Reactions of polyfluoroaromatic compounds with electrophilic agents in the presence of tris(dialkylamino)phosphines

8.* Replacement of fluorine by hydrogen in polyfluoroaromatic compounds

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When reacted with $P(NEt_2)_3$ and a proton donor, pentafluoropyridine, 3-chlorotetrafluoropyridine, pentafluorobenzonitrile, and octafluorotoluene yield products of replacement of the fluorine atom by hydrogen at position 4. This process is accompanied by the side reaction of aminodefluorination. In the case of 3-H-heptafluorotoluene and octafluoronaphthalene, aminodefluorination is the main reaction. Reactions of perfluoro-4-isopropyltoluene, 4-H-heptafluorotoluene, and 4-methylheptafluorotoluene do not occur under the above-mentioned conditions.

Key words: polyfluoroarenes, reduction, tris(diethylamino)phosphine.

Previously,[1] we have developed a simple method for preparing polyfluoroarenes containing one or two H atoms in the aromatic ring by reduction of polyfluoroarylchlorides, -bromides, or -iodides under the action of $P(NEt_2)_3$ and a proton donor. In this case, protodefluorination was not observed. However, it was found[2] that this process can occur in the case of pentafluoropyridine and pentafluorobenzenes RC_6F_5 containing electron-withdrawing substituents R. In this work, the reactions of $P(NEt_2)_3$ with C_5F_5N (**1**), C_6F_5CN (**2**), octafluoronaphthalene $C_{10}F_8$ (**3**), the derivatives $RC_6F_4CF_3$ (R = F (**4**), 3-H (**5**), 4-H (**6**), 4-Me, or 4-$(CF_3)_2CF$), and 3-chlorotetrafluoropyridine (**7**) in the presence of a proton donor (H_2O or MeOH) were studied with the aim of developing a general method of modification of polyfluoroaromatic compounds.

It was established that in aqueous ether, pyridine **1** is converted to 2,3,5,6-tetrafluoropyridine (**8**) and 4-diethylamino-2,3,5,6-tetrafluoropyridine (**9**). In more polar aqueous DMF, compound **9** is the major product.

$$\underset{\mathbf{1}}{C_5F_5N} + P(NEt_2)_3 + H_2O \xrightarrow[Et_2O,\ 20\ ^\circ C]{} \underset{\mathbf{8}}{4\text{-}HC_5F_4N} + \underset{\mathbf{9}}{4\text{-}Et_2NC_5F_4N}$$

Competitive reactions of protodefluorination and aminodefluorination were also observed in the case of compounds **2** and **4** (Table 1). The relative rate of consumption of **4** was substantially lower (*cf.* Ref. 3). In boiling aqueous dioxane, the rate of conversion of toluene **4** increased, but 4-diethylaminoheptafluorotoluene (**10**) was formed as the major product.

$$\underset{\mathbf{2}}{C_6F_5CN} + P(NEt_2)_3 + H_2O \xrightarrow{Et_2O} \underset{\mathbf{11}}{4\text{-}HC_6F_4CN} + \underset{\text{(traces)}}{4\text{-}Et_2NC_6F_4CN}$$

$$\underset{\mathbf{4}}{C_6F_5CF_3} + P(NEt_2)_3 + H_2O \xrightarrow{Et_2O} \underset{\mathbf{7}}{4\text{-}HC_6F_4CF_3} + \underset{\mathbf{10}}{4\text{-}Et_2NC_6F_4CF_3}$$

Less electrophilic polyfluoroaromatic compounds (4-H-heptafluorotoluene, 4-methylheptafluorotoluene, and perfluoro-4-isopropyltoluene) did not react with $P(NEt_2)_3$ in aqueous ether (22 °C, 3 days). Under these conditions, 3-H-heptafluorotoluene **5** gave 4-diethylamino-2,3,6-trifluorobenzotrifluoride (**12**), which was demonstrated using the reaction of a mixture of 2-, 3-,

Table 1. Protodefluorination of polyfluoroarenes Ar_FF

Ar_FF	*N*/mmol		*V*/mL		Time	Products
	Ar_FF	$P(NEt_2)_3$	H_2O	Et_2O	/h	(yield (%))
1	2.0	7.0	0.1	7[a]	1	**8** (traces), **9** (93)
1	2.0	2.0	0.1	5	1	**8** (38), **1** (62)[b]
1	2.0	4.0	0.1	5	1	**8** (73), **9** (27)[b]
2	6.2	15.5	0.32	10	1	**11** (74)
4	5.2	14.5	0.15	18	22	**7** (82), **10** (7)
4	7.8	21	0.2	21[c]	6	**7** (5), **10** (90)

[a] DMF. [b] The yield according to the data of ^{19}F NMR spectroscopy. [c] In boiling dioxane.

