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# Electrochemically Enabled Intramolecular Aminooxygenation of Alkynes via Amidyl Radical Cyclization

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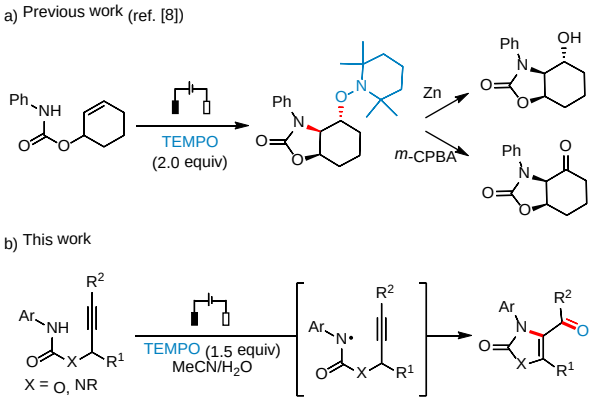
**Summary of main observation and conclusion** An electrochemical synthesis of oxazol-2-ones and imidazol-2-ones has been developed via 5-*exo*-*dig* cyclization of propargylic carbamates- and ureas-derived amidyl radicals. The electrosynthesis relies on the dual function of TEMPO as a redox mediator for amidyl radical formation and an oxygen atom donor. The reactions are conducted under mild conditions using a simple setup and provide convenient access to functionalized oxazol-2-ones and imidazol-2-ones from readily available materials.

## Background and Originality Content

Nitrogen-centered radicals (NCRs) are versatile synthetic intermediates for organic synthesis and can participate in reactions such as hydrogen atom transfer and addition to π-systems.[1] Particularly, the addition reactions provide access to nitrogen-containing compounds, which are prevalent in chemistry and biology. Probably due to the importance of nitrogen-containing compounds, addition reactions of NCRs have been attracting increasing interests. Among the addition reactions that have been investigated, reactions with alkynes are much less common compared to those with alkenes.[2] Further expansion of the synthetic utility of NCRs hinges on the development of efficient methods for their formation from readily available precursors.

Organic electrochemistry is emerging as a useful tool for promoting radical reactions.[3] In this context, we have developed several electrochemical methods for the generation of NCRs from N–H precursors.[4] The electrochemically generated NCRs participate in intramolecular cyclization reactions with arenes,[5] alkenes[6] and alkynes[7] to afford various N-heterocycles. Particularly, we have shown that TEMPO can serve as both a redox mediator for amidyl radical formation and an oxygen atom donor to achieve intramolecular alkene aminooxygenation.[8] In these reactions, TEMPO is incorporated into the final product as an alkoxyamine moiety, which can be cleaved reductively to a hydroxyl group or oxidatively to a keto group. Herein, we report a TEMPO-mediated, electricity-driven intramolecular aminooxygenation reaction of alkynes. Unlike the reactions of alkenes, these reactions of alkynes afford acyl-substituted oxazolone and imidazolone products that do not contain TEMPO-derived alkoxyamine moiety. Oxazolones and imidazolones are useful synthetic intermediates and are also structural motifs present in several bioactive compounds.[9]

**Scheme 1** Electrochemical aminooxygenation of alkenes and alkynes

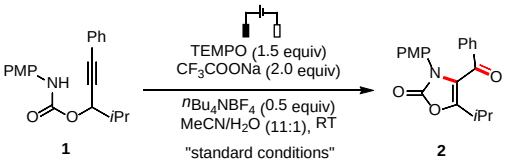



## Results and Discussion

We first selected carbamate **1** as a model substrate for optimization of the electrolysis conditions. The electrochemical reaction was carried out in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum cathode at a constant current of 5 mA (Table 1). Oxazol-2-one **2** was isolated in 85% yield when the reaction was conducted at room temperature for 1.2 h in the presence of 1.5 equiv of TEMPO and 2.0 equiv of $CF_3COONa$ in a mixed solvent of $MeCN/H_2O$ (11:1) under argon atmosphere (entry 1). Electricity was indispensable for success (entry 2). Reduction of the amount of TEMPO to 0.5 equiv (entry 3) or conducting the electrolysis without $CF_3COONa$ (entry 4) resulted in a lower yield of **2**. Other basic additives such as $Na_2CO_3$ (entry 5), $NaHCO_3$ (entry 6), NaOAc (entry 7) and $CF_2ClCOONa$ (entry 8) failed to give better results. Moderate yield of **2** was obtained when the electrolysis was performed in the absence of $n$Bu$_4$NBF$_4$ (entry 9) or under air atmosphere (entry

10).

