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Visible-Light Photocatalyzed Oxidation of Oxamic Acids: A Green Route to Urethanes and Ureas

Govind Goroba Pawar,[a] Frédéric Robert,[a] Etienne Grau,[b] Henri Cramail,*[b] and Yannick Landais*[a]

A unique and sustainable metal-free route to urethanes and ureas based on a photocatalyzed synthesis of isocyanates using oxamic acids is described. This includes *in situ* generation of isocyanates using a light source, which triggers a free-radical decarboxylation of an oxamic acid derivative in the presence of an organic dye as a photocatalyst and an hypervalent iodine reagent as an oxidant. This protocol successfully avoids the isolation, purification and storage of carcinogenic isocyanates and allows elaboration of urethanes and ureas in a one-pot process from commercially available resources.

Carbamates display attractive biological activities and constitute key structural motifs in many targets having clinical potential.[1] This functional group is present in many FDA approved drugs. They show, as amides, bond resonance, albeit to a smaller extent as compared to amides.[2] Carbamates exhibit excellent proteolytic stabilities[3] and, as a consequence, are often used as peptide bond surrogates.[4] Carbamates are also widely used as amine protecting groups,[5] showing orthogonality and stability towards acids, bases or hydrogenation. Numerous methods have been developed to access carbamates and among the best known, the Hofmann amide rearrangement,[6] the Curtius rearrangement from acyl azide,[7] or the addition of amines to mixed carbonates.[8] Sustainable procedures using CO_2 as a phosgene surrogate have been described recently.[9] Finally, the addition of alcohols to isocyanates is probably the most reliable method to access carbamates.[10] This strategy is commonly employed to access polyurethanes (PUs), an important class of polymers with a wide range of applications.[11] However, this approach suffers from the use of highly hazardous phosgene as a precursor during the preparation of isocyanates. Strategies to avoid such toxic activated carbonyl species have flourished and have been reviewed recently.[12] Oxamic acid prepared through the coupling between amines and oxalic acid derivatives are potent precursors of isocyanates. Minisci originally oxidized such α-amidoacid derivatives into isocyanates using Ag(I) and Cu(II) salts as catalysts and stoichiometric amount of $K_2S_2O_8$ as an oxidant in a water-CH_3CN medium.[13] Although the reaction led to the desired isocyanates, yields were moderate and large amount of amine was also observed due to partial hydrolysis of the isocyanate in the reaction medium. We propose here to investigate a metal-free catalytic system to overcome these problems, developing an environmentally friendly synthetic route to isocyanates and urethanes, which may also be extended to ureas. Our strategy includes the in situ generation of isocyanates using a photocatalyst and a visible light source,[14] which triggers a free-radical decarboxylation of an oxamic acid derivative in the presence of an organic oxidant (Figure 1).[15] This protocol successfully avoids the isolation, purification and storage of the carcinogenic isocyanates and allows elaboration of urethanes, ureas in a one-pot process from commercially available sources.

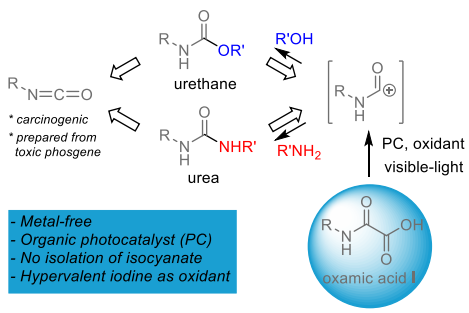

Figure 1 Visible-light mediated access to urethanes and ureas from oxamic acids

Reaction conditions were first optimized as to access in a one-pot process carbamate **3a** from oxamic acid **1a** (Table 1). The transformation was first carried out in the presence of photoredox catalyst $Ru(bpy)_3Cl_2H_2O$ and $(NH_4)_2S_2O_8$ as an

