



Cite this: *RSC Adv.*, 2022, 12, 35649

# Metal-free hydrosulfonylation of $\alpha,\beta$ -unsaturated ketones: synthesis and application of $\gamma$ -keto sulfones†

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Received 27th October 2022  
Accepted 8th December 2022

DOI: 10.1039/d2ra06784f

rsc.li/rsc-advances

$\gamma$ -Keto sulfones are versatile building blocks and valuable intermediates in organic synthesis and pharmaceutical chemistry. Motivated by their excellent properties, we herein report a green, convenient, metal-free hydrosulfonylation method for a variety of ynones, vinyl ketones, and sodium sulfinates in the absence of stoichiometric oxidants. This operationally simple protocol provides straightforward and practical access to a wide range of  $\gamma$ -keto sulfones with broad functional group tolerance from easily available starting materials. Moreover, the  $\beta,\gamma$ -unsaturated keto sulfones could further react with 2,3-butadienoate to generate cyclopentenes in phosphine-mediated [3 + 2] cycloaddition.

As a useful common structural fragment in a broad number of pharmaceuticals<sup>1</sup> and functional materials,<sup>2</sup> keto sulfones are usually present in promising biologically active molecules such as *Casodex*,<sup>3</sup> *VCAM-1* (ref. 4) and *anti-HIV-1* (ref. 5) (Fig. 1). Furthermore, a valuable synthetic impression is associated with the role of reactive intermediates in various high-demand synthetic transformations,<sup>6</sup> including total synthesis.<sup>7</sup> Owing to their excellent properties, and efficient and practical synthesis methods keto sulfones are in high demand.

In the past decades, a variety of protocols have been developed to construct  $\beta$ -keto sulfones.<sup>8</sup> Whereas succinct synthetic routes toward structurally related  $\gamma$ -keto sulfones are scarce,<sup>9</sup> traditionally,  $\gamma$ -keto sulfones were synthesized *via* the nucleophilic substitution of sodium sulfinates by 2-chlorovinyl ketones,<sup>10</sup> the elimination of the bromo derivatives of saturated keto sulfones<sup>11</sup> and the oxidation of the corresponding sulfides

or sulfoxides.<sup>12</sup> However, the principal drawback is that these procedures were strongly limited by multiple steps, narrow substrate scope, or poor stereoselectivity.

Indeed, several streamlined strategies for the preparation of  $\gamma$ -keto sulfones involves addition reaction of alkenes or alkynes have been developed.<sup>13</sup> Li's group<sup>14</sup> reported the synthesis of (*E*)-vinyl sulfones through Pd-catalyzed conjugate additions of alkynes with 1,2-bis(phenylsulfonyl)ethane. In 2013 Jiang and co-workers<sup>15</sup> showed that a Pd-catalyzed sulfonylation of alkyne with sodium sulfinates affords  $\gamma$ -keto sulfones (Scheme 1a). Li and coworkers<sup>16</sup> reported that BPO triggered the hydro-sulfonylation of chalcones with arylsulfonyl hydrazides producing  $\gamma$ -keto sulfones. Subsequently, Bi's group<sup>17</sup>

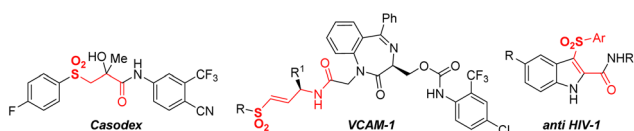


Fig. 1 Representative biologically active  $\gamma$ -keto sulfones.

