Bis(2-methoxyethyl)aminosulfur Trifluoride: A New Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability

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Bis(2-methoxyethyl)aminosulfur trifluoride, $(CH_3OCH_2CH_2)_2NSF_3$ (Deoxo-Fluor reagent), is a new deoxofluorinating agent that is much more thermally stable than DAST $(C_2H_5)_2NSF_3$ and its congeners. It is effective for the conversion of alcohols to alkyl fluorides, aldehydes/ketones to the corresponding *gem*-difluorides, and carboxylic acids to the trifluoromethyl derivatives with, in some cases, superior performance compared to DAST. The enhanced stability is rationalized on the basis of conformational rigidity imposed by a coordination of the alkoxy groups with the electron-deficient sulfur atom of the trifluoride.

Introduction

The introduction of fluorine into medicinal and agrochemical products can profoundly alter their biological properties.[1−4] Fluorine mimics hydrogen with respect to steric requirements and contributes to an alteration of the electronic properties of the molecule, often resulting in favorable increased lipophilicity and oxidative stability properties.[5] 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]

A widely used synthetic technique involves the conversion of carbon−oxygen to carbon−fluorine bonds (deoxofluorination) by nucleophilic fluorinating sources. This transformation has routinely been accomplished with the dialkylaminosulfur trifluorides, mostly with DAST (NEt_2SF_3), in small laboratory scale reactions, usually at near-ambient conditions.[6] However, the use of DAST at more forcing conditions and at a large scale has been severely curtailed owing to its well-known thermal instability.[7,8] Thermal analysis studies of DAST and related R_2NSF_3 compounds by Middleton et al.[9] indicate that decomposition of these aminosulfur trifluorides occurs in two stages. A slow reaction is seen at ∼90 °C with evolution of SF_4 and formation of a bis(dialkylamino)sulfur difluoride, $R_2NSF_2NR_2$, presumably by a molecular disproportionation mechanism. On heating to higher temperatures, the samples exploded or detonated, resulting in a black char and unidentified gaseous byproducts.

In our attempts to arrive at more thermally stable and safer deoxofluorinating reagents, we sought to prepare aminosulfur trifluorides that primarily would not yield significant gaseous byproducts on thermal decomposition. Since such R_2NSF_3 reagents are expected to be a facile source of fluoride, a very strong base, compounds in which the R groups are relatively resistant to proton abstraction were chosen. Perhaps more importantly, we surmised that the presence of sterically hindered groups in the vicinity of the reactive SF_3 moiety would militate against the postulated bimolecular disproportionation[9] seen with DAST and hence lead to a more thermally robust reagent. Such a sterically rigid entity could, in principle, be realized by having very bulky groups on nitrogen or preferably by employing electron-rich alkoxy groups that could coordinate to the electron-deficient sulfur atom. In this context, there was some indication in the literature of a greater thermal stability of a cyclic monoalkoxy aminosulfurane.[10] Our efforts led to bis(2-methoxyethyl)aminosulfur trifluoride, $(CH_3OCH_2CH_2)_2NSF_3$, (Deoxo-Fluor reagent, **1**) which was found to be significantly more thermally stable than DAST with, consequently, a greater range and scope of applicability. We report here a synthesis of **1**, results of thermal analysis studies, and illustrations of the reagent's significant broad-spectrum utility, as in the conversion of alcohols to alkyl fluorides, aldehydes/ketones to *gem*-difluorides, and carboxylic acids to the corresponding trifluoromethyl derivatives. A preliminary report of some of this work has appeared.[11]

Results

Synthesis. The Deoxo-Fluor reagent **1** was obtained in a manner analagous to that used for preparing DAST[12]

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(4) Banks, R. E. *Fluorine in Agriculture*; Fluorine Technology Limited: Sale, Chesire, U.K., 1995 (ISBN: 1-85957-033-X).
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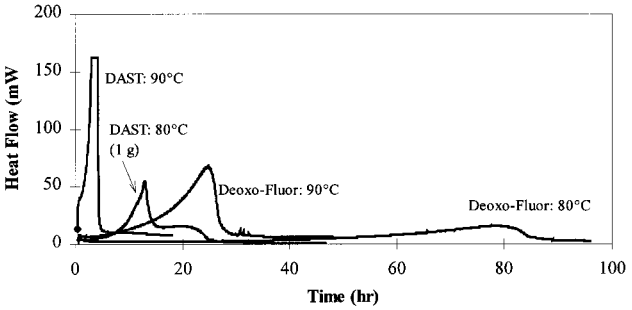


Figure 1. Isothermal calorimetry of DAST and Deoxo-Fluor (**1**) reagents.

