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Journal of Fluorine Chemistry 101 (2000) 45–60

JOURNAL OF FLUORINE CHEMISTRY

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Preparation and reactions of 2,3,4,6-tetrafluoropyridine and its derivatives

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Received 16 April 1999; accepted 3 August 1999

Abstract

A reliable route to 2,3,4,6-tetrafluoropyridine has been established starting from the readily available 3,5-dichlorotrifluoropyridine by halogen exchange under controlled conditions to give 3-chlorotetrafluoropyridine and its subsequent hydrodechlorination using hydrogen over palladium on alumina at 250–270°C. The formation and reactions of the 3-lithio derivative have been studied with the aim of obtaining 3,4-disubstituted trifluoropyridines. Routes to such materials have been developed and their conversion to deazapurine derivatives as potential substrates for the generation of anti-sense nucleosides are reported.

Keywords: Exchange reactions; Hydrodechlorination; 2,3,4,6-tetrafluoropyridine; Polyfluoropyridyl lithium reagents; Deazapurine derivatives

1. Introduction

We have, for some time, been interested in the use of fluorine containing deazapurines as precursors of potential anti-viral agents and as compounds for studies in anti-sense nucleosides. There is some evidence that replacement of a ring nitrogen in ribovirin derivatives with a CF-group has a beneficial effect on antiviral activity [1]. We decided that polyfluoropyridines were potential starting materials for this project, particularly if it were possible to obtain 3,4- disubstituted compounds. There has been only one significant paper concerned with the preparation of these compounds when the 3-substituent is not a halogen. Chambers [2] showed that amination of 4-nitro-tetrafluoropyridine **1** affords significant amounts of the 3-amino-4-nitrocompound **2**, this is the same pattern of substitution that was observed in a similar reaction with pentafluoronitrobenzene [3]. Reduction of **2** affords 3,4-diamino-trifluoropyridine **3**, which would be a possible precursor in our deazpurine synthesis. However, the original reaction was complicated by the formation of significant quantities of 4-aminotetrafluoropyridine **4**, formed by aminodenitration and 2-amino-4-nitrotrifluoropyridine **5** as shown in Scheme 1. This mixture of products was difficult to separate, which when allied with the somewhat hazardous oxidation of amino to nitro groups to obtain the starting material, did not suggest this was a viable route to the desired diamine **3**. We thus decided to look for a more feasible route to our target. It has been shown that some amine nucleophiles will give a significant amount of product with ortho substitution on reaction with polyfluorocarboxylic acids [4]. Thus, it seemed likely to us that if we could prepare tetrafluoronicotinic acid **6** (see Scheme 3) it could react in the 4-position with ammonia to give us a potentially useful intermediate. This reaction should be very likely to succeed as the 4-position in polyfluoropyridines is known to be the most active towards nucleophilic substitution and together with the added activating effect of the carboxyl group be even more likely to lead to the desired product. Tetrafluoronicotinic acid **6** has been prepared previously by Chambers [5] from 2,3,4,6-tetrafluoropyridine **7** which in turn was prepared by the hydrogenation of 3-chloro-tetrafluoropyridine **8**. This work has not been pursued, possibly due to the relative lack of available starting material. The attraction of this route led us to reinvestigate both the formation of 3-chloro-tetrafluoropyridine **8** the starting material in the Chambers' study and its hydrogenation to 2,3,4,6-tetrafluoropyridine **7**. We also proposed to make a more detailed study of the reactions of **7**.

Earlier work concerned with the preparation of polyfluoropyridines [6,7] was of two types. Firstly, uncatalysed reactions of fluoride ion with pentachloropyridine in dipolar aprotic solvents such as sulpholane at 190–200°C, or secondly by reaction of pentachloropyridine and potassium fluoride in an autoclave without solvent at 400–480°C. In the reaction in solvents both groups reported that the principal product obtained was 3,5-dichlorotrifluoropyridine **9** with only relatively small amounts of 3-chlorotetrafluoropyridine **8** and only trace amounts of pentafluoropyridine **10**

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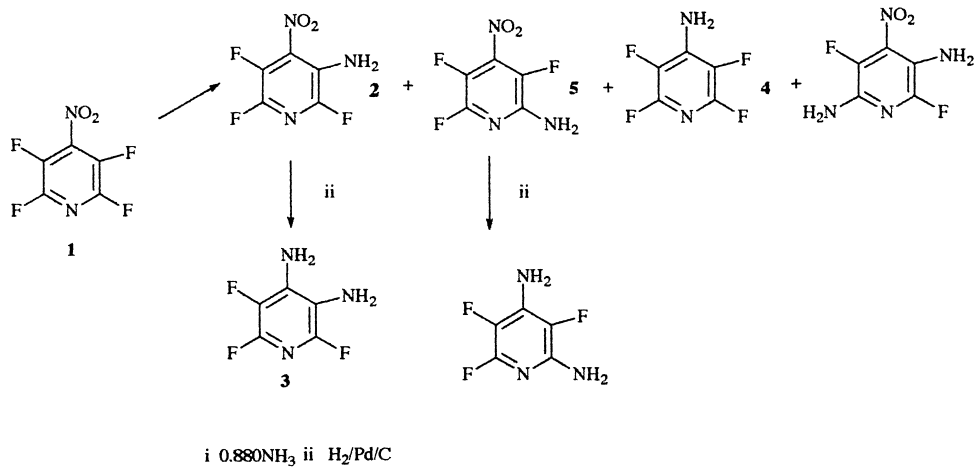
0022-1139/00/$ – see front matter
PII: S0022-1139(99)00189-X



Scheme 1.

being formed. In autoclave reactions it was found that at ca. 450°C the main products were the 3-chloro-tetrafluoropyridine **8** and pentafluoropyridine **10**. When the temperature was raised to 480°C the major component (80–90%) was pentafluoropyridine **10**. Although the latter reaction show excellent results for the formation of pentafluoropyridine **10** it suffers from the drawback of requiring somewhat specialist equipment and can only be used on a relatively limited batch size. We required a route which, without the use of specialist equipment, would lead to good yields of the 3-chlorotetrafluoropyridine as the major product. For the next step in our proposed route we required good yields of 2,3,4,6-tetrafluoropyridine **7**. The preparation of this compound on a relatively small-scale has been reported by Chambers [5] and we decided to re-investigate the hydrogenation route. Having obtained reasonable quantities of the desired compound **7** the aim of the project was then to study its reactions in the hope of finding a route to the required deazapurine.

2. Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR spectra (75 MHz) were measured on a Bruker AC 300 NMR spectrometer unless stated otherwise. ^{1}H 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. 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.

2.1. Fluorination of 3,5-dichlorotrifluoropyridine 9 with potassium fluoride: a typical procedure

Sufolane (previously distilled in vacuo) (300 g), spray-dried potassium fluoride (re-dried in a vacuum oven at 60°C for 12 h) (44 g, 0.759 mol) and tetraphenyl phosphonium bromide (10 g, 0.024 mol) were heated together in vacuo until ca. 30 cm^3 of distillate were obtained. The flask was allowed to cool to below 50° C when **9** (105 g, 0.505 mol) was added. The mixture was magnetically stirred at 200° C for 7 h under total reflux. After this time the mixture was fractionally distilled from the solvent to yield a mixture of polyfluoropyridines (77.8 g) boiling between 80°C and 160°C. GC analysis of the mixture showed three peaks attributable, by comparison with a known mixture, to pentafluorpyridine **10** (28.7%) [6,7], 3-chlorotetrafluoropyridine **8** (65%) [6,7] and unreacted starting material **9** (6.3%).

A mixture from five similar runs (590 g) was then re-fractionated to yield (i) pentafluoropyridine **10** (25.5 g) b.p. 83–84°C cited 84°C [6], (ii) mixed fractions of **8** and **10** (24.9 g) b.p. 85–118°C (iii) 3-chlorotetrafluoropyridine **8** (189 g) b.p. 119–120°C cited 119°C [6] and a 1 : 1 mixture of **8** and **9** (162 g), the latter was recycled in further experiments. All the pure products were identified by comparison of their spectra with authentic samples.

2.2. Preparation of tetraphenylphosphonium bromide 11

Triphenylphosphine (52.4 g, 0.20 mol), nickel bromide (36.46 g, 0.11 mol), bromobenzene (37.5 g, 0.24 mol) in benzonitrile (25 cm^3) were heated together under reflux

using a Dean and Stark trap. When no more water was observed in the trap, heating was continued for 3 h under total reflux. The mixture was cooled and then the product was steam distilled from the residual solids. The organic layer of the steam distillate, which solidified on standing, was dissolved in dichloromethane (400 cm^3), the aqueous layer was extracted with dichloromethane (2 × 25 cm^3), the combined extracts and the original solution were dried ($MgSO_4$) and the solvent removed to leave a slush. This latter was washed with ether (300 cm^3) to leave a crystalline solid which was filtered off and the residue washed with ether several times to leave, after drying in vacuo, pure tetraphenylphosphonium bromide (71.8 g, 85.6%) m.p. 290–295°C cited 287°C [9]; (Found: C, 68.4; H, 4.7% $C_{24}H_{20}BrP$ requires C, 68.7; 4.8%) δ_H (acetone d6) 7.54 (m, 2H, 2-H), 7.73 (m, 2H, 3-H), 7.83 (m, 1H, 4-H); δ_C 117.4 (d, $^1J_{PC}$ 89.5, 1-C), 130.9 (d, $^2J_{PC}$ 12.9, 2-C), 134.3 (d, $^3J_{P,3\text{-}C}$ 10.3, 3-C), 135.8(d, $^4J_{PC}$ 2.8, 4-C); *m/z* 339 (M^+ [Ph_4P]), 262, 185, 108.

2.3. Hydrogenolysis of 3-chlorotetrafluoropyridine **8**

In a typical experiment **8** (19.7 g) was dripped at a rate of 0.22 g/min onto the column head of a vertically mounted quartz column (2.5 cm × 15 cm heated length) packed with 0.5% palladium on alumina pellets (ex Johnson Matthey) held in place by plugs of quartz wool and fused alumina. The column was heated at 275° C and a stream of hydrogen at 50 cm^3/min was passed through during the addition of **8**. The products were collected in a trap cooled in liquid air. At the end of the addition the gas flow was continued for 30 min when the products (16.7 g) were collected from the trap. GC analysis showed the presence of 2,3,4,6-tetrafluoropyridine **7** (76%) and 3-chlorotetrafluoropyridine **8** (24%). No products from hydrodefluorination were observed. The products from several runs (128 g) were fractionated through a Spaltrohr column to yield (i) 2,3,4,6-tetrafluoropyridine **7** (65.4 g) b.p. 97–98°C (cited [5] 89–90°C); δ_H (acetone d6) 7.29 (dddd, 1H, $^5J_{HF}$ 1.5, $^3J_{HF}$ 2.5, $^4J_{HF}$ 4.0, $^3J_{HF}$ 6.0, 5-H); δ_F (acetone d6) −67.6 (bs, 1F, 6-F), −83.6 (bs, 1F, 2-F), −113.0 (ddd, 1F, J_{FF} 9.2, J_{FF} 33.6, J_{FF} 18.3, 4-F), −169 9 (m, 1F, 3-F); δ_C (acetone d6) −98.3 (dddd, $^2J_{FC}$ 43.1, $^2J_{FC}$ 21.2, $^4J_{FC}$ 6.6, $^4J_{FC}$ 2.1, 5-C), 134.0 (dddd, $^1J_{FC}$ 255.4, $^2J_{FC}$ 28.5, $^2J_{FC}$ 14.2, $^4J_{FC}$ 8.5, 3-C), 150.6 (dm, $^1J_{FC}$ 260.8, 2-C), 155.9 (dm, $^1J_{FC}$ 244.3, 6-C), 161.0 (dm, $^1J_{FC}$ 263.4, 4-C); *m/z* 151 (M^+), 132 (M^+–F), 120 (M^+–CF), 106 (M^+–NCF), 93 (M^+–NCF–CH), 87 (M^+–NCF–F), 82 (M^+–CF–F–F), 75 (M^+–NCF–CF).