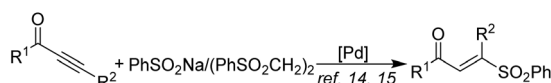
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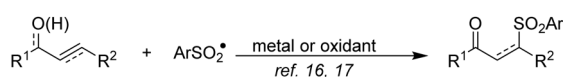
† Electronic supplementary information (ESI) available. CCDC 2181007. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2ra06784f>

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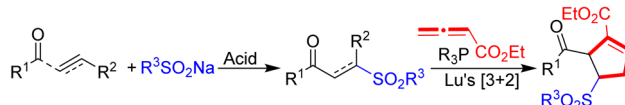
### a) Palladium-Catalyzed Cross-Coupling Reaction



### b) Metal-catalyzed or Metal-free Radical Cascade Reaction



### c) This work: Acid-Promoted Sulfonylation of $\alpha,\beta$ -Unsaturated Ketones



- Metal-free, no oxidant
- High functional group tolerance
- Mild, efficient and high yield
- Broad substrate scope
- Lu's [3+2] cycloaddition of  $\gamma$ -Keto Sulfones

Scheme 1 Methods for the synthesis of  $\gamma$ -keto sulfones.



developed a  $\text{Ag}_2\text{CO}_3$ -promoted sulfonylation of allyl/propargyl alcohols with sodium sulfinates for the preparation of  $\gamma$ -keto sulfones (Scheme 1b). Nevertheless, most cases still have to use large excess oxidants, noble metal catalysts, or require high temperatures. Accordingly, an efficient, mild and practical method to furnish  $\gamma$ -keto sulfones is worthwhile studying.

With growing demand for sustainable chemistry, an "ideal" reaction system for such transformations would be "metal-free" due to cost efficiency and possible advantages regarding toxicity, as well as selectivity. With this intent, we herein describe a simple and efficient acid-mediated sulfonylation of sodium sulfinates and  $\alpha,\beta$ -unsaturated ketones for the selective synthesis of  $\gamma$ -keto sulfones (Scheme 1c). The significant advantages of this method are high efficiency, metal-free and mild reaction conditions, thus providing a potential application in natural product synthesis and medicinal chemistry.

Further studies were commenced with the optimization of the conditions for the hydrosulfonylation of the ynone **1f** with sodium benzenesulfonate **2a** (Table 1). Acetate buffer solution (pH = 3.5)<sup>13e</sup> and acetyl chloride/ $\text{H}_2\text{O}$ ,<sup>19</sup> as used in the previous

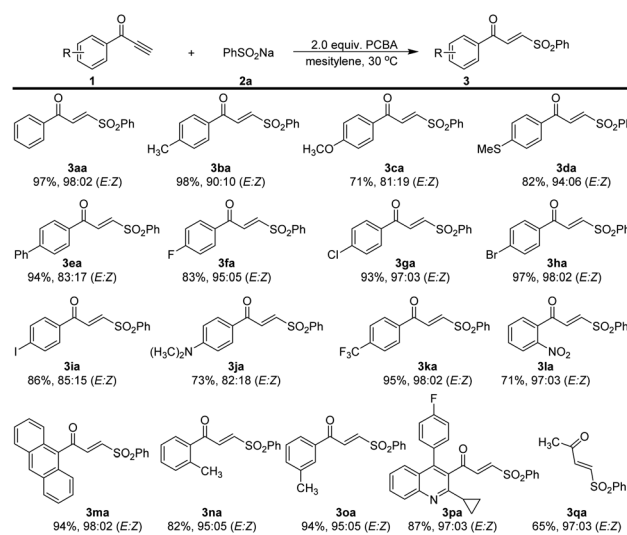
study, were completely ineffective due to several unknown complex products being formed (entry 1). Gratifyingly, the desired  $\gamma$ -keto sulfone **3fa** was isolated in a 49% yield ( $E/Z = 90 : 10$ ) as the major product for the reaction mediated by AcOH (entry 3). Encouraged by this initial result, we screened an array of acids. The results showed that 4-chlorobenzoic acid (PCBA) gave the best result, leading to the isolation of  $\gamma$ -keto sulfone **3fa** in a yield of 80% ( $E/Z = 98 : 02$ ) (entries 4–15). Solvent screening indicated that mesitylene could improve the yield to 85% ( $E/Z = 95 : 05$ ) (entry 21). Further investigations on the reduced usage of PCBA to 2.0 equivalents, the yield of **3fa** was slightly reduced (entry 22, 83% yield,  $E/Z = 95 : 05$ ). The amounts of sodium benzenesulfonate **2a** and the reaction temperature have deleterious effects on the reaction yields (entries 23–27). Thus, the optimized reaction conditions were successfully established as **1f** (1.0 equiv.), **2a** (2.5 equiv.), PCBA (2.0 equiv.), and mesitylene (2.0 mL) at 30 °C in this process.

