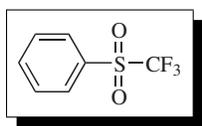


## Trifluoromethyl Phenyl Sulfone



[426-58-4]  $C_7H_5F_3O_2S$  (MW 210.18)  
 InChI = 1/C7H5F3O2S/c8-7(9,10)13(11,12)6-4-2-1-3-5-6/h1-5H  
 InChIKey = UPGBQYFXKAKWQC-UHFFFAOYAH

(reductive trifluoromethylating agent;<sup>1</sup> alkoxide- or hydroxide-induced nucleophilic trifluoromethylating agent;<sup>2</sup> benzenesulfonylation agent to prepare phenyl sulfones<sup>3</sup> and benzenesulfonic acid derivatives<sup>2,4,5</sup>)

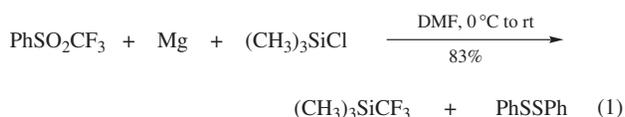
*Physical Data:* bp 205 °C;  $d$  1.423 g cm<sup>-3</sup> (20 °C).<sup>6</sup>

*Solubility:* soluble in alcohols, ethers, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, DMF, and DMSO.

*Form Supplied in:* colorless liquid; often prepared by the oxidation of trifluoromethyl phenyl sulfide using aqueous hydrogen peroxide in acetic acid.<sup>7</sup>

*Handling, Storage, and Precautions:* PhSO<sub>2</sub>CF<sub>3</sub> has high reactivity with bases and reducing metals; store under anhydrous, neutral conditions; use in a fume hood.

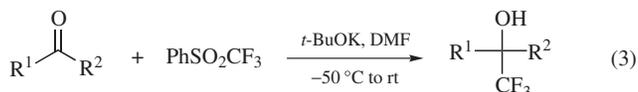
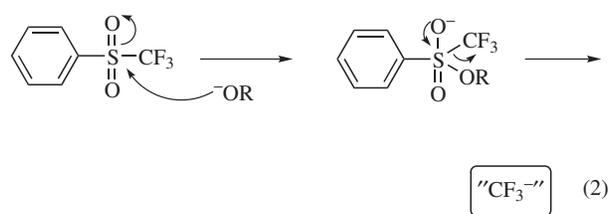
**Reductive Trifluoromethylation.** Since the trifluoromethanesulfonyl group (CF<sub>3</sub>SO<sub>2</sub>-) is a substituent with extreme electron-acceptor properties, trifluoromethyl phenyl sulfone can readily accept one electron to form a radical anion species.<sup>8</sup> Magnesium metal has been found to be a good single-electron transfer (SET) agent for trifluoromethyl phenyl sulfone and other similar systems.<sup>1,9,10</sup> The trifluoromethyl phenyl sulfone radical anion undergoes carbon-sulfur bond cleavage to give the trifluoromethyl anion (CF<sub>3</sub><sup>-</sup>) species, which acts as a nucleophilic trifluoromethylating source for electrophiles. Hence, when trifluoromethyl phenyl sulfone reacts with magnesium metal and chlorotrimethylsilane in DMF at 0 °C, (trifluoromethyl)trimethylsilane (TMS-CF<sub>3</sub>) is formed in high yield (eq 1).<sup>1</sup> Diphenyl disulfide is also formed as a by-product. It is well known that trifluoromethyl phenyl sulfone can be readily prepared from trifluoromethane (CF<sub>3</sub>H) and diphenyl disulfide. So the reductive trifluoromethylation method provides a novel and useful catalytic pathway (in diphenyl disulfide) for the production of TMS-CF<sub>3</sub> from trifluoromethane and chlorotrimethylsilane.<sup>1</sup>



The magnesium-mediated reductive trifluoromethylation also works for other structurally diverse chlorosilanes. Chlorotriethylsilane, *t*-butyldimethylsilyl chloride, and tris(trimethylsilyl)silyl chloride have been applied to prepare corresponding trifluoromethyl-containing silanes.<sup>1</sup> However, the reductive trifluoromethylation did not take place with other electrophiles such as aldehydes, ketones, allyl bromide, benzyl chloride, or tributyltin chloride. Even tributyltin hydride and allyltrimethylsilane showed no reactivity.<sup>1</sup> The reason for such behavior is not clear. Probably,

chlorosilanes play an important role during the reductive trifluoromethylation both as a silylating agent and a single-electron transfer promoter.

**Alkoxide- or Hydroxide-induced Nucleophilic Trifluoromethylation.** By using a nucleophilic base such as an alkoxide or hydroxide, the carbon-sulfur bond of trifluoromethyl phenyl sulfone can be cleaved to give a trifluoromethyl anion (CF<sub>3</sub><sup>-</sup>) synthon that can undergo addition to carbonyl compounds (eq 2).<sup>2</sup> The driving force for this substitution is the formation of a strong S–O bond (348–551 kJ mol<sup>-1</sup>) and the high polarity of the C–S bond of trifluoromethyl phenyl sulfone. The generation of pseudohalide CF<sub>3</sub><sup>-</sup> species is somewhat similar to the reaction between benzenesulfonyl halides with alkoxides.<sup>2</sup> Bases such as potassium *t*-butoxide, sodium methoxide, and potassium hydroxide can all be used as nucleophiles to activate the C–S bond cleavage of trifluoromethyl phenyl sulfone and thus accomplish the trifluoromethylation to nonenolizable carbonyl compounds. Potassium *t*-butoxide was found to be the best choice in terms of reaction yields, and DMF or DMSO can be used as the reaction medium. Various nonenolizable aldehydes and ketones have been trifluoromethylated by this method to give corresponding trifluoromethyl-containing carbinols in good yields (eq 3).<sup>2</sup> An excess amount of potassium *t*-butoxide was found to be helpful to achieve high yields in the trifluoromethylation reactions for several reasons.<sup>2</sup> Due to the lower reactivity of ketones compared with aldehydes, the ketone reactions need a slightly longer time (2–3 h) for completion. With enolizable aldehydes and ketones, however, only low yields (10–30%) of trifluoromethylated products were observed because of the competing and facile aldol reactions. Another advantage of the reaction is the simple workup procedure. The by-product of the reaction is *t*-butyl benzenesulfonate, and it can be readily hydrolyzed into *t*-butyl alcohol and benzenesulfonic acid derivatives. Aqueous washing thus can remove most of the by-products and simplifies the purification process.

