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Copper electron-transfer induced trifluoromethylation with methyl fluorosulphonyldifluoroacetate[†]

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Abstract

Treatment of halogen compounds, RX, with methyl fluorosulfonyldifluoroacetate and copper powder in dimethylformamide for 4 h at 65–80 °C resulted in the corresponding trifluoromethylated products, RCF_3, in good yield. In the absence of halogen compounds and at 100 °C, methyl triflone ($CF_3SO_2CH_3$) was synthesized readily in 20–30% yield from the same reaction system. The fact that the reaction was suppressed by oxygen, *p*-dinitrobenzene or in darkness suggested that a copper-induced electron-transfer process was involved in this new trifluoromethylating system.

Introduction

The introduction of trifluoromethyl groups into organic compounds has recently been the subject of increasing research activity. The interest is related to the synthesis of trifluoromethyl-containing pharmaceutical and agricultural chemicals relative to their unique physical and biochemical properties [1]. Numerous trifluoromethylating agents have been employed for the trifluoromethylation of aryl halides [2–4]. Among them Burton's reagent ($Cu–CF_2X_2$–amide) appears to have good promise because this trifluoromethylating agent is produced *in situ* from readily available commercial precursors [2a, b]. We have also reported a new trifluoromethylating agent, methyl fluorosulfonyldifluoroacetate (**1**), which reacts with halogenides to give the corresponding trifluoromethylated products in the presence of catalytic amounts of CuI in dimethylformamide (DMF) [3]. The mechanism of this reaction has been proposed as a nucleophilic substitution of $[CF_3CuI]^-$ on the organic halides. In connection with the copper-induced electron-transfer (ET) reaction of fluorosulphonyldifluoromethyl iodide, which has been employed as a direct trifluoromethylating agent [4], we envisaged that compound **1** may undergo a similar process during its reaction with organic halides in the presence of copper.

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[†] Dedicated to Professor Wei-Yuan Huang on the occasion of his 70th birthday.

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Experimental

All boiling points and melting points are uncorrected. ^{1}H NMR and ^{19}F NMR spectra were recorded on a Varian EM-360 (60 MHz) instrument with TMS and CF_3COOH (positive for upfield shifts) as external references, respectively. Mass spectra were recorded on a GC–MS 4021 spectrometer. IR spectra were measured on a Shimadzu IR-440 instrument. All reagents and solvent were purified before use and all experiments were carried out under pure nitrogen unless noted otherwise.

Compound **1** was prepared from FO_2SCF_2COF as described in the literature [5].

Direct trifluoromethylation of alkyl halides with 1 in the presence of copper powder

The typical procedure adopted was Copper powder (0.096 g, 1.5 mmol), **2b** (3.1 g, 12.5 mmol), DMF (10 ml) and **1** (0.78 ml, 6 mmol) were placed in a 25 ml three-necked round-bottom flask fitted with a magnetic stirrer and a reflux condenser connected with a dry-ice trap. The mixture was stirred for 3 h at 65 °C. ^{19}F NMR spectrometry showed that the conversion of **1** was 100%. Sulfur dioxide was quantitatively collected in the cold trap. The gas mixture was then passed through a solution of sodium hydroxide to eliminate carbon dioxide quantitatively. The residual gas was identified as methane (40 ml, 30%) and a small amount of HCF_3 by GC–MS spectrometry. The reaction mixture was washed with 5 ml water, extracted with ethyl ether (20 ml × 3) and the combined organic layer was washed with water, dried over sodium sulfate and the solvent was evaporated. Distillation gave **3b** (0.8 g, 82%). The reaction data are summarized below in Table 1 and the relevent analytical data are as follows:

Compound: **3a:** b.p., 102–103 °C (lit. value [6], 102–107 °C). ^{19}F NMR: $\delta = -12.6$ (s) ppm; ^{1}H NMR: $\delta = 6.64$ (m) ppm.

3b:m.p., 40–42 °C (lit. value [7], 40–41 °C).

3c:b.p., 139–141 °C (lit. value [6], 138.9 °C). ^{19}F NMR: $\delta = -13.6$ (s) ppm; ^{1}H NMR: $\delta = 7.12$ (m) ppm. MS (*m/z*, rel. int.): 180 (M^+, 100.00), 161 ($M^+ - F$, 23.25).

3d:b.p., 116–118 °C (lit. value [8], 115–120 °C.

3f:b.p., 51–53 °C/10 mm Hg (lit. value [9], 60–62 °C/20 mm Hg).

