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Synthesis of Aryl(chalcogen-heteroaryl)methyl Sulfones via Sulfuric Acid-Promoted Three-Component Reaction in Water

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Abstract: A facile and efficient three-component reaction in presence of Brønsted acid in water was developed to synthesize aryl(chalcogen-heteroaryl)methyl sulfones in good to very high yields with broad substrate scope. Our protocol is eco-friendly, metal free, and atom economic. The sulfone products may be efficiently transformed into a bactericidal agent analogue and an aryl heteroaryl ketone.

Sulfones are extensively used as biologically active compounds,^[1] natural products,^[2] agrochemicals, such as Syngenta's popular herbicide mesotrione^[3] and pharmaceuticals, such as γ -secretase inhibitor which is a drug to prevent Alzheimer's disease.^[4] Sulfones are also mostly used as valuable intermediates in organic synthesis.^[5]

On the other hand, chalcogen heterocyclic scaffolds shows biological activity such as antitumor^[6] and antiproliferative.^[7] In that, thiophene, furan and selenium containing compounds are well known to exhibit various biological activities, such as anti-inflammatory agents,^[8] anti-HIV PR inhibitors,^[9] inhibitors of NQO2[^{10]} and anti-cancer agents.^[11] Most recently the structure-activity relationship (SAR) of α-branched heterocyclic benzyl sulfones was set out to explore in medicinal chemistry projects.^[12] Based on this importance, our interest was grown to synthesize aryl(chalcogen-heteroaryl)methyl sulfones.

In traditional methods, several reports^[13-20] available on synthesis of sulfone and related sulfonamide arylations. Only few reports available on aryl(het)methylsulfones. For example, Beletskaya et. al.^[21] synthesized by palladium catalyzed arylation of strongly CH-acidic sulfones (scheme 1a).

Knauber et. al.^[12] synthesized palladium catalyzed α heteroarylation of sulfones (scheme 1b) under inert atmosphere at 130 °C. In recent reports Prapurna et al.^[22] synthesized sulfonated thiophenephenyl methane which is involved in low atom-economic two-step reaction (scheme 1c): one is moisture-

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sensitive Grignard reaction and the other is Lewis acid-catalyzed condensation. Crudden et. al.^[23] synthesized phenyl thiophenemethyl sulfone by second step intermediate alcohol substitution with sodium benzenesulfinate under inert atmosphere in 16 h in DCM solvent (Scheme 1d). However, in earlier reports they used metal catalyst, organic solvents, dry conditions and two step reaction to synthesize aryl(heteroaryl)methyl sulfones. The usage of organic solvents may have diverse harmful characters to environment, such as flammable and explosive, they may be toxic and persistent, so there is a need to use environmentally benign solvent such as water.^[24]

Scheme 1a (Ref. 13)



Scheme 1b (Ref. 12)

$$R' O R'' + Br R''' + Br R''' + Br R''' + CR'' + CR''' + CR'' + CR''' + CR'' + CR''' + CR'' + CR''$$

Scheme 1c (Ref. 14)



Scheme 1d (Ref. 15)



Scheme 1. Synthesis of aryl(chalcogen-heteroaryl)methyl sulfones.

On the other hand, the focus on metal-free transformations has become one of the main research topics in organic synthesis and green chemistry, because the metal-free catalytic process is favorable to cost-saving, elimination of metal toxicity and reduction of environmental pollution.^[25-27]

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In view of this and as our ongoing research in organosulfur chemistry,^[28-31] here we report a Brønsted acid-catalyzed metal-free three-component reaction in water to obtain aryl(chalcogen-heteroaryl)methyl sulfones with broad substrate scope (Scheme 1-1e), and product transformation into other valuable molecules such as bactericidal agent analogue via new reactions are also demonstrated.

Initially we chose benzaldehyde (1a), sodium phenylsulfinate (2a) and 2-methylthiophene (3a) as substrates to obtain product 4aaa with 69% yield in DCM solvent in presence of H_2SO_4 at room temperature (Table 1, entry 1).

Table 1. Optimization of reaction conditions.^[a]



^[a] Reaction conditions: resin (100%, weight percentage according to **3a**) or Bronsted /Lewis acid (1 equivalent according to **3a**), benzaldehyde **1a** (1.3 mmol), **2a** (1.0 mmol) and **3a** (1.0 mmol), reaction time 12 h, under air, unless otherwise noted. ^[b] Reaction time 7 h, H₂SO₄ (0.5 mmol).

