Supporting Electrolyte-Free Anodic Oxidation of Oxamic Acids into Isocyanates: An Expedient Way to Access Ureas, Carbamates, and Thiocarbamates

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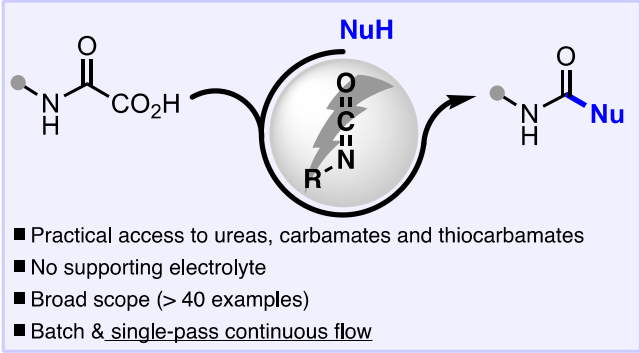


ABSTRACT:

We report a new electrochemical supporting electrolyte-free method for synthesising ureas, carbamates, and thiocarbamates *via* the oxidation of oxamic acids. This simple, practical, and phosgene-free route includes the *in situ* generation of an isocyanate intermediate *via* anodic decarboxylation of an oxamic acid in the presence of an organic base, followed by a one-pot addition of a suitable nucleophile to afford the corresponding ureas, carbamates and thiocarbamates. This procedure is applicable to different amines, alcohols, and thiols. Furthermore, by using single-pass continuous electrochemical flow conditions and running this reaction in a carbon graphite C_{gr}/C_{gr} flow cell urea compounds could be obtained in high yields within a 6 minutes residence time, unlocking access to substrates that were inaccessible under batch conditions while being easily scalable.

KEYWORDS:

Isocyanates, electrosynthesis, urea, carbamates, phosgene-free, flow electrosynthesis, anodic decarboxylation, oxamic acids

INTRODUCTION

Carbamates, thiocarbamates, and ureas have found numerous applications across fields ranging from medicinal chemistry to material chemistry.[1-4] They are mostly used to produce poly(urea-urethanes) or PUreas, which are valuable polymers in the manufacture of flexible and rigid foams, coating, and adhesives.[5, 6] For instance, a biodegradable polymer, such as poly(propylene carbonate), is a widely used packing material and medicinal material.[7] Up to 24 million tons of polyurethane are produced annually mainly using aromatic isocyanates, such as toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI).[8] Additionally, numerous medicinal

compounds bear carbamate or urea groups, such as sorafenib (a multi-kinase inhibitor for hepatocellular carcinoma and advanced renal cell carcinoma), ritonavir (an antiretroviral used to treat HIV/AIDS) and albendazole (a drug used to treat parasitic worm infestations) (Figure 1).[9, 10]

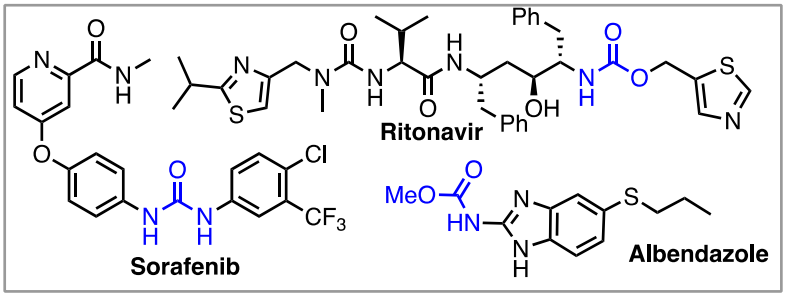


Figure 1. Examples of APIs containing carbamates and ureas

Carbamates and ureas are also useful protecting groups in organic synthesis due to their high stability and selective cleavage conditions.[6, 11-14] Conventionally, these are synthesised *via* isocyanates, which can be prepared *in situ* by treating primary amines with phosgene (Figure 2).[15, 16] Although industrial processes still use stoichiometric amounts of the highly toxic phosgene[17] there is a growing impetus for the development of greener and less harmful approaches to prepare isocyanates. Alternative methods do exist and include the Hofmann, Curtius, and Lossen rearrangements which divert away from the use of phosgene or phosgene derivatives.[18-24] They generate isocyanates under relatively mild conditions but still require the use of toxic reagents or elaborate precursors. For instance, the use of an alkaline solution of bromine in the Hofmann rearrangement and the formation of potentially explosive azides in the Curtius rearrangement limit their use for large scale synthesis.[25] As an alternative, the Lossen rearrangement provides access to isocyanates under relatively mild conditions, but still requires the synthesis of a potentially unstable hydroxamic acid.[26, 27] Some recent developments using dehydrating agents, such as carbonyldiimidazole (CDI)[28] and activating reagents, such as dimethyl carbonate (DMC),[27] have received a particular attention (Figure 2). Additional developments, such as amine carboxylation

using CO_2 as the carbon source,[29-33] reductive carboxylation of nitroaromatics,[34] and carbamate metathesis,[35] have emerged.[36-39] However, these methods still suffer from the limited availability and stability of the commercial starting materials, metal catalysts,[40] and toxic gas reagents, which could be disfavoured by industries.

