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METHYL CHLORODIFLUOROACETATE A CONVENIENT TRIFLUOROMETHYLATING AGENT

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Summary: Treatment of methyl chlorodifluoroacetate with organic halides in the presence of KF and CuI at 100-120°C for 7 -8 h in DMF gave the corresponding trifluoromethylated derivatives in moderate to high yields.

In the past years, considerable effort has been devoted to develop novel methods for introducing trifluoromethyl group into organic compounds because of its effect on physicochemical properties and biological activities[1]. Recently, the following trifluoromethylating 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] all of which involved the formation of CF_3^- from $:CF_2$ and F^-. We envisaged the use of methyl chlorodifluoroacetate (**1**) for the purpose. The compound **1** is readily available[4], and has been employed either as a precursor of difluorocarbene or as a source of chlorodifluoromethide ion[5]. We report here the preliminary account of **1** with halogen compounds.

Heating **1** with organic halides **2** in the presence of KF and CuI in DMF gave the corresponding trifluoromethyl compounds **3** in moderate to high yields with simultaneous elimination of CO_2 and methyl halides. The results with various organic halides are listed in Table.

$$\underset{\mathbf{1}}{ClCF_2CO_2Me} + \underset{\mathbf{2}}{RX} \xrightarrow{KF} \underset{\mathbf{3}}{RCF_3} + CH_3X + CO_2 + KF$$

RX: **a** C_6H_5I, **b** C_6H_5Br, **c** CH_2=CH-CH_2Br, **d** CH_2=CH-CH_2I, **e** C_6H_5CH=CHBr, **f** $C_6H_5CH_2Br$, **g** $C_6H_5CH_2Cl$, **h** 1-Iodonaphthalene, **i** p-ClC_6H_4I, **j** p-$NO_2C_6H_4I$, **k** CH_2=CHBr, **l** $ClCH_2CO_2Et$

Typical procedure: Copper(I) iodide (2.0g, 10mmol), dry KF (0.58g, 10mmol), **2a** (2.04g, 10mmol), and **1** (2.90g, 20mmol) in DMF (20mL) were heated with stirring to 120°C for 8 h under nitrogen atmosphere. After the reaction mixture was treated as described before[3], **3a** was obtained in 88% yield (1.28g).

The presence of CuI is essential to the reaction; in its absence, **2a** did not react with **1** in DMF at 120°C. CuCl instead of CuI did not decompose **1** which was recovered completely. An equivalent of KF is necessary, otherwise the yield was quite low. Gases evolved from the reaction were identified by GC-MS to be CH_3Cl or a mixture of CH_3Cl and CH_3Br, and a trace of C_2F_4, CF_3I and CHF_3. No CH_3F, HCF_2Cl and chlorodifluoromethylated products were detected. Addition of 2,3-dimethylbut-2-ene, a trapping agent for $:CF_2$, to the reaction mixture of **1** and **2a** in the presence of CuI and KF gave no cyclopropane derivative; only **3a** was obtained. As expected, the chloride **2l** gave only a poor yield of **3l**[6].

The results can be rationalized by the sequence shown below. The first formation of Cu salt from **1** (or complex)[3] followed by its decarboxylation produces $:CF_2$, which with added F^- is in equilibrium with CF_3^-. In the presence of CuI, the equilibrium readily shifts to CF_3CuI^-, which reacts with organic halide to give the trifluoromethylated products.

Dedicated to Professor Qi-Yi Xing on the occassion of his 80th birthday

Table. Reactions of **1** with **2** in the presence of KF and CuI (**1**:**2**:KF:CuI=2:1:1:1)[a]

Entry	RX	Temperature (°C)	Period (h)	Yield of **3**[b] (%)
1	**2a**	100-120	8	88
2[c]	**2a**	100	8	80
3	**2b**	110-120	8	60
4	**2c**	110-120	8	82
5	**2d**	110-120	8	85
6	**2e**	110-120	8	81
7	**2f**	110-120	8	84
8	**2g**	110-120	8	46
9	**2h**	100-120	8	94
10	**2i**	100	8	81[d]
11	**2j**	100	8	89
12	**2k**	100	10	56
13	**2l**	110-120	8	5

a: In DMF unless noted otherwise. b: Isolated yields based on **2**, all the products are known and their physical constants (^1H, ^{19}F NMR, MS) are consistent with those of the authentic samples. c: In HMPA. d: No p-$CF_3C_6H_4CF_3$ was detected.

$$ClCF_2CO_2Me + CuI \longrightarrow ClCF_2CO_2Cu + CH_3I$$

$$ClCF_2CO_2Cu \xrightarrow{-CO_2,\ -CuCl} CF_2: \underset{}{\overset{F^-}{\rightleftharpoons}} CF_3^- \underset{}{\overset{CuI}{\rightleftharpoons}} CF_3CuI^- \xrightarrow{RX} RCF_3 + CuI + X^-$$

Because HCF_2Cl and the compound with $ClCF_2$ group are absent in the products, the CF_2Cl^- seems to be absent in the reaction in contrary to the case of the decomposition of **1** by LiCl[5]. Therefore the decomposition 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 implies that CH_3I reacted with CuI to give CH_3Cl and regenerated CuI during the reaction. Control experiment has proved the possibility. The trace of $CF_2{=}CF_2$ and CHF_3 observed may be ascribed to the following reaction.

$$CF_3CuI^- + :CF_2 \longrightarrow CF_3CF_2CuI^- \longrightarrow CF_2{=}CF_2 + F^- + CuI$$

$$CF_3^- + H_2O(\text{trace}) \longrightarrow CF_3H + OH^-$$

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References and Notes:

1. R. Filler, Y. Kobayashi. "*Biomedicinal Aspects of Fluorine Chemistry*", Elsevier, Amsterdam, **1982**. N. Dieter, K. Juergen, *J. Fluorine Chem.*, **1990**, *46*, 265; J. H. Clark, M. A. McClinton, C. W. Jones, D. Bishop, R. J. Blade, *Tetrahedron Lett.*, **1989**, *30*, 2133; M. Zupan, Z. Bregar, *ibid.*, **1990**, *23*, 3357
2. D. J. Burton, D. M. Wiemers, *J. Am. Chem. Soc.*, **1985**, *107*, 5014; **1986**, *108*, 832.
3. a. Q.-Y. Chen, S.-W. Wu, *J. Chem. Soc.*, Perkin Trans. 1, **1989**, 2385. b. *Idem. J. Chem. Soc., Chem. Commun.*, **1989**, 705.
4. Compound **1** is in Aldrich Catalog and can also be prepared in laboratory as follows: Treatment of 2-chloro-1-iodotetrafluoroethane, prepared by bubbling tetrafluoroethene into ICl, with fuming sulfuric acid gives $ClCF_2COF$ which then is reacted with methanol to afford **1**. The overall yield is nearly quantitative.
5. G. A. Wheaton, D. J. Burton, *J. Fluorine Chem.*, **1977**, *9*, 25. *Idem. J. Org. Chem.* **1978**, *13*, 2643
6. Y. Kobayashi, K. Yamamoto, and I. Kumadaki, *Tetrahedron Lett.* **1979**, 4071.

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