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Exploratory study of the reaction of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor^{TM} reagent) with diaryl sulfoxides: novel routes to Ar_2SF_2 and $Ar_2SF(OTf)$ via sulfoxide activation

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Abstract

Neither bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor^{TM} reagent) nor HF/pyridine alone can fluorinate diaryl sulfoxides. S-fluorination can be effected by activating the sulfoxide via protonation with HF/pyridine (70:30) to form sulfoxonium ions in equilibrium which are then S-fluorinated in situ with Deoxofluor^{TM} to give Ar_2SF_2 compounds. Conversions depend strongly on steric factors and the reactions require the use of excess Deoxofluor^{TM} and HF/pyridine. NMR data for the resulting diarylsulfur difluorides are gathered and discussed. Sulfoxide activation via diaryl (trifloxy) sulfonium triflate generated in situ from Ar_2SO with triflic anhydride at low temperature represents another strategy for S-fluorination with Deoxofluor^{TM} to generate $Ar_2S(OTf)F$.

Keywords: Bis(2-methoxyethyl)aminosulfur trifluoride; Diaryl sulfoxides; HF/pyridine

1. Introduction

The recent discovery of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor^{TM} reagent), $(MeO–CH_2CH_2)_2NSF_3$ **1** by Lal et al. [1,2] as a more selective and thermally stable analogue of DAST (Et_2NSF_3) has opened up a new chapter in selective fluorination.

By and large the area of greatest focus in fluorination with **1** (as with DAST itself and its analogues) has been in carbonyl and thiocarbonyl compounds, and in comparison studies dealing with fluorination of sulfoxides and sulfides have been rather limited [2–6].

When at least one α-hydrogen is present, the outcome of fluorination with DAST is the formation of α-fluorosulfides with both ArS(=O)R and ArSR. Reagent **1** reacts in a similar fashion and the reactions are catalyzed by $SbCl_3$ or ZnI_2. It has been suggested that this transformation occurs via a fluoro-Pummerer type rearrangement [2,7]. However, there are no reported studies which examined the interaction of **1** or DAST with diaryl sulfoxides under Lewis or protic acid catalysis.

Janzen and co-workers [8] had earlier reported on the oxidative fluorination of Ph_2S **2** with XeF_2 leading to Ph_2SF_2, whereas with Me_2S the outcome was α-fluorination (as with DAST and its analogues). α-Fluorosulfides are also formed from sulfides by fluorination with various NF reagents [6]. Formation of α-fluorosulfoxides and α-fluorosulfones from sulfoxides and sulfones have also been documented in some cases [6]. Ruppert synthesized Ph_2SF_2 from Ph_2S by direct fluorination or by reaction with AgF_2 [9].

Over a decade ago, we reported a one-pot synthesis of symmetrical and non-symmetrical (mixed) diaryl sulfoxides by reacting simple arenes with $FSO_3H{\cdot}SbF_5$ (1:1)/SO_2, proceeding via in situ generation of $ArSO^+$ and its arylation [10a]. Diaryl sulfoxide formation was accompanied by minor formation of the sulfide whose origin was traced to the *O*-protonated sulfoxonium ions (Ar_2SOH^+) and the dimeric mono- and disulfonium ions ($Ar_2S^+–O–S(OH)Ar_2$ and $Ar_2S^+–O–S^+Ar_2$) as key intermediates [10].

Independent protonation of diaryl sulfoxides with $FSO_3H{\cdot}SbF_5$ (1:1)/SO_2 and quenching furnished the sulfides. Low temperature reaction of authentic ditolyl sulfoxide **3** with $HF{\cdot}SbF_5$ (1:1)/SO_2 followed by quenching gave Ar_2S (90%) and a by-product proposed to be Ar_2SF_2. Independent reaction of Ar_2SO with SbF_5 in Freon-113 solvent did not give Ar_2S but gave the same by-product in increased amounts (19%).

In an effort to broaden the scope of S-fluorination in Ar_2SO, we report here an exploratory study on the reactions of various diaryl sulfoxides with Deoxofluor^{TM} and show

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that HF/pyridine and triflic anhydride can be used to activate the sulfoxide towards S-fluorination.

