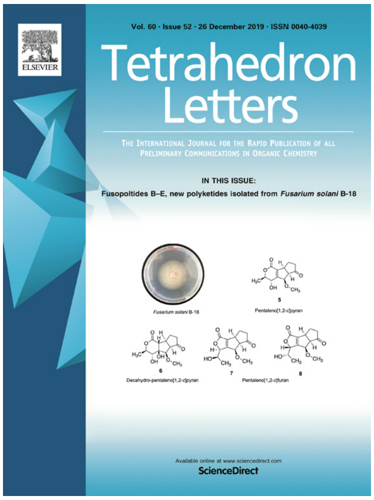

Facile synthesis of diarylsulfones from arenes and $3CdSO_4 \cdot xH_2O$ *via* mechanochemistry

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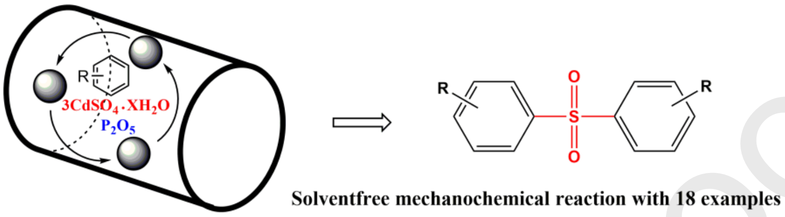

Solventfree mechanochemical reaction with 18 examples

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Facile synthesis of diarylsulfones from arenes and $3CdSO_4·xH_2O$ *via* mechanochemistry

Shuai Qin, Pu Zhang⁎, Yu-Jun Qin, and Zhi-Xin Guo*

Department of Chemistry, Renmin University of China, Beijing 100873, China

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ABSTRACT

A variety of substituted diarylsulfones could be synthesized by simple arenes and $3CdSO_4·xH_2O$ in the presence of P_2O_5 under high-speed ball milling. It was suggest the aromatic sulfonation was performed by arene and *in situ* generated H_2SO_4, following-up by electrophilic substitution with another arene to give diarylsulfone.

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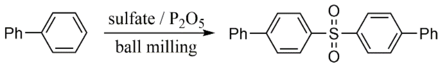
⁎ Corresponding authors. E-mail: gzhixin@ruc.edu.cn, zhangpu@ruc.edu.cn molecules which have found wide utilities in pharmaceuticals, agrochemicals, and functional materials [1-4]. In the meantime, diarylsulfones are also important intermediates in organic transformation [5]. Traditionally, these sulfones were synthesized via aromatic sulfonating [6-10], the oxidation of sulfides and sulfoxides [11-13], and transition-metal catalyzed arylation of sulfinate salts [14-15]. Despite their usefulness, these methods have some limitations, such as harsh reaction conditions, requiring prefunctionalized starting materials, or employing high temperature, expensive catalysts, toxic solvents. Although a number of new methods have been developed recently [16-19], development of a general, facile, and efficient synthetic protocol to diarylsulfone is still highly desirable.

In recent years, mechanochemical organic methodologies have been explored as a powerful tool for organic chemists [20-26]. The application of mechanical forces to solvent-free or solventless reaction mixtures through the use of ball-mills offers many advantages over traditional solvent-based strategies. During our continuous exploration of high-speed ball milling (HSBM) reactions [27-32], we recently found that by taking $Bi(NO_3)_2 \cdot 9H_2O$ or $Fe(NO_3)_3 \cdot 9H_2O$ as the nitrification reagents, $MgSO_4$ or P_2O_5 as the auxiliaries, respectively, arenes could be nitrated in excellent yields under HSBM condition. In this context, acetophenones could also be converted to diacylfuroxans in high or moderate yields [32]. While the nitrate salts with P_2O_5 together can perform the aromatic nitration very well, likewise, we propose that the combination of certain sulphate salt with P_2O_5 may also achieve the aromatic sulfonation. Herein, we report an unprecedented synthesis of diarylsulfones by reacting arenes with $3CdSO_4 \cdot xH_2O$ and P_2O_5 under HSBM condition.