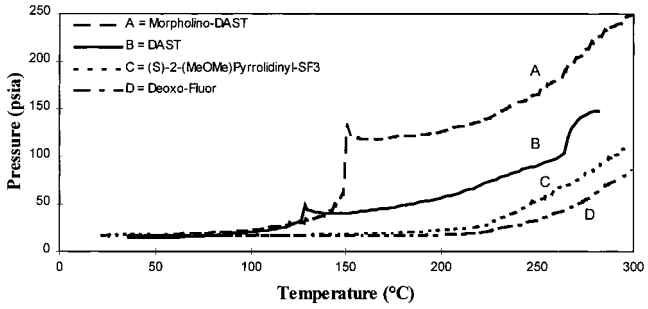


Figure 2. Comparison of recorded pressure data from the thermal decompositon of the Deoxo-Fluor (**1**), DAST, and morpholino-DAST reagents in the Radex instrument.

by reacting the *N*-trimethylsilyl derivative of bis(2-methoxyethyl)amine with SF_4 in Et_2O, followed by distillation of the crude product at 71 °C (0.4 mmHg). It was characterized by elemental and spectroscopic analyses: ^{1}H NMR ($CDCl_3$) δ 3.5 (t, J = 5.30 Hz, 4H), 3.15 (t, J = 5.30 Hz, 4H), 3.05 (s, 6H); ^{19}F NMR ($CDCl_3$) δ 40 (s, br, 3F); with added fluoride scavenger, e.g., NEt_2SiMe_3,[10] ^{19}F NMR ($CDCl_3$) δ 55 (s, br, 2F), 28 (s, br, 1F). As prepared, the reagent is a light yellow liquid, colorless after distillation. It is currently commercially available.[13]

Thermal Analysis Studies. The thermal decomposition profiles of **1**, of DAST, and in some cases, of morpholino-DAST were examined by isothermal calorimetry, differential scanning calorimetry (DSC), Radex, and accelerating rate calorimetry (ARC). The instrumentation and procedures are succinctly described in the Experimental Section.

(a) Isothermal Heat Evolution Measurements. A Setaram C80 calorimeter, operating in an isothermal mode, was used to provide data on the decomposition characteristics of reagent **1** and DAST. Results are reported in Figure 1, which gives heat flow data (reaction exotherms) for samples that were held isothermally at 90 and 80 °C for periods of hours to days. At 90 °C, DAST decomposes within a few hours, with a high rate of heat release (>160 mW). However, for **1** at 90 °C, the time to maximum reaction rate is 25 h, about six times longer than for DAST, and the maximum heat flow is substantially lower (~67 mW); both are indications of improved thermal stability for **1**. This is also the case at the lower temperature (80 °C), where the DAST sample reaches its maximum rate of decomposition (55 mW) in about 12 h, whereas **1** requires about 80 h (>3 days) to reach its maximum (15 mW). Note that for the test with DAST at 80 °C the sample size was reduced from 3 to 1 g to avoid over-ranging the calorimeter. This affects the magnitude of the heat flow signal but not its position on the time scale; as a result, rates of heat evolution cannot be directly compared.

The data in Figure 1 also indicate that both materials decompose by an autocatalytic mechanism, because the maximum rate of heat evolution occurs after some elapsed time. Clearly, the decomposition rate of both compounds depends on the generation of some catalyst, and this is hypothesized to be hydrogen fluoride. Because HF is known to catalyze deoxofluorination reactions with aminosulfur trifluorides,[12] its effect on the decomposition of **1** was investigated by calorimetry. Addition of a small amount of 70% HF−pyridine (30 mg/2.5 g of **1**) decreased the time to maximum reaction rate at 90 °C by 1−2 h. With a higher concentration (130 mg/3.0 g of **1**), this time decreased by about 6 h, but the maximum heat flux was about the same with and without HF−pyridine. In both cases however, the total heat evolved was about the same as that measured for neat **1**. Interestingly, the addition of triethylamine (90 mg/3.0 g of **1**) resulted in a greatly accelerated decomposition of the reagent, with a maximum rate occurring at only 1−2 h after equilibration at 90 °C. Similar results were observed when triethylamine was added to DAST; at 80 °C, the time to maximum reaction rate decreased from 13 h to less than 2 h.

(b) Heat Evolution and Pressure Rise Data on Thermal Ramping. Preliminary testing by DSC on very small (~3 mg) samples of DAST and **1** indicated that, although both begin to decompose at about the same temperature (~140 °C), DAST releases more heat (1700 vs 1100 J/g) and does so at significantly higher rates (see Figure 1 in ref 11). These results have now been confirmed with larger samples (~300 mg) utilizing the Radex instrumentation.

Of equal importance to heat evolution is the rate of formation of gaseous decomposition products, which determines the size of emergency relief devices in process vessels. In Figure 2 are summarized the pressure versus temperature data obtained for DAST, morpholino-DAST, and reagent **1**, using the Radex instrument. DAST and morpholino-DAST exhibit dramatic rates of gas evolution on heating, as evidenced by the nearly vertical slope of the pressure curves during their decomposition exotherms (~130 and 150 °C, respectively). The Deoxo-Fluor reagent (**1**) does not exhibit such a rapid increase in pressure during decomposition. It is also interesting to note that the cyclic alkoxy sulfurane, (*S*)-2-methoxymethyl-pyrrolidin-1-ylsulfur trifluoride[10] showed a decomposition profile similar to that of **1** up to ~160 °C, but somewhat higher pressures were recorded above this temperature.