2. Results and discussion

2.1. Reaction of Ar_2SO with Deoxofluor^{TM} 1

2.1.1. Preliminary studies

Sample of **1** received from Air Products had a purity of ca. 95% (estimated from ^{1}H NMR). Its ^{19}F NMR spectrum (using internal $CFCl_3$ as reference and $CDCl_3$ as solvent) exhibited a major broad peak centered at δ 33.4 for the $(MeOCH_2CH_2)_2N–SF_3$ (lit.[1a]: δ 40) and small sharp peaks at -152.5 (in correct range for BF_4^-!), 56.2 and 75.0 ppm (HF is a reasonable candidate).

Reaction of **3** with **1** in CH_2Cl_2 at room temperature (RT) was extremely sluggish. After 45 h stirring at RT, >98% of the sulfoxide was still unreacted (^{1}H and ^{19}F NMR).

In subsequent experiments, the catalytic effects of Lewis acids $B(C_6F_5)_3$ and $SbCl_3$ were explored in RT reactions in CH_2Cl_2 solvent using sulfoxide to Deoxofluor^{TM} to Lewis acid molar ratios of 1:2:0.1, respectively. With $B(C_6F_5)_3$ after 18 h, tiny new resonances appeared in the ^{1}H NMR spectrum and the fluorine NMR spectrum showed small resonances which matched closely the reported values for $[B(C_6F_5)_3F]^-$ [11] in addition to a peak at δ -129.6 and the usual impurities (at δ -151.4 and 56.3). With $SbCl_3$ after 2 days a mixture of products were formed but the total conversion did not increase beyond 10%.

In another experiment, *p*-chlorophenyl sulfoxide **4** was allowed to react with **1** in benzene solvent initially at RT for several hours and subsequently under reflux for 30 min. NMR analysis (in $CDCl_3$ following the removal of benzene) indicated ~1% conversion to the diaryl sulfur difluoride (δ ^{19}F -13.9, see further for additional examples). The reported fluorine chemical shift for Ph_2SF_2 is δ -5.43 (in CD_2Cl_2 with added fluoride scavenger $(TMS)_2NH$) [8] (in [9], the ^{19}F chemical shift for Ph_2SF_2 was reported at δ 6.8). In addition, the ^{19}F NMR spectrum exhibited a major broad peak at δ -133.7 (plus those δ -152.5 and δ 56.2). See also further for comparative and tabulated data (Tables 1 and 2).

2.1.2. Protic activation

Looking back at our previous studies of diaryl sulfoxides in superacids [10], protic activation to generate sulfoxonium ions and subsequent S-fluorination with **1** appeared a more reasonable approach. For this purpose, commercially available HF/pyridine (70:30 (w/w)) seemed most convenient.

At the onset, in a control experiment, when *p*-ditolyl sulfoxide **3** was allowed to react with HF/pyridine (four-fold excess) for 40 h in CH_2Cl_2 at RT in the absence of **1**, the NMR spectrum of the reaction mixture (after venting off the HF) was essentially that of unreacted sulfoxide.

Several experiments were then performed using reagent **1** in which the ratio of the Deoxofluor^{TM} and HF/pyridine was varied. The reactions were analyzed directly by NMR after venting off the HF under a fast stream of dry nitrogen. These studies illustrated that maximum conversions to Ph_2SF_2 could be achieved when both Deoxofluor^{TM} and the HF/

Table 1
Fluorine resonances observed in different reactions

Entry	Ar_2SO	Ar_2SO:Deoxofluor^{TM}:HF/pyridine	^{19}F NMR resonances
1	**4**	1:1.1:0	-133.7 (major); -152.5; -13.9 (Ar_2SF_2); 56.2
2	**2**	1:1.4:2.8	-130.0 (major, ex); -128 (ex); -153.2; -146.3; -78.7
3	**2**	1: 1.3:1.4	-165.8 (major); -129.6; -152.1 (trace); -78.7 (trace); -14.2 (Ar_2SF_2) (trace); 37.7 (trace)
4	**2**	1:2.2:1.2	-152.0; -145.0; -129.4 (major); -128.5
5	**2**	1:3.2:3.4	-166.2 (major); -152.6 (trace); -14.0 (Ar_2SF_2); 37.7 (trace)
6	**3**	1:3.2:3.3	-168.6 (major); -151.7; -14.0 (Ar_2SF_2); 73.7 (trace)
7	**4**	1:3.3:3.4	-166 (major, ex); -151.6; -129.5 (ex); -14.4 (Ar_2SF_2); 37.7 (trace)
8	**5**	1:3.4:5.1	-155.0; -14.1 (Ar_2SF_2); 37.4; 56.4; 60.4; 75.0
9	**6**	1:3.8:3. 8	-153.3 (br); -129.5; -78.9
10	**7**	1:2:2.7	-160.5 (br); -151.8; -129.2 (major)

