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Reactions of HMPA with hexafluorobenzene, pentafluorochlorobenzene and pentafluorophenol

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ABSTRACT

Hexamethylphophoramide (HMPA) reacted with hexafluorobenzene and its derivatives with good conversion to give dimethylaminated products and phosphorofluoridates, even in unfavorable reaction stoichiometries. An aromatic nucleophilic mechanism might be involved.

1. Introduction

Generally, hexafluorobenzene is very stable in common solvents, such as DMSO, THF and DMEU. Indeed, many nucleophilic substitution reactions of hexafluorobenzene can be safely performed in these solvents [1,2]. Hexafluorobenzene, as a solvent, is very soluble, and could favor the intramolecular cyclization of dialkynyl imidazoles and products separation in much higher yields [3]. In some conditions, however, the cleavage of C–F bond of hexafluorobenzene and its derivatives is known to occur in the presence of nucleophiles. The nucleophilic replacement of the C–F bond always need wild conditions like high temperature, strong base or violent nucleophiles [1,4–8]. The use of HMPA to effect *N*,*N*-dimethylamination of aromatic substrates has captured wide interest previously, for example, the reaction of HMPA with halogenated aromatics containing electron-withdrawing groups [9–11]. The synthetic usefulness of the *N*,*N*-dimethylamination of fluoroaromatics has been well documented [3,12–16]. However, to the best of our knowledge, the reaction between HMPA and hexafluorobenzene or its derivatives has never been reported. In the investigation of the reaction of hexafluorobenzene with nucleophiles in HMPA in our laboratory, we found unexpectedly a *N*,*N*-dimethylamination of hexafluorobenzene with HMPA. Herein, we present the results.

2. Results and discussion

The reaction between HMPA and hexafluorobenzene was carried out in a sealed tube. **2a** could be obtained in good yield at 140 °C for 40 h (entry 4, Table 1), while **2b** and **2c** were formed at 160 °C for 82 h (entry 9, Table 1), which was determined by ^{19}F NMR.

As indicated in Table 1, this reaction is much influenced by the reaction time, temperature and the ratios of the reactants. Lower temperature and shorter reaction time will favor mono-substitution. 1-(*N*,*N*-dimethylamino)pentafluorobenzene was formed as the main product at 140 °C for 40 h or at 160 °C for 12 h (entries 4 and 5). Increasing the ratio of HMPA to C_6F_6 resulted in rapid conversion of hexafluorobenzene to 1,4-bis(*N*,*N*-dimethylamino)-tetrafluorobenzene (entries 10 and 14). 1,2,4-Tris(*N*,*N*-dimethylamino)trifluorobenzene still remains trace as the temperature increases (entries 1 and 2, entries 3 and 6, entries 4 and 7, entry 13). However, tetra-substitution were never observed in these conditions even with prolonged reaction time (entries 7, 8, 9, 11 and 12). The disubstituted product began to form substantially only in the second 12 h at 160 °C (entries 5 and 6). Similarly, the formation of trisubstituted product required longer reaction time (entries 7 and 8). This prompts us to assume that the first introduction of the *N*,*N*-dimethylamino group deactivated the second substitution

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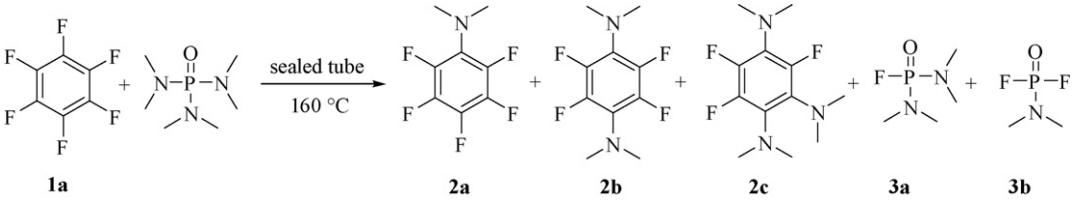
Table 1
Reaction of C_6F_6 with HMPA



