Polyhalogenated heterocyclic compounds. Part 47.[1] Syntheses of multi-substituted pyridine derivatives from pentafluoropyridine

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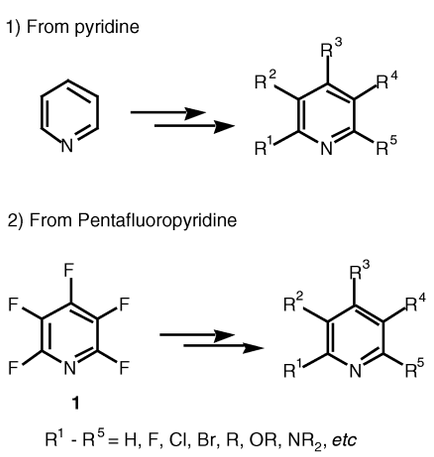
A sequence of nucleophilic aromatic substitution and palladium catalysed coupling processes were used to transform pentafluoropyridine into various pyridine derivatives that bear five different functional groups.

Introduction

Heteroaromatic systems have, of course, a vast chemistry[2] and a great number of materials, pharmaceuticals and other life-science products are heterocyclic derivatives. In the ongoing search for novel biologically active "lead" compounds, the life-science industries have extensive discovery programmes focussed upon the synthesis of a wide range of structurally diverse, multi-functional systems, including those based upon heterocyclic "scaffolds" that, ideally, can be accessed by parallel synthesis. Consequently, development of effective methodology for the synthesis of heterocyclic derivatives bearing several different functional groups has become a topic of great interest particularly in the drug discovery arena where the search for novel pharmacophores is a primary goal. 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 in this journal[3] and the requirement for short, high yielding, regioselective and flexible routes to multiply functionalised heteroaromatic derivatives has been emphasised.[4] A sequence of substitution processes involving the functionalisation of a heteroaromatic "core scaffold" is a strategy frequently employed. This idea is illustrated in Scheme 1 in which

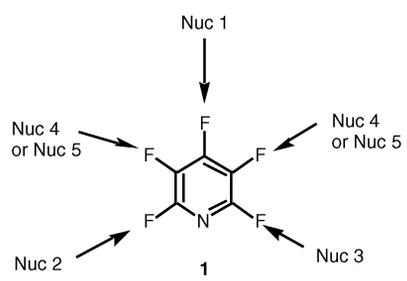


Scheme 1 Penta-functional pyridine derivatives.

pyridine is the parent of heterocyclic systems bearing up to five different substituents R^1–R^5.

Our approach towards the synthesis of highly functionalised heteroaromatic derivatives utilises perfluorinated heterocyclic systems as starting materials (Scheme 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 continues to emerge.[5,6] Indeed, a number of commercially significant fibre-reactive dyes are prepared on a large scale by such processes.[7]

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[5,6] that, in general, the order of activation towards nucleophilic attack follows the sequence 4-fluorine > 2-fluorine > 3-fluorine. Consequently, for a succession of five nucleophilic substitution steps, where Nuc1 is the first nucleophile, Nuc2 is the second, *etc*., the order of substitution is predicted to be selective as outlined in Scheme 2, although a few exceptions to these general rules have been reported.[8]



Scheme 2

A very limited number of relatively highly reactive polychloroheterocyclic derivatives such as trichloro-*s*-triazine have been used recently as substrates for parallel synthesis.[9] However, the vastly increased reactivity of carbon–fluorine bonds in heterocyclic systems towards nucleophiles compared with corresponding carbon–chlorine bonds, the enhanced selectivity of perfluorinated heterocycles towards nucleophilic attack as compared to corresponding perchlorinated derivatives (for example, pentachloropyridine gives a mixture of 2- and 4-substituted products on reaction with sodium ethoxide,[10,11] whereas pentafluoropyridine gives 4-substitution exclusively[12]) and the opportunity for using ^{19}F NMR as a structural probe

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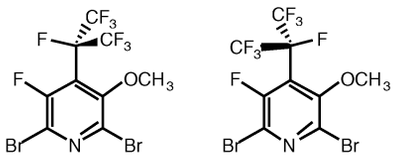


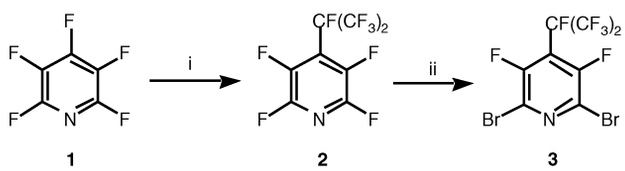
Fig. 1 Conformers **4a** and **4b**.

make perfluorinated heterocyclic systems much more preferable substrates for analogue synthesis than the corresponding chlorinated derivatives.

In this paper, we describe an approach to the synthesis of a range of penta-substituted pyridine derivatives in which the heteroaromatic ring bears up to five different substituents by a sequence of substitution processes using pentafluoropyridine as the starting material.[13]

Results and discussion

Perfluoroalkylation of pentafluoropyridine **1** was achieved by reaction with hexafluoropropene and a catalytic amount of a tertiary amine to afford perfluoroisopropylpyridine **2**, as described previously.[14] This methodology, which is suitable for scale-up, allows ready isolation of the perfluoroisopropyl derivative **2** by simple distillation from the crude reaction mixture. Bromination of **2** by a superacidic hydrogen bromide–aluminium tribromide mixture[15] gave the dibromopyridine derivative **3** in high yield (Scheme 3).



Scheme 3 *Reagents and conditions*: i, CF_2=CF–CF_3, tetrakis(dimethylamino)ethylene, 60 °C; ii, $AlBr_3$ (2.2 equiv.), HBr (2.2 equiv.), 160 °C, 48 h.

The bromofluoroheterocyclic derivative **3** was expected to be a very versatile "building block" because we have recently established[15] that in reactions involving polybromo-fluoroheterocyclic systems fluorine is preferentially substituted by "hard" nucleophiles whereas bromine is substituted by "soft" nucleophiles. With this type of reactivity profile in mind, we explored reactions between **3** and representative oxygen and nitrogen nucleophiles.

Reaction of **3** with methoxide gave products that depended upon reaction conditions. Fluorine is substituted by methoxide to give **4** and **5** upon reaction of **3** with one or two equivalents of sodium methoxide respectively (Scheme 4) and these results are consistent with the HSAB rationale established previously.[15] Reaction of **3** with an excess of sodium methoxide under more forcing conditions does, however, lead to bromine substitution and **6** was isolated (Scheme 4).

Rotation of the perfluoroisopropyl group in **4** is restricted by the 5-methoxy substituent to such an extent that two conformers, **4a** and **4b** (Fig. 1), can be observed by ^{19}F NMR at room temperature.[16] Large through space coupling ($^4J_{FF}$ = 96 Hz) is recorded when two fluorine atoms are in close proximity such as in conformer **4a**. The two conformers **4a** and **4b** were also characterised by X-ray analysis (Fig. 2).

