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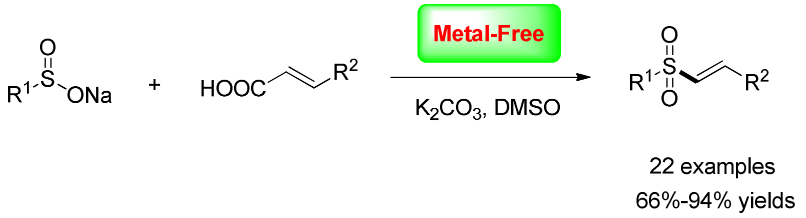

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Cite this: DOI: 10.1039/c0xx00000x
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ARTICLE TYPE

Transition-Metal-Free Synthesis of Vinyl Sulfones via a Tandem Cross-Decarboxylative/Coupling Reaction of Sodium Sulfinates and Cinnamic Acids *

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

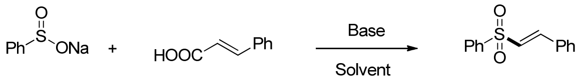
Transition-metal-free synthesis of vinyl sulfones utilizing sodium sulfinates and cinnamic acids through a tandem cross-decarboxylative/coupling reaction has been developed. This transformation is simple, efficient and environmentally benign, with a wide range of substrate scope and exceptional good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

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

Vinyl sulfones are valuable synthetic targets[3] 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. The conventional methods for the synthesis of vinyl sulfones involve the oxidation of the corresponding sulfides,[5] manipulation of acetylenic sulfones,[6] condensation of aromatic aldehydes with sulfonylacetic acids,[7] and β-elimination of selenosulfones or halo-sulfones.[8] In recent years, there have been replaced by a new and more efficient Pd- or Cu-catalyzed cross-coupling of sulfinate salts with vinyl halides,[9] vinyl tosylates,[10] vinyl triflates,[11] alkenyl boronic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 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 vinyl sulfones with high regioselectivity is still needed.

Cinnamic acids are relatively stable, simple to handle, and readily prepared by Perkin reaction from aromatic aldehydes. As our continuous interest in sodium sulfinates as substrates,[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 with the use of DMSO as the oxidant. This reaction performed under transition-metal-free conditions, giving good yields of coupling products and tolerating a variety of functional groups.

Table 1. Optimization of Reaction Conditions.[a]



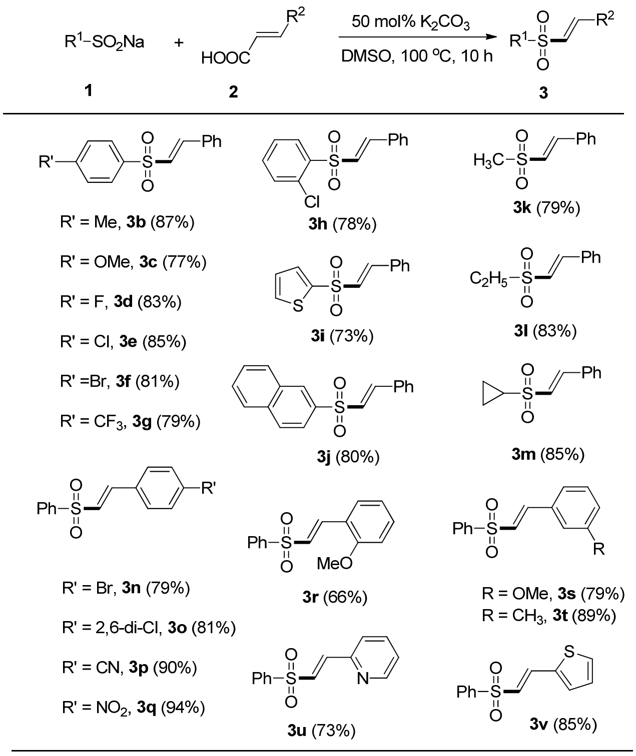
1a **2a** **3a**

Entry	Base	Solvent	Yield (%)[b]
1	-	DMSO	32
2	CH_3COONa	DMSO	55
3	CH_3COOK	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[f]	K_2CO_3	1,4-dioxane	83
17[g]	K_2CO_3	DMSO	90 (78)

[a] Reaction conditions: unless otherwise noted, all 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. Data in parentheses is the yield of isolated product. [c] The reaction performed under N_2 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 o 1,4-dioxane/ DMSO (v/v = 1:1); [g] Conditions: **1a** (7.5mmol), **2a** (5mmol), K_2CO_3 (2.5mmol), DMSO (4.0 mL), 12 h.

