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Visible-Light Mediated Carbamoyl Radical Addition to Heteroarenes

Ashique Hussain Jatoi, Govind Goroba Pawar, Frédéric Robert, and Yannick Landais*

The generation of carbamoyl radicals, followed by their addition to heteroarenes was performed under mild conditions through a metal-free photocatalyzed oxidative decarboxylation of oxamic acids. The process has been applied to the carbamoylation of heteroaromatic bases using α -aminoacid-derived oxamic acids leading to the corresponding amides without racemization.

Carbamoyl radicals constitute a useful class of reactive intermediates, exhibiting a relatively long lifetime as compared to that of their acyl analogues, which tend to decarbonylate easily to generate alkyl radicals.¹ Although these radical species have attracted less interest than acyl radicals, they were shown to efficiently add, both inter- and intramolecularly, to unsaturated systems, including alkenes and alkynes,² arenes³ and heteroarenes.⁴ Loss of hydrogen under oxidative conditions also allow their conversion into useful isocyanates.⁵ Carbamoyl radicals are accessible through essentially three main routes: (1) the C-X bond cleavage in $R_2N(C=O)X$ precursors ($X = H$,^{4,6} xanthate,⁷ SPh,⁸ Co(salen),⁹..), (2) the photoredox reductive decarboxylation of N-hydroxyphthalimido oxamides³ and (3) the oxidative decarboxylation of oxamic acids.^{5,10} These acids are readily available by combination of amines and oxalic acid derivatives¹¹ and constitute potent precursors of carbamoyl radicals. The generation of carbamoyl radicals from oxamic acids is particularly useful as it circumvents the problem of regioselectivity encountered for instance during the C-H abstraction in formamides ($R_2N(C=O)H$), which occurs concurrently at CHO and α to nitrogen, leading to a mixture of products.⁴ Oxidative decarboxylation of oxamic acids may be carried out in the presence of Ag(I) and Cu(II) salts, with stoichiometric amount of $K_2S_2O_8$ as an oxidant in a biphasic medium, as originally proposed by Minisci and co-workers.⁵ These conditions however suffer from the presence of large amount of metal catalysts, and water was shown to be detrimental to the process efficiency, as observed for instance during the preparation of isocyanates. We recently showed that the oxidative decarboxylation of oxamic acid could also be performed conveniently under metal-free conditions in an organic solvent, using an organo-photocatalyst under visible-light irradiation, leading to the corresponding isocyanates in good yields.¹² When the reaction was carried out in the presence of alcohols, the corresponding urethanes were isolated in excellent yields in a one-pot process. Our mechanistic studies unambiguously showed that a carbamoyl radical was generated under these conditions, which was trapped by unsaturated substrates. We thus report here an extension of this work, with the visible-light mediated addition of oxamic acids onto heteroaromatic bases using a visible-light photoredox catalysis¹³ and an hypervalent iodine reagent as an oxidant (Figure 1). This metal-free procedure enables the amidation of heteroarenes in generally good yields under mild conditions. The method was extended to the carbamoylation of heterocycles using α -aminoacid-derived oxamic acids, which occurred without racemization.

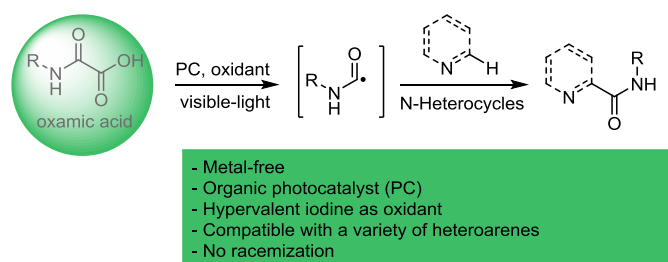
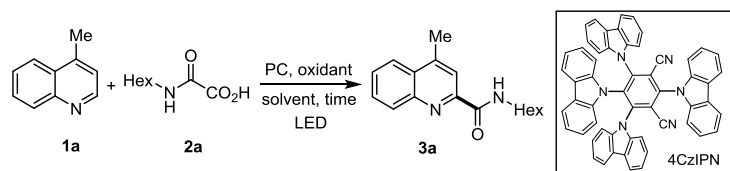