On the other hand, reaction of **3** with a "softer" nucleophile, such as piperidine, gave **7** arising from bromine substitution (Scheme 5). Thus, these reactions demonstrate that the regioselectivity of nucleophilic substitution depends critically on the choice of nucleophile.

In order to widen the range of selective functionalisation reactions possible for bromofluoroheterocycles, such as **3**,

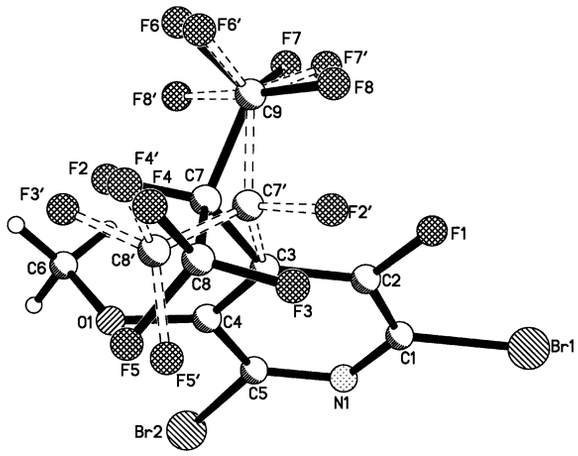
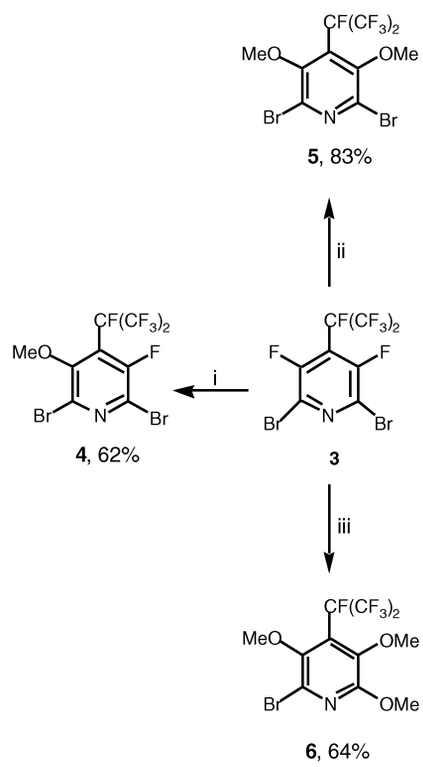
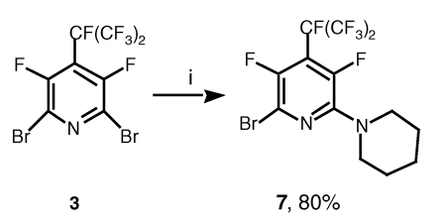


Fig. 2 X-Ray structure of **4**.



Scheme 4 *Reagents and conditions*: i, NaOMe (1.5 equiv.), MeOH, reflux, 24 h; ii, NaOMe (3 equiv.); iii, NaOMe (6 equiv.).



Scheme 5 *Reagents and conditions*: i, piperidine (2 equiv.), MeCN, 80 °C, 24 h.

beyond nucleophilic aromatic substitution processes, we turned our attention to the use of the bromine substituents as functional groups in various metallation and palladium catalysed processes.

Other functional groups may be attached to the heterocyclic ring by lithiation of **3** using *n*-butyllithium followed by trapping of the intermediate carbanionic species **8** by an electrophile (Scheme 6). Lithiation of **3** gave **8** and reaction of a solution of **8** in THF with ethanol and trimethylsilyl chloride gave **9** and **10** respectively.

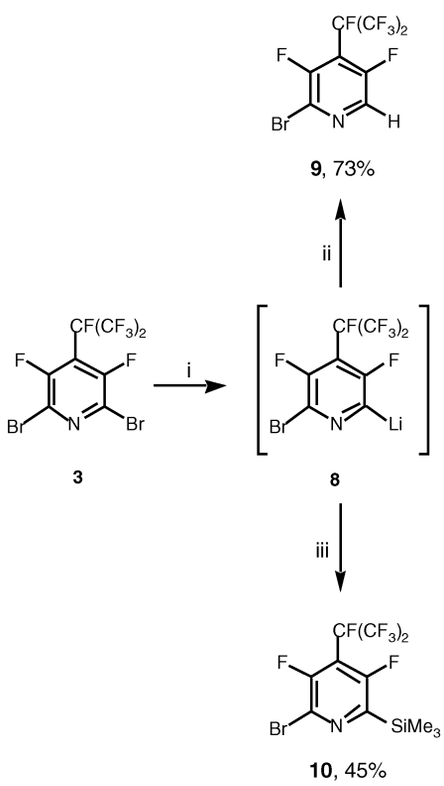
Palladium catalysed reactions,[17] involving coupling between **3** and pent-1-yne (Sonogashira reactions) were carried out and gave **11** and **12** after reaction of **3** with one or two equivalents of pent-1-yne, a palladium catalyst and triethylamine respectively (Scheme 7). By a similar procedure, bis-phenylalkynylation of **3** was carried out by stirring an excess of phenylacetylene with **3** and a Pd catalyst. Mono- and bis-phenylalkynylated products **13** and **14** were separated by column chromatography.

A consideration of the mechanism[17] for palladium catalysed coupling reactions (Scheme 8), allows the effect of perfluoroalkyl substituents on such processes to be assessed. Insertion of the palladium catalyst into the carbon–bromine bond can be envisaged as a nucleophilic attack by the palladium centre and this will be aided by the presence of the highly electron withdrawing perfluoroalkyl group located on the pyridine ring. The coordination of the nucleophilic alkynyl group with the palladium atom, however, is the more likely rate determining step and, again, this will be aided by the perfluoroalkyl group which renders the metal site more electrophilic in nature.

In the final stage of synthesis, reaction of heterocycles, **4**, **7**, **11** and **13**, each bearing four different substituents, yielded penta-substituted systems upon reaction with a further nucleophile (Scheme 9 and Scheme 10). Reaction of **4** with piperidine gave a mixture of isomers **15** and **16** in approximately equal amounts, as estimated by ^{19}F NMR and GC–MS analysis (Scheme 9). However, in contrast, reaction of the piperidyl system **7** with methoxide gave predominantly isomer **15**, arising from substitution of the fluorine atom located *ortho* to the piperidyl group, and only a trace quantity of **16** by GC–MS analysis. The structure of **15** was confirmed by X-ray crystallography (Fig. 3).

Methoxylation of the phenylethynylpyridine derivative **13** gave predominantly **17**, resulting from the substitution of the fluorine atom *para* to the phenylethynyl group (Scheme 10). A small amount (5%) of isomer **18** was formed but was not isolated. Purification and isolation of the major product **17** was achieved by column chromatography.

