Pergamon

Tetrahedron Letters, Vol. 37, No. 44, pp. 7983-7986, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01788-1

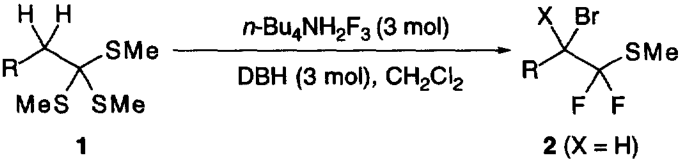
Difluorination of 2-Substituted 1,1,1-Tris(methylthio)ethanes by Oxidative Desulfurization-Fluorination. A New Route to Partially Fluorinated Olefins

Satoru Furuta and Tamejiro Hiyama*

Research Laboratory of Resources Utilization, Tokyo Institute of Technology
4259 Nagatsuta, Midori-ku, Yokohama, Kanagawa 226, JAPAN

Abstract: Oxidative desulfurization-fluorination of $RCH_2C(SMe)_3$ using n-$Bu_4NH_2F_3$ and 1,3-dibromo-5,5-dimethylhydantoin gave $RCHBrCF_2SMe$ in good yields. The products were converted into difluorobromo olefins. Under similar conditions $ArCH_2C(SMe)_3$ afforded $ArCBr_2CF_2SMe$. The mechanism of the partial difluorination accompanied by bromination is discussed. Copyright © 1996 Elsevier Science Ltd

The oxidative desulfurization-fluorination[1] converts C-S bond(s) of dithio esters or dithio acetals into C-F bond(s), and thus provides us with a convenient synthetic method for organofluorine compounds useful as agrochemicals and pharmaceuticals.[2] Orthothio esters as the substrate attracted our attention because various types of orthothio esters are readily available. McCarthy has reported trifluorination of aromatic orthothio esters.[3] Recently, we have reported $RCH(OH)C(SMe)_3$ are transformed to difluoro(methylthio)methyl ketones.[4] We further studied the utility of orthothio esters and found fluorination of 2-substituted 1,1,1-tris(methylthio)ethanes (**1**) readily takes place to give 2-substituted 2-bromo-1,1-difluoro-1-methylthio ethanes (**2**) or its 2,2-dibromo derivatives **3** on treatment with tetrabutylammonium dihydrogentrifluoride (n-$Bu_4NH_2F_3$) and 1,3-dibromo-5,5-dimethylhydantoin (DBH). The sulfur functionality in **2** is readily removed to difluorobromo olefins.

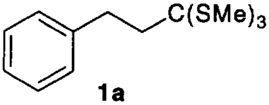
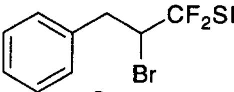
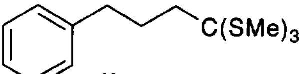
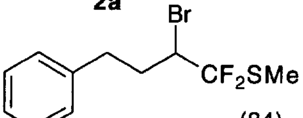
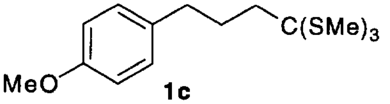
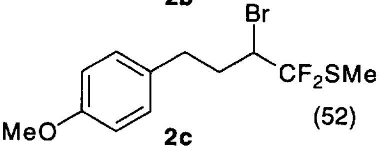
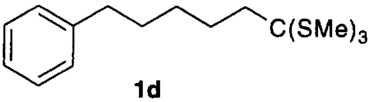
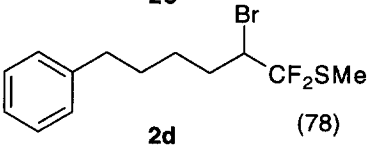
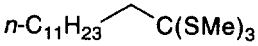
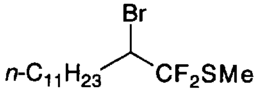
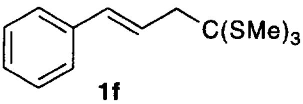
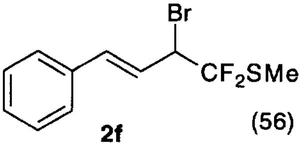
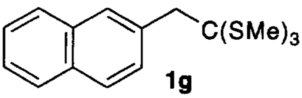
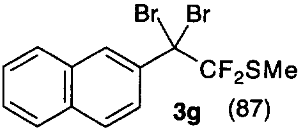
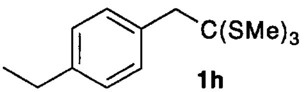
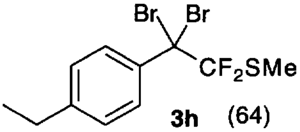
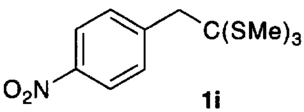
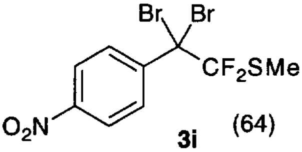


