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Letter

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Photoredox Catalysis: Construction of Polyheterocycles via Alkoxycarbonylation/Addition/Cyclization Sequence

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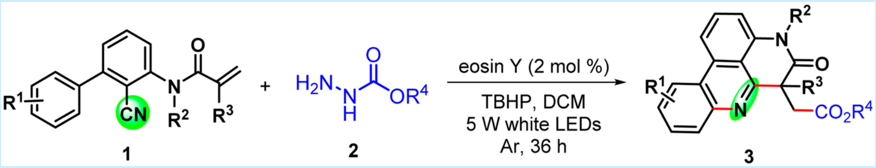
Ⓢ *Supporting Information*



ABSTRACT: A novel visible-light-induced cascade reaction for the preparation of ester-functionalized polyheterocycles was developed under metal-free conditions, which was initiated by an intermolecular radical addition to a carbon−carbon double bond of *N*-arylacrylamide derivatives using alkyl carbazate as the ester source followed by cyano-mediated cyclization. The desired phenanthridine derivative products were isolated in moderate to high yields with broad substrate scope.

The importance of heterocyclic compounds in organic and pharmaceutical chemistry is undoubted, thus the synthesis of these molecules is one of the most important works for organic chemists, and many efforts have been made for this purpose over the course of a century.[1] Visible-light-induced radical reactions have aroused more and more attention in recent years because of their simplicity, efficiency, and unique activation, as well as atom economy.[2] This strategy has been successfully used for the synthesis of heterocycles,[3] and a series of pioneering and significant methods were developed in this field. Many of these heterocyclization reactions were initiated via the addition of radicals to carbon−carbon double bonds. For example, by the addition of several radicals to *N*-acryloyl benzamides, isoquinoline-1,3(2*H*,4*H*)-diones were synthesized;[4] the addition to *N*-arylacrylamides generated oxoindoles;[5] the addition to cinnamamides resulted in quinolone-2-ones or 1-azaspiro[4.5]-decanes;[6] intramolecular oxy- and aminoarylation of alkenes with a aryl radical produced tetrahydrofuran and pyrrolidine derivatives;[7] the difunctionalization of styrenes using ammonium thiocyanate yielded 1,3-oxathiolanes.[8] The radical addition plays an increasingly significant role in the synthesis of heterocyclic compounds.

Cyano is a versatile functional group in organic synthesis because it can be used as an important precursor for a multitude of transformations.[9] Cyano-participated radical addition/cyclization for the formation of cyclic compounds has aroused much interest in recent years. A series of reports involved the application of a cyano group to be used as the carbonyl source in the construction of various substituted quinoline diones[10] and some other cyclic ketones.[11] Furthermore, several intramolecular radical cascade cyclizations through the addition to a cyano group to construct fused N-heterocyclic compounds were developed.[12] These significant approaches stimulated us to further explore the application of this group in the synthesis of functionalized polycyclic heterocycles. In this letter, we wish to report a novel visible-light-induced cascade alkoxycarbonylation/addition/cyclization to obtain tetracyclic compounds 2-(5-oxo-5,6-dihydro-4*H*-pyrido[4,3,2-*gh*]phenanthridin-6-yl)-acetates, in which cyano acted as the key mediator.

