Polyhalogenoaromatic Compounds. Part 53.[1] Substitution in Polyfluoroaromatic Compounds by Bulky Nucleophiles

Catherine L. Cheong and Basil J. Wakefield *
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT

Potassium t-butoxide in THF is highly reactive towards polyfluoroaromatic compounds. The position(s) of substitution are generally similar to those observed with other nucleophiles, though octafluoronaphthalene undergoes *ca.* 30% 2,7-disubstitution. Hexafluorobenzene, octafluoronaphthalene, pentafluoropyridine, and 3,5-dichlorotrifluoropyridine also undergo substitution by lithium di-isopropylamide; in the last case substitution occurs in the 2-position.

We have reported that, contrary to expectations, polychloroaromatic compounds undergo substitution when made to react with potassium t-butoxide in tetrahydrofuran (THF), despite the steric hindrance to the reaction.[2] We speculated that an electron transfer mechanism might be involved. In order to obtain more information on the scope of such reactions, and possibly on their mechanisms, we have now investigated some reactions of polyfluoroaromatic compounds with potassium t-butoxide and with the even bulkier lithium di-isopropylamide (LDA).

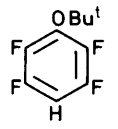
Under the conditions which led to monosubstitution in hexachlorobenzene by potassium t-butoxide in THF,[2] hexafluorobenzene gave much disubstitution; with 2 mol equiv. of t-butoxide a single disubstituted product (**1**) was obtained in 90% yield. The position of the t-butoxy substituents was proved by the equivalence of all the fluorine atoms in the ^{19}F n.m.r. spectrum. Pentafluoroanisole is similarly substituted in the *para*-position by ethoxide[3] (although with methoxide both *ortho*- and *meta*-substitution also occur[4]). When the temperature was held between −8 °C and 0 °C it was possible to obtain the mono-t-butoxy compound (**2**) in 77% yield. This high reactivity of potassium t-butoxide in THF may be contrasted with the report that one hour under reflux with an excess of potassium hydroxide in t-butyl alcohol was required to give pentafluorophenol, with no disubstitution observed.[5]

LDA is popularly regarded as 'non-nucleophilic', although examples of nucleophilic attack by this reagent are known.[6] Prior to our work it would certainly not have been expected to attack hexafluorobenzene under mild conditions. (A reaction with sodium diphenylamide in dioxane required 2 h under reflux;[7] on the other hand results comparable to ours have been reported for some N-substituted lithium anilides in THF.[8]) However, after only 15 min at room temperature, a reaction between equimolar amounts of hexafluorobenzene and LDA in

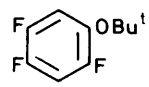
(**1**) R = OBu^t
(**3**) R = NPr^i_2

(**2**) R = OBu^t
(**4**) R = NPr^i_2

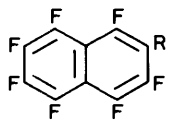
(**5**) R = OBu^t
(**6**) R = NPr^i_2



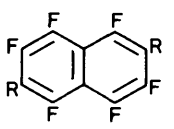
(**7**)



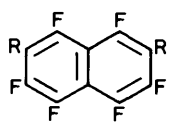
(**8**)



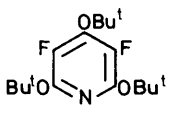
(**9**) R = OBu^t
(**12**) R = NPr^i_2



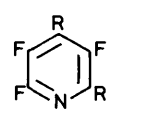
(**10**) R = OBu^t
(**13**) R = NPr^i_2



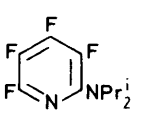
(**11**) R = OBu^t
(**14**) R = NPr^i_2



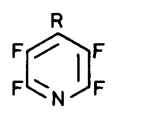
(**16**)



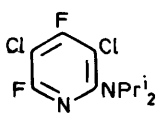
(**15**) R = OBu^t
(**17**) R = NPr^i_2



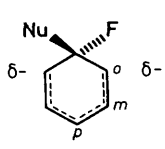
(**18**)



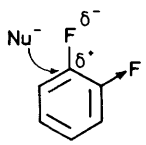
(**19**) R = NPr^i_2
(**20**) R = OBu



(**21**)



(**22**)



(**23**)

