A New Method for the Syntheses of Aryl and Heteroaryl Trifluoromethyl Sulfides

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Aryl trifluoromethyl sulfides are obtained mainly by chlorination of aryl methyl sulfides and subsequent fluorination of the aryl trichloromethyl sulfides with antimony trifluoride[1] or hydrogen fluoride[2,3]. A disadvantage of this method is that many of the aryl trichloromethyl sulfides, especially *ortho*-substituted derivatives[3], are virtually inobtainable. For example, during chlorination of *o*-nitrothioanisole and *o*-methylthio-benzoyl chloride a splitting of the C—S bond occurs, followed by formation of the corresponding phenylsulfenyl chloride derivatives[3].

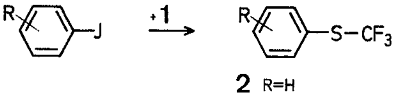
Methods are known for the direct introduction of trifluoromethylthio groups by means of heating trifluoromethylsulfenyl chloride with aromatic compounds[4] or by means of interaction of the former with arylmagnesium halides[5]. However, in the first case the reaction proceeds smoothly only if the ring contains some strong electron-donating substituents. In the absence of such substituents the use of drastic conditions and of boron trifluoride as catalyst is required. Both methods often lead to a mixture of products which are difficult to separate and thus they are not suited practically for the synthesis of aryl trifluoromethyl sulfides with electron-withdrawing substituents. Heteroaryl trifluoromethyl sulfides are even more difficult to obtain. They are generated predominantly via cyclization reactions[6].

We have developed a method for direct introduction of the trifluoromethylthio group on to aromatic and heterocyclic rings by the action of trifluoromethylthiocopper (**1**) on aryl and heteroaryl iodides. Trifluoromethylthiocopper was previously obtained[7] from bis[trifluoromethylthio] mercury and copper powder in autoclave (the yield was not reported here). An attempt to repeat this reaction led to the product in a yield not exceeding 10%.

We have found a convenient method of synthesising trifluoromethylthiocopper[8] which results in a quantitative yield and starts from accessible trifluoromethylthiosilver[9] and copper bromide in acetonitrile or tetrahydrofuran.

$$AgSCF_3 + CuBr \longrightarrow \underset{\mathbf{1}}{CuSCF_3} + AgBr$$

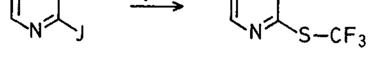
In the reactions of aryl iodides containing electron-withdrawing substituents with trifluoromethylthiocopper (**1**), the iodine atoms are smoothly replaced by the trifluoromethylthio group to give the products in 70–75% yield. As in the case of the Ullmann reaction[10], the presence of substituents in *ortho*-positions relative to the iodine atom do not decrease the yields of products resulting from the reaction.



2 R=H
3 R=4-H$_3$C
4 R=2-O$_2$N
5 R=4-O$_2$N
6 R=2-O=CH

Electron-donating substituents have a deactivating effect on this reaction, the yields being decreased to 30–55%. Excess of the initial aryl iodide can be separated by passing chlorine through the solution of products in chloroform at 0–5°. Low-soluble, high-melting aryl iododichlorides precipitate while aryl trifluoromethyl sulfides remain in solution.

The proposed method is also well-suited for synthesizing trifluoromethylthio-derivatives of nitrogen heterocycles.



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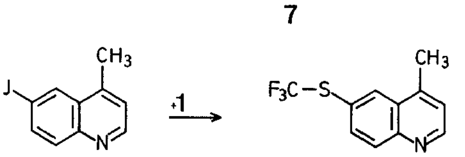

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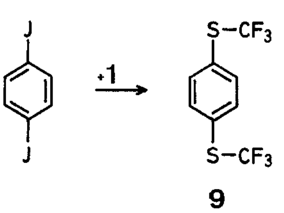
In reactions of diiodo-derivatives with trifluoromethylthiocopper both of the iodine atoms are replaced by trifluoromethylthio groups.



