Article

Electrochemical TEMPO-Catalyzed Oxidative Ugi-Type Reaction

Na Pan, Maegan Xinen Lee, Louis Bunel, Laurence Grimaud,* and Maxime R. Vitale*

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ABSTRACT: Oxidative isocyanide-based multicomponent reactions (oxidative IMCRs) are very useful tools for the rapid construction of molecular diversity starting from readily available and stable substrates. Despite all their benefits, such multicomponent reactions are underdeveloped and strictly limited to 3-component processes. Indeed, in the presence of several reaction partners, the oxidation event needs to be rigorously chemoselective, which becomes incredibly more intricate as the number of reactive components increases. Nonetheless, we could overcome this significant pitfall and reach the first oxidative Ugi-type 4-IMCR by capitalizing on a very mild and green TEMPO-catalyzed electro-oxidation process. Employing alcohols as aldehyde surrogates and in the notable absence of any supporting electrolyte, this transformation proved to be extremely chemoselective in the presence of an amine and was compatible with a wide range of alcohols, amines, isocyanides, and carboxylic acids.

KEYWORDS: *Oxidative Ugi reaction, Muticomponent reaction, Electrosynthesis, Indirect anodic oxidation, TEMPO*
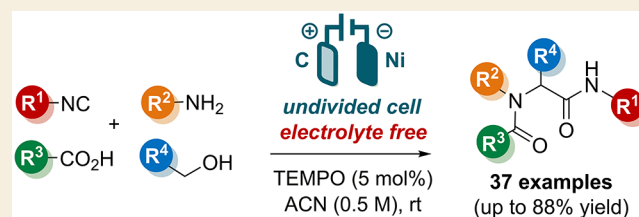
INTRODUCTION

Multicomponent reactions (MCRs) are now established as very efficient tools for the rapid and efficient preparation of elaborated chemicals, starting from relatively simple building blocks.[1] Inasmuch as they meet many of the criteria dictated by green chemistry,[2−5] this sustainable strategy has found many applications ranging from the production of fine chemicals to various uses in material sciences.[1,6−11] Isocyanide-based processes (IMCRs) have partaken substantially to the blossoming of this field. Since Passerini and Ugi demonstrated that the ambivalent reactivity of isocyanides could be successfully harnessed in multicomponent processes,[12,13] IMCRs have not ceased to bring stimulating developments.[1,6−11,14−21] Nevertheless, one of the major impediments of IMCRs is that, because often relying on the use of $Csp^2{=}O$ or $Csp^2{=}N$ partners, such reactions largely rely on the use of carbonyl/imine derivatives, which may reveal themselves to be unstable enough to impede their preparation and, accordingly, their use.

To circumvent this problem, the concept of generating the adequate carbonyl/imine electrophiles by means of the in situ oxidation of the corresponding alcohol/amine emerged.[22,23] As the first milestone in oxidative IMCRs, Zhu et al. succeeded in performing an alcohol-based 3-component Passerini reaction by employing 2-iodoxybenzoic acid (IBX) as the stoichiometric oxidant (Scheme 1, eq (a)).[24] Whereas a catalytic version of this multicomponent process was later reported,[25,26] more attention was subsequently paid to oxidative 3-component Ugi−Joullié-type IMCRs, in which an amine or an aniline derivative serves as the imine/iminium precursor (Scheme 1, eq (b)).[27−41]

Scheme 1. Oxidative IMCRs—Aim of This Work
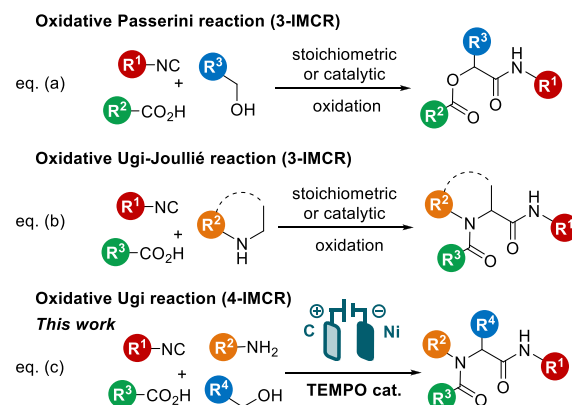
Despite all of these significant achievements, neither catalytic nor stochiometric methods could be applied to related 4-component processes so far. This significant pitfall probably results from the problematic, yet compulsory, chemoselective oxidation required by the presence of an additional reactant. In particular, the 4-component Ugi coupling based on the use of alcohols remains an unsolved challenge, with the amine partner being also prone to
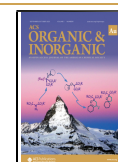
oxidation. In fact, alcohol-based Ugi-type processes could only be performed via a one-pot two-step sequence, wherein the stoichiometric or catalytic oxidation of an alcohol to its aldehyde form is achieved first, followed by the subsequent addition of the other three components.[42−45]

