



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

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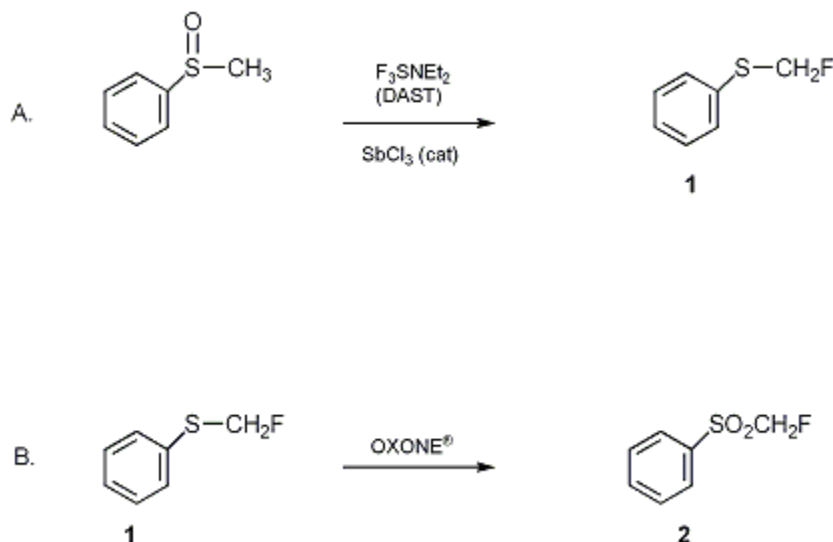
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 9, p.446 (1998); Vol. 72, p.209 (1995).*

## REACTION OF SULFOXIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE: FLUOROMETHYL PHENYL SULFONE, A REAGENT FOR THE SYNTHESIS OF FLUOROALKENES

[Benzene, [(fluoromethyl)sulfonyl]-]



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### 1. Procedure

**CAUTION!** All reactions should be conducted in an efficient fume hood.

A. *Fluoromethyl phenyl sulfide (1)*. To a 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, air condenser and thermometer are added methyl phenyl sulfoxide (25.2 g, 0.18 mol) (Note 1) and chloroform (150 mL) (Note 2). The flask is placed in a cooling bath containing 3 L of water kept at 20°C (Note 3). Diethylaminosulfur trifluoride (DAST) (38.5 g, 31.6 mL, 0.24 mol) (Note 4) is added to the flask, followed by antimony trichloride (0.50 g, 0.0022 mol) (Note 5), and an additional 50 mL of chloroform. The light yellow reaction mixture is stirred under an argon atmosphere. After 2 to 8 hr, an exothermic reaction is observed and the solution turns dark orange (Note 6). The reaction mixture is poured slowly with stirring into 600 mL of ice-cold, saturated, aqueous sodium bicarbonate containing 10 g (0.25 mol) of sodium hydroxide (CAUTION: gas evolution). After 10 min, the chloroform layer is separated and the remaining aqueous layer is extracted with additional chloroform (3 × 100 mL). The combined organic layers are washed with saturated aqueous sodium bicarbonate (250 mL), saturated aqueous sodium chloride, and dried over potassium carbonate. The chloroform is removed with a rotary evaporator at 30–40°C and the crude fluoromethyl phenyl sulfide **1** (ca. 29 g), obtained as a yellow orange oil, is used immediately in the next step (Note 7) and (Note 8).

B. *Fluoromethyl phenyl sulfone (2)*. To a 3-L, three-necked, round-bottomed flask, equipped with an overhead stirrer, thermometer, and 1-L addition funnel with sidearm are added Oxone (221.0 g, 0.36 mol) (Note 9) and water (700 mL). The mixture is cooled to 5°C and a solution of the crude fluoromethyl phenyl sulfide (**1**) in methanol (700 mL) is placed in the addition funnel and added in a slow stream to the stirring slurry. After addition of the sulfide, the reaction mixture is stirred at room temperature for 4 hr, (Note 10) and the methanol is removed on a rotary evaporator at 40°C. The remaining solution is extracted with methylene chloride (2 × 500 mL). The combined organic layers are

dried over [magnesium sulfate](#), concentrated to ca. 150 mL, filtered through a plug of silica gel (230–400 mesh, 300 mL, 10 × 6.5 cm), and washed with an additional 500 mL of [methylene chloride](#) ([Note 11](#)). The colorless filtrate is concentrated and the resulting oil or solid is dried under vacuum (0.1 mm) at room temperature to provide 29 g of crude [fluoromethyl phenyl sulfone \(2\)](#) as a solid white mass. The solid is recrystallized from 250 mL of hot [hexane](#) (forms two layers) by cooling the two phase solution to room temperature with vigorous stirring and adding a seed crystal. The resulting white crystals of [fluoromethyl phenyl sulfone \(2\)](#) (25.0–28.5 g, 80–90%) are collected by filtration, mp 53–55°C ([Note 12](#)) and ([Note 13](#)).

