Methyl 3-Oxo- ω -fluorosulfonylperfluoropentanoate: a Versatile Trifluoromethylating Agent for Organic Halides

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Methyl 3-oxo- ω -fluorosulfonylperfluoropentanoate FSO₂CF₂CCP₂CCP₂CO₂Me 1, prepared through the reaction of readily available ICF₂CF₂OCF₂CF₂SO₂F and SO₃ followed by MeOH, is a very convenient trifluoromethylating agent; in the presence of copper(ι) iodide, 1 not only reacts with vinyl, benzyl allyl, phenyl iodides and bromides, but also with aryl chlorides to give the corresponding trifluoromethyl compounds in moderate to high yield; a probable reaction mechanism is proposed.

Owing to the increasing interest of trifluoromethylated compounds in biochemistry and material science,1 various methods for introducing trifluoromethyl groups into organic molecules have been reported, 2 e.g. fluorination of carboxylic acid with SF_4 , 3 conversion of CX_3 to CF_3 group with Swarts' reagent⁴ and addition of the trifluoromethyl radical to unsaturated molecules.5A widely used trifluoromethylating agent is trifluoromethylcopper or its complex, which is prepared from copper powder with CF₃I,⁶ (CF₃)₂Hg,⁷ CF₃N(NO)SO₂CF₃⁸ or CF₃SiMe₃/CuI.⁹ Using a copper anode, an electrochemical method for preparing this species employing the low cost and readily available CF₃Br¹⁰ has been reported. Recently, a number of reports described the utilization of compounds containing the difluorocarbene moiety as precursors to trifluoromethylcopper, such as $CF_2XY(X=Y=Br;X=Br,Y=Cl)$, 11 ICF_2SO_2F , 12 $XCF_2CO_2Me^{13}$ (X=FSO₂, Cl, Br, I) and BrCF₂CO₂K.¹⁴ All the reagents have been found to react with vinyl, allyl, benzyl and aryl iodides and bromides.

$$FSO_{2}CF_{2}CF_{2}CCF_{2}CO_{2}Me + CuI \longrightarrow FSO_{2}CF_{2}CF_{2}CCF_{2}CO_{2}Cu + MeI$$

$$F + 2CF_{2}: + CF_{2}O + SO_{2} + Cu^{+}$$

$$F - C - F$$

$$F - C - F$$

$$H - C - NMe_{2}$$

$$F - C = O$$

$$CO_{2} + HCF_{2}NMe_{2} \longrightarrow HCF = NMe_{2}^{+}$$

$$F - C - NMe_{2}$$

$$F - C = O$$

Scheme 1

$$FSO_2CF_2CF_2CCO_2Me + Cul \longrightarrow 2CF_2: + 2F + 2CO_2 + SO_2$$

In the presence of the cocatalyst CdI₂–CuI, ClCF₂CO₂Me can be used to convert even genuine saturated alkyl halides into the trifluoromethylated derivatives.¹⁵ However, they are inert towards aryl chlorides unless strong electron-withdrawing groups, *i.e.* NO₂, CN, are present on the *ortho* and/or *para* position of the benzene ring.¹⁶

In connection with our previous report that methyl haloand fluoro-sulfonyldifluoroacetate¹³ are convenient trifluoromethylating agents, we envisaged that methyl 3-oxo-ωfluorosulfonylperfluoropentanoate, FSO₂CF₂CF₂OCF₂CO₂-Me, could serve this same purpose because it is analogous to XCF₂CO₂Me provided FSO₂CF₂CF₂O⁻ acts as a leaving group and we, herein, report the results.

Methyl 3-oxo-ω-fluorosulfonylperfluoropentanoate¹⁷ is easily prepared in high yield by treatment of ICF₂CF₂OCF₂CF₂SO₂F with SO₃ followed by MeOH. The starting material, ICF₂CF₂OCF₂CF₂SO₂F, is available commercially or can be produced by the reaction of tetrafluoroethylene, 1,2-tetrafluoroethanesultone, KF and ICl in diglyme.¹⁸

Treatment of FSO₂CF₂CF₂OCF₂CO₂Me with organic halides in dimethylformamide (DMF) with 1 equiv. of copper(1) iodide at 100–120 °C for 6–10 h gives the corresponding trifluoromethylated compounds. The results are listed in Table 1.

$$FSO_{2}CF_{2}CF_{2}OCF_{2}CO_{2}Me + RX \xrightarrow{DMF} \\ RCF_{3} + CO_{2} + SO_{2} + MeX \\ 3 \\ RX = a; C_{6}H_{5}I & k; p-Cl-C_{6}H_{4}CHO \\ b; p-lC_{6}H_{4}I & l; p-ClC_{6}H_{4}CO_{2}Et \\ c; p-ClC_{6}H_{4}I & m; p-ClC_{6}H_{4}NO_{2} \\ d; C_{6}H_{5}Br & n; m-ClC_{6}H_{4}NO_{2} \\ e; C_{6}H_{5}CH_{2}Br & o; 2-Cl-pyridine \\ f; C_{6}H_{5}CH=CHBr & p; p-MeO-C_{6}H_{4}Cl \\ g; 2-Br-pyridine & q; C_{6}H_{5}Cl \\ h; C_{6}H_{5}CH_{2}Cl & r; C_{6}H_{5}CH=CHCl \\ i; p-MeC_{6}H_{4}Cl & s; CH_{2}=CHCH_{2}Br \\ j; o-MeC_{6}H_{4}Cl & s; CH_{2}=CHCH_{2}Br \\ \end{bmatrix}$$

The presence of copper(1) iodide is essential to the reaction, in its absence, the ester did not decompose.

