A NOVEL TRIFLUOROMETHYLATION METHOD OF SATURATED ORGANIC HALIDES

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Abstract: Treatment of methyl chlorodifluoroacetate with aliphatic halides
in the presence of equivalent ammount of potassium fluoride,copper iodide
and cadmium iodide at 120°C in HMPA for 8 h gave the corresponding tri-
fluoromethyl derivatives in moderate yields.

Recently, much attention has been devoted to finding novel methods for
introducing the trifluoromethyl group into organic compounds because of
increasing demands in medicine and biochemistry[1]. Although numerous tri-
fluoromethylating reagents for organic halides have been reported[2], they
are generally succeeded only in displacement of halogens in aryl, benzyl,
vinyl and allyl halides. To our knowledge few "genuine" saturated organic
halides could be trifluoromethylated by known methods.The only one example
was the trifluoromethylation of n-decyl iodides with pre-prepared $CF_3Cu/$
hexamethylphosphoric amide(HMPA) in 48% yield by Kabayashi[3].The report on
the synthesis of 1,1,1-trifluoroheptane from hexyl iodide and sodium tri-
fluoroacetate is now recognized as erroneous[4]. In connexion with our
recent finding that methyl halodifluoroacetate is a good trifluoromethyl-
ating agent[2b,2c], it would be interesting to develop it for trifluoro-
methylating the saturated alkyl halides. This paper presents the results
of using methyl chlorodifluoroacetate or bromodifluoroacetate in the pre-
sence of a co-catalyst, i.e. copper(1) iodide and cadmium iodide as the
trifluoromethylating agent.

Treatment of methyl chlorodifluoroacetate(1) with saturated alkyl hali-
des(2) in the presence of equivalent ammount of potassium fluoride,copper
iodide and cadmium iodide in HMPA at 120°C for 6-8 h gave the correspond-

ing trifluoromethyl derivatives (3) in satisfactory yields with simultaneous elimination of CO_2 and methyl iodide (see Table 1).

$$XCF_2CO_2Me + RY + KF \xrightarrow{\text{CuI, CdI}_2} RCF_3 + CO_2 + MeX(Y)$$
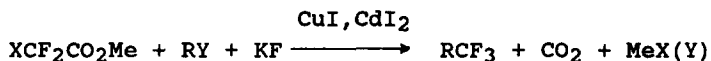
$$\text{(1)} \qquad \text{(2)} \qquad\qquad \text{(3)}$$

X=Cl(**1a**), Br(**1b**)

RY: n-$C_8H_{17}I$(a)   n-$C_7H_{15}Br$(b)   n-C_4H_9I(c)

            n-C_4H_9Br(d)   n-$C_6H_{13}Br$(e)   n-C_3H_7I(f)

            CH_3I(g) CH_2I_2(h)   Cyclohexyl bromide(i)

Table 1   Reaction of (**1**) with (**2**) in the presence of potassium fluoride, copper iodide and cadmium iodide (**1**:**2**:KF:CuI:CdI_2=2:1:1:1:1) in HMPA for 6-8h[a]

Entry	1	RY	T/°C	Conv.% of 2	3%[b]
1	**1a**	**2a**	120	73	77
2	**1a**	**2b**	120	43	73
3	**1a**	**2c**	120	75	74
4	**1a**	**2d**	120	41	67
5	**1a**	**2e**	120	37	72
6	**1a**	**2f**	120	71	73
7	**1a**	**2g**	110	74	81
8	**1a**	**2h**	120	81	78[c]
9	**1b**	**2a**	90	70	72
10	**1b**	**2b**	95	44	69
11	**1b**	**2g**	90	71	75
12	**1b**	**2i**	90	43	68

a: all the products were known and their MS, ^{19}F NMR and ^{1}H NMR were consistent with those of the authentic samples.

b: isolated yield based on the conversion of **2**.
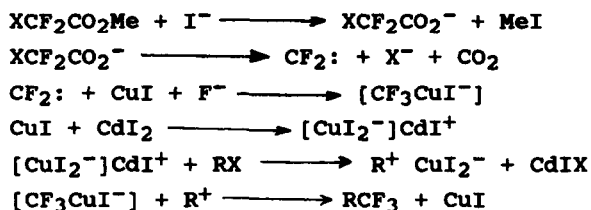
c: only ICH_2CF_3 was obtained.