Since **17** did not give crystals suitable for X-ray analysis, its structure was assigned by a consideration of less reliable ^{19}F NMR calculations, using substituent chemical shift data. The



Scheme 6 *Reagents and conditions*: i, *n*-BuLi (1.2 equiv.), THF, −78 °C; ii, excess EtOH, −78 °C–rt; iii, Me_3SiCl (4 equiv.), −78 °C–rt.

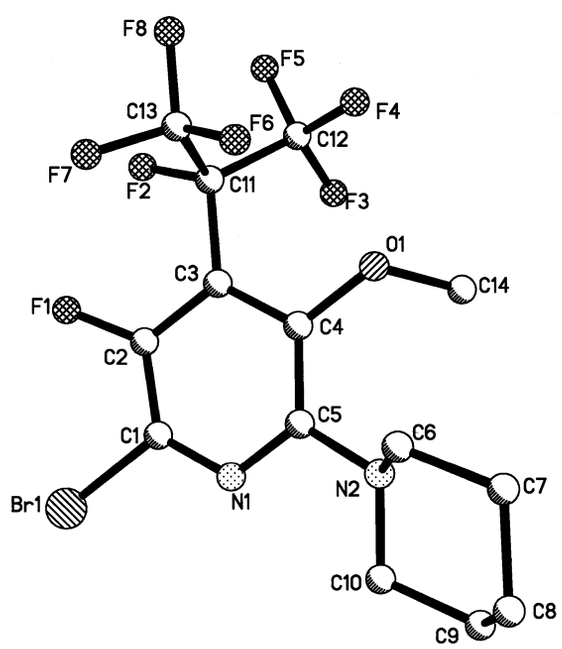
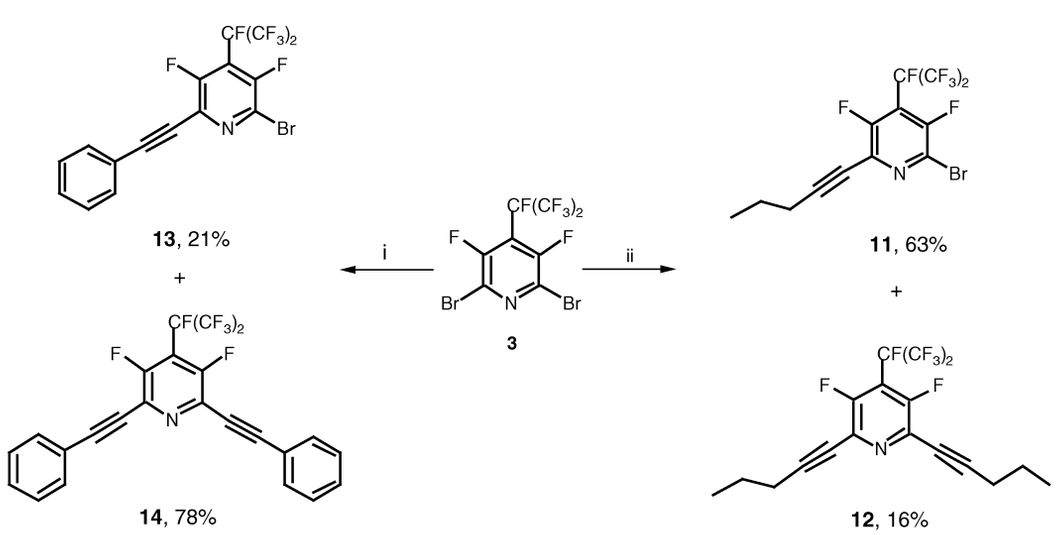
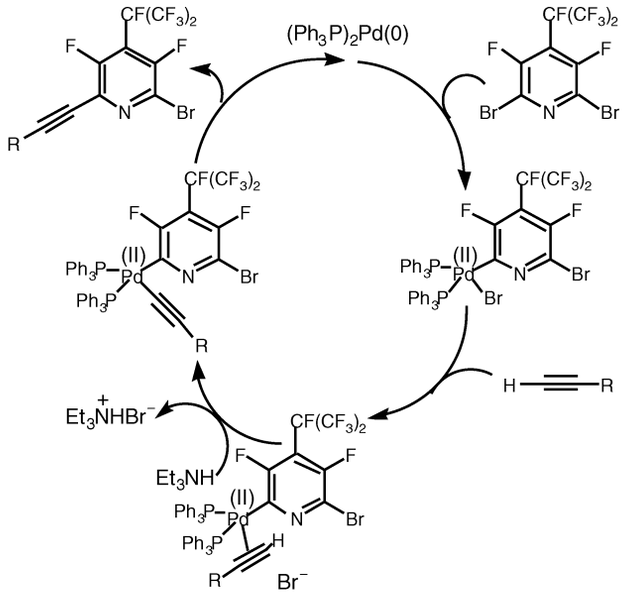


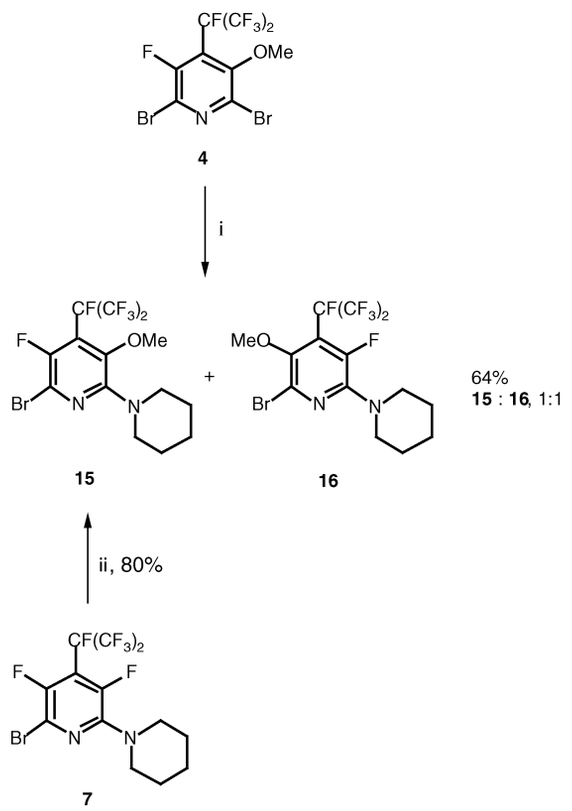
Fig. 3 X-Ray structure of **15**.



Scheme 7 *Reagents and conditions*: i, pent-1-yne (2 equiv.), CuI, $Pd(OAc)_2$, PPh_3, Et_3N, rt, 3 days; ii, phenylacetylene (2 equiv.), CuI, $(Ph_3P)_2PdCl_2$, Et_3N, rt, 16 h.

