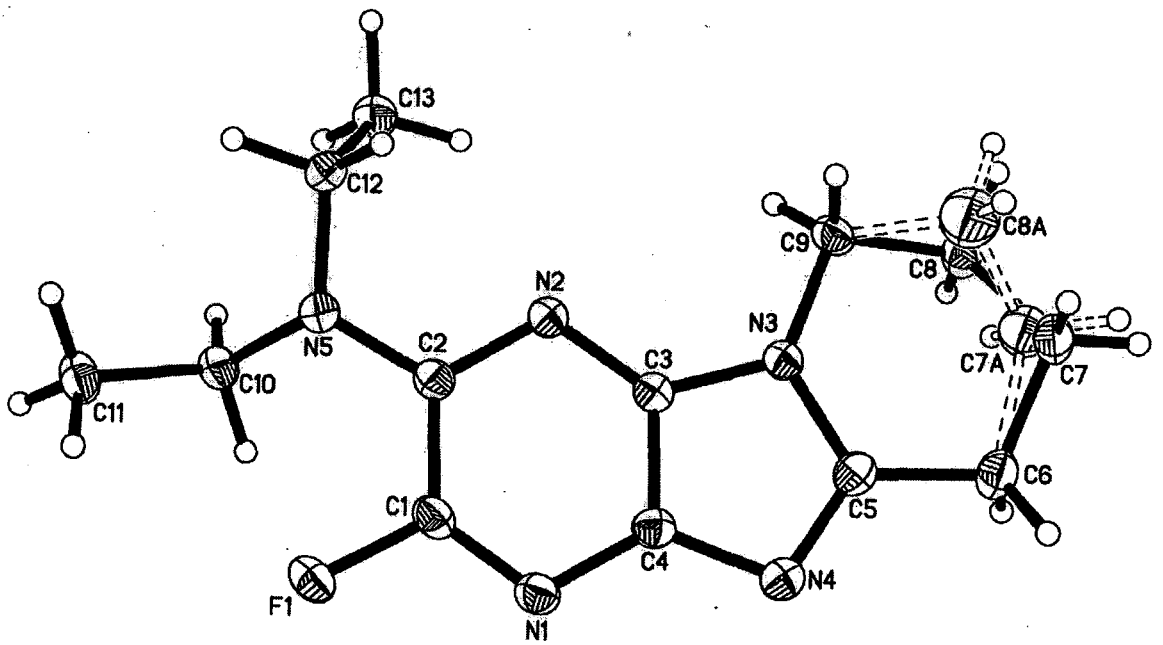
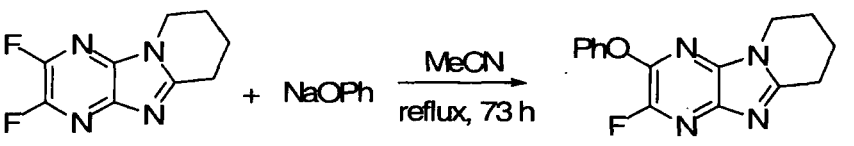


Figure 5.5 The x-ray crystallography structure of compound **348**

Compound **341** was reacted with sodium phenoxide and this also resulted in the nucleophilic substitution of the fluorine atom that was *para* to that of the N=C bond. Confirmation of this structure can be seen from the ^{19}F NMR studies which showed a single peak at -93.08 ppm.



341 54%, **349**

Scheme 5.20

Mechanistically the reason for the orientation of nucleophilic substitution in both of the above examples can be attributed to the Meisenheimer model of the transition state which shows delocalisation of the intermediate negative charge around the [5,6] ring-fused system is more stabilising than if the incoming nucleophile is *meta* to the N=C bond.

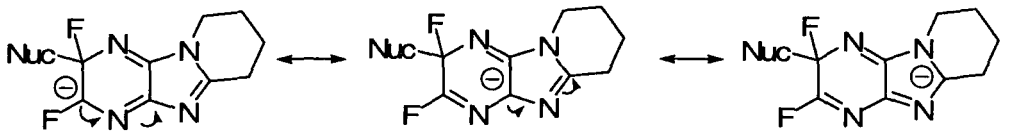


Figure 5.6

Nucleophilic attack *meta* to the N=C bond does not allow for delocalisation of the intermediate charge around the full ring system making attack unfavourable.

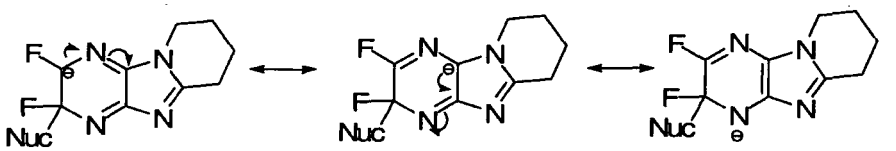
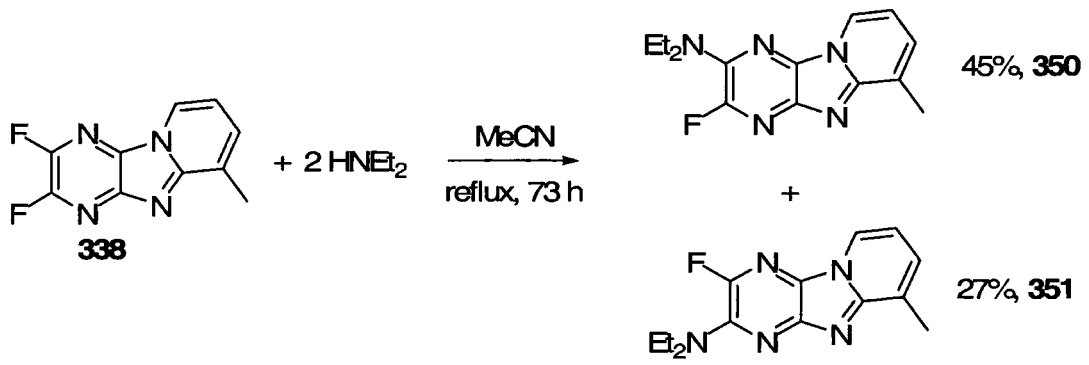


Figure 5.7

In order to demonstrate the utility of compound **338** as a scaffold it was reacted with diethylamine which resulted in a mixture of isomers of compound **350** and **351** in a 1:1 ratio. Both isomers could be clearly differentiated by the ^{19}F NMR spectrum which contained two individual peaks at -75.20 ppm for compound **350** and -84.35 ppm for compound **351**. Each compound also gave individual peaks in mass spectrometry with a mass at m/z = 273.

Separation of the isomers through chromatographic and recrystallisation methods proved to be unsuccessful. Final separation of the isomers was achieved through the use of mass directed automated purification which utilises reverse phase chromatography and a mass ion detector to collect the desired isomers. Crystallisation from MeOH provided a crystal that was subjected to x-ray analysis to confirm compound **350**.



Scheme 5.22

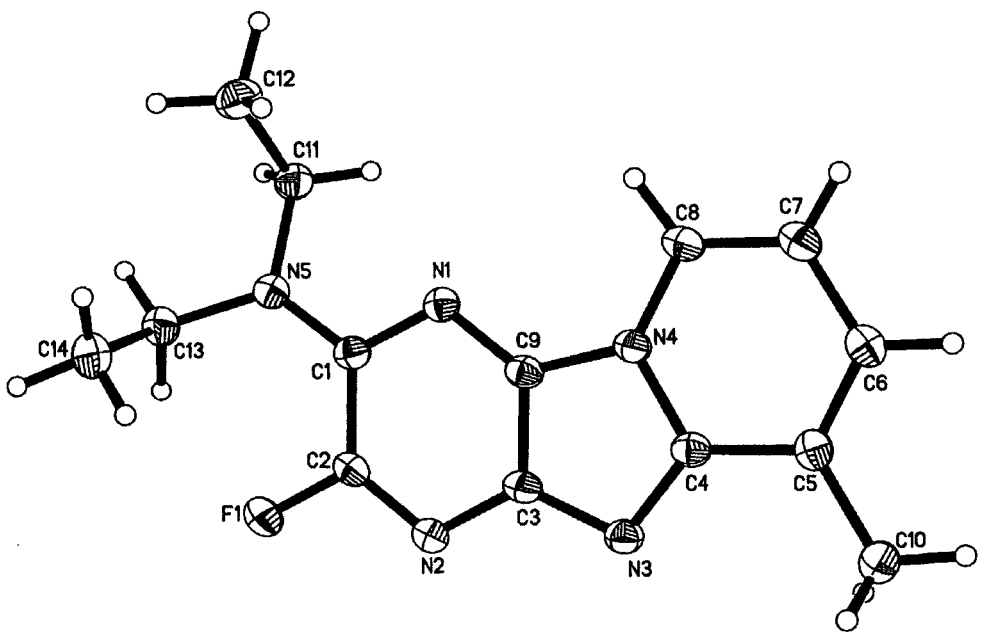
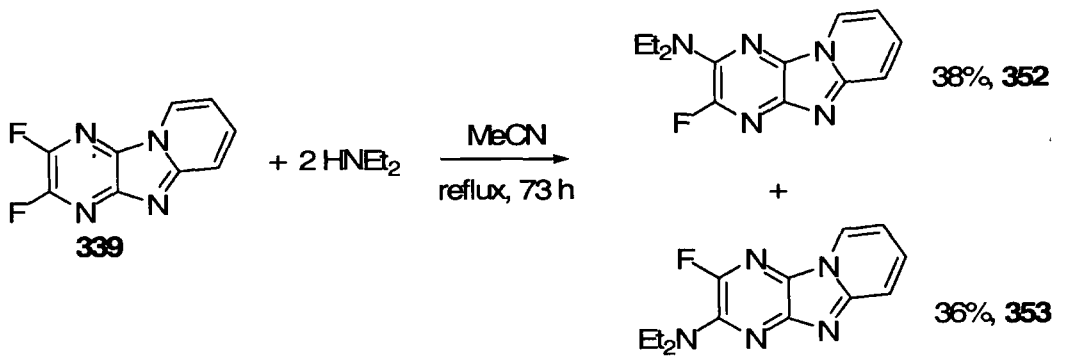


Figure 5.8 The x-ray crystallography structure of compound **350**

Similarly reaction of compound **339** with diethylamine also resulted in the formation of two isomers in a 1:1 ratio. Both isomers could be clearly differentiated by the ^{19}F NMR spectrum which contained two individual peaks at -75.20 ppm for compound **352** and -

84.35 ppm for compound **353**. The mass spectrum of the crude reaction mixture showed two separate compounds with the same mass of 273 which also confirmed the presence of two distinct isomers. Separation of the isomers was achieved through the use of mass directed automated purification. Again a single crystal grown from MeOH was subjected to x-ray analysis to give further proof compound **352**.



Scheme 5.24

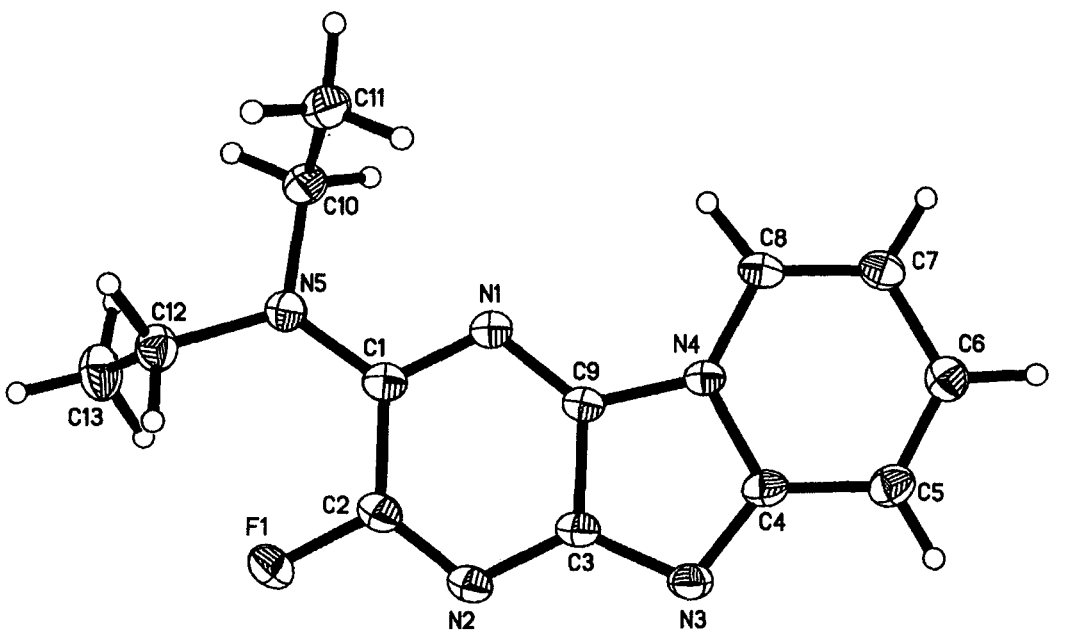
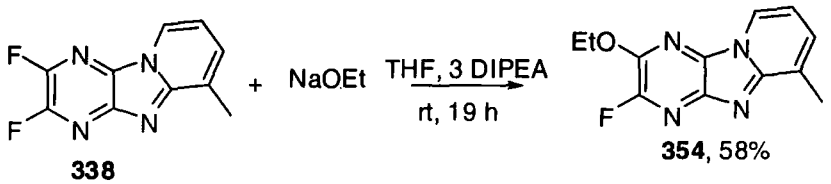


Figure 5.9 The x-ray crystallography structure of compound **352**

It was previously postulated that if the incoming nucleophile approaches *para* to the C=N bond delocalisation of the intermediate negative charge around the [5,6] ring-fused system

is more stabilising and thus approach to the *meta* position is disfavoured. These results have shown that this is not always true and could be due to each position being equivalent in compounds **338** and **339**.

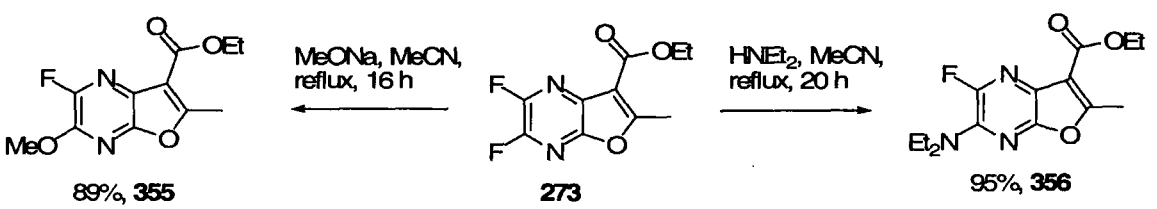
Reaction of compound **338** with sodium ethoxide gave substitution of one fluorine atom as the only product. This may also indicate that the position attacked in such systems also depends upon the hard or soft nature of the incoming nucleophile.



Scheme 5.23

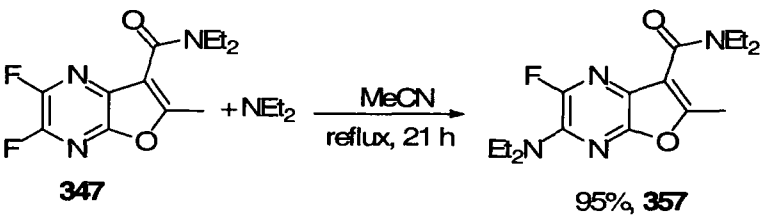
5.6.2 Reaction of Furo[2,3-b]pyrazines with Nitrogen and Oxygen Mono Nucleophiles

Compound **273** was reacted with a selection of mono nucleophiles. Reaction of compound **273** gave products where substitution of the fluorine that was *para* to the C=C bond. This result can be rationalised using the same model as previously cited for compound **338** (see section 5.6.1)



Scheme 5.25

Reaction of compound **347** with diethylamine gave the same selectivity of substitution which is *para* to the C=C bond.



Scheme 5.26

5.7 Conclusion

This chapter has demonstrated the utility of tetrafluoropyrazine for the synthesis of novel [5,6] and [6,7] ring-fused pyrazine systems, demonstrated in Figure 5.10 below, when reacted with N,N and C,O dinucleophiles.

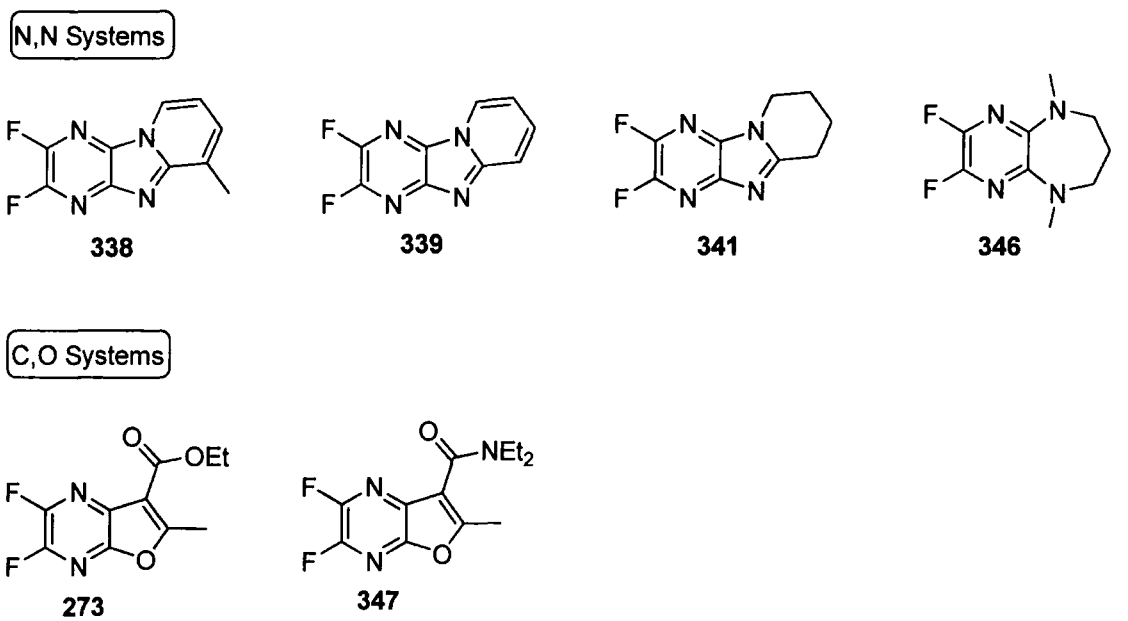


Figure 5.10 A summary of the reaction of tetrafluoropyrazine, **116**, with N,N and C,O dinucleophiles

Moreover, the resulting annulated products have been shown to react with nucleophiles to furnish polyfunctional nitrogen, and oxygen-substituted heterocycles due to the remaining fluorine atoms that readily undergo nucleophilic aromatic substitution.

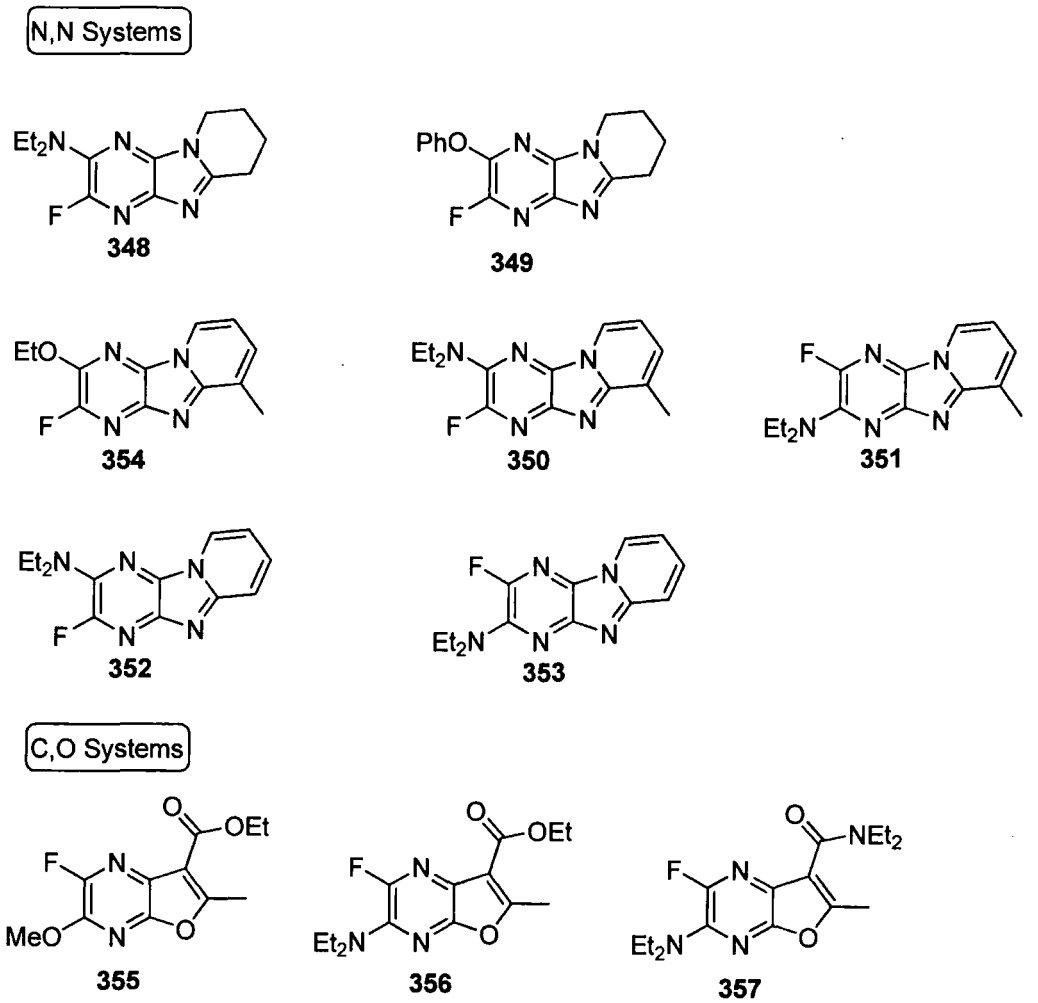


Figure 5.11 The reaction of Imidazo[4,5-*b*] and Furo[2,3-b]pyrazines with mono nucleophiles

Thus, it has been demonstrated that starting from tetrafluoropyrazine, **116** and reacting with nucleophiles, can in a few short and high yielding steps, lead to a series of novel pyrazines. Such a methodology has the applicability to be used to synthesise libraries of molecules that have potential for further development and could have uses as therapeutic agents.