2.4. Preparation of 2,4,5,6-tetrafluoronicotinic acid **6**

(i) *Using butyllithium and gaseous carbon dioxide.* To 2,3,4,6-tetrafluoropyridine (1.00 g, 6.62 mmol) and dry ether (100 cm^3) cooled to −78°C was added butyllithium in hexane (1.6M, 4.20 cm^3, 6.72 mmol) over 20 min so that the internal temperature did not rise above −65°C. The reaction was stirred for a further 60 min at −78°C when the reaction was allowed to warm to −55°C and carbon dioxide (dried by passing down a calcium chloride tube) was bubbled into the solution. A white precipitate formed immediately and the temperature began to rise. After two hours of passing carbon dioxide through the solution all the solvent had evaporated to leave a white paste. Hydrochloric acid (2M, 40 cm^3) and ether (40 cm^3) were added to the reaction flask until all solids had dissolved. The ether layer was separated, washed with brine (30 cm^3), dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator to leave, after recrystallisation from hexane, 2,4,5,6-tetrafluoronicotinic acid **6** (1.29 g, 6.56 mmol, 89.1%), m.p. 120–121°C (cited [5] 121–122°C); δ_F (acetone d6) −65.9 (1F, m, 2-F), −81.4 (1F, m, 6-F), −112.5 (ddd, 1F, $^4J_{FF}$ 23.4, $^3J_{FF}$ 19.1, $^4J_{FF}$ 10.6, 4-F), −167.0 (ddd, 1F, $^5J_{FF}$ 23.5, $^3J_{FF}$ 22.2, $^3J_{FF}$ 19.2, 5-F); δ_C (acetone d6) 105.8 (m, 3-C), 134.4 (dddd, $^1J_{CF}$ 257.9, $^2J_{CF}$ 28.0, $^2J_{CF}$ 15.0, $^4J_{CF}$ 8.5, 5-C), 151.5 (dddd, $^1J_{CF}$ 245.0, $^2J_{CF}$ 18.3, $^3J_{CF}$ 12.9, $^3J_{CF}$ 7.5, 6-C), 154.2 (dddd, $^1J_{CF}$ 249.3, $^3J_{CF}$ 16.2, $^3J_{CF}$ 9.7, $^4J_{CF}$ 3.2, 2-C), 160.1 (dddd, $^1J_{CF}$ 71.8, $^2J_{CF}$ 10.8, ^3J_C, or $^3J_{CF}$ 7.6, $^3J_{CF}$ or $^3J_{CF}$ 6.5, 4-C), 175.0 (s, CO_2H); *m/z* 195 (M^+), 178 (M^+–OH), 167 (M^+–CO), 151 (M^+–CO_2), 150 (M^+–CO_2H or M^+–NCF).

(ii) A repeat of this experiment (on a smaller scale) was also carried out in hexane with a yield of 0.24 g of tetrafluoronicotinic acid **6** (65%).

(iii) *Using butyllithium and solid carbon dioxide*. A repeat of the experiment in which the carbon dioxide was added as dry ice worked well giving good yields (in excess of 70% as standard) on a small-scale (less than 1 g of 2,3,4,6-tetrafluoropyridine). Increasing the scale of the reaction up to 7.50 g of 2,3,4,6-tetrafluoropyridine failed and a yield of only 10% of **6** was obtained along with a large amount of polymeric material.

2.5. Using lithium di-isopropylamide (LDA) and solid carbon dioxide

2,3,4,6-Tetrafluoropyridine (0.2 cm^3, 0.30 g, 1.99 mmol) was added to a solution of LDA in THF (25 cm^3) at −78°C and the mixture stirred for 40 min. The cooling bath was removed and crushed (solid) carbon dioxide was added to the solution. A white precipitate formed as the temperature began to rise towards room temperature. After 4 h water (5 cm^3) was added and the reaction mixture poured into 2M hydrochloric acid (20 cm^3) and ether (20 cm^3), the ether layer was separated and washed with saturated sodium bicarbonate solution until the aqueous layer remained basic to pH paper. The ether layer was removed and discarded. The aqueous layer was acidified with 2M hydrochloric acid and extracted with ether (3 × 50 cm^3). The combined ether layers were washed with brine (30 cm^3) and dried ($MgSO_4$), filtered and the solvent removed to leave 2,4,5,6-tetrafluoronicotinic acid **6** (0.11 g, 0.56 mmol, 28.1%).

2.6. Preparation of ethyl tetrafluoroisonicotinate **25**

2,3,5,6-Tetrafluoropyridine (5.00 g, 33.11 mmol) and dry THF (60 cm^3) were cooled to −78° C and butyllithium (1.6M, 20.6 cm^3, 32.96 mmol) in hexane was added over 30 min and the mixture stirred for a further 30 min. Freshly distilled ethyl chloroformate (4.00 g, 36.87 mmol) in ether (5 cm^3) was added to the red solution at −78°C and the reaction stirred at this temperature for 1 h. The solution was allowed to warm to room temperature and then stirred for 18 h. Water (5 cm^3), hydrochloric acid (2M, 60 cm^3) and ether (60 cm^3) were added successively. The organic layer was separated, washed with brine (30 cm^3), dried ($MgSO_4$), filtered and most of the volatile components removed on a rotary evaporator to leave a clear liquid. This was then carefully distilled at room temperature and then residue re-distilled under vacuum to give ethyl tetrafluoroisonicotinate **25** (4.64 g, 20.80 mmol, 63%) (n.c.) b.p. 67–69°C/9 mmHg; (Found: C, 42.8; H, 2.18% $C_8H_5F_4NO_2$ requires C, 43.1; H, 2.3%); δ_H (acetone d6) 1.40 (t, 3H $^3J_{HH}$ 0.7 Hz, 3H, CH_2CH_3), 4.52 (q, 2H, $^3J_{HH}$ 0.7, CH_2CH_3); δ_F (acetone d6) −90.6 (m, 2F, 2-F, 6-F), −141.7 (m, 2F, 3-F, 5-F); *m/z* 223 (M^+), 195 (M^+–CH_2CH_2), 178 (M^+–NCF or EtO), 150 (M^+–CO_2Et), 131 (M^+–CO_2Et–F), 105 (M^+–CO_2Et–NCF).

2.7. Preparation of 2,3,4,6-tetrafluoro-5-trimethylsilylpyridine **17**

(i) *Using butyllithium*. To dry ether (12 cm^3) and 2,3,4,6-tetrafluoropyridine (0.6 cm^3, 0.90 g, 5.96 mmol), cooled to below −70°C butyllithium in hexanes (1.6M, 3.73 cm^3, 5.97 mmol) was added over 30 min so that the internal temperature did not rise above −55°C. The reaction was stirred for a further 40 min at −70°C. An excess of trimethylsilyl chloride (0.90 cm^3, 0.77 g, 7.10 mmol) was added and the reaction stirred for 2 h at −70°C. The solution warmed to room temperature and was stirred a further 30 min. Water (30 cm^3) and ether (30 cm^3) were added, the ether layer separated, washed with brine (30 cm^3), dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator to leave a clear liquid (0.93 g). By ^{19}F NMR analysis, two components were present in a ratio of 70 : 30. With the help of GCMS analysis they were identified as 2,3,4,6-tetrafluoro-5-trimethylsilylpyridine **17** and 2-butyl-3,4,6-trifluoro-5-trimethylsilylpyridine **18**. The mixture was separated by column chromatography (silica, hexane/ethyl acetate 4 : 1) to give (i) 2,3,4,6-tetrafluoro-5-trimethylsilylpyridine 17 (0.52 g) (n.c.) b.p. 71–73°C/20 mmHg; (Found: C, 42.8; H, 4.3%,$C_8H_9F_4NSi$ requires C, 43.0; H, 4.1%); δ_H (acetone d6) 0.1 (s, 9H, $Si(CH_3)_3$); δ_F (acetone d6) −57.1 (bs, 1F, 6-F), −87.1 (bm, 1F, 2-F), −104.9 (m, 1F, 4-F), −170.8 (q, 1F, J_{FF} 21.4, 3-F); δ_C (acetone d6) 2.0 (s, CH_3), 108.1 (m, C-5), 133.7 (dm, $^1J_{FC}$ 256.6, 3-F), 151.6 (dm, $^1J_{FC}$ 241.6, 2-C), 151.8 (dm, $^1J_{FC}$ 238.1, 6-C), 158.8 (dm, $^1J_{FC}$ 240.3, 4-C); *m/z* 223 (M^+), 208 (M^+–CH_3), 148 (M^+–$(CH_3)_2$–NCF), 133 (M^+–$(CH_3)_3$–NCF), 101 ($(CH_3)_2SiCCF$) and (ii) 2-butyl-3,4,6-trifluoro-5-trimethylsilylpyridine **18** (0.18 g) (n.c.) b.p. 95–98°C/20 mmHg; (Found: C, 55.9; H, 6.8% $C_{12}H_{18}F_3NSi$ requires C, 55.2; H, 6.9%); δ_H (acetone d6) 0.40 (s, 9H, $Si(CH_3)_3$), 0.95 (t, $^3J_{HH}$ 7.5 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.40 (sextet, 2H, $^3J_{HH}$ 7.5, $CH_2CH_2CH_2CH_3$), 1.69 (quintet, 2H, $^3J_{HH}$ 7.5, $CH_2CH_2CH_2CH_3$), 2.75 (dt, 2H, $^3J_{HH}$ 7.5, J_{HF} 2.5, $CH_2CH_2CH_2CH_3$); δ_F (acetone d6) −56.0 (m, 1F, 6-F), −110.7 (t, 1F, $^3J_{FF} = 4$, J_{FF} 18.3, 4-F), −157.0 (m, 1F, 3-F); *m/z* 261 (M^+), 260 (M^+–H), 246 (M^+–CH_3), 232 (M^+–CH_3CH_2), 219 (M^+–$CH_3CH_2CH_2$), 218 (M^+–CH_3CH_2–CH_3), 204 (M^+–$CH_3CH_2CH_2CH_2$), 203 (M^+–$CH_3CH_2CH_2$–CH_3), 177 (M^+–$CH_3CH_2CH_2$–CH_3–C), 163 (M^+–$CH_3CH_2CH_2$–CH_3–CN).

(ii) *Using LDA*. 2,3,4,6-Tetrafluoropyridine (0.2 cm^3, 0.30 g, 1.99 mmol) was added at −78° C to LDA (2.22 mmol in ether 15 cm^3) and the mixture stirred for 40 min. Trimethylsilyl chloride (0.26 cm^3, 0.22 g, 2.03 mmol) was added and the reaction stirred for 4 h at −70° C. The solution was warmed to room temperature and stirred for 30 min. Water (30 cm^3) and ether (30 cm^3) were added, the ether layer was separated, washed with brine (30 cm^3), dried ($MgSO_4$), filtered and the solvent removed to leave a clear liquid (0.18 g). Two components were present in a ratio of 65 : 35. These were identified as 2,3,4,6-tetrafluoro-5-trimethylsilylpyridine **17** (65%) and 2-(*N*, *N*-diisopropylamino)-3,4,6-trifluoro-5-trimethylsilylpyridine **17a** (35%). Separation by column chromatography (silica, hexane/ethyl acetate) gave (i) **17** and (ii) 2-(*N*,*N*-diisopropylamino)-3,4,6-trifluoro-5-trimethylsilylpyridine **17a**; δ_F (acetone d6) −56.9 (bs, 1F, 6-F), −112.9 (m, 1F, 4-F), −163.8 (m, 1F, 3-F).