Looking for appropriate reaction conditions, we selected *N*-(2-cyano-[1,1′-biphenyl]-3-yl)-*N*-methylmethacrylamide (**1a**) and methyl carbazate (**2a**) as the model substrates. Under the irradiation of 5 W white LEDs, using eosin Y as photocatalyst and in the presence of TBHP (*tert*-butyl hydroperoxide), the fused heterocycle product methyl 2-(4,6-dimethyl-5-oxo-5,6-dihydro-4*H*-pyrido[4,3,2-*gh*]phenanthridin-6-yl)acetate (**3a**) was obtained in 48% yield after 16 h, whereas less than 10% byproduct **3a′** that was generated via a cyclization on the 6-position of the benzene ring of **1a** was observed. Encouraged by this result, we optimized the reaction conditions (Table 1). Oxidants were first screened. Without oxidant, no desired product **3a** was obtained (entry 2). Compared with TBHP, the oxidants H_2O_2, DTBP (di-*tert*-butyl peroxide), TBPB (*tert*-butyl peroxybenzoate), and DCP (dicumyl peroxide) showed lower efficiency for this reaction (entries 3−6). Sequential screening of solvents found that the highest yield of 57% was obtained when the reaction was performed in DCM, whereas other solvents gave lower yields (entries 7−11). In view of the important impact of the catalyst on photoredox catalysis, we next examined several other photocatalysts such as eosin B, rhodamine B, acid red 94, fluorescein, and $Ru(bpy)_3Cl_2$ (entries 12−16). Nevertheless, no results better than those of eosin Y were observed. The experimental results also revealed that a 2 mol % catalyst loading was appropriate for this reaction (entries 17 and 18). In the dark, the reaction could not take place at all (entry 19). The irradiation

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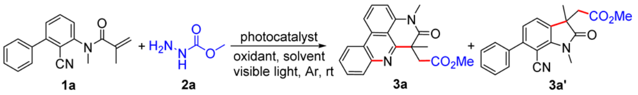
Table 1. Optimization of Reaction Conditions[a]



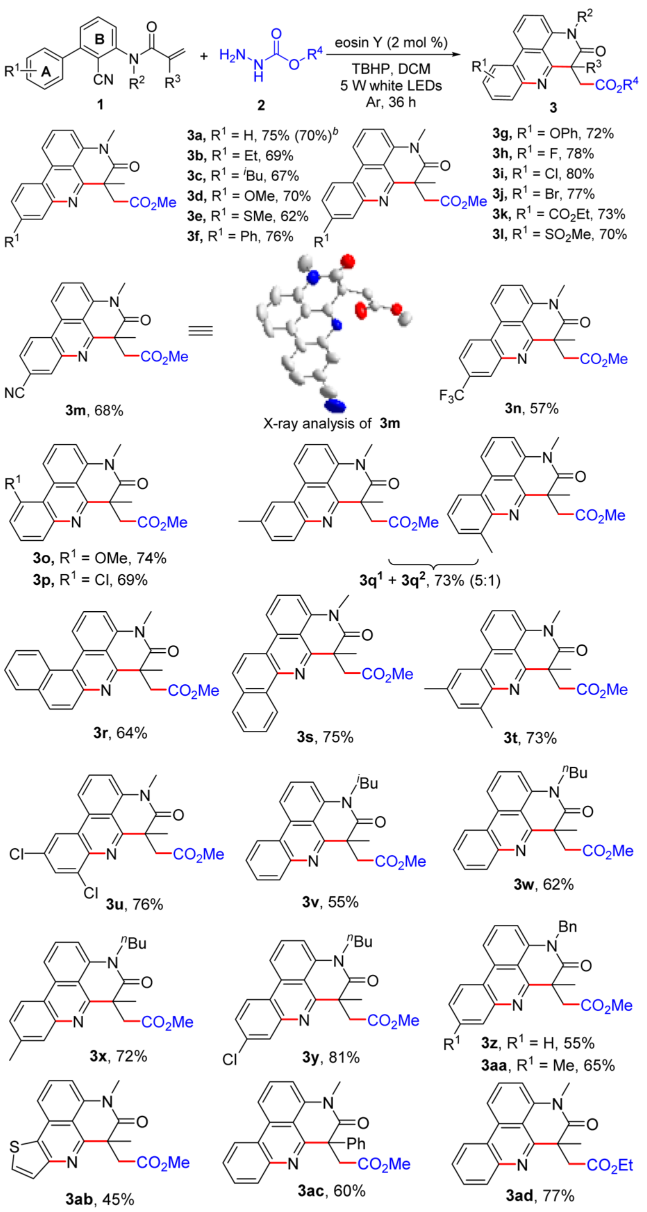
entry	catalyst (mol %)	oxidant	solvent	3a yield (%)	3a′ yield (%)
1	eosin Y (2)	TBHP	CH_3CN	48	<10
2	eosin Y (2)		CH_3CN	0	0
3	eosin Y (2)	H_2O_2	CH_3CN	38	0
4	eosin Y (2)	DTBP	CH_3CN	42	<10
5	eosin Y (2)	TBPB	CH_3CN	46	<10
6	eosin Y (2)	BPO	CH_3CN	0	0
7	eosin Y (2)	TBHP	DCE	55	trace
8	eosin Y (2)	TBHP	DCM	57	trace
9	eosin Y (2)	TBHP	acetone	40	<10
10	eosin Y (2)	TBHP	DMSO	32	<10
11	eosin Y (2)	TBHP	DMF	20	<10
12	eosin B (2)	TBHP	DCM	trace	0
13	rhodamine B (2)	TBHP	DCM	46	trace
14	acid red 94 (2)	TBHP	DCM	40	0
15	fluorescein (2)	TBHP	DCM	0	0
16	$Ru(bpy)_3Cl_2$ (2)	TBHP	DCM	41	<10
17	eosin Y (1)	TBHP	DCM	42	0
18	eosin Y (3)	TBHP	DCM	55	trace
19[b]	eosin Y (2)	TBHP	DCM	0	0
20[c]	eosin Y (2)	TBHP	DCM	54	trace
21[d]	eosin Y (2)	TBHP	DCM	43	0
22[e]	**eosin Y (2)**	**TBHP**	**DCM**	**75**	**trace**