5.8 References

1 T. Suzuki, Y. Nagae, and K. Mitsuhashi, *J. Heterocycl. Chem.*, 1986, **23**, 1419-1421.

2 M. Cartwright, 'Highly Functionalised Fused Heterocycle Synthesis from Fluoropyridines', Durham University, 2006.

3 R. Slater, 'Polyfunctional Ring Fused Heterocyclic Compounds', Durham University, 2005.

Chapter 6

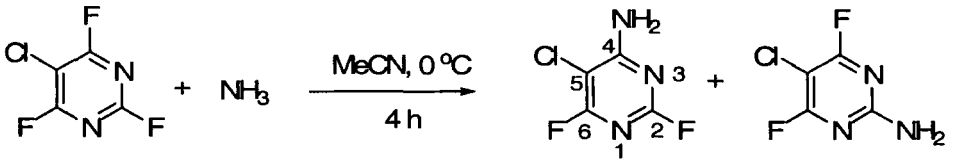
Experimental for Chapter 2

Technical Detail

Ratios of products were calculated from ^{19}F NMR spectra of reaction mixture unless otherwise stated. All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem) or from GlaxoSmithKline's chemical stores, Stevenage. DIPEA bound resins were obtained from Biotage. Microwave reactions were performed in a Biotage Initiator 60 EXP with a power range of 0-400 W at 2.45 GHz. All solvents were dried using either literature procedures or via an Innovative Technology solvent purification system. Mass Directed Automated Preparative HPLC was carried out using Supleco LCABZ++ column and MicroMass MassLynx v4.0 software. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040-0.063 mm) or using a 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. Accurate mass measurements were determined on a Micromass Autospec Mass Spectrometer at the national spectrometry centre, Swansea. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless stated and are uncorrected. The progress of each reaction was monitored by either ^{19}F NMR spectroscopy or LCMS analysis. All crystallographic data were 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 methods and refined by full-matrix least squares minimisation 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.

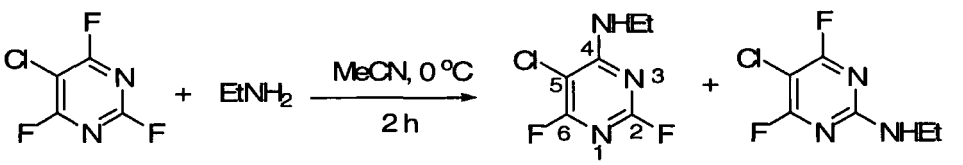
5-Chloro-2,6-difluoropyrimidin-4-amine, 121



112 **121** **122**

A solution of 5-chloro-trifluoropyrimidine **112** (0.50 g, 6.1 mmol) and ammonia (0.5 M in dioxan, 1.49 cm^3) in acetonitrile (50 cm^3) was stirred at 0 °C for 4 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to 5-chloro-2,6-difluoropyrimidin-4-amine **121** (-48.18 and -69.47 ppm) and 5-chloro-4,6-difluoropyrimidin-2-amine **122** (-65.44 ppm) in a 9:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 5-chloro-2,6-difluoropyrimidin-4-amine **121** and 5-chloro-4,6-difluoropyrimidin-2-amine **122** as a white solid (0.68 g). Recrystallisation from ethyl acetate yielded 5-chloro-2,6-difluoropyrimidin-4-amine **121** (0.56 g, 57%) as white solid; mp 161-162 °C; δ_c (d^3-acetonitrile) 92.7 (dd, $^2J_{CF}$ 39, $^4J_{CF}$ 8, C-5), 159.4 (dd, $^1J_{CF}$ 235, $^4J_{CF}$ 23, C-2), 166.1 (dd, $^1J_{CF}$ 260, $^3J_{CF}$ 20, C-6), 165.2 (m, C-4); δ_F -46.72 (1F, s, C-6), -65.63 (1F, s, C-2); *m/z* (EI^+) 165 ($[M]^+$, 52%), 124(4), (ES^+) (Found: $[M+H]^+$ 165.9978 $C_4H_2ClF_2N_3$ requires: $[M+H]^+$ 165.9978)

(5-Chloro-2,6-difluoro-pyrimidin-4-yl)-ethylamine, 276

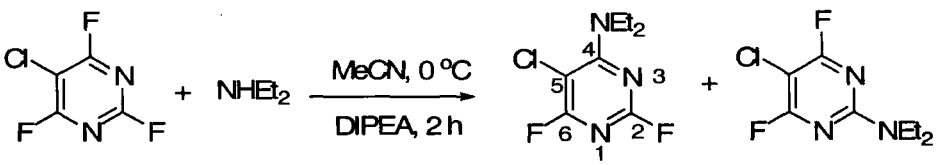


112 **276** **277**

A solution of 5-chloro-trifluoropyrimidine **112** (0.50 g, 6.4 mmol), 2.0 M ethylamine in THF (2.99 cm^3) in acetonitrile (50 cm^3) was stirred at stirred at 0 °C for 2 h after which

time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to 5-chloro-*N*-ethyl-2,6-difluoropyrimidin-4-amine **276** (-47.48 and -70.83 ppm) and 5-chloro-*N*-ethyl-4,6-difluoropyrimidin-2-amine **277** (-63.59 ppm) in an 8:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 5-chloro-*N*-ethyl-2,6-difluoropyrimidin-4-amine **276** and 5-chloro-*N*-ethyl-4,6-difluoropyrimidin-2-amine **277** as a yellow oil (0.54 g). Column chromatography (silica, DCM: *n*-hexane, 1:1) gave 5-chloro-*N*-ethyl-2,6-difluoropyrimidin-4-amine **276** (0.36 g, 57%) as a white solid; mp 37-38 °C; (Found: C, 37.5; H, 3.2; N, 21.6 $C_6H_6ClF_2N_3$ requires: C, 37.2; H, 3.1; N, 21.7%); δ_H 1.22 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.51 (2H, q, $^3J_{HH}$ 7.2, CH_2); δ_c 14.8 (s, CH_3), 37.3 (s, CH_2), 113.45 (dd, $^2J_{CF}$ 38, $^4J_{CF}$ 8, C-5), 158.9 (dd, $^1J_{CF}$ 216, $^3J_{CF}$ 22, C-2), 162.7 (dd, $^3J_{CF}$ 24, $^5J_{CF}$ 6, C-4), 165.0 (dd, $^1J_{CF}$ 263, $^3J_{CF}$ 24, C-6); δ_F -46.14 (1F, s, C-6), -68.59 (1F, s, C-2); *m/z* (EI^+) 193 ($[M]^+$, 44%), 178(62).

5-Chloro-*N,N*-diethyl-2,6-dipyrimidin-4-amine, 278

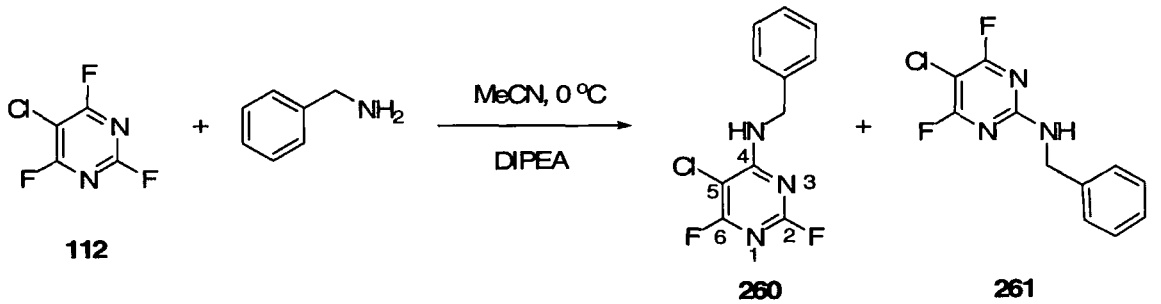


112 **278** **279**

A solution of 5-chloro-trifluoropyrimidine **112** (1.01 g, 6.0 mmol) and diethylamine (0.43 g, 6.0 mmol), DIPEA (2.31 g, 8.9 mmol) in acetonitrile (100 cm^3) was stirred at 0 °C for 2 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to 5-chloro-*N,N*-diethyl-2,4-dipyrimidin-6-amine **278** (-47.81 and -64.26 ppm) and 5-chloro-*N,N*-diethyl-2,4-dipyrimidin-6-amine **279** (-65.35 ppm) in a 5:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 5-chloro-*N,N*-diethyl-2,4-dipyrimidin-6-amine **278** and 5-chloro-*N,N*-diethyl-2,6-dipyrimidin-4-amine **279** as a yellow oil (0.71 g). Column chromatography (silica, DCM: *n*-hexane, 1:2) gave 5-

chloro-*N,N*-diethyl-2,6-dipyrimidin-4-amine **278** (0.63 g, 47%) as a colourless oil; δ_H 1.25 (6H, t, $^3J_{HH}$ 7.2, CH_3), 3.68 (4H, q, $^3J_{HH}$ 7.2, CH_2); δ_c 13.9 (s, CH_3), 45.2 (s, CH_2), 92.5 (dd, $^2J_{CF}$ 22, $^4J_{CF}$ 9, C-5), 158.5 (dd, $^1J_{CF}$ 190, $^3J_{CF}$ 24, C-2), 161. 5 (dd, $^3J_{CF}$ 13, $^5J_{CF}$ 5, C-4), 168.0 (dd, $^1J_{CF}$ 233, $^3J_{CF}$ 19, C-6); δ_F -47.81 (1F, s, C-6), -64.26 (1F, s, C-2); *m/z* (EI^+) 221.0 ($[M]^+$, 80%), 206(86), 192(88), 178(98), (ES^+) (Found: $[M+H]^+$ 222.0605 $C_8H_{10}ClF_2N_3$ requires: $[M+H]^+$ 222.0604)

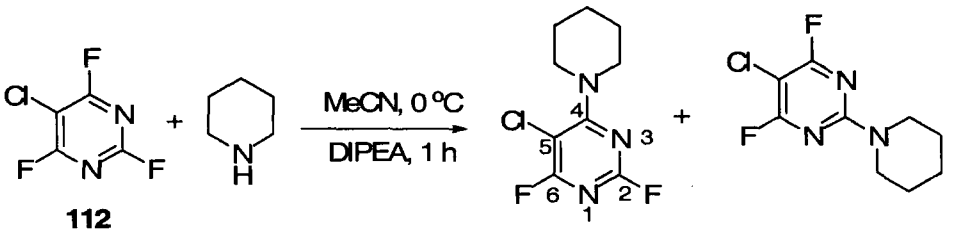
_N_-Benzyl-5-chloro-2,6-difluoropyrimidin-4-amine, 260



A solution of 5-chloro-trifluoropyrimidine **112** (0.50 g, 3.0 mmol), benzylamine (0.32 g, 3.0 mmol) and DIPEA (1.15 g, 8.9 mmol) in acetonitrile (50 cm^3) was stirred at 0 °C for 2 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to *N*-benzyl-5-chloro-2,6-difluoropyrimidin-4-amine **260** (-45.80 and -67.84 ppm) and *N*-benzyl-5-chloro-2,4-difluoropyrimidin-6-amine **261** (-48.09 ppm) in a 5:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N*-benzyl-5-chloro-2,6-difluoropyrimidin-4-amine **260** and *N*-benzyl-5-chloro-2,4-difluoropyrimidin-6-amine **261** as a yellow solid (0.54 g). Recrystallisation from *n*-hexane yielded *N*-benzyl-5-chloro-2,6-difluoropyrimidin-4-amine **260** (0.31 g, 41%) as a white solid; mp 57-59 °C; IR (neat, *v* cm-1): 3408, 3281, 2364, 2169, 1739, 1612, 1528, 1447, 1349, 1129, 695; (Found: C, 51.7; H, 3.1; N, 16.6 $C_{11}H_8ClF_2N_3$ requires: C, 51.7; H, 3.15; N, 16.4%); δ_H 4.74 (2H, d, $^2J_{HH}$ 5.8, CH_2), 7.39 (5H, m, Ar-H); δ_c 46.2 (s, CH_2), 93.1 (dd, $^2J_{CF}$ 21.4, $^4J_{CF}$ 8.0, C-5), 128.1 (s, Ar-CH), 128.4 (s, Ar-CH), 129.2 (s, Ar-CH), 136.9 (s, Ar-CH), 159.3 (dd, $^1J_{CF}$ 222, $^3J_{CF}$ 22.1 C-2), 162.6 (dd, $^3J_{CF}$ 13, $^5J_{CF}$ 5.4, C-4), 164.5 (dd,

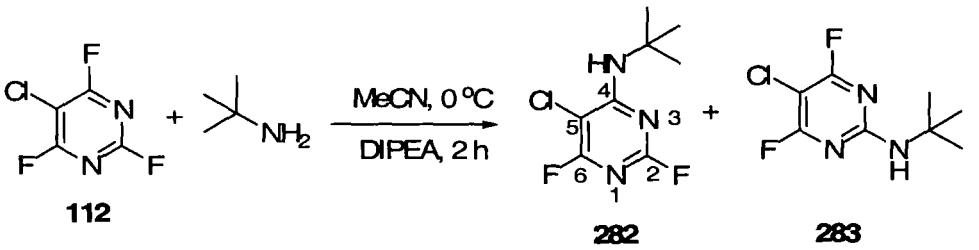
$^1J_{CF}$ 236.2, $^3J_{CF}$ 18.7, C-6); δ_F -45.8 (1F, s, C-6), -67.9 (1F, s, C-2); *m/z* (EI^+) 255 ($[M]^+$, 40%), 218(10), 178(12).

5-Chloro-2,4-difluoro-6-(piperidin-1-yl)pyrimidine, 284



A solution of 5-chloro-trifluoropyrimidine **112** (0.50 g, 6.6 mmol), piperidine (0.25 g, 6.3 mmol) and DIPEA (1.15 g, 8.9 mmol) in acetonitrile (50 cm^3) was stirred at 0 °C for 1 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to 5-chloro-2,4-difluoro-6-(piperidin-1-yl)pyrimidine **284** (-48.49 and -65.88 ppm) and 5-chloro-4,6-difluoro-2-(piperidin-1-yl)pyrimidine **285** (-63.38 ppm) in a 3:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 5-chloro-2,4-difluoro-6-(piperidin-1-yl)pyrimidine **284** and 5-chloro-4,6-difluoro-2-(piperidin-1-yl)pyrimidine **285** as a yellow oil (0.61 g). Column chromatography (silica, DCM: *n*-hexane, 10:1) gave 5-chloro-2,4-difluoro-6-(piperidin-1-yl)pyrimidine **284** (0.34 g, 49%) as an colourless oil; (Found: C, 46.4; H, 4.4; N, 17.9 $C_9H_{10}ClF_2N_3$ requires: C, 46.3; H, 4.3; N, 18.0%); δ_H 1.64 (6H, m, CH_2), 3.73 (4H, m, CH_2); δ_c 24.5 (s, CH_2), 26.2 (s, CH_2), 49.2 (s, CH_2), 94.7 (dd, $^2J_{CF}$ 21, $^4J_{CF}$ 9, C-5), 158.3 (dd, $^1J_{CF}$ 222, $^3J_{CF}$ 22, C-2), 162.6 (dd, $^3J_{CF}$ 13, $^5J_{CF}$ 5, C-4), 164.5 (dd, $^1J_{CF}$ 236, $^3J_{CF}$ 19, C-6); δ_F -47.63 (1F, s, C-6), -64.17 (1F, s, C-2); *m/z* (EI^+) 233 ($[M]^+$, 70%), 204(100).

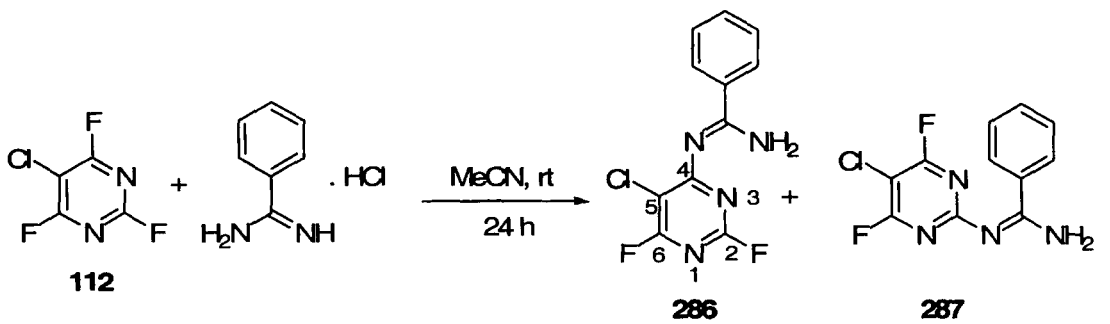
***N-tert*-Butyl-5-chloro-2,6-difluoropyrimidin-4-amine, 282**



112 282 283

A solution of 5-chloro-trifluoropyrimidine **112** (0.50 g, 6.6 mmol), *tert*-butylamine (0.23 g, 6.3 mmol) and DIPEA (1.15 g, 8.9 mmol) in acetonitrile (50 cm^3) was stirred at 0 °C for 2 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to *N-tert*-butyl-5-chloro-2,6-difluoropyrimidin-4-amine **282** (-47.07 and -69.75 ppm) and *N-tert*-butyl-5-chloro-4,6-difluoropyrimidin-2-amine **283** (-63.47 ppm) in a 3:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N-tert*-butyl-5-chloro-2,6-difluoropyrimidin-4-amine **282** and *N-tert*-butyl-5-chloro-4,6-difluoropyrimidin-2-amine **283** as a colourless solid (0.59 g). Recrystallisation from *n*-hexane yielded, N-*tert*-butyl-5-chloro-2,6-difluoropyrimidin-4-amine **282** (0.32 g, 49%) as an colourless solid; mp 52-54 °C; (Found: C, 43.4; H, 4.6; N, 19.1 $C_8H_{10}ClF_2N_3$ requires: C, 43.4; H, 4.6; N, 19.0%); δ_H 1.12 (m, CH_3); δ_c 28.9 (s, CH_3), 54.0 (s, CCH_3), 93.0 (dd, $^2J_{CF}$ 21, $^4J_{CF}$ 8, C-5), 159.8 (dd, $^1J_{CF}$ 193, $^3J_{CF}$ 23, C-2), 162.1 (dd, $^3J_{CF}$ 20, $^5J_{CF}$ 5, C-4), 164.3 (dd, $^1J_{CF}$ 263, $^3J_{CF}$ 19, C-6); δ_F -47.02 (1F, s, C-6), -69.70 (1F, s, C-2); *m/z* (EI^+) 221 ($[M]^+$, 38%), 206(100).

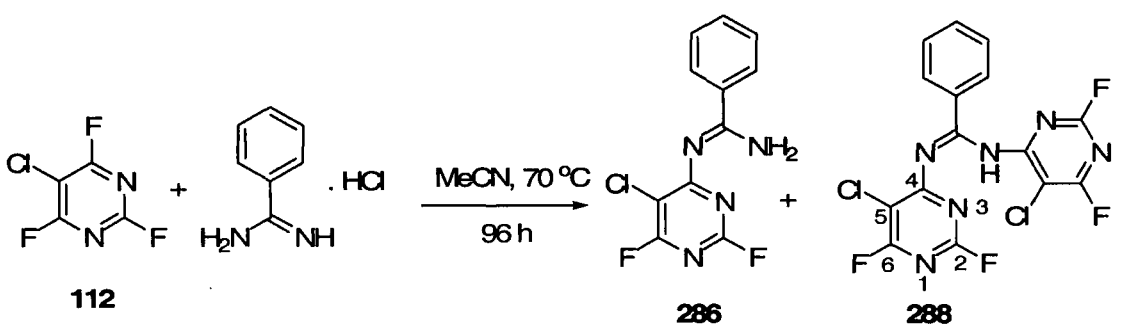
N-(5-Chloro-2,6-difluoropyrimidine-4-yl)benzamidine, 286



112 286 287

A solution of 5-chloro-trifluoropyrimidine **112** (1.10 g, 6.6 mmol), benzamidine hydrochloride (0.95 g, 6.3 mmol) and sodium carbonate (2.99 g, 3.6 mmol) in acetonitrile (300 cm^3) was stirred at room temperature for 24 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to *N*-(5-chloro-2,6-difluoropyrimidine-4-yl)benzamidine **286** (-47.75 and -62.91 ppm) and *N*-(5-chloro-4,6-difluoropyrimidine-2-yl)benzamidine **287** (-111.93 ppm) in a 40:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3) and HCl (5 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N*-(5-chloro-2,6-difluoropyrimidine-4-yl)benzamidine **286** and *N*-(5-chloro-4,6-difluoropyrimidine-2-yl)benzamidine **287** as a yellow solid (1.34 g). Recrystallisation from acetonitrile yielded *N*-(5-chloro-2,6-difluoropyrimidine-4-yl)benzamidine **286** (1.21 g, 69%) as an off white solid; mp 164-165 °C; (Found: C, 48.9; H, 2.6; N, 20.7 $C_{11}H_7ClF_2N_4$ requires: C, 49.2; H, 2.6; N, 20.9%); δ_H (d^6-DMSO) 7.50 (2H, m, C*H*), 7.59 (1H, m, Ar-H), 7.61 (2H, m, Ar-H); δ_c (d^6-DMSO) 103.8 (dd, $^2J_{CF}$ 14, $^4J_{CF}$ 10, C-5), 129.4 (s, Ar-C), 129.9 (s, Ar-C) 133.5 (s, Ar-C), 135.2 (s, Ar-C), 158.2 (dd, $^1J_{CF}$ 193, $^3J_{CF}$ 23, C-6), 162.7 (s, C=N), 169.0 (dd, $^1J_{CF}$ 225, $^3J_{CF}$ 19, C-2), 170.3 (m, C-4); δ_F (d^6-DMSO) -47.49 (1F, s, C-6), -66.06 (1F, s, C-2); *m/z* (EI^+) 268 ($[M]^+$, 12%), 233(36). Crystals suitable for x-ray analysis were grown from acetonitrile.