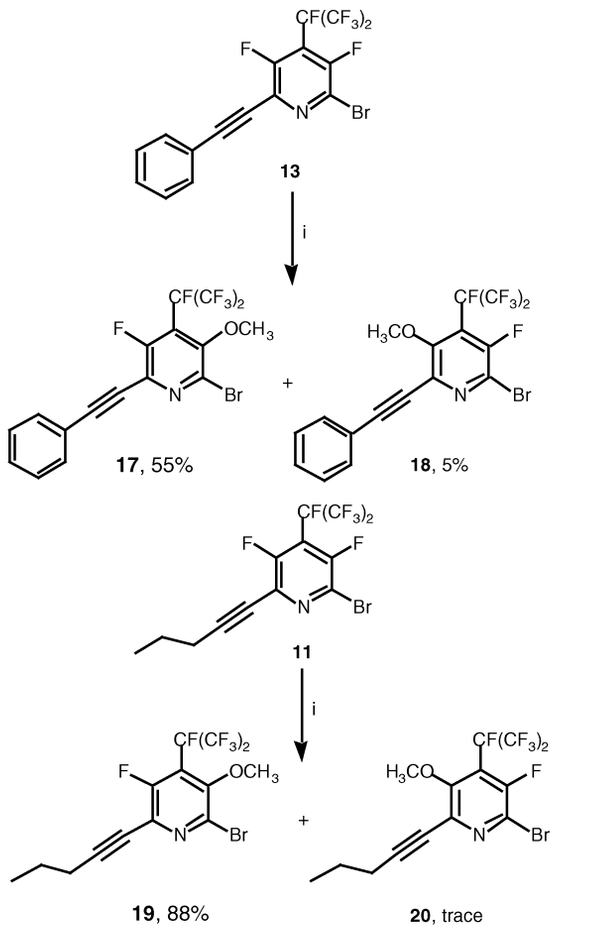


Scheme 8



Scheme 9 *Reagents and conditions*: i, piperidine, THF, reflux, 16 h; ii, NaOMe (1.7 equiv.), MeOH, reflux, 24 h.

^{19}F NMR shift of the ring fluorine substituent in **4**, where the structure was proved unambiguously by X-ray crystallography (Fig. 1), is −104.3/−106.5 ppm (two conformers). A comparison of the published ^{19}F NMR data of bromopentafluorobenzene[18] (F-*ortho* −132.6; F-*meta* −161.2; F-*para*, −155.2 ppm) with 1-phenylethynylpentafluorobenzene[19] (F-*ortho* −136.7; F-*meta* −162.7; F-*para*, −153.7 ppm) reveals that replacement of a bromine substituent by a phenylethynyl group in an aromatic ring causes chemical shifts of −4.1 for *ortho*-fluorine, −1.5 for *meta*-fluorine and +1.5 ppm for *para*-fluorine. Thus, we can predict that the ring fluorine in **17** should have a shift of −108.4/−110.6 ppm whereas in **18** the chemical shift is calculated to be −102.8/−105.0. A comparison of these predicted chemical shift values with the observed resonances,



Scheme 10 *Reagents and conditions*: i, NaOMe (1.7 equiv.), MeOH, reflux, 24 h.

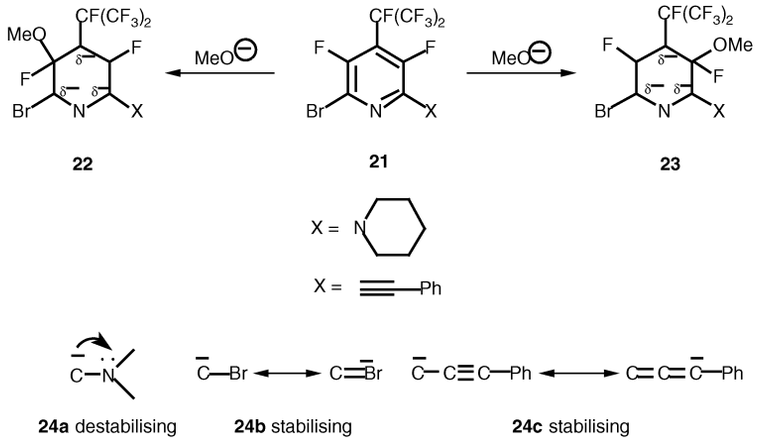
major product δ_F = −109.6/−112.0 ppm and minor product δ_F = −100.0/−102.4 ppm, confirms the structures of the products **17** and **18**.

Similarly, reaction of **11** with sodium methoxide gives **19**, arising from substitution of the fluorine located *para* to the alkynyl group and a trace amount of isomer **20** (Scheme 10).

The regiochemistry of each nucleophilic substitution reaction in Schemes 9 and 10 can be explained by the following mechanistic rationale. In principle, reaction of **21** with methoxide could give two transition states resembling **22** and **23** depending on the site of nucleophilic attack (Scheme 11).

Since the electronegativity of bromine is not significantly different to that of nitrogen, there is no real difference in the electrophilicity of the 3 and 5 ring carbon atoms in the initial state for **21** (X = piperidyl) and therefore the relative stabilities of the anionic transition states determine the regiochemistry of the reaction. If the negative charge density in the transition states **22** (X = piperidyl) and **23** (X = piperidyl) is considered to be greater at the carbon atoms *para* to the sites of nucleophilic attack, then the transition state **23** (X = piperidyl), in which the carbon bearing the highest negative charge density is attached to the bromine substituent, will be more stable than the transition state **22** (X = piperidyl), in which the carbon bearing negative charge is bonded to the piperidyl group (destabilising **24a**). It seems reasonable, therefore, to conclude that nucleophilic substitution occurs at the site that leads to greater charge density adjacent to bromine, rather than nitrogen, in the transition state and, of course, this leads to the product **15**.

Similarly, we can conclude that methoxylation of **21** (X = C≡C–Ph) leads to the more stable transition state **22** (X = C≡C–R) because, in this case, the C≡C–R group is more stabilising than a bromine substituent, due to further delocalisation of charge **24c**, giving product **17**. Finally,



Scheme 11

substitution of bromine in **4** by piperidine gives a mixture of products **15** and **16** because there is not a large difference in the ability of fluorine and methoxy to stabilise carbanion centres where, in each case, stabilising inductive electron withdrawal is offset by electron pair repulsions. The latter are known to be more important when the attached carbanion centre is planar.

In summary, we have outlined an approach for the synthesis of a range of pyridine derivatives that bear four or five different substituents by carrying out a short, efficient sequence of substitution (nucleophilic, palladium catalysed, lithiation, *etc.*) processes on pentafluoropyridine starting material. Clearly, pentafluoropyridine and, by analogy, other highly fluorinated heterocyclic systems, can be utilised as core units for the synthesis of a range of highly substituted heterocyclic derivatives.

