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Eosin Y as a direct hydrogen-atom transfer photocatalyst for the C3-H acylation of quinoxalin-2(*1H*)-ones

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ABSTRACT

Visible light promoted eosin Y catalyzed selective C3-H acylation of quinoxalin-2(*1H*)-ones has been developed in a green and sustainable manner. In contrast to the conventional anionic eosin Y-based photoredox process, neutral eosin Y acts as the actual catalyst, which was responsible for the hydrogen-atom transfer (HAT) process to generate the acyl radical with readily available aldehydes as the radical precursor.

Introduction

Photocatalysis has emerged as a viable tool to realize cross-coupling reactions over the past decade. [1] This subtle organic photosynthesis is generally achieved with various iridium and ruthenium complexes as well as organic dyes as photocatalysts. [2] In contrast to the classical two-electron pathways, single electron transfer (SET) or energy transfer (ET) process of the excited photocatalysts occurs in these reactions to generate the reactive radical species. However, new activation modes of the photoexcited catalysts are being explored by chemists aside from their commonly utilized ones. [3]

Eosin Y, as an economic and ecological photocatalyst, has been widely applied as the photoredox (Fig. 1) catalyst in organic synthesis (Scheme 1a). [4] It was recognized that anionic forms of eosin Y were responsible for the photocatalytic activity in the majority of the previously reported photo-reactions whereas the neutral forms were considered to be inactive. [5] However, recent results reported by Wu's and Wang's groups indicated that the excited neutral eosin Y act as the direct hydrogen atom transfer (HAT) photocatalyst, which opened a new door for the use of eosin Y in photocatalysis (Scheme 1b) [6].

Quinoxalin-2(*1H*)-ones are valuable heterocyclic compounds due to their rich biological activities. [7] In recent years, a variety of methods have been developed for the direct functionalization of the versatile quinoxalin-2(1*H*)-one scaffold. [8] Among these, C3-H acylation *via* radical process is emerging as an efficient way for the preparation of C3-acylated quinoxalin-2(*1H*)-ones. [9] However, novel and green methods are still demanding considering that harsh conditions [9] and unstable radical precursors [9] are usually required for the previous methods. Herein, we reported a visible light promoted eosin Y catalyzed C3-H acylation of quinoxalin-2(*1H*)-ones. Compared to the unstable and complex acyl radical precursors, [10] easily accessible aldehydes were utilized as the radical precursors directly to generate the acyl radical via HAT process (Scheme 1c).

Reaction conditions were optimized with quinoxalin-2(*1H*)-one (**1a**) and benzaldehyde (**2a**) as the model substrates, and the selected results were shown in Table 1 (see Table S1 for more details). After extensive trials, low catalyst loading (Na_2-eosin Y, 0.5%) in CH_3CN under 20 W blue LED irradiation gave the desired product in a 97% yield (entry 1–3, Table 1). Less or trace product was formed with other photocatalysts or without catalyst (entry 4–6, Table 1). Yield decreased dramatically under air or with $K_2S_2O_8$ as the oxidant, and shorter reaction time gave the product in a lower yield (entry 7–9, Table 1). Control experiment without light gave no product, confirming the significance of light (entry 10, Table 1).

