Studies on Organic Fluorine Compounds. Part 27.[1] Abnormal Reactions in the Trifluoromethylation of Aromatic Compounds with Trifluoromethyl Iodide and Copper Powder

By **Yoshiro Kobayashi** * and **Itsumaro Kumadaki**, Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192–03, Japan

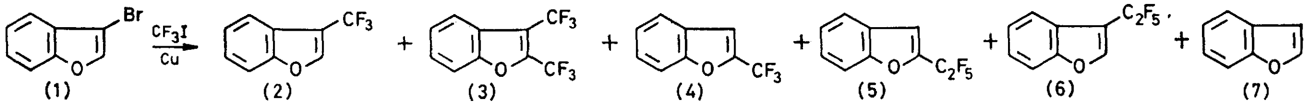
Reaction of 3-bromobenzofuran with trifluoromethyl iodide and copper powder in pyridine gave 2-(trifluoromethyl)-, 2- and 3-(pentafluoroethyl)-, and 2,3-bis(trifluoromethyl)-benzofuran, as well as the expected product, 3-(trifluoromethyl)benzofuran. Bromoanisole also gave (trifluoromethyl)anisole and (pentafluoroethyl)anisole, but introduction of the perfluoroalkyl group occurred at the position originally occupied by the bromine. Formation of pentafluoroethyl compounds is explained by decomposition of trifluoromethylcopper to cuprous fluoride and difluorocarbene, which can then react with a further molecule of trifluoromethylcopper to form pentafluoroethylcopper. This then reacts with aryl halide to give pentafluoroethyl compounds. Perfluoroalkylcopper is thermally cleaved to perfluoroalkyl radical, which then reacts with pyridine to give perfluoroalkylpyridines. This mechanism must be involved in the formation of 2,3-bis(trifluoromethyl)benzofuran. Introduction of a perfluoroalkyl group to the position originally unoccupied with halogen might be due to the rather localized double bond in benzofuran.

In previous papers, we have reported the trifluoromethylation of aryl halides with trifluoromethyl iodide [2] or bromide [3] in the presence of copper powder in aprotic solvents, with some data showing the effect of solvents and pre-treatment of copper powder on this reaction.

Recently, we applied this reaction to 3-bromobenzofuran (1) and found that some abnormal reactions occurred when the reaction was carried out in pyridine and/or at rather high temperature; thus, as well as a small amount of the expected product 3-(trifluoromethyl)benzofuran (2), 2,3-bis(trifluoromethyl)benzofuran (3), 2-(trifluoromethyl)benzofuran (4), 2-(pentafluoroethyl)benzofuran (5), 3-(pentafluoroethyl)benzofuran (6), and benzofuran (7) were also obtained when pyridine was used as a solvent. Furthermore, while the reaction in dimethylformamide (DMF) at 110 °C gave (2) in a fairly good yield, a rise in the reaction temperature to 140 °C resulted in the formation of (4)—(6) although in this case yields of these by-products were much smaller than those in the reaction in pyridine. These results are shown in Table 1.

Table 1

Product yields (%) in the reaction of 3-bromobenzofuran



	(2)	(3)	(4)	(5)	(6)	(7)
In pyridine	9	45	27	9	9	trace
In DMF (140 °C)	66	0	11	9	14	trace

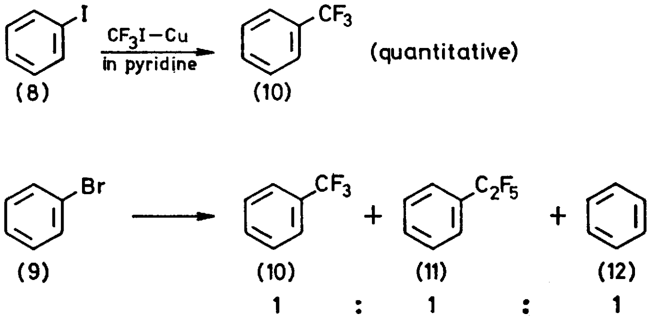
The structures of (2) and (4) were determined by comparison of ^1H and ^{19}F n.m.r. spectra with those of authentic samples.[4] Compound (3) shows two quartet peaks due to the trifluoromethyl groups in the ^{19}F n.m.r. spectrum, and a peak at *m/e* 254 in the mass spectrum. Treatment of (2) or (4) in the same reaction conditions in pyridine gave (3). Therefore, (3) was determined to be 2,3-bis(trifluoromethyl)benzofuran. The structures of (5) and (6) were determined to be 2- and 3-(pentafluoroethyl)-benzofuran, respectively, based on the spectral data: *i.e.* the presence of a pentafluoroethyl group from the ^{19}F n.m.r. spectrum, a peak at *m/e* 226 (M^+) in the mass spectrum, and the similarity of the ^1H n.m.r. spectra of both compounds to those of (4) and (2), respectively.