Experimental

All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem). Compound **2** was prepared according to literature procedures.[14] 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. 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 was 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).

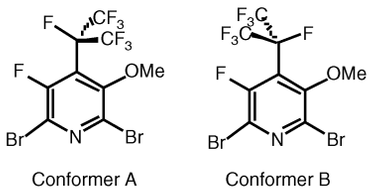
2,6-Dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 3

A Hastalloy autoclave was charged with aluminium bromide (34.1 g, 0.13 mol), 2,3,5,6-tetrafluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine **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 ($MgSO_4$) 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 (4 mmHg) (Found: C, 21.8; N, 3.1. $C_8Br_2F_9N$ requires C, 21.8; N, 3.2%); δ_F −75.8 (6F, m, CF_3), −103.7 and −105.8 (2F, br s, F-3), −180.0 (1F, m, C*F*CF$_3$); δ_C 91.5 (dsept, $^1J_{CF}$ 216, $^2J_{CF}$ 36.0, *C*FCF$_3$), 114.1 (dt, $^2J_{CF}$ 22.5, $^2J_{CF}$ 13.3, C-4), 119.7 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.1, CF_3), 124.0–126.2 (br m, C-2), 148.0–155.0 (br m, C-3); *m*/*z* (EI$^+$) 443 (M$^+$, 33%), 441 (M$^+$, 41), 439 (M$^+$, 48), 343 (11), 341 (11), 324 (24), 322 (48), 320 (27), 212 (15), 193 (18), 162 (32), 124 (20), 69 (100).

Reactions of 2,6-dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 3 with methoxide

General procedure. Under an atmosphere of dry nitrogen, sodium metal was added to methanol (20 ml) and stirred until hydrogen evolution was complete. Compound **3** was added to the solution which was stirred at reflux temperature for 24 h before water (25 ml) was added. The mixture was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to yield crude material which was purified by column chromatography on silica gel, using dichloromethane and hexane (2 : 1) as the eluent.

2,6-Dibromo-3-fluoro-5-methoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 4. Sodium methoxide (0.38 g, 6.9 mmol) gave *2,6-dibromo-3-fluoro-5-methoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **4** (1.26 g, 62%) as a colourless liquid; bp 254–255.6 °C (Found: C, 23.8; H, 0.6; N, 3.1. $C_9H_3Br_2F_8NO$ requires C, 23.8; H, 0.7; N, 3.1%); conformer A: δ_H 3.99 (s, CH_3); δ_F −74.6 (6F, m, CF_3), −106.5 (d, $^4J_{FF}$ 96, F-3), −176.3 (d, $^4J_{FF}$ 96, C*F*CF$_3$); δ_C 62.3 (s, CH_3), 92.2 (dsept, $^1J_{CF}$ 216, $^2J_{CF}$ 34.7, *C*FCF$_3$), 119.9 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.4, CF_3), 121.1 (m, C-4), 124.6 (d, $^2J_{CF}$ 27.7, C-2), 129.6 (s, C-6), 151.6 (d, $^1J_{CF}$ 268, $^3J_{CF}$ 21, C-3), 151.9 (br s, C-5); conformer B: δ_H 3.88 (s, CH_3); δ_F −74.6 (6F, m, CF_3), −104.3 (s, F-3), −181.5 (s, C*F*CF$_3$); δ_C 63.2 (s, CH_3), 92.2 (dsept, $^1J_{CF}$ 216, $^2J_{CF}$ 34.7, *C*FCF$_3$), 119.9 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.4, CF_3), 120.1 (m, C-4), 124.1 (d, $^2J_{CF}$ 28.9, C-2), 134.1 (s, C-6), 153.6 (d, $^1J_{CF}$ 278, C-3), 153.5 (br s, C-5); *m*/*z* (EI$^+$) 455 (M$^+$, 14%), 453 (M$^+$, 31), 451 (M$^+$, 20), 305 (31), 303 (34), 290 (13), 288 (13), 69 (100).



2,6-Dibromo-3,5-dimethoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 5. Sodium methoxide (0.76 g, 13.9 mmol)

gave *2,6-dibromo-3,5-dimethoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **5** (1.75 g, 83%) as a white solid; mp 72.7–74.0 °C (Found: C, 26.1; H, 1.3; N, 2.9. $C_{10}H_6Br_2F_7NO_2$ requires C, 25.8; H, 1.3; N, 3.0%); δ_H 3.90 (3H, s, OCH_3), 4.00 (3H, s, OCH_3); δ_F −73.9 (6F, m, CF_3), −177.2 (m, C*F*CF_3); δ_C 62.0 (s, CH_3), 63.0 (s, CH_3), 93.3 (dsept, $^1J_{CF}$ 213, $^2J_{CF}$ 35.1, *C*FCF_3), 119.9 (qd, $^1J_{CF}$ 292, $^2J_{CF}$ 27.9, CF_3), 126.4 (d, $^2J_{CF}$ 19.8, C-4), 129.4 (s, C-2), 133.1 (s, C-6), 152.0 (s, C-3), 153.8 (m, C-5); *m*/*z* (EI^+) 467 (M^+, 29%), 465 (M^+, 70), 463 (M^+, 52), 317 (61), 315 (66), 260 (36), 221 (24), 205 (28), 93 (22), 69 (100).

2-Bromo-3,5,6-trimethoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 6. Sodium methoxide (1.5 g, 27.5 mmol) gave *2-bromo-3,5,6-trimethoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **6** (1.2 g, 64%) as a colourless liquid; bp 260.5–262 °C (Found: C, 31.6; H, 2.0; N, 3.3. $C_{11}H_9BrF_7NO_3$ requires C, 31.7; H, 2.2; N, 3.4%); δ_H 3.8, 3.9 and 4.0 (all 3H, all s, CH_3); δ_F (major conformer) −74.2 (6F, m, CF_3), −179.3 (1F, m, C*F*CF_3); δ_F (minor conformer) −74.2 (6F, m, CF_3), −176.7 (1F, m, C*F*CF_3); δ_C (major conformer) 54.4 (s, CH_3), 60.4 (s, CH_3), 62.5 (s, CH_3), 93.5 (dsept, $^1J_{CF}$ 210, $^2J_{CF}$ 35.1, *C*FCF_3), 120.5 (qd, $^1J_{CF}$ 287, $^2J_{CF}$ 28.3, CF_3), 123.5 (d, $^2J_{CF}$ 20.2, C-4), 127.8 (m, C-2), 141.1 (s, C-3), 146.9 (s, C-5), 152.6 (s, C-6).

