Efficient Conversions of Thioethers to α-Fluoro Thioethers with DAST or DAST/Antimony(III) Chloride[1]

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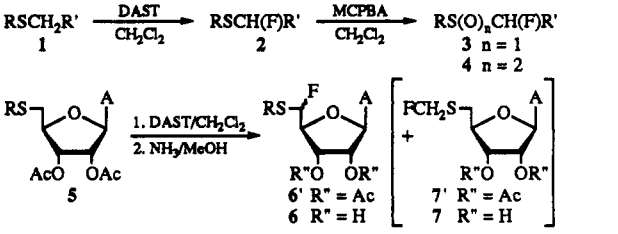
Summary: Dialkyl or alkyl aryl thioethers, including nucleoside thioethers, undergo virtually quantitative conversion to α-fluoro thioethers with (diethylamino)sulfur trifluoride (DAST) in dichloromethane at ambient temperature. Antimony(III) chloride catalyzes the process.

α-Fluoro thioethers have recently been employed in syntheses of novel biologically active compounds[2-4] and in preparations of α-fluoro sulfoxides,[5,6] sulfones,[7] and sulfoximines[8] which have been used to construct terminal vinyl fluorides[9] by alternatives to "fluoromethylene-Wittig"[10] chemistry. We now report efficient direct transformations of thioethers to α-fluoro thioethers with (diethylamino)sulfur trifluoride (DAST) and antimony(III) chloride catalysis.

Prior direct conversions of thioethers to α-fluoro thioethers have employed xenon difluoride,[11] *N*-fluoropyridinium triflates,[12] and electrochemical oxidation with $Et_3N{\cdot}3HF$ as the fluorine source.[13] Rigorously dried potassium fluoride/18-crown-6 ether converted α-chloro to α-fluoro thioethers.[14] McCarthy *et al.*[5] treated dialkyl and alkyl aryl sulfoxides with DAST and obtained α-fluoro thioethers by a "fluoro-Pummerer rearrangement" which has been widely used.[2-5,7,8,15] We discovered the potent and generally applicable[16-18] catalysis of this sulfoxide/DAST transformation by antimony(III) chloride.[2] We now report that the oxidation of thioethers to sulfoxides is unnecessary; thioethers are converted to α-thioethers readily with DAST or DAST/$SbCl_3$ at ambient temperature.

Table I. Conditions and Yields for Fluorination Reactions



compd	R	R'	time,[a] h	yield,[b] (%)
1–4a	4-$MeOC_6H_4$	H	1 (3)	quant (95)[c]
b	C_6H_5	H	3 (9)	quant (94)[c]
c	4-ClC_6H_4	H	7 (22)	98 (92)[c,d]
d	C_6H_5	$(CH_2)_2CO_2Et$	3	quant[c] (85)[e]
e	C_6H_5	$(CH_2)_6CH_3$	2	quant[c] (88)[e]
f	$PhCH_2$	H	<1 (3)	75[c,f] (55)[f,g]
g	CH_3	H	6	(82)[g]
h	C_2H_5	H	4	(88)[g]
5–6a	CH_3		2 (14)	(41)[f,h–j]
b	4-$MeOC_6H_4$		12	(59)[i–k]
c	C_6H_5		20	(48)[j,l,m]

[a] Reactions with 1.4 equiv of DAST, except as noted, were catalyzed with $SbCl_3$ (0.07 equiv) (times in parentheses are for uncatalyzed reactions). [b] Estimated by ^1H NMR; values in parentheses are for isolated products after column chromatography. [c] **2**. [d] With $SbCl_3$ and 1.6 equiv of DAST. Without $SbCl_3$, **2c**/**1c** (~9:1) was obtained. [e] **3** (overall yield). [f] Combined yield of fluorination products. [g] **4** (overall yield). [h] **6a** (R = CH_3) plus **7**. [i] Fluorination was complete (yield after deprotection and purification). [j] With $SbCl_3$ and 2.2 equiv of DAST. [k] **6b**. [l] **6c**. [m] Unreacted **5c** (~10%) was recovered as 5′-*S*-phenyl-5′-thioadenosine by Dowex 1 × 2 (OH^-) chromatography.

(Methylthio)benzene (**1b**) was treated with DAST (1.4 equiv) in anhydrous CH_2Cl_2 at ambient temperature for 9 h to give [(fluoromethyl)thio]benzene (**2b**) quantiatively [^1H NMR δ 5.70 (d, $^2J_{H,F}$ = 52.8 Hz, SCH_2F)]. Conversion of **1b** to **2b** was ~80% in 3 h with 1.4 equiv of DAST and quantitative in 4 h with 2 equiv of DAST. The small-scale process was general for dialkyl, alkyl aryl, and nucleoside 5′-thioethers, but it became *vigorously exothermic* with larger scale reactions.

