# Green Chemistry

## Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: K. Xu, L. Li, W. Yan, Y. Wu, Z. Wang and S. Zhang, *Green Chem.*, 2017, DOI: 10.1039/C7GC01847A.



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 **author guidelines**.

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 ethical guidelines, outlined in our <u>author and reviewer resource centre</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.



rsc.li/green-chem

### Journal Name



# Dual roles of sulfonyl hydrazides in the catalyst-free sulfonylation of unsaturated benzylic alcohols in water

Received 00th January 20xx, Accepted 00th January 20xx

Kun Xu, Lijun Li, Wen Yan, Yuanyuan Wu, Zhiqiang Wang and Sheng Zhang\*

DOI: 10.1039/x0xx00000x

www.rsc.org/

An atom-economic sulfonylation of unsaturated benzylic alcohols in water is described. In this transformation, dual roles of sulfonyl hydrazides serving as both sulfonyl source and reductant have been demonstrated, which enabled a facile and green method to synthesize alkyl sulfones from unsaturated benzylic alcohols. Moreover, this approach provides a practical access to deuterated alkanes from the corresponding alkenes by employing the combination of sulfonyl hydrazides and the solvent D<sub>2</sub>O.

Atom economy is regarded as one of the most important principles of green chemistry, which generally requires maximal incorporation of all materials used in the process into the final product.<sup>1</sup> In other words, fully utilizing an organic reagent in the transformations is the ultimate goal of organic chemists. Given this requirement in modern organic chemistry, recent efforts have focused on the exploitation of multiple functions of a versatile reactant in a single reaction.<sup>2</sup> Among various synthetically useful reagents, sulfonyl hydrazides have been extensively explored to construct sulfonyl- or sulfenylcontaining compounds,<sup>3-5</sup> which are prevalent in diverse biologically valued molecules.<sup>6</sup> However, in most of these protocols, sulfonyl hydrazides were always treated as the sulfonylating or sulfenylating reagents, the functions of hydrazine moiety in sulfonyl hydrazides were not used simultaneously. In 2014, the dual functions of sulfonyl hydrazides was reported by Wan and coworkers in a cobaltcatalyzed reaction to access fully substituted pyrazoles (Scheme 1).<sup>2a</sup> Dispite this advance, the development of new reactions exploiting the multifunctions of sulfonyl hydrazides in a green manner is still highly desired.



Scheme 1 The dual roles of sulfonyl hydrazides in the synthesis of substituted pyrazoles.

Sulfonylation of alcohols as a conventional approach to construct sulfones typically needs preactivation of hydroxy group into halide or mesylate.<sup>7</sup> To avoid the tedious steps, direct sulfonylation of alcohols catalyzed by Pd(II) or Fe(III) was disclosed by Chandrasekhar<sup>8</sup> and Sreedhar groups<sup>9</sup>, respectively (Scheme 2a). Tian and coworkers also described a byproduct-catalyzed sulfonylation of benzylic and allylic alcohols using sulfinyl chlorides as the sulfonylating reagents (Scheme 2b).<sup>10</sup> Promoted by these backgrounds together with the reported results that sulfonyl hydrazides could serve as reductants,<sup>11</sup> we envisioned that the dual roles of sulfonyl hydrazides would be achieved for the reaction with unsaturated alcohols (Scheme 2c). Herein, we report a catalyst



College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, 473061 P. R. China

E-mail: shengzhang@nynu.edu.cn

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

#### COMMUNICATION

Journal Name

free sulfonylation and simultaneous reduction of unsaturated benzylic alcohols with sulfonyl hydrazides to furnish a wide array of alkyl sulfones in water.<sup>12</sup> Moreover, this protocol also provides a practical route to access deuterated alkanes from the corresponding alkenes with the combination of sulfonyl hydrazides and the solvent  $D_2O$ .

