

# Polyhalogenated heterocyclic compounds. Part 48.<sup>1</sup> Synthesis of perfluoroisopropyl-2,2'-bipyridyl derivatives

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**Dedicated to Professor Charles Rees on the occasion of his 75<sup>th</sup> birthday**

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## Abstract

The synthesis of a highly halogenated 2,2'-bipyridyl system using organometallic methodology is reported.

**Keywords:** Heterocyclic, organofluorine, bipyridyl, polyhalogenated

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## Introduction

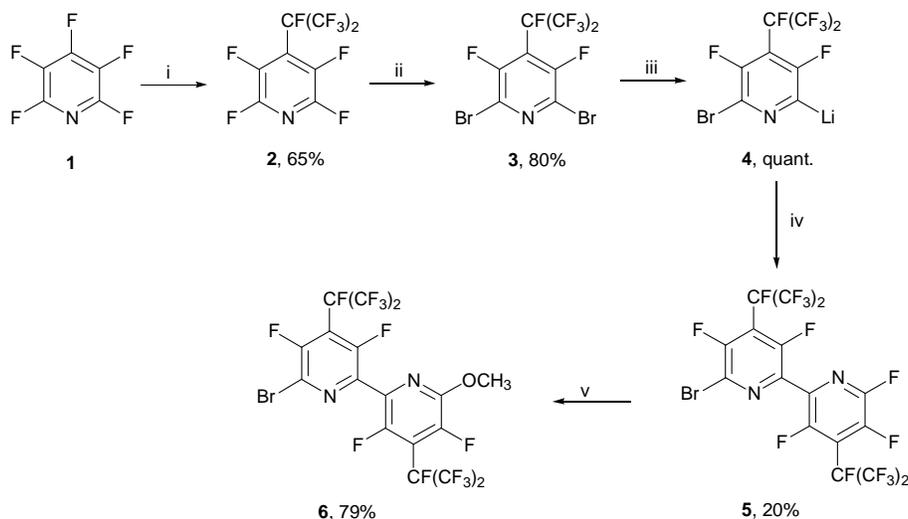
The chemistry of highly fluorinated bipyridyl derivatives remains relatively undeveloped. Earlier work from this laboratory includes synthesis of octafluoro-3,3'-bipyridyl by Ullman coupling of 3-chlorotetrafluoropyridine,<sup>2</sup> halogen exchange reactions, by heating octachloro-bipyridine derivatives with potassium fluoride at high temperature gave octafluoro-2,2'-bipyridyl<sup>3</sup> and electrochemical reduction, involving the generation and coupling of perfluoropyridyl radical anions, gave octafluoro-4,4'-bipyridyl.<sup>4</sup> So far as we are aware, these are the only synthetically realistic methods for the synthesis of these systems that have been reported,<sup>5</sup> together with some studies of factors effecting the orientation of nucleophilic attack in perfluoro-3,3'-bipyridyl.<sup>2</sup>

In this paper, we report the synthesis of a 2,2'-bipyridyl derivative using organometallic methodology.

## Results and Discussion

Perfluoroalkylation of pentafluoropyridine **1** was achieved by heating with hexafluoropropene and a catalytic amount of tetrakis(dimethylamino)ethylene (TDAE), following a procedure described earlier.<sup>6</sup> Bromination of perfluoro-4-isopropylpyridine **2** by heating with hydrogen

bromide and aluminium tribromide in an autoclave, proceeded efficiently to give the 2,6-dibromo pyridine derivative **3** in high yield.<sup>1</sup> The subsequent reaction of **3** with *n*-butyl lithium in THF at low temperature afforded the lithio derivative **4** and then addition of one equivalent of the heterocycle **2**, which is highly susceptible to nucleophilic attack, led to 2,2'-bipyridyl derivative **5** in moderate yield. (Scheme 1) However, we have not yet probed the factors that may lead to an increase in the yield of **5**. Characterisation of **5** followed readily from elemental analysis, mass spectrometry and <sup>19</sup>F n.m.r.



