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Reactions of polyfluoropyridines with bidentate nucleophiles: attempts to prepare deazapurine analogues

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Abstract

Reactions of pentafluoropyridine with guanidine, thiourea and urea with the hope of preparing derivatives which may be cyclised to polyfluorodeazapurines are described The reactions with urea and thiourea produced, somewhat unexpectedly, bis-(2,3,5,6-tetrafluoro-4-pyridyl)amine and bis-(2,3,5,6-tetrafluoro-4-pyridyl)sulfide, respectively, the structure of the amine was confirmed by X-ray crystallography. The product from the guanidine reaction was the expected 4-substituted tetrafluoropyridine derivative. Attempts to cyclise the latter are described and a rationalisation to explain the unexpected melamine derivatives which were produced is given.

Keywords: Polyfluoropyridines; Bidentate nucleophiles; Cyclisation; Deazapurines

1. Introduction

In a previous paper [1], we have described work directed towards the formation of fluorodeazapurine derivatives as potential precursors for anti-viral agents and more importantly as precursors in the preparation of anti-sense nucleosides. Part of the rationale for this work was the discovery that the replacement of nitrogen by the isoelectronic CF group in ribovirin analogues albeit in a five-membered ring afforded compounds with significant anti-influenza activity [2]. As part our program in the study of antiviral agents it was of interest to see if similar replacement of a purine nitrogen both in the imidazole ring akin to the work of Townsend and coworkers [3] and also in the pyrimidine ring would lead to activity. We were able to prepare 3-deaza-2,3,6-trifluoro-8-hydroxypurine (**1**) (see Scheme 1) that could after reduction and suitable nucleophilic substitution lead to 3-fluoro-3-deazaguanine or the corresponding 2,3-difluoro-3-deaza-adenine analogues. Unfortunately, we could not deoxygenate **1** to the required purine using a variety of methods and hence we were unable to study the elaboration of the molecule to the desired derivatives.

Thus, in a different approach, we decided to investigate the possibility of preparing 4-substituted polyfluoropyridine derivatives using bidentate nucleophiles containing suitable functional groups which could either spontaneously or in a two-step process cyclise to the desired ring systems. This kind of process has been exemplified by the reaction of dimethyl-2-(*S*-(tetrafluoro-4-pyridyl)fumarate (**2**) leading to **3** [4] and by the work of Herkes [5] who showed that polyfluorobenzothiazoles (**4**) could be prepared by cyclisation of polyfluorothioanilides which in turn can be prepared by thioacylation of the corresponding anilines as shown in Scheme 1. There are relatively few examples of reactions of fluorinated aromatic compounds with bidentate nucleophiles as indicated in a recent comprehensive review of the area [6]. There is, to our knowledge, only one example in the benzenoid series in which the first attack by nitrogen is followed by a spontaneous cyclisation, this is the formation of 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydroquinoxaline (**5**) reported by Burdon et al. [7] who reacted hexafluorobenzene with ethylene diamine at high temperature over a prolonged period The reason for this is almost certainly the very high deactivating effect of nitrogenous functions on nucleophilic substitutions of fluoroaromatics [8]. Most other nitrogen heterocycles described in this field are prepared by reactions of suitable vicinal diamines in standard heterocyclic syntheses.

A search of the literature reveals only one report of a successful reaction between guanidine and a fluoroaromatic by Popova [9] who showed that 2,4,6-trifluoropyrimidine, a highly reactive species, afforded 2-guanidino-4,6-difluoropyrimidine. We found no reports of reactions between urea

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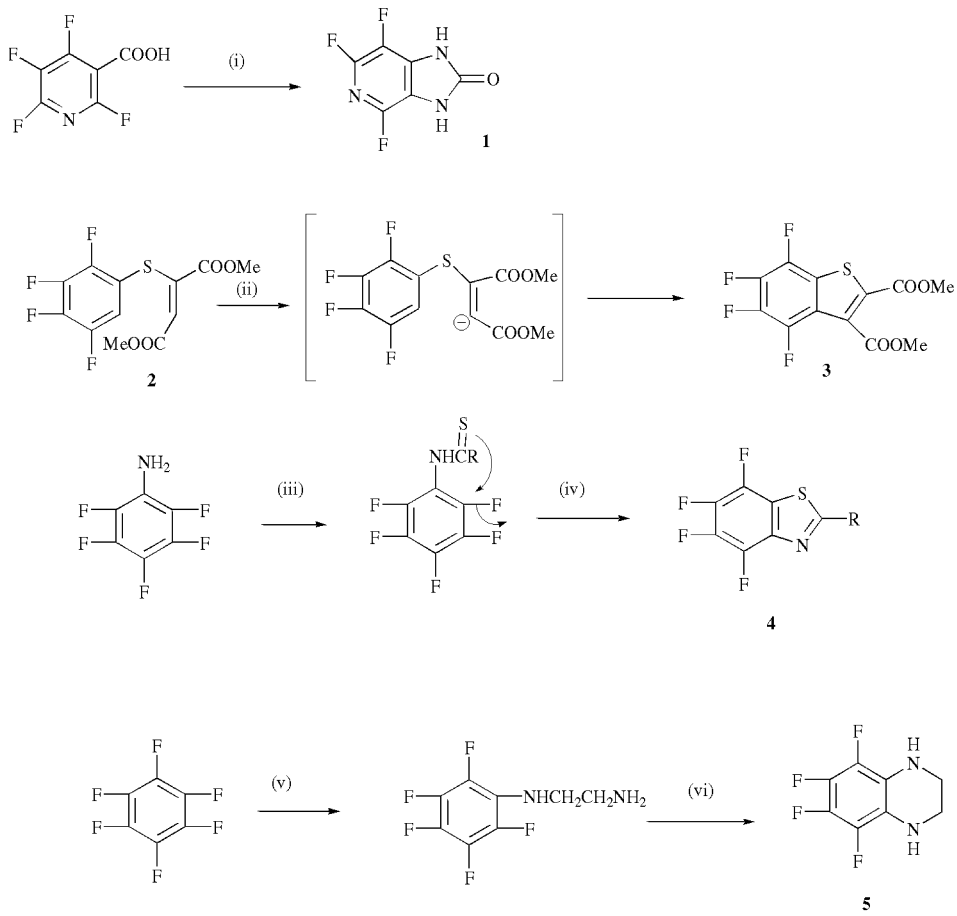


(i) $(PhO)_2PON_3/Et_3N$/ t-BuOH / heat (ii) base (iii) RCSX R= NH_2, R'NH , OEt CF_3 CF_2Cl X =F, Cl

