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# Catalyst-free regioselective sulfonylation of phenoxazine with sulfonyl hydrazides in H<sub>2</sub>O/HFIP†

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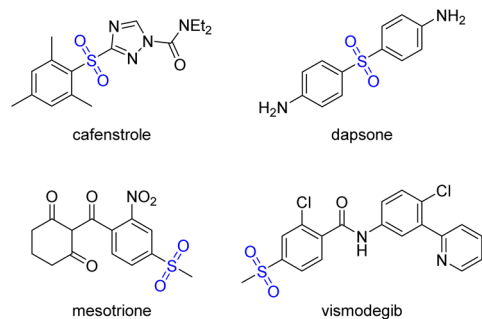
A facile catalyst-free sulfonylation of phenoxazine with sulfonyl hydrazides was efficiently developed in H<sub>2</sub>O/HFIP without any catalyst. This metal- and catalyst-free protocol is suitable for aromatic and aliphatic reagents to afford the corresponding sulfones in moderate to high yields. A gram-scale experiment was performed to assess the practicability of the method.

## Introduction

Green and sustainable chemistry represents a transformative approach in modern chemical practices, focusing on minimizing the use and generation of harmful substances while efficiently synthesizing target products.<sup>1</sup> To achieve this goal, chemists have made remarkable strides in developing innovative approaches, particularly in metal-free synthesis<sup>2</sup> and aqueous-phase reactions.<sup>3</sup> Metal-free synthesis has gained significant traction in green chemistry for its environmental friendliness and cost-effectiveness. By eliminating the need for often toxic and expensive metal catalysts, this approach reduces both environmental contamination and production costs. Simultaneously, water as a solvent offers many advantages in

chemical processes. Water is not only safe and abundantly available but also non-flammable and non-toxic, making it an ideal medium for sustainable reactions. Thus, conducting sulfonylation reactions in aqueous medium under metal-free conditions is highly anticipated as a green synthesis pathway.

Sulfones are widely distributed in nature products and pharmaceutical drugs,<sup>4</sup> such as cafenstrole, dapsone, mesotrione and vismodegib (Scheme 1).<sup>5</sup> Over the past decades, numerous methodologies have been developed to synthesize sulfones, including oxidation of sulfides,<sup>6</sup> sulfur dioxide insertion,<sup>7</sup> and corresponding cross coupling reactions,<sup>8</sup> *etc.* However, these methods usually do not meet the requirements of green chemistry, as they frequently involve the use of strong oxidants, metal catalysts, or are conducted in organic solvents. Therefore, there is a growing requirement to develop a facile, green, and economical friendly protocol for synthesizing sulfones. Sulfonyl hydrazides are ideal sulfonylation agents due



Scheme 1 Typical examples of sulfones.

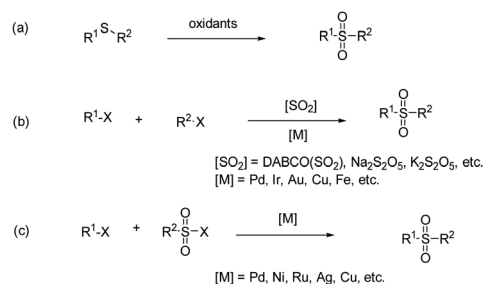
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previous work:



• Metal free • Catalyst free • Gram scale • C3 regioselectivity

Scheme 2 Study on reactions to synthesize sulfones.