We then sought to explore the generality of the method for the synthesis of  $\alpha,\beta$ -unsaturated  $\gamma$ -keto sulfones, using various ynones in reactions with **2a** under the optimized conditions (Scheme 2). The reaction of the 1-phenylprop-2-yn-1-one **1a** with **2a** proceeded reasonably to provide an excellent yield of the corresponding  $\gamma$ -keto sulfone **3aa** (97% yield,  $E/Z = 98 : 02$ ). To our delight, the reaction worked successfully with a range of ynones **1** bearing various substituents on the aromatic ring. Substituents such as methyl, thiomethylmethoxy, phenyl, halogen and dimethylamino atoms could be tolerated and gave the corresponding products **3ba–3ja** with high to excellent yields (71–98% yield) and stereoselectivity ( $E/Z = 82 : 18$  to  $98 : 02$ ). Trifluoromethyl and nitro substituents on the aromatic ring were also compatible and products **3ka** and **3la** were afforded 95% and 71% yields, respectively. 9-Anthracene-derived ynone successfully afforded **3ma** in a 94% yield ( $E/Z = 98 : 02$ ). The methyl group in the *ortho* or *meta* positions of the aromatic ring

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Acid (x equiv.)	Solvent	Yield <sup>b</sup> (%)	$E/Z^c$
1	Buffer (pH = 3.5)	DMF	NR	—
2	Acetyl chloride/ $\text{H}_2\text{O}$	$\text{CHCl}_3$	NR	—
3	AcOH (3.0)	Toluene	49	90 : 10
4	$\text{HCO}_2\text{H}$ (3.0)	Toluene	23	85 : 15
5	HCl (3.0)	Toluene	36	80 : 20
6	$\text{HNO}_3$ (3.0)	Toluene	36	87 : 13
7	Benzoic acid (3.0)	Toluene	66	96 : 04
8	<i>p</i> -Toluic acid (3.0)	Toluene	52	96 : 04
9	4-Acetylbenzoic acid (3.0)	Toluene	57	96 : 04
10	4-Fluorobenzoic acid (3.0)	Toluene	73	98 : 02
11	PCBA (3.0)	Toluene	80	98 : 02
12	4-Bromobenzoic acid (3.0)	Toluene	72	95 : 05
13	PNBA (3.0)	Toluene	57	88 : 12
14	2-Naphthoic acid (3.0)	Toluene	48	94 : 06
15	2-Nitrobenzoic acid (3.0)	Toluene	29	94 : 06
16	PCBA (3.0)	<i>o</i> -Xylene	73	92 : 08
17	PCBA (3.0)	<i>p</i> -Xylene	70	90 : 10
18	PCBA (3.0)	<i>m</i> -Xylene	72	96 : 04
19	PCBA (3.0)	DMF	NR	—
20	PCBA (3.0)	MeOH	68	89 : 11
21	PCBA (3.0)	Mesitylene	85	95 : 05
22	PCBA (2.0)	Mesitylene	83	95 : 05
23	PCBA (1.2)	Mesitylene	76	91 : 09
24	PCBA (0.5)	Mesitylene	44	73 : 27
25 <sup>d</sup>	PCBA (2.0)	Mesitylene	79	90 : 10
26 <sup>e</sup>	PCBA (2.0)	Mesitylene	80	95 : 05
27 <sup>f</sup>	PCBA (2.0)	Mesitylene	53	97 : 03

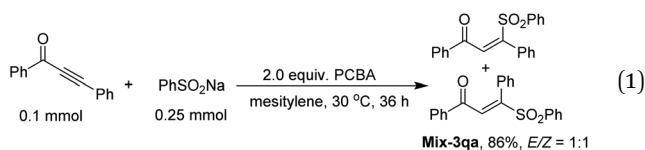
<sup>a</sup> Reaction conditions: **1f** (0.1 mmol), **2a** (0.25 mmol), acid (x equiv.), solvent (1.0 mL), 30 °C, 48 h. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by RP-HPLC. <sup>d</sup> With 2.0 equiv. **2a**. <sup>e</sup> 50 °C. <sup>f</sup> 80 °C. PCBA = 4-chlorobenzoic acid. PNBA = *p*-nitrobenzoic acid.



