Fluorination of Thiocarbonyl Compounds with Bis(2-methoxyethyl)aminosulfur Trifluoride (Deoxo-Fluor Reagent): A Facile Synthesis of *gem*-Difluorides

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A variety of thiocarbonyl derivatives (thioketone, thioester, thioamide, dithioester, and dithiocarbamate) were converted to the corresponding *gem*-difluorides in excellent yields on reaction with the fluorinating agent, bis(2-methoxyethyl)aminosulfur trifluoride, in the presence of $SbCl_3$.

Introduction

The introduction of fluorine into organic compounds can profoundly alter their chemical, physical, and biological properties.[1−5] As a result, there has been a considerable interest in the development of pharmaceuticals and plant protection agents that contain fluorine in their structures. In view of this, efforts aimed at the development of simple, safe, and efficient methods for the synthesis of organofluorine compounds have escalated in recent years.[6]

The direct transformation of the carbonyl group of aldeydes and ketones into the *gem*-difluoride can in many cases be accomplished with reagents such as SF_4[7] and aminosulfur trifluorides[8] with relative ease. However, extreme conditions are required and low yields are obtained when similar transformations are conducted with electron-deficient ketones, esters, and amides.[7] Alternative methods involve the reaction of carbonyl-derived hydrazones[9] and diazo compounds[10] with the strong oxidative fluorinators, iodine monofluoride or fluorine. *gem*-Difluorides can also be prepared by the oxidative desulfurization−fluorination of ortho thioesters,[11] dithiolanes,[12] and thiocarbonyl derivatives with electrophilic halonium species in the presence of fluoride ions.[13] The synthesis of α,α-difluoroethers from the reaction of thioesters with diethylaminosulfur trifluoride (DAST)[14] is the only report of a thiocarbonyl to *gem*-difluoride conversion using aminosulfur trifluorides.

We recently reported on the preparation and the general synthetic utility of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor Reagent, **1**)[15] a compound that has been found to be significantly more thermally stable and therefore of broader applicability than DAST. Herein, we describe a simple, efficient route to a variety of *gem*-difluorides by the reaction of thioketones, thioesters, thioamides, dithioesters, and dithiocarbamates with **1.** These compounds are not readily accessible directly from their carbonyl precursors.

Results and Discussion

The direct conversion of benzophenone to the *gem*-difluoride with SF_4 is known to be quite difficult. It takes place only at 180 °C in the presence of a large excess of HF.[16] Alternatively, the product can be obtained by reacting the dithiolane derivative with excess DBH in HF−pyridine[12a] or with I_2/F_2.[12b] We observed no reaction when benzophenone was heated with neat **1** at 90 °C for 16 h. However, we found that the thiono derivative of bezophenone obtained from the reaction of benzophenone with P_4S_{10}[17] reacted readily with **1** in CH_2Cl_2 in the presence of a catalytic amount of $SbCl_3$ (Table 1) to produce the difluoride in excellent yield.

† Air Products and Chemicals Inc. summer interns (1998 and 1999, respectively) from Cedar Crest College, Allentown, PA.

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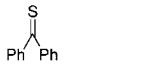
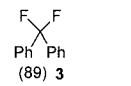
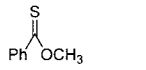
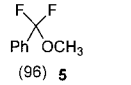
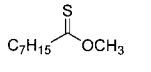
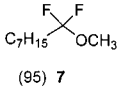
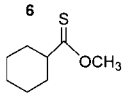
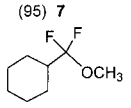
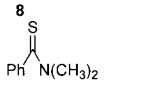
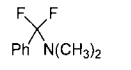
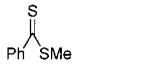
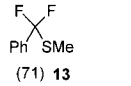
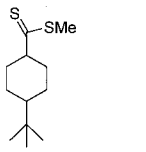
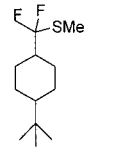
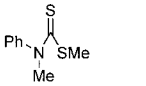
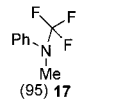
Table 1. Fluorination of Thiocarbonyl Compounds with 1

