

## Studies on Fluoroalkylation and Fluoroalkoxylation. Part 33.† Direct Trifluoromethylation of Aryl Halides with Fluorosulphonyldifluoromethyl Iodide in the Presence of Copper: an Electron Transfer Induced Process

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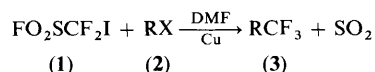
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Aryl halides are readily trifluoromethylated with fluorosulphonyldifluoromethyl iodide (**1**) in the presence of copper in DMF in high yield. A single electron transfer (s.e.t.) scavenger, *p*-dinitrobenzene, and free radical inhibitor, hydroquinone, partly suppress the reaction. Addition of 2,3-dimethylbut-2-ene to the reaction mixture gives a free radical addition-elimination product and difluorocarbene derivatives besides the trifluoromethyl displaced compound. A copper SET-induced mechanism is proposed.

Previously, we have shown that alkenes and trimethylsilylacetylenes can be fluoroalkylated with fluoroalkyl iodides<sup>1,2</sup> in the presence of copper *via* a single electron transfer (s.e.t.) mechanism. However, the co-existence of radical and carbene intermediates was also observed in the case of the reaction of fluorosulphonyldifluoromethyl iodide, FO<sub>2</sub>SCF<sub>2</sub>I (**1**) with olefins.<sup>3</sup> Recently, we<sup>4</sup> and others<sup>5</sup> found that copper or cuprous halide is able to catalyze the addition of fluoride ion to difluoromethylene carbon with the formation of a trifluoromethyl group. Thus, it would be interesting to develop (**1**) to be a new trifluoromethylating agent in the presence of copper. This paper presents the results of trifluoromethylation of aryl halides with (**1**) and the possible mechanisms of the copper-induced reactions are discussed.

### Results and Discussion

Treatment of aryl halides with fluorosulphonyldifluoromethyl iodide (**1**) in the presence of copper [(**1**): Cu molar ratio 1:2.2] in dimethylformamide (DMF) at 60–80 °C for 6–7 h gave high yields of the product (**3**), together with white cuprous iodide. The results are summarized in Table 1, where the order of reactivity is seen to be RI > RBr ≫ RCl. Although the bromo derivative is seen to be quite effective, there was no displacement of chlorine in (**2b**) after iodine had been substituted by the trifluoromethyl group even at a ratio of (**1**):(**2**) of 3:1.



**Scheme 1.** RX = PhI (**a**), *p*-ClC<sub>6</sub>H<sub>4</sub>I (**b**), *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I (**c**), 1-iodonaphthalene (**d**), 1-bromonaphthalene (**e**), Cl(CF<sub>2</sub>)<sub>4</sub>C<sub>6</sub>H<sub>4</sub>I-*p* (**f**), *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>Br (**g**), PhCH<sub>2</sub>Br (**h**), PhCH<sub>2</sub>I (**i**), PhCH=CHBr (**j**), CH<sub>2</sub>=CHCH<sub>2</sub>Br (**k**), CH<sub>2</sub>=CHCH<sub>2</sub>I (**l**)

The amount of copper powder used had a significant influence on the conversion of (**1**) but not on the yield. Table 2 shows the optimum molar ratio of (**1**): Cu is 1:2.2.

The presence of single electron transfer (s.e.t.) scavenger, *p*-dinitrobenzene (*p*-DNB) or free radical inhibitor, hydroquinone (HQ) in DMF partly suppressed the reaction. The results are shown in Table 3.

