# POLYHALOGENATED HETEROCYCLIC COMPOUNDS. PART 48.+ MULTISUBSTITUTED BIS-PYRIDYL DERIVATIVES FROM PENTAFLUOROPYRIDINE

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*Dedicated to the memory of our friend Professor Miloš Hudlický.*

Various polyfunctional and ring-fused bis-pyridine systems have been synthesised from pentafluoropyridine by nucleophilic substitutions.

**Keywords**: Heterocycles; Fluorine; Polysubstituted heterocycles; Pentafluoropyridine; Pyridines; Perfluoroalkylations; Nucleophilic substitutions.

In the ongoing search for novel biologically active lead compounds, the life-science industries have extensive discovery programmes focused upon the synthesis of a wide range of structurally diverse, multifunctional systems that can be accessed by the developing *privileged structures* strategy[2]. Privileged structures are typically low-molecular-weight rigid polycyclic systems possessing a range of functionalities in a well defined structural system that can interact with a variety of unrelated receptor sites.

Heteroaromatic systems have, of course, a vast chemistry[3] and could, potentially, act as ideal privileged structures. Methodology for the synthesis of ranges of structurally diverse heteroaromatic derivatives is, therefore, under continuing development and application of, for example, sequential electrophilic substitution and palladium-catalysed coupling reactions to the synthesis of many heterocyclic analogues (rapid analogue synthesis, RAS) has been reviewed recently[4]. The requirement for short, high-yielding, regioselective and flexible routes to multiply functionalised heteroaromatic derivatives has been emphasised.

+ Part 47, see ref.[1]


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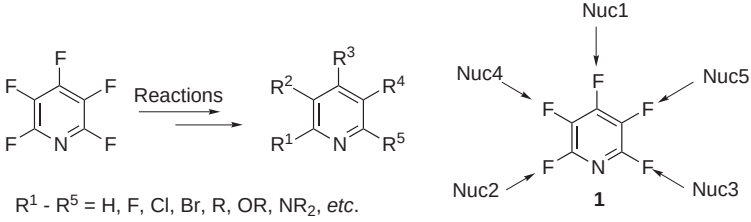
Our approach towards the synthesis of highly functionalised heteroaromatic derivatives utilises perfluorinated heterocyclic systems as starting materials[1]. Highly fluorinated heteroaromatic systems are very susceptible towards nucleophilic attack and an extensive chemistry principally involving substitution of fluorine by a variety of nucleophiles has emerged[5,6]. Pentafluoropyridine (**1**) is a very versatile building block because, in principle, all five fluorine substituents in pentafluoropyridine could be substituted by nucleophiles. Therefore, potentially, a range of polysubstituted systems could be derived from this core molecule by nucleophilic aromatic substitution processes. Furthermore, it is well established that, in general, the order of activation towards nucleophilic attack follows the sequence 4-F > 2-F > 3-F. Consequently, for a succession of five nucleophilic substitution steps, where Nuc1 is the first nucleophile, Nuc2 is the second, *etc.*, the order of substitution could be selective as outlined below, although a few exceptions to these general rules have been reported[7].

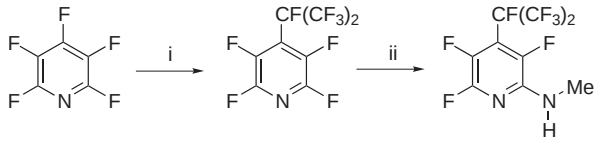



The wide range of nucleophiles available (O-, N-, C-, S-centred) makes the theoretical number of highly functionalised pyridine systems that could be accessed by this methodology very large indeed.

We have already described various synthetic strategies[1] for the preparation of pyridine derivatives that bear five different substituents, using pentafluoropyridine (**1**) as the starting core molecule. In this paper, we extend our studies in this area and report the ready synthesis of various polyfunctional and ring-fused bis-pyridine systems from pentafluoropyridine.

