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Catalyst-free regioselective sulfonylation of phenoxazine with sulfonyl hydrazides in H_2O/HFIP†

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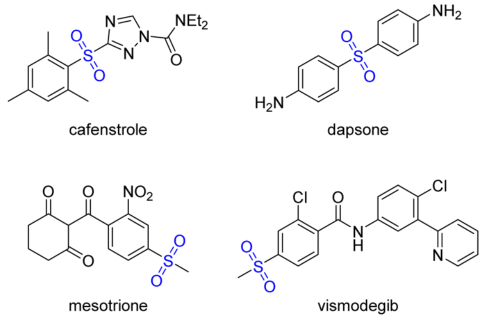
A facile catalyst-free sulfonylation of phenoxazine with sulfonyl hydrazides was efficiently developed in H_2O/HFIP without any catalyst. This metal- and catalyst-free protocol is suitable for aromatic and aliphatic reagents to afford the corresponding sulfones in moderate to high yields. A gram-scale experiment was performed to assess the practicability of the method.

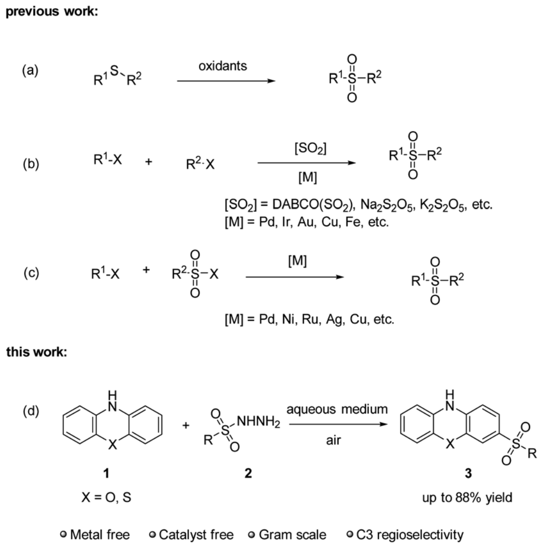
Introduction

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.[1] To achieve this goal, chemists have made remarkable strides in developing innovative approaches, particularly in metal-free synthesis[2] and aqueous-phase reactions.[3] 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.



Scheme 1 Typical examples of sulfones.

Sulfones are widely distributed in nature products and pharmaceutical drugs,[4] such as cafenstrole, dapsone, mesotrione and vismodegib (Scheme 1).[5] Over the past decades, numerous methodologies have been developed to synthesize sulfones, including oxidation of sulfides,[6] sulfur dioxide insertion,[7] and corresponding cross coupling reactions,[8] *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 2 Study on reactions to synthesize sulfones.

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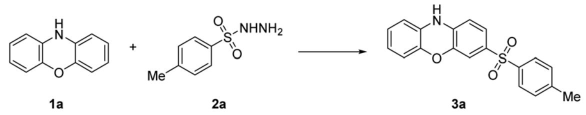
to their ease of handling, stability, moisture compatibility, noncorrosive nature and eco-friendly conversion.[9] To best of our knowledge, the sulfonylation reaction of phenoxazine has not been explored yet. Herein, we reported our recent work to develop a sulfonylation reaction of phenoxazine with sulfonyl hydrazides in aqueous medium under metal-free conditions (Scheme 2). This sulfonylation reaction exhibits a good tolerance to air and water. Notably, in this sulfonylation reaction, regioselective C3–SO_2 bond is formed instead of N–SO_2 bond.

Results and discussion

We commenced our initial trials by selecting phenoxazine **1a** and 4-methylbenzenesulfonohydrazide **2a** as the model substrates (Table 1). The reaction was carried out in water at 100 °C in a Schlenk tube, affording the desired product **3a** in 48% yield (entry 1). When water was replaced with organic solvents (entries 2–10), the yields of **3a** decreased, except when using HFIP (entry 10), which afforded a 65% yield of the target product **3a**. Therefore, we investigated the influence of mixed solvents on the reaction (entries 11–13), H_2O/HFIP (v/v 1.5 : 0.5) was identified as the optimum choice (entry 13), giving **3a** in 85% yield. Changing the temperature did not improve the yield of **3a** (entries 14–15). Conducting this reaction under nitrogen atmosphere negatively affected the yield (entry 16). Thus, the optimal reaction conditions (entry 13) were determined as described below: the sulfonylation reaction was carried out in H_2O/HFIP (v/v 1.5 : 0.5) under air atmosphere at 100 °C in a Schlenk tube.