The results obtained seem to indicate that trifluoromethylation of aryl halides with (**1**) in the presence of copper in DMF might involve a s.e.t. mechanism. However, there was uncertainty over this in view of the need to postulate a difluorocarbene intermediate which must then be transformed

**Table 1.** Reaction of (**1**) with (**2**) in DMF in the presence of Cu<sup>a</sup>

Entry	RX	(1):(2)	T/°C	t/h	Conversion (%) <sup>b</sup>	Product (3)(%) <sup>c</sup>
1	( <b>2a</b> )	1:2	80	7	100	80
2	( <b>2b</b> )	1:2	80	6	91	78.7
3		3:1	80	6	92	84.4
4	( <b>2c</b> )	1:2.5	80	6	100	83.2
5	( <b>2d</b> )	1:2	80	6.5	100	84
6	( <b>2e</b> )	1:2.5	80	7	100	78
7	( <b>2f</b> )	1:1.8	80	7	100	90.4
8	( <b>2g</b> )	1:2	90	7	98	84
9	( <b>2h</b> )	1:2.5	90	6.5	83	72
10	( <b>2i</b> )	1:2	90	5.5	100	78.7
11	( <b>2j</b> )	1:2	80	7	100	74
12	( <b>2k</b> )	1:3	60	6	100	74.3
13	( <b>2l</b> )	1:3	60	6	100	78

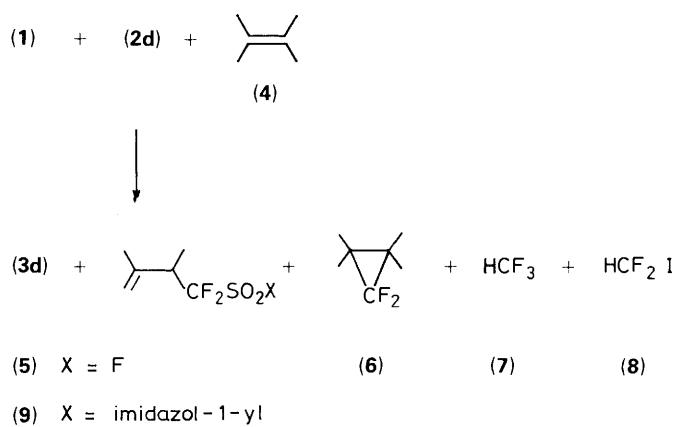
<sup>a</sup> (**1**):Cu molar ratio 1:2.2. <sup>b</sup> Conversion(%) was determined by <sup>19</sup>F n.m.r. <sup>c</sup> Isolated yields based on (**1**) except entry 3.

to trifluoromethanide. In order to establish the existence or otherwise of a difluorocarbene, an equivalent of 2,3-dimethylbut-2-ene (**4**) was added to a reaction mixture of (**1**) and (**2d**) in the presence of catalytic amounts of copper [12 mol% relative to (**1**)] and the mixture kept at 80 °C for 6.5 h. On work-up both (**3d**) and an addition-elimination product (**5**) were obtained, together with the difluorocarbene derivatives (**6**), (**7**), and (**8**) [29% conversion of (**1**)]. Compound (**5**) was isolated as its derivative (**9**).<sup>3</sup>

It is noteworthy that in the presence of 2.2 equiv. of copper in the same reaction the conversion of (**1**) increased to 100% and the yield of (**3d**) also improved significantly at the expense of (**5**), (**6**), and (**7**) (see Table 4).

The appearance of (**6**), (**7**), and (**8**) provides good evidence for the presence of a difluorocarbene intermediate and of (**5**) for the intermediacy of a fluorosulphonyldifluoromethyl radical. This together with the above inhibition by *p*-DNB and *p*-HOC<sub>6</sub>H<sub>4</sub>OH suggests that the three-competing processes, [i.e. difluorocarbene insertion (path A), free radical addition-elimination (path B), and trifluoromethylation (path C)] and the results obtained can be explained in terms of a copper s.e.t.-induced mechanism. For path C, there is, seemingly, an equilibrium between CF<sub>2</sub>: plus F<sup>-</sup> and CF<sub>3</sub><sup>-</sup>. The presence of an

† For Part 32 see Ref. 3.



Scheme 2.

Table 2. Reaction of (1) with (2a) or (2j) with different amounts of copper in DMF at 80 °C.