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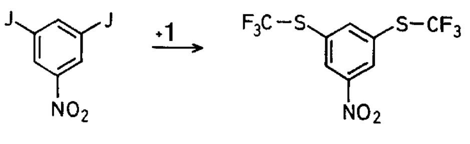

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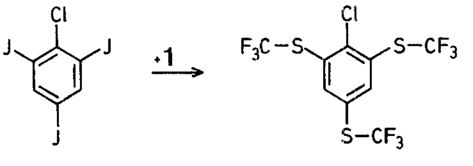
This reaction also enables the introduction of three trifluoromethylthio groups, but the yields are rather low.



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It is more reasonable to obtain 1,3,5-tris[trifluoromethylthio]-benzene (**14**) from compound **10** by successive reduction up to the appropriate amino compound **12**, transformation of this into 3,5-bis[trifluoromethylthio]iodobenzene, and reaction of the latter with trifluoromethylthiocopper (see Table 1).

Table 1. Aryl and Heteroaryl Trifluoromethyl sulfides

Compound	Yield (%)	B.p./torr	n_D^{20}	Elemental Analyses			
2[1]	55	140°/754	1.4649	—	—	—	
3[a]	30	166–167°/756	1.4707	—	—	—	
4[12]	75	122–123°/22	1.5219	—	—	—	
5[6, b]	70	125–126°/23	—	—	—	—	
6	65	95°/20	1.5073	$C_8H_5F_3OS$	calc.	F 27.71	
				(206.1)	found	27.48	
7	63	130°/754	1.4756	$C_6H_4F_3NS$	calc.	F 31.82	
				(179.1)	found	31.90	
8[c]	70	—	—	—	—	—	
9[d]	55	—	—	—	—	—	
10	75	75°/0.4	1.4969	$C_8H_3F_6NO_2S_2$	calc.	F 35.27	
				(323.2)	found	35.08	
11	30	74°/17	1.4776	$C_9H_2ClF_9S_3$	calc.	C 26.19	H 0.48
				(412.7)	found	26.24	0.48
12[e]	80	—	—	$C_8H_5F_6NS_2$	calc.	F 38.88	
				(293.2)	found	39.01	
13[f]	80	73°/0.3	—	$C_8H_3F_6JS_2$	calc.	J 31.40	
				(404.1)	found	31.61	
14[g]	60	93°/18	1.4588	$C_9H_3F_9S_3$	calc.	C 28.57	H 0.79
				(378.3)	found	28.40	0.75

[a] L. M. Yagupolskii, M. S. Marenets, N. V. Kondratenko, *Zh. Obshch. Khim.* **35**, 377 (1965).

[b] M.p. 34°.

[c] M.p. 78°. Z. Y. Krainer, P. F. Gudz, L. M. Yagupolskii, *Khim. Geterotsikl. Soedin.* **1973**, 237.

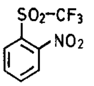
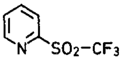
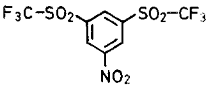
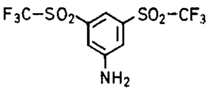
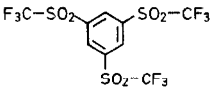
[d] M.p. 43°. L. M. Yagupolskii, V. V. Orda, *Zh. Obshch. Khim.* **34**, 1979 (1964).

[e] M.p. 56–57°.

[f] M.p. 36–37°.

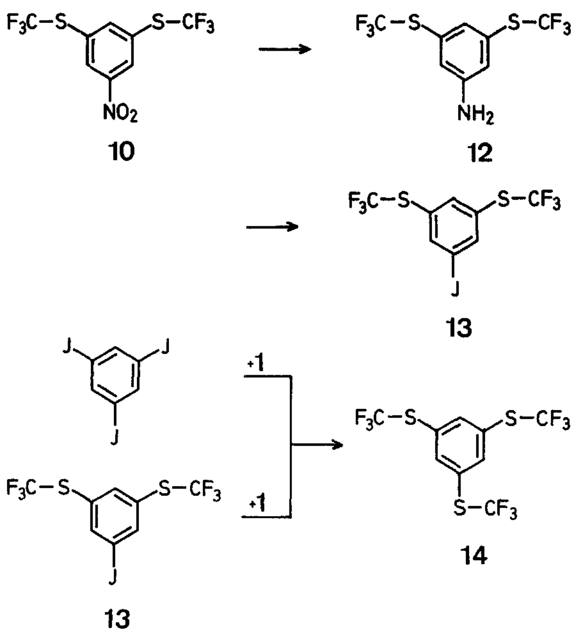
[g] ^{1}H-N.M.R. (CCl$_4$): δ (ppm) = 8.42; ^{19}F-N.M.R. (CCl$_4$): δ (ppm) = −9.54 relative to trifluoromethylbenzene, as external standard.