**Table 1** Optimization of reaction conditions[a]

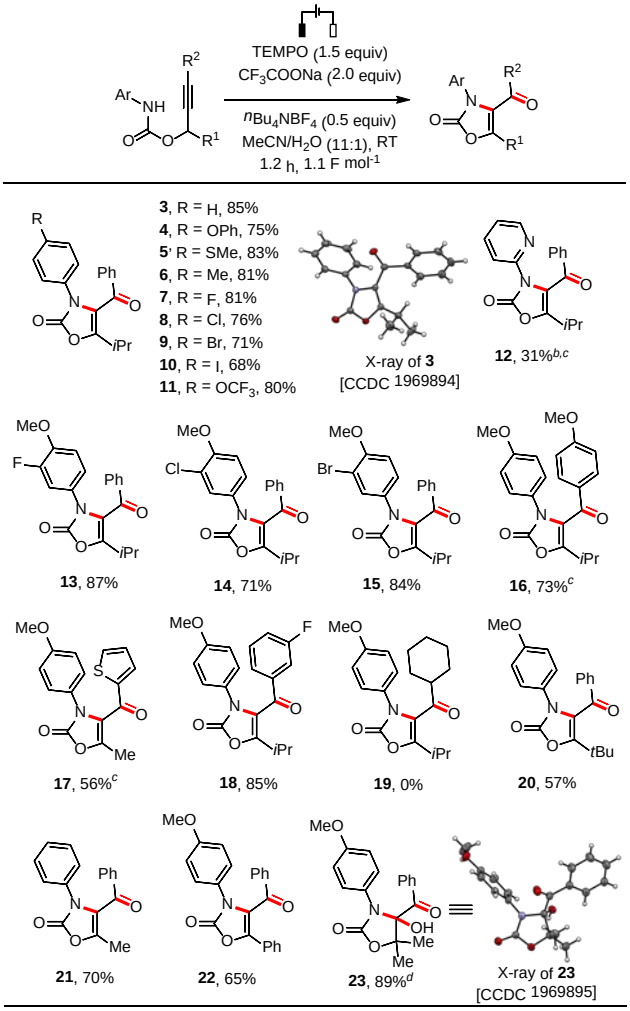



| Entry | Deviation from standard conditions | Yield[b]/% |
|---|---|---|
| 1 | None | 85[c] |
| 2 | no electricity | 0 (99) |
| 3 | entry 1 but TEMPO (0.5 equiv) | 40 (34) |
| 4 | entry 1 but no $CF_3COONa$ | 32 |
| 5 | entry 1 but $Na_2CO_3$ (2.0 equiv) as base | 28 |
| 6 | entry 1 but $NaHCO_3$ (2.0 equiv) as base | 36 |
| 7 | entry 1 but NaOAc (2.0 equiv) as base | 65 |
| 8 | entry 1 but $CF_2ClCOONa$ (2.0 equiv) as base | 73 |
| 9 | entry 1 but no $nBu_4NBF_4$ | 70 |
| 10 | entry 1 but under air | 67 |

[a]Reaction conditions: RVC anode, Pt cathode, **1** (0.2 mmol), TEMPO (0.3 mmol), $CF_3COONa$ (0.4 mmol), $nBu_4NBF_4$ (0.1 mmol), MeCN (5.5 mL), $H_2O$ (0.5 mL), argon, 5 mA, 1.2 h (1.1 F $mol^{-1}$). [b]Yield determined by $^1$H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard, unreacted **1** in parenthesis. [c]Isolated yield. PMP = *p*-methoxyphenyl.

After the optimized reaction conditions were defined, we investigated the substrate scope of the electrosynthesis (Scheme 2). The phenyl ring of the aniline moiety tolerated substituents of diverse electronic properties, including electron-donating groups such as OPh (**4**), SMe (**5**) and Me (**6**), halogens (F, Cl, Br, I; **7**–**10**), and electron-withdrawing groups such as $OCF_3$ (**11**). The structure of **3** was confirmed by single crystal X-ray diffraction studies. 2-Aminopyridine-derived substrate afforded the corresponding oxazol-2-one **12** in 31% yield. Substrates with a disubstituted *N*-aryl ring were also suitable for the electrochemical cyclization reaction (**13**–**15**). While the reaction is compatible with 4-methoxyphenyl (**16**), 2-thiophenyl (**17**) or 3-fluorophenyl (**18**) substituted alkynes, alkyl substituted alkynes failed to afford any desired products (**19**). Furthermore, carbamates bearing a tert-butyl (**20**), methyl (**21**) or phenyl (**22**) group at the propargylic position also reacted successfully to produce the desired oxazol-2-ones. Interestingly, substate without propargylic proton reacted to afford a hydroxyl oxazolidone (**23**).

