ARTICLE

Electrochemical TEMPO-Catalyzed Multicomponent C(sp³)-H α -Carbamoylation of Free Cyclic Secondary Amines.

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We report here an original electrosynthetic method allowing the straightforward C(sp³)-H α -carbamoylation of free cyclic secondary amines. Based on a TEMPO-catalyzed indirect anodic oxidation and a multicomponent coupling, a wide variety of *N*-acyl α -carboxamides have been obtained in remarkably mild and sustainable reaction conditions.

Introduction

Electrosynthesis is in its very essence a “green” technology which permits the safe production of chemicals while limiting our impact on the environment.^[1] Indeed, by employing electrons as inherently clean reagents, this method may allow the modulation of the redox state of reactants without the generation of the toxic by-products that is often associated with the use of stoichiometric promoters.^[1] As such, electrosynthesis represents a matchless opportunity to conceive safer and more sustainable chemical processes, as in the case of the C(sp³)-H α -functionalization of amine derivatives.^[1-8]

As soon as 1966, Weinberg and Brown showed that, in methanolic solution, the anodic oxidation of electron rich tertiary anilines afforded the corresponding α -methoxylated derivatives.^[3] This seminal work, in which an electro-generated electrophilic iminium species is trapped by a nucleophilic solvent molecule, has opened some new perspectives for the straightforward and sustainable preparation of advanced nitrogen-based building blocks. In parallel of a strong enthusiasm for Shono’s electro-alkoxylation reaction and Yoshida’s cation-pool method, which are both restricted to the use of *N*-protected amines,^{[4],[5]} the development of a wider set of electrochemical α -functionalization of free amine derivatives has been comparatively narrowly investigated.^{[1b],[6-8]}

In this field, the use of carbon based nucleophiles remains mainly limited to the use of cyanide sources,^[6] even if in specific

cases malonates and *in situ* generated enamines have been employed (Scheme 1, eq. (a)).^{[7],[8]}

Based on our experience in multicomponent reactions (MCRs),^[9] we questioned the feasibility of an electrochemical α -carbamoylation reaction of unprotected secondary amines. More specifically, provided that the presence of an isocyanide and a carboxylic acid would not interfere with the anodic oxidation of the amine partner, we envisioned to develop an electro-Ugi/Joullié type MCR (Scheme 1, eq. (b)).^[10] Seminal work by the group of Zhu and others showed that direct one-pot oxidative Ugi MCRs are achievable using stoichiometric oxidants^[11] or metal-based catalytic systems.^{[12],[13]} However, such multicomponent processes present several severe limitations such as the over-stoichiometric generation of waste and/or the necessity to use easily oxidizable amine partners (tetrahydroisoquinolines (THIQs), benzylamines or dialkylanilines).^[14] In this particular context, we wish to report here a remarkably mild and sustainable electrochemical multicomponent C(sp³)-H carbamoylation of non-activated free secondary amines (Scheme 1, eq. (c)).

Scheme 1: State of the art – Aim of this work

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Electronic Supplementary Information (ESI) available: [More details concerning cyclic voltammetry and optimization studies are provided. Experimental protocols and descriptions of all new compounds are available, together with copies of NMR spectra.]. See DOI: 10.1039/x0xx00000x

Results and discussion

At the onset of this study, we decided to achieve the desired multicomponent reaction under indirect electrolysis so as to promote an oxidative process with a functional group tolerance as wide as possible.^[15] In line with recent work from the group of Stahl,^{[6b],[16]} we chose the nitroxyl radical TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as redox mediator since the anodic generation of the corresponding oxoammonium species (TEMPO⁺) reported to be prone to oxidize amines.^{[6b],[17],[18]} To test the feasibility of our approach, we initially performed some cyclic voltammetry studies (Figure 1). Whereas isocyanides, such as *tert*-butyl isocyanide (**2a**), proved to be non-electroactive in the range of potentials examined ((a), Figure 1), a clear increase of the anodic current corresponding to the oxidation of TEMPO (+0.65 V vs SCE) was observed when a 10-fold excess of pyrrolidine (**1a**) was added ((b) vs (c), Figure 1). This result was particularly encouraging as, in addition to the loss of the reversibility which was also observed, it supported a possible electrocatalytic process in which TEMPO was partially regenerated at the anode after the oxidation of pyrrolidine (E_p^{ox} ≈ +1.20 V vs SCE) by TEMPO⁺.^[19] Further addition of an excess of acetic acid (**3a**, 25 equiv) reduced this electrocatalytic effect but, in these reaction conditions, the non-reversible nature of the TEMPO oxidation was still maintained, which indicated that TEMPO⁺ could still promote the oxidation of pyrrolidine ((c) vs (d), Figure 1). Such a decrease of the anodic current is consistent with a low concentration of free pyrrolidine, as a result of the acid/base equilibrium taking place when acetic acid is present in the reaction media, and/or a slower regeneration of TEMPO. In these conditions, the second oxidation peak was attributed to the oxidation of pyrrolidine which, for the same reason, operates at a potential 0.2 V more important.^[19] Hence, the presence of both an isocyanide and a carboxylic acid did not seem to preclude the TEMPO-catalyzed electrochemical oxidation of pyrrolidine to take place and, thereby, hinted the feasibility of our strategy.^[19]

Figure 1: Preliminary Cyclic Voltammetry (0.3 M of *n*-Bu₄NBF₄ in MeCN, 20°C, 0.5 V.s⁻¹, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode).