During our studies, a stainless milling beaker of 2.5 mL along with one stainless milling ball (ø = 6.0 mm) was used. The mechanochemical reaction was performed in a MM400 mixer mill at 28 Hz for 5 hours at room temperature. Biphenyl was chosen as the standard substrate to screen if any reaction could be performed. Initially, the molar ratios of the biphenyl, sulfate salt, and P2O5 were fixed as 1:2:3. All the reagents were added to the stainless milling beaker (2.5 mL), along with one stainless milling ball (ø = 6.0 mm). The beaker was sealed and milled at 28 Hz for 5 hours in the MM400 mixer mill (Table 1, entries 1, 2, 8–17, 32–34, 41). When anhydrous sulfates were employed, no or only trace amount of 4,4'-sulfonyldibiphenyl was observed (Table 1, entries 1, 9, 11, 16, and 33). For hydrated sulfates with relatively large amount crystal waters, the result was almost the same (Table 1, entries 8, 10, 12–15, and 32). However, when $MgSO_4 \cdot H_2O$, $3CdSO_4 \cdot xH_2O$ (x ≈ 1, the same below), and $CaSO_4 \cdot 0.5H_2O$ was taking as sulfate, 4,4'-sulfonyldibiphenyl could be obtained in 14%, 10%, and 12% yield, respectively (Table 1, entries 2, 17, and 34). For these three sulfates, the HSBM reaction condition was further optimized by adjusting the molar ratios of each sulfate and P_2O_5 related to biphenyl to a variety of values, in order to get higher yield (Table 1, entries 2–7, 17–31, and 34–40). By keeping the molar ratios of biphenyl, $MgSO_4 \cdot H_2O$, and P_2O_5 as 1:7:3, 43% of the desired sulfone could be obtained. When the molar ratios of biphenyl, $CaSO_4 \cdot 0.5H_2O$, and P_2O_5 were 1:4:3, 39% of the corresponding sulfone could be obtained. Most gratifyingly, when the molar ratios of biphenyl, $3CdSO_4 \cdot xH_2O$, and P_2O_5 were kept as 1:3.5:11, 72% of 4,4'-sulfonyldibiphenyl was obtained. In this case, $3CdSO_4 \cdot xH_2O$ was chosen as the appropriate sulfate and the molar ratios of substituent/$3CdSO_4 \cdot xH_2O$/P_2O_5 = 1:3.5:11 were selected for the HSBM reaction in the further studies.

It was reported that mechanochemistry process parameters usually have a strong influence on the outcomes [33-40]. In order to obtain the best HSBM reaction condition, the combined assessment of the grinding time and vibration frequency as well as the influence of ratios between the milling ball and the milling materials were carried out, respectively. When the reaction time % to 52% and 63% along with the frequency was elevated from 20 to 25 and 28 Hz, respectively. However, when the reaction time was setting as 6 or 7 hours, the yields were almost the same with the frequency at 25 and 28 Hz, respectively. This implies that compared with vibration frequency, the grinding time is more important in this HSBM reaction (Figure 1(a) and Table S1 in ESI).

Table 1. The choice and optimization of sulfate salts*



Entry	Sulfate	Molar ratio†	Yield (%)‡
1	$MgSO_4$	1:2:3	trace
2	$MgSO_4 \cdot H_2O$	1:2:3	14
3		1:6:3	35
4		1:7:3	43
5		1:8:3	31
6		1:7:4	33
7		1:3.5:11	5
8	$MgSO_4 \cdot 7H_2O$	1:2:3	N.D.
9	Na_2SO_4	1:2:3	trace
10	$Na_2SO_4 \cdot 10H_2O$	1:2:3	N.D.
11	$Fe_2(SO_4)_3$	1:2:3	N.D.
12	$FeSO_4 \cdot 7H_2O$	1:2:3	N.D.
13	$CoSO_4 \cdot 7H_2O$	1:2:3	N.D.
14	$NiSO_4 \cdot 6H_2O$	1:2:3	N.D.
15	$ZnSO_4 \cdot 7H_2O$	1:2:3	N.D.
16	$CdSO_4$	1:2:3	N.D.
17	$3CdSO_4 \cdot xH_2O$	1:2:3	10
18		1:2:6	14
19		1:2:7	28
20		1:2:8	50
21		1:3:10	65
22		1:3:11	52
23		1:3:12	63
24		1:3.5:11	72
25		1:3..5:12	61
26		1:4:12	59
27		1:4:13	64
28		1:4:14	60
29		1:5:13	58
30		1:5:14	62
31		1:5:15	55
32	$3CdSO_4 \cdot 8H_2O$	1:2:3	N.D.
33	$CaSO_4$	1:2:3	trace
34	$CaSO_4 \cdot 0.5H_2O$	1:2:3	12
35		1:3:3	24
36		1:4:3	39
37		1:5:3	31
38		1:6:3	20
39		1:4:4	28
40		1:3.5:11	8
41	$CaSO_4 \cdot 2H_2O$	1:2:3	trace