## RESULTS AND DISCUSSION

Perfluoroalkylation of pentafluoropyridine (**1**) to give **2** was achieved by reaction of hexafluoropropene and a catalytic amount of a tertiary amine, tetrakis(dimethylamino)ethene[8]. Subsequent amination of **2**, giving **3**, occurred in high yield upon heating **2** with a slight excess of methylamine[9] (Scheme 1).

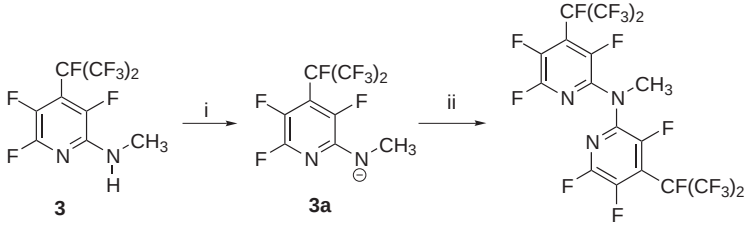



**1** **2**, 58% **3**, 76%

(i) $(Me_2N)_2C=C(NMe_2)_2$, $CF_2=CF-CF_3$, 60 °C; (ii) $MeNH_2$, r.t., 24 h

SCHEME 1

We found that aminopyridine **3** can be used as a building block for the synthesis of a variety of bis-pyridyl systems. Deprotonation of **3**, by addition of butyllithium in THF at low temperature, gave anion **3a**, which can, of course, act as a nucleophile and was trapped by addition of a further equivalent of pyridine **2** giving bis-pyridyl derivative **4** (Scheme 2).



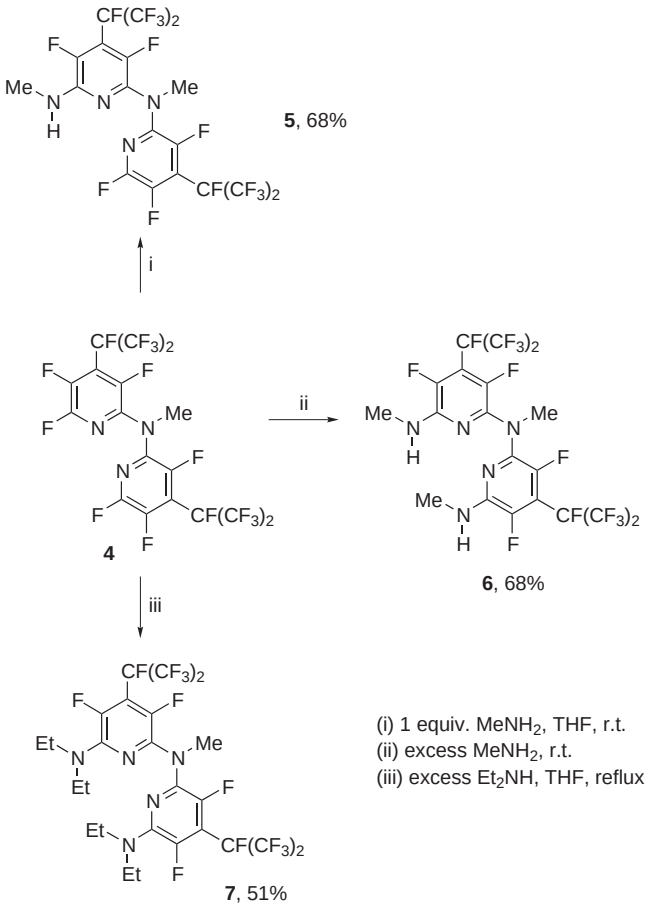

**3** **3a** **4**, 52%

(i) BuLi, THF, -78 °C; (ii) **2**, r.t.