[a] Reactions conditions (unless otherwise specified): **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (2 mol %), oxidant (4 equiv), and solvent (2 mL) were placed in a sealed tube under Ar atmosphere upon irradiation of 5 W white LEDs for 16 h. [b] In the dark. [c] Using 5 W blue LEDs. [d] Using 23 W CFL. [e] The reaction time was 36 h.

with 5 W blue LEDs or 23 W CFL instead of 5 W white LEDs provided lower yields of **3a** (entries 20 and 21). Furthermore, the yield could be increased to 75% when the reaction time was extended to 36 h (entry 22).

With the optimized conditions in hand, the substrate scope in this visible-light-induced alkoxycarbonylated cyclization was investigated (Scheme 1). The effect of the substituents on the benzene ring **A** of reactant **1** was first examined. As shown in Scheme 1, for the substrates with both electron-donating groups (alkyl, alkoxy, alkylthiol, etc.) and electron-withdrawing groups (halogen, ester, sulfonyl, cyano, etc.) on the *para*-position of benzene ring **A**, the reactions proceeded smoothly, and the yields had no significant difference (**3a**−**3m**). The structure of the product **3m** was further confirmed by crystal X-ray diffraction (CCDC number 1538715). In the presence of a strong electron-withdrawing substituent, trifluoromethyl, a lower yield of 57% was obtained (**3n**). The *ortho*-MeO- or Cl-substituted reactants also gave high yields (**3o** and **3p**), in which no steric hindrance was observed. For the *meta*-methyl-substituted reactant (**1q**), a mixture of the products **3q**^{1} and **3q**^{2} were separated from the reaction mixture in a ratio of 5:1. The reaction could also take place on the naphthalene ring, and the pentacyclic compounds were obtained from this visible-light-induced cascade cyclization (**3r** and **3s**). For disubstituted substrates, the reaction gave results similar to those of monosubstituted substrates (**3t** and **3u**). The effect of different substituents on nitrogen was then studied. The comparable yields were obtained from *N*-^{n}butyl reactants (**3w**−**3y**), whereas *N*-isobutyl- or benzyl-substituted derivatives gave the products in moderate yields (**3v**, **3z**, and **3aa**). It is worth mentioning that a thieno[3,2-*c*]isoquinoline motif was constructed via the cyclization on the thiophene ring (**3ab**), which demonstrated that this cascade cyclization was appropriate for the synthesis of more types of fused heterocyclic compounds. The reaction could still perform well when R^3 was phenyl, and the desired product **3ac** with 60% yield was obtained under the same conditions. In addition, when ethyl carbazate was employed as the ester group source, the cascade cyclization reaction also proceeded smoothly to afford product **3ad** in 77% yield.