Initially, the solvent effect on the direct sulfonylation of unsaturated alcohol 1a with p-toluene sulfonhydrazide 2a was investigated. As shown in the Table 1, the protonic solvent ethanol and water proved to be superior to other solvents (3aa). To conduct the reaction in a greener version, the environmentally benign water was chose as the optimal solvent. With these optimized conditions identified, the scope of benzylic alcohols was examined in the direct sulfonylation reaction (Table 1). Firstly, a range of readily accessible orthohydroxyl substituted homoallylic alcohols were tested. It was found that the reaction performance is largely independent from the arene substitution pattern in the substrates. For instance, electron-rich substituents as well as bromide group at the aryl group are well tolerated delivering the products 3aa-3fa with moderate to excellent yields. Ortho-amino substituted substrate also tolerated well to furnish the product 3ga in 87% yield. Changing the hydroxyl group to para position led to formation of product 3ha in 73% yield. Replacing of hydroxyl group with dimethyl amino group gave the corresponding product 3ia in 75% yield.



<sup>*a*</sup> The reaction of **1** (0.5 mmol) with **2a** (1 mmol) was performed in water at 120  $\,^{\circ}$  for 12 h. The product was isolated by column chromatography.

Subsequently, we probed the generality of sulfonyl hydrazides in the reaction with the homoallylic alcohol **1a**. As shown in Table 2, the reaction was tolerant of electronically and sterically diverse substituents on the phenyl ring, giving sulfones **3ab-3am** in 65-90% yields. The multiple substituted sulfonyl hydrazides proved to be compatible in this reaction, providing the desired products **3an** and **3ao** in 62% and 67% yields, respectively. Additionally, the fused ring substituted product **3ap** was also readily afforded in 83% yield. It is noteworthy that aliphatic hydrazide was also a suitable



#### **Table 2** The scope of sulfonyl hydrazides in the direct sulfonylation.<sup>a</sup>



 $^{a}$  The reaction of **1a** (0.5 mmol) with **2** (1 mmol) was performed in water at 120  $\,^{\circ}$ C for 12 h. The product was isolated by column chromatography.

In order to expand the utility of this methodology, homopropargyl, allyl and non-allyl alcohols were also tested under the standard conditions (Scheme 3). For homopropargyl alcohol 4, the reaction underwent smoothly to give alkyl sulfone **3aa** in 63% yield; In the case of non-allylic alcohol **5**, the corresponding sulfone **6** was obtained in 71% yield. With respect to the allyl alcohol **7**, an unexpected reductive dehydroxy alkane **8** was obtained with 80% yield. This exceptional result might be attributed to the conjugation effect of the olefin moiety.

Published on 01 August 2017. Downloaded by University of Windsor on 01/08/2017 16:28:33

Journal Name

7

Scheme 3 Other types of substrates.

3aa, 63% yield

6, 71% yield

OH

8, 80% yield

#### COMMUNICATION

nemistry Accepted



To shed light on the reaction mechanism, control experiments were performed as shown in Scheme 4. First, the reactant sulfonyl hydrazide was replaced with sulfinic acid 9 to investigate the possible intermediate in the reaction (Scheme 4a). A direct sulfonylation product 10 was detected without reduction of the carbon-carbon double bond in the substrate, even under the hydrogen atmosphere. These results illustrate that the sulfinic acid is a key intermediate in the sulfonylation process, while the hydrazine moiety in sulfonyl hydrazide would play an important role in the reduction process. To identify the reduction role of sulfonyl hydrazide, deuteration reaction were subsequently perfomed. When unsaturated alcohol 1a was reacted with deuterated sulfonyl hydrazide 11 in H<sub>2</sub>O, product **3aa** was obtained in 82% yield (Scheme 4b); when unsaturated alcohol 1a was reacted with sulfonyl hydrazide **2a** in  $D_2O$ , deuterated product **d<sup>2</sup>-3aa** was obtained in 81% yield (Scheme 4c). These results may attribute to the H,D-exchange between the reactive intermediates with water.

TsNHNH

2a

2a

22

120 °C

H<sub>2</sub>O

120 °C

H<sub>2</sub>O 120 °C



On the basis of the control experiments and the related report,<sup>4a,5a</sup> a plausible reaction pathway for the formation of **d<sup>2</sup>-3aa** was proposed (Scheme 5). Initially, the tosylhydrazide is decomposed into active species sulfinic acid (TsH) and diimide *via* an elimination process under high temperature. The *in-situ* generated TsH and diimide could readily undergo H,D-exchange with D<sub>2</sub>O to give TsD and d<sup>2</sup>-diimide. Protonation of alcohol **1a** gives intermediate **12**, which undergoes a

subsequent nucleophilic substitution reaction Arandonira simultaneous reduction reaction by d<sup>2</sup>ປີທີ່ທຳປີປ<sup>2</sup> ອີບິດຊີທິບ<sup>2</sup> ຖືກຳລຳ product **d<sup>2</sup>-3aa**.



