

Urethanes synthesis from oxamic acids under electrochemical conditions

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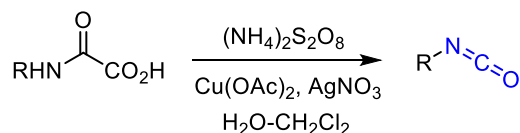
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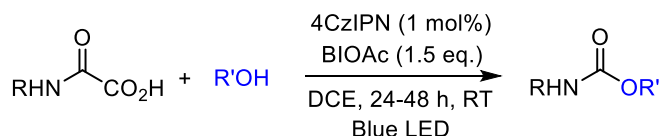
Urethanes synthesis *via* oxidative decarboxylation of oxamic acids under mild electrochemical conditions is reported. This simple phosgene-free route to urethanes involves an *in-situ* generation of isocyanates by anodic oxidation of oxamic acids in an alcoholic medium. The reaction is applicable to a wide range of oxamic acids, including chiral ones, and alcohols furnishing the desired urethanes in a one-pot process without the use of a chemical oxidant.

The urethane (or carbamates) functional group is present in a large number of substrates of pharmaceutical and agrochemical interest.¹ Urethanes exhibit excellent proteolytic stabilities² and are consequently used frequently as a peptide bond surrogate.³ Carbamates have been popularized in organic synthesis as amine protecting groups,⁴ showing convenient orthogonality and stability towards acids, bases or reducing conditions depending on the nature of the substituent. The addition of alcohols to isocyanates is likely one of the most reliable method to access urethanes, but also polyurethanes (Bayer reaction).⁵ However, the known isocyanates carcinogenicity and the synthesis of the latter from toxic phosgene constitute a major limit to the use of this reaction. Isocyanates may also be conveniently accessed from parent oxamic acids. The latter have emerged as versatile synthons for the synthesis of amide-containing organic compounds.⁶ Oxamic acids are stables⁷ and easily accessible through the coupling between amines and oxalic acid derivatives.⁸ Minisci and co-workers originally showed that oxamic acids are useful precursors of isocyanates.⁹ This approach involved the use of ammonium persulfate as an oxidant in the presence of Ag(I) and Cu(II) salts as catalysts to achieve oxidative decarboxylation of oxamic acid into isocyanate (Figure 1a). However, the reaction performed in a two-phase medium (H₂O-CH₂Cl₂) did not allow for a direct access to urethane without isolation of the carcinogenic isocyanate and led to the latter with moderate yields. Leveraging this, we recently showed that urethanes can be accessed through a one-pot metal-free visible light-mediated oxamic acids decarboxylation, thereby generating isocyanates *in-situ*, which in the presence of an alcohols furnished urethanes in good to excellent yields (Figure 1b).^{8a} This strategy involved the use of an organophotocatalyst and hypervalent iodine (III) as an oxidant to trigger the free-radical conversion of oxamic acids into isocyanates.

(a) Minisci synthesis of isocyanates from oxamic acids (Ref. 9)



(b) Urethanes from oxamic acids using visible light/hypervalent iodine oxidation (Ref. 8a)



(c) Urethanes through electrochemical decarboxylation of oxamic acids (this work)

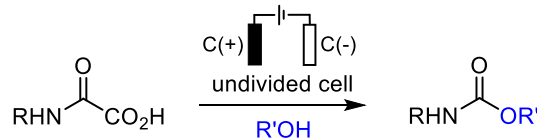


Figure 1 Oxamic acids as green precursors of urethanes

Encouraged by these results, we sought to simplify further this useful process, designing a metal-, photocatalyst-, light- and oxidant-free route relying on electrochemistry to mediate single electron transfers during the oxamic acid decarboxylation. There is an increasing interest in the use of simple electrochemical set-up in organic synthesis due to its simplicity, promising environmental benefits and sustainability, limiting the recourse to expensive chemicals and minimizing waste.¹⁰ We thus report herein a practical urethane synthesis via a mild anodic oxidation of oxamic acids.