McCarthy noted that 4-methoxyphenyl (alkyl) sulfoxides gave markedly increased rates of reaction with DAST and yields of α-fluoro thioethers relative to phenyl substrates.[5] We found that 4-methoxy(methylthio)benzene (**1a**) reacted with DAST to give **2a** only ~3 times faster than the phenyl analogue **1b** to give **2b**. Problems with reproducibility of fluorination yields with phenyl alkyl sulfoxides and DAST with ZnI_2 catalysis[5] resulting from competing reduction of sulfoxides to unflorinated sul-

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fides[2,4,8] had led to the use of the expensive 4-methoxyphenyl substrates.[3a-c,5] In contrast, even with the deactivating *p*-chloro substituent present, our new thioether/DAST transformation affords the α-fluoro thioether **2c** efficiently from 4-chloro(methylthio)benzene (**1c**).

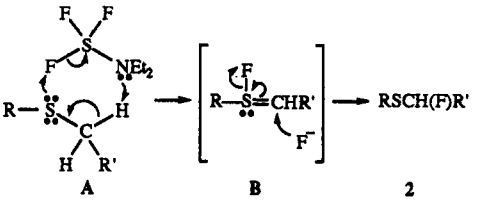
Antimony(III) chloride exerts less dramatic catalysis of this thioether process relative to its acceleration of the fluoro-Pummerer reaction.[16] $SbCl_3$ (0.05–0.07 equiv) caused 3–5-fold acceleration of **1b** + DAST → **2b** [DAST (1.2 equiv)/$SbCl_3$ gave ~85% conversion to **2b** (^1H NMR) in 2 h; ~10 h without catalyst]. The ratios of DAST/thioether required for complete conversions were the same for catalyzed and uncatalyzed reactions, depended strongly on the DAST quality, and varied slightly with the thioether (1.4–1.6 equiv). Larger quantities of $SbCl_3$ (0.75–1.0 equiv) inhibited the α-fluorination and gave dark mixtures.

Treatment of α-fluoro thioethers with XeF_2[11a] or electrochemically,[13] or α-fluoro sulfoxides with DAST,[5] gave α,α-difluoro thioethers. However, our new DAST/thioether procedure did not perform this second fluorination. Treatment of **2a** with DAST (3 equiv)/$SbCl_3$ (0 or 0.07 equiv)/CH_2Cl_2/20 h/Δ gave dark mixtures which contained mainly unreacted **2a** (~85%).

Dialkyl thioethers were converted to α-fluoro thioethers efficiently with DAST. Treatment of (methylthio)ethane (**1h**) with DAST/$SbCl_3$ for 4 h resulted in regiospecific formation of [(fluoromethyl)thio]ethane (**2h**) which was oxidized in situ (3-chloroperoxybenzoic acid, *m*-CPBA) to the stable, less volatile sulfone **4h** (88% from **1h**) for analysis. DAST converted the benzyl methyl thioether (**1f**) into a regioisomeric mixture[12] (~1:1) of **2f** and the labile α-fluoro-α-(methylthio)toluene which decomposed (2 h, ambient, $CHCl_3$ solution) to give benzaldehyde. A ^1H NMR spectrum of the crude mixture immediately after workup at 0 °C had peaks at δ 5.38 (d, $^2J_{H,F}$ = 52.9 Hz, SCH_2F), 6.61 (d, $^2J_{H,F}$ = 55.6 Hz, PhC*H*FS), and 10.02 (s, PhC*H*O) (**2f**/**5**/benzaldehyde, ~2:1:1; the δ 6.61 signal diminished with increasing intensity of the signal at δ 10.02 upon standing). The labile dialkyl α-fluoro thioethers **2** were directly oxidized in situ to stable sulfoxides **3** or sulfones **4**. The expected[15] major sulfoxide diastereomers (*R*-sulfur) were obtained (**3d**, ~2.6:1; **3e**, ~2.1:1).

Treatment of 2′,3′-di-*O*-acetyl-5′-*S*-methyl-5′-thioadenosine (**5a**) with DAST (2.2 equiv) or DAST/$SbCl_3$ gave the labile 2′,3′-di-*O*-acetyl-5′-fluoro-5′-(methylthio) (**6′a**) diastereomers and 2′,3′-di-*O*-acetyl-5′-*S*-(fluoromethyl)-5′-thioadenosine (**7′**). ^{19}F NMR peaks[2] were diagnostic for the isomeric composition. Silica chromatography gave **6′a**/**7′** (~2.2:1; 60%) which could be deacetylated, purified, and resolved to give **6a** plus **7** directly by ion-exchange chromatography [Dowex 1×2 (OH^-), MeOH].[4a] The 5′-*S*-(4-methoxyphenyl) (**5b**) and phenyl (**5c**) nucleoside derivatives were converted directly to their 5′-fluoro analogues[2] **6′** by this procedure. The 4-methoxy derivative **5b** reacted more readily to give **6′b** [**6b** (5′*R*/*S* (~1:1.7)) after deacetylation], but the phenyl diastereomers **6c** (5′*R*/*S* (~1:1.6)) were obtained in comparable yields.

Fluorination might occur via 6-membered transition state **A** with transfer of fluorine from DAST to the thioether sulfur atom and abstraction of an α-proton by the electron pair on nitrogen. A postulated intramolecular



3-centered fluorine rearrangement[11b,12] or conjugate nucleophilic attack by external fluoride on intermediate **B** would complete the transformation to **2**.

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Supplementary Material Available: Experimental details and spectral data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.