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Metal-free hydrosulfonylation of α,β -unsaturated ketones: synthesis and application of γ -keto sulfones*

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 γ -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 γ -keto sulfones with broad functional group tolerance from easily available starting materials. Moreover, the β , γ -unsaturated keto sulfones could further react with 2,3butadienoate to generate cyclopentenes in phosphine-mediated [3 + 2] cycloaddition.

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As a useful common structural fragment in a broad number of pharmaceuticals¹ and functional materials,² keto sulfones are usually present in promising biologically active molecules such as Casodex,³ 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,⁶ including total synthesis.⁷ 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 β-keto sulfones.8 Whereas succinct synthetic routes toward structurally related y-keto sulfones are scarce,9 traditionally, γ -keto sulfones were synthesized via the nucleophilic substitution of sodium sulfinates by 2-chlorovinyl ketones,10 the elimination of the bromo derivatives of saturated keto sulfones11 and the oxidation of the corresponding sulfides



Indeed, several streamlined strategies for the preparation of γ -keto sulfones involves addition reaction of alkenes or alkynes have been developed.¹³ Li's group¹⁴ 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-workers¹⁵ showed that a Pd-catalyzed sulfonylation of alkynoates with sodium sulfinates affords y-keto sulfones (Scheme 1a). Li and coworkers¹⁶ reported that BPO triggered the hydrosulfonylation of chalcones with arylsulfonyl hydrazides producing γ-keto sulfones. Subsequently, Bi's group¹⁷



Representative biologically active γ -keto sulfones. Fig. 1



Scheme 1 Methods for the synthesis of γ -keto sulfones.

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developed a Ag₂CO₃-promoted sulfonylation of allyl/propargyl alcohols with sodium sulfinates for the preparation of γ -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 γ -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 α , β -unsaturated ketones for the selective synthesis of γ -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 benzosulfonate **2a** (Table 1). Acetate buffer solution (pH = 3.5)^{13e} and acetyl chloride/H₂O,¹⁹ as used in the previous

Table 1 Optimization of the reaction conditions^a Acid SO₂Ph PhSO₂Na Solvent, T 1f 2a 3fa $Yield^{b}$ (%) Solvent E/Z^{c} Entrv Acid (x equiv.) Buffer (pH = 3.5) DMF NR 1 2 Acetyl chloride/H₂O CHCl₃ NR 3 AcOH (3.0) Toluene 49 90:10 4 $HCO_{2}H(3.0)$ Toluene 85:15 23 5 80:20 HCl (3.0) Toluene 36 6 $HNO_{3}(3.0)$ Toluene 36 87:13 7 Benzoic acid (3.0) Toluene 66 96:04 8 p-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 98:0211 PCBA (3.0) Toluene 80 98:0212 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 94:06 152-Nitrobenzoic acid (3.0) Toluene 29 94:06 16 o-Xylene 73 92:08 PCBA (3.0) 17 PCBA (3.0) p-Xylene 70 90:1018 PCBA (3.0) *m*-Xylene 72 96:04 DMF 19 PCBA (3.0) NR 20 PCBA (3.0) MeOH 89:11 68 21PCBA (3.0) Mesitylene 85 95:05 2.2 PCBA (2.0) Mesitylene 95:05 83 23 PCBA (1.2) Mesitvlene 76 91:09 24 PCBA (0.5) Mesitylene 44 73:27 25^d PCBA (2.0) Mesitylene 79 90:10 26 PCBA (2.0) Mesitylene 80 95:05 27^f PCBA (2.0) Mesitylene 53 97:03

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

study, were completely ineffective due to several unknown complex products being formed (entry 1). Gratifyingly, the desired γ -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 γ -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 benzosulfonate 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 α,β -unsaturated γ -keto sulfones, using various vnones 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 γ -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-Anthracenee-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



Scheme 2 Sulfonylation reaction of various terminal alkynones 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 γ -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 alkynone **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 PhSO₂Na at 30 °C for 36 h. The reaction provided *E* and *Z*- β -sulfonyl- α , β -unsaturated carbonyl mixed compounds **3qa**^{13e} (86% yield, *E*/*Z* = 1 : 1).

The results of ynone **1a** reacting with a number of sodium sulfinates 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-napthyl and cyclopropyl substituted sodium sulfinates 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 alkynone (1a) with sodium Sulfinates. 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 sulfinates. 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. ^aAt 80 °C for 72 h.

Interestingly, the treatment of the vinyl ketone **4a** with PhSO₂Na (**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 (OCH₃ 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 γ -keto sulfone in excellent yields. We were pleased to find that the β -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 γ -keto sulfones obtained by the present method was explored (Scheme 5). Gramscale ynone **1a** was reacted with sodium benzosulfonate **2a** to form product **3aa** with an excellent E/Z ratio (**A**). Lu's [3 + 2] cycloaddition of 2,3-butadienoate with α , β -unsaturated γ -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, γ -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 N₂ atmosphere also successfully delivered **3a** in 97% yield.²⁰ 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*-



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.²⁰ 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 α , β -unsaturated ketones **1** (**4**) to afford intermediate **I** or tautomerize to intermediate **II**. Finally, sulfonyl anion can



Scheme 6 Mechanistic studies.

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 γ -keto sulfones from sodium sulfinates and α , β -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 α , β -unsaturated γ -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.

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