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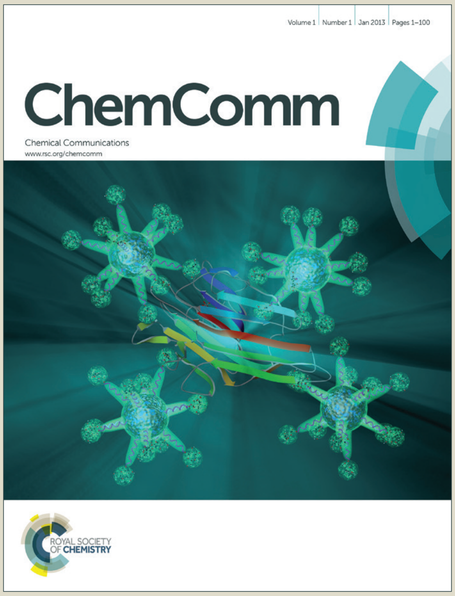

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COMMUNICATION

Ammonium iodide-induced sulfonylation of alkenes with DMSO and water toward the synthesis of vinyl methyl sulfones†

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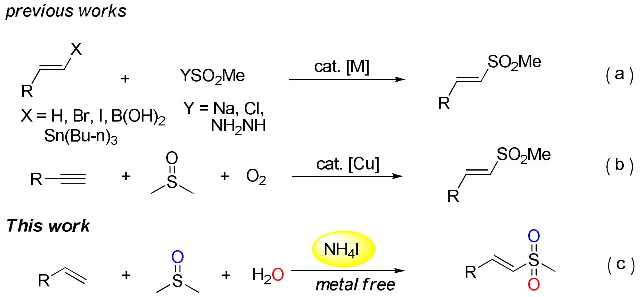
A novel ammonium iodide-induced sulfonylation of alkenes with DMSO and water toward the synthesis of vinyl methyl sulfones is described. The process proceeded smoothly under metal-free conditions with high stereoselectivity and good functional group tolerance. The reaction mechanism was revealed to proceed through a domino reaction of oxidation and elimination after the radical addition to alkenes.

Vinyl sulfones are important compounds in organic and medicinal chemistry due to their versatile reactivities and potential biological activities.[1] In the last decades, the synthesis of vinyl sulfones has attracted more and more attention from chemists.[2-6] Traditional pathways for the preparation of vinyl sulfones typically include the direct oxidation of vinyl sulfides and Heck reaction of ary halides with vinyl sulfones.[2,3] However, these methods suffer from poor selectivity or expensive starting materials. In recent years, some efficient metal-catalyzed approaches have been investigated such as cross-coupling reactions of olefins and its derivatives (vinyl halides, stannanes, and arylboronic acids) with sulfone reagents including sulfinate salts, sulfonyl chlorides, or sulfonyl hydrazides (Scheme 1a).[4] Recently, some researchers have achieved this transformation in the absence of transition-metal catalysts.[5] Despite remarkable improvement and efficiency of such reactions, the discovery of sulfone sources from inexpensive and readily available reagents is highly desired. Very recently, Loh and co-workers published an alternative Cu-catalyzed methyl sulfonylation of alkynes using DMSO and O_2 as a methyl sulfone source ($-SO_2Me$) (Scheme 1b).[6] Herein, we disclose a novel and efficient ammonium iodide-induced sulfonylation of alkenes in which DMSO and H_2O are used as the starting materials to provide the source of $-SO_2Me$ (Scheme 1c). To the best of our knowledge, such a route for the synthesis of vinyl methyl sulfones has not been reported under metal free conditions.

