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Fluorodesulfurization of Aliphatic Orthothioesters

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ABSTRACT: *In contrast with aromatic orthothio esters that undergo desulfurative fluorination to produce trifluoromethyl substituted aromatics, aliphatic orthothio esters react with BrF with replacement of only one or two methylthio groups by fluorine. An elimination step often follows the first sulfur replacement to produce novel unsaturated fluorinated systems.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 31–34, 1999

Fluorodesulfurization involves replacement of sulfur by fluorine. The process generally is successful for replacement of thiols [1], sulfides [2], thioketals [3] and acetals [4,5], thioesters and dithioesters [6] with fluorine obtained from mixed halogens [6], mercuric fluoride [4], or diethylaminosulfur trifluoride [7]. Complete replacement of three sulfur atoms occurs only in aromatic orthothio esters [6]. Aliphatic orthothioesters have received little attention, but the few known examples show either elimination without fluorination [1] or fluorination accompanied by rearrangements or oxidation [5].

We observe that fluorodesulfurization of several selected aliphatic orthothio esters occurs smoothly with replacement of one or two fluorine atoms followed by elimination to produce unique unsaturated fluorinated systems. The present study describes our results of fluorodesulfurization with several aliphatic orthothio esters obtained through nucleophilic substitution with tris(methylthio)methyl lithium [8]. Reaction of 1-indanone (**1**) with $(CH_3S)_3CLi$ provides **2** in 77% yield. Reaction of **2** with excess BrF, prepared from dibromohydantoin and HF/pyridine [6], occurs smoothly to give **3** in 82% yield (Scheme 1). Compound **2** likely loses water and CH_3SF under the acidic conditions to produce the unsaturated intermediate **A**. Rearrangement and fluorination leads to the final product observed (**3**).

Styrene oxide (**4**) reacts with $(CH_3S)_3CLi$ to give the trimethylthio alcohol **5** in 77% yield. Fluorodesulfurization of **5** gave the difluoro adduct **6** in 68% yield in which the alcohol function is replaced by bromine (Scheme 2). In this case, the thiomethyl groups are replaced by fluorine until two fluorines are present. Further fluorination is stopped because an unstable difluoro cation would be required.

Benylideneacetophenone (**7**) gave the Michael addition product **8** in 84% yield. Fluorodesulfurization of **8** gave both the monofluoro product **9** (48%) and the difluoro ketone **10** (34%) (Scheme 3). Both **9** and **10** can arise from a common intermediate **B** that undergoes further rearrangement and fluorination under the acidic conditions.

In Scheme 4, a brief general rationalization of the results is shown. Reactions of this type follow a known carbocation mechanism [1,3,6]. After initial fluorination, **C** is converted to cation **D,** which fluorinates further to **E** or eliminates to **F.** Elimination and rearrangement routes occur when the cation can be conjugated with the aromatic system. Without elimination, the difluoromethylthio is observed, as seen in **6.** Two fluorine atoms destabilize the further formation of cations.

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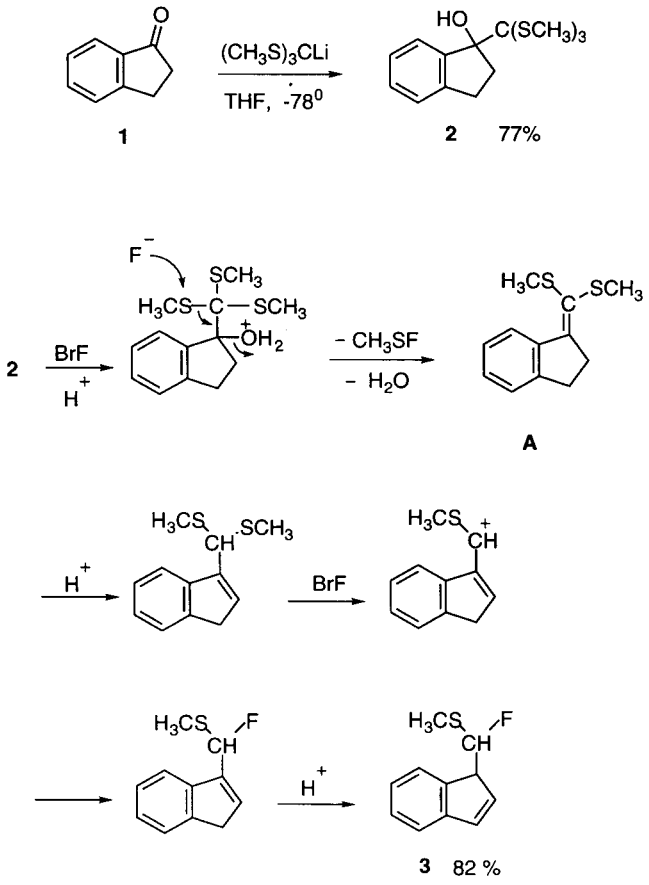
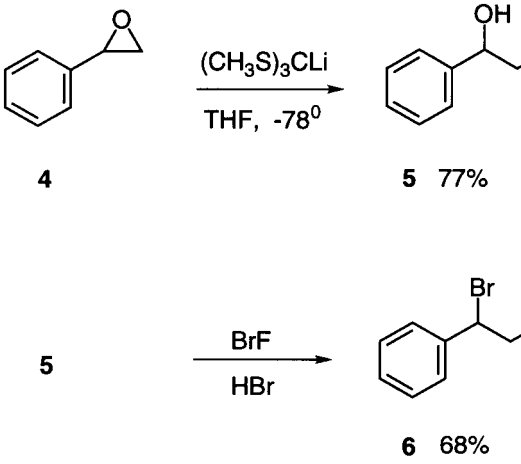


