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

7.* Replacement of a halogen by hydrogen in halogenopolyfluoroaromatic compounds

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A method was developed for the replacement of chlorine, bromine, and iodine in halopolyfluoroaromatic compounds by hydrogen under the action of $P(NEt_2)_3$ and a proton donor.

Key words: polyfluoroaryl halides, reduction, tris(diethylamino)phosphine.

Several general methods are used for the preparation of polyfluoroarenes containing hydrogen atoms in the aromatic ring. Polyfluoroaryl chlorides, bromides, and iodides are reduced by hydrogen over palladium, by heating with copper powder and water in an autoclave, by zinc in acetic acid, or by protolysis of the corresponding organomagnesium or organolithium compounds. Oxidation of polyfluoroarylhydrazines by copper(II) salts, decarboxylation of polyfluoroarenecarboxylic acids, or replacement of fluorine using lithium aluminum hydride also afford partially fluorinated aromatic compounds.[2–4] Recently,[5] protodehalogenation of polyfluorinated benzene and pyridine derivatives under the action of Zn (Cu) in aqueous DMF has been described. It was reported[6] that tetrafluoro-4-iodo-*N*,*N*-dimethylaniline is transformed into 2,3,5,6-tetrafluoro-*N*,*N*-dimethylaniline under the action of Ph_3P in a yield of 7%. Protodehalogenation of tetrafluoro-4-iodo(bromo)-phenyltrimethylammonium triflate occurs in higher yields. However, in the case of $C_6F_5NMe_3^+ \cdot OTf^-$, demethylation rather than replacement of fluorine by hydrogen occurs (hereinafter, we shall use the term "halogen" to mean chlorine, bromine, or iodine, but not fluorine). Iodopentafluorobenzene is reduced smoothly by rongalite $HOCH_2SO_2Na \cdot 2H_2O$, sodium sulfite, or sodium dithionite to pentafluorobenzene, whereas chloropentafluorobenzene does not react with Na_2SO_3 or $Na_2S_2O_4$ and is transformed into 1,2,4,5-tetrafluoro-3-chlorobenzene under the action of rongalite.[7] In the course of our systematic studies of interactions of halopolyfluoroaromatic compounds with electrophilic agents under the action of tris(dialkylamino)phosphine,[1,8–13] we developed a new simple method for the replacement of chlorine, bromine, or iodine by hydrogen.

Results and Discussion

Chloropentafluorobenzene (**1**) does not react with H_2O and $P(NEt_2)_3$ in DMF at ~20 °C (5 days). Reduction of bromopentafluorobenzene (**2**) and iodopentafluorobenzene (**3**), on the other hand, is completed at ~20 °C in a few minutes (Scheme 1). Pentafluorobenzene (**4**) can be easily isolated from the reaction mixture by steam distillation. The products of the conversion of tris(diethylamino)phosphine were not analyzed, although, by analogy with the data obtained previously,[14] it can be suggested that phosphorus(III) is oxidized to phosphorus(V).

Scheme 1

$$C_6F_5X + H_2O \xrightarrow{P(NEt_2)_3,\ DMF} C_6F_5H$$

2,3 **4**

X = Br (**2**), I (**3**)

Methanol can be used instead of water and can also serve as the solvent. Thus when bromopentafluorobenzene **2** was treated with $P(NEt_2)_3$ in MeOH (22 °C, 5—10 min), it was transformed into C_6F_5H in quantitative yield.

Previously,[1,9,10] we have demonstrated that the introduction of an electron-withdrawing substituent R, instead of fluorine, into a C_6F_5X compound accelerates the replacement of X by a trimethylsilyl, triethylgermyl, or trialkylstannyl group under the action of YMR'_3 (Y = Cl or Br; M = Si, Ge, or Sn; R' = alkyl) and $P(NEt_2)_3$, whereas electron-donor substituents in the polyfluoroaromatic ring inhibit the reaction. This is also true for the protodehalogenation of the halopolyfluoroaromatic compounds. For example, 4-chloroheptafluorotoluene

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* For Part 6, see Ref. 1.

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(**5**) and 4-bromoheptafluorotoluene (**6**) were reduced to 4-H-heptafluorotoluene (**7**) at 20 °C in 15—30 min (Scheme 2). However, unlike bromoheptafluorotoluene **6**, conversion of chlorine analog **5** under the action of 1 equiv. of $P(NEt_2)_3$ did not exceed 40%, and an excess of $P(NEt_2)_3$ was required for complete conversion.

Scheme 2

$$\underset{\mathbf{5,6}}{4\text{-}XC_6F_4CF_3} + H_2O \xrightarrow{P(NEt_2)_3,\ DMF} \underset{\mathbf{7}}{4\text{-}HC_6F_4CF_3}$$

X = Cl (**5**), I (**6**)

In spite of the presence of electron-donor substituents, 4-bromo-2,3,5,6-tetrafluoroanisole (**8**) and 4-bromo-2,3,5,6-tetrafluoro-1-piperidinobenzene (**9**) also undergo protodebromination under the action of $P(NEt_2)_3$ in methanol or aqueous DMF to form 2,3,5,6-tetrafluoroanisole (**10**) and 2,3,5,6-tetrafluoro-1-piperidinobenzene (**11**), respectively (Scheme 3).

