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Oxidative Desulfurization-Fluorination of Methyl Arenedithiocarboxylates. A Convenient Synthesis of Trifluoromethylated Aromatic Compounds†

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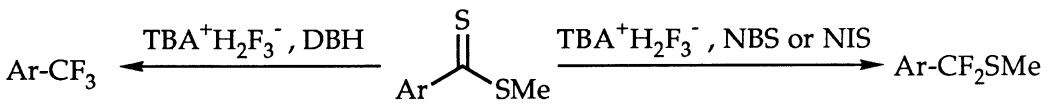
Trifluoromethyl-substituted aromatic compounds were obtained by oxidative desulfurization-fluorination reaction of methyl arenedithiocarboxylates using *n*-$Bu_4N^+H_2F_3^-$ and 1,3-dibromo-5,5-dimethylhydantoin (DBH). Use of *N*-bromosuccinimide or *N*-iodosuccinimide instead of DBH afforded difluoro(methylthio)methyl-substituted aromatics.

Aromatic compounds when functionalized by CF_3 group raise the lipophilicity or lower the viscosity of the parent compounds to effect often remarkable biological activities and/or physical properties. Accordingly,[1] a lot of synthetic drugs, agrochemicals and liquid crystalline materials have been developed that involve a CF_3-substituted aromatic moiety. To ease synthesis of CF_3-substituted aromatics, a regio- and chemoselective method for introduction of trifluoromethyl group should be established.

Compounds of type Ar-CF_3 are accessible by conversion of Ar-C(O)OH with SF_4,[2] halogen-exchange of Ar-CCl_3 with SbF_3[3] or HF,[4] treatment of Ar-H with CCl_4/HF,[5] trifluoromethylation of Ar-H by $CF_3\cdot$ or CF_3^+ equivalents, or substitution of Ar-Br with CF_3-metal reagents.[6] However, these methods suffer severe limitations like harmful reaction conditions and use of a highly toxic and/or unstable reagent in addition to low yield and low regioselectivity.

Oxidative desulfurization-fluorination reaction allows us to introduce fluorine atom(s) into an organic molecule under very mild reaction conditions.[7] Extension of this concept has led us to find that methyl arenedithiocarboxylates (Ar-C(S)SMe) are readily converted into Ar-CF_3[8] by treatment with tetrabutylammonium dihydrogentrifluoride[9] ($TBA^+H_2F_3^-$) and 1,3-dibromo-5,5-dimethylhydantoin (DBH). Replacing DBH by *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) has given rise to new compounds of type $ArCF_2SMe$.

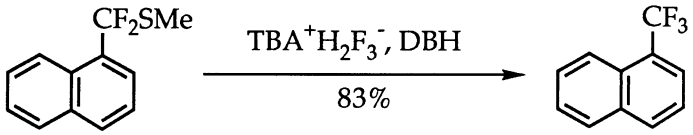


†Dedicated to Professor Emeritus Osamu Simamura of The University of Tokyo on the occasion of his 80th birthday.

Starting materials Ar-C(S)SMe are readily accessible by reaction of $ArCH_2X$ and sulfur in the presence of sodium methoxide[10] followed by treatment with MeI or, alternatively, by the reaction of Ar-metal with CS_2 and subsequently with MeI.[11] A general procedure for transformation of Ar-C(S)SMe to Ar-CF_3 follows. To a dichloromethane (1.5 mL) solution of Ar-C(S)SMe (0.5 mmol) and $TBA^+H_2F_3^-$ (1.5 mmol) was added DBH (2 mmol) in one portion at 0 °C, and the resulting mixture was stirred for 1 h at room temperature. Work-up[12] followed by chromatographic purification afforded Ar-CF_3 in good yields.

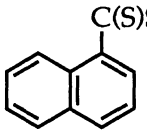
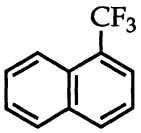
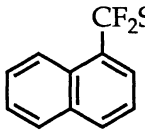
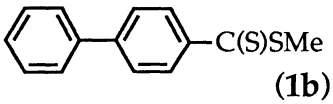
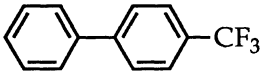
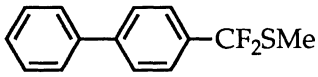
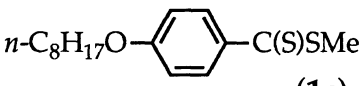
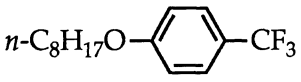
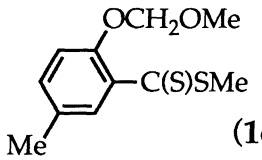
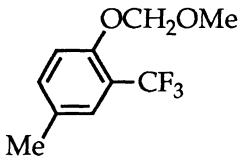
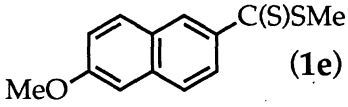
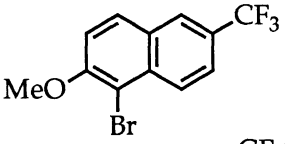
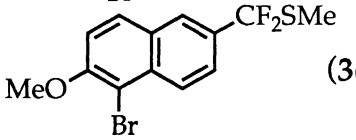
Results are summarized in Table 1. Starting materials unsubstituted or substituted by an electron-donating group gave trifluorinated products in good yields (entries 1, 8, 12, and 13), whereas those bearing such an electron-withdrawing group as bromine gave only a complex mixture of products. In this case, the target trifluorination product was obtained by use of HF/pyridine (HF/Py, 70/30 wt%) as fluoride ion source (entry 16). Moreover, in combination with HF/Py, any of DBH, NIS, NBS, and NCS gave 1-trifluoromethylnaphthalene from methyl 1-naphthalenedithiocarboxylate in yields of 79%, 63%, 43% and 29%, respectively (entries 2, 3, 4, and 5). On the other hand, substrates containing an electron-rich aromatic ring suffered ring bromination during trifluoromethylation (entry 14). As the starting material of entry 13 was prepared through selective *ortho*-lithiation[13] of methoxymethyl ether of *p*-cresol followed by treatment with CS_2 and MeI, this example demonstrates the electrophilic and regioselective introduction of a CF_3 group into the aromatic nucleus.