2.8. Preparation of 2,3,4,6-tetrafluoro-5-tributylstannylpyridine **19**

Butyllithium (1.6M, 1.24 cm^3, 1.98 mmol) in hexanes was added to 2,3,4,6-tetrafluoropyridine (0.2 cm^3, 0.30 g, 1.99 mmol) in dry ether (12 cm^3) at −78°C over 20 min at such a rate that the internal temperature did not rise above −65°C. The reaction was stirred for a further 90 min at −70°C when tributylstannyl chloride (0.54 cm^3, 0.65 g, 2.00 mmol) was added and the reaction stirred for 2 h at −70°C. The solution warmed to room temperature and was stirred for 30 min, water (30 cm^3) and ether (30 cm^3) were then added. The ether layer was separated, washed with brine (30 cm^3), dried over $MgSO_4$, filtered and the solvent removed to leave a clear liquid. By ^{19}F NMR analysis, only one component was present and was identified as 2,3,4,6-tetrafluoro-5-tributylstannylpyridine (0.64 g, 73.3%) (n.c.) b.p. 125°C/20 mmHg; (Found: C, 46.2; H, 6.3% $C_{17}H_{27}F_4NSn$ requires C, 46.4; H 6.2%); δ_H 0.880 (t, 9H, $^3J_{HH}$ 7, CH_3), 1.04 (t, 6H, $^3J_{HH}$ 8, CH_2), 1.33 (sextet, 6H, $^3J_{HH}$ 7, CH_2), 1.52 (q, 6H, $^3J_{HH}$ 7, CH_2); δ_F (acetone d6) −55.3 (m, 1F, 6-F), −89.0 (m, 1F, 2-F), −100.2 (m, 1F, 4-F), −170.8 (m, 3-F); *m/z* 440 (M^+), 383, 326, 269.

2.9. Preparation of 2,3,4,6-tetrafluoro-5-iodopyridine **20**

Butyllithium in hexanes (1.6M, 1.24 cm^3, 1.98 mmol) was added over 10 min to 2,3,4,6-tetrafluoropyridine (0.2 cm^3, 0.30 g, 1.99 mmol) in dry ether (20 cm^3) at −78°C so that the internal temperature did not rise above −70°C. The reaction was stirred for a further 30 min at −78°C. Iodine (0.75 g, 2.95 mmol) was added and the reaction stirred for 30 min at −78°C. The solution allowed to warm to room temperature over 1 h and stirred for a further 1 h when water (5 cm^3) was added. Aqueous sodium thiosulphate was added, the ether layer was separated, washed with sodium bicarbonate (20 cm^3), brine (20 cm^3) and dried ($MgSO_4$). The solution was filtered and most of the ether removed, distillation using a Kugelrohr distillation apparatus to give 2,3,4,6-tetrafluoro-5-iodopyridine **20** (0.29 g) (n.c.) b.p. 143–145°C; (Found: C, 21.4; N, 4.9% C_5F_4IN requires C, 21.7; N, 5.1%); δ_F (acetone d6), −58.9 (bm, 1F, 6-F), −88.0 (bm, 1F, 2-F), −96.6 (dt, 1F, $^4J_{FF} = {}^3J_{FF}$ 21.4, $^3J_{FF}$ 12.2, 4-F), −165.3 (q, 1F, $^5J_{FF} = {}^3J_{FF} = {}^3J_{FF}$ 21, 3-F); δ_C (acetone d6) 62.9 (dddd, $^2J_{CF}$, 49.3, $^2J_{CF}$ 26.8, $^3J_{CF}$ 7.5, $^4J_{CF}$ 4.3, 5-C), 133.3 (dddd, $^1J_{CF}$ 259.5, $^2J_{CF}$ 29.0, $^2J_{CF}$ 16.1, $^4J_{CF}$ 8, 3-C), 150.8 (dddd, $^1J_{CF}$ 241.0, $^2J_{CF}$ 17.2, $^3J_{CF}$ 13.9, $^4J_{CF}$ 7.5, 2-C), 153.3 (dddd, $^1J_{CF}$ 234.9, $^3J_{CF}$ 15.0, $^3J_{CF}$ 9.6, $^4J_{CF}$ 3.2, 6-C), 161.1 (dddd, $^1J_{CF}$ 257.4, $^2J_{CF}$ 10.7, $^3J_{CF}$ 8.6, $^3J_{CF}$ 6.4, 4-C); *m/z* 277 (M^+), 150 (M^+–I), 127 (I^+), 105 (M^+–I–NCF), 100 (M^+–I–CF–F), 93 (M^+–CI–NCF), 86 (M^+–I–F–NCF), 74 (M^+–I–NCF–CF); Accurate *m/z* 276.9013262 (calc. for C_5F_4IN 276.901164).

2.10. Preparation of tetrafluoronicotinaldehyde **15** and 2,5,6-trifluoro-4-hydroxynicotinaldehyde **16**

2,3,4,6-Tetrafluoropyridine (0.2 cm^3, 0.30 g, 1.99 mmol) in dry ether (20 cm^3) was cooled to below −78°C, butyllithium in hexane (1.6M, 1.24 cm^3, 1.98 mmol) was added over 10 min so that the internal temperature did not rise above −75°C. The reaction was stirred for a further 30 min at −78°C. *N*-Methylformanilide (0.25 cm^3, 0.27 g, 2.000 mmol) was added and the reaction stirred for 2 h at −78°C when the solution allowed to warm to room temperature over 2 h. The reaction mixture was poured into saturated ammonium chloride solution, the ether layer was separated, combined with extracts of the aqueous layer (2 × 25 cm^3), dried ($MgSO_4$). The ether was removed by rotary evaporation to leave a slightly coloured liquid (0.39 g), which crystallised on standing. Recrystallisation from hexane/benzene 10 : 1 afforded tetrafluoronicotinaldehyde **15** (0.3 g) m.p. 59–61°C (cited [16] 59–60°C); δ_H (acetone d6) 10.18 (t, $^4J_{HF} = {}^4J_{HF}$ 1.1 Hz, C*H*O); δ_F (acetone d6) −71.2 (bm, 1F, 2-F), −76.9 (bm, 1F, 6-F), −118.4 (m, 1F, 4-F), −166.8 (m, 1F, 5-F); *m/z* 179 (M^+), 178 (M^+–H), 150 (M^+–CHO), 100 (M^+–CHO–CF–F).

In a repeat of this experiment but using a non-acidic work-up we obtained, as the sole product, 2,5,6-trifluoro-4-hydroxynicotinaldehyde **16** (0.28 g) (n.c.) b.p. 90°C/2 mmHg; (Found: C, 40.4; H, 1.3% $C_6H_2F_3NO_2$ requires C, 40.7; H, 1.1%); δ_H (acetone d6) 10.20 (d, $J_{H,2\text{-}F}$ 1.8 Hz, C*H*O); δ_F (acetone d6) −75.2 (bm, 1F, 2-F), −80.4 (bm, 1F, 6-F), −170.0 (1F, m, 1F, 5-F); *m/z* 177 (M^+), 176 (M^+–H), 148 (M^+–CHO), 131 (M^+–CHO–OH), 120 (M^+–CHO–CO), 119 (M^+–CHO–HO–C).

2.11. Attempted preparation (and subsequent oxidation) of tetrafluoro-5-nitrosopyridine

Nitrosyl chloride (pre-prepared from sodium nitrite and conc. HCl) was bubbled through tetrafluoro-3-lithiopyridine prepared as above from **7** (0.30 g) at −78°C. The reaction mixture was slowly warmed to −60°C and kept at this temperature for 2 h. The solution was allowed to warm to room temperature over 2 h during the whole of this time a constant supply of nitrosyl chloride being passed through the solution. The reaction was stirred at room temperature for a further 2 h and then dry air was drawn through the mixture for several hours. Immediately after this oxidation was stopped ^{19}F NMR analysis of the mixture was carried out which showed that there were three types of aromatic ring in the mixture, from either two or three compounds. The peaks were at −71.7 (bm), −72.7 (bm), −75.7 (bm), −78.4 (bm), −80.0 (bm), −80.7 (bm), −114.9 (bm), −119.1 (m), −163.0 (m), −163.1 (m), −166.1 (m). In the light of later results, shown below, the products are suggested to be bis-(2,4,5,6-tetrafluoro-3-pyridyl)amine **21**, bis-(2,4,5,6-tetrafluoro-3-pyridyl)hydroxylamine **22** and bis-(2,4,5,6-tetrafluoro-3-pyridyl)nitroxide **23**.

2.12. Attempted preparation (and subsequent amination) of tetrafluoro-5-nitrosopyridine

Tetrafluoro-3-lithiopyridine was reacted as above with nitrosyl chloride but instead of the oxidation step 0.880 ammonia was added to the reaction and the solution turned black immediately. The reaction was stirred for a further 18 h before being poured into concentrated hydrochloric acid (60 cm^3). Ether (30 cm^3) was added, the ether layer separated, dried ($MgSO_4$), and after filtration the solvents were removed by rotary evaporation. The residue (0.15 g) was a black semi-solid. ^{19}F analysis of this showed the presence of two compounds which were readily separated by column chromatography (silica, hexane/ethyl acetate 4 : 1) as (i) bis-(2,4,5,6-tetrafluoro-3-pyridyl)amine **21** and (ii) *N*-(4′-amino-2′,5′,6′-trifluoro-3′-pyridyl)-3-amino-tetrafluoropyridine **24** (see below for characterisation) in about equal amounts.

2.13. Attempted preparation (and subsequent reduction) of tetrafluoro-5-nitrosopyridine

Tetrafluoro-3-lithiopyridine (from **7** 1.8 g) was reacted as above with nitrosyl chloride. At the end of the addition of

the nitrosyl chloride the solvents were removed by rotary evaporation, water (30 cm^3) and zinc powder (8.50 g) were then added followed by the dropwise addition of concentrated hydrochloric acid (60 cm^3). The final colour of the solution (after all the zinc had been used up) was pale yellow. The ether layer was separated, washed with water (30 cm^3) and dried ($MgSO_4$). After filtration most of the solvent was removed on a rotary evaporator to leave a residue (2 g) which was separated by column chromatography (silica, dichloromethane) to give bis-(2,4,5,6-tetrafluoro-3-pyridyl)amine **21** (1.20 g, 63%) (n.c.) m.p. 86–87°C as a yellow solid; (Found: C, 38.3; H, 0.28% $C_{10}HF_8N_3$ requires C, 38.1; H, 0.32%); δ_F (acetone d6) −80.1 (bm, 1F 6-F), −93.2 (bm, 1F 2-F), −127.1 (m, 1F, 4-F), −165.9 (m, 1F, 5-F); δ_C (acetone d6) 115.0 (m, 3-C), 133.6 (dm, $^1J_{CF}$ 258.3, 5-C), 144.1 (dm, $^1J_{CF}$ 239, 6-C), 147.5 (dm, $^1J_{CF}$ 241.0, 2-C), 153.1 (dm, $^1J_{FF}$ 260.5, 4-C); *m/z* 315 (M^+), 296 (M^+–F), 295 (M^+–HF), 277 (M^+–F–F), 276 (M^+–HF–F), 269 (M^+–NCF–H), 250 (M^+–NCF–HF), 245 (M^+–CF–HF–F), 231 (M^+–NCF–HF–F), 119 (M^+–C_5F_4N–NH–CF), 100 (M^+–C_5F_4N–NH–CF–F).

2.14. Reaction of 2,4,5,6-tetrafluoro-3-pyridyllithium with nitrosonium tetrafluoroborate

Tetrafluoro-3-lithiopyridine was prepared as above. The reaction was stirred for a further 30 min at −78 °C when nitrosonium tetrafluoroborate (0.94 g, 8.034 mmol) was added and the reaction stirred for a further 2 h at −78°C. The solution was warmed to room temperature and the reaction stirred for 30 min. Hydrochloric acid (2M, 20 cm^3) was then slowly added. The ether layer was separated, dried ($MgSO_4$) and the solvent removed on a rotary evaporator to leave a yellow liquid (0.40 g) which crystallised on standing. The ^{19}F NMR spectrum of the crude product showed it to be very largely **21**.