Table 1 Optimization of reaction conditions[ab]

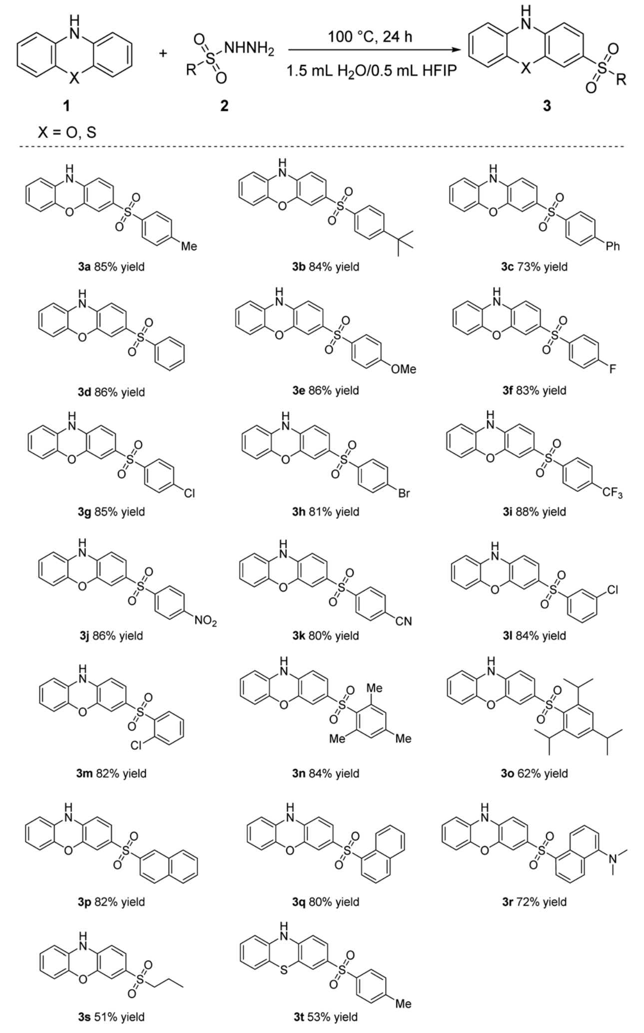


Entry	Solvent	Temp. (°C)	Yield[b] (%)
1	H_2O	100	48
2	CH_3CN	100	18
3	EtOAc	100	15
4	Toluene	100	12
5	DMF	100	n.d.
6	THF	100	11
7	CH_3OH	100	16
8	DMSO	100	8
9	CH_2Cl_2	100	29
10	HFIP	100	65
11	0.5 mL H_2O/1.5 mL HFIP	100	63
12	1.0 mL H_2O/1.0 mL HFIP	100	77
13	1.5 mL H_2O/0.5 mL HFIP	100	85
14	1.5 mL H_2O/0.5 mL HFIP	90	73
15	1.5 mL H_2O/0.5 mL HFIP	110	85
16[c]	1.5 mL H_2O/0.5 mL HFIP	100	52

[a] Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2a** (0.5 mmol), solvent (2.0 mL) in a Schlenk tube for 24 h. [b] Isolated yield. [c] Under nitrogen atmosphere.

With the optimized conditions established, the substrate scope for the sulfonylation reactions was explored (Table 2). Initially, the electronic effect of the substrates was investigated by varying the *para* position substituent groups of the phenyl ring of R. Substrates with hydrogen (**3d**), electron-donating groups, such as methyl (**3a**) *tert*-butyl (**3b**) and methoxy (**3e**) groups, electron-withdrawing groups, such as halogens (**3f–3h**), or strong electron-withdrawing groups, such as trifluoromethyl (**3i**), nitro (**3j**) and nitrile (**3k**) groups provided the corresponding products in 80% to 88% yields. These results demonstrated that the electronic effect has minimal influence on this reaction. Afterwards, the steric effect on the phenyl ring was investigated. A broad range of benzenesulfonohydrazides substituted with a chlorine group in any position (*ortho*, *meta*, *para*) furnished the corresponding sulfone products in high yields (**3g**, **3l**, **3m**). The Substrate bearing a phenyl group (**3c**) affording the target product in 73% yield. Substrates bearing multi-substituted groups, such as tri-methyl (**3n**), tri-isopropyl (**3o**)

Table 2 Substrate scope[ab]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), and solvent 2.0 mL (1.5 mL H_2O/0.5 mL HFIP) at 100 °C in a Schlenk tube for 24 h. [b] Isolated yield.