The abnormal features of this reaction are the introduction of perfluoroalkyl groups at a position different from that substituted with bromine, formation of bis(trifluoromethyl) compounds, formation of pentafluoroethyl compounds, and reductive cleavage of bromine. Furthermore, (perfluoroalkyl)pyridines were detected in the reaction mixture by g.l.c.

These abnormalities might be ascribed to the following causes: (*a*) the solvent effect; (*b*) the low reactivity of aryl bromide compared with aryl iodide; [2] (*c*) the electron-donating effect of benzofuran; and (*d*) the specific nature of the benzofuran ring. We therefore tried to determine which of these effects was operative in the present case.

The solvent effect seems to be a rather relative one, since some of the abnormal products were formed even in DMF at high temperature as shown above. To see the effect of the halogen of aryl halide, the reactions of iodobenzene (8) and bromobenzene (9) were examined in pyridine. The results are shown in Scheme 1.

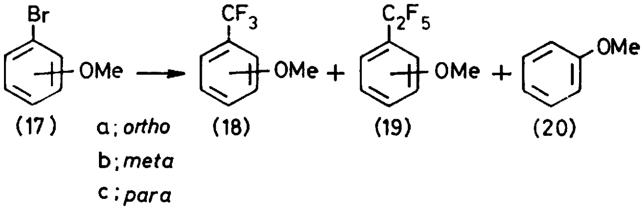
Only (trifluoromethyl)benzene (10) was obtained from (8), while (pentafluoroethyl)benzene (11) and benzene (12), as well as (10), were formed from (9). The ratio (10) : (11) was *ca.* 1 : 1 on the basis of intensities in the ^{19}F n.m.r. spectrum, and the ratio (11) : [(10) + (12)] was 1 : 2 on the basis of peak areas in g.l.c. Separation of (11) from (10) and (12) was performed by preparative g.l.c., but separation of (10) and (12) was unsuccessful even by analytical g.l.c. Compound (11) was identified with an authentic sample by comparison of retention times in g.l.c., and by ^{19}F n.m.r. spectroscopy. Formation of (11) was confirmed by a peak at *m/e* 196 (M^+) in the mass spectrum, and comparison of the ^{19}F n.m.r. spectrum with that of an authentic sample obtained by the reaction of (8) with pentafluoroethyl iodide in the presence of copper powder. This result showed that the formation of the pentafluoroethyl compound and the reduced product occurred when the less active aryl bromide was used. In this case, it was not obvious whether rearranged products were formed, since (9) had no substituent other than bromine. Therefore, the reactions of bromoanisoles were examined, because anisole is a π-electron-rich compound like benzofuran, and formation of rearranged products could be easily detected by reference to the methoxy-group. The results are summarized in Table 2. The products were isolated by preparative g.l.c., and each (trifluoromethyl)anisole was identified by comparison of the ^{19}F and ^{1}H n.m.r. spectra with those of authentic samples. The presence of (pentafluoroethyl)anisoles was confirmed by peaks at *m/e* 226 (M^+) in the mass spectra, signals due to C_2F_5 groups in the ^{19}F n.m.r. spectra, and similarities of patterns in their ^{1}H n.m.r. spectra with those of the corresponding (trifluoromethyl)anisoles.



