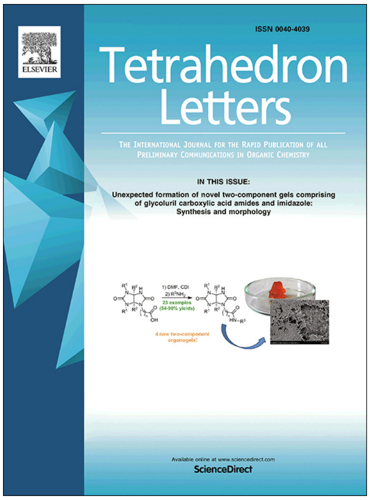

Photocatalysed eosin Y mediated C(sp^3)−H alkylation of amine substrates via direct HAT

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Graphical Abstract

Photocatalysed eosin Y mediated C(sp^3)−H alkylation of amine substrates via direct HAT

Vishal Srivastava[a] Pravin K. Singh[a] and Praveen P. Singh*[b]

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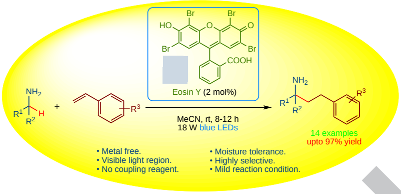

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Photocatalysed eosin Y mediated C(sp^3)−H alkylation of amine substrates via direct HAT

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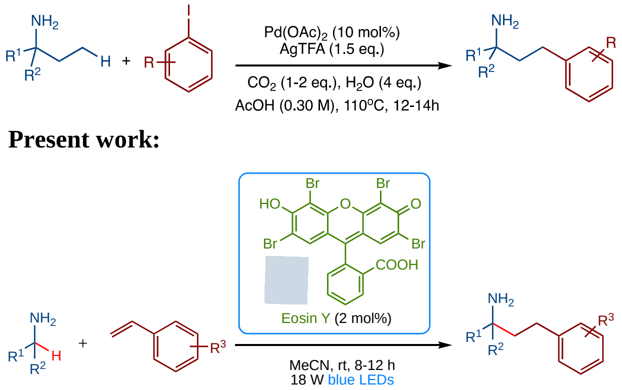
ABSTRACT

A visible light promoted, photoredox catalysed, green one-pot approach for the alkylation of amine substrates with sp^2 carbon has been developed. This eosin Y based organic transformations, can behave as an effective direct hydrogen-atom transfer catalyst for coupling reaction. The proposed strategy includes simple procedure which can make adduct product with sp^2 carbon. This eosin Y based photocatalytic hydrogen-atom transfer strategy may hold great potential for diverse functionalization of a wide range of native C-H bonds in an economical and sustainable manner.

Amines are important substituents in many biologically active compounds. Amines acts like a key functional group in agrochemicals [1] as well as materials. [2,3] Aliphatic amines are ubiquitously present in pharmaceuticals with a wide range of biological activities [4-8]. In recent years, a number of medicines containing aliphatic amine moieties are among the top 100 best-selling drugs. The persistent need from drug discovery programmes for elaborate amine containing architectures has led to pioneering developments in the C(sp^3)–H functionalization of amines [9,10]. Due to the extreme popularity and importance of aliphatic amines, development of efficient and straightforward methods for the synthesis and derivatization of these compounds is of great research interest in organic chemistry and medicinal sciences [11,12]. Tertiary amine moiety has been extensively found in many popular prodrugs [13], fluorescence anti-collapse drilling fluid [14,15] etc. Tertiary amine drug, promethazine hydrochloride [16] used as an antiemetic, antihistamine, allergies, sedative and nauseas. Amine moiety is also found in popular prodrugs like Rolitertracycline. [17] New researches [18,19] are also in progress on amine prodrug due to their specific physical and chemical properties.

A potential of developing new synthetic methodologies using visible light has recently received much attention from a number of research groups [20-23]. This is because solar energy (visible light) is clean, easy to handle and an unlimited energy source having great prospects for the development of sustainable and eco-friendly protocols for organic synthesis [24]. Some pioneering researchers have dedicated to converting solar energy into chemical energy for chemical transformations [25,26] which includes a promising strategy for the application of photoredox catalysts to initiate single electron transfer (SET) processes [27,28]. Visible light photoredox catalysis has recently received much attention in organic synthesis owing to ready availability, sustainability, non-toxicity and ease of handling [29-32] Recently, a superior alternative to transition metal photoredox catalysts, especially metal-free organic dyes such as eosin Y, fluorescein, rose bengal, nile red, perylene and rhodamine B have been used as economically and ecologically superior surrogates for Ru(II) and Ir(II) complexes in visible-light promoted organic transformations involving SET [35-37]. These organic dyes have great potential for applications in visible-light-mediated organic synthesis [38-41] which fulfils the basic principle of green chemistry.

