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Manjula Singh, Arvind K. Yadav, Lal Dhar S. Yadav, R.K.P. Singh

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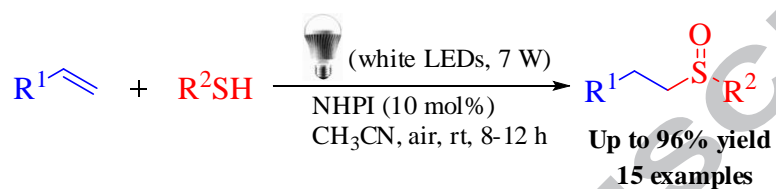
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Graphical Abstract

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Visible-light-activated selective synthesis of sulfoxides via thiol-ene/oxidation reaction cascade

Manjula Singh,^a Arvind K. Yadav,^b Lal Dhar S. Yadav^{b*} R. K. P. Singh^{a*}

^a Electrochemical laboratory, Department of Chemistry, University of Allahabad, Allahabad 211002, India

^b Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211002, India

* Corresponding author. Tel.: +91 532 2500652; fax: +91 532 2460533; E-mail address: ldsyadav@hotmail.com (L.D.S. Yadav)

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ABSTRACT

A convenient, highly selective and metal-free synthesis of sulfoxides from alkenes and thiols using NHPI as an inexpensive and reusable organophotoredox catalyst is reported. The protocol involves radical thiol-ene/oxidation reaction cascade and utilizes visible light and air (O₂) as inexpensive, readily available, non-toxic and eco-sustainable reagents to afford up to 96% yields of the product at room temperature.

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Posner in 1905 reported the radical hydrothiolation of alkenes with thiols,¹ which was later termed as the thiol-ene click (TEC) reaction by Schlaad² due to its efficiency, atom economy and regioselectivity.³ The reaction is synthetically very useful for the formation of carbon-sulfur bonds in various pharmaceuticals and natural products,⁴ polymers and organic materials⁵ as well as ligands and chiral auxiliaries.⁶ The TEC reaction involves the anti-Markovnikov radical addition of thiols to alkenes and provides one of the most common methods for the synthesis of thioethers.⁷ Owing to its high efficiency and desired functional groups compatibility, the reaction is of particular importance in biological and material sciences.⁸

Recently, the research groups of Yoon⁹ and Stephenson¹⁰ have demonstrated novel applications of visible light for the activation of radical thiol-ene reactions employing Ru(bpy)₃(PF₆) and Ru(bpy)₃Cl₂, respectively as the photoredox catalysts. Although these transition metal based complexes are highly efficient visible light photoredox catalysts, they suffer from disadvantages such as high cost, potential toxicity and problematic removal of their undesired traces from products. Alternatively, we have very recently used benzophenone as an inexpensive visible light organophotocatalyst in radical thiol-ene reactions.¹¹

Sulfoxides constitute a class of sulfur compounds that are significantly important in natural products, medicinal chemistry and organic synthesis.¹² Traditional synthetic approaches to sulfoxides rely on the oxidation of sulfides with stoichiometric amounts of oxidants such as peroxides¹³ and hypervalent¹⁴ iodine reagents in the presence of a variety of transition metal catalysts.¹⁵ A few reports are also available on the application of visible light photocatalysis to the oxidation of sulfides to sulfoxides.¹⁶ All these methods require at least two operationally separate steps, that is, the

preparation of sulfides and their oxidation. In addition, most of them use hazardous oxidants and some toxic metal reagents, and also suffer from overoxidation of sulfoxides to sulfones.

