Trifluoromethylation of organic halides with methyl halodifluoroacetates — a process via difluorocarbene and trifluoromethide intermediates

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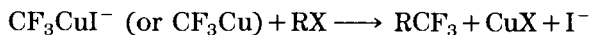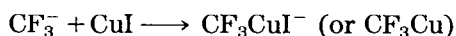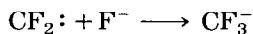
Abstract

Treatment of methyl halodifluoroacetates, XCF_2CO_2Me (X = Cl, Br, I), with organic halides RY in the presence of KF and CuI at an appropriate temperature in DMF gave the corresponding trifluoromethylated derivatives, RCF_3, in moderate to high yields. A process involving difluorocarbene and trifluoromethide intermediates is suggested.

Introduction

In the past years, considerable efforts have been devoted to develop novel methods for introducing the trifluoromethyl group into organic compounds because of their effect on physicochemical properties and biological activities [1]. Numerous trifluoromethylating agents have been employed for the trifluoromethylation of aryl halides. Recently, the following trifluoromethylation approaches were proposed: CF_2XY/M (XY = Cl, Br; M = Zn, Cd/CuI) [2], ICF_2SO_2F/Cu [3a] and $FSO_2CF_2CO_2Me/CuI$ [3b]. They are characterized by the formation of the trifluoromethide ion from difluorocarbene and fluoride ion during their decomposition.

$$CF_2\!: + F^- \longrightarrow CF_3^-$$

$$CF_3^- + CuI \longrightarrow CF_3CuI^- \text{ (or } CF_3Cu)$$

$$CF_3CuI^- \text{ (or } CF_3Cu) + RX \longrightarrow RCF_3 + CuX + I^-$$

Based on this possible mechanism, we envisaged the use of methyl halodifluoroacetates, XCF_2CO_2Me (X = Cl (**1a**), Br (**1b**), I (**1c**)) for the purpose. All these acetates are readily available or can be easily prepared in the laboratory (see Experimental section). Methyl chlorodifluoroacetate (**1a**) has been employed either as a precursor of difluorocarbene [4] or as a source of the chlorodifluoromethide ion [5]. Whereas methyl bromodifluoroacetate (**1b**) was also capable of producing the bromodifluoromethide ion [5], no

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difluorocarbene generation was apparent. With methyl iododifluoroacetate (**1c**), only the Reformatsky reaction with carbonyl compounds and coupling reactions with organic halides or alkene have been reported [6], i.e. neither the generation of the iododifluoromethide ion nor of difluorocarbene has been reported from **1c**. In a preliminary paper [7], we briefly indicated that **1a** could be utilized as a trifluoromethylating reagent for organic halides through the agency of difluorocarbene and trifluoromethide intermediates. This new methodology has now been extended to compounds **1b** and **1c**. We report the detailed results in this paper.

Experimental

All boiling points are reported uncorrected. ^{1}H NMR spectra were obtained on EF-360 (60 MHz) and XL-200 (200 MHz) NMR spectrometers. CDCl$_3$ was used as the solvent with TMS as the external reference. ^{19}F NMR spectra were obtained on an EM-360L (60 MHz) NMR spectrometer with CFCl$_3$ as the external reference (negative for upfield shifts). Mass spectra was recorded with a GC–MS model 4021 spectrometer. All reagents and solvents were purified prior to use.

Compound **1a** is obtainable from Aldrich and can also be prepared as follows: treatment of chlorotetrafluoroethyl iodide (**2**) (prepared by bubbling tetrafluoroethylene into ICl) with fuming sulfuric acid gave ClCF$_2$COF which was then reacted with methanol to afford **1a**. The overall yield was nearly quantitative. Compound **1b** was prepared via methods described in ref. 8, while compound **1c** was synthesized according to those given in ref. 6.

Trifluoromethylation of organic halides RY with 1 in the presence of KF and CuI in DMF

The typical procedure employing **1a** was as follows. A mixture of dry KF (0.58 g, 10 mmol), CuI (2.0 g, 10 mmol), C$_6$H$_5$I (2.0 g, 10 mmol) and DMF (30 ml) was placed in a 50 ml three-necked round-bottomed flask fitted with stirrer bar, dry ice condenser and thermometer. The solution was heated to 120 °C under an N$_2$ atmosphere for 0.5 h. Then ClCF$_2$CO$_2$Me (**1a**) (2.89 g, 10 mmol) was added over 3 h and the contents stirred for a further 4 h. After reaction was completed, the reactants were poured into ice water (200 ml). The solution was filtered and the residue washed with ethyl ether (3×20 ml) and the aqueous layer was extracted with ethyl ether (3×20 ml). The combined extract was washed with water (30 ml) and dried over Na$_2$SO$_4$. After evaporation of the ether, distillation gave **3a** (1.3 g, 88% yield). Gases evolved from the reaction mixture were identified as CH$_3$Cl, F$_2$C=CF$_2$ and CF$_3$H by GC–MS methods. The reaction data are summarized in Table 1 and the relevant analytical data are as follows.