Previous work: J. Am. Chem. Soc. 2018, 140, 6818−6822.



Scheme 1. Eosin Y mediated C(sp^3)−H alkylation of amine substrates via direct hydrogen atom transfer (HAT)

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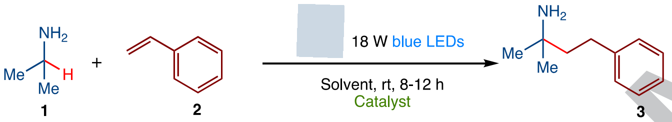
Recent developments in photocatalysis over the past decade have enabled previously inaccessible transformations [42-45]. In addition to SET and energy transfer, HAT has been frequently involved in photocatalysis, which can activate substrates without the limitation of redox potentials, offering enormous opportunities for C-H activations [46,47]. Upon light absorption, HAT catalysis is normally achieved in three different ways: direct HAT process, indirect HAT process [48,49] and proton-coupled electron transfer (PCET) process [50,51]. Among these three pathways, direct HAT catalysis represents the most reagent and redox economical method, in which the activated photocatalyst behaves as a HAT catalyst to abstract a H atom from a substrate. The catalytic cycle is subsequently turned over through a reverse hydrogen atom transfer (RHAT) to one of the generated intermediates [52-56]. Thus, photoredox catalysis in conjugation with HAT is an attractive approach to activating organic molecules. Although, transition metal catalysed arylation of amine substrate has been reported so far, [57], to the best of our knowledge, this study represents the first example of photocatalysed coupling of amine substrate with substituted styrene via direct HAT. In continuation of our work on development of environmentally benign synthesis [58-67] herein we report a simple, visible light irradiated, efficient green protocol for the eosin Y mediated $C(sp^3)$−H alkylation of amine substrates via direct HAT.

Table 1. Optimization of reaction conditions.[a]



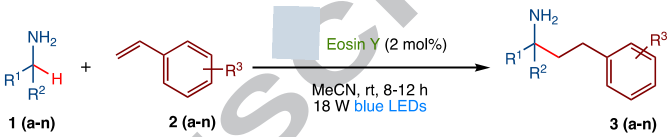
Entry	Catalyst	Catalyst loading (mol%)	Solvent	Time (h)	Yield[b] (%)
1	Eosin Y	2	MeCN	8	97
2	Quinones	2	MeCN	8	35
3	Benzophenones	2	MeCN	8	5
4	Fluorescein	2	MeCN	8	12
5	Rhodamine B	2	MeCN	8	10
6	Eosin Y	2	DCM	8	75
7	Eosin Y	2	THF	8	68
8	Eosin Y	1	MeCN	8	65
9	Eosin Y	3	MeCN	8	92
10	Eosin Y	2	MeCN	12	Trace[c]
11	-	-	MeCN	12	Nd[d]
12	Eosin Y	2	MeCN	12	78[e]

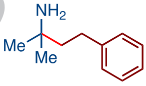
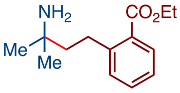
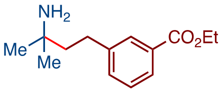
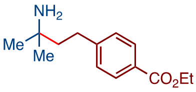
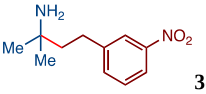
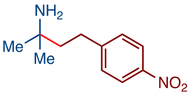
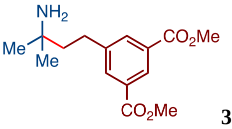
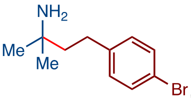
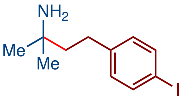
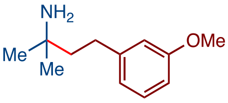
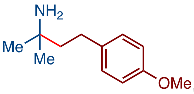
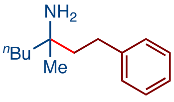
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), catalyst (mol%), in 3 mL solvent irradiated using high power blue LEDs [18 W] at rt for 8–12 h. [b] Isolated yield of the pure product **3**. [c] Reaction was performed in the dark. [d] Reaction was carried out without the catalyst. [e] 18 W CFL (compact fluorescent lamp, Philips) was used.

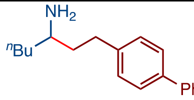
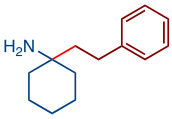
In order to realise our idea and optimise the reaction conditions, the key reaction of substituted amine **1** and substituted styrene **2** with a catalytic amount of eosin Y in a solvent under irradiation with blue LEDs [18 W, $\lambda = 469$ nm] was carried out (Table 1).

