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Transition-Metal-Free Synthesis of (*E*)-Vinyl Sulfones from Vinyl Halides in Water

Shuai Liang,[a] Ruo-Yi Zhang,[a] Gao Wang,[a] Shan-Yong Chen,*[a] and Xiao-Qi Yu*[a]

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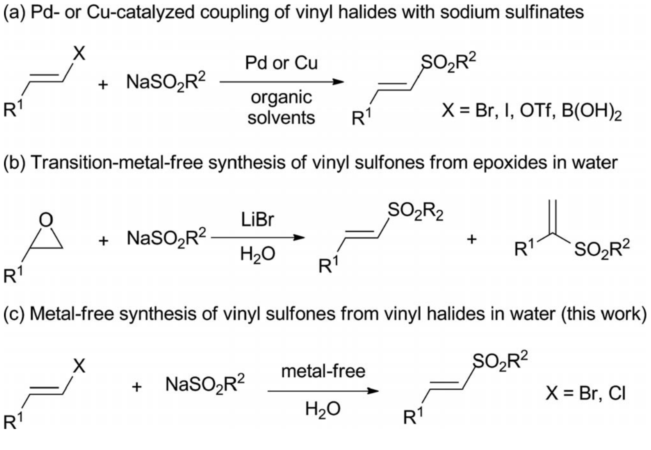
A practical transition-metal-free procedure for the synthesis of (*E*)-vinyl sulfones through the coupling of vinyl halides with sodium sulfinates in water is reported. The reaction is strongly influenced by the presence of acids, and the use of *n*Bu_4NBr promotes its efficiency.

Introduction

The use of water as a reaction medium for organic synthesis has attracted much interest in recent years, because water is cheap, readily available, nontoxic, nonflammable, and the most abundant liquid on our planet. Using water as an alternative solvent in organic synthesis complies with green chemistry protocols and provides an answer to the growing concerns associated with the environmental impact of chemical processes.[1]

Vinyl sulfones have received considerable attention in organic and medicinal chemistry because of their interesting synthetic utilities and potential biological activities. From a synthetic perspective, the activating and electron-withdrawing nature of the sulfone moiety in vinyl sulfones enables them to undergo highly stereoselective conjugate addition and cycloaddition reactions.[2] Furthermore, the sulfone group can be readily exchanged by hydrogen, an alkyl group, a hydroxy group, or a nucleophile at the end of a synthetic sequence, which allows the sulfonyl group to function as a temporary activating group.[3] In medicinal chemistry, substituted vinyl sulfones represent a new class of small-molecule inhibitors of some enzymatic processes, such as cysteine proteases[4] and inducible VCAM-1 expression,[5] which make them candidates for drug designing.

Traditional methods to prepare vinyl sulfones include the Horner–Emmons reaction, aldol condensation, and the oxidation of vinyl sulfides.[6] Recently, these traditional methods have been replaced by more efficient Pd- or Cu-catalyzed cross-coupling reactions of sulfinate salts[7] with vinyl bromides, vinyl triflates, alkenylboronic acids, or alkenes (Scheme 1a). In spite of the remarkable efficiency and generality of such reactions, they are still insufficient from a green chemistry point of view because of the use of toxic metals or organic solvents. Very recently, Yadav et al. reported a simple and green route to vinyl sulfones from terminal epoxides and sodium sulfinates[8] (Scheme 1b). Inefficiently, this reaction gave two regioisomers (linear and branched vinyl sulfones) in most cases, which made separation difficult. Therefore, the development of a practical and environmentally friendly method to construct vinyl sulfones is still highly desirable.



Scheme 1. Recent routes to vinyl sulfones. Tf = (trifluoromethyl)-sulfonyl.

Recently, transition-metal-free coupling reactions of heteroatoms with aryl halides have received increasing attention.[9] We envisioned that vinyl halides could also be coupled with heteroatoms without a transition-metal catalyst to afford various vinyl heteroatom compounds. Herein, we report a transition-metal-free route to (*E*)-vinyl sulfones from the coupling of vinyl halides with sodium sulfinates in water.

