

Oxidative desulfurization–fluorination of alkanol xanthates. Control of the reaction pathway to fluorination or trifluoromethoxylation

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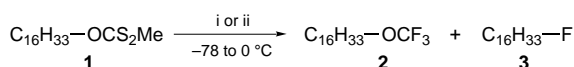
The reagent consisting of 70% HF–py (py = pyridine) and a halonium oxidant converts R–OCS₂Me into either R–OCF₃ (R = primary) or R–F (R = secondary, tertiary or benzylic) whereas the 50% HF–py system converts R–OCS₂Me (R = secondary) into R–OCF₃.

Exploitation of novel and efficient fluorination reactions has been the subject of extensive research,¹ because organofluorine compounds very often play key roles in material and pharmaceutical science. The oxidative desulfurization–fluorination reaction² recently disclosed by us transforms the xanthates derived from phenols and primary alkanols to the corresponding trifluoromethyl ethers.³ To achieve this transformation, a readily available reagent system consisting of hydrogen fluoride and 30% pyridine (70% HF–py)⁴ and a halonium oxidant is extremely effective.

Very recently, Motherwell and his co-workers reported that the xanthates of primary and secondary alkanols were converted into the corresponding fluorides by means of 4-methyl(difluoroiodo)benzene (TolIF₂).⁵ This paper, indicating that the xanthates of primary alkanols gave different products, prompted us to study in more detail the oxidative desulfurization–fluorination of the xanthates of various secondary and tertiary alkanols. Herein we report that R–OCS₂Me (R = primary) could be converted into R–OCF₃, whereas R–OCS₂Me (R = secondary, tertiary or benzylic) was fluorinated to give R–F. Furthermore, we also found that 50% HF–py could convert R–OCS₂Me (R = secondary) into the corresponding R–OCF₃ with R–F being undetected. According to the presented method, secondary alkyl trifluoromethyl ethers are prepared for the first time from the corresponding alcohols.

To compare the selectivity of the reagent 70% HF–py–X⁺ with TolIF₂, we first chose *O*-hexadecyl *S*-methyl dithiocarbonate **1** for the model substrate. Upon treatment with TolIF₂, **1** was reportedly converted into 1-fluorohexadecane **3** in 48% yield.⁵ When **1** was treated with 1,3-dibromo-5,5-dimethylhydantoin (DBH, 3.0 mol) and 70% HF–py (80 mol) in dichloromethane at –78 to 0 °C for 1 h, 1-trifluoromethoxyhexadecane **2** was isolated in 95% yield, and no trace of **3** could be detected. To confirm the difference between the two reagents, we used bis(trifluoroacetoxy)iodobenzene (3.0 mmol) in place of DBH; trifluoromethyl ether **2** was obtained again as the sole product in 67% yield (Scheme 1). Thus, the reagent system consisting of 70% HF–py and an oxidant exhibits unique reactivity, contrasting sharply to TolIF₂, and the reaction pathway appears to be governed by a fluorinating agent rather than by an oxidant.

In contrast to the xanthates of primary alcohols, those of benzylic, secondary or tertiary alcohols underwent the fluorination reaction under the standard oxidative desulfurization–

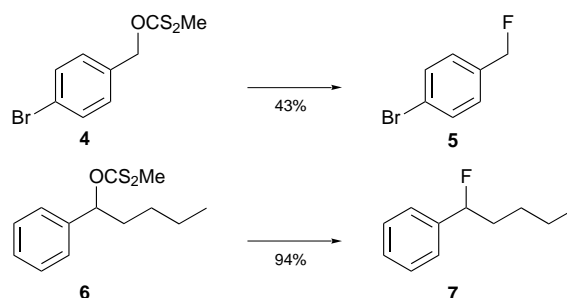


Scheme 1 Reagents and conditions: i, 70% HF–py, DBH, **2** 95%; ii, 70% HF–py, PhI(OCOCF₃)₂, **2** 67%

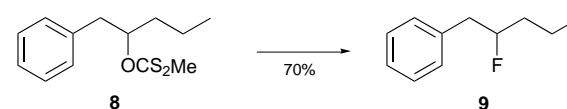
fluorination conditions. Examples are the reactions of the benzylic xanthates **4**† and **6**; both gave fluorination products **5** and **7**, respectively (Scheme 2).

