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COMMUNICATION

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

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A sustainable metal-free route to urethanes and ureas based on a photocatalyzed oxidative decarboxylation of oxamic acids is described. The reaction includes *in situ* generation of an isocyanate from the oxamic acid, using an organic dye as a photocatalyst, a hypervalent iodine reagent as an oxidant and a light source, which trigger the free-radical decarboxylation. 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 sources.

Urethanes display attractive biological activities and constitute key structural motifs in many targets having clinical potential, being present in many FDA approved drugs.[1] This functional group shows, as amides, bond resonance, albeit to a smaller extent.[2] Urethanes exhibit excellent proteolytic stabilities,[3] and as a consequence, are often used as peptide bond surrogates.[4] They 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 urethanes, 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 urethanes.[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 carcinogenic isocyanates. Strategies to avoid such toxic activated carbonyl species have flourished and have been reviewed recently.[11,12] Oxamic acids 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 (PC) and a visible light source,[14] which trigger the free-radical decarboxylation of oxamic acids in the presence of an organic oxidant (Figure 1).[15] This protocol avoids the isolation, purification and storage of the carcinogenic isocyanates and allows elaboration of urethanes and ureas in a one-pot process from readily available starting material.

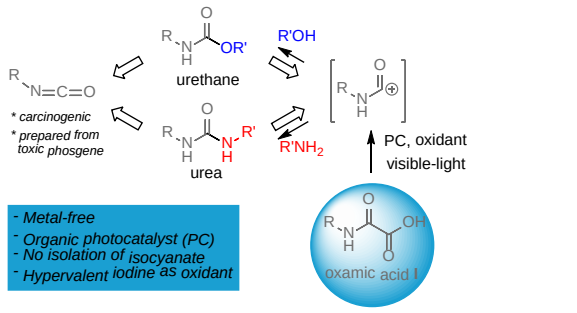

Figure 1 Visible-light mediated access to urethanes and ureas from oxamic acids

Reaction conditions were first optimized as to access in a one-pot process urethane **3a** from oxamic acid **1a** (Table 1). The transformation was first carried out in the presence of photoredox catalyst (PC) $Ru(bpy)_3Cl_2H_2O$ and $(NH_4)_2S_2O_8$ as an oxidant in CH_2Cl_2/H_2O (1:1) at rt under visible light irradiation (Blue LEDs, λ_{max} = 452 nm, SI). Pleasingly, in our first attempt the

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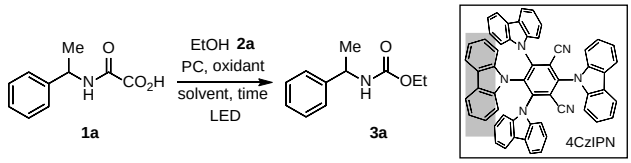
corresponding carbamate **3a** was isolated in 30% yield (entry 1). The use of water-soluble oxidants such as $K_2S_2O_8$ or $Na_2S_2O_8$ provided poor results (yields <15%). Removal of water from the reaction medium and use of $(^nBu_4N)_2S_2O_8$ in CH_2Cl_2 led only to trace amounts of **3a**, due to the low solubility of the persulfate (entry 2). When more lipophilic hypervalent iodine (BI-OH)[16] was introduced as an oxidant, **3a** was formed in good yield (entry 3). Changing BI-OH for acetoxybenziodoxole (BI-OAc) led to improved yield, likely as a result of the better leaving group ability of OAc (entry 4). Gratifyingly, the reaction proceeded readily in DCE using 1.0 mol% of photocatalyst affording **3a** in 91% isolated yield (entry 5).