Table. ^{19}F N.m.r. spectra of disubstituted hexafluoronaphthalenes

	2,6-Di-t-butoxy (**10**)	2,6-Dimethoxy[9a]	2,7-Di-t-butoxy (**11**)	2,7-Dimethoxy[9]	2,6-Bis(di-isopropylamino) (**13**)	2,6-Dipiperidino[11]	2,7-Bis(di-isopropylamino) (**14**)
				δ_F			
1-F	−29.5 (dd)	−23.7	−31.0 (m)	−24.4	−31.0 (dd)	−27.4	−32.5 (m)
3-F	−17.3 (d)	−13.9	−18.0 (m)	−13.9	−19.0 (d)	−16.9	−19.5 (m)
4-F	−15.4 (dq)	−16.9	−14.0 (m)	−16.1	−16.5 (dq)	−11.7	−15.5 (m)
5-F	−29.5 (dd)	−23.7	−14.0 (m)	−16.1	−31.0 (dd)	−27.4	−15.5 (m)
6-F	—	—	−18.0 (m)	−13.9	—	—	−19.5 (m)
7-F	−17.3 (d)	−13.9	—	—	−19.0 (d)	−16.9	—
8-F	−15.4 (dq)	−16.9	−31.0 (m)	−24.4	−16.5 (dq)	−11.7	−32.5 (m)
				J_{F-F}			
1,8	65				64	67	
3,4	21				21		
4,5	65	*a*			64	68	
5,8	16				16	15	
7,8	21				21		
1,4	16				16	15	

[a] See ref. 11 for alternative partial assignments and some coupling constants.

THF gave the products of monosubstitution (**4**) (44%) and 1,4-disubstitution (**3**) (11%).

The only products we isolated from reactions of t-butoxide and LDA with chloropentafluorobenzene were those of monosubstitution in the 4-position, (**5**) and (**6**) respectively, although in the latter case the yield was low.

In reactions of nucleophiles with pentafluorobenzene and tetrafluorobenzenes, complications may arise from deprotonation (and consequent aryne formation),[9] but the 'normal' position of substitution in pentafluorobenzene is *para* to the unsubstituted position.[10] All the fluorine-bearing positions in 1,2,4,5-tetrafluorobenzene are equivalent, and this compound is very much less reactive towards nucleophiles than hexafluorobenzene and pentafluorobenzene, since each fluorine-bearing position is influenced by one deactivating *para*-fluorine and only one activating *ortho*-fluorine. Addition of potassium t-butoxide in THF to pentafluorobenzene at room temperature led to an exothermic reaction. The main product was 1,2,4,5-tetrafluoro-3-t-butoxybenzene (**7**) (60%); a trace of a compound with M^+ at *m/z* 370, corresponding to an octafluoro-t-butoxybiphenyl, was also obtained. As expected, the reaction of 1,2,4,5-tetrafluorobenzene with t-butoxide was much slower, and required several hours at room temperature for completion. The sole product identified was the mono-t-butoxy compound (**8**) (41%). In the presence of 18-crown-6, the reaction was faster, but the yield of the substitution product (**8**) dropped to 24% and several other products were formed. They could not be purified and characterised, but appeared from their mass spectra to be bi-and ter-phenyl derivatives; presumably the crown ether had promoted deprotonation, and the oligophenyls were formed *via* aryne intermediates.

Octafluoronaphthalene undergoes nucleophilic substitution mainly at the 2-position (although minor amounts of 1-substitution have been observed).[11,12,13] Further substitution of the 2-substituted heptafluoronaphthalenes occurs mainly at the 6-position,[14] although disubstitution of octafluoronaphthalene by methoxide gives a little of the 2,7-dimethoxy compound.[12] The reaction between octafluoronaphthalene and t-butoxide was difficult to control. With 0.5 mol equiv. of t-butoxide at 0 °C, heptafluoro-2-t-butoxynaphthalene (**9**) was obtained in 36% yield and octafluoronaphthalene (60%) was recovered. When a total of 1.75 mol equiv. of t-butoxide was added in portions at −5 °C, the 2-butoxy compound (**9**) was obtained in 56% yield, together with an inseparable mixture of disubstituted compounds. Analysis of the ^{19}F n.m.r. spectrum of the mixture (Table) showed that it consisted of the 2,6- (**10**) and 2,7-disubstituted (**11**) compounds (2:1). Reactions of octafluoronaphthalene with LDA gave mixtures under all the conditions tried (an additional complication being traces of n-butoxy compounds arising from contamination of the n-butyl-lithium used to generate the LDA). From these mixtures we succeeded in isolating low yields of 2-di-isopropylaminoheptafluoronaphthalene (**12**) and of a mixture of the 2,6-(**13**) and 2,7-disubstituted (**14**) compounds in a ratio of 2:1.