Starting material	Reaction conditions	Product (% Yield)	^{19}FNMR ($CDCl_3$) δ (ppm)
 **2**	CH_2Cl_2, **1**, $SbCl_3$ (0.05 eq), 48h, RT	 (89) **3**	- 90
 **4**	CH_2Cl_2, **1**, $SbCl_3$ (0.05 eq), 4h, RT	 (96) **5**	- 72
 **6**	CH_2Cl_2, **1**, $SbCl_3$ (0.05 eq), 2h, RT	 (95) **7**	- 79
 **8**	CH_2Cl_2, **1**, $SbCl_3$ (0.05 eq), 30 min, RT	 (95) **9**	- 86
 **10**	CH_2Cl_2, **1**, $SbCl_3$ (0.1 eq), 48h, RT	 (78) **11**	- 72
 **12**	CH_2Cl_2, **1**, $SbCl_3$ (0.1 eq), 1h, RT	 (71) **13**	- 76
 **14**	CH_2Cl_2, **1**, $SbCl_3$ (0.1 eq), 1h, RT	 (74) **15**	- 82
 **16**	CH_2Cl_2, **1**, (2eq), $SbCl_3$ (0.05eq), 4h, RT	 (95) **17**	- 62

When thioesters prepared from Lawesson reagent[18] in xylenes at 150 °C were reacted with **1** in CH_2Cl_2, in the presence of 0.01 equiv of $SbCl_3$, the *gem*-difluoride products were obtained in virtually quantitative yields from the corresponding esters (Table 1). The reaction could be applied to a variety of struturally diverse substrates including aliphatic, alicyclic, and aromatic thioesters. Much lower overall yields of products were obtained when these thioesters, prepared from the reaction of the carboxylic esters with Lawesson reagent in refluxing toluene, were treated with DAST in the absence of any added Lewis acid catalyst.[14] Our mild, high yielding procedure to α,α-difluorethers should provide ready access to this unique class of fluorinated compounds.

A similar reaction of **1** with the thioamide derivative of *N*,*N*-dimethylbenzamide[18] furnished the corresponding α,α-difluoroamine[19] in a very good yield (Table 1). In contrast to the reaction with the thioesters this conversion was much slower, requiring 48 h for complete consumption of starting material.

The methyldithio esters of benzoic acid and 4-*tert*-butylcyclohexane carboxylic acid were prepared by reacting the appropriate acyl chloride with methanethiol followed by reaction with Lawesson reagent.[13e] These were used to generate the corresponding α,α-difluorothioether on reaction with **1** under reaction conditions similar to those described above (Table 1). While the reaction proceeded in high yields with the aryl or 2° alkyl substituted dithioesters (**12** and **14** in Table 1), we obtained only a complex mixture of products from the 1° alkyl substituted compounds. This result is in sharp contrast to that of the reported reaction of DAST with similar dithioesters where none of the desired products were obtained.[20]

Aryl(trifluoromethyl)amines are becoming an important class of liquid-crystalline materials.[21] This class of compounds is also accessible with our current fluorination protocol (Table 1). For example, the methyldithiocarbamate derivative of *N*-methylaniline[22] afforded an excellent yield of the trifluoride **17**.[22] Significantly and in contrast with the fluorination by **1** of all the other thiocarbonyl compounds described herein, no difluoride formation was seen. Our method represents an improvement over alternative procedures which utilize toxic and/or corrosive reagents[23] or via *N*-haloimides in the presence of HF where brominated byproduct formation can be substantial.[13b,22]