* See ESI for reaction details; † Molar ratio = biphenyl: sulfate: P_2O_5;
‡ Yields were determined by ^{1}HNMR; N.D. = Not detected.

I [illegible] ball and the milling materials was another key parameter for the yields of the ball milling reaction [35-40]. In the HSBM reaction, stainless steel balls with different sizes were investigated under the same reaction condition (Figure 1(b), Table S2 in ESI). Obviously, when the ratio between the milling ball and the milling materials was 3.7 (the ball's diameter is 6.0 mm), the best yield of 72% was obtained, indicating that the best weight ratio between the milling ball and the milling materials is around 3.7. Combining with the results of assessment of the grinding time and vibration frequency, the best HSBM condition for this ball-milling reaction is grinding 5 hours under the vibration frequency of 28 Hz with the weight ratio of 3.7 between the milling ball and the milling materials.

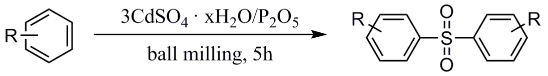
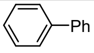
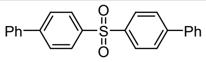
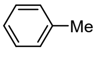
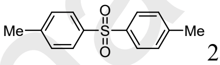
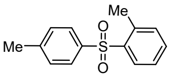
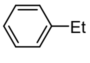
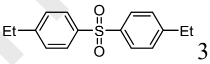
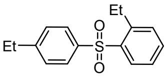
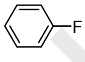
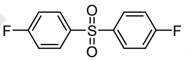
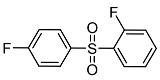
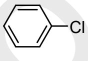
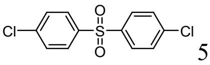
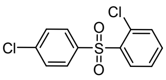
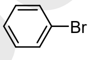
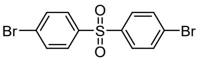
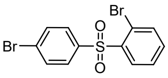
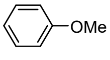
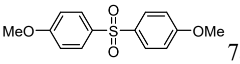
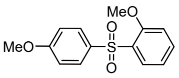
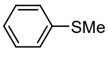
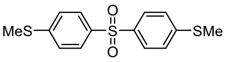
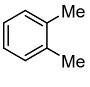
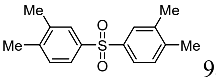
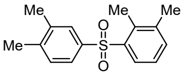
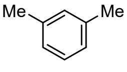
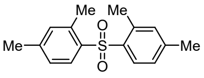
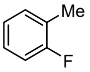
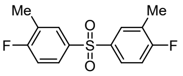
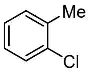
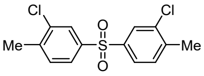
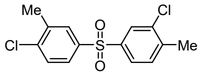
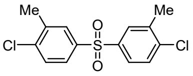
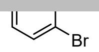
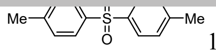
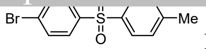
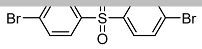
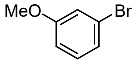
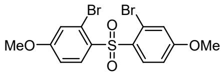
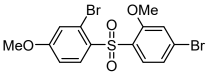
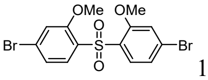
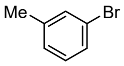
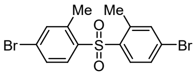
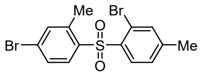
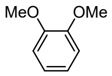
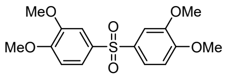
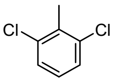
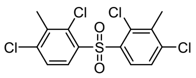
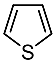
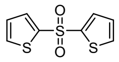


Figure 1. Optimization of mechanochemical parameters. (a) Influence of time/frequency; (b) Influence of the weight ratios of milling ball/milling materials.