Scheme 3

$$\underset{\mathbf{8}}{4\text{-}BrC_6F_4OCH_3} + H_2O \xrightarrow{P(NEt_2)_3,\ DMF} \underset{\mathbf{10}}{4\text{-}HC_6F_4OCH_3}$$

$$\underset{\mathbf{9}}{4\text{-}BrC_6F_4NC_5H_{10}} \xrightarrow[H_2O\text{—}DMF\text{ or }MeOH]{P(NEt_2)_3,} \underset{\mathbf{11}}{4\text{-}HC_6F_4NC_5H_{10}}$$

If a polyfluoroarene molecule contains more than one bromine (iodine) atom, one would expect the consecutive replacement of these atoms by hydrogen. Actually, when 1,3-dibromotetrafluorobenzene (**12**) was treated with 1 equiv. of $P(NEt_2)_3$, 2-bromo-1,3,4,5-tetrafluorobenzene (**13**) and 1,2,3,5-tetrafluorobenzene (**14**) formed (Scheme 4). In the presence of an excess of $P(NEt_2)_3$, both bromine atoms were replaced by hydrogen.

Scheme 4

$$\underset{\mathbf{12}}{1,3\text{-}Br_2C_6F_4} + H_2O \xrightarrow{P(NEt_2)_3,\ DMF} \underset{\mathbf{13}}{2\text{-}Br\text{-}1,3,4,5\text{-}C_6F_4H} + \underset{\mathbf{14}}{1,2,3,5\text{-}C_6F_4H_2}$$

Under analogous conditions (1.2 equiv. of $P(NEt_2)_3$), 1,4-dibromotetrafluorobenzene (**15**) was transformed partially into 3-bromo-1,2,4,5-tetrafluorobenzene (**16**) and 1,2,4,5-tetrafluorobenzene (**17**). Analogously, 3-iodo-1,2,4,5-tetrafluorobenzene (**19**) and tetrafluorobenzene **17** formed from 1,4-diiodotetrafluorobenzene (**18**) (conversion of compound **18** was 82%). In the presence of an excess of $P(NEt_2)_3$, both compounds, **15** and **18**, were reduced rapidly to tetrafluorobenzene **17** (Scheme 5).

Scheme 5

$$\underset{\mathbf{15,\ 18}}{1,4\text{-}X_2C_6F_4} + H_2O \xrightarrow[DMF]{P(NEt_2)_3} \underset{\mathbf{16,19}}{3\text{-}X\text{-}1,2,4,5\text{-}C_6F_4} + \underset{\mathbf{17}}{1,2,4,5\text{-}C_6F_4H_2}$$

X = Br (**15**), I (**18**) X = Br (**16**), I (**19**)

Reduction of dihalotetrafluorobenzenes **12**, **15**, and **18** with water and 1 equiv. of $P(NEt_2)_3$ yields tetrafluorobenzenes **14** and **17**, which is indicative of a slight difference in the rates of the reaction of $X_2C_6F_4$ and HC_6F_4X compounds with identical mutual arrangement of the substituents other than fluorine. However, this difference becomes more pronounced in the reduction of 1,2-dibromotetrafluorobenzene (**20**). Treatment of the latter with 1 equiv. of $P(NEt_2)_3$ in aqueous DMF or with 1 equiv. of tris(piperidino)phosphine in a MeOH—CH_2Cl_2 mixture affords 1-bromo-2,3,4,5-tetrafluorobenzene (**21**) and a small amount of 1,2,3,4-tetrafluorobenzene (**22**) (Scheme 6). Further replacement of bromine in bromobenzene **21** occurs slowly. Thus, treatment of 1,2-dibromotetrafluorobenzene **20** with H_2O and 2 equiv. of $P(NEt_2)_3$ for 84 h yields compounds **21** and **22** in a ratio of 23 : 77.

Table 1. Protodehalogenation of halopolyfluorobenzenes Ar_FX

Ar_FX	Number of moles		V/mL		Time /min	Products (yield, %)
	Ar_FX	$P(NEt_2)_3$	H_2O	DMF		
2	4.8	6.5		5[a]	10	**4** (100)[b]
2	10	10	0.2	7.5	15	**4** (72)
3	6.5	8	0.15	6	10	**4** (94)
5	2	7	0.2	3	30	**7** (100)[b]
6	6.0	21	0.6	8	15	**7** (77)
8	10	10	0.25	10	120	**10** (67)
9	3.2	4.8	0.32	6	80	**11** (81)
9	3.2	4.8		5[a]	20	**11** (92)
12	0.9	0.9	0.04	2.5	30	**13** (41), **14** (22)[b,c]
12	1.0	2.5	0.1	2.5	30	**14** (100)[b]
15	0.6	0.7	0.03	2	30	**16** (33), **17** (39)[b,c]
15	2.9	11	0.45	3	40	**17** (93)
18	1.2	1.4	0.1	3	20	**19** (55), **17** (27)[b,c]
18	1.2	3.5	0.2	5	15	**17** (72)
20	1.6	1.6	0.04	3	30	**21** (96), **22** (4)[b]
20	1.6	3.4	0.04	3	84 h	**21** (50), **22** (50)[b]

[a] MeOH. [b] The yield according to the data of ^{19}F NMR spectroscopy. [c] Conversions of compounds **12**, **15**, and **18** were 63%, 72%, and 82%, respectively.