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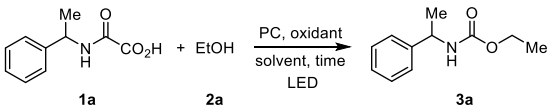
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

oxidant in CH_2Cl_2/H_2O (1:1) at room temperature under visible light irradiation (Blue LEDs, λ_{max} = 452 nm, SI). Pleasingly, in our first attempt the corresponding carbamate **3a** was isolated in 30% yield (entry 1). The use of other oxidants such as $K_2S_2O_8$, or $Na_2S_2O_8$ provided poor results (yields <15%). Removal of water from the reaction medium and use of $(^nBu_4N)_2S_2O_8$ in CH_2Cl_2 led only to trace amounts of **3a** (entry 2). However, when hypervalent iodine (BI-OH) was introduced as an oxidant, the desired product was formed in good yields (entry 3).[16] Changing BI-OH for the more reactive acetoxybenzodioxole (BI-OAc) led to improved yield (entry 4). Gratifyingly, the reaction proceeded readily in DCE using 1.0 mol% of photocatalyst affording **3a** in 94% yield (entry 5).

Table 1 Oxidative decarboxylation of oxamic acids. Optimization conditions

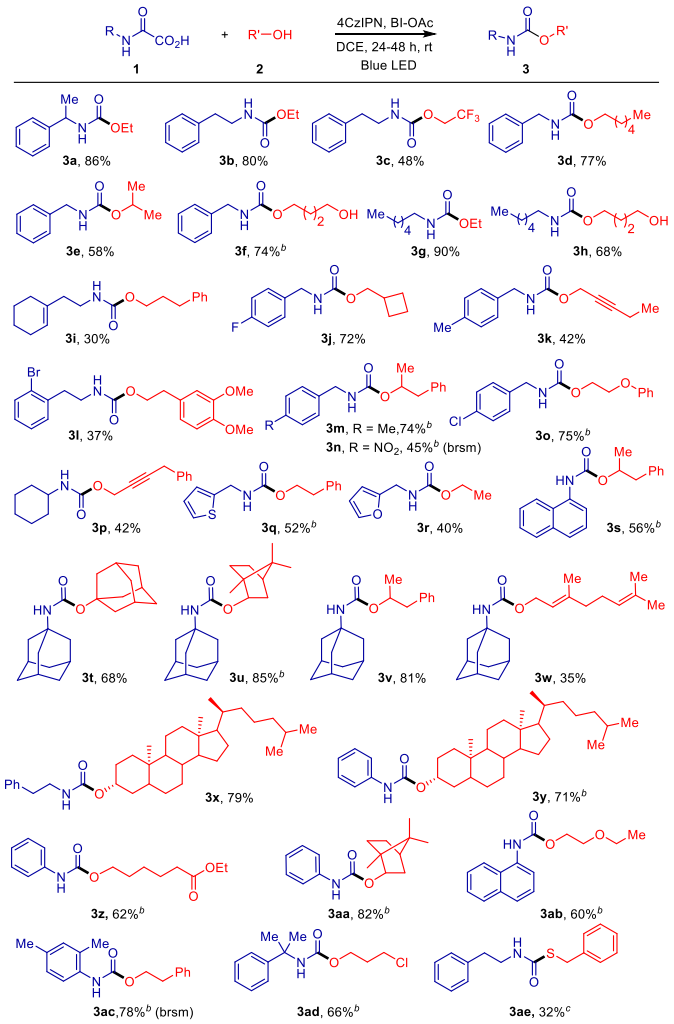


entry[a]	PC	oxidant	solvent	t (h)	Yield (%)[b]
1	$Ru(bpy)_3Cl_2,6H_2O$	$(NH_4)_2S_2O_8$	CH_2Cl_2/H_2O[c]	15	30
2	$Ru(bpy)_3Cl_2,6H_2O$	$(^nBu_4)_2S_2O_8$	CH_2Cl_2	15	Trace
3	$Ru(bpy)_3Cl_2,6H_2O$	BI-OH	CH_2Cl_2	15	75
4	$Ru(bpy)_3Cl_2,6H_2O$	BI-OAc	CH_2Cl_2	15	86
5	$Ru(bpy)_3Cl_2,6H_2O$	BI-OAc	DCE	15	94(91)[d]
6	4CzIPN	BI-OAc	DCE	15	76
7	4CzIPN	BI-OAc	DCE	24	91(86)[d]
8	$AcrMes^+ClO_4^-$	BI-OAc	DCE	24	80
9	4CzIPN	BI-OAc	CH_2Cl_2	24	84
10	4CzIPN	BI-OAc	THF	24	46
11	4CzIPN	BI-OAc	MeCN	24	52
12	4CzIPN	BI-OAc	DMF	24	30
13	4CzIPN	BI-OAc	DMSO	24	NA
14	-	BI-OAc	DCE	24	NA
15	4CzIPN	-	DCE	24	NA
16	4CzIPN	BI-OAc	DCE	24	NA[f]