Chemical oxidation of oxamic acids into isocyanates using peroxydisulfate in the presence of a Cu or Ag catalyst was first disclosed in 1995 by Minisci.[41] We have previously reported that the anodic oxidation of oxamic acid derivatives in methanol led cleanly to the formation of the corresponding methylcarbamate *via* the formation of an isocyanate.[42] Afterwards, Landais *et al.* applied this method towards the preparation of a variety of carbamates.[43] Unfortunately, the methodology is limited to the synthesis of simple carbamates that could very often be accessed more rapidly by using the commercially available chloroformate. Indeed, Landais's methodology is only compatible with alcohols as nucleophiles and requires them to be stable toward anodic oxidation and be used in a vast excess as the solvent. A wasteful supporting electrolyte is also needed (0.1 equiv) and the reaction is run at extremely low current densities (5 $mA.cm^{-2}$). In this work, we have developed an improved electrolytic method for the generation of isocyanates from oxamic acids, which is applicable to the synthesis of ureas, carbamates, and thiocarbamates (Figure 2). This anodic decarboxylation of oxamic acids into isocyanates uses no supporting electrolyte and is compatible with a wide range of nucleophiles without having to use them in significant excess.

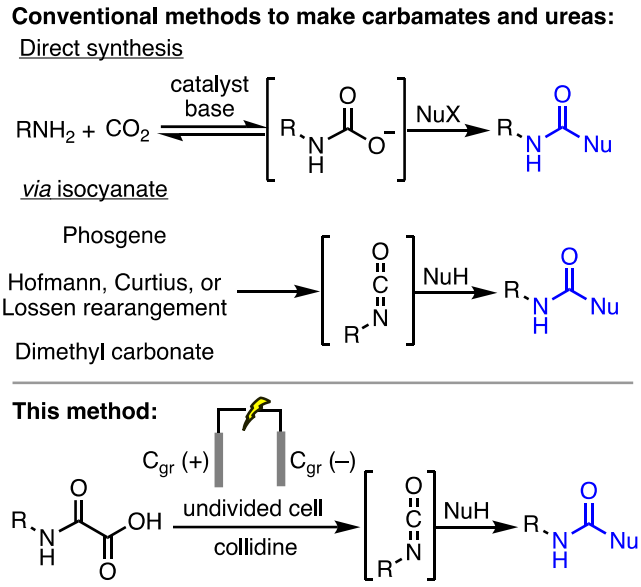


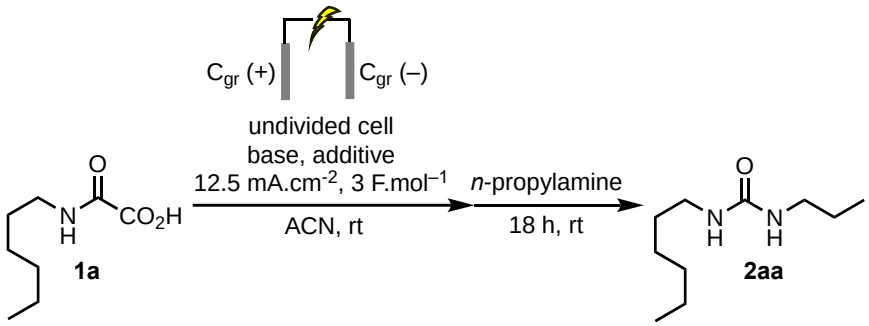
Figure 2. Overview of the synthesis of carbamates and ureas

Our general strategy relies on the use of a cheap electrode material (graphite) and easily synthesised oxamic acid derivatives in combination with collidine to generate an *in-situ* carboxylate ion. In a typical experiment, the oxamic acid is first electrolysed, a nucleophile is then added to the solution post-electrolysis and allowed to react with the anodically formed isocyanate. An acidic workup followed by a rapid filtration over silica gel allows the isolation of the pure coupled product. We firstly investigated the synthesis of ureas from electro-generated isocyanates. The electrochemical conditions for the anodic decarboxylation of oxamic acid **1a** were optimised by screening bases and additives with *n*-propylamine as a nucleophile (Table 1). Encouragingly, GC-MS analyses of the reaction mixture confirmed the formation of 1-isocyanatohexane.

Much to our delight, the electrolysis of **1a** in the presence of 2.5 equivalents of collidine led to the quantitative formation of the desired urea **2aa** (Table 1, entry 1). The exact effect of collidine remains unclear and is under further investigation. Interestingly, GC-MS analyses of the reaction shown that collidine is found intact at the end of the reaction. Both decreasing and increasing the

amount of collidine led to a decrease in the urea yield (Table 1, entries 6–9). Changing the base to DMAP, methylimidazole or triethylamine led to a similar drop in yield, whilst using an inorganic base as Cs_2CO_3 gave no trace of the desired urea **2aa** (Table 1, entries 2–5). The addition of a supporting electrolyte, such as $LiClO_4$, was shown to be detrimental (Table 1, entry 10). Moreover, using molecular sieves to remove possible traces of moisture was shown to be unnecessary (Table 1, entry 11). Doubling the concentration of oxamic acid still led to the quantitative formation of the desired urea and allowed to run the electrolysis at a higher current due to the solution's increased conductivity, shortening the electrolysis time per mmol of substrate. (Table 1, entry 12). Finally, attempts to replace acetonitrile with other solvents, such as DMSO, DMF or DCM led to poor yields and complex mixtures of products that were challenging to separate.

