

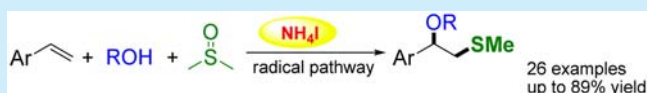
# NH<sub>4</sub>I-Mediated Three-Component Coupling Reaction: Metal-Free Synthesis of $\beta$ -Alkoxy Methyl Sulfides from DMSO, Alcohols, and Styrenes

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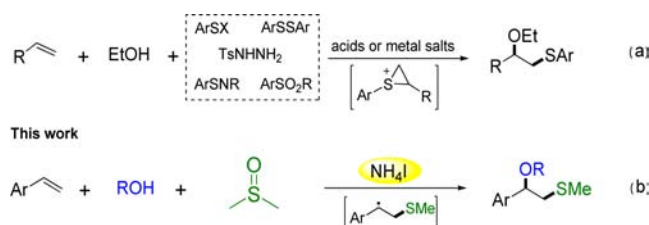
**S** Supporting Information

**ABSTRACT:** A novel synthesis recipe for  $\beta$ -alkoxy methyl sulfides was developed via NH<sub>4</sub>I-mediated three-component oxysulfenylation reaction of styrenes with DMSO and alcohols. This method features simple operation and readily available starting materials, and it provides an alternative sulfenylating agent generated from DMSO for oxysulfenylation reactions.



The simultaneous introduction of two different functional groups to the carbon–carbon double bonds of alkenes is a fundamentally important process in organic synthesis.<sup>1</sup> Among the numerous difunctionalization reactions reported, the oxysulfenylation of alkenes for synthetically useful 1,2-hydroxy sulfides<sup>2</sup> has attracted much attention, due to their interesting synthetic utilities and biological activities.<sup>3</sup> However, the sulfenylating agents applied in the previous investigations mainly focused on aromatic sulfur, such as sulfonyl halides,<sup>2a–d</sup> disulfides,<sup>2e–i</sup> sulfenamides,<sup>2j–l</sup> sulfonate esters,<sup>2m,n</sup> and sulfonyl hydrazides<sup>2o</sup> (Scheme 1 (a)). In contrast, the introduction of

## Scheme 1. Three-Component Oxysulfenylation Reaction of Alkenes



alkyl sulfides into alkenes for  $\beta$ -alkoxy sulfides has been rarely explored. The only disclosure was reported by Capozzi<sup>4</sup> and co-workers and Tiecco<sup>5</sup> and co-workers who employed (methylthio)-sulfonium salt and sodium methanethiolate as alkyl sulfide agents for the three-component oxysulfenylation of alkenes. However, these systems suffered from low selectivities, expensive reagents, and harsh reaction conditions. Thus, the discovery of new sources of alkyl sulfenylating agents generated in situ from simple and readily available reagents for the oxysulfenylation of alkenes is highly desirable.

Dimethyl sulfoxide (DMSO), as a cheap and commercially available solvent, has been widely used in organic synthesis. Actually, besides being an effective polar reaction medium, DMSO has also been used as a multipurpose precursor for the –O, –SMe, –CH<sub>2</sub>SMe, –Me, –CN, and –CHO units, etc.<sup>6</sup> Based on our previous work on the utilization of DMSO,<sup>7</sup> we

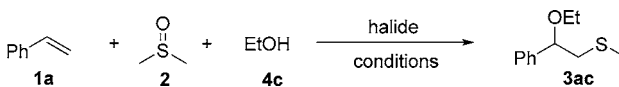
envisioned that DMSO could serve as a sulfenylating agent in the oxysulfenylation reactions of alkenes. Herein, we report the realization of this idea via ammonium iodide mediated three-component oxysulfenylation reaction of styrenes with DMSO and alcohols (Scheme 1 (b)).

Initially, we employed the oxysulfenylation of styrene **1a**, ethanol **4c**, and DMSO as a model reaction to screen the reaction conditions. To our delight, the three-component coupling reaction resulted in formation of the desired product **3ac** in 47% yield in the presence of NH<sub>4</sub>I (Table 1, entry 1). Further investigation revealed that the yield improved dramatically when increasing the amount of DMSO (Table 1, entries 2–5). The reaction efficiency did not change obviously even the amount of EtOH was decreased to 2.0 equiv (Table 1, entry 6). It is noteworthy that NH<sub>4</sub>I concentration and reaction temperature had a significant effect on the yield of **3ac** (Table 1, entries 7–10 and 13–16). Shortening the reaction time to 13 h led to only 33% yield, while prolonged reaction time did not promote the reaction (Table 1, entries 11–12). Hence, the optimal reaction conditions were determined to be NH<sub>4</sub>I (3.0 equiv), EtOH (0.5 mL), DMSO (2.5 mL), with **1a** (1.0 mmol) at 125 °C for 26 h, which provided **3ac** in 89% yield (Table 1, entry 5).