Figure 1 Visible-light mediated amidation of *N*-heterocycles

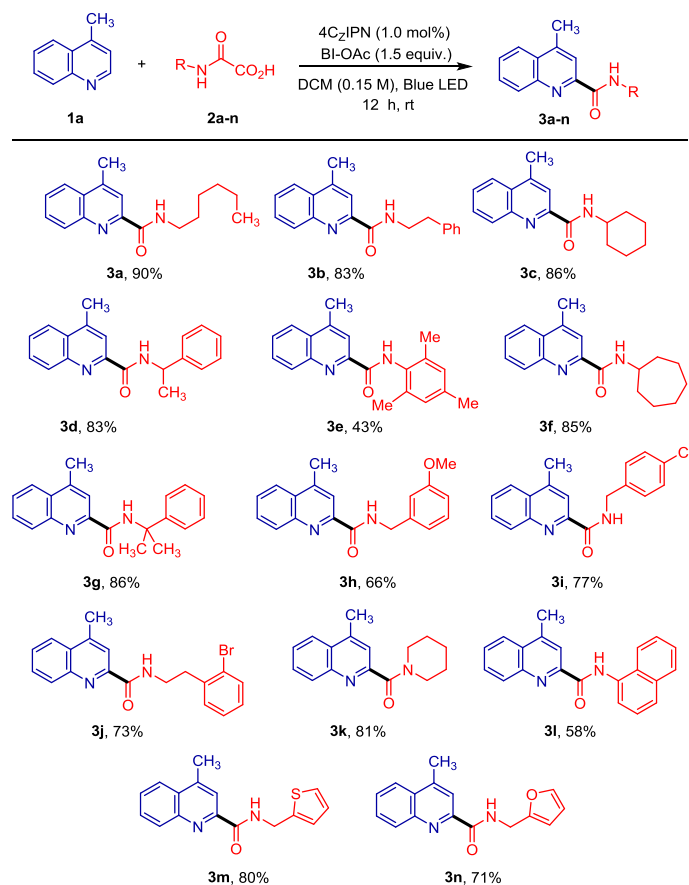
Reaction conditions were first optimized, as summarized in Table 1, to access carboxamide **3a** from oxamic acid **2a** and lepidine **1a** as a model heteroaromatic base (Table 1). Photocatalyst 4CzIPN¹⁴ was first tested considering its efficiency in our previous study. Blue LEDs were also selected regarding the maximum UV-vis absorption of 4CzIPN. Preliminary results using hypervalent iodine oxidants such as $PhI(OAc)_2$ (PIDA), $PhI(TFA)_2$ (PIFA) and BI-OH afforded **3a** in good yields (entries 1-3). However, changing these oxidants for BI-OAc¹⁵ remarkably improved the yield, due to the presence of a better leaving group (OAc) at the iodine center (entry 4).¹² Eosin-Y and rose Bengal were also tested as photocatalysts, but led only to traces of **3a** (entries 6-7), while an acridinium salt¹⁶ provided 70% conversion (entry 5). 1.0 mol % of 4CzIPN, 0.75 mmol of BI-OAc in CH_2Cl_2 for 12 h were thus selected as optimal conditions (entry 4). Solvents were also varied, indicating that CH_2Cl_2 and DCE were superior (entries 4 and 8), while THF, MeCN, DMF and DMSO led to lower yields (entries 9-12). Finally control experiments were carried out, showing that, photocatalyst, oxidant and light were all essential for the process to occur (entries 13-15).

Table 1 Addition of oxamic acid **2b** to lepidine **1a**.

