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Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents

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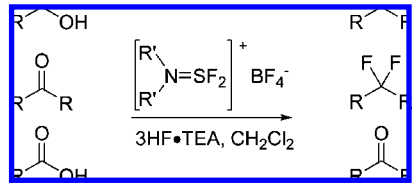
ABSTRACT



Aminodifluorosulfinium tetrafluoroborate salts were found to act as efficient deoxofluorinating reagents when promoted by an exogenous fluoride source and, in most cases, exhibited greater selectivity by providing less elimination byproduct as compared to DAST and Deoxo-Fluor. Aminodifluorosulfinium tetrafluoroborates are easy handled crystalline salts that show enhanced thermal stability over dialkylaminosulfur trifluorides, are storage-stable, and unlike DAST and Deoxo-Fluor do not react violently with water.

Fluorines are of high importance in pharmaceuticals and agrochemicals because their presence in organic molecules can advantageously alter their chemical and biological profiles, including stability, lipophilicity, and bioavailability. In fact, 30−40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine atoms.[1] As such, there is an increasing need for safe, selective, and efficient methods to introduce fluorine atoms in molecules, and a common practice is to produce fluorides from alcohols and *gem*-difluorides from carbonyl functional groups. These transformations are commonly referred to as deoxofluorinations.

It was recognized early that SF_4 can perform deoxofluorinations, but in practice, handling of this highly toxic gas necessitates extensive safety measures.[2] Reactions using SF_4 are often undertaken under pressure, require high temperatures (typically 100 °C), and lead to undesired products. Later, liquid-state diethylaminosulfur trifluoride (DAST, **1**) was developed by Middleton as a superior alternative to gaseous SF_4.[3] Unfortunately, it was soon recognized that this liquid was thermally unstable and highly explosive in nature.[4] In an effort to develop a safer reagent, Lal et al. have reported that bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor, **2**) was more thermally stable.[5] In this context, it has been shown by differential scanning calorimetry (DSC) that DAST and Deoxo-Fluor have the same decomposition temperature, but DAST degrades more rapidly with somewhat larger heat evolution.

DAST (**1**) and Deoxo-Fluor (**2**) are the most widely used deoxofluorinating reagents.[6] These reagents are fuming liquids that are difficult to handle in humid environments, react violently with water, and do not offer the convenience of handling solids from a manufacturing standpoint. The liquids also discolor with aging and sometimes require redistillation to be satisfactory.[7] As a consequence of their

(1) Thayer, A. M. *Chem. Eng. News* **2006**, *84* (23), 15.
(2) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, *82*, 543.
(3) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(4) (a) Cochran, J. *Chem. Eng. News* **1979**, *57* (12), 74. (b) Middleton, W. *J. Chem. Eng. News* **1979**, *57* (21), 43. (c) Messina, P. A.; Mange, K. C.; Middleton, W. J. *J. Fluor. Chem.* **1989**, *42*, 137.
(5) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *71*, 7048.
(6) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561.

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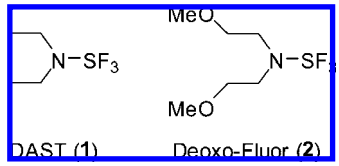


Figure 1. Structures of popular dialkylaminosulfur trifluorides.

explosiveness, DAST-type reagents are subject to strict legal provisions and shipping restrictions. There is therefore a need for deoxofluorinating reagents that do not suffer from the aforementioned deficiencies of dialkylaminosulfur trifluorides. Ideally, the deoxofluorinating reagents would be stable from handling, storage, and process safety standpoints, would be cost-efficient, and could be prepared in high yield and isolated efficiently in a solid-state form by simple filtration. Herein, we report that dialkylaminodifluorosulfinium salts can be employed as surrogates of aminosulfur trifluorides and provide a safer alternative reagent thereof.

Distinctly isolated and characterized dialkylaminodifluorosulfinium salts have been known for over three decades. Markovskii et al. first reported that DAST (**1**) and the dimethylamino, piperidino, and morpholino analogues all react with BF_3•Et_2O to form the corresponding dialkylaminodifluorosulfinium tetrafluoroborates **3**−**6**.[8,9] Since this initial discovery, other dialkylaminodifluorosulfinium salts (**7**−**9**) have been reported, all of which were prepared by the reaction of a DAST-type reagent with fluoride ion acceptors such as BF_3, PF_5, SeF_4, SbF_5, and AsF_5.[10] Besides fluorination of silylamines,[8,10d] the reactivity of dialkylaminodifluorosulfinium salts as reagents has been scarcely studied. To the best of our knowledge, not a single deoxofluorination reaction of an alcohol, aldehyde, ketone, or carboxylic acid has ever been reported. Moreover, their thermal stability has not been evaluated.