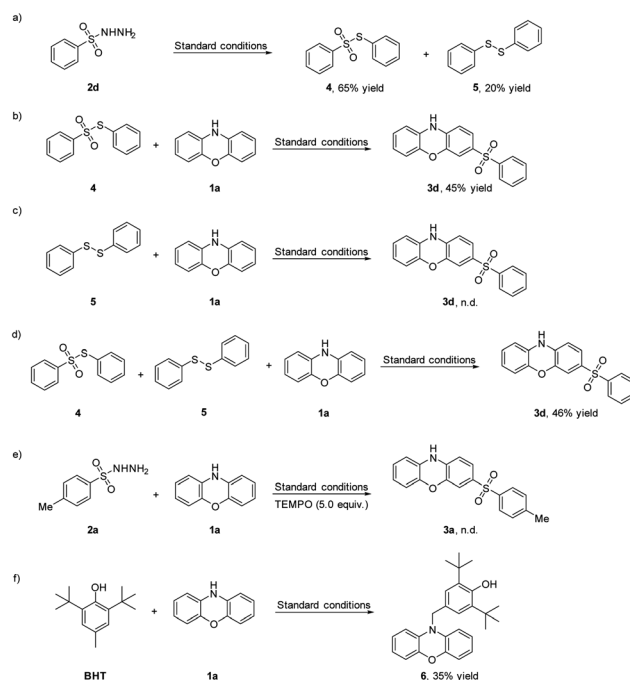
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groups on the phenyl ring provided the corresponding products in 84% and 62% yields, respectively, due to the steric effect. When R were 1-naphthyl (**3q**) and 2-naphthyl (**3p**) groups, the corresponding products were obtained in high yields. Changing R to *N,N*-dimethyl-1-naphthyl-5-amine group (**3r**) was tolerated but resulted in a slightly lower yield. Pleasingly, with a substrate bearing an aliphatic group, *n*-propyl group, target product **3s** was isolated in moderate yield, which increased the significance of this sulfonylation strategy. Moreover, phenothiazine (**3t**) was also compatible with this reaction system, giving the corresponding product in 53% yield.

To demonstrate the synthetic application of this sulfonylation protocol, a gram scale reaction of phenoxazine **1a** and 4-methylbenzenesulfonylhydrazide **2a** was carried out (Table 3). To our delight, the target product **3a** was gained with an 84% isolated yield.

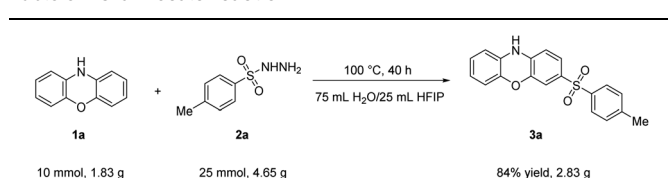
To gain further insight into the reaction mechanism, several control experiments were conducted (Scheme 3). First, when the reaction was carried out under standard conditions without phenoxazine **1a**, *S*-phenyl benzenesulfonylthioate **4** and 1,2-diphenyldisulfane **5** were obtained from benzenesulfonylhydrazide **2d** in 65% and 20% yields, respectively (Scheme 3a). Replacing the substrate **2d** by *S*-phenyl benzenesulfonylthioate **4** provided the corresponding product **3d** in 45% yield (Scheme 3b). However, when the substrate **2d** was replaced by 1,2-diphenyldisulfane **5**, the target product **3d** was not detected (Scheme 3c). Then the substrate **2d** was replaced by *S*-phenyl benzenesulfonylthioate **4** and 1,2-diphenyldisulfane **5**, the target product **3d** was obtained in 46% yield (Scheme 3d). These results indicated that **5** was not involved to generate **3d**. These results indicated that **4** may be generated as an intermediate in the reaction. When the model reaction was conducted in the presence of radical scavenger 2,2,6,6-tetramethylpiperidinoxy (TEMPO, 5.0 equiv.) under standard conditions, no **3a** was detected (Scheme 3e), suggesting that the reaction involves a radical process. When the substrate **2** was replaced by BHT under standard conditions, **6** was obtained in 35% yield, implying N-centered radical was produced (Scheme 3f).

Based on the aforementioned experimental results and previous reports,<sup>10</sup> a plausible mechanism is proposed (Scheme 4). First, two plausible competitive reaction pathways to generate intermediate **7** are proposed. According to control experiments Scheme 3a–c, pathway I is proposed. Initially, benzenesulfonylhydrazide **2d** transforms into minor product **5** and major intermediate **4** which can dissociate into radicals **7**

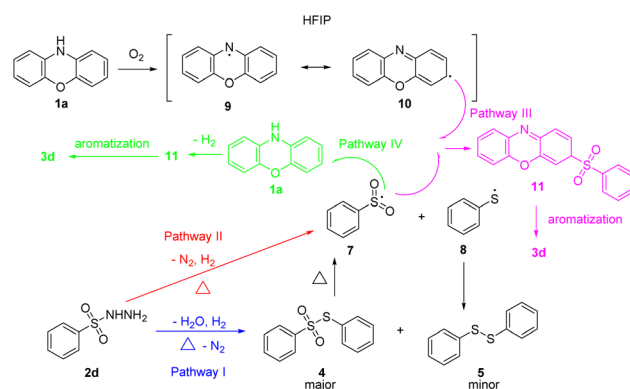


Scheme 3 Control experiments.