SCHEME 2

Bis-pyridyl system **4** is, potentially, a very versatile synthetic building-block because, in principle, all fluorine atoms located on both of the pyridine rings are susceptible towards nucleophilic attack. In order to establish the regioselectivity of nucleophilic substitution for this novel bis-pyridyl system, we carried out reactions between **4** and some representative nitrogen nucleophiles (Scheme 3). Reaction of **4** with one equivalent of methylamine gave **5**, arising from the displacement of the fluorine atom located on carbon adjacent to nitrogen. Similarly, reaction of **4** with two equivalents of methylamine and diethylamine gave **6** and **7**, respectively (Scheme 3).

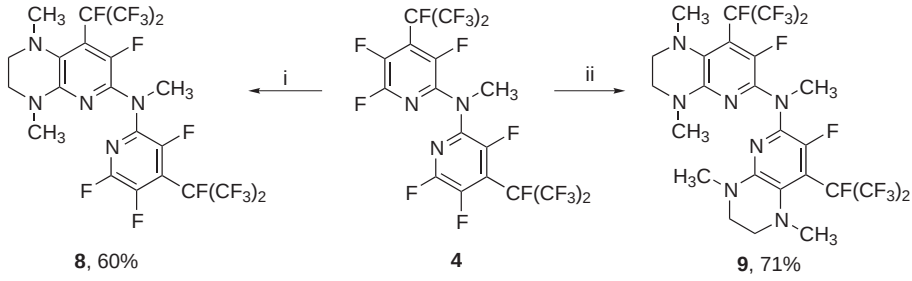
In principle, three possible products could arise from nucleophilic substitution of each of the ring fluorine atoms in **4**. However, it is well established that ring nitrogen significantly activates *alpha* and *gamma* positions[5] and so the attack at the 6-position, leading to **5**–**7**, is preferred.




SCHEME 3

Reaction of **4** with a difunctional nucleophile, *N*,*N*′-dimethylethane-1,2-diamine, gave ring-fused systems that showed that fluorine atoms located *meta* to the nitrogen atom can also be attacked by nucleophiles. The fused pyridine systems **8** and **9** were formed in high yield by reaction of **4** with one and two equivalents of the diamine, respectively (Scheme 4).

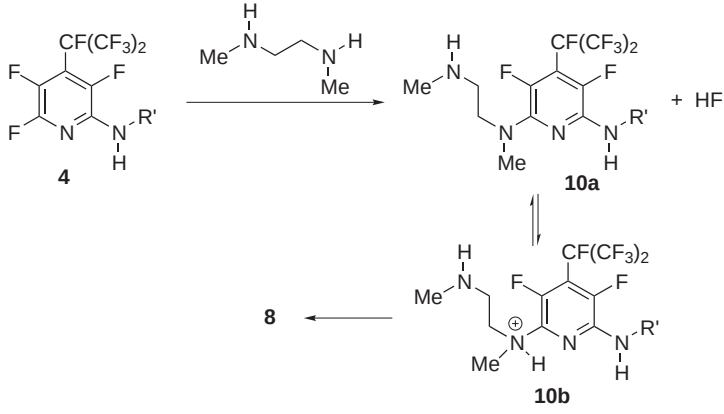
These cyclisation processes occur very readily and are perhaps surprising considering that positions *beta* to ring nitrogen in highly fluorinated systems are usually of relatively low reactivity. Furthermore, the intermediate **10a** should be very significantly deactivated by the alkylamino and dialkylamino groups at the 2- and 6-positions, respectively. Obviously, the 4-perfluoroisopropyl group offsets this deactivation and the intramolecular




(i) 1 equiv. MeNH-$CH_2CH_2$-NHMe, THF, reflux, 40 h
(ii) 2 equiv. MeNH-$CH_2CH_2$-NHMe, THF, reflux, 40 h

SCHEME 4

nature of the conversion **10a** to **10b** is clearly beneficial (Scheme 5). However, we cannot rule out the possibility that cyclisation proceeds *via* even a very small concentration of a protonated species such as **10a** and, clearly, the NHMeR group would now be strongly activating, instead of deactivating.




