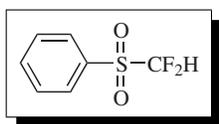


Difluoromethyl Phenyl Sulfone



[426-58-4] $C_7H_6F_2O_2S$ (MW 192.18)
 InChI = 1/C7H6F2O2S/c8-7(9)12(10,11)6-4-2-1-3-5-6/h1-5,7H
 InChIKey = LRHDNAVPELLXDL-UHFFFAOYAP

[reductive difluoromethylating agent for preparation of structurally diverse (difluoromethyl)trialkylsilanes;¹ nucleophilic (benzenesulfonyl)difluoromethylating agent for synthesis of (benzenesulfonyl)difluoromethylated carbinols;² stereoselective difluoromethylenating agent for synthesis of 2,2-difluoropropane-1,3-diols;³ a difluorocarbene precursor⁴]

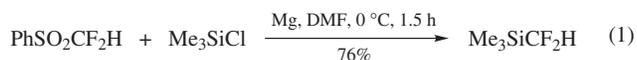
Physical Data: mp 24.7–25.0 °C; bp 115–120/7 Torr; d 1.3241 g cm⁻³.⁴

Solubility: soluble in alcohols, ethers, CH₂Cl₂, CHCl₃, DMF, and DMSO.

Form Supplied in: colorless liquid; often prepared by the oxidation of difluoromethyl phenyl sulfide using aqueous hydrogen peroxide in acetic acid.

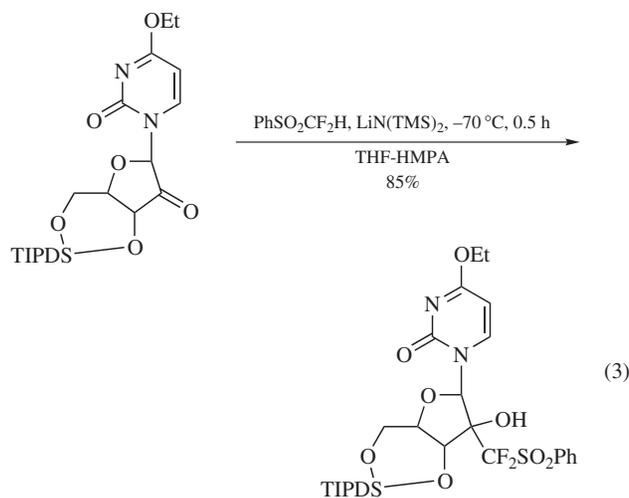
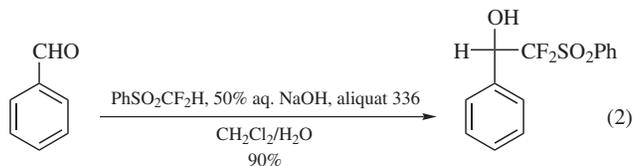
Handling, Storage, and Precautions: PhSO₂CF₂H has high reactivity with bases and reducing metals; it has certain acidity; store under anhydrous, neutral conditions; use in a fume hood.

Reductive Difluoromethylation. Under the induction of reducing metals, difluoromethyl phenyl sulfone can act as a difluoromethyl anion (CF₂H⁻) synthon. For instance, difluoromethylsilanes (R₃SiCF₂H) can be prepared from the magnesium-metal-mediated reductive difluoromethylation of chlorosilanes using difluoromethyl phenyl sulfone (eq 1).¹ The magnesium metal acts as a single-electron transfer (SET) source for difluoromethyl phenyl sulfone to generate the difluoromethyl anion species, which reacts with chlorosilanes to produce difluoromethylsilanes. (Difluoromethyl)trimethylsilane and (difluoromethyl)triethylsilane have been prepared by this method.¹ These (difluoromethyl)trialkylsilanes can be further used as difluoromethylating agents for other electrophiles such as carbonyl compounds.⁵

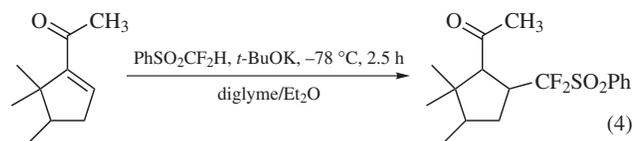


Nucleophilic (Benzenesulfonyl)difluoromethylation. Difluoromethyl phenyl sulfone can be readily deprotonated by a common base such as sodium hydroxide, to generate (benzenesulfonyl)difluoromethide (PhSO₂CF₂⁻). The in situ generated (benzenesulfonyl)difluoromethide has been shown to react with nonenolizable aldehydes to give (benzenesulfonyl)difluoromethylated carbinols in high yields (eq 2).² These (benzenesulfonyl)difluoromethylated carbinols can be further transformed into many other important fluorine-containing compounds, such as difluoromethyl carbinols (after reductive desulfonylation) and 1,1,2-trifluoro-1-alkenes (after fluorination and elimination).² By applying different bases, simi-