* For Part 7, see Ref. 1.

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and 4-H-heptafluorotoluenes as an example. Octafluoronaphthalene **3** gave 2-diethylaminoheptafluoronaphthalene (**13**) under the action of $P(NEt_2)_3$ and H_2O in ether (20—22 °C, 145 h) or in boiling dioxane (20 h), while compound **13** and 2-H-heptafluoronaphthalene were not obtained by boiling naphthalene **3** with $P(NEt_2)_3$ in anhydrous dioxane. In the latter case, a solid product was isolated. This product is insoluble in hot dioxane and chloroform. The ^{19}F NMR spectrum of the filtrate has only signals of phosphorane $(Et_2N)_3PF_2$. It can be suggested that the resulting product is perfluoropolynaphthylene because it is known that derivatives of diphenyl are formed in the reaction of C_6F_5R (R = CF_3 or COOMe) with $P(NEt_2)_3$ in ether.[4] Condensation of methylpentafluorobenzoate, octafluorotoluene,[4] and octafluoronaphthalene under the action of $P(NEt_2)_3$ is a reaction of a nucleophilic intermediate, which is generated from $P(NEt_2)_3$ and one perfluoroarene molecule, with the second perfluoroarene molecule, which acts as an electrophile. On the other hand, aminodefluorination of polyfluoroaromatic compounds under the action of $P(NEt_2)_3$ and H_2O is apparently attributable to the formation of Et_2NH during hydrolysis of $P(NEt_2)_3$. An analogous process occurred when $P(NR_2)_3$ was heated with alcohols,[5] and this is consistent with an increase in the yields of (diethylamino)polyfluoroarenes as the reaction temperature increases. It should be noted that one of the probable causes of formation of 4-$Et_2NC_6F_4CF_3$ (a by-product) in the reaction of toluene **4** with $P(NEt_2)_3$ and $ClGeEt_3$ along with 4-$Et_3GeC_6F_4CF_3$ (the major product)[2] can be the exchange reaction

$$P(NEt_2)_3 + ClGeEt_3 \rightleftharpoons P(NEt_2)_2Cl + Et_3GeNEt_2,$$

in which the aminating agent Et_3GeNEt_2 is generated.

It was demonstrated[1] that 3- and 4-chloroheptafluorotoluenes were reduced to the corresponding heptafluorotoluenes under the action of $P(NEt_2)_3$ in aqueous ether. Replacement of F atoms by H atoms was not observed. Under the analogous conditions, reduction of chlorine in 3-chlorotetrafluoropyridine **7** does not occur. Addition of $P(NEt_2)_3$ (0.3 equiv.) to a solution of pyridine **7** in ether containing MeOH yielded 2,3,6-trifluoro-5-chloropyridine (**14**), 2-diethylamino-5-chlorotrifluoropyridine (**15**), and 4-diethylamino-5-chlorofluoropyridine (**16**). The ^{19}F NMR spectrum has also the signals of the initial chloropyridine **7**, the doublets at δ 103.46 ($J_{F,P}$ = 692 Hz), 98.78 ($J_{F,P}$ = 1192 Hz), and 65.97 ($J_{F,P}$ = 1020 Hz) belonging to (diethylamino)fluorophosphoranes and/or (diethylamino)fluorophosphonium salts, the signals at δ 87.02 and 0.34 (presumably 2,4-bis(diethylamino)-5-chlorodifluoropyridine; *cf.* the spectrum of 2,4-bis(dimethylamino)trifluoropyridine[6]), and unidentified signals at δ 73.79 and 0.2. The signals of fluorine atoms of 2,3,4,6-tetrafluoropyridine and 2,3,6-trifluoropyridine were not observed.

Therefore, chloropyridine **7** reacts with $P(NEt_2)_3$ and a proton donor analogously to its perfluorinated analog **1**. If the attack of tris(diethylamino)phosphine on the chlorine atom occurs under kinetically-controlled conditions, a comparison of the results of the reactions of $P(NEt_2)_3$ with 3-chlorotetrafluoropyridine and with 3-chloroheptafluorotoluene allows one to conclude that in the first case, the rate of the chlorophile attack is substantially lower than that of competitive protodefluorination. In other words, the activation effect of the trifluoromethyl group in 3-chloroheptafluorotoluene is not as pronounced as that of the nitrogen atom in 3-chlorotetrafluoropyridine, which leads to protodechlorination of 3-chloroheptafluorotoluene rather than to protodefluorination. Compounds **6**, **8**, **10**, **11**, **13**, and **14** were identified based on the ^1H and ^{19}F NMR spectra described in the literature. The derivatives of pyridine **15** and **16** and the derivative of toluene **12** were prepared by an independent synthesis.