With the optimal conditions in hand, a series of styrenes (**1**) were investigated to evaluate the generality of this reaction (Scheme 2). In general, both electron-withdrawing and -donating styrenes could be successfully converted to the corresponding  $\beta$ -alkoxy methyl sulfides in good to excellent yields. Adding the substituted group at different positions on the phenyl ring of styrenes (Scheme 2, **3b–d**) had no obvious influence on the yields (77–82%). Sterically hindered 2,4,6-trimethylstyrene and 4-*tert*-butylstyrene worked well under the standard conditions, leading to the desired products **3e** and **3f** in 75% and 78% yields, respectively. Moreover, the heteroaryl substrate also participated in the reaction under the optimized conditions (Scheme 2, **3g**). Halides remained untouched in the

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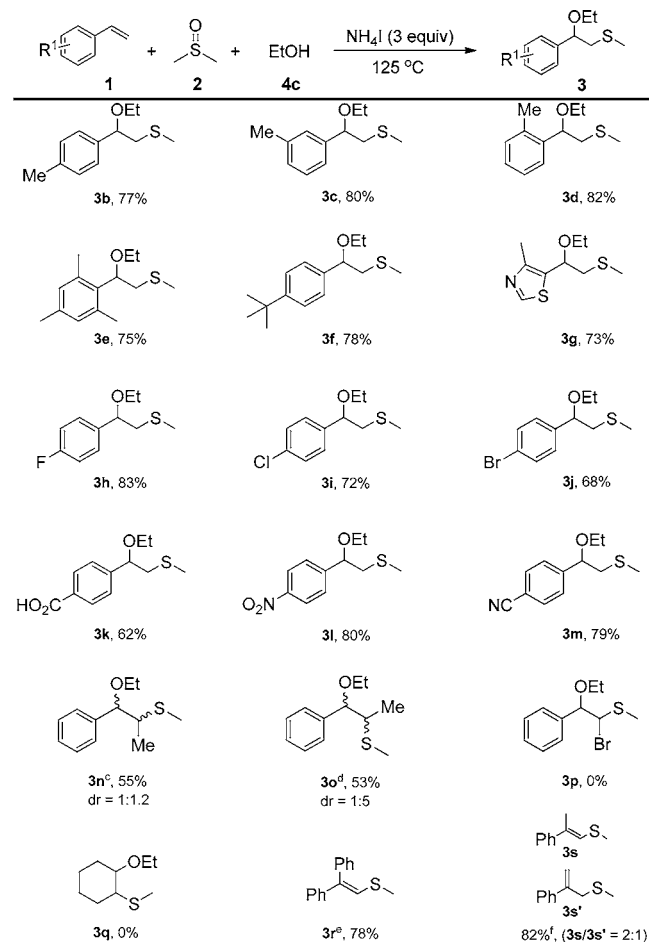
Table 1. Optimization of Reaction Conditions<sup>a</sup>


entry	halide (equiv)	solvent (v/v)	temp (°C)/time (h)	yield <sup>b</sup> (%)
1	NH <sub>4</sub> I (4)	DMSO/EtOH (2:1)	130/24	47
2	NH <sub>4</sub> I (3)	DMSO/EtOH (1:1)	125/26	53
3	NH <sub>4</sub> I (3)	DMSO/EtOH (2:1)	125/26	64
4	NH <sub>4</sub> I (3)	DMSO/EtOH (3:1)	125/26	72
5	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	125/26	89
6 <sup>c</sup>	NH <sub>4</sub> I (3)	DMSO/EtOH	125/26	75
7	NH <sub>4</sub> I (1)	DMSO/EtOH (5:1)	125/26	37
8	NH <sub>4</sub> I (2)	DMSO/EtOH (5:1)	125/26	69
9	NH <sub>4</sub> I (4)	DMSO/EtOH (5:1)	125/26	85
10	NH <sub>4</sub> I (5)	DMSO/EtOH (5:1)	125/26	49
11	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	125/13	33
12	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	125/32	68
13	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	100/26	35
14	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	110/26	47
15	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	120/26	71
16	NH <sub>4</sub> I (3)	DMSO/EtOH (5:1)	135/26	38
17	KI (3)	DMSO/EtOH (5:1)	125/26	0
18	<i>n</i> -Bu <sub>4</sub> NI (3)	DMSO/EtOH (5:1)	125/26	0
19	NH <sub>4</sub> Br (3)	DMSO/EtOH (5:1)	125/26	0
20	NH <sub>4</sub> Cl (3)	DMSO/EtOH (5:1)	125/26	0
21 <sup>d</sup>	HI	DMSO/EtOH (5:1)	125/26	39, 33
22 <sup>e</sup>	I <sub>2</sub>	DMSO/EtOH (5:1)	125/26	38, 23

<sup>a</sup>Reaction conditions: **1a** (1.0 mmol), **4c** (0.5 mL). <sup>b</sup>Isolated yield. <sup>c</sup>EtOH (2.0 equiv), DMSO (2.5 mL). <sup>d</sup>HI (0.1 and 0.05 mL). <sup>e</sup>I<sub>2</sub> (0.5 and 0.1 equiv).