1a **2a** **2b** **2c** **3a** **3b**

Entry	C_6F_6:HMPA[a]	Temperature (°C)	Time (h)	**1a**:**2a**:**2b**:**2c**[b]
1	1:5	120	8	100:0:0:0
2	1:5	140	11	75:25:0:0
3	1:5	140	23	30:70:0:0
4	1:5	140	40	5:94:1:0
5	1:5.3	160	12	2:95:3:0
6	1:5.3	160	24	0:79:21:0
7	1:5.3	160	41	0:50:44:6
8	1:5.3	160	63	0:12:77:11
9	1:5.3	160	82	0:12:69:19
10	1:20	160	14	0:45:43:12
11	1:20	160	38	0:5:77:18
12	1:20	160	65	0:0:83:17
13	1:20	180	15	0:54:36:10
14	1:50	160	6	0:15:85:0
15[c]	1:5	120	9	100:0:0:0
16[c]	1:5	140	23	98:2:0:0
17	1:5.3	160	2	79:21:0:0
18	1:5.3	160	4	69:31:0:0
19[d]	1:5.3	160	2	77:23:0:0
20[d]	1:5.3	160	4	68:32:0:0
21	1:5.3	180	2	10:88:2:0
22	1:5.3	180	4	0:91:9:0
23[e]	1:5.3	180	2	9:89:2:0
24[e]	1:5.3	180	4	0:90:10

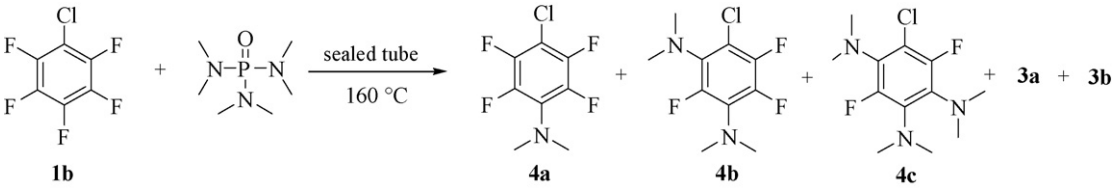
[a] Molar ratio.
[b] Molar ratio, determined by ^{19}F NMR.
[c] NaF was added in the reaction system and the molar ratio of NaF to C_6F_6 was 1:1.
[d] *p*-Hydroquinone was added and the molar ratio of *p*-hydroquinone to C_6F_6 was 1:5.
[e] The reaction was conducted in darkness.

of hexafluorobenzene. And the second introduction of *N*,*N*-dimethylamino group would intensively deactivate further substitution. Therefore, tri-substitution products always remain in low yield (entries 7–13). Probably this can be explained in terms of the strongly electron-donating effect of *N*,*N*-dimethylamino group which retarded the further nucleophilic attack of *N*,*N*-dimethylamino anion to **2a**, **2b** and **2c**. Addition of fluoride ion could not make the reaction condition milder but greatly inhibit the reaction (entries 1 and 15, entries 3 and 16), which indicated that the generation of dimethylamino anion would not be induced by fluoride ion. Thermal cleavage of P–N bond was then assumed to be the most probable way to dimethylamino anion. Furthermore, the reaction could not be suppressed by the addition of free-radical inhibitor, *p*-hydroquinone (entries 17 and 19, entries 18 and 20) and could not be inhibited either even in dark environment (entries 21 and 23, entries 22 and 24), which indicated that there might be no free radical generated in these reactions. Even though mono-, di-, and tri-substituted products were formed almost simultaneously in most cases, the desired substitution type could still be obtained by choosing proper reaction time, temperature and the reactant ratios. These three dimethylaminated products were easily separated by column chromatography.