Using styrene (**1a**) and DMSO as the substrates, optimal conditions were first examined for the sulfonylation. After screening a variety of reaction parameters, the sulfonylation of **1a** gave **2a** in an excellent yield with sole stereoselectivity under the standard conditions (Table 1, entry 1: 4.0 equiv NH_4I, 0.5 mL H_2O, 1.0 mL DMSO, at 130 °C for 24 h; optimization details, see SI). The effects of the other factors on the reaction are shown in entries 2–13. Neither the organic tetrabutylammonium iodide (n-Bu_4NI) nor the inorganic KI did afford the desired product (entries 2 and 3), suggesting that iodide anion is not the real form for NH_4I participated in this conversion. No desired transformation was observed employing similar ammonium salt NH_4Br (entry 4), ruling out the function of NH_4^+ in this reaction. When using 2.0 equiv of I_2 instead of 4.0 equiv of NH_4I, **2a** was not obtained with only benzoic acid as the product, whereas 15% yield of **2a** was determined with 0.5 equiv of I_2 (entries 5 and 6). In addition, when the reaction was performed with aqueous ammonia, the yield of the product was not improved (entry 7). However, in the presence of catalytic amounts of I_2, no desired product was obtained only recovering the unreacted styrene (entry 8). These results clearly indicated that I_2 was indeed the actual form to promote this conversion and its concentration had a great impact on the selectivity of reaction. It was also observed that both the adding amount of NH_4I and reaction temperature were important parameters for a high yield (entries 10–12). In the absence of water, the yield of the target product dramatically decreased (entry 13).



Scheme 1 Different routes for the synthesis of vinyl methyl sulfones.

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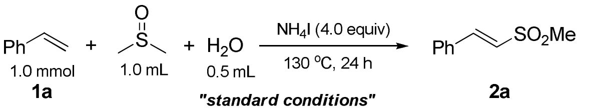
Table 1 Effect of various factors on the reaction.



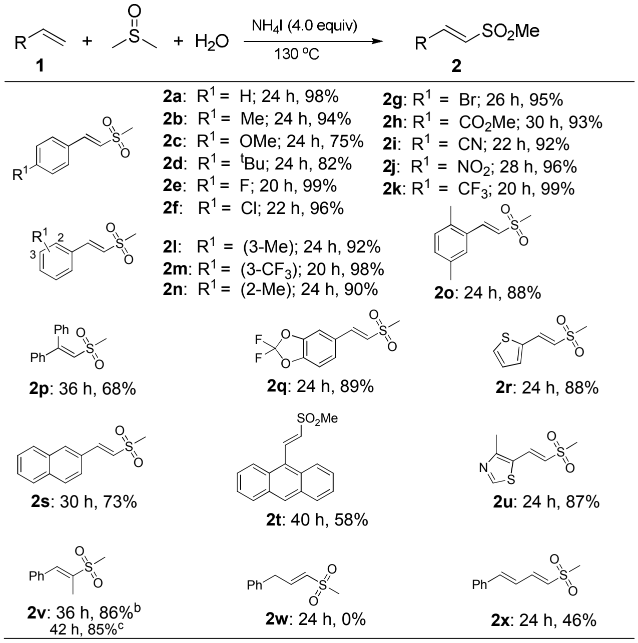
Entry	Variation from the standard conditions	Yield/%[a]
1	none	98
2	Bu_4NI instead of NH_4I	0
3	KI instead of NH_4I	0
4	NH_4Br instead of NH_4I	0
5	2.0 equiv of I_2 instead of NH_4I	0
6	0.5 equiv of I_2 instead of NH_4I	15
7	0.5 equiv of I_2 + 0.5mL $NH_3.H_2O$ instead of NH_4I	17
8	10 mol % I_2 instead of NH_4I	0
9	HI instead of NH_4I	8
10	1.0 equiv of NH_4I	0
11	100 °C instead of 130 °C	0
12	120 °C instead of 130 °C	39
13	without adding H_2O	12
14[b]	under N_2 atmosphere	91
15[c]	adding TEMPO	0
16[c]	adding BHT	0

[a] Determined by ^1H NMR (internal standard: 1,3,5-trimethyl benzene). [b] Run for 32 h. [c] 1.0 equiv of radical trapper was used.