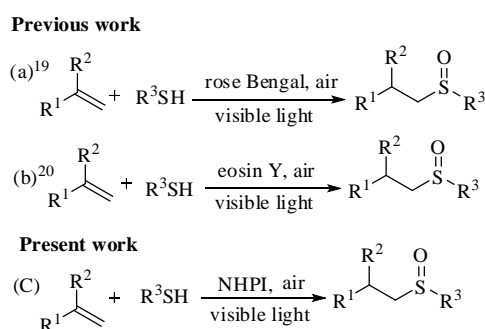
Recently, Klusmann¹⁷ and Chi¹⁸ have reported one-pot synthesis of sulfoxides from alkenes and thiols using methanesulfonic acid (MsOH) and *N*-fluorobenzene sulfonimide (NFSI), respectively. In continuation of this advancement, the research groups of Wang¹⁹ and Aleman²⁰ have demonstrated the elegant synthesis of sulfoxides via thiol-ene/oxidation tandem reaction using rose Bengal (Scheme 1a) and eosin Y (Scheme 1b), respectively as visible light photocatalysts. Although the reactions are efficient and performed under an air atmosphere, both the photocatalysts are unstable and they decompose under visible light irradiation,²¹ hence their recovery from the reaction mixture for reutilization is problematic. This prompted us to go for a stable, more efficient and reusable photocatalyst suitable for thiol-ene/oxidation tandem reaction. Based on the effectiveness of recently reported²² visible light organophotoredox catalyst, NHPI (*N*-hydroxyphthalimide), we opted to use it throughout the present study. NHPI generates PINO (phthalimide-*N*-oxyl) radicals under visible light irradiation.²²

In view of the above points and our current focus on the development of visible light organophotoredox catalyzed new synthetic routes,^{22,23} we assumed that the thiyl radicals could be easily generated photochemically from thiols using NHPI as the catalyst, which would lead to the formation of sulfoxides through thiol-ene reaction and subsequent oxidation with atmospheric oxygen under the same reaction conditions (Scheme 1c). To the best of our knowledge, this is the first example to generate thiyl radicals employing NHPI under visible light irradiation.

To realize our assumed protocol and optimize the reaction conditions, a model reaction was performed with a mixture of

styrene **1a** (1 mmol) and thiophenol **2a** (1 mmol) in acetonitrile (3 mL) in the presence of catalytic amount of NHPI (10 mol%) under an air atmosphere and irradiation with 7 W white LEDs (white light emitting diodes) at room temperature (Table 1). We were delighted to get the desired product sulfoxides **3a** in 89% yield (Table 1, entry 1). We demonstrated that there was no product formation when the reaction was conducted in the dark (Table 1, entry 1 versus 2). Then, the control experiments were carried out, which show that a photocatalyst, NHPI and visible light are essential for the reaction because in the absence of NHPI the desired product was not detected (Table 1, entry 1 versus 3).

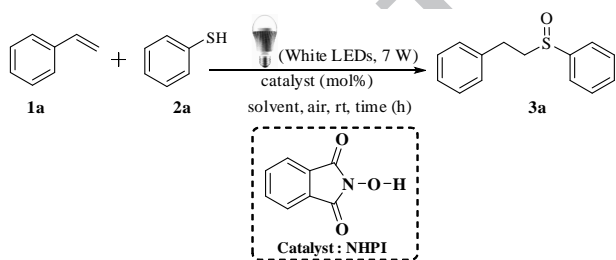
Next, we optimized the reaction for a suitable solvent. It was found that acetonitrile was the best among the tested solvents, viz. DCE, DMF, DMSO and THF to afford the desired product in excellent yield (Table 1, entry 1 versus 4, 5, 6 and 7), hence it was used throughout the present study. The optimum amount of the photocatalyst NHPI required for the reaction was 10 mol%. On decreasing the amount of the catalyst NHPI



Scheme 1. Visible-light-promoted synthesis of sulfoxides.

Table 1

Optimization of reaction conditions^a



| Entry | Reaction conditions | Time (h) | Yield (%) ^b |
|-------|---|----------|------------------------|
| 1 | NHPI (10 mol%), CH ₃ CN, white LEDs | 8 | 89 |
| 2 | NHPI (10 mol%), CH ₃ CN, in the dark | 12 | n.d. |
| 3 | No catalyst, CH ₃ CN, white LEDs | 12 | n.d. |
| 4 | NHPI (10 mol%), DCE, white LEDs | 8 | 58 |
| 5 | NHPI (10 mol%), DMF, white LEDs | 8 | 68 |
| 6 | NHPI (10 mol%), DMSO, white LEDs | 8 | 73 |
| 7 | NHPI (10 mol%), THF, white LEDs | 8 | 65 |
| 8 | NHPI (5 mol%), CH ₃ CN, white LEDs | 8 | 54 |
| 9 | NHPI (15 mol%), CH ₃ CN, white LEDs | 8 | 89 |
| 10 | NHPI (10 mol%), CH ₃ CN, 80 °C | 8 | 53 ^c |
| 11 | NHPI (10 mol%), CH ₃ CN, white LEDs | 8 | 89 ^d |
| 12 | NHPI (10 mol%), CH ₃ CN, white LEDs | 8 | 89 ^e |

^aReaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), NHPI (5–15 mol%), in 3 mL solvent irradiated under an air atmosphere at rt using white LEDs (7 W) for 8–12 h.