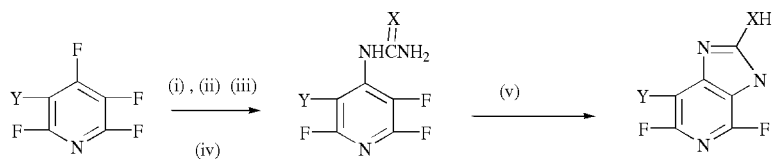
(iv) Δ, DMF 120-140°C (v) base/ $NH_2CH_2CH_2NH_2$ (vi) reflux DMF

Scheme 1.

and any fluoroaromatics. We showed earlier [10] that reaction between thiourea and its *N*-substituted derivatives and polyfluorobenzenes yielded polyfluorodiarylsulphides. We therefore, decided to investigate the reactions of these three reagents with polyfluoropyridines, in particular pentafluoropyridine (**6**) and 3-chlorotetrafluoropyridine (**7**), in the hope of obtaining the corresponding 4-substituted compounds, which is the expected orientation for nucleophilic substitution in these pyridines. The possibility of cyclisation of these products to the desired deazapurine analogues, as shown in Schemes 2 and 3, would then be investigated, hopefully leading to the desired deazapurines.

2. Results and discussion

The first reaction we studied was that between guanidine (as its hydrochloride) and pentafluoropyridine (**6**) in the presence of excess sodium hydride firstly to release the free base and secondly to generate the anion from it. The



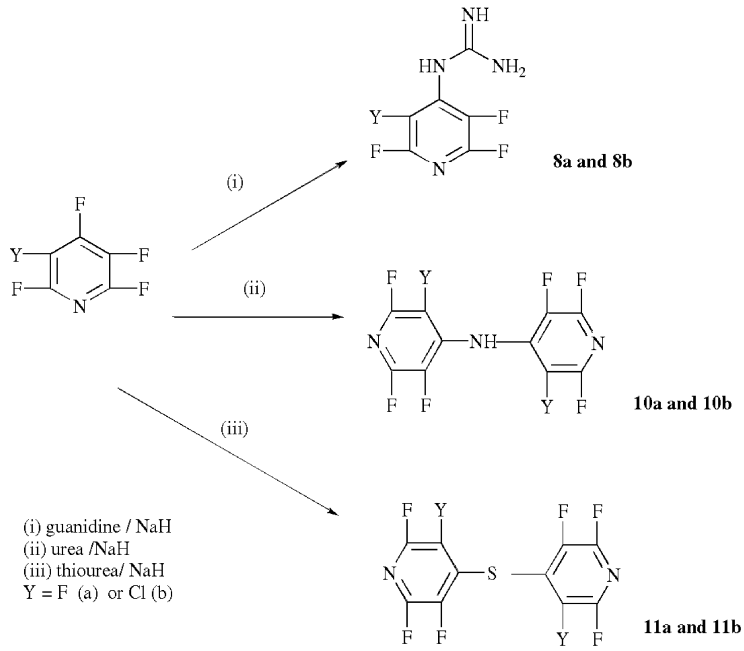
6 Y= F
7 Y =Cl

8a Y = F, 8 b Y = Cl
X= NH

9a Y = F, 9 b Y = Cl
X= NH

(i) urea (ii) guanidine (iii) thiourea (iv) base Y =F (a) or Cl (b) X = O ,S, NH_2 (v) heat

Scheme 2.



Scheme 3.

reaction, monitored by TLC, proceeded rather slowly but yielded a single compound in 63% yield after reaction for 2 days in refluxing ether. The product was identified by a combination of physical techniques. The ^{1}H NMR spectrum showed only a broad singlet which disappeared on shaking the sample with D_2O, indicating the presence of exchangeable protons. The ^{19}F NMR spectrum showed the characteristic bands at δ −97.2 and −154.9 for 4-substituted tetrafluoropyridines [11] and the ^{13}C NMR spectrum was consistent with this pattern showing four bands attributable to the 2 and 6, 3 and 5, and 4 ring and guanidino carbon atoms, respectively. The mass spectral and elemental analysis data confirmed the structure as *N*-(2,3,5,6-tetrafluoropyridyl)guanidine (**8a**). In the same way 3-chlorotetrafluoropyridine (**7**) afforded *N*-(3-chloro-2,5,6-trifluoro-4-pyridyl)guanidine (**8b**) identified as above for **8a** by similar physical methods (see Section 3 for details). We found using different solvents (ethanol, THF or acetonitrile) with or without added base were of no advantage, indeed without the addition of two equivalents of base very little reaction occurred. Attempts to cyclise **8a** or **8b** to the desired deazapurine derivatives **9a** and **9b** are described below. This result is interesting in that a similar reaction with hexafluorobenzene gave no reaction at low temperature and at higher temperature in a sealed tube gave only polymeric material [12]. This presumably reflects the greater reactivity of polyfluorofluoropyridines towards nucleophiles vis-a-vis hexafluorobenzene and is in keeping with the results obtained by Popova with 2,4,6-trifluoropyrimidine.

The next reaction we tried was that of urea with **6**. The rationale for this choice was that urea is frequently used as a bidentate nucleophile in purine and deazapurine synthesis [13]. We found that substitution did not occur under the conditions described above for the reaction with guanidine. We changed the solvent from ether to the higher boiling dimethoxyethane and after heating the reaction for 18 h obtained a single compound in 92% yield as a white crystalline solid. The ^{1}H NMR spectrum showed a broad peak exchangeable with D_2O, the ^{19}F NMR spectrum again showed the characteristic bands for a 4-substituted tetrafluoropyridine at δ −92.7 and −153.9. The ^{13}C spectrum was at first somewhat puzzling showing bands for only the ring carbon atoms again characteristic of a 4-substituted tetrafluoropyridine. The mass spectrum and elemental analysis indicated that the product had the molecular formula $C_{10}HF_8N_3$. This latter, together with the above data suggested that the compound was bis-(2,3,5,6-tetrafluoro-4-pyridyl)amine (**10a**). This compound has been reported previously by a different route [14–16]. The structure was confirmed by X-ray analysis[1] on a single crystal as shown in Fig. 1 (Tables 1 and 2). A similar reaction occurred with 3-chlorotetrafluropyridine (**6**) to yield the corresponding amine **10b**. **Caution! We subsequently found that both of these compounds have very high biological activity as**

[1] The X-ray data was collected using a Rigaku *R*-axis II area detector refracrometer using graphite monochoromated Mo Kα radiation. The structure was determined by direct methods (molecular structure corp. TEXSAN single crystal structure analysis software version 1.6 and G.M. Sheldrick SHELXL-93 program for crystal structure refinement. The data and analysis was carried out by Dr. T.A. Hamor of the School of Chemistry, University of Birmingham. The formula of the compound is $C_{10}HN_3F_8$ and its Found mass is 315.004239 and the required mass is 315.004273, the error is 0.1 ppm.