With the optimal conditions in hand, we next evaluated the substrates scope and limitations of our protocol (Table 2 and 3). In general, the reactions of alkenes bearing electron-withdrawing groups gave slightly higher yields of product than those containing electron-donating moieties, as well as much faster reaction rates (**2a–2n**). All of the reactions proceeded with excellent regioselectivity, and various functional groups such as methyl, methoxyl, fluoro, chloro, bromo, ester, cyanide, nitro, and trifluoromethyl groups at the meta or para positions of the aromatic ring were reasonably well tolerated under the standard conditions. The reaction of disubstituted alkenes was also efficient (**2o,2q**). Polyaryl substrates such as 2-naphthalene and 9-phenanthrene retarded the reaction even after an extended reaction time, albeit in moderate yields (**2s–2t**), possibly due to the steric interference. In addition, heteroaromatic olefins proceeded smoothly to afford the target products in good yields (**2r, 2u**). Gratifyingly, interminal alkenes were also productive, exclusively forming (*E*)-sulfonyl product (**2v**) either from the *cis*- or *trans*-β-methyl styrene. However, allylbenzene failed to give the corresponding product (**2w**), and the similar result was also observed with alkyl alkenes as substrates. On the contrary conjugated diene afforded the target product in a moderate yield (**2x**), indicating that conjugative effect played an important role in stabilizing the intermediate.[7]

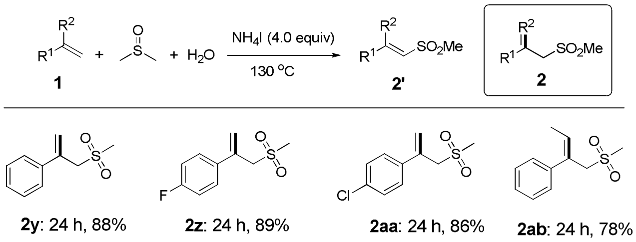
Interestingly, when *α*-methylstyrene (**1y**) was applied as substrate, isomerization product (**2y**) was obtained instead of the desired vinyl sulfone (Table 3). Other similar olefins were tested under the standard conditions, obtaining the isomerized products in good yields (**2z–2ab**) as well. These results suggested that a different elimination protocol was existed for 1,1-disubstituted olefins. This isomerization result is consistent with the previous studies by Jiang [4b] and Li.[5c]

Table 2 Scope of alkene substrates.[a]



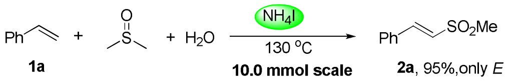
[a] Reaction conditions: alkene (1 mmol), NH_4I (4.0 equiv), H_2O (0.5 mL), DMSO (1.0 mL) and 130 °C . Isolated yield. [b] Cis-β-methyl styrene. [c] Trans-β-methyl styrene.

Table 3 Scope of 1,1-disubstituted alkene substrates.[a]

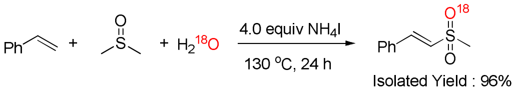


[a] Reaction conditions: as shown in Table 2. Isolated yield.

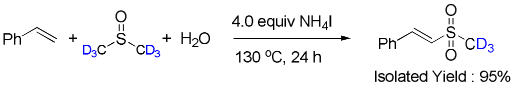
Moreover, the reaction is scalable and practical as an excellent yield (95%) of **2a** was obtained when the reaction was performed on a 10.0 mmol scale (eq 1).[8]



(1)



(2)



(3)

In order to investigate the reaction mechanism, a series of control experiments were carried out. Under the protection of N_2, the target product **2a** could be obtained in an excellent yield (Table 1, entry 14), indicating that the oxygen atom of