^bIsolated yield of the pure product **3a** (For general procedure, see experimental section); n.d.= not detected.

^cReaction was conducted at 80 °C in the dark.

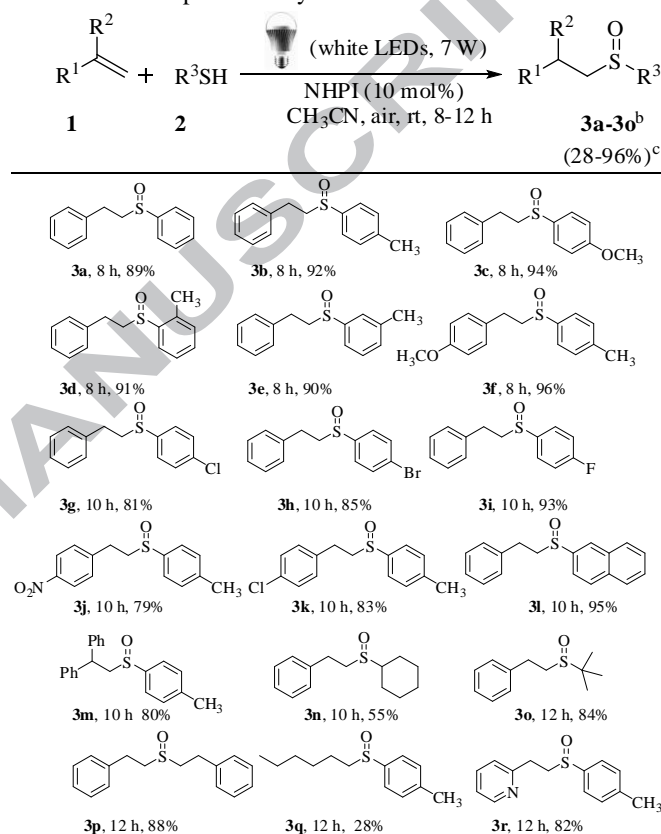
^dCatalyst was recovered in 93% yield.

^eRecovered catalyst was used.

from 10 mol% to 5 mol%, a significant decrease in the yield of **3a** was observed (Table 1, entry 1 versus 8), while an increase in the amount of the photocatalyst from 10 mol% to 15 mol% does not affect the yield of the product (Table 1, entry 1 versus 9). Moreover, the catalyst NHPI also works under thermal conditions but gives a considerably lower yield of the desired product **3a** (Table 1, entry 1 versus 10). Advantageously, the catalyst was recovered in high yield after the reaction (Table 1, entry 11) and reused with the same efficiency (Table 1, entry 12).

Table 2

Substrate scope for the synthesis of sulfoxides^a



^aFor experimental procedure, see ref. 24.

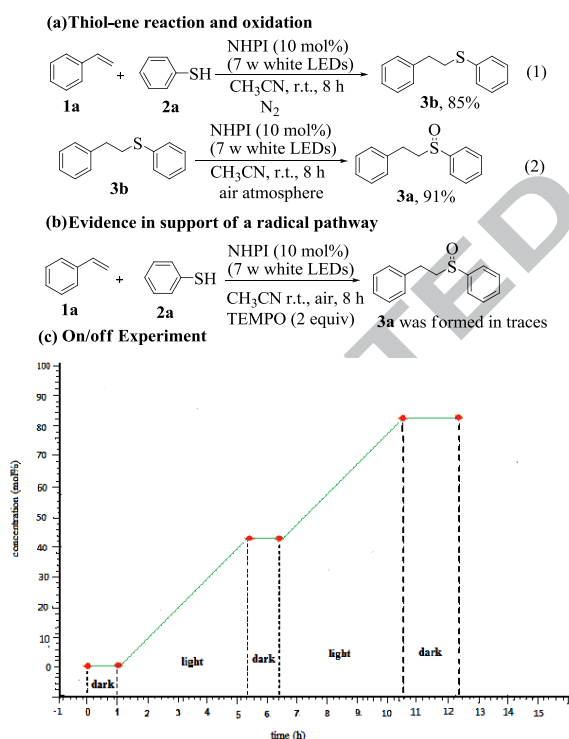
^bAll compounds are known and were characterized by comparison of their spectral data with those reported in the literature.^{17,18,19}