2.15. Amination of ethyl tetrafluoroisonicotinic acid

Ethyl2,3,5,6-tetrafluoroisonicotinate (3.12 g, 13.99 mmol) was dissolved in ether (200 cm^3) in a round bottomed flask and ammonia gas was bubbled through for 6 h. After 1 h the solution became yellow but even after 6 h no precipitate of ammonium fluoride was seen. ^{19}F NMR analysis showed that only ethyl 2,3,5,6-tetrafluoroisonicotinate remained. The ether was mostly distilled off using an Oldershaw column and the residue from this experiment and 0.880 ammonia (20 cm^3) were stirred at room temperature for 18 h. The solution was acidified and ether (40 cm^3) was added. The ether layer was washed with water (25 cm^3), brine (25 cm^3), dried ($MgSO_4$) and the solvent removed on a rotary evaporator to yield a yellow solid (2.6 g). Column chromatography (hexane-ethyl acetate, 1 : 2) on a small sample (0.5 g) of the product gave (i) 2-amino-3,5,6-trifluoroisonicotinamide **27** (0.38 g) (n.c.) m.p. 216–218°C; (Found: C, 37.31; H, 2.36; N 21.60. $C_6H_3F_3N_2O_2$ requires C, 37.71; H, 2.11; N, 21.99%); δ_H (acetone d6) 6.05 (bs, 2H, NH_2), 7.50 and 7.75 (broad s, 2H, $CONH_2$ (protons are not equivalent)); δ_F (acetone d6) −94.3 (dd, 1F, $^3J_{FF}$ 24.4, $^5J_{FF}$ 30.5, 6-F), −144.2 (dd, 1F, $^4J_{FF}$ 6.1, $^5J_{FF}$ 33.6, 3-F), −160.3 (dd, 1F, $^3J_{FF}$ 27.5, $^4J_{FF}$ 6.1, 5-F); δ_C (acetone d6) 126.7 (t, $^2J_{FC} = {}^2J_{FC}$ 19.5, 4-C), 131.9 (dd, $^1J_{FC}$ 247.2, $^2J_{FC}$ 32.5, 5-C), 140.0 (dd, $^1J_{FC}$ 252.2, $^3J_{FC}$ 4.9, 3-C), 143.9 (t, $^3J_{FC} = {}^2J_{FC}$ 16.2 H, 2-C), 145.8 (dd, $^1J_{FC}$ 229.0 Hz, $^2J_{FC}$ 13.8, C-2), 160.8 (s, $CONH_2$); *m/z* 191 (M+), 148 (M^+–CONH), 121 (M^+–CONH–CNH), 101 (M^+–CONH–CNH_2–F), 75 (M^+–CONH–CNH_2–NCF).

Two other compounds were obtained in small amounts but could not be fully characterised. On the basis of their ^{19}F NMR spectra we believe these compounds to be ethyl-2-amino-3,5,6-trifluoroisonicotinate **28** δ_F (acetone d6) −94.3 (m, 1F, 6-F), −144.3 (dd, 1F, $^4J_{FF}$ 6.1, $^5J_{FF}$ 30.5, 3-F), −162.0 (dd, 1F, $^3J_{FF}$ 24.4, $^4J_{FF}$, 6.1, 5-F) and 2,3,5,6-tetrafluoroisonicotinamide **29** δ_F (acetone d6) −90.4 (m, 1F, 2-F), −141.7 (m, 1F, 3-F).

2.16. Amination of tetrafluoronicotinic acid

2,4,5,6-Tetrafluoronicotinic acid (2.56 g, 13.13 mmol) and 0.880 ammonia (30 cm^3) were stirred together for 15 h. Ether (60 cm^3) was added followed by 5M hydrochloric acid until the aqueous layer was acidic. The ether layer was separated, washed with saturated sodium bicarbonate solution (40 cm^3), the basic layer removed and re-acidified and ether (40 cm^3) was added. The ether was separated, washed with water (25 cm^3), brine (25 cm^3) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to leave 4-amino-2,5,6-trifluoronicotinic acid **26** (1.87 g, 71.9 %) (n.c.), m.p. 216–218°C; (Found: C, 37.4; H, 1.82; N 14.9%. $C_6H_3F_3N_2O_2$ requires C, 37.52; H, 1.57; N, 14.6 %). δ_F (acetone d6) (at 400 MHz) −60.5 (dd, 1F, $^5J_{FF}$ 23.4, $^4J_{FF}$ 8.3, 2-F), −90.6 (dd, 1F, $^3J_{FF}$ 20.8, $^4J_{FF}$ 9.9, 6-F), −170.8 (dd, 1F, $^5J_{FF}$ 23.7, $^3J_{FF}$ 20.9, 2-F); δ_C (acetone d6) 94.8 (dm, $^2J_{FC}$ 30.8, 3-C), 131.5 (ddd, $^1J_{FC}$ 243.3, $^2J_{FC}$ 27.4, $^5J_{FC}$ 5.8, 5-C), 150.2 (ddd, $^1J_{FC}$ 237.3, $^2J_{FC}$ 21.1, $^3J_{FC}$ 13.1, 6-C), 152.5 (m, 4-C), 157.3 (dm, $^1J_{FC}$ 247.6, C-2), 166.8 (d, $^3J_{FC}$ 7.6, CO_2H); *m/z* 192 (M^+), 174 (M^+–OH–H), 147 (M^+–CO_2H or M^+–NCF).

2.17. Preparation of 4-aminotrifluoronicotinic acid from 2,3,4,6-tetrafluoropyridinein a "one pot" reaction

Tetrafluoro-3-lithiopyridine from **7** (6 g) as above in ether (100 cm^3) was stirred for 40 min at −78°C and then allowed to warm to −55°C, carbon dioxide (dried by passing down a calcium chloride tube) was bubbled into the solution for 3 h when all the solvent had evaporated. 0.880. Ammonia (60 cm^3) was then carefully added, the mixture was stirred for 15 h, 6M hydrochloric acid was then very carefully added until the solution was acidic. A white solid precipitated as more hydrochloric acid was added. The solution was left to cool for 30 min and ether (80 cm^3) was added.

The ether layer was separated and washed with saturated sodium bicarbonate solution (40 cm^3), the basic aqueous layer was removed and re-acidified, ether (80 cm^3) was added. The ether layer was separated, washed with water (40 cm^3), brine (40 cm^3) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to leave 4-amino-2,5,6-trifluoronicotinic acid **31** (6.30 g, 32.81 mmol, 82.6%).

2.18. Amination of bis-(2,4,5,6-tetrafluoro-3-pyridyl)amine

To bis-(2,4,5,6-tetrafluoro-3-pyridyl)amine (1.00 g, 3.175 mmol) was added 880 ammonia (10 cm^3). The reaction mixture, which went black immediately, was then stirred for 20 h before being poured into concentrated hydrochloric acid (200 cm^3). Ether (50 cm^3) was added, the ether layer separated, dried ($MgSO_4$) and the solvents removed by rotary evaporation. The residue (0.80 g) was a black semi-solid. A sample of this solid (0.5 g) was separated by column chromatography (silica, hexane/ethylacetate 4 : 1) to give (i) unreacted starting material 0.2 g) and (ii) *N*-(2,4,5,6-tetrafluoro-3-pyridyl)-*N*-(4-amino-2,5,6-trifluoro-3-pyridyl)amine **29** (0.23 g) (n.c.) m.p. 106–108°C; (Found: C, 38.2; H, 0.8; N, 17.8% $C_4H_3F_7N_4$ requires C, 38.5; H, 0.97; N, 17.9%); δ_F −83.5 (bm, 2′-F), −83.6 (bm, 2-F), −95.1 (bq, 6′-F), −99.3 (bm, 6-F), −133.1 (m, 4-F), 167.1(q, 3-F) and −168.2 (t, 3′-F) ppm.

2.19. Attempted direct nitration of 2,3,4,6-tetrafluoropyridine

Fuming (90%) nitric acid (0.93 cm^3, 13.26 mmol) was added slowly to sulfolane (4 cm^3) at 0°C, boron trifluoride/dihydrate (0.84 cm^3, 1.38 g, 13.27 mmol) was then added dropwise. 2,3,4,6-Tetrafluoropyridine (1.00 g, 6.62 mmol) was added and the stirred mixture heated to, and maintained at 75°C for 2 h. After cooling, the mixture was poured onto crushed ice and the organic material was extracted with dichloromethane. ^{19}F NMR analysis of this dichloromethane layer showed only the presence of the starting material.

2.20. Curtius reactions of 4-amino-2,5,6-trifluoronicotinic acid using diphenyl phosphorazidate (DPPA)

4-Aminotrifluoronicotinic acid **26** (1.00 g, 5.21 mmol) in t-butanol (20 cm^3), triethylamine (0.3 cm^3, 0.53 g, 5.24 mmol) and DPPA (1.12 cm^3, 1.43 g, 5.20 mmol) were stirred together under reflux for 4 h. The solvents were evaporated, the residue dissolved in ether (30 cm^3) the solution was washed with water (25 cm^3) and then brine (25 cm^3). The ether layer was dried ($MgSO_4$) and evaporated to give a yellow residue. Column chromatography (silica, hexane-ethyl acetate, 1 : 1) gave 3-deaza-2,3,6-trifluoro-8-hydroxypurine (0.17 g, 19.3%) m.p. 239–241°C. (Found: C, 37.9; H, 0.9; N, 21.9% $C_6H_2F_3N_3O$ requires C, 38.1; H 1.1; N 22.2%); δ_H (DMSO) 11.8 (s, D_2O exchangeable, N–H), 12.4 (s, D_2O exchangeable, N–H); δ_F (acetone d6) −92.0 (dd, 1F, J_{FF} 27.5, J_{FF} 14.2, 6-F), −99.0 (dd, 1F, J_{FF} 22.6, J_{FF} 14.2, 2-F), −166.6 (dd, 1F, J_{FF} 27.5, J_{FF} 22.6, 3-F); δ_C (acetone d6) 112.2 (dm, $^2J_{FC}$ 34.5, 5-C), 128.6 (ddd, $^1J_{FC}$ 249.2, $^2J_{FC}$ 32.6, $^5J_{FC}$ 7.1, 3-C), 130.0 (m, 4-C), 137.9 (dd, $^1J_{FC}$ 231.7, $^2J_{FC}$, 15.0, coupling between 2-C and 6-F must be too small to be seen), 147.6 (ddd, $^1J_{FC}$ 231.0, $^3J_{FC}$ 14.5, $^4J_{FC}$ 14.5 Hz, C-6), 155.2 (s, 8-C); *m/z* 189 (M^+), 170 (M^+–F), 161 (M^+–CO), 142 (M^+–FCO), 134 (M^+–CO–CHN), 107 (M^+–CO–CHN–CHN

2.21. Reaction of 2,4,5,6-tetrafluoro-3-pyridyllithium with benzaldehyde

Tetrafluoro-3-lithiopyridine (from **7** 0.30 g) in dry ether (20 cm^3) was reacted at −78°C with freshly distilled benzaldehyde (0.21 cm^3, 0.22 g, 2.07 mmol) and the reaction stirred for 30 min at −78°C. The solution was allowed to warm to room temperature over one hour and was then stirred at room temperature for a further 1 h. Sulphuric acid (4M, 30 cm^3) was added the ether layer was separated, washed with water (20 cm^3), brine (20 cm^3) and dried ($MgSO_4$) and the ether removed by rotary evaporation to leave a yellow oil which was distilled in vacuo using a Kugelrohr apparatus to give phenyl-(2,4,5,6-tetrafluoro-3-pyridyl)methanol **33** (0.36 g, 1.40 mmol, 70.7%) (n.c.) b.p. 120–125°C/0.1 mmHg; (Found: C, 56.1; H, 2.6% $C_{12}H_7F_4N$ requires C, 56.0; H, 2.7%), δ_H (acetone d6) 6.2 (1H, s, C*H*–OH), 7.1–7.5 (5H, m, Ar); δ_F (acetone d6) −71.4 (bm, 1F, 2-F), −87.6 (bm, 1F, 6-F), −117.0 (m, 1F, 4-F), −168.0 (m, 1F, 3-F); δ_C (acetone d6) 66.6 (s, *C*H–OH), 126.3 (s, 2′-C, 6′-C), 128.3 (s, 4′-C), 129.1 (s, 3′-C, 5′-C), 142.8 (s, 1′-C) (signals for 2-C, 3-C, 4-C, 5-C and 6-C are all too small to be interpretable due to extensive C-F coupling); *m/z* 256 (M^+–H), 236 (M^+–H–HF), 180 (M^+–Ph), 164 (M^+–Ph–HF), 150 ($C_5F_4N^+$), 149 (M^+–Ph–CF), 130 (M^+–Ph–NCF), 107 (M^+–C_5F_4N), 77 (Ph^+).