Compound **3a**: b.p., 102–103 °C (lit. value [9], 102.7 °C). ^{1}H NMR δ: 6.57–6.88 (m) ppm. ^{19}F NMR δ: −66 (s) ppm. MS (*m/e*): 146 (M$^+$, 78.2); 145 (M$^+$−1, 39.6); 77 (M$^+$−CF$_3$, 42.5); 69 (CF$_3$, 100); 127 (M$^+$−F, 95.2).

TABLE 1

Reaction of **1a** with **2** in the presence of KF and CuI (**1a/2/KF/CuI** = 2:1:1:1)[a]

Entry No.	RX	Temp. (°C)	Time (h)	Yield of **3** (%)[b]
1	**2a**	120	8	88
2[c]		100	8	80
3[d]		110–120	8	10
4	**2b**	110–120	8	60
5	**2c**	110–120	8	82
6	**2d**	110–120	8	85
7	**2e**	110–120	8	81
8	**2f**	110–120	8	84
9	**2g**	110–120	8	46
10	**2h**	100–120	8	94
11	**2i**	100	8	81[e]
12	**2j**	100	8	89
13	**2k**	100	10	56
14	**2l**	110–120	8	5

[a]In DMF, unless noted otherwise.
[b]Isolated yields based on **2**.
[c]In HMPA.
[d]In the absence of KF.
[e]No $p\text{-}CF_3C_6H_4CF_3$ was detected.

The procedures for **1b** and **1c** were similar to that of **1a** except for different reaction temperatures and times. The results are listed in Table 2. All the trifluoromethylated compounds obtained were known and their physical constants (b.p. ^{1}H NMR, ^{19}F NMR, MS) were the same as those for authentic samples.

Results and discussion

Heating methyl chlorodifluoroacetate (**1a**) with organic halides RY (**2**) in the presence of equivalent quantities of copper iodide and potassium fluoride in dimethylformide (DMF) for 7–8 h at 100–120 °C gave the corresponding trifluoromethylated compounds RCF_3 (**3**) in moderate to high yields with the simultaneous elimination of CO_2 and methyl halides. The results with various organic halides are listed in Table 1.
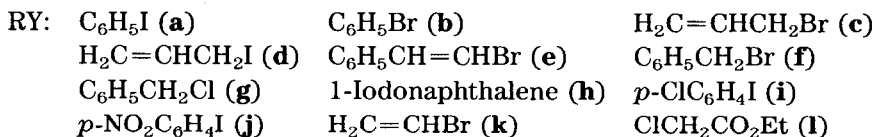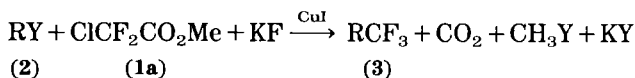
$$RY + ClCF_2CO_2Me + KF \xrightarrow{CuI} RCF_3 + CO_2 + CH_3Y + KY$$
(2)   (1a)   (3)

RY: C_6H_5I (**a**) C_6H_5Br (**b**) $H_2C{=}CHCH_2Br$ (**c**)
   $H_2C{=}CHCH_2I$ (**d**) $C_6H_5CH{=}CHBr$ (**e**) $C_6H_5CH_2Br$ (**f**)
   $C_6H_5CH_2Cl$ (**g**)   1-Iodonaphthalene (**h**) $p\text{-}ClC_6H_4I$ (**i**)
   $p\text{-}NO_2C_6H_4I$ (**j**) $H_2C{=}CHBr$ (**k**) $ClCH_2CO_2Et$ (**l**)

TABLE 2

Reaction of **1b** and **1c** with **2** in the presence of KF and CuI (1/2/KF/CuI = 2:1:1:1) at 85–90 °C and 80 °C for 5 h, respectively[a]

Entry No.	1b + 2	Yield of 3 (%)[b]	1c + 2	Yield of 3 (%)[c]
1	2a	81	2a	75.4
2[d]	2a	79		
3[e]	2a	25		
4	2b	67.2	2b	61
5	2c	70.2	2c	81.2
6	2d	72.9		
7	2f	60.7	2f	62
8	2g	41	2g	32
9	2h	84.2		
10	2j	80.2		
11	2k	67.5		
12[f]	2m	70.8		

[a]In DMF, unless noted otherwise.
[b]Isolated yields based on **2**.
[c]Determined by ^{19}F NMR spectroscopy.
[d]In HMPA.
[e]Without KF.
[f]**2m** = 1-bromonaphthalene.