Xanthate **8** also was successfully fluorinated to give **9** in 70% yield using *N*-iodosuccinimide (NIS) as the oxidant (Scheme 3). With DBH, bromination of the phenyl ring accompanied the fluorination reaction.§

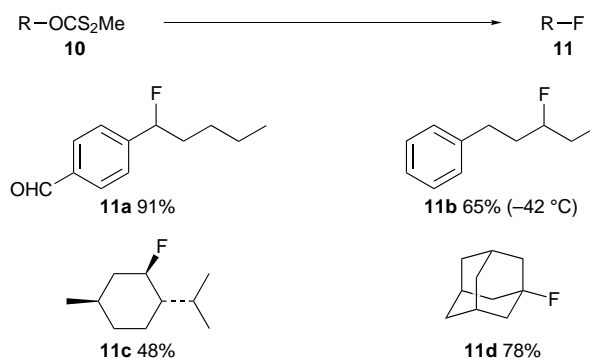
The fluorination conditions were applied to the xanthates derived from secondary or tertiary alcohols. The isolated yield is shown below the formula of each product (Scheme 4). As readily seen, both secondary and tertiary alkyl fluorides could be prepared in good yields.¶ The xanthate of menthol gave **11c** as an isolable single product. Although the reaction appears to have proceeded with retention of configuration, we consider **11c** was produced through a carbocationic intermediate. Similar stereochemical results are reported with other fluorination reactions.^{5,6}



Scheme 2 Reagents and conditions: 70% HF–py (40 mol), DBH (3.0 mol), CH₂Cl₂, –78 to 0 °C, 1 h



Scheme 3 Reagents and conditions: 70% HF–py (20 mol), NIS (3.0 mol), CH₂Cl₂, –42 °C, 1 h

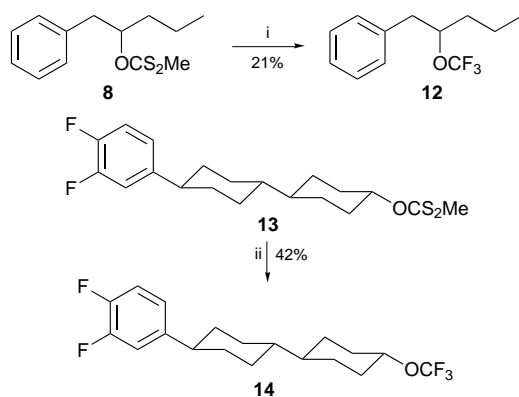


Scheme 4 Reagents and conditions: 70% HF–py (40 mol), NIS (3.0 mol), CH₂Cl₂, –78 to 0 °C, 0.5–1 h

The fluorination reaction may be attributed to an easy elimination of the $-\text{OCS}_2\text{Me}$ group from secondary and tertiary aliphatic xanthates under the acidic conditions, followed by the subsequent fluoride attack at the resulting electrophilic carbon to complete the fluorination. Hence we envisaged that, if the acidity of the reaction conditions was controlled by proper choice of the reagent system, we could switch the reaction pathway to the trifluoromethyl ether formation. Thus, we used 50% HF-py as the fluorinating reagent that was prepared by dilution of 70% HF-py with pyridine. Indeed, xanthate **8** afforded the corresponding trifluoromethyl ether **12** in 21% yield by treatment with 50% HF-py (40 mol) and *N*-bromosuccinimide (NBS, 5.0 mol) at -78 to 0°C for 30 min (Scheme 5).^{||} Herein no trace of alkyl fluoride **9** could be detected. Furthermore, xanthate **13** was also converted into the corresponding trifluoromethyl ether **14** in 42% yield.

