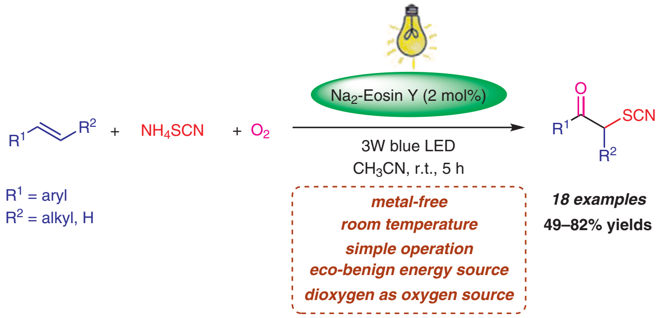
Visible-Light-Promoted Difunctionalization of Olefins Leading to α-Thiocyanato Ketones

Guangming Nan*[a]
Huilan Yue*[b]

[a] University and College Key Lab of Natural Product Chemistry and Application in Xinjiang, School of Chemistry and Environmental Science, Yili Normal University, Yining 835000, China
nanguangming02@sohu.com
[b] Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology, Chinese Academy of Sciences and Qinghai Provincial Key Laboratory of Tibetan Medicine Research, Qinghai 810008, China
hlyue@nwipb.cas.cn



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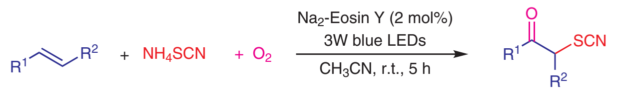
Abstract A simple and convenient visible-light-induced difunctionalization of alkenes with ammonium thiocyanate and dioxygen has been developed at room temperature. A series of α-thiocyanato ketones could be easily and efficiently obtained in moderate to good yields through the formation of C–S and C=O bonds simply by using nontoxic and inexpensive Na_2-Eosin Y as a photocatalyst.

Key words visible-light catalysis, difunctionalization, alkenes, ammonium thiocyanate, α-thiocyanato ketones

As an important functionality, the thiocyanato group is widely present in a number of natural products and biologically-active compounds.[1] Furthermore, organic thiocyanates are of great importance in various areas of organosulfur chemistry because they are key synthetic intermediates to access diverse valuable sulfur-containing compounds.[2] In particular, α-thiocyanato carbonyl compounds can serve as versatile precursors for the construction of sulfur-containing heterocycles such as thiazoles and 2-amino-1,3-thiazines,[3] some of which are associated with herbicidal and other useful biological activities.[4] As a consequence, considerable research efforts have been dedicated to construct α-thiocyanato ketones. In general, α-thiocyanato ketones are prepared by the nucleophilic reaction of the thiocyanate anion with halocarbonyl compounds[5] or α-tosyloxycarbonyls.[6] However, these classical methods usually require harsh reaction conditions and suffer from low yields that are due to the poor nucleophilicity of the thiocyanate anion. In recent years, alternative methods such as the direct α-thiocyanation of ketones mediated by I_2,[7a] heteropolyacid,[7b] $FeCl_3$,[7c] NBS,[7d] and copper,[7e] the oxidative thiocyanation of enol ethers,[8] and the thiocyanation reaction of styrenes in the presence of a stoichiometric amount of cerium(IV) ammonium nitrate (CAN), cis-1,4-bis(triphenylphosphonium)-2-buteneperoxodisulfate (BTPBPD), or AcOH have also been developed.[9] Nevertheless, many of these methods still involve multi-step synthetic sequences, the use of a large excess of expensive and strong oxidants, or toxic metal catalysts and metal thiocyanates, which may limit their practical applications in synthetic and pharmaceutical chemistry. Therefore, the development of mild, convenient, economic, and environmentally benign methods to prepare α-thiocyanato ketones is still highly desirable.