and **8** under heating conditions. Due to the yields of product **3d** were decreased in control experiments **3b** and **3d**, competitive pathway II is proposed. Benzenesulfonylhydrazide **2d** transforms into intermediate **7** under heating conditions directly. Afterwards, two plausible competitive reaction pathways to generate product **3d** are also proposed. According to control experiment Scheme 3f, pathway III is proposed. Under oxygen atmosphere, **1a** was oxidized to generate to intermediate **9**. The intermediate **9** transforms into C-centered radical **10** immediately, and then reacts with SO<sub>2</sub>-radical **7** to form transition state **11**. Subsequently, transition state **11** transforms into final product **3d** via aromatization. HFIP plays a role in stabilizing radicals.<sup>11</sup> According to entry 16 in Table 1, competitive pathway IV is proposed. Without oxygen, the SO<sub>2</sub>-radical **7** reacts with **1a** directly to form transition state **11**. Subsequently, transition state **11** transforms into final product **3d** via aromatization.

Table 3 Gram scale reaction<sup>ab</sup>

<sup>a</sup> Reaction conditions: **1a** (10 mmol), **2a** (25 mmol), and solvent 100 mL (75 mL H<sub>2</sub>O/25 mL HFIP) at 100 °C in a Schlenk tube for 40 h. <sup>b</sup> Isolated yield.



Scheme 4 Plausible mechanism.