^cYields of isolated pure compounds **3**.

Employing the optimized reaction conditions, we continued to survey the generality and scope of the present protocol across a range of alkenes **1** and thiols **2**, incorporating various functionalities such as Me, OMe, NO₂, F, Cl, and Br (Table 2). The reaction works efficiently in all the cases, however, styrenes and thiophenols bearing an electron-donating group on the aromatic ring appear to react faster and afford marginally higher yields in comparison to those bearing an electron-withdrawing group on the aromatic ring (Table 2, products **3b–3f** versus **3g–3l**). This is probably because an electron-donating group stabilizes the electron-deficient thiyl and benzylic radical intermediates **C** and **D** involved in the reaction (Scheme 2). The reaction was also applicable to aliphatic alkenes and thiols but in this case the yield was lower as compared to styrenes and thiophenols (Table 2, **3n–3q**). The much lower yield (28%) of the sulfoxide **3q** might be due to the formation of less stable alkyl radicals from the corresponding aliphatic alkene as compared to the resonance stabilized benzylic radicals in case of styrenes. Notably, a heterocyclic aromatic alkene also performed well in this reaction to give the product **3r** in 82%

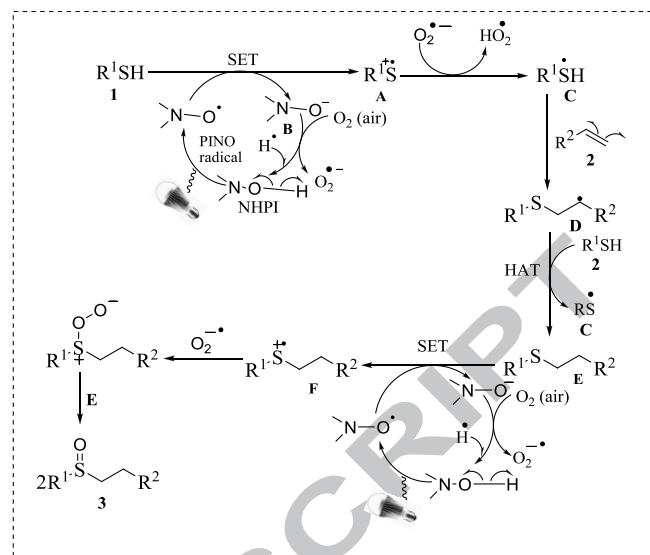
yield. The reaction also worked with a trisubstituted double bond to give a good yield (Table 2, product **3m**).

In order to have insights into a plausible mechanism for the thiol-ene/oxidation tandem reaction, several experiments were further conducted (Scheme 2) besides those summarized in Table 1. The product **3a** was not detected when the model reaction was conducted under a nitrogen atmosphere (Scheme 2a, eqn 1). This indicates that air (O_2) is essential for this reaction. Two independent reactions were carried out to ensure that the two individual steps of the cascade reaction (thiol-ene reaction and oxidation) were involved, and it was observed that only sulfide was formed in 85% yield instead of the sulfoxide **3a** (Scheme 2a, eqn 1). When the sulfide was subjected to the standard reaction conditions in an air atmosphere, the sulfoxide **3a** was formed in an excellent yield (Scheme 2a, eqn 2). Moreover, on addition of a traditional radical scavenger TEMPO (2,2,6,6-tetramethylpiperidyl-1-oxyl) (2 equiv), the desired product **3a** was detected in traces, which indicates that a radical pathway is involved (Scheme 2b). Next, an on/off experiment was conducted to verify the effect of irradiation of visible light in promoting the process, and the graph thus obtained establishes the necessity of continuous irradiation with visible light to realize the present protocol (Scheme 2c).