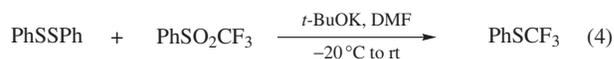


R<sup>1</sup> = Ph, R<sup>2</sup> = H, 77%;

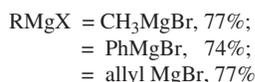
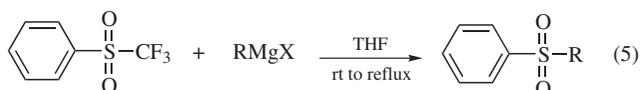
R<sup>1</sup> = Ph, R<sup>2</sup> = Ph, 86%

The similar alkoxide- or hydroxide-induced trifluoromethylation was also found to work with other electrophiles.<sup>2</sup> Diphenyl disulfide can be trifluoromethylated to give trifluoromethyl phenyl sulfide in 87% yield (eq 4). Methyl benzoate can be trifluoromethylated to generate 2,2,2-trifluoroacetophenone in 30% yield at temperatures between -50 °C and -20 °C. Trifluoromethylcopper (CF<sub>3</sub>Cu) can be generated in situ with trifluo-

romethyl sulfone, *t*-BuOK, and copper iodide (CuI), and it then further reacts with iodobenzene at 80 °C for 20 h to give  $\alpha,\alpha,\alpha$ -trifluorotoluene in 26% yield.<sup>2</sup>



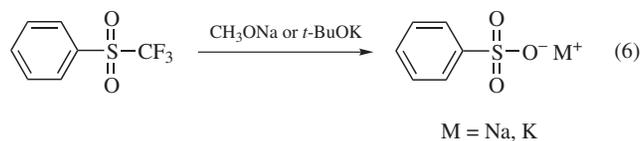
**Benzenesulfonylation Reactions.** Besides oxygen nucleophiles, carbon nucleophiles such as Grignard reagents and alkyllithiums also readily attack the sulfur center of trifluoromethyl phenyl sulfone to cleave the carbon-sulfur bond. Thus, trifluoromethyl phenyl sulfone can be used as a benzenesulfonylation agent with carbon nucleophiles to form phenyl sulfones (eq 5).<sup>3</sup> Primary saturated and allylic Grignard reagents are suitable for the reaction to give alkyl phenyl sulfones or allyl phenyl sulfones, with the yields ranging from 56 to 83%. Secondary Grignards can also react with trifluoromethyl phenyl sulfone satisfactorily, although elevated temperature is required in the case of isopropyl magnesium chloride.<sup>3</sup> *tert*-Butyl magnesium chloride did not react with trifluoromethyl phenyl sulfone even after reflux in THF overnight. When aryl Grignards are treated with trifluoromethyl phenyl sulfone, corresponding diaryl sulfones can be obtained in good yields. However, with vinyl magnesium bromide, consumption of trifluoromethyl phenyl sulfone without formation of the desired sulfone was observed at various temperatures.<sup>3</sup> *n*-Butyllithium also reacts with trifluoromethyl phenyl sulfone to give *n*-butyl phenyl sulfone in 38% yield.



The advantage of this methodology for sulfone preparation is that it can substantially avoid the formation of 1,1-disulfone, especially compared to the method using sulfonyl fluoride with organometallic reagents (such as Grignards and organolithium reagents). For the latter case, when an aliphatic organometallic species bearing an  $\alpha$  proton is treated with a sulfonyl fluoride, 1,1-disulfones tend to arise through further deprotonation and sulfonylation of the initial product.<sup>4,5</sup> With the method using trifluoromethyl phenyl sulfone, no 1,1-disulfones were observed from

the reactions with aliphatic Grignards or alkyllithium reagents.<sup>3</sup> The alkyl phenyl sulfone reaction products were undoubtedly metallated under the reaction conditions, but the resulting species were not sulfonylated by trifluoromethyl phenyl sulfone in contrast to their facile sulfonylation by sulfonyl fluoride.<sup>3</sup>

Another application of trifluoromethyl phenyl sulfone is in the preparation of benzenesulfonic acid (or metal benzenesulfonate) using oxygen nucleophiles. Trifluoromethyl phenyl sulfone is readily transformed into benzenesulfonate salt upon treatment with an alkoxide or hydroxide (eq 6).<sup>2,6,7</sup> This is particularly useful for the convenient transformation of a polymer-supported trifluoromethyl phenyl sulfone into polymer-supported sulfonic acid (or sulfonate) ion-conducting materials.<sup>8–12</sup>



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