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[a] Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University,
Chengdu 610064, P. R. China
E-mail: chensy@scu.edu.cn
xqyu@scu.edu.cn
http://www.scu.edu.cn/

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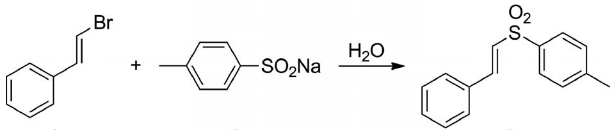
Results and Discussion

The coupling of phenylvinyl bromide with sodium *p*-toluenesulfinate was chosen as a model reaction for optimization studies. After stirring the reaction mixture at 100 °C in air for 10 h, no indication of product formation was observed in water[10] (Table 1, Entry 1). Fortunately, upon adding HCl (3 mol-%) to the reaction mixture, the desired product was isolated in 38% yield (Table 1, Entry 2). An increase in the amount of HCl (30 mol-%) added resulted in an increase in the yield to 90% (Table 1, Entry 3). Other acids such as H_2SO_4 and acetic acid gave the same results. We further found that the addition of an acid and a phase-transfer catalyst as a co-catalyst was more effective (Table 1, Entry 4). If only $n\mathrm{Bu}_4\mathrm{NBr}$ was added, no indication of product formation was detected (Table 1, Entry 5). These results show that the acid played a key role in the reaction.

Table 1. Optimization of the reaction conditions.[a]



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

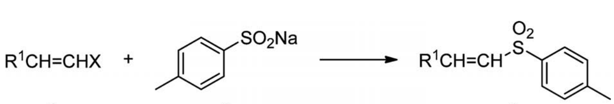
Entry	Additive (mol-%)	Yield[b] [%]
1	–	trace
2	HCl (3)	38
3	HCl (30)	90
4	HCl (30), $n\mathrm{Bu}_4\mathrm{NBr}$ (5)	99
5	$n\mathrm{Bu}_4\mathrm{NBr}$ (5)	trace
6	$\mathrm{CH_3COOH}$ (30), $n\mathrm{Bu}_4\mathrm{NBr}$ (5)	94

[a] Conditions: **1a** (0.3 mmol), **2a** (0.5 mmol), H_2O (2 mL), 100 °C, 10 h. [b] Yield of isolated product.

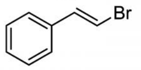
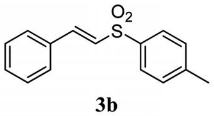
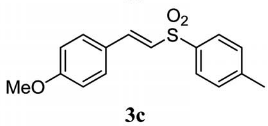
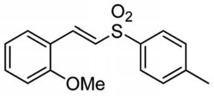
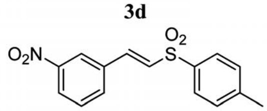
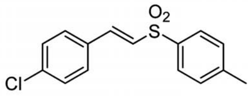
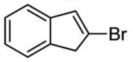
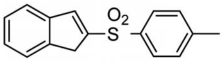
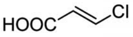
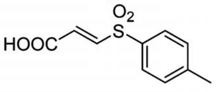
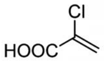
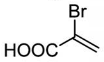
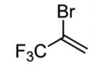
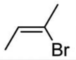
With the optimized reaction conditions in hand, we extended our approach towards the synthesis of various vinyl sulfones. Arylvinyl bromides bearing either an electron-donating substituent or an electron-withdrawing substituent afforded vinyl sulfones in good yields under the standard conditions (Table 2, Entries 1–5). Interestingly, arylvinyl chloride **1f** was also a good substrate for this reaction, and it afforded vinyl sulfone **3b** in 99% yield (Table 2, Entry 6). Notably, vinyl chlorides are less reactive than vinyl bromides, and they perform poorly in transition-metal-based systems. Both bromo- and chloroacrylic acid afforded the target products in moderate yields and both α- and β-substrates ended up with β-substituted products (Table 2, Entries 8–10). Alkylvinyl bromides **1k** and **1l** did not undergo this reaction (Table 2, Entries 11 and 12).

Besides sodium *p*-toluenesulfinate, other sulfinate salts were also good sulfonating reagents (Table 3, Entries 1–4). Benzenesulfinate, 4-methoxybenzenesulfinate, 4-chlorobenzenesulfinate, and 4-fluorobenzenesulfinate afforded the products in high yields. Naphthalenesulfinate **2f**, thiophenesulfinate **2g**, and methanesulfinate **2h** gave moderate yields (Table 3, Entries 5–7).