Scheme 2 Sulfonylation reaction of various terminal alkynes with **2a**. All reactions were carried on 0.2 mmol scale in mesitylene (2.0 mL) and used 2.5 equiv. of **2a**, 2.0 equiv. PCBA, at 30 °C. Yields of isolated products are reported.  $E/Z$  ratios were determined by RP-HPLC.

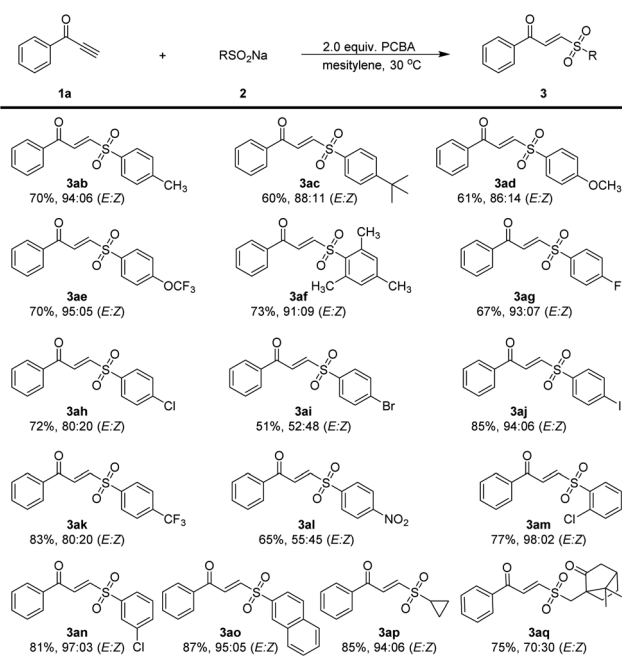


gave the desired  $\gamma$ -keto sulfones in 82% and 94% yield, respectively. The desired product **3pa** bearing a pitavastatin unit could be readily prepared in a yield of 87%. When alkyl terminal alkyne **1q** was subjected to the reaction, affording the desired product **3qa** in 65% yield ( $E/Z = 97 : 03$ ).

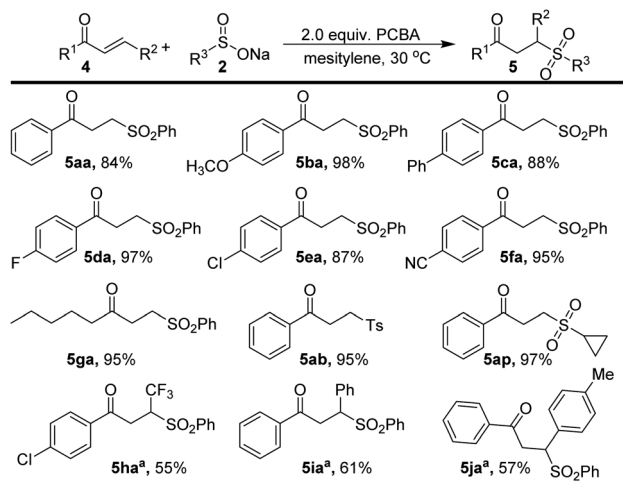


Inspired by the above results, the nonterminal alkyne was used as the substrate to react with  $\text{PhSO}_2\text{Na}$  at 30 °C for 36 h. The reaction provided *E* and *Z*- $\beta$ -sulfonyl- $\alpha,\beta$ -unsaturated carbonyl mixed compounds **3qa**<sup>13c</sup> (86% yield,  $E/Z = 1 : 1$ ).