Further comparisons of DAST and **1** were provided by ARC. Here temperature and pressure in the test cell are measured as the sample undergoes runaway reaction at near adiabatic conditions, and these signals can be converted to rates of temperature and pressure rise. In Figure 3, the log of the measured self-heating rate is plotted versus inverse absolute temperature for DAST and **1**. A smaller sample size was used for DAST to prevent rupture of the test cell by excessive pressure. Exothermic activity is first detected at a slightly higher temperature for **1** than for DAST (100 vs 85 °C); however,

(13) Aldrich Chemical Co., Milwaukee, WI, 53201 and Air Products and Chemicals, Inc., 7201 Hamilton Blvd., Allentown, PA 18195-1501: ref. to G. Saba, Tel: 610-481-7510, Fax: 610-481-3765, E-mail: sabagt@apci.com.

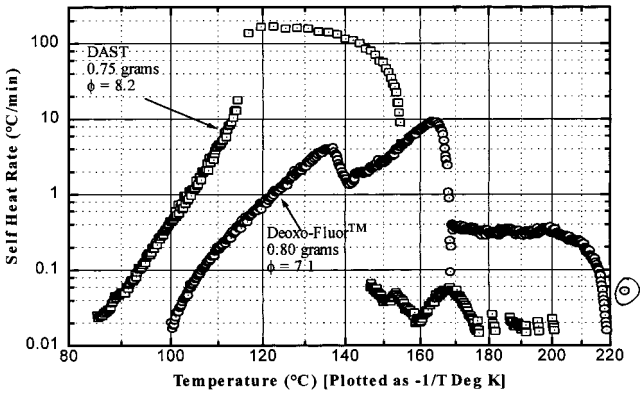
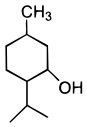
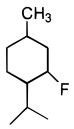
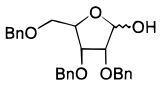
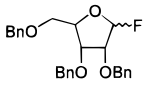
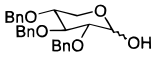
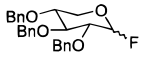


Figure 3. Accelerating rate calorimetry of DAST and Deoxo-Fluor reagents.

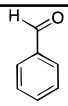
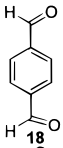
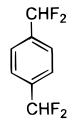
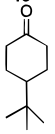
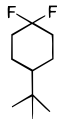
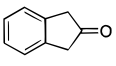
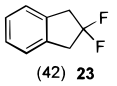
Table 1. Fluorination of Alcohols with 1

Starting Material	Reaction Conditions	Product (Yield)
$PhCH_2CH_2OH$ **2**	**1**,CH_2Cl_2, RT,16h	$PhCH_2CH_2F$ (85) **3**
$PhCH_2OH$ **4**	**1**,CH_2Cl_2, -78°C, 3h	$PhCH_2F$ (96) **5**
 **6**	**1**,CH_2Cl_2, -78°C, 2h RT, 2h	 (44) **7**
$CH_3CH(OH)CO_2Et$ **8**	**1**,CH_2Cl_2, -78°C, 2h RT, 3h	$CH_3CH(F)CO_2Et$ (73) **9**
$CH_3CCH_3(OH)CO_2Et$ **10**	**1**,CH_2Cl_2, -78°C, 2h RT,8h	$CH_3CCH_3(F)CO_2Et$ (89) **11**
 **12**	**1**,CH_2Cl_2, RT,30 min	 (98) α/β = 9/91 **13**
 **14**	**1**,CH_2Cl_2, RT,30 min	 (98) α/β = 28/72 **15**

heat generation rates are about an order of magnitude higher for DAST at any temperature. The accompanying rate of pressure increase data provided an even more pronounced contrast in the thermal behavior of the two reagents. For DAST, pressure generation rates of 1000 psi/min were recorded at 115 °C with a sample size of <1 g. On the same scale, **1** exhibited a maximum pressure rise rate of 50 psi/min, at a higher temperature (160 °C).

Fluorination Reactions with the Deoxo-Fluor Reagent (1). (a) Alcohols. Alcohols are readily converted to alkyl fluorides (Table 1). Excellent to moderate yields were obtained with a variety of structurally diverse substrates (1°, 2°, 3°, benzylic, and anomeric hydroxyl groups). For most of the compounds examined, fluorination proceeded at −78 °C; however, in some cases it was necessary to warm the reaction mixture to room temperature to ensure a more rapid and complete conversion. The rate of reaction was greatly dependent on the structure of the compound with benzylic >2° > 3° > 1°. Within any particular class of alcohol, the rate is controlled by the steric hindrance of the compound; e.g., menthol was more slowly fluorinated than ethyl lactate under the same reaction conditions. The replacement of the anomeric hydroxyls of both ribose and glucose derivatives readily yielded the corresponding fluorides in virtually quantitative yields. This procedure for the anomeric functionalization of carbohydrates, which has been performed with DAST,[14,15] should be more efficient than previous reported methodologies, avoiding multistep procedures.[16]

Table 2. Fluorination of Aldehydes and Ketones with 1

Starting Material	Reaction Conditions	Product (Yield)
 **16**	**1**, (1.7eq), CH_2Cl_2 RT, 16h	 (95) **17**
 **18**	**1**, (3.0eq), CH_2Cl_2 Reflux, 16h	 (94) **19**
 **20**	**1**, (1.7eq), CH_2Cl_2 RT, 16h, 0.2eq. HF	 (85) **21**
 **22**	**1**, (1.7eq), CH_2Cl_2 RT, 16h, 0.2eq. HF	 (42) **23**
$PhOCH_2COCH_3$ **24**	**1**, (1.7eq), CH_2Cl_2 RT, 16h, 0.2eq. HF	$PhOCH_2CF_2CH_3$ (98) **25**
$PhCOCOOEt$ **26**	**1**, (1.7eq), CH_2Cl_2 RT, 16h, 0.2eq. HF	$PhCF_2COOEt$ (81) **27**
$PhCOCH_3$ **28**	**1**, (1.5eq), neat 85°C, 16h	$PhCF_2CH_3$ (92) **29**