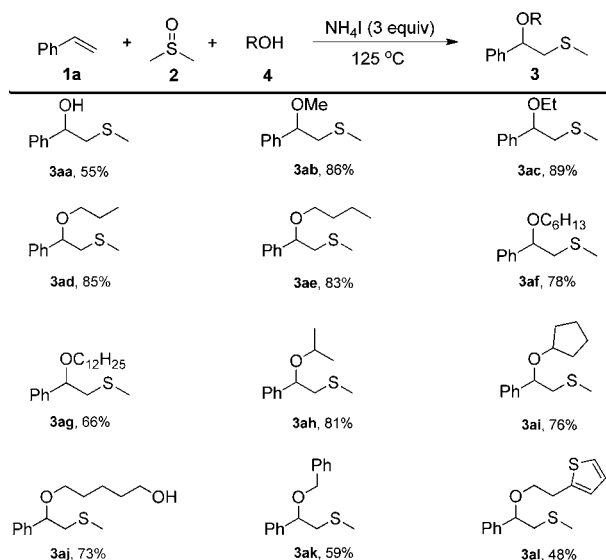
reaction system, which provided the possibility for further functionalization (Scheme 2, **3h–j**). In addition, substrates bearing electron-withdrawing groups such as carboxyl, cyano, and nitro proceeded smoothly to afford the target products in moderate to good yields (62–79%). Furthermore, the optimized reaction conditions turned out to be equally successful for internal alkenes *cis*- or *trans*- $\beta$ -methylstyrene **1n** and **1o**, affording the desired products in moderate yields with a diastereoselective ratio of 1:1.2 and 1:5, respectively (Scheme 2, **3n**, **3o**). However, *cis*- $\beta$ -bromostyrene **1p**, cyclohexene **1q**, and even allylbenzene failed to give the corresponding products.

To further explore the potential of our methodology, a variety of alcohols were investigated (Scheme 3). Generally, aliphatic primary alcohols reacted well with styrene **1a** and DMSO to afford **3ab–af** in good yields (78–89%). To our delight, bulky alcohol **4g** was also transformed into the desired product (Scheme 3, **3ag**) in 66% yield. When secondary alcohols were subjected to the reaction conditions, such as 2-propanol and cyclopentanol, oxysulfenylated products **3ah** and **3ai** were obtained in 81% and 76% yields, respectively. However, the reaction was not applicable to tertiary alcohols such as *tert*-butyl alcohol. Pentane-1,5-diol, an alkyl glycol, also worked for this reaction, and the corresponding product **3aj** was obtained in 73% yield. Moreover, aromatic alcohol **4k** also proved to be suitable for the three-component oxysulfenylation reaction with the formation of **3ak** in moderate yield (59%). Heterocyclic alcohol such as 2-(thiophen-2-yl) ethanol gave the desired product in 48% yield. When alcohol was replaced with water, the reaction gave the product **3aa** with a moderate yield of 55%.

Scheme 2. Substrate Scope for Reaction of Styrenes<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (1.0 mmol), NH<sub>4</sub>I (3.0 equiv) and **4c** (0.5 mL) in DMSO (2.5 mL) at 125 °C for 26 h. <sup>b</sup>Isolated yield. <sup>c</sup>*cis*- $\beta$ -Methylstyrene (0.5 mmol), 32 h. <sup>d</sup>*trans*- $\beta$ -Methylstyrene (0.5 mmol), 32 h. <sup>e</sup>1,1-Diphenylethene (1.0 mmol) was used as substrate. <sup>f</sup> $\alpha$ -Methylstyrene (1.0 mmol) was used as substrate.