Pentafluoropyridine was so reactive towards potassium t-butoxide that a monosubstituted product could not be obtained. Under optimum conditions, however (two mol equiv. of butoxide, room temp., 30 min), 2,3,5-trifluoro-4,6-di-t-butoxypyridine (**15**) was obtained in 91% yield. Under more forcing conditions even a small amount of the tri-t-butoxy compound (**16**) (a rare example of a trialkoxypyridine) was formed. As in the case of octafluoronaphthalene, reactions of pentafluoropyridine with LDA gave mixtures. Under appropriate conditions the 2,4-disubstituted compound (**17**) was obtained in fair yield (56%), but the monosubstituted products (**18**) and (**19**) were obtained only in poor yields. The formation of the 2-substituted isomer (**18**), which was fully characterised, is noteworthy, as only 4-monosubstitution in pentafluoropyridine is normally observed even with quite bulky nucleophiles.[15] [The 4-di-isopropylamino compound (**19**) was contaminated by the n-butoxy compound (**20**)] The 2-substituted compound (**21**) was the only compound isolated, albeit in low yield, from a reaction of LDA with 3,5-dichlorotrifluoropyridine.

The scope of the reactions of bulky nucleophiles with polyfluoroaromatic compounds may be summarised briefly. As expected, the polyfluoroaromatic compounds are even more reactive than the corresponding polychloroaromatic compounds. They react under even milder conditions, undergo substitution even by LDA, and in some cases undergo a higher degree of substitution. These results, however, throw little further light on the mechanism of the reactions. The position(s) of substitution are generally similar to those reported for other nucleophilic substitutions (though modified by steric hindrance in the case of the pyridines).

The position of nucleophilic substitution in polyfluoroaromatic compounds may be predicted by use of the generalisation that fluorine atoms *ortho* or *meta* to the site of attack are activating, whereas *para*-fluorine atoms are slightly

deactivating.[16] In polycyclic systems the fluorine atoms in rings other than the one attacked may be similarly classified as pseudo-*ortho*, pseudo-*meta*, or pseudo-*para*, although their effect is weaker.[17,18] These generalisations have been rationalised in various ways, but the best current view is summarised by the conclusions of Chambers *et al.*[16] Thus, the effects of *meta*- and *para*-fluorine may be accounted for on the basis of known effects of fluorine on adjacent or attached carbanionic sites applied to the corresponding Meisenheimer complexes (**22**), whereas the activating influence of *ortho*-fluorine is a composite of stabilisation of the Meisenheimer complex and 'initial state' ion-dipole interactions (**23**).

Since the positions of substitution observed in our experiments are in agreement with those previously reported for other nucleophiles, and with the generalisations outlined above, it seems most likely that the relative rates of substitution in alternative positions are governed by similar considerations. What still requires explanation is the high reactivity of t-butoxide and di-isopropylamide in THF. Our hypothesis to account for their anomalous reactivity is that the formation of a Meisenheimer complex intermediate is preceded by a fast electron transfer step. Attempts were made to detect any radical intermediates by e.s.r. No signals were observed from a reaction between pentafluoropyridine and potassium t-butoxide in THF at −70 °C, but this reaction was fairly fast even at that temperature. The reaction between potassium t-butoxide and 1,2,4,5-tetrafluorobenzene was sufficiently slow at room temperature to enable the reaction mixture to be placed in the e.s.r. cavity and the instrument to be tuned while the reaction was still proceeding. Under these conditions a weak signal was observed at g = 1.965, but it was broad and could not be identified. The lack of convincing direct evidence for radical intermediates does not of course invalidate our hypothesis, since such intermediates may only be present in low stationary concentrations. Possible investigations of the effect of radical scavengers on the reactions were frustrated by the reactivity of t-butoxide towards commonly used traps. Nitro compounds are known to react with t-butoxide in THF,[19] and a blank reaction of t-butoxide with benzoquinone in THF resulted in the almost instantaneous precipitation of quinhydrone. These reactions do provide further evidence of the capacity of t-butoxide to act as a single electron donor.[20] Single electron transfer reactions of di-isopropylamide are also documented.[20,21]

Clearly, more searching physicochemical investigations will be required in order to determine whether the reactions reported here do involve an electron transfer step, or whether solvation effects are responsible for the high reactivity of potassium t-butoxide and LDA in THF.[22]

Experimental

All the preparations were carried out under an inert atmosphere, with THF freshly distilled from benzophenone ketyl as solvent. Butyl-lithium was used in the form of a 15% solution in hexane (Lithium Corporation of Europe) and standardised by Gilman double titration. Column chromatography (medium pressure or 'flash') was carried out with the appropriate grade of Merck Kieselgel 60. Light petroleum refers to the fraction b.p. 40—60 °C. ^{1}H and ^{13}C N.m.r. spectra were recorded with TMS as internal reference. ^{19}F N.m.r. spectra were recorded with hexafluorobenzene as external reference; the signal for hexafluorobenzene is 164.9 p.p.m. upfield from that for trichlorofluoromethane. E.s.r. spectroscopy was carried out with a JEOL FE-3-X instrument.