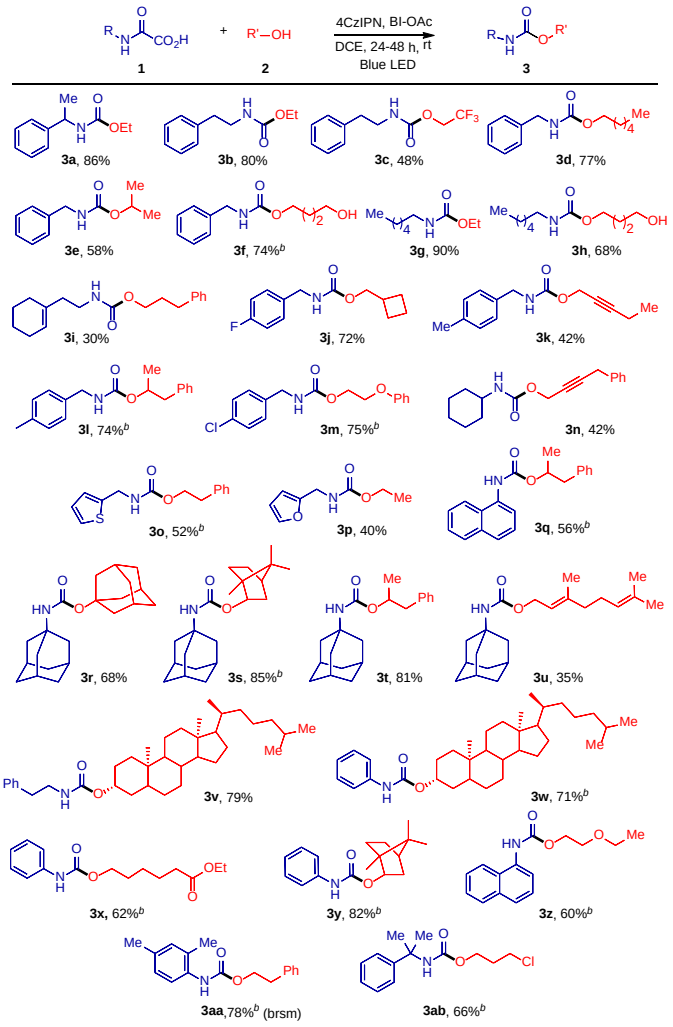
Table 1 Oxidative decarboxylation of oxamic acids. Optimization studies.



entry[a]	PC (mol%)	Oxidant (1.5 eq.)	solvent	t (h)	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$ (2)	$(NH_4)_2S_2O_8$	CH_2Cl_2/H_2O[c]	15	30
2	$Ru(bpy)_3Cl_2$ (2)	$(^nBu_4)_2S_2O_8$	CH_2Cl_2	15	Trace
3	$Ru(bpy)_3Cl_2$ (2)	BI-OH	CH_2Cl_2	15	75
4	$Ru(bpy)_3Cl_2$ (2)	BI-OAc	CH_2Cl_2	15	86
5	$Ru(bpy)_3Cl_2$ (1)	BI-OAc	DCE	15	94(91)[d]
6	4CzIPN (2)	BI-OAc	DCE	15	76
7	$AcrMes^+ClO_4^-$ (1)	BI-OAc	DCE	24	80
8	4CzIPN (1)	BI-OAc	DCE	24	91(86)[d]
9	4CzIPN (1)	BI-OAc	CH_2Cl_2	24	84
10	4CzIPN (1)	BI-OAc	THF	24	46
11	4CzIPN (1)	BI-OAc	MeCN	24	52
12	4CzIPN (1)	BI-OAc	DMF	24	30
13	4CzIPN (1)	BI-OAc	DMSO	24	NA
14	-	BI-OAc	DCE	24	NA
15	4CzIPN (1)	-	DCE	24	NA
16	4CzIPN (1)	BI-OAc	DCE	24	NA[e]

[a] Unless otherwise mentioned, all reactions were performed with **1a** (1 eq.), **2a** (3 eq.), PC (1-2 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 external standard 1,3,5-trimethylbenzene [c] 1:1 mixture. [d] Isolated yields of **3a**. [e] 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[17] showed efficiency comparable to that of metal photocatalysts (entry 6). Similarly, acridinium salt[18] provided 80% of conversion (entry 7). 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 8). 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 8 and 9), as use of THF, MeCN, DMF, or DMSO, significantly decreased the yields (entries 10-13). 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 14-16). With these optimal conditions in hand, the scope of the reaction was then established, varying the nature of oxamic acids **1** and alcohols **2** (Conditions **A**, 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.* **3r-u**, **3aa**, **3ab**), although reaction time needs to be increased with steric bulk of the alcohol. Using diols, only monofunctionalization occurs as shown with **3f** and **3h**. The reaction conditions are mild, allowing functional groups on both partners, including alcohols, halides, alkynes, strained rings, heteroarenes or esters.