Table 2. Aryl and Heteroaryl Trifluoromethyl Sulfones

Compound	Chromic oxide (mol-equiv)	Time (h)	Yield (%)	m.p. (solvent)	Elemental Analyses			
	10	15	92	45–46° (pentane)	$C_7H_4F_3NO_4S$	calc.	F 22.34	
					(255.1)	found	22.50	
	8	6	60	55–56° (hexane)	$C_6H_4F_3NO_2S$	calc.	F 27.00	
					(211.1)	found	26.79	
	10	15	89	143–144° (hexane)	$C_8H_3F_6NO_6S_2$	calc.	F 29.44	
					(387.2)	found	29.80	
	—	—	80[a]	139–140° (benzene/hexane)	$C_8H_5NF_6O_4S_2$	calc.	F 31.91	
					(357.2)	found	31.67	
	12	20	80[b]	206–207° (acetone)	$C_9H_3F_9O_6S_3$	calc.	C 22.78	H 0.63
					(474.3)	found	22.70	0.70

[a] Obtained by means of reduction of 1,5-bis[trifluoromethylsulfonyl]nitrobenzene.

[b] ^{1}H-N.M.R. (acetone): δ (ppm) = 8.87; ^{19}F-N.M.R. (acetone): δ (ppm) = 14.68.



Oxidation of aryl and heteroaryl trifluoromethyl sulfides resulted in the synthesis of the corresponding sulfones. Thus, the synthesis of various compounds containing one of the most electron-withdrawing substituents known, i.e. the trifluoromethylsulfonyl group[11], has become possible. For example, oxidation of *o*-nitrophenyl trifluoromethyl sulfide leads to *o*-nitrophenyl trifluoromethyl sulfone which was previously synthesized by multi-stage methods[12], and from 1,3,5-tris[trifluoromethylthio]benzene (**14**) an analog of 1,3,5-tris[nitro]benzene was generated, i.e. 1,3,5-tris[trifluoromethylsulfonyl]benzene (see Table 2).

Trifluoromethylthiocopper:
Copper bromide (0.01 mol) is added to the solution of trifluoromethylthiosilver (0.01 mol) in dry acetonitrile (10 ml). The mixture is then stirred in a stream of nitrogen at 60–70° for 30 min. Silver bromide is filtered and acetonitrile is evaporated in vacuo; yield: 100%.

$CCuF_3S$	calc.	F 34.75
(164.61)	found	34.42

Aryl and Heteroaryl Trifluoromethyl Sulfides; General Procedure: The aryl or heteroaryl iodide (0.005 mol) is stirred in dry nitrogen with trifluoromethylthiocopper (0.01 mol) in *N*-methylpyrrolidone, chinoline, or dimethylformamide (10 ml) at 150–165° for 7 h, whereupon it is cooled, diluted with water, and the product is extracted with ether. The ether solution is washed with water (in case of chinoline use 15% hydrochloric acid/water solution) and then dried (see Table 1).

In case of di- and triiodoarenes, the reaction is run in a similar way, the trifluoromethylthiocopper quantity being increased proportionally.

Aryl and Heteroaryl Trifluoromethyl Sulfones; General procedure: The aryl or heteroaryl trifluoromethyl sulfide (0.01 mol) is boiled and stirred with chromic anhydride (8–12 mol-equiv) in acetic acid (5 ml) for 6–20 h. The mixture is then diluted with water and the sulfones are filtered and dried (see Table 2).

Received: July 11, 1975

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