The results of ynone **1a** reacting with a number of sodium sulfonates under the optimized condition are depicted in Scheme 3. Gratifyingly, no matter whether the phenyl ring of sodium sulfinate was substituted with either a sterically hindered, electron-donating, or electron-withdrawing group, all of them smoothly furnished the corresponding products in moderate to excellent yields with a high range of  $E/Z$  ratios from 52 : 48 to 97 : 03 (**3ab–3an**). Likewise, 2-naphthyl and cyclopropyl substituted sodium sulfonates were both effective in this reaction with a yield of 87% and 85%, respectively (**3ao** and **3ap**). Additionally, *L*-10-camphorsulfonyl sulfinate **2q** was also suitable for this reaction.



**Scheme 3** Sulfonylation reaction of terminal alkyne (**1a**) with sodium Sulfonates. All reactions were carried on 0.2 mmol scale in mesitylene (2.0 mL) and used 2.5 equiv. of **2**, 2.0 equiv. PCBA, at 30 °C. Yields of isolated products are reported.  $E/Z$  ratios were determined by RP-HPLC.



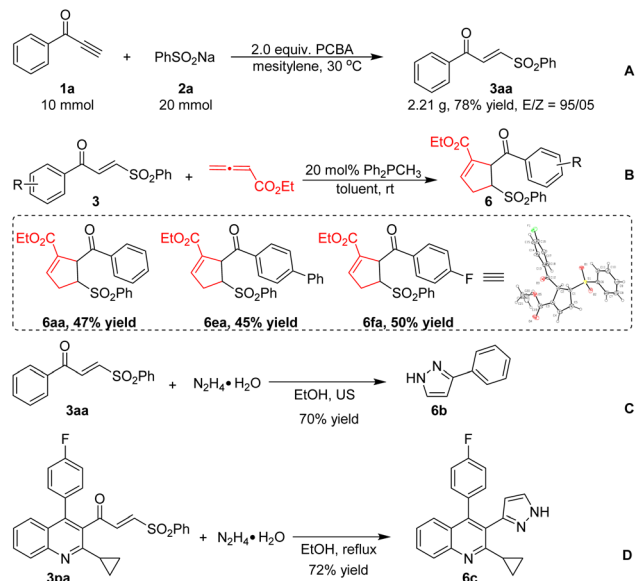
**Scheme 4** Sulfonylation reaction of vinyl ketone with sodium sulfonates. All reactions were carried on 0.2 mmol scale in mesitylene (2.0 mL) and used 2.0 equiv. of **2a**, 2.0 equiv. PCBA, at 30 °C. Yields of isolated products are reported. <sup>a</sup>At 80 °C for 72 h.

Interestingly, the treatment of the vinyl ketone **4a** with  $\text{PhSO}_2\text{Na}$  (**2a**) under the standard conditions furnished sulfone **5aa** (Scheme 4). The substrate scope was also explored in Scheme 4. Delightfully, it was perfectly tolerable to introduce both electron-donating ( $\text{OCH}_3$  and Ph) and electron-withdrawing (F, Cl, and CN) groups at the *para* position of the phenyl ring, affording the corresponding products (**5ba–5fa**) in excellent yields. 4-Toluene sulfonate and cyclopropane sulfonate also reacted well with substrate **2a** to form  $\gamma$ -keto sulfone in excellent yields. We were pleased to find that the  $\beta$ -trifluoromethylated enone **4h** and *trans*-chalcone (**4i–4j**) could be successfully employed to give desired products (**5ha–5ja**, 55–61% yields). Unfortunately, no reaction occurred for 2-cyclopentenone.

Additionally, the synthetic utility of the  $\gamma$ -keto sulfones obtained by the present method was explored (Scheme 5). Gram-scale ynone **1a** was reacted with sodium benzenesulfonate **2a** to form product **3aa** with an excellent  $E/Z$  ratio (**A**). Lu's [3 + 2] cycloaddition of 2,3-butadienoate with  $\alpha,\beta$ -unsaturated  $\gamma$ -keto sulfones **3** mediated by phosphine produced cycloadducts **6** (ref. 18) in good yields (**B**). Moreover, pyrazole derivative **6b** could be efficiently obtained from **3aa** under ultrasound (US) irradiation conditions (**C**). Next,  $\gamma$ -keto sulfone **3pa** derived from the biologically active pitavastatin could also react with hydrazine to give a high yield of **6c** (**D**).