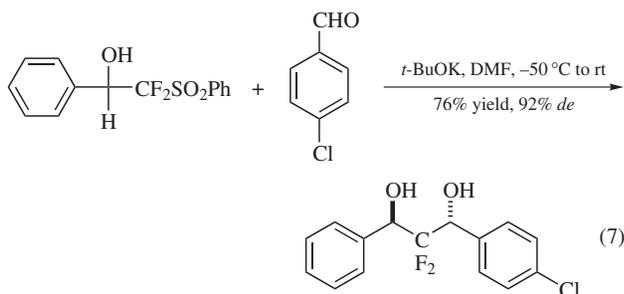
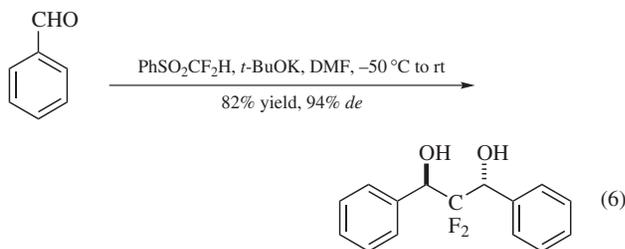
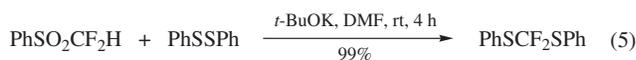
lar nucleophilic (benzenesulfonyl)difluoromethylations involving cyclic ketones and α,β -unsaturated ketones have been reported (eqs 3 and 4).^{6,7} 1,4-addition products were formed as the major products in the case of α,β -unsaturated ketones (eq 4).⁷ These (benzenesulfonyl)difluoromethylated products are useful precursors to 2'-deoxy-2'-difluoromethylene nucleosides and 16 β -difluoromethyl or 16-difluoromethylene steroids.^{6,7} Besides the carbonyl compounds, similar base-induced (benzenesulfonyl)difluoromethylation works for diaryl disulfides to produce (aryltio)difluoromethyl phenyl sulfones.^{2,3}



TIPDS = 3',5'-*O*-tetrakisopropylidisiloxane-1,3-diyl group

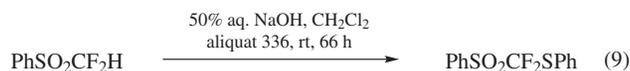
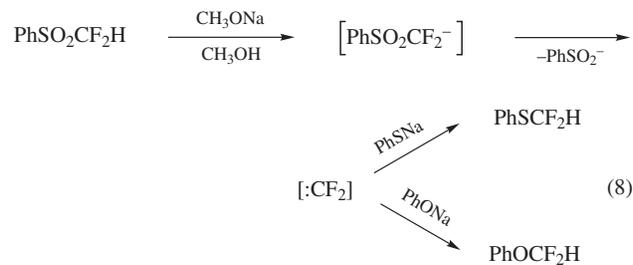


Stereoselective Difluoromethylation. Due to the rather high acidity of its CF₂H hydrogen and high polarity of its S-C bond, difluoromethyl phenyl sulfone can also act as a difluoromethylene dianion (CF₂⁻) equivalent.³ Hence, using potassium *t*-butoxide as both a base and a nucleophile, difluoromethyl phenyl sulfone reacts with two molecules of diphenyl disulfide to give bis(phenylthio)difluoromethane in almost quantitative yield (eq 5). Similarly, it can couple with two molecules of nonenolizable aldehydes to give *anti*-2,2-difluoropropane-1,3-diols with high diastereoselectivity (up to 94% *de*) (eq 6).³ This unusual high diastereoselectivity is obtained by means of an intramolecular charge-charge repulsion effect rather than the traditional steric control (based on Cram's rule). Besides symmetrical *anti*-2,2-difluoropropane-1,3-diols, this methodology can also be used to synthesize unsymmetrical *anti*-2,2-difluoropropane-1,3-diols when difluoro(phenylsulfonyl)methyl-substituted alcohols are applied as the substrate to react with structurally different aldehydes (eq 7).³



Difluorocarbene Reactions. (Benzenesulfonyl)difluoromethide, readily generated from the deprotonation of the difluoromethyl phenyl sulfone by a base, was found to undergo α -elimination of the benzenesulfonyl group [leaving as benzenesulfinate, PhS(O)O^-] to give difluorocarbene.⁴ The difluorocarbene generation from difluoromethyl phenyl sulfone can be facilitated by applying a strong base, especially in the absence of proper electrophiles (such as carbonyl compounds, disulfides) in the system. The generated difluorocarbene was found to react with sodium thiophenoxide to give difluoromethyl phenyl sulfide, or react with sodium methoxide to give difluoromethyl methyl ether (eq 8).⁴ It has been reported that difluoromethyl phenyl sulfone

reacts with aqueous sodium hydroxide solution alone over 66 h to give (benzenesulfonyl)difluoromethyl phenyl sulfide as the sole product (eq 9).² The mechanism of this unusual reaction was proposed as follows: the difluorocarbene generated reacts with the side-product sodium benzenesulfinate to give the diphenyl disulfide, which reacts further with (benzenesulfonyl)difluoromethide to give (benzenesulfonyl)difluoromethyl phenyl sulfide.²



- (a) Prakash, G. K. S.; Hu, J.; Olah, G. A., *J. Org. Chem.* **2003**, *68*, 4457. (b) Prakash, G. K. S.; Hu, J.; Olah, G. A., WO 2003048033.
- Stahly, G. P., *J. Fluorine Chem.* **1989**, *43*, 53.
- Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A., *Angew. Chem. Int. Ed.* **2003**, *42*, 5216.
- Hine, J.; Porter, J. J., *J. Am. Chem. Soc.* **1960**, *82*, 6178.
- (a) Hagiwara, T.; Fuchikami, T., *Synlett* **1995**, 717. (b) Hu, J., Ph.D dissertation, University of Southern California, 2002.
- Sabol, J. S.; McCarthy, J. R., *Tetrahedron Lett.* **1992**, *33*, 3101.
- Edwards, J. A.; Fried, J. H.; Mills, J. S., US 3705182 (1972).

G. K. Surya Prakash & Jinbo Hu
University of Southern California, Los Angeles, CA, USA