In this specific context, we recently began to study the synergistic merger of electrosynthesis with IMCRs. Performing an anodic oxidation, direct or indirect, is particularly appealing as it avoids the use of stoichiometric oxidants by employing perfectly sustainable reagents: electrons and protons.[46−51] Moreover, such oxidation methods are typically very mild, giving better chances to reach better chemoselectivity. After establishing the proof of concept via the development of an electrochemical oxidative Ugi−Joullié reaction,[41] we now report the first alcohol-based oxidative Ugi reaction, thanks to an indirect anodic oxidation process (Scheme 1, eq (c)).

■ RESULTS AND DISCUSSION

At the onset of this work, we decided to study the model oxidative Ugi reaction between *tert*-butylisocyanide **1a** (1.5 mmol, 1 equiv), benzylamine **2a** (1.1 equiv), acetic acid **3a** (2.5 equiv), and methanol **4a** (3 equiv). TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was chosen as the redox mediator to promote the oxidation of methanol into formaldehyde (Table 1).[52,53]

Table 1. Optimization of the Reaction Conditions

entry	variation from above	yield (%)[a]
1	none	68 (70)[b]
2	*t*BuNC (0.5 mmol), [0.17 M]	39
3	DCM[c] as solvent	75
5	Ni foam as cathode	69
6	stainless steel as cathode	68
7	Ni as anode	54
8	stainless steel as anode	53
9	MeCO$_2$H (1.5 equiv)	57
10	MeCO$_2$H (3.5 equiv)	69
11	MeOH (1.5 equiv)	59
12	MeOH (6 equiv)	74
13	TEMPO (5 mol %)	70 (72)[b]
14	TEMPO (20 mol %)	67
15	no TEMPO	40
16	no electrolyte	78 (74)[b]
17	**no electrolyte, TEMPO (5 mol %)**	76 (74)[b]
18	no electricity	NR[d]

[a]NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]Dichloromethane. [d]No reaction.