To understand the reaction mechanism, control reactions of **1a** with **2a** were examined (Scheme 6a). When **1a** and **2a** was subjected to the standard reaction conditions except using deuterated 4-chlorobenzoic acid system, the **3a** were detected with 80% yield. An attempt to run the reaction of **1a** and **2a** in a anhydrous solvent system under an  $\text{N}_2$  atmosphere also successfully delivered **3a** in 97% yield.<sup>20</sup> The results unambiguously disclosed that the incorporated hydrogen atoms in **3a** originated from acid rather than water. The reaction using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,4-di-*tert*-





Scheme 5 Gram-scale preparation and further synthetic utilization.

butyl-4-methylphenol (BHT) as the radical scavengers showed no observable radical intermediates and unaffected desired products formation, which suggests that the radical process could be ruled out.<sup>20</sup> On the basis of the results presented above and previous reports, we propose the following mechanism in Scheme 6b. The 4-chlorobenzoic acid activates the carbonyl group in  $\alpha,\beta$ -unsaturated ketones **1** (**4**) to afford intermediate **I** or tautomerize to intermediate **II**. Finally, sulfonyl anion can

add to the unsaturated bond of intermediate **II** to afford the products **3** (**5**).

## Conclusions

In summary, we developed a simple and efficient acid-mediated approach for the formation of  $\gamma$ -keto sulfones from sodium sulfonates and  $\alpha,\beta$ -unsaturated ketones. This environmentally friendly methodology features a convenient, mild, efficient, C-S sulfonylation approach without the use of any metal catalysts and stoichiometric oxidants. The procedure results in good to excellent yields with various substituted ynones or vinyl ketones, as well as good functional group tolerance. The sulfonylation was easily scaled up and successfully integrated into Lu's [3 + 2] cycloaddition based on transformations of  $\alpha,\beta$ -unsaturated  $\gamma$ -ketosulfones (**3**). All these advantages make the new method highly attractive to the organic chemist in both academia and industry.

## Conflicts of interest

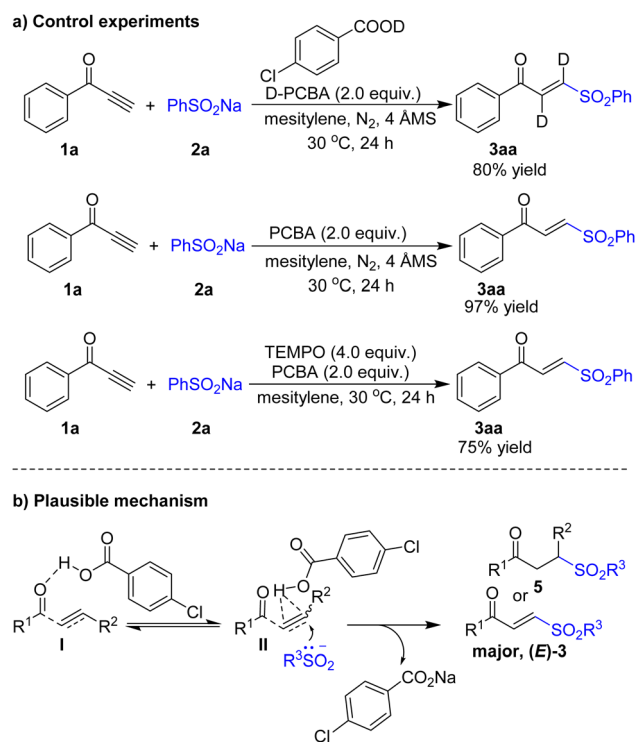
There are no conflicts to declare.

## Acknowledgements

Financial support for this work from the National Natural Science Foundation of China (No. 21977042), the Hunan Provincial Natural Science Foundation of China (No. 2022JJ40362). We thank Professor Wei-Min He (USC) for helpful discussions on this manuscript.

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Scheme 6 Mechanistic studies.





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