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# Visible-light-induced direct α-C($sp^3$)–H thiocyanation of tertiary amines

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ABSTRACT

Visible-light-induced, eosin Y catalyzed aerobic oxidative α-C($sp^3$)–H thiocyanation of tertiary amines is reported. The reaction proceeds through visible-light-induced in situ generation of the iminium ion followed by attack of $^{-}$SCN nucleophile. This is the first example of visible-light-initiated formation of C($sp^3$)–S bond employing organo-photoredox catalysis. Mild reaction conditions and use of air and visible light as the greenest and sustainable reagents at room temperature are the salient features of the protocol.

Chemical community desires a sustainable, environment friendly, and highly efficient protocol with selectivity. Thus, the continued efforts for the development of more effective synthetic protocols that fulfill these criteria are of global relevance. In this regard, photoredox catalysis has recently offered a great opportunity by utilizing unending resources like visible light and air in organic synthesis.[1] Certain electron rich substrates are capable of engaging in single electron transfer (SET) for photoredox catalysis processes to generate radicals, radical ions, or ions as intermediates to bring about the desired transformations.[2]

The success of this strategy started with the pioneering work of MacMillan,[3a] Yoon,[3b,c] and Stephenson et al.[3d] involving the use of photocatalysts such as $Ru(bpy)_3Cl_2$ (bpy = 2,2′-bipyridine) and Ir$(dtbbpy)_3Cl_2$ (dtbbpy = 4,4′-di-*tert* butyl-2,2′-bipyridine), which absorb light in the visible region. Photocatalysts possess one common characteristic, that is, a facile intersystem crossing (ISC) that allows the conversion of the initially formed singlet photoexcited state to the relatively long-lived triplet photoexcited state, which undergoes single-electron transfer with organic molecules such as amines. Tertiary amines act as sacrificial electron donors to reductively quench the photoexcited state while they are oxidized to amine radical cations, which are easily converted to its iminium ion.

The in situ formation of iminium ion has attracted considerable attention of synthetic organic chemists for the α-C($sp^3$)–H functionalization of tertiary amines.[2] This is a tool that allows easy construction of C–C and C–X bonds (X = N, P, O) adjacent to tertiary amines through: (i) in situ formation of iminium ion transient and (ii) attack of C, N, P, or O centered nucleophile (Scheme 1a).[1] The photoredox catalysis is of great interest because it allows utilization of visible light and atmospheric oxygen as the greenest and readily available reagents in organic syntheses. Moreover, an alternative to the photochemistry of Ru(II) and Ir(II), eosin Y (EY)[4], a long known dye has recently been widely applied as an organo-photoredox catalyst for the construction of C–C and C–X bonds particularly in the field of pharmaceuticals, where traces of metals are undesirable. Recently, our group has also applied eosin Y as an organo-photoredox catalyst to bring about various synthetically useful transformations.[5]

Several communications have appeared on utilization of these photocatalysts (Ru(II), Ir(II), and eosin Y etc.) during the last five years for the α-functionalization of C($sp^3$)–H of tertiary amines.[2] We have already extended the scope of this methodology by applying it to aza-Baylis–Hillman adducts to access γ-functionalized tertiary amines.[2d] To the best of our knowledge, there is no report on the C–S bond construction on C($sp^3$)–H carbon adjacent to tertiary amines using visible light photoredox catalysis.

Incorporation of thiocyanate function in organic molecules enhances their scope of biological and chemical applications,[6] because it allows the functional group manipulation in a

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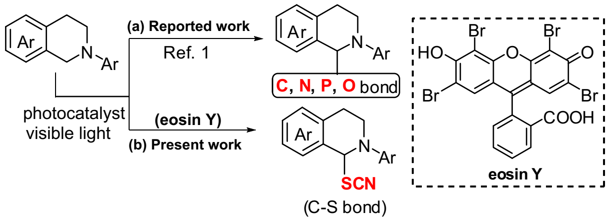
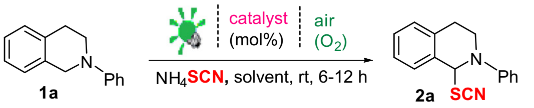


**Scheme 1.** Visible-light-induced α-C($sp^3$)–H functionalization of tetrahydroisoquinolines (THIQs).

**Table 1**
Optimization of reaction conditions[a]



| Entry | Catalyst (mol %) | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Eosin Y (1) | $CH_3CN$ | 6 | 90 |
| 2 | Rose bengal (1) | $CH_3CN$ | 6 | 68 |
| 3 | Eosin Y (1) | THF | 6 | 73 |
| 4 | Eosin Y (1) | DMF | 6 | 86 |
| 5 | Eosin Y (1) | DMSO | 6 | 81 |
| 6 | Eosin Y (0.5) | $CH_3CN$ | 6 | 64 |
| 7 | Eosin Y (2) | $CH_3CN$ | 6 | 90 |
| 8 | Eosin Y (1) | $CH_3CN$ | 12 | Traces[c] |
| 9 | Eosin Y (1) | $CH_3CN$ | 12 | Traces[d] |
| 10 | – | $CH_3CN$ | 12 | 0[e] |
| 11 | Eosin Y (1) | $CH_3CN$ | 12 | Traces[f] |
| 12 | Eosin Y (1) | $CH_3CN$ | 12 | 63[g] |
| 13 | Eosin Y (1) | $CH_3CN$ | 12 | 58[h] |
| 14 | Eosin Y (1) | $CH_3CN$ | 6 | 91[i] |

[a] Reaction conditions: **1a** (1.0 mmol), $NH_4SCN$ (1.0 mmol), catalyst (mol %), in 3 mL solvent irradiated using Luxeon Rebel high power green LEDs [2.50 W, $\lambda = 535$ nm] under an air atmosphere at rt for 6–12 h.