Table 1. Optimisation of Reaction Conditions for the Electrosynthesis of Isocyanates and One-pot Synthesis of Urea 2aa



Entry[a]	Base	Equiv	Additive (y equiv)	Yield 2aa (%)[b]
1	Collidine	2.5	–	Quantitative
2	DMAP	2.5	–	72
3	Methylimidazole	2.5	–	39
4	Cs_2CO_3	2.5	–	0
5	NEt_3	2.5	–	39
6	Collidine	1	–	60

7	Collidine	2	–	92
8	Collidine	5	–	93
9	Collidine	10	–	95
10	Collidine	2.5	$LiClO_4$ (1)	72
11[c]	Collidine	2.5	4Å MS	Quantitative
12[d]	**Collidine**	2.5	**–**	**Quantitative[e]**

[a]Reaction conditions: **1a** (0.32 mmol), *n*-Propylamine (3 equiv), ACN (5 mL) in a 10 mL Electrasyn vial, C_{gr}/C_{gr} electrodes, 12.5 $mA.cm^{-2}$, 3 $F.mol^{-1}$, alternating polarity (30 sec) at rt. [b]Yields are determined by ^1H NMR spectroscopy post-workup using CH_2Br_2 as an internal standard. [c] 25 mg of 4Å molecular sieves were used. [d]**1a** (0.64 mmol), ACN (5 mL) in a 5 mL Electrasyn vial at 25 $mA.cm^{-2}$.[e] Isolated yield.

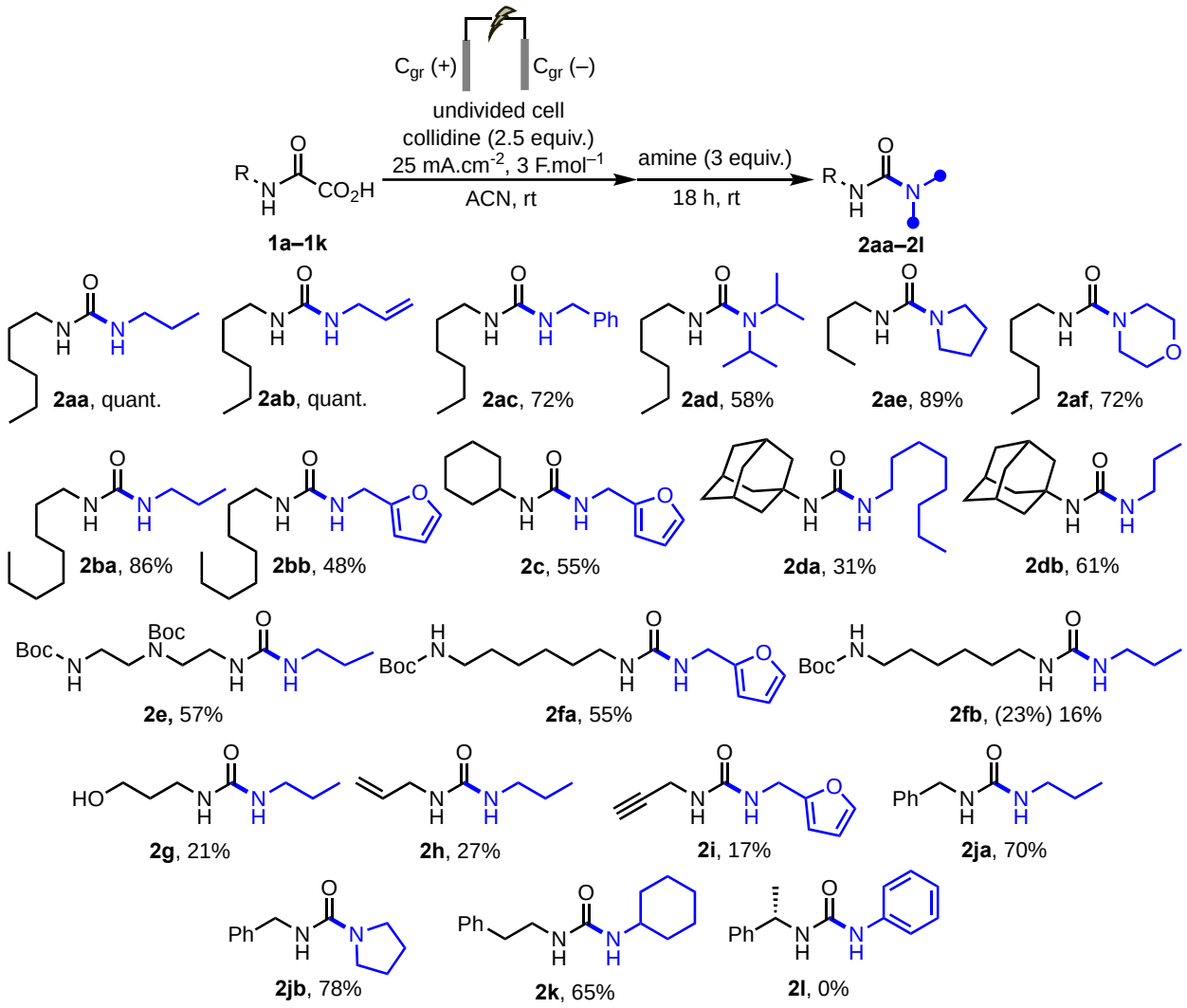
Cyclic voltammetry measurements performed on **1a** showed an ill-defined oxidation at ca. 2.25V *vs* Fc/Fc^+ in acetonitrile (See SI). The addition of 0.5 equivalents of triethylamine resulted in the formation of **1a**'s anion, which displayed a lower oxidation potential (E_{pa} = 0.75 V *vs* Fc/Fc^+). However, upon adding more than 1 equivalent of base, a secondary feature at a lower potential (E_{pa} = 0.52 V *vs* Fc/Fc^+) was observed, arising from the anodic oxidation of the excess triethylamine. At least two equivalents of base are needed to generate the desired isocyanate and triethylamine would be unsuitable for our reaction since it would be oxidised before the oxamate anion. The use of collidine as an alternative base was investigated due to its high tolerance towards anodic oxidation. As in the previous case, upon titration with 0.5 equivalent of collidine, an anion with a lower oxidation potential (E_{pa} = 0.87 V vs Fc/Fc^+) was formed, with no additional redox processes observed upon further addition of base up to 2.5 total equivalents. In both cases, anodic fouling of the electrode was observed when potentials greater than 1.75 V were applied (See SI).

