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Graphical Abstract

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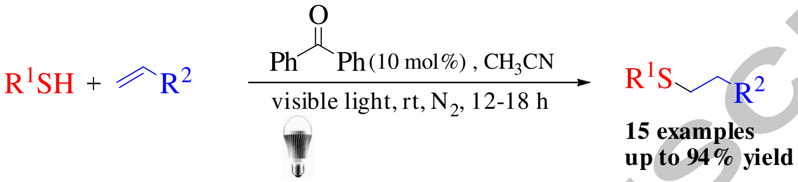

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Visible light photocatalysis with benzophenone for radical thiol-ene reactions

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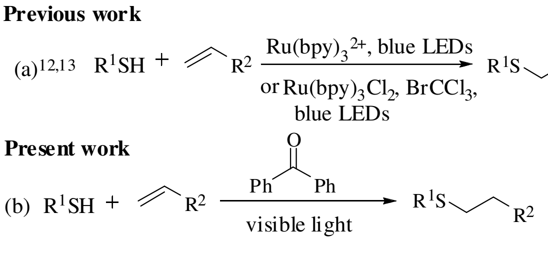
ABSTRACT

We report herein a simple, metal- and oxidant-free visible light promoted strategy for an anti-Markovnikov hydrothiolation of unactivated olefins using benzophenone as an inexpensive photocatalyst at room temperature. Anti-Markovnikov adducts of a wide variety of olefins and thiols are formed in highly regioselective manner and good to excellent yields. The present radical thiol-ene reaction is operationally simple and well tolerates a variety of functional groups.

The hydrothiolation of alkenes is a long known synthetically useful transformation,[1] described as the thiol-ene click (TEC) reaction by Schlaad.[2] The reaction has emerged as a powerful tool for the construction of carbon-sulfur bonds in natural products, pharmaceuticals,[3] polymers and organic materials[4] as well as sulfur-containing ligands and chiral auxillaries.[5] The radical TEC reaction[6] is one of the most common methods for effecting the synthesis of thioethers involving the anti-Markovnikov radical addition of thiols to alkenes (Scheme 1).[7] Particularly, this reaction is of significant importance in materials and biological sciences owing to its high efficiency and compatibility with a variety of functional groups.[8]

Over the past several years, the application of visible light photoredox catalysis for the convenient generation of free radicals has stimulated their targeted use in organic synthesis. Basically, the success of this strategy relies on the pioneering work of the research groups of McMillan,[9] Yoon,[10] and Stephenson,[11] who have used ruthenium and iridium transition metal complexes as efficient photoredox catalysts. Recently, Yoon and co-workers[12] have reported novel applications of visible light photoredox catalysis in radical thiol-ene reactions employing the ruthenium complex Ru(bpz)$_3$(PF$_6$) (Scheme 1a). Stephenson and co-workers[13] have also reported radical thiol-ene reactions under visible light irradiation (blue LEDs) using ruthenium complex Ru(bpy)$_3$Cl$_2$ as the photoredox catalyst (Scheme 1a). However, the use of transition metal complexes as photoredox catalysts is disadvantageous because of high cost, potential toxicity and problematic removal of their undesired traces from products. In requisite of metal-free, cost effective, operationally simple and ecofriendly catalysts, some organic dyes,[14] diarylketones[15] and *N*-hydroxyphthalimide[16] have shown enough promise for high photocatalytic performance. It is known that after photoexcitation with visible light, diarylketones selectively abstract a hydrogen atom attached to a heteroatom.[15] Based on earlier reports[15] on successful use of benzophenone as a photocatalyst, it was chosen as a catalyst in the present study. Movassagh and Navidi have reported water promoted catalyst-free anti-Markovnikov addition of thiols to styrenes but the method is not applicable to aliphatic thiols and nonstyrenic alkenes.[17]

In view of the above points and our continued efforts focused on visible light mediated synthetic routes,[14b,18] we hypothesized that photoexcited benzophenone could bring about a metal- and oxidant-free radical thiol-ene reaction under visible light irradiation (Scheme 1b).

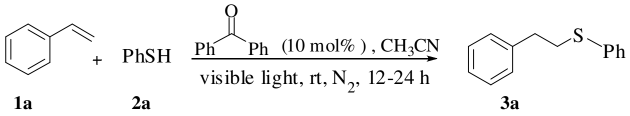


Scheme 1. Visible light mediated radical thiol-ene reactions.