Table 2
Multinuclear NMR Data for Ar_2SF_2 compounds

Compound	^{1}H	^{19}F	^{13}C
Ph_2SF_2	7.56 (m); 7.51 (m); 7.34 (m)	-14.2	142.8 (br, C-1); 130.6; 129.4 (br); 128.7 (br, C-2/C-6)
$(4\text{-}MeC_6H_4)_2SF_2$	7.60 (d, J = 8.5 Hz); 7.52 (d, J = 8.5 Hz); 2.49 (s)	-14.1	144.9 (br, C-1); 142.0 (br); 131.1; 129.5 (C-2/C-6); 21.2 (Me)
$(4\text{-}ClC_6H_4)_2SF_2$	7.88 (d, J = 9 Hz); 7.51 (d, J = 9 Hz)	-14.4	147.7 (br, C-1); 129.5; 129.2; 125.0 (C-2/C-6)
$(2,4\text{-}Me_2C_6H_3)_2SF_2$	7.89 (d, J = 8.5 Hz); 7.26 (br, s); 7.22 (d, J = 8.5 Hz) 2.44 and ca. 2.46 (Me)	-14.2	146.9 (br, C-1); 138.8; 133.7; 130.1; 127.3 (C-2/C-6) 21.5 and 20.1 (Me)

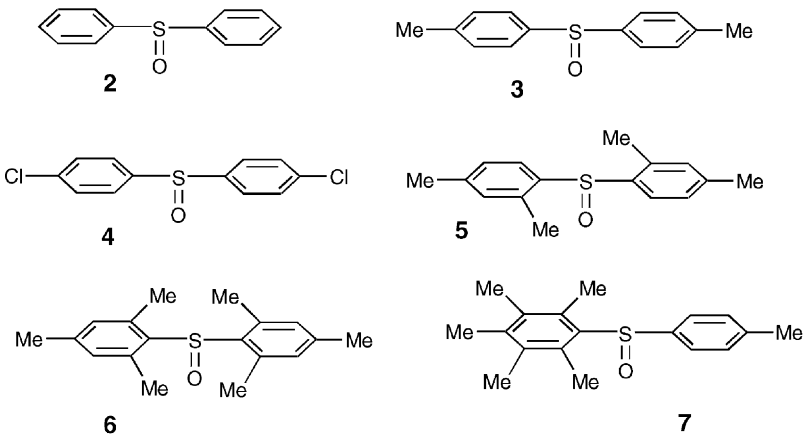


Fig. 1. Substrates examined.

pyridine were used in excess (three molar equivalents), whereas employing slight excess of either one resulted in little or no conversion. Thus, optimal conversions were achieved with Ar_2SO:**1**:HF/pyridine = 1:3.2:3.4, respectively.

The ^{19}F resonance for the polyhydrogen fluoride species in HF/pyridine (70:30) has been reported at 188 ppm (a quintet at −60 °C; each fluorine is surrounded by four hydrogens) [12]. A peak in this range is no longer observed in the ^{19}F NMR spectrum of mixtures of Ar_2SO, Deoxofluor™ and HF/pyridine. Table 1 sketches a summary of ^{19}F resonances observed at RT in different reactions. In entry 2, the major resonance from Deoxofluor™/HF/pyridine system appears around −130 ppm and dynamic exchange is apparent between this signal and a nearby smaller peak at δ −128. In other entries, the major signal is dramatically upfield shifted and appears in the −166 to −169 ppm range depending on the reaction. It is conceivable that these resonances are due to Deoxofluor™–sulfeniminium/HF_2^- equilibrium, analogous to equilibrium fluoride removal from DAST by ZnI_2 proposed by McCarthy et al. [7a].

2.1.3. Survey of diaryl sulfoxides

Availability of several diaryl sulfoxides synthesized via the previously developed one-pot procedure [10a] provided the opportunity to examine structural effects on the course of Ar_2SO fluorination using **1**/HF/pyridine. Substrates examined were diphenyl sulfoxide **2**, *p*-tolyl sulfoxide **3**, *p*-chlorophenyl sulfoxide **4**, 2,4-dimethylphenyl sulfoxide **5**, 2,4,6-trimethylphenyl sulfoxide **6** and pentamethylphenyl tolyl sulfoxide **7** (Fig. 1).