Visible-light photoredox catalysis has attracted great attention as a powerful tool to develop sustainable synthetic processes because of its advantageous properties: clean and safe application and easy availability of visible light, which is a renewable energy source.[10] In recent years, various synthetically useful chemical transformations have been successfully established by visible-light-driven catalysis under the mild conditions.[11] On the other hand, the direct utilization of dioxygen as an oxidant and oxygen source in organic synthesis meets the demands of green chemistry because of its economic and environmentally benign features. Visible-light photoredox catalysis has opened up a new and attractive avenue for aerobic oxidation, where molecular oxygen is usually used as an oxidant to regenerate the photoredox catalyst after its reductive quenching to finish the catalytic cycle.[12]

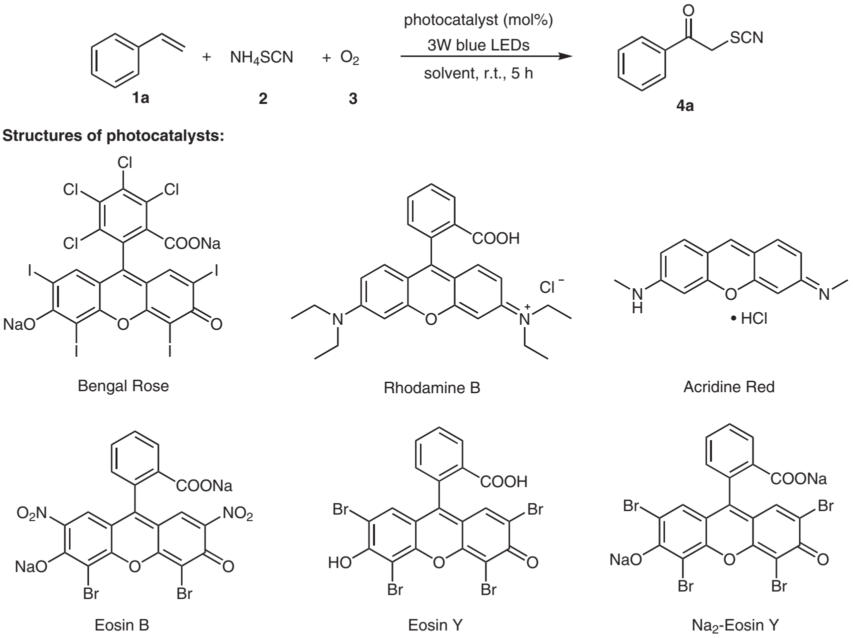


Scheme 1 Visible-light-induced difunctionalization of alkenes with ammonium thiocyanate and dioxygen

Herein, we report a mild and convenient visible-light-enabled method for the construction of α-thiocyanato carbonyl compounds through Na_2-Eosin Y catalyzed difunctionalization of alkenes with ammonium thiocyanate and dioxygen (Scheme 1), in which the C–S and C=O bonds are formed in a one-pot procedure under mild and metal-free conditions.

We started our investigation by using the combination of styrene (**1a**), NH_4SCN, and Eosin B (2 mol%) in MeCN (5 mL) under O_2 at room temperature as the model reaction. The reaction was conducted under irradiation with a 3W blue LED lamp. To our delight, the desired α-thiocyanato ketone **4a** was obtained in 36% yield after five hours (Table 1, entry 1). In the screening of photocatalysts Na_2-Eosin Y was the best one leading to the desired product **4a** in 79% yield (Table 1, entry 7), while others such as Rhodamine B, Acridine Red, Rose Bengal, Eosin Y, and $Ru(bpy)_3Cl_2$ were less effective in this transformation (Table 1, entries 2–6). The choice of solvent was also crucial for this oxythiocyanation reaction. Replacing CH_3CN with other solvents dramatically decreased the yield of **4a** (Table 1, entries 8–17). Low to moderate yields were obtained when the reaction was carried out in ether solvent such as THF, DME, or 1,4-dioxane (Table 1, entries 8–10). DCE, toluene, DMF, H_2O, acetone, EtOH, and CH_3CN/H_2O all resulted in no transformation or low efficiency (Table 1, entries 11–17). Increasing or decreasing the loading of Na_2-Eosin Y failed to improve the reaction efficiency (Table 1, entries 18–19). Furthermore, replacing NH_4SCN by KSCN gave the desired product **4a** in only 34% yield (Table 1, entry 20). Moreover, the target product could also be isolated in moderate yield when the model reaction was carried out under air (Table 1, entry 21). Notably, only a lower amount of the desired product was obtained when the reaction was conducted in absence of the photocatalyst (Table 1, entry 22). In contrast, the oxythiocyanation of alkene did not at all occur in the dark (Table 1, entry 23).