To further investigate the properties of dialkylaminodifluorosulfinium salts, several derivatives were prepared using a modified version of the original Markovskii procedure, including the novel salt **11** derived from Deoxo-Fluor. We were pleased to observe the ease at which dialkylaminodifluorosulfinium tetrafluoroborate salts precipitated directly out of solution upon the reaction of the corresponding dialkylaminosulfur trifluorides and BF_3•Et_2O. From a manufacturing standpoint, this constitutes a direct-drop process, which greatly simplifies the isolation procedure.[11] In fact, the solid-state salts are easily filterable and dried under inert atmosphere. The DAST-derived salt **4** had an amorphous appearance, was pale yellow and somewhat hygroscopic. The crude salt was therefore recrystallized in 1,2-dichloroethane to obtain white microcrystalline flakes melting at 83−84 °C, whereas Markovskii reported obtaining needles melting at

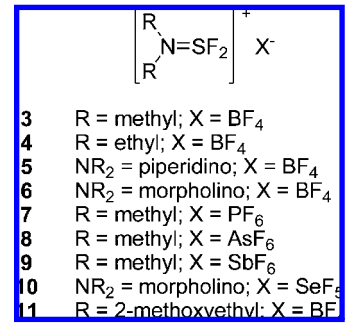


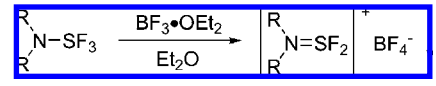
Figure 2. Dialkylaminodifluorosulfinium salts.

74−76 °C using the same solvent. The recrystallized material exhibits better handling properties, can be manipulated in ambient conditions, and is storage-stable.[12]

We next assessed the thermal stability by performing a preliminary hazard study of diethylaminodifluorosulfinium tetrafluoroborate (**4**). DSC analysis showed a decomposition temperature at 215 °C with an exothermic heat ($-\Delta H$) of 661 J/g. In comparison, DAST decomposes at 140 °C, releasing 1700 J/g, and Deoxo-Fluor decomposes at 140 °C with 1100 J/g of energy.[5] In general, a higher decomposition temperature and a lower exothermic heat generated during decomposition is indicative of a more stable compound and provides greater safety.

The physical attributes and the thermal stability of morpholino and bis(2-methoxyethyl)aminodifluorosulfinium tetrafluoroborate salts were also investigated. DSC analysis of the latter (**11**) showed decomposition at 193 °C with a release of 367 J/g. Although less energetic than the diethylamino analogue **4**, the decomposition occurs at a lower temperature. Moreover, the salt **11** has a low melting point of 35−38 °C, is highly hygroscopic, deliquescent, and as such, not easily handled. On the other hand, the morpholino analogue **6** has a high melting point of 122−125 °C and is more stable on the basis of both decomposition temperature and amount of energy released. In fact, morpholinodifluorosulfinium tetrafluoroborate (**6**) decomposed at 242 °C while releasing only 388 J/g, which favorably compares to Deoxo-Fluor (140 °C with 1100 J/g).

Table 1. Preparation of Dialkylaminodifluorosulfinium Tetrafuoroborate Salts and DSC Analyses



			DSC	
compound	yield (%)	mp (°C)	T_{dec} (°C)	$-\Delta H_{dec}$ (J/g)
4	82	83−84	215	661
6	75	122−125	242	388
11	78	35−38	193	367
DAST			140	1700
Deoxo-Fluor			140	1100

(7) Fauq, A. H.; Singh, R. P.; Meshri, D. T. In *Handbook of Reagents for Organic Synthesis−Fluorine Containing Reagents*; Paquette, L. A., Ed.; John Wiley & Sons Ltd.: England, 2007; pp 180−194.

(8) Markovskii, L. N.; Pashinnik, V. E.; Saenko, E. P. *Zh. Org. Khim.* **1977**, *13*, 1116.