[a] Unless otherwise mentioned, all reactions were performed with **1a** (0.5 mmol), **2a** (1.5 mmol), PC catalyst (0.01 mmol), and oxidant (0.75 mmol) in 0.2 M solvent, in a sealed tube (entry 1-6). [b] Yields of **3a** determined by ^1H NMR with external standard 1,3,5-triemethylbenzene [c] 1:1 mixture. [d] Isolated yields of **3a**. [e] PC catalyst (0.005 mmol) (entry 7-13). [f] absence of Blue LED.

Encouraged by these results, replacement of non-sustainable metal photoredox catalyst with cheaper organic dyes was then investigated, using BI-OAc as the oxidant and DCE as a solvent. While Eosin-Y, rose-Bengal led only to traces of **3a**, 4CzIPN[18] showed efficiency comparable to that of metal photocatalysts (entry 6). Similarly, acridinium salt[17] provided 80% of conversion (entry 8). Remarkably, decreasing the amount of 4CzIPN to 1.0 mol % and increasing the reaction time up to 24 h finally offered optimal conditions with 91% yield (entry 7). Among hypervalent iodine reagents examined, BI-OAc was the most effective oxidant for this reaction as compared to BI-OH, BI-OMe, $PhI(OAc)_2$, and $PhI(TFA)_2$. An evaluation of solvents showed that reaction proceeds more efficiently with DCE or CH_2Cl_2 (entries 7-8), as use of THF, MeCN, DMF, or DMSO, significantly decreased the yields (entries 9-13). Finally, control experiments indicated that both photocatalyst and oxidant, as well as light were necessary for this transformation, as no desired product was observed in their absence (entries 14-15).

With these optimal conditions in hand, the scope of the reaction was then established, varying the nature of oxamic acids **1** and alcohols **2** (Scheme 1). As highlighted in Scheme 1, the one-pot process was shown to be rather general, with yields ranging between 30% and 90%. Primary, secondary and tertiary alcohols react smoothly even with hindered isocyanates (*i.e.* **3t-w**, **3ac**, **3d**), although reaction time needs to be increased with steric bulk of the alcohol. The reaction conditions are mild, allowing functional groups on both partners, including alcohols, halides, alkynes, strained rings, hetero-aromatic groups or esters.



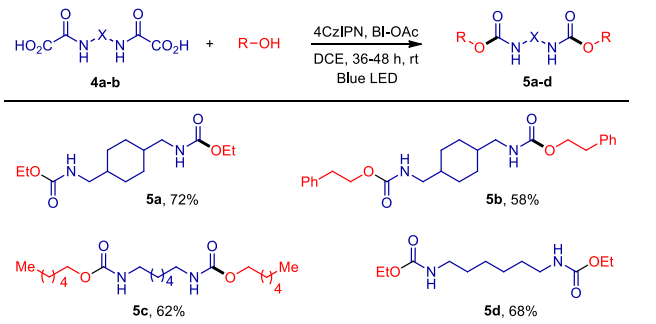
[a] **Conditions A:** The reactions were carried out with Oxamic Acid (0.5 mmol), ROH (1.0-1.5 mmol), PC catalyst (0.005 mmol), and oxidant (0.75 mmol) in DCE (0.2 M), in a sealed tube. [b] **Conditions B:** The reaction was conducted with ROH (0.25 mmol), Oxamic Acid (0.75 mmol), PC catalyst (0.005 mmol), and oxidant (0.75 mmol) in DCE (0.1 M), in a sealed tube. [c] Oxamic Acid (0.5 mmol), PC catalyst (0.005 mmol), and oxidant (0.75 mmol), in DCE (0.1 M), then Et_3N (1.0 mmol), RSH (0.75 mmol), under Ar atm, 30°C , 4-6 h.