In reactions with some alcohols, better yields were obtained with **1** than with DAST. For example, under the same reaction conditions, fluorination of cyclooctanol afforded an 85% yield of cyclooctyl fluoride with **1** and only a 70% yield on reaction with DAST.[17] This difference can be attributed to a higher proportion of the olefin elimination product (cyclohexene) in the DAST reaction. Surprisingly, reaction of the earlier cited[10] alkoxy aminosulfurane, (*S*)-2-(methoxymethyl)pyrrolidin-1-ylsulfur trifluoride, with cyclooctanol was relatively unselective, giving only a 17% yield of cyclooctyl fluoride and considerable elimination byproducts under the same reaction conditions. Thus, despite the apparent thermal stability of this compound, its poor fluorinating ability coupled with the relatively high cost and low availability of the starting amine used in its preparation will likely limit its synthetic utility.

(b) Aldehydes and Ketones. The fluorination of several structurally different aldehydes and ketones was also investigated (Table 2). These reactions were conducted in CH_2Cl_2 at room temperature in the presence of 0.1 equiv of HF, generated in situ, with added EtOH. Fluorination of benzaldehyde and terephthaldicarbox-

(14) Rosenbrook, W., Jr.; Riley, D. A.; Lartez, P. A. *Tettrahedron Lett.* **1985**, *26* (1), 3.
(15) Posner, G. H.; Haines, S. R. *Tettrahedron Lett.* **1985**, *26* (1), 5.
(16) Withers, S. G.; Rupitz, K.; Street, I. P. *J. Biol. Chem.* **1988**, *263*, 7929.
(17) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

Table 3. Fluorination of Carboxylic Acids and Acid Chloride with 1

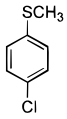
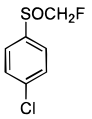
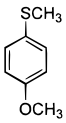
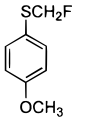
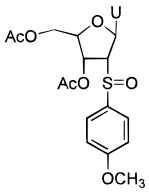
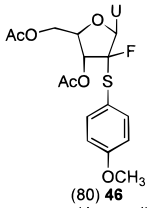
Starting Material	Reaction Conditions	Product (Yield)
PhCOOH **30**	**1**, CH_2Cl_2, 0°C, 30 min	PhCOF (96) **31**
$C_{11}H_{23}COOH$ **32**	**1**, CH_2Cl_2, 0°C, 30 min	$C_{11}H_{23}COF$ (97) **33**
PhCOCl **34**	**1**, CH_2Cl_2, 0°C, 30 min	PhCOF (95) **31**
PhCOF **31**	**1**,neat, 85°C,48h	$PhCF_3$ (58) **35**
$C_{11}H_{23}COF$ **33**	**1**,neat, 85°C, 48h	$C_{11}H_{23}CF_3$ (63) **36**

aldehyde proved to be surprisingly facile. The former aldehyde afforded a 96% yield of benzal fluoride (3 h), and the latter resulted in a 95% yield after 6 h of refluxing. Deoxofluorination of the ketone 4-*tert*-butylcyclohexanone afforded a mixture of 1-*tert*-butyl-4,4-difluorocyclohexane and 4-*tert*-butyl-1-fluoro-1-cyclohexene (5.25:1 ratio). Under the same conditions, DAST gave a 2.03:1 ratio of difluoride to vinyl fluoride.[17] A virtually quantitative yield of the *gem*-difluoride was obtained on fluorinating the straight chain ketone 3-phenoxy-2-propanone. Good yields of products were also obtained on fluorination of the keto-ester, ethyl benzoylformate and the electron-deficient ketone, acetophenone. For the fluorination of the latter, no reaction was seen at room temperature and only ~70% conversion was realized in refluxing hexanes. However, using the neat reagent at 85 °C, there was an almost complete conversion to the difluoride. This illustrates that it is possible to take advantage of the greater thermal stability of **1** to fluorinate relatively unreactive substrates.

(c) Carboxylic Acids and Acid Chlorides. Trifluoromethylated compounds are an important class of specialty chemicals that are usually prepared by fluoride ion displacement reactions from the corresponding trichloride or via multistep processes.[18] The direct conversion of carboxylic acids to the trifluoromethyl derivatives by SF_4 (usually done at forcing conditions) is well-known.[19] DAST has not generally been employed for the fluorination of carboxylic acids, and as far as we are aware only the conversion of benzoic acid to benzotrifluoride in the presence of NaF has been reported.[20]

We have found that **1** can be used for the synthesis of trifluoromethyl-substituted aromatic and aliphatic compounds from the corresponding carboxylic acid or acid chloride (Table 3). A facile initial conversion to the carbonyl fluoride is achieved by reaction of **1** with the carboxylic acid or acid chloride at 0 °C. (The acid chloride transformation can also be carried out using other reagents, e.g., pyridine/HF.[21]) The monofluoro product is then heated in neat **1** at 85 °C to obtain the trifluoromethyl derivative. This method proved to be useful for aromatic and 1° alkyl-substituted carboxylic acids, but only low yields (<10%) of products were obtained from 2° alkyl-substituted acids. In this conversion, the greater thermal stability of **1** is again exploited for the fluorination of relatively unreactive compounds.