SCHEME 1



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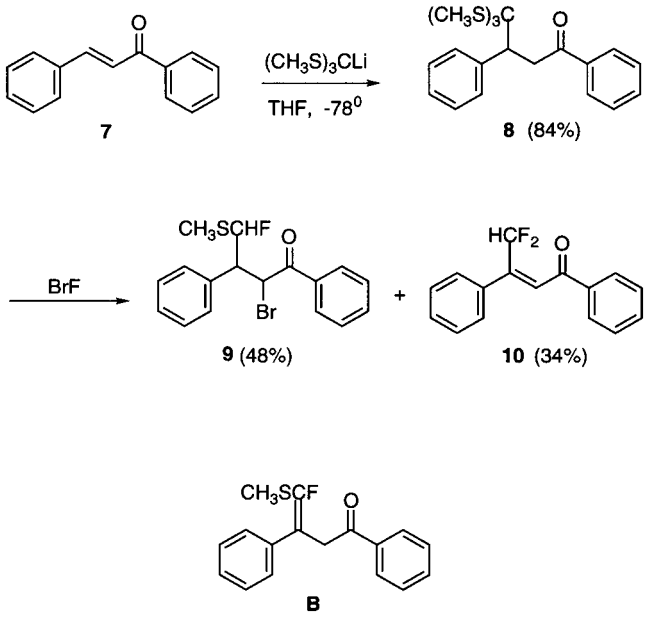

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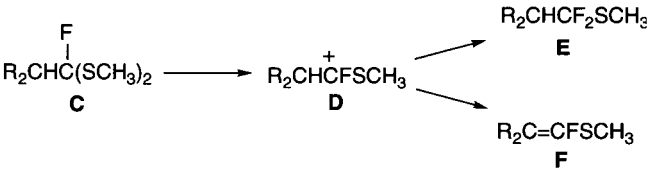

SCHEME 4

EXPERIMENTAL

1-Tris(methylthio)methyl-1-indanol (**2**)

In a 25 mL round-bottom flask, under dry nitrogen, were placed 1.0 mL (7.5 mmol) of tris(methylthio)methane and 10 mL of dry THF. The mixture was cooled to −78°C in a dry ice–acetone bath. *n*-Butyllithium (2.5 M in THF, 3.0 mL, 7.5 mmol) was added dropwise by syringe. The reaction mixture was allowed to stir until a white solid formed, approximately 5 minutes. A solution of 1-indanone (0.690 g, 5.22 mmol in 5 mL THF) was added dropwise. The reaction mixture was allowed to stir for 1.5 hours at −78°C after which 1 mL 1:1 acetic acid:ethanol was added, and the reaction mixture was allowed to come to room temperature. Saturated sodium bicarbonate (20 mL) was added to the reaction mixture, and the THF was taken off with a rotary evaporator. Three 20 mL methylene chloride extracts of the aqueous layer were combined and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator, and the

residue was purified by chromatography. The yield was 0.816 g, 77%, mp 62–64°C, R_f = 0.42 (20% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$) δ 1.99 (9H, s, CH_3), 2.22–3.24 (5H, m, CH_2CH_2-COH), 7.2–8.0 (4H, m, Ar); ^{13}C NMR ($CDCl_3$), 15.0 (s, CH_3), 31.3 (s, CH_2), 40.5 (s, CH_2), 75.7 (s, CS), 94.0 (COH), 124.8–129.1 (4 peaks, Ar). Mass spectrum: *m/z* (relative intensity), 285 (3) $[(M + H) - H_2]^+$: IR 3500 cm^{-1} (OH).