2.22. Preparation of 1,1-bis-(2,4,5,6-tetrafluoro-3-pyridyl)ethyl acetate **36**

Acetyl chloride (0.28 cm^3, 0.31 g, 3.974 mmol) was added at –78°C to tetrafluoro-3-lithiopyridine prepared as above from **7** (0.6 g) and the reaction stirred for 30 min at −70°C, the solution was then allowed to warm to room temperature over 1 h, at about −20°C the solution became cloudy, and the reaction was stirred at room temperature for a further hour. 4M Hydrochloric acid (30 cm^3) was added, the ether layer separated, washed with sodium bicarbonate (20 cm^3), brine (20 cm^3) and dried ($MgSO_4$). The ether was removed by rotary evaporation to leave a pale yellow viscous liquid shown after distillation in vacuo to be 1,1-bis-(2,4,5,6-tetrafluoro-3-pyridyl)ethyl acetate **36** (0.62 g, 1.606 mmol, 80.8%) (n.c.) b.p. 175°C 4.5 mmHg; (Found: C, 43.43; H, 1.62; N, 7.04%. $C_{14}H_6F_8N_2O_2$ requires C,

43.54; H, 1.57; N, 7.25%); δ_H (acetone d6) 2.14 (s, 3H, OCOCH_3), 2.36 (q, 3H, J_{HF} 2.0, CCH_3); δ_F (acetone d6) −65.0 (bm, 1F, 2-F), −85.8 (bm, 1F, 6-F), −112.4 (m, 1F, 4-F), −166.3 (m, 1F, 5-F); δ_C (acetone d6) 21.3 (s, 9-C), 25.4 (q, $J_{CF} = J_{CF}$ 3.8, C-10), 78.0 (s, 7-C), 113.7 (m, 3-C), 134.4 (dddd, $^1J_{CF}$ 257.1, $^2J_{CF}$ 28.4, $^2J_{CF}$ 16.2, $^4J_{CF}$ 7, 5-C), 149.0 (dm, $^1J_{CF}$ 177.9, 6-C), 152.2 (dm, $^1J_{CF}$ 178.6, 2-C), 158.6 (dm, $^1J_{CF}$ 268.2, 4-C), 169.3 (s, C-8); *m/z* 386 (M^+), 327 (M^+–CO_2Me), 326 (M^+–HCO_2Me via McLafferty rearrangement), 307 (M^+–HCO_2Me–F), 287 (M^+–HCO_2Me–F–HF), 178 (C_5F_4NCO), 150 (C_5F_4N); Accurate *m/z* 386.031304 (calc. for $C_{14}H_6F_8N_2O_2$ 386.030154).

2.23. Preparation of 1,1-bis-(2,4,5,6-tetrafluoro-3-pyridyl)-2,2,2-trifluoroethanol **37**

Tetrafluoro-3-lithiopyridine from **7** (0.3 g) was stirred for 30 min at −70°C when trifluoroacetic anhydride (0.28 cm^3, 0.42 g, 2.000 mmol) was added and the reaction stirred for 30 min at −70°C. The solution was warmed to room temperature over 1 h and stirred for a further 1 h. Sulphuric acid (4M, 30 cm^3) was added, the ether layer was separated washed with water (40 cm^3), sodium bicarbonate (20 cm^3) and dried ($MgSO_4$). The ether was removed by rotary evaporation to leave a clear liquid which after distillation afforded 1,1-bis-(2,4,5,6-tetrafluoro-3-pyridyl)-2,2,2-trifluoroethanol **37**(0.45 g) (n.c.) b.p. 156°C/2 mmHg; (Found: C, 36.3; H, 0.4% $C_{12}HF_{11}N_2$ requires C, 36.2; H, 0.3%); δ_F (acetone d6) −62.9 (bm, 2F, 2-F), −77.8 (q, 3F, J_{FF} and J_{FF} 15.3, CF_3), −83.4 (bm, 2F, 6-F), −109.8 (m, 2F, 4-F), −165.5 (m, 2F, 5-F); δ_C (acetone d6) 75.6 (q, $^2J_{CF}$ 36.6, C–OH), 109.8 (m, 3-C), 124.4 (q, $^1J_{CF}$ 285.8, CF_3), 134.2 (dddd, $^1J_{CF}$ 258.2, $^2J_{CF}$ 28.2, $^2J_{CF}$ 15.9, $^4J_{CF}$ 7.9, 5-C), 150.4 (dm, $^1J_{CF}$ 244.5, 6-C), 152.2 (dm, $^1J_{CF}$ 245.0, 2-C), 159.3 (dm, $^1J_{CF}$ 270.3, 4-C); *m/z* 398 (M^+), 381 (M^+–OH), 379 (M^+–F), 362 (M^+–OH–F), 359 (M^+–HF–F), 329 (M^+–CF_3), 309 (CF_3–HF), 293 (CF_3–F–OH), 281 (CF_3–CF–OH), 262 (CF_3–CF–OH–F), 248 (M^+–C_5F_4N) or (M^+–CF_3–NCF–OH–F), 236 (M^+–CF_3–NCF–OH–F), 231 (M^+–CF_3–CF–CF–OH–F), 178 (M^+–C_5F_4N–CF_3–H), 150 (C_5F_4N).

2.24. Preparation of 2-(2,4,5,6-tetrafluoro-3-pyridyl) propan-2-ol **34**

Acetone (1.00 cm^3, 0.79 g, 13.62 mmol) was added to a solution of tetrafluoro-3-lithiopyridine from **7** (0.3 g) and the reaction stirred for 30 min at −78°C. The solution was warmed to room temperature over 1 h and stirred for a further 1 h. Sulphuric acid (4M, 30 cm^3) was added, the mixture separated and the ether layer washed with water (20 cm^3), brine (20 cm^3) and dried ($MgSO_4$). The ether removed by rotary evaporation to leave a clear liquid which was identified as 2-(2,4,5,6-tetrafluoro-3-pyridyl)-propan-2-ol **34** (0.38 g) (n.c) (Found: C, 46.1: H, 3.2% $C_8H_7F_4NO$ requires C,45.9; H 3.4%), δ_H (acetone d6) 1.7 (t, $J_{H,\,(4\text{-F and }2\text{-F})}$ 2.0); δ_F (acetone d6) −64.3 (bm, 1F, 2-F), −89.7 (bm, 1F, 6-F), −112.6 (m, 1F, 4-F), −168.2 (m, 1F, 3-F); δ_C (acetone d6) 30.7 (t, J_{CF}) 3.8, *C*H_3), 44.5 (s, *C*–OH), 119.4 (m, 3-C), 134.1 (dddd, $^1J_{CF}$ 255.7, $^2J_{CF}$ 28.5, $^2J_{CF}$ 16.9, $^4J_{CF}$ 8.0, 5-C), 148.1 (dm, $^1J_{CF}$ 239.2, 6-C), 152.7 (dm, $^1J_{CF}$ 247.3, 2-C), 159.2 (dm, $^1J_{CF}$ 265.8, 4-C); *m/z* 194 (M^+–CH_3), 178 (M^+–CH_2–OH), 174 (M^+–CH_3–HF), 164 (M^+–CH_3–O–CH_2) or (M^+–CH_3–CF), 150 ($C_5F_4N^+$), 146 (M^+–CH_3–OH–CF), 132 (M^+–CH_3–OH–NCF), 59 (Me_2C–OH^+). It was impossible to obtain a boiling point of **34** as it decomposed on heating even at low temperature in vacuo to the corresponding alkene.

2.25. Dehydration of 2-(2,3,4,6-tetrafluoropyridyl) propan-2-ol **35**

Alcohol **34** (0.3 g) was heated at 180°C with phosphoric oxide (0.5 g) in a small distillation apparatus. The product which distilled off at ca. 160°C was re-distilled to yield 2-(2,3,4,6-tetrafluoropyridyl) prop-2-ene **35** (0.2 g) (n.c.) b.p. 160–165°C; (Found: C, 50.2; H, 2.52% $C_8H_5F_4N$ requires C, 50.27; H, 2.64%), δ_H (acetone d6) 2.10 (dd, 3H, $^3J_{HH}$ 1.5, $^3J_{HH}$ 1.0, CH_3), 5.28 (distorted, 1H, =CH_2), 5.58 (q, 1H, $^3J_{HH} = {}^1J_{HH}$, 1.5, =CH_2); δ_F (acetone d6) −71.5 (bm, 1F, 6-F), −88.7 (bm, 1F, 2-F), −117.2 (m, 1F, 4-F), −168.3 (m, 1F, 5-F); δ_C (acetone d6) 22.5 (s, CH_3), 122.2 (s, =CH_2), (s, C–CH_3), 112 (m, 3-C), 131.8 (s, =C(Ar)Me), 135 ((d)m, 5-C), 149 ((d)m, 6-C), 153 ((d)m, 6-C), 158 ((d)m, 4-C); *m/z* 191 (M^+), 190 (M^+–H), 176 (M^+–CH_3), 172 (M^+–F), 164 (M^+–C_2H_3), 156 (M^+–CH_3–HF), 106 (M^+–C_3H_4–NCF).

3. Results and discussion

It seemed clear from the above discussion that any desirable route to 3-chlorotetrafluoropyridine **8** should be solvent based and take place at a reasonable temperature. Since the early work of Banks and Chambers there have been a number of developments in so-called "Halex" chemistry and particularly in the use of quaternary salts as catalysts. The area has been subject to a number of reviews [8]. We chose first to investigate the use of tetraphenylphosphonium bromide **11** as a catalyst. This compound is commercially available but is very expensive. We have developed a cheap synthesis of **11** based on the existing literature preparation [9] involving the metal catalysed reaction between bromobenzene and triphenylphosphine in benzonitrile. A number of salts worked well and nickel bromide was found to be the best. In the course of our work we found that the desired salt was very soluble in ether whereas the remaining byproducts and unchanged triphenylphosphine are very insoluble in ether thus making purification very simple. Using this modification to the procedure we were able to obtain very pure **11** in multi-gram quantities in a matter of hours in 86% isolated yield.

3,5-Dichlorotrifluoropyridine **9** is now commercially available in bulk quantities and we used this as our starting material. We found that the best conditions to obtain the desired 3-chlorotetrafluoropyridine **8** were to react **9** with a slight excess of spray dried potassium fluoride using a catalytic quantity of the salt **11** in sulfolane at 180–190°C and to remove product as it was formed. Using these conditions we obtained a mixture of pentafluoropyridine **10** (21%), the required 3-chlorotetrafluoropyridine **8** (61%) and unreacted starting material (13%). We have been able to repeat this work on the kilogram scale.

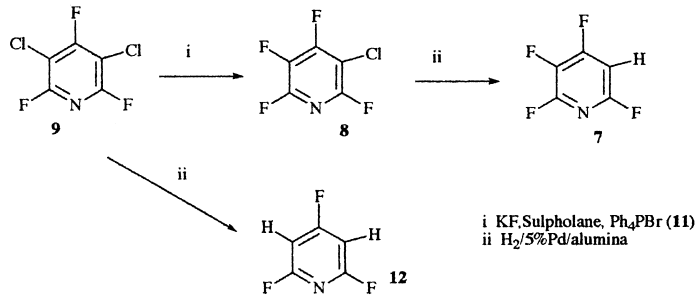
We next investigated the reduction of 3-chlorotetrafluoropyridine **8** under a variety of conditions to attempt to find a clean large scale route to 2,3,4,6-tetrafluoropyridine **7**. There are reports [5,10] of the reduction of chlorine to hydrogen in polyhalobenzenes and polyhalopyridines by hydrogen and metal catalysts and of hydrodefluorination by complex metal hydrides, in perfluoroarenes and heteroarenes [11,12]. In the latter case the reaction is only of synthetic value if the fluorine atom to be reduced is activated. In our study we were concerned with the hydrodechlorination of 3-chlorotetrafluoropyridine **8** in particular. Literature evidence [13] clearly indicates that in reactions of polyfluoro- and chloropolyfluoro-pyridines with complex metal hydrides, preferential hydrodefluorination at the 4-position was the most likely outcome. Thus, we turned our attention to the use of hydrogen and metal catalysts as a means of achieving our objective. McNamara and Cook [14] have shown that 4-amino-3,5-dichlorodifluoropyridine can be reduced to 4-amino-2,6-difluoropyridine by reaction with hydrogen at 3 bar pressure with palladium on carbon as catalyst at room temperature using methanol/acetic acid as the solvent, albeit rather slowly, over 3 days. It therefore seemed sensible to study the reaction of **8** under the same conditions. This reaction resulted in complete recovery of the starting material, and so we concluded that the amino function was in some way contributing to the successful reduction of 4-amino-3,5-dichlorodifluoropyridine. We changed the solvent system to either neat triethylamine or better to triethylamine/ether. We found that using one equivalent of triethylamine gave complete conversion of the starting material after 13 days and although the GC yield of product was 74%, it was extremely difficult to isolate the pyridine from the reaction medium without resort to preparative GC.