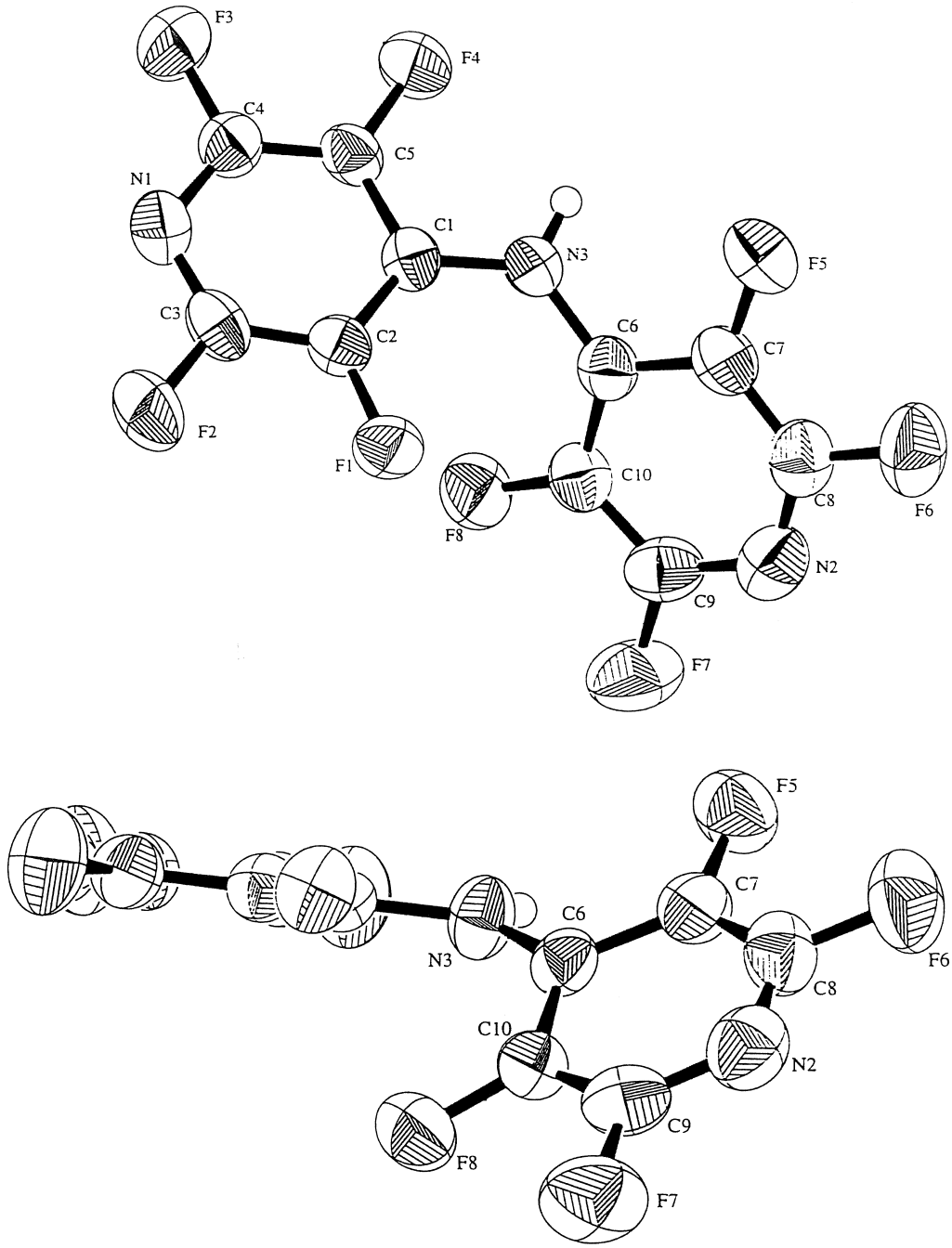


Fig. 1.

insecticides but also may well have very high mammalian toxicities and should be treated with extreme caution [17]. Compound **10a** has been reported in a list of compounds in a patent, but with no experimental details, as being bioactive [16]. Although these reactions were in themselves unusual and provided some biologically interesting compounds they did not enable us to proceed further towards our original goal. We, therefore, investigated the reaction of pentafluoropyridine (**6**) with the more reactive thiourea. We found that reaction in ethanol in the absence of added base afforded a crystalline product in 71% yield. ^{1}H, ^{19}F and ^{13}C NMR data indicated that the product contained 4-substituted tetrafluoropyridyl residues and no other carbon atoms and that there were no protons present in the molecule. Mass spectral and elemental analysis data confirmed the molecular formula as $C_{10}N_2F_8S$ and all the data together confirms the compound to be bis-(2,3,5,6-tetrafluoro-4-pyridyl)sulfide (**11a**). This compound has been reported as a byproduct in the formation of tetrafluoro-4-mercaptopyridine [18]. In a similar way the pyridine (**7**) and thiourea gave the sulfide (**11b**). These results particularly in the urea reactions were somewhat surprising although in the thiourea case