Table 4. Fluorination of Sulfides, Sulfoxides, and Thioester with 1

Starting Material	Reaction Conditions	Product (Yield)
 **37**	**1**, CH_2Cl_2, $SbCl_3$ (cat.) 18h; then NBS, MeOH/H_2O, 0°C,30min	 (94) **38**
 **39**	**1**, CH_2Cl_2, $SbCl_3$ (cat.) 48h; then NBS, MeOH/H_2O, 0°C,30min	 (95) **40**
 **41**	**1**, CH_2Cl_2, $SbCl_3$ (cat.) 3h;	 (83) **42**
$PhSOCH_3$ **43**	**1**, CH_2Cl_2, $SbCl_3$ (cat.) 16h;	$PhSCH_2F$ (82) **44**
 U = uracil **45**	**1**, CH_2Cl_2, $SbCl_3$ (cat.) 16h;	 (80) **46** U = uracil
PhCSOMe **47**	**1**, CH_2Cl_2, $SbCl_3$ (cat.) 3h;	$PhCF_2OMe$ (96) **48**

(d) Sulfides, Sulfoxides, and Thioesters. The α-fluorosulfides have proven to be important fluorinated intermediates to *β*-lactams, amino acids, and other medicinally active compounds.[22] They are obtained in moderate yields from sulfides by various electrochemical processes or via the use of electrophilic fluorinating agents.[23] The reaction of DAST with sulfoxides and sulfides bearing α-hydrogen atoms can also furnish these compounds.[24]

Compound **1** reacts with sulfides in a manner analogous to DAST to produce α-fluorosulfides (Table 4). Excellent yields were obtained on fluorination of various aryl−alkyl and dialkyl sulfides in CH_2Cl_2 containing 0.01 equiv of a $SbCl_3$ catalyst. Most of the α-fluorosulfides are not stable to standard purification techniques and were oxidized to the sulfoxides or sulfone prior to isolation.

McCarthy and co-workers,[25] as well as Robbins and Wnuk,[26] demonstrated the transformation of sulfoxides to α-fluorosulfides using DAST, with or without Lewis acid catalysis, via the Pummerer rearrangement mechanism. We have found that a similar conversion can be effected with **1** (Table 4). This was applied to the simple sulfoxide, phenyl methyl sulfoxide, as well as to the more

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(25) McCarthy, J. R.; Peet, N. P.; Le Tourneau, M. E.; Inbasekaran, M. J. *Am. Chem. Soc.* **1985**, *107*, 735.
(26) Wnuk, S. F.; Robbins, M. J. *J. Org. Chem.* **1990**, *55*, 4757.

complicated 2′-aryl sulfoxide substituted nucleoside, 3′,5′-di-*O*-acetyl-2′-*S*-(4-methoxyphenyl)-2′-sulfinyluridine. For the latter, a higher yield (80%) of the fluorinated product was obtained with **1** than was reported using DAST (56%).[27] The fluoronucleoside was obtained as a mixture of diastereomers (2′ R/S = 9:91 as determined by ^{19}F NMR) with stereoselectivity similar to that seen for the reaction with DAST (2′ R/S = 87:13).[27]

Although the geminal difluorination of the carbonyl group of esters is generally too difficult to perform with DAST[12] or SF_4,[19] Bunnelle and co-workers[28] demonstrated a simple synthesis of α,α-difluoroethers by reacting thioesters with DAST. For example, methyl thionobenzoate obtained from methyl benzoate and the Lawesson reagent[28] in refluxing toluene afforded the corresponding difluoroether in an overall yield of ∼42%. When the thionation was carried out at 150 °C in xylenes and fluorination was done with **1** in the presence of a catalytic amount of $SbCl_3$ (0.01 equiv), a virtually quantitative yield of the difluoride (**48**) was realized (Table 4).

Discussion

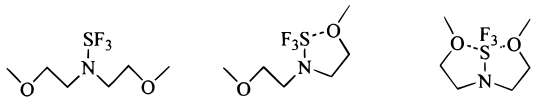
Stability of Reagent 1 Relative to Structure. The thermal analysis studies clearly point to an enhanced thermal stability of the Deoxo-Fluor reagent **1** vis-à-vis DAST and even morpholino-DAST, which is cited as being the most stable of the aminosulfur trifluorides.[9] Under isothermal conditions at 80−90 °C, DAST decomposes much more rapidly and with greater heat evolution than **1** (Figure 1). In the temperature ramping DSC,[11] Radex, and ARC experiments, a similar contrast is seen between **1** and DAST: the latter undergoes much more rapid thermal degradation at generally lower temperatures. Perhaps more important from a process safety point of view, **1** surprisingly yields far less gaseous byproducts on decomposition than DAST (Figure 2).