_N'_-(5-Chloro-2,6-difluoropyrimidin-4-yl)benzamidine, 286 and _N'N'_-Bis-(5-chloro-2,6-difluoro-pyrimidin-4-yl)-benzamidine, 288



112 286 288

A solution of 5-chloro-trifluoropyrimidine **112** (1.07 g, 6.4 mmol), benzamidine hydrochloride (0.94 g, 6.0 mmol) and sodium carbonate (2.97 g, 3.6 mmol) in acetonitrile

(300 cm^3) was stirred at reflux for 96 h after which time ^{19}F NMR spectroscopy indicated complete consumption of the starting material to *N*'-(5-chloro-2,6-difluoropyrimidin-4-yl)benzamidine **286** and *N'N'*-Bis-(5-chloro-2,6-difluoro-pyrimidin-4-yl)-benzamidine **288** in a 2:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3) and HCl (5cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N*'-(5-chloro-2,6-difluoropyrimidin-4-yl)benzamidine **286** and *N'N'*-Bis-(5-chloro-2,6-difluoro-pyrimidin-4-yl)-benzamidine **288** (0.65 g). Column chromatography was performed (silica, *n*-hexane: DCM, 1:10) to yield;

(i) *N*'-(5-chloro-2,6-difluoropyrimidin-4-yl)benzamidine **286** (0.40 g, 23%). Analysis as was found previously.

(ii) *N'N'*-Bis-(5-chloro-2,6-difluoro-pyrimidin-4-yl)-benzamidine **288** (0.24 g, 8%) as a yellow solid; mp 111-113 °C; (Found: C, 43.1; H, 1.4; N, 20.2 $C_{15}H_6Cl_2F_4N_6$ requires C, 43.2; H, 1.5; N, 20.2%); δ_H (d^6-acetone) 7.47 (4H, m, CH), 7.60 (2H, m, CH), 7.71 (4H, m, CH); δ_c (d^6-acetone) 128.92 (s, Ar-C) 129.8 (s, Ar-C), 133.1 (s, Ar-C), 133.9 (s, Ar-C), 156.8 (s, C=N), 159.2 (dd, $^1J_{CF}$ 158, $^3J_{CF}$ 17, C-6), 168.1 (dd, $^1J_{CF}$ 183, $^3J_{CF}$ 14, C-2), 205.5 (s, C-4); δ_F (d^6-acetone) -48.00 (2F, s, C-6), -64.40 (2F, s, C-2); *m/z* (EI^+) 416 ($[M]^+$, 2%), 381(4), 339(2), 252(54).

Chapter 7

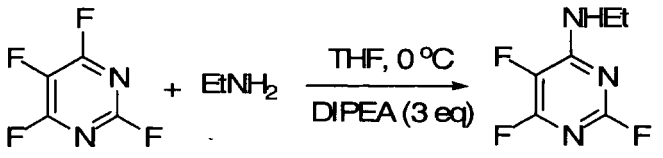
Experimental to Chapter 3

2,4,5,6-Tetrafluoropyrimidine, 113

112 **113**

A stainless steel, oven dried 0.5 dm^3 autoclave was charged with flame-dried potassium fluoride (125 g, 4 mol) and 5-chloro-2,4,6-trifluoropyrimidine, **112** (50 g, 0.6 mol). The autoclave was sealed and heated to 480 °C for 19 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-tetrafluoropyrimidine* **113** (30 g, 67%), as a colourless oil; bp 80 °C; (Found: C, 31.3; N, 18.5 $C_4N_2F_4$ requires: C, 31.6; N, 18.4%); δ_c 132.5 (dtd, $^1J_{CF}$ 249, $^2J_{CF}$ 24, $^4J_{CF}$ 10, C-5), 154.1 (dtd, $^1J_{CF}$ 222, $^3J_{CF}$ 21, $^4J_{CF}$ 5, C-2), 162.3 (dm, $^1J_{CF}$ 256, C-4); δ_F -47.15 (1F, m, C-2), -73.49, (2F, m, C-4), -171.44 (1F, m, C-5); *m/z* (EI^+) 152 ($[M]^+$, 100%), 133(30)

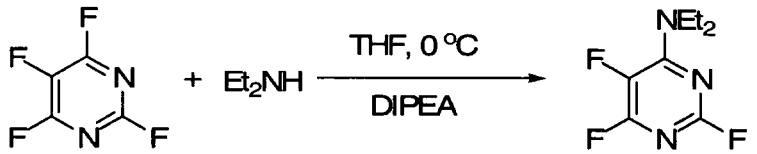
N-Ethyl-2,5,6-trifluoropyrimidin-4-amine, 292



113 **292**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (2.02 g, 13.3 mmol), ethylamine 2 M in THF (6.65 cm^3, 13.3 mmol) and DIPEA (5.16 g, 39 mmol) in THF (200 cm^3) was stirred at 0 °C for 2 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude yellow solid (2.28 g). Column chromatography (silica, ethyl acetate: *n*-hexane, 1:4) yielded *N-ethyl-2,5,6-trifluoropyrimidin-4-amine*, **292** (1.76 g, 75%) as a yellow solid; mp 57-58 °C; IR (neat, ν cm^{-1}): 3313, 3001, 1644, 1596, 1448, 1389, 1276, 1136, 1039, 788, 760; (Found: C, 40.7; H, 3.4; N, 23.7 $C_6H_6F_3N_3$ requires: C, 40.7; H, 3.4; N, 23.7%); δ_H 1.29 (3H, t, $^3J_{HH}$ 6.8, CH_3), 3.56 (2H, q, $^3J_{HH}$ 6.8, CH_2); δ_c 14.2 (s, CH_3), 36.2 (s, CH_2), 127.4 (ddd, $^1J_{CF}$ 250, $^2J_{CF}$ 23, $^4J_{CF}$ 9, C-5), 154.7 (ddd, $^1J_{CF}$ 217, $^3J_{CF}$ 21, $^4J_{CF}$ 3, C-2), 155.4 (ddd, $^1J_{CF}$ 247, $^2J_{CF}$ 19, $^3J_{CF}$ 13, C-6), 156.1 (ddd, $^2J_{CF}$ 18, $^3J_{CF}$ 11, $^3J_{CF}$ 6, C-4); δ_F -48.80 (1F, d, $^4J_{FF}$ 25, C-2), -87.72 (1F, d, $^3J_{FF}$ 16, C-6), -174.15 (1F, s, C-5); *m/z* (ES^+) 176 ($[M+H]^+$, 85%)

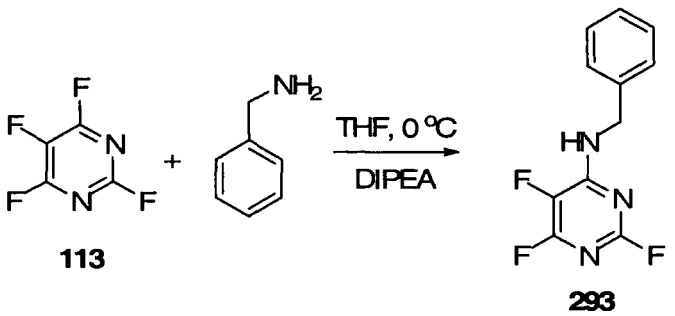
***N,N*-Diethyl-2,5,6-trifluoropyrimidin-4-amine, 294**



113 **294**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (1.02 g, 6.7 mmol), diethylamine (0.49 g, 6.7 mmol) and DIPEA (2.71 g, 20.1 mmol) in THF (50 cm^3) was stirred at 0 °C for 1 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (0.98 g). Recrystallisation from DCM yielded *N,N-diethyl-2,5,6-trifluoropyrimidin-4-amine*, **294** (0.34 g, 26%) as a colourless solid; mp 45-49 °C; (Found: C, 46.6; H, 4.9; N, 20.4 $C_8H_{10}F_3N_3$ requires: C, 46.8; H, 4.9; N, 20.5%); δ_H 1.26 (3H, t, $^3J_{HH}$ 8, CH_3), 3.60 (2H, q, $^3J_{HH}$ 8, CH_2); δ_c 13.6 (s, CH_3), 44.7 (d, 6.5, 2 CH_2), 128.5 (ddd, $^1J_{CF}$ 250, $^2J_{CF}$ 26, $^3J_{CF}$ 9, C-5), 154.1 (dt, $^2J_{CF}$ 19, $^3J_{CF}$ 5, C-4), 154.3 (dd, $^1J_{CF}$ 212, $^4J_{CF}$ 23, C-2), 159.0 (ddd, $^1J_{CF}$ 245, $^2J_{CF}$ 19, $^3J_{CF}$ 16, C-6); δ_F -47.61 (1F, d, $^4J_{FF}$ 15, C-2), -86.76 (1F, s, C-6), -177.38 (1F, d, $^3J_{FF}$ 26, C-5); *m/z* (ES^+) 206 ($[M+H]^+$, 100 %)

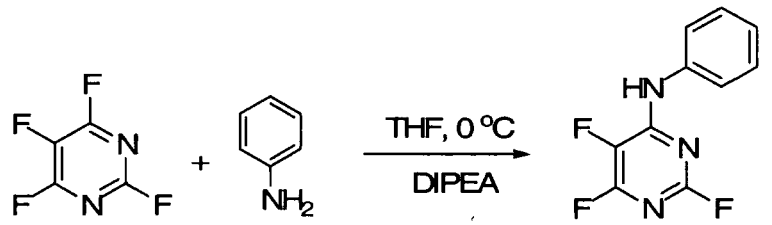
***N*-Benzyl-2,5,6-trifluoropyrimidin-4-amine, 293**



113 **293**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (1.16 g, 7.7 mmol), benzylamine (0.82 g, 7.7 mmol) and DIPEA (1.678 g, 22.9 mmol) in THF (50 cm^3) was stirred at 0 °C for 1 h, after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow oil (1.62 g). Column chromatography (silica, ethyl acetate:*n*-hexane, 1:3) yielded *N-benzyl-2,5,6-trifluoropyrimidin-4-amine*, **293** (1.09 g, 59%) as a yellow solid; mp 69-70 °C; (Found: C, 54.9; H, 3.3; N, 17.3 $C_{11}H_8F_3N_3$ requires: C, 55.2; H, 3.4; N, 17.6%); δ_H 4.71 (2H, d, $^3J_{HH}$ 4, CH_2), 7.38 (5H, m, Ar-H); δ_c 45.5 (s, CH_2), 127.9 (ddd, $^1J_{CF}$ 251, $^2J_{CF}$ 23, $^3J_{CF}$ 9, C-5), 127.9 (s, Ar-CH), 128.2 (s, Ar-CH), 128.9 (s, Ar-CH), 136.7 (s, Ar-CH), 155.0 (ddd, $^1J_{CF}$ 218, $^3J_{CF}$ 21, $^4J_{CF}$ 4, C-2), 156.1 (ddd, $^1J_{CF}$ 247, $^2J_{CF}$ 19, $^3J_{CF}$ 12, C-6), 156.3 (ddd, $^2J_{CF}$ 19, $^3J_{CF}$ 11, $^3J_{CF}$ 6, C-4); δ_F -47.21 (1F, d, $^4J_{FF}$ 25, C-2), -86.61 (1F, d, $^3J_{FF}$ 16, C-6), -180.69 (1F, s, C-5); *m/z* (ES^+) 239 ($[M+ H]^+$, 100%)

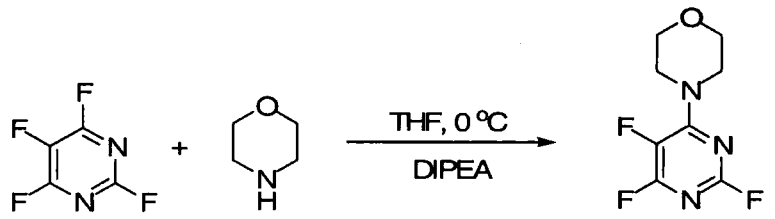
2,5,6-Trifluoro-*N*-phenylpyrimidin-4-amine, 139



113 **139**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (1.01 g, 6.6 mmol), aniline (0.6 g, 6.6 mmol) and resin bound DIPEA (3 g (4 mmol per g), 12 mmol) in THF (150 cm^3) was stirred at 0 °C for 2 h after which time ^{19}F NMR indicated 100% conversion of the start material. The solution was filtered to remove the resin and the reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude cream solid (1.36 g). Recrystallisation from *n*-hexane yielded *2,5,6-trifluoro-N-phenylpyrimidin-4-amine*, **139** (0.64 g, 43%) as a cream solid; mp 91-93 °C; IR (neat, ν cm^{-1}): 3413, 2364, 1628, 1583, 1536, 1478, 1446, 1390, 1290, 1228, 751; (Found: C, 53.0; H, 2.7; N, 18.4 $C_{10}H_6F_3N_3$ requires: C; 53.3; H; 2.7; N; 18.7%); δ_H 7.26 (1H, m, Ar-H), 7.42 (1H, m, Ar-H), 7.58 (1H, m, Ar-H); δ_c 121.4 (s, Ar-CH), 125.7 (s, Ar-CH), 127.3 (ddd, $^1J_{CF}$ 278, $^2J_{CF}$ 32, $^4J_{CF}$ 9, C-5), 129.7 (s, Ar-CH), 154.1 (m, C-4), 154.2 (ddd, $^1J_{CF}$ 218, $^3J_{CF}$ 21, $^4J_{CF}$ 3, C-2), 155.5 (ddd, $^1J_{CF}$ 283, $^2J_{CF}$ 32, $^3J_{CF}$ 9, C-6) ; δ_F -46.1 (1F, d, $^4J_{FF}$ 27, C-2), -84.1 (1F, d, $^3J_{FF}$ 18, C-6), -177.8 (1F, m, C-5); *m/z* (EI^+) 224 ([M^+], 100%), 205(10), 186(6)

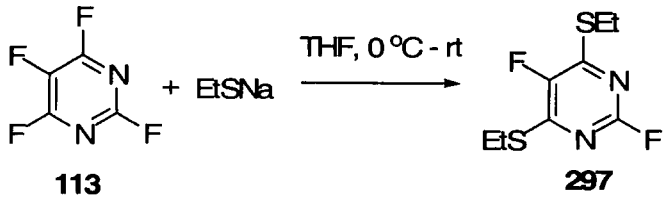
2,4,5-Trifluoro-6-morpholinopyrimidine, 295



113 **295**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (1.01 g, 6.6 mmol), morpholine (0.6 g, 6.6 mmol) and resin bound DIPEA (2 g (4 mmol per g), 8 mmol) in THF (150 cm^3) was stirred at 0 °C for 2 h after which time ^{19}F NMR indicated 100% conversion of the start material. The solution was filtered to remove the resin and the reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude cream solid (1.76 g). Recrystallisation from *n*-hexane yielded *2,4,5-trifluoro-6-morpholinopyrimidine*, **295** (1.22 g, 84%) as a white solid; mp 65-66 °C; (Found: C, 43.7; H, 3.7; N, 19.2 $C_8H_8F_3N_3O$ requires: C, 43.8; H, 3.7; N, 19.2%); δ_H 3.79 (4H, m, CH_2), 3.85 (4H, m, CH); δ_c 46.9 (d, $^4J_{CF}$ 9, CH_2), 66.8 (s, CH_2), 129.5 (ddd, $^1J_{CF}$ 251, $^2J_{CF}$ 25, $^4J_{CF}$ 9, C-5), 154.4 (ddd, $^1J_{CF}$ 217, $^3J_{CF}$ 23, $^4J_{CF}$ 4, C-2), 154.5 (dt, $^2J_{CF}$ 16, $^3J_{CF}$ 6, C-4), 159.7 (ddd, $^1J_{CF}$ 281, $^2J_{CF}$ 35, $^3J_{CF}$ 16, C-6); δ_F -47.90 (1F, d, $^4J_{FF}$ 26, C-2), -84.66 (1F, d, $^3J_{FF}$ 17, C-6), -172.39 (1F, m, C-5); *m/z* (EI^+) 219 ([M^+], 32%), 176(60), 134(100)

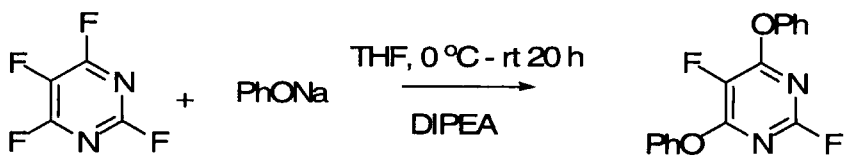
4,6-Bis(ethylthio)-2,5-difluoropyrimidine, 297



113 **297**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (3.03 g, 19 mmol), and sodium ethanethiolate (1.67 g, 19 mmol) in THF (250 cm^3) was stirred at 0 °C for 1 h and then for 19 h at room temperature, after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude containing *4,6-bis(ethylthio)-2,5-difluoropyrimidine*, **297** (2.56 g, 54%) as a yellow solid; mp 48-50 °C; (Found: C, 40.4; H, 4.3; N, 11.9 $C_8H_{10}F_2N_2S_2$ requires: C, 40.7; H, 4.3; N, 11.9%); δ_H 1.34 (3H, t, $^3J_{HH}$ 8, CH_3), 3.13 (2H, q, $^3J_{HH}$ 8, CH_2); δ_c 14.7 (s, CH_3), 24.1 (s, CH_3), 150.7 (dd, $^1J_{CF}$ 249, $^4J_{CF}$ 7, C-5), 157.3 (dd, $^1J_{CF}$ 214, $^4J_{CF}$ 9, C-2), 158.0 (dd, $^2J_{CF}$ 33.9, $^3J_{CF}$ 16, C-4); δ_F -50.25 (1F, d, $^5J_{FF}$ 30, C-2), -139.16 (1F, m, C-5); *m/z* (EI^+) 236 ([M^+], 100%), 203(81), 175(63)

2,5-Difluoro-4,6-bis(phenyloxy)pyrimidine, 296

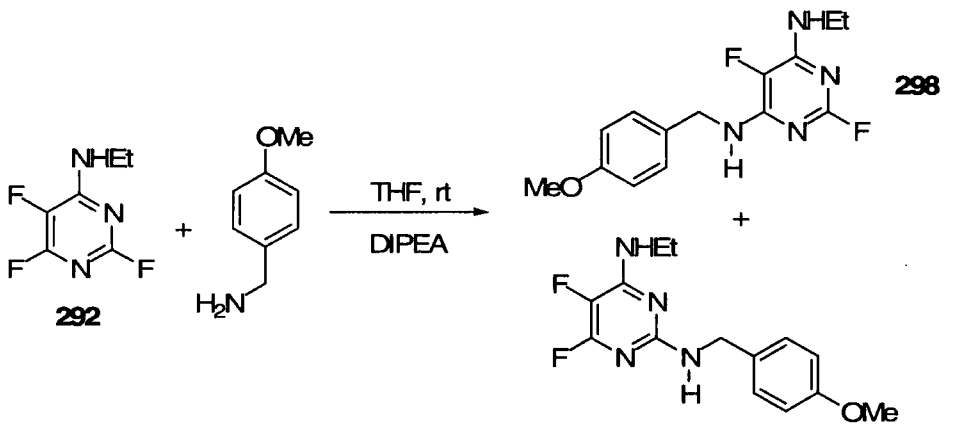


113 **296**

A solution of 2,4,5,6-tetrafluoropyrimidine, **113** (1.05 g, 6.9 mmol), and sodium phenoxide (0.80 g, 6.9 mmol) in THF (150 cm^3) was stirred at 0 °C for 2 h and then for 20 h at room

temperature after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude white solid (0.96 g). Recrystallisation from *n*-hexane yielded *2,5-difluoro-4,6-bis(phenyloxy)pyrimidine*, **296** (0.89 g, 43%) as a white solid; mp 67-68 °C; (Found: C, 63.8; H, 3.3; N, 9.2 $C_{16}H_{10}F_2N_2O_2$ requires: C, 64.0; H, 3.4; N, 9.3%); δ_H 7.26 (2H, m, Ar-H), 7.37 (2H, m, Ar-H), 7.50 (2H, m, Ar-H); δ_c 121.7 (s, Ar-CH), 126.7 (s, Ar-CH), 130.2 (s, Ar-CH), 130.4 (dd, $^1J_{CF}$ 258, $^4J_{CF}$ 10, C-5), 152.2 (s, COC), 152.94 (dd, $^1J_{CF}$ 221, $^4J_{CF}$ 5, C-2); δ_F -45.9 (1F, s, C-2), -174.2 (1F, s, C-5); *m/z* (ES^+) 301 ($[M+H]^+$, 100%)

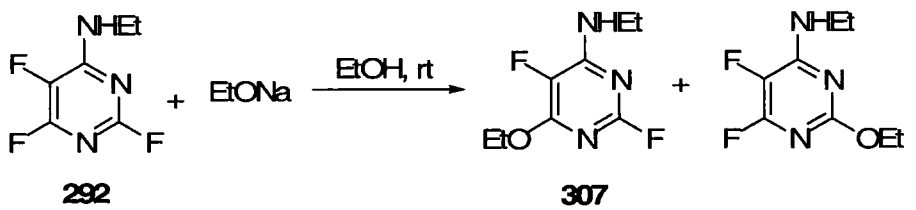
N-Benzyl-N'-ethyl-2,5-difluoropyrimidine-4,6-diamine, 298



A solution of *N*-ethyl-2,5,6-trifluoropyrimidin-4-amine, **292** (1.03 g, 5.8 mmol), 4-methoxybenzylamine (0.8 g, 5.8 mmol) and DIPEA (3.04 cm^3, 17 mmol) in THF (100 cm^3) was stirred at room temperature for 12 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid containing *N*-benzyl-*N'*-ethyl-2,5-difluoropyrimidine-4,6-diamine and *N*-benzyl-*N'*-ethyl-6,5-difluoropyrimidine-2,4-diamine (1.21 g) in a 19:1 ratio. Recrystallisation from *n*-hexane

yielded *N-benzyl-N'-ethyl-2,5-difluoropyrimidine-4,6-diamine*, **298** (1.09 g, 61%) as a white solid; mp 77-79 °C; (Found: C, 57.2; H, 5.5; N, 18.8 $C_{14}H_{16}F_2N_4O$ requires: C, 57.1; H, 5.5; N, 19.0%); δ_H 1.25 (3H, t, $^3J_{HH}$ 7.6, CH_3), 3.48 (2H, m, CH_2), 3.82 (3H, s, OCH_3), 4.56 (2H, d, $^2J_{HH}$ 5.6, CH_2), 4.66 (1H, s, NH), 4.87 (1H, s, NH), 6.89 (2H, m, Ar-H), 7.28 (2H, m, Ar-H); δ_c 14.8 (s, CH_3), 35.4 (s, CH_2), 43.9 (s, CH_2), 54.8 (s, OCH_2), 113.6 (s, Ar-CH), 128.4 (dd, $^1J_{CF}$ 232, $^4J_{CF}$ 7, C-5), 128.7 (s, Ar-CH), 130.1 (s, Ar-CH), 150.7 (dd, $^2J_{CF}$ 11, $^3J_{CF}$ 10, C-6), 151.3 (dd, $^2J_{CF}$ 11, $^3J_{CF}$ 10, C-4), 156.3 (dd, $^1J_{CF}$ 206, $^4J_{CF}$ 2, C-2), 158.7 (s, OCH_3); δ_F -49.58 (1F, s, C-2), -186.07 (1F, s, C-5); *m/z* (ES$^+$) 295 ([M+ H]$^+$, 100%)