With the optimised conditions in hand, the scope and limitations of the newly developed anodic synthesis of ureas were explored (Scheme 1). Using **1a** under the previously optimised conditions,

the corresponding ureas were obtained in high yields (72%–quant) in the presence of a primary amine (Scheme 1, **2aa–2ac**). Diisopropyl amine, as a nucleophile, led to a slightly decreased yield of 58% in **2ad**, presumably due to its higher steric hindrance, leaving unreacted isocyanate, which degrades over time and during the workup. However, with pyrrolidine and morpholine as nucleophiles, ureas **2ae** and **2af** were obtained in 89% and 72%, respectively. Oxamic acids with linear and cyclic alkane chains **1b–1d** gave moderate to good yields (31–86%) of urea compounds with either aliphatic or aromatic amines (Scheme 1, **2ba–2db**).

Impressively, this method tolerates *N*-protected groups where the corresponding isocyanate led to the urea compounds **2e–2fb** in moderate yields (16–57%). Electrolysing alkene- and alkyne bearing oxamic acids, 2-(allylamino)-2-oxoacetic acid **1h** and 2-oxo-2-(prop-2-yn-1-ylamino)acetic acid **1i**, gave ureas **2h** and **2i** in modest yields. This procedure is also compatible with oxamic acids bearing benzylic groups with ureas **2ja** and **2jb** obtained in 70% and 78% yield, respectively, in addition to homo-benzylic groups, which yielded urea **2k** in 65% with cyclohexyl amine. Most of the lower yields are due to substrates that are either less conductive or that form highly reactive isocyanates. Unfortunately, this method does not seem to tolerate aryl amines as nucleophiles, as shown by the inability to prepare **2l**.

Scheme 1. Scope of Urea Compounds



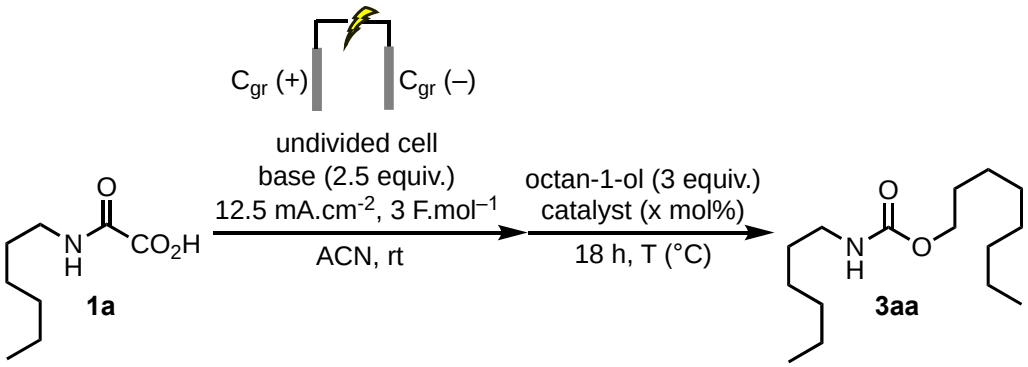
Yields in brackets are determined by ^{1}H NMR spectroscopy post-workup using CH_2Br_2 as an internal standard.

Encouraged by the positive results obtained for the synthesis of ureas, we investigated the possibility of transposing the methodology to the synthesis of carbamates. Unfortunately, low yields were obtained. Instead of the desired carbamate, the unreacted alcohol and amine (generated by the hydrolysis of the unreacted isocyanate) were found to be the primary products at the end of the reaction (Table 2). Again, this observation seems to be in line with collidine's ability to moderate the reactivity of isocyanates. For instance, when **1a** was electrolysed under our optimal conditions and let to react with octan-1-ol (3 equiv.) for 18 h at room temperature, the expected

carbamate **3aa** was only formed in 7% yield (Table 2, entry 1). Increasing the temperature after addition of the alcohol led to slightly improved yields (up to 23%) (Table 2, entries 2–4). Changing the base to either methylimidazole or DMAP only led to traces of the carbamates (Table 2, entries 5 and 6). However, using 10 mol% of dibutyltin dilaurate (DBTDL), a well-known catalyst for adding alcohols onto carbonyl groups, gave **3aa** in 63% (Table 2, entry 7). Increasing the reaction temperature after the addition of octan-1-ol to 60 °C in the presence of DBTDL (10 mol%) further increased the yield to 73% (Table 2, entry 8). Attempts to replace DBTDL with $BF_3{\cdot}OEt_2$, or DBU led to lower yields, and no trace of the desired carbamate was observed when $FeCl_3$ was employed (Table 2, entry 9–11). Finally, as discussed previously, increasing the concentration of the oxamic acid in the electrochemical cell increased the rate of electrolysis by running it at 25 $mA.cm^{-2}$. Under such conditions, using DBTDL (10 mol%) at 60 °C, the desired carbamate **3aa** was obtained in 67% (Table 2, entry 12).