This enhanced stability of **1** was admittedly surprising, and we attempted to rationalize it in terms of our starting postulates relating to C−H bond acidities and steric effects, now quantified by *ab initio* quantum-mechanical calculations. Heterolytic bond dissociation energies for specific C−H linkages in **1**, DAST, morpholino-DAST, and diethylamine as a reference molecule were calculated using the Hartree−Fock method with a 6-31G** basis set;[29,30] these energies are collected in Table 5. It is evident that the aminosulfuranes are generally in this sense more acidic than Et_2NH, but except perhaps for the C−H_β proton data, there is not a marked contrast between **1** and DAST. This is consistent with the observation that the thermal decomposition of both of the reagents is accelerated by triethylamine. The distinctively higher acidities for DAST vis-à-vis morpholino-DAST may be an indication of the marginally greater thermal stability of the latter.

It appears, however, that the relatively greater stability of **1** can be more satisfactorily rationalized on the basis of conformational structures where there is bonding between the ether oxygen and sulfur. Density functional theory (DFT) calculations using the B3LYP functional[29,30] with a 6-31G** basis set were carried out considering the following structures:

Table 5. Heterolytic C−H Bond Dissociation Energies (kcal/mole) for Aminosulfuranes and Diethylamine

	C-H_α	C-H_β	C-H_γ
$(CH_3OCH_2CH_2)_2NSF_3$ (**1**)	377.22	364.90	364.19
$(CH_3CH_2)_2NSF_3$ (DAST)	378.75	371.12	
 (Morpholino-DAST)	387.89	425.31	
$(CH_3CH_2)_2NH$	452.91	447.09	



(a) **(*b*)** **(*c*)**

The single ring structure (b) is calculated to be more stable, in electronic energy terms, than the open molecule (a) by 2.8 kcal/mol, while (c) is too sterically strained at N to be energetically feasible. In (b) the optimized S−O bond distance is 2.95 Å, indicating a weak bonding as a result of the partial charge transfer from S to O. We thus postulate that the single ring folded structure (b) stabilizes **1** by shielding the reactive SF_3 group with the ether side chain, making the reagent less prone to decomposition by bimolecular disproportionation reactions, as putatively occurs with DAST.[9]

DFT calculations done on (S)-2-methoxymethyl-pyrrolidin-1-ylsulfur trifluoride[10] show that a five-membered ring structure similar to (b) is the most stable conformation. However, the S−O bond with a bond distance of 3.15A° is much weaker than observed for **1** as a result of steric hindrance around the $-SF_3$ group.

Reactivity and Applications of the Deoxo-Fluor Reagent (1). The broad applicability of **1** as in the fluorination of alcohols, aldehydes/ketones, carboxylic acids, sulfides, sulfoxides and thioesters is evident from the examples in Tables 1−4. The reagent's reaction chemistry generally parallels that of DAST, although in some cases significantly higher selectivities for the desired fluorinated compounds with concomitantly less elimination products were realized. Pertinent examples are the conversion of cyclooctanol to cyclooctyl fluoride (Table 1) and of 4-*tert*-butylcyclohexanone to 1-*tert*-butyl-4,4-difluorocyclohexane (Table 2). The most distinguishing feature of **1** is its greater thermal stability, which should encourage its use not only in larger scale processes but also in reactions that require more forcing conditions, as in the fluorination of electron-deficient ketones and carboxylic acids, which are traditionally less reactive substrates (Tables 2 and 3).

Experimental Section

All of the substrates and bis(2-methoxyethyl)amine, $SbCl_3$, NBS, and MCPBA reagents were obtained from Aldrich and used as received; the sulfoxide (**45** in Table 4) was prepared

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(30) Jaguar 3.5; Schrodinger Inc.: Portland, OR, 1998.

by a standard literature method.[27] Sulfur tetrafluoride was acquired from Air Products and Chemicals, Inc.

^{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 ionization detector. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, TN.

The Hartree−Fock and DFT quantum chemistry calculations were done using the Jaguar 3.5 package.[30]

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

Synthesis of Bis(2-methoxyethyl)aminosulfur Trifluoride (1). A solution of bis(2-methoxyethyl)amine (3.3 g, 25 mmol) in hexane (12 mL) contained in a three-neck, 100 mL round-bottom flask equipped with a N_2 inlet tube, a rubber septum and magnetic stirring bar was cooled to −78 °C and treated with 2.5 M BuLi (10 mL, 25 mmol, in hexanes). The mixture was brought to 0 °C and treated with chlorotrimethylsilane (2.72 g, 3.2 mL) dissolved in 10 mL of hexanes. After 30 min at 0 °C, the mixture was filtered, and the solvent was evaporated in vacuo to obtain the silylamine, $(CH_3OCH_2CH_2)_2$-$NSi(CH_3)_3$; ^{1}H NMR ($CDCl_3$) δ 3.25 (t, 4H), 3.25 (s, 6H), 2.95 (t, 4H), 0.0 (s, 9H). This product was reacted with SF_4 as described below.