The following general method of work-up was used. The reaction mixture was added to water (50 ml). The resulting mixture was saturated with sodium chloride and extracted with chloroform (3 × 50 ml). The combined extracts were washed with water (5 × 50 ml), dried ($MgSO_4$), and evaporated.

Reactions of Hexafluorobenzene.—(*a*) Potassium t-butoxide (0.3 g, 2.7 mmol) was added to a stirred solution of hexafluorobenzene (1.0 g, 5.4 mmol) in THF (50 ml) at −8 °C. T.l.c. of the resulting orange solution showed a single spot. Further potassium t-butoxide (0.3 g) was added, the mixture was stirred and maintained at −8 °C to 0 °C for 30 min, and then worked up. Chromatography of the residue (alumina, light petroleum) gave *pentafluoro-t-butoxybenzene* (1.0 g, 77%), colourless oil, δ 1.4 (s) (Found: C, 50.4; H, 3.9%; M^+, 240. $C_{10}H_9F_5O$ requires C, 50.0; H, 3.9%; *M*, 240).

(*b*) Potassium t-butoxide (1.2 g, 10.7 mmol) was added to a stirred solution of hexafluorobenzene (1.0 g, 5.4 mmol) in THF (50 ml). The resulting exothermic reaction produced an orange solution which was allowed to cool to room temperature and then worked up to give *tetrafluoro-1,4-di-t-butoxybenzene* (1.15 g, 90%), m.p. 54—55 °C (purified by sublimation); δ_H 1.4 (s); δ_F −9.0 (s) (Found: C, 57.0; H, 6.0%; M^+, 294. $C_{14}H_{18}F_4O_2$ requires C, 57.1; N, 6.2%; *M*, 294).

(*c*) Butyl-lithium (5.3 mmol) was added dropwise to a solution of di-isopropylamine (0.54 g, 5.3 mmol) in THF (50 ml). Hexafluorobenzene (1.0 g, 5.4 mmol) was added, and the resulting red-brown solution was stirred during 15 min. Work-up as described above gave, in order of elution, (i) (*di-isopropylamino*)*pentafluorobenzene* (0.62 g, 44%), colourless oil, δ_H 1.05 (12 H, d) and 3.6 (2 H, m) [Found: C, 54.2; H, 5.3; N, 5.2%; $M^+ + 1$ (c.i.), 268. $C_{12}H_{14}F_5N$ requires C, 53.9; H, 5.3; N, 5.2%; *M*, 267]; (ii) 1,4-*bis*(*di-isopropylamino*)*tetrafluorobenzene* (0.2 g, 11%), colourless oil, δ_H 1.05 (24 H, d) and 3.6 (4 H, m) (Found: M^+, 348.2176. $C_{18}H_{28}F_4N_2$ requires *M*, 348.2188).

Reactions of Chloropentafluorobenzene.—(*a*) Potassium t-butoxide (0.28 g, 2.5 mmol) was added to a stirred solution of chloropentafluorobenzene (0.5 g, 2.5 mmol) in THF (30 ml), resulting in an exothermic reaction. After 15 min the reaction mixture was worked up as described above to give 4-*chloro*-2,3,5,6-*tetrafluoro*-1-*t-butoxybenzene* (0.55 g, 87%), colourless oil, δ_H 1.4 (s); δ_F −12.5 (2 F, m) and −20.0 (2 F, m) (Found: C, 47.2; H, 3.7%; M^+, 256. $C_{10}H_9ClF_4O$ requires C, 46.8; H, 3.5%; *M*, 256).

(*b*) Butyl-lithium (4.9 mmol) was added dropwise to a solution of di-isopropylamine (0.5 g, 4.9 mmol) in THF (50 ml). Chloropentafluorobenzene (1.0 g, 4.9 mmol) was added and the solution was stirred during 30 min. Work-up followed by flash chromatography [silica; eluant dichloromethane–light petroleum (1:9)] gave 1-*chloro*-4-*di-isopropylamino*-2,3,5,6-*tetrafluorobenzene* (0.2 g, 14%), colourless oil, δ_H 1.05 (12 H, d) and 3.6 (2 H, m); δ_F −1.85 (2 F, m), and −4.85 (2 F, m) (Found: C, 50.7; H, 4.6; N, 4.9%; M^+, 283.0775. $C_{12}H_{14}ClF_4N$ requires C, 50.8; H, 5.0; N, 4.9%; *M*, 283.0751).