3,3,3-Tris(methylthio)-1-phenyl-1-propanol (**5**)

In a 100 mL round-bottom flask, under dry nitrogen, was placed (4.0 mL, 30 mmol) of tris(methylthio)methane in 40 mL of dry THF. The mixture was cooled to −78°C in a dry ice–acetone bath. *n*-Butyllithium (2.5 M in THF, 12.0 mL, 30 mmol) was added dropwise by syringe. The reaction mixture was allowed to stir until a white solid formed, approximately 5 minutes. Styrene oxide (2.28 mL, 20 mmol) in 20 mL of dry THF was added dropwise by syringe. The reaction mixture was stirred 23 hours at −78°C after which 3.5 mL of 1:1 acetic acid:ethanol was added, and the reaction mixture was allowed to come to room temperature. Saturated sodium bicarbonate (80 mL) was added to the reaction mixture, and the THF was taken off with a rotary evaporator. Three 80 mL methylene chloride extracts of the aqueous layer were combined and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporator, and the residue was purified by flash chromatography. The yield was 4.26 g, 77%. R_f = 0.39 (10% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$) δ 2.17 (9H, s, CH_3), 2.27–2.53 (2H, m, CH_2), 3.89 (1H, d, J = 3 Hz, OH), 5.29 (1H, dt, J_1 = 7 Hz, J_2 = 3 Hz, CH), 7.24–7.38 (5H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 13.1 (s, CH_3), 46.5 (s, CH_2), 70.2 (s, CS), 71.7 (s, CHOH), 125.9–144.4 (m, Ar): mass spectrum 227 (49) $[(M + H)\text{-}SCH_3]^+$: IR 3400 cm^{-1} (OH).

4,4,4-Tris(methylthio)-1,3-diphenyl-1-butanone (**8**)

In a 50 mL round-bottom flask, under dry nitrogen, were placed 1.0 mL (7.5 mmol) of tris(methylthio)methane and 8 mL of dry THF. The mixture was cooled to −78°C in a dry ice–acetone bath. *n*-Butyllithium (2.5 M in THF, 3.0 mL, 7.5 mmol) was added dropwise by syringe. The reaction mixture was allowed to stir until a white solid formed, approximately 5 minutes. A solution of benzylideneacetophenone (1.00 g, 4.84 mmol) in 5 mL dry THF was added dropwise by syringe. The reaction mixture was allowed to stir for 1 hour at −78°C after which 1 mL of 1:1 acetic acid:ethanol was added, and the reaction mixture was allowed to come to room temperature. Saturated sodium carbonate, 20 mL, was added to the reaction mixture, and the THF was taken off with a rotary evaporator. Three 20 mL methylene chloride extracts of the aqueous layer were combined and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporator, and the residue was purified by chromatography. Further purification by mild heating under vacuum to remove low boiling contaminants was required. The yield was 0.99 g, 84%. R_f = 0.04 in 10% methylene chloride in hexanes: ^{1}H NMR ($CDCl_3$) δ 1.94 (9H, s, CH_3), 3.49–4.00 (3H, m, $CHCH_2$), 7.11–7.91 (10H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 14.3 (s, CH_3), 42.0 (s, CH_2), 50.5 (s, CH), 126.7–133.2 (m, Ar), 197.6 (s, C=O): IR 1680 cm^{-1} (C=O); mass spectrum 315 (19) $[(M + H)\text{-}SCH_3]^+$.

