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Graphical Abstract

$K_2S_2O_8$-mediated decarboxylative oxysulfonylation of cinnamic acids: A transition-metal-free synthesis of β-keto sulfones

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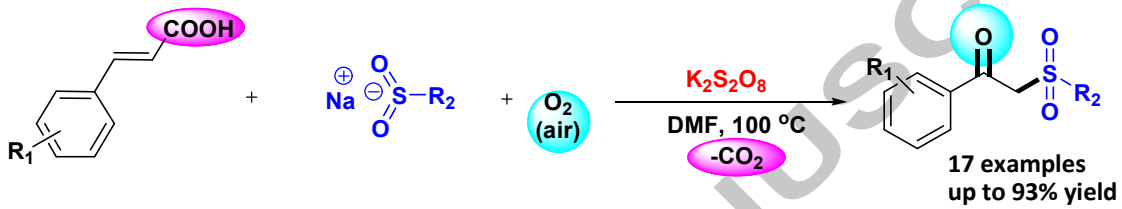

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$K_2S_2O_8$-mediated decarboxylative oxysulfonylation of cinnamic acids: A transition-metal-free synthesis of β-keto sulfones

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ABSTRACT

A new paradigm of the oxidative decarboxylative sulfono functionalization of cinnamic acids with sulfinate salts mediated by $K_2S_2O_8$ under aerobic conditions to afford synthetically and biologically relevant β-keto sulfones has been described. It is the first report on the transition-metal-free synthesis of β-keto sulfones from cinnamic acids, which employs environmentally benign, readily available and inexpensive starting materials and oxidants, viz. air and $K_2S_2O_8$.

Oxidative coupling, the coupling of two nucleophilic reagents with the help of oxidants, is a rapidly thriving field [1]. Particularly, the decarboxylative coupling reactions of α,β-unsaturated carboxylic acids have drawn significant attention over the last few years [1e,2].Their straightforward preparation using Perkin reaction, simple handling, non-toxicity, cost-effectiveness and stability to air and moisture, in general, make cinnamic acids attractive starting materials in organic synthesis. Moreover, the credibility of the decarboxylative coupling reactions is also leveraged by the ease of their operation and formation of relatively less toxic by-products.

The C=C bond in α,β-unsaturated carboxylic acids is an extra reactive site, which is highly susceptible to attack by radicals. Under suitable conditions, radical attack followed by decarboxylation or oxidation and decarboxylation lead to olefination or oxyfunctionalized products, respectively (Fig. 1) [1e]. However, reports on the synthesis of the latter products via oxidative decarboxylative coupling are relatively scarce. In addition, extensive work has been done in the field of decarboxylative coupling reactions for the formation of C-C bonds but the number of reports on the C-S bond formation is limited [3]. All the previous reports on the decarboxylative coupling reaction of α,β-unsaturated carboxylic acids leading to C-S bond formation employ the coupling of these acids with sulfonyl radical precursors to obtain vinyl sulfones via the olefinic route under transition-metal [4] as well as transition-metal-free conditions [5] (Scheme 1a). Based on this strategy, Liu et al. reported a synthesis of 2-sulfonylbenzo[*b*]furans from *trans*-2-hydroxycinnamic acids and sodium sulfinates mediated by the $CuCl_2.2H_2O$/AgTFA system via a protodecarboxylation/ sulfonylation/cyclization cascade (Scheme 1b) [4a]. To the best of our knowledge, there is no report in the literature on the transition-metal-free oxidative coupling of α,β-unsaturated carboxylic acids with sulfinate salts, which can lead to the synthesis of valuable β-keto sulfones.

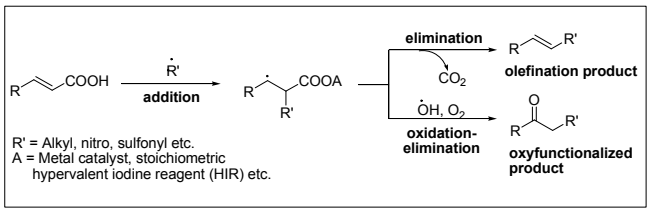
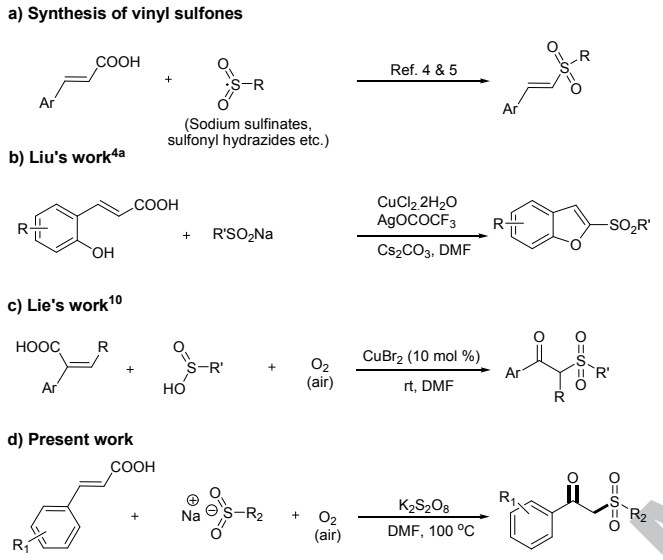


Fig. 1 Radical functionalizations of α,β-unsaturated carboxylic acids.