Table 1
Data for X-ray crystallography

Temperature (K)	293
Wavelength (Å)	0.71069
Crystal system	Orthorhombic
Space group	*Pnma*
Unit cell dimensions	
a (Å)	13.027
b (Å)	15.018
c (Å)	11.435
Volume (Å^3)	2237.2
Z	8
Density (Mg m^3)	1.871
Absorption coefficient (mm^{-1})	0.210
R indices	0.0577
Bond length (Å)	
F(1)–C(2)	1.349 (5)
F(2)–C(3)	1.348 (5)
F(3)–C(4)	1.346 (5)
F(4)–C(5)	1.351 (4)
F(5)–C(7)	1.353 (5)
F(6)–C(8)	41.33 (5)
F(7)–C(9)	1.357 (5)
F(8)–C(10)	1.345 (5)
N(1)–C(3)	1.315 (6)
N(1)–C(4)	1.318 (5)
N(2)–C(9)	1.300 (6)
N(2)–C(8)	1.318 (6)
N(3)–C(1)	1.375 (5)
N(3)–C(6)	1.397 (5)
C(1)–C(2)	1.392 (6)
C(1)–C(5)	1.396 (6)
C(2)–C(3)	1.364 (6)
C(4)–C(5)	1.354 (6)
C(6)–C(7)	1.393 (6)
C(6)–C(10)	1.396 (6)
C(7)–C(8)	1.365 (7)
C(9)–C(10)	1.378 (7)
Bond angles (°)	
C(3)–N(1)–C(4)	114.8 (4)
C(9)–N(2)–C(8)	116.0 (5)
C(1)–N(3)–C(6)	128.6 (4)
N(3)–C(1)–C(2)	125.9 (4)
N(3)–C(1)–C(5)	119.0 (4)
C(2)–C(1)–C(5)	115.0 (4)
F(1)–C(2)–C(3)	120.6 (4)
F(1)–C(2)–C(1)	120.3 (4)
C(3)–C(2)–C(1)	119.0 (4)
N(1)–C(3)–F(2)	115.9 (4)
N(1)–C(3)–C(2)	125.9 (4)
F(2)–C(3)–C(2)	118.2 (4)
N(1)–C(4)–F(3)	115.7 (4)
N(1)–C(4)–C(5)	124.9 (4)
F(3)–C(4)–C(5)	119.4 (4)
F(4)–C(5)–C(4)	120.9 (4)
F(4)–C(5)–C(1)	118.8 (4)
C(4)–C(5)–C(1)	120.3 (4)
C(7)–C(6)–C(10)	115.4 (4)
C(7)–C(6)–N(3)	119.3 (4)
C(10)–C(6)–N(3)	125.1 (4)
F(5)–C(7)–C(8)	121.0 (4)
F(5)–C(7)–C(6)	119.0 (4)
C(8)–C(7)–C(6)	119.9 (5)
N(2)–C(8)–F(6)	116.1 (5)
N(2)–C(8)–C(7)	124.4 (5)
F(6)–C(8)–C(7)	119.5 (5)
N(2)–C(9)–F(7)	116.4 (5)
N(2)–C(9)–C(10)	125.3 (5)
F(7)–C(9)–C(10)	118.3 (5)
F(8)–C(10)–C(9)	120.7 (4)
F(8)–C(10)–C(6)	120.5 (4)
C(9)–C(10)–C(6)	118.8 (4)

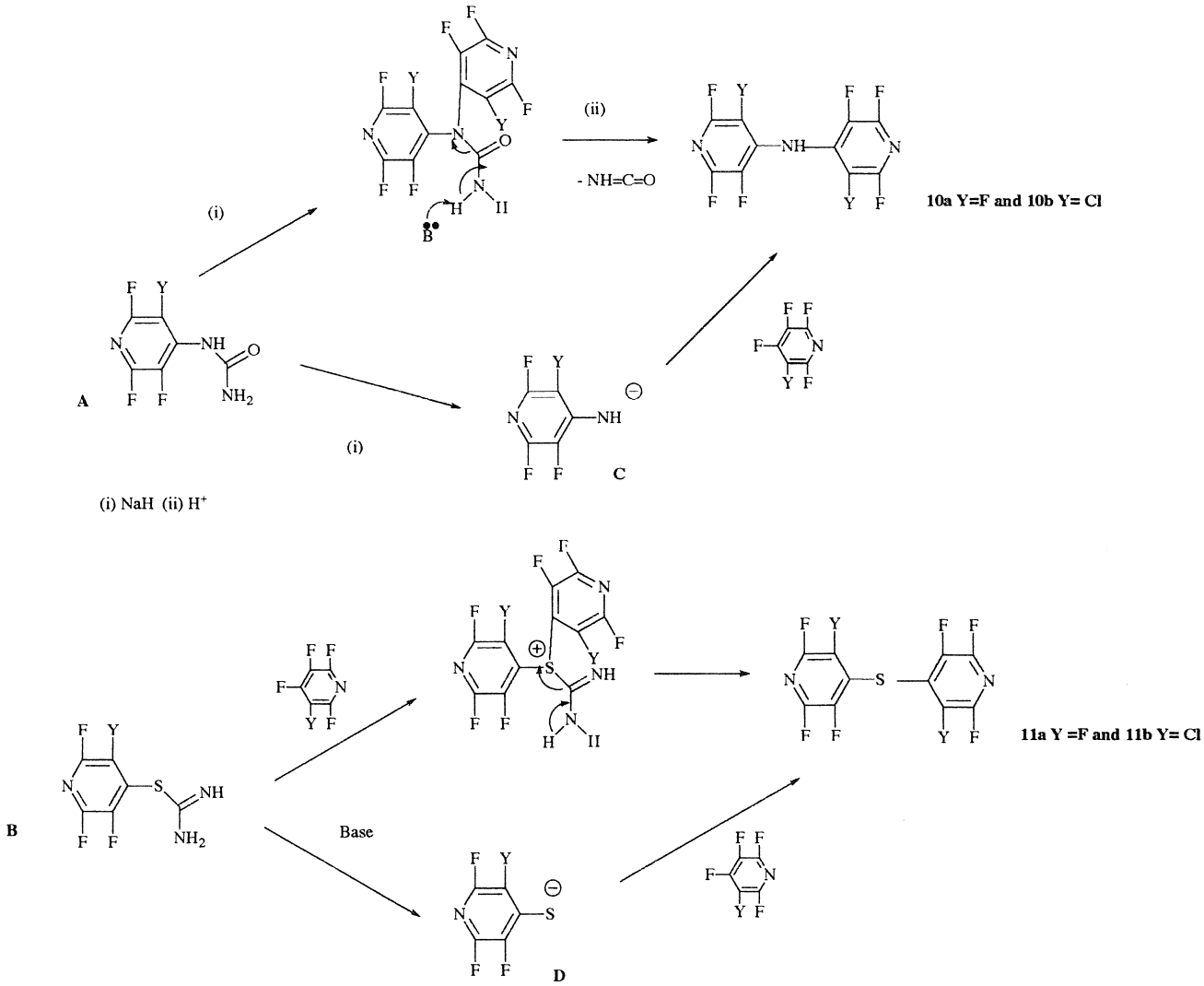
the formation of the sulfide may have been expected based on the results we obtained from a similar reaction with hexafluorobenzene [10].