Reaction of 3 with piperidine

6-Bromo-3,5-difluoro-2-piperidyl-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 7. A solution of **3** (1.0 g, 2.3 mmol) and piperidine (0.4 g, 4.5 mmol) in acetonitrile (15 ml) was stirred at reflux temperature for 24 h. Water (30 ml) was added and the mixture was filtered and extracted into dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated affording a liquid (1.9 g). Flash-column chromatography, using dichloromethane as the eluent, yielded *6-bromo-3,5-difluoro-2-piperidyl-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **7** (1.62 g, 80.2%) as a yellow liquid; bp 284.5–286.6 °C (Found: C, 35.2; H, 2.0; N, 6.3. $C_{13}H_{10}BrF_9N_2$ requires C, 35.1; H, 2.2; N, 6.3%); δ_H 1.6 (3H, m, CH_2), 3.3 (2H, m, CH_2N); δ_F −73.3 (6F, m, CF_3), −117.6 and −120.2 (1F, br m, F-3), −120.3 and −122.8 (1F, br m, F-5), −177.3 (m, C*F*CF_3); δ_C 24.4 (s, CH_2), 25.6 (s, *C*H_2CH_2N), 49.2 (s, CH_2N), 91.8 (dsept, $^1J_{CF}$ 214, $^2J_{CF}$ 38.2, *C*FCF_3), 113.9 (br s, C-4), 120.2 (qd, $^1J_{CF}$ 287, $^2J_{CF}$ 27.5, CF_3), 120–122 (br m, C-6), 142.0–149.0 (br m, C-2,3,5); *m*/*z* (EI^+) 446 (M^+, 28%), 444 (M^+, 33), 417 (20), 415 (21), 361 (20), 84 (46), 69 (100).

Lithiation of 3 and trapping by electrophiles

General procedure. A solution of *n*-butyllithium (3.5 ml of 1.6 M solution in hexanes, 5.5 mmol) was added, under an atmosphere of dry nitrogen, to a cooled (−78 °C), stirred solution of **3** (2.0 g, 4.5 mmol) in tetrahydrofuran (25 ml). The electrophile was added and the mixture was stirred for a further 30 min at −78 °C, before being allowed to warm to rt. Water (30 ml) was added and the organic components were extracted into dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to give a residue which was purified by column chromatography on silica gel.

2-Bromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine 9. Ethanol (30 ml), 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-trifluoromethylethyl)pyridine* **9** (1.2 g, 73%) as a colourless liquid; bp 180.6–182.2 °C (Found: C, 26.4; H, 0.2; N, 3.8. C_8HBrF_9N requires C, 26.5; H, 0.3; N, 3.9%); δ_H 8.27 (s); δ_F −71.2 (6F, m, CF_3), −97.0 and −100.0 (1F, br s, F-3), −116.0 and −119.0 (1F, s, F-5), −175.6 (m, C*F*CF_3); δ_C 91.5 (dsept, $^1J_{CF}$ 214, $^2J_{CF}$ 36.2, *C*FCF_3), 113.8 (dt, $^2J_{CF}$ 22.4, $^2J_{CF}$ 12.3, C-4), 119.8 (qd, $^1J_{CF}$ 291, $^2J_{CF}$ 27.5, CF_3), 127.0 (br m, C-2), 135.4 (br m, C-6), 150.0–158.0 (br m, C-3,5); *m*/*z* (EI^+) 363 (M^+, 18%), 361 (M^+, 18), 244 (23), 242 (22), 69 (100).

2-[6-Bromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2-pyridyl]-2-methyl-2-silapropane 10. Trimethylsilyl chloride (2.4 g, 22.2 mmol), after column chromatography, using hexane and dichloromethane (6 : 1) as the eluent, gave *2-[6-bromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2-pyridyl]-2-methyl-2-silapropane* **10** (0.9 g, 48%) as a colourless liquid; bp 211.0–212.1 °C (Found: C, 30.3; H, 2.0; N, 3.2. $C_{11}H_9BrF_9NSi$ requires C, 30.4; H, 2.1; N, 3.2%); δ_H 0.38 (s); δ_F −73.4 (6F, m, CF_3), −100.4 and −103.0 (1F, br s, F-3), −108.6 and −110.6 (1F, s, F-5), −177.3 (1F, m, C*F*CF_3); δ_C −1.8 (s, CH_3), 91.8 (dsept, $^1J_{CF}$ 214, $^2J_{CF}$ 36.3, *C*FCF_3), 111.9 (m, C-4), 120.1 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.1, CF_3), 128.2 (br m, C-6), 152.0–160.0 (br m, C-2,3,5); *m*/*z* (EI^+) 420 ($M^+ - CH_3$, 14%), 418 ($M^+ - CH_3$, 14), 270 (11), 232 (16), 170 (16), 77 (100).

Palladium catalysed coupling reactions of 3

General procedure. A mixture consisting of **3**, the alkyne derivative, copper(I) iodide, palladium(II) acetate, triphenylphosphine and triethylamine was stirred at rt, under an atmosphere of dry nitrogen, for 3 d. Water (30 ml) was added and the mixture was filtered and extracted into dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to give a crude product which was purified by column chromatography.

Reaction with pent-1-yne. Pent-1-yne (0.31 g, 4.5 mmol), **3** (1.0 g, 2.3 mmol), copper(I) iodide (0.01 g, 0.05 mmol), palladium(II) acetate (0.04 g), triphenylphosphine (0.08 g) and triethylamine (15 ml), after column chromatography using hexane–DCM (1 : 2) as the eluent, gave *6-bromo-3,5-difluoro-2-pent-1-ynyl-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-pyridine* **11** (0.6 g, 63%) as white crystals; mp 55.2–56.5 °C (Found: C, 36.5; H, 1.6; N, 3.2. $C_{13}H_7BrF_9N$ requires C, 36.5; H, 1.6; N, 3.3%); δ_H 1.05 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.67 (2H, sex, $^3J_{HH}$ 7.2, C$H_2$$CH_3$), 2.48 (2H, t, $^3J_{HH}$ 7.2, CH_2); δ_F −75.4 (6F, m, CF_3), −101.2 and −104.2 (1F, m, F-5), −111.9 and −114.2 (1F, m, F-3), −179.8 (1F, m, C*F*CF_3); δ_C 13.4 (s, CH_3), 21.4 (s, *C*H_2CH_3), 72.3 (s, *C*-CH_2), 91.5 (dsept, $^1J_{CF}$ 215, $^2J_{CF}$ 36.2, *C*FCF_3), 101.4 (s, Ar-C), 113.5 (m, C-4), 119.8 (qd, $^1J_{CF}$ 276, $^2J_{CF}$ 25.6, CF_3), 124–135 (br m, C-2,6), 150–158 (br m, C-3,5); *m*/*z* (EI^+) 429 (M^+, 38%), 427 (M^+, 50), 414 (24), 412 (100), 345 (49), 343 (52), 200 (33); and, *3,5-difluoro-2,6-dipent-1-ynyl-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **12** (0.15 g, 16.4%) as a yellow oil (bp >300 °C) (Found: C, 52.2; H, 3.4; N, 3.3. $C_{18}H_{14}F_9N$ requires C, 52.0; H, 3.4; N, 3.4%); δ_H 0.95 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.57 (2H, sex, $^3J_{HH}$ 7.2, C$H_2$$CH_3$), 2.38 (2H, t, $^3J_{HH}$ 7.2, CH_2); δ_F −76.1 (6F, m, CF_3), −111.2 and −113.7 (2F, m, F-3), −180.5 (1F, m, C*F*CF_3); δ_C 12.9 (s, CH_3), 21.2 (s, *C*H_2CH_3), 21.3 (s, CH_2), 72.7 (s, *C*-CH_2), 91.6 (dsept, $^1J_{CF}$ 214, $^2J_{CF}$ 35.8, *C*FCF_3), 99.1 (s, Ar-C), 112.1 (m, C-4), 119.8 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.5, CF_3), 128–132 (br m, C-2), 150–159 (br m, C-3); *m*/*z* (EI^+) 415 (M^+, 100%), 400 (72), 387 (72), 358 (34), 331 (31), 302 (27), 252 (27).