6-Ethoxy-*N*-ethyl-2,5-difluoropyrimidin-4-amine, 307

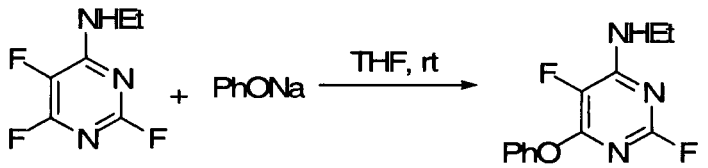


292 **307**

A solution of *N*-ethyl-2,5,6-trifluoropyrimidin-4-amine, **292** (1.00 g, 5.71 mmol), and sodium ethoxide (0.66 g, 5.71 mmol) in ethanol (150 cm^3) was stirred at room temperature for 17 h after which time ^{19}F NMR indicated 100% conversion with the formation of 6-ethoxy-*N*-ethyl-2,5-difluoropyrimidin-4-amine and 2-ethoxy-*N*-ethyl-4,5-difluoropyrimidin-4-amine in a 6:1 ratio. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing 6-ethoxy-*N*-ethyl-2,5-difluoropyrimidin-4-amine and 2-ethoxy-*N*-ethyl-4,5-difluoropyrimidin-4-amine (1.34 g). Recrystallisation from *n*-hexane yielded *6-ethoxy-N-ethyl-2,5-difluoropyrimidin-4-amine*, **307** (0.88 g, 77%) as a white solid; mp 81-83 °C; (Found: C, 47.3; H, 5.5; N, 20.7 $C_8H_{11}F_2N_3O$ requires: C, 47.3; H, 5.5; N, 20.7%); δ_H 1.24 (3H, t, $^3J_{HH}$ 7, CH_3), 1.41 (3H, t, $^3J_{HH}$ 7, CH_3), 3.49 (2H, q, $^3J_{HH}$ 6, NCH_2), 4.41 (2H, q, $^3J_{HH}$ 6, OCH_2), 4.87 (1H, s, NH); δ_c 14.8 (s, CH_3), 15.3 (s, CH_3), 36.3 (s, CH_2), 63.8 (s, CH_2), 130.5 (dd, $^1J_{CF}$ 231, $^4J_{CF}$ 9, C-5), 154.5 (dd, $^2J_{CF}$ 30, $^3J_{CF}$ 11, C-4), 154.8 (dd, $^1J_{CF}$ 214, $^4J_{CF}$

4, C-2), 156.3 (dd, $^{2}J_{CF}$ 27, $^{3}J_{CF}$ 10, C-6); δ_F -49.33 (1F, d, $^{5}J_{FF}$ 27, C-2), -186.07 (1F, d, $^{5}J_{FF}$ 27, C-5); *m/z* (EI$^+$) 203 ([M]$^+$, 32%), 188(40)

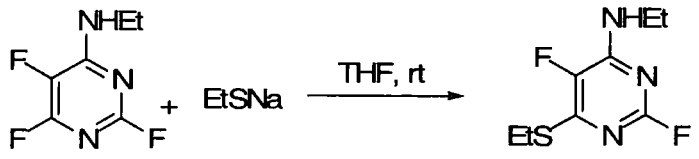
_N_-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine, 304



292 **304**

A solution of *N*-ethyl-2,5,6-trifluoropyrimidin-4-amine, **292** (1.01 g, 5.7 mmol), and sodium phenoxide (0.66 g, 5.7 mmol) in THF (50 cm^3) was stirred at room temperature for 17 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude yellow solid (1.56 g). Recrystallisation from *n*-hexane yielded *N-ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine*, **304** (0.91 g, 63%) as a white solid; mp 97-99 °C; (Found: C, 57.3; H, 4.3; N, 16.6 $C_{12}H_{11}F_2N_3O$ requires: C, 57.4; H, 4.4; N, 16.7%); δ_H 1.32 (3H, t, $^{3}J_{HH}$ 7.2, CH_3), 3.58 (2H, m, CH_2), 7.20 (2H, m, Ar-H), 7.29 (1H, m, Ar-H), 7.43 (2H, m, Ar-H); δ_c 14.3 (s, CH_3), 35.7 (s, CH_2), 120.4 (s, Ar-CH), 124.9 (s, Ar-CH), 128.0 (dd, $^{1}J_{CF}$, $^{4}J_{CF}$, C-5), 129.0 (s, Ar-CH), 151.8 (s, COC), 152.7 (m, C-6), 153.8 (dd, $^{1}J_{CF}$, $^{4}J_{CF}$, C-2), 157.8 (m, C-4); δ_F -47.8 (1F, s, C-2), -180.2 (1F, s, C-5); *m/z* (ES$^+$) 252 ([M+ H]$^+$, 100%)

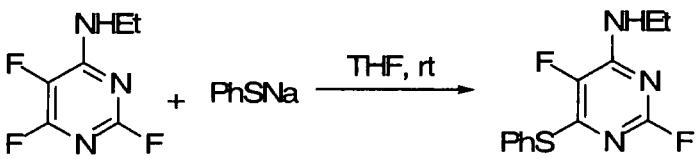
_N_-Ethyl-6-(ethylthio)-2,5-difluoropyrimidin-4-amine, 310



292 **310**

A solution of *N*-ethyl-2,5,6-trifluoropyrimidin-4-amine, **292** (1.50 g, 8.5 mmol), and sodium ethanethiolate (0.71 g, 8.5 mmol) in THF (50 cm^3) was stirred at room temperature for 17 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (1.56 g). Recrystallisation from *n*-hexane yielded *N-ethyl-6-(ethylthio)-2,5-difluoropyrimidin-4-amine*, **310** (0.95 g, 51%) as a yellow solid; mp 54-55 °C; (Found: C, 43.6; H, 5.0; N, 18.9 $C_{12}H_{11}F_2N_3O$ requires: C, 43.8; H, 5.1; N, 19.2%); δ_H 1.25 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.35 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.15 (2H, q, $^3J_{HH}$ 7.2,, CH_2), 3.49 (2H, m, CH_2); δ_c 14.3 (s, CH_3), 14.4 (s, CH_3), 24.0 (s, CH_2), 36.2 (s, CH_2), 138.7 (dd, $^1J_{CF}$ 230, $^4J_{CF}$ 8, C-5), 152.1 (m, C-4), 153.4 (m, C-6), 153.8 (dd, $^1J_{CF}$ 210, $^4J_{CF}$ 5, C-2); δ_F -56.67 (1F, s, C-2), -167.93 (1F, s, C-5); *m/z* (EI^+) 219 ([M^+], 90%), 186(100), 176(75)

_N_-Ethyl-2,5-difluoro-6-(phenylthio)pyrimidin-4-amine, 311

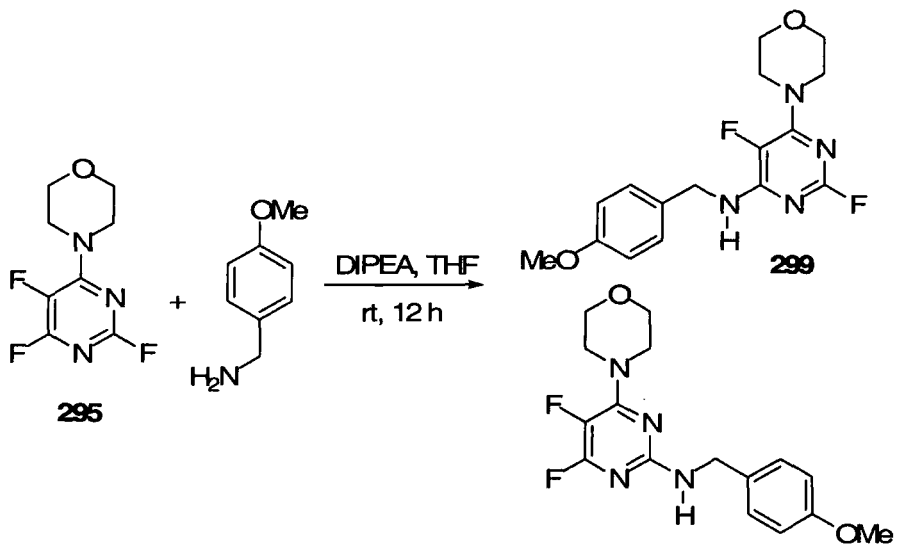


292 **311**

A solution of *N*-ethyl-2,5,6-trifluoropyrimidin-4-amine, **292** (1.52 g, 8.5 mmol), and sodium benzenethiol (0.71 g, 8.5 mmol) in THF (50 cm^3) was stirred at room temperature

for 17 h after which time ^{19}F NMR indicated 100% conversion with the formation of *N*-ethyl-2,5-difluoro-6-(phenylthio)pyrimidin-4-amine. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (1.56 g). Recrystallisation from *n*-hexane yielded *N-ethyl-2,5-difluoro-6-(phenylthio)pyrimidin-4-amine*, **311** (1.35 g, 60%) as a yellow solid; mp 99-100 °C; (Found: C, 53.9; H, 4.1; N, 15.7 $C_{12}H_{11}F_2N_3S$ requires: C, 53.9; H, 4.2; N, 15.7%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.54 (2H, m, CH_2), 5.16 (1H, s, NH), 7.40 (2H, m, Ar-H), 7.55 (1H, m, Ar-H); δ_c 14.9 (s, CH_3), 36.3 (s, CH_2), 127.3 (s, CSC), 129.4 (s, Ar-CH), 129.7 (s, Ar-CH), 135.4 (s, Ar-CH), 140.9 (dd, $^1J_{CF}$ 239, $^4J_{CF}$ 7, C-5); δ_F -48.55 (1F, d, $^5J_{FF}$ 27, C-2), -159.3 (1F, d, $^5J_{FF}$ 25, C-5); *m/z* (ES^+) 268 ($[M+H]^+$, 85%)

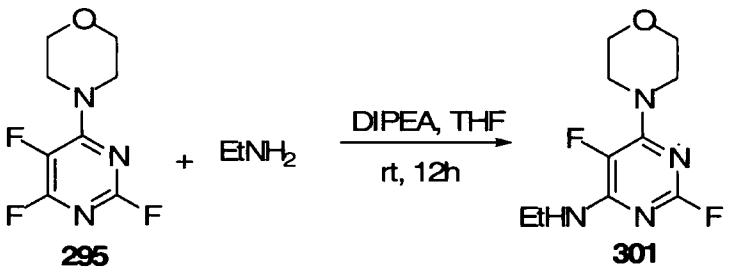
N-(4-Methoxybenzyl)-2,5-difluoro-6-morpholinopyrimidin-4-amine, 299



A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **295** (1.03 g, 4.7 mmol), 4-methoxybenzylamine (0.64 g, 4.7 mmol) and DIPEA (3.04 cm^3, 17 mmol) in THF (100 cm^3) was stirred at room temperature for 12 h after which time ^{19}F NMR indicated 100% conversion of the start material with the formation of *N*-benzyl-*N'*-ethyl-2,5-difluoropyrimidine-4,6-diamine and *N*-benzyl-*N'*-ethyl-6,5-difluoropyrimidine-2,4-diamine

in a 16:1 ratio. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid containing *N*-benzyl-*N'*-ethyl-2,5-difluoropyrimidine-4,6-diamine and *N*-benzyl-*N'*-ethyl-6,5-difluoropyrimidine-2,4-diamine (1.21 g). Recrystallisation from *n*-hexane yielded *N-benzyl-N'-ethyl-2,5-difluoropyrimidine-4,6-diamine* **299** (1.04 g, 66%) as a white solid; mp 85-87 °C; (Found: C, 57.0; H, 5.4; N, 16.6 $C_{16}H_{18}F_2N_4O_2$ requires: C, 57.1; H, 5.4; N, 16.7%); δ_H 3.65 (4H, m, CH_2), 3.74 (4H, m, CH_2), 3.65 (3H, s, CH_3), 4.56 (2H, d, $^3J_{HH}$ 5.6, CH_2), 6.87 (2H, m, Ar-H), 7.24 (2H, m, Ar-H); δ_c 44.8 (s, CH_2), 46.7 (d, $^4J_{CF}$ 7, CH_2), 55.6 (s, CH_3), 67.0 (s, CH_2), 114.4 (s, Ar-CH), 128.7 (dd, $^1J_{CF}$ 240, $^4J_{CF}$ 8, 5-CF), 130.5 (s, CCN), 150.4 (dd, $^2J_{CF}$ 18, $^4J_{CF}$ 4, C-4), 154.8 (dd, m, C-6), 155.4 (dd, $^1J_{CF}$ 209, $^4J_{CF}$ 4, 2-CF), (ddd, $^2J_{CF}$ 18, $^3J_{CF}$ 11, $^3J_{CF}$ 6, 4-CN); δ_F -49.99 (1F, d, $^5J_{FF}$ 28, C-2), -175.45 (1F, d, $^5J_{FF}$ 25, C-5); *m/z* (ES^+) 337 ([M+ H]$^+$, 100%)

N-Ethyl-2,5-difluoro-6-morpholin-4-ylpyrimidin-4-amine, 301

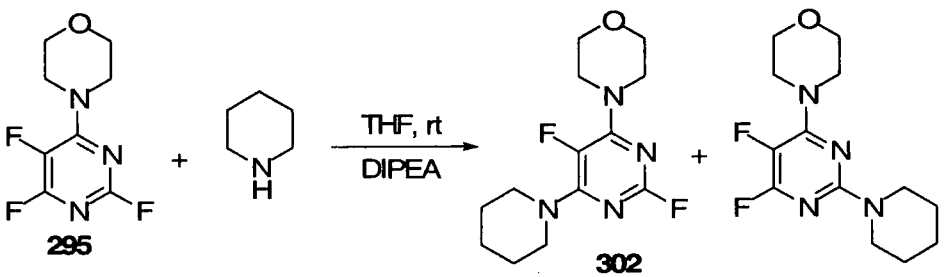


295 **301**

A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **295** (1.03 g, 4.7 mmol), ethylamine (0.21 g, 4.7 mmol) and DIPEA (3.04 cm^3, 17 mmol) in THF (100 cm^3) was stirred at room temperature for 12 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (1.33 g). Recrystallisation from *n*-hexane yielded *N-ethyl-2,5-difluoro-6-morpholin-4-ylpyrimidin-4-amine*, **301** (0.68 g, 61%) as a white solid; mp 61-62 °C; (Found: C, 49.2; H, 5.8; N, 22.8 $C_{10}H_{14}F_2N_4O$ requires: C, 49.2; H, 5.8; N, 22.9%); δ_H 1.23 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.47 (2H, m, CH_2), 3.67 (4H, m, CH_2),

3.75 (4H, m, CH_2), 4.81 (1H, NH); δ_c 15.3 (s, CH_3), 36.2 (s, CH_3), 46.7 (d, $^4J_{CF}$ 7, CH_2), 67.0 (s, CH), 128.0 (dd, $^1J_{CF}$ 228, $^4J_{CF}$ 7, C-5), 150.1 (dd, $^2J_{CF}$ 14, $^4J_{CF}$ 4, C-4), 154.9 (m, C-6), 157.1 (dd, $^1J_{CF}$ 206, $^4J_{CF}$ 3, C-2); δ_F -50.11 (1F, d, $^5J_{FF}$ 28, C-2), -175.77 (1F, d, $^5J_{FF}$ 26, C-5); *m/z* (ES^+) 245 ($[M+H]^+$, 100%)

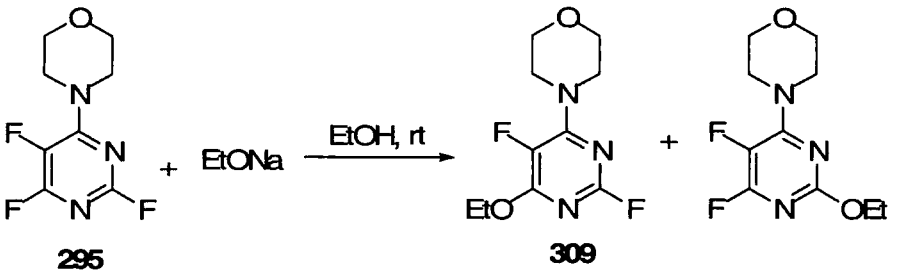
2,5-Difluoro-*N*-phenyl-6-(piperidin-1-yl)pyrimidin-4-amine, 302



295 302

A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **295** (1.01 g, 4.7 mmol), piperidine (0.39 g, 4.7 mmol) and DIPEA (3.04 cm^3, 17mmol) in THF (100 cm^3) was stirred at room temperature for 14 h after which time ^{19}F NMR indicated 100% conversion with the formation of two products including 2,5-difluoro-4-morpholino-6-(piperidin-1-yl)pyrimidine and 4,5-difluoro-4-morpholino-2-(piperidin-1-yl)pyrimidine in a 1:1 ratio. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid containing 2,5-difluoro-*N*-phenyl-6-(piperidin-1-yl)pyrimidin-4-amine and 2,5-difluoro-*N*-phenyl-6-(piperidin-1-yl)pyrimidin-4-amine in a 3:1 ratio. Column chromatography (silica, ethyl acetate:*n*-hexane, 1:3) yielded *2,5-difluoro-N-phenyl-6-(piperidin-1-yl)pyrimidin-4-amine*, **302** (0.68 g, 51%) as white solid; mp 59-60 °C; (Found: C, 54.7; H, 6.4; N, 19.5 $C_{13}H_{18}F_2N_4O$ requires: C, 54.9; H, 6.4; N, 19.7%); δ_H 1.61 (6H, m, CH_2), 3.63 (8H, m, CH_2), 7.78 (4H, m, CH_2), 7.43 (2H, m, CH_2); δ_c 24.9 (s, CH_2), 26.3 (s, CH_2), 47.5 (d, $^4J_{CF}$ 7, CH_2), 48.3 (d, $^4J_{CF}$ 7, CH_2), 67.1 (s, CH_2), 128.0 (dd, $^1J_{CF}$ 240, $^4J_{CF}$ 8, C-5), 154.1 (m, C-4), 154.2 (m, C-6), 153.8 (dd, $^1J_{CF}$ 203, $^4J_{CF}$ 2, C-2); δ_F -50.66 (1F, d, $^5J_{FF}$ 27, C-2), -163.61 (1F, d, $^5J_{FF}$ 27, C-5); *m/z* (ES^+) 285 ($[M+H]^+$, 100%)

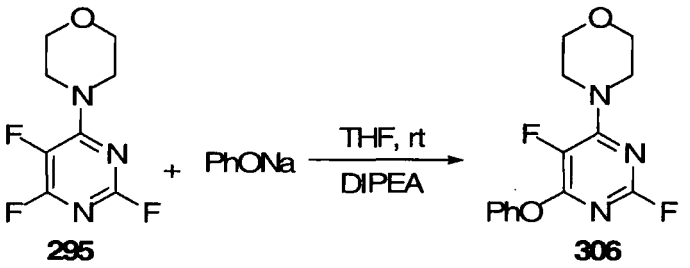
4-(6-Ethoxy-2,5-difluoropyrimidin-4-yl)morpholine, 309



295 309

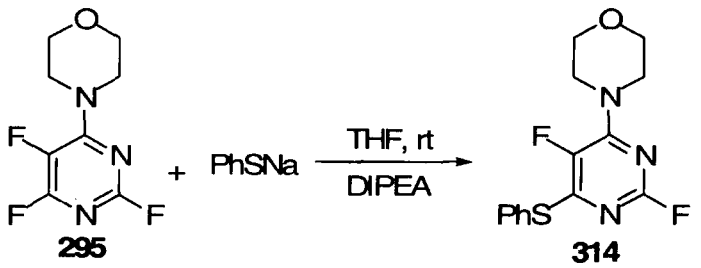
A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **295** (1.00 g, 5.7 mmol), and sodium ethoxide (0.31 g, 5.7 mmol) in ethanol (150 cm^3) was stirred at room temperature for 18 h after which time ^{19}F NMR indicated 100% conversion with the formation of 4-(6-ethoxy-2,5-difluoropyrimidin-4-yl)morpholine and 4-(2-ethoxy-4,5-difluoropyrimidin-4-yl)morpholine in a 6:1 ratio. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing 4-(6-ethoxy-2,5-difluoropyrimidin-4-yl)morpholine and 4-(2-ethoxy-4,5-difluoropyrimidin-4-yl)morpholine (1.48 g). Recrystallisation from *n*-hexane yielded *4-(6-ethoxy-2,5-difluoropyrimidin-4-yl)morpholine*, **309** (0.79 g, 71%) as a white solid; mp 97-98 °C; (Found: C, 48.8; H, 5.3; N, 17.1 $C_{10}H_{13}F_2N_3O_2$ requires: C, 49.0; H, 5.3; N, 17.1%); δ_H 1.42 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.76 (8H, m, CH_2), 4.43 (2H, q, $^3J_{HH}$ 7.2, CH_2); δ_c 14.7 (s, CH_3), 47.0 (d, $^4J_{CF}$ 7, NCH_2), 64.2 (s, CH_2), 66.9 (s, OCH_2), 128.4 (dd, $^1J_{CF}$ 244, $^4J_{CF}$ 9, C-5), 152.6 (dd, $^2J_{CF}$ 22, $^3J_{CF}$ 4, C-4), 154.0 (dd, $^1J_{CF}$ 210, $^4J_{CF}$ 3, C-2), 160.7 (m, C-6); δ_F -49.59 (1F, d, $^5J_{FF}$ 27, C-2), -172.81 (1F, m, C-5); *m/z* (ES^+) 246 ($M^+ + H^+$, 100%)