DCM

DCM

DCM

40

40

40

21%

NA

NA

PTSA

FeCl₃

ZnCl₂

14

15

16

To optimize reaction conditions, in this model reaction were further screened different acid catalysts such as Amberlyst 15, IR-120(H) acid resins in ethanol or water as solvent, respectively, but poor yields were got (Table 1, entries 2~5). So investigation was continued with H_2SO_4 as catalyst in water with different temperatures and different equivalents of H_2SO_4 (Table 1, entries 6~9), and 82% yield of **4aaa** was obtained with 0.5 equivalent of H_2SO_4 at 60 °C (Table 1, entry 8), which was a very good yield. Further we tried to improve yield of **4aaa** with acids such as NaHSO₄, HCI, HBF₄ and AcOH in water at various temperatures (Table 1, entries 10~14), and poor yields were observed. In the case of PTSA in DCM also observed poor yield (Table 1, entries 14). Next we also tried with Lewis acids such as FeCl₃, ZnCl₂ (Table 1, entries 14-15) in DCM solvent, but product **4aaa** was not observed. So finally based on the above screened reactions, 0.5 equivalent of H₂SO₄ at 60 °C in water to give 82% yield of **4aaa** in 7 h time (Table 1, entry 8) was chosen as optimized reaction condition, which was metal free and environmentally benign solvent contained reaction condition.

With the optimized condition in hand, we explored the substrate scope of aldehydes **1.** Various aryl/heteroaryl/alkyl aldehydes (**1a-k**) were individually examined by reacting with substrates **2a** and **3a** via three-component reaction (Table 2).

Table 2. Substrate scope of the aldehydes (1).^[a]

о , Ц +	SO2	H_2SO + H_2SO Wate	O ₄ (0.5 eq)	
1a-k	2a	3a	2	R laaa-kaa
Entry	1	R	4	Yield (%)
1	1a	Phenyl	4aaa	82
2	1b	4-Fluorophenyl	4baa	89
3	1c	2-Chlorophenyl	4caa	88
4	1d	4-Chlorophenyl	4daa	88
5	1e	2-bromophenyl	4eaa	86
6	1f	2-Hydroxyphenyl	4faa	77
7	1g	4-Methylphenyl	4gaa	77
8	1h	н	4haa	72
9	1i	Methyl	4iaa	74
10	1j	2-Furan	4jaa	69
11	1k	3-Thiophene	4kaa	71

 $^{[a]}$ Reaction conditions: H₂SO₄ (0.5 mmol), benzaldehyde **1** (1.3 mmol), **2a** (1.0 mmol) and **3a** (1.0 mmol), 7 h, water (4 mL) under air atmosphere.

When the aromatic aldehyde substrates with electronwithdrawing groups on phenyl ring, such as F (1b), Cl (1c, 1d), and Br (1e), the yields of 4baa (89%), 4caa (88%), 4daa (88%) and 4eaa (86%) were very good. When we used aromatic aldehydes with electron-donating group such as hydroxyl (1f), methyl (1g) and alkyl aldehydes (1h and 1i) as substrates, the yields of 4faa-4jaa were reduced to 77%, 77%, 72% and 74%, respectively, when compared to aromatic aldehyde substrates with electron-withdrawing group afforded product (4baa-4eaa). When we used heterocyclic substrates (1j and 1k) in this three component reaction, the yields of 4jaa and 4kaa were decreased to 69% and 71%, respectively (Table 2). In a word, it seems that there is a rule that electron-withdrawing groups on aldehydes afforded higher yields than electron-donating groups including

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electron-rich heteroaryl groups, perhaps electron-withdrawing groups on aldehydes benefit stability of reactive intermediates. Next, we explored the substrate scope of 2. Various sodium aryl/alkylsulfinates (2a-i) were examined by reacting with substrates 1a and 3a under the optimized reaction condition (Table 3). The aromatic sulfinate substrates 2 bearing electron withdrawing groups, such as F (2b), CF₃ (2c) and Cl (2d) on phenyl ring at ortho- or para- position were tolerated, and afforded the desired products (4aba-4aca) in very good yields and aromatic sulfinate substrates 2e bearing electron withdrawing group F, at meta-position was afforded product 4aea in less yield when compared to yields of products 4aba-4aca which were afforded by substrates (2b-d) with electron withdrawing groups, on phenyl ring at ortho- or para- position. Also we observed that decreasing yields in case of aromatic sulfinate 2 with electrondonating group, such as tertiary-butyl (2f), methyl (2g) and alkyl sulfinate (2h and 2i) substrates afforded products (4afa-4aia, Table 3).

Table 3. Substrate scope of sodium aryl/alkylsulfinates (2)



 $^{[a]}$ Reaction conditions: H₂SO₄ (0.5 mmol), benzaldehyde **1a** (1.3 mmol), **2** (1.0 mmol) and **3a** (1.0 mmol), 7 h, water (4 mL) under air atmosphere.

Finally, we explored the substrate scope of **3**. Diverse thiophene/furans and selenophene (**3a-i**) were examined individually by reacting with substrates **1a** and **2a** via threecomponent reaction under the optimized reaction condition (Table 4). The thiophene substrates **3** with electron donating groups such as methyl, ethyl, hydroxyethyl and thiomethyl at ortho position, were afforded products (**4aaa-4aad**) in very good yields, whereas simple thiophene afforded product **4aae** yield was a little less. It is also observed that in the case of various substituted furan substrates' and selenophene's products **4aaf-4aai** were obtained in less yields when compared to diverse thiophene substrate's products (Table 4). In overall, the electron-rich thiophene substrates afforded desired product **4** in very good yield, and various furans and selenophene afforded desired product **4** in good yield.