In initial reaction conditions, employing an undivided cell, TEMPO (10 mol %), Et$_4$NBF$_4$ (1 equiv) as supporting electrolyte in acetonitrile (0.5 M), with a nickel plate cathode and a carbon graphite anode, we were pleased to observe the desired 4-component IMCR adduct **5a** in 70% isolated yield after 2.7 F/mol of electricity (Table 1, entry 1). This result was very encouraging as, despite the presence of benzylamine **2a**, this oxidation method allowed the desired selective oxidation
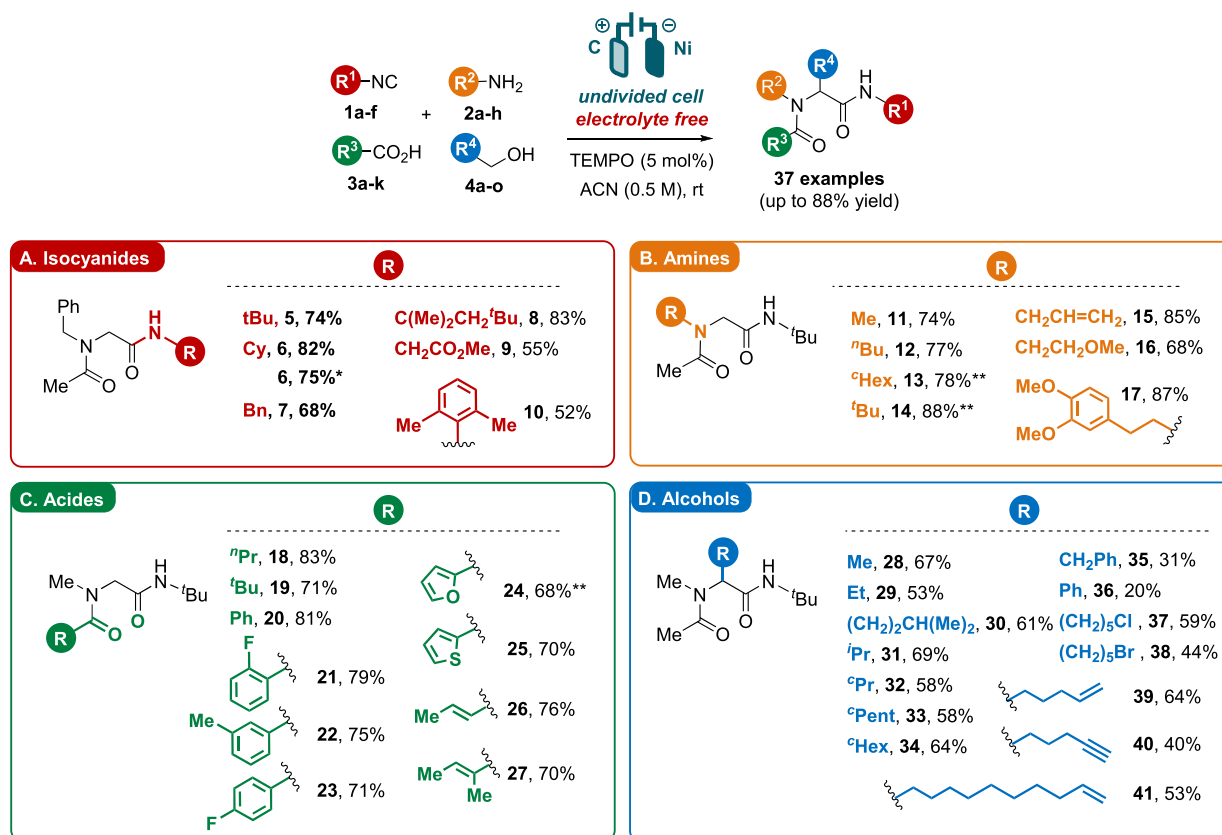
of methanol **4a**, without interfering with the concomitant multicomponent coupling. Moreover, it showcased the synthetic utility of this strategy, with which it became possible to avoid the use of toxic formaldehyde in Ugi processes.

Therefore, we embarked on the optimization of the reaction conditions. Whereas lowering the reaction concentration was detrimental (Table 1, entry 2), using dichloromethane as solvent or changing the cathode material to nickel foam or stainless steel had little influence over the reaction efficiency (Table 1, entries 3−6). On the other hand, substituting the graphite anode by other electrode materials gave lower yields (Table 1, entries 7 and 8). We then evaluated the influence of the starting quantities of acetic acid and methanol. Lowering them up to 1.5 equiv resulted in a noticeable diminution of yields, whereas increasing them did not significantly improve the formation of **5** (Table 1, entries 9−12). Pleasingly, this reaction was equally efficient when employing only 5 mol % of TEMPO (Table 1, entry 13), whereas the use of 20 mol % had no positive impact (Table 1, entry 14). The fact that some product was obtained without TEMPO indicated that direct anodic oxidation of methanol may happen, although with lesser efficiency (Table 1, entry 15). Most interestingly, likely because of the intrinsic conductivity of the reaction mixture, this electro-oxidative Ugi reaction could be achieved in the absence of any supporting electrolyte, using either 10 or 5 mol % of TEMPO (Table 1, entries 16 and 17). In the latter reaction conditions, which we kept for the rest of our study, the desired 4-IMCR adduct **5** was isolated in satisfying 74% yield, equaling a fair 55% Faraday yield.