Table 1 Optimization of Reaction Conditions[a]



Entry	Photocatalyst (mol%)	Solvent	Yield (%)[b]
1	Eosin B (2)	CH_3CN	36
2	Rhodamine B (2)	CH_3CN	34
3	Acridine Red (2)	CH_3CN	33
4	Rose Bengal (2)	CH_3CN	33
5	Eosin Y (2)	CH_3CN	41
6	$Ru(bpy)_3Cl_2$ (2)	CH_3CN	56
7	Na_2-Eosin Y (2)	CH_3CN	79

Table 1 (continued)

Entry	Photocatalyst (mol%)	Solvent	Yield (%)[b]
8	Na_2-Eosin Y (2)	THF	12
9	Na_2-Eosin Y (2)	DME	16
10	Na_2-Eosin Y (2)	1,4-dioxane	54
11	Na_2-Eosin Y (2)	DCE	0
12	Na_2-Eosin Y (2)	toluene	0
13	Na_2-Eosin Y (2)	DMF	0
14	Na_2-Eosin Y (2)	H_2O	0
15	Na_2-Eosin Y (2)	EtOH	trace
16	Na_2-Eosin Y (2)	acetone	trace
17	Na_2-Eosin Y (2)	CH_3CN/H_2O	18
18	Na_2-Eosin Y (5)	CH_3CN	49
19	Na_2-Eosin Y (1)	CH_3CN	63
20	Na_2-Eosin Y (2)	CH_3CN	34[c]
21	Na_2-Eosin Y (2)	CH_3CN	50[d]
22	–	CH_3CN	22
23	Na_2-Eosin Y (2)	CH_3CN	0[e]

[a] *Reaction conditions*: **1a** (0.2 mmol), **2** (0.4 mmol), photocatalyst (1–5 mol%), solvent (5 mL), 3W blue LED lamps, r.t., O_2, 5 h.
[b] Isolated yields based on **1a**.
[c] KSCN was used instead of NH_4SCN.
[d] Under air.
[e] In the dark.

After the establishment of the optimal reaction conditions, the substrate scope in this visible-light-promoted difunctionalization of alkenes was examined. As listed in Scheme 2, in general, reactions of aromatic alkenes containing electron-donating or electron-withdrawing groups with ammonium thiocyanate and dioxygen worked well under the standard conditions and their corresponding α-thiocyanato ketones were obtained in moderate to good yields. The reaction efficiency was not obviously affected by the steric effect, and substrates bearing a methyl group in the *para*, *meta*, or *ortho* position of the aryl ring were all suitable for this reaction (**4b–d**). A series of functionalities such as methoxy, chloromethyl, acetoxy, or halogen groups survived well leading to **4f–n**, which could be potentially employed for further modifications. 2-Vinylnaphthalene also performed well in this reaction to give the expected product **4o** in 82% yield. Notably, an internal aromatic alkene such as (*E*)-prop-1-enylbenzene could smoothly be converted into the desired α-thiocyanato ketone **4p** in 51% yield. Nevertheless, none of the desired products (**4q** and **4r**) were detected when stilbene and an aliphatic alkene such as hex-1-ene were employed in this reaction system.

Subsequently, we turned our attention to the possible reaction mechanism. As demonstrated in Scheme 3 (a), the model reaction was significantly inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT) was added under standard conditions, indicating that a radical process might be involved in this transformation. Furthermore, only a trace amount of product **4a** was detected when the model reaction was carried out under a nitrogen atmosphere (Scheme 3, b), which suggests that dioxygen should be the key oxidant and oxygen source in the present reaction system. Moreover, to certify the effect of photo irradiation, on/off visible-light irradiation experiments were performed. The result demonstrated that the continuous irradiation of visible-light is essential for this reaction (Figure 1).