**Scheme 2** Scope of oxazol-2-one synthesis[a]



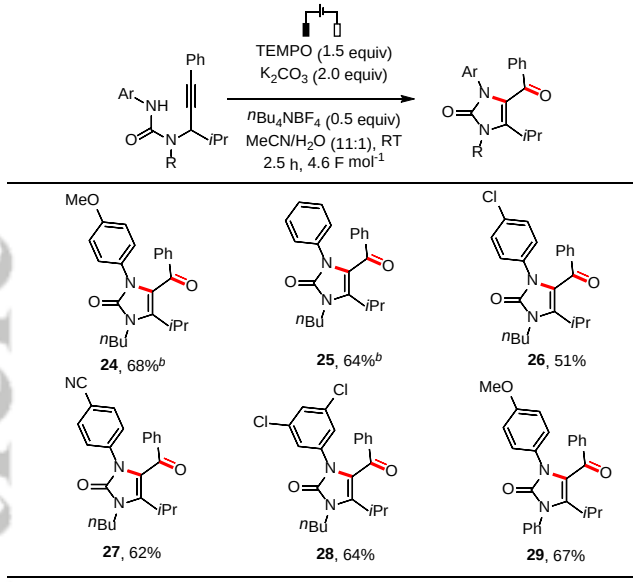

[a]Reaction conditions: Table 1, entry 1 unless otherwise mentioned. All yields are isolated yields. [b]Reaction with NaOAc (2.0 equiv) instead of $CF_3COONa$. [c]Reaction for 4 h. [d]Reaction for 2.5 h.

Next, we applied the electrochemical strategy to the synthesis of imidazol-2-ones from propargylic ureas (Scheme 3). Urea substrates bearing 4-methoxy phenyl (**24**) and phenyl (**25**) groups reacted to afford the corresponding imidazol-2-ones in 68% and 64% yields, respectively. 4-Chlorophenyl (**26**), 4-cyanophenyl (**27**) and 3,5-dichlorophenyl (**28**) substituted ureas reacted successfully under modified conditions with $K_2CO_3$ as the base at a constant current of 10 mA. The substitutent on the linking nitrogen also tolerated variation as demonstrated with a N-Ph urea (**29**).



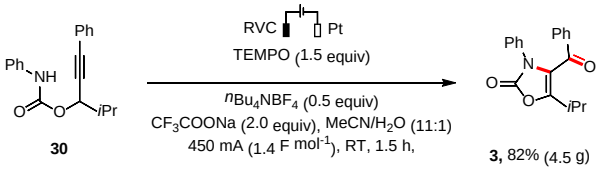
**Scheme 3** Scope of imidazol-2-one synthesis[a]




[a]Reaction conditions: urea (0.2 mmol), TEMPO (0.3 mmol), $K_2CO_3$ (0.4 mmol), $nBu_4NBF_4$ (0.1 mmol), MeCN (5.5 mL), $H_2O$ (0.5 mL), argon, 10 mA, 2.5 h (4.6 F $mol^{-1}$). All yields are isolated yields. [b]Reaction under the conditions of Table 1, entry 1 for 4 h.

The practicality of our method was further demonstrated by the gram scale reaction of **30** to give oxazolone **3** in 82% yield (Scheme 4). Note that larger electrodes were employed to allow the use of higher current to increase productivity.

**Scheme 4** Gram-scale synthesis of oxazol-2-one **3**




To shine light on the reaction mechanism, we first recorded cyclic voltammograms (CVs) of TEMPO under different conditions (Figure 1). The CVs of TEMPO did not change when either the substrate **30** (curve b) or **30** together with $CF_3COONa$ was added (curve c), suggesting that the neutral substrate **30** did not react with anodically generated $TEMPO^+$. However, a catalytic current was observed in the presence of $nBu_4NOH$, along with complete disappearance of reduction current (curve d). A comparison of curve d with curve e, the voltammogram of the conjugate base of **30**, suggested the current increase of curve d was not due to the oxidation of the substrate anion. These studies indicated that effective electron transfer occurred between $TEMPO^+$ and the conjugate base of **30** but not the neutral **30**.

