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Carbamoyl Radicals via Photoredox Decarboxylation of Oxamic Acids in Aqueous Media: Access to 3,4-Dihydroquinolin-2(1*H*)-ones

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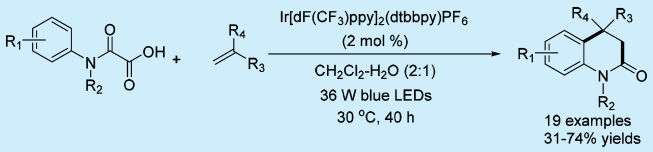
Supporting Information

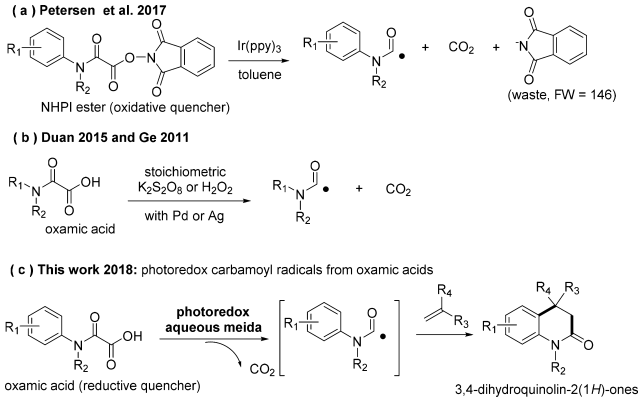
ABSTRACT: The first visible-light-mediated photoredox oxidative approach for generating carbamoyl radicals from oxamic acids is disclosed. Reaction of the generated carbamoyl radicals with electron-deficient alkenes opens efficient access to 3,4-dihydroquinolin-2(1*H*)-ones under mild conditions through a sequence of intermolecular radical addition, cyclization, and aromatization. The process is compatible with a variety of oxamic acids and electron-deficient alkenes, and a wide variety of 3,4-dihydroquinolin-2(1*H*)-ones were prepared.



Visible-light photoredox catalysis has emerged as a powerful, eco-friendly synthetic platform for forming carbon−carbon or carbon-heteroatom bonds by employing ruthenium/iridium polypyridyl complexes or organic dyes as photoredox catalysts.[1] Excited with visible light, photoredox catalysts could act as both excellent one-electron reductants and oxidants, which react with organic or organometallic molecules to generate reactive alkyl, aryl, and acyl radicals to engage in reaction process, enabling a wide array of previously inaccessible transformations could be accomplished under extraordinary mild conditions. In this context, photoredox decarboxylative functionalization of carboxylic acids have attracted significant attention.[2] Many types of acids, such as α-oxocarboxylic acids,[3] α-amino acids,[4] and α-oxy acids[5] could undergo direct decarboxylation to afford the corresponding radicals under photoredox conditions. In particular, conversion of carboxylic acid to the corresponding *N*-hydroxyphthalimide (NHPI) ester has been wide explored and demonstrated as a versatile and powerful tool for site-specific decarboxylation to afford alkyl or acyl radicals,[6] as *N*-hydroxyphthalimide motif could easily undergo single-electron reduction by the excited photocatalyst, followed by rapid decarboxylative fragmentation to liberate 1 equiv of CO_2 and $^{-}$NPhth as byproducts.[7]

A carbamoyl radical is a versatile reaction intermediate for synthesizing molecules with amide functionality and nitrogen-containing heterocycles. Thus, development of novel strategies for generation of carbamoyl radicals is highly desirable. Very recently, employing *N*-hydroxylphthalimide as decarboxylative auxiliary, Petersen and co-workers[8] disclosed a photoredox-neutral approach for generation of carbamoyl radicals from *N*-hydroxyphthalimido oxamides using $Ir(ppy)_3$ as a catalyst (Scheme 1a). Although this method was shown to possess a wide substrate scope, the starting *N*-hydroxyphthalimido oxamides must be prepared under relative harsh conditions (low temperature, dry solvent), stored in darkness, and the phthalimide subunit, containing around half of the molecular weight (formula weight (FW) = 146) becomes part of waste after the reaction.

Scheme 1. Methods for Generation of Carbamoyl Radicals



From the viewpoint of atom-economy, preparation handling, and stability, direct conversion of readily available oxamic acid to a carbamoyl radical, although challenging, would be much more appealing. Existing methods for carbamoyl radical generation from oxamic acid usually employ stoichiometric $K_2S_2O_8$ or H_2O_2 as an oxidant, along with Pd or Ag as a catalyst[9] (see Scheme 1b). To the best of our knowledge, photoredox catalysis for the generation of carbamoyl radicals from oxamic acids has not been reported yet.