SCHEME 1

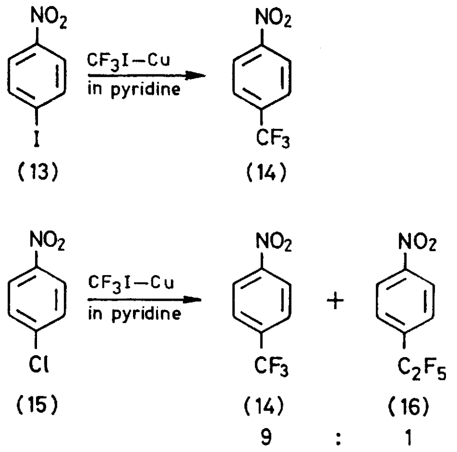
TABLE 2

Reaction products of bromoanisoles and their spectral data



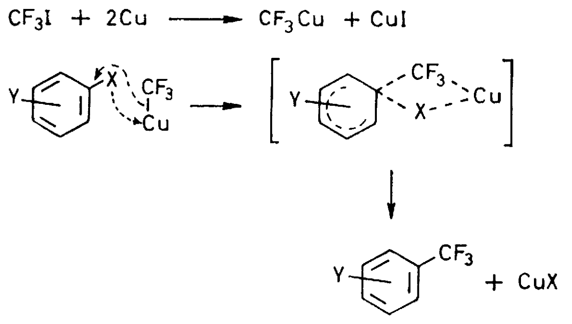
Starting material	Product (%)	Retention time/min	δ_H	δ_F	*m/e* (M^+)	Accurate mass measurement	
						Calc.	Found
(17a)	(18a) (83)	6.0	3.75 (Me), 6.7—7.8 (m)	−0.8(CF_3)	176		
	(19a) (16)	3.9	3.82 (Me), 6.7—7.8 (m)	21.4(CF_3)	226	226.0417	226.0437
	(20) (trace)	5.6		52.0(CF_2)			
(17b)	(18b) (77)	4.0	3.73 (Me), 6.6—7.4 (m)	0.0(CF_3)	176		
	(19b) (10)	3.1	3.72 (Me), 6.8—7.5 (m)	23.0(CF_3)	226	226.0417	226.0436
	(20) (13)	5.6		55.6(CF_3)			
(17c)	(18c) (30)	5.0	3.82 (Me), 6.97 (d) 7.60 (d)	−1.4(CF_3)	176		
	(19c) (30)	3.6	3.83 (Me), 6.93 (d) 7.52 (d)	23.8(CF_3) 53.2(CF_2)	226	226.0417	226.0437
	(20) (40)	5.6					

In this case, pentafluoroethyl compounds and reduction products were obtained as in the case of 3-bromobenzofuran, but no rearrangement products were detected. The reaction of *p*-iodoanisole gave only *p*-(trifluoromethyl)anisole.[2] Therefore, formation of the pentafluoroethyl compounds must be due to the low reactivity of bromo-compounds, although the electronic effect of the anisole ring might also be involved. It seems that the formation of rearrangement products is due to the specific nature of the benzofuran ring.