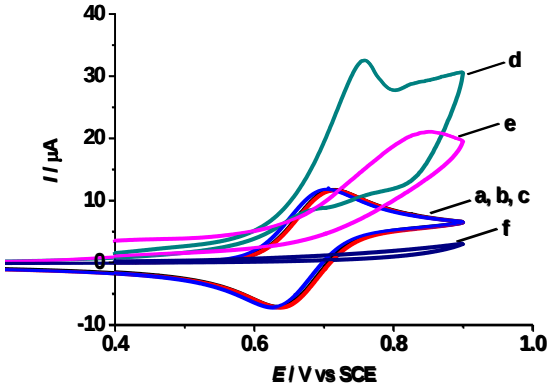


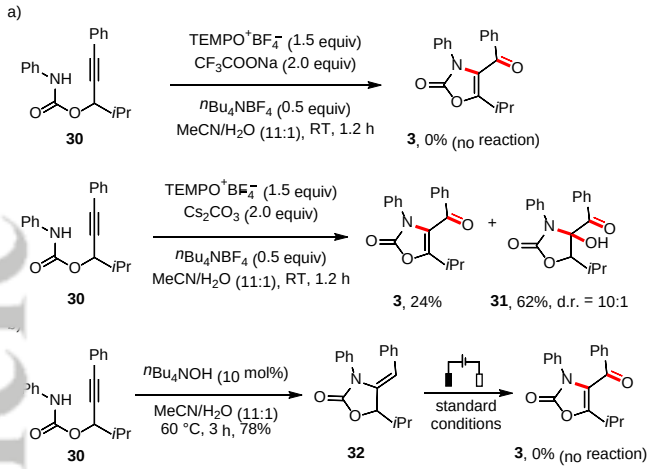

**Figure 1** Cyclic voltammograms in MeCN, $nBu_4NBF_4$ (0.1 M). a: TEMPO (3 mM). b: TEMPO (3 mM) + **30** (10 mM). c: b + $CF_3COONa$ (10 mM). d: b + $nBu_4NOH$ (10 mM). e: **30** (10 mM) + $nBu_4NOH$ (10 mM). f: $nBu_4NOH$ (10 mM).

Next, we performed a series of mechanistic experiments (Scheme 5). The oxidation of **30** was investigated with oxoammonium salt ($TEMPO^+BF_4^-$) under electricity-free conditions (Scheme 5a). While no reaction occurred in the presence of $CF_3COONa$, oxazolone **3** was formed in 24% along with hydroxy ketone **31** in 62% when $Cs_2CO_3$ was employed as a base. These results, together with the CV studies, clearly showed that a base strong enough to deprotonate the carbamate was needed for the aminooxygenation reaction to occur. The inferior results obtained using stoichiometric oxidant also highlighted the advantage of our electrochemical method. The alkyne substrates are known to undergo base promoted hydroamidation reaction.[7c,10] For example, propargyl carbamate **30** underwent efficient hydroxide-promoted ionic cyclization to afford oxazolidinone **32** in 78% yield. However, electrolysis of **32** under the standard conditions resulted in no oxazolone **3** and the recovery of 92% of **32** (Scheme 5b). These results suggested that **32** was not an intermediate for the electrochemical synthesis of **3**.



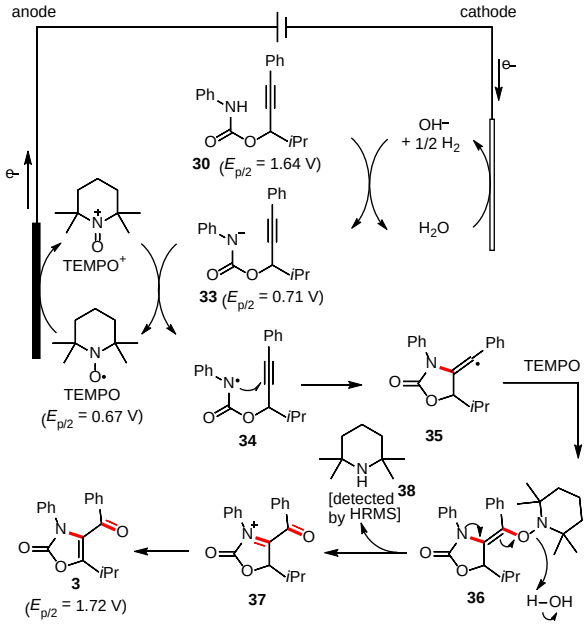
  

**Scheme 5** Mechanistic experiments




Based on the above studies and previous reports,[8,11] a possible mechanism for the electrochemical cyclization reaction was proposed using carbamate **30** as a model substrate (Scheme 6). At the anode, TEMPO ($E_{p/2}$ = 0.67 V vs SCE) is oxidized through single electron transfer (SET) to afford $TEMPO^+$. Simultaneously, the cathodic reduction of $H_2O$ forms $H_2$ and $HO^-$. The cathodically generated base $HO^-$ deprotonates **30** ($E_{p/2}$ = 1.64 V vs SCE) to give the nitrogen anion intermediate **33** ($E_{p/2}$ = 0.71 V vs SCE), which is easily oxidized by $TEMPO^+$ via SET to furnish nitrogen-centered radical **34**. The 5-*exo*-*dig* cyclization of **34** affords vinyl radical **35**, which is trapped by TEMPO to give tetrasubstituted alkene **36**. The sterically crowded alkene **36** undergoes N–O bond cleavage to afford iminium **37** and 2,2,6,6-