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sulfone group in **2a** does not come from O_2. The isotopic labeling experiment with $H_2{}^{18}O$ was conducted (eq 2).[8] These experimental results make sure that one oxygen atom of the sulfone group of **2a** is from H_2O and the other results from DMSO. The deuterium labeling experiment with DMSO-d_6 (eq 3) confirms that methylthiyl (MeS) originates from DMSO. Further, a reaction profile was obtained in the sulfonylation of styrene (**1a**) under the standard conditions (Figure 1). Within reaction time 4 h, 2-(methylthio)-1-phenylethanol (**3a**) was firstly detected in 20% yield, and then 2-(methylsulfonyl)-1-phenylethanol (**4a**) and (*E*)-(2-(methylsulfonyl)vinyl) benzene (**2a**) were produced. During the reaction process, **3a** and **4a** remained a low concentration in the reaction mixture and disappeared at the end of reaction. Simultaneously, the concentration of **2a** increased with the reaction time, thus implying that **3a** and **4a** were the intermediates in this conversion. Indeed, discrete **3a** and **4a** both could be completely converted to **2a** under the otherwise identical conditions.[8] In addition, when the reaction was performed in the presence of a stoichiometric amount of TEMPO or BHT under the standard conditions, **2a** was not obtained (Table 1, entries 15 and 16). These results suggested that the present reaction presumably proceeded through a radical pathway.

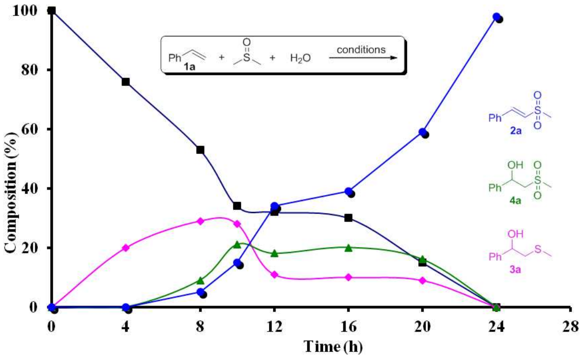
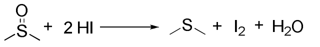


Figure 1 Reaction profile in the NH_4I-induced sulfonylation of **1a**.

Based on the above results, a plausible reaction mechanism is proposed in Scheme 2. First, the radical initiator I_2 and precursor MeSH are generated through a series of reactions, as shown in equations 4–6.[9-11] Then, I_2 is decomposed to form iodine radical (eq 7),[12] which attacks on MeSH to give a methylthiyl radical MeS· (eq 8).[13] Subsequently, the radical MeS· is added to the alkene to generate a radical intermediate **I**.[14] At the same time, The MeS· abstracts hydrogen from water to afford hydroxyl radical (OH·). The rapid coupling reaction between the radical intermediate **I** and OH· produces intermediate **3a,** which is further oxidized by DMSO[15] and H_2O_2 resulting from self-coupling of the radical OH·,[16] to form intermediate **4a**. Finally, with the assistance of newly formed sulfone group, **2a** is generated via acid-catalysed dehydration of **4a**.

In conclusion, we have developed a novel and efficient protocol of ammonium iodide-induced sulfonylation of olefins with DMSO and water, achieving excellent stereoselectivity and high functional group tolerance. In addition, this procedure provides a new valuable method of generating methylthiyl radical (MeS·) from DMSO. Further studies on the details of reaction mechanism and applications in organic synthesis are currently underway in our laboratory.

$$NH_4I \xrightarrow{\Delta} NH_3 + HI \qquad (4)$$

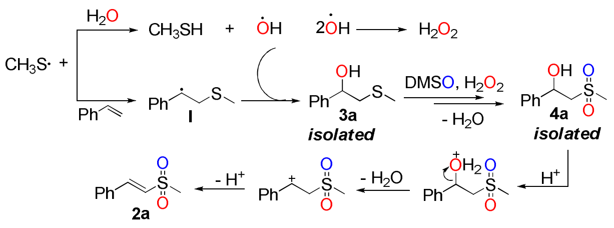

(5)

$$CH_3S(O)CH_3 + 2\,HI \longrightarrow CH_3SCH_3 + I_2 + H_2O \qquad (5)$$

$$(CH_3)_2SO \longrightarrow CH_3SH + HCHO \qquad (6)$$

$$I{-}I \underset{}{\overset{\Delta}{\rightleftharpoons}} 2\,I\cdot \qquad (7)$$

$$I\cdot + CH_3SH \longrightarrow CH_3S\cdot + HI \qquad (8)$$



Scheme 2 Proposed reaction mechanism.

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