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Oxidative Desulfurization-Fluorination of 1-Substituted 2,2,2-Tris(methylthio)ethanol Induces Difluorination under Oxidation or Rearrangement

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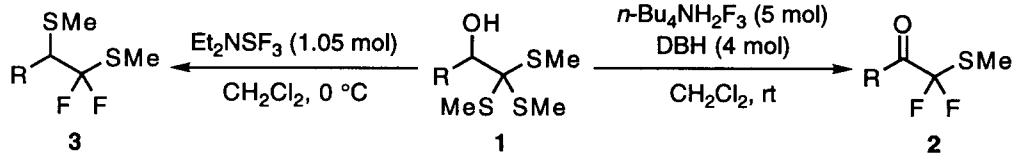
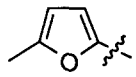
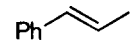
Abstract: Oxidative desulfurization-fluorination of $RCH(OH)C(SMe)_3$ using n-$Bu_4NH_2F_3$ and 1,3-dibromo-5,5-dimethylhydantoin gave $RC(O)CF_2SMe$, whereas treatment of the same substrates with Et_2NSF_3 afforded $RCH(SMe)CF_2SMe$.

Since organofluorine compounds often exhibit unique biological activities and/or material properties, their synthetic methods have been studied in various ways.[1] We have demonstrated that oxidative desulfurization-fluorination,[2] which converts C-S bond into C-F bond. For example, difluoromethylene moiety can be derivatized from dithio acetal.[3] We have extended this method to orthothioesters and found that β-hydroxy orthothioesters **1** could be converted into difluoro(methylthio)methyl ketones **2** and/or 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethanes **3**, depending on the reagent used.[4]



The substrate **1** was prepared by the aldehyde addition of $LiC(SMe)_3$[5] in good yields. The β-hydroxy orthothioester **1** was added to a mixture of n-$Bu_4NH_2F_3$ (5 mol) and 1,3-dibromo-5,5-dimethylhydantoin (DBH, 4 mol) in CH_2Cl_2 at room temperature. The resulting mixture was stirred at room temperature for 10 min and poured into sat. Na_2SO_3 aq solution. Extractive workup and purification by silica gel column chromatography gave difluoro(methylthio)methyl ketone **2**. Results summarized in Table 1 show that the substrates **1** derived from both aromatic and aliphatic aldehydes were successfully converted into the desired products **2** in good to moderate yields. Trifluorination did not take place even after prolonged reaction time. Bromofluorination of C=C bonds was not observed in the transformation of **1i** to **2i**.[6] However, the substrate derived from a ketone gave only a complex mixture of products.

Table 1. Fluorination of **1** with DBH/*n*-$Bu_4NH_2F_3$ or Et_2NSF_3

	R	DBH/*n*-$Bu_4NH_2F_3$[a]		Et_2NSF_3[a]	
1a	1-Naph-	**2a**	(95)	-[b]	
1b	2-Naph-	**2b**	(71)	**3b**	(50)
1c	4-Ph-C_6H_4-	**2c**	(44)	**3c**	(55)
1d	4-O_2N-C_6H_4-	-[b]		**3d**	(56)
1e	$PhCH_2CH_2$-	-[b]		**3e**	(70)
1f		**2f**	(56)	-[b]	
1g	*n*-$C_{11}H_{23}$-	**2g**	(44)	**3g**	(71)
1h	*c*-Hex-	**2h**	(28)	-[b]	
1i		**2i**	(31)	**3i**	(8)

a) Isolated yields are given in parentheses.
b) Not performed.

Formation of **2** is ascribed to (1) oxidation of sulfur by Br^+, (2) nucleophilic substitution of C-S bond by fluoride ion to form C-F bond, and (3) oxidation of the hydroxyl group. When the corresponding acetate $RCH(OAc)C(SMe)_3$ (R = 1-Naph) was treated under similar conditions (0 °C, 10 min), $RCH(OAc)CF_2SMe$ was obtained in 70% yield with a by-product $RCH(OAc)C(O)SMe$ (14%). Hydrolysis of $RCH(OAc)CF_2SMe$ (NaOH) or reduction of **2** ($NaBH_4$) gave $RCH(OH)CF_2SMe$ in 64% or 93% yield, respectively (R = 1-Naph).

On the other hand, when **1** was treated with Et_2NSF_3 at 0 °C for 10 min, 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethane **3** was obtained probably *via* dehydroxylation, rearrangement, fluorination, and oxidative desulfurization-fluorination.[7] The substrates derived from aromatic and aliphatic aldehydes gave the corresponding products (**3b**, **3e**, and **3g**) in good yields, whereas allyl alcohol **1i** gave **3i** in only 8% yield. Substrates derived from ketones gave complex mixtures of products. Trifluorination did not take place in this reaction also.

In summary, we have demonstrated here that difluoro(methylthio)methyl ketones and/or 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethanes are readily prepared from β-hydroxy ortho-thioesters *via* oxidative desulfurization-fluorination. Further synthetic applications of these products are being studied in our laboratories.

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