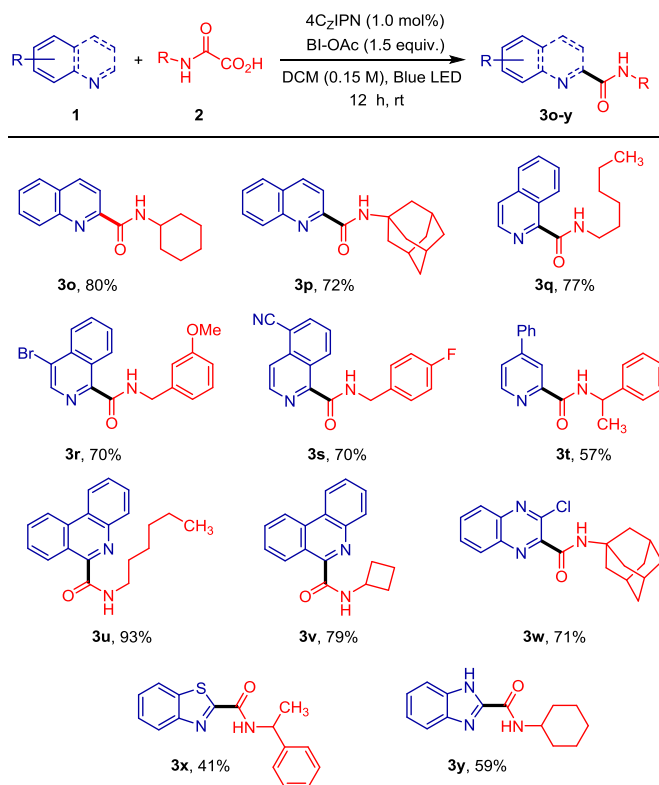
entr y	PC	oxidant	solvent	Time (h)	Yield (%)
1	4CzIPN	PhI(OAc) ₂	CH ₂ Cl ₂	12	76
2	4CzIPN	PhI(TFA) ₂	CH ₂ Cl ₂	12	65
3	4CzIPN	BI-OH	CH ₂ Cl ₂	12	69
4	4CzIPN	BI-OAc	CH ₂ Cl ₂	12	95
5	AcrMes ⁺ ClO ₄ ⁻	BI-OAc	CH ₂ Cl ₂	12	70
6	Eosin Y	BI-OAc	CH ₂ Cl ₂	15	Trace
7	Rose Bengal	BI-OAc	CH ₂ Cl ₂	12	NA
8	4CzIPN	BI-OAc	DCE	12	85
9	4CzIPN	BI-OAc	THF	12	33
10	4CzIPN	BI-OAc	MeCN	12	58
11	4CzIPN	BI-OAc	DMF	12	51
12	4CzIPN	BI-OAc	DMSO	12	NA
13	-	BI-OAc	CH ₂ Cl ₂	12	NA
14	4CzIPN	-	CH ₂ Cl ₂	12	NA
15	4CzIPN	BI-OAc	CH ₂ Cl ₂	12	NA ^d

^a Unless otherwise mentioned, all reactions were performed with **1a** (1.0 eq.), **2b** (2.0 eq.), PC (1.0 mol%) and oxidant (1.5 eq.) in the indicated solvent (0.2 M), in a sealed tube. ^b Yields of **3a** determined by ¹H NMR with 1,3,5-trimethylbenzene as an external standard ^d Isolated yields of **3a**. ^e Absence of blue LED.

With these results, in hands, the substrate scope was extended varying the nature of oxamic acids **2** in the presence of Lepidine **1a** (Scheme 1). The mild reaction conditions allowed the formation of various amides **3a-n** in generally good yields. For oxamic acids bearing sterically hindered substituents, amides were isolated in somewhat lower yields (e.g. **3e**). **3m-n**, having benzylic substituents sensitive to oxidations were also obtained in high yields.