We decided therefore to abandon this route and to concentrate our attention on the Chambers gas phase route [5]. In this method the starting chlorofluoropyridines were passed in a stream of hydrogen over 10% palladium on carbon at 250°C and the product collected in liquid air. In this way it was found possible to obtain 2,3,4,6-tetrafluoropyridine **7** from 3-chlorotetrafluoropyridine **8**, 2,4,6-trifluoropyridine **12** from 3,5-dichlorotrifluoropyridine **9** and interestingly at higher temperatures 2,3,5,6-tetrafluoropyridine **13** from pentafluoropyridine **10**, in the latter case in relatively low yield with considerable decomposition. This latter result is in accord with the work of Pummer and Wall [10] who showed it was possible to reduce hexafluorobenzene to penta- and tetrafluorobenzenes under similar conditions but using platinum based catalysts. We attempted to repeat the literature process using fresh palladium on carbon with hydrogen and 3-chlorotetrafluoropyridine **8**, without success. In an attempt to explain the difference between our results and the literature procedure we repeated reaction in exactly the same manner but then continued to pass the carrier gas for 36 h, when we found that we obtained approximately the same yield of product as had been reported. We believe that there was a difference in the activation and probably the nature of the carbon supports used in the different sets of experiments. It is known that fluorocompounds are strongly absorbed by active carbon, a process that can be readily reversed by heating the carbon strongly [15]. We next tried a reduction of **8** using commercially available 0.5% palladium on alumina as catalyst. We found that at temperatures between 250°C and 285°C we were able to obtain, under the best conditions, a smooth reduction of **8** to a mixture of the desired 2,3,4,6-tetrafluoropyridine **7** and a little unchanged starting material. Table 1.

Table 1
Reduction results of **8** using 0.5% palladium on fused alumina catalyst[a]

Run	Input (g)	T (°C)	H_2 flow (ml/min)	Addition rate (g/min)	Mass output (g)	3-H (%)	3-Cl (%)	3-H yield (%)
1	5	250	50	0.07	0.3	91	9	
2	5	250	55	0.12	0.8	88	12	
3	19.7	275	50	0.22	16.7	76	24	79
4	50	285	50	0.83	46.2	26	74	30
5	46.2	285	65	0.49	41	71	29	72
6	41	285	70	0.46	40	82	18	81
7	50	280	75	0.53	44	33	67	15
8	44	275	60	1.0	42	43	57	44
9	42	275	50	0.84	39.5	67	33	65
10	39.5	285	60	0.88	36	71	29	68
11	53	290	60	0.44	49.7	86	10	77

[a] All experiments were run on the same column (packed and heated length 2.5 × 15 cm) containing 0.5% Pd on fused alumina. Temperature is the average over the time taken to add substrate. Addition rate calculated as the ratio of mass added to time of addition. 3-H is 2,3,4,6 tetrafluoropyridine, 3-Cl is 3-chlorotetrafluoropyridine. % Composition calculated from GC traces using a calibration curve obtained from known mixtures.

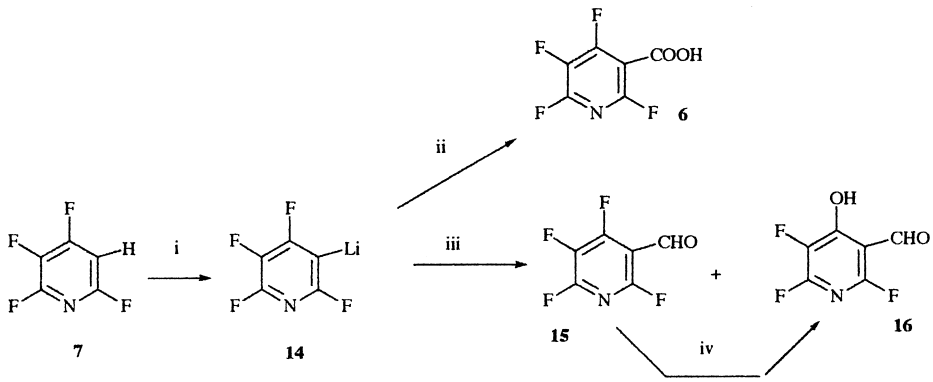


Scheme 2.

It appears that there is only a small temperature effect within the temperature range used. Similarly the hydrogen flow rate and mass input also have only small effects. The main effect on conversion seems to be the rate and mode of addition of the pyridine since the yields improved if the pyridine was added dropwise to the top of a vertical pyrolysis tube rather than by volatilisation into the hydrogen stream. We also found that it was possible to re-pyrolyse the products from runs which contained higher amounts of starting material without any over reduction. The desired 2,3,4,6-tetrafluoropyridine **7** was obtained in high purity by fractional distillation of the combined products from several pyrolyses. This phase of our study is summarised in Scheme 2.

We next extended the study of the reactions of 2,3,4,6-tetrafluoropyridine **7** that we believed would lead to the 3,4-disubstituted tetrafluoropyridines we required for our deazapurine synthesis. Two areas appeared to be promising, firstly, to extend the organometallic work reported previously [5], taking into account some other reported reactions of tetrafluoro-3-lithiopyridine **14** to make the 3-formyl tetrafluoropyridine **15** and the corresponding 3-formyl-4-hydroxy derivative **16** [16,17]. Secondly, to probe the nucleophilic displacement reactions of 2,3,4,6-tetrafluoropyridine **7** and compounds derived from it (see Scheme 3).

We tried first to optimise the yield of tetrafluoronicotinic acid **6**. There have been some examples reported of quite dramatic solvent effects in the carbonation of organometallic reagents in the fluoroarene series. Early work by ourselves showed that pentafluorophenyl Grignard and lithium reagents derived from the bromo or iodo compounds reacted normally with most electrophiles in ether or ether/hexane but under these conditions would not react with carbon dioxide [18,19]. These observations were confirmed by Tamborski [20] who found that it was necessary to use ether/THF to obtain good yields of the carboxylic acid. He also generated the lithium reagent from pentafluorobenzene by deprotonation with butyl lithium and his system was then essentially salt free. In the original work [5] to prepare tetrafluoronicotinic acid, hexane was used as the solvent and the acid was obtained in 62% yield. In this work the CO_2 was added to the reagent as a gas. We repeated the literature reaction exactly as reported and also obtained a 65% yield of the desired acid. The reaction was then repeated on the literature scale (3.3 mmol) but solid carbon dioxide was added, we obtained a 75% yield but when we scaled up the reaction to 50 mmol we obtained only a 10% yield with much polymerisation. We have no firm evidence to explain this result which was consistent over several experiments. However, we



Scheme 3.

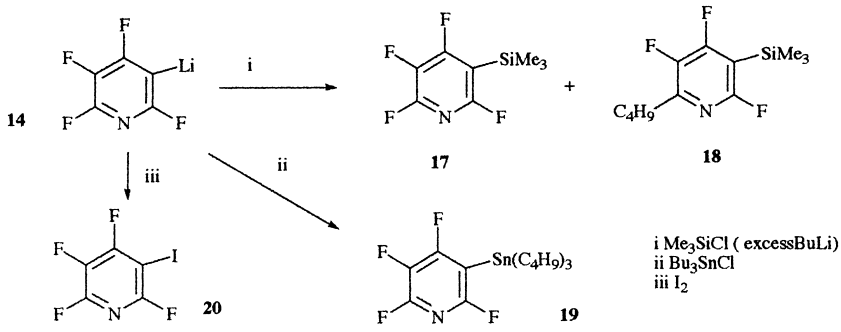
believe it may be a temperature effect, in that addition of the solid, CO_2 maintains a low temperature in the reaction mixture for a long period of time and the CO_2 probably does not react at −78°C. When the gaseous addition is used the reaction mixture is slowly allowed to warm to ambient temperature with the CO_2 still flowing. We then changed the solvent system to either ether/hexane or THF/ether/hexane with gaseous CO_2 addition. Over a number of large-scale (50 mmol or greater) experiments, we obtained consistently yields in the region of 75%. This afforded sufficient of the acid for further study. During the course of this part of the work we also used lithium diisopropylamide (LDA) as the base to form the lithio derivative. Although the reaction proceeded smoothly, the yields were generally lower and products were isolated, which on the basis of their NMR spectra, arose from reaction of the diisopropylamine generated in the reaction with the first formed product, presumably at the now very highly active 4-position (see below). We wished to prepare the 3-formyl-tetrafluoropyridine (tetrafluoronicotinaldehyde) **15**, which has been suggested to be too reactive towards nucleophiles, particularly in the 4-position, to be used to prepare other derivatives [16]. Since we wished to make 3,4-disubstituted compound it seemed logical that we should investigate this report further. Thus, reaction of the 3-lithio-tetrafluoropyridine **14** with *N*-methylformanilide in ether/hexane afforded, after work-up under strongly acidic conditions, the known tetrafluoronicotinaldehyde **15** in 57% yield as a crystalline solid. However, work-up with only the addition of water or aqueous ammonium chloride gave a mixture of the aldehyde **15** and 2,5,6-trifluoro-4-hydroxynicotinaldehyde **16**. If water was added and the mixture was heated for 30 min prior to isolation the product was solely **16** in 67% yield. Both structures were confirmed by physical means. We have thus been able to confirm that the earlier suggestion is correct and further to show that it is possible to use the very high reactivity of the 4-position to advantage in order to obtain potentially useful 3,4-disubstituted compounds. We did not in the event carry out a similar reaction with ammonia to get the 4-amino compound since we found (see below) a much simpler and more reliable route. These reactions are summarised in Scheme 3.

An attractive possibility would be to obtain tetrafluoro-5-nitro-pyridine since this, almost certainly, would aminate under very mild conditions at the 4-position to give us our desired pyridine derivative after a simple reduction step. It seemed very unlikely that direct nitration of 2,3,4,6-tetrafluoropyridine **7** would occur and indeed we readily confirmed this view by reacting **7** with fuming nitric acid and boron trifluoride/hydrate in sulfolane under conditions we used to nitrate pentafluorobenzene [21]. Unreacted starting material was recovered almost quantitatively. To our knowledge no other direct electrophilic substitution reactions have been reported for any highly fluorinated pyridines. In the light of our recent work with trimethylsilylated polyfluorobenzenes [22] where we were able to effect nitro and bromo desilylation reactions, we felt it might be possible to similarly nitrodesilylate or nitrodestannylate appropriate derivatives of 2,3,4,6-tetrafluoropyridine **7**. We thus carried out the reaction of 3-lithio-tetrafluoropyridine **14** with chlorotrimethylsilane and in this case somewhat surprisingly obtained two products which could be separated by column chromatography to give the desired 5-trimethylsilyl derivative **17** as the major product (70%) and 2-butyl-3,4,6-trifluoro-5-trimethylsilylpyridine **18** 30% as the minor product. The structure of both products was confirmed by analysis of their NMR spectra, elemental analysis and mass spectrometry (see Section 3).

