ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxx

COMMUNICATION

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

Xiaofang Gao, Xiaojun Pan, Jian Gao, Huawen Huang, Gaoqing Yuan*, and Yingwei Li*

Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX 5 DOI: 10.1039/b000000x

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 10 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 15 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 20 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) 25 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 ³⁰ 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 O₂ as a methyl sulfone source (– SO_2Me) (Scheme 1b).⁶ Herein, we disclose a novel and
- ³⁵ efficient ammonium iodide-induced sulfonylation of alkenes in which DMSO and H₂O are used as the starting materials to provide the source of -SO₂Me (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.
- ⁴⁰ Using styrene (1a) and DMSO as the substrates, optimal conditions were first examined for the sulfonylation. After

previous works



⁵⁰ Scheme 1 Different routes for the synthesis of vinyl methyl sulfones.

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 55 NH₄I, 0.5 mL H₂O, 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-Bu₄NI) nor the inorganic KI did afford the desired product (entries 2 and 3), suggesting 60 that iodide anion is not the real form for NH₄I participated in this conversion. No desired transformation was observed employing similar ammonium salt NH₄Br (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 NH₄I, **2a** was not obtained with only 65 benzoic acid as the product, whereas 15% yield of 2a was determined with 0.5 equiv of I₂ (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 I₂, no desired product 70 was obtained only recovering the unreacted styrene (entry 8). These results clearly indicated that I₂ 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 NH₄I and reaction 75 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).

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, 510640, P. R. China

⁴⁵ E-mail: gqyuan@scut.edu.cn, liyw@scut.edu.cn † Electronic Supplementary Information (ESI) available: Detailed experimental procedures, characterization of products, and NMR spectral charts. See DOI: 10.1039/b000000x/

Table 1 Effect of various factors on the reaction.

Ph 1.0 mmol 1a	+ $\stackrel{O}{\stackrel{H}{\underset{1.0 \text{ mL}}{}}}$ + H_2O $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{\underset{130 ^{\circ}C, 24 \text{ h}}{}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$ Ph $\stackrel{\text{NH}_4I (4.0 \text{ equiv})}{{\underset{130 ^{\circ}C, 24 \text{ h}}{}}}$.SO ₂ Me
Entry	Variation from the standard conditions	Yield/% ^a
1	none	98
2	Bu ₄ NI instead of NH ₄ I	0
3	KI instead of NH ₄ I	0
4	NH ₄ Br instead of NH ₄ I	0
5	2.0 equiv of I2 instead of NH4I	0
6	0.5 equiv of I2 instead of NH4I	15
7	0.5 equiv of I ₂ + 0.5mL NH ₃ .H ₂ O instead of	17
	NH ₄ I	
8	10 mol % I2 instead of NH4I	0
9	HI instead of NH ₄ I	8
10	1.0 equiv of NH ₄ I	0
11	100 °C instead of 130 °C	0
12	120 °C instead of 130 °C	39
13	without adding H ₂ O	12
14 ^b	under N ₂ atmosphere	91
15 ^c	adding TEMPO	0
16 ^c	adding BHT	0
^a Determined by ¹ H 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 5 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 ¹⁰ 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 (20,2q). Polyaryl ¹⁵ 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).
- ²⁰ 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
- ²⁵ 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 ³⁰ 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 $_{35}$ consistent with the previous studies by Jiang 4b and Li. 5c

 Table 2 Scope of alkene substrates.^a



⁴⁰ ^a Reaction conditions: alkene (1 mmol), NH₄I (4.0 equiv), H₂O (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



^aReaction 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

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 ⁵⁵ yield (Table 1, entry 14), indicating that the oxygen atom of 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 determinent and the labeling experiment with DMSO d

- ⁵ DMSO. The deuterium labeling experiment with DMSO-d₆ (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-
- ¹⁰ 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.
- ¹⁵ 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
- ²⁰ 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 sulforylation of 1a.

- Based on the above results, a plausible reaction ³⁰ mechanism is proposed in Scheme 2. First, the radical initiator I₂ and precursor MeSH are generated through a series of reactions, as shown in equations 4-6.⁹⁻¹¹ Then, I₂ is decomposed to form iodine radical (eq 7),¹² which attacks on MeSH to give a methylthiyl radical MeS· (eq 8).¹³ ³⁵ 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
- ⁴⁰ further oxidized by DMSO¹⁵ and H₂O₂ resulting from selfcoupling 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 ⁴⁵ 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

⁵⁰ the details of reaction mechanism and applications in organic synthesis are currently underway in our laboratory.

$$S_{+} 2 H \longrightarrow 5S_{+} I_2 H \longrightarrow 5S_{+}$$

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

$$I \rightarrow 2I$$
 (7)

I• + CH₃SH → CH₃S• + HI



Scheme 2 Proposed reaction mechanism.

