Direct Trifluoromethylthiolation of Aryl Halides using Methyl Fluorosulfonyldifluoroacetate and Sulfur

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In the presence of S₈ and copper(i) iodide, methyl fluorosulfonyldifluoroacetate **1** reacts with aryl halides **2** in hexamethylphosphoramide (HMPA) or *N*-methylpyrrolidinone (NMP) at 100–110 °C to give the corresponding trifluoromethylthiolated derivatives **3** in good yields.

Trifluoromethylthio and trifluoromethylsulfonyl groups are important aromatic substituents in the preparation of potential new dyes¹ and medicinal agents.² Previous methods for introducing these groups suffered from harsh conditions or toxic reagents.³ For example, the commonly used trifluoromethylthio silver and copper reagents have to be prepared from expensive silver metal at high temperature^{3b} and even in

$RX + FSO_2CF_2CO_2Me + S_2$	$\xrightarrow{\text{Cul}}$ RSCF ₂ + SO ₂ + CO ₂ + MeX
2 1	3
	60-74%
RX; 2	
$\mathbf{a} = C_6 H_5 I$	$\mathbf{b} = C_6 H_5 Br$
$\mathbf{c} = p - ClC_6H_4I$	$\mathbf{d} = \mathbf{IC}_6 \mathbf{H}_4 \mathbf{I}$
$\mathbf{e} = p \cdot \mathbf{NO}_2 \mathbf{C}_6 \mathbf{H}_4 \mathbf{I}$	$\mathbf{f} = \mathbf{C}_{10}\mathbf{H}_{7}\mathbf{I}$
$\mathbf{g} = p \cdot \mathrm{MeC}_{6}\mathrm{H}_{4}\mathrm{Br}$	

Table 1 Reaction of aryl iodides **2** with fluorosulfonyldifluoroacetate **1** in the presence of copper iodide and sulfur (mol ratio: $1:2:CuI:S_8 = 1:1:1:0.125)^a$

Entry	RX	Solvent	T/°C	t/h	3 (%) ^b
1	2a	HMPA	110	8	60
2		DMF-HMPA	100	8	51
3		NMP	100	8	57
4	2b	DMF	100	7	0
5		HMPA	100	7	0
6		NMP	100	8	43
76	2c	HMPA	100	7	63
8		NMP	100	7	61
9c	2d	HMPA	100	7	63
10		DMF	100	7	0
11	2e	HMPA	100	6	74
12	2f	HMPA	110	7	64
13	2g	NMP	100	7	41
	0				

^{*a*} Isolated yields based on **2**, all the compounds were known and gave ¹H NMR, ¹⁹F NMR and mass spectra consistent with authentic samples. ^{*b*} Only *p*-ClC₆H₄SCF₃ was detected. ^{*c*} 1:2:CuI:S₈ (molar ratio) = 2:1:2:0.25, and only *p*-CF₃SC₆H₄SCF₃ was obtained. an autoclave.^{3c} Although both bis(trifluoromethylthio)mercury $Hg(SCF_3)_2^{3a}$ and trifluoromethyldisulfide $CF_3SSCF_3^{3c}$ are good trifluoromethylthiolating agents, they are toxic and must be converted to the corresponding copper agent. The condensation of bromotrifluoromethane with potassium thiophenoxides requries dry potassium thiophenoxide and under pressure.⁴ Previously we have found⁵ that methyl fluorosulfonyldifluoroacetate **1** is a good trifluoromethylating agent.

Reaction of 1 with alkyl halides gives trifluoromethylated products and a trifluoromethyl copper complex, which was proposed to be the reaction intermediate. It has also been shown that the trifluoromethylcopper could react with sulfur to form a trifluoromethylthiocopper reagent.^{3a} Therefore, we envisaged using 1 for the synthesis of trifluoromethylthio compounds and here we report the results. Compound 1, obtained from TCI America, can also be readily obtained from the corresponding acid fluoride,⁶ which is a starting material for the commercial ion-exchange resin, Nafion-H.⁷

Treatment of aryl iodides $2,\dagger$ in the presence of an equivalent amount of copper(1) iodide and sulfur, with methyl fluorosulfonyldifluoracetate 1 in either HMPA, NMP or a cosolvent DMF (dimethylformamide)-HMPA [3:1 (v/v)] at