Scheme 2. Preliminary mechanistic investigations.

On the basis of our above experimental observations and the relevant literature reports,^{19,22} a plausible mechanistic pathway is depicted in Scheme 3. On irradiation with visible light NHPI undergoes photolysis to generate the PINO radical, which upon SET (single electron transfer) with thiol **2** forms a radical cation **A** and PINO anion **B**. The air oxidation of **B** generates NHPI and $O_2^{\cdot-}$. Subsequently, the radical cation **A** might be deprotonated by $O_2^{\cdot-}$ to give the thiyl radical **C**. Next, the addition of thiyl radical **C** to alkene **1** could lead to the formation of alkyl radical **D**, which undergoes a hydrogen atom transfer (HAT) with thiol **2** to afford the sulfide intermediate **E**. Finally, the sulfide **E** could undergo SET with NHPI to form **F**, which reacts with $O_2^{\cdot-}$ and **E** to afford the desired product **3**.



Scheme 3. Plausible mechanism for NHPI catalyzed synthesis of sulfoxides.

In conclusion, we have developed an operationally simple, highly anti-Markovnikov selective and metal-free photocatalytic synthesis of sulfoxides from readily available diversified olefins and thiols. The synthesis proceeds through radical thiol-ene/oxidation tandem reaction in the presence of NHPI, a reusable efficient organophotoredox catalyst, and there is no problem of overoxidation of sulfoxides formed to sulfones. The protocol utilizes air and visible light as inexpensive, clean and eco-sustainable reagents to afford up to 96% yields of sulfoxides at room temperature.

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24. *General procedure for the synthesis of sulfoxides 3:* A mixture of olefin **1** (1 mmol), NHPI (10 mol%), thiol **2** (1 mmol) and acetonitrile (3 mL) was stirred at rt under air and irradiation with visible light (7 W white light emitting diodes) (7 W LEDs) for 8-12 h (Table 2). After completion of reaction (monitored by TLC), water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The

combined organic phase was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The resulting crude product was purified by silica gel chromatography using a mixture of hexane/ethyl acetate (4:1) as eluent to afford an analytically pure sample of product **3**. All the compounds **3** are known and were characterized by comparison of their spectral data with those reported in the literature.¹⁷⁻¹⁹ Characterization data of representative compounds **3** are given below :

Compound **3a**:¹⁹ ¹H NMR (400 MHz, CDCl₃) δ: 7.66-7.62 (m, 2H), 7.57-7.46 (m, 3H), 7.34-7.28 (m, 2H), 7.21-7.14 (m, 3H), 3.11-2.98 (m, 3H), 2.90-2.84 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 143.6, 138.9, 131.0, 129.2, 128.7, 128.5, 126.6, 124.0, 58.2, 28.3; HRMS (EI): calc. for C₁₄H₁₄OS 230.0765, found 230.0761.

Compound **3g**:¹⁹ ¹H NMR (400 MHz, CDCl₃) δ: 7.56 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 3.12-3.01 (m, 3H), 2.90-2.86 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 142.1, 138.5, 137.4, 129.5, 128.7, 128.4, 126.7, 125.5, 58.3, 28.2; HRMS (EI): calc. for C₁₄H₁₃ClOS 264.0376, found 264.0379.

Compound **3p**:¹⁹ ¹H NMR (400 MHz, CDCl₃) δ: 7.23 (t, *J* = 7.2 Hz, 4H), 7.21-7.15 (m, 6H), 3.09-2.98 (m, 4H), 2.91-2.88 (m, 2H), 2.82-2.78 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 137.7, 127.9, 127.5, 125.7, 52.8, 28.0; HRMS (EI): calc. for C₁₆H₁₈OS 258.1078, found 258.1074.

Highlights

- Metal-free one-pot protocol for the synthesis of sulfoxides.
- Visible light-mediated radical thiolene/oxidation tandem reaction.
- Utilization of NHPI as a reusable and efficient organophotoredox catalyst.
- Highly selective synthesis of sulfoxides using air oxidation.

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