We then investigated the scope of this new oxidative IMCR (Scheme 2). The tolerance to various isocyanides was surveyed first (Scheme 2, red box). Employing benzylamine, acetic acid, and methanol, this reaction was amenable for the use of diverse alkyl- or benzyl-substituted isocyanides **1b−e**. The corresponding multicomponent adducts **5−8** were obtained in good yields ranging from 74 to 83%. Using less nucleophilic and/or more sterically demanding partners such as methyl isocyanoacetate **1f** or 2,6-xylyl isocyanide **1g** resulted in a small decrease of reaction efficiency. Nevertheless, the desired Ugi products **9** and **10** were isolated in acceptable 55 and 52% yields, respectively. Of note, this electrochemical multicomponent reaction could be transposed to gram-scale, demonstrating its genuine synthetic utility and versatility. Indeed, while this scope evaluation was realized on a typical 1 mmol scale, starting from 5.0 mmol of isocyanide **1b** straightforwardly yielded 1.08 g of adduct **6** (75% yield).

Next, different amine partners were evaluated (Scheme 2, orange box). Replacing benzylamine **2a** with primary amines such as methylamine **2b** or *n*-butylamine **2c** had no detrimental impact over the reaction efficiency. A similar trend was also observed when employing bulkier α,α-di- or α,α,α-trisubstituted primary amines, such as cyclohexylamine **2d** and *tert*-butylamine **2e**, provided that 5% (v/v) of water was added to ensure the homogeneity of the reaction mixture. In these cases, **13** and **14** were obtained in respectable 78 and 88% yields. More elaborated amine partners could also be used successfully; allylamine **2f**, methoxyethylamine **2g**, and 3,4-dimethoxyphenyl ethylamine **2h** all afforded the desired Ugi adducts **15−17** in good yields, up to 87%.

Several carboxylic acids **3b−k** were also tested (Scheme 2, green box). Aliphatic acids were well-tolerated in this reaction, as witnessed by the good yields which were obtained when butyric acid **3b** and pivalic acid **3c** were employed (83 and

Scheme 2. Scope of the Electrochemical Oxidative Ugi Reaction[a]

A. Isocyanides

tBu, **5**, 74%   C(Me)$_2$CH$_2^t$Bu, **8**, 83%
Cy, **6**, 82%   CH$_2$CO$_2$Me, **9**, 55%
6, 75%*
Bn, **7**, 68%   **10**, 52%

B. Amines

Me, **11**, 74%   CH$_2$CH=CH$_2$, **15**, 85%
^{n}Bu, **12**, 77%   CH$_2$CH$_2$OMe, **16**, 68%
^{c}Hex, **13**, 78%**   **17**, 87%
^{t}Bu, **14**, 88%**

C. Acides

^{n}Pr, **18**, 83%
^{t}Bu, **19**, 71%   **24**, 68%**
Ph, **20**, 81%
21, 79%   **25**, 70%
22, 75%   **26**, 76%
23, 71%   **27**, 70%

D. Alcohols

Me, **28**, 67%   CH$_2$Ph, **35**, 31%
Et, **29**, 53%   Ph, **36**, 20%
(CH$_2$)$_2$CH(Me)$_2$, **30**, 61%   (CH$_2$)$_5$Cl, **37**, 59%
^{i}Pr, **31**, 69%   (CH$_2$)$_5$Br, **38**, 44%
^{c}Pr, **32**, 58%   **39**, 64%
^{c}Pent, **33**, 58%   **40**, 40%
^{c}Hex, **34**, 64%   **41**, 53%

[a]Reaction conditions: isocyanide **1** (1.5 mmol, 1 equiv), amine **2** (1.65 mmol, 1.1 equiv), carboxylic acid **3** (3.75 mmol, 2.5 equiv), and alcohol **4** (4.5 mmol, 3 equiv) in acetonitrile (3 mL, [0.5 M]) at room temperature; graphite as working electrode, Ni as counter electrode, constant current electrolysis (i = 14.5 mA, j = 5 mA cm^{-2}) for 7.5 h, 2.7 F mol^{-1}. *Gram-scale reaction starting from 5.0 mmol isocyanide **1b** (1.08 g of multicomponent adduct **6** was obtained). **Water 5% (v/v) was added.