Various substituted arenes were tested as substrates under the optimized conditions. Table 2 summarizes the results. Arenes with only one activating substituent such as methyl (Table 2, entry 2), ethyl (Table 2, entry 3), and methoxy (Table 2, entry 7) gave [illegible]no-halogen substituted arenes also gave similar results (Table 2, entries 4-6). All of the mono-substituted arenes above gave para-substituted sulfones as the major products accompanied with small amount of ortho-substituted counterparts, implying these regioselectivity outcomes were determined by the steric hinderance effect. In this context, biphenyl (Table 2, entry 1) and methylthiobenzene (Table 2, entry 8) resulted in only para diarylsulfones, most probably due to the relative big steric effect of the phenyl and methylthio group, respectively. However, mono-substituted arenes with deactivating substituents such as nitro, cyano, acetyl, acetylamino, and ethoxycarbonyl all failed to give the desired products, almost all the starting arenes were recovered. These results agree well with the synthesis of sulfones in traditional solution chemistry by taking either benzenesulfonic acid or benzenesulfonyl chloride as electrophilic reagents [6-10], implying an electrophilic substitution process may be involved in the HSBM process. For those arenes with multi-substituents, m-dimethylbenzene (Table 2, entry 10), 1,2-dimethoxybenzene (Table 2, entry 16), and 2,6-dichlorotoluene (Table 2, entry 17) resulted in only one regioisomer, respectively. For the three 2-halogenotoluenes (Table 2, entries 11 – 13), 2-fluorotoluene shown specific regioisomerization and only the 4,4'- sulfone was obtained (Table 2, entry 11). It was reported that when these 2-halogenotoluenes were sulfonated, the degree of 5-substitution decreased from ~ 90% for the fluoro, to ~ 70% for the chloro, and to ~ 60% for the bromo compound, respectively [41]. Thus the directing effect of the fluoro is more dominant than those of chloro and bromo. This maybe the reason for the specific regioisomerism of 2-fluorotoluene in the reaction. All of the other substrates gave more than one regioisomers, and the distribution should be resulted from the balance of the electronic

Table 2. Various diarylsulfones formed via the mechanochemical reaction*

Entry	Arene	Sulfone and yield**
1		 1a, 72% (65%)
2		 2a, 68% (60%)  2b, 23% (16%)
3		 3a, 74%  3b, 15%
4		 4a, 49% (43%)  4b, 13% (10%)
5		 5a, 53%  5b, 14%
6		 6a, 59%  6b, 16%
7		 7a, 80%  7b, 15%
8		 8a, 52%
9		 9a, 85%  9b, 11%
10		 10a, 74%
11		 11a, 61%
12		 12a, 33%  12b, 28%  12c, 16%

13		 13a, 39%	 13b, 31%	 13c, 20%
14		 14a, 48% (42%)	 14b, 33% (28%)	 14c, 10% (8%)
15		 15a, 45%		 15b, 26%
16			 16a, 70%	
17			 17a, 57%	
18			 18a, 46%	

* See ESI for reaction details. The yields in the brackets were from the PTEF milling beakers. ** Isolated yields.

character of the substituent groups. This results agree well with Rao's report by taking $K_2S_2O_8$ as sulfonating reagents in solution chemistry [13]. It is worth to mention that the only regioisomeric diarylsulfones obtained in this research may be further converted to fused diaryl sulfones, which show a great significance due to their prospective application in pharmaceutical and material areas [36]. In addition, aromatic heterocyclics such as thiophene could also be converted to the corresponding sulfone with a good yield (Table 2, entry 18), implying that heterocyclic sulfones could also be obtained by this HSBM method. In the meantime, this reaction could also be performed well in big PTFE milling beaker (35 mL) with a PTFE ball (entries, 1, 2, 4, and 14).

As far as we know, this is the first observation for the synthesis of diarylsulfones via HSBM reaction. Since the above experimental results imply an electrophilic substitution process, we suggest that the aromatic sulfonic acid should be the key intermediate. In order to obtain this intermediate, the HSBM reaction by taking biphenyl as substituent was re-investigated. Since aromatic sulfonic acid may have relatively large solubility in methanol, the reaction mixture was extracted with methanol. The solvent was removed *via* rot-vap, and the residue was purified by column chromatography using dichloromethane/methanol (15:1, v/v) as eluent. A white solid was obtained, the structure of which was confirmed as 4-biphenyl sulfonic acid by ^{1}H NMR, ^{13}C NMR, and HRMS (ESI).