To explore the scope of this new carbamate synthesis, a series of oxamic acids were electrolysed and subsequently treated with an alcohol in the presence of a catalytic amount of DBTDL at 60 °C (Scheme 2). Thiocarbamate formation was also briefly explored with the same substrates by using a thiol instead of an alcohol under similar conditions. When oxamic acid **1a** was electrolysed and then treated with 1-prop-2-yn-1-ol or phenol, the corresponding carbamates **3ab** and **3ac**

Table 2. Re-optimization of Reaction Conditions for the Electrosynthesis Carbamate 3aa

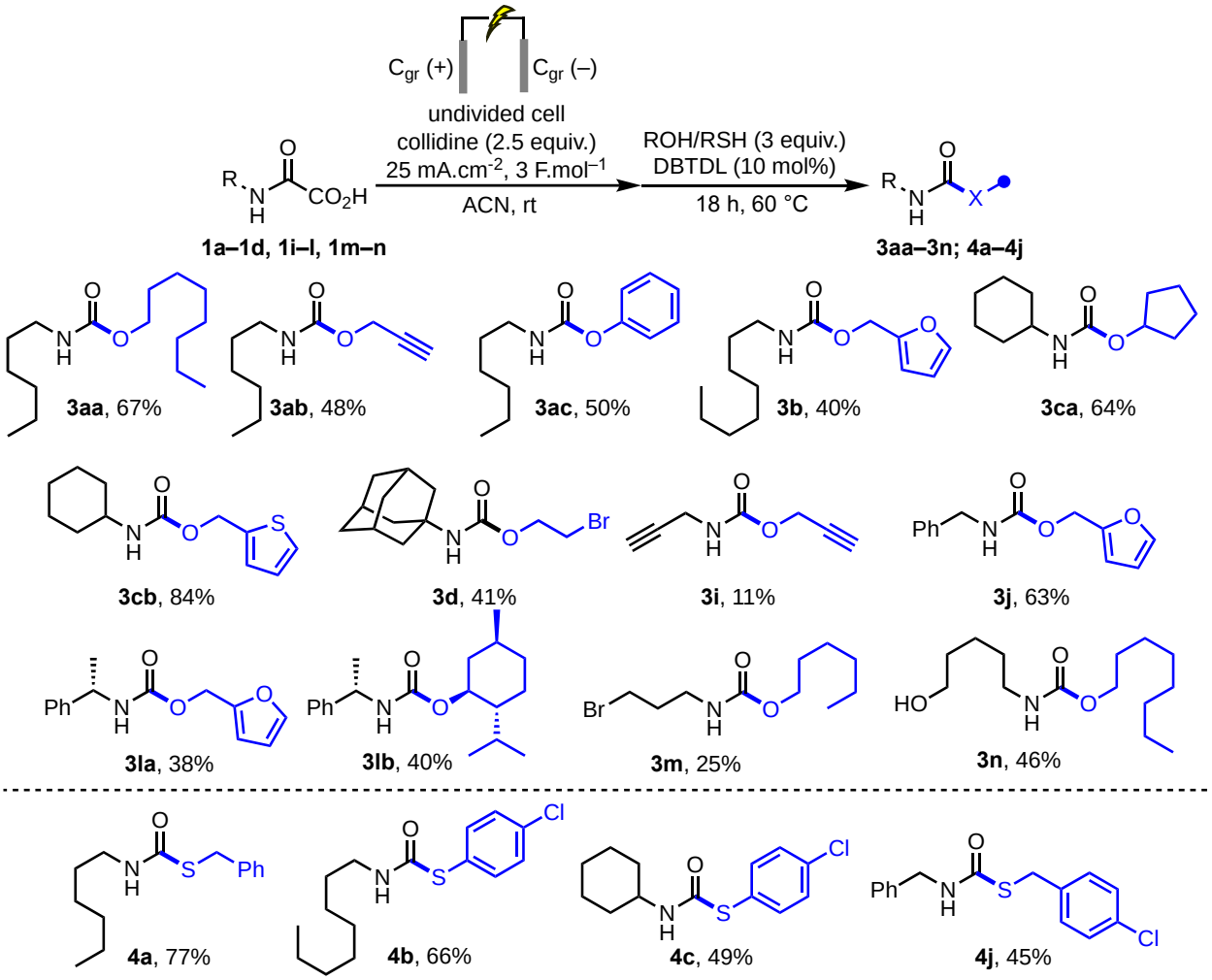


Entry[a]	T (°C)	Base	Catalyst (x mol%)	Yield 3aa (%)[b]
1	rt	Collidine	–	7
2	40	Collidine	–	12
3	60	Collidine	–	23
4	80	Collidine	–	23
5	rt	Methylimidazole	–	traces
6	rt	DMAP	–	traces
7	rt	Collidine	DBTDL (10)	63
8	60	Collidine	DBTDL (10)	73
9	60	Collidine	$BF_3 \cdot OEt_2$ (10)	28
10	60	Collidine	DBU (10)	9
11	60	Collidine	$FeCl_3$	0
12[c]	**60**	**Collidine**	**DBTDL (10)**	**67[d]**