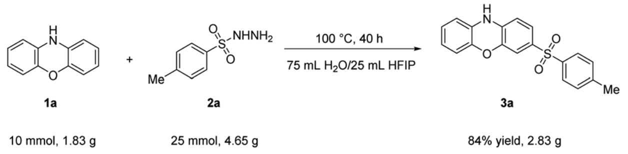
groups on the phenyl ring provided the corresponding products in 84% and 62% yields, respectively, due to the steric effect. When R were 1-naphthyl (**3q**) and 2-naphthyl (**3p**) groups, the corresponding products were obtained in high yields. Changing R to *N*,*N*-dimethyl-1-naphthyl-5-amine group (**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-methylbenzenesulfonohydrazide **2a** was carried out (Table 3). To our delight, the target product **3a** was gained with an 84% isolated yield.

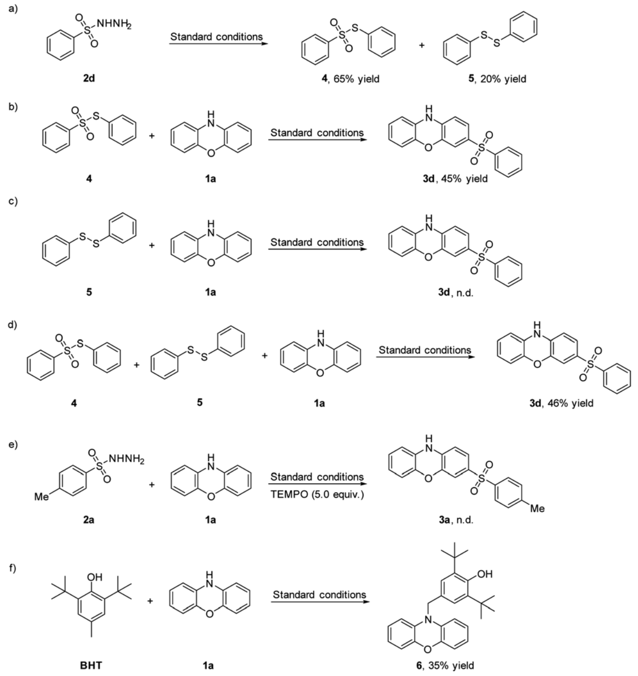
To gain further insight into the reaction mechanism, several control experiments were conducted (Scheme 3). First, when the reaction was carried out under standard conditions without phenoxazine **1a**, *S*-phenyl benzenesulfonothioate **4** and 1,2-diphenyldisulfane **5** were obtained from benzenesulfonohydrazide **2d** in 65% and 20% yields, respectively (Scheme 3a). Replacing the substrate **2d** by *S*-phenyl benzenesulfonothioate **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 benzenesulfonothioate **4** and 1,2-diphenyldisulfane **5**, the target product **3d** was obtained in 46% yield (Scheme 3d). These results indicated **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-tetramethylpiperidinooxy (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,[10] 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, benzenesulfonohydrazide **2d** transforms into minor product **5** and major intermediate **4** which can dissociate into radicals **7** 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. Benzenesulfonohydrazide **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 oxidated to generate to intermediate **9**. The intermediate **9** transforms into C-centered radical **10** immediately, and then reacts with SO_2-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.[11] According to entry 16 in Table 1, competitive pathway IV is proposed. Without oxygen, the SO_2-radical **7** reacts with **1a** directly to form transition state **11**. Subsequently, transition state **11** transforms into final product **3d** *via* aromatization.

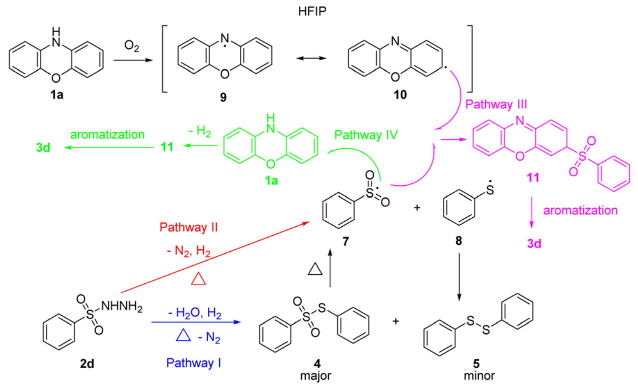
Table 3 Gram scale reaction[ab]



[a] Reaction conditions: **1a** (10 mmol), **2a** (25 mmol), and solvent 100 mL (75 mL H_2O/25 mL HFIP) at 100 °C in a Schlenk tube for 40 h. [b] Isolated yield.



Scheme 3 Control experiments.



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.

Acknowledgements

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