The process was first optimized, as summarized in Table 1, using oxamic acid **1a** as a model compound, and MeOH **2a**, both as a solvent and a nucleophile, to trap the isocyanate generated in situ. Unless indicated, graphite electrodes were used both as cathode and anode. The reaction was first conducted under basic conditions using triethylamine (TEA), and a constant current of 60 mA was applied.¹¹ Gratifyingly, the corresponding methyl carbamate **3a** was obtained in 72% yield along with 20% of 1,1-diethyl-3-phenethylurea as a result of the amine oxidation¹² (see **8**, vide infra) (Table 1, entry 1). Decreasing the amount of the base to 0.1 eq resulted in a slight increase in yield (entry 2) and the absence of urea. Replacement of TEA with other bases including ammonia, or guanidines such as TBD or MTBD did not help improving the yield of **3a** (entries 3-5). The reaction time was equally extended to 8h, but no significant effect was observed on the yield (entry 6). Furthermore, when the current was lowered to 5 mA and reaction time increased up to 12h, conversion into **3a** reached 80% (entry 7). Interestingly, the reaction worked also well in the absence of a base, **3a** being isolated in 77% (84% conversion) without any additives (entry 8). Under these conditions, the reaction time was further extended to 18 h, without yield improvement (entry 9). The role of a supporting electrolyte was also studied, showing that tetrabutylammonium perchlorate (*n*-Bu₄NClO₄)^{11b} did not bring any improvement (entry 10), while *n*-Bu₄NI led to a drastic decrease in yield, possibly as a result of its competitive decomposition at the anode (entry 11).¹³ Finally, the nature of electrodes was investigated. The use of a platinum anode significantly decreased the yield (entry 12), while stainless steel did not provide the product at all (entry 13). Nickel foam exhibited a similar performance as graphite anode (entry 14), in good agreement with literature precedent, showing that graphite and nickel anodes favour Hofer-Moest type reactions, as multi-electron transfer is improved due to a better absorption on foam as compared to metallic surface.^{11b,14} The reaction was finally performed in air with success, indicating that the process could proceed appreciably without much precautions to exclude air (entry 15).

Under these optimal conditions (entry 8), substrate scope was extended by varying the nature of oxamic acids in the presence of MeOH **2a** as a nucleophile and solvent (Scheme 1). These conditions thus allowed the conversion of a wide range of oxamic acids **1a-m**, furnishing methyl carbamates **3a-m** in moderate to high yield (Scheme 1). These mild conditions were found compatible with arenes bearing electron-withdrawing (**3b**, **3e-f**) or electron-donating (**3c**) substituents. Interestingly, while oxamic acids having benzylic substituents (**1b-c**, **1e-h**) were shown to be sensitive to oxidation, using our previous photocatalytic conditions,^{8a} the corresponding urethanes were obtained in good yields under electrochemical conditions. Bis-oxamic acids **1k-m** were also shown to undergo the reaction, resulting in the corresponding bis(methyl carbamates) **3k-m** in satisfying yields. In this case, supporting electrolyte was used in small quantities as it was shown to improve conductivity and conversion.

