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Oxidative Desulfurization-Fluorination of Xanthates. A Convenient Synthesis of Trifluoromethyl Ethers and Difluoro(methylthio)methyl Ethers

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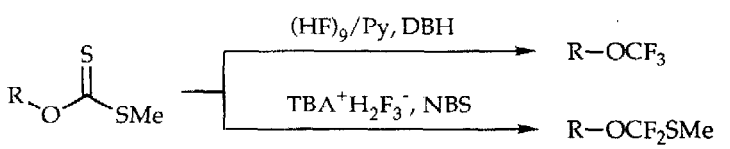
Key Words: oxidative desulfurization-fluorination; xanthates; trifluoromethyl ethers

Abstract: Treatment of xanthates R-OC(S)SMe with $(HF)_9$/Py and 1,3-dibromo-5,5-dimethylhydantoin gives trifluoromethyl ethers R-OCF_3 through intermediates R-OCF_2SMe, which could be isolated upon treatment of xanthates with *n*-$Bu_4N^+H_2F_3^-$ and *N*-bromosuccinimide.

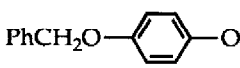
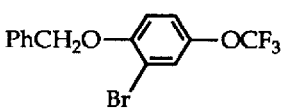
Trifluoromethyl group often contributes to remarkable enhancement and/or modification of biological activity and/or physical property of materials.[1] For example, CF_3-O group attached to an aromatic ring increases lipophilicity of biologically active compounds[2] and decreases viscosity of liquid crystalline compounds.[3] Introduction of CF_3-O group has been achieved by halogen-exchange of CCl_3-O group with $SbF_3/SbCl_5$[4] or HF,[5] by alkylation of phenols with CCl_4/HF,[6] or by fluorination of ArOC(O)F or ArOC(S)Cl with SF_4[7] or MoF_6,[8] respectively. However, these reactions suffer severe limitations like difficult accessibility of starting materials, dangerous reaction conditions, highly toxic reagents, and low yields.

Of various fluorination reactions, oxidative desulfurization-fluorination reaction of organosulfur compounds is characterized as a method which allows us to synthesize organofluorine compounds under extremely mild conditions.[9] Herein we report (1) methyl xanthates R-OC(S)SMe are easily converted into trifluoromethyl ethers R-OCF_3 by treatment with HF-pyridine complex ($(HF)_9$/Py) and 1,3-dibromo-5,5-dimethylhydantoin (DBH), (2) the same substrates are converted into difluoro(methylthio)methyl ethers R-OCF_2SMe with tetrabutylammonium dihydrogen-trifluoride ($TBA^+H_2F_3^-$)[10] and *N*-bromosuccinimide (NBS).



To a dichloromethane (3.0 mL) suspension of DBH (1.5 mmol) were added $(HF)_9$/Py (1 mL, 4.4 mmol, 40 mmol of F^-) and methyl xanthate[11] (0.5 mmol) at -78 °C, and the resulting mixture was stirred at 0 °C for 1 h. Workup[12] followed by chromatography or distillation afforded trifluoromethyl ethers in good yields. Results are summarized in Table 1. As readily seen, both *O*-alkyl and *O*-aryl trifluoromethyl ethers could be prepared. For substrate having an aromatic ring without an electron-withdrawing group, exactly 3 eq of DBH should be used to avoid further ring bromination. This side reaction occurred particularly when a substrate contained an alkoxy-substituted aromatic nucleus. For example, methyl 4-benzyloxyphenyl xanthate was converted into 4-benzyloxy-3-bromophenyl trifluoromethyl ether with $(HF)_9$/Py (80 eq of F^-) and 4 eq of DBH (entry 6), but a complex reaction mixture resulted with 3 eq of DBH.

Table 1. Synthesis of Trifluoromethyl Ethers from Xanthates[a]

Entry	Starting Material	Product	Yield/%[b]
1	4-*n*-Pr-C_6H_4-OC(S)SMe	4-*n*-Pr-C_6H_4-OCF_3	58
2	4-*n*-Hex-C_6H_4-OC(S)SMe	4-*n*-Hex-C_6H_4-OCF_3	50
3	4-Br-C_6H_4-OC(S)SMe	4-Br-C_6H_4-OCF_3	62
4	3-MeOC(O)-C_6H_4-OC(S)SMe	3-MeOC(O)-C_6H_4-OCF_3	48
5	4-(4-AcO-C_6H_4)-C_6H_4-OC(S)SMe	4-(4-AcO-C_6H_4)-C_6H_4-OCF_3	80
6[c]			56
7	*n*-$C_{10}H_{21}$-OC(S)SMe	*n*-$C_{10}H_{21}$-OCF_3	80

[a]Unless otherwise noted, $(HF)_9$/Py (80 eq of F^-) and DBH (3 eq) were used. [b]Isolated yields. [c]DBH (4 eq) was used.

