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ARTICLE TYPE

Visible-light-induced selective synthesis of sulfoxides from alkenes and thiols using air as the oxidant†

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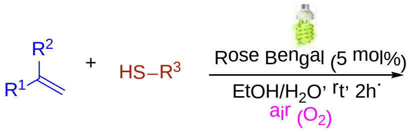
A highly selective synthesis of sulfoxides from alkenes and thiols was established by visible-light photoredox catalysis at room temperature. This metal-free transformation protocol, which uses inexpensive Rose Bengal as the photocatalyst and air as the green oxidant, opens a new door toward the facile and practical construction of sulfoxides.

Sulfoxides are extremely valuable organic compounds, which are not only frequently found in a large number of nature products and pharmacologically active molecules,[1] but also serve as the versatile building blocks for the construction of various important chemicals[2] and therapeutic agents such as antiulcer,[3] antifungal[4] and antiatherosclerotic[5] agents in both academic and industrial communities. Consequently, sulfoxide functionality strongly attracts synthetic pursuit of chemists owing to its structural diversity and remarkable biological functions. Traditionally, the approaches for the synthesis of sulfoxides rely heavily on the oxidation of sulfides using stoichiometric amount of peroxides[6] and hypervalent iodine reagents[7] with the assistance of various transition-metal-catalysts such as iron,[8] vanadium,[9] copper,[10] titanium,[11] cobalt,[12] magnesium,[13] silver[14] and zinc[15] salts. Unfortunately, most of these methods involve the use of some toxic metal reagents, and hazardous oxidants or complex reaction procedures, which led to the generation of a large volume of wastes. Another problematic scenario pertaining to traditional methods is that most of them are usually accompanied by over oxidation of sulfoxide to the sulfone. Recently, the metal-free reactions of alkenes and thiols under dioxygen leading to β-oxy sulfoxides and β-keto sulfoxides were independently reported by Yadav[16] and Lei,[17] in which the co-oxidation of the olefin carbon to form C-O or C=O bond occurred concurrently. In 2016, Klussmann and co-workers reported a methanesulfonic acid (MsOH)-catalyzed selective sulfoxidation of alkenes with thiols for the construction of sulfoxides in the presence of *tert*-butyl hydroperoxide.[18] Very recently, Chi et al. also presented a one-pot selective synthesis of sulfoxides from alkenes and thiols using N-fluorobenzenesulfonimide (NFSI) as a radical initiator and oxidant under nitrogen atmosphere.[19] Gracefully successive as these metal-free methods could be, there is still a great demand for the development of more mild, economic, efficient, and environmentally-benign methods to selectively construct sulfoxides.

Visible-light has long been recognized as an ideal chemical energy to promote the organic synthetic transformations due to its clean, inexpensive, and renewable features. In recent years, especially after 2008, visible-light photoredox catalysis has emerged as a highly versatile and powerful tool for the construction of various valuable organic compounds via the formation of C-C and C-heteroatom bonds under the mild conditions.[20] Very recently, we also presented a new visible-light induced oxysulfonylation of alkenes with sulfinic acids for the synthesis of β-ketosulfones with the assistance of excess amounts of THBP.[21] Molecular oxygen is a green oxidant and oxygen source in view of economic and environmental points. Thus, developing a dioxygen activation by photoredox catalysis for the functionalization of organic molecules has recently attracted significant interests from the synthetic community.[22] As a part of our continued studies focusing on the synthesis of sulfur-containing compounds,[23] herein, we wish to report a facile and efficient visible-light-induced method for the selective construction of sulfoxides via Rose Bengal-catalyzed sulfoxidation of alkenes with thiols using molecular oxygen (air) as the oxidant and oxygen source (eqn (1)).