We thank the National Natural Science Foundation of 55 China (21172079, 21322606, and 21436005), and Guangdong Natural Science Foundation (10351064101000000) for financial support.

Notes and references

(

- For reviews, see: (a) B. A. Frankel, M. Bentley, R. G. Kruger and D.
 McCafferty, J. Am. Chem. Soc., 2004, **126**, 3404; (b) M.V. Reddy, N.
 M. Iqbal, K. A. Robell, A. D. Kang and E. P. Reddy, J. Med. Chem., 2008, **51**, 86; (c) J.-N. Desrosiers and A. B. Charette, Angew. Chem., Int. Ed., 2007, **46**, 5955.
- 2 (a) M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli and M.
 ⁶⁵ Montanucci, J. Org. Chem., 1983, 48, 4795; (b) P. Caramella, E.
 Albini, T. Bandiera, A. C. Coda, P. Grünanger and F. M. Albini, Tetrahedron, 1983, 39, 689.
- 3 A. Battace, T. Zair, H. Doucet and M. Santelli, *Synthesis*, 2006, 20, 3495.
- 70 4 (a) N. Taniguchi, *Synlett.* 2011, 9, 1308; (b) X. Li, Y. Xu, W. Wu, C. Jiang, C. Qi and H. Jiang, *Chem. Eur. J.*, 2014, 20, 1; (c) M. Bian, F. Xu and C. Ma, *Synthesis.* 2007, 19, 2951; (d) S. S. Labadie, *J. Org. Chem.*, 1989, 54, 2496; (e) F. Huang and R. A. Batey, *Tetrahedron*, 2007, 63, 7667; (f) A. Kar, I. A. Sayyed, W. F. Lo, H. M. Kaiser, M.Beller and M. K. Tse, *Org. Lett.*, 2007, 9, 3405.
- 5 (a) S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu and A. Lei, *Chem. Commun.*, 2014, **50**, 4496; (b) Y. Xu, X. Tang, W. Hu, W. Wu and H. Jiang, *Green Chem.*, 2014, **16**, 3720; (c) X. Li, X. Xu and C. Zhou, *Chem. Commun.*, 2012, **48**, 12240; (d) S. Liang, R. Zhang, G. Wang,
- S. Chen and X. Yu, *Eur. J. Org. Chem.*, 2013, 7050; (e) P. Katrun, S. Chiampanichayakul, K. Korworapan, M. Pohmakotr, V. Reutrakul, T. Jaipetch and C. Kuhakarn, *Eur. J. Org. Chem.*, 2010, 5633.
- 6 Y. Jiang and T.-P. Loh, *Chem. Sci.*, DOI: 10.1039/c4sc01901f.
- 7 B. Giese, Angew. Chem., Int. Ed., 1983, 22, 753.
- 85 8 See the Surporting Information for details.
 - 9 A. Smith and R. P. Calvert, J. Am. Chem. Soc., 1914, 36, 1363.
 - 10 H. Gilman and J. Eisch, J. Am. Chem. Soc., 1955, 77, 3862.
 - 11 V. J. Traynelis and W. L. Hergenrother, J. Org. Chem., 1964, 29, 221.
 - 12 J. Gromada and K. Matyjaszewski, Macromolecules, 2001, 34, 7664.
- 90 13 A. Fava, G. Reichenbach and U. Peron, J. Am. Chem. Soc., 1967, 89, 6696.
 - (a) C. Walling and W. Helmreich, J. Am. Chem. Soc., 1959, 81, 1144;
 (b) L. Lunazzi, G. Placucci and L. Grossi, J. Chem. Soc., Perkin Trans. 2, 1981,703.
- 95 15 S. S. Jr and H. R. Hays, J. Org. Chem., 1958, 23, 2028.
 - 16 (a) E. Brillas and I. Sirés, *Chem. Rev.*, 2009, **109**, 6570; (b) J. Kiwi, K. Kalyanasundaram and M. Graetzel, *Struct. Bonding (Berlin)*, 1982, **49**, 39.

(8)