## 2. Notes

1. [Methyl phenyl sulfoxide](#) was purchased from Aldrich Chemical Company, Inc., and used as received.
2. *Chloroform is a suspected carcinogen.* Follow manufacturer's recommended procedures for handling, storage, and disposal.
3. Both a sizable head space and a large heat sink are essential for this reaction since a vigorous, but latent, exothermic reaction occurs (see ([Note 5](#))). This reaction was run twelve times without incident on a 25–125-g scale following these precautions.
4. [Diethylaminosulfur trifluoride](#) (DAST) should be handled using appropriate safety equipment (rubber gloves and goggles). DAST was purchased from Carbolabs, Inc., and used as received.
5. [Antimony trichloride](#) was purchased from Aldrich Chemical Company, Inc. and used as received. Excess [antimony trichloride](#) can cause a vigorous reaction.
6. Progress of the reaction can be followed by gas chromatography, TLC ([ethyl acetate/hexane](#) 1:5) or <sup>1</sup>H NMR. (Probe reactions can be carried out in CDCl<sub>3</sub> in an NMR tube).
7. Alternatively, the [chloroform](#) solution can be treated with 2 equiv of 3-chloroperbenzoic acid (MCPBA) to provide [fluoromethyl phenyl sulfone](#) (see reference <sup>2</sup>).
8. The crude sulfide is readily purified by Kugelrohr distillation (bp 80–90°C, 0.8 mm), but the colorless liquid polymerizes to a white solid on standing overnight. A solution of the sulfide in [chloroform](#) was stored at –10°C for 2 days on one occasion with no decomposition, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 5.72 (d, 2 H, J = 52.9), 7.29–7.52 (m, 5).
9. Oxone (potassium peroxymonosulfate, 2 KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>) was purchased from Aldrich Chemical Company, Inc.
10. Progress of the oxidation can be followed by TLC ([ethyl acetate/hexane](#) 1:5). The checkers found that the product crystallized from water when the [methanol](#) was removed.
11. Alternatively, the organic layer is concentrated to an oil and **2** is purified by Kugelrohr distillation, bp 120–125°C (1 mm).
12. The two step reaction was run on a 125-g scale with an overall yield of 88%.
13. The physical properties are as follows: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 5.15 (d, 2 H, J = 47.1), 7.60–8.00 (m, 5 H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ: –211.2 (t, J = 47.4); MS (EI) m/z 175 (M<sup>+</sup>); Anal. Calcd for C<sub>7</sub>H<sub>7</sub>FO<sub>2</sub>S: C, 48.26; H, 4.05. Found: C, 48.35, H, 3.94.

## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

The first step of the present procedure is an example of the fluoro Pummerer or DAST Pummerer reaction<sup>3</sup> and describes a convenient method for the synthesis of  $\alpha$ -fluoro sulfides.  $\alpha$ -Fluoro sulfides can subsequently be oxidized to the corresponding sulfoxide or sulfone. For aromatic sulfoxides, use of the 4-anisyl group can dramatically improve the yield and facility of the reaction. The submitters originally found that [zinc iodide](#) catalyzes the reaction.<sup>3</sup> Recently, Robins and co-workers<sup>4,5</sup> have reported that [antimony trichloride](#) is a superior catalyst for this transformation, eliminating the need for a 4-methoxy group for the conversion of aryl sulfoxides to  $\alpha$ -fluoro sulfides. The submitters have subsequently utilized this catalyst in place of [zinc iodide](#).<sup>2,6</sup>

In most cases, the fluoro Pummerer reaction can be carried out with 1.33 to 2.0 equiv of DAST and

a "catalytic" amount of [antimony trichloride](#) in either refluxing [methylene chloride](#) or [chloroform](#) at room temperature or 50°C. In the synthesis of [fluoromethyl phenyl sulfide](#), however, the induction period makes room temperature conditions the preferred method for large scale synthesis.

Electron-withdrawing groups decrease the rate of the fluoro Pummerer reaction, which, in certain cases,<sup>7</sup> allows a DAST-mediated deoxygenation to compete with the introduction of fluorine alpha to sulfur. The reaction is compatible with a number of functional groups and can readily be carried out with nucleosides. Robins and co-workers<sup>4</sup> reported the synthesis of a [5'-fluoro-5'-S-phenyladenosine](#) analog using [antimony trichloride](#) as catalyst at room temperature. It should be noted that  $\alpha$ -fluoro sulfoxides provide a convenient entry to terminal fluoroalkenes.<sup>3,8,9,10</sup>

In most cases, introduction of fluorine adjacent to sulfur can be monitored by proton NMR for small-scale probe reactions run in CDCl<sub>3</sub>. The CHF peaks in the proton NMR are generally found between  $\delta$  5 and 6 ppm (with proton-fluorine coupling constants around 55) and fall below the range for protons on DAST.

For the synthesis of the title compound, [Oxone](#) or [3-chloroperbenzoic acid](#)<sup>2</sup> can be used to oxidize the sulfide to the sulfone. The title compound is a key reagent for the preparation of fluoroalkenes from aromatic<sup>11</sup> and aliphatic<sup>2</sup> aldehydes. Recently, a stereospecific method to (E)- and (Z)-fluoroalkenes was reported using this reagent.<sup>12,13,14</sup>

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 442](#)

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## References and Notes

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## Appendix

### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

DAST

3-chloroperbenzoic acid (MCPBA)

Oxone (potassium peroxymonosulfate,  $2 \text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ )

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

oxone (37222-66-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

antimony trichloride (7647-18-9)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

argon (7440-37-1)

zinc iodide

Methyl phenyl sulfoxide (1193-82-4)

Diethylaminosulfur trifluoride (38078-09-0)

3-chloroperbenzoic acid (937-14-4)

Fluoromethyl phenyl sulfone,  
Benzene, [(fluoromethyl)sulfonyl]- (20808-12-2)

Fluoromethyl phenyl sulfide (60839-94-3)

5'-fluoro-5'-S-phenyladenosine