3g:b.p., 64 °C/1.5 mm Hg. Analysis: 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%. IR (ν_{max}): 3030, 1620, 1270, 1020–1170, 920 (cm^{-1}). ^{19}F NMR: $\delta = -13.5$ (3F), 4.1 (2F), 34.1 (3F) and 42.2 (2F) ppm; ^{1}H NMR: $\delta = 7.74$ (s) ppm. MS (*m/z*, rel. int.): 381 ($M^+ + 1$, 0.39), 380 (M^+, 1.08), 361 (5.75), 195 (100.00), 145 (19.38).

3h:m.p. 90–92 °C (lit. value [10], 90 °C). ^{19}F NMR: $\delta = -17.6$ (s) ppm; ^{1}H NMR: $\delta = 6.92$–7.43 (m) ppm. MS (*m/z*, rel. int.):

TABLE 1

Reaction of **1** with **2** in the presence of Cu (12 mol%)

Entry	RX	Ratio of **1:2**	Temp. (°C)	Time (h)	Percentage conversion of **1**[a]	Yield of **3** (%)[b]
1	**2a**	1:2.5	65	4	93	84
2[c]		1:2.5	65	4	43	56
3[d]		1:2.5	65	4	48	54
4	**2b**	1:2	65	3	100	82
5[e]		1:2	65	3	53	77
6	**2c**	1:2	70	3	90	70
7	**2d**	1:2	80	3	100	70
8[e]		1:2	80	3	62	70
9	**2e**	1:2	80	3	100	80
10	**2f**	1:2	60	4	100	72
11	**2g**	1:2	70	3	90	68
12	**2h**	1:2	80	4	100	90
13	**2i**	1:1.5	80	5	100	76

[a] As determined by ^{19}F NMR spectroscopy.
[b] Isolated yield.
[c] In darkness.
[d] In the presence of O_2.
[e] In the presence of *p*-DNB.

196 (M^+, 100.00), 177 (18.6), 157 (2.40), 127 (9.74). **3i**:b.p., 100 °C/2.5 mm Hg. Analysis: Found: C, 51.55; H, 6.58; N, 6.76; F, 27.48%. $C_9H_{14}NOF_3$ requires: C, 51.66; H, 6.76; N, 6.70; F, 27.24%. IR (ν_{max}): 1650, 1450, 1350, 1245, 1100–1180 (cm^{-1}). ^{19}F NMR: $\delta = -15.5$ (t, $J_{H-F} = 21$ Hz) ppm; ^{1}H NMR: $\delta = 1.1$ (d, 3H), 1.53 (s, 9H), 3.1 (q, 2H) ppm. MS (*m/z*, rel. int.): 209 (M^+, 0.47), 140 ($M^+ - CF_3$, 7.23), 58 (100.00).

Preparation of methyl triflone (4)

As described above, the mixture of DMF (40 ml), copper powder (0.2 g) and **1** (2.6 ml, 20 mmol) was stirred for 45 min to 1 h at 100–110 °C when 0.84 g (95.5%) CO_2, 0.60 g (46%) SO_2 and 190 ml (42%) methane were collected. The crude product was distilled out, washed with water, extracted with ethyl ether (20 ml × 3), and the combined organic layer was dried over sodium sulfate and evaporated. Redistilled of the product gave **4** (0.74 g, 25.0%). Analytical data: b.p., 127–129 °C (lit. value [11], 128.9 °C/737 mmHg). ^{1}H NMR: $\delta = 3.11$ ppm; ^{19}F NMR: $\delta = 3\ 6$ ppm. MS (*m/z*): 148 (M^+).

Preparation of trans-*2-(dimethylamino)-vinyl triflone (5)*

The reaction was continued for 6 h before separation of methyl triflone from the reaction mixture. The reaction mixture was extracted with ethyl acetate and the combined organic layer was dried over sodium sulfate, evaporated, separated on a silica gel column and crystallized from ethyl acetate to give **5** (1.62 g, 40.0%). Analytical data: m.p., 92–93 °C (lit. value [12], 91–93 °C). ^{19}F NMR: $\delta=5.8$ ppm; ^{1}H NMR: $\delta=3.98$ (s, 3H), 3.26 (s, 3H), 4.86 (d, 1H), 7.50 (d, 1H, $J=12$ Hz) ppm.

Preparation of 4 in the presence of CuI

When the above reaction was carried out in the presence of CuI (10 mol%) instead of copper powder, **4** was obtained in 20–30% yield.