Scheme 3. Mechanistic Proposal

Indirect Anodic Oxidation   *Ugi 4-IMCR*
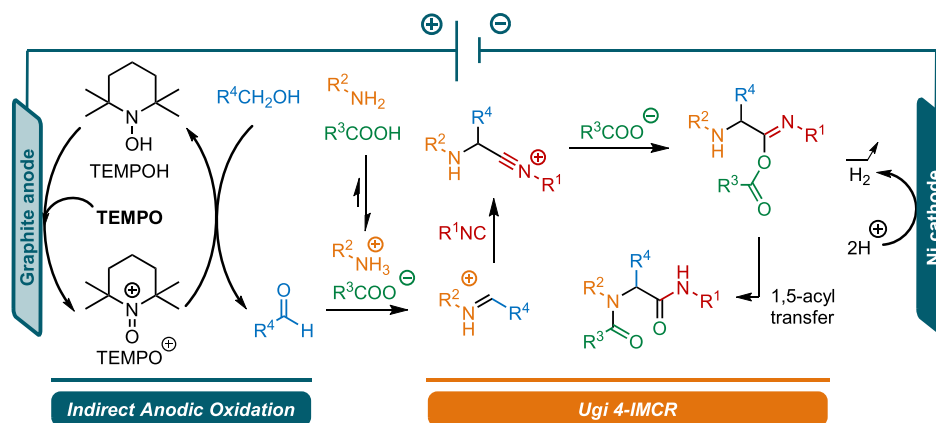
71%). This oxidative multicomponent process also appeared to be compatible with various aromatic and heteroaromatic acids **3d−i**, as well as acrylic acids **3j,k**, with which the corresponding coupling products **20−27** were isolated likewise with satisfactory yields (68−81%).

We next questioned if this unconventional oxidative IMCR was specific for the use of methanol (Scheme 2, blue box). A wide range of alcohol partners was also compatible with this electro-oxidative process. Different aliphatic alcohols **4b−h** led straightforwardly to the corresponding Ugi adducts **28−34** in

reasonable yields (53−69%). On the other hand, 2-phenyl-ethanol **4i** and benzyl alcohol **4j**, possibly less nucleophilic due to the presence of the aromatic ring, afforded only little of the desired products **35** and **36**. Halogen-, alkene-, and alkyne-substituted alcohols **4k−o** also proved to be suitable reaction partners. The corresponding multicomponent coupling products **37−41** were isolated in 40−64% yields.

Based on our previous work and literature,[14−21,41,52−54] we propose that TEMPO is oxidized at the graphite anode to generate the corresponding oxoammonium species TEMPO$^+$.

The latter would, in turn, promote the selective oxidation of the alcohol partner into the corresponding aldehyde, leaving the amine partner untouched. At this stage, we surmise that the presence of the carboxylic acid is critical for chemoselectivity. Indeed, it probably ensures the protection of the amine via an acid/base equilibrium in favor of the non-nucleophilic ammonium carboxylate form, thereby preventing it to interact with TEMPO$^+$. Then, the newly formed aldehyde, as in a classical 4-component Ugi reaction, would generate the corresponding iminium, electrophilic enough to react with the isocyanide. The resulting nitrilium cation would be trapped by the remaining carboxylate anion, and after 1,5-acyl transfer, the multicomponent product would be formed. To complete the catalytic cycle, either through comproportionation or direct anodic oxidation,[54] TEMPO$^+$ would be regenerated and, to keep the electroneutrality of the global system, proton reduction would occur at the nickel cathode.

CONCLUSION

In conclusion, we have developed the first oxidative 4-IMCR by implementing a very chemoselective TEMPO-catalyzed electrochemical process. This alcohol-based Ugi-type reaction allows the use of unstable/toxic aldehydes to be avoided (such as formaldehyde) and is compatible with a wide range of alcohols, amines, isocyanides, and carboxylic acids. A small library of the corresponding Ugi adducts (37 examples) was rapidly obtained, showcasing the synthetic utility of this approach for the rapid construction of high molecular diversity in a sustainable manner. Further studies concerning this promising synergistic merger of electrosynthesis with IMCRs is currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00003.

All experimental details including further optimization studies, detailed procedures, and proper characterization of all products; copies of ^{1}H and ^{13}C NMR (PDF)

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Notes

The authors declare no competing financial interest.

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