2,5-Difluoro-4-morpholino-6-phenoxypyrimidine, 306



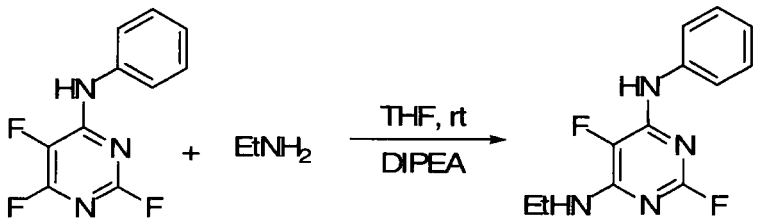
A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **295** (1.00 g, 0.49 mmol), and sodium phenoxide (0.53 g, 0.49 mmol) in THF (100 cm^3) was stirred at room temperature for 19.5 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude containing yellow solid (1.05 g). Recrystallisation from *n*-hexane yielded *2,5-difluoro-4-morpholino-6-phenoxypyrimidine*, **306** (1.05 g, 78%) as a white solid; mp 128-130 °C; (Found: C, 57.3; H, 4.5; N, 14.3 $C_{14}H_{13}F_2N_3O_2$ requires: C, 57.3; H, 4.5; N, 14.3%); δ_H 3.79 (8H, m, CH_2), 7.16 (2H, m, CH), 7.25 (1H, m, CH), 7.40 (2H, m, CH); δ_c 46.8 (d, $^4J_{CF}$ 7, NCH_2), 66.9 (s, OCH_2), 121.4 (s, Ar-CH), 126.0 (s, Ar-CH), 129.9 (Ar-CH), 132.0 (dd, $^1J_{CF}$ 244, $^4J_{CF}$ 9, C-5), 152.5(s, COC), 153.6 (m, C-4), 154.0 (dd, $^1J_{CF}$ 213, $^4J_{CF}$ 3, C-2), 159.9 (m, C-6); δ_F -48.3 (1F, d, $^5J_{FF}$ 28, C-2), -170.7 (1F, d, $^5J_{FF}$ 28, C-5); *m/z* (ES^+) 294 ($[M+H]^+$, 100%)

2,5-Difluoro-4-morpholino-6-(phenylthio)pyrimidine, 314



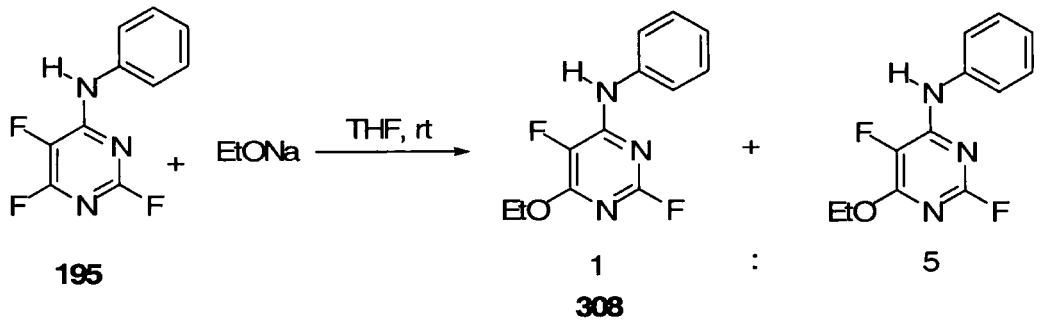
A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **295** (1.00 g, 4.6 mmol), and sodium thiophenolate (0.66 g, 5.0 mmol) in THF (100 cm^3) was stirred at room temperature for 19 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing yellow solid (1.23 g). Recrystallisation from *n*-hexane yielded *2,5-difluoro-4-morpholino-6-(phenylthio)pyrimidine*, **314** (0.76 g, 54%) as a yellow solid; mp 120-122 °C; (Found: C, 54.5; H, 4.2; N, 13.4 $C_{14}H_{13}F_2N_3OS$ requires: C, 54.4; H, 4.2; N, 13.6%); δ_H 3.7 (8H, m, CH_2), 7.4 (3H, m, CH_2), 7.6 (2H, m, CH); δ_c 46.8 (d, $^4J_{CF}$ 8, CH_2), 66.9 (s, CH_2), 47.5 (d, $^4J_{CF}$ 7, CH_2), 48.3 (d, $^4J_{CF}$ 7, CH_2), 67.1 (s, CH_2), 128.0 (dd, $^1J_{CF}$ 240, $^4J_{CF}$ 8, C-5), 154.1 (m, C-4), 154.2 (m, C-6), 153.8 (dd, $^1J_{CF}$ 203, $^4J_{CF}$ 2, 2-CF); δ_F -49.1 (1F, s, 2-CF), -149.2 (1F, s, 5-CF); *m/z* (ES^+) 310 ($[M+ H]^+$, 100%)

N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine, 300



A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **139** (1.01 g, 4.4 mmol), ethylamine (0.20 g, 4.4 mmol) and DIPEA (3.04 cm^3, 17 mmol) in THF (100 cm^3) was stirred at 40 °C for 12 h after which time ^{19}F NMR indicated 100% conversion with the formation of N^4-ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (1.09 g). Recrystallisation from *n*-hexane yielded *N^4-ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine*, **300** (0.99 g, 88%) as a orange solid; mp 131-132 °C; (Found: C, 57.3; H, 4.8; N, 22.2 $C_{12}H_{12}F_2N_4$ requires: C, 57.6; H, 4.8; N, 22.4%); δ_H 1.28 (3H, t, $^3J_{HH}$ 7, CH_3), 3.51 (2H, q, $^3J_{HH}$ 6, CH_2), 4.81 (1H, s, NH), 6.58 (1H, s, NH), 7.16 (1H, s, Ar-H), 7.34 (2H, m, Ar-H), 7.52 (2H, m, Ar-H); δ_c 15.4 (s, CH_3), 36.2 (s, CH_2), 120.5 (s, Ar-CH), 123.8 (s, Ar-CH), 128.2 (dd, $^1J_{CF}$ 234, $^4J_{CF}$ 7 5-CF), 129.5 (s, Ar-CH), 138.4 (s, CNC), 148.6 (dd, $^2J_{CF}$ 29, $^3J_{CF}$ 9, 4-CN), 152.6 (dd, $^2J_{CF}$ 31, $^3J_{CF}$ 11, 6-CN), 157.4 (dd, $^1J_{CF}$ 207, $^4J_{CF}$ 3, 2-CF); δ_F -49.1 (1F, s, 2-CF), -149.2 (1F, s, 5-CF); *m/z* (ES^+) 251 ($[M+ H]^+$, 100%)

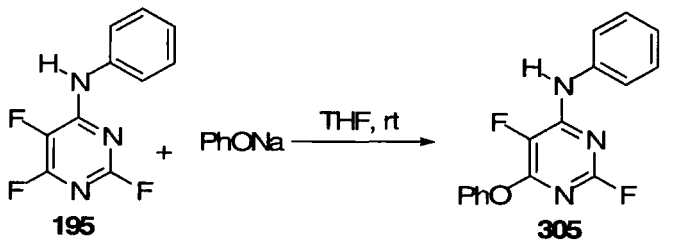
6-Ethoxy-2,5-difluoro-*N*-phenylpyrimidin-4-amine, 308



195 → 1 (308) : 5

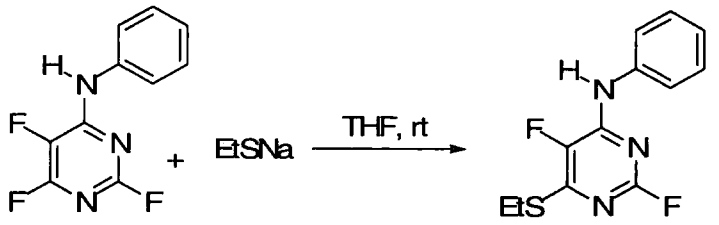
A solution of 2,4,5-trifluoro-6-morpholinopyrimidine, **195** (1.00 g, 4.4 mmol), and sodium ethoxide (0.31 g, 4.4 mmol) in ethanol (150 cm^3) was stirred at room temperature for 18 h after which time ^{19}F NMR indicated 100% conversion with the formation of 6-ethoxy-2,5-difluoro-*N*-phenylpyrimidin-4-amine and 2-ethoxy-5,6-difluoro-*N*-phenylpyrimidin-4-amine in a 5:1 ratio. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing 6-ethoxy-2,5-difluoro-*N*-phenylpyrimidin-4-amine and 2-ethoxy-5,6-difluoro-*N*-phenylpyrimidin-4-amine (1.48 g). Recrystallisation from *n*-hexane yielded *6-ethoxy-2,5-difluoro-N-phenylpyrimidin-4-amine*, **308** (0.56 g, 50%) as a pink solid; mp 105-106 °C; (Found: C, 57.2; H, 4.4; N, 16.9 $C_{12}H_{11}F_2N_3O$ requires: C, 57.4; H, 4.4; N, 16.7%); δ_H 1.47 (3H, t, $^3J_{HH}$ 7, CH_3), 4.49 (3H, t, $^3J_{HH}$ 7, CH_2), 7.16 (1H, m, Ar-H), 7.53 (2H, m, Ar-H), 7.57 (2H, m, Ar-H); δ_c 14.7 (s, CH_3), 64.3 (s, CH_2), 120.8 (s, Ar-CH), 124.5 (s, Ar-CH), 128.9 (dd, $^1J_{CF}$ 253, $^4J_{CF}$ 9, C-5), 129.4 (s, Ar-CH), 137.8 (s, OCH_2), 151.5 (dd, $^2J_{CF}$ 29, $^3J_{CF}$ 9, C-4), 154.4 (dd, $^1J_{CF}$ 216, $^4J_{CF}$ 4, C-2), 158.0 (dd, $^2J_{CF}$ 27, $^3J_{CF}$ 10, C-4); δ_F -49.97 (1F, d, $^5J_{FF}$ 28, C-2), -179.31 (1F, m, 5-CF); *m/z* (ES^+) 252 ($[M+H]^+$, 100%)

2,5-Difluoro-6-phenoxy-*N*-phenylpyrimidin-4-amine, 305



A solution of 2,5,6-trifluoro-*N*-phenylpyrimidin-4-amine, **195** (1.02 g, 4.4 mmol), and sodium phenoxide 0.57 g, 4.4 mmol) in THF (100 cm^3) was stirred at room temperature for 19 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product as a yellow solid. (1.32 g). Recrystallisation from *n*-hexane yielded *2,5-difluoro-6-phenoxy-N-phenylpyrimidin-4-amine*, **305** (0.98 g, 70%) as a white solid; mp 128-130 °C; (Found: C, 64.1; H, 3.7; N, 14.0 $C_{16}H_{11}F_2N_3O$ requires: C, 64.2; H, 3.7; N, 14.0%); δ_H 6.9 (1H, NH), 7.2 (3H, m, Ar-CH), 7.3 (1H, m, Ar-CH), 7.4 (4H, m, Ar-CH), 7.5 (2H, m, Ar-CH); δ_c 121.0 (s, Ar-CH), 121.4 (s, Ar-CH), 124.9 (s, Ar-CH), 126.1 (s, Ar-CH), 129.1 (dd, $^1J_{CF}$ 248, $^4J_{CF}$ 9, C-5), 129.2 (s, Ar-CH), 129.9 (s, Ar-CH), 137.4 (s, CNC), 152.4 (s, 4-CN), 152.5 (dd, $^2J_{CF}$ 10, $^3J_{CF}$ 9, 6-CO), 154.3 (dd, $^1J_{CF}$ 217, $^4J_{CF}$ 4, 2-CF), 156.6 (dd, $^2J_{CF}$ 10, $^3J_{CF}$ 7, 6-CO); δ_F -46.5 (1F, s, C-2), -176.9 (1F, s, C-5); *m/z* (EI^+) 299 ([M^+], 17%), 259(5)

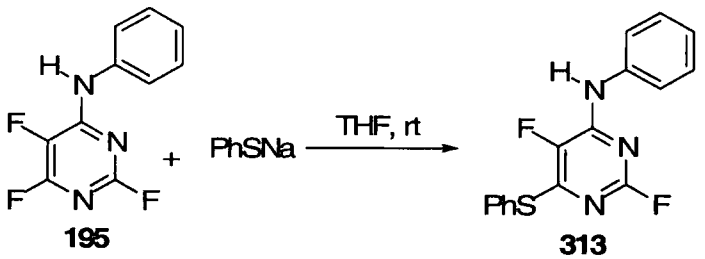
6-(Ethylthio)-2,5-difluoro-*N*-phenylpyrimidin-4-amine, 312



195 **312**

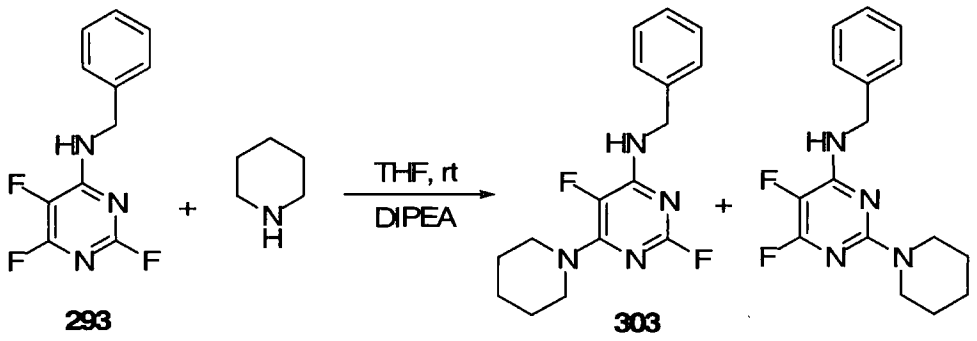
A solution of 2,5,6-trifluoro-*N*-phenylpyrimidin-4-amine, **195** (1.03 g, 4.4 mmol), and sodium ethanethiolate 0.37 g, 4.4 mmol) in THF (100 cm^3) was stirred at room temperature for 19 hrs after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude product as a yellow solid. (1.39 g) Recrystallisation from *n*-hexane yielded *6-(ethylthio)-2,5-difluoro-N-phenylpyrimidin-4-amine*, **312** (0.83 g, 69%) as a yellow solid; mp 101-102 °C; (Found: C, 53.8; H, 4.1; N, 15.8 $C_{12}H_{11}F_2N_3S$ requires: C, 53.9; H, 4.2; N, 15.7%); δ_H 1.44 (3H, t, $^3J_{HH}$ 7.4, CH_3), 3.23 (3H, q, $^3J_{HH}$ 7.4, CH_2), 6.82 (1H, NH), 7.20 (1H, m, Ar-H), 7.39 (2H, m, Ar-H), 7.61 (2H, m, Ar-H); δ_c 15.1 (s, CH_3), 24.0 (s, CH_3), 121.0 (s, Ar-CH), 124.8 (s, Ar-CH), 129.4 (s, Ar-CH), 137.4 (s, CNC), 139.1 (dd, $^1J_{CF}$ 252, $^4J_{CF}$ 7, C-5), 150.2 (dd, $^2J_{CF}$ 40, $^3J_{CF}$ 11, 4-CN), 155.2 (t, $^3J_{CF}$ 17, 6-CS), 155.6 (dd, $^1J_{CF}$ 246, $^4J_{CF}$ 3, 2-CF); δ_F -48.5 (1F, d, $^5J_{FF}$ 29, C-2), -158.5 (1F, d, $^5J_{FF}$ 29, C-5); *m/z* (EI^+) 267 ([M^+], 100%), 234(74)

2,5-Difluoro-*N*-phenyl-6-(phenylthio)pyrimidin-4-amine, 313



A solution of 2,5,6-trifluoro-*N*-phenylpyrimidin-4-amine, **195** (1.02 g, 4.4 mmol), and sodium thiophenolate (0.61 g, 9.8 mmol) in THF (100 cm^3) was stirred at room temperature for 19 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid. (1.32 g) Recrystallisation from *n*-hexane yielded *2,5-difluoro-N-phenyl-6-(phenylthio)pyrimidin-4-amine*, **313** (0.46 g, 32%) as a yellow solid; mp 143-144 °C; (Found: C, 61.0; H, 3.5; N, 13.4 $C_{16}H_{11}F_2N_3S$ requires: C, 60.9; H, 3.5; N, 13.3%); δ_H 6.92 (1H, NH), 7.35 (1H, m, Ar-H), 7.45 (5H, m, Ar-H), 7.62 (4H, m, Ar-H); δ_c 121.0 (s, Ar-CH), 125.0 (s, Ar-CH), 126.6 (s, CSC), 129.5 (s, Ar-CH), 129.6 (s, Ar-CH), 130.0 (s, Ar-CH), 135.7 (s, Ar-CH), 137.2 (s, CNC), 138.5 (dd, $^1J_{CF}$ 248, $^4J_{CF}$ 9, C-5), 150.8 (dd, $^2J_{CF}$ 20, $^3J_{CF}$ 11, C-6), 154.2 (m, 6-CNH), 155.4 (dd, $^1J_{CF}$ 210, $^4J_{CF}$ 8, C-2); δ_F -47.3 (1F, d, $^5J_{FF}$ 29, C-2), -157.1 (1F, d, $^5J_{FF}$ 26, C-5); *m/z* (ES^+) 316 ([M+ H]$^+$, 100%)

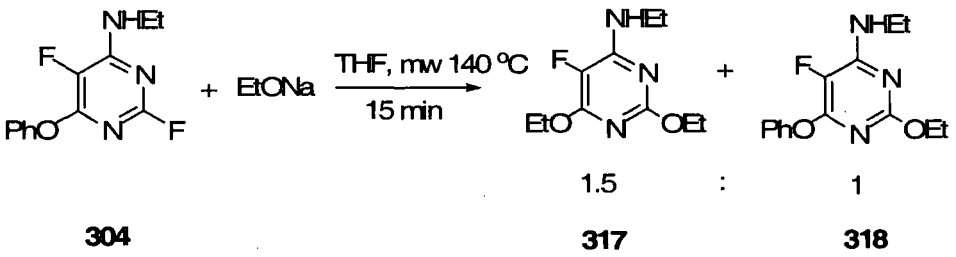
2,5-Difluoro-*N*-(phenylmethyl)-6-(1-piperidinyl)-4-pyrimidinamine, 303



293 303

A solution of *N,N*-diethyl-2,5,6-trifluoropyrimidin-4-amine, **293** (100 mg, 0.49 mmol), piperidine (36 mg, 0.42 mmol) and DIPEA (0.333 ml, 1.47 mmol) in THF (10 cm^3) was stirred at room temperature for 19 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing 2,5-difluoro-*N*-(phenylmethyl)-6-(1-piperidinyl)-4-pyrimidinamine and 5,6-difluoro-*N*-(phenylmethyl)-2-(1-piperidinyl)-2-pyrimidinamine in a 1:1 ratio (65 mg). Mass-directed auto-preparation HPLC purification gave *5,6-difluoro-N-(phenylmethyl)-2-(1-piperidinyl)-4-pyrimidinamine*, **303** (46 mg, 36%) as a red solid; mp 133-135 °C; δ_H 1.56 (6H, m, CH_2), 3.64 (4H, m, CH), 4.66 (2H, d, $^3J_{HH}$ 6, CH_2), 5.08 (1H, m, NH), 7.34 (5H, m, Ar-H); δ_c 24.7 (s, CH_2), 28.3 (s, CH_2), 47.3 (d, $^4J_{CF}$ 7, CH_2), 47.6 (d, $^4J_{CF}$ 7, CH_2), 128.3 (dd, $^1J_{CF}$ 240, $^4J_{CF}$ 8, C-5), 126.8 (s, Ar-CH), 127.4 (s, Ar-CH), 129.3 (s, Ar-CH), 140.1 (s, NNC), 143.1 (m, C-4), 144.2 (m, C-2), 153.8 (dd, $^1J_{CF}$ 203, $^4J_{CF}$ 2, C-6); δ_F -50.1 (1F, s, C-2), -194.3 (1F, s, C-5); *m/z* (ES^+) 305 ($[M+H]^+$, 100%). Crystals suitable for x-ray analysis were grown from MeOH.

2,6-Diethoxy-*N*-ethyl-5-fluoropyrimidin-4-amine, 317 and 2-ethoxy-*N*-ethyl-5-fluoro-6-phenoxypyrimidin-4-amine, 318



304 **317** **318**

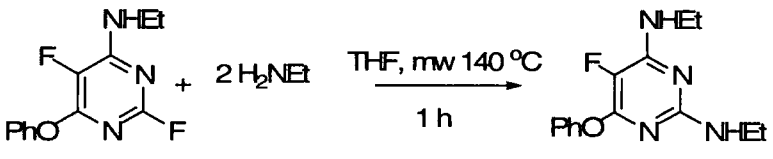
A solution of *N*-ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine, **304** (1.01 g, 4.1 mmol), and sodium ethoxide (0.59 g, 8.7 mmol) in THF (50 cm^3) was stirred in a microwave at 140 °C for 15 min after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (1.56 g) and this was passed through a silica plug to yield a crude white solid containing 2,6-diethoxy-*N*-ethyl-5-fluoropyrimidin-4-amine and 2-ethoxy-*N*-ethyl-5-fluoro-6-phenoxypyrimidin-4-amine in a 1.5:1 ratio. Chromatography was performed using a reverse phase column with a gradient running from 5%:95% MeCN:H_2O (0.1% formic acid in both) to 85%:15% to yield;

(i) *2,6-diethoxy-N-ethyl-5-fluoropyrimidin-4-amine*, **317** (0.15 g, 16%) as a white solid; mp 58-60 °C; (Found: C, 52.3; H, 7.0; N, 18.3 $C_{12}H_{16}FN_3O_2$ requires: C, 52.4; H, 7.0; N, 18.3%); δ_H 1.27 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.38 (6H, t, $^3J_{HH}$ 7.2, CH_3), 3.49 (2H, q, $^3J_{HH}$ 6, CH_2), 3.49 (4H, m, CH_2); δ_c 14.8 (s, CH_3), 14.9 (s, CH_3), 15.5 (s, CH_3), 36.1 (s, CH_2), 62.8 (s, CH_2), 63.4 (s, CH_2), 127.3 (d, $^1J_{CF}$ 237, C-5), 153.7 (d, $^2J_{CF}$ 10, C-4), 156.2 (d, $^2J_{CF}$ 9, C-6), 158.6 (d, $^4J_{CF}$ 4, C-2); δ_F -191.2 (1F, s, C-5); *m/z* (EI^+) 229 ([M^+], 40%), 214(44), 201(42). Crystals suitable for x-ray analysis were grown from MeOH.