Direct trifluoromethylation of iodobenzene in the presence of copper(I) iodide

As previously described [3], treatment of **1** with **2a** in DMF in the presence of catalytic amounts of copper(I) iodide (12 mol%) for 2.5 h at 70 °C gave **3a** (80%). The generated gases were identified as sulfur dioxide, carbon dioxide and iodomethane. No methane was detected.

Reaction of 1 with 2a in darkness

A Pyrex tube fitted with a screw cap was charged with copper powder (0.069 g, 1.5 mmol), **1** (0.78 ml, 6 mmol), DMF (10 ml) and the compound **2a** (3.0 g, 15 mmol). The mixture was stirred for 4 h at 65 °C in darkness. Only 43% conversion of **1** was observed and **3a** (0.50 g, 56%) was obtained.

In a similar fashion, the reaction of **1** with **2a** in the presence of O_2 (bubbled with air) or *p*-DNB under laboratory illumination resulted in decreased conversion of **1** and decreased yield of **3a** (see Table 1).

Decomposition of 1 in the presence of p-*DNB, HQ or* O_2

The mixture of copper powder (0.13 g, 2 mmol), DMF (20 ml), **1** (1.3 ml, 10 mmol) and *p*-DNB (0.08 g, 0.5 mmol) was stirred at 100–110 °C for 1 h. The yield of **4** was 16%. Similarly, no **4** was produced in the presence of hydroquinone (0.11 g, 1 mmol) or O_2 (bubbled with air) (see Table 2 below).

Results and discussion

Treatment of methyl fluorosulfonyldifluoroacetate (**1**) with organic halides (**2**) in the presence of catalytic amounts of copper in DMF for 4 h at 65–80 °C gave the corresponding trifluoromethylated compounds RCF_3 (**3**) in high yields (Scheme 1). The gases collected were identified as methane (~30%) in addition to quantitative amounts of carbon dioxide and sulfur dioxide. The results are summarized in Table 1.

The presence of the single electron-transfer scavenger, *p*-dinitrobenzene (*p*-DNB) or free-radical inhibitor, oxygen, in DMF partly suppressed the reaction. When the reaction was carried out in darkness, both the conversion of **1** and the yield of **3** were decreased (see entries 2, 3, 5 and 8 in Table 1).

TABLE 2

Preparation of **4** and **5**

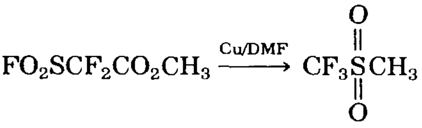
Entry	Temp. (°C)	Time (h)	Yield of **4** (%)[a]	Yield of **5** (%)[a]
1	80	4	0	0
2	100	1	30[b]	10[b]
3	100	2	24	18
4	100	4	12	32
5	100	6	5	35
6[c]	100	1	16	0
7[d]	100	1	0	0
8[e]	100	1	0	0

[a] Determined by ^{19}F NMR spectroscopy unless noted otherwise.
[b] Isolated yield.
[c] In the presence of *p*-DNB.
[d] In the presence of HQ (hydroquinone).
[e] In the presence of O_2.

$$\underset{(1)}{FO_2SCF_2CO_2CH_3} + \underset{(2)}{RX} \xrightarrow{Cu/DMF} \underset{(3)}{RCF_3} + SO_2 + CO_2 + CH_4$$

2a: $R = Ph$, $X = I$
b: $R = p\text{-}O_2NC_6H_4$, $X = I$
c: $R = p\text{-}ClC_6H_4$, $X = I$
d: $R = C_6H_5CH_2$, $X = Br$
e: $R = C_6H_5CH_2$, $X = I$
2f: $R = C_6H_5CH{=}CH$, $X = Br$
g: $R = p\text{-}C_6H_4(CF_2)_4Cl$, $X = I$
h: $R =$ naphthyl, $X = I^{\alpha}$
i: $R = CH_2CONEt_2$, $X = Br$

Scheme 1.