A 300 mL stainless steel Parr reactor, equipped with a magnetic stirrer, was charged with the silylamine (5.05 g) dissolved in Et_2O (100 mL). The reactor vessel was cooled to −30 °C and connected via an entry port to a vacuum/pressure metal manifold, through which SF_4 (37 mmol) was slowly added. After the vessel was sealed, it was brought to 0 °C, and the contents were stirred under autogenous pressure for 3 h. Gaseous volatiles were then removed by pumping through a soda lime trap, and the remaining liquid contents of the vessel were transferred to a 250 mL glass flask. Evaporation in a vacuum resulted in 2.6 g (51% yield) of **1**, as a light yellow liquid. It was purified by distillation in glass at 71 °C (0.4 mmHg) to a colorless liquid. Elemental analysis calculated for $C_6H_{14}F_3NO_2S$: C, 32.57; H, 6.37; F, 25.76; N, 6.33; S, 14.49. Found: C, 32.61, H, 6.46; F, 25.56; N, 6.44; S, 14.59. For NMR see the Results section.

General Procedure for Fluorination of Alcohols. The alcohol (10 mmol) in dry CH_2Cl_2 (3.0 mL) was added at the temperature indicated in Table 1, under N_2, to a solution of the aminosulfur trifluoride **1** (2.43 g, 11 mmol) in CH_2Cl_2 (2.0 mL) in a 50 mL, three-neck flask equipped with a N_2 inlet tube, septum, and a magnetic stirring bar. The reaction was monitored by GC/MS for disappearance of the starting material. On completion, the mixture was poured into saturated $NaHCO_3$ (25 mL), and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in hexane/ethyl acetate afforded the pure products: 2-fluoroethylbenzene[17] (**3**, 1.05 g, 85%); benzyl fluoride[17] (**5**, 1.05 g, 96%); 1-fluoro-2-isopropyl-5-methylcyclohexane[17] (**7**, 695 mg, 44%); ethyl 2-fluoropropionate[17] (**9**, 876 mg, 73%); ethyl 2-fluoro-2-methylpropionate[31] (**11**, 1.19 g, 89%); 1-fluoro-2,3,5-tri-*O*-benzyl-D-arabinofuranose[14] (**13**, 4.13 g, 98%, α/β = 9:91); 1-fluoro-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[15] (**15**, 5.32 g, 98%, α/β = 28:72).

Fluorination of Aldehydes and Ketones. A solution of aldehyde (**16**, **18**) or ketone (**20**, **22**, **24**, **26**) (10 mmol) in CH_2Cl_2 (3.0 mL), contained in a 25 mL Teflon bottle equipped with a N_2 inlet tube and stirring bar, was treated with a solution of **1** (3.76 g, 17 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. EtOH (92 mg, 116 μL, 2 mmol) was added, and the mixture was stirred at room temperature. The progress of the reaction was monitored by GC/MS. On completion, the solution was poured into saturated $NaHCO_3$, and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in hexanes/Et_2O afforded the pure products: benzal fluoride[17] (**17**, 1.22 g, 95%); α,α,α′,α′-tetrafluoro-*p*-xylene[32] (**19**, 1.67 g, 94%); 1,1-difluoro-4-*tert*-butylcyclohexane[33] (**21**, 1.50 g, 85%); 2,2-difluoroindan[34] (**23**, 647 mg, 42%); 2,2-difluoro-1-phenoxypropane (**25**, 1.68 g, 98%). ^{1}H NMR ($CDCl_3$) δ 7.35 (t, J = 7, 8.5 Hz, 2H), 7.05 (t, J = 7 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 4.10 (t, J = 12 Hz, 2H), 1.80 (t, J = 18 Hz, 3H). ^{19}F NMR ($CDCl_3$) δ − 102 (s, br). Elemental analysis calculated for $C_9H_{10}OF_2$: C, 62.88; H, 5.85; F, 22.07. Found: C, 63.58; H, 5.88; F, 22.20. Ethyl 2-phenyl-2,2-difluoroacetate[35] (**27**, 1.62 g, 81%); 1,1-difluoroethylbenzene[17] (**29**, 1.32 g, 92%).

Fluorination of Carboxylic Acids. (a) Carboxylic Acid to Acyl Fluoride. A solution of the carboxylic acid (10 mmol) in CH_2Cl_2 (5.0 mL) was added to the aminosulfur trifluoride **1** (2.43 g, 11 mmol) under N_2 and stirred for 16 h at room temperature. The progress of the reaction was monitored by GC/MS. On completion, the solution was poured into saturated $NaHCO_3$, and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in hexanes/Et_2O afforded the pure products: benzoyl fluoride[36] (**31**, 1.19 g, 96%); dodecanoyl fluoride[37] (**33**, 1.96 g, 97%).

(b) Acyl Fluoride to the Trifluoromethyl Derivative. The acyl fluoride (10 mmol) prepared as described above was added to the aminosulfur trifluoride **1** (4.42 g, 20 mmol) contained in a Teflon bottle equipped with a N_2 inlet tube, and the mixture was heated at 85 °C. The progress of the reaction was monitored by GC/MS. On completion, the solution was poured into saturated $NaHCO_3$, and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in hexanes/Et_2O afforded the pure products: α,α,α-trifluorotoluene[36] (**35**, 847 mg, 58%); 1,1,1-trifluorododecane[38] (**36**, 1.41 g, 63%).