RX	(1):Cu	t/h	Conv'n(%) <sup>a</sup>	Product (3)(%) <sup>b</sup>
(2a)	4:1	6	10	73.5
	2:1	6	22	74.2
	1:1	6	40	75.6
	1:2	6	78	74
	1:2.2	7	100	80
(2j)	4:1	7	12	74.5
	2:1	7	28	73.2
	1:1	7	48	75
	1:2	7	86	74.8
	1:2.2	7	100	74

<sup>a</sup> Conversion(%) was determined by <sup>19</sup>F n.m.r. <sup>b</sup> Isolated yields based on (1).

Table 3. Reaction of (1) with (2d) in the presence of *p*-DNB or HQ in DMF at 80 °C for 6.5 h

Conv'n(%) <sup>a</sup>	Molar ratio (Cu/ <i>p</i> -DNB) (Cu/HQ)	5:0	5:1	1:1
		100	44	9
		100	40	8

<sup>a</sup> Conversion(%) was determined by <sup>19</sup>F n.m.r.

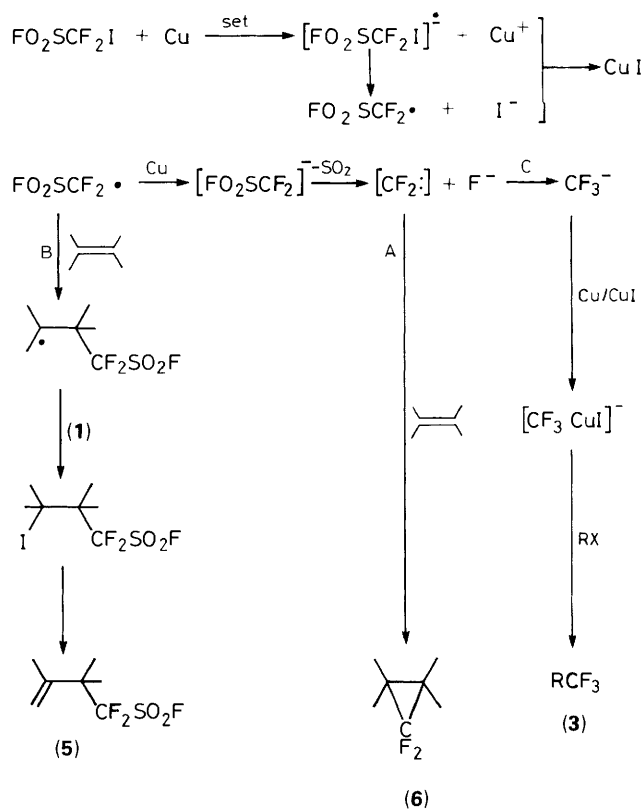
Table 4. Reaction of (1), (2d), and (4) (1:2:1) in the presence of copper in DMF at 80 °C for 6.5 h

Cu:(1)	Conv'n(%) <sup>a</sup>	Yield(%) <sup>b</sup>				
		(3d)	(5)	(6)	(7)	(8)
0.12	29	5	43.5	13	19	Trace
2.2	100	43	27	10	10	—

<sup>a,b</sup> As noted in Table 2.

excess of copper or cuprous iodide\* produced during the reaction course much favours the shifting of equilibrium toward CF<sub>3</sub><sup>-</sup> then to [CF<sub>3</sub>CuI]<sup>-</sup> and subsequently depresses path A and path B. In the absence of (4) path C predominates leading to the high yield of (3). The possible mechanisms of the reaction are shown in Scheme 3.

\* We found that cuprous iodide does not induce the reaction under similar conditions.



Scheme 3.

### Experimental

All b.p.s are uncorrected. G.c. product analyses were performed on a Shanghai analytical instrument, Model 103 with column packing consisting of oxaperfluoroalkyltriazine polymer on 100 mesh Celite 102 support. <sup>1</sup>H and <sup>19</sup>F n.m.r. spectra were recorded on a Varian EM-360 (60 MHz) instrument with SiMe<sub>4</sub> and CF<sub>3</sub>CO<sub>2</sub>H (positive for upfield shifts) as external references, respectively. Mass spectra were recorded on a GC-MS-4021 spectrometer. I.r. spectra were measured on a Shimadzu IR-440. All reagents and solvents were purified before use, and all experiments were carried out under pure nitrogen.