A rationalisation of these observations is shown in Scheme 4. We believe the first step in these reactions is the expected nucleophilic attack by nitrogen and sulfur, respectively, to give the first formed products **A** and **B** which under any conditions reacted rapidly and could not be isolated. In the case of the urea reaction there are now two possible reactions, either direct attack of **A** on another molecule of pentafluoropyridine, or attack of the base (NaH) on **A**. Loss of isocyanic acid or carbodiimide leaves the corresponding anion **C** attack of which on a further molecule of the starting pyridine yields **10a** or **10b**. In the case of the thiourea reaction the same pathways are both possible via **B**. However, for the anion **D** to form it is necessary to postulate ethanol acting as the base since the reaction proceeds without the addition of base. *Iso*-thiouronium salts of the type **B** normally require strong bases for

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å^2 $\times 10^3$)[a]

	x	*y*	*z*	*U* (eq)
F(1)	4282 (2)	618 (2)	437 (2)	64 (1)
F(2)	6098 (2)	896 (2)	1492 (3)	86 (1)
F(3)	4795 (2)	3016 (2)	3860 (3)	88 (1)
F(4)	2885 (2)	2801 (2)	2967 (2)	76 (1)
F(5)	1134 (2)	1931 (2)	−438 (2)	74 (1)
F(6)	258 (2)	580 (2)	−1718 (2)	90 (1)
F(7)	2000 (3)	−1511 (2)	310 (3)	98 (1)
F(8)	2893 (2)	−273 (2)	1700 (2)	75 (1)
N(1)	5446 (3)	1948 (3)	2688 (3)	62 (1)
N(2)	1152 (3)	−456 (3)	−714 (4)	70 (1)
N(3)	2515 (3)	1588 (3)	1259 (3)	57 (1)
C(1)	3491 (3)	1670 (3)	1704 (4)	46 (1)
C(2)	4355 (3)	1208 (3)	1323 (4)	50 (1)
C(3)	5275 (3)	1364 (3)	1855 (4)	58 (1)
C(4)	4632 (3)	2406 (3)	3018 (4)	57 (1)
C(5)	3677 (3)	2303 (3)	2572 (4)	52 (1)
C(6)	2099 (3)	887 (3)	610 (4)	50 (1)
C(7)	1385 (3)	1073 (3)	−264 (4)	56 (1)
C(8)	949 (4)	394 (4)	−882 (4)	65 (1)
C(9)	1803 (4)	−636 (3)	115 (5)	66 (1)
C(10)	2283 (3)	−15 (3)	813 (4)	56 (1)
H(1)	2091 (39)	1982 (32)	1493 (43)	79 (17)

[a] *U* (eq) is defined as one-third of the traces of the orthogonolised U_{ij} tensor.



Scheme 4.

their hydrolysis/decomposition and it seems that proton abstraction by ethanol is unlikely in this case. We may, therefore, have to postulate that the *iso*-thiouronium salts react as shown in a different way, e.g. ethanol acting as a nucleophile leading to formation of the anion which then reacts with more starting material.

Thus, only in the reaction with guanidine we were able to isolate a product with the potential for cyclisation to the desired deazapurine analogues. In the light of the literature evidence, we would expect the cyclisation process to be difficult for two reasons; firstly the lone pair on the nitrogen atom when attached to a polyfluoroaryl ring has a powerful deactivating effect on the positions *ortho* and *para* to it [7]. Secondly, the 3-position in polyfluoropyridines has been shown to be unreactive towards most nucleophiles [19]. We, therefore, decided to use forcing conditions to attempt the cyclisation reaction. To achieve cyclisations of the type we required the previous studies have indicated that the use of relatively high boiling dipolar aprotic solvents or poly ethers such as diglyme is required [20], frequently base, usually a tertiary amine or sodium hydride, is added. We tried a series of reactions using a wide range of conditions and obtained some interesting and potentially useful results. In all cases in the absence of base we recovered only starting materials when **8a** or **8b** were heated below 100°C. Heating of **8a** in DMF, NMP, sulpholane or DMSO at temperatures between 80 and 200°C in the presence of sodium hydride or triethylamine afforded only 4-amino-tetrafluoropyridine (**12**) as the sole isolable product. Thus, our attempts to prepare the desired deazapurine structure by this method failed. However, when **8a** was heated in refluxing anisole (154°C) without base a different reaction occurred and we obtained a mixture of four products, the major one of which was unchanged starting material. Separation of the mixture by column chromatography afforded starting material 65%, 4-amino-tetrafluoropyridine (**12**) (10%) identical to an authentic sample, and crystalline solids **13** and **14**. The first of these **13** was identified by physical methods. The ^{1}H

NMR spectrum showed a broad single band which was exchangeable with D_2O at δ 9.5 indicative of an amino function, whilst the ^{19}F spectrum showed a set of bands with very similar chemical shifts to those found for 4-amino-tetrafluoropyridine. An accurate mass measurement gave a mass peak corresponding to a molecular formula of $C_{18}H_3F_{12}N_9$. These data together are compatible with the structure of **13** as tris-(*N*-[tetrafluoro-4-pyridyl])melamine. Compound **14** was, in a similar manner indicated, to be bis-(*N*-[tetrafluoro-4-pydridyl])melamine (see Section 3 for details). The origin of these latter compounds is interesting and possible mechanisms which account for the products are shown in Scheme 5. The loss of carbodiimide from the guanidine derivative **8a** under the influence of base leads directly to the formation of anion of 4-amino-tetrafluoro-pyridine (**12**) which would readily protonate. We believe, as shown, that the thermal reaction leading to **12**, **13** and **14** takes a different course. The rationale for this comes firstly from the early work of Davis and Underwood [20] who showed that heating of guanidine carbonate in an open tube led to the formation of cyanamide and ammonia whereas heating the carbonate with a condensing system in a sublimation apparatus led to the formation of melamine. Subsequent work, notably by Pankratov [21], has shown that heating of *N*-arylcyanamides leads to the formation of *N*-aryl-melamine derivatives possibly via dicyanamide and the isomelamine derivative. The latter has been shown to rearrange irreversibly to the melamine at temperatures in the range 150–200°C [22]. We believe that the first step in the reaction follows the literature precedent to give 4-cyanamido-tetrafluoropyridine. This latter then has two possible reaction pathways either direct thermal trimerisation to give the observed melamine, a known process [21] or the sequential nucleophilic addition process as shown. This has the merit that it more satisfactorily explains the formation of the dimeric product. Our preferred route is via the stepwise build up, but we have no evidence to support one mechanism against the other.

Thus, we conclude that although we have been unable to prepare the desired deazapurine precursors by this approach we have discovered some unexpected and potentially useful reactions. The melamines and their method of synthesis could lead to the production of some unusual and interesting ligands since by careful choice of pyridine derivatives we could in principle prepare a range of nine co-ordinate ligands which may have interesting properties. As indicated above some of the compounds we have made have shown extremely potent biological activities and work is continuing to study structure activity relationships with a range of their analogues.