[a]Reaction conditions: **1a** (0.32 mmol), octan-1-ol (3 equiv), ACN (5 mL) in a 10 mL Electrasyn vial, C_{gr}/C_{gr} electrodes, 12.5 $mA.cm^{-2}$, 3 $F.mol^{-1}$, alternating polarity (30 sec) at rt. [b]Yields are determined by ^1H NMR spectroscopy post-workup using CH_2Br_2 as an internal standard. [c]**1a** (0.64 mmol), ACN (5 mL) in a 5 ml Electrasyn vial at 25 $mA.cm^{-2}$.[d]Isolated yield.

were obtained in moderate yields (48 and 50%). In comparison, thiocarbamate **4a** was formed in 77% yield when treated with phenyl methanethiol. 2-(Octylamino)-2-oxoacetic acid **1b,** 2-(cyclohexylamino)-2-oxoacetic acid **1c** and 1-(adamantan-1-yl)amino)-2-oxoacetic acid **1d** resulted in carbamates **3b**–**3d** in moderate to good yields (40–86%) and thiocarbamates **4b**–**4c** in moderate yields. Alkynyl and benzylic oxamic acids were compatible under the optimised electrolytic conditions as well as for the synthesis of carbamates **3i**–**3lb** and thiocarbamate **4j**. The new methodology tolerates not only alkyl halides but pleasingly free hydroxyl groups are also compatible, as shown by the successful syntheses of **3m** and **3n** in 25% and 46% yield, respectively.

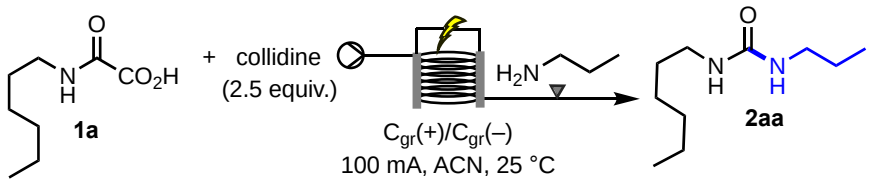
Scheme 2. Scope of Carbamates and Thiocarbamates



To further streamline this synthetic method and emphasise its usefulness industrially, we decided to translate it into a continuous flow setup. The use of flow electrochemistry has been gaining significant traction over the past few years and is amongst the most efficient ways to conduct electrosynthesis on a large scale.[44-48] The small interelectrode gap and the high electrode surface area to reaction volume ratio significantly decreases resistance.[49, 50] In this study, we aimed at having a method in flow that works as efficiently as in batch, while also resolving issues with substrates that were inaccessible due to high reactivity or low conductivity. Initially, we sought to investigate flow conditions using urea **2aa** from 2-(hexylamino)-2-oxoacetic acid **1a** and propylamine (Table 3). A complete description of the flow systems used can be found in the

Supporting Information. A solution of the oxamic acid (0.15 M) was prepared in acetonitrile with 2.5 equivalents of collidine and introduced into a flow cell equipped with two graphite electrodes at various flow rates while also changing the interelectrode gap (*i.e.*, changing the spacer) and hence the volume of the flow cell. The power supply was set to a maximum of 100 mA, and output was then introduced into stirring propyl amine (excess) to trap the isocyanate. It was found that at significantly small interelectrode gaps (0.25 mm), no conversion was observed due to the small volume and hence short residence time of the oxamic acid in the cell (3 min) (Table 3, entry 1). The impedance was so low with a 0.25 mm spacer that the electrolysis of the solvent itself, without any supporting electrolyte, allowed to reach 100 mA at a maximum voltage of 30 V. Using thicker spacers (0.5 and 1 mm) resulted in the formation of the desired urea in 48% and 70%, respectively (Table 3, entries 2 and 3). Running the reaction at a doubled flow rate (200 µL/min) while using a 1 mm spacer allowed a residence time of 6 min and gave urea **2aa** in a quantitative yield (Table 3, entry 4). Increasing the concentration of the oxamic acid to 0.3 M reduced conversions, as did increasing the flow rate to 400 µL/min (Table 3, entries 5 and 6). This successful translation into flow conditions allows faster reaction times (12 min vs 1h40 on a 0.6 mmol scale) with comparable yields.

Table 3. Optimisation of Flow Conditions for the Electrosynthesis Carbamate 2aa



Entry[a]	Interelectrode gap (mm)	V_{cell} (mL)	fr (µL/min)	Residence time (min)	Yield 2aa (%)[b]
1	0.25	0.3	100	3	N.R.