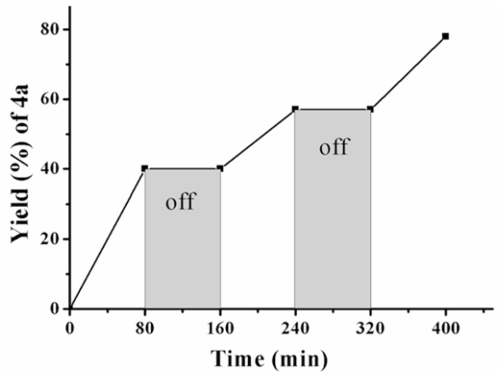
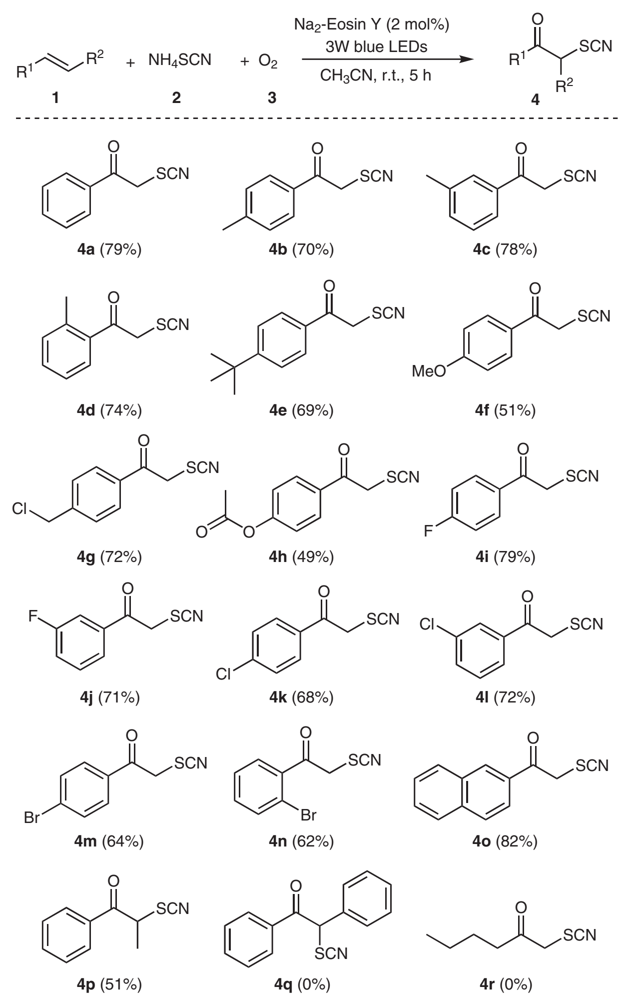
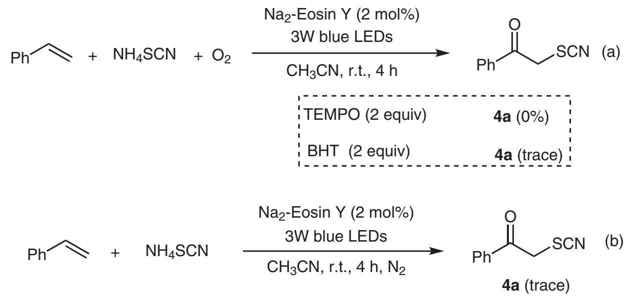


Figure 1 On/off experiments



Scheme 2 Results for visible-light-induced difunctionalization of alkenes leading to α-thiocyanato ketones. *Reaction conditions*: **1** (0.2 mmol), **2** (0.4 mmol), Na$_2$-Eosin Y (2 mol%), CH$_3$CN (5 mL), 3W blue LED lamps, r.t., O$_2$, 5 h. Isolated yields are based on **1**.



Scheme 3 Prelimininary mechanistic study

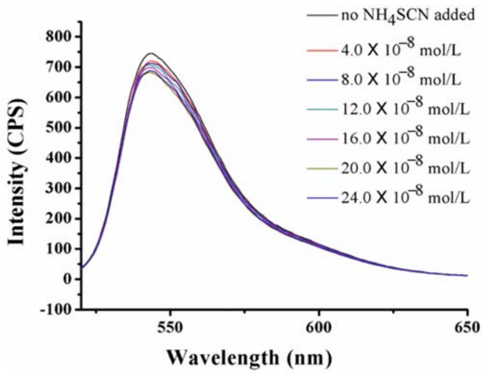


Figure 2 Quenching of Na$_2$-Eosin Y fluorescence emission in the presence of NH$_4$SCN