Compound (1) was prepared from FO<sub>2</sub>SCF<sub>2</sub>COF as described in the literature.<sup>6</sup> In our previous paper,<sup>3</sup> compound (1) was prepared from FO<sub>2</sub>SCF<sub>2</sub>CO<sub>2</sub>H by the following procedure: FO<sub>2</sub>SCF<sub>2</sub>CO<sub>2</sub>H was converted into the corresponding silver salt, FSO<sub>2</sub>SCF<sub>2</sub>CO<sub>2</sub>Ag (>90%) with Ag<sub>2</sub>CO<sub>3</sub> at room temperature. After thorough drying treatment of the silver salt with I<sub>2</sub> gave (1) (49.9%), b.p. 82–84 °C.

*Direct Trifluoromethylation of Alkyl Halides with (1) in the Presence of Copper: Typical Procedure.*—A Pyrex tube fitted with a screw cap was charged with copper powder (0.7 g, 11 mmol) under pure nitrogen. Compound (2c) (3.1 g, 12.5 mmol), DMF (10 ml), and (1) (1.3 g, 5 mmol) were then added. After addition, the mixture was stirred for 6 h at 80 °C: white cuprous iodide appeared in the tube. <sup>19</sup>F N.m.r. spectrometry, showed that the conversion of (1) was 100%. The reaction mixture was filtered and the solid was washed twice with ether, the combined extracts were poured into water. The aqueous layer was extracted with ether (×3) and the combined extracts were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. Distillation under reduced pressure gave (3c) (0.8 g, 83.2%). The results are summarized in Table 1.

Compound (3a), b.p. 102–103 °C (lit;<sup>7</sup> b.p. 102.7 °C),  $\delta_F$  –12.6 (s) p.p.m.;  $\delta_H$  6.64 (m).

Compound (3b), b.p. 139–141 °C (lit;<sup>7</sup> b.p. 138.9 °C),  $\delta_F$  –13.6 (s) p.p.m.;  $\delta_H$  7.12 (m);  $m/z$  180 ( $M^+$ , 100%), 161 ( $M^+$  – F, 23.35), 145 ( $M^+$  – Cl, 23.52), 123 (3.58), 111 (4.46), and 76 (2.32).

Compound (3c), m.p. 40–42 °C (lit;<sup>8</sup> m.p. 40–41 °C).

Compound (3d), m.p. 90–92 °C (lit;<sup>9</sup> 90 °C),  $\delta_F$  –17.6 (s) p.p.m.;  $\delta_H$  6.92–7.43 (m);  $m/z$  196 ( $M^+$ , 100%), 177 ( $M^+$  – F, 18.60), 157 (2.40), and 127 (9.74).

Compound (3f), b.p. 64 °C/1.5 mmHg (Found: C, 34.45; H, 0.9; Cl, 9.45; F, 54.3.  $C_{11}H_4ClF_{11}$  requires C, 34.71; H, 1.06; Cl, 9.31; F, 54.91%),  $v_{max}$ . 3 030, 1 620, 1 270, 1 020–1 170, and 920  $cm^{-1}$ ;  $\delta_F$  –13.5 (3F), 4.1 (2F), 34.1 (3F), and 42.2 (2F) p.p.m.;  $\delta_H$  7.74 (s);  $m/z$  381 ( $M^+$  + 1, 0.39), 380 ( $M^+$ , 1.08), 362 (1.84), 361 ( $M^+$  – F, 5.75), 345 ( $M^+$  – Cl), 326 (0.41), 325 (4.32), 295 (0.65), 257 (0.62), 245 (1.65), 226 (3.28), 196 (9.61), 195 (100), 146 (1.50), 145 (19.38), 126 (3.68), 107 (1.06), 88 (0.66), and 76 (0.66).

Compound (3g), m.p. 64–66 °C (lit;<sup>8</sup> m.p. 65–66 °C),  $\delta_F$  –12.4 (t) p.p.m.;  $\delta_H$  8.22 (d, 2H), 7.48 (d, 2H), and 3.50 (q, 2H),  $J_{H,F}$  10.5 Hz).