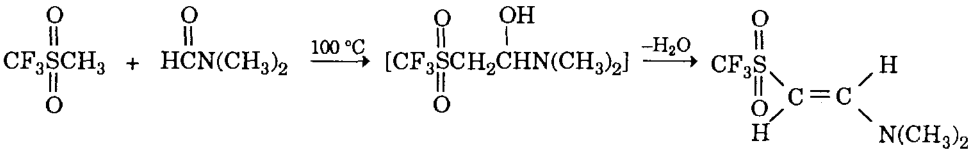


$$\underset{(1)}{FO_2SCF_2CO_2CH_3} \xrightarrow{Cu/DMF} \underset{(4)}{CF_3\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}CH_3}$$

(1) (4)

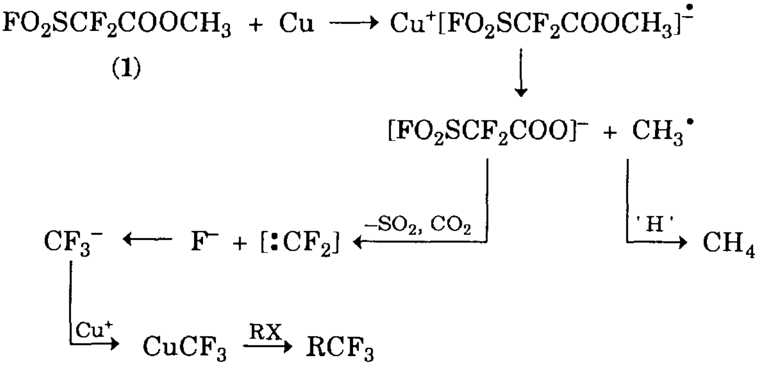
Scheme 2.

It is interesting to note that in the absence of the substrate RX, the Cu-induced decomposition of **1** for 45 min at 100 °C resulted in triflone (**4**) in 20–30% yield with simultaneous elimination of SO_2 (46%), CO_2 (95.5%) and CH_4 (42%) (Scheme 2). Continuing the reaction for 5–6 h led to the formation of *trans*-2-(dimethylamino)-vinyltriflone (**5**) in 30–40% yield (Scheme 3). Triflone (**4**) has been synthesized previously through a multistep process whereas **5** has, in fact, been prepared from the reaction of **4** with DMF [11]. *p*-DNB, oxygen or hydroquinone were also capable of partly or completely suppressing the reaction (see entries 6, 7 and 8 in Table 2). The results are shown in Table 2.



(5)

Scheme 3.



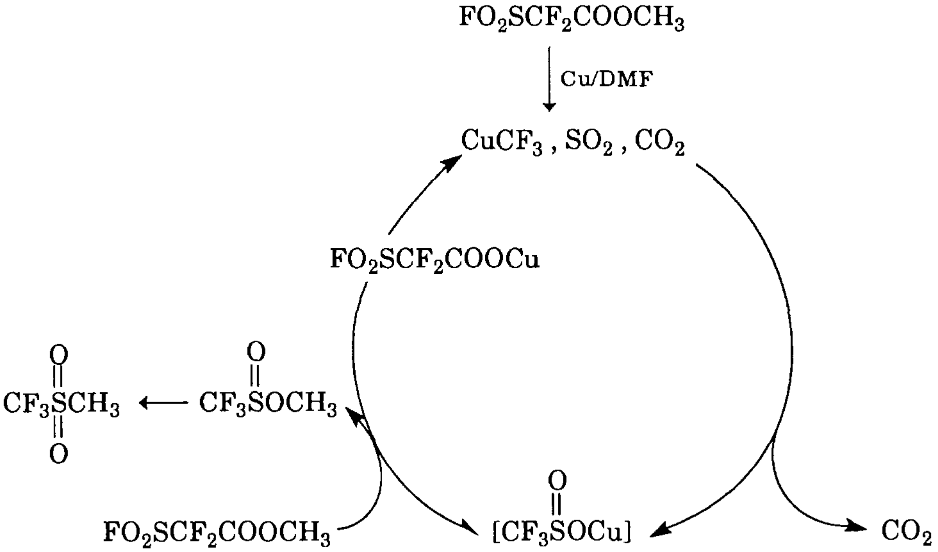
Scheme 4.

$$FO_2SCF_2COOCH_3 + RX \xrightarrow{CuI} RCF_3 + CH_3X + CO_2 + SO_2$$

Scheme 5.