Table 2. Synthesis of vinyl sulfones from vinyl halides.[a]



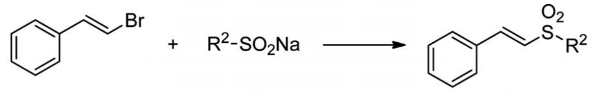
1 **2a** **3**

Entry	1	3	Yield [%]
1	**1a** 	**3a** 	99 90[b]
2	**1b** $R^1 = p\text{-MeOC}_6H_4$ X = Br	**3b** 	99 86[b]
3	**1c** $R^1 = o\text{-MeOC}_6H_4$ X = Br	**3c** 	99
4	**1d** $R^1 = m\text{-NO}_2C_6H_4$ X = Br	**3d** 	96
5	**1e** $R^1 = p\text{-ClC}_6H_4$ X = Br	**3e** 	95
6	**1f** $R^1 = p\text{-MeOC}_6H_4$ X = Cl	**3b**	99
7	**1g** 	**3f** 	40[c]
8	**1h** 	**3g** 	59[c]
9	**1i** 	**3g**	55[c]
10	**1j** 	**3g**	59[c]
11	**1k** 	**3h**	n.d.[d,e]
12	**1l** 	**3i**	n.d.[e]

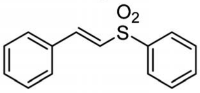
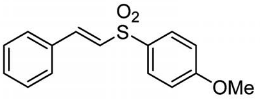
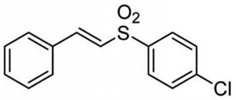
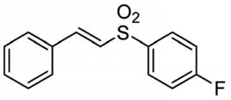
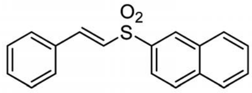
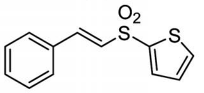
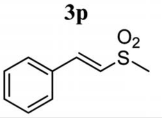
[a] Standard conditions: **1** (0.3 mmol), **2** (0.5 mmol)., HCl (30 mol-%) $n\mathrm{Bu}_4\mathrm{NBr}$ (5 mol-%) H_2O (2 mL), 100 °C, 10 h. [b] Without $n\mathrm{Bu}_4\mathrm{NBr}$. [c] $n\mathrm{Bu}_4\mathrm{NBr}$ (30 mol-%). [d] 50 °C. [e] n.d. = not determined.

In support of the utility of this method, we conducted the reaction on a gram scale, whereupon the product was obtained with almost no change in yield (Scheme 2). To further demonstrate its practical utility, we tested the recyclability of the catalysts. After each run, the products were extracted from the crude mixture with ethyl acetate. After the first run, only the vinyl halide (i.e., **1a**, 1 equiv.) and the sodium sulfinate (i.e., **2a**, 1.5 equiv.) were added to the

Table 3. Synthesis of vinyl sulfones from vinyl halides.[a]

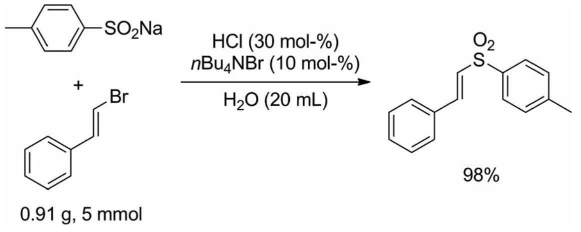


1a **2** **3**

Entry	2	3	Yield [%]
1	**2b** $R^2 = C_6H_5$	**3j** 	93 60[b]
2	**2c** $R^2 = p\text{-MeOC}_6H_4$	**3k** 	94[b]
3	**2d** $R^2 = p\text{-ClC}_6H_4$	**3l** 	91 61[b]
4	**2e** $R^2 = p\text{-FC}_6H_4$	**3m** 	86 64[b]
5	**2f** $R^2 = \beta\text{-C}_{10}H_7$	**3n** 	61
6	**2g** R^2 = 2-thienyl	**3o** 	51[c]
7	**2h** $R^2 = CH_3$	**3p** 	53[c]

[a] Standard conditions: **1** (0.3 mmol), **2** (0.5 mmol), HCl (30 mol-%), nBu$_4$NBr (5 mol-%), H_2O (2 mL), 100 °C, 10 h. [b] Without nBu$_4$NBr. [c] nBu$_4$NBr (30 mol-%).

recovered residue after the extraction. As shown in Table 4, the reaction gave very high yields in each run, and consequently, the catalysts (HCl and nBu$_4$NBr) maintained their efficiency (Table 4).