(ii) *2-ethoxy-N-ethyl-5-fluoro-6-phenoxypyrimidin-4-amine*, **318** (0.14 g, 13%) as a white solid; mp 109-110 °C; (Found: C, 60.39; H, 5.80; N, 15.15 $C_{14}H_{16}FN_3O_2$ requires: C, 60.64; H, 5.82; N, 15.15%); δ_H 1.25 (3H, m, CH_3), 1.29 (6H, m CH_3), 3.55 (2H, q, $^3J_{HH}$ 6, CH_2),

4.13 (4H, m, CH_2), 7.32 (5H, m, Ar-CH); δ_c 14.6 (s, CH_3), 15.3 (s, CH_3), 36.2 (s, CH_2), 63.6 (s, CH_2), 121.2 (s, *C*H), 125.0 (s, *C*H), 127.7 (d, $^1J_{CF}$ 241, C-5), 129.5 (s, *C*H), 153.20 (s, *C*O), 154.7 (d, $^2J_{CF}$ 9, C-4), 154.8 (d, $^2J_{CF}$ 10, C-6), 158.7 (d, $^4J_{CF}$ 4, C-2); δ_F -185.2 (1F, s, C-5); *m/z* (EI^+) 277 ([M^+], 20%), 262(8), 234(10). Crystals suitable for x-ray analysis were grown from MeOH.

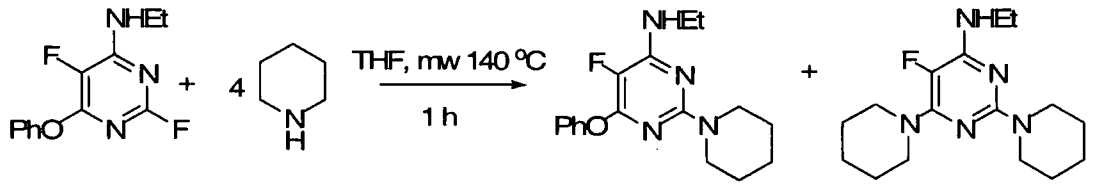
N^2-Butyl-N^4-ethyl-5-fluoro-6-phenoxypyrimidine-2,4-diamine, 316



304 **316**

A solution of *N*-ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine, **304** (1.02 g, 4.1 mmol), and ethylamine (0.34 g, 8.2 mmol) in THF (50 cm^3) was stirred in a microwave at 140 °C for 1 h after which time ^{19}F NMR indicated 100% conversion with the formation of. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude brown solid (1.12 g). Recrystallisation from *n*-hexane yielded *N^2,N^4-diethyl-5-fluoro-6-phenoxypyrimidine-2,4-diamine*, **316** (0.91 g, 63%) as a light brown solid; mp 88-89 °C; (Found: C, 60.7; H, 6.2; N, 20.3 $C_{14}H_{17}FN_4O$ requires: C, 60.9; H, 6.2; N, 20.3%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.38 (2H, m, CH_2), 3.44 (2H, m, CH), 4.56 (1H, s, NH), 7.07 (3H, m, CH), 7.26 (2H, m, CH); δ_c 15.2 (s, CH_3), 15.4 (s, CH_3), 36.0 (s, CH_2), 36.8 (s, CH_2), 121.0 (s, CH), 124.6 (s, CH), 125.4 (d, $^1J_{CF}$ 237, C-5), 129.3 (s, CH), 153.8 (s, COC), 154.2 (d, $^2J_{CF}$ 10, C-4), 154.5 (d, $^2J_{CF}$ 8, C-6), 156.8 (d, $^4J_{CF}$ 6, C-2); δ_F -189.8 (1F, s, C-5); *m/z* (EI^+) 276 ([$M]^+$, 100%), 234(70). Crystals suitable for x-ray analysis were grown from MeOH.

_N_-Ethyl-5-fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-amine, 315

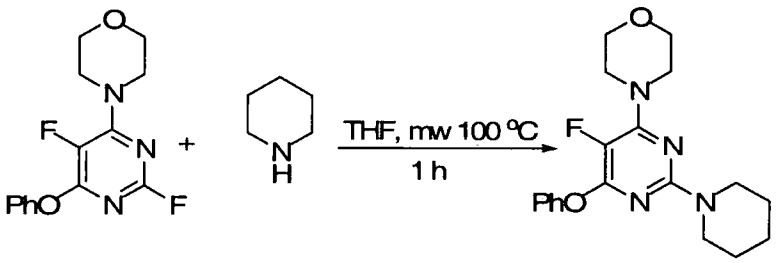


6 : 1

304 **315**

A solution of *N*-ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine, **304** (1.01 g, 4.1 mmol), and piperidine (1.37 g, 16.0 mmol) in THF (50 cm^3) was stirred in a microwave at 140 °C for 15 min after which time ^{19}F NMR indicated 100% conversion with the formation of *N*-ethyl-5-fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-amine and *N*-ethyl-5-fluoro-2,6-di(piperidin-1-yl)pyrimidin-4-amine in a 6:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude yellow solid (1.56 g). Column chromatography (silica, ethyl acetate:*n*-hexane, 1:15) yielded *N-ethyl-5-fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-amine*, **315** (0.92 g, 73%) as a yellow solid; mp 78-80 °C; (Found: C, 64.5; H, 6.6; N, 17.4 $C_{17}H_{21}FN_4O$ requires: C, 64.5; H, 6.7; N, 17.7%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.38 (2H, m, CH_2), 3.44 (2H, m, CH), 4.56 (1H, s, NH), 7.07 (3H, m, Ar-H), 7.26 (2H, m, Ar-H); δ_c 15.4 (s, CH_3), 25.0 (s, CH_2), 25.8 (s, CH_2), 36.0 (s, CH_2), 45.3 (s, CH_2), 120.9 (s, Ar-CH), 124.3 (s, Ar-CH), 125.4 (d, $^1J_{CF}$ 238, C-5), 129.2 (s, Ar-CH), 153.9 (s, COC), 153.9 (d, $^2J_{CF}$ 10, C-4), 154.1 (d, $^2J_{CF}$ 8, C-6), 156.1 (d, $^4J_{CF}$ 4, C-2); δ_F -190.7 (1F, s, C-5); *m/z* (ES^+) 317 ([M+H]$^+$, 100%)

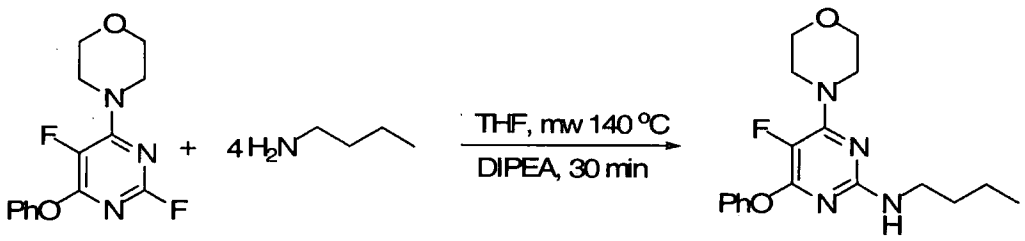
4-(5-Fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-yl)morpholine, 320



306 320

A solution of 2,5-difluoro-4-morpholino-6-phenoxypyrimidine, **306** (1.00 g, 3.4 mmol), and piperidine (0.29 g, 3.4 mmol) in THF (15 cm^3) was stirred in a microwave at 100 °C for 1 h after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude yellow solid (1.45 g). Recrystallisation from *n*-hexane yielded *4-(5-fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-yl)morpholine*, **320** (1.10 g, 90%) as a white solid; mp 128-130 °C; (Found: C, 64.0; H, 6.6; N, 15.4 $C_{19}H_{23}FN_4O_2$ requires: C, 63.7; H, 6.5; N, 15.6%); δ_H 1.49 (6H, m, CH_2), 3.44 (4H, m, CH_2), 3.70 (4H, m, CH), 3.79 (4H, m, CH), 7.16 (3H, m, CH), 7.23 (2H, m, CH); δ_c 24.4 (s, CH_2), 24.8 (s, CH_2), 44.3 (s, CH_2), 46.5 (s, CH_2), 66.5 (s, CH_2), 120.4 (s, Ar-CH), 124.0 (s, Ar-CH), 126.5 (d, $^1J_{CF}$ 243, C-5), 129.8 (s, Ar-CH), 153.2 (s, 4-CN), 153.6 (s, COC), 156.0 (m, 2-CN), 158.1 (m, 6-CO); δ_F -180.0 (1F, s, C-5); *m/z* (ES^+) 359 ($[M+ H]^+$, 100%). Crystals suitable for x-ray analysis were grown from MeOH.

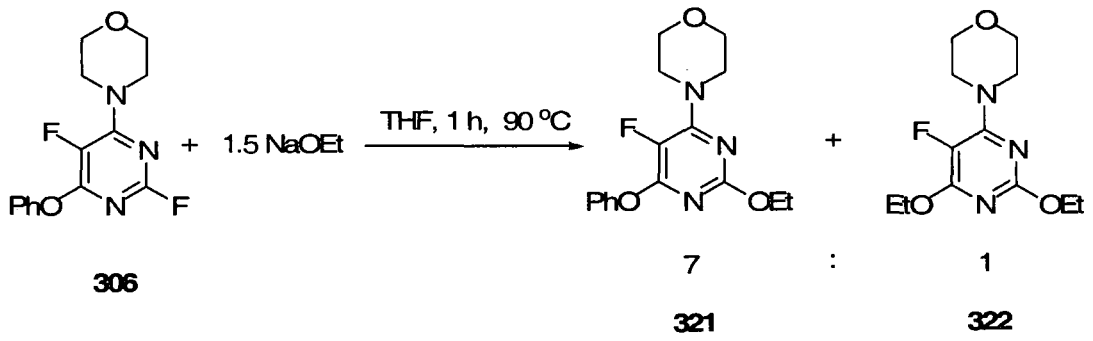
_N_-Butyl-5-fluoro-4-morpholino-6-phenoxypyrimidin-2-amine, 319



306 **319**

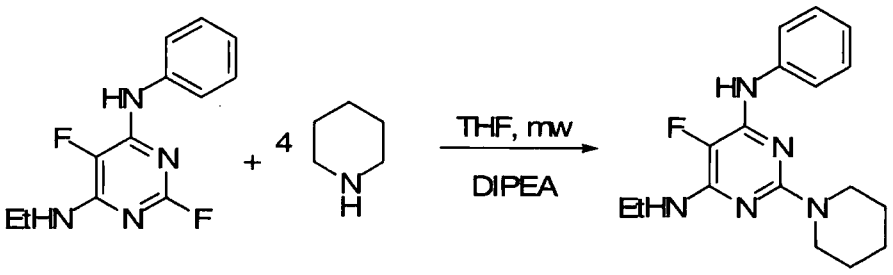
A solution of 2,5-difluoro-4-morpholino-6-phenoxypyrimidine, **306** (1.00 g, 3.4 mmol), and butylamine (0.99 g, 13.6 mmol) in THF (15 cm^3) was stirred in a microwave at 140 °C for 30 min after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude white solid (1.46 g). Recrystallisation from *n*-hexane yielded *N-butyl-5-fluoro-4-morpholino-6-phenoxypyrimidin-2-amine*, **319** (0.59 g, 50%) as a white solid; mp 126-127 °C; (Found: C, 62.4; H, 6.7; N, 16.1 $C_{18}H_{23}FN_4O_2$ requires: C, 62.4; H, 6.7; N, 16.2%); δ_H 0.89 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.28 (2H, m, CH_2), 1.44 (2H, m, CH_2), 3.16 (2H, m, CH_2), 3.71 (4H, m, CH_2), 3.79 (4H, m, CH_2), 4.76 (1H, NH), 7.13 (3H, m, CH_2), 7.35 (2H, m, CH_2); δ_c 14.1 (s, CH_3), 20.3 (s, CH_2), 32.0 (s, CH_2), 41.7 (s, CH_2), 46.9 (d, $^4J_{CF}$ 7.3, CH_2), 67.1 (s, CH_2), 121.4 (s, Ar-CH), 124.8 (s, Ar-CH), 127.5 (d, $^1J_{CF}$ 240, C-5), 129.4 (s, Ar-CH), 152.8 (s, 4-CN), 153.3 (s, COC), 154.2 (m, 2-CN), 158.4 (m, 6-CO); δ_F -179.4 (1F, s, C-5); *m/z* (ES^+) 347.2 ($[M+ H]^+$, 100%). Crystals suitable for X-ray analysis were grown from MeOH.

4-(2-Ethoxy-5-fluoro-6-phenoxypyrimidin-4-yl)morpholine, 321



A solution of 2,5-difluoro-4-morpholino-6-phenoxypyrimidine, **306** (0.50 g, 1.7 mmol), and sodium ethoxide (0.17 g, 2.55 mmol) in THF (50 cm^3) was stirred in a microwave at 90 °C for 1 h after which time ^{19}F NMR indicated 67% conversion with the formation of *4-(2-ethoxy-5-fluoro-6-phenoxypyrimidin-4-yl)morpholine* and *4-(2,6-diethoxy-5-fluoropyrimidin-4-yl)morpholine* in a 7:1 ratio. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude cream solid (0.68g). Column chromatography (silica, *n*-hexane: Ethyl acetate, 12:1) of the solid was performed and the solid recrystallised from *n*-hexane yielded *4-(2-ethoxy-5-fluoro-6-phenoxypyrimidin-4-yl)morpholine*, **321** (0.14 g, 26%) as a white solid; mp 87-88 °C; (Found: C, 59.96; H, 5.73; N, 13.36 $C_{16}H_{18}FN_3O_3$ requires: C, 60.18; H, 5.68; F, 5.95; N, 13.16; O, 15.03%); δ_H 1.23 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.79 (8H, m, CH_2), 4.15 (2H, q, $^3J_{HH}$ 7.2, CH_2), 7.18 (2H, m, Ar-H), 7.19 (1H, m, Ar-H), 7.39 (2H, m, Ar-H); δ_c 14.1 (s, CH_3), 46.6 (s, CH_2), 63.4 (s, CH_2), 66.7 (s, CH_2), 120.4 (s, Ar-CH), 125.8 (s, Ar-CH), 129.5 (d, $^1J_{CF}$ 244, C-5), 129.8 (s, Ar-CH), 153.1 (s, 4-CN), 153.5 (s, COC), 157.8 (m, 2-CN), 158.2 (m, 6-CO); δ_F -175.0 (1F, s, C-5); *m/z* (EI^+) 319 ($[M]^+$, 90%), 234(100)

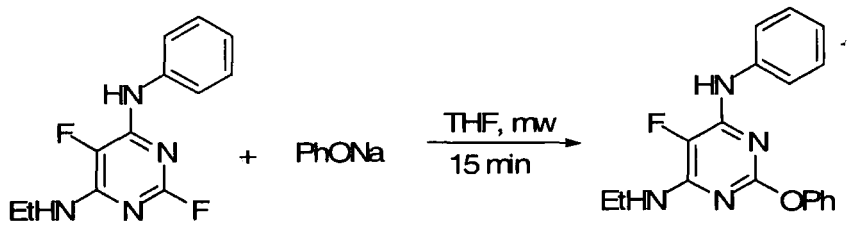
***N*-Ethyl-5-fluoro-*N'*-phenyl-2-piperidin-1-ylpyrimidine-4,6-diamine**



300 **328**

A solution of N^4-ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine, **300** (1.03 g, 4.0 mmol), piperidine (1.40 g, 16.1 mmol) and DIPEA resin (3.0 g (4 mmol per g), 12 mmol) in THF (15 cm^3) was stirred in a microwave at 140 °C for 15 min after which time ^{19}F NMR indicated 90% conversion. The solution was filtered to remove the resin and the reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude orange solid (1.59 g). Recrystallisation from *n*-hexane:DCM yielded *N-ethyl-5-fluoro-N'-phenyl-2-piperidin-1-ylpyrimidine-4,6-diamine*, **328** (1.86 g, 56%) as a peach solid; mp 131-132 °C; (Found: C, 64.6; H, 7.0; N, 22.1 $C_{17}H_{22}FN_5$ requires: C, 64.7; H, 7.0; N, 22.2%); δ_H 1.25 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.60 (6H, m, CH_2), 3.47 (2H, m, CH_2), 3.68 (4H, m, CH_2), 4.23 (1H, s, NH), 6.16 (1H, s, NH), 6.96 (1H, m, Ar-H), 7.29 (1H, m, Ar-H); δ_c 15.7 (s, CH_3), 25.2 (s, CH_2), 26.0 (s, CH_2), 35.8 (s, CH_2), 45.3 (s, CH_2), 45.7 (s, CH_2), 119.4 (s, Ar-CH), 122.0 (s, Ar-CH), 127.5 (d, $^1J_{CF}$ 223, C-5), 129.0 (s, Ar-CH), 140.2 (s, 4-CNC), 147.0 (d, $^2J_{CF}$ 7, C-4), 151.1 (d, $^2J_{CF}$ 8, C-6), 156.8 (d, $^4J_{CF}$ 4, C-2); δ_F -191.96 (1F, s, C-5); *m/z* (ES^+) 316 ($[M+ H]^+$, 100%)

***N*-Ethyl-5-fluoro-2-phenoxy-*N'*-phenylpyrimidine-4,6-diamine, 329**



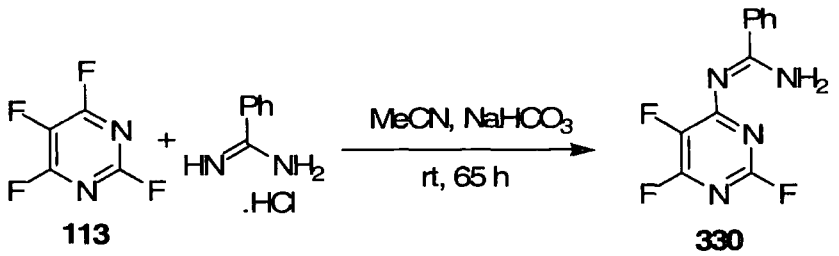
300 **329**

A solution of N^4-ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine, **300** (1.01 g, 4.0 mmol), and sodium phenoxide (0.46 g, 4.1 mmol) in THF (15 cm^3) was stirred in a microwave at 140 °C for 15 min after which time ^{19}F NMR indicated 100% conversion with the formation of *N*-ethyl-5-fluoro-2-phenoxy-*N'*-phenylpyrimidine-4,6-diamine. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing *N-ethyl-5-fluoro-2-phenoxy-N'-phenylpyrimidine-4,6-diamine* as a white solid (1.59 g). Recrystallisation from *n*-hexane:DCM yielded *N-ethyl-5-fluoro-2-phenoxy-N'-phenylpyrimidine-4,6-diamine*, **329** (1.06 g, 79%) as a white solid; mp 124-112 °C; (Found: C, 66.7; H, 5.3; N, 17.4 $C_{18}H_{17}FN_4O$ requires: C, 66.7; H, 5.3; N, 17.3%); δ_H 1.22 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.58 (2H, m, CH_2), 4.76 (1H, NH), 6.42 (1H, NH), 6.98 (2H, m, CH), 7.19 (2H, m, CH), 7.23 (4H, m, CH), 4.41 (2H, m, CH); δ_c 15.5 (s, CH_3), 36.1 (s, CH_2), 119.2 (s, CH), 122.6 (s, CH), 122.7 (s, CH), 125.0 (s, CH), 127.4 (d, $^1J_{CF}$ 235, C-5), 129.4 (s, CH), 139.2 (s, 4-CNC), 147.3 (d, $^2J_{CF}$ 8, C-4), 152.3 (d, $^2J_{CF}$ 10, C-6), 153.9 (s, 2-COC), 156.8 (d, $^4J_{CF}$ 4, C-2); δ_F -186.3 (1F, s, C-5); *m/z* (ES^+) 325 ($[M+ H]^+$, 100%)

Chapter 8

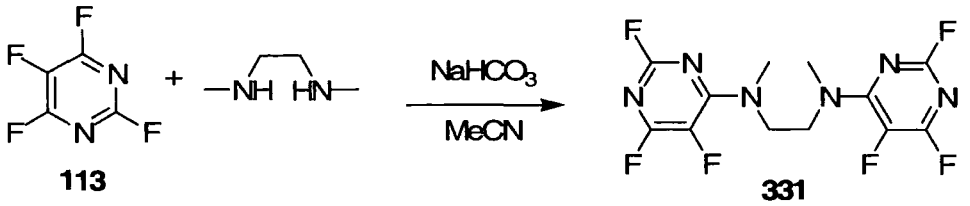
Experimental to Chapter 4

_N_-(2,4,6-Trifluoropyrimidine-4-yl)benzamidine, 330



A solution of tetrafluoropyrimidine, **113** (0.50 g, 3.3 mmol), benzamidine hydrochloride (0.52 g, 3.3 mmol) and sodium bicarbonate (1.10 g, 13.2 mmol) in acetonitrile (200 cm^3) was stirred at room temperature for 65 h after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude white solid (0.46 g). Recrystallisation from acetonitrile yielded *N-(2,4,6-trifluoropyrimidine-4-yl)benzamidine*, **330** (0.41 g, 50%) as a colourless solid; mp 151-153 °C; (Found: C, 52.3; H, 2.8; N, 22.2 $C_{11}H_7F_3N_4$ requires: C, 52.4; H, 2.8; N, 22.2%); δ_H 7.54 (2H, m, Ar-CH), 7.60 (1H, m, Ar-CH), 8.03 (2H, m, Ar-CH); δ_c 128.6 (s, Ar-C), 129.2 (s, Ar-C), 132.7 (s, Ar-C), 134.5 (s, Ar-C), 135.3 (dd, $^2J_{CF}$ 9.6, $^3J_{CF}$ 10.6, C-5), 148.3 (ddd, $^1J_{CF}$ 188, $^2J_{CF}$ 17.2, $^3J_{CF}$ 4.5, C-6), 159.5 (ddd, $^1J_{CF}$ 211.2, $^3J_{CF}$ 14.5, $^4J_{CF}$ 4.9, C-2), 162.3 (m, C-4), 162.2 (s, Ar-C); δ_F –48.6 (1F, s, C-6), -84.6 (1F, s, C-5), -166.7 (1F, m, C-2); *m/z* (EI^+) 268 ($[M]^+$, 12%), 233 (36).