SCHEME 5

In summary, pentafluoropyridine can be used as a building block for the synthesis of multifunctional bis-pyridyl derivatives that react with a variety of nitrogen nucleophiles to give a variety of polysubstituted and ring-fused heterocyclic derivatives. These experiments further illustrate the concept of using highly fluorinated heterocycles as core molecules for the synthesis of highly substiuted heterocyclic derivatives.

## EXPERIMENTAL

All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem), **2** and **3** were prepared according to literature procedures[8,9]. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer operating at 400 MHz ($^1$H NMR), 376 MHz ($^{19}$F NMR) and 100 MHz ($^{13}$C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Mass spectra were recorded on a Fisons VG-Trio 1000 spectrometer coupled with a Hewlett–Packard 5890 series II gas chromatograph using a 25-m HP1 (methylsilicone) column. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure, unless otherwise stated, and are uncorrected. The progress of reactions were monitored by either $^{19}$F NMR or gas chromatography on an Shimadzu GC8A system using an SE30 column. Distillation was performed using a Fischer Spaltrohr MS220 microdistillation apparatus. Column chromatography was carried out on silica gel (Merck No. 109385, particle size 0.040–0.063 nm) and TLC analysis was performed on silica gel TLC plates (Merck).

### Methyl Bis{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2-pyridyl}-amine (**4**)

Under an atmosphere of dry nitrogen, butyllithium (5.8 g, 91 mmol) was added to a solution of 3,5,6-trifluoro-*N*-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine-2-amine (**3**) (30 g, 91 mmol) in THF (300 ml) cooled to –78 °C and then stirred for 1 h before 2,3,5,6-tetrafluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine (**2**) (29.0 g, 91 mmol) was added. The mixture was then stirred for a further 3 h before water (200 ml) was added. The organic material was extracted with dichloromethane, dried with anhydrous $MgSO_4$ and then evaporated to yield crude material (58 g). Distillation under reduced pressure afforded **4** (29.8 g, 52%) as a yellow solid; b.p. 95 °C (8 Pa); m.p. 81.2–83 °C. For $C_{17}H_3F_{20}N_3$ (629.2) calculated: 32.4% C, 0.5% H, 6.7% N; found: 32.7% C, 0.6% H, 7.0% N. $^1$H NMR: 3.5 (m). $^{19}$F NMR: –75.5 (12 F, m, $CF_3$); –86.6 and –87.8 (2 F, m, F-6); –124.0 and –126.3 (2 F, m, F-3); –138.8 and –141.8 (2 F, m, F-5); –179.9 (2 F, m, C**F**$CF_3$). $^{13}$C NMR: 37.8 (s, $CH_3$); 91.9 (d sept, $^1J_{CF}$ = 213.7, $^2J_{CF}$ = 40.8, $CFCF_3$); 117.0 (m, C-4); 119.9 (qd, $^1J_{CF}$ = 293.8, $^2J_{CF}$ = 27.1, $CF_3$); 137.0–149.0 (overlapping m, C-2, 3, 5, 6). MS ($EI^+$), *m/z* (%): 629 ($M^+$, 7), 329 (100), 314 (28), 301 (12), 260 (18).

### 3,5-Difluoro-*N*,*N*′-dimethyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*N*-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2-pyridyl}pyridine-2,6-diamine (**5**)