Noteworthy observation is that difluorination products of type Ar-CF_2SMe were obtained upon treatment of the same substrates with $TBA^+H_2F_3^-$ and a halonium ion-generating agent such as bromine (1.5 mmol, entry 7), NBS (1.5 mmol, entry 9), *N*-bromoacetamide (NBA, 1.5 mmol, entry 10) or *N*-iodosuccinimide (NIS, 1.5 mmol, entries 6 and 11). Ring bromination occurred again of an electron-rich substrate **1e** (entry 15). The products Ar-CF_2SMe are assumed to be precursors of Ar-CF_3, since Ar-CF_2SMe could be converted into Ar-CF_3 by DBH and $TBA^+H_2F_3^-$.[14] For example, 1-trifluoromethylnaphthalene was obtained from 1-[difluoro-(methylthio)methyl]naphthalene in 83% yield.

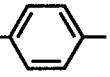
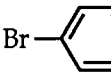


The present method allows us an easy preparation of Ar-CF_3 or Ar-CF_2SMe under extremely mild conditions using readily accessible starting materials, arenedithiocarboxylates. Furthermore, CF_3 group can be introduced as planned through regioselective metalation of aromatic compounds. Thus, this methodology should find wide applications particularly in the synthetic study of new drugs, agrochemicals, and electro-optical materials. Studies along this line are progressing in our laboratories.

Table 1. Oxidative desulfurization-fluorination of methyl arenedithiocarbonates[a)]

Entry	Starting material	X^+ (mol equiv.)	Product	Yield/%[b)]
1	 (1a)	DBH (4.0)	 (2a)	63
2[c)]	1a	DBH (4.0)	2a	79
3[c)]	1a	NIS (4.0)	2a	63
4[c)]	1a	NBS (4.0)	2a	43
5[c)]	1a	NCS (4.0)	2a	29
6	1a	NIS (3.0)	 (3a)	61
7	1a	Br_2 (3.0)	3a	38
8	 (1b)	DBH (4.0)	 (2b)	52
9	1b	NBS (3.0)	 (3b)	69
10	1b	NBA (3.0)	3b	66
11	1b	NIS (3.0)	3b	86
12	 (1c)	DBH (4.0)	 (2c)	62
13	 (1d)	DBH (4.0)	 (2d)	71
14	 (1e)	DBH (4.0)	 (2e)	78
15	1e	NBS (3.0)	 (3e)	62

(*Table 1 continued*)

16[d]		DBH	(4.0)		(2f)	82

a) All the reactions were performed on 0.5 mmol scale. $TBA^+H_2F_3^-$ (2.5 mmol) was used unless otherwise noted. b) Isolated yields. c) HF/Py (1.15 mmol, F^-: 10.4 mmol) was used as a fluorinating agent. d) HF/Py (4.4 mmol, F^-: 40 mmol) was employed in place of $TBA^+H_2F_3^-$.

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8) Alternative synthesis of Ar-CF_3 from Ar-C(S)SH with XeF_2: M. Zupan and Z. Bregar, *Tetrahedron Lett.*, **31**, 3357 (1990); that from $ArC(SR)_3$ with HF/Py and DBH or NBS: D. P. Matthews, J. P. Whitten, and J. R. McCarthy, *Tetrahedron Lett.*, **27**, 4861 (1986).
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12) The reaction mixture was poured into an aqueous solution of $NaHCO_3$ and $NaHSO_3$ and extracted with diethyl ether. The ethereal layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography or thin layer chromatography.
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14) The reaction is considered to be initiated by electrophilic reaction of halonium ion with Ar-C(S)SMe to generate Ar-C(=S^+X)SMe. Subsequent nucleophilic attack by fluoride ion to the carbocationic center makes C-F bond. The resulting Ar-CF(SX)SMe is again oxidized and substituted by fluoride ion to give a difluorination product Ar-CF_2SMe. Repeated oxidation and substitution of the sulfide bond gives a trifluorination product Ar-CF_3.

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