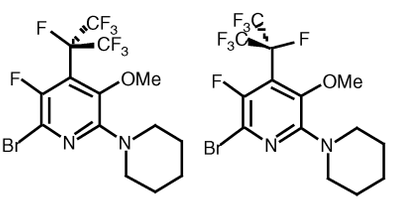
Reaction with phenylacetylene. Phenylacetylene (0.5 g, 4.5 mmol), **3** (1.0 g, 2.3 mmol), copper(I) iodide (0.01 g, 0.05 mmol), bis(triphenylphosphine)palladium dichloride (0.04 g, 0.06 mmol) and triethylamine (10 ml), after column chromatography using hexane–DCM (1 : 2) as the eluent, gave *6-bromo-3,5-difluoro-2-phenylethynyl-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **13** (0.23 g, 21%) as white crystals; mp 84.7–86.2 °C (Found: C, 41.9; H, 1.1; N, 3.1. $C_{16}H_5BrF_9N$ requires C, 41.6; H, 1.1; N, 3.0%); δ_H 7.3–7.6 (5H, m, ArH); δ_F −75.2 (6F, m, CF_3), −100.2 and −103.0 (1F, m, F-5), −110.7 and −113.0 (1F, m, F-3), −179.7 (1F, m, C*F*CF_3); δ_C 80.1 (s, *C*-C_6H_5), 91.6 (dsept, $^1J_{CF}$ 215, $^2J_{CF}$ 35.8, *C*FCF_3), 98.6 (m, Ar-C), 114.2 (dt, $^2J_{CF}$ 22.1, $^2J_{CF}$ 13.3, C-4), 119.9 (qd, $^1J_{CF}$ 290,

$^2J_{CF}$ 27.1, CF_3), 121.0 (s, Ar_{ipso}), 128.8 (s, Ar_{meta}), 130.4 (s, Ar_{para}), 132.5 (s, Ar_{ortho}), 126–132 (br m, C-2,6), 150–160 (br m, C-3,5); *m/z* (EI^+) 463 (M^+, 94%), 461 (M^+, 100), 313 (26), 293 (30), 244 (66), 69 (68); and *2,6-bis(2-phenylethynyl)-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)pyridine* **14** (0.86 g, 78%) as white crystals; mp 172.8–173.2 °C (Found: C, 59.5; H, 2.0; N, 2.8. $C_{24}H_{10}F_9N$ requires C, 59.6; H, 2.1; N, 2.9%); δ_H 7.33 (3H, m, ArH), 7.55 (2H, m, ArH); δ_F −75.3 (6F, m, CF_3), −108.5 and −110.9 (2F, m, F-3), −179.9 (1F, m, C*F*CF_3); δ_C 80.3 (m, *C*-C_6H_5), 91.8 (dsept, $^1J_{CF}$ 215, $^2J_{CF}$ 35.9, *C*FCF_3), 97.4 (m, Ar-C), 112.9 (dt, $^2J_{CF}$ 22.1, $^2J_{CF}$ 13.1, C-4), 120.2 (qd, $^1J_{CF}$ 306, $^2J_{CF}$ 27.5, CF_3), 121.3 (s, Ar_{ipso}), 128.8 (s, Ar_{meta}), 130.2 (s, Ar_{para}), 132.5 (s, Ar_{ortho}), 126–132 (br m, C-2,6), 150–160 (br m, C-3,5); *m/z* (EI^+) 483 (M^+, 100%), 344 (13), 242 (75), 182 (30).

Penta-substituted derivatives—reactions with methoxide

General procedure. Under an atmosphere of dry nitrogen, sodium methoxide (0.3 g, 5.9 mmol) was added to methanol (35 ml) and stirred. The heterocyclic derivative was added to the solution and then stirred at reflux temperature for 24 h before water (25 ml) was added. The mixture was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to yield crude material which was purified by column chromatography, using dichloromethane and hexane (1 : 1) as the eluent.

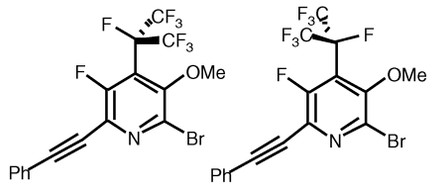
4-(1,2,2,2-Tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-fluoro-5-methoxy-6-piperidinopyridine 15. Sodium methoxide (0.3 g, 5.9 mmol) in methanol (35 ml) and **7** (1.5 g, 3.4 mmol), gave *4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-fluoro-5-methoxy-6-piperidinopyridine* **15** (1.2 g, 80%) as a white solid; mp 81.1–83.0 °C (Found: C, 36.6; H, 2.8; N, 6.0. $C_{14}H_{13}BrF_8N_2O$ requires C, 36.8; H, 2.8; N, 6.1%); δ_H 1.5–1.65 (6H, m, CH_2), 3.2 (4H, m, CH_2N), 3.7 (3H, s, CH_3O); δ_F (minor conformer B) −73.6 (6F, m, CF_3), −116.0 (1F, m, F-3), −179.3 (1F, m, C*F*CF_3); δ_F (major conformer A) −73.4 (6F, m, CF_3), −118.4 (1F, d, $^4J_{FF}$ 95.9, F-3), −174.9 (1F, d, $^4J_{FF}$ 95.9, C*F*CF_3); δ_C (major conformer A) 24.3 (s, CH_2), 25.8 (s, CH_2), 49.2 (m, CH_2N), 57.7 (br s, CH_3O), 92.8 (dsept, $^1J_{CF}$ 211, $^2J_{CF}$ 35.1, *C*FCF_3), 120.4 (qd, $^1J_{CF}$ 287, $^2J_{CF}$ 28.2, CF_3), 120.8 (m, C-4), 121.5 (d, $^2J_{CF}$ 28.2, C-2), 143.3 (m, C-6), 148.1 (d, $^1J_{CF}$ 267, C-3), 151.5 (m, C-5); *m/z* (EI^+) 458 (M^+, 36%), 456 (M^+, 36), 443 (23), 441 (23), 69 (83), 41 (100).