In conclusion, the reagent system consisting of 70% HF-py and a halonium ion oxidant is extremely effective for the conversion of $\text{R}-\text{OCS}_2\text{Me}$ (R = alkyl) into either $\text{R}-\text{OCF}_3$ (R = primary) or $\text{R}-\text{F}$ (R = benzylic, secondary or tertiary), depending on the structure of the substrate. In particular, the xanthates of primary alcohols give trifluoromethyl ethers in striking contrast to the reaction with ToIF_2 . The difference may be attributed to the difference between the reactive species involved.^{5,6} Furthermore, the synthesis⁷ of secondary alkyl trifluoromethyl ethers is achieved with a readily adjustable reagent system consisting of 50% HF-py and NBS. Thus, the reaction pathway to secondary alkyl fluoride or to trifluoromethyl ether is controlled simply by an appropriate choice of the fluorination reagent starting with the same substrate.

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Scheme 5 Reagents and conditions: i, 50% HF-py (40 mol), NBS (5.0 mol), CH_2Cl_2 , -78 to 0°C , 0.5 h; ii, 50% HF-py (40 mol), NBS (5.0 mol), CH_2Cl_2 , 0°C , 1 h

Footnotes

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‡ To obtain the product in high yield, 40 mol of 70% HF-py was enough. When 80 mol of 70% HF-py was used, halogenation of the aromatic moiety simultaneously took place, and a mixture of monobromo, dibromo and tribromo derivatives resulted.

§ When 40 mol of 70% HF-py was used, iodination of the phenyl group occurred to some extent.

¶ A procedure for the synthesis of 4-(1-fluoropentyl)benzaldehyde **11a** is representative. To a suspension of NIS (1.5 mmol) in dichloromethane (2.5 ml) were added 70% HF-py⁴ (0.5 ml, 2.2 mmol, 20 mmol of F^-) and *O*-{1-(4-formylphenyl)pentyl} *S*-methyl dithiocarbonate (0.5 mmol) at -78°C . The mixture was stirred at 0°C for 1 h, poured into a $\text{pH} = 10$ buffer solution (NaHCO_3 , NaHSO_3 and NaOH) and extracted with diethyl ether three times. The combined ethereal layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (hexane- Et_2O , 20:1) afforded **11a** in 91% yield.

|| A procedure for the preparation of trifluoromethyl ether **12** is as follows. To a suspension of NBS (5.0 mmol) in dichloromethane (2.5 ml) was added pyridine (0.46 ml); subsequently 70% HF-py (1.0 ml, 4.4 mmol, 40 mmol of F^-) was slowly added dropwise at -78°C , and the resulting mixture was stirred at room temp. for 5 min and then recooled to -78°C . A dichloromethane (2.5 ml) solution of xanthate **8** (1.0 mmol) was added dropwise to the suspension at -78°C . The resulting mixture was stirred at 0°C for 30 min, poured into a $\text{pH} = 10$ buffer solution (NaHCO_3 , NaHSO_3 and NaOH) and extracted with diethyl ether three times. The combined ethereal layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (cyclohexane) afforded 1-phenylpent-2-yl trifluoromethyl ether **12** in 21% yield.

** Under the similar conditions, trifluoromethyl ethers of β -cholestanol and 1-phenylpentan-3-ol were prepared in 24 and 16% yield, respectively.

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- β -Fluoroalkyl trifluoromethyl ethers are prepared alternatively by treatment of alkenes with CF_3OF , albeit in low yields. See: D. H. R. Barton, L. J. Dankas, A. K. Ganguly, R. H. Hesse, G. Tarzia and M. M. Pechet, *J. Chem. Soc., Chem. Commun.*, 1969, 227; S. Rozen, *Chem. Rev.*, 1996, **96**, 1717; C. Corvaja, F. Cremonese, W. Navarrini, C. Tonelli and V. Tortelli, *Tetrahedron Lett.*, 1995, **36**, 3543.

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