

Synthesis of Symmetric Diaryl Sulfones with Dimethyl Sulfate

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In this procedure dimethyl sulfate was used for preparation of symmetric diaryl sulfones. First, dimethyl sulfate was treated with pyridine, then activated by TiF_2O to generate SO_2 as the functional group for synthesis of diaryl sulfones. It is noticeable that this reaction was carried out in moderate conditions and products obtained in short times and good yields.

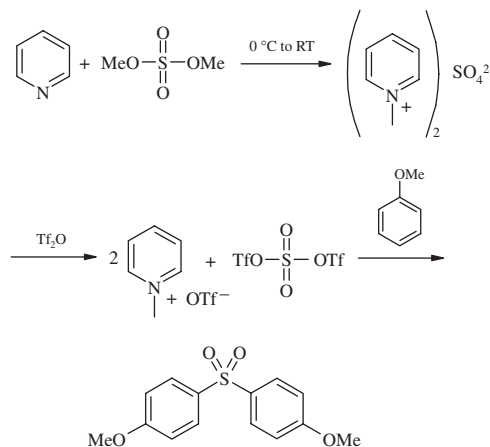
Aryl sulfones are of great use in organic synthesis and industry.^{1,2} Diaryl sulfones are important drugs active against leishmaniasis, malaria, and infections in patients with AIDS discoid lupus erythematosus.^{3,4} Various methods for the synthesis of sulfones involve the oxidation of sulfides,⁵ sulfonylation of arenes using an arylsulfonyl halide in the presence of Lewis acids,⁶ and reaction of sulfonyl fluorides with organometallic reagents.⁷ Catalysts such as AlCl_3 and SbF_5 ,⁸ BiCl_3 /triflic acid,⁹ metal-exchanged k-10 Montmorillonites,¹⁰ $\text{Sn}(\text{OTf})_2$,¹¹ $\text{In}(\text{OTf})_3$,¹² Nafion-H,¹³ Zn-exchanged zeolites,¹⁴ and InCl_3 /triflic acid¹⁵ have been used to promote Friedel–Crafts reactions. Also, very recently Zhang et al. reported the sulfonylation of aromatic compounds with sulfonamide using TiF_2O .¹⁶

Most of the above procedures lead to unsymmetrical diaryl sulfones and methods that lead to symmetric diaryl sulfones via electrophilic aromatic substitution have been less reported. Therefore, the development of new methods, especially those leading to symmetric diaryl sulfone in situ electrophilic aromatic substitution is highly desirable.

In continuation of our studies on diaryl sulfone in situ aromatic substitution,¹⁷ we would like to report the use of dimethyl sulfate as the source of SO_2 functional groups to produce symmetric diaryl sulfone in situ with pyridine and triflic anhydride (TiF_2O).

The activity of dimethyl sulfate under these reaction conditions was investigated with anisole as an aromatic model compound (Scheme 1). First, dimethyl sulfate was treated with pyridine to produce bis(*N*-methylpyridinium) sulfate [IR (neat)/ cm^{-1} 1205, 1049 (SO_2). ^1H NMR (DMSO- d_6 , 200 MHz): δ 4.32 (s, 3H), 8.05 (t, 2H), 8.52 (t, 1H), 8.93 (d, $J = 5.3$ Hz, 2H). ^{13}C NMR (DMSO- d_6 , 50 MHz): δ 48.3, 128.1, 145.5, 145.9]. Then this salt was activated by TiF_2O to create ditriflate sulfone [IR (neat)/ cm^{-1} 1306, 1028 (SO_2). ^{13}C NMR (DMSO- d_6 , 50 MHz): δ 120.6 (CF_3 , q, $J = 318.7$ Hz) (The chemical shifts of quartet are: 111.0, 117.4, 123.7, 130.1)] having two excellent leaving groups, and finally anisole was added. The corresponding sulfone, bis(4-methoxyphenyl) sulfone, was obtained after 15 min in 82% yield (Table 1). The amount of other isomers were ignorable. To demonstrate the generality of this method, we next investigated the scope of this reaction and the results are summarized in Table 1.

It is shown in Table 1, the best result was obtained for mesitylene and dimesityl sulfone achieving 95% yield after



Scheme 1.