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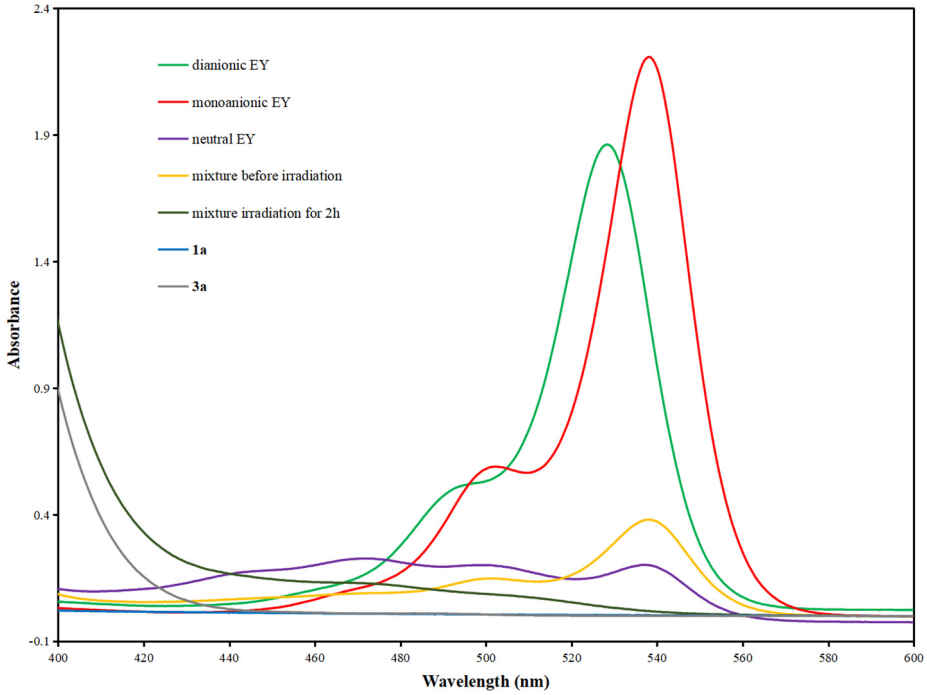
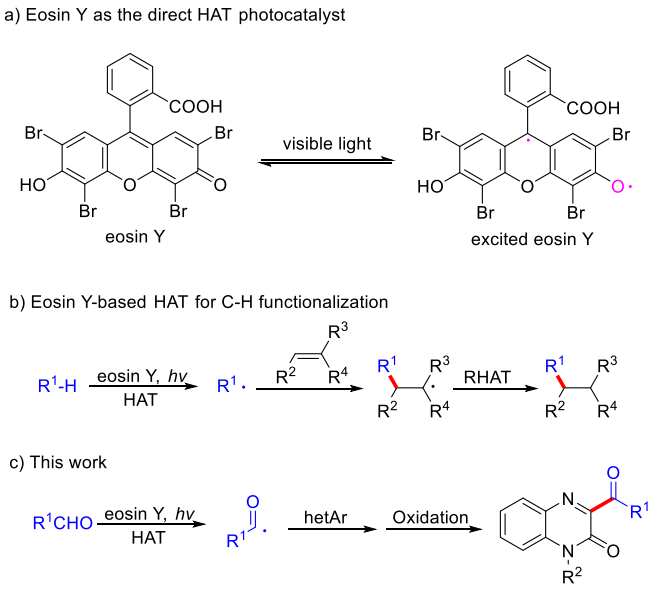
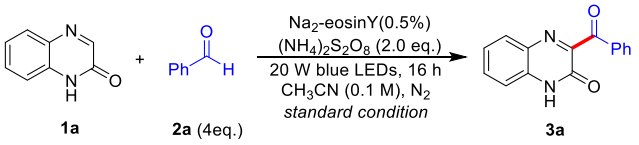


Fig. 1. UV–Vis of different forms of eosin Y and reaction solution. Acetonitrile solution: dianionic eosin Y (40 μM Na_2-eosin Y); monoanionic eosin Y (40 μM eosin Y + 40 μM TFA); neutral eosin Y (1 mM eosin Y + 3 mM TFA); **1a** (1 mM); **3a** (1 mM).



Scheme 1. Eosin Y as the HAT photocatalyst.

Table 1
Optimization of reaction conditions[a]