β-Keto sulfones, as a class of organosulfur compounds, are well-recognized for their synthetic and biological importance [6]. As building blocks, they are used for the synthesis of γ-sulfonyl δ-lactones, β-sulfonyl styrenes, polyfunctionalized *4H*-pyrans, quinolines, sulfonyl phenanthrenes and vinylcyclopropanes [7]. As regards their biological significance, they are bestowed with exceptional pharmaceutical properties such as anti-fungal, anti-bacterial, inhibitors of LpxC, MMP and CES1 [8]. Accordingly, a number of methods have been developed for the synthesis of β-keto sulfones [9]. However, the decarboxylative sulfonylation approach for their synthesis is only limited to the use of arylpropiolic acids [9b,d] and β-keto acids [9f] as their precursors. α,β-Unsaturated carboxylic acids have never been used to synthesize β-keto sulfones under transition-metal-free conditions. Nevertheless, a $CuBr_2$-

catalyzed decarboxylative oxysulfonylation of arylacrylic acids using sulfinic acids has been reported for their synthesis by Lei et al. in 2015 [10].Transition-metal-free conditions are highly desirable in the pharmaceutical industry because it makes any protocol free from the adverse traits of transition-metals, viz. toxicity, sensitivity to air or moisture and need of additional co-catalysts/ligands. All the above facts and our previous work on the synthesis of sulfones [11] inspired us to develop a transition-metal-free protocol for the synthesis of β-keto sulfones from α,β-unsaturated carboxylic acids and sodium sulfinates mediated by $K_2S_2O_8$ under aerobic conditions (Scheme 1d).

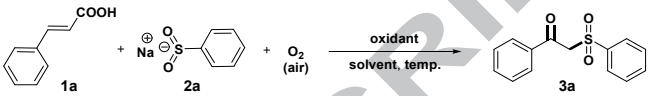


Scheme 1. Decarboxylative sulfonylation of α,β-unsaturated carboxylic acids.

At the outset of our investigation, a model reaction was set up between cinnamic acid **1a** (1.0 mmol) and sodium benzene sulfinate **2a** (1.5 mmol) using $K_2S_2O_8$ (1.5 mmol) as an oxidant in DMF (5 mL) at 80 °C in an open flask. To our satisfaction, the desired β-keto sulfone **3a** was formed in 68% yield in 12 hours (Table 1, entry 1). Encouraged by this preliminary success, we next focused our efforts towards the optimization of the reaction conditions. Since the external oxidant was the cornerstone of our strategy, we first scrutinized other oxidants for our protocol which included $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, $KHSO_5$ and DTBP but none of them was found to be more effective than $K_2S_2O_8$ (entries 2-5 versus entry 1). In fact, in the presence of DTBP, vinyl sulfone was obtained as the major product (entry 5). The product formation could not be detected in the absence of any oxidant (entry 6). Therefore, $K_2S_2O_8$, an inexpensive, readily available and versatile inorganic oxidant [12], remained our choice for the role of an oxidant in the reaction. Any further increase in the amount of the oxidant did not affect the yield of **3a** much (entry 7) but a decrease in the amount of $K_2S_2O_8$ to 1.0 mmol led to a substantial decrease in the yield (entry 8).

In order to decide the best solvent, the model reaction was also performed using different solvents (entries 9-12). Decent yield of the product was obtained in DMSO (entry 9) but the aqueous environment was not conducive to the formation of product (entry 10) which is in accordance with earlier observations [13]. Low yield of the product in toluene (entry 11) and MeCN (entry 12) can be attributed to the low solubility of the model substrate/reagent in these solvents, thus establishing DMF as the best solvent for our developed protocol. When the temperature of the reaction was increased to 100 °C, the yield of the product improved to 83% (entry 13). Increasing the reaction time to 14 hours produced no significant change in the yield of **3a** (entry 14) but decreasing the reaction time to 10 hours was detrimental to the yield (entry 15). On dilution, the yield of the product decreased (entry 16), whereas when 3 mL of DMF was used, the reaction became more complex (entry 17).