As expected, the bromo- and iodo-difluoroacetates **1b** and **1c** also reacted with **2** to give the trifluoromethylated products (**3**) under similar conditions except for lower reaction temperatures (for **1b**, 85–90 °C; for **1c**, 80 °C). The data obtained are shown in Table 2.

$$XCF_2CO_2Me + RY + KF \xrightarrow{CuI} RCF_3 + CH_3Y + CO_2 + KX$$

$$(1) \qquad (2) \qquad\qquad (3)$$
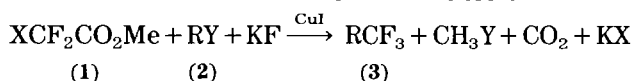
X = Br (**1b**)
RY = **2a–2d**, **2f–2h**, **2j**, **2k** and **2m** (**2m** = 1-bromonaphthalene)
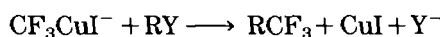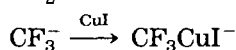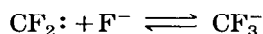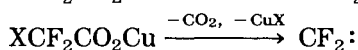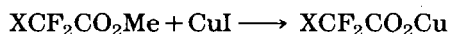X = I (**1c**)
RY = **2a–2c**, **2f** and **2g**

DMF is a suitable solvent for the reaction although hexamethylphosphoric amide (HMPA) can also be used with comparable yields.

The results in Tables 1 and 2 show the order of reactivity to be RI > RBr ≫ RCl, although the use of the bromo derivatives is also quite efficient. However, the chlorine in p-chloroiodobenzene (**2i**) (Entry 11 in Table 1) was not displaced after substitution of the iodine by a trifluoromethyl group even in large excess (**1a/2i** = 2:1).

The presence of CuI was essential for reaction. In its absence, **2a** did not react with **1a** and **1b** at 120 °C and at 85–90 °C, respectively, over 5–8 h. Substituting CuCl for CuI did not lead to the decomposition of **1a** which was completely recovered. The use of 1 equiv of KF was necessary, otherwise the yield was quite low (see Entry 3 in Table 1 and Entry 3 in Table 2).

The gases evolved from the reaction were identified by GC–MS methods as CH_3Cl or a mixture of CH_3Cl and CH_3Br, a trace of $F_2C=CF_2$, CF_3I and CF_3H. No CH_3F, HCF_2Cl (for **1a**), HCF_2Br (for **1b**) and halodifluoromethylated products (RCF_2Cl for **1a** and RCF_2Br for **1b**) were detected. Addition of 2,3-dimethylbutene, a trapping agent for CF_2:, to the reaction mixture of **1a** or **1b** and **2a** in the presence of CuI and KF gave no cyclopropane derivatives; only **3a** was obtained. As expected, **2l** reacted with **1a** to give **3l** but only in very poor yield [10].
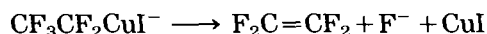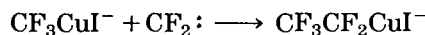
The results can be rationalized by the sequence shown below. The formation of the CuI salt of **1** (or a complex) [6] followed by its decarboxylation yields CF_2: which reacts with F^- to establish an equilibrium with CF_3^-. In the presence of CuI, the equilibrium is readily shifted to the right to give the species CF_3CuI^- which reacts with organic halides to afford the final products.

$$XCF_2CO_2Me + CuI \longrightarrow XCF_2CO_2Cu$$

$$XCF_2CO_2Cu \xrightarrow{-CO_2, \ -CuX} CF_2:$$

$$CF_2: + F^- \rightleftharpoons CF_3^-$$

$$CF_3^- \xrightarrow{CuI} CF_3CuI^-$$

$$CF_3CuI^- + RY \longrightarrow RCF_3 + CuI + Y^-$$

Because of the absence of HCF_2X and halodifluoromethylated compounds from the products, the halodifluoromethide ion, CF_2X^- ($X = Cl$, Br, I), does not seem to exist in the reaction contrary to the situation in the decomposition of **1** with LiBr (LiCl) [5]. Hence the decarboxylation of the salt is a concerted rather than a stepwise process. As **1** is inert to CuCl, and CH_3Cl and/or CH_3Br are present in the reaction mixture, it appears that CH_3I reacts with CuX ($X = Br$, Cl) to give the halomethane CH_3Cl and/or CH_3Br and regenerate CuI during the reaction. A control experiment has proved this possibility. Treatment of CH_3I with CuCl in DMF at 120 °C for 8 h led to CH_3Cl in almost quantitative yield:

$$CH_3I + CuCl \longrightarrow CH_3Cl + CuI$$
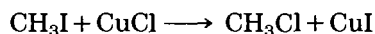
The trace of $F_2C=CF_2$ and HCF_3 observed may be ascribed to the following reactions:

$$CF_3CuI^- + CF_2: \longrightarrow CF_3CF_2CuI^-$$

$$CF_3CF_2CuI^- \longrightarrow F_2C=CF_2 + F^- + CuI$$

$$CF_3^- + H_2O(trace) \longrightarrow CF_3H$$

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