Experimental

The ^1H (200 MHz) and ^{19}F (188.28 MHz) NMR spectra were recorded on a Bruker WP 200 SY spectrometer (Me_4Si and C_6F_6 as internal standards). The IR spectra were recorded on a Specord M-80 spectrophotometer in CCl_4.

Protodefluorination of polyfluoroaromatic compounds (general procedure). $P(NEt_2)_3$ was added to a stirred solution of polyfluoroarenes in aqueous ether (DMF or dioxane). After completion of the reaction, the etheral layer was washed with H_2O and a 50% H_2SO_4 solution and dried with $CaCl_2$. The solvent was distilled off. The residue was distilled. Products were isolated from solutions in dioxane or DMF by steam distillation (see Table 1).

Reaction of a mixture of 4-$RC_6F_4CF_3$ (R = F or Me) with $P(NEt_2)_3$ and H_2O. $P(NEt_2)_3$ (20.3 g, 82 mmol) was added to a stirred solution of octafluorotoluene **4** (6.8 g, 29 mmol), 4-$MeC_6F_4CF_3$ (2.8 g, 12 mmol), and H_2O (2 mL) in Et_2O (60 mL). After 36 h, the reaction mixture contained compounds **6**, **10**, and 4-$MeC_6F_4CF_3$ (~10 : 1 : 4.2) (^{19}F NMR). During the next 72 h, no changes occurred. The reaction mixture was washed with water (200 mL) and a 50% H_2SO_4 solution (50 mL) and dried with $CaCl_2$. The solvent was distilled off. The residue was distilled. Toluene **6** and 4-$MeC_6F_4CF_3$ were obtained in yields of 4.2 g (65%) and 1.9 g. The nonvolatile residue contained aminotoluene **10** (^{19}F NMR).

4-Diethylamino-2,3,6-trifluorobenzotrifluoride (12). ***A.*** A solution of heptafluorotoluenes 2-, 3-, and 4-$C_6HF_4CF_3$ (the molar ratio was 5 : 66 : 29) (1.0 g, 4.6 mmol), H_2O (0.2 g), and $P(NEt_2)_3$ (3.0 g, 12.1 mmol) in ether (4 mL) was stirred for 96 h. According to the data of ^{19}F NMR spectroscopy, aminotoluene **12** was formed, and unconsumed heptafluorotoluene **6** (~2 : 1) remained (products of conversion of 2-H-heptafluorotoluene were not analyzed).

B. A solution of heptafluorotoluenes 2-, 3-, and 4-$HC_6F_4CF_3$ (5 : 66 : 29) (4.3 g, 20 mmol) and Et_2NH (3.0 g, 41 mmol) in dioxane (12 mL) was boiled for 3 h. The reaction mixture was diluted with water. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with H_2O and dried with $MgSO_4$. Distillation gave aminotoluene **12** in a yield of 2.6 g

(72%), b.p. 104—105 °C (5 Torr). Traces of 4-diethylamino-2,3,5-trifluorobenzotrifluoride were present as evidenced by the signals in the ^{19}F NMR spectrum at δ 101.4, 38.50, 20.30, and 19.11. Found (%): C, 48.70; H, 4.44; F, 42.80; N, 6.00. $C_{11}H_{11}F_6N$. Calculated (%): C, 48.70; H, 4.06; F, 42.10; N, 5.17. ^1H NMR (CCl_4), δ: 6.20 (C_{arom}—H); 3.36 (CH_2); 1.20 (Me, J = 7 Hz). ^{19}F NMR (CCl_4), δ: 106.85 (CF_3); 44.71 (F-2); 25.43 (F-6); 4.19 (F-5). IR, ν/cm^{-1}: 2980, 2935, 2875, 1645, 1570, 1530, 1516, 1483, 1461, 1425, 1380, 1363, 1300, 1225, 1183, 1168, 1135, 1053, 895.

Reaction of octafluoronaphthalene 3 with $P(NEt_2)_3$. *A.* A solution of naphthalene **3** (0.54 g, 2 mmol) and $P(NEt_2)_3$ (1.5 g, 6 mmol) in ether (5 mL) containing H_2O (0.1 g) was stirred at 20—22 °C for 145 h. According to the data of ^{19}F NMR spectroscopy, naphthalene **3** was quantitatively converted to aminonaphthalene **13**.