1a **2a** (4eq.) **3a**

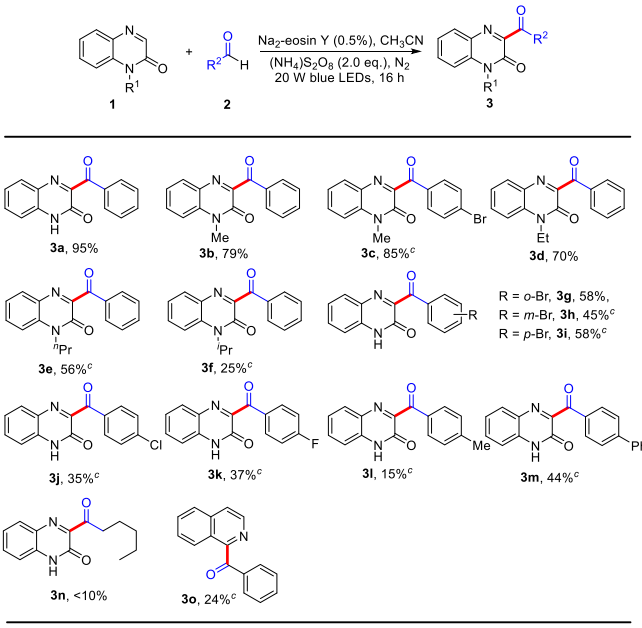
Entry	Deviation from standard conditions	Yield[b]
1	none	97%
2	1% of Na_2-eosin Y	95%
3	0.25% of Na_2-eosin Y	80%
4	Without Na_2-eosin Y	10%
5	$Ru(bpy)_3Cl_2·6H_2O$ as catalyst	14%
6	$Ir(ppy)_3$ as catalyst	<5%
7	$K_2S_2O_8$ as the oxidant	14%
8	Reaction under air	8%
9	Reaction for 7 h	47%
10	Without blue LED light at 45 °C	trace

[a]All reactions were conducted at 0.3 mmol scale of **1a** in 3.0 mL of acetonitrile in a closed flask under nitrogen atmosphere with 20 W blue led (450–455 nm) at around 40 °C.
[b]Yield determined by HPLC using 4-acetylbiphenyl as internal standard.

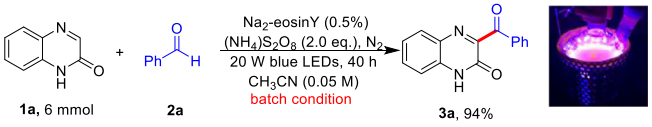
Under the optimal reaction condition, the substrate scope of quinoxalin-2(*1H*)-ones and aldehydes were examined, and results were compiled in Table 2. It was found that unprotected quinoxaline-2(*1H*)-ones were well tolerated in this acylation reaction under the optimal reaction condition. Generally, the photocatalytic C3-H acylation reaction of N1-substituted quinoxalin-2(*1H*)-ones proceeded well to give the product **3b**-**3f** in moderate to good yield. Aromatic aldehyde **2** with electron-withdrawing group (**3 g**-**3 k**) or electron-donating group (**3 l** and **3 m**) provided the desired products in a lower yield. Product **3 l** was only obtained in a 15% yield, which might be due to the benzylic Csp3-H of *p*-methyl benzaldehyde might participate in the HAT process [6]. More hindered aldehyde performed well to form the desired product (3 g) in a 58% yield. Aliphatic aldehyde was also tested, though generating the product (**3n**) in a quite low yield, indicating that the aliphatic acyl radical was inert to the C=N bond of quinoxalin-2(*1H*)-one. [9] In addition to the quinoxalin-2(*1H*)-one, isoquinoline was found to be compatible with our protocol to give the product (**3o**) in a 24% yield.

To demonstrate the utility of the C3-H acylation reaction, a gram-scale reaction was carried out under the standard condition. To our delight, with a longer reaction time and lower concentration, this acylation reaction could be easily scaled up to gram scale, affording the desired product **3a** in an excellent yield (94%) (Scheme 2).

Table 2
Scope of quinoxalin-2(1H)-ones and aldehyde[a,b]

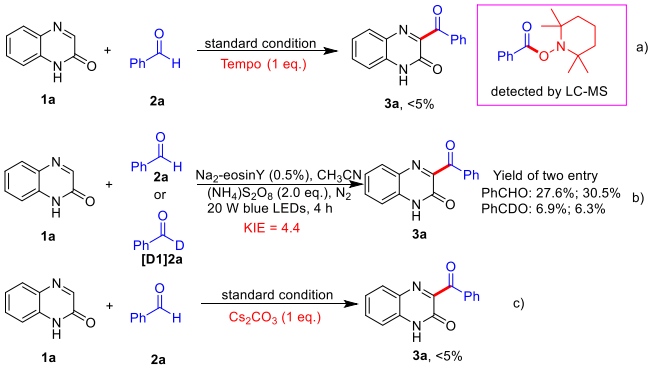


[a]All reactions were conducted at 0.3 mmol scale of **1** in 3.0 mL of CH_3CN in a closed flask under nitrogen atmosphere with 20 W blue led (450–455 nm) at around 40 °C.
[b]Isolated yield.
[c]Reaction conducted for 24 h.

