

Efficient Conversions of Thioethers to α -Fluoro Thioethers with DAST or DAST/Antimony(III) Chloride¹

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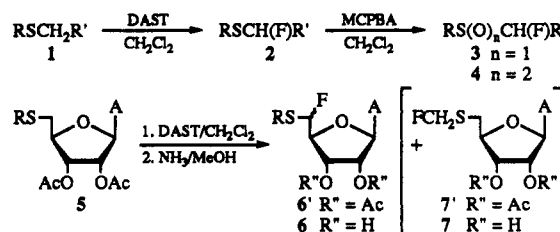
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Summary: Dialkyl or alkyl aryl thioethers, including nucleoside thioethers, undergo virtually quantitative conversion to α -fluoro thioethers with (diethylamino)sulfur trifluoride (DAST) in dichloromethane at ambient temperature. Antimony(III) chloride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

α -Fluoro thioethers have recently been employed in syntheses of novel biologically active compounds²⁻⁴ and in preparations of α -fluoro sulfoxides,^{5,6} sulfones,⁷ and sulfoximines⁸ which have been used to construct terminal vinyl fluorides⁹ 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 Et₃N·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 applicable¹⁶⁻¹⁸ catalysis of this sulfoxide/DAST transformation by antimony(III) chloride.² We now

Table I. Conditions and Yields for Fluorination Reactions



compd	R	R'	time, ^a h	yield, ^b (%)
1-4a	4-MeOC ₆ H ₄	H	1 (3)	quant (95) ^c
b	C ₆ H ₅	H	3 (9)	quant (94) ^c
c	4-ClC ₆ H ₄	H	7 (22)	98 (92) ^{c,d}
d	C ₆ H ₅	(CH ₂) ₂ CO ₂ Et	3	quant ^c (85) ^e
e	C ₆ H ₅	(CH ₂) ₆ CH 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 ₂ H ₅	H	4	(88) ^g
5-6a	CH ₃		2 (14)	(41) ^{f,h-j}
b	4-MeOC ₆ H ₄		12	(59) ^{i-k}
c	C ₆ H ₅		20	(48) ^{j,l,m}

^a Reactions with 1.4 equiv of DAST, except as noted, were catalyzed with SbCl₃ (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 SbCl₃ and 1.6 equiv of DAST. Without SbCl₃, 2c/1c (~9:1) was obtained. ^e 3 (overall yield). ^f Combined yield of fluorination products. ^g 4 (overall yield). ^h 6a (R = CH₃) plus 7. ⁱ Fluorination was complete (yield after deprotection and purification). ^j With SbCl₃ 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.

report that the oxidation of thioethers to sulfoxides is unnecessary; thioethers are converted to α -thioethers readily with DAST or DAST/SbCl₃ at ambient temperature.

(Methylthio)benzene (**1b**) was treated with DAST (1.4 equiv) in anhydrous CH₂Cl₂ at ambient temperature for 9 h to give [(fluoromethyl)thio]benzene (**2b**) quantitatively [¹H NMR δ 5.70 (d, ³J_{H,F} = 52.8 Hz, SCH₂F)]. 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 catalysis⁵ resulting from competing reduction of sulfoxides to unfluorinated 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 SbCl₃ (0.05–0.07 equiv) caused 3–5-fold acceleration of 1b + DAST $\rightarrow$ 2b [DAST (1.2 equiv)/SbCl₃ gave $\sim$ 85% conversion to 2b (¹H NMR) in 2 h; $\sim$ 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 SbCl₃ (0.75–1.0 equiv) inhibited the α -fluorination and gave dark mixtures.

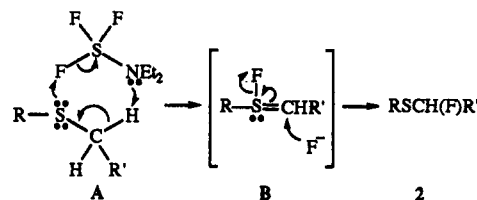
Treatment of α -fluoro thioethers with XeF₂^{11a} or electrochemically,¹³ or α -fluoro sulfoxides with DAST,⁵ gave α,α -difluoro thioethers. However, our new DAST/thioether procedure did not perform this second fluorination. Treatment of 2a with DAST (3 equiv)/SbCl₃ (0 or 0.07 equiv)/CH₂Cl₂/20 h/ Δ gave dark mixtures which contained mainly unreacted 2a ($\sim$ 85%).

Dialkyl thioethers were converted to α -fluoro thioethers efficiently with DAST. Treatment of (methylthio)ethane (1h) with DAST/SbCl₃ 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 mixture¹² ($\sim$ 1:1) of 2f and the labile α -fluoro- α -(methylthio)toluene which decomposed (2 h, ambient, CHCl₃ 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, SCH₂F), 6.61 (d, ²J_{H,F} = 55.6 Hz, PhCHFS), and 10.02 (s, PhCHO) (2f/5/benzaldehyde, $\sim$ 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

sulfoxes 4. The expected¹⁵ major sulfoxide diastereomers (*R*-sulfur) were obtained (3d, $\sim$ 2.6:1; 3e, $\sim$ 2.1:1).

Treatment of 2',3'-di-*O*-acetyl-5'-*S*-methyl-5'-thioadenosine (5a) with DAST (2.2 equiv) or DAST/SbCl₃ 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'). ¹⁹F NMR peaks² were diagnostic for the isomeric composition. Silica chromatography gave 6'a/7' ($\sim$ 2.2:1; 60%) which could be deacetylated, purified, and resolved to give 6a plus 7 directly by ion-exchange chromatography [Dowex 1 $\times$ 2 (OH⁻), MeOH].^{4a} The 5'-*S*-(4-methoxyphenyl) (5b) and phenyl (5c) nucleoside derivatives were converted directly to their 5'-fluoro analogues² 6' by this procedure. The 4-methoxy derivative 5b reacted more readily to give 6'b [6b (5'*R*/*S*) ($\sim$ 1:1.7)) after deacetylation], but the phenyl diastereomers 6c (5'*R*/*S*) ($\sim$ 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.