B. A solution of naphthalene **3** (1.0 g, 3.6 mmol) and $P(NEt_2)_3$ (3.2 g, 13.0 mmol) in dioxane (7 mL) containing H_2O (0.3 mL) was boiled for 20 h. According to the data of ^{19}F NMR spectroscopy, substrate **3** was converted to aminonaphthalene **13** and, apparently, to 2,6-bis(diethylamino)hexafluoronaphthalene (signals at δ 31.95 (F-1, F-5); 19.49 (F-3, F-7); and 13.50 (F-4, F-8), *cf.* Ref. 7). The reaction mixture was diluted with benzene (30 mL), washed with H_2O, concentrated HCl, and water, and dried with $MgSO_4$. The solvent was distilled off. 2-Diethylaminoheptafluoronaphthalene was isolated by chromatography on a short column (silica gel, pentane as the eluent). The yield was 0.5 g (43%) (colorless oil). Found (%): C, 51.20; H, 3.00; F, 40.50; N, 4.30. $C_{14}H_{10}F_7N$. Calculated (%): C, 51.70; H, 3.08; F, 40.90; N, 4.31. ^1H NMR (CCl_4), δ: 3.26 (CH_2); 1.08 (Me, J = 7 Hz). ^{19}F NMR (CCl_4), δ: 31.31 (F-1); 21.00 (F-3); 16.18 (F-8); 14.81 (F-5); 13.65 (F-4); 5.28 (F-7); 4.60 (F-6); $J_{1,4}$ = 15 Hz; $J_{1,8}$ = 69 Hz; $J_{3,4}$ = 16 Hz; $J_{4,5}$ = 57 Hz; $J_{5,6}$ = 16 Hz; $J_{5,8}$ = 16 Hz; $J_{6,7}$ = 18 Hz; $J_{7,8}$ = 16 Hz. IR, ν/cm^{-1}: 2982, 2940, 2880, 1662, 1643, 1545, 1482, 1463, 1452, 1407, 1225, 1195, 1162, 1117, 956, 860.

C. A mixture of naphthalene **3** (0.54 g, 2 mmol) and $P(NEt_2)_3$ (1.2 g, 4.9 mmol) was boiled with stirring in anhydrous dioxane (3 mL) for 2 h. The reaction mixture was cooled, and a solid brown product, which was insoluble in hot dioxane and $CHCl_3$, was filtered off in a yield of 0.5 g. The ^{19}F NMR spectrum of the filtrate has only the signals of $P(NEt_2)_3F_2$.

Reaction of 3-chlorotetrafluoropyridine 7 with $P(NEt_2)_3$ and MeOH. $P(NEt_2)_3$ (0.25 g, 1 mmol) was added dropwise to a stirred solution of chloropyridine **7** (0.63 g, 3.4 mmol) and MeOH (0.15 g, 4.9 mmol) in ether (2 mL). The reaction mixture was stirred for 30 min. According to the data of ^{19}F NMR spectroscopy, the reaction mixture contained the starting chloropyridine **7**, compounds **14**, **15**, and **16**, and presumably 2,4-bis(diethylamino)-5-chlorofluoropyridine (5 : 3 : 1 : 1 : 1).

5-Chloro-2-diethylaminotrifluoropyridine (15) and 3-chloro-4-diethylaminotrifluoropyridine (16). Compounds **15** and **16** (1 : 1, without separation of isomers) (0.28 g, 73%) were synthesized from 3-chlorotetrafluoropyridine (0.30 g, 1.6 mmol) and Et_2NH (0.28 g, 3.8 mmol) according to a procedure described previously.[8] Found (%): C, 45.00; H, 4.20; Cl, 14.20; F, 23.10; N, 12.20. $C_9H_{10}ClF_3N_2$. Calculated (%): C, 45.30; H, 4.19; Cl, 14.90; F, 23.90; N, 11.70.

Pyridine 15. ^1H NMR (CCl_4), δ: 3.49 (CH_2); 1.20 (Me, J = 7 Hz). ^{19}F NMR (CCl_4), δ: 89.92 (F-6); 38.74 (F-4); −1.30 (F-3); $J_{3,4}$ = 17 Hz; $J_{3,6}$ = 26 Hz; $J_{4,6}$ = 11.6 Hz.

Pyridine 16. ^1H NMR (CCl_4), δ: 3.37 (CH_2); 1.15 (Me, J = 7 Hz). ^{19}F NMR (CCl_4), δ: 88.38 (F-2); 70.61 (F-6); 8.10 (F-3); $J_{2,5}$ = 22 Hz; $J_{2,6}$ = 13.5 Hz; $J_{5,6}$ = 21 Hz.

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