Scheme 1 Oxidative decarboxylation of oxamic acids. Substrate scope.

Two main limitations were however observed; (1) reaction using benzylic alcohols did not provide the desired compounds

due to the oxidation of the alcohol under the reaction conditions; (2) somewhat lower yields were observed when oxamic acids derived from anilines and benzylamines were used. This was attributed to the decarbonylation of the putative carbamoyl radical intermediate forming a more stable anilinyl radical[13b] and the oxidation of benzylic position to the corresponding aldehyde respectively. It is worth mentioning that the use of an excess of oxamic acids in these cases overcomes the limitation and increases the yields of the corresponding carbamates (**Conditions B**).

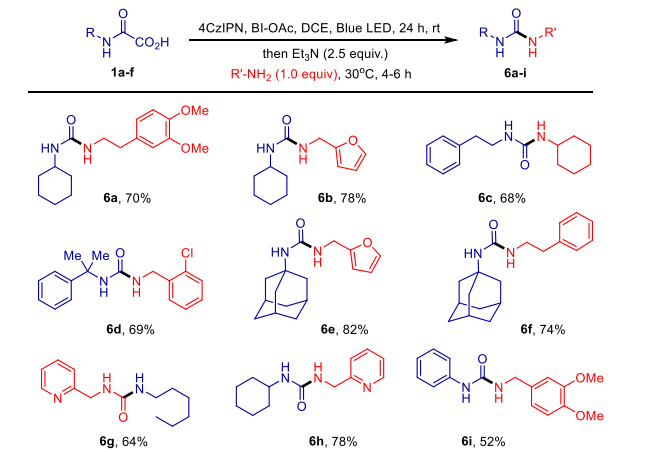
Bis-oxamic acids **4a-b** were also shown to react cleanly with alcohols under the optimal reaction conditions to afford the corresponding bis-carbamates **5a-d** in good yields (Scheme 2). This result is noteworthy as it opens the way to the synthesis of polyurethanes using diols.



[a] The reactions were carried out with oxamic Acid (0.5 mmol), ROH (1.5 mmol), PC catalyst (0.01 mmol), and oxidant (1.0 mmol) in DCE (0.2 M), in a sealed tube.

Scheme 2 Bis-oxamic acids as urethane precursors

The results obtained in the carbamate series then prompted us to extend the methodology to the preparation of unsymmetrical ureas. The one-pot protocol established for the carbamate was however not found suitable for a direct access

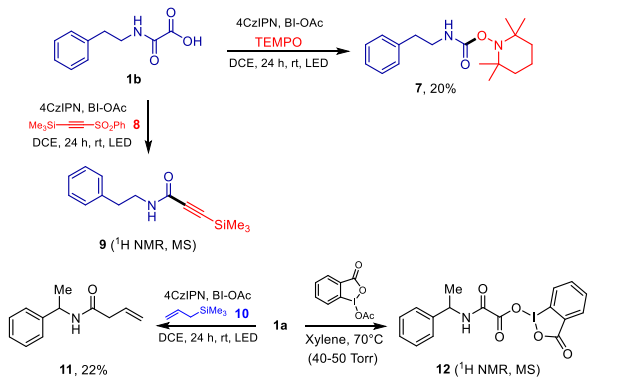


[a] The reactions were carried out with oxamic Acid (0.5 mmol), PC catalyst (0.005 mmol), and oxidant (0.75 mmol), in DCE (0.1 M), then Et_3N (1.5 mmol), RNH_2 (0.25 mmol), under Ar atm, 30°C , 4-6 h.

Scheme 3 Oxidative decarboxylation of oxamic acids. Synthesis of unsymmetrical ureas.

to ureas, likely due to the oxidation of the amine partner under the reaction conditions. Moreover, the presence of benzoic acid residue resulting from the reaction of the oxidant BI-OAc clearly obstructed the formation of ureas. These drawbacks could however be circumvented adding, in the same pot, 3.0 equiv. of Et_3N prior to the addition of the amine. This two-steps one-pot protocol proved its efficiency affording a variety of ureas **6a-i** in reasonable to good yields (Scheme 3).