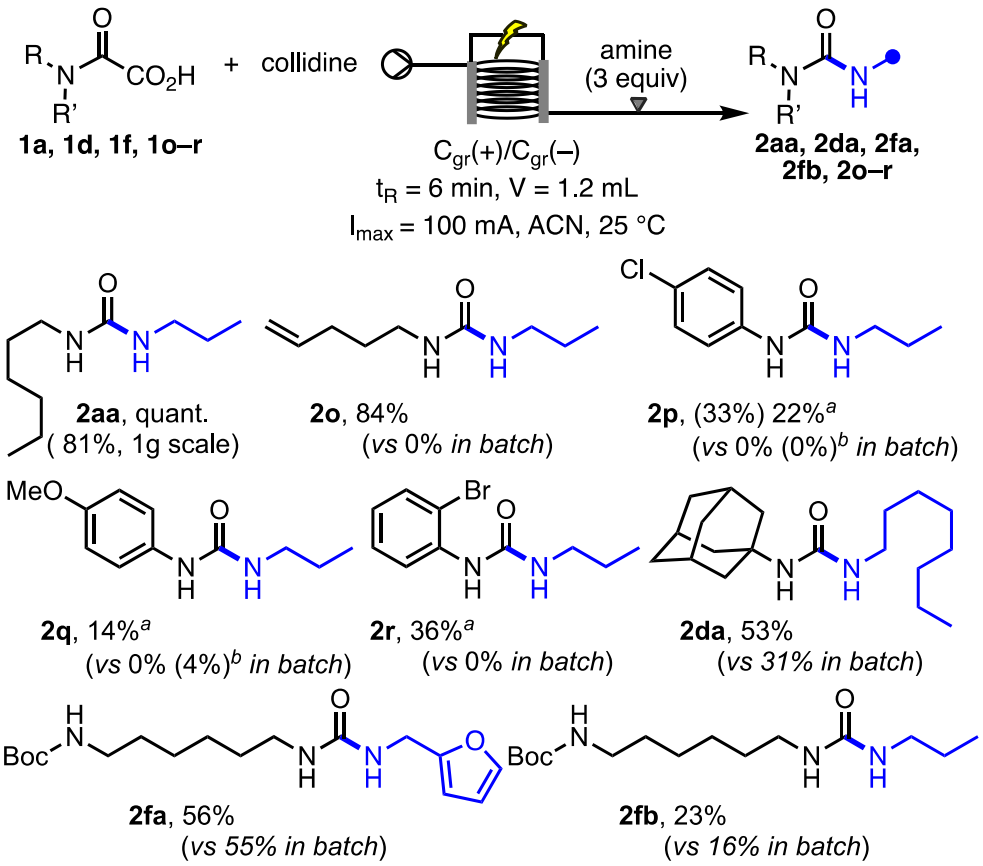
2	0.5	0.6	100	6	48
3	1	1.2	100	12	70
4 [c]	**1**	**1.2**	**200**	**6**	**Quantitative**
5[d]	1	1.2	200	6	53[e]
6	1	1.2	400	3	44[e]

[a]Reaction conditions: **1a** (0.3 mmol) and collidine (2.5 equiv) in ACN (0.15 M) are injected into a flow cell equipped with C_{gr}/C_{gr} electrodes and a spacer at set flow rates at rt and the collection unit is equipped with a vial containing propyl amine (1 mL). [b]Yields are determined by ^{1}H NMR post-workup using CH_2Br_2 as an internal standard. [c]3 equiv of propylamine were used. [d] [**1a**] = 0.3 M. [e]Incomplete conversion.

The reaction of 2-(hexylamino)-2-oxoacetic acid **1a** under the optimised reaction conditions gives quantitative yields of urea **2aa** at 0.3 mmol scale. When run at 1 g scale (5.37 mmol), the desired urea is obtained in 81%. The slightly decreased yield during scale-up can be explained by the fouling of the electrodes during a longer electrolysis run, resulting in the incomplete conversion of the oxamic acid. This could possibly be improved by alternating the electrodes' polarity and adapting the cell design to accommodate large scale electrolyses. During our screening of substrates, the absence of a supporting electrolyte proved that conductivity is highly substrate-dependent. Substrates that resulted in low conductivity were selected to be run under the optimised flow conditions. Indeed, 2-oxo-2-(pent-4-en-1-ylamino)acetic acid **1o** and aryl oxamic acids **1o–1r** suffered from poor conductivities in batch and no isocyanate was formed. When oxamic acids **1p–1r** were electrolysed, no trace of the desired urea was obtained under standard batch conditions. The addition of a supporting electrolyte did not lead to any improvements; **2p** was only obtained in 4% while no trace of **2q** was observed. However, in continuous flow, solutions of **1o–1r** with collidine were sufficiently conductive to be electrolysed and led to the clean formation of their corresponding urea after reaction with propylamine (Scheme 3). Urea **2o** was obtained in 84% from 2-oxo-2-(pent-4-en-1-ylamino)acetic acid **1o**. Aryl oxamic acids bearing *p*-Cl, *p*-OMe, or *m*-

Br substituents led to the desired urea compounds **2p–2r**, whereas in batch no traces were obtained, albeit in low yields. Ureas **2da, 2fa,** and **2fb** were also made under flow conditions in an attempt to improve yields compared to batch and slightly increased yields were obtained; hence, a substrate-specific optimisation would be required to address these. Even though no significant increase in yield was obtained in these cases, it is worth noting that these single-pass flow reactions are not only faster than batch electrolyses but also much cleaner. Performing a simple acidic workup at the end of the flow reaction is enough to obtain the pure urea without further chromatographic purifications (see SI).