3. Experimental

^1H NMR (300 MHz) and ^{13}C NMR spectra (75 MHz) were measured on a Bruker AC 300 NMR spectrometer unless stated otherwise. ^1H NMR spectra (400 MHz) were measured on a Bruker AMX 400 NMR spectrometer. ^{19}F NMR spectra were carried out either on a Jeol NMR spectrometer, type FX 90 Q (84.26 MHz) or on a Bruker AC 300 NMR spectrometer (282.4 MHz); tetramethylsilane and fluorotrichloromethane were used as internal references. For the characterisation of the signals the following abbreviations are used: s: singlet; d: doublet, t: triplet, q: quartet, quin: quintet, sext: sextet, m: multiplet, dd: doublet of doublets, dt: doublet of triplets, quin: pseudo-quintet, etc. *J* values are given in Hz. The mass spectra (CI-MS/EI-MS) were measured on a VG-Prospec-triple focusing mass spectrometer. For GC-MS analysis, a Carlo Erba, 8000 series GC was used with a 50 m column, BPX 5 (helium carrier gas, 70 eV, electron impact).

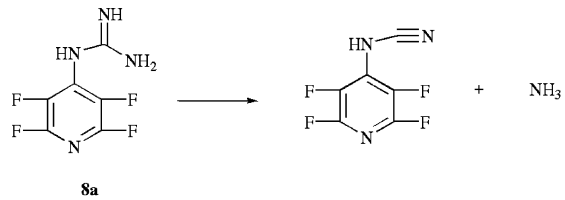
Thin layer chromatography was performed on TLC plastic sheets silica gel 60 F_{254}, pre-coated with a layer thickness of 0.2 mm from Merck, Art. 5735. Gas chromatographic analysis was carried out using a Philips PYE Unicam, Series 304 chromatograph with a 50 m CD-SIL-CB 19 column. The data were registered by a JCL 600 chromatography data system.

3.1. Materials

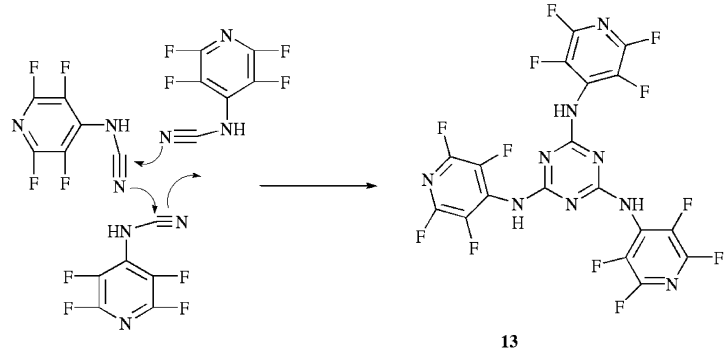
Pentafluoropyridine and 3-chlorotetrafluoropyridine were prepared as previously described [1] although they are commercially available at relatively high cost (Aldrich). All other reagents were obtained from Aldrich.

3.1.1. Preparation of N-(2,3,5,6-tetrafluoro-4-pyridyl) guanidine (8a)

Sodium hydride (0.236 g of 60% dispersion in oil, washed three times with dry ether) was suspended in dry ether (40 cm^3). The suspension was cooled in ice and dry guanidine hydrochloride (0.283 g, 2.96 mmol) was added and the mixture stirred for 30 min after which pentafluoropyridine (**6**) (0.5 g, 2.95 mmol) was added dropwise. The mixture was heated at reflux for 2 days when TLC and GLC of the liquid showed all the pyridine had reacted. Saturated ammonium chloride solution (30 cm^3) was carefully added, all the solids dissolved in the aqueous phase. The ether layer and the combined extracts of the aqueous phase (3×20 cm^3) were dried ($MgSO_4$) and the solvent evaporated to yield a small amount of an oil which contained no fluorinated products. The aqueous phase was made basic (saturated Na_2CO_3) and re-extracted with ether (3×50 cm^3). After drying ($MgSO_4$) the ether layer was evaporated to afford *N*-(2,3,5,6-tetrafluoro-4-pyridyl)guanidine (**8a**) (nc) (0.4 g, 64%) mp 134–135°C (from hexane/ethyl acetate); (Found: C, 34.4; H, 2.1; N, 26.6% $C_6H_4N_4F_4$ requires C, 34.6; H, 1.9; N, 26.9%). δ_H (DMSO-d_6) 6.15 (bs, equivalent NH), δ_F (DMSO-d_6) −97.2 (m, 2F, 2F and 6F), −154.9 (m, 2F, 3F and 5F), δ_C (DMSO-d_6) 156.3 (s, C7), 143.6 (dm, $^1J_{FC}$ 233.4, C2), 143.5 (m, C4), 136.1 (dm, $^1J_{FC}$ 247.4, 3C); *m/z* 208 $[M]^+$, 192 $[M - NH_2]^+$, 166 $[M - NHCNH]^+$.



8a



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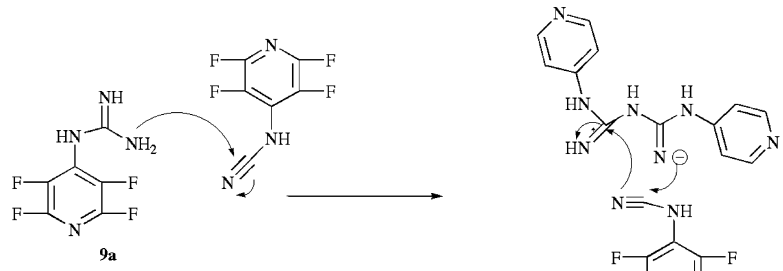
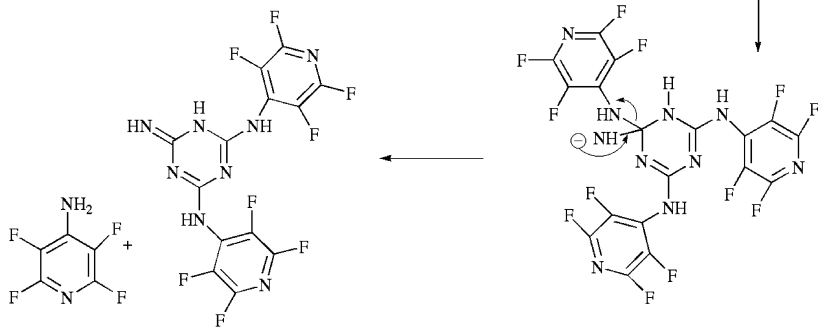
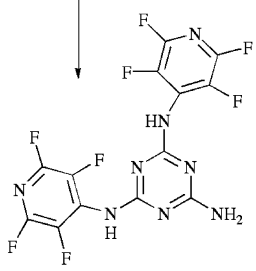


9a



12



14

Scheme 5.