We were delighted to obtain the desired substituted product **3**, in 97% yield (Table 1, entry 1). Then, the control experiments were carried out, which show that eosin Y and visible light are essential for the reaction, because in the absence of any of the reagents/reaction parameters either the product was not detected or was formed in traces (Table 1, entries 1 versus 11 and 10). By application of quinones, benzophenones, fluorescein and rhodamine B the yield of product become very less (Table 1, entries 2, 3, 4 and 5). By using solvent DCM and THF with eosin Y (2 mol%) results increase in yield of desired product (Table 1, entries 6 and 7). Using MeCN as a solvent with eosin Y (1 mol%) results decrease in yield of desired product (Table 1, entry 8). Using MeCN as a solvent with eosin Y (2 mol%) in presence of 18W CFL results decrease yield of desired product in comparison to blue LED (Table 1, entry 12 vs entry 1). The scope of the present protocol across a range of amine and styrene incorporating various substituents were studied. It was found that substituted styrene 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). It was found that the yield of product decreases due to the ortho substituent as well as it increases at meta and para position respectively.

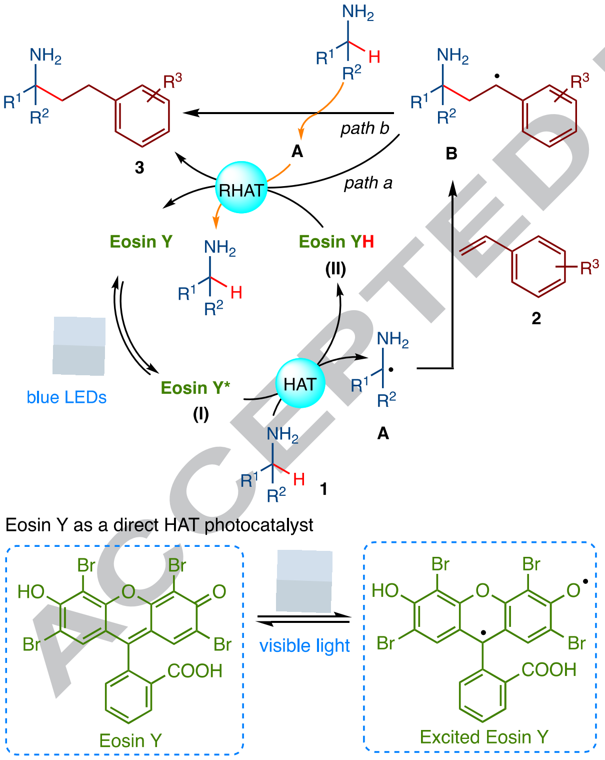
Table 2. Scope of the reaction.



Entry	Product	Yield
1	 **3a**	93
2	 **3b**	75
3	 **3c**	85
4	 **3d**	88
5	 **3e**	78
6	 **3f**	65
7	 **3g**	72
8	 **3h**	90
9	 **3i**	83
10	 **3j**	97
11	 **3k**	95
12	 **3l**	80

13	 **3m**	68
14	 **3n**	72

On the basis of our observations and the literature reports, [57] a plausible mechanistic pathway is depicted in Scheme 2. It has been illustrated that the anionic forms of eosin Y were the active catalysts that promote SET-based redox catalytic cycles in majority of previous studies, where neutral eosin Y was considered inactive [68,69]. In order to elucidate the actual species of eosin Y in the HAT-based catalytic cycle, various control experiments were performed in presence of blue LED with excellent yield [70]. The formation of a carbon-centered radical was promoted by visible-light activated *eosin Y through a HAT process. The derived carbon radical was subsequently trapped by an electron deficient styrene to selectively form radical adduct **B**. The RHAT process between eosin Y-H **II** and radical **B** exhibited a high free energy barrier (path a). Instead, another amine molecule and radical **B** might undergo a reversible HAT process to deliver the desired product, followed by RHAT between amine radical **A** and eosin Y-H **II** to regenerate ground state eosin Y catalyst (path b).



Scheme 2. Plausible mechanistic pathway.

In conclusion, we have developed a novel, one-pot photocatalysed C(sp^3)−H alkylation of amine substrates using eosin Y as a catalyst via direct HAT. Thus, it is a superior alternative to the existing method with respect to green and sustainable chemistry (better atom and step-economy). Due to metal-free, readily available, eco-sustainable, economical nature and in addition to light absorption in the visible region makes eosin Y an ideal direct HAT photocatalyst. Thus, it would become a novel protocol for coupling between amine substrate and styrene in the repertoire of chemistry and biology might be paved with the implementation of our developed strategy.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

- A mild and efficient one-pot visible light-induced method
- Metal-free organic dyes have been used
- Functionalization of a wide range of native C-H bonds in an economical and sustainable manner