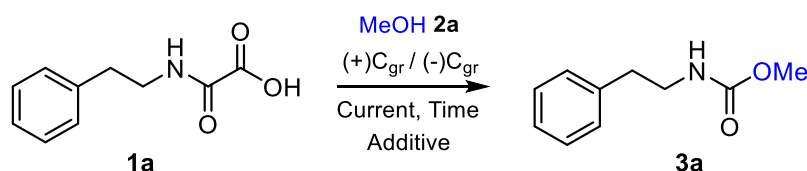
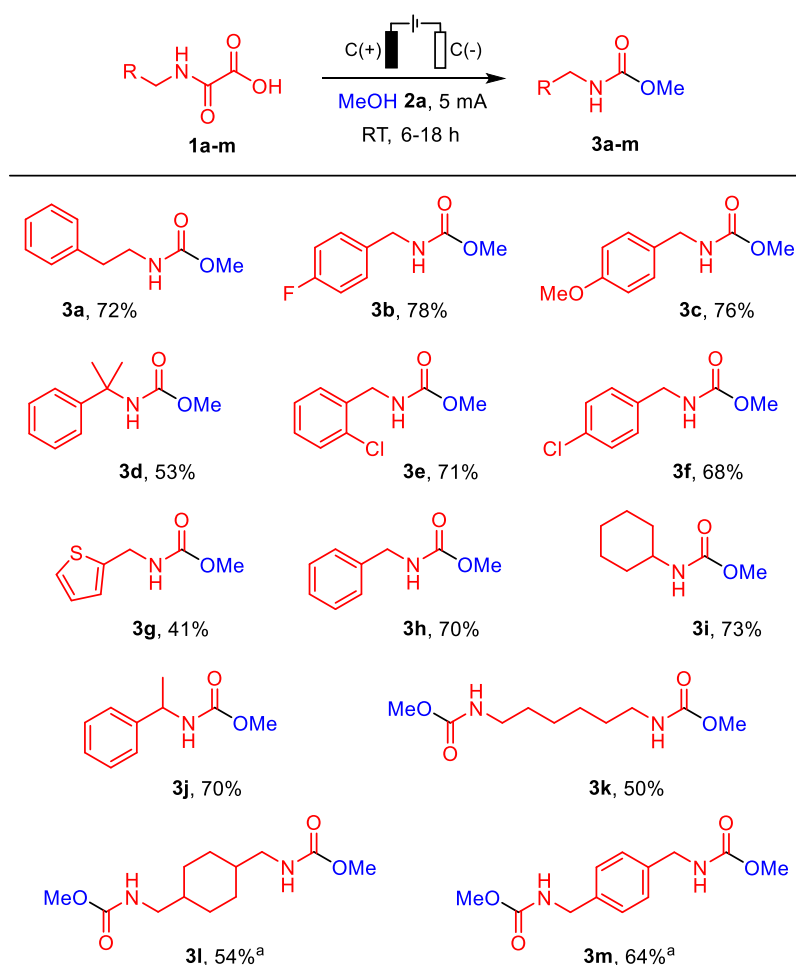


Table 1 Electrochemical conversion of oxamic acid **1a** into urethane **3a**.