Table 1: Optimization studies

Entry	Variation from above	Yield (%) ^[a]
1	none	54
2	HFIP ^[b] as solvent	< 5
3	DCM ^[c] as solvent	46
4	With 1 equiv of HFIP as additive	35
5	With 1 equiv of H ₂ O as additive	45
6	<i>n</i> Bu ₄ NBF ₄ (1 equiv) as supporting salt	42
7	<i>n</i> Bu ₄ NBF ₄ (5 equiv) as supporting salt	37
8	<i>n</i> Bu ₄ NOAc (1 equiv) as supporting salt	<10
9	No supporting electrolyte	20
10	Without TEMPO	32
11	With 30 mol% of TEMPO	40
12	With 4-(NHAc)-TEMPO instead of TEMPO	50
13	Pt as CE	47
14	Reaction time of 8 hours (7.2 F)	66 {58} ^[d]
15	Pyrrolidine (1.5 mmol), [0.5 M]	64 {60}^[d]

^[a] HPLC yields using *N*-cyclohexylformamide as internal standard. ^[b] 1,1,1,3,3,3-Hexafluoro-propan-2-ol. ^[c] Dichloromethane. ^[d] Isolated yield.

To probe this further, employing an undivided cell, the targeted TEMPO-catalyzed electrochemical α -carbamoylation reaction was next investigated on preparative scale (Table 1).

To our delight, the desired reactivity was reached by running a 3 hour-galvanostatic electrolysis (with a current density of 5 mA.cm⁻²) in acetonitrile (0.17 M) in the presence of 10 mol% TEMPO and tetraethylammonium tetrafluoroborate as electrolyte (1 equiv). Employing graphite as working electrode (WE) and nickel as counter electrode (CE), the expected carbamoylated product **4** was obtained in an encouraging 54% HPLC yield after 2.7 F of electricity (Table 1, entry 1). Further optimization studies indicated that other solvents such as DCM and HFIP were less adequate (Table 1, entries 2 & 3), while the use of protic additives did not improve the reaction efficiency (Table 1, entries 4 & 5). Several electrolytes were tested but none proved superior to Et₄NBF₄, even at higher concentration (Table 1, entries 6-9).

Direct electrolysis (without TEMPO) resulted in a less efficient electrochemical process, as a probable consequence of deleterious electrode fouling. Nevertheless, rising the TEMPO catalytic charge to 30 mol% proved detrimental as well (Table 1, entries 10-11). On the other hand, using 4-NHAc-TEMPO as redox mediator did not significantly affect the reaction yield (Table 1, entry 12). Other CE materials could be used (Table 1 entry 13), although we opted for keeping a nickel cathode since it is both cheap and well-known to induce a low overpotential for proton reduction.^[1e] Drastically prolonging the reaction time to 8 hours (*i.e.* increasing the total charge to 7.2 F) allowed a small increase of the reaction yield (Table 1, entry 14). However, in a more convenient way, rising the initial concentration of pyrrolidine to 0.5 M resulted in a more efficient process, as

acids did not impede the reaction. 2-Ethylbutyric acid (**3d**), cyclopentylacetic acid (**3e**) and pivalic acid (**3f**) allowed the preparation of the corresponding products **7**, **8** and **9** with good efficiency (59, 62 and 69% yields). This electrochemical reaction was also amenable to the use of phenylacetic and hydrocinnamic acids (**3g** and **3h**), as well as that of more elaborated acidic partners such *N*-Boc glycine (**3i**) and 5-hexynoic acid (**3j**). Accordingly, the α -functionalized pyrrolidines **10-13** were obtained in the range of 43% to 68% yield. Interestingly, the reaction proved to be completely chemoselective with amino acids **3i**. Indeed, no product resulting of the insertion of *tert*-butyl isocyanide **2a** at the α position of the Boc-protected nitrogen atom could be detected. Different acrylic acids **3k-m** were tested then, in which case the corresponding unsaturated α -carbamoylated products **14-16** were isolated in 34-51% yield.