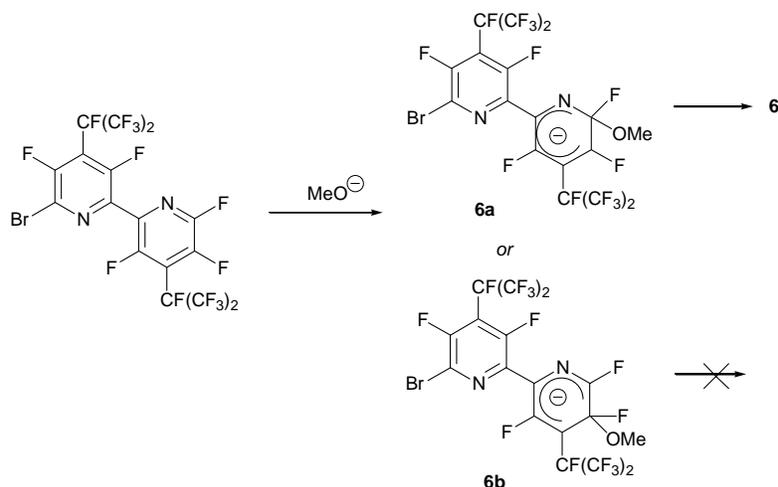
### Scheme 1

#### Reagents and Conditions

(i) CF<sub>3</sub>-CF=CF<sub>2</sub>, TDAE, 60°C; (ii) AlBr<sub>3</sub> (2.2 equiv.), HBr (2.2 equiv.), 160°C, 48 h; (iii) *n*-BuLi (1.2 equiv.), THF, -78°C; (iv) **2**, -78°C - r.t.; (v) NaOMe, MeOH, reflux, 24h

Bipyridyl derivative **5** is, of course, still very reactive towards nucleophiles. Heating **5** with sodium methoxide lead to the major product **6**, in which the fluorine atom located *ortho* to ring nitrogen was substituted. This was deduced by the disappearance of the diagnostic resonance at -83.1 ppm, assigned to the *ortho* ring fluorine substituent in **4**, in the <sup>19</sup>F nmr spectrum.

In principle, nucleophilic attack on the perfluorinated ring could occur at sites both *ortho* and *meta* to the ring nitrogen which would lead to transition states approximating to **6a** and **6b** respectively. (Scheme 2)



## Scheme 2

Transition state **6b** would be stabilised by delocalisation of the negative charge into the pyridine ring attached to the carbon atom *para* to the site of nucleophilic attack. However, the product **5** obtained indicates that the *ortho/para* activating influence of ring nitrogen is the dominant factor in these processes leading to preferential *ortho* substitution. Of course, the bromine atom could, in principle, be displaced because this substituent is also located *ortho* to ring nitrogen. However, replacement of the *ortho* fluorine is predominant because, in this case, the ‘hard’ oxygen nucleophile preferentially attacks the ‘harder’ carbon-fluorine bond rather than the ‘softer’ carbon-bromine bond, in line with previous findings.<sup>7</sup>

In summary, methodology for the preparation of bipyridyl derivatives in which a perfluoropyridyl lithium derivative is trapped by another equivalent of a perfluoropyridine has been established and many similar bis-heterocyclic systems, synthesised by analogous methodology, can be envisaged.

## Experimental Section

**General Procedures.** All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as an internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl -silicone) column. Elemental analyses were obtained on an 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 determined by either <sup>19</sup>F-NMR or gas-chromatography on a Shimadzu GC8A system using a 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 0.040-0.063nm) and TLC analysis was performed on silica gel TLC plates.

Perfluoro-4-isopropylpyridine **1**, was synthesised by literature procedures.<sup>6</sup>

**2,6-Dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-pyridine (3).** A Hastalloy autoclave was charged with aluminium bromide (34.1 g, 0.13 mol), **2** (19.2 g, 0.06 mol) and hydrogen bromide gas (10.2 g, 0.13 mol). The autoclave was heated at 160°C for 48 h. After cooling excess hydrogen bromide was neutralised by release into a sodium hydrogen carbonate solution. The autoclave was opened and ice/water was cautiously added to the solid contents. This mixture was then extracted with dichloromethane and the extracts were dried (MgSO<sub>4</sub>) and distilled under reduced pressure to give *2,6-dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-pyridine 3* (21.6 g, 80%) as a colourless liquid; bp 56°C (4mmHg); (Found C, 21.8; N, 3.1. C<sub>8</sub>Br<sub>2</sub>F<sub>9</sub>N requires C, 21.8; N, 3.2%); δ<sub>F</sub> -75.8 (6F, m, CF<sub>3</sub>), -103.7 and -105.8 (2F, br s, F-3), -180.0 (1F, m, CFCF<sub>3</sub>); δ<sub>C</sub> 91.5 (dsept, <sup>1</sup>J<sub>CF</sub> 216, <sup>2</sup>J<sub>CF</sub> 36.0, CFCF<sub>3</sub>), 114.1 (dt, <sup>2</sup>J<sub>CF</sub> 22.5, <sup>2</sup>J<sub>CF</sub> 13.3, C-4), 119.7 (qd, <sup>1</sup>J<sub>CF</sub> 289, <sup>2</sup>J<sub>CF</sub> 27.1, CF<sub>3</sub>), 124.0 – 126.2 (br m, C-2), 148.0 – 155.0 (br m, C-3); *m/z* (EI<sup>+</sup>) 443 (M<sup>+</sup>, 33%), 441 (M<sup>+</sup>, 41%), 439 (M<sup>+</sup>, 48%), 343 (11), 341 (11), 324 (24), 322 (48), 320 (27), 212 (15), 193 (18), 162 (32), 124 (20), 69 (100).