Herein, we report a visible-light-mediated approach for generating a carbamoyl radical from oxamic acid and its reaction with alkenes to afford 3,4-dihydroquinolin-2(1*H*)-ones, which is a privileged structure subunit existing in many biologically active natural products and pharmaceuticals,[10] via a

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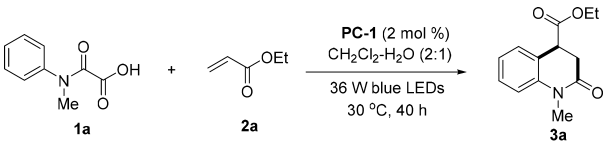
sequence of intermolecular radical addition, intramolecular cyclization, and aromatization.

A gram-scale synthesis of oxamic acids was carried out through an operating-simple sequence:

(1) reaction of *N*-alkylaniline with methyl 2-chloro-2-oxoacetate at room temperature in the presence of $NaHCO_3$;
(2) hydrolysis of the resulting methyl ester in THF with aqueous KOH; and
(3) acidification of the aqueous layer with HCl, followed by filtration and extraction.

The reaction conditions for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones were then optimized using *N*-methyl-*N*-phenyloxamic acid **1a** and ethyl acrylate **2a** as model substrates. Some selected examples are listed in Table 1. Gratifyingly, by irradiating the mixture of *N*-methyl-*N*-phenyloxamic acid **1a** and 3 equiv of ethyl acrylate **2a** in CH_2Cl_2–H_2O (v/v = 2:1) with 36 W blue LEDs, in the presence of 2 mol % of **PC-1** as photocatalyst at 30 °C for 40 h, the desired 3,4-dihydroquinolin-2(1*H*)-one **3a** was observed in 68% yield, according to ^1H NMR analysis, and isolated in 64% yield (entry 1 in Table 1). **PC-1** is crucial for the transformation, as much lower yields were observed when **PC-2**, Eosin Y, and 2,4,6-triphenylpyrylium fluoroborate were employed as photocatalysts (entries 2–4 in Table 1). Increasing the amount of ethyl acrylate **2a** to 5 equiv could improve neither reaction efficiency nor yield (entry 5 in Table 1). Elevating the reaction temperature to 55 °C resulted in a decreased yield of 24%, which is due to the formation of *N*-methyl-*N*-phenylformamide (entry 6 in Table 1). Solvent screening indicated that aqueous CH_2Cl_2 was optimal, and the addition of H_2O had a beneficial effect (entries 7–13 in Table 1). It was found that basic additives had a deleterious effect, as lower yields were observed, ranging from 35% to 42% (entries 14–16 in Table 1). On the other hand, the addition of acetic acid could also achieve the comparable yields with those adding base (entry 17 in Table 1). Interestingly, the amount of oxygen seemed important for achieving high yield, as lower yields were observed under both O_2 and N_2 atmosphere (entries 18 and 20 in Table 1) and comparable yield was achieved without N_2 bubbling (entry 19 in Table 1). The presence of more O_2 was prone to demethylation of the target **3a** to form 4-ethoxycarbonyl-3,4-dihydroquinolin-2(1*H*)-one (entry 18 in Table 1). Control experiments confirmed that both photocatalyst and visible light were essential for significant conversion to the product (entries 21 and 22 in Table 1), as no product was observed in the absence of both light and photocatalyst.

Table 1. Optimization of Reaction Conditions[a]



entry	variation from the standard conditions	yield[b] (%)
1	none	68 (64)
2	**PC-2** instead of **PC-1**	38
3	**PC-3** instead of **PC-1**[c]	trace
4	**PC-4** instead of **PC-1**	trace
5	with 5 equiv of **2a**	65
6	performed at 55 °C	24[d]
7	H_2O instead of CH_2Cl_2–H_2O	trace
8	CH_2Cl_2 instead of CH_2Cl_2–H_2O	18
9	acetone-H_2O instead of CH_2Cl_2–H_2O	22
10	CH_3CN–H_2O instead of CH_2Cl_2–H_2O	16
11	DMSO-H_2O instead of CH_2Cl_2–H_2O	trace
12	THF-H_2O instead of CH_2Cl_2–H_2O	13
13	EtOH-H_2O instead of CH_2Cl_2–H_2O	12
14	with 1.5 equiv of KH_2PO_4	39
15	with 1.5 equiv of $K_3PO_4.3H_2O$	35
16	with 1.5 equiv of K_2CO_3	42
17	with 1.5 equiv of CH_3COOH	44
18	under O_2 atmosphere	(34)[e]
19	without N_2 bubbling	62 (60)
20	N_2 through "freeze-pump-thaw" cycle	(35)
21	no blue light	0
22	no **PC-1**	0