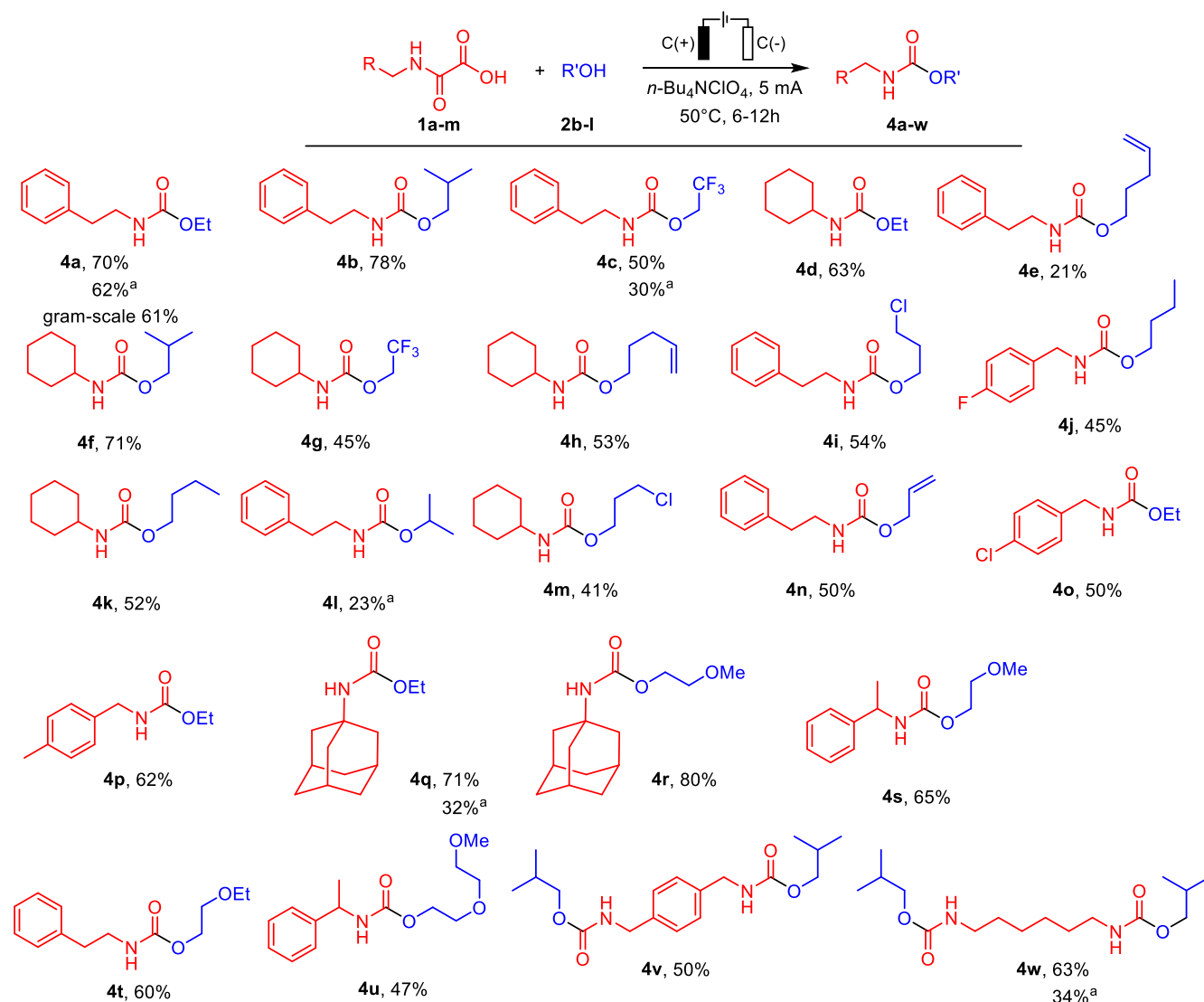
entry ^a	Current (mA)	Additive (eq.)	Time (h)	Yield (%) ^b
1	60	TEA (1.0)	5	72
2	60	TEA (0.1)	5	78 (72)
3	60	NH ₃ (0.1)	5	76
4	60	TBD (0.1)	5	70
5	60	MTBD (0.1)	5	68
6	60	TEA (0.1)	8	79
7	5	TEA (0.1)	12	80
8	5	-	12	84 (77)
9	5	-	18	84
10	5	<i>n</i> -Bu ₄ NClO ₄ (0.1)	12	83
11	5	<i>n</i> -Bu ₄ Ni (0.1)	12	26
12 ^c	5	-	12	40
13 ^d	5	-	12	ND
14 ^e	5	-	12	83
15 ^f	5	-	12	84

^a Unless otherwise mentioned, all reactions were performed with **1a** (0.5 mmol), **2a** (3 mL), graphite anode and cathode, under argon atmosphere unless indicated, in an ElectraSyn vial, undivided cell at room temperature. ^b Yields of **3a** determined by ¹H NMR with 1,3,5-trimethylbenzene as an external standard (Isolated yields of **3a** under brackets). ^c Platinum anode. ^d Stainless steel anode. ^e Nickel anode. ^f Reaction in air.



Scheme 1 Electrochemical decarboxylation of oxamic acids in the presence of MeOH **2a**. Oxamic acid scope. ^a (*n*-Bu₄)NClO₄ (0.1 eq.) was added.