1

2 (X = H)
3 (X = Br)

The substrates **1** were prepared by alkylation of $LiC(SMe)_3$ with alkyl halides[5] in good yields. A typical procedure of the oxidative desulfurization-fluorination is as follows. DBH (3 mol equivalents) was added to a dichloromethane solution of **1** and n-$Bu_4NH_2F_3$ (3 mol equivalents) at

Table 1. Oxidative Desulfurization-Fluorination of orthothio esters **1** with n-$Bu_4NH_2F_3$ and DBH

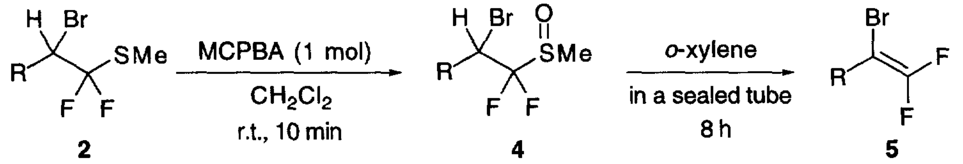
Run	Orthothio ester (**1**)	Conditions	Products (% yields)[a]
1	 **1a**	0 °C to r.t. 20 min	 **2a** (79)
2	 **1b**	0 °C to r.t. 20 min	 **2b** (84)
3	 **1c**	-10 °C 10 min	 **2c** (52)
4	 **1d**	0 °C to r.t. 20 min	 **2d** (78)
5	 **1e**	0 °C to r.t. 20 min	 **2e** (83)
6	 **1f**	-10 °C 5 min	 **2f** (56)
7	 **1g**	0 °C to r.t. 1 h	 **3g** (87)
8	 **1h**	0 °C to r.t. 1 h	 **3h** (64)
9	 **1i**	0 °C to r.t. 1 h[b]	 **3i** (64)

a) Isolated yield. b) The amounts of the fluorinating reagent and the oxidant were, respectively, 5 mol equivalents.

0 °C, and the resulting mixture was stirred at room temperature for 20 min. Workup[6] gave difluorinated product **2** or **3** in good yields. The results summarized in Table 1 show difluorination was always accompanied by bromination or dibromination. Even after prolonged reaction time trifluorination did not take place.

When R in **1** was aliphatic (runs 1-5), the reaction leading to **2** proceeded smoothly. With a substrate having a C=C bond (run 6), a similar reaction occurred and no trace of a bromofluorination product was obtained. With the substrates **1** (R = aryl), dibromodifluoro products **3** were produced (runs 7-9). Substrates having a weak electron-donating or an electron-withdrawing group on aryl underwent the fluorination reaction cleanly. The substrate having an electron-donating group gave a complex mixture of products.

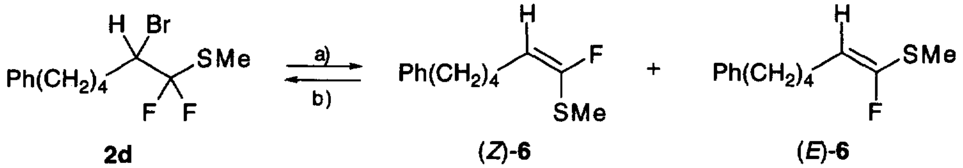
The synthetic utility of products **2** is demonstrated by removal of the remaining sulfur functionality.[7] Oxidation of **2** with a stoichiometric amount of MCPBA at room temperature yielded sulfoxides **4**, which were pyrolized at 160-170 °C in a sealed tube to afford 2-bromo-1,1-difluoroalkenes (**5**).