[a]Reaction conditions: *N*-methyl-*N*-phenyloxamic acid **1a** (0.3 mmol), ethyl acrylate **2a** (0.9 mmol), photocatalyst (2 mol %), organic solvent (4 mL), H_2O (2 mL), N_2(bubbling for 5 min), 36 W blue LEDs, 30 °C, 40 h. [b]Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. The value given in the parentheses is the isolated yield. [c]Irradiating with 36 W green LEDs. [d]*N*-methyl-*N*-phenylformamide was observed in 10% yield. [e]4-Ethoxycarbonyl-3,4-dihydroquinolin-2(1*H*)-one was isolated in 10% yield.

With the optimized conditions in hand, we next sought to investigate the substrate scope of both alkenes and oxamic acids in this new photoredox carbamoyl radical generation, radical addition, and cyclization process. To simplify operation, reactions were carried out without N_2 bubbling and the results are summarized in Scheme 2. A wide array of monosubstituted electron-deficient alkenes, such as *n*-butyl acrylate, *t*-butyl acrylate, *N*,*N*-dimethylacrylamide, ethyl vinyl ketone, phenyl vinyl sulfone, and acrylonitrile were first subjected to the reaction with *N*-methyl-*N*-phenyloxamic acid under the standard conditions, affording the corresponding 3,4-dihydroquinolin-2(1*H*)-ones **3b**–**3g** in 31%–60% yields. Moreover, 1,1-disubstituted alkenes was also compatible with the process. Particularly, the reaction of α-methylene-γ-butyrolactone with *N*-methyl-*N*-phenyloxamic acid proceeded smoothly to provide the spirocyclic lactone lactam **3i** in 41% yield, which was slightly lower than that of Donald's, using *N*-hydroxyphthalimido oxamide as the carbamoyl radical precursor. A series of oxamic acids with different substitutions on the phenyl subunit was then investigated. To our delight, the oxamic acids with both electron-withdrawing (−Cl, −F, and $-CF_3$) and electron-donating (−Me and −OMe) groups could provide the desired 3,4-dihydroquinolin-2(1*H*)-ones **3j**–**3o** in moderate yields, ranging from 41% to 56%. Finally, two types of oxamic acids with different groups on the N atom were investigated. Pleasingly, both *N*-benzyl- and *N*-allyl-substituted oxamic acids could undergo a similar process smoothly, providing the desired products **3p**–**3s** in 50%–74% yields, although they have potential reactions on both the benzyl and allyl motifs.

Mechanism studies were then carried out. In the reaction of *N*-methyl-*N*-phenyloxamic acid with ethyl acrylate under the standard conditions, a trace amount of *N*-methyl-*N*-phenylformamide was isolated.[11] Moreover, when a radical scavenger (TEMPO) was added to the same reaction, only a trace amount of **3a** was detected. Both results indicated that the reaction probably proceeded via the formation of a carbamoyl radical. A