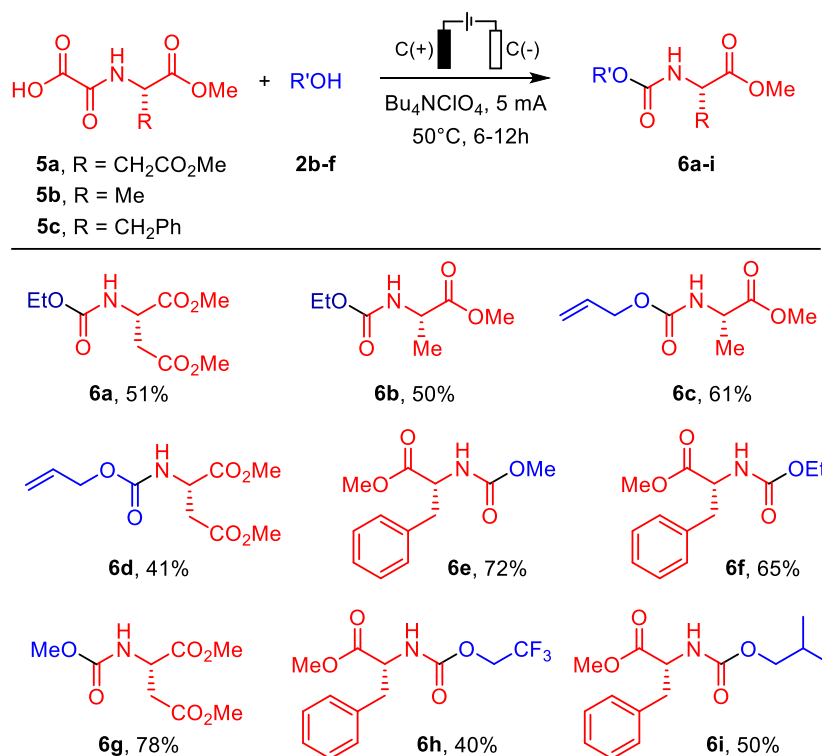
Other alcohols **2b-l** were then submitted to the optimal reaction conditions above. Although alcohols with higher molecular weight than MeOH **2a** display lower electrical conductivity,¹⁵ they were shown to be competent solvents and nucleophiles in the presence of a supporting electrolyte, affording the desired urethanes in moderate to good yields (Scheme 2).



Scheme 2 Electrochemical decarboxylation of oxamic acids in the presence of alcohols **2b-l**. Alcohol scope. ^a room temperature.

Improved yields were obtained by heating up the electrochemical cell during electrolysis. Beside a known enhanced reactivity of alcohols towards isocyanates with increasing temperature,^{5a} the mild heating increases the conductivity of the medium,¹⁵ and also likely improves the solubility and mass transport of ions to the electrodes.¹⁶ The reaction conditions are compatible with alcohols bearing a Cl (**4i**, **4m**), ethers (**4r-u**) and CF₃ groups (**4c**, **4g**) as well as a double bond (**4h**, **4n**). The reaction was equally shown to work appreciably well in a one gram-scale experiment, furnishing the product **4a** in 61%. Double addition was also observed with bis-oxamic acids leading to the corresponding bis-urethanes **4v-w** in reasonable yields. Some limitations were however noticed during this study. For instance, oxamic acids derived from anilines were not successful under these conditions, as already observed using the photocatalyzed process,^{8a} due to the competitive decarbonylation of the putative carbamoyl radical intermediate (vide infra).^{9b} Degradation was also observed using benzyl alcohol (oxidation) or 2-bromoethanol, which led instead to the ester of the oxamic acid (ESI). It is worth noticing that although the alcohol is used as a solvent, vacuum distillation at the end of the process was successful, allowing about 90% alcohol recovery with satisfying purity (¹H NMR).

Finally, chiral oxamic acids **5a-c** derived from the corresponding (L)-amino acids,^{8b} were also submitted to the above electrochemical conditions (Scheme 3), leading to the expected urethanes **6a-i** in satisfying yields without racemization, as shown by chiral HPLC on racemic and homochiral **6f** (ESI).



Scheme 3 Electrochemical decarboxylation of amino-acids derived oxamic acids in the presence of alcohols **2b-c**.

A tentative mechanism for the electrochemical decarboxylation of oxamic acids is finally proposed, as depicted in Figure 2. Oxidation of oxamic acid **A** at the anode should generate a ketocarboxyl radical **I**, which would then suffer decarboxylation leading to the carbamoyl radical **II**.¹⁷ A second oxidation event would then convert **II** into the carbamoyl cation **III** (that may also be written as a protonated isocyanate **IV**), the reaction of which with alcohol **B** furnishing the urethane **C** along with one proton. Reduction of H⁺ at the cathode produces in turn hydrogen.