Under an atmosphere of dry nitrogen, methylamine (1.24 g, 40.0 mmol) was added to a solution of **4** (10.1 g, 16 mmol) in THF (75 ml) and the mixture was stirred at room temperature for 20 h before water (100 ml) was added. The mixture was continuously extracted with dichloromethane, dried with anhydrous $MgSO_4$ and evaporated to yield crude material (10.1 g). Column chromatography, using hexane and ether (3 : 1) as the eluent, afforded **5** (7.0 g, 68%) as a yellow solid; m.p. 60.2 °C. For $C_{18}H_7F_{19}N_4$ (640.3) calculated: 33.8% C, 1.1% H, 8.7% N; found: 33.5% C, 1.1% H, 8.7% N. $^1$H NMR: 2.9 (3 H, m, NHC**H**$_3$); 3.5 (3 H, s, $CH_3$); 4.7 (1 H, br s, NH). $^{19}$F NMR: –76.0 (12 F, m, $CF_3$); –88.6 and –89.7 (1 F, m, F-6); –125.1 (1 F, m, F-3); –130 to –148.0 (3 F, m, F-3′, 5, 5′); –180.0 (2 F, m, C**F**$CF_3$). $^{13}$C NMR: 27.7 (s,

$NHCH_3$); 37.4 (s, $NCH_3$); 91.8 (m, $CFCF_3$); 111.9 (m, C-4, 4′); 119.7 (m, $CF_3$); 138–148 (overlapping m, ring C). MS ($EI^+$), *m/z* (%): 640 ($M^+$, 45), 621 (11), 341 (42), 69 (100).

3,3′,5,5′-Tetrafluoro-*N*,*N*′-dimethyl-4,4′-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-6,6′-(methylimino)di(pyridin-2-amine) (**6**)

Under an atmosphere of dry nitrogen, methylamine (0.6 g, 19.4 mmol) was added to a solution of **4** (3.1 g, 4.9 mmol) in THF (100 ml) and the mixture was stirred at room temperature for 20 h before water (100 ml) was added. The mixture was extracted with dichloromethane, dried with anhydrous $MgSO_4$ and evaporated to yield crude **6** (3.3 g). Column chromatography, using hexane and dichloromethane (2 : 1) as the eluent, afforded pure **6** (2.2 g, 68%) as a blue liquid; b.p. 105 °C (8 Pa). For $C_{19}H_{11}F_{18}N_5$ ( 651.3) calculated: 35.0% C, 1.7% H, 10.8% N; found: 34.5% C, 1.7% H, 10.5% N. $^1$H NMR: 2.91 (3 H, s, NHC**H**$_3$); 2.92 (3 H, s, NHC**H**$_3$); 3.5 (3 H, s, $NCH_3$); 4.6 (2 H, br s, NH). $^{19}$F NMR: –75.6 (12 F, m, $CF_3$); –140.0 to –146.0 (4 F, overlapping m, ring F); –179.8 (2 F, m, C**F**$CF_3$). $^{13}$C NMR: 27.8 (s, $NCH_3$); 36.9 (s, $NHCH_3$); 92.2 (d sept, $^1J_{CF}$ = 211.8, $^2J_{CF}$ = 35.1, $CFCF_3$); 111.9 (br m, C-4); 120.3 (qd, $^1J_{CF}$ = 288.4, $^2J_{CF}$ = 27.1, $CF_3$); 139.5–144.5 (overlapping m, ring C). MS ($EI^+$), *m/z* (%): 651 ($M^+$, 9), 340 (38), 325 (100).

3,3′,5,5′-Tetrafluoro-*N*,*N*,*N*′,*N*′-tetraethyl-4,4′-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)-ethyl]-6,6′-(methylimino)di(pyridin-2-amine) (**7**)