Scheme 2. Preparative-scale experiment.

To obtain some insight into this reaction, we analyzed the reaction mixture by using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Indeed, 0.03–0.05 ppm of Pd, Cu, Fe, and other metal species were detected.[11] When 10 times the amount of Cu was added, only a trace amount of the product was detected in the absence of an acid. The addition of 100 times the amount of Pd or Fe was still inefficient. These results excluded the effect of transition-metal species.

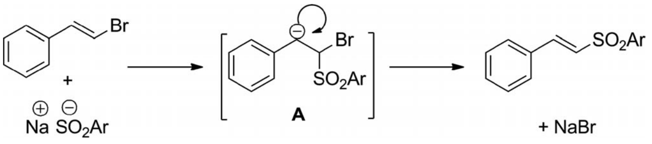
Table 4. Catalyst-recycling experiments.

Run	Yield [%]
1[a]	99
2[b]	99
3[b]	98
4[b]	99

[a] Conditions: **1a** (0.3 mmol), **2a** (0.5 mmol), HCl (30 mol-%), nBu$_4$NBr (10 mol-%), H_2O (2 mL), 100 °C, 10 h. [b] The aqueous phase from the previous run was reused instead of recharging the catalysts and water.

Then, several control experiments were performed (for details, see the Supporting Information). (1) By using DMSO or *N*,*N*-dimethylacetamide (DMAc) as the solvent, the reaction performed efficiently without an acid. (2) By using D_2O as the solvent, no deuterated starting materials or products were detected. These results suggest that an acid may not take part in the chemical transformation. Although the exact role of the acid is not certain, we infer from the observed results that it may work to enhance the solubility of the vinyl halides in water.[12] (3) Upon adding an excess amount of HCl, the reaction did not occur, which suggests the nucleophilicity of the sodium sulfinate is crucial to this transformation.

On the basis of the above experiments, a tentative mechanism is proposed. First, intermediate **A** is generated through nucleophile addition of sodium sulfinate to phenylvinyl bromide. The anion of the intermediate is stabilized by the benzene ring (or electron-withdrawing groups such as the carboxy group). Then, elimination of the bromine anion gives the desired product (Scheme 3).[13]



Scheme 3. Proposed mechanism.

Conclusions

We have reported a transition-metal-free method for the synthesis of (*E*)-vinyl sulfones from the coupling of vinyl halides with sodium sulfinates in water. The protocol complies with several attributes of green chemistry such as recycling of the catalyst, using water as an alternative medium, and avoiding the use of toxic catalysts and intermediates.

Experimental Section

General Procedures for Vinyl Sulfones: A 10 mL flask was charged with vinyl bromide (0.3 mmol), sodium sulfinate (0.5 mmol), *n*Bu_4NBr (0.015 mmol), concentrated HCl (12 M, 8 µL, 0.3 equiv.), and deionized water (2 mL), and the reaction mixture was stirred at 100 °C for 10 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (15 mL), and the organic layer was washed with water (3 × 15 mL). After drying with Na_2SO_4, the combined ethyl acetate extracts were concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel to give the product.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

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[9] For selected examples: a) J. Zhao, Y.-F. Zhao, H. Fu, *Angew. Chem.* **2011**, *123*, 3853; *Angew. Chem. Int. Ed.* **2011**, *50*, 3769; b) K. M. Maloney, J. T. Kuethe, K. Linn, *Org. Lett.* **2011**, *13*, 102.

[10] For details of the selection of the solvents, see the Supporting Information. Only three vinyl sulfones were prepared from vinyl halides under transition-metal-free conditions; they were obtained in 31, 24, and 17% yield, respectively; see: B. R. Baker, M. V. Querry, *J. Org. Chem.* **1950**, *15*, 417. The reaction presented by Querry et al. was carried out under alkaline conditions, whereas this reaction was carried out in acidic solution.

[11] For specific experiments, see the Supporting Information.

[12] We found that acids slightly promoted the solubility of phenylvinyl bromide in water.

[13] A similar mechanism was described in this paper: H.-L. Kao, C.-F. Lee, *Org. Lett.* **2011**, *13*, 5204.

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