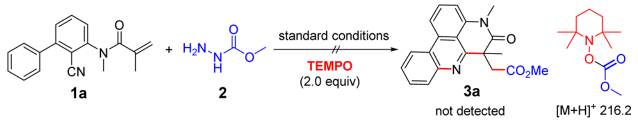
Scheme 1. Synthesis of Pyrido[4,3,2-*gh*]phenanthridin-6-yl)acetate Derivatives[a]



[a] Reactions conditions: **1** (0.2 mmol), **2** (0.4 mmol), eosin Y (2 mol %), TBHP (4 equiv), and DCM (2 mL) were placed in a sealed tube under Ar atmosphere upon irradiation of 5 W white LEDs for 36 h. [b] At 1 mmol scale.

To understand the reaction mechanism adequately, a control experiment was carried out, as shown in Scheme 2. When 2 equiv of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy

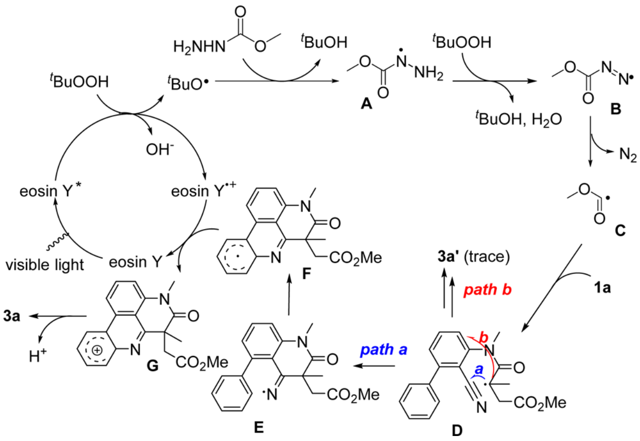
Scheme 2. Control Experiment



(TEMPO) was added to the reaction mixture of **1a** under the standard reaction conditions, the reaction was entirely suppressed and no desired product **3a** was found; the TEMPO−$COOCH_3$ adduct was detected by LC-MS, which indicated that this reaction might proceed through a radical pathway.

On the basis of the above experimental results and previous reports, a plausible mechanism for this transformation is proposed in Scheme 3. Initially, the photocatalyst eosin Y was irradiated by visible light to form the excited-state species eosin Y*. Eosin Y* readily underwent a single electron transfer with TBHP to give a *tert*-butoxyl radical, which captured a hydrogen from methyl carbazate (**2a**) to give the nitrogen radical intermediate **A**.[13] The sequential dehydrogenation of **A** by TBHP gave alkoxycarbonyl diazo radical **B**, which released a molecular nitrogen to form an alkoxycarbonyl radical **C**.[14] The addition of alkoxycarbonyl radical **C** to the carbon−carbon double bond of the reactant **1a** generated the radical intermediate **D**.[4,5] Radical **D** then underwent an intramolecular cyclization with a cyano group to give the radical intermediate **E** (path a). The subsequent addition of **E** to the benzene ring produced the conjugated radical **F**.[12] The oxidation of intermediate **F** by the eosin Y cation radical species gave the carbocation **G**. Finally, a fused heterocyclic product **3a** was produced via deprotonation of intermediate **G**, and the photocatalyst eosin Y was regenerated to go to the next catalytic cycle. In contrast, the intramolecular cyclization for the construction of oxindole derivative **3a′** via radical **D** addition to electron-deficient *ortho*-carbon was unfavorable (path b).

Scheme 3. Proposed Reaction Mechanism



In summary, we have developed a novel visible-light-induced cascade cyclization reaction for the synthesis of ester-functionalized pyrido[4,3,2-*gh*]phenanthridind derivatives using alkyl carbazate as the ester source under metal-free conditions. The process showed considerable advantages such as mild reaction conditions, simplicity of the reaction procedure, and high atom economy. This present work provides an efficient strategy for constructing polycyclic heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01553.

Experimental procedures, characterization data, and NMR spectra for **1** and **3** (PDF)
X-ray data for **3m** (CIF)

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Notes

The authors declare no competing financial interest.

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