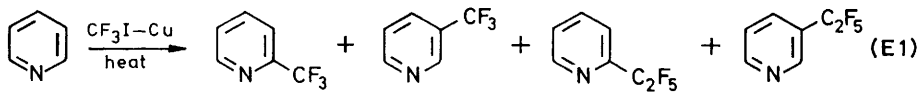


SCHEME 2

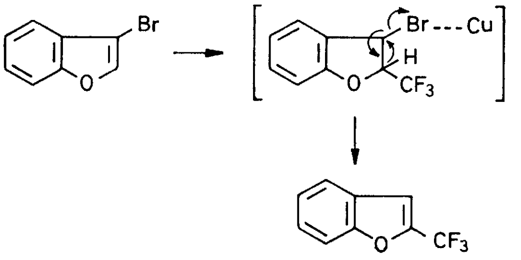
To elucidate the effects of the aromatic ring, the reaction of *p*-nitrohalogenobenzenes was examined. While *p*-nitroiodobenzene (13) gave only *p*-nitro(trifluoromethyl)benzene (14), *p*-nitrochlorobenzene (15) gave *p*-nitro(pentafluoroethyl)benzene (16) as well as (14), but the amount of (16) was much smaller than that of the analogous *p*-methoxy-compound (Scheme 2). Since our previous work had shown that the order of reactivity of halogens is I > Br > Cl, the chloro-compound (15) would have given a larger amount of the pentafluoroethyl compound than bromobenzene, if the halogen reactivity alone controlled the formation of pentafluoroethyl compounds. Therefore, activation by the *p*-nitro-group seems to compensate for the lower reactivity of aryl chloride. This suggests that the trifluoromethylation starts with the simultaneous attack by trifluoromethyl anion on the halogenated carbon and by cuprous ion on halogen, as shown in Scheme 3. If the reactivity of aryl halide is low, trifluoromethylcopper can decompose competitively to give cuprous fluoride and difluorocarbene. The latter can then react with another molecule of trifluoromethylcopper to give pentafluoroethylcopper, which then gives pentafluoroethyl compounds on reaction with aryl halides.



SCHEME 3



The formation of rearranged products in the case of benzofuran might be due to the addition of trifluoromethyl anion to the rather localized double bond between the 2- and 3-positions, followed by the migration of hydride ion and the elimination of bromide ion, as shown in Scheme 4.



SCHEME 4

Heating trifluoromethyl iodide with copper powder in pyridine without aryl halides resulted in the formation of (trifluoromethyl)- and (pentafluoroethyl)-pyridines [equation E1)]. This result shows that perfluoroalkylcopper compounds decompose to some extent to perfluoroalkyl radicals, which attack the aromatic ring. Formation of 2,3-bis(trifluoromethyl)benzofuran might be due to this radical reaction.

EXPERIMENTAL

General procedure.—The aryl halide was sealed with CF_3I (measured in liquid form at −78 °C) and Cu powder in the designated solvent in a stainless steel tube and heated with shaking for 20 h.[2] The reaction mixture was treated with ice–ether, steam-distilled, and extracted with ether. The ether solution was analysed by g.l.c. using a Shimazu 3AF apparatus (column DEGS, diameter 3 mm, length 3 m; carrier gas N_2; inlet pressure, 1 atm). The ratio of the products was estimated from the ratio of peak areas. For the preparative work, the ether solution was concentrated using a Vigreux tube and the residue was separated using a Varian Aerograph 705 apparatus (column, DEGS, diameter 10 mm, length 4 m; carrier gas N_2). ^1H and ^{19}F N.m.r. spectra were recorded on a Varian T 60 spectrometer; ^{19}F chemical shifts are referred to (trifluoromethyl)benzene, positive values to high field. Combustion analyses of our compounds did not give satisfactory values, but rather lower values, probably due to high volatility or incomplete combustion. Therefore, we used high-resolution mass spectroscopy for elemental analyses. The purity of each compound was confirmed by g.l.c. and ^{19}F and ^1H n.m.r. spectroscopy.

Reaction of 3-*Bromobenzofuran* (1).—(*a*) A solution of (1) (1 g) in pyridine (10 ml) was treated with Cu powder (2 g) and CF_3I (3 ml) at 140 °C. After steam-distillation, the ether extract was analysed by g.l.c. at 115 °C to give the following compounds (retention times in parentheses) (3) (3.2 min); (5) (4.5 min); (6) (5.0 min); (4) (6.0 min); (2) (6.8 min); and (7) (15.5 min). After evaporation of solvent, the residue was distilled. Crude oil (b.p. 140—185 °C) was collected (0.7 g), and the products separated by preparative g.l.c. Compounds (2), (4),[4] and (7) were identified by comparison with authentic samples of g.l.c., n.m.r., and i.r. spectra. Compound (3) is a colourless oil, b.p. 170—180 °C (bath temperature); δ_F 7.2—7.8 (no peak due to 2- and 3-H); δ_H 0.0 and −5.7 (both q, J_{FF} 7.9 Hz); *m*/*e* 254 (M^+) (Found: M^+ 254.017 3. Calc. for $C_{10}H_4F_6O$: M^+ 254.016 6).