[†] *Typical procedure* for trifluoromethylthiolation of ArI and oxidation of **3**: CuI (2.0 g, 10 mmol), S₈ (0.32 g, 10 mmol), C₆H₅I (2.04 g, 10 mmol), FSO₂CF₃CO₂Me (10 mmol), and 30 ml HMPA were placed in a 50 ml three-necked round-bottomed flask equipped with dry ice condenser under a nitrogen atmosphere. After stirring at 100 °C for 8 h (monitored by ¹⁹F NMR), the reaction mixture was poured into 50 ml ice water, the residue was filtered and extracted with diethyl ether. The aqueous solution was filtered and extracted with diethyl ether (3 × 20 ml). The combined ether extracts were dried with anhydrous Na₂SO₄ and the diethyl ether was removed. Distillation gave **3a** C₆H₅SCF₃ (1.03 g, 60%) (70–72 °C, 350 mmHg) (lit.:⁴ 77–78 °C, 754 mmHg). $\delta_{\rm F}$ (solvent CDCl₃, standard CFCl₃, downfield positive): –42.3, $\delta_{\rm H}$ (standard Me₄Si): 6.8 (m) **3a** (1.0 g) was oxidized with H₂O₂ in AcOH at 40 °C for 5 h and gave CF₃SO₂C₆H₅ (1.0 g, 77%), b.p. 110 °C/30 mmHg (lit.:⁸ m.p. 100 °C), $\delta_{\rm H}$: 8.35–755, $\delta_{\rm F}$: –79. IR v/cm⁻¹ (film): 1595m, 1355s, 1270s, 1150s, 1075s, 775m, 720s.

$$\operatorname{ArSCF}_{3} + \operatorname{H}_{2}\operatorname{O}_{2} \xrightarrow{40 \,^{\circ}\mathrm{C}} \operatorname{ArSO}_{2}\operatorname{CF}_{3} + \operatorname{H}_{2}\operatorname{O}$$

3: 3a, b and d

Table 2 Reaction of 3 with H_2U_2 in MeCU ₂ H at 20-40°	Table	2 Reaction	of 3 with	H ₂ O ₂ in	MeCO ₂ H	at 20-40 °C
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Entry	3	<i>t</i> /h	Yield $4(\%)^a$	
1	a	6	74	
2	b	7	77	
3	d	6	73	

^a Isolated yields based on 3, all the compounds were known and gave ¹H NMR, ¹⁹F NMR and mass spectra consistent with authentic samples.

100-120 °C for 5-8 h gave the corresponding trifluoromethylthic compounds $\vec{3}$ in the yields of $6\dot{0}$ -74%.

The results listed in Table 1 show that the reaction solvent plays an important role in the reaction. If DMF alone was used, then the reaction did not occur. When a cosolvent [i.e. DMF-HMPA = 3:1 (v/v)] was employed in the reaction of 1, 2a and sulfur, the yield of 3a was reduced by 10%, compared with using HMPA; further dilution of HMPA with DMF resulted in lower yields of 3a. Bromobenzenes under similar conditions failed to react. However, it was found that NMP was a more suitable reaction solvent for both aryl iodides and bromides.[‡] For example bromobenzene and *p*-methylbromobenzene reacted with 1 and sulfur giving the expected products in moderate yield in (entries 6 and 13). Besides the role of the solvent, copper(1) iodide was also essential to the reaction, in its absence no trifluoromethylthio compounds were formed. The data in Table 1 also show that aryl iodides are more reactive than aryl bromides even in NMP. The aryl chlorides were found to be inert to reaction, e.g. the chlorine in 2c cannot be substituted by the trifluoromethylthio group. p-IC₆H₄I **2d** lead to only p-CF₃SC₆H₄SCF₃. No monosubstituted products p-IC₆H₄SCF₃ and HCF₂SO₂F were formed in any of the reactions. Gases evolved from the reaction system were shown by GC-MS to be SO₂, CO₂ and MeI.

The oxidation of 3 with H_2O_2 gave the aryl trifluoromethyl sulfone 4 in good yields, which further confirmed the

‡ We thank a referee for suggesting the use of solvents other than HMPA.

structures of the products 3. The reaction results are listed in Table 2.

The reaction mechanism may be proposed to be similar to the trifluoromethylation of 2 with organic halides⁵ as follows. The methyl ester \mathbf{i} may first be attacked by copper(1) iodide to form the copper salt FSO₂CF₂CO₂Cu with formation of methyl iodide. As no HCF2SO2F was detected in all the reactions, copper fluorosulfonyldifluoroacetate may decompose in a concerted manner giving difluorocarbene, F-, SO₂ and CO₂. In the presence of copper iodide, the difluorocarbene and F- generated combine to afford trifluoromethylcopper (or complex) which then reacts with sulfur to give trifluoromethylthiocopper. The incorporation of trifluoromethylthiocopper with aryl iodides gives the final products [see eqns. (1)-(5)].

$$FSO_2CF_2CO_2Me + CuI \longrightarrow FSO_2CF_2CO_2Cu + MeI$$
(1)

$$FSO_2CF_2CO_2Cu \longrightarrow CuF + CF_2: + SO_2 + CO_2$$
 (2)

$$CF_2: + F^- + CuI \longrightarrow CF_3CuI^-$$
 (3)

 $CF_3CuI^- + S \longrightarrow CF_3SCu + I^-$ (4)

$$CF_3SCu + ArI \longrightarrow CF_3SAr + CuI$$
 (5)

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