The data in Table 1 show that 1 not only reacted with benzyl, vinyl, allyl, aryl iodides and bromides, but also with the normally unreactive aryl chlorides (entry 19). Previously, we and others have reported that aryl chlorides containing ortho- and/or para-electron-withdrawing groups, such as NO₂, CF₃, react with trifluoromethylating agents, e.g. XCF₂CO₂Me(X=Cl, Br, FSO₂)¹³ and CF₂XY(X=Cl, Br)¹¹ giving trifluoromethylated derivatives in high yields whereas aryl chlorides with only one electron-withdrawing group gave very low yields. However, in the present case, aryl chlorides bearing one strong or even weak electron-withdrawing group e.g. NO₂, CHO, CO₂Et did react with 1 to afford the desired products in good yields (entries 13-16 in Table 1). Furthermore, the presence of an electron-donating group, i.e. Me, MeO, in chlorobenzene did not interfere much, though the yields were not high (entries 11, 12, 18). Different from the previous report^{12,13} that the chlorine in p-IC₆H₄Cl cannot be

Table 1 Reaction of 1 and 2 in the presence of CuI (1:2:CuI (molar ratio) = 1:1:1) in dimethylformamide

Entry	RX	<i>t</i> /h	T/°C	Yields 3 (%)a
1	2a	8	100	80
2^b	2a	6	100	61
2 ^b 3	2b	8	100	62^c
4	2c	8	100	82
5^d	2c	8	120	52
6	2d	8	110	73
7	2e	8	120	62
8	2f	8	120	67
9	2g	8	120	70
10	2h	8	120	42
11	2i	8	120	34
12	2j	8	120	32
13	2k	8	120	56
14	21	8	120	52
15	2m	8	120	67
16	2n	8	120	72
17	20	8	120	64
18	2p	8	120	37
19	$\hat{\mathbf{2q}}$	8	110-120	52
20	2r	8	120	67
21	2s	8	120	81

^a Isolated yields based on 2, all the compounds are known and their ¹⁹F NMR, ¹H NMR and MS were consistent with those of the authentic samples. ^b 1:2a = 1:2, isolated yield based on 1. ^c only $p\text{-CF}_3\text{C}_6\text{H}_4\text{CF}_3$ was obtained. ^d 1:2c = 2:1 and only $p\text{-CF}_3\text{C}_6\text{H}_4\text{CF}_3$ was isolated.

displaced even using a large excess of trifluoromethylating agents, e.g. ClCF₂CO₂Me, ICF₂SO₂F, mono or bis(trifluoro)methylated products can be obtained depending on the ratio of 1 to p-IC₆H₄Cl used (entries 4, 5 in Table 1). Substitution of chlorine or bromine in 2-halopyridine without an activating group with CF₃CO₂Na/CuI/HMPA¹⁹ has been reported to be very difficult. However, using 1 as a trifluoromethylating agent for 2-chloro- and 2-bromo-pyridine, good yields of the expected products were obtained (entries 9, 17 in Table 1).

In the absence of alkyl halides, the difluorocarbene generated from 1 and copper(1) iodide was trapped by 2,3-dimethylbut-2-ene (DMB, a good difluorocarbene trapping agent) giving 1,1-difluoro-2,2,3,3-tetramethylcyclopropane in a yield of 46% (based on 1). The gases evolved from the reaction were identified by GC-MS to be CO₂, SO₂ (molar ratio nearly 2:1) and a small amount of CF₃H. Neither FSO₂CF₂CF₂OCF₂H or FSO₂CF₂H were detected.

The mechanism of the reaction, similar to that of XCF₂CO₂Me,^{11,12} may be proposed as follows. The methyl ester may first be attacked by copper iodide generating the corresponding copper salt, FSO₂CF₂CF₂OCF₂CO₂Cu. As no FSO₂CF₂CF₂OCF₂H and FSO₂CF₂H were detected, the salt formed may decarboxylate in a concerted manner to give CF₂:, F-, SO₂, CO₂ and CF₂O.²⁰ In view of the existence of difluorocarbene and the molar ratio of CO₂ to SO₂ produced being 2:1, difluorophosgene may react with DMF giving CO₂ and F-.²¹ The difluorocarbene and fluoride ion generated are in equilibrium with the trifluoromethide ion. In the presence of copper(1) iodide, the equilibrium shifts to the right in favour of the formation of trifluoromethyl copper or its complex, which then reacts with aryl halides affording the final products:

The advantage of our reagent 1 may be ascribed to the high activity, and higher concentrations of fluoride ion and difluoro-carbene generated *in situ* in the reaction. Compound 1 (1 equiv.) can produce 2 equiv. of both fluoride ion and difluorocarbene, which may favour the formation of trifluoromethyl copper or its complex in the presence of CuI. Thus, 1

is a good trifluoromethylating agent for all of organic halides especially for the unactivated aryl chlorides.

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