Besides the dimethylamination products, the phosphorofluoridates (**3a** and **3b**), which have been demonstrated to be good selective phosphorylating agents and efficient inhibitors of several classes of enzyme [17–19], were also formed in these reactions. They were easily determined by ^{19}F NMR, according to the literatures [17–23]. There have been several approaches for the synthesis of these P–F compounds, which required the use of some special phosphorus precursors [19–21]. This reaction might thus become a more practical and straightforward method to construct the phosphorofluoridates. Treatment of hexafluorobenzene with HMPA at 160 °C for 12 h could give **3a** in 36% yield and **3b** in 25% yield, which were determined by ^{19}F NMR using trifluoroacetic acid as an internal standard (entry 5, Table 1).

In the case of pentafluorochlorobenzene, similar results were achieved, as described in Table 2. Different products were also observed at different reaction time, temperature and reactant ratios (entries 1–3, entries 4 and 8). The *para*-substitution of pentafluorochlorobenzene with HMPA occurred at 160 °C at first (entry 3). The di-substitution and the subsequent tri-substitution happened gradually with the extension of time (entries 5–7 and 8–11). The product **4b** and **4c** were fully characterized by ^1H NMR, ^{19}F NMR, elementary analysis and MS. The substitution position of the second and the third dimethylamino group was confirmed by the ^{19}F NMR and ^1H NMR, as mentioned in the literatures [24,25]. A doublet with ^5J (F–H) 2.1 Hz and a triplet with ^5J (F–H) 1.8 Hz in the ^1H NMR of **4b** indicated that there exist two kinds of proton, in which one was coupled with one fluorine and the other with two [25]. This means that the first dimethylamino group was adjacent to two fluorine. Only doublets or multiplets would be observed in ^1H NMR specta if the substitution happened at C2. Therefore, the introduction of the second dimethylamino group should be at C3 (**4b**) (Scheme 1). As for **4c**, 5-substitution could be excluded for the

Table 2
Reaction between C_6F_5Cl and HMPA

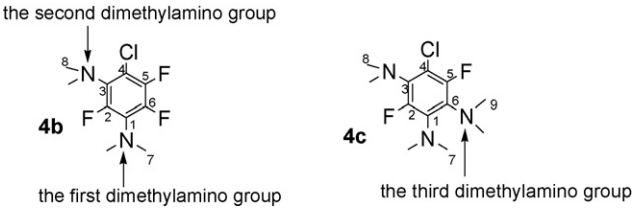


Entry	C_6F_5Cl:HMPA[a]	Temperature (°C)	Time (h)	**1b**:**4a**:**4b**:**4c**[b]
1	1:1.21	140	5	99:1:0:0
2	1:1.21	160	5	58:42:0:0
3	1:1.21	160	10	2:97:1:0
4	1:4.7	160	5	0:91:9:0
5	1:4.7	160	10	0:74:26:0
6	1:4.7	160	44	0:23:69:8
7	1:4.7	160	82	0:7:65:28
8	1:10	160	5	0:69:31:0
9	1:10	160	10	0:16:70:14
10	1:10	160	44	0:0:28:72
11	1:10	160	82	0:0:12:88

[a] Molar ratio.
[b] Molar ratio, determined by ^{19}F NMR.