Compound (3h), b.p. 116–118 °C (lit;<sup>10</sup> b.p. 115–120 °C).

Compound (3j), b.p. 51–53 °C/10 mmHg (lit;<sup>11</sup> b.p. 60–62 °C/20 mmHg).

Compound (3k), b.p. 10–12 °C (lit;<sup>12</sup> b.p. 10.6 °C).

**Reaction of (1) with (2a) and Varying Amounts of Copper.**—To a mixture of copper powder (80 mg, 1.25 mmol), (2a) (2.0 g, 10 mmol), and DMF (10 ml) was added (1) (1.3 g, 5 mmol). The mixture was stirred for 6 h at 80 °C. <sup>19</sup>F N.m.r. spectrometric analyses showed that the conversion of (1) was 10% and the yield of (3a) was 73.5%. The results for varying amounts of copper in this reaction are summarized in Table 2.

**Reaction of (1) with (2d) in the Presence of p-DNB or HQ.**—To a mixture of copper powder (0.7 g, 11 mmol), p-DNB (1.8 g, 11 mmol), (2d) (2.5 g, 10 mmol), and DMF (10 ml) was added (1) (1.3 g, 5 mmol) and the mixture was stirred at 80 °C for 6.5 h. The conversion of (1) was 9% as shown by <sup>19</sup>F n.m.r. spectrometry. However, the conversion was 44% if p-DNB (0.37 g, 2.2 mmol) was used under the same conditions.

Similarly, the conversions of (1) were 8 and 40% in the presence of hydroquinone (1.2 g, 11 mmol) and (0.24 g, 2.2 mmol) respectively (See Table 3).

**Reaction of (1) with (2d) in the Presence of 2,3-Dimethylbut-2-ene.**—To a mixture of copper powder (80 mg, 1.2 mmol), (2d) (5.0, 20 mmol), 2,3-dimethylbut-2-ene (0.84 g, 10 mmol), and DMF (10 ml) was added (1) (2.6 g, 10 mmol) and the mixture was stirred at 80 °C for 6.5 h. <sup>19</sup>F N.m.r. showed that the

conversion of (1) was 29%. Compounds (3d), (5)–(8) were obtained and (5) was completely converted into (9) with imidazole anion.<sup>3</sup> Compounds (7) and (8) were identified by g.c.—m.s. However, in the presence of copper (2.2 equiv.) in the same reaction the conversion of (1) was 100% and (3d), (5), (6), and (7) were obtained (see Table 4).

Compound (6), b.p. 90–92 °C (lit;<sup>13</sup> b.p. 90–91 °C),  $\delta_F$  –71.0 (m) p.p.m.;  $\delta_H$  1.0 (t);  $m/z$  134 ( $M^+$ , 4.39%), 119 (59.45), 84 (8.43), 77 (9.57), 69 (21.52), and 43 (100).

Compound (9), m.p. 23 °C (lit;<sup>3</sup> m.p. 23 °C),  $v_{max}$ . 3 400, 3 100, 3 000, 1 835, 1 725, 1 700, 1 640, 1 530, 1 460, 1 400, 1 345, 1 245, 1 185, 1 155, 1 100, 1 045, 1 000, 950, 920, 900, 860, 825, 750, and 620  $cm^{-1}$ ;  $\delta_F$  20.0 (s) p.p.m.;  $\delta_H$  1.45 (s, 6H), 1.85 (s, 3H), 4.97 (s, 2H), 6.94 (s, 1H), 7.13 (s, 1H), and 7.70 (s, 1H);  $m/z$  265 ( $M^+$  + 1, 8.48%), 264, (1.00), 201 (38.91), 175 (11.48), 133 (31.76), 129 (10.21), 113 (29.65), 109 (19.89), 93 (20.14), 91 (24.82), 85 (13.72), 83 (23.39), 77 (20.82), 73 (26.61), 69 (100), 68 (83.12), 67 (25.93), 61 (71.46), 55 (28.28), 43 (94.42), and 41 (76.82).

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