All these results seem to show that the reaction of **1** with or without organic halides in the presence of catalytic amounts of copper can be rationalized in terms of a copper-induced electron-transfer process. First, an electron transferred from the copper to **1** gives Cu^+ and the corresponding radical anion, which decomposes to yield $[:CF_2]$ with the simultaneous elimination of SO_2, CO_2 and the methyl radical. The difluorocarbene combines with F^- to form $[CF_3^-]$, which can be immediately stabilized by combination with Cu^+ to form $[CuCF_3]$, whereas $CH_3\cdot$ abstracts a hydrogen atom from the solvent to give CH_4 (Scheme 4). Organic halides react with $CuCF_3$ to afford the final product, RCF_3 and CuX. Because **1** and CuI are able to give the same products in the presence of RX as described previously (Scheme 5) [3], both trifluoromethyl substitution of $[CF_3CuI]^-$ and $CuCF_3$ on alkyl halides may be involved.

The fact that no methane has been detected in the reaction system $FO_2SCF_2COOCH_3$/CuI in DMF (Scheme 5) suggests that copper is essential to form methane; indeed with 30% methane being collected in the process, this may imply that these two approaches can proceed competitively.



Scheme 6.

In the absence of RX and at temperatures up to 100 °C, the $CuCF_3$ generated would combine with SO_2 to produce $[\mathrm{CF_3\overset{\overset{O}{\|}}{S}OCu}]$, which could then react with **1** to form $\mathrm{CF_3\overset{\overset{O}{\|}}{S}OCH_3}$ and unstable $FO_2SCF_2CO_2Cu$. The $\mathrm{CF_3\overset{\overset{O}{\|}}{S}OCH_3}$ formed readily isomerizes to **4** [12], which then reacts with DMF to give **5** (see Scheme 6).

Because sulfur dioxide is very easily reduced [13], copper may transfer an electron to sulfur dioxide to form a radical anion, *i.e.* $SO_2^{\bullet -}$, which can react readily with $CuCF_3$ to yield the intermediate CF_3SO_2Cu, as described in Scheme 7.

$$Cu + SO_2 \rightleftharpoons Cu^+SO_2^{\bullet -}$$

$$Cu^+SO_2^{\bullet -} + CuCF_3 \longrightarrow CF_3SO_2Cu + Cu$$

Scheme 7.

When the reaction was catalyzed by copper(I) iodide, triflone was also obtained in comparable yield. The mechanism of this process is not very clear and is still under investigation.

Acknowledgement

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References

1 (a) R. Filler and Y. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, Kodonsha and Elsevier, New York, 1982; (b) R. E. Banks, *Organic Compounds and their Applications*, Ellis Horwood Ltd, Chichester, 1979; (c) N. V. Konderatanko, E P. Vechirk and L. M. Yagupolskii, *Synthesis*, (1980) 932; (d) K. Matsui, E. Tobita, M. Ando and K. Kondo, *Chem. Lett.*, (1981) 1719; (e) T. Umemoto and S. Ishihara, *Tetrahedron. Lett.*, *25* (1990) 3579.

2 (a) D. J. Burton and D. M. Wiemers, *J. Am. Chem. Soc.*, *107* (1985) 5014; (b) D. M. Wiemers and D. J. Burton, *J. Am. Chem. Soc.*, *108* (1986) 832; (c) T. Kitazume and N. Ishikawa, *Chem Lett.*, (1981) 1679.

3 Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc.*, *Chem. Commun.*, (1989) 705.

4 Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc.*, *Perkin Trans. 1*, (1989) 2385.

5 M. A. Dimitriev, G. A. Sokolski and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1960) 1227; D. C. England, M. A. Dietrich and R. V. Lindsey, *J. Am. Chem. Soc.*, *82* (1960) 7181.

6 H. Freiser, M. E. Hobbs and P. M. Gross, *J. Am. Chem. Soc.*, *71* (1949) 111.

7 N. V. Kondratenko, E. P. Vechirko and L. M. Yagupolskii, *Synthesis*, (1980) 932.

8 *US Pat. 3 408 411* (1968) to V. C. R. McLoughlin and J. Thrower; *Chem. Abstr.*, *70* (1969) 57375.

9 L. M. Yagupolskii and Yu. A. Fialkov, *Zh. Obshch. Khim.*, *30* (1960) 1293.

10 A. F. Benning and H. B. Gottlieb, *US Pat. 2 273 922* (1942); *Chem. Abstr.*, *36* (1942) 3812.

11 W. E. Truce, G. H. Birum and E. T. McBee, *J. Am. Chem. Soc.*, *74* (1952) 3594.

12 J. B. Hendrickson and P. L. Shipper, *Tetrahedron*, *32* (1976) 1627.

13 H. J. Wille, D. Knittel, B. Kastening and J. Meryel, *J. Appl. Electrochem.*, *10* (1980) 489.