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Transition-metal-free synthesis of vinyl sulfones via tandem cross-decarboxylative/coupling reactions of sodium sulfinates and cinnamic acids†

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A transition-metal-free synthesis of vinyl sulfones, utilizing sodium sulfinates and cinnamic acids through tandem cross-decarboxylative/coupling reactions, has been developed. This transformation is simple, efficient and environmentally benign, with a wide range of substrate scope and exceptional functional group tolerance.

The development of environmentally benign, operationally simple, and efficient tandem cross-coupling strategies for the construction of privileged molecular skeletons continues to attract broad interest, due to their economical and environmental impact.¹ Recently, such protocols which avoid or minimize the use of transition metals in tandem cross-coupling reactions, have been intensively pursued by the synthetic community, as the alternatives are sometimes toxic, expensive, hard to handle, difficult to dispose of properly in large quantities, and may possibly leave toxic traces of metals in the products.²

Vinyl sulfones are valuable synthetic targets³ and constitute a significant component in naturally occurring products and in drug discovery,⁴ and therefore have attracted considerable interest from organic chemists in pursuing synthetic efficiency. Conventional methods for the synthesis of vinyl sulfones involve the oxidation of the corresponding sulfides,⁵ the manipulation of acetylenic sulfones,⁶ the condensation of aromatic aldehydes with sulfonylacetic acids,⁷ or the β -elimination of selenosulfones or halo-sulfones.⁸ In recent years, these have been replaced by new and more efficient Pd- or Cu-catalyzed cross-coupling reactions of sulfinate salts with vinyl halides,⁹ vinyl tosylates,¹⁰ vinyl triflates,¹¹ alkenyl boronic acids,¹² or alkenes.¹³ In spite of the efficiency and generality of these reactions, it is still not enough for green chemistry because of the use of toxic metals. Very recently, Yadav *et al.* have reported a simple and green method for the synthesis of vinyl sulfones from terminal epoxides and sodium sulfinates, and two regioisomers (linear and branched vinyl sulfones) were obtained in most cases, which made the separation difficult.¹⁴ Therefore, the development of efficient, environment-friendly, and practical synthetic methods for synthesising vinyl sulfones with high regioselectivity is still needed.

Cinnamic acids are relatively stable, simple to handle, and readily prepared by the Perkin reaction from aromatic aldehydes. As our interest in sodium sulfinates as substrates continues,¹⁵ we wish to describe a concise and efficient tandem cross-decarboxylative/coupling reaction for the synthesis of vinyl sulfones from sodium sulfinates and cinnamic acids, using DMSO as the oxidant. This reaction, performed under transition-metal-free conditions, gives coupling products in good yields, and tolerates a variety of functional groups.

We commenced our study by using benzenesulfinic acid sodium salt (1a) and trans-cinnamic acid (2a) as model substrates under various conditions and the results are summarized in Table 1. In the absence of a base, the reaction between 1a and 2a gave a low yield of (E)-(2-(phenylsulfonyl)vinyl)benzene (3a) (Table 1, entry 1). When this reaction was performed in the presence of bases, such as CH₃COONa, CH₃COOK, NaHCO₃, Li₂CO₃, Na₂CO₃, K₂CO₃, and Cs₂CO₃, the yield of 3a increased (Table 1, entries 2-7 and 9). The reaction performed with 50 mol% Cs₂CO₃ gave the best result (95% GC yield) (Table 1, entry 9). Considering the costs of Cs_2CO_3 and K_2CO_3 , we used K_2CO_3 to further optimize this transformation. Notably, not much influence on the yield of 3a was observed by GC-MS when the reaction was performed in the presence of 50 mol% K₂CO₃ in DMSO under a N₂ atmosphere (Table 1, entry 8). Screening of different solvents revealed that DMSO was the best solvent for this process (Table 1, entry 7 vs. 10-12 and 14). No 3a was detected by GC-MS when using toluene or 1,4-dioxane as solvents (Table 1, entries 12 and 14), while 37% and 46% yields of 3a were obtained when it was performed in a mixture of toluene-DMSO (v/v = 10:1) or 1,4-dioxane-DMSO (v/v = 10:1), respectively (Table 1, entries 13 and 15). In

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O II Ph ^{-S} \Of 1a	Na + HOOC ^{Ph} 2a	Base Solvent	O Ph [∽] S O 3a
Entry	Base	Solvent	Yield ^b (%)
1	_	DMSO	32
2	CH ₃ COONa	DMSO	55
3	CH ₃ COOK	DMSO	52
4	NaHCO ₃	DMSO	39
5	Li_2CO_3	DMSO	62
6	Na_2CO_3	DMSO	75
7	K_2CO_3	DMSO	92 (82)
8 ^c	K_2CO_3	DMSO	90
9	Cs_2CO_3	DMSO	95
10	K_2CO_3	DMF	27
11	K_2CO_3	H_2O	<10
12	K_2CO_3	Toluene	nd
13^d	K_2CO_3	Toluene	37
14	K_2CO_3	1,4-Dioxane	nd
15^e	K_2CO_3	1,4-Dioxane	46
16 ^{<i>f</i>}	K_2CO_3	1,4-Dioxane	83
17 ^g	K_2CO_3	DMSO	90 (78)