This method was likewise compatible with aromatic carboxylic acids. Benzoic acid (**3n**) allowed the formation of the *N*-benzoyl compound **17** in 70% yield, while different groups at ortho or meta position (Me, CF₃, F, Br Cl) yielded the expected products **18-23** (32-82% yield). In some cases (**20-22**), the poor solubility of the starting acids (**3q-s**) in acetonitrile led us to add 5% (v/v) water in the reaction media. Even then, *para*-methyl and *para*-hydroxy benzoic acids (**3u** and **3v**) remained poorly soluble such that the corresponding heterogeneous reactions failed. Nevertheless, the 4-fluoro substituted acid **3w**, for which better solubility was assessed, allowed to obtain the 2-carboxamide pyrrolidine **26** in good 70% yield, attesting that *para*-substituted benzoic acids are indeed compatible. Worthy of note, more electron-rich 2-furyl and 2-thienyl carboxylic acids **3x** and **3y** were also compatible.

Under otherwise identical conditions, by employing pyrrolidine (**1a**) and hydrocinnamic acid (**3h**), a broader range of isocyanides (**2b-i**) were evaluated next. This multicomponent electrochemical reaction well performed with cyclohexyl (**2b**), benzyl (**2c**), *tert*-octyl (**2d**) and 2-(3,4-dimethoxyphenyl)-ethyl (**2g**) isocyanides, with which the corresponding carbamoylation products **29, 30, 31** and **34** were obtained in satisfactory 42-66% yields. On the other hand, isocyanoacetates **2e** and **2f**, as well as 2,6-dimethylphenyl isocyanide **2h**, tended to give lower yields (28-34%). This trend suggests that more electron-deficient or sterically demanding isocyanides are less efficient reaction partners, as a probable consequence of their poorer ability to trap the electro-generated transient imine, prior to its competitive degradation in the reaction conditions. We then demonstrated that this reaction is not restricted to the use of pyrrolidine **1a** and that it is compatible with a wider set of cyclic free secondary amines **1b-f**.^{[20],[21]} Indeed, although with slightly diminished yields (36-44%), piperidines **1b** and **1c** reacted with *tert*-butyl isocyanide **2a** and different carboxylic acids (**3a, 3h** and **3f**) to provide the corresponding pipecolic acid derivatives **36-39**. In addition, the multicomponent coupling occurred with complete diastereoselectivity in favour of the 2,4-*trans* product **39** when 4-phenylpiperidine **1c** was employed, as recently reported by Ruijter and Orru.^[22] The use of morpholine (**1d**) was also amenable, with which the α -carbamoylated IMCR adducts **40** and **41** were obtained in 44 and 48%, respectively. In somewhat lower yields (22-43%), azepane **1e** reacted too and gave access to the corresponding 7-membered ring products

42-45. Finally, this method was also adequate for the α -carbamoylation of tetrahydroisoquinoline **1f**, which allowed us to obtain the desired α -functionalized THIQs **46-48** in 52-67% yields.

On the basis of our results and the literature,^{[10],[18]} we propose the following mechanism for this electrochemical multicomponent process (Scheme 3). In an initial stage, catalytic TEMPO is oxidized at the anode to generate the corresponding oxoammonium species TEMPO⁺. The latter then reacts with the free cyclic secondary amine to provide, after hydride transfer, the cyclic iminium **A** and TEMPOH, which, as independently reported the groups of Kato and Stahl,^{[23],[24]} is in equilibrium with its protonated form TEMPOH₂⁺. While TEMPOH -or its conjugated acid- can further regenerate TEMPO⁺ upon the loss of one proton -or two- and a *bis*-electronic anodic oxidation, the transient cyclic iminium is trapped by the isocyanide present in the reaction media to deliver the nitrilium **B**. Upon the nucleophilic attack of the carboxylic partner, the acyl imidate **C** which is formed subsequently evolves, through 1,5-acyl transfer, toward the desired carbamoylation product.

Conclusions

In summary, we have developed an original electrochemical TEMPO-catalyzed multicomponent process allowing the direct C(sp³)-H α -carbamoylation of free cyclic secondary amines. This new method, which likely operates under catalytic indirect anodic oxidation followed by a Ugi-Joullié isocyanide-based multicomponent reaction, avoids the use of stoichiometric oxidants or metal-based catalytic systems, and could be applied to the straightforward preparation of a wide variety of *N*-acyl α -carboxamides. Further developments, including electrolyte-free reaction conditions, are currently studied and will be reported in due course.

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Scheme 3. Mechanistic proposal.

Conflicts of interest

There are no conflicts to declare.

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- See Electronic Supplementary Information for further electroanalytical descriptions.
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Graphical Abstract

The electrochemical α -Carbamoylation of free cyclic secondary amines has been realized under an original TEMPO-catalyzed multicomponent coupling.