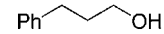
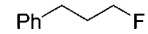
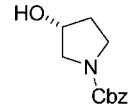
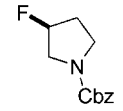
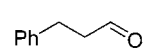
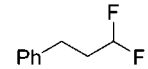
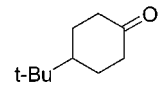
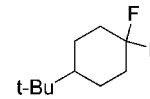
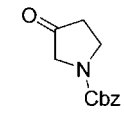
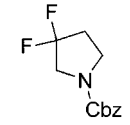
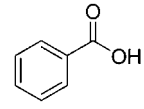
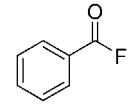
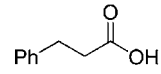
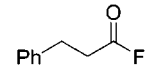
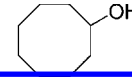
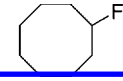
Since the reactivity of aminodifluorosulfinium salts toward hydroxyls and carbonyls was unknown as of yet, the potential use of such salts as deoxofluorinating reagents was next assessed. In preliminary trials, we found that diethylaminodifluorosulfinium tetrafluoroborate (**4**) alone was incapable of performing deoxofluorination of carbonyls, whereas alcohols did convert into the desired fluorides, albeit sluggishly. For example, when 4-*tert*-butylcyclohexanone was treated with the foregoing salt, no detectable conversion to 1-*tert*-butyl-4,4-difluorocyclohexane was observed even after 4 days at room temperature. This result was unexpected since Lal et al. had claimed that BF_3•Et_2O catalyzes the dialkylaminosulfur trifluoride mediated deoxofluorination of ketones.[13] However, Merck has reported that 10 mol % of BF_3•Et_2O substantially retards the rate of reaction in the deoxofluorination of a ketone by Deoxo-Fluor.[14] All indications suggest that BF_3•Et_2O does not act as a Lewis acid but rather as an irreversible fluoride ion acceptor to form dialkylaminodifluorosulfinium tetrafluoroborate salts with attenuated reactivity.

From a mechanistic perspective, it is recognized that the reaction of DAST and alcohols produces a dialkylaminodifluorosulfane intermediate along with HF, the latter of which serves as a fluoride source for the final displacement in the synthetic pathway leading to the alkyl fluoride.[3,15] By analogy, we surmised that the electrophilic dialkylaminodifluorosulfinium species is capable of reacting with an alcohol to provide an alkoxy-*N*,*N*-dialkylaminodifluorosulfane, but since tetrafluoroboric acid is released instead of the requisite HF, the overall process cannot be completed. In this context, an exogenous source of fluoride would be required.

After much investigation, we were pleased to observe that complete conversion of 3-phenylpropanol to 1-fluoro-3-phenylpropane could be achieved when the reaction was performed in the presence of 3HF•Et_3N as a promoter (Table 2, entry 1). *It is noteworthy that, unlike Olah's reagent (i.e., pyridinium polyhydrogen fluoride) and anhydrous hydrogen fluoride, 3HF•Et_3N is much less corrosive, is almost pH neutral, and can be handled in borosilicate glassware up to 150 °C without corrosion.*[16]

Gratifyingly, the 3HF•Et_3N-promoted deoxofluorination using diethylaminodifluorosulfinium tetrafluoroborate was found generally applicable to a wide variety of substrates including alcohols, aldehydes, ketones, and carboxylic acids (Table 2).[17] An additional advantage of diethylaminodifluorosulfinium tetrafluoroborate over DAST and Deoxo-Fluor became apparent in the deoxofluorination of 4-*tert*-butylcyclohexanone (entry 4). Typically, a major side reaction observed in the deoxofluorination of ketones is the production of the corresponding olefinic fluoride side product. In fact, the reactions of DAST/HF and Deoxo-Fluor/HF with 4-*tert*-butylcyclohexanone were reported to produce 33% and 16% of olefinic fluoride side product, respectively,[5] whereas diethylaminodifluorosulfinium tetrafluoroborate exhibited higher selectivity by leading to only 4% of olefinic fluoride using the same substrate.

Table 2. Deoxofluorinations Using Diethylaminodifluorosulfinium Tetrafuoroborate **4**[a,b]

entry	substrate	product	% yield[a]
1			85
2			60 (18)[9]
3			83
4			85 (4)[b]
5			53
6			88
7			94
8			84 (23)[9]

[a] Isolated yield. [b] Combined yield of product and elimination side product (the percentage yield of side product in the isolated mixture calculated from ^1H and ^{19}F NMR).

(9) Compounds **4** and **6** can be obtained from the Aldrich Chemical Co. (catalogue nos. 719439 and 719447, respectively)

(10) (a) Cowley, A. H.; Pagel, D. J.; Walker, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 7065. (b) Mews, R.; Henle, H. *J. Fluor. Chem.* **1979**, *14*, 495. (c) Pauer, F.; Erhart, M.; Mews, R.; Stalke, D. *Z. Naturforsch., B: Chem. Sci.* **1990**, *45*, 271. (d) Pashinnik, V. E.; Martynyuk, E. G.; Shermolovich, Y. G. *Ukr. Khim. Zh.* **2002**, *68*, 83.