*3.1.2. Preparation of N-(3-chloro-2,5,6-trifluoro-4-pyridyl)guanidine (**8b**)*

In the same manner as above, the chloropyridine (**7**) (0.24 g, 2.96 mmol) afforded *N*-(3-chloro-2,5,6-trifluoro-4-pyridyl) guanidine (**8b**) (0.4 g) mp 131–134°C (from hexane/ethyl acetate); (Found: C, 32.2; H, 1.5; N, 24.8% $C_6H_4ClN_4F_3$ requires C, 32.1; H, 1.8; N, 24.9%); δ_H (DMSO-d_6) 6.2 (bs, equivalent NH), δ_F (DMSO-d_6) −78.4 (dd, 1F, $^5J_{FF}$ 21.4, $^4J_{FF}$ 15.3, F2) −96.2 (dd, 1F, $^5J_{FF}$ 21.4, $^4J_{FF}$ 15.3, 6F), −155.4 (t, 1F, $^5J_{FF} = {}^3J_{FF}$ 21.4,5F), δ_C (DMSO-d_6) 156. (s, C7), 151.4 (m, C4), 151.1 (dd, $^1JC_{FC}$ 232.6, $^3J_{FC}$ 17.7, C2),147.1 (dt, $^1J_{FC}$ 235.9, $^2J_{FC} = {}^3J_{FC}$ 17.8, C6), 135.7 (ddd, $^1J_{FC}$ 246.6, $^3J_{FC}$ 24.9, $^4J_{FC}$ 5.4, C5), 105.7 (m, C3); *m/z* 224/226 $[M]^+$, 208/210 $[M - NH_2]^+$, 182/184 $[M - NHCNH]^+$.

*3.1.3. Preparation of bis-(tetrafluoro-4-pyridyl)amine (**10a**)*

Sodium hydride (0.237 g as a suspension 60% in mineral oil) which had been washed with dry hexane (2 × 10 cm^3) then with dry ether (2 × 10 cm^3) and finally with diglyme (5 cm^3) was suspended in diglyme (20 cm^3). A solution of urea (0.178 g, 2.97 mmol) in diglyme (20 cm^3) was added dropwise; when the initial evolution of hydrogen has subsided pentafluoropyridine **6** (0.5 g, 2.96 mmol) was added and the reaction heated at reflux for 18 h. The mixture was cooled and the solvent evaporated to leave a gum to which a mixture of ether (40 cm^3), water (10 cm^3) and 3 M HCl (20 cm^3) was added. The solution was separated and the ether layer dried ($MgSO_4$) and the solvent evaporated to a leave a crystalline mass, which was recrystallised from ether to yield bis-(tetrafluoro-4-pyridyl)amine (**10a**) (0.43 g, 93%) mp 144–146°C (cited 149–151°C [14,15]); (Found: C, 38.1; H, 0.4; N, 13.2% $C_{10}HF_8N_3$ requires C, 38.1; H, 0.3;N, 13.3%); δ_H (acetone-d_6) 9.6 (bs, D_2O exchangeable NH); δ_F (acetone-d_6) −92.7 (m, 2F, F2 and F6), −153.8 (m, 2F, F3 and F5); δ_C (acetone-d_6) 144.3 (ddt, $^1J_{FC}$ 238.6, $^2J_{FC} = {}^3J_{FC}$ 16.6 $^4J_{FC}$ is seen as an outer band of triplets but is too small to measure, C2), 135.9 (dm, $^1J_{FC}$ 256, C3); *m/z* 315 $[M]^+$ 296 $[M - F]^+$. Found mass, 315.00423. Required mass ($C_{10}HF_8N_3$), 315.00427.

*3.1.4. Preparation of bis-(3-chloro-trifluoro-4-pyridyl)amine (**10b**)*

In the same manner as above reaction of 3-chloro-tetrafluoropyridine (**7**) (2.0 g, 10.8 mmol) afforded, after purification by column chromatography (hexane: ethyl acetate 1:1 as eluant), bis-(3-chloro-trifluoro-4-pyridyl) amine **10b** (nc) (1.8 g, 96%) as a gum; (Found: C, 34.6; H, 0.4; N, 12.0% $C_{10}HCl_2F_6N_3$ requires C, 34.5; H, 0.3; N, 12.1%); δ_H ($CDCl_3$) 7.0 (bs, D_2O, exchangeable NH); δ_F ($CDCl_3$), −73.7 (dd, 1F, $^4J_{FF}$ 12.2, $^5J_{FF}$ 24.4, F2), −88.9 (dd, $^4J_{FF}$ 12.2, $^3J_{FF}$ 21.4, F5), −153.8 (dd, 1F, $^3J_{FF}$ 21.4, $^5J_{FF}$ 24.4, F5); δ_C ($CDCl_3$) 151.3 (ddd, $^1J_{FC}$ 241, $^3J_{FC}$ 15, $^4J_{FC}$2, C2) 147.5 (dt, $^1J_{FC}$ 244.2, $^2J_{FC} = {}^3J_{FC}$ 15.3, C6), 138.9 (m, C4), 135.3 (ddd, $^1J_{FC}$ 258.3, $^2J_{FC}$ 29.4, $^4J_{FC}$ 6.8, C5), 104.9 (dd, $^2J_{FC}$ 37.5, $^3J_{FC}$ or $^4J_{FC}$ 6.2, C3); *m/z* 347/349/351 $[M]^+$. Found mass, 346.94517. Required mass ($C_{10}HCl_2F_6N_3$), 346.94517.