(1)

Initially, we started the investigation of visible-light-induced sulfoxidation reaction using styrene **1a** and 4-methylbenzenethiol **2a** as the model substrates in the presence of Eosin Y (5 mol %). The model reaction was carried out by exposure to air in CH_3CN/H_2O (v/v = 1/1) under irradiation with 3 white LED lamps. To our delight, the desired product **3a** was obtained in 15% yield after 2 h (Table 1, entry 1). Inspired by this result, a series of metal-free photocatalysts such as Na_2-eosin Y, Eosin B, Rose Bengal, Rhodamine B, and Acridine Red were investigated (Table 1, entry 2-6). Among the above photocatalysts tested, Rose Bengal was demonstrated the highest catalytic activity leading to the desired product **3a** in 53% yield (Table 1, entry 4).

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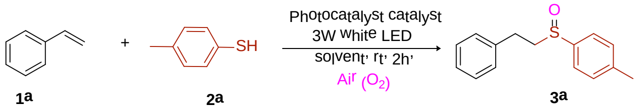
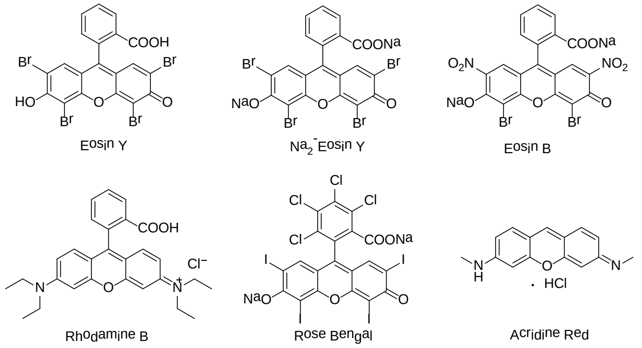
† Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b000000x/

Table 1 Optimization of the reaction conditions



Structures of Photocatalysts:



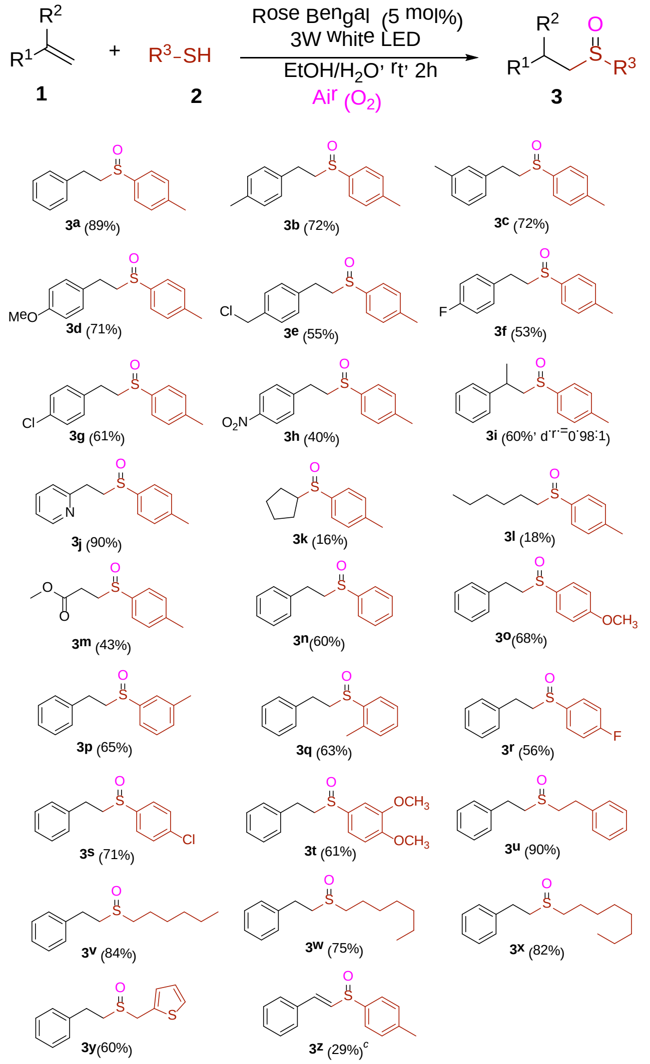
Entry	Photocatalyst (mol%)	Solvent	Yield (%)[b]
1	Eosin Y (5)	CH_3CN/H_2O (1:1)	15
2	Na_2-eosin Y (5)	CH_3CN/H_2O (1:1)	36
3	Eosin B (5)	CH_3CN/H_2O (1:1)	26
4	Rose Bengal (5)	CH_3CN/H_2O (1:1)	53
5	Rhodamine B (5)	CH_3CN/H_2O (1:1)	16
6	Acridine Red (5)	CH_3CN/H_2O (1:1)	14
7	Rose Bengal (5)	DME/H_2O (1:1)	35
8	**Rose Bengal** (5)	**EtOH/H_2O (1:1)**	**89**
9	Rose Bengal (5)	THF/H_2O (1:1)	7
10	Rose Bengal (5)	DCE/H_2O (1:1)	45
11	Rose Bengal (5)	Toluene/H_2O (1:1)	17
12	Rose Bengal (5)	1,4-dioxane/H_2O (1:1)	21
13	Rose Bengal (5)	Acetone/H_2O (1:1)	20
14	Rose Bengal (5)	EtOH/H_2O (2:1)	69
15	RoseBengal (5)	EtOH	32
16	RoseBengal (5)	H_2O	46
17	RoseBengal (1)	EtOH-H_2O (1:1)	17
18	RoseBengal (2)	EtOH-H_2O (1:1)	23
19	RoseBengal (10)	EtOH-H_2O (1:1)	84
20	Rose Bengal (5)	EtOH-H_2O (1:1)	67[c]
21	Rose Bengal (5)	EtOH-H_2O (1:1)	62[d]
22	RoseBengal (5)	EtOH-H_2O (1:1)	0[e]
23	--	EtOH-H_2O (1:1)	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), photocatalyst (1-10 mol %), solvent 2 ml), 3W white LED lamps, rt, air, 2h. DME: 1,2-dimethoxyethane; DCE: 1,2-dichloroethane; THF: tetrahydrofuran; [b] Isolated yields based on **1a**. [c] 3W blue LED lamps. [d] 3W green LED lamps. [e] Without visible-light irradiation.