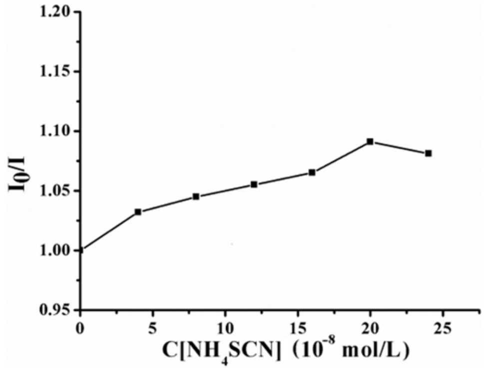
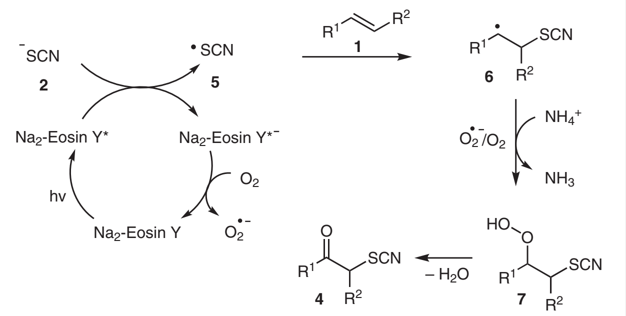


Figure 3 Stern–Volmer plot

In addition, an energy transfer process between Na$_2$-Eosin Y and NH$_4$SCN was proved by a series of fluorescence-quenching (Stern–Volmer) experiments. As shown in Figures 2 and 3, the emission intensity of excited Na$_2$-Eosin Y gradually decreased along with increasing concentration of NH$_4$SCN. On the contrary, when Na$_2$-Eosin Y and styrene **1a** were mixed separately, such effect was not observed (see Supporting Information). These results strongly suggest that a single-electron transfer process occurred between Na$_2$-Eosin Y and NH$_4$SCN under the standard reaction conditions.

On the basis of the above results and previous reports,[9,13–15] a possible reaction mechanism is described in Scheme 4. Initially, Na$_2$-Eosin Y* is generated from Na$_2$-Eosin Y in the presence of blue LED light. Subsequently, a single-electron transfer (SET) from thiocyanate anion **2** to Na$_2$-Eosin Y* gives the thiocyanate radical **5** and Na$_2$-Eosin Y$^{\bullet-}$ radical anion.[13] The oxidation of Na$_2$-Eosin Y$^{\bullet-}$ by dioxygen forms the ground-state Na$_2$-Eosin Y and O$_2^{\bullet-}$. Then, the selective addition of thiocyanate radical **5** to alkene **1** produces alkyl radical **6**. Next, the interaction of radical **6** with O$_2^{\bullet-}$ or O$_2$ and NH$_4^+$ would lead to the formation of hydroperoxide intermediate **7**.[14] Finally, the elimination of water from **7** affords the corresponding product **4**.[9,15]



Scheme 4 Postulated reaction pathway

In summary, a facile and efficient visible-light-enabled method has been developed for the construction of α-thiocyanato ketones through Na$_2$-Eosin Y catalyzed difunctionalization of alkenes with ammonium thiocyanate and dioxygen at room temperature.[16] Such a "green" protocol provides an attractive approach to access various α-thiocyanato ketones because of its operational simplicity, mild reaction conditions, eco-friendly energy source, and cheap and nontoxic catalyst. Further studies on the scope and application of this reaction are underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609443.

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(16) **Preparation of 1-Phenyl-2-thiocyanatoethanone (4a)**
To a solution of NH_4SCN (**2**) (30.4 mg, 0.4 mmol) and Na_2-EosinY (2.8 mg, 0.004 mmol, 2 mol%) in CH_3CN (5 mL) was added alkene **1a** (20.8 mg, 0.2 mmol). The reaction mixture was stirred under the irradiation of 3W blue LED under an oxygen atmosphere at r.t. for 5 h. After completion of the reaction, the solution was concentrated under vacuum. The residue was purified by using a mixture of ethyl acetate and petroleum ether (1:10) as eluent to give the desired product **4a**. Yield: 30 mg (79%). ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ = 7.95 (d, J = 8.0 Hz, 2 H), 7.68 (t, J = 7.3 Hz, 1 H), 7.54 (t, J = 7.7 Hz, 2 H), 4.75 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ = 190.8, 134.8, 134.0, 129.2, 128.5, 111.9, 43.0. HRMS: m/z $[M + Na]^+$ calcd for C_9H_7NOSNa: 200.0146; found 200.0149.