Finally, a series of intermediate trapping experiments were carried out as to establish the mechanism of the photocatalyzed oxidative decarboxylation of oxamic acids. First, **1a** was treated under the standard conditions, but in the presence of TEMPO, which led to the formation of compound **7**, albeit in low yield, supporting the radical nature of the process (Scheme 3). According to the seminal mechanistic proposal by Minisci,[13b] decarboxylation of oxamic acid under oxidative conditions should proceed through the formation of a carbamoyl radical (RNHCO·) intermediate,[19] which further oxidation would generate the corresponding cation or protonated isocyanate ($RNHC^{+}=O \leftrightarrow RN^{+}H=C=O$). When oxamic acid **1a** was treated under conditions above, but in the presence of alkynylsulfone **8**,[20] amide **9** was obtained, supporting the presence of a carbamoyl radical intermediate, reacting onto **8** through an addition-elimination process to form **9**. The same reaction was repeated using allylsilane **10**, which led to the formation of amide **11** in 22% yield. Although this experiment was originally intended to support the presence of a cationic species (or protonated isocyanate) at some stage, the allylsilane may also trap the carbamoyl radical, to form a β-silyl radical, which upon oxidation (possibly by $4CzIPN^{\cdot+}$ the semi-oxidized form of the photocatalyst) would lead to a β-silyl cation collapsing to afford **8** (*vide infra*).



Scheme 4 Mechanistic studies

Decarboxylation of oxamic acid is thought to proceed through the intermediary of an hypoiodite such as **12** as recently proposed for the related oxidative decarboxylation of α-ketoacids.[15] In order to give credit to this hypothesis, we first attempted to prepare **12** through coupling between oxamic acid **1a** and BIOAc. Although we were unable to purify **12** in pure form, mass spectrometry supported its formation. On the basis of these mechanistic studies and related literature,[15,21] a plausible mechanism was thus proposed starting with a reductive quenching of photocatalyst (4CzIPN) in its ? excited state by an hypoiodite of type **I** (Figure 2).[21] This would generate the resulting radical-anion **II**, then collapsing to afford the corresponding ketocarboxyl radical. Decarboxylation of the latter would then form carbamoyl

radical **III**, along with the *o*-iodobenzoic acid anion. **III** would then be oxidized further by the photocatalyst radical cation $PC^{\cdot+}$ into the corresponding protonated isocyanate **IV**, returning PC in its ground state. **IV** would finally loose a proton to afford the desired isocyanate, or react *in situ* with alcohols and amines to give urethanes and ureas, respectively.

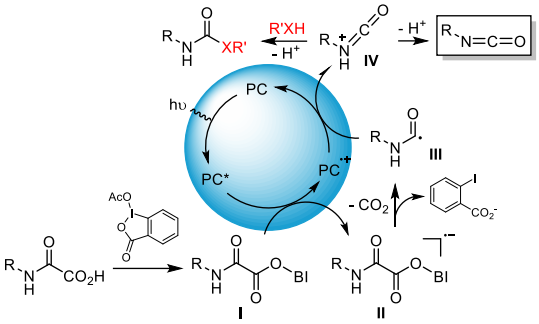


Figure 2 Mechanism of the photocatalyzed oxidative decarboxylation of oxamic acids.

Conclusions

In summary, we reported a "metal-free" photocatalyzed oxidative decarboxylation of oxamic acids, which provides a straightforward and environmentally benign entry toward urethanes and ureas, after coupling of the isocyanate, generated *in situ*, with alcohols and amines respectively. Mechanistic studies suggest that hypervalent BIOAc used as terminal oxidant reacts with the oxamic acid to generate an instable hypoiodide, the source of carboxyl radical. Decarboxylation of the latter and further oxidation led to the desired isocyanates. Work is now ongoing in our laboratories to apply this strategy to the synthesis of bio-sourced polyurethanes.

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Conflicts of interest

"There are no conflicts to declare".

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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