This result is unusual, as we would have expected the second substitution of the butyl group to occur in the 4-position. We could explain the result on steric grounds in that the vicinal arrangement of the butyl and trimethylsilyl groups is unfavourable. We have NMR evidence that a second product obtained when we carried out a similar reaction but using LDA as base was in fact the analogous 2-*N*,*N*-diisopropylamino derivative but we were unable to isolate sufficient of it to obtain full characterisation, thus again indicating the selective substitution para to the trimethylsilyl group rather than the expected 4-substitution. An argument could also be advanced suggesting that the empty d-orbitals on silicon can readily stabilise the negative charge on C5 of the canonical structure. There is evidence for such species being important in nucleophilic attack on halosilane derivatives [23].

We next carried out a similar reaction of 3-lithio-tetrafluoropyridine **14** with tributylstannyl chloride and obtained a clear liquid as the sole product in 73% yield which was readily identified by physical means as the expected 5-tributylstannyl-2,3,4,6-tetrafluoropyridine **19**. The absence of the butylated moiety analogous to **18** can be readily explained by the much greater reactivity towards nucleophiles of the tributylstannylchloride relative to its silicon counterpart. Reaction of the lithio-reagent **14** with iodine readily afforded the expected 2,3,4,6-tetrafluoro-5-iodopyridine **20** in 52% yield again identified by physical means. This compound could be useful as a reactive starting material in copper(1) mediated reactions which could be used to prepare our target deazapurine. These reactions are summarised in Scheme 4.

In the light of the observed high level of reactivity towards electrophiles of the lithio compound **14** we decided to investigate the possibility of forming a C–N bond directly. It has been shown that reaction of organometallic reagents with nitrogen dioxide afforded oximes [26,27], whilst reaction with nitrosyl chloride yielded nitroso compounds e.g from phenylmagnesium bromide and nitrosyl chloride, nitrosobenzene was obtained in 56% yield [28]. As a result of the high reactivity of tetrafluoronicotinaldehyde 15 towards nucleophiles which we have described above, we were concerned about a suitable work-up procedure and equally in view of the known properties of pentafluoronitrosobenzene, we were concerned about the volatility and

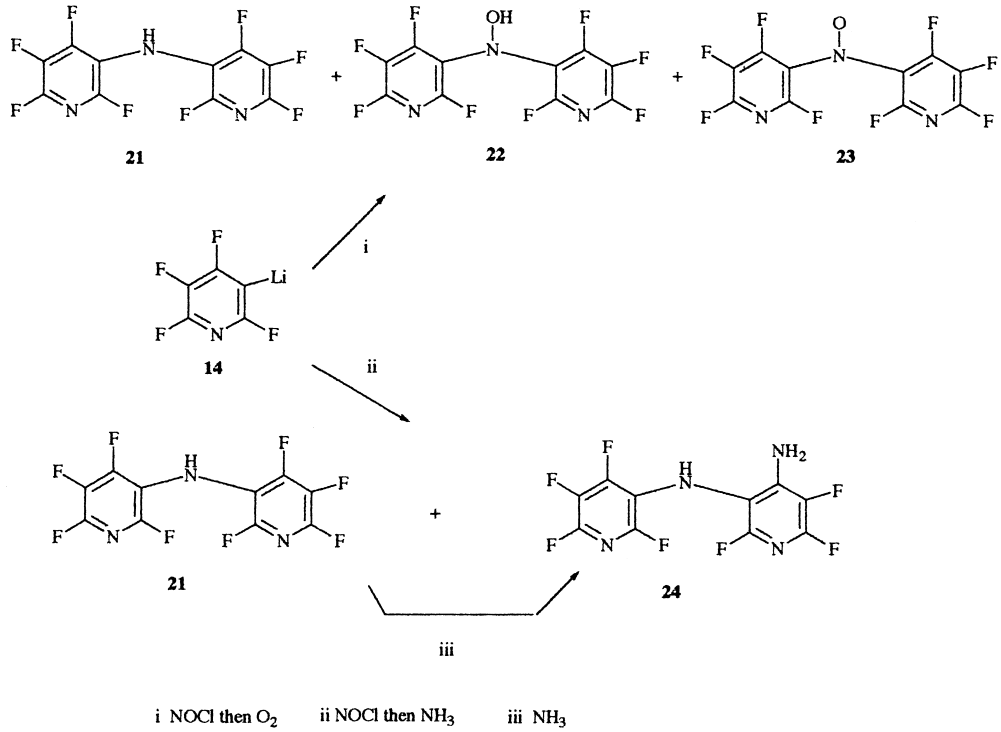


Scheme 4.

possible toxicity of the nitrosopyridine. We decided in the first instance not to try to isolate the nitroso compound but to either oxidise it to the nitro- compound, a known species, or to aminate it to the nitrosoamine, or to reduce it to the 3-amino compound. We proposed to do all of these reactions in situ. The lithium reagent **14** was reacted at −78°C with gaseous nitrosyl chloride fed into the reaction from an external reservoir of the liquid as a steady stream of the gas diluted with dry nitrogen. During the passage of the gas the solution of **14** was raised slowly to room temperature (over about 2 h). The reaction mixture was then stirred at room temperature for a further 2 h when the flow of nitrosyl chloride was stopped and air was drawn through the solution for 6 h. After this time an aliquot of the solution was examined by ^{19}F NMR spectroscopy. The spectrum showed three sets of signals attributable to three compounds containing polyfluoropyridine rings. Although the three components could be observed by TLC, none could be separated into a pure component by column chromatography. In the light of later results which allowed us to compare NMR data from pure compounds with the spectra of the mixture we were able to identify the three components as bis-(2,4,5,6-tetrafluoro-3- pyridyl) amine **21**, bis-(2,4,5,6-tetrafluoro-3-pyridyl)hydroxylamine **22** and bis-(2,4,5,6-tetrafluoro-3-pyridyl)nitroxide **23**. We then repeated the experiment except that 0.880M ammonia was added after the addition of nitrosyl chloride was stopped. Work-up of the reaction afforded a very dark crystalline solid in ca. 30% yield. TLC showed two spots of equal intensity but no clean separation was possible using column chromatography. The ^{19}F NMR spectrum of the mixture showed two sets of signals attributable to bis-(2,4,5,6-tetrafluoro-3-pyridyl) amine **21** and *N*-(4-amino-2,5,6-trifluoro-3-pyridyl)-3-aminotetrafluoropyridine **24** by comparison with authentic samples (see below). The reaction was repeated but at the end of the addition of the nitrosyl chloride, water and zinc powder were added to the reaction mixture, work-up afforded a pale yellow solid. This product was confirmed as bis-(2,4,5,6-tetrafluoro-3-pyridyl)amine **21** by the usual combination of physical methods. This and the previous two experiments again indicated the high reactivity of the lithium reagent **14**. The activating effect of the tetrafluoropyridyl ring on neighbouring electrophilic centres is again apparent since again it appears that the first formed product is much more reactive than the starting material. This results in the formation, as we found in the reaction with acetyl chloride and trifluoroacetic anhydride, of the disubstituted products (see below). The results of this set of reactions are illustrated in Scheme 5.

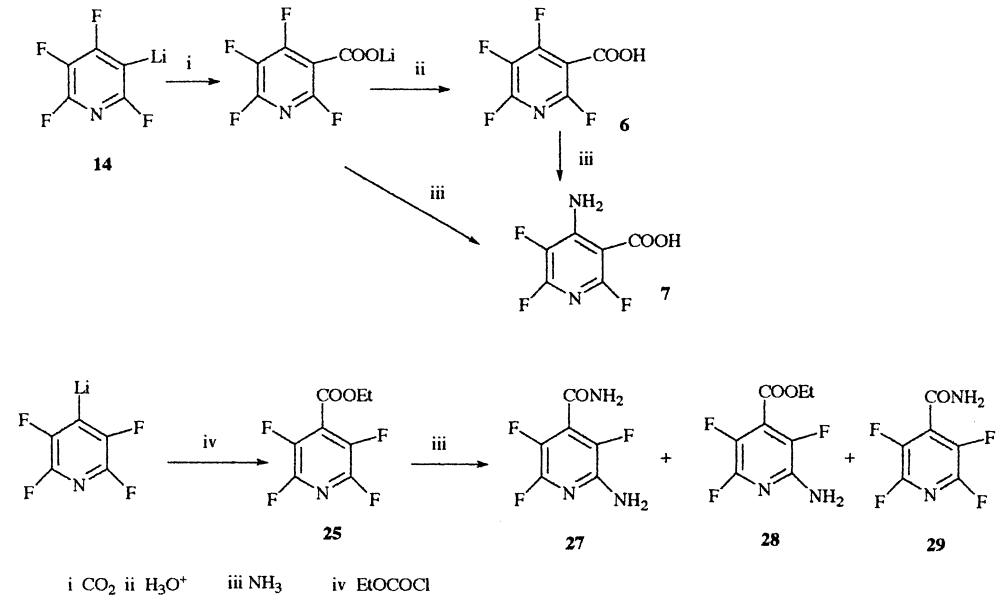
Having obtained a pure sample of **21** we were able to react it with 0.880 ammonia to obtain an amine. Analysis of the structure by physical means showed it to be identical to compound **24** above thus confirming the structure of **24**. We also carried out a number of unsuccessful experiments with **14** and nitrosonium tetrafluoroborate (NO^+BF_4) and with nitronium tetrafluoroborate ($NO_2^+BF_4$) to make the nitroso and nitrocompounds, respectively.

We next investigated the reaction of some of the compounds we had prepared. Firstly we studied some chemistry of tetrafluoronicotinic acid **6**. Much to our surprise, we found it impossible to directly esterify **6**, using a variety of procedures. Further we failed to obtain the ester directly by reaction of the lithiocompound **14** with purified ethyl chloroformate, a reaction which readily proceeded with 2,3,5,6-tetrafluoro-4-lithiopyridine to yield ethyl tetrafluoroisonicotinate **25**. At present we have no satisfactory explanation for these observations. From previous observations and from the result we obtained in the attempted preparation of the aldehyde **15** above, when we isolated the 4-hydroxy compound as the major product, we expected that the 4-fluorine atom in tetrafluoronicotinic acid **6** would be very reactive towards nucleophiles. This proved to be the case since treatment of the acid **6** with excess 0.880 ammonia at room temperature gave 4-amino-2,5,6-trifluoronicotinic acid **26** in 72% yield, which was fully characterised by physical methods. We found no evidence for the formation of the analogous 2-amino compound. We subsequently discovered that we could carry out the carbonation and amination successively in a 'one-pot reaction' in 83% yield. Tetrafluoroisonicotinic acid and its ethyl ester **25** are readily available and it is reported that pentafluorobenzoic acid will, under carefully controlled conditions, give a high proportion of the *ortho* substituted product in nucleophilic substitution reactions [4]. We felt therefore that we should investigate

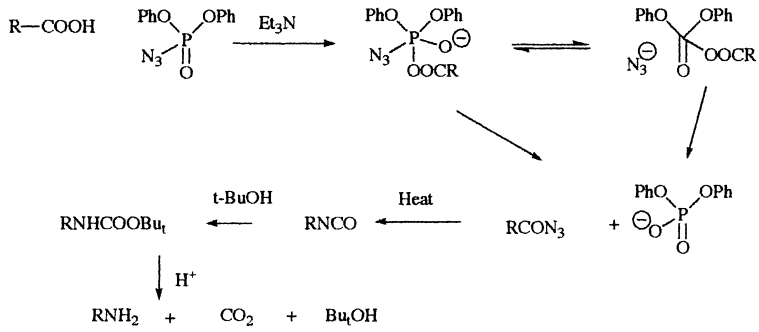


Scheme 5.

the reaction of **25** with ammonia. Thus, we treated ethyl tetrafluoroisonicotinate **25** with 0.880 ammonia. In addition to unreacted starting material we obtained 2-amino-3,5,6-trifluoroisonicotinamide **27** in 33% yield, ethyl-2-amino-3,5,6-trifluoroisonicotinate **28** 12% and a small amount of 2,3,5,6-tetrafluoroisonicotinamide **29**, but none of the desired 3-amino products were observed. This result suggests that the activating effect of the ring nitrogen atom is still sufficiently potent to overcome any directing effect of the ester function and that derivatives of tetrafluoroisonicotinic acid are likely to be of little value in the quest for suitable substrates for deazapurine formation. The results of these reactions are shown in Scheme 6. Not surprisingly, in the light of the failed direct nitration reported above,



Scheme 6.