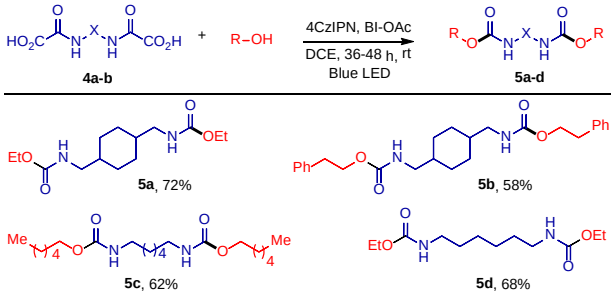


[a] **Conditions A:** The reaction was carried out with oxamic acid (1 eq.), R'OH (2-3 eq.), PC (1 mol%) and oxidant (1.5 eq.) in DCE (0.2 M) in a sealed tube. [b] **Conditions B:** The reaction was conducted with oxamic acid (3 eq.), R'OH (1 eq.), PC (1 mol%) and oxidant (2 eq.) in DCE (0.1 M), in a sealed tube.

Scheme 1 Oxidative decarboxylation of oxamic acids. Substrate scope.

Two main limitations were however observed; (1) reaction using benzyl alcohols did not provide the desired compounds due to the oxidation of the alcohol under the reaction conditions **A**. Similarly, oxamic acids from benzylamines tend to oxidize at the benzylic position to form the corresponding

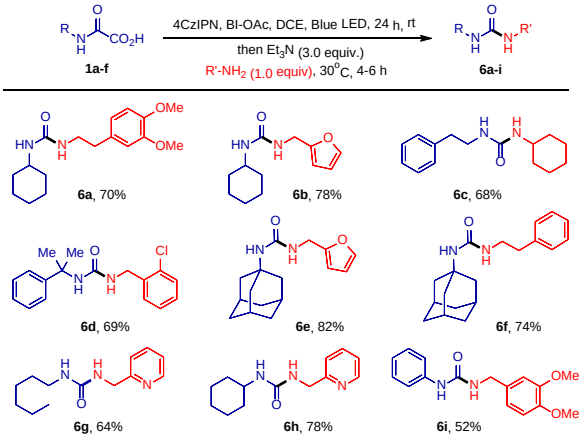
aldehyde; (2) somewhat lower yields were observed with oxamic acids derived from anilines due to the known decarbonylation of the putative carbamoyl radical intermediate *(vide infra)*.[13b] These limitations were however overcome using an excess of oxamic acid (Conditions **B**), leading to improved yields of the corresponding urethanes (*i.e.* **3w-z**). Bis-oxamic acids **4a-b** were also shown to react cleanly with alcohols 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] **Conditions C:** the reactions were carried out with oxamic acid (1 eq.), ROH (3 eq.), PC (2 mol%) and oxidant (2 eq.) in DCE (0.2 M), in a sealed tube.

Scheme 2 Bis-oxamic acids as bis-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

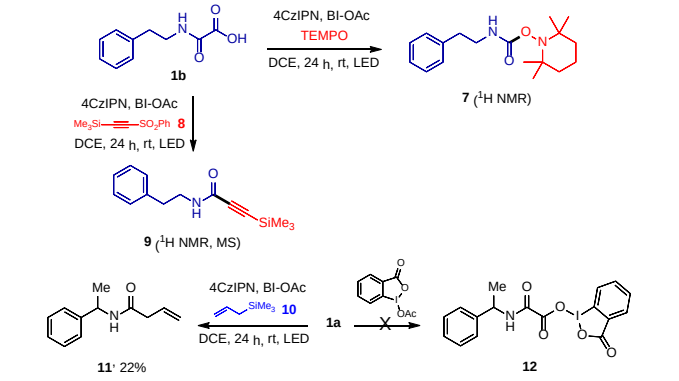


[a] **Conditions D:** the reactions were carried out with oxamic acid (2.0 eq.), PC (1 mol%) and oxidant (1.5 eq.) in DCE (0.1 M), then Et_3N (3 eq.), $R'NH_2$ (1.0 eq.), under Ar atm, 30°C , 4-6 h.