Table 1
Optimization of experimental conditions[a]



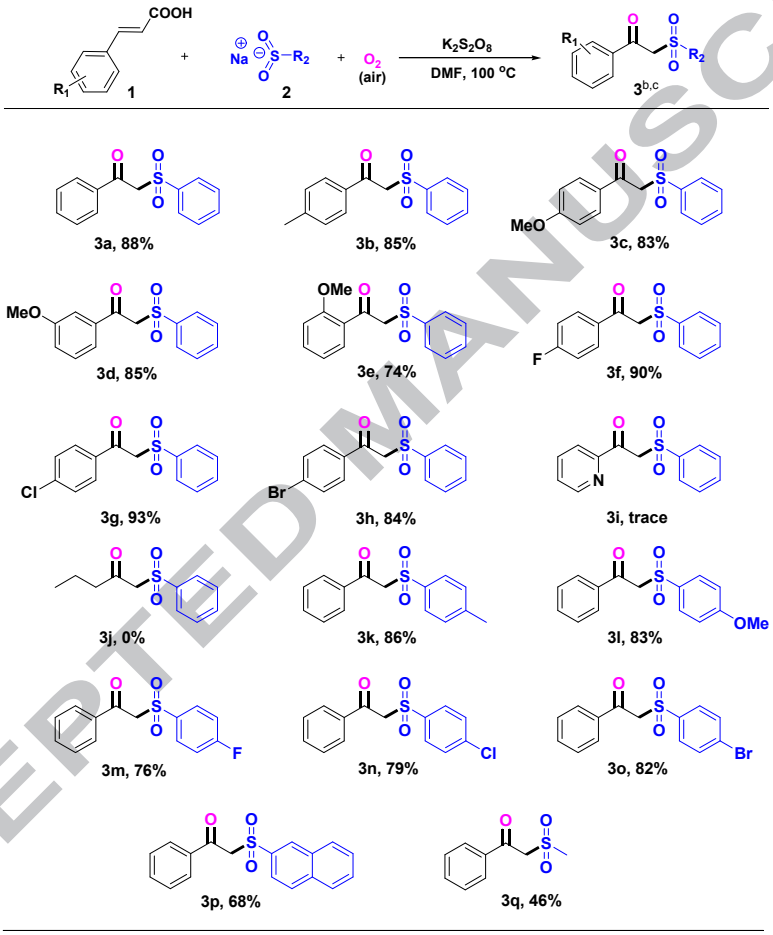
Entry	Oxidant	Solvent	Temper-ature (°C)	Time (h)	Yield (%)[b]
1	$K_2S_2O_8$ (1.5 mmol)	DMF	80	12	68
2	$Na_2S_2O_8$ (1.5 mmol)	DMF	80	12	32
3	$(NH_4)_2S_2O_8$ (1.5 mmol)	DMF	80	12	30
4	$KHSO_5$ (1.5 mmol)	DMF	80	12	61
5	DTBP (1.5 mmol)	DMF	80	12	18[c]
6	-	DMF	80	12	n.d.
7	$K_2S_2O_8$ (2.0 mmol)	DMF	80	12	70
8	$K_2S_2O_8$ (1.0 mmol)	DMF	80	12	47
9	$K_2S_2O_8$ (1.5 mmol)	DMSO	80	12	65
10	$K_2S_2O_8$ (1.5 mmol)	H_2O	80	12	traces
11	$K_2S_2O_8$ (1.5 mmol)	Toluene	80	12	25
12	$K_2S_2O_8$ (1.5 mmol)	MeCN	80	12	32
13	$K_2S_2O_8$ (1.5 mmol)	DMF	100	12	88
14	$K_2S_2O_8$ (1.5 mmol)	DMF	100	14	89
15	$K_2S_2O_8$ (1.5 mmol)	DMF	100	10	71
16[d]	$K_2S_2O_8$ (1.5 mmol)	DMF	100	12	66
17[e]	$K_2S_2O_8$ (1.5 mmol)	DMF	100	12	59

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 equiv.), oxidant, solvent 5 mL, in an open-flask.
[b] Isolated yield, n.d. = not detected.
[c] Corresponding vinyl sulfone was obtained in 57% yield.
[d] Solvent 7 mL.
[e] Solvent 3 mL.