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Table 4. Substrate scope of chalcogen heteroarenes (3)



^a Reaction conditions: H_2SO_4 (0.5 mmol), benzaldehyde **1a** (1.3 mmol), **2a~2i** (1.0 mmol) and **3a** (1.0 mmol), 7 h, water (4 mL) under air atmosphere.

To study the reaction mechanism, control experiments were carried out under the optimized reaction condition. The results were showed that reaction of **1a** and **3a** produced intermediates **A** (Identified by ESI-HRMS and available in supporting information) and **B**^[32] (NMR spectrum available in supporting information) in 42% yield (Scheme 2, equation a). Reaction of **1a** and **2a** did not (Scheme 2, equation b) produce intermediate **C**.



Scheme 2. Control experiments.

4aai (67%)

Based on the control experiments (Scheme 2), and earlier reports^[32-33] a reaction mechanism for one-pot three-component reaction between **1a**, **2a** and **3a** is proposed (Scheme 3). Initially, the oxygen atom of aldehyde **1a** grasps a proton of sulfuric acid to form intermediate **D**. The electron-rich carbon of **3a** attacks on protonated aldehyde **D** to form intermediate **E**, which subsequently forms intermediate **A** by losing a molecule of water. Here one more **3a** attacks on the intermediate **C** to form

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intermediate **B**. However intermediate **B** will disappear after 50 minutes, which was observed by TLC, since the transformation between **A** and **B** is a reversible reaction. Next the sulfur atom of sodium phenylsulfinate **2a** attacks on intermediate **A** and forms the stable targeted product **4aaa**.



Scheme 3. A plausible reaction mechanism.

We also demonstrating application of one of the above products **4baa** by C-SO₂ bond activation, by synthesizing valuable ketone compound **5** and bactericidal agent ^[34] analogue **6**. Sulfone **4baa** to ketone compound **5** ^[35] was obtained in 71% yield in presence of sodium t-butoxide base in acetonitrile at room temperature (Scheme 4) by new and advanced route. The other transformation is synthesis of bactericidal agent analogue **6** in 62% yield from **4baa** in the presence of FeCl₃ and DCM at room temperature (Scheme 4).



Scheme 4. Further transformation of product 4baa to 5 and 6, an analogue to a bactericidal agent 7.

In summary, we have developed a facile and efficient Brønsted acid-catalyzed three-component reaction in water to synthesize aryl(chalcogen-heteroaryl)methyl sulfones in good to very good yields with broad substrate scope. Aryl(chalcogen-heteroaryl)methyl sulfones were synthesized in single step by C-C and C-S bond formation. We also demonstrated product transformation to synthesize valuable bactericidal agent analogue and ketone.

Experimental Section

General procedure for the synthesis of compounds 4

To a 25 mL glass test tube equipped with a stir bar were added the corresponding aldehyde 1 (1.5 mmol), heteroarene 3 (1 mmol), sulfuric acid (0.5 equiv) and 2 mL water. The test tube was stirred in an oil bath preheated at 60°C for 15 minutes, and then slowly added sodium sulfinate 2 (1 mmol). The reaction mixture was stirred at 60°C. After 6 h, the reaction progress was checked by TLC and confirmed reaction was completed. The reaction mixture was cooled to room temperature. Then water (10 mL) was added to the reaction mixture, which was extracted with ethyl acetate (10 mL) for three times. The combined organic layer was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Petroleum ether : Ethyl acetate = 10 : 1 used as eluents), to give the desired product **4**.

Typical procedure for synthesis of compound 5

The compounds **4baa** (0.28 mmol) was taken into CH₃CN (2 mL) which was already added in 25mL dried glass reaction tube, then added sodium tertiary butoxide (1.2 equiv) and stirred the reaction mixture for 4 h at room temperature. By using the TLC, we confirmed that the reaction was completed after 4 h. Then the reaction mixture was concentrated by using a rotary evaporator. And then water was added to the concentrated reaction mixture, which was extracted with ethyl acetate (3x 5mL). The combined organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Petroleum ether used as eluent) to obtain pure product **5**.

Typical procedure for synthesis of compound 6

To a 25 mL dried glass reaction tube equipped with a stir bar were added compounds **4baa** (0.28 mmol), 1,3,5-trimethoxybenzene (0.3 mmol), DCM (2 mL), FeCl₃ (10 mol%). The reaction mixture was stirred for 8 h at room temperature. By using TLC, we confirmed that the reaction was completed after 8h. Then the reaction mixture was concentrated with a rotary evaporator. Water (10 mL) was added to the concentrated reaction mixture. The resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Petroleum ether : Ethyl acetate = 20 : 1 used as eluents) to obtain pure product **6**.

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Keywords: Sulfones • Sulfuric acid • Three component reaction • Chalcogen heteroaryl • Bactericidal agent

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A straitforward sulfuric acid-promoted three-component reaction in water for synthesis of synthesis of aryl(chalcogen-heteroaryl)methyl sulfones was developed.

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Synthesis of Aryl(chalcogenheteroaryl)methyl Sulfones via Sulfuric Acid-Promoted Three-Component Reaction in Water