Further optimization of solvents found that the reaction performed in EtOH/H_2O (v:v = 1/1) gave the best yield (89%) of **3a** (Table 1, entries 7-16). Notably, this visible-light-induced sulfoxidation reaction also proceeded smoothly in water (Table 1, entry 16). The increase or reduction of the amount of photoredox catalysts did not improve the reaction efficiencies (Table 1, entries 17-19). In addition, the desired product was also obtained in 67% and 62% yields when the reaction was conducted under irradiation with 3 W blue and green LED lamps (Table 1, entries 20 and 21). It should be noted that this sulfoxidation reaction did not occur in the absence of visible-light irradiation and only a trace amount of product was detected without photocatalyst (Table 1, entries 22 and 23).

With the optimized conditions in hand, we then examined the generality of this visible-light initiated sulfoxidation of alkenes with thiols (Table 2). Gratifyingly, both electron donating and electron-withdrawing aromatic substituents were tolerated in the terminal alkenes, and the reaction worked well with the styrene bearing electron donating groups (**3a-3h**). It should be noted that a range of functional groups such as methoxy, halogen, chloromethyl and nitro groups were compatible with this reaction, and the corresponding products could be used for further transformation. The reaction of more sterically demanding α-methylstyrene with 4-methylbenzenethiol proceeded smoothly to produce the desired product **3i** in 60% yield. Notably, heterocycle aromatic alkene such as 2-vinylpyridine could also work well in this reaction to give the expected product **3j** in 90% yield. Nevertheless, the corresponding products (**3k-3m**) were obtained in relatively low yields when aliphatic alkenes such as cyclopentene, hex-1-ene, and methyl acrylate were used as the substrates. The scope of this sulfoxidation reaction was further expanded to a series of thiols. In general, aryl thiols bearing electron-rich or -poor groups on the aryl rings were all suitable

Table 2 Results for visible-light inditated sulfoxidation of alkenes with thiols leading to sulfoxides [ab]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Rose Bengal (5.0 mol%), EtOH-H_2O (2 mL, v_1/v_2=1:1), 3W white LED lamps, rt, air, 2h. [b] Isolated yields based on **1**. [c] phenylacetylene was used (0.2 mmol).