R	Isolated yield	Temperature	Isolated yield
$Ph(CH_2)_4$	98 %	170 °C	63 %
n-$C_{11}H_{23}$-	54 %	160 °C	51 %

The bromine and fluorine functional groups in **2** are removed in a reductive way. For example, treatment of **2d** with zinc powder in acetic acid gave an E/Z mixture of α-fluorovinyl sulfide **6** in 66% yield. The product **6** is assumed to be a key intermediate of the oxidative desulfurization-fluorination of **1** giving **2**. Indeed, treatment of the E/Z mixture of **6** with n-$Bu_4NH_2F_3$ and DBH produced **2d** in 42% yield. Thus, formation of **2** should involve (1) first electrophilic attack of Br^+ at sulfur of **1**, (2) substitution of Me-S-Br by the fluoride ion to give $RCH_2CF(SMe)_2$, (3) second electrophilic attack of Br^+ at sulfur of this intermediate followed by elimination of Me-S-Br with the fluoride ion[8] to produce RCH=CFSMe (**6**), and (4) bromofluorination[9] of the C=C bond of **6**.

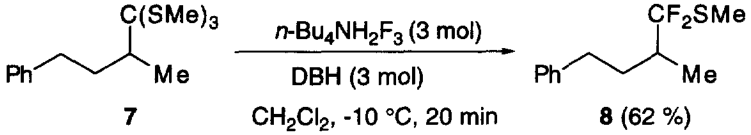
Formation of the dibromodifluoro product **3** is explained as follows: (1) first electrophilic attack of Br^+ at sulfur followed by elimination of Me-S-Br to give $ArCH=C(SMe)_2$, (2) bromofluorination of this dithioketene acetal to give $ArCHBr-CF(SMe)_2$, (3) second electrophilic attack of Br^+ at sulfur followed by elimination of Me-S-Br to produce ArCBr=CFSMe, and (4) bromofluorination of the olefin intermediate to give **3**.



a) Zn (3 mol), AcOH - H_2O, 0 °C to r.t., 30 min, 28 % (*Z*) and 38 % (*E*)

b) *n*-$Bu_4NH_2F_3$ (1.5 mol), DBH (1.5 mol), CH_2Cl_2, 0 °C to r.t., 20 min, 42 %

An exception in the reaction was observed with the substrate **7** which gave difluoro product **8** without any bromination. Probably because of steric hindrance, the olefin formation induced by the fluoride ion did not take place, and oxidative desulfurization-fluorination only proceeded.



In summary, we have demonstrated difluorination of 2-substituted 1,1,1-tris(methylthio)ethanes (**1**) occurs under the oxidative desulfurization-fluorination conditions. Depending on the substituent, bromination or dibromination was found to accompany the reaction.

ACKNOWLEDGMENT: The present work was partially supported by a Grant-in-Aid from Asahi Glass Foundation (Japan) for the Promotion of Science and by Grant-in-Aid for Scientific Research No. 07405042 from the Ministry of Education, Science and Culture.

REFERENCES AND NOTES

1. Kuroboshi, M.; Hiyama, T. *Yuki Gosei Kagaku Kyokai Shi* **1993**, *51*, 1124-1133 and references cited therein.
2. a) *Biomedical Aspects of Fluorine Chemistry*, Filler, R.; Kobayashi, Y., Ed.; Kodansha Ltd. and Elsevier Biomedical: Tokyo and Amsterdam, **1982**. b) Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197-204. c) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley and Sons, Inc.: New York, 1979. d) Kusumoto, T.; Hiyama, T.; Takehara, S. *Dyestuffs & Chemicals* **1994**, *39*, 6-17.
3. Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *Tetrahedron Lett.* **1986**, *27*, 4861-4864.
4. Kuroboshi, M.; Furuta, S.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 6121-6122.
5. Barbero, M.; Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R. *J. Chem. Soc. Perkin Trans.* 1 **1993**, 2075-2080.
6. The reaction mixture was diluted with a 10 : 1 mixture of hexane and diethyl ether, and the resulting insoluble material was filtered through a short silica gel column. The filtrate was washed with an aqueous solution of $NaHCO_3$ and $NaHSO_3$, and then with brine. The organic 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.
7. Kim, K.; McCarthy, J. R. *Tetrahedron Lett.* **1996**, *37*, 3223-3226.
8. Clark, J. H. *Chem. Rev.* **1980**, *80*, 429-452.
9. Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1799-1805.

(*Received in Japan* 19 *August* 1996; *revised* 9 *September* 1996; *accepted* 10 *September* 1996)