Reaction of Pentafluorobenzene.—Potassium t-butoxide (0.67 g, 6.0 mmol) was added to a stirred solution of pentafluorobenzene (1.0 g, 6.0 mmol) in THF (50 ml). The mixture was stirred while the exothermic reaction subsided (*ca.* 15 min). Work-up and chromatography gave 1,2,4,5-*tetrafluoro*-3-*t-butoxybenzene* (0.8 g, 61%), colourless oil, δ_H 1.4 (9 H, s), and 6.8 (1 H, m); δ_F −11.0 (2 F, m) and −22.5 (2 F, m) (Found: C, 54.4; H, 4.8%; M^+, 222. $C_{10}H_{10}F_4O$ requires C, 54.1; H, 4.5%; *M*, 222).

Reactions of 1,2,4,5-*Tetrafluorobenzene.*—(*a*) Potassium t-butoxide (0.37 g, 3.3 mmol) was added to a stirred solution of 1,2,4,5-tetrafluorobenzene (0.5 g, 3.3 mmol) in THF (30 ml) and stirring was continued during 4 h. Work-up and chromato-

graphy gave 2,4,5-*trifluoro*-1-*t*-*butoxybenzene* (0.28 g, 41%), colourless volatile oil, δ_H 1.4 (9 H, s), and 6.7 (2 H, m); δ_F −22.5 (1 F, m), −24.0 (1 F, dt), and −36.0 (1 F, m) (Found: C, 59.7; H, 5.4. $C_{10}H_{11}F_3O$ requires C, 58.8; H, 5.4%).

(*b*) Potassium t-butoxide (0.37 g, 3.3 mmol) was added to a stirred solution of 1,2,4,5-tetrafluorobenzene (0.5 g, 3.3 mmol) in THF (30 ml). After 30 min stirring 18-crown-6 (0.18 g, 0.7 mmol) was added; the solution immediately became yellow. The mixture was stirred during 1 h. Work-up and chromatography gave, in order of elution, (i) 2,4,5-trifluoro-1-t-butoxybenzene (0.16 g, 24%); (ii) a mixture, shown by g.c.m.s. to consist of two components, *m/z* 276.0204 ($C_{10}H_5F_5O_2$ requires 276.0210) and 406.0250 ($C_{18}H_6F_8O_2$ requires 406.0240).

Reactions of Octafluoronaphthalene.—(*a*) Potassium t-butoxide (0.2 g, 1.8 mmol) was added to a stirred solution of octafluoronaphthalene (1.0 g, 3.6 mmol) in THF (50 ml) at 0 °C. The bright yellow solution was stirred during 15 min. Work-up followed by flash chromatography [silica; eluant chloroform–light petroleum (5:95)] gave, in order of elution, (i) octafluoronaphthalene (0.6 g, 60%); (*ii*) *heptafluoro*-2-*t*-*butoxynaphthalene* (0.2 g, 36%), m.p. 74—75 °, δ_H 1.5 (s); δ_F −7.0 (2 F, m, 6-F and 7-F), −15.3 [1 F, dt, $J_{5,4}$ 58 Hz, $J_{5,6}$ and $J_{5,8}$ 16 Hz, 5-F (or 4-F)], −16.5 [1 F, dt, $J_{4,5}$ 58 Hz, $J_{4,3}$ and $J_{4,1}$ 17, 15 Hz, 4-F (or 5-F)], −18.0 (1 F, dt, $J_{8,1}$ 68 Hz, $J_{8,5}$ and $J_{8,7}$ 16 Hz, 8-F), −19.8 (1 F, d, $J_{3,4}$ 17 Hz, 3-F) and −30.5 (1 F, dd, $J_{1,8}$ 68 Hz, $J_{1,4}$ 15 Hz, 1-F) (Found: C, 51.8; H, 2.55%; M^+, 326. $C_{14}H_9F_7O$ requires C, 51.55; H, 2.8%; *M*, 326); (iii) unidentified material (0.12 g).