[b] Isolated yield of the pure product **2a**.

[c] Reaction was performed under nitrogen.

[d] Reaction was carried out in the dark.

[e] Reaction was carried out in the absence of catalyst.

[f] Reaction was quenched with 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO (1.0 mmol).

[g] 18 W CFL (compact fluorescent lamp, Philips) was used.

[h] KSCN was used as instead of $NH_4SCN$.

[i] $O_2$ balloon was used.

straightforward and atom economical fashion.[7] Organic thiocyanates usually serve as synthetic precursors that can be conveniently converted into various sulfur-containing derivatives, including thiophenols,[7a] thioethers,[7b] and disulfides by using $SmI_2$,[7c] and thiocarbamates on acid hydrolysis.[7d] Moreover, the SCN functionality undergoes intramolecular heterocyclization to afford 1,3-oxathiolane, an important biologically and pharmaceutically active five member heterocycle.[8] Thus, a new protocol that successfully installs the SCN group into C($sp^3$)–H of organic molecules is of considerable interest.

Thiocyanates can be prepared via two classic routes, one is the direct electrophilic thiocyanation of enolisable ketones in the presence of an oxidant[7a] and the other is the direct nucleophilic substitution by $^-$SCN.[7,9] However, the major drawback associated with most of them is atom economy, use of oxidant, low regio- and chemo-selectivity, as well as narrow substrate scope.[7] Intrigued by the earlier reports on the application of eosin Y in the visible light photoredox process for the iminium ion formation[4] and of our work on the introduction of SCN functionality,[9] we report herein a pot efficient, eco-friendly, and novel method for the incorporation of SCN into α-C($sp^3$)–H of tertiary amines (Scheme 1b).

To realize our idea and optimize the reaction conditions, the key reaction of THIQ (**1a**) with $NH_4SCN$ was carried out using a catalytic amount of eosin Y in $CH_3CN$ under irradiation with green LEDs [2.50 W, $\lambda = 535$ nm][10] in open air (Table 1). We were delighted to get the desired product **2a** in 90% yield (Table 1, entry 1). Then, the control experiments were carried out, which show that eosin Y, air ($O_2$), and visible light are essential for the reaction, because in the absence of any of the reagents/reaction parameters the product was not detected/formed in traces (Table 1, entry 1 vs 8–10). The reaction was quenched with TEMPO (1 mol %), which indicates that a radical intermediate may be involved in the reaction (Table 1, entry 1 vs 11). The optimum amount of eosin Y required for the reaction was 1 mol %. On decreasing the amount of eosin Y from 1 mol % to 0.5 mol % the yield was considerably reduced (Table 1, entry 6), whereas the yield was not enhanced even on the use of 2 mol % of eosin Y (Table 1, entry 7). The use of another photo-organocatalyst like rose bengal (1 mol %) was not so effective as eosin Y (1 mol %) (Table 1, entry 1 vs 2). For the photo-activation of eosin Y, green LEDs give a much better result than the normal house hold light (Table 1, entry 12). When $O_2$ balloon was used instead of open air, there was no appreciable enhancement in the yield (Table 1, entry 14).

Next, the reaction was optimized for an effective solvent system and source of SCN ion. It was found that $CH_3CN$ was the best among the tested solvents THF, DMF, DMSO, and $CH_3CN$, hence it was used throughout the present study (Table 1, entry 1 vs 3–5). As the SCN sources, $NH_4SCN$ was better than KSCN in terms of the yield and reaction time (Table 1, entry 1 vs 13).

Under the established reaction conditions, we surveyed the generality and scope of the present protocol across a range of THIQ incorporating various substituents like Me, Et, MeO, COOEt, $NO_2$, Br, and Cl in the aryl moiety, and THIQ substrates bearing an *N*-alkyl or *N*-heteroaryl moiety (Table 2). The reaction worked well in all the cases and afforded products **2** in good to excellent yields (74–95%). However, THIQs **1** 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 **2b**–**2e** and **2h**–**2j** vs **2f**, **2g**, **2k**, **2l**). Tertiary amines other than THIQs were also well compatible with the present protocol (Table 2, entries **2m**, **2n**, and **2o**).

Intrigued by our previous work,[2d] we applied the present protocol to the aza-Baylis–Hillman adduct **1r** containing benzylic amine in conjugation with the double bond. Under the photoreox catalysis, it generates 4π-conjugated iminium ion, which selectively affords the expected γ-thiocyanated product **2r** with $NH_4SCN$ in 89% yield (Scheme 2).

On the basis of our observations and the literature reports,[1–5] a plausible mechanistic pathway is depicted in Scheme 3. Eosin Y (EY) on absorption of light goes to its excited state (EY*). Single electron transfer between **1** and EY* affords **A** and $EY^{\cdot-}$,[4] The photoredox cycle of eosin Y is completed by the aerobic oxidation of $EY^{\cdot-}$ by $O_2$ to its ground state (EY). The in situ generated superoxide radical anion ($O_2^{-\cdot}$) abstracts a proton from α-position of **A** to form iminium ion **B**, which is further attacked by $^-$SCN nucleophile to afford the final product **2**. The formation of superoxide radical anion ($O_2^{-\cdot}$) during the reaction was confirmed by the detection of the resulting $H_2O_2$ ($HO_2^- + NH_4^+ \rightarrow H_2O_2 + NH_3$) using KI/starch indicator.[12]

In conclusion, we have disclosed an efficient protocol for the α-C($sp^3$)–H thiocyanation of tertiary amines at room temperature using readily available and inexpensive $NH_4SCN$ as the source of $^-$SCN. It is also applicable to aza-Baylis–Hillman adduct to afford the γ-thiocyanated product. The present protocol extends the