#### Conclusions

In conclusion, dual roles of sulfonyl hydrazide as sulfonyl source and reductant have been achieved in the reaction with unsaturated benzylic alcohols in water. The environmentalbenign medium, catalyst-free reaction conditions, and high atom-economy make this reaction a green and practical approach to sulfones synthesis. Moreover, this protocol also provides a straightforward route to access deuterated alkanes from the corresponding alkenes by using the combination of sulfonyl hydrazides and the solvent  $D_2O$ .

#### Acknowledgements

We are grateful to the Natural Science Foundation of China (21602119, U1504208), and acknowledged the financial support from Nanyang Normal University (ZX2017016, QN2017037).

#### Notes and references

- (a) B. M. Trost, Science, 1991, 254, 1471; (b) B. M. Trost, Angew. Chem. Int. Ed., 1995, 34, 259; (c) P. T. Anastas and J. C. Warner, in Green Chemistry: Theory and Practice, Oxford University Press, New York, 1998; (d) B. M. Trost, Acc. Chem. Res., 2002, 35, 695; (e) C.-J. Li and B. M. Trost, Proc. Natl. Acad. Sci. U. S. A., 2008, 105, 13197. (f) P. T. Anastas and N. Eghbali, Chem. Soc. Rev., 2010, 39, 301. (g) C.-J. Li and P. T. Anastas, Chem. Soc. Rev., 2012, 41, 1413.
- 2 (a) J. Zhang, Y. Shao, H.-X. Wang, Q. Luo, J.-J. Chen, D.-M. Xu and X.-B. Wan, Org. Lett., 2014, 16, 3312 (b) H. Bounar, Z.-H. Liu, L. Zhang, X.-X. Guan, Z.-L. Yang, P.-Q Liao, X.-H. Bi and X.-Q. Li, Org. Biomol. Chem., 2015, 13, 8723; (c) J.-J. Zhang, Q.-H. Gao, X. Wu, X. Geng, Y.-D. Wu and A.-X. Wu, Org. Lett., 2016, 18, 1686.
- 3 Forming hydrazones and heterocycles, see: (a) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560; (b) J. Barluenga and C. Valdés, *Angew. Chem. Int. Ed.*, 2011, **50**, 7486; (c) R. O. Hutchins and M. K. Hutchins, in Comprehensive Organic Synthesis, Vol. 8 (Eds.: B. M. Trost and I. Fleming), Pergamon, Oxford, 1991, p. 327.
- Using sulfonyl hydrazides as sulfonyl reagents, see: (a) A. Deavin and C. W. Rees, J. Chem. Soc., 1961, 4970; (b) T. Taniguchi, A. Idota and H. Ishibashi, Org. Biomol. Chem., 2011, 9, 3151; (c) X.-Q. Li, X.-S. Xu and C. Zhou, Chem. Commun., 2012, 48, 12240; (d) S. Tang, Y. Wu, W.-Q. Liao, R.-P. Bai, C. Liu and A.-W. Lei, Chem. Commun., 2014, 50, 4496;

**Green Chemistry Accepted Manuscript** 

#### Journal Name

View Article Online DOI: 10.1039/C7GC01847A

(e) K. Xu, V. Khakyzadeh, T. Bury, and B. Breit, *J. Am. Chem.* Soc., 2014, **136**, 16124; (f) Y.Yang, L. Tang, S. Zhang, X.-F. Guo, Z.-G. Zha and Z.-Y. Wang, *Green Chem.*, 2014, **16**, 4106; (g)

COMMUNICATION

Z.-Z. Chen, S. Liu, W.-J. Hao, G. Xu, S. Wu, J.-N. Miao, B. Jiang, S.-L. Wang, S.-J. Tu and G.-G. Li, *Chem. Sci.*, 2015, **6**, 6654; (*h*) G. C. Senadi, B.-C. Guo, W.-P. Hu and J.-J. Wang, *Chem. Commun.*, 2016, **52**, 11410. (*i*) L. Tang, Y. Yang, L.-X. Wen, X.-K. Yang and Z.-Y. Wang, *Green Chem.*, 2016, **18**, 1224. (*j*) F.-L. Yang and S.-K. Tian, *Tetrahedron Lett.*, 2017, **58**, 487.