**2-Bromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-6-lithiopyridine (4).** A solution of *n*-butyllithium (3.5 cm<sup>3</sup>, 5.5 mmol of 1.6 M solution in hexanes) was added to a solution to **3** (2.0 g, 4.5 mmol) in tetrahydrofuran (25 cm<sup>3</sup>) at -78°C, with stirring, under an atmosphere of dry nitrogen.

**2-Bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl]-6-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}pyridine (5).** **2** (7.1 g, 22.2 mmol) was added to a solution of **4** as prepared above and the mixture was stirred for 0.5 h at -78°C, then warmed to room temperature. Water (30 cm<sup>3</sup>) was added and the organic components were extracted into dichloromethane. The dichloromethane solution was dried (MgSO<sub>4</sub>) and evaporated to give a residue which after column chromatography, using hexane and dichloromethane (4:1) as the eluent, gave *2-bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl]-6-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}pyridine 5* (0.6 g, 20%) as a white solid; mp 68-69.5°C; (Found C, 29.1; N, 4.2. C<sub>16</sub>BrF<sub>19</sub>N<sub>2</sub> requires C, 29.1; N, 4.2%); δ<sub>F</sub> -75.2 (12 F, m, CF<sub>3</sub>), -82.9 and -83.8 (1 F, br m, F-2'), -97.3 and -99.5 (1 F, br m, F-3'), -115.0 and -119.8 (2 F, br m, F-5, 5'), -124.7 and -127.5 (1 F, br m, F-3), -179.6 (2 F, m, CFCF<sub>3</sub>); *m/z* (EI<sup>+</sup>) 662 (M<sup>+</sup>, 8%), 660 (M<sup>+</sup>, 9%), 69 (100).

**2-{6-Bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl](2-pyridyl)3,5,-}difluoro-6-methoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine (6).** Under an atmosphere of dry nitrogen, sodium metal (0.02 g, 0.8 mmol) was added to methanol (20 cm<sup>3</sup>) and stirred until hydrogen evolution was complete. **5** (0.5 g, 0.8 mmol) was added to the solution which was stirred at reflux temperature for 24 h. Water (30 cm<sup>3</sup>) was added and the organic components were extracted into dichloromethane. The dichloromethane solution was dried (MgSO<sub>4</sub>) and evaporated to give a residue which after column chromatography, using hexane

and dichloromethane (4:1) as the eluent, gave 2-{6-bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl](2-pyridyl)}{3,5,-difluoro-6-methoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine **6** (0.4 g, 79%) as a white solid; mp 79.8-81.6°C (Found: C, 30.3; H, 0.4, N, 4.2. C<sub>17</sub>H<sub>3</sub>BrF<sub>18</sub>N<sub>2</sub>O requires C, 30.3; H, 0.5; N, 4.2%);  $\delta_{\text{H}}$  4.0 (s, CH<sub>3</sub>);  $\delta_{\text{F}}$  -75.4 (12 F, m, CF<sub>3</sub>), -97.3 and -99.5 (1 F, br m, F-3), -115.2 and -119.6 (2 F, m, F-5,5'), -124.7 and -127.1 (1 F, m, F-3'), -179.9 (2 F, m, CFCF<sub>3</sub>);  $m/z$  (EI<sup>+</sup>) 674 (M<sup>+</sup>, 48%), 672 (M<sup>+</sup>, 56%), 659 (11), 657 (11), 469 (16), 467 (17), 343 (11), 293 (15), 248 (20), 69 (100).

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