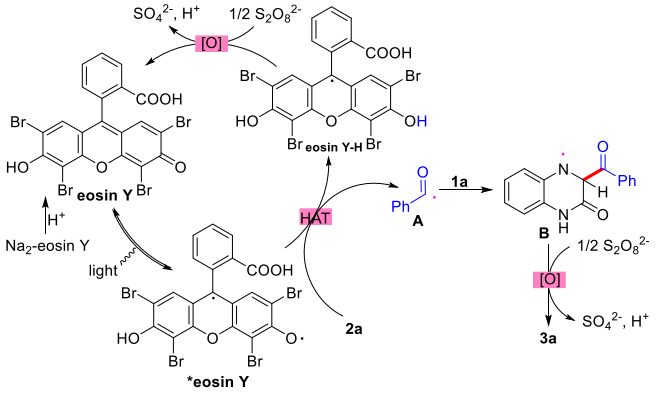


Scheme 2. Gram scale reaction.

In order to gain some insight into the reaction mechanism, several control experiments were conducted. Addition of 1 equivalent of TEMPO into the standard reaction almost inhibited the acylation reaction with the TEMPO adduct detected by LC-MS, demonstrating that a radical process was likely to be involved in this reaction (Scheme 3a). Furthermore, a kinetic isotope effect value of 4.4 was determined through comparation of parallel reaction yields of **2a** and [D1]**2a** under the standard reaction condition, which indicated that the C—H elimination step might be involved in the rate-determining step (Scheme 3b).



Scheme 3. Mechanistic study.



Scheme 4. Proposed mechanism.

To elucidate the actual species of eosin Y in the catalytic cycle, UV/Vis analysis and control experiments were performed (Fig. 1).

UV/Vis analysis revealed that Na_2-eosin Y exhibited dianionic form in acetonitrile, and monoanionic and neutral form of eosin Y were generated with the addition of CF_3COOH, which was in accordance with literature. [6] Monoanionic form of the reaction mixture before irradiation was observed while this monoanionic form peak disappeared after irradiation for 2 h. These results demonstrated that neutral eosin Y should be the actual specie in the catalytic cycle to undergo HAT process for the formation of acyl radical, [6] which was further confirmed by the result that the acylation reaction could not proceed with the addition of 1 equivalent of Cs_2CO_3.

According to the above experiments and literature [6,8,9], a plausible mechanism was proposed (Scheme 4). Initially, Na_2-eosin Y was acidified by NH_4^+ to give the neutral eosin Y, which was excited by blue light irradiation to give the excited eosin Y. Through a HAT process, the acyl radical was generated as well as the eosin Y-H, and oxidization of eosin Y-H by $S_2O_8^{2-}$ regenerate the neutral eosin Y. Then, addition of **A** to C=N bond of quinoxalin-2(*1H*)-one gave the nitrogen-centered radical **B**, and the following oxidative deprotonation of **B** afforded the final product **3**.

In conclusion, visible light promoted eosin Y catalyzed selective C3-H acylation of quinoxalin-2(*1H*)-ones has been achieved in a green and sustainable way. It is noteworthy that readily available aldehydes act as the radical precursors, and low catalyst loading was required for this reaction. In addition, this method could be easily scaled up to gram-scale under batch condition, which provided a very convenient way for photo-promoted gram-scale synthesis. Mechanistic study revealed that reaction proceeded via radical process, and neutral eosin Y was the actual species in the catalytic cycle to undergo HAT process for the formation of acyl radicals. This simple and green protocol would provide a complementary way for the functionalization of nitrogen-containing heterocycles both in pharmaceutical chemistry and organic chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152915.

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