Scheme 3. Flow Synthesis of Urea Compounds



[a]Reaction run at 100 μL/min, 12 min residence time. [b] $LiClO_4$ (0.1 M) was used as supporting electrolyte. Yields in brackets are determined by ^1H NMR spectroscopy post-workup using CH_2Br_2 as an internal standard.

At last, we propose a mechanism for the anodic oxidation of oxamic acids (Figure 3). First, the oxamic acid **1** is deprotonated by collidine to form the corresponding anion **A** which undergoes an electrostatic attraction to the positive anode. At the same time, the protonated collidine gets reduced at the cathode and regenerate the free base. At the anode, A's oxidation generates an acyloxy radical **I**, which subsequently undergoes an anodic decarboxylation (Hofer-Moest type mechanism) to form the carbamoyl cation **III**. The latter is then deprotonated to give the isocyanate intermediate **V**. Finally, the addition of a nucleophile would lead to the formation of the desired urea, carbamate or thiocarbamate **B**.

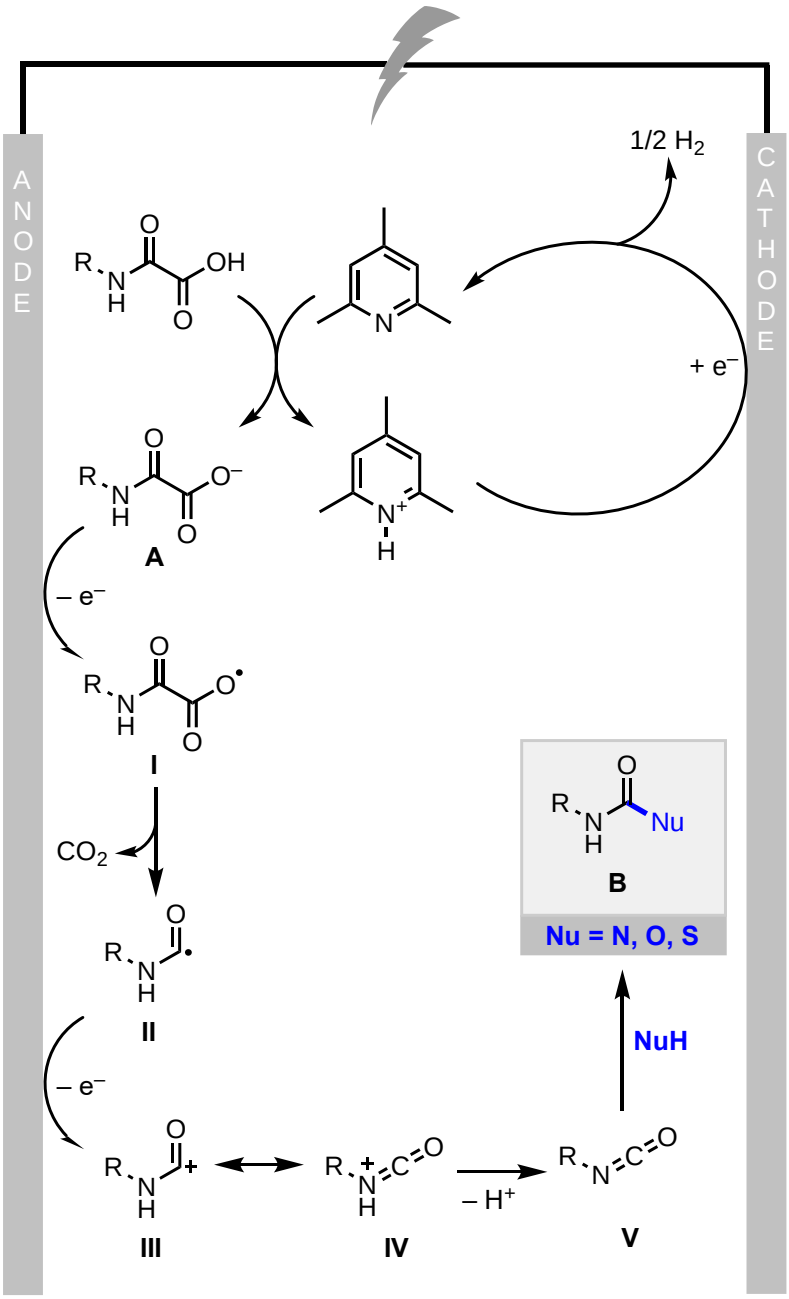


Figure 3. Proposed mechanism for the anodic oxidation of oxamic acids

CONCLUSION

In summary, we have developed an original method for the batch and flow electrochemical synthesis of carbamates, ureas, and thiocarbamates *via* oxidative decarboxylation of oxamic acids. This practical approach gives rapid and easy access to highly functionalised unsymmetrical ureas,

carbamates, and thiocarbamates. The newly developed procedure allows to obtain under mild and oxidant free conditions the desired products in moderate to excellent yields, without the use of any toxic reagents or the isolation of highly reactive and toxic isocyanates. Lastly, this one-pot synthesis has shown broad functional group compatibility and represents an efficient and practical way to access pharmaceutical targets on both laboratory and industrial scales.

ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge.

Supporting Information. Experimental details and procedures, including copies of NMR spectra, can be found in the Supporting Information (PDF).

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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