(*b*) Potassium t-butoxide (0.2 g, 1.8 mmol) was added to a stirred solution of octafluoronaphthalene (1.0 g, 3.6 mmol) in THF (50 ml) at −5 °C and the mixture was stirred during 2 h. Potassium t-butoxide (0.5 g, 4.5 mmol) was added in portions until only a trace of starting material remained (t.l.c.). Work-up followed by flash chromatography [silica; eluant dichloromethane–light petroleum (1:9)] gave, in order of elution, (i) octafluoronaphthalene (trace); (ii) heptafluoro-2-t-butoxynaphthalene (0.7 g, 58%); and (iii) an inseparable mixture (0.19 g, 14%), m.p. 68—98 °C of hexafluoro-2,6-di-t-butoxynaphthalene and 2,7-di-t-butoxynaphthalene, δ_H 1.45 (s); δ_F, see Table. (Found: C, 56.6; H, 4.6%; M^+, 380. Calc. for $C_{18}H_{18}F_6O_2$: C, 56.85; H, 4.8%; *M*, 380).

(*c*) Butyl-lithium (4.0 mmol) was added dropwise to a stirred solution of di-isopropylamine (0.4 g, 4.0 mmol) in THF (50 ml). Octafluoronaphthalene (1.1 g, 4.0 mmol) was added, giving a deep purple mixture which was stirred until the exothermic reaction had subsided (*ca.* 20 min). Work-up followed by flash chromatography (silica; eluant light petroleum) gave, in order of elution, (i) octafluoronaphthalene (0.24 g, 22%); (ii) a mixture, the ^1H n.m.r. spectrum of which revealed the presence of a di-isopropylamino group and a butoxy group; and (iii) an inseparable mixture (0.1 g, 6%), m.p. 92—100 °C, of 2,6-bis(di-isopropylamino)hexafluoronaphthalene and 2,7-bis(di-isopropylamino)hexafluoronaphthalene, δ_H 1.1 (d) and 3.7 (m); δ_F see Table. (Found: C, 60.9; H, 6.4%; M^+, 434. Calc. for $C_{22}H_{28}F_6N_2$: C, 60.8; H, 6.5%; *M*, 434).

(*d*) An experiment was carried out as described in (*c*), except that after the initial reaction had subsided a second equivalent of LDA was added and reaction was continued for a further 20 min. The products obtained were (i) octafluoronaphthalene (9%); (ii) a mixture, which was separated by chromatography on alumina to give 2-*di-isopropylaminoheptafluoronaphthalene* (14%), colourless oil, δ_H 1.1 (12 H, d) and 3.7 (2 H, m); δ_F (principal couplings only given) −5.5 (d, *J* 17 Hz, 6-F), −7.0 (t, *J* 17 Hz, 7-F), −13.5 (dt, *J* 58, 16 Hz, 4-F), −15.5 (dt, *J* 58, 17 Hz, 5-F), −18.0 (dt, *J* 71, 17 Hz, 8-F), −28.0 (d, *J* 21 Hz, 3-F), and −42.5 (dd, *J* 71, 16 Hz, 1-F) (Found: C, 54.3; H, 4.1; N, 4.0%; M^+, 353. $C_{16}H_{14}F_7N$ requires C, 54.4; H, 4.0; N, 4.0%; *M*, 353) and butoxyheptafluoronaphthalene (20 mg, 3%), δ_H 1.1 (3 H, m), 1.7 (4 H, m), and 4.3 (2 H, t); M^+, 326; and (iii) a mixture (0.13 g, 15%) of 2,6- and 2,7-bis(di-isopropylamino)hexafluoronaphthalene.

Reactions of Pentafluoropyridine.—(*a*) Potassium t-butoxide (0.66 g, 6.0 mmol) was added to a stirred solution of pentafluoropyridine (1.0 g, 6.0 mmol) in THF (50 ml). The mixture was stirred during *ca.* 30 min and heated under reflux during 2 h. Work-up and chromatography (alumina; eluant light petroleum) gave 3,5,6-*trifluoro*-2,4-*di*-*t*-*butoxypyridine* (0.65 g, 34%), b.p. 58 °C/2 mmHg, δ_H 1.45 (s) and 1.6 (s); δ_F −2.75 (d, 5-F), −14.0 (d, 3-F), and −72.0 (t, 6-F) (Found: C, 56.3; H, 6.4; N, 5.3%; $M^+ + 1$, 278. $C_{13}H_{18}F_3NO_2$ requires C, 56.3; H, 6.5; N, 5.05%; $M + 1$, 278).

(*b*) A similar experiment, but with potassium t-butoxide (1.32 g, 12.0 mmol) gave trifluoro-2,4-di-t-butoxypyridine (1.49 g, 91%).