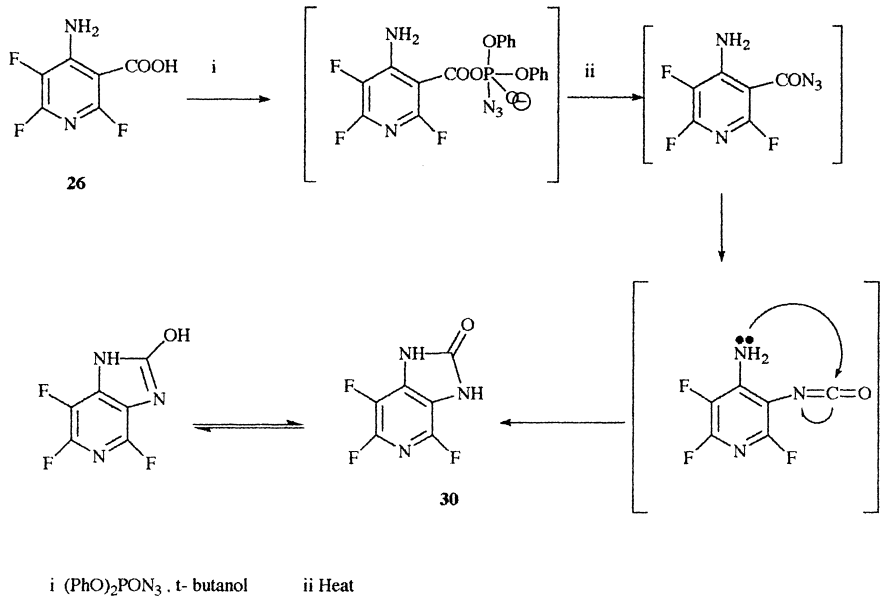
Scheme 7.

nitrodesilyl- and nitrodestannylation reactions of **17** and **18** under conditions we had found gave reasonable results in the polyfluorobenzene series [22] gave only unreacted starting materials.

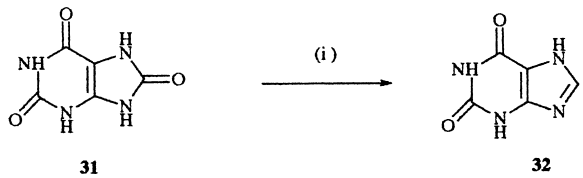
The conversion of the carboxyl group in 4-aminotrifluoronicotinic acid **26** to an amine should be possible by one of several methods, e.g. the Hofmann degradation known to proceed with tetrafluorophthalimide [29] to yield tetrafluoroanthranilic acid, or the Curtius reaction and its variations. In the light of possible substitution at the 2 or 6 positions in the amino-acid **26** by hydroxide in the strongly basic conditions required for the Hofmann degradation, we decided to investigate the Curtius reaction and the Schmidt variation of it. We tried the Schmidt variation without success, the only recoverable material was unreacted **26**. A relatively recent modification of the Curtius reaction has been reported to work well with relatively unactivated carboxylic acids [30,31]. This modification uses diphenyl phosphoraziate as the azide source. The rationale behind the reaction is that the carbonyl group in the acid is activated by reaction at the phosphorus ultimately leading to the required acylazide. This reaction is in some ways akin to the well-known Mitsonobu reaction. The acyl azide so formed leads, in the expected manner, by the Wolf-type rearrangment to the isocyanate which then reacts with *t*-butanol to form the carbamate ester which on acidic hydrolysis affords the desired amine as its salt. This method was very attractive to us since one of the cited examples of its efficiency was the formation of 2-aminopyridine from pyridine-2-carboxylic acid in 73% yield [31]. This reaction sequence is shown in Scheme 7. The initial reaction we carried as a trial using tetrafluoronicotinic acid was not very encouraging, it gave a mixture of a number of products which could not be readily separated. This is perhaps not too surprising since in this acid we still have the highly reactive 4-fluorine atom present which, especially in the presence of triethylamine, could easily react with *t*-butanol, the preferred reaction solvent, and any other nucleophilic species present or generated in the reaction. We then reacted the amino acid **26** under the literature conditions and obtained a single product albeit in a rather low yield (19%). The ^{19}F spectrum proved to be very useful in elucidating the structure of the product, the signals in the spectrum of the starting **26** at δ −61, −91 and −170 had been replaced by signals at δ −92, −99 and −167; these values compare very favourably with those reported by Chambers [2] for 3,4-diaminotrifluoropyridine at δ −94, −104 and −169. This led us to believe we had produced a trifluoropyridine with amino functions at the 3- and 4-positions. Clearly it was not the free diamine or a salt of it since it had a sharp melting point at 239–241°C, whereas the diamine as reported by Chambers had a melting point of 117–118°C. The mass spectrum showed a peak of *m/z* 189 as the highest mass fitted with an empirical formula $C_6H_2F_4N_3O$ and this was confirmed by the elemental analysis as being the molecular formula. The ^{13}C NMR spectrum showed a signal at δ 155.2 indicative of a carbonyl group; this was confirmed by the J-modulated spin echo spectrum. This data lead us to assign the structure of the product as 3-deaza-2,3,6-trifluoro-8-hydroxypurine (3-deaza-2,3,6-triflurouric acid) **30**. The proposed reaction sequence leading to this unexpected product is shown in Scheme 8.

The standard route for the conversion of uric acid **31** and its derivatives to purines of the kind we required is by reflux of **31** with acid amides. To obtain 8-unsubstituted compounds, formamide itself is used, as exemplified by the preparation of xanthine **32** from uric acid (Scheme 9). We investigated the reaction of **30** under conditions which had given us a good yield of **32** in a trial experiment, with no success. A wide range of different reduction methods we then tried all failed giving either unchanged **30** or in tar formation. Thus, our final goal eluded us.

We next decided to study the reactions of **14** with carbon and nitrogen electrophiles and these reactions proved to be much more interesting than we expected. Reaction of the lithiocompound **14** and benzaldehyde, gave phenyl-(2,4,5,6- tetrafluoro-3-pyridyl)-methanol **33** in 71% yield, identified by physical means. The reaction with propanone proceeded smoothly to give a clear liquid in >90% yield, the ^{1}H NMR spectrum of which indicated it to be almost pure 2-(2,4,5,6-tetrafluoro-3-pyridyl) propan-2-ol **34**. The spectrum was notable for an unusual coupling pattern, a quintet with a coupling constant of 2 Hz for the methyl groups. However, all our attempts to completely purify **34** either by

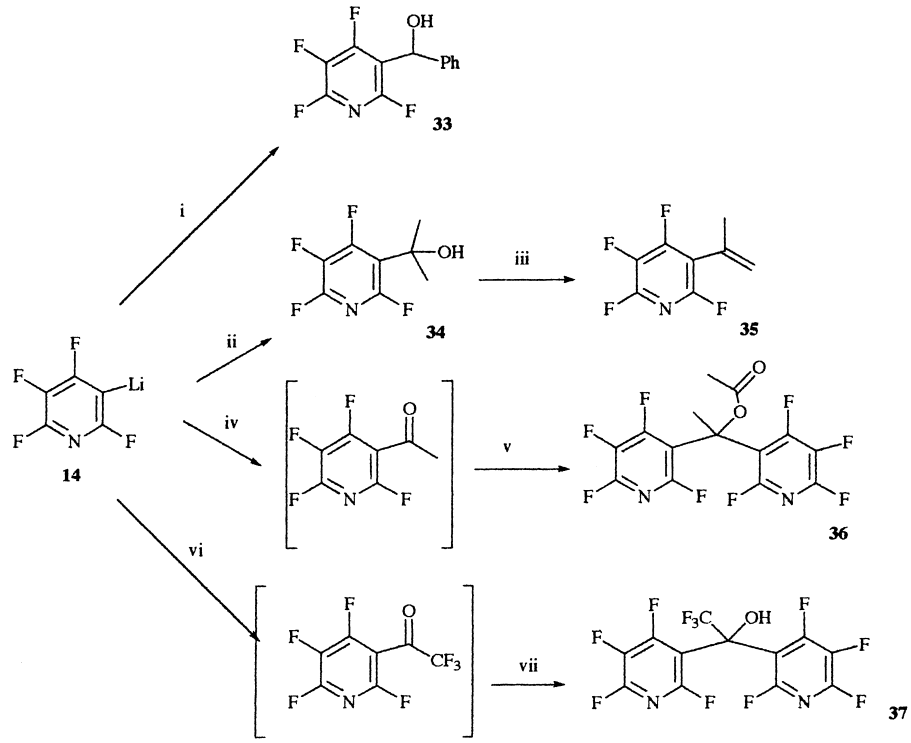


Scheme 8.



Scheme 9.

high vacuum distillation at low temperature or by column chromatography failed. Distillation at various temperatures and pressures always afforded 2-(2,4,5,6-tetrafluoro-3-pyridyl) prop-2-ene **35**, the dehydration product of **34**, whilst chromatography gave a mixture of **34** and **35**. We were able to obtain **35** more simply by distillation of **34** with a trace of added *p*-toluenesulphonic acid. However, we were unable to obtain a sample of **34** pure enough for either elemental analysis or accurate mass measurement, although we were able to obtain NMR parameters and a mass spectrum (GC/MS) as partial characterisation. This ready dehydration of polyfluoroaryl methanols has been noted previously in the pentafluorobenzene series [18]. The reaction of **14** with an excess of acetyl chloride, which we had thought would give the methyl ketone analogous to the reaction of pentafluorophenylorganometallics [24] gave a somewhat unexpected result. The ^{1}H NMR spectrum of the crude product, obtained in 80% yield, showed the presence of two methyl groups, one of which was at δ 2.14 as a singlet and the second one was at δ 2.36, again, as noted above for **34**, a quintet with a coupling of 2 Hz. The mass spectrum indicated a RMM of 386 and the IR spectrum showed the presence of a carbonyl function consistent with the presence of an ester. These data together with the ^{19}F and ^{13}C NMR spectra, accurate mass measurement and the elemental analysis confirm the empirical formula as $C_{14}H_6F_8O_2$, consistent with the structure being 1,1-bis(2,4,5,6-tetrafluoro-3-pyridyl)ethyl acetate **36**. The origin of the unexpected multiplicity of the methyl signal we believe is best explained by a coupling to the *ortho* fluorine atoms of each of the pyridine rings, a study of models of the compound reveals that the methyl groups and these atoms are very close together. This kind of coupling has been observed previously in other fluoroarenes [25] but whether it is a "through space" or a long-range through bond coupling is not clear. This result clearly indicated that the pyridyl lithium **14** is very reactive and interestingly that the presumed first formed ketone, the expected product of the reaction, appears to be more reactive than acetyl chloride at least in the system we were using. A similar reaction using trifluoroacetic anhydride afforded a single product, the ^{1}H NMR spectrum showed a broad signal characteristic of an OH group at δ 5.2 which disappeared on shaking with D_2O. The IR spectrum showed no carbonyl group to be present. The ^{19}F spectrum in addition to signals for the fluorine atoms of the pyridine ring system showed a quintet at δ −77.8, characteristic of a CF_3 group and interestingly showing as a quintet again clearly coupled to the ring fluorine atoms. The mass spectrum and elemental analysis further confirmed the structure as 1,1-bis(2,4,5,6-tetrafluoro-3- pyridyl)-2,2,2-trifluoroethanol **37**, again arising from rapid attack of **14** onto the first formed trifluoromethyl ketone. Thus, we have further demonstrated in these experiments the reactivity of 2,4,5.6-tetrafluoro-3-pyridyllithium. These results are shown in Scheme 10.



Scheme 10.

4. Conclusion

We believe that we have considerably widened the scope of polyfluropyridine chemistry, particularly the development of the preparation and reactions of 2,3,4,6-tetrafluoropyridine.

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