Compound (5) was a colourless oil, b.p. 170—180 °C (bath temperature); $\delta_H(CDCl_3)$ 7.2—7.8 (m), 7.20 (br s, 3-H) [pattern of multiplet is quite similar to that in ^1H n.m.r. of (4)]; δ_F 23.0 (t, J_{FF} 2.9 Hz, CF_3) and 55.3 (m, CF_2); *m*/*e* 236 (M^+) (Found: M^+ 236.027 3. Calc. for $C_{10}H_5F_5O$: M^+ 236.026 0); (6) colourless oil, b.p. 170—180 °C (bath temperature); $\delta_H(CDCl_3)$ 7.2—7.8 (m), 7.88 (t, J_{HF} 1.7 Hz, 2-H) [pattern of multiplet quite similar to that of ^1H n.m.r. of (2)]; ^{19}F n.m.r. δ_F 24.3 (t, J_{FF} 2.9 Hz, CF_3) and 55.6 (m, CF_2); *m*/*e* 236 (M^+) (Found: M^+ 236.027 3. Calc. for $C_{10}H_5F_5O$: M^+ 236.026 0).

Compounds (5) and (6) were obtained by treatment of the corresponding bromobenzofurans (1 g) with C_2F_5I (3 ml) and Cu powder (3 g) in DMF (20 ml) at 110—130 °C in the same manner as the general procedure for trifluoromethylation, b.p. 170—180 °C (bath temperature) yield 0.7 g.

Reaction of Iodobenzene (8).—Compound (8) (5 g) was treated with CF_3I (4 ml) and Cu powder (10 g) in pyridine (20 ml). (Trifluoromethyl)benzene (10) was obtained in quantitative yield, and no other by-products were detected.

Reaction of Bromobenzene (9).—Compound (9) (4 g) was treated with CF_3I (4 ml) and Cu powder (10 g) in pyridine (20 ml). The ether extract was analysed by g.l.c. at 70 °C. Two peaks [(pentafluoroethyl)benzene (11) and a mixture of (trifluoromethyl)benzene (10) and benzene (12)] were observed, ratio 1 : 2. The extract was carefully concentrated using a Vigreux tube, and the residue was analysed by ^{19}F n.m.r. Three peaks were observed, δ_F 0.0 [CF_3 of (10)], 25.2 [t, J_{FF} 1.7 Hz, CF_3 of (11)], and 55.6 [m, CF_2 of (11)]. The intensity ratio of the first two peaks was 1 : 1.

Compound (11) was isolated by preparative g.l.c. and identified by comparison of the ^{19}F n.m.r. spectrum with that of an authentic sample obtained by the reaction of (8) (2 g) with C_2F_5I (3 ml) and Cu powder (10 g) in DMF (20 ml) at 120—135 °C. This compound was also obtained by the reaction of ωωω-trifluoroacetophenone with sulphur tetrafluoride according to the literature.[5]

Reaction of p-*Nitroiodobenzene* (13).—Compound (13) (1 g) was treated with CF_3I (1 ml) and Cu powder (3 g) in pyridine (10 ml) at 110—120 °C. Analysis of the ether extract by g.l.c. and n.m.r. showed that *p*-nitro(trifluoromethyl)benzene (14) was the only product. After evaporation of solvent, the residue was distilled to give 0.7 g of a yellow oil, b.p. 110 °C at 30 mmHg.

Reaction of p-*Nitrochlorobenzene* (15).—Compound (15) (1 g) was treated with CF_3I (1 ml) and Cu powder (3 g) in pyridine (10 ml) at 110—120 °C. The ether extract was analysed by ^{19}F n.m.r. spectroscopy and shown to be a mixture of (14) and *p*-(pentafluoroethyl)nitrobenzene (16) (9 : 1). (14) δ −0.5; (16) δ_F 21.2 (CF_3) and 54.2 (CF_2). Further separation of the residual oil (0.3 g) after evaporation of solvent was not attempted, but the ^1H n.m.r. spectrum of this mixture was quite similar to that of (14).