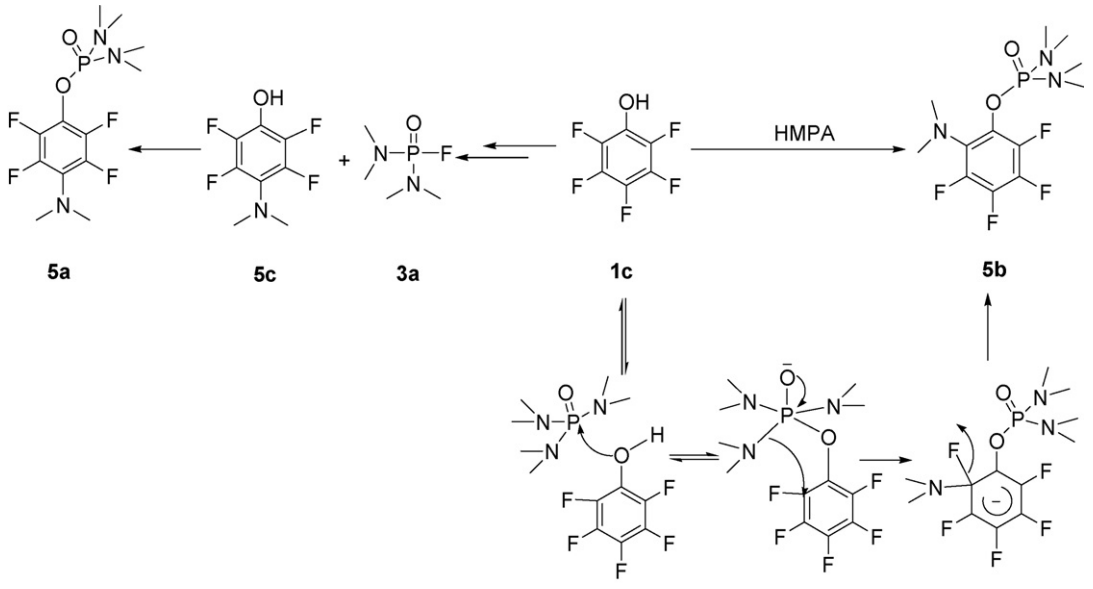
reason that two kinds of signals were found in the ^{19}F NMR specta. In addition, the signal appeared as a doublet with J (F–F) 7.8 Hz was not from the *ortho* F–F coupling [25]. Thus the third dimethylamino group should be bonded to C6 (**4c**) (Scheme 1). Besides, the ^{19}F chemical shifts confirmed further the substitution position of the dimethylamino groups [24].

In order to gain deep insight into these reactions, we extended our investigation to pentafluorophenol, as shown in Scheme 2. Phosphordiamidates **5a** and **5b** (1:2) were formed when pentafluorophenol reacted with HMPA at 140 °C for 20 h. As for the formation of **5a**, 4-(*N*,*N*-dimethylamino)tetrafluorophenol (**5c**) was presumed to be the most probable intermediate. The reaction between **5c** and **3a** was very fast. Therefore, no **5c** could be detected by ^{19}F NMR. On the other hand, the *ortho*-substituted phosphordiamidate **5b** was obtained as the major product in the reaction of HMPA with pentafluorophenol (Scheme 2). An intramolecular nucleophilic substitution was supposed to occur after the phosphorylation of pentafluorophenol with HMPA (Scheme 2).

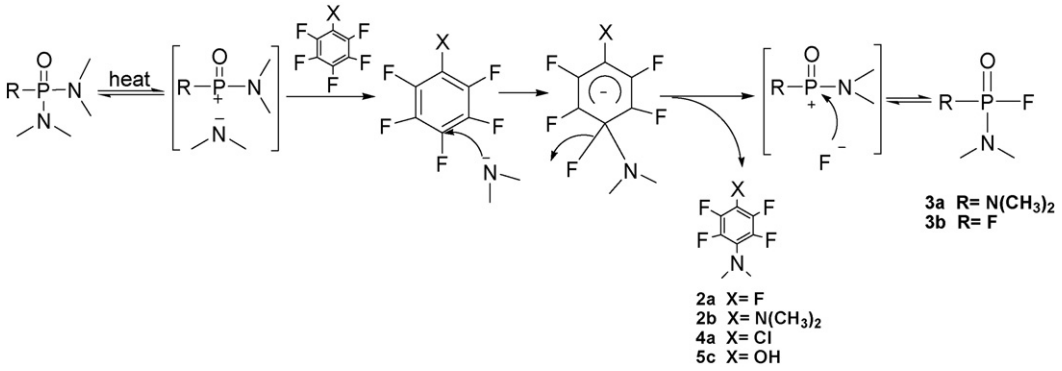


Scheme 1.