*3.1.5. Preparation of bis-(tetrafluoro-4-pyridyl)sulfide (**11a**)*

Pentafluoropyridine (**6**) (1.50 g, 8.88 mmol) and thiourea (7.5 g, 98.7 mmol) were heated together in ethanol (50 cm^3) at reflux for 20 h. The mixture was cooled and the unreacted thiourea was filtered off. The filtrate and the ether washings of the precipitate were combined and the solvents evaporated to leave a residual solid which was re-extracted with cold ether (2 × 20 cm^3) to leave a further quantity of thiourea. The ether layer was washed successively with 2M HCl (20 cm^3) and water (20 cm^3), dried ($MgSO_4$) and the solvent evaporated to leave a pale yellow solid which was freed from any residual thiourea by column chromatography (hexane:ethyl acetate 1:1 as eluant) to yield bis-(tetrafluoro-4-pyridyl)sulfide (**11a**) (1.05 g, 71%) mp 43–46°C (cited 52–53 [18]); (Found: C, 36.0; N, 8.4% $C_{10}F_8N_2S$ requires C, 36.1; N, 8.4%); δ_F ($CDCl_3$) −90.4 (m, F2 and F6), −135.1 (m, F3 and F5); δ_C ($CDCl_3$) 144.3 (dm, $^1J_{FC}$ 245.3, 2C and 6C), 143.2 (dm, $^1J_{FC}$ 259.8, C3 and C5), 125.2 (m, C4); *m/z* 332 $[M]^+$.

*3.1.6. Preparation of bis-(3-chloro-trifluoro-4-pyridyl)sulfide (**11b**)*

In the same manner as above 3-chloro-tetrafluoropyridine (**7**) (1 g, 5.4 mmol) and thiourea (5.0 g, 65.8 mmol) afforded bis-(3-chlorotrifluro-4-pyridyl)sulfide (**11b**) (nc) (0.25 g, 25%) mp 33–36°C; (Found: C, 33.0; N, 7.7% $C_{10}Cl_2F_6N_2S$ requires C, 32.9; N, 7.7%); δ_F ($CDCl_3$) −73.0 (dd, 2F, $^5J_{FF}$, 27.5, $^4J_{FF}$ 12.2, F2), −88.5 (dd, 2F, $^3J_{FF}$ 21.4, $^4J_{FF}$ 12.2, F6), −133.7 (dd, 2F, $^3J_{FF}$ 21.4, $^5J_{FF}$ 27.5, F5); δ_C ($CDCl_3$) 151.9 (dd, $^1J_{FC}$ 242.6, $^3J_{FC}$ 13.4, C2), 148.1 (ddd, $^1J_{FC}$ 246.9, $^2J_{FC}$ 17.1, $^3J_{FC}$ 15.1, C6), 143.7 (ddd, $^1J_{FC}$ 258.7, $^2J_{FC}$ 28.3, $^4J_{FC}$6.1, C5) 136.5 (dm, $^2J_{FC}$ 15.3, C4), 116.8 (m, C3); MS *m/z* 364/366/368$[M]^+$.

*3.1.7. Reaction of N-(tetrafluoro-4-pyridyl)guanidine (**8a**) with sodium hydride*

The guanidine derivative **8a** (0.5 g, 2.4 mmol) in NMP (50 cm^3) was treated with sodium hydride (0.1 g, 2.4 mmol, 60% dispersion in oil washed from the oil as described above) at 100°C for 20 h. The mixture was cooled and ether (100 cm^3) and 2 M HCl (100 cm^3) were added and the mixture was continuously extracted for 24 h. The ether layer was dried ($MgSO_4$) and the solvent evaporated to leave a solid (0.15 g) which was identified as 4-amino-tetrafluoropyridine (**12**) [23] by comparison with an authentic sample.Similar reactions in other solvents, e.g. diglyme, DMSO, DMF and THF all gave essentially the same results.

*3.1.8. Thermal decomposition of **8a***

Heating in refluxing anisole for 2 days. The guanidine derivative **8a** (1.0 g) was heated in anisole (15 cm^3) at the

reflux temperature for 2 days. The reaction mixture was cooled, water (15 cm^3), saturated sodium bicarbonate solution (20 cm^3) and ether (30 cm^3) were added. The ether layer was separated, dried ($MgSO_4$) and the solvents evaporated to leave a pasty solid. TlC showed the presence of four components the major of which had an identical R_f value to starting material. The mixture was separated by column chromatography with ether:hexane (1:1) to yield (i) 4-amino-tetrafluoropyridine (**12**) (0.08 g, 10%) mp 84–85°C (cited [23] 85–86°C) identified by comparison with an authentic sample, (ii) Tris-(*N*-[tetrafluoro-4-pyridy])melamine (**13**) (nc) (0.04 g, 4.4%) mp 142–143°C; (Found: C, 37.4; H, 0.4; N, 21.8% $C_{18}H_3F_{12}N_9$ requires C, 37.7; H, 0.5; N, 22%); δ_H (acetone-d_6) 9.5 (bs, exchangeable with D_2O, NH); δ_F (acetone-d_6) −97.2 (m, 2F, F2 and F6), −145.3 (m, 2F, F3 and F5); MS *m/z* 573 $[M]^+$, 554 $[M-F]^+$. Found mass, 573.032980. Required mass ($C_{18}H_3F_{12}N_9$), 573.032922, (iii) bis-(*N*-[tetrafluoro-4-pyridyl])melamine (**14**) (nc) (0.07 g, 6.9%) mp 206–207°C; (Found: C, 37.1; H, 1.1; N, 26.2% $C_{13}H_4F_8N_8$ C, 36.8; H, 1.0; N, 26.4%); δ_H (acetone-d_6) 9.1 (bs,2H, D_2O exchangeable, 2 × NH), 0.6 (bs, 2H, D_2O exchangeable, NH_2), δ_F (acetone-d_6) −93.6 (m, 2F, F2 and F6) −145.7 (m, 2F, F3 and F5); δ_C (acetone-d_6) 168.9 (s, CNH_2), 165.6 (s, CNH), 144.3 (dt, $^1J_{FC}$ 239.6, $^2J_{FC} = {}^3J_{FC}$ 16.4, $^4J_{FC}$ too small to measure, C2), 138.6 (ddm, $^1J_{FC}$ 258, $^2J_{FC}$ 35.3, C3), 131.8 (m, C4); *m/z* 424 $[M]^+$, 405 $[M-F]^+$. Found mass, 424.043118. Required mass ($C_{13}H_4F_8N_8$), 424.0425145. and (iv) starting material (0.4 g).

In a repeat of the above reaction but with heating for 10 days under reflux we obtained complete reaction of the starting material to afford a mixture (0.6 g) which was separated as above to give(i) 4-amino-tetrafluoropyridine 46%, (ii) tris-(*N*-[tetrafluoro-4-pyridyl])melamine 20% and (iii) bis-(*N*-[tetrafluoro-4-pyridyl])melamine 34%, these ratios are approximately the same as we found in the 2-day experiment.

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