- 5 Using sulfonyl hydrazides as as sulfenylating reagents, see: (a)
  F.-L. Yang and S.-K. Tian, Angew. Chem. Int. Ed., 2013, 52, 4929; (b) R. Singh, D. S. Raghuvanshi and K. N. Singh, Org. Lett., 2013, 15, 4202; (c) F.-L. Yang, F.-X. Wang, T.-T. Wang, Y.-J. Wang and S.-K. Tian, Chem. Commun., 2014, 50, 2111; (d)
  X. Zhao, L.-P. Zhang, T.-J. Li, G.-Y. Liu, H.-M. Wang and K. Lu, Chem. Commun., 2014, 50, 13121; (e) A. K. Bagdi, S. Mitra, M. Ghosh and A. Hajra, Org. Biomol. Chem., 2015, 13, 3314; (f) X. Zhao, Z.-J. Deng, A.-Q. Wei, B.-Y. Li and K. Lu, Org. Biomol. Chem., 2016, 14, 7304; (g) Y. Yang, S. Zhang, L. Tang, Y.-B. Hu, Z.-G. Zha and Z.-G. Wang, Green Chem., 2016, 18, 2609.
- 6 For sulfur containing drugs, see: (a) E. A. Ilardi, E. Vitaku and J. T. Njardarson, J. Med. Chem., 2014, 57, 2832; (b) M.-H. Feng, B.-Q.Tang, S.-H. Liang and X.-F. Jiang, Curr Top Med Chem., 2016, 16, 1200.
- 7 (a) J. K. Crandall and C. Pradat, J. Org. Chem., 1985, 50, 1327;
  (b) T. Murakami and K. Furusawa, Synthesis, 2002, 4, 479; (c)
  Y.-H Ju, D. Kumar and R. S. Varma, J. Org. Chem., 2006, 71, 6697; (d) F. Zhao, Q. Tan, F.-H. Xiao, S.-F. Zhang and Guo-Jun Deng, Org. Lett., 2013, 15, 1520;
- 8 S. Chandrasekhar, V. Jagadeshwar, B. Saritha and C. Narsihmulu, *J. Org. Chem.*, 2005, **70**, 6506.
- 9 M. A. Reddy, P. S. Reddy and B. Sreedhar, *Adv. Synth. Catal.*, 2010, **352**, 1861.
- 10 H.-H. Li, D.-J. Dong, Y.-H. Jin and S.-K. Tian, *J. Org. Chem.*, 2009, **74**, 9501.
- Using sulfonyl hydrazides as reductants, see: (a) N. J. Cusack, C. B. Reese, A. C. Risius and B. Roozpeikar, *Tetrahedron*, 1976, **32**, 2157; (b) D. J. Pasto and R. T. Taylor, *Org. React.*, 1991, **40**, 91; (c) K. R. Buszek and N. Brown, *J. Org. Chem.*, 2007, **72**, 3125; (d) B. J. Marsh and D. R. Carbery, *J. Org. Chem.*, 2009, **74**, 3186.
- Other method for alkyl sulfones synthesis, see: (a) X.-W. Feng, J. Wang, J. Zhang, J. Yang, N. Wang and X.-Q. Yu, Org. Lett., 2010, 12, 4408; (b) C. S. Richards-Taylor, D. C. Blakemoreb and M. C. Willis, Chem. Sci., 2014, 5, 222; (c) W.-C. Yang, P. Dai, K. Luo and L. Wu, Adv. Synth. Catal., 2016, 358, 3184; (d) P. K. Shyam and H.-Y. Jang, J. Org. Chem., 2017, 82, 1761; (e) M. W. Johnson, S. W. Bagley, N. P. Mankad, R. G. Bergman, V. Mascitti and F. D. Toste, Angew. Chem. Int. Ed., 2014, 53, 4404; (f) A. Shavnya, K. D. Hesp, V. Mascitti and A. C. Smith, Angew. Chem. Int. Ed., 2015, 54, 13571; (g) J.-J. Chen, W. Guo, Z.-R. Wang, L. Hu, F. Chen and Y.-Z. Xia, J. Org. Chem., 2016, 81, 5504.



254x190mm (96 x 96 DPI)