Scheme 6

$$\underset{\textbf{20}}{1,2\text{-}C_6Br_2F_4} + H_2O \xrightarrow{P(NEt_2)_3,\ DMF} \underset{\textbf{21}}{1\text{-Br-}2,3,4,5\text{-}C_6F_4H} + \underset{\textbf{22}}{1,2,3,4\text{-}C_6F_4H_2}$$

It is noteworthy that in 1-bromotetrafluorobenzene **21**, the replacement of bromine by a trimethylsilyl group does not occur under the action of $ClSiMe_3$ and $P(NEt_2)_3$ in less polar solvents (hexane or dichloromethane).[1]

The dependence of the rate of replacement of a halogen atom by an electrophile under the action of $P(NEt_2)_3$ on the mutual arrangement of the halogen atom and the CF_3 group was observed in the competitive reduction of 3-chloroheptafluorotoluene (**23**) and 4-chloro isomer **5** in aqueous ether by the successive addition of 0.45 and 1.0 equiv. of $P(NEt_2)_3$. As a result, 5-H-heptafluorotoluene (**24**) and the 4-H-isomer **7** form, and *para* isomer **5** is predominantly consumed.

A comparison of our results with the data[1] on silyldehalogenation of tetrafluorobenzene derivatives RC_6F_4X by chlorotrimethylsilane and $P(NEt_2)_3$ allows one to conclude that there exist general regularities for the replacement of chlorine, bromine, and iodine atoms by electrophiles in halopolyfluoroaromatic compounds. This fact is confirmed also by the fact that the decrease in the rate of protodehalogenation in the series $C_6F_5Br > C_6F_5I >> C_6F_5Cl$, coincides with that for silyldehalogenation,[1] which has been demonstrated in a competitive reaction of bromo- and iodopentafluorobenzenes. The treatment of an equimolar mixture of **2** and **3** with 1 equiv. of $P(NEt_2)_3$ in aqueous DMF yielded pentafluorobenzene. The ratio of unconsumed compounds **2** and **3** was ~1 : 4.

The ^1H and ^{19}F NMR spectra of the compounds obtained agree with those of compounds reported in the literature.

Experimental

The ^1H (200 MHz) and ^{19}F (188.28 MHz) spectra were recorded on a Bruker WP 200 SY spectrometer (Me_4Si and C_6F_6 as internal standards).

Protodehalogenation of halopolyfluoroaromatic compounds (general procedure). $P(NEt_2)_3$ was added dropwise to a stirred solution of halopolyfluoroarene in MeOH or aqueous DMF cooled with cold water. The mixture was stirred at ~20 °C and diluted with 3—4 volumes of water. The product was steam distilled. The organic layer was separated and dried with $CaCl_2$ (Table 1).

Reduction of dibromotetrafluorobenzene **20** (2.92 mmol) in MeOH (0.5 mL) and CH_2Cl_2 (1 mL) was carried out by adding $P(NC_5H_{10})_3$ (2.92 mmol) in CH_2Cl_2 (1 mL). After 30 min, the reaction mixture was washed with water, dilute H_2SO_4, and water, and dried with $CaCl_2$. Bromotetrafluorobenzene **21** was isolated by distillation (yield 42%).

Competitive reaction of C_6F_5Br and C_6F_5I with H_2O and $P(NEt_2)_3$. $P(NEt_2)_3$ (2 mmol) was added dropwise to a stirred solution of C_6F_5Br (2 mmol), C_6F_5I (2 mmol), and water (0.1 mL) in DMF (4 mL). After 10 min, the contents of C_6F_5Br, C_6F_5I, and C_6F_5H were 12, 46, and 42%, respectively (^{19}F NMR).

Reaction of chloroheptafluorotoluenes $ClC_6F_4CF_3$ with H_2O and $P(NEt_2)_3$. Tris(diethylamino)phosphine was added in two portions to a stirred solution of chloroheptafluorotoluenes **23** and **5** (3 : 1) (0.61 g, 2.4 mmol)[*] and water (0.1 mL) in ether (3 mL). After each addition, the reaction mixture was stirred for 1 h, and the composition of the mixture was analyzed by ^{19}F NMR spectroscopy. The ratios of compounds **23** : **5** were 84 : 16 (0.45 equiv. of $P(NEt_2)_3$) and 90 : 10 (1 equiv. of $P(NEt_2)_3$).

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[*] The mixture also contained 10 mol.% of $2\text{-}ClC_6F_4CF_3$. Products of the conversion of $2\text{-}ClC_6F_4CF_3$ were not analyzed.