For these reactions, excess **1** (3–3.8 molar equivalent) and excess HF/pyridine were employed (3.4–5.1 molar equivalent). Whereas parent Ph_2SF_2 is reasonably stable and was previously isolated [8,9], substituted Ar_2SF_2 appear to be considerably less stable. In our hands, attempted isolation of $(4\text{-}MeC_6H_4)_2SF_2$ by crystallization or small-scale column chromatography led to decomposition. It was, therefore, decided to analyze the reaction mixtures directly by multinuclear NMR. Under these conditions, conversion to Ar_2SF_2 was ∼90% for **2** and 93% for **3**. Introduction of *p*-Cl groups (**4**) reduced the conversion to 27%. Introduction of *ortho* methyl groups (**5**) reduced the yield of Ar_2SF_2 to ∼10%.[2]

Based on AM1 minimizations the dihedral angle between the two aryl rings in Ph_2SOH^+ ($\mathbf{1}H^+$) is 46.6° and does not change to any noticeable extent when *para* substituents are introduced (as in $\mathbf{3}H^+$ and $\mathbf{4}H^+$). Steric crowding in $\mathbf{5}H^+$ and $\mathbf{6}H^+$ causes one aryl ring to twist out of plane leading to dihedral angles of −40.4 and −71.0°, respectively. The observed reactivity pattern reflects both the stability of the sulfoxonium ion and steric problems associated with nucleophilic attack by Deoxofluor™ on the sulfoxonium ion. The following mechanistic scenario seems reasonable (Scheme 1).

The NMR data for the resulting Ar_2SF_2 compounds are summarized in Table 2. Notable features are minimal sensitivity of the fluorine chemical shifts to substituent effects, observation of small long-range C/F couplings in the ^{13}C spectra, and the deshielding of the proton resonances relative to the starting sulfoxides. The ^2J C/F and ^3J C/F couplings for Ph_2SF_2 were reported as 4.5 and 6.7 Hz, respectively [8] (in [9], they are 4.5 and 4.5 Hz). In Deoxofluor™/HF/pyridine system dynamic fluorine exchange averages these small couplings leading to broadening of the *ipso* and *ortho* ring carbons. Minimal sensitivity of the fluorine chemical shifts to substituent effects was previously noted by Furin et al. [13] in $XC_6H_4SF_3$

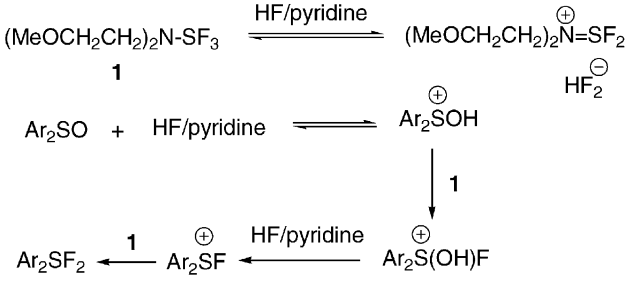
[2] The following experimental observations are noteworthy:

(i) yields depend critically on the structure of the diaryl sulfoxide;

(ii) the experiments were performed under very similar reaction conditions;

(iii) in selected cases NMR monitoring of the progress of the reactions clearly showed that the resonances for Ar_2SO decrease and new peaks for the product appear and increase in the mixture (for confirmation, in some cases, authentic Ar_2SO was added into the NMR tube);

(iv) in the absence of HF/pyridine the fluorine resonance assigned to Ar_2SF_2 was not observed.



Scheme 1.

(X = H, F, CF_3). With **6** and **7**, a combination of steric crowding to S-fluorination by Deoxofluor™ and increased stability of the derived benzenium ions (*ipso* attack competing with sulfoxonium ion formation), favored dearylation. Thus, for the reaction of **6** with **1** and HF/pyridine major fluorine resonances are seen at d −153.3 (br) and δ −129.5 (fluoromesitylene) and for **7** at δ −164.2 and δ −129.2 (fluoropentamethylbenzene) with corroboratory evidence from the proton spectra.