Fluorination of Benzoyl Chloride. A solution of benzoyl chloride (1.41 g, 10 mmol) in CH_2Cl_2 (5.0 mL) was added to **1** (2.43 g, 11 mmol) under N_2 and stirred for 16 h at room temperature. After workup as above, benzoyl fluoride[36] (**31,** 1.18 g) was obtained in 95% yield.

Fluorination of Sulfides. A solution of the sulfide (10 mmol) in CH_2Cl_2 was added dropwise to a solution of **1** (3.09 g, 14 mmol) in CH_2Cl_2 (20 mL) under N_2 in a three-neck, 50 mL, round-bottomed flask. This was followed by addition of solid $SbCl_3$ (114 mg, 0.5 mmol), and the mixture was stirred at room temperature until GC/MS analysis indicated completion. The solution was poured into CH_2CL_2 (25 mL), washed with saturated $NaHCO_3$, dried, and filtered. The filtrate was treated successively with MeOH (15 mL), H_2O (1.5 mL), and NBS (3.56 g, 20 mmol). After 30 min of stirring, the resulting solution was washed with 0.1 M aqueous sodium thiosulfate (25 mL), 5% H_2SO_4 (25 mL), saturated $NaHCO_3$ (25 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography on silica gel in hexane/ethyl acetate to obtain the pure products: fluoromethyl phenyl sulfoxide[24] (**38**, 1.48 g, 94%); *p*-chlorophenyl fluoromethyl sulfoxide[39] (**40**, 1.82 g, 95%); *p*-methoxyphenyl fluoromethyl sulfide[24] (**42**, 1.56 g, 83%) was isolated as such and not further oxidized.

Fluorination of Sulfoxides. A solution of the sulfoxide (10 mmol) in CH_2Cl_2 (10 mL) was added to **1** (4.42 g, 20 mmol) under N_2. $SbCl_3$ (0.1 mmol) was added, and the mixture was stirred at room temperature for 16 h. The solution was quenched with saturated $NaHCO_3$ (25 mL). After CO_2 evolu-

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tion ceased, the CH_2Cl_2 extract was dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in ethyl acetate/hexanes afforded the pure products: fluoromethyl phenyl sulfide[24] (**44**, 1.15 g, 82%); 3′,5′-di-*O*-acetyl-2′-fluoro-2′-*S*-(4-methoxyphenyl)-2′-thiouridine[27] (**46**, 3.75 g, 80%, R/S = 9/91).

Fluorination of Thioester. Lawesson reagent (4.04 g, 10 mmol) was added under N_2 to a solution of methyl benzoate (1.3 mL, 10 mmol) in xylenes (15 mL) contained in a three-neck, round-bottom flask equipped with a N_2 inlet tube, septum, and a magnetic stirring bar. The mixture was heated at 150 °C for 16 h. On cooling to room temperature, the mixture was treated with hexane (35 mL), the resulting precipitate was filtered, and the filtrate was evaporated in vacuo. The thioester thereby obtained was dissolved into CH_2Cl_2 (5.0 mL) and transferred to a three-neck, round-bottom flask under N_2. This solution was then treated with $SbCl_3$ (114 mg, 0.5 mmol) and the aminosulfur trifluoride **1** (3.09 g, 14 mmol) and stirred for 3 h. The solution was quenched with saturated $NaHCO_3$ (25 mL). After CO_2 evolution ceased, the mixture was extracted with CH_2Cl_2 (2 × 25 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in diethyl ether/hexanes afforded the pure product: α,α-difluorobenzyl methyl ether[28] (**48**, 1.52 g, 96%).

Thermal Analysis Procedures. The Radex Thermal Hazards Screening System (Astra Scientific International, Inc.; Pleasanton, CA) is similar in principle to a heat-flux differential scanning calorimeter but uses larger sample sizes and is equipped with a transducer to monitor pressure inside the test cell (8 cm^3 internal volume). For the Radex tests, samples were heated at 2 °C per minute from 30 to 350 °C. Relatively small (~300 mg) samples were used to avoid overpressurization of the stainless steel cell. Either Viton or ethylene−propylene (EP) O-rings were used for the flange closure.

The Setaram C80 (Setaram/SFIM, Inc.; Grand Prairie, TX) is a high sensitivity heat-flux (Calvet-type) calorimeter. Its standard high pressure 316 stainless steel cells (8 cm^3 internal volume) were used, with a Teflon O-ring seal. The calorimeter was heated to operating temperature (usually 80 or 90 °C, nominal) and allowed to stabilize before insertion of the test cell.

Typically, the ARC instrument (Arthur D. Little, Inc.; Cambridge, MA) operates in a "heat-wait-search mode", i.e., it heats the sample to a predetermined temperature, waits for thermal transients to subside, then searches for exothermic activity at a detection limit of 0.02 °C per minute of self-heating. Accumulation of heat causes the system temperature to rise, which results in an increase in the rate of reaction. Acceleration of the rate continues exponentially. The typical heat-wait-search profiles were done from 50 to 350 °C, using 5 °C steps and 15−20 min wait times. The thermal inertia factor (ϕ) cited in Figure 3 is the ratio of the heat capacity of the cell plus sample to that of the sample alone and indicates the amount of heat lost to the test cell relative to that generated by the sample.

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