While the mechanism of the fluorination of thiocarbonyls by **1** has not been elucidated it should be similar to that proposed for the reaction of carbonyl compounds with SF_4.[8] It is clear that the Lewis acid $SbCl_3$ greatly facilitates this process. $SbCl_3$ catalysis of other reactions with DAST has been previously observed.[24] An examination of the products formed on reaction of **1** with $SbCl_3$ in CH_2Cl_2 showed that the highly electrophilic dialkylaminosulfiminium species $(NR_2{-}SF_2)^+$, R = $CH_2CH_2OCH_3$, (^{19}F NMR in $CDCl_3$, δ = 12 ppm) was predominantly obtained. However, the identity of the counteranion could not be easily characterized. A similar product was observed by Markovskii et al.[25a] for the reaction of BF_3 with DAST, and a similar intermediate was proposed by McCarthy et al.[25b] for the reactions of DAST catalyzed by ZnI_2. The fluorodesulfurization is undoubtedly aided by the highly nucleophilic nature of the thione sulfur atom. It is interesting to note that other Lewis acids such as HF and ZnI_2 were not as effective as $SbCl_3$, requiring much longer reaction times.

The $SbCl_3$-catalyzed fluorination of thiocarbonyl compounds with the Deoxo-Fluor Reagent (**1**) provides a simple, mild, and selective process for the preparation of a variety of interesting and potentially useful *gem*-difluoride synthons.

Experimental Section

The thioketone,[17] thioesters,[18] thioamide,[18] dithioesters,[13e] and dithiocarbamate[22] substrates were obtained by standard literature methods. $SbCl_3$ and Lawesson reagent were obtained from Aldrich and used as received. Bis(2-methoxyethyl)-aminosulfur trifluoride (**1**) was acquired from Air Products and

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Chemicals, Inc.[26] ^{1}H and ^{19}F NMR spectra were recorded at 300 and 282 MHz, respectively. Chemical shifts were referenced to neat $CFCl_3$ (^{19}F) or neat TMS (^{1}H). GC/MS were done using a GC with a 30 m × 0.25 mm SPB-5 column and a MS with an EI detector. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, TN.

CAUTION: Compound **1** reacts rapidly and exothermically with water liberating HF. It is recommended that reactions with **1** be carried out at <90 °C.

General Procedure for Preparation of *gem*-Difluorides. A solution of the thiocarbonyl compound (10 mmol) in CH_2Cl_2 (3.0 mL) was added to a three-neck round-bottom flask fitted with a rubber septum, stopper and a N_2 inlet tube. To this solution were added $SbCl_3$ (0.01−0.1 equiv; as indicated in Table 1) and Deoxo-Fluor Reagent, **1** (3.09 g, 2.57 mL,14 mmol). The resulting solution was stirred under N_2, and the reaction was monitored by GC/MS for disappearance of the starting material. On completion, the mixture was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$. After CO_2 evolution ceased, the mixture was extracted into CH_2Cl_2, dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel with hexanes/ethyl acetate (98/2) as eluent (**3**, **5**, **7**, **9**) or by bulb to bulb distillation (**11**, **13**, **15**, **17**) to afford the pure products: difluorodiphenylmethane[16] (**3**, 89%); (difluoromethoxymethyl)-benzene[14] (**5**, 96%); 1,1-difluoro-1-methoxyoctane[14] (**7**, 97%); (difluoromethoxymethyl)cyclohexane[14] (**9**, 95%); α,α-difluoro-*N*,*N*-dimethylbenzylamine[19] (**11**, 78%); [difluoro(methylthio)-methyl]benzene (**13**, 71%); ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2H), 7.45−7.35 (m, 3H), 2.40 (s, 3H); ^{19}F NMR($CDCl_3$) δ −75 (s); elemental analysis calculated for $C_8H_8F_2S$ C, 55.16; H, 4.63; F, 21.81; S, 18.40; found C, 55.05; H, 4.52; F, 21.52; S, 18.15; 1-[difluoro(methylthio)methyl]-4-*tert*-butylcyclohexane (**15**, 74%); ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.0−1.90 (m, 2H), 1.90−1.70 (m, 3H), 1.35−1.10 (m, 2H), 0.9−1.05 (m, 3H), 0.85 (s, 9H); ^{19}F NMR ($CDCl_3$) δ −82 (s); elemental analysis calculated for $C_{12}H_{22}F_2S$ C, 60.98; H, 9.38; F, 16.07; S, 13.56; found C, 60.85; H, 9.26; F, 15.93; S, 13.34; *N*-methyl-*N*-trifluoroaniline[22] (**17**, 95%).

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