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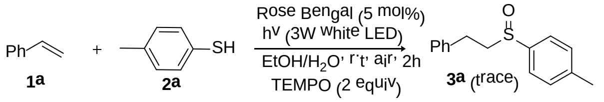
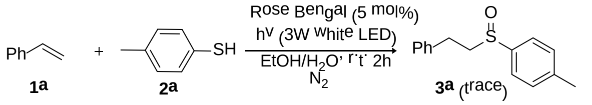
substrates leading to the corresponding products in moderate to good yields (**3n**–**3t**). It was found that various aliphatic thiols with the long aliphatic chains were also well compatible with the reactions to deliver the corresponding products **3u-3x** in good yields. To our delight, heterocycle alkylthiol such as thiophen-2-ylmethanethiol could also be employed in this transformation to give the product **3y** in 60% yield. In addition, when aromatic alkyne such as phenylacetylene was tested in the present reaction system, the corresponding vinylsulfoxide product **3z** was obtained in 29% yield. Nevertheless, only a trace amount of product was detected when aliphatic alkyne such as hex-1-yne was employed in this reaction system.

A series of control experiments were further carried out to better understand the possible mechanism of this transformation. As shown in eqn (2), when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known radical scavenger) was added in the model reaction system, the reaction was extremely inhibited and only a trace amount of product **3a** was detected, suggesting that a radical process might be involved in the present reaction. Moreover, only a trace amount of product **3a** was detected when the model reaction was conducted under nitrogen atmosphere (eqn (3)). Also, ^{18}O-labeling experiment was performed to determine the source of oxygen in sulfoxide. When the reaction of **1a** and **2a** was conducted in the presence of EtOH/H_2O^{18} under air, the corresponding product **3a** was isolated in 80% yield and none of O^{18}-**3a** was detected (eqn (4)). These results indicate that air (O_2) is essential for this reaction and the oxygen atom of sulfoxide came from dioxygen (air). Furthermore, none of the desired product was detected when the reaction of styrene **1a** with 1,2-diphenyldisulfane was carried out under standard conditions, which showed the disulfide might not be involved in this transformation (eqn (5)). In addition, when the model reaction was carried out for 20 min, the desired product **3a** was obtained in 14% yield along with the formation of sulfide **7a** in 74% yield (eqn (6)). Furthermore, when the preformed sulfide **7a** was added separately under the standard conditions, the desired product **3a** was obtained in 77% yield, suggesting that sulfide might be the key intermediate in the present reaction system (eqn (7)).



(2)



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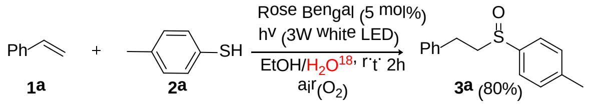

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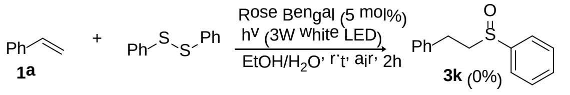

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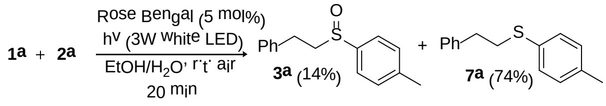

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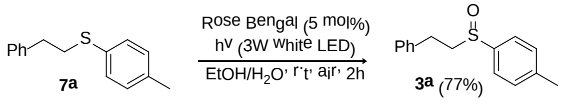


(7)

Moreover, an on/off visible light irradiation experiment was carried out to verify the effect of photo irradiation, and showing that the continuous irradiation of visible light is necessary for promoting the present transformation (Figure 1). In addition, fluorescence quenching experiments were also investigated to prove an energy transfer process between thiol **2a** and Rose Bengal (Stern-Volmer studies) (see Figures 2 and 3). Indeed, it was found that the emission intensity of excited Rose Bengal (RB*) was dramatically diminished along with the increasing of the amount of thiol **2a**. On the contrary, none of such effect was observed when styrene **1a** was added separately (see ESI†).