5 min. The reactions of xylene derivatives under the same reaction conditions were also studied and the results for *o*- and *m*-xylene were desirable, but in the case of *p*-xylene no product was achieved. The reason for this fact may be arisen from the steric effect and low activity of *p*-xylene. However, in the case of *m*-xylene, the steric effect still exist but the position of the reaction can be activated by two methyl groups. Also, some active derivatives of anisole (Entries 5–8) were applied and their reactions were performed and the corresponding products were obtained in good yields.

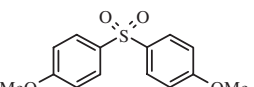
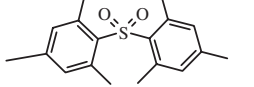
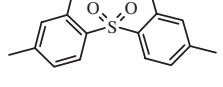
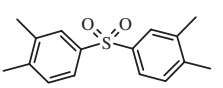
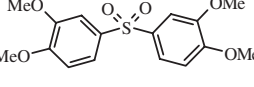
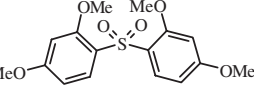
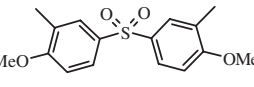
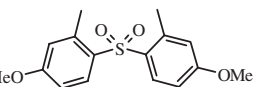
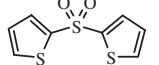
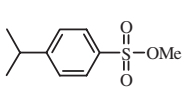
Reaction of cumene under these conditions was unsuccessful. However, when the temperature was increased to 80 °C, methyl 4-isopropylbenzenesulfonate instead of the corresponding diaryl sulfone was obtained that shows ^1H NMR peaks at 1.30 (d, 6H), 3.03 (m, 1H), 3.79 (OMe, s, 3H), 7.48 (d, 2H), and 7.85 (d, 2H). Activity of toluene was investigated in different temperatures and various solvents, but no product was observed. Among of heterocyclic aromatic compounds, thiophene and indole were chosen and tested. The reaction of thiophene was successful and di-2-thienyl sulfone was obtained in 90% yield but the reaction of indole afforded a mixture of products.

Instead of dimethyl sulfate and pyridine, some inorganic salts such as Na_2SO_4 , $(\text{NH}_4)_2\text{SO}_4$ were allowed to react with TiF_2O and anisole, but no reaction was observed. This means that the reaction between dimethyl sulfate and pyridine produces the organic salt [bis(*N*-methylpyridinium) sulfate] that can easily react in organic media.

In conclusion, we have described a novel approach to produce symmetric diaryl sulfones via activation of dimethyl sulfate with pyridine and TiF_2O under mild conditions.¹⁸

The authors thank the Razi University Research Council for financial assistance.

Table 1. Synthesis of symmetric diaryl sulfone with dimethyl sulfate

Entry	Aromatic	Product	Time/min	Yield/% ^a
1			15	83
2			5	95
3			10	88
4			10	85
5			10	88
6			15	90
7			10	87
8			15	90
9			5	90
10			60	40

^aIsolated product.**References and Notes**

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- General procedure: To a 25 mL flask, dimethyl sulfate (0.5 mmol, 0.05 mL) and pyridine (1 mmol, 0.08 mL) were added at 0 °C and allowed the mixture stirred at room temperature for 30 min. Then Tf₂O (1 mmol, 0.16 mL) and aromatic compound (1 mmol) were added to the mixture and after the appropriate time (Table 1), 10 mL of water was added. The resulting precipitated crude product was purified by recrystallization from a mixture of dichloromethane and *n*-hexane (1:2). Selected spectroscopic data: [Bis(4-methoxyphenyl) sulfone, Entry 1]. ¹H NMR (CDCl₃, 200 MHz): δ 3.83 (s, 3H), 6.94 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (CDCl₃, 50 MHz): δ 55.9, 114.4, 129.5, 133.8, 163.1. [Bis(3,4-dimethylphenyl) sulfone, Entry 3]. ¹H NMR (CDCl₃, 200 MHz): δ 2.22 (s, 6H), 2.30 (s, 6H), 6.95 (s, 2H), 7.10 (d, *J* = 8 Hz, 2H), 7.99 (d, *J* = 8 Hz, 2H). ¹³C NMR (CDCl₃, 50 MHz): δ 19.9, 21.3, 126.6, 130.1, 133.2, 136.2, 137.5, 144.0.