N,N'-dimethyl-N,N'-bis(2,5,6-trifluoropyrimidin-4-yl)ethane-1,2-diamine, 331

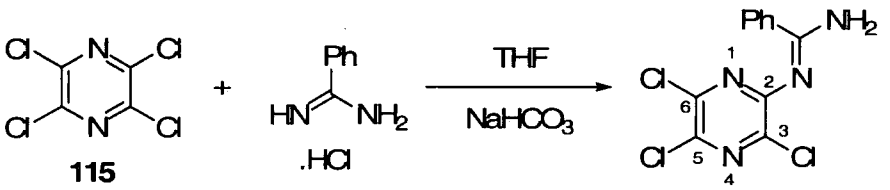


A solution of tetrafluoropyrimidine, **113** (2.05 g, 13 mmol), *N,N'*-dimethyl-ethylene-1,2-diamine (1.16 g, 13 mmol) and sodium hydrogen carbonate (4.40 g, 52 mmol) in acetonitrile (300 cm^3) was stirred at reflux for 127 h after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude colourless solid (3.29 g). Recrystallisation from ethyl acetate gave *N,N'-dimethyl-N,N'-bis(2,5,6-trifluoropyrimidin-4-yl)ethane-1,2-diamine*, **331** (2.16 g, 45%) as a colourless solid; mp 100-102 °C; (Found: C, 40.7; H, 2.8; N, 23.7 $C_{12}H_{10}F_6N_6$ requires: C, 40.9; H, 2.9; N, 23.9%); δ_H 3.24 (3H, s, CH_3), 3.87 (2H, s, CH_2); δ_c 38.6 (s, CH_3), 49.7 (s, CH_2), 130.7 (ddd, $^1J_{CF}$ 234, $^2J_{CF}$ 15, $^4J_{CF}$ 9, C-5), 154.7 (ddd, $^1J_{CF}$ 187, $^2J_{CF}$ 21, $^3J_{CF}$ 3, C-2), 155.6 (dt, $^2J_{CF}$ 19, $^3J_{CF}$ 5, C-4), 160.1 (ddd, $^1J_{CF}$ 241, $^2J_{CF}$ 21, $^3J_{CF}$ 9, C-6); δ_F –48.8 (1F, d, $^4J_{FF}$ 25, C-2), -87.7 (1F, d, $^3J_{FF}$ 16, C-6), -174.2 (1F, s, C-5); *m/z* (ES^+) 353 ($[M+H]^+$, 100%)

Chapter 9

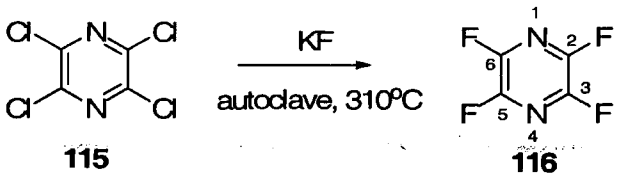
Experimental to Chapter 5

N-(3,5,6-Trichloro-pyrazin-2-yl)-benzamidine, 344



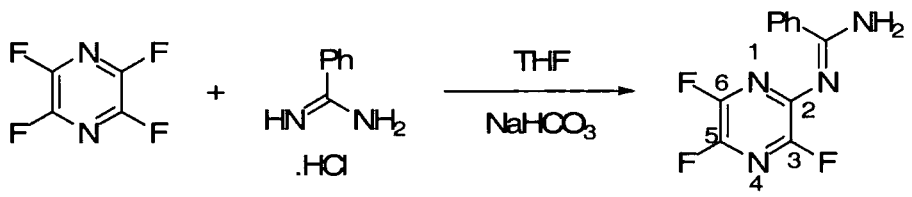
A solution of tetrachloropyrazine, **115** (1.06 g, 4.5 mmol), benzamidine hydrochloride (0.72 g, 4.5 mmol) and sodium carbonate (1.54 g, 18 mmol) in acetonitrile (300 cm^3) was stirred at reflux for 99 h after which time TLC indicated 100% conversion form the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N*-(3,5,6-Trichloro-pyrazin-2-yl)-benzamidine as a yellow solid. Recrystallisation from acetonitrile yielded *N-(3,5,6-Trichloro-pyrazin-2-yl)-benzamidine*, **344** (1.12 g, 76%) as a yellow solid; mp 199-201 °C; (Found: C, 43.8; H, 2.3; N, 18.4, $C_{11}H_7Cl_3N_4$ requires: C, 43.8; H, 2.3; N, 18.6%); δ_H 7.57 (4H, m, Ar-H), 8.07 (1H, m, Ar-H); δ_c 128.4 (s, Ar-CH), 129.1 (s, Ar-CH), 132.4 (s, Ar-CH), 133.69 (s, CCN), 135.04 (s, C-3), 140.31 (s, C-5), 141.47 (s, C-6), 154.27 (s, CN), 160.26 (C-2) *m/z* (ES^+) 301 ($[M + H]^+$, 100%)

2,3,5,6-Tetrafluoropyrazine, 116



A stainless steel, oven dried 0.5 dm^3 autoclave was charged with flame-dried potassium fluoride (125 g, 4 mol) and tetrachloropyrazine, **115** (50 g, 0.6 mol). The autoclave was sealed and heated to 310 °C for 19 h after which time the reaction mixture was allowed to cool to 200 °C. The gaseous tetrafluoropyrazine, **116** was removed under reduced pressure and condensed in a Young's tap-equipped vessel. Analysis as outlined by Chambers et al. [1]

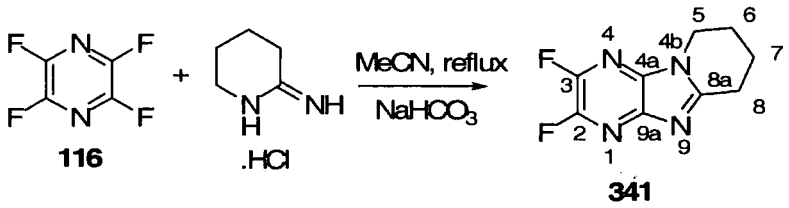
_N_-(3,5,6-Trifluoro-pyrazin-2-yl)-benzamidine, 342



116 **342**

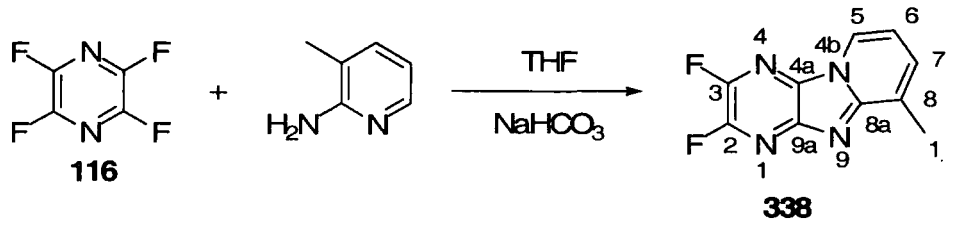
A solution of tetrafluoropyrazine, **116** (1.00 g, 6.6 mmol), benzamidine hydrochloride (1.24 g, 6.6 mmol) and sodium hydrogen carbonate (2.21 g, 26 mmol) in acetonitrile (300 cm^3) was stirred at reflux for 101 h after which time ^{19}F NMR indicated 82% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3) and HCl (5 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N*-(3,5,6-trifluoro-pyrazin-2-yl)-benzamidine (1.87 g) as an yellow solid. Recrystallisation from ethyl acetate yielded *N-(3,5,6-trifluoro-pyrazin-2-yl)-benzamidine*, **342** (1.09 g, 67%) as an yellow solid; mp 121-123 °C; (Found: $[M+H]^+$ 253.0698 $C_{11}H_7F_3N_4$ requires: $[M+H]^+$ 253.0696); δ_H 7.45 (3H, m, Ar-H), 7.91 (2H, m, Ar-H); δ_c 128.3 (s, Ar-CH), 129.1 (s, Ar-CH), 132.2 (s, Ar-CH), 135.3 (s, Ar-CH), 136.6 (dm, $^1J_{CF}$ 191, C-6), 140.4 (dm, $^1J_{CF}$ 175, C-5), 142.3 (m, C-3), 147.1 (dm, $^1J_{CF}$ 205, C-2), 160.4 (s, C=N); δ_F -87.29 (1F, dd, $^1J_{FF}$ 54, $^3J_{FF}$ 17, C-2), -97.78 (1F, dd, $^1J_{FF}$ 39, $^3J_{FF}$ 31, C-3), -105.02 (1F, dd, $^1J_{FF}$ 18, $^3J_{FF}$ 13, C-5); *m/z* (EI^+) 252 ($[M]^+$, 12%), 233(16), 216(2),

2,3-Difluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine, 341



A solution of tetrafluoropyrazine, **116** (1.02 g, 6.7 mmol), 2-iminopiperidine hydrochloride (1.33 g, 9.9 mmol) and sodium hydrogen carbonate (3.31 g, 40 mmol) in acetonitrile (300 cm^3) was stirred at reflux for 105 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 2,3-difluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine (1.82 g) as an yellow solid. Recrystallisation from DCM gave *2,3-difluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-b]pyrazine*, **341** (1.12 g, 79%) as an yellow solid; mp 144-146 °C; (Found: $[M+ H]^+$ 211.0792 $C_9H_8F_2N_4$ requires: $[M+ H]^+$ 211.0790); δ_H 1.97 (2H, m, CH_2), 2.05 (2H, s, CH_2), 3.06 (2H , t, $^3J_{HH}$ 6.4, CH_2), 4.13 (2H , t, $^3J_{HH}$ 6, CH_2); δ_c 19.9 (s, CH_2), 21.9 (s, CH_2), 26.1 (s, CH_2), 42.5 (s, CH_2), 134.2 (d, $^3J_{CF}$ 10, C-9a), 140.3 (dd, $^1J_{CF}$ 210, $^2J_{CF}$ 33.1, C-2), 141.9 (dd, $^1J_{CF}$ 210, $^2J_{CF}$ 33.1, C-3), 142.1 (dd, $^3J_{CF}$ 12, $^4J_{CF}$ 4, C-4a), 154.7 (dd, $^1J_{CF}$ 207, $^2J_{CF}$ 31, C-8a); δ_F -98.41 (1F, dd, $^3J_{FF}$ 25, C-2), -100.38 (1F, dd, $^3J_{FF}$ 27, C-3); *m/z* (EI^+) 210 ($[M]^+$, 100%), 182(68), 155(30)

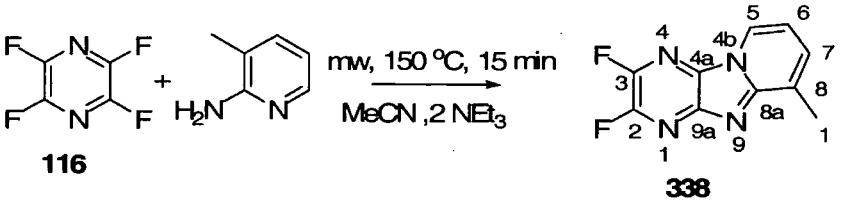
2,3-Difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine, 338



338

A solution of tetrafluoropyrazine, **116** (1.50 g, 10 mmol), 2-amino-3-picoline (1.57 g, 15 mmol) and sodium carbonate (3.32 g, 39 mmol) in THF (300 cm^3) was stirred at room temperature for 19 h after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 2,3-difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine (3.21 g). Recrystallisation from ethylacetate yielded *2,3-difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine*, **338** (1.04 g, 30%) as brown solid; mp 213-215 °C; (Found: C, 54.4, H, 2.7, N, 25.5 $C_{10}H_6F_2N_4$ requires: C, 54.6, H, 2.8, N, 25.5%); δ_H (d^6-DMSO) 2.57 (3H, s, CH_3), 7.15 (1H, m, Ar-H), 7.61 (1H, m, Ar-H), 8.74 (1H, m, Ar-H); δ_c (d^6-DMSO) 18.5 (s, CH_3), 117.9 (s, C-8), 122.0 (s, Ar-CH), 129.0 (s, Ar-CH), 129.1 (m, C-4a), 132.1 (s, Ar-CH), 140.2 (dd, $^1J_{CF}$ 377, $^2J_{CF}$ 35, C-3), 143.9 (m, C-9a), 144.1 (dd, $^1J_{CF}$ 374, $^2J_{CF}$ 31, C-2), 151. 3 (s, C-8a); δ_F (d^6-DMSO) -89.52 (1F, d, $^3J_{FF}$ 27, C-2), -98.62 (1F, d, $^3J_{FF}$ 27, C-3); *m/z* (EI^+) 220 ([M] $^+$, 100%), 192(6), 167(2)

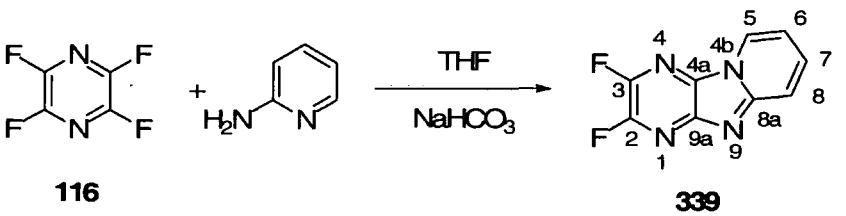
2,3-Difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine, 338



116 **338**

A solution of tetrafluoropyrazine, **116** (100 mg, 0.66 mmol), 2-amino-3-picoline (70 mg, 0.66 mmol) and diethylamine (180 mg, 1.38 mmol) in acetonitrile (1 cm^3) was stirred in a microwave for 5 min at 150 °C after which time ^{19}F NMR indicated 87% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 2,3-difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine (130 mg). Recrystallisation from ethyl acetate yielded *2,3-difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine* as brown solid (90 mg, 56%). Analysis data is as found previously.

2,3-Difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine, 339

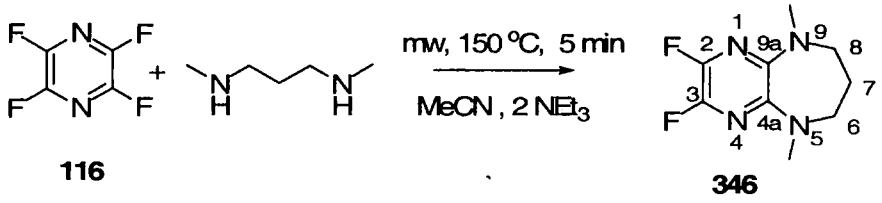


116 **339**

A solution of tetrafluoropyrazine, **116** (0.50 g, 3.3 mmol), 2-amino-pyridine (0.93 g, 10 mmol) and sodium carbonate (3.32 g, 39 mmol) in THF (20 cm^3) was stirred was stirred in a microwave for 5 min at 150 °C after which time ^{19}F NMR indicated 87% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The

mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 2,3-difluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine (1.21 g). Recrystallisation from methanol yielded *2,3-difluoropyrido[1',2':1,2]imidazo[4,5-b]pyrazine*, **339** (0.22 g, 32%) as brown solid; mp 217-219 °C; ([M + H]$^+$ 214.1022 $C_9H_4F_2N_4$ requires; [M + H]$^+$ 214.1025); δ_H 6.93 (1H, m, Ar-H), 7.11 (1H, m, Ar-H), 7.53 (1H, m, Ar-H), 8.31 (1H, m, Ar-H); δ_c 111.8 (s, Ar-CH), 116.0 (s, Ar-CH), 119.3 (s, Ar-CH), 127.9 (s, Ar-CH), 128.0 (d, $^3J_{CF}$ 9, C-3), 131.5 (s, CH_2), 145.2 (dd, $^1J_{CF}$ 377, $^2J_{CF}$ 35, C-5), 143.9 (dd, $^1J_{CF}$ 374, $^2J_{CF}$ 31, C-6); δ_F - 89.67 (1F, d, $^3J_{FF}$ 27, 2-C*F*), -96.72 (1F, d, $^3J_{FF}$ 27, 3-C*F*); *m/z* (EI) 207 (M$^+$, 100%), 192(6), 167(2)

2,3-Difluoro-6,7,8,9-tetrahydro-5,9-dimethyl-5H-pyrazino[2,3-*b*][1,4]diazepine, 346

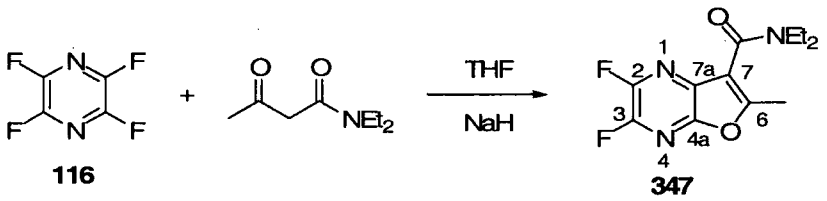


116 **346**

A solution of tetrafluoropyrazine, **116** (1.00 g, 6.6mmol), N^1,N^2-dimethylethane-1,2-diamine (0.58 g, 6.6mmol) and diethylamine (1.80 g, 13 mmol) in acetonitrile (10 cm^3) was stirred in a microwave for 5 min at 150 °C after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing 2,3-difluoro-6,7,8,9-tetrahydro-5,9-dimethyl-5H-pyrazino[2,3-*b*][1,4]diazepine (1.14 g). The sample was then dissolved into ethyl acetate and passed through a silica plug to yield *2,3-difluoro-6,7,8,9-tetrahydro-5,9-dimethyl-5H-pyrazino[2,3-b][1,4]diazepine*, **346** (1.09 g, 67%) as an brown solid; mp 18-19 °C; (Found: [M+ H]$^+$ 214.1022 $C_9H_{12}F_2N_4$ requires: [M+ H]$^+$ 214.1025); δ_H 1.89 (2H, q, $^3J_{HH}$ 6, CH_2), 2.86 (6H, s, CH_3), 3.38 (4H, t, $^3J_{HH}$ 6.2, CH_2); δ_c 25.8 (s, CH_2), 40.2 (s, CH_2), 51.4 (s, CH_2), 138.6 (dd, $^1J_{CF}$ 202, $^2J_{CF}$ 34, C-2 and C-

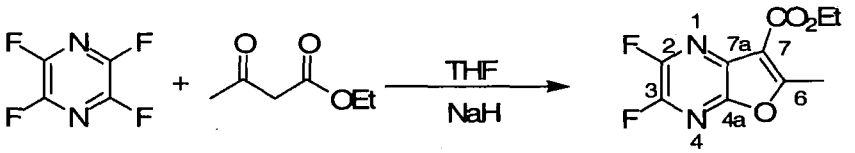
3), 143.1 (m, C-4a and C-9a); δ_F -115.73 (2F, s, C-2); *m/z* (EI^+) 213.9 ($[M]^+$, 82%), 185(100), 171(26)

_N,N_-Diethyl-2,3-difluoro-7-methylfuro[2,3-b]pyrazine-6-carboxamide, 347



N,N'-diethylacetoacetamide (4.40 g, 30 mmol) and sodium hydride (60% in mineral oil, 1.31 g, 30 mmol) was added to tetrahydrofuran (400 cm^3) and stirred at room temperature for 2 h before the addition of 2,3,5,6-tetrafluoropyrazine, **116** (2.07 g, 14 mmol). The reaction mixture was then stirred at reflux for 23 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N,N*-diethyl-2,3-difluoro-7-methylfuro[2,3-b]pyrazine-6-carboxamide (5.43 g). Column chromatography (silica, ethylacetate:*n*-hexane, 1:4) gave *N,N-diethyl-2,3-difluoro-7-methylfuro[2,3-b]pyrazine-6-carboxamide*, **347** (2.04 g, 60%) as yellow crystals; mp 73-75 °C; (Found: C, 53.7; H, 4.9; N, 15.4 $C_{12}H_{13}F_2N_3O_2$ requires: C, 53.5; H, 4.9; N, 15.6%); δ_H 1.04 (3H, t, $^3J_{HH}$ 6.8, CH_3), 1.17 (3H, t, $^3J_{HH}$ 6.8, CH_3), 2.56 (1H, s, CH_3), 3.30 (2H, q, $^3J_{HH}$ 7.2, CH_2), 3.50 (2H, q, $^3J_{HH}$ 7.2, CH_2); δ_c 13.6 (s, CH_3), 14.3 (s, CH_3), 15.1 (s, CH_3), 39.6 (s, CH_2), 43.3 (s, CH_2), 114.2 (s, C-7), 131.9 (dd, $^4J_{CF}$ 7, $^5J_{CF}$ 5, C-7a), 144.5 (dd, $^1J_{CF}$ 215, $^2J_{CF}$ 34, C-2) 147.2 (dd, $^1J_{CF}$ 133, $^2J_{CF}$ 22, C-3), 147.4 (s, C-4a), 147.5 (s, C=O), 161.4 (s, 6-C); δ_F -95.80 (1F, d, $^3J_{FF}$ 23, C-2), -97.37 (1F, d, $^3J_{FF}$ 25, C-3); *m/z* (EI^+) 269 ($[M]^+$, 48%), 196(100), 141(18)

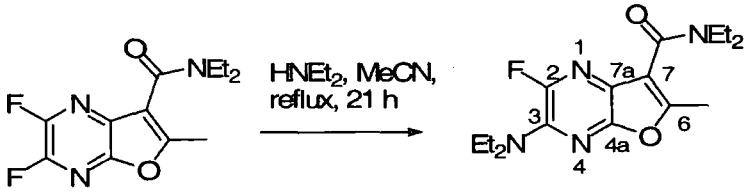
Ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate, 273



116 **273**

Ethylacetoacetate (2.56 g, 13 mmol) and sodium hydride (60% in mineral oil, 0.75 g, 19 mmol) was added to tetrahydrofuran 250 cm^3 and stirred at room temperature for 2 h before the addition of 2,3,5,6-tetrafluoropyrazine, **116** (1.5 g, 10 mmol). The reaction mixture was then stirred at reflux for 26 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate (2.52 g). Column chromatography (silica, ethylacetate:*n*-hexane, 1:4) gave *ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate*, **273** (1.70 g, 71%). Analysis as outlined in Rachel Slater thesis.[2] Crystals suitable for x-ray analysis were grown from MeOH.