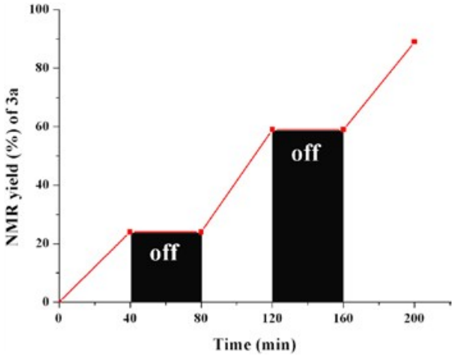


Figure 1. Visible light irradiation on/off experiment

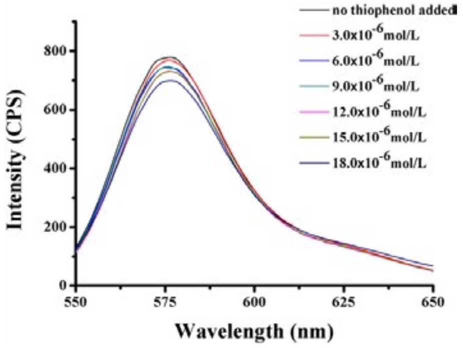


Figure 2 Quenching of Rose Bengal fluorescence emission in the presence of thiol **2a**.

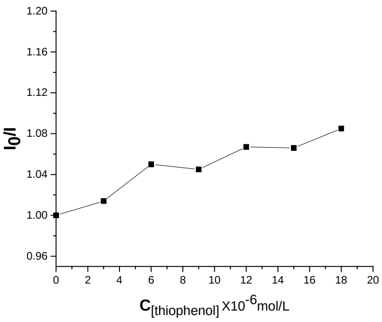
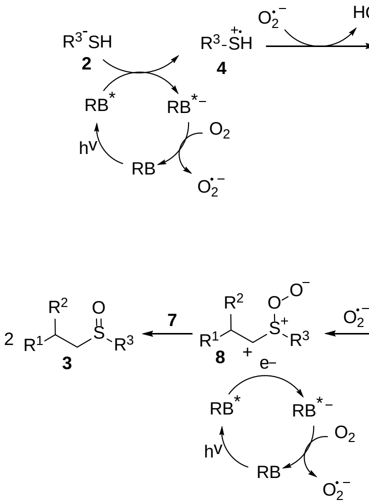


Figure 3. Stern-volmer plots.

On the basis of the above results and referring to previous literatures,[24,25] a possible reaction pathway was thus proposed as shown in Scheme 1. Initially, Rose Bengal was converted to the excited RB* under the visible-light irradiation. Then, a single electron transfer from thiol **2** to RB* afforded the radical cation **4** and $RB^{\bullet-}$ radical anion. The oxidation of $RB^{\bullet-}$ by dioxygen (air) generated the ground state Rose Bengal and $O_2^{\bullet-}$. Subsequently, the radical cation **4** is deprotonated by $O_2^{\bullet-}$ leading to the stabilized thiyl radical **5**. Next, the addition of thiyl radical **5** to alkene **1** would lead the formation of alkyl radical **6**. Furthermore, a hydrogen atom transfer (HAT) process underwent between thiol **2** and alkyl radical **6** to give sulfide intermediate **7** along with the regeneration of the thiyl radical **5**. Finally, the sensitized photooxidation of sulfide **7** with dioxygen produced the desired sulfoxide **3**.[25]



Scheme 1. Postulated reaction pathway

In summary, a rapid and facile approach to the visible-light induced selective sulfoxidation reaction of alkenes with thiols has been developed using air as the environmentally-benign oxidant. A series of biologically important sulfoxides could be conveniently and efficiently prepared in moderate to good yields using of simple and readily available materials. The present method is of great value from both green chemistry and organic synthesis perspectives because of its desirable features including operation simplicity, high atom efficiency, eco-energy source, green solvent, metal-free catalysis and ambient conditions. The application of this powerful system to the synthesis of other sulfur-containing compounds is currently underway in our laboratory.

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