(11) Anderson, N. G. *Org. Process Res. Dev.* **2004**, *8*, 260.

(12) A sample of salt **4** stored at room temperature under inert nitrogen was analyzed after 90 days with no detectable degradation.

(13) Lal, G. S.; Pez, G. P. U.S. patent 6,222,064 B1, 2001.

(14) Mase, T.; Houpis, I. N.; Akao, A.; Dorzoitis, I.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lunch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775.

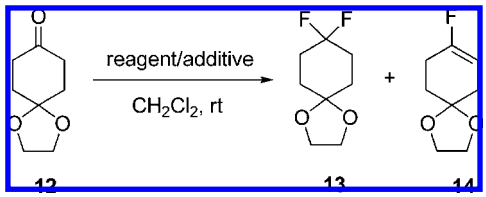
(15) (a) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090. (b) Sutherland, A.; Vederas, J. C. *Chem. Commun.* **1999**, 1739.

(16) (a) Haufe, G. *J. Prakt. Chem.* **1996**, *338*, 99. (b) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31. (c) Gatner, K. *Pol. J. Chem.* **1993**, *67*, 1155. (d) Franz, R. *J. Fluorine Chem.* **1980**, *15*, 423.

(17) **General procedure for deoxofluorination.** To a stirred suspension of diethylaminodifluorosulfinium tetrafluoroborate (4.0 mmol) in dichloromethane (25 mL) at room temperature was added the substrate (2.67 mmol) and triethylamine trihydrofluoride (4.0 mmol). The resulting mixture was stirred under nitrogen over the prescribed amount of time. The reaction was then quenched at room temperature with a 5% sodium bicarbonate aqueous solution and stirred for 15 minutes, and the resulting mixture was extracted twice using dichloromethane. The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated. The residual oil was purified by SiO_2 chromatography.

As mentioned above, deoxofluorinations on six-membered ring systems are notoriously prone to elimination, and the monoprotected 1,4-cyclohexanedione **12** is no exception (Table 3). In fact, Deoxo-Fluor predominantly leads to

Table 3. Case Study: Deoxofluorination Reaction Outcome of Cyclohexanone **12**



entry	reagent (equiv)	additive (equiv)	**13**:**14** ratio
1	Deoxo-Fluor (1.2)	none	0.8:1
2	Deoxo-Fluor (1.2)	BF_3•OEt_2 (0.1)	1.4:1
3	Deoxo-Fluor (1.2)	3HF•TEA(0.3)	1.0:1
4	**11** (2.0)	none	no conv
5	**11** (2.0)	3HF•TEA(1.0)	6.9:1

olefinic fluoride **14**, whereas the addition of promoters modestly increases the selectivity. More specifically, 0.1 equiv of BF_3•Et_2O almost doubles the selectivity, but increasing further the amount of the additive slowed down the reaction rate and led to intractable mixtures. Ultimately, no conversion to **13** was observed when equimolar amounts of Deoxo-Fluor and BF_3•Et_2O, i.e., the salt **11**, was employed. We were pleased to observe, however, an 8-fold increase in selectivity when promoted with 3HF•Et_3N with an isolated yield of 63%.[18]

In summary, results of this preliminary investigation have shown that dialkylaminodifluorosulfinium tetrafluoroborate salts are considerably more stable than dialkylaminosulfur trifluorides, both in terms of higher decomposition temperature and lower amount of energy released. These salts are capable of performing deoxofluorinations of hydroxyls and carbonyls when promoted by an exogenous fluoride source, i.e., 3HF•Et_3N and, in most cases, led to fewer elimination byproducts as compared to DAST and Deoxo-Fluor. These desirable attributes, combined with the ease of handling and storage stability of dialkyaminodifluorosulfinium tetrafluoroborate salts, make these reagents a useful and safer option to perform deoxofluorination reactions, especially on a large scale. Further investigations into mechanistic aspects and substrate scope are currently underway and will be reported in due course.

Acknowledgment. We thank Mahmoud Mirmehrabi (Wyeth Research, Canada) for conducting the DSC analyses.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H, ^{13}C, and ^{19}F NMR and DSC spectras. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902039Q

(18) Unoptimized yield of a mixture of **13** and **14**.