In order to realize our hypothesis and optimize the reaction conditions, a model reaction of styrene (**1a**) with thiophenol (**2a**) was performed using catalytic amount of benzophenone in a solvent under nitrogen and irradiation with a household 18 W compact fluorescent lamp (18 W CFL) (Table 1). We were delighted to get the desired product (**3a**) in 87% yield (Table 1, entry 1). Then, the control experiments were carried out, which show that benzophenone and visible light are essential for the reaction because in the absence of any of the reagents/reaction parameters the product was not detected (Table 1, entry 1 versus 6 and 7).The optimum amount of the photocatalyst benzophenone required for the reaction was 10 mol%. On decreasing the amount of benzophenone from 10 mol% to 5 mol% the yield was considerably reduced (Table 1, entry 1 versus 4), whereas the yield was not enhanced even on use of 15 mol% of benzophenone (Table 1, entry 1 versus 5). The use of other organic catalyst was not so effective as benzophenone (Table 1, entry 1, versus 2 and 3).

Table1

Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)[b]
1	Benzophenone (10%)	CH_3CN	12	87
2	Acetone (10%)	CH_3CN	12	67
3	Acetophenone (10%)	CH_3CN	12	62
4	Benzophenone (5 %)	CH_3CN	12	58
5	Benzophenone (15 %)	CH_3CN	12	87
6	Benzophenone (10 %)	CH_3CN	24	n.d.[c]
7	-	CH_3CN	24	n.d.[d]
8	Benzophenone (10%)	CH_3CN	24	traces[e]
9	Benzophenone (10%)	EtOH	12	53
10	Benzopnenone (10%)	DMF	12	71
11	Benzophenone (10%)	DMSO	12	76

[a] Reaction conditions: **1a** (1.0 mmol), thiophenol (1.0 mmol), catalyst (mol%), in 3 mL solvent irradiated with a household 18 W compact fluorescent lamp Philips (18 W CFL) under nitrogen atmosphere at rt for 12-24 h. [b] Isolated yield of the pure product **3a**. [c] Reaction was performed in the dark, n.d. = not detected. [d] Reaction was carried out without catalyst. [e] Reaction was quenched with 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) (2 equiv).

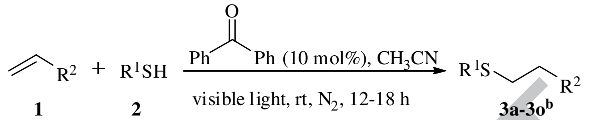
Moreover, the reaction was quenched with traditional radical seavenger 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) (2 equiv) indicating that the reaction might follow a radical pathway (Table 1, entry 6).

Next, the reaction was optimized for an effective solvent system. It was found that CH_3CN was the best among the tested solvents EtOH, DMF, DMSO and CH_3CN (Table 1, entry 1 versus 9-11) hence it was used throughout the present study.

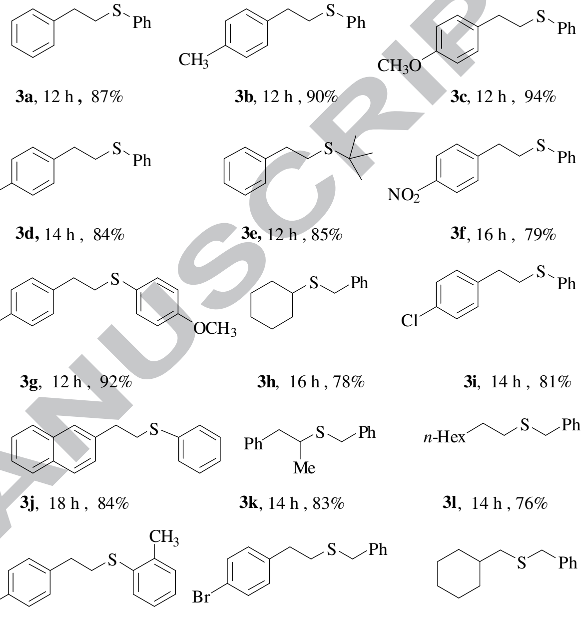
Under the established reaction conditions, we surveyed the generality and scope of the present thiol-ene reaction across a range of olefins **1** and thiophenols **2** incorporating various substituents like Me, MeO, NO_2, Cl, and Br. The reaction worked well in all the cases and afforded sulfides **3** in good to excellent yields and high purity. Styrenes and thiophenols with 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 (Table 2, products **3b and 3c** versus **3d**, **3f** and **3i**).This is probably because an electron-donating group stabilizes the electron-deficient benzylic and thiyl radical intermediates **C** and **D** involved in the reaction (Scheme 2). The protocol was also applicable to aliphatic alkenes and thiols to give satisfactory results (Table 2, **3e**, **3h**, **3k**, and **3o**). However, in this case the yield was slightly lower as compared to styrenes and thiolphenols.