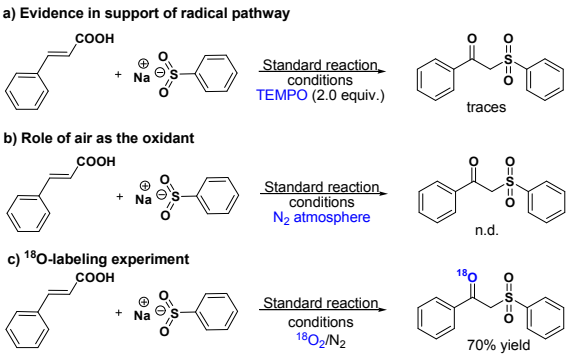
After deciding the optimal reaction conditions, our next goal was to examine the substrate scope of the reaction with respect to both the starting materials (Table 2). Cinnamic acids with both electron-donating or -withdrawing group and halogens on the phenyl ring reacted with sodium benzene sulfinate to produce the desired sulfones **3a-h** in good to excellent yields (74-93%). The developed protocol could be successfully applied irrespective of the position of the methoxy group at the *ortho*-, *meta*- or *para*- position of the aryl ring in cinnamic acids with not much difference in the efficiency of the transformation (**3c-e**). The heterocyclic derivative, 3-(pyridin-2-yl)acrylic acid and the corresponding alkyl derivative (hex-2-enoic acid) of cinnamic acid were not amenable to our oxidative decarboxylative protocol (compounds **3i** and **j**). Similarly, in the case of sulfinate salts, a broad range of substituents on the aromatic ring were well tolerated (**3k-o**). In general, the sulfinate salts with electron-donating groups on the aryl ring gave better yield of the products (**3k** and **3l**) than those with electron-withdrawing groups on the ring (**3m-o**). The methodology could be extended successfully to naphthyl (**3p**) and alkyl sulfinates (**3q**) as well.

In view of gaining insight into the mechanism of the reaction, a number of control experiments were performed (Scheme 2). In the presence of 2 equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) under standard conditions, the product was formed in traces which suggested a radical pathway (Scheme 2a). In the absence of oxygen (N_2 atmosphere), no product formation could be detected (Scheme 2b). On the basis of this result, we concluded that the source of keto oxygen atom in the synthesized sulfones was atmospheric oxygen. This was further confirmed by isotopic labeling experiments (Scheme 2c). With these results in hand and on the basis of literature precedents [13], a tentative mechanism has been proposed in Scheme 3. Initially, $K_2S_2O_8$ oxidizes sulfinate salt to sulfone radical **I**. The attack of radical **I** on cinnamic acid with ensuing addition of atmospheric oxygen would produce the peroxide radical **II**. The decomposition of **II** could form the radical intermediate **III**, which is subsequently transformed into **IV** by $K_2S_2O_8$. Then, the compound **IV** undergoes decarboxylation via the cyclization process under the standard conditions to give **V**, which finally ketonises to the product **3**.

Table 2
Scope of α,β-unsaturated carboxylic acids and sulfinate salts[a]

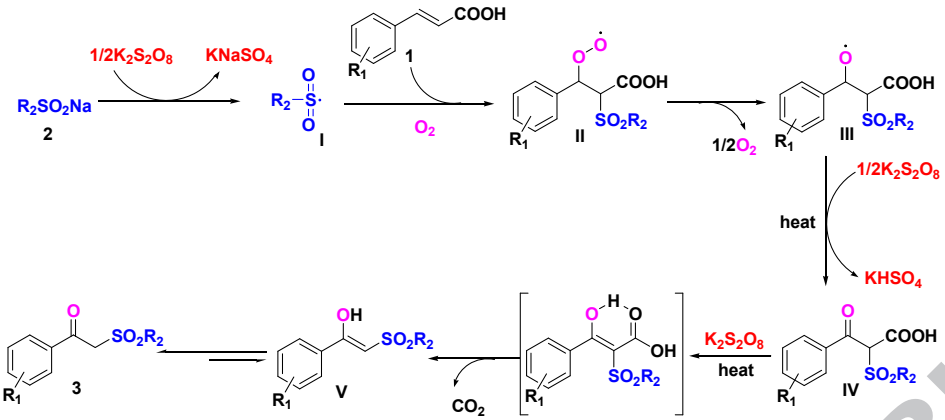


[a] For experimental procedure, see Supplementary data.
[b] Isolated yield of the purified products **3**.
[c] All compounds gave satisfactory spectral (^{1}H NMR, ^{13}C NMR and HRMS) data [9c,10].



Scheme 2. Control experiments.

In conclusion, we have developed the first transition-metal-free route to β-keto sulfones from cinnamic acids and sulfinate salts mediated by $K_2S_2O_8$. Experimental evidences suggest that atmospheric oxygen is the source of keto oxygen atom in the synthesized sulfones and the developed method follows a radical pathway. The aerobic oxidative decarboxylative approach for the synthesis β-keto sulfones capitalizes on the use of inexpensive, easily accessible and environmentally benign substrates/oxidant. The use of cinnamic acids as the precursors to β-keto sulfones under transition-metal-free conditions is the highlight of the developed protocol.



Scheme 3. Plausible mechanism for the formation of β-keto sulfones.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/xxxxxxxxxxxxxxxxxxx.

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Highlights

- Metal-free one-pot approach to β-keto sulfones.

- Use of air and $K_2S_2O_8$ as eco-friendly and inexpensive oxidants.
- Decarboxylative oxysulfonylation of cinnamic acids.
- A synthetically useful radical pathway is developed.