When NBS (2 mmol) was added to a dichloromethane (1.5 mL) solution of methyl xanthates (0.5 mmol) and $TBA^+H_2F_3^-$ (1.5 mmol) at 0 °C and the resulting mixture was stirred for 1 h at room temperature, difluoro(methylthio)methyl ethers were obtained after workup and purification (Table 2). Hereby no trifluoromethyl ethers could be detected. Aryl difluoro(methylthio)methyl ethers were obtained in fair yields from *O*-aryl xanthates (entries 1 to 9), whereas the corresponding alkyl ether (entry 10) was isolated albeit in unsatisfactory yield. In contrast to trifluorination, aromatic rings having an alkoxyl group did not suffer ring halogenation during difluorination (entries 3 and 4).

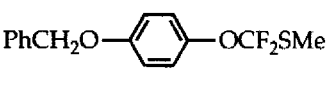
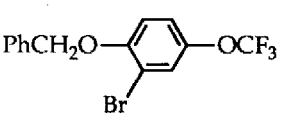
Table 2. Synthesis of Difluoro(methylthio)methyl Ethers from Xanthates

Entry	Product	Yield/%[a]	Entry	Product	Yield/%[a]
1	4-*n*-Pr-C_6H_4-OCF_2SMe	58	6	4-Ph-C_6H_4-OCF_2SMe	23
2	4-*n*-Hex-C_6H_4-OCF_2SMe	36	7	4-(4-Br-C_6H_4)-C_6H_4-OCF_2SMe	28
3	4-MeO-C_6H_4-OCF_2SMe	33	8	3-MeOC(O)-C_6H_4-OCF_2SMe	31
4	4-$PhCH_2O$-C_6H_4-OCF_2SMe	43	9	4-*n*-PrOC(O)-C_6H_4-OCF_2SMe	42
5	4-Br-C_6H_4-OCF_2SMe	44	10	$Ph(CH_2)_3$-OCF_2SMe	15

[a]Isolated yields.

The reagent system $(HF)_9$/Py-DBH is also effective for conversion of R-OCF_2SMe into R-OCF_3. Treatment of R-OCF_2SMe with $(HF)_9$/Py (80 eq of F^-) and DBH (1 eq) afforded R-OCF_3 (Table 3). This transformation could be carried out without ring bromination by use of 1 eq of DBH, except for substrates having an aromatic ring substituted by an alkoxyl group. Thus, difluoromethyl ethers R-OCF_2SMe are shown to be precursors of trifluoromethyl ethers.[13]

Table 3. Conversion of R-CF_2SMe into R-CF_3[a]

Entry	Starting Material	Product	Yield/%[b]
1	4-*n*-Pr-C_6H_4-OCF_2SMe	4-*n*-Pr-C_6H_4-OCF_3	42
2	3-MeOC(O)-C_6H_4-OCF_2SMe	3-MeOC(O)-C_6H_4-OCF_3	51
3[c]			62
4	$Ph(CH_2)_3$-OCF_2SMe	$Ph(CH_2)_3$-OCF_3	41

[a]Unless otherwise noted, $(HF)_9$/Py (80 eq of F^-) and DBH (1 eq) were used. [b]Isolated yields. [c]DBH (2 eq) was used.

We have demonstrated that easily accessible methyl xanthates are transformed effectively to trifluoromethyl ethers by oxidative desulfurization-fluorination. Through appropriate tuning of the reagents, difluoro(methylthio)methyl ethers, a new type of compounds, could be isolated, which might be derivatized to various fluorinated materials other than trifluoromethyl ethers.

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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.
13. The reaction is considered to be initiated by electrophilic reaction of halonium ion (X^+) with thiocarbonyl of R-OC(S)SMe to generate a carbocation R-OC^+(SX)SMe; subsequent nucleophilic attack by fluoride ion to the cationic center makes C-F bond. The resulting R-OCF(SX)SMe is again oxidized and fluorinated to give the difluorination product R-OCF_2SMe. Further oxidation and fluorination gives the trifluorination product R-OCF_3.

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