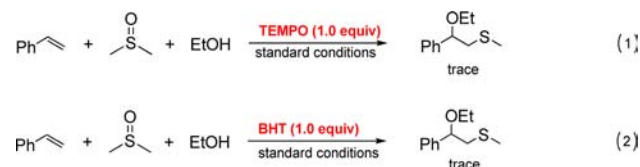
To gain insight into the reaction mechanism, several control experiments were conducted. No desired product was detected when NH<sub>4</sub>I was replaced with KI or *n*-Bu<sub>4</sub>NI, which indicated that iodide anion was not the real species for NH<sub>4</sub>I participating in this conversion (Table 1, entries 17 and 18). Nevertheless, similar ammonium salts including NH<sub>4</sub>Br and NH<sub>4</sub>Cl failed to promote the formation of the desired **3ac**, ruling out the function of NH<sub>4</sub><sup>+</sup> in this reaction (Table 1, entries 19 and 20). It was important to find that when HI and I<sub>2</sub> were used as mediator instead of NH<sub>4</sub>I, the target product **3ac** could be produced (Table 1, entries 21 and 22). When 0.1 mL of HI or 0.5 equiv of I<sub>2</sub> was used, styrene **1a** was totally converted but with a poor selectivity of the desired product **3ac** (38–39%). Decreasing the amount of HI or I<sub>2</sub> did not improve the yield of **3ac** (23–33%), and almost half of the styrene was unreacted in both cases. These results suggested that HI and I<sub>2</sub> could be the real forms of NH<sub>4</sub>I that participated in this reaction. Moreover, the concentration of HI was well controlled in the case of NH<sub>4</sub>I since its decomposition was a reversible process, which avoided the oxidation of styrene into benzaldehyde and benzoic acid when iodine was used directly as mediator. Thus, the good selectivity of **3ac** was ensured when NH<sub>4</sub>I was employed as mediator in this reaction. In addition, we found that the three-

Scheme 3. Substrate Scope for Reaction of Alcohols<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1a** (1.0 mmol),  $\text{NH}_4\text{I}$  (3.0 equiv), and ROH or  $\text{H}_2\text{O}$  (2.0 equiv) in DMSO (2.5 mL) at 125 °C for 26 h. <sup>b</sup>Isolated yield.

component coupling reaction was completely inhibited by the addition of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) (Scheme 4, eqs 1 and 2). The results suggested that the present

Scheme 4. Preliminary Mechanism Studies

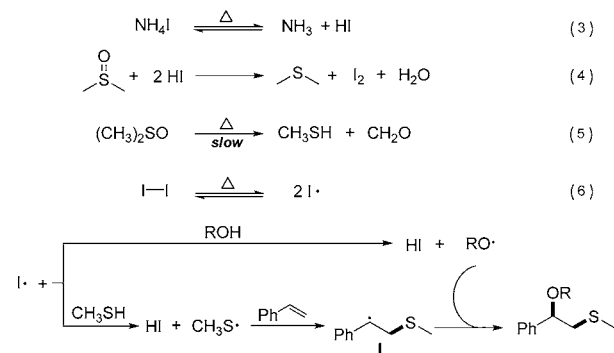


reaction presumably proceeded through a radical pathway. In addition, when 1,1-diphenylethene **1r** was used, methyl 2,2-diphenylethenyl sulfide **3r** was obtained in 78% yield (Scheme 2, **3r**). Moreover,  $\alpha$ -methylstyrene **1s** afforded a mixture of **3s** and **3s'** under the optimized conditions (Scheme 2, **3s**, **3s'**). The generation of vinyl sulfides **3r**, **3s**, and **3s'** indicated that methylthiyl radical ( $\text{MeS}^\bullet$ ) was probably involved in this procedure.

According to the above results and previous relevant studies, a plausible reaction mechanism is proposed in Scheme 5. First, the radical initiator  $\text{I}_2$  and precursor MeSH are generated through a series of reactions, as shown in eqs 3–5.<sup>8–10</sup> Then, iodine radical can be formed by thermal decomposition of the in situ generated  $\text{I}_2$  (eq 6),<sup>11</sup> which could react with MeSH to give a methylthiyl radical ( $\text{MeS}^\bullet$ )<sup>12</sup> and concurrently abstract hydrogen atom from alcohols to afford alkoxy radicals ( $\text{RO}^\bullet$ ).<sup>13</sup> Subsequently, the methylthiyl radical adds to the C=C double bond of styrene, leading to a radical intermediate **I**.<sup>14</sup> Finally, the rapid combination of  $\text{RO}^\bullet$  and the intermediate **I** produces the desired product. Because of the involvement of  $\text{NH}_3$  and  $\text{I}_2$  in this reaction system, the possibility of formation and involvement of nitrogen triiodide might exist, even though we did not detect it in our experiments.<sup>15</sup>

In summary, we have developed a novel ammonium iodide mediated oxysulfenylation of styrenes with DMSO and alcohols

Scheme 5. Proposed Reaction Mechanism



for the synthesis of  $\beta$ -alkoxy methyl sulfides under metal-free conditions. The reaction proceeds smoothly with excellent regioselectivity, broad substrate scope, and high functional group tolerance. Furthermore, this process is simple in operation and makes use of inexpensive and readily available starting materials. Investigation of the detailed mechanism and application of methylthiyl radical based on the  $\text{NH}_4\text{I}$ -DMSO system for other transformations are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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