Scheme 3 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, after completion of the decarboxylation process, 3.0 equiv. of Et_3N prior to the addition of the amine (Conditions **D**). This two-steps one-pot protocol proved its efficiency affording a variety of ureas **6a-i** in satisfying yields (Scheme 3).

Finally, a series of intermediate trapping experiments were carried out as to establish the mechanism of this photocatalyzed oxidative decarboxylation of oxamic acids. First, **1b** 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 4). According to the seminal mechanistic proposal by Minisci,[13b] decarboxylation of oxamic acid under oxidative conditions proceeds through the formation of a carbamoyl radical intermediate ($RNHCO^{\cdot}$),[19] which further oxidation generates the corresponding cation or protonated isocyanate ($RNHC^{+}=O \leftrightarrow RHN^{+}=C=O$). When oxamic acid **1a** was treated under conditions above, replacing R'OH with alkynylsulfone **8**, amide **9** was detected (^{1}H NMR, MS), supporting the presence of a carbamoyl radical intermediate, reacting onto **8** through an addition-elimination process[20] to form **9**. The same reaction was repeated using oxamic acid **1a** and allylsilane **10**, which led to the formation of amide **11** in 22% yield. Although this experiment was originally intended to support the presence of the cationic species ($RNHC^{+}=O$), we cannot rule out at this stage that allylsilane **10** may also trap the carbamoyl radical, to form a β-silyl radical, the oxidation of which (possibly by $4CzIPN^{\cdot+}$, the semi-oxidized form of the photocatalyst) would lead to a β-silyl cation collapsing to afford **11** (*vide infra*). Finally, it was envisioned that decarboxylation of oxamic acid would proceed through the intermediary of a benziodoxole-oxamic acid complex such as **12** (having a weak O-I bond) as recently proposed for the related oxidative decarboxylation of α-ketoacids.[16c] However, all our efforts to prepare **12** through coupling between oxamic acid **1a** and BIOAc unfortunately met with failure.



Scheme 4 Intermediate trapping experiments.

On the basis of these trapping experiments and related literature,[15,16] a plausible mechanism was proposed, starting with the quenching of photocatalyst (PC: 4CzIPN) in its excited state by an intermediate of type **I** formed through ligand exchange at the iodine center (Figure 2).[16c] This would generate the resulting radical-anion **II**, then collapsing to afford the corresponding amidocarboxyl radical. Decarboxylation of the latter would form carbamoyl radical **III**, along with the *o*-iodobenzoic acid anion. **III** would then be oxidized further by the photocatalyst radical cation PC^{+} into the corresponding

protonated isocyanate **IV**, returning PC in its ground state. **IV** would finally loose a proton to afford the desired isocyanate,[21] or react in situ with alcohols and amines to give urethanes and ureas respectively.

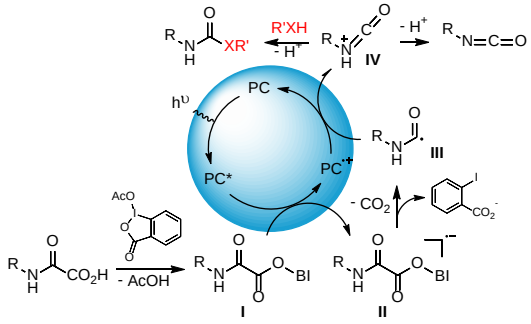


Figure 2 Mechanism of the oxidative decarboxylation of oxamic acids.

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. The methodology uses readily available starting material as well as standard photocatalyst and organic oxidant sources. Intermediate trapping experiments suggest that BIOAc used as terminal oxidant reacts with the oxamic acid to generate an instable benziodoxole-oxamic acid complex, the source of the amidocarboxyl radical. Decarboxylation of the latter and further oxidation lead to the desired isocyanate. Work is actively pursued in our laboratories to apply this strategy to the synthesis of bio-sourced polyurethanes, which will be reported soon.

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Conflicts of interest

"There are no conflicts to declare".

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21 When the oxidation was carried out in the absence of R'OH (Scheme 1), corresponding isocyanates were formed in good yields.

Graphical Abstract

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

Oxidative decarboxylation of oxamic acids under visible-light irradiation in the presence of alcohols or amines provides urethanes or ureas.