Conformer A Conformer B

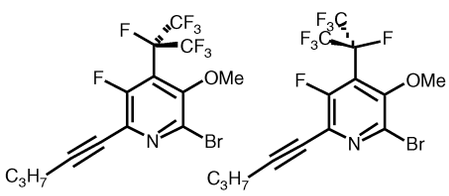
4-(1,2,2,2-Tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-methoxy-5-fluoro-6-(2-phenylethynyl)pyridine 17. Sodium methoxide (0.3 g, 5.9 mmol) in methanol (35 ml) and **13** (1.8 g, 4.0 mmol) gave *4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-methoxy-5-fluoro-6-(2-phenylethynyl)pyridine* **17** (1.0 g, 55%) as a yellow oil; bp >300 °C (Found: C, 42.6; H, 1.6; N, 2.8. $C_{17}H_8BrF_8NO$ requires C, 43.0; H, 1.7; N, 2.9%); δ_H 3.91 and 3.99 (3H, br s, CH_3O), 7.3–7.5 (5H, m, ArH); δ_F (major conformer B) −72.9 (6F, m, CF_3), −109.6 (1F, m, F-5), −179.6 (1F, m, C*F*CF_3); δ_F (minor conformer A) −72.9 (6F, m, CF_3), −112.0 (1F, d, $^4J_{FF}$ 89.9, F-5), −174.6 (1F, d, $^4J_{FF}$ 89.9, C*F*CF_3); *m/z* (EI^+) 475 (M^+, 34%), 473 (M^+, 40), 325 (100), 262 (11), 256 (25), 237 (13).

A minor product, *4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-fluoro-5-methoxy-6-(2-phenylethynyl)pyridine* **18** (5% by ^{19}F NMR integration) was observed in the crude product mixture; δ_F (two conformers) −72.6 (6F, m, CF_3), −100.0 and −102.4 (1F, m, F-5), −179.6 (1F, m, C*F*CF_3); *m/z* (EI^+) 475 (M^+, 32%), 473 (M^+, 32), 305 (38), 303 (36), 182 (45), 155 (54).



Conformer A Conformer B

4-(1,2,2,2-Tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-methoxy-5-fluoro-6-pent-1-ynylpyridine 19. Sodium methoxide (0.3 g, 5.9 mmol) in methanol (35 cm^3) and **11** (1.7 g, 4.0 mmol) gave *4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2-bromo-3-methoxy-5-fluoro-6-pent-1-ynylpyridine* **19** (1.5 g, 88%) as a yellow oil; bp >300 °C (Found: C, 38.5; H, 2.2; N, 3.2. $C_{14}H_{10}BrF_8NO$ requires C, 38.2; H, 2.3; N, 3.2%); δ_H 0.99 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.61 (2H, sex, $^3J_{HH}$ 7.2, C$H_2$$CH_3$), 2.41 (2H, t, $^3J_{HH}$ 7.2, Ar-CH_2), 3.86–3.96 (3H, br m, OCH_3); δ_F (major conformer B) −74.9 (6F, m, CF_3), −112.6 (1F, m, F-5), −181.5 (1F, m, C*F*CF_3); δ_F (minor conformer A) −74.9 (6F, m, CF_3), −115.1 (1F, d, $^4J_{FF}$ 96.0, F-5), −176.6 (1F, d, $^4J_{FF}$ 96.0, C*F*CF_3); *m/z* (EI^+) 441 (M^+, 81%), 439 (M^+, 100).



Conformer A Conformer B

Reaction of 4 with piperidine

A mixture consisting of **4** (0.80 g, 1.7 mmol), piperidine (0.17 g, 2.0 mmol) and THF (20 ml) was heated at reflux temperature for 16 h. The reaction mixture was cooled before water (25 ml) was added. The mixture was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to yield crude material which consisted of **15** and **16** (0.51 g, 64%) in a 1 : 1 ratio by GC–MS analysis; no further purification was attempted and spectral data for **15** were as described above.

X-Ray crystal structures.† All single crystal data were collected on a Bruker SMART-CCD diffractometer (ω-scan, 0.3°/frame) at 120.0(2) K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The data were corrected for absorption and systematic errors using the SADABS procedure. The structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL software.[20]

Crystal data for ***4****.* $C_9H_3Br_2F_8NO$, M = 452.94, monoclinic, space group $P2_1/c$, a = 10.446(2), b = 7.122(1), c = 17.251(4) Å, β = 93.71(3)°, U = 1280.8(4) $Å^3$, $F(000)$ = 856, Z = 4, D_c = 2.349 mg m^{-3}, μ = 6.424 mm^{-1}. 12605 reflections (1.95 ≤ θ ≤ 27.5 °) were collected yielding 2941 unique data (R_{merg} = 0.032). $CF(CF_3)_2$ group of the molecule is disordered over two positions which were refined with equal occupancy. Final $wR_2(F^2)$ = 0.1435 for all data (176 refined parameters), conventional $R(F)$ = 0.0528 for 2346 reflections with $I \geq 2\sigma$, GOF = 1.008. The largest peak on the residual map (1.341 e $Å^{-3}$) is located in

† CCDC reference numbers 167082 and 167083. See http://www.rsc.org/suppdata/p1/b1/b105950p/ for crystallographic files in .cif or other electronic format.

the vicinity of one of the bromine atoms and caused by termination errors.

Crystal data for ***15***. $C_{14}H_{13}BrF_8N_2O$, $M = 457.17$, monoclinic, space group $P2_1/c$, $a = 10.530(2)$, $b = 13.802(3)$, $c = 11.485(2)$ Å, $\beta = 90.86(3)°$, $U = 1669.1(4)$ Å^3, $F(000) = 904$, $Z = 4$, $D_c = 1.819$ mg m^{-3}, $\mu = 2.553$ mm^{-1}. 17323 reflections ($1.93 \leq \theta \leq 27.5°$) were collected yielding 3834 unique data ($R_{merg} = 0.028$). The $CF(CF_3)_2$ group of the molecule is severely disordered. Final $wR_2(_F^2) = 0.1802$ for all data (238 refined parameters), conventional $R(F) = 0.0692$ for 3118 reflections with $I \geq 2\sigma$, GOF = 1.118. The largest peak on the residual map is located in the vicinity of the bromine atom and caused by termination errors.

Acknowledgements

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