2.1.4. Sulfoxide activation by triflic anhydride (Tf_2O)

Trifloxysulfonium triflate is formed in situ when DMSO or Ph_2SO are reacted with Tf_2O at low temperature, and subsequently undergo nucleophilic attack at sulfur by a variety of nucleophiles [14]. In the context of present study, we have found that trifloxysulfonium triflate Ph_2S^+–OTf OTf^- formed at low temperature in dry methylene chloride reacts with Deoxofluor™ **1** to form $Ph_2SF(OTf)$ which appears as a white solid when the solvent and most of the unreacted Tf_2O are removed. The ^{19}F NMR spectrum of the residue dissolved in $CDCl_3$ exhibits one resonance at δ 11.5 together with a peak at δ −78.9 for the residual Tf_2O (possibly there is intermolecular OTf exchange between $Ph_2SF(OTf)$ and residual Tf_2O which is fast at RT). Based on the ^1H NMR spectrum the conversion is about 90% based on the sulfoxide. The ring protons for $Ph_2SF(OTf)$ (δ 8.06 (d), 7.97 (t) and 7.83 (d)) are more deshielded relative to Ph_2SF_2.

In summary, we have shown that S-fluorination of diaryl sulfoxides to form Ar_2SF_2 can be effected with reagent **1**, following sulfoxide activation with HF/pyridine. It is essential that both Deoxofluor™ and HF/pyridine are used in excess. The conversions are strongly influenced by the structure of the diaryl sulfoxide substrates and the yields decrease as steric crowding around the sulfoxonium moiety increases. The resulting Ar_2SF_2 compounds were not stable enough for isolation and could only be analyzed in the mixture by multinuclear NMR. The ^{19}F NMR spectra for the mixtures of Ar_2SO/Deoxofluor™/HF/pyridine give evidence for equilibrium fluoride ion exchange and depend strongly on the ratios of these reagents. It has also been shown that Deoxofluor™ reagent reacts with diphenyl(trifloxy)sulfonium triflate generated in situ from Ph_2SO and Tf_2O to generate $Ph_2S(OTf)F$.

3. Experimental

Phenyl sulfoxide **2**, *p*-chlorophenyl sulfoxide **4** and HF/pyridine were high purity commercial samples (Aldrich) which were used as received. Methylene chloride (Aldrich) was distilled from P_2O_5 and benzene was distilled over sodium.

Diaryl sulfoxides **3**, **5**, **6** and **7** were high purity samples synthesized as part of our previous study [10a]. Deoxofluor™ (Air Products) was used as received. Reactions involving HF/pyridine were carried out in Nalgene bottles under argon whereas others were performed in Schlenk tubes (under argon). NMR spectra were recorded in $CDCl_3$ at RT on a Varian INOVA 500 MHz instrument using a 5 mm broad-band probe. Proton and carbon chemical shifts are relative to internal TMS or $CDCl_3$ (δ 77.23) and fluorine shifts are relative to internal $CFCl_3$. AM1 minimizations were carried out using Hyperchem Pro. Release 6 program.

3.1. Reaction of Ar_2SO with deoxofluor in HF/pyridine (typical run)

To solution of phenyl sulfoxide (102 mg, 0.5 mmol) in dry CH_2Cl_2 (charged into Nalgene bottle) was added under an argon atmosphere the Deoxofluor™ reagent (331 mg, 1.49 mmol) followed by HF/pyridine (258 mg), and the mixture was stirred at RT for 40 h. Then a stream of dry nitrogen was bubbled through the reaction mixture to vent off the HF and to remove most of the solvent. The residue was dissolved in $CDCl_3$ and analyzed directly by multinuclear NMR.

3.2. Reaction of Ar_2SO with Deoxofluor™ in benzene solvent without HF/pyridine

Sulfoxide **3** (99 mg, 0.37 mmol) was charged into small Schlenk tube and dry benzene (~10 ml) was added (sulfoxide is only partly soluble), followed by Deoxofluor™ (92 mg, 0.42 mmol) under argon. The resulting mixture was stirred at RT for 3 h (white solution) and then refluxed for 30 min (yellow solution). The solvent was removed under vacuum and the residue was taken up in $CDCl_3$ and analyzed directly by multinuclear NMR (Table 2).

3.3. Reaction of Ph_2SO with Deoxofluor™ and triflic anhydride Tf_2O

The sulfoxide (111.7 mg, 0.55 mmol) was charged into a small Schlenk tube and dissolved in dry methylene chloride. The tube was cooled to dry ice/acetone temperature and Tf_2O (1.154 g, 4.09 mmol) was added followed by Deoxofluor™ (240.3 mg, 1.08 mmol) to form a yellow solution. The temperature was then slowly raised while stirring. At −30 °C a white solid was formed which subsequently disappeared overtime upon raising temperature under stirring, to eventually produce a yellow solution at RT. The solvent and excess Tf_2O

were removed under vacuum, the residue (white solid) was taken up in $CDCl_3$ and analyzed directly by NMR.

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