General Procedure for Reaction of **2**, **5**, *and* **8** *with Bromine Fluoride*

In a 25 mL round-bottom flask under nitrogen were placed dibromohydantoin (1.25 g, 4.8 mmol) and 10 mL of dry methylene chloride. The mixture was cooled to −20°C (dry ice–carbon tetrachloride). The trismethylthio substrate (**2**, **5**, or **8**, 0.97 mmol) in 1 mL of dry methylene chloride was added dropwise to the stirred mixture. After 5 minutes, pyridinium poly(hydrogen fluoride) (1 mL, 4.4 mmol) was added dropwise by syringe. The reaction mixture was allowed to come to room temperature over 60 minutes. Saturated sodium carbonate solution was added very slowly for neutralization. Three 20 mL methylene chloride extracts were combined and dried with magnesium sulfate. The solution was concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel. The products were isolated as oils.

Results for the individual experiments are subsequently given.

1-Tris(methylthio)methyl-1-indanol (**2**) gave after chromatography with 60% methylene chloride in hexanes (R_f = 0.53) compound **3** in 82% yield as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 2.34 (3H, s, CH_3), 4.60 (1H, dd, J_{HH} = 7.0 Hz, J_{HF} = 14.0 Hz, CH), 4.76 (1H, dd, J_{HH} = 7.0 Hz, J_{HF} = 44 Hz, CHF), 6.7 (1H, d, J = 4.0 Hz, vinyl), 7.36 (5H, m, Ar and vinyl); ^{13}C NMR (TMS) δ 29.3 (CH_3), 39.7 (d, J_{CF} = 24 Hz, CH), 81.0 (d, J = 273 Hz, CHF), 124–131 (Ar and vinyl): ^{19}F NMR (trifluoroacetic acid that is 76.5 ppm upfield from the common standard $CFCl_3$) δ-52.7 (d, J = 44 Hz): mass spectrum, 175 $[(M + H)\text{-}HF]^+$. Anal. calcd for $C_{11}H_{11}FS$: C, 68.04; H, 5.67. Found: C, 68.20; H, 5.76. A minor amount of material thought

possibly to contain a trifluoromethyl group was also obtained but could not be sufficiently purified.

3,3,3,-Tris(methylthio)-1-phenyl-1-propanol (**5**) gave after chromatography with 50% methylene chloride in hexane (R_f = 0.73) one major component identified as **6** in 68% yield: ^{1}H NMR δ 2.39 (3H, s, CH_3), 2.33 (2H, m, CH_2), 5.41 1H, (m, CH), 7.25 (5H, m, Ar); ^{13}C NMR δ 8.9 (SCH_3), 56.8 (m, CH_2), 72.2 (m, CH), 114.8 (t, J = 268 Hz, CF_2), 123–148 (Ar); ^{19}F NMR δ + 2.66 (m). Mass Spectrum, 242 [(M + H)-HF]$^+$. Anal. calcd for $C_{10}H_{11}BrF_2S$: C, 45.82; H, 4.22. Found. C, 45.77; H, 4.00.

4,4,4-Tris(methylthio)-1,3-diphenyl-1-butanone (**8**) produced two main components. Chromatography with 40% methylene chloride in hexane gave **9** (R_f = 0.21) in 48% yield: ^{1}H NMR δ 1.93 (3H, m, CH_3), 4.49, 4.60 (1H, m, CH, CHBr), 4.95 (1H, d, J_{HF} = 52 Hz, CHF), 7.4 (m, Ar); ^{13}C NMR δ 13.8 (CH_3), 56.0 (d, J = 37 Hz, CH), 58.1 (CHBr), 92.5 (d, J = 178 Hz, CHF), 170 (C=O); ^{19}F NMR δ − 73.9 (dd, $^2J_{HF}$ = 52 Hz, $^3J_{HF}$ = 15 Hz). Anal. calcd for $C_{17}H_{16}BrFOS$: C, 56.60; H, 4.36. Found. C, 56.66; H, 4.22. The second component was **10** (R_f = 0.13) in 34% yield: ^{1}H NMR δ 6.27 (1H, dt, J_{HF} = 63 Hz, J_{HH} = 5 Hz, CHF_2), 7.23 (11H, Ar and vinyl); ^{13}C NMR δ 100 (t, J = 270 Hz, CF_2), 123–148 (Ar and vinyl), 190.1 (C=O): ^{19}F NMR δ − 14.3 (dd, J_{HF} = 63 Hz, J_{HH} = 5 Hz). Mass spectrum, 259 (M + H)$^+$. Anal. calcd for $C_{16}H_{12}F_2O$: C, 74.42; H, 4.65. Found: C, 74.40; H, 4.71.

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