Based on these observations, the single electron transfer (SET) mechanism [26] was not supposed to be involved in these substitution reactions. The product profile and the inhibition experiments (entries 17–24 in Table 1) did not support a free radical mechanism. The relative reactivity between hexafluorobenzene and pentafluorochlorobenzene with HMPA (entry 5 in Table 1 and entry 4 in Table 2) and the preferential *para*-substitution of pentafluorochlorobenzene and pentafluorophenol in HMPA (**2a**, **2b**, **4a** and **5c** in



Scheme 2.



Scheme 3.

Scheme 3 and **5a** in Scheme 2) prompt us to assume that a typical nucleophilic aromatic substitution might be involved in these reactions [27,28], as outlined in Scheme 3. The *ortho*-effect [27] was also observed among them. Furthermore, the formation of **5a** also confirmed the existence of the phosphorofluoridate **3a**, which was found in the previous reactions of hexafluorobenzene and pentafluorochlorobenzene.

3. Conclusion

The aromatic nucleophilic substitution between HMPA and hexafluorobenzene or its derivatives could occur smoothly, which offers a simple and efficient method for the transformation of the polyfluoroaromatics to the corresponding dimethylaminated derivatives and a new procedure for the preparation of phosphorofluoridates. When HMPA was used as the solvent for polyfluorobenzenes and other activated halo-aromatic compounds, the potential reactions between them should be considered.

4. Experimental

4.1. General

NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on Mercury 300 at 300 MHz (^{1}H NMR) and 282 MHz (^{19}F NMR). Chemical shifts were reported in parts per million relative to tetramethylsilane and trichlorofluoromethane (positive for downfield shifts) as external standards. Mass spectra were recorded on a Shimadzu LCMS instrument. The IR spectra were recorded on a Shimadzu IR-440 spectrometer. Column chromatography was carried out on silica gel H (10–40 μm). All starting materials were obtained commercially. HMPA was distilled from CaH_2 before use.

4.2. Typical procedure

The polyfluorobenzene (4.67 mmol) was placed in a sealed tube equipped with a magnetic stir bar. HMPA (4 ml) was added and the system was flushed with nitrogen. The sealed tube was kept at 160 °C for 82 h. Then the reaction mixture was cooled and poured into water (20 ml), extracted with ethyl acetate (30 ml), washed with water (4 ml × 15 ml) and dried over anhydrous Na_2SO_4. The crude products were purified by column chromatography.

4.3. 1-(*N*,*N*-dimethylamine)pentafluorobenzene (2a)

Yield 69%, ^{1}H NMR: δ 2.90 (t, *J* = 2.4 Hz, 6H) ^{19}F NMR: δ −150.8 (dm, *J* = 22.4 Hz, 2F), −164.1 (tm, *J* = 22.4 Hz, 22.2 Hz, 2F), −164.8 (tm, *J* = 22.2 Hz, 1F).

4.4. 1,4-Di(*N*,*N*-dimethylamine)tetrafluorobenzene and 1,2,4-tri(*N*,*N*-dimethylamine)trifluorobenzene (2b, 2c)

2b: Yield 63%, ^{1}H NMR: δ 2.88 (s, 12H) ^{19}F NMR: δ −152.8 (s, 4F). **2c**: Yield 9.5%, ^{1}H NMR: δ 2.86 (t, *J* = 1.8 Hz, 6H), 2.83 (d, *J* = 1.8 Hz, 6H), 2.79 (d, *J* = 1.8 Hz, 6H) ^{19}F NMR: δ −136.0 (d, *J* = 6.3 Hz, 1F), −151.2 (d, *J* = 20.4 Hz, 1F), −152.3 (dd, *J* = 20.4 Hz, 6.3 Hz, 1F).

4.5. 4-Chloro-1-(*N*,*N*-dimethylamine)tetrafluorobenzene (4a)

Yield 36%, ^{1}H NMR: δ 2.95 (t, *J* = 2.7 Hz, 6H) ^{19}F NMR: δ −143.9 (dm, *J* = 20.4 Hz, 2.7 Hz, 2F), −150.9 (d, *J* = 20.4 Hz, 2F).