(*c*) Experiments using equimolar amounts of potassium t-butoxide and pentafluoropyridine and initial temperatures of −10 °C and −70 °C gave the same product in yields of 30% and 67%, respectively.

(*d*) Potassium t-butoxide (1.0 g, 9.0 mmol) was added to a stirred solution of pentafluoropyridine (0.5 g, 3.0 mmol) in THF (50 ml) at room temperature. The mixture was heated under reflux during 1 h, allowed to cool to room temperature, and worked up to give a clear oil (0.86 g) which on standing deposited large crystals. Column chromatography [alumina, eluant diethyl ether–light petroleum (2:98)] gave trifluoro-2,4-di-t-butoxypyridine (0.09 g, 11%) and 3,5-*difluoro*-2,4,6-*tri*-*t*-*butoxypyridine* (0.10 g, 10%), m.p. 43—45 °C; δ_H 1.4 (18 H, s) and 1.55 (9 H, s) (Found: C, 61.7; H, 8.3; N, 4.4%; $M^+ + 1$, 332. $C_{17}H_{27}NO_3$ requires C, 61.6; H, 8.2; N, 4.2%; $M + 1$, 332).

(*e*) Butyl lithium (4.0 mmol) was added dropwise to a solution of di-isopropylamine (0.4 g, 4.0 mmol) in THF (40 ml). Pentafluoropyridine (0.67 g, 4.0 mmol) was added (exothermic reaction) and the solution was stirred during 15 min. Work-up gave an oil (0.55 g) which on chromatography [alumina; eluant dichloromethane–light petroleum (5:95)] gave (i) 2-*di*-*isopropylaminotetrafluoropyridine* (40 mg, 4%), colourless oil, δ_H 1.3 (12 H, d) and 3.9 (2 H, m); δ_F 13.0 (1 F, m, 5-F), −8.5 (1 F, m, 3-F), −22.0 (1 F, m, 4-F), −77.0 (1 F, m, 6-F) (Found: M^+, 250.108. $C_{11}H_{14}F_4N_2$ requires *M*, 250.109), and (ii) a mixture (0.28 g) containing 4-di-isopropylaminotetrafluoropyridine, δ_H 1.15 (d) and 3.7 (m); δ_F −17.5 (m) and −71.5 (m), and 4-butoxytetrafluoropyridine, δ_H 1.0 (t), 1.2—2.0 (m), and 4.5 (m); δ_F −3.0 (m) and −74.0 (m) in a ratio of 2.5:1 (n.m.r).

(*f*) An experiment was carried out as in (*e*) except that LDA (8.0 mmol) was used. Chromatography of the crude product (silica; gradient elution with dichloromethane in light petroleum) gave (i) 2-di-isopropylaminotetrafluoropyridine (0.1 g, 10%); (ii) 4-di-isopropylaminotetrafluoropyridine (0.07 g, 7%); and (iii) 2,4-*bis*(*di*-*isopropylamino*)*trifluoropyridine* (0.73 g, 56%), colourless oil, δ_H 1.2 (m) and 3.75 (m); δ_F −9.5 (d, *J* 28 Hz, 5-F), −32.5 (d, *J* 28 Hz, 3-F), and −71.0 (t, *J* 28 Hz, 6-F) (Found: C, 61.3; H, 8.4; N, 12.3%; M^+, 331. $C_{17}H_{28}F_3N_3$ requires C, 61.6; H, 8.52; N, 12.7%; M^+, 331).

Reactions of 3,5-*Dichlorotrifluoropyridine.*—(*a*) Potassium t-butoxide (1.1 g, 10.0 mmol) was added to a stirred solution of 3,5-dichlorotrifluoropyridine (1.0 g, 5.0 mmol) in THF (50 ml). The mixture was stirred (30 min) while the exothermic reaction subsided. Work-up and chromatography (silica; gradient elution with chloroform in light petroleum) gave 2,4-*di*-*t*-*butoxy*-3,5-*dichloro*-6-*fluoropyridine* (0.38 g, 25%), colourless oil, δ_H 1.55 (s) and 1.65 (s); δ_F −2.15 (s); δ_C 28.3, 29.7, 83.1, 88.3, 104.9 (d, $J_{5C,6F}$ 29 Hz, C-5), 112.9 (d, C-3), 116.2 (d, C-4), 155.3 (d, $J_{6-C,6-F}$ 236 Hz, C-6), and 156.2 (d, $J_{2-C,6-F}$ 17 Hz,

C-2) (Found: M^+, 309.868. $C_{13}H_{18}Cl_2FNO_2$ requires M, 309.870).