To make the mechanism of this HSBM reaction more clearly, the changing of the inorganic components ($3CdSO_4{\cdot}xH_2O$ and P_2O_5) involved after the HSBM reaction was also investigated. After the standard HSBM reaction procedure, the reaction mixture was extracted thoroughly by chloroform in order to remove any organic components. Then the residue was rinsed with 20 mL of 5 N NaOH solution for a while and then centrifuged. The resulting solid was fully dried to give a white solid. FT-IR and Raman spectroscopy was employed to investigate its possible structure, respectively (Figure 2).

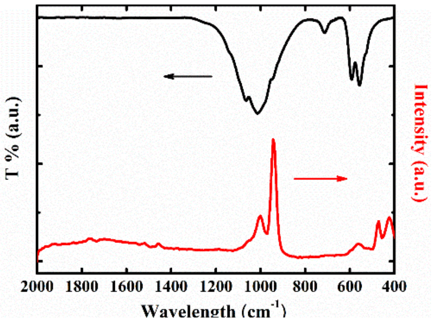
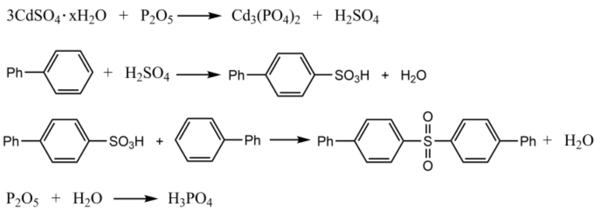


Figure 2. FT-IR (black) and Raman (red) spectrum of the white solid.

The FTIR spectrum obtained is almost the same with pristine $Cd_3(PO_4)_2$ measured by He et al [37]. Basically, the peak at 1012 cm^{-1} as well as the should peak at 1065 cm^{-1} can be assigned to the asymmetric stretching modes of P=O group. The peak around 550 cm^{-1} is the asymmetric bending modes of O-P-O [38]. Correspondingly, the symmetric stretching modes of P-O bands is at 940 cm^{-1} in the Raman spectrum [39]. The above spectroscopic results strongly suggest the existence of phosphate anion in the tested substance. Considering the only possible metal existed in the solid was Cadmium, and $Cd_3(PO_4)_2$ could not be dissolved in water, therefore, the white solid should contain $Cd_3(PO_4)_2$ as the dominant component. Combined with 4- biphenyl sulfonic acid separated above, a plausible mechanism for HSBM sulfonation reaction is depicted in Scheme 1.



Scheme 1. Plausible mechanism for HSBM sulfonation reaction by taking biphenyl as substituent

As shown in Scheme 1, firstly, $3CdSO_4{\cdot}xH_2O$ reacted with P_2O_5 to produce H_2SO_4 (a). The biphenyl was sulfonated by this *in situ* generated H_2SO_4 to give 4-biphenyl sulfonic acid (b). Accordingly, 4-biphenyl sulfonic acid reacted with another biphenyl through electrophilic substitution process to give the final product of 4,4'-sulfonyldibiphenyl (c). The *in situ* generated water during the reaction was adsorbed by the excessive P_2O_5 to produce phosphoric acid (d). This process would move water from the products which would also promoted the HSBM reaction forward.

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sulfate salts with certain amount of crystal waters and P_2O_5 can successfully convert arenes to diarylsulfones. Among a variety of sulfate salts tested, $3CdSO_4 \cdot xH_2O$ gives the best results. This method is facile and eco-friendly and exhibits advantages in terms of safety and easier operation. We suggest H_2SO_4 We suggest H_2SO_4 generated *in situ* from the reaction of the sulfate salts with P_2O_5, could perform the aromatic sulfonation with arene to produce aryl sulfonic acid. The aryl sulfonic acid thus formed could conduct further electrophilic substitution reaction with another arene to give diarylsulfone.

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Supplementary Material

Supplementary data to this article can be found online at XXX.

Highlights

- Solvent-free mechanochemical synthesis of sulfones
- $3CdSO_4 \cdot xH_2O$ as the alterative reagent instead of sulfonic acid
- Facile, safe, and eco-friendly method with high yield

Declaration

The authors declare no competing financial interest