## Conclusions

In conclusion, we have developed a sulfonylation reaction of phenoxazine with sulfonyl hydrazides in aqueous medium under metal-free conditions. This sulfonylation can be performed under environmentally benign conditions without the need for any catalyst and ligand. A variety of corresponding sulfones were obtained in moderate to high yields. Moreover, a gram scale of the sulfonylation reaction was achieved.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- (a) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford Press, 2000; (b) *The Role of Green Chemistry in Biomass Processing and Conversion*, ed. H. B. Xie and N. Gathergood, Wiley, 2013.
- (a) A. B. Cuenca, R. Shishido, H. Ito and E. Fernández, *Chem. Soc. Rev.*, 2017, **46**, 415; (b) M. Z. Rahman, M. G. Kibria and C. B. Mullins, *Chem. Soc. Rev.*, 2020, **49**, 1887; (c) S. Roy, S. Panja, S. R. Sahoo, S. Chatterjee and D. Maiti, *Chem. Soc. Rev.*, 2023, **52**, 2391.
- (a) C. J. Li, *Chem. Rev.*, 1993, **93**, 2023; (b) Y. Hayashi, *Angew. Chem.*, 2006, **118**, 8281; (c) Y. Jung and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492; (d) C. F. Pan and Z. Y. Wang, *Coord. Chem. Rev.*, 2008, **252**, 736; (e) M. O. Simon and C. J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415; (f) A. Dhakshinamoorthy, A. M. Asiri and H. Garcia, *Chem. Commun.*, 2014, **50**, 12800; (g) Y. N. Li, Y. K. Huang, Y. Gui, J. N. Sun, J. D. Li, Z. G. Zha and Z. Y. Wang, *Org. Lett.*, 2017, **19**, 6416; (h) M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2021, **12**, 4237; (i) B. H. Lipshutz, *Green Chem.*, 2024, **26**, 739.
- (a) M. H. Feng, B. Q. Tang, S. H. Liang and X. F. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200; (b) K. A. Scott and J. T. Njardarson, *Top. Curr. Chem.*, 2018, **376**, 5.
- (a) Y. M. Ma, R. H. Liu, X. Y. Gong, Z. Li, Q. C. Huang, H. S. Wang and G. H. Song, *J. Agric. Food Chem.*, 2006, **54**, 7724; (b) R. Beaudegnies, A. J. F. Edmunds, T. E. M. Fraser, R. G. Hall, T. R. Hawkes, G. Mitchell, J. Schaezter, S. Wendeborn and J. Wibley, *Bioorg. Med. Chem.*, 2009, **17**, 4134; (c) A. Chakraborty, A. K. Panda, R. Ghosh and A. Biswas, *Arch. Biochem. Biophys.*, 2019, **665**, 107.
- (a) A. Ivachtchenko, E. Golovina, M. Kadieva, O. Mitkin, S. Tkachenko and I. Okun, *Bioorg. Med. Chem.*, 2013, **21**, 4614; (b) R. Fu, W. J. Hao, Y. N. Wu, N. N. Wang, S. J. Tu, G. G. Li and B. Jiang, *Org. Chem. Front.*, 2016, **3**, 1452; (c) N. W. Liu, S. Liang and G. Manolikakes, *Synthesis*, 2016, **48**, 1939.
- (a) G. Y. S. Qiu, K. D. Zhou and J. Wu, *Chem. Commun.*, 2018, **54**, 12561; (b) S. Q. Ye, G. Y. S. Qiu and J. Wu, *Chem. Commun.*, 2019, **55**, 1013; (c) J. Zhang, P. Q. Wang, Y. Z. Li and J. Wu, *Chem. Commun.*, 2023, **59**, 3821.
- (a) C. Shen, P. F. Zhang, Q. Sun, S. Q. Bai, T. S. A. Hor and X. G. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291; (b) Y. Q. Li and Y. H. Fan, *Synth. Commun.*, 2019, **49**, 3227; (c) D. Joseph, M. A. Idris, J. J. Chen and S. Lee, *ACS Catal.*, 2021, **11**, 4169.
- (a) Y. Yang, L. Tang, S. Zhang, X. F. Guo, Z. G. Zha and Z. Y. Wang, *Green Chem.*, 2014, **16**, 4106; (b) L. Tang, Y. Yang, L. X. Wen, X. K. Yang and Z. Y. Wang, *Green Chem.*, 2016, **18**, 1224; (c) Y. Yang, Y. J. Bao, Q. Q. Guan, Q. Sun, Z. G. Zha and Z. Y. Wang, *Green Chem.*, 2017, **19**, 112; (d) F. L. Yang and S. K. Tian, *Tetrahedron Lett.*, 2017, **58**, 487; (e) A. Hosseini, S. Arshadi, S. Sarhandi, A. Monfared and E. Vessally, *J. Sulfur Chem.*, 2019, **40**, 289; (f) S. T. Zhao, K. J. Chen, L. Zhang, W. G. Yang and D. Y. Huang, *Adv. Synth. Catal.*, 2020, **362**, 3516.
- (a) G. C. Senadi, B. C. Guo, W. P. Hu and J. J. Wang, *Chem. Commun.*, 2016, **52**, 11410; (b) Y. Yang, S. Zhang, L. Tang, Y. Hu, Z. Zha and Z. Wang, *Green Chem.*, 2016, **18**, 2609; (c) B. Wang, L. Tang, L. Liu, Y. Li, Y. Yang and Z. Wang, *Green Chem.*, 2017, **19**, 5794; (d) J. Meesin, M. Pohmakotr, V. Reutrakul, D. Soorukram, P. Leowanawat and C. Kuhakarn, *Org. Biomol. Chem.*, 2017, **15**, 3662; (e) B. Wang, Z. C. Yan, L. Y. Liu, J. W. Wang, Z. G. Zha and Z. Y. Wang, *Green Chem.*, 2019, **21**, 205.
- (a) A. A. Folgueiras-Amador, K. Philipps, S. Guilbaud, J. Poelakker and T. Wirth, *Angew. Chem., Int. Ed.*, 2017, **56**, 15446; (b) I. Colomer, *ACS Catal.*, 2020, **10**, 6023; (c) S. Ghosh, Z. W. Qu, S. Pradhan, A. Ghosh, S. Grimme and I. Chatterjee, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115272; (d) W. J. Wang, X. X. Yang, R. H. Dai, Z. X. Yan, J. L. Wei, X. D. Dou, X. Qiu, H. L. Zhang, C. Wang, Y. M. Liu, S. Song and N. Jiao, *J. Am. Chem. Soc.*, 2022, **144**, 13415.