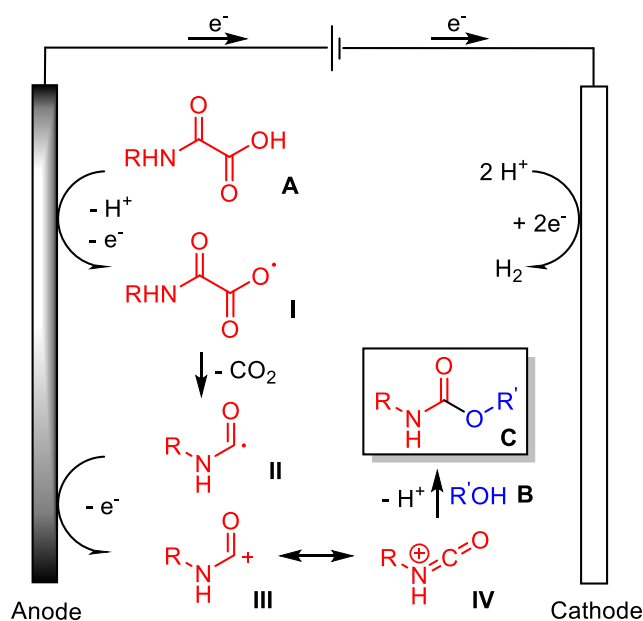
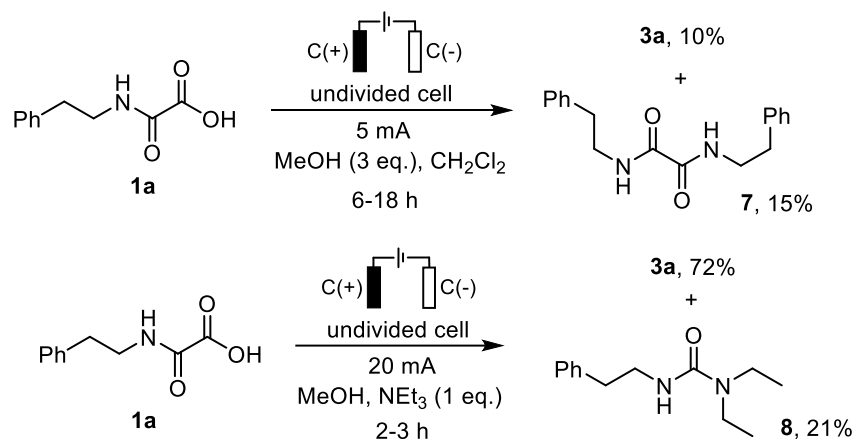


Figure 2 Mechanism of the electrochemical decarboxylation of oxamic acids.

The formation of the intermediate carbamoyl radical is supported by the formation of diamide **7** during electrolysis of oxamic acid **1** in the presence of MeOH **2a** in CH₂Cl₂ (Scheme 4). The presence of the coupling product **7** also suggests that the oxidation of radical **II** into **III** is a slow process, in good agreement with Minisci's observations.⁹ As mentioned above, when TEA was used as a base, competing oxidation of the amine occurs, which is in line with the oxidative potential of NEt₃ and oxamic acids respectively of +0.95 V¹⁸ and +1.17 V^{6g} (vs SCE). Electrochemical oxidation of Et₃N is known to lead, in the presence of traces of water, to formaldehyde and diethylamine,¹² the latter then adding to carbamoyl cation **IV** to afford **8**, thus supporting the formation of **IV** as an intermediate.



Scheme 4 Mechanistic studies supporting the formation of carbamoyl radical **II** and cation **III-IV**.

In summary, we reported the preparation of urethanes from oxamic acids and alcohols through a practically simple electrochemical process. The method allows the formation of various urethanes in moderate to good yields without isolation of the carcinogenic isocyanates generated in situ and directly trapped by alcohols. This metal-, photocatalyst-, light- and oxidant-free reaction proceeds under mild conditions and should serve as a useful tool to access these important targets of pharmaceutical interest.

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