Reaction of Bromoanisoles.—Bromoanisole (17a, b, or c) (5 g) was treated with CF_3I (7 ml) and Cu powder (15 g) in pyridine (25 ml) at 140 °C. The ether extract was analysed by g.l.c. The retention times at 140 °C, inlet pressure 0.9 atm, and the area ratios are summarized in Table 2. Before the peaks due to products appeared, other peaks were observed, most of which were identified with (trifluoromethyl)- and (pentafluoroethyl)-pyridines. Distillation of the residues after evaporation of ether gave pale yellow oils, b.p. 150—180 °C, yield 3—3.5 g.

Each crude oil was separated by preparative g.l.c. (Trifluoromethyl)anisoles were identified by comparison with authentic samples, obtained by the reaction of chloro(trifluoromethyl)benzene with sodium methoxide according to the literature.[6] They were also obtained by the reaction of iodoanisoles with CF_3I and Cu powder in DMF in the same manner as in the general procedure.[2] Authentic (pentafluoroethyl)anisoles were obtained by the reaction of iodoanisoles (1 g) with C_2F_5I (3 ml) and Cu powder (3 g) in DMF (20 ml) in the same method as in the general procedure. Colourless oils, b.p. 160—175 °C (bath temperature) were obtained, yield *ca.* 70% for each. The pattern of the ^1H n.m.r. spectrum of a (pentafluoroethyl)anisole was quite similar to that of the corresponding (trifluoromethyl)anisole.

Reaction of Pyridine.—Pyridine (5 g) was treated with CF_3I (5 ml) and Cu powder (10 g) at 140 °C for 20 h. The ether extract was washed with 1% AcOH and dried over Na_2SO_4. G.l.c. of the extract showed four main peaks together with some very small peaks. The area ratio of the four peaks was 29 : 15 : 40 : 36. Evaporation of the solvent under a Vigreux tube gave a crude oil (3 g), which was separated by preparative g.l.c. The products corresponding to the second and fourth peaks were identified by comparison with authentic samples of 3- and 2-(trifluoromethyl)pyridine,[7] respectively. From the comparison of the ^1H n.m.r. spectra of the first and the third products with those of 3- and 2-(trifluoromethyl)pyridine,[7] products 1 and 3 were believed to be 3- and 2-(pentafluoroethyl)pyridine, respectively. 3-(Pentafluoroethyl)pyridine: $\delta_H(CDCl_3)$ 8.81 (2- and 6-H), 7.93 (d, 4-H), 7.5 (dd, 5-H); δ_F 22.8 (CF_3) and 56.8 (CF_2); *m/e* 197 (M^+) (Found: M^+ 197.027 8. Calc. for $C_7H_4F_5N$: M^+ 197.026 4). 2-(Pentafluoroethyl)pyridine: δ_H ($CDCl_3$) 8.83 (d, 6-H) and 8.1—7.3 (m); δ_F 21.0 (CF_3) and 58.5 (CF_2); *m/e* 197 (M^+) (Found: M^+ 197.027 8. Calc. for $C_7H_4F_5N$: M^+ 197.026 4).

[9/008 *Received, 3rd January,* 1979]

REFERENCES

[1] Part 26, Y. Kobayashi, T. Nakano, R. Takahashi, and I. Kumadaki, *J.C.S. Perkin I*, 1979, 2253.

[2] Y. Kobayashi and I. Kumadaki, *Tetrahedron Letters*, 1969, 4095; Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, and E. Chikami, *Chem. Pharm. Bull.* (*Japan*), 1970, **18**, 2334.

[3] Y. Kobayashi, I. Kumadaki, A. Ohsawa, and T. Yamada, *Chem. Pharm. Bull.* (*Japan*), 1972, **20**, 1839.

[4] Y. Kobayashi, I. Kumadaki, and Y. Hanzawa, *Chem. Pharm. Bull.* (*Japan*), 1977, **25**, 3009.

[5] W. R. Hasek, W. C. Smith, and W. A. Engelhardt, *J. Amer. Chem. Soc.*, 1960, **82**, 543.

[6] T. McBee, R. O. Bolt, P. J. Graham, and R. F. Tebbe, *J. Amer. Chem. Soc.*, 1947, **69**, 957.

[7] M. S. Raash, *J. Org. Chem.*, 1962, **27**, 1406.