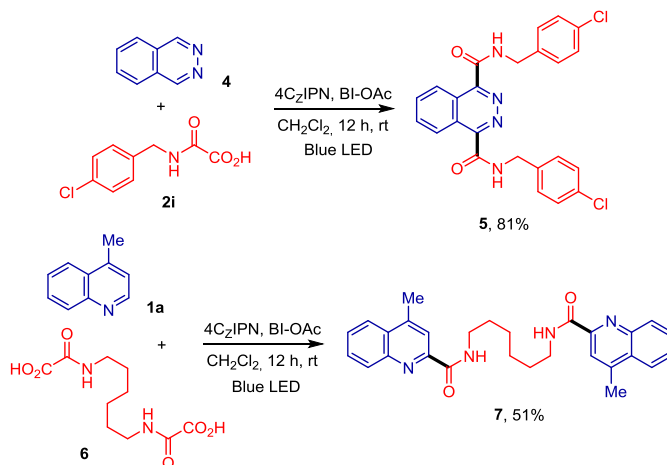
**Scheme 1** Oxidative decarboxylation of oxamic acids in the presence of lepidine **1a**. Oxamic acid scope.

Other heteroaromatic compounds were submitted to the optimal reaction conditions above, showing that the method is general, the addition occurring regioselectively β - to the nitrogen (Scheme 2).¹⁷ Interestingly, in cases where two regioisomers may be formed as in **3q**, **3r** and **3s**, only one was observed. Benzimidazole and benzothiazole were found to be competent substrates for the carbamoyl addition, albeit lower yields were observed (e.g. **3x-y**). A similar reactivity was observed for 4-phenylpyridine, which led to amide **3t** in moderate yield. In these cases, the absence of extended aromatic systems probably explain the lower reactivity, the radical intermediate formed upon addition of the carbamoyl radical being less stabilized (vide infra). This may also explain the failure of the addition with several other heteroarenes, including 4-*i*Pr-pyridine, 4-DMAP, indole, furane, (+)-cinchonine, caffeine or pyrrole (see ESI). Considering that carbamoyl radicals are nucleophilic in nature, their addition was also attempted on electron-poor arenes such 1,3-dicyanobenzene or 1,3-(CF₃)₂benzene, but again not addition was observed under these conditions.



Scheme 2 Oxidative decarboxylation of oxamic acids in the presence of heteroarenes **1a**. heteroarenes scope.

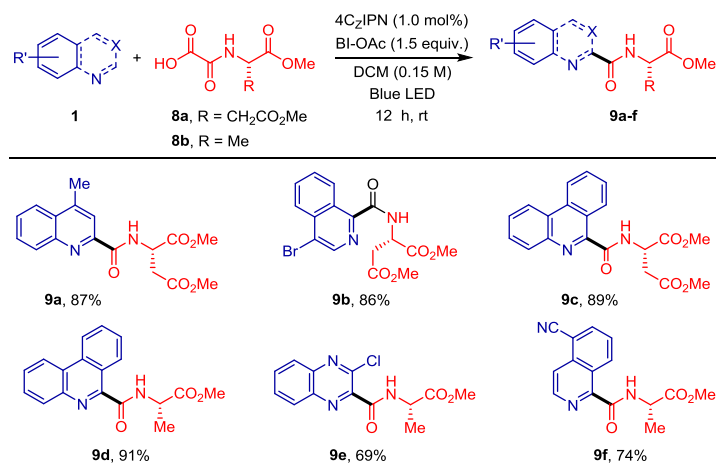
Interestingly, double addition was observed between phthalazine **4** as a heteroaromatic base and oxamic acid **2i**, affording bis-amide **5** in excellent yield (Scheme 3). We were unable to detect the mono-addition product, when using only one equivalent of **2i**, suggesting that the mono-amide was much more reactive than **4**, the first amidation increasing the electron-deficiency of the heteroarene, thus accelerating the second addition.^{17c} In parallel, bis-amide **7** was prepared in moderate yield by coupling two equivalents of lepidine **1a** with bis-oxamic acid **6**.



^a The reaction was carried out with heteroaromatic bases **4**, oxamic acid **2i**, PC (1 mol%) and oxidant (1.5 eq.) in DCE (0.15 M) in a sealed tube. ^b The reaction was carried out with lepidine **1a**, oxamic acid **6**, PC (1 mol%) and oxidant (1.5 eq.) in DCE (0.15 M) in a sealed tube.

Scheme 3 Double oxidative decarboxylation of oxamic acids in the presence of heteroarenes.