2-(Diethylamino)-*N,N*-diethyl-3-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxamide, 357

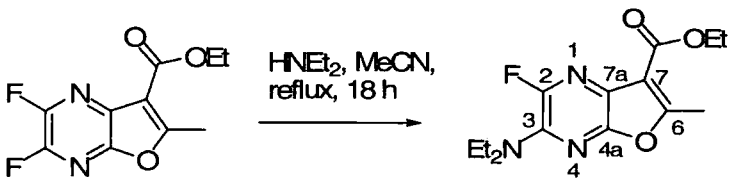


347 **357**

N,N-diethyl-2,3-difluoro-7-methylfuro[2,3-b]pyrazine-6-carboxamide, **347** (0.50 g, 1.9

mmol) and diethylamine (0.28 g, 3.8 mmol) in acetonitrile (40 cm^3) was stirred at reflux for 21 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *2-(diethylamino)-N,N-diethyl-3-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxamide*, **357** (0.56 g, 95%) as yellow crystals; mp 66-68 °C, IR (neat, ν cm^{-1}): 2973, 2361, 1702, 1590, 1510, 1453, 1431, 1400, 1265, 1028, 993; (Found: C, 59.4; H, 7.2; N, 17.2 $C_{16}H_{23}FN_4O_2$ requires: C, 59.6; H, 7.2; N, 17.4%); δ_H 1.03 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.17 (3H, m, CH_3), 2.41 (3H, s, CH_3), 2.28 (1H, q, $^3J_{HH}$ 7.2, CH_3), 3.48 (2H, m, 7.2, CH_2); δ_c 13.7 (s, CH_3), 13.8 (s, CH_3), 14.0 (s, CH_3), 15.1 (s, CH_3), 39.6 (s, CH_2), 43.2 (s, CH_2), 44.8 (d, $^4J_{CF}$ 5.7, CH_2), 113.7 (s, C-7), 120.8 (d, $^3J_{CF}$ 13.4, C-7a), 140.7 (d, $^2J_{CF}$ 25.9, 3-CN), 148.1 (d, $^1J_{CF}$ 244, C-2), 151.1 (s, C-4a), 154.1 (s, C-6), 162.5 (s, C=O); δ_F -83.54 (1F, s, C-2); *m/z* (EI^+) 322 ($[M]^+$, 96%), 249(100), 221(94)

2-(Diethylamino)-3-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate, 356

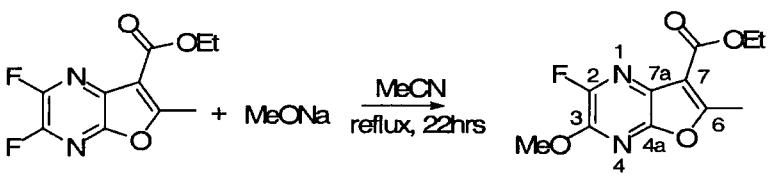


273 **356**

Ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate, **273** (0.42 g, 1.7 mmol) and diethylamine (0.25 g, 3.4 mmol) in acetonitrile (50 cm^3) was stirred at reflux for 18 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing ethyl *2-(diethylamino)-3-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate*, **356** (0.48 g, 95%) as a

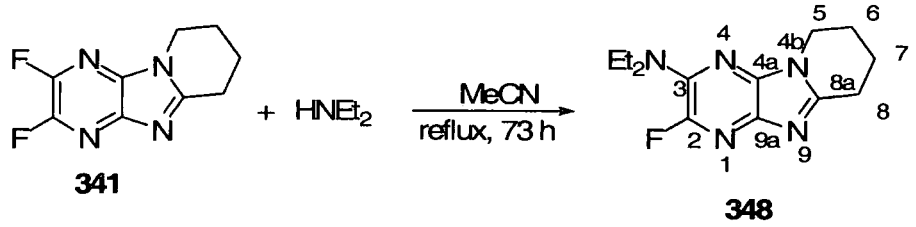
yellow solid; mp 43-45 °C; (Found: C, 56.7; H, 6.2; N, 14.2 $C_{14}H_{18}FN_3O_3$ requires: C, 56.9; H, 6.1; N, 14.2%); δ_H 1.19 (3H, t, $^3J_{HH}$ 7, CH_3), 1.37 (3H, t, $^3J_{HH}$ 7, CH_3), 2.68 (3H, s, CH_3), 3.52 (1H, q, $^3J_{HH}$ 7.5, CH_3), 4.37 (1H, q, $^3J_{HH}$ 7.5, CH_3); δ_c 13.8 (s, CH_3), 14.7 (s, CH_3), 15.0 (s, CH_3), 44.9 (d, $^4J_{CF}$ 5.4, CH_2), 61.0 (s, CH_2), 109.2 (s, C-7), 120.4 (d, $^3J_{CF}$ 11.1, C-7a), 141.0 (d, $^2J_{CF}$ 21, 3-CN), 148.3 (s, C-4a), 151.4 (d, $^1J_{CF}$ 196, C-2), 161.8 (s, C-6), 163.2 (s, C=O); δ_F -82.54 (1F, s, C-2); *m/z* (EI^+) 295 ($[M]^+$, 52%), 280(100), 249(62)

Ethyl 2-fluoro-3-methoxy-6-methylfuro[2,3-b]pyrazine-7-carboxylate, 355



A solution of Ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate, **273** (300 mg, 1.2 mmol), and sodium methoxide (60 mg, 1.2 mmol) in methanol (50 cm^3) was stirred at room temperature for 16 h after which time ^{19}F NMR indicated 100% conversion. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing ethyl 2-fluoro-3-methoxy-6-methylfuro[2,3-b]pyrazine-7-carboxylate. Recrystallisation from ethyl acetate yielded *ethyl 2-fluoro-3-methoxy-6-methylfuro[2,3-b]pyrazine-7-carboxylate*, **355** (270 mg, 89%) as white needles; mp 159-160 °C; IR (neat, ν cm^{-1}): 1706, 1589, 1503, 1456, 1399, 1321, 1150, 1031, 800; (Found: C, 51.7; H, 4.3; N, 10.8 $C_{11}H_{11}FN_2O_4$ requires: C, 52.0; H, 4.4; N, 11.0%); δ_H 1.37 (3H, t, $^3J_{HH}$ 7, CH_3), 2.75 (3H, s, CH_3), 4.03 (3H, s, OCH_3), 4.39 (2H, q, $^3J_{HH}$ 7, CH_3); δ_c 14.63 (s, CH_3), 15.14 (s, CH_3), 55.18 (s, OCH_3), 61.26 (s, CH_2), 109.60 (s, C-7), 125.01 (d, $^3J_{CF}$ 12.4, C-7a), 145.01 (d, $^2J_{CF}$ 30.5, C-3), 147.09 (d, $^1J_{CF}$ 248, C-2), 149.11 (s, C-4a), 162.71 (s, C-6), 164.29 (s, C=O); δ_F -91.90 (1F, s, C-2); *m/z* (EI^+) 254 ($[M]^+$, 14%), 208(100), 180(82)

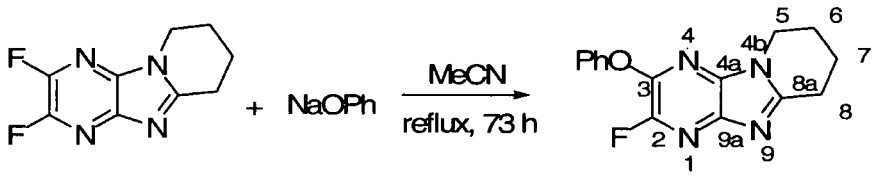
_N,N_-Diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-_b_]pyrazin-2-amine, 348



341 **348**

A solution of 2,3-difluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine, **341** (0.30 g, 1.4 mmol) and diethylamine (0.63 g, 8.6 mmol) in acetonitrile (50 cm^3) was stirred at reflux for 73 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with ethyl acetate (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N,N*-diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine (0.28 g). Recrystallisation from DCM gave *N,N-diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-b]pyrazin-2-amine*, **348** (0.26 g, 69%) as yellow solid; mp 89-91 °C; (Found: C, 59.2; H, 6.9; N, 26.5 $C_{13}H_{18}FN_5$ requires: C, 59.3; H, 6.9; N, 26.6%); δ_H 1.15 (3H, t, $^3J_{HH}$ 7, CH_3), 2.06 (4H, m, CH_2), 3.00 (2H , t, $^3J_{HH}$ 6.4, CH_2), 3.48 (4H, q, $^3J_{HH}$ 5.4, CH_2) 4.03 (2H ,t, $^3J_{HH}$ 6, CH_2); δ_c 13.7 (s, CH_3), 20.7 (s, CH_2), 22.5 (s, CH_2), 26.0 (s, CH_2), 41.7 (s, CH_2), 44.8 (d, $^4J_{CF}$ 5.7, CH_2), 135.5 (d, $^3J_{CF}$ 13.4, C-9a), 136.0 (s, C-4a), 140.8 (d, $^2J_{CF}$ 13.4, C-3), 145.79 (d, $^1J_{CF}$ 247, C-2), 151.03 (m, C-8a); δ_F -84.37 (s, C-2); *m/z* (ES^+) 264 ($[M + H]^+$, 100%),

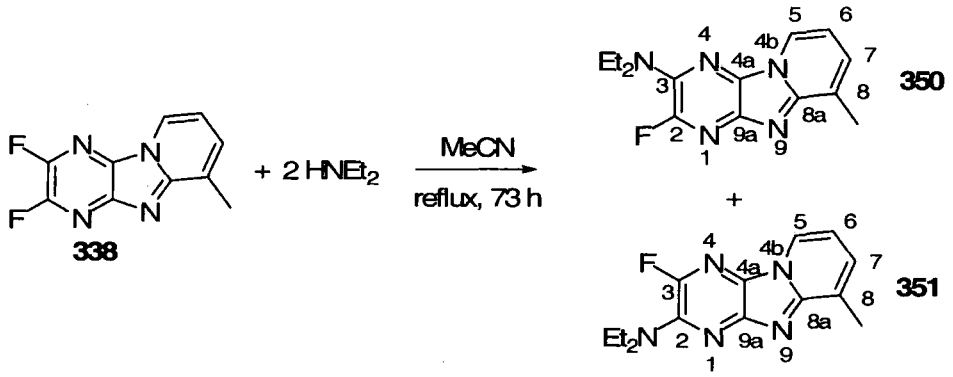
_N,N_-Diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-_b_]pyrazin-2-amine, 349



341 **349**

A solution of 2,3-difluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine, **341** (0.30 g, 1.4 mmol) and sodium phenoxide (0.63 g, 8.6 mmol) in acetonitrile (50 cm^3) was stirred at reflux for 73 h after which time ^{19}F NMR indicated 100% conversion of the start material. The reaction solvent was evaporated *in vacuo* and the sample dissolved into water (40 cm^3). The mixture was extracted with DCM (3 × 40 cm^3), the organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product containing *N,N*-diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine (0.28 g). Recrystallisation from hexane gave *N,N-diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1',2':1,2]imidazo[4,5-b]pyrazin-2-amine*, **349** (0.22 g, 54%) as a white solid; mp 108-110 °C; (Found: C, 63.2; H, 4.6; N, 19.6 $C_{15}H_{13}FN_4O$ requires: C, 63.4; H, 4.6; N, 19.7%); δ_H 2.07 (4H, m, CH_2), 3.13 (2H , t, $^3J_{HH}$ 6, CH_2), 4.04 (4H, t, $^3J_{HH}$ 5, CH_2), 7.14 (1H, m, Ar-H), 7.25 (1H, m, Ar-H), 7.39 (4H, m, Ar-H); δ_c 20.8 (s, CH_2), 22.6 (s, CH_2), 26.5 (s, CH_2), 42.7 (s, CH_2), 120.6 (s, Ar-CH), 125.4 (s, Ar-CH), 130.3 (s, Ar-CH), 134.9 (d, $^4J_{CF}$ 2, C-9a), 140.9 (d, $^3J_{CF}$ 12, C-4a), 143.5 (d, $^2J_{CF}$ 30, C-3), 149.0 (d, $^1J_{CF}$ 247, C-2), 154.9 (s, C-8a), 155.8 (d, $^4J_{CF}$ 2, CO); δ_F -93.08 (s, C-2); *m/z* (EI^+) 284 ($[M]^+$, 90%), 255(77), 206(33)

_N,N_-Diethyl-2-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-_b_]pyrazin-3-amine, 350 and _N,N_-Diethyl-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-_b_]pyrazin-2-amine, 351



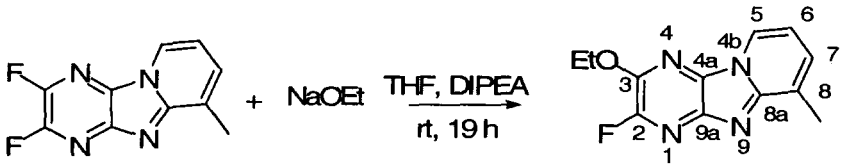
A solution of 2,3-difluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine, **338** (200 mg, 0.9 mmol), diethylamine (140 mg, 1.8 mmol) and DIPEA (376 mg, 2.7 mmol) in THF (50 cm^3) was stirred at room temperature for 20 h after which time LCMS indicated 100% conversion with the formation *N,N*-diethyl-3-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine and *N,N*-diethyl-2-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine in a 1:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing *N,N*-diethyl-2-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine and *N,N*-diethyl-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine (149mg). Mass-directed auto-preparation HPLC purification yielded;

(i) *N,N-diethyl-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazin-2-amine*, **351** which was then recrystallised from methanol to give *N,N*-diethyl-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine (34 mg, 27%) as a yellow solid; mp 159 °C, (Found: C, 61.3; H, 5.9; N, 25.7 $C_{14}H_{16}FN_5$ requires: C, 61.5; H, 5.9; N, 25.6%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7, CH_3), 2.68 (3H, s, CH_3), 3.68 (2H, q, $^3J_{HH}$ 6, CH_2), 6.85 (1H, m, Ar-H), 7.22 (1H, m, Ar-H), 8.33 (1H, m, Ar-H); δ_c 13.7 (s, CH_3), 17.3 (s, CH_3), 45.0 (d, $^4J_{CF}$ 6, CH_2), 111.6 (s, C-8), 121.7 (s, Ar-CH), 126.9 (s, Ar-CH), 128.3 (s, Ar-CH), 130.3 (s, C-

9a), 137.3 (d, $^3J_{CF}$ 15, C-4a), 140.6 (d, $^2J_{CF}$ 26, C-2), 147.2 (d, $^1J_{CF}$ 115, C-3), 149.9 (s, C-8a); δ_F -84.45 (1F, s, C-3), *m/z* (ES^+) 274 ($[M + H]^+$, 85%)

(ii) *N,N-diethyl-2-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazin-3-amine*, **350** which was then recrystallised from methanol to yield *N,N*-diethyl-2-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine (56 mg, 45%) as a brown solid; mp 146-147 °C; (Found: C, 61.5; H, 5.9; N, 25.9 $C_{14}H_{16}FN_5$ requires: C, 61.5; H, 5.9; N, 25.6%); δ_H 1.28 (3H, t, $^3J_{HH}$ 7, CH_3), 2.67 (3H, s, CH_3), 3.64 (2H, q, $^3J_{HH}$ 6, CH_2), 6.82 (1H, m, Ar-H), 7.18 (1H, m, Ar-H), 8.37 (1H, m, Ar-H); δ_c 13.9 (s, CH_3), 17.3 (s, CH_3), 44.9 (d, $^4J_{CF}$ 6, CH_2), 111.8 (s, C-8), 121.1 (d, $^3J_{CF}$ 11, C-9a), 121.6 (s, Ar-CH), 127.7 (s, Ar-CH), 127.8 (s, Ar-CH), 143.6 (d, $^1J_{CF}$ 256, C-2), 144.7 (d, $^2J_{CF}$ 28, C-3), 145.9 (s, C-8a), 148.7 (d, $^4J_{CF}$ 6, C-4a); *m/z* (ES^+) 274 ($[M + H]^+$, 85%)

2-(Ethyloxy)-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine, 354

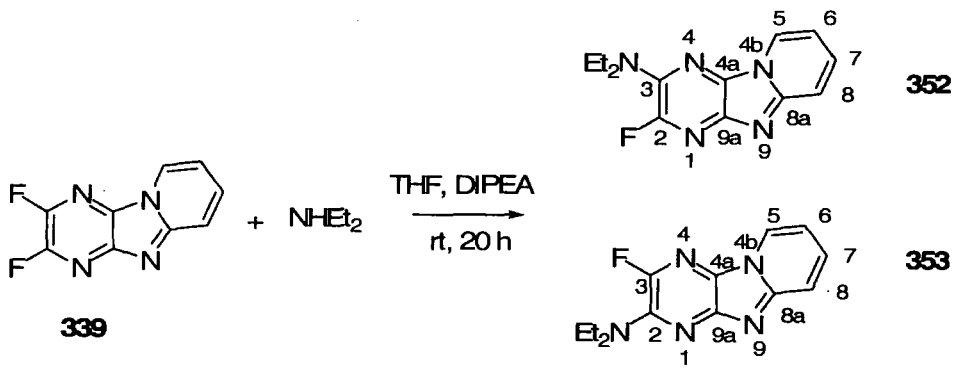


338 **354**

A solution of 2,3-difluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine, **338** (100 mg, 0.45 mmol), sodium ethoxide (32 mg, 0.45 mmol) and DIPEA (175 mg, 1.36 mmol) in THF (10 cm^3) was stirred at room temperature for 16 h after which time LCMS indicated 100% conversion with the formation 2-(ethyloxy)-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing 2-(ethyloxy)-3-fluoro-6-methylpyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine (111 mg). Recrystallisation from methanol gave *2-(ethyloxy)-3-fluoro-6-*

methylpyrido[1',2':1,2]imidazo[4,5-b]pyrazine, **354** (65 mg, 58%) as a orange solid; mp 125-126 °C; (Found: C, 58.5; H, 4.5; N, 22.6 $C_{12}H_{11}FN_4O$ requires: C, 58.5; H, 4.5; N, 22.8;%); δ_H 1.53 (6H, m, CH_3), 2.68 (3H, s, CH_3), 4.60 (2H, q, $^3J_{HH}$ 8, CH_2), 4.68 (2H, q, $^3J_{HH}$ 8, CH_2), 6.85 (1H, m, Ar-H), 7.18 (1H, m, Ar-H), 8.38 (1H, m, Ar-H); δ_c 13.9 (s, CH_3), 17.3 (s, CH_3), 44.9 (d, $^4J_{CF}$ 6, CH_2), 111.8 (s, C-8), 121.1 (d, $^3J_{CF}$ 11, C-4a), 121.6 (s, Ar-CH), 127.7 (s, Ar-CH), 127.8 (s, Ar-CH), 143.6 (d, $^1J_{CF}$ 256, C-2), 144.7 (s, C-8a), 148.0 (d, $^2J_{CF}$24, C-3), 148.9 (s, C-9a); *m/z* (ES^+) 247 ([M+ H]$^+$, 100%)

N,N-Diethyl-3-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine, 352 and N,N-Diethyl-2-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine, 353



A solution of 2,3-difluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine, **339** (200 mg, 0.9 mmol), diethylamine (140 mg, 1.8 mmol) and DIPEA (376 mg, 2.7 mmol) in THF (50 cm^3) was stirred at room temperature for 20 h after which time LCMS indicated 100% conversion with the formation *N,N*-diethyl-3-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine and *N,N*-diethyl-2-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine in a 1:1 ratio by ^{19}F NMR. The reaction solvent was evaporated *in vacuo*, DCM (40 cm^3) and brine (40 cm^3) was added and passed through a hydrophobic frit to collect the DCM layer. The DCM was evaporated *in vacuo* to give a crude containing *N,N*-diethyl-3-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine and *N,N*-diethyl-2-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine (269 mg). Mass-directed auto-preparation HPLC purification gave;

(i) *N,N-diethyl-3-fluoropyrido[1',2':1,2]imidazo[4,5-b]pyrazin-2-amine*, **352** which was then recrystallised from methanol to give *N,N*-diethyl-3-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-2-amine as a brown solid (96 mg, 38%), mp 134-137 °C; (Found: C, 61.5; H, 5.9; N, 25.9 $C_{14}H_{16}FN_5$ requires: C, 61.5; H, 5.9; N, 25.6%); δ_H 1.25 (3H, t, $^3J_{HH}$ 7, CH_3), 3.65 (2H, q, $^3J_{HH}$ 6, CH_2), 6.95 (1H, m, Ar-H), 7.42 (1H, m, Ar-H), 7.77 (1H, m, Ar-H), 8.23 (1H, m, Ar-H); δ_c 13.7 (s, CH_3), 45.0 (d, $^4J_{CF}$ 6, CH_2), 111.6 (s, Ar-CH), 121.7 (s, Ar-CH), 126.9 (s, Ar-CH), 128.3 (s, Ar-CH), 129.9 (s, C-9a), 137.8 (d, $^3J_{CF}$ 14, C-4a), 141.1 (d, $^2J_{CF}$ 26, C-2), 146.6 (d, $^1J_{CF}$ 163, C-3), 150.0 (s, C-8a); δ_F -75.2 (1F, s, C-2); *m/z* (ES^+) 274 ([M+ H]$^+$, 85%)

(ii) *N,N-diethyl-2-fluoropyrido[1',2':1,2]imidazo[4,5-b]pyrazin-3-amine*, **353** which was then recrystallised from methanol to give *N,N*-diethyl-2-fluoropyrido[1',2':1,2]imidazo[4,5-*b*]pyrazin-3-amine as a yellow solid (94 mg, 36%), mp 139-140 °C, (Found: C, 61.3; H, 5.9; N, 25.7 $C_{14}H_{16}FN_5$ requires: C, 61.5; H, 5.9; N, 25.6%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7, CH_3), 2.68 (3H, s, CH_3), 3.68 (2H, q, $^3J_{HH}$ 6, CH_2), 6.85 (1H, m, Ar-H), 7.22 (1H, m, Ar-H), 8.33 (1H, m, Ar-H); δ_c 12.6 (s, CH_3), 43.9 (d, $^4J_{CF}$ 6, CH_2), 110.8 (s, Ar-CH), 116.5 (s, Ar-CH), 120.5 (d, $^3J_{CF}$ 5, C-9a), 124.2 (s, Ar-CH), 128.5 (s, Ar-CH), 143.7 (d, $^1J_{CF}$ 257, C-2), 145.1 (d, $^2J_{CF}$ 22, C-3), 145.7 (s, C-8a), 148.0 (d, $^4J_{CF}$ 4, C-4a); δ_F -84.45 (1F, s, C-3), *m/z* (ES^+) 274 ([M+ H]$^+$, 85%)

References

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2 R. Slater, 'Polyfunctional Ring Fused Heterocyclic Compounds', Durham University, 2005.