4.6. 4-Chloro-2,5,6-trifluoro-*N*,*N*,*N*,*N*-tetramethylbenzene-1,3-diamine and 5-chloro-3,6-difluoro-*N*,*N*,*N*,*N*,*N*,*N*-hexamethylbenzene-1,2,4-triamine (4b, 4c)

4b: Colorless liquid. Yield 47%, ^{1}H NMR: δ 2.90 (t, *J* = 1.8 Hz, 6H), 2.83 (d, *J* = 2.1 Hz, 6H) ^{19}F NMR: δ −134.3 (s, 1F), −141.7 (dm, *J* = 19.6 Hz, 1F), −149.2 (d, *J* = 19.6 Hz, 1F); ESIMS (*m*/*e*): 253.0 $[M+H]^+$ (100); IR (KBr): 2933, 2852, 2803, 1499, 1452, 1432, 1060, 989, 914, 878, 801 cm^{-1}. Anal. Calcd for $C_{10}H_{12}ClF_3N_2$: C, 47.54; H, 4.79; N, 11.09. Found: C, 47.92; H, 5.11; N, 10.92. **4c**: Colorless liquid. Yield 54%, ^{1}H NMR: δ 2.83–2.84 (m, 12H), 2.80 (d, *J* = 2.1 Hz, 6H) ^{19}F NMR: δ −126.6 (d, *J* = 7.8 Hz, 1F), −134.2 (s, 1F); ESIMS (*m*/*e*): 278.0 $[M+H]^+$ (100); IR (KBr): 2979, 2933, 2871, 2839, 2796, 1494, 1448, 1214, 1051, 1000, 927, 874, 776 cm^{-1}. Anal. Calcd for $C_{12}H_{18}ClF_2N_3$: C, 51.89; H, 6.53; N, 15.13. Found: C, 51.72; H, 6.51; N, 14.72.

4.7. 4-(Dimethylamino)-2,3,5,6-tetrafluorophenyl-*N*,*N*,*N*,*N*-tetramethylphosphordiamidate and 2-(dimethylamino)-3,4,5,6-tetrafluorophenyl-*N*,*N*,*N*,*N*-tetramethylphosphordiamidate (5a, 5b)

5a: Red liquid. Yield 15%, ^{1}H NMR: δ 2.89 (t, *J* = 2.4 Hz, 6H), 2.78 (d, *J* = 9.9 Hz, 12H) ^{19}F NMR: δ −153.0 (d, *J* = 19.2 Hz, 2F), −158.6 (d, *J* = 19.2 Hz, 2F); ESIMS (*m*/*e*): 344.1 $[M+H]^+$ (100); IR (KBr): 2938, 2901, 2858, 2814, 1519, 1497, 1459, 1438, 1312, 1234, 1123, 1027, 985, 866, 796, 761, 506, 475 cm^{-1}. Anal. Calcd for $C_{12}H_{18}F_4N_3O_2P$: C, 41.99; H, 5.29; N, 12.24. Found: C, 42.40; H, 5.43; N, 12.06. **5b**: Red liquid. Yield 29%, ^{1}H NMR: δ 2.87 (t, *J* = 1.8 Hz, 6H), 2.78 (d, *J* = 10.8 Hz, 12H). ^{19}F NMR: δ −143.5 (s, 1F), −149.8 (d, *J* = 21.9 Hz, 1F), −157.5 (d, *J* = 22.5 Hz, 1F), −165.2 (td, *J* = 22.5 Hz, 1F); ESIMS (*m*/*e*): 344.1 $[M+H]^+$ (100), IR (KBr): 2937, 2900, 2857, 2812, 1514, 1492, 1454, 1312, 1234, 1000, 987, 873, 792, 759, 474 cm^{-1}. Anal. Calcd for $C_{12}H_{18}F_4N_3O_2P$: C, 41.99; H, 5.29; N, 12.24. Found: C, 42.42; H, 5.48; N, 11.98.

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