^{*a*} Reaction conditions: unless otherwise noted, all of the reactions were performed with **1a** (0.45 mmol), **2a** (0.3 mmol), 0.5 equiv. base, in solvent (2.0 mL) at 100 °C (bath temperature) for 10 h. ^{*b*} Determined by GC using dodecane as the internal standard. The data in parentheses are the yields of the isolated products. ^{*c*} The reaction was performed under a N₂ atmosphere. ^{*d*} 2.0 mL of toluene–DMSO (v/v = 10:1). ^{*e*} 2.0 mL of 1,4-dioxane–DMSO (v/v = 10:1). ^{*f*} 2.0 mL of 1,4-dioxane–DMSO (v/v = 10:1). *f* 2.0 mL of 1,4-dioxane–DMSO (v/v = 1:1). ^{*g*} Conditions: **1a** (7.5 mmol), **2a** (5 mmol), K₂CO₃ (2.5 mmol), DMSO (4.0 mL), 12 h.

addition, the GC-yield of **3a** was up to 83% when the reaction was performed in a mixture of 1,4-dioxane–DMSO (v/v = 1 : 1), which suggested that DMSO could play some unique role in this process (Table 1, entry 16). Therefore, the best conditions for this transformation involved 50 mol% K_2CO_3 , in DMSO at 100 °C for 10 h. Besides, the reaction was scalable and practical since a satisfactory yield (78%) could be obtained in the presence of 50 mol% K_2CO_3 when the reaction was performed on a 5 mmol scale (Table 1, entry 17).

Using the optimal conditions, various sulfinic acid sodium salts and cinnamic acids were explored as substrates, and the results are summarized in Table 2. A series of para-substituted sulfinic acid sodium salts, including some with electron-donating groups (R' = OMe, Me), and some with electron-withdrawing groups (R' = F, Cl, Br, CF_3), proceeded smoothly and afforded the desired vinyl sulfone products in high yields. Other substituted sulfinic acid sodium salts such as 2-chlorobenzene sulfinic acid sodium salt, could also provide the desired product in a 78% yield. These results showed that this transformation was tolerant towards the electronic and steric effects of the aromatic ring. In addition, a 73% yield of 3i was obtained when 2-thienylsulfinic acid sodium salt reacted with 2a. More sterically hindered substrates, such as 2-naphthylsulfinic acid sodium salt, reacted with 2a giving the desired product 3j in an 80% yield. Moreover, methane sulfinic acid sodium salt, ethane sulfinic acid sodium salt and cyclopropane-

Table 2 Synthesis of vinyl sulfones^{a,b}



^{*a*} Reaction conditions: unless otherwise noted, all of the reactions were performed with 1 (0.75 mmol), 2 (0.5 mmol), and K_2CO_3 (0.25 mmol), in DMSO (2.0 mL) at 100 °C (bath temperature) for 10 h. ^{*b*} The data in parentheses are the yields of the isolated products.

sulfinic acid sodium salt, were also good substrates for this transformation, affording the corresponding products **3k–3m** in excellent yields.

Substituted cinnamic acids bearing electron-donating groups such as Me or OMe, or electron-withdrawing groups such as Cl, Br, CN, or NO₂, on the aromatic ring performed well in this process, and led to the formation of the expected vinyl sulfones in good to excellent yields. On the whole, cinnamic acids with an electron-withdrawing group on the benzene ring gave the corresponding products in higher yields than those with an electron-donating group on the benzene ring. In addition, both (*E*)-3-(pyridin-2-yl)acrylic acid and (*E*)-3-(thiophen-2-yl)acrylic acid showed high reactivities, and the desired products $3\mathbf{u}$ and $3\mathbf{v}$ were obtained in 73% and 85% yields, respectively.

To investigate the reaction mechanism, several control experiments were conducted (Scheme 1). The reaction failed to give the desired product 3a when benzenesulfinic acid sodium salt (1a) was treated with styrene under the standard conditions (eq (1)). No 3a was detected in the presence of the radical scavengers TEMPO or BHT (eq (2)), which indicated that a radical pathway could be involved. According to the above results, a possible mechanism is proposed in Scheme 2. An oxygen centered radical generated by the oxidation of



Scheme 1 Mechanistic investigations for the tandem cross-decarboxylative/coupling reaction.



Scheme 2 Plausible reaction mechanism.

sulphinate by DMSO, resonates with the sulphonyl radical intermediate A,¹⁶ followed by radical addition to **B** (formed from cinnamic acid under basic conditions). This leads to the formation of intermediate **C**. The loss of carbon dioxide results in intermediate **D**, which gives the vinyl sulfone products under the DMSO conditions.^{13,15*b*,17}

In summary, we have developed a simple and efficient metal-free synthesis of vinyl sulfones through the cross-decarboxylative/coupling reactions of sodium sulfinates and cinnamic acids. The reaction presents a convenient method with good functional group tolerance for the preparation of vinyl sulfones in medicinal chemistry. Due to its simplicity, this protocol may have potential applications in organic synthesis, and further studies on the applications of vinyl sulfones in drug design are currently ongoing in our laboratory.

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Communication

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