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 base, the reaction between **1a** and **2a** gave lower yield of (*E*)-(2-(phenylsulfonyl)vinyl)benzene (**3a)** (Table 1, entry 1). When this reaction performed in the presence of bases, such as CH_3COONa, CH_3COOK, $NaHCO_3$, Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, the yield of **3a** was increased (Table 1, entries 2-7 and 9), and the reaction performed along with 50 mol% Cs_2CO_3 gave the best result (95% GC yield) (Table 1, entry 9). Considering the cost of Cs_2CO_3 and K_2CO_3, we used K_2CO_3 to further optimize this transformation. Notably, no much influence on the yield of **3a** was observed by GC-MS when the reaction was performed in the presence of 50 mol% K_2CO_3 in DMSO under N_2 atmosphere (Table 1, entry 8). Screening of different solvents revealed that DMSO was the best solvent for this process (Table 1, entries 7 *vs* 10-12 and 14). No product **3a** was detected by GC-MS when using toluene or 1,4-dioxane as solvent (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 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 should play some unique role in this process (Table 1, entry 16). Therefore, the best condition 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).

Table 2. Synthesis of Vinyl Sulfones. [a-b]

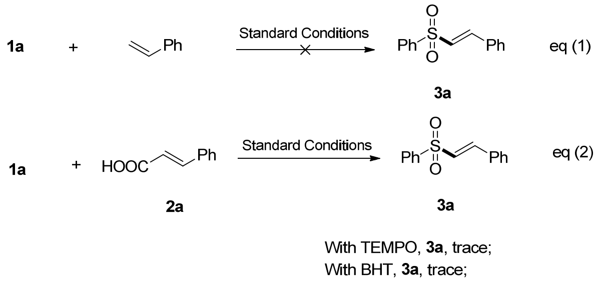


[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1** (0.75 mmol), **2** (0.5 mmol), K_2CO_3 (0.25 mmol) in DMSO (2.0 mL) at 100 °C (bath temperature) for 10 h. [b] Yields of isolated products.

Under the optimal conditions, various sulfinic acid sodium salts and cinnamic acids were explored, 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 products of vinyl sulfones in high yields. Other substituted sulfinic acid sodium salts such as 2-chloro benzene sulfinic acid sodium, could also provide the desired product in 78% yield. These results showed that this transformation was tolerant toward electronic and steric effects of the aromatic ring. In addition, 73% yield of **3i** was obtained when 2-thienylsulfinic acid sodium salt reacted with **2a**. More steric substrates such as 2-naphthylsulfinic acid sodium salt, treated with **2a** giving the desired product **3j** in 80% yield as well. Moreover, methane sulfinic acid sodium salt, ethane sulfinic acid sodium salt and cyclopropanesulfinic acid sodium salt were also good substrates for this transformation, affording the corresponding products **3k**-**3m** in excellent yields.

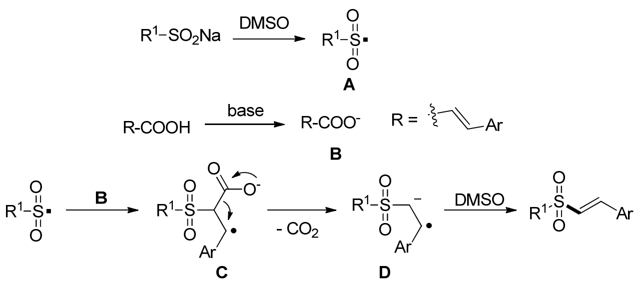
Besides, substituted cinnamic acids bearing electron-donating groups such as Me, OMe or electron-withdrawing groups such as Cl, Br, CN, NO_2 on the aromatic ring were performed well in this process, and led to the formation of the expected vinyl sulfones in good to excellent yields. On the whole, cinnamic acids having 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 **3u** and **3v** were obtained in 73% and 85% yields, respectively.

Scheme 1. Mechanistic Investigations for the Tandem Cross-Decarboxylative/Coupling Reaction.



To investigate the reaction mechanism, several controlled 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 condition. No product **3a** was detected in the presence of the radical scavenger TEMPO or BHT (eq 2), which indicated that a radical pathway should be involved. According to the above results, a possible mechanism is proposed in Scheme 2. An oxygen centered radical generated by the oxidation of sulphinate with DMSO resonates with a sulphonyl radical intermediate **A**,[16] and followed by radical addition to **B** (formed from cinnamic acid under basic condition) led to the formation of intermediate **C**. Subsequently, followed by the loss of carbon dioxide resulted in intermediate **D**, giving the vinyl sulfones products under the DMSO condition.[13, 15b, 17]

Scheme 2. Plausible Reaction Mechanism.



In summary, we have developed a simple and efficient metal-free synthesis of vinyl sulfones through cross-decarboxylative/coupling reaction 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 application in organic synthesis, and further studies on the applications of vinyl sulfones in drug design are currently ongoing in our laboratory.

We thank the National Natural Science Foundation of China (21172076), the National Basic Research Program of China (973 Program) (2011CB808600), the Guangdong Natural Science Foundation (10351064101000000) and the Fundamental Research Funds for the Central Universities (2014ZP0004 and 2014ZZ0046) for financial support.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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