(*b*) Butyl-lithium (2.4 mmol) was added dropwise to a stirred solution of di-isopropylamine (0.17 g, 2.4 mmol) in THF (30 ml) at 0 °C. 3,5-Dichlorotrifluoropyridine (0.46 g, 2.3 mmol) was added and the mixture was stirred until the exothermic reaction had subsided. Work-up gave a deep red oil (0.6 g) from which was obtained by chromatography (silica; eluant light petroleum) 3,5-*dichloro*-2,4-*difluoro*-6-*di-isopropylaminopyridine* (0.12 g, 18%), colourless oil, δ_H 1.4 (d) and 4.0 (m); δ_F 4.0 (d) and −21.0 (d); δ_C 22.0, 49.6, 94.0 (dd, *J* 42, and 22 Hz, C-3), 104.2 (dd, *J* 26 Hz, C-5), 153.5 (dd, *J* 7 and 5 Hz, C-6), 154.3 (dd, *J* 234 and 9 Hz, C-2), and 162.9 (dd, *J* 257 and 7 Hz, C-4) (Found: C, 47.0; H, 5.0; N, 9.5%; M^+, 283. $C_{11}H_{14}Cl_2F_2N_2$ requires C, 49.7; H, 5.0; N, 9.9%; *M*, 283).

Acknowledgements

We thank S.E.R.C. for a maintenance grant to C. L. C.

References

1 Part 52, J. H. Brady, N. Tahir, and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2425.
2 J. H. Brady and B. J. Wakefield, *Synthesis*, 1984, 33.
3 J. H. James, M. E. Peach, and C. R. Williams, *J. Fluorine Chem.*, 1985, **27**, 91.
4 J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 5152.
5 J. M. Birchall and R. N. Haszeldine, *J. Chem. Soc.*, 1959, 13.
6 J. L. Herrmann, G. R. Kieczykowskii, and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, 2433; T. Uyehara, N. Asao, and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1987, 1411.
7 J. Burdon, J. Castaner, and J. C. Tatlow, *J. Chem. Soc.*, 1964, 5017.
8 R. Koppang, *J. Organomet. Chem.*, 1972, **46**, 193; R. Koppang, *J. Fluorine Chem.*, 1976, **8**, 389 and 1977, **9**, 449.
9 R. J. Harper, E. J. Soloski, and C. Tamborski, *J. Org. Chem.*, 1964, **29**, 2385; D. E. Fenton, A. J. Park, D. Shaw, and A. G. Massey, *J. Organomet. Chem.*, 1964, **2**, 437; D. D. Callender, P. L. Coe, and J. C. Tatlow, *Tetrahedron*, 1966, **22**, 419.
10 G. M. Brooke, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1962, 3253; J. Burdon, W. Hollyhead, C. R. Patrick, and K. V. Wilson, *ibid.*, 1965, 6375.
11 B. Gething, C. R. Patrick, and J. C. Tatlow, *J. Chem. Soc.*, 1962, 186.
12 R. Bolton and J. P. B. Sandall, *J. Chem. Soc., Perkin Trans. 2*, 1978, 746.
13 J. Burdon and T. W. Rimmington, *J. Fluorine Chem.*, 1985, **27**, 257.
14 D. Price, H. Suschitzky, and J. I. Hollies, *J. Chem. Soc. C*, 1969, 1967.
15 R. D. Chambers and C. R. Sargent, *Adv. Heterocycl. Chem.*, 1981, **28**, 48.
16 R. D. Chambers, M. J. Seabury, D. L. H. Williams, and N. Hughes, *J. Chem. Soc., Perkin Trans. 1*, 1988, 255.
17 R. D. Chambers, M. J. Seabury, D. L. H. Williams, and N. Hughes, *J. Chem. Soc., Perkin Trans. 1*., 1988, 251.
18 R. K. Atwal and R. Bolton, *Aust. J. Chem.*, 1987, **40**, 241.
19 R. D. Guthrie and D. E. Nutler, *J. Am. Chem. Soc.*, 1982, **104**, 7478.
20 E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Org. Chem.*, 1981, **46**, 2429; P. Huszthy, K. Lempert, G. Simig, and J. Tamas, *J. Chem. Res.*, 1985, (*S*), 309; (*M*), 3419.
21 G. R. Newkome and D. C. Hager, *J. Org. Chem.*, 1982, **47**, 599.
22 J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.

Received 28*th January* 1988; *Paper* 8/00318A