Under an atmosphere of dry nitrogen, diethylamine (0.94 g, 13.1 mmol) was added to a solution of **4** (2.0 g, 3.18 mmol) in THF (50 ml) and the mixture was stirred at reflux temperature for 20 h before water (100 ml) was added. The organic material was extracted with dichloromethane, dried with anhydrous $MgSO_4$ and then evaporated to yield crude **7** (2.3 g). Column chromatography using hexane and ethyl acetate (8 : 1) as the eluent, afforded pure **7** (1.2 g, 51%) as a yellow solid; m.p. 74.6–76 °C. For $C_{25}H_{23}F_{18}N_5$ (735.5) calculated: 40.8% C, 3.1% H, 9.5% N; found: 40.8% C, 3.1% H, 9.4% N. $^1$H NMR: 1.16 (12 H, m, $CH_3$); 3.41 (8 H, m, $CH_2$); 3.48 (3 H, s, $NCH_3$). $^{19}$F NMR: –75.5 (12 F, m, $CF_3$); –135.0 and –137.0 (2 F, F-3); –139.0 and –142.0 (2 F, m, F-5); –179.4 (2 F, m, C**F**$CF_3$). MS ($EI^+$), *m/z* (%): 735 ($M^+$, 21), 353 (53).

7-Fluoro-1,4-*N*-dimethyl-8-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*N*-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2-pyridyl}-1,2,3,4-tetrahydropyrido-[2,3-*b*]pyrazin-6-amine (**8**)

Under an atmosphere of dry nitrogen, *N*,*N*′-dimethylethylene-diamine (0.28 g, 3.2 mmol) was added to a solution of **4** (2.0 g, 3.18 mmol) in THF (50 ml) and the mixture was stirred at reflux temperature for 40 h before water (100 ml) was added. The organic material was extracted with dichloromethane, dried ($MgSO_4$) and then evaporated to yield crude material (2.1 g). Column chromatography, using hexane and ethyl acetate (8 : 1) as the eluent, afforded **8** (1.3 g, 60%) as a yellow solid; m.p. 112.4–113.0 °C. For $C_{21}H_{13}F_{18}N_5$ (677.3) calculated: 37.2% C, 1.9% H, 10.3% N; found: 37.2% C, 1.9% H, 10.1% N. $^1$H NMR: 2.6 (3 H, s, $NCH_3$); 2.92 (2 H, s, $CH_2$); 2.98 (3 H, s, $NCH_3$); 3.38 (2 H, m, $CH_2$); 3.44 (3 H, m, $NCH_3$). $^{19}$F NMR: –75.5 (12 F, m, $CF_3$); –89.1 and –90.4 (1 F, m, F-2); –125.6 and –126.5 (1 F, F-5); –140.5 (1 F, m, F-3); –145.7 and –148.7 (1 F, m, F-3′); –179.0 (2 F, m, C**F**$CF_3$). MS ($EI^+$), *m/z* (%): 677 ($M^+$, 21), 662 (25), 339 (63).

Bis{7-fluoro-1,4-dimethyl-8-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-6-yl}methylamine (**9**)

Under an atmosphere of dry nitrogen, *N*,*N*′-dimethylethane-1,2-diamine (0.13 g, 1.48 mmol) was added to a solution of **4** (0.5 g, 0.79 mmol) in THF (50 ml) and the mixture was stirred at reflux temperature for 40 h before water (100 ml) was added. The organic layer was extracted with dichloromethane, dried with anhydrous $MgSO_4$ and then evaporated to yield crude **9** (0.6 g). Column chromatography, using hexane and ethyl acetate (6 : 1) as the eluent, afforded **9** (0.38 g, 71%) as a green solid; m.p. 169.3–170.2 °C. For $C_{25}H_{23}F_{16}N_7$ (725.5) calculated: 41.4% C, 3.2% H, 13.5% N; found: 41.4% C, 3.2% H, 13.5% N. $^1$H NMR: 2.6 (6 H, s, $CH_3$); 2.99 (4 H, m, $CH_2$); 3.1 (6 H, s, $CH_3$); 3.44 (4 H, m, $CH_2$); 3.51 (3 H, s, $CH_3$). $^{19}$F NMR: –74.8 (12 F, br m, $CF_3$); –141.3 (2 F, m, F-3); –178.9 (2 F, m, C**F**$CF_3$). MS ($EI^+$), *m*/*z* (%): 725 ($M^+$, 13), 363 (20), 336 (17), 42 (100).

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