The suitable reaction temperature for **1a** was 120°C, for **1b** 90°C and the yields with **1a** or **1b** were comparable.

The results in Table 1 show that the alkyl iodides are more reactive

than the corresponding bromides, though the use of bromoderivatives was also effective. However alkyl chlorides did not react with 1 under the similiar conditions.

The presence of copper iodide and cadmium iodide was essential to the reaction, in the absence of either ones, no trifluoromethylated products were obtained. As expected, diiodomethane only gave monosubstituted derivative, ICH_2CF_3 [5]. In the absence of alkyl halides, a small ammount of CF_3CH_3 (10%) and CH_3Cl (60% yield based on 1a) was obtained. Gases evolved from the reaction were identified by GC - MS to be CO_2 and a small amount of CF_3H and $CF_2=CF_2$.

The mechanism of the trifluoromethylation of alkyl halides might be proposed as follows: The first step is the attack of iodide ion on methyl carbon of 1 to afford the corresponding copper salt, followed by its decomposition in a concerted process to give difluorocarbene and CO_2. The combination of difluorocarbene with fluoride ion added and copper iodide produces trifluoromethyl copper complex $[CF_3CuI^-]$[2b,2c]. The complex then reacts with alkyl cation, generated in situ from alkyl halides with CdI_2 and CuI[6] to give the final products:

$$XCF_2CO_2Me + I^- \longrightarrow XCF_2CO_2^- + MeI$$
$$XCF_2CO_2^- \longrightarrow CF_2: + X^- + CO_2$$
$$CF_2: + CuI + F^- \longrightarrow [CF_3CuI^-]$$
$$CuI + CdI_2 \longrightarrow [CuI_2^-]CdI^+$$
$$[CuI_2^-]CdI^+ + RX \longrightarrow R^+ CuI_2^- + CdIX$$
$$[CF_3CuI^-] + R^+ \longrightarrow RCF_3 + CuI$$

The terminal alkenes(detected by GC-MS) obtained from the reaction of 1a with 2a or 2b (5% and 8%,respectively) may be a good indication of the existence of carbonium ion.

The byproducts fluoroform and tetrafluoroethylene may come from reactions of $[CF_3CuI]^-$ with H_2O and dimerization of difluorocarbene respectively[2b]:

$$CF_3CuI^- + H_2O \longrightarrow CF_3H$$
$$2CF_2 \longrightarrow CF_2=CF_2$$
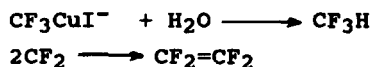
Typical procedure for the reaction may be described as follows: To a three necked 50 mL round-bottomed flask, equipped with dry ice condensor, thermometer and magnetic stirrer, a mixture of CuI (2.0g 10mmol), CdI_2 (3.5g, 10mmol), dry KF (0.58g 10mmol), HMPA (30 mL), $ClCF_2CO_2Me$ (2.9g, 20mmol) and $n-C_8H_{17}I$ (2.0g, 10mmol) was added under nitrogen atomosphere.

After heating at 120°C for 8h. The reaction mixture was poured into H_2O, the residue was filtered off and the solution was extracted with ethyl thermometer and magnetic stirrer, a mixture of CuI (2.0g 10mmol), CdI_2 ether (3 X 30 mL). The combined extracts were dried over Na_2SO_4. After evaporated off the ether, distillation(110-113°C) gave 3a[7](1 g,Yield 77%) and 2a(0.54g, recovery 27%).

3a: $_F$(solvent: $DCCl_3$) -65.2 ppm, $_H$ 2.1 ppm (m, 2H), 0.8-1.5ppm (m, 15H). m/z 182(M^+, 4.3), 113($C_8H_{17}^+$,2.3),84($C_6H_{12}^+$,34.0),70($C_5H_{10}^+$,55.4), 69(CF_3^+, 14.2), 43($C_3H_7^+$, 82.4), 41($C_3H_5^+$, 100).

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