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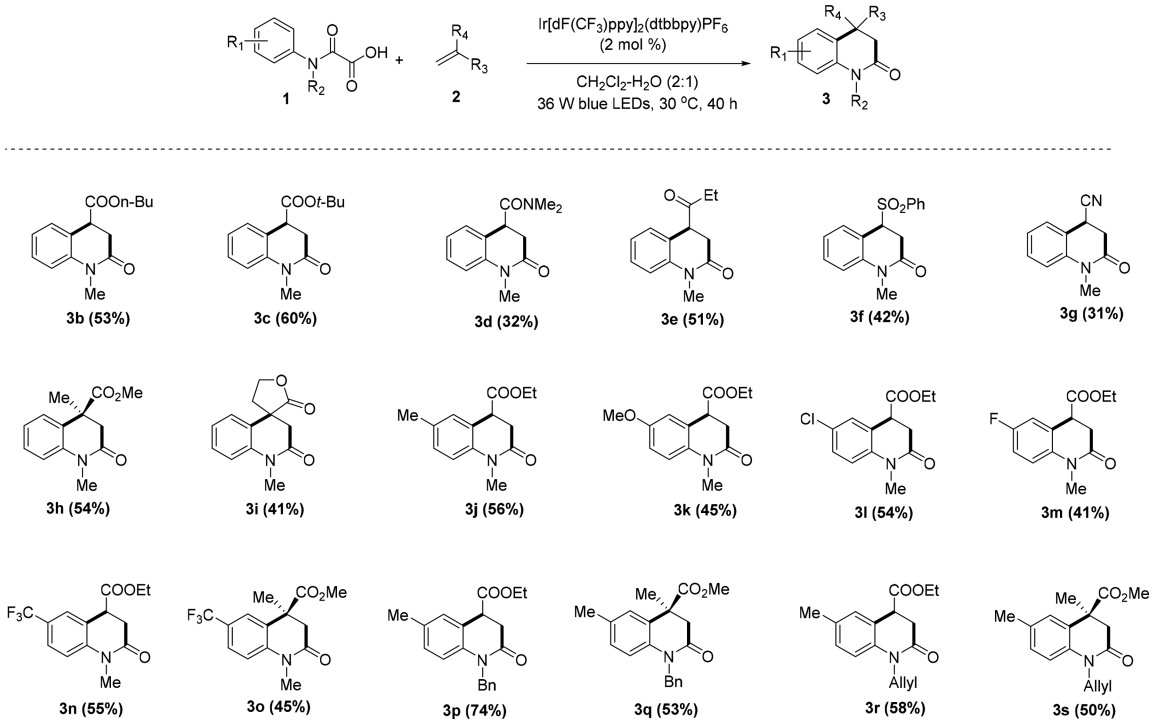
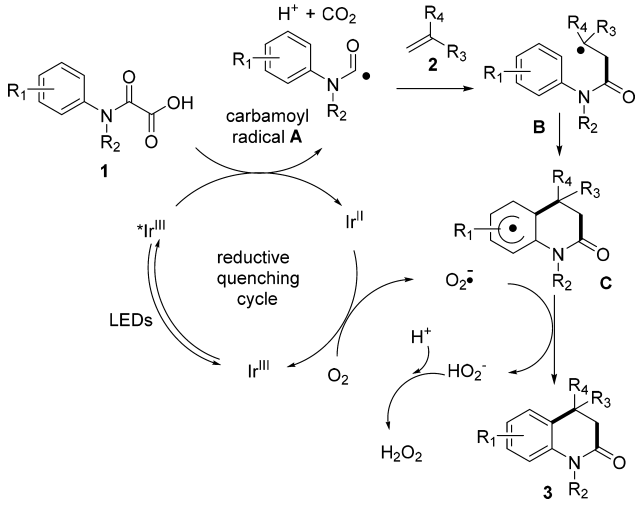
Scheme 2. Substrate Scope Investigation



plausible mechanism is illustrated in Scheme 3. Irradiation of Ir^{III} with blue light generated long-lived photoexcited catalyst

Scheme 3. Proposed Reaction Mechanism



Ir^{III}*, which was then reductively quenched with oxamic acid to afford Ir^{II}, carbamoyl radical intermediate **A**, and CO_2. Intermolecular nucleophilic addition of the carbamoyl radical to electron-deficient alkene then occurred to generate new radical **B**, which could then engage in intramolecular homolytic aromatic substitution to deliver cyclohexadienyl radical **C**. The reduced Ir^{II} was then oxidized by the residue oxygen in the reaction tube to regenerate the ground state Ir^{III} to complete the catalytic cycle. Meanwhile, the generated oxygen radical anion abstracted a hydrogen atom from cyclohexadienyl radical **C** to provide the desired 3,4-dihydroquinolin-2(1*H*)-one **3** and HO_2^-. Finally, HO_2^- anion was protonated to form H_2O_2.

In conclusion, we have disclosed a new visible-light-mediated decarboxylative approach toward a carbamoyl radical from oxamic acid. As an example for application of the present methodology, the generated carbamoyl radical was subjected to the reaction with electron-deficient alkenes, enabling efficient access to 3,4-dihydroquinolin-2(1*H*)-ones via a sequence of intermolecular radical addition, intramolecular cyclization, and aromatization. The process is compatible with a variety of oxamic acids and electron-deficient alkenes. Moreover, comparing with *N*-hydroxyphthalimido oxamide as the reductive carbamoyl radical precursor, oxamic acid is not only more atom-economical, stable, and easily prepared, but it also undergoes the reaction in an oxidative manner under photoredox catalysis, thus providing a basis for the development of carbamoyl radical chemistry. Synthesis of other heterocycles via visible-light-mediated decarboxylative generation of carbamoyl radical from oxamic acid is under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00449.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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