Finally, oxamic acids **8a-b** were prepared from the corresponding (L)-amino acids, through an efficient two-steps procedure, involving the treatment of the amine-free amino-ester with ClCOCOt-Bu, followed by the removal of the *t*-Bu substituent using TFA (ESI).¹¹ **8a-b** were then submitted to the photocatalyzed oxidative decarboxylation in the presence of several heterocycles **1**, leading to the corresponding chiral amides **9a-f** in excellent yields (Scheme 4). The reaction was also carried out with *rac*-**8a**, and the HPLC signatures of *rac*-**9a** and homochiral **9a** compared (ESI), to show unambiguously that no racemization occurred during the oxidative process. It is also worth noticing that treatment of **9a** with Lewis acids such as Eu(hfc)₃ or strong bases (Cs₂CO₃) led to **9a** with unchanged optical rotation, emphasizing on the high configurational stability of these chiral amides.



Scheme 4 Oxidative decarboxylation of amino-acids derived oxamic acids.

A tentative mechanism for the carbamoylation of heteroarenes under photoredox conditions is finally proposed, based on our previous trapping experiments (Figure 2).¹² These studies showed that the key carbamoyl radical **III** likely results from the formation of a radical-anion **II**, itself issued from the hypiodite species **I**, formed in situ through the coupling between the oxamic acid and BIOAc.¹⁸ The quenching of the photocatalyst in its excited state by hypiodite **I**, would form **II**, while returning the photocatalyst in its semi-oxidized form (PC⁺). Cleavage of the weak O-I bond in **II** would then lead to the corresponding amidocarboxyl radical (not shown), which decarboxylation would generate **III** and *o*-iodobenzoic acid. Radical addition of the carbamoyl radical **III** onto the heteroaromatic base would form intermediate **IV**, the oxidation of which, by the radical-cation PC⁺, generating cationic species **V**. Deprotonation of the latter and rearomatization would finally give the corresponding amide.^{17a,c} An alternative mechanism may also be proposed, considering the protonation of the heteroaromatic base under the reaction conditions (AcOH is formed), as suggested by Minisci in his seminal studies on the addition of related formamide (HC(=O)NH₂) onto heteroarenes.^{4,17a} Such a protonation would activate the heteroarene toward the addition of the electron-rich carbamoyl radical to form N-protonated-**IV**. The ensuing loss of the α -C-H proton would produce a rather stable allylic captodative radical species, which oxidation (by PC⁺) would give the final protonated amide. This mechanism cannot be formally ruled out at this stage, although our conditions are much less acidic than those in Minisci's work (H₂SO₄).

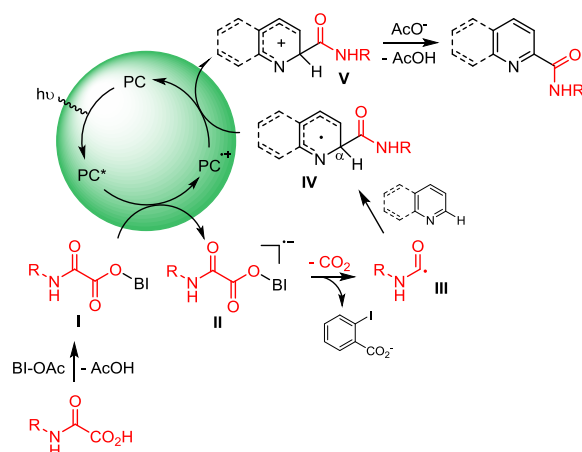


Figure 2 Mechanism of the photocatalyzed decarboxylative amidation of oxamic acids.

In summary, we reported the addition, onto heteroaromatic bases, of carbamoyl radical species generated through a “metal-free” photocatalyzed oxidative decarboxylation of oxamic acids. This strategy allows a straightforward and environmentally benign carbamoylation of a variety of *N*-heterocycles. The methodology uses readily available starting material as well as standard photocatalyst and organic oxidant sources. Reaction conditions are mild, offering an access to heteroaryl amides derived from amino-acids without racemization.

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