Table 2

Substrate scope for the radical thiol-ene reaction



1 **2** **3a-3o**[b] (75-94%)[c]



3a, 12 h , 87% **3b**, 12 h , 90% **3c**, 12 h , 94%

3d, 14 h , 84% **3e,** 12 h , 85% **3f**, 16 h , 79%

3g, 12 h , 92% **3h**, 16 h , 78% **3i**, 14 h , 81%

3j, 18 h , 84% **3k**, 14 h , 83% **3l**, 14 h , 76%

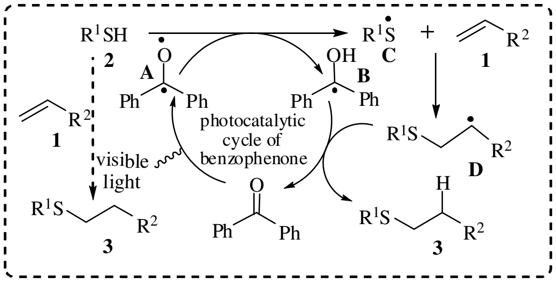
3m , 14 h , 82% **3n**, 14 h , 81% **3o**, 16 h , 75%

[a] For experimental procedure, see ref. 19.

[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[12b,20]

[c] Yields of isolated pure compounds **3**.

On the basis of our observations and the literature reports,[12,15a] a plausible mechanistic pathway is depicted in Scheme **2**. As already reported,[15a] on irradiation with visible light, benzophenone is photoexcited to **A**, which abstracts a hydrogen radical from thiol **2** to generate the thiyl radical **C** and the ketyl radical **B** in the present case. The thiyl radical **C** adds to olefin **1** to form a radical intermediate **D**, which abstracts a hydrogen radical from the ketyl radical **B** to complete the photocatalytic cycle of benzophenone and afford the final product **3**. The excitation of benzophenone by the visible light was ensured by using a 400 nm long-pass filter.[15a]



Scheme 2. Plausible mechanism for anti-Markovnikov thiol-ene reaction.

In conclusion, we have developed a convenient and highly regioselective synthesis of sulfides from readily available and diversified olefins and thiols. The present radical thiol-ene reaction utilizes visible light as the greenest energy source and benzophenone as an inexpensive organophotocatalyst to afford sulfides in good to excellent yields and high purity at ambient temperature. The protocol is metal-and oxidant-free, operationally simple and compatible with a variety of functional groups in both the reaction partners.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi…

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19. *General procedure for the synthesis of sulfides* **3:** A mixture of olefin **1** (1 mmol), benzophenone (10 mol%), thiol **2** (1 mmol) and nitrile (3 mL) was stirred at rt under N_2 atmosphere and irradiation with visible light (18 W compact fluorescent lamp) for 12-18 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 Na_2SO_4, 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.[12b,20] Characterization data of representative compounds **3** are given below:
    Compound **3a**:[20a] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.40 (m, 2H), 7.38-7.31 (m, 4H), 7.29-7.23 (m, 4H), 3.28-3.22 (m, 2H), 3.00-2.99 (m, 2H) ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 140.8, 136.7, 129.7, 129.3, 128.9, 128.5, 126.8, 126.3, 36.1,35.6; HRMS (EI): calcd for $C_{14}H_{14}S$ 214.0816, found 214.0812.
    Compound **3i**:[20a] ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.47-7.23 (m, 7H), 7.16 (m, 2H), 3.29-3.19 (m, 2H), 2.99-2.92 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 138.6, 136.3, 132.1, 131.4, 130.0, 129.5, 129.0, 128.5, 35.1, 34.8; HRMS (EI): calcd for $C_{14}H_{13}ClS$ 248.0427, found 248.0430.
    Compound **3m**:[20a] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, *J* =7.3 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.40-7.28 (m, 5H), 7.16 (d, *J*=7.9 Hz, 2H), 3.26-3.19 (m, 2H), 3.05-2.95 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 141.3, 139.9, 136.7,135.3,134.5, 133.4, 132.8, 130.7, 130.2, 129.5, 129.1, 127.7, 127.5, 127.3, 36.3, 35.7, 21.6; HRMS (EI): calcd for $C_{21}H_{20}S$ 304.1286, found 304.1283.
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Highlights

- Metal- and oxidant-free one-pot protocol for the synthesis of thioethers.
- Visible light-mediated radical thiol-ene click (TEC) reactions.
- Utilization of benzophenone as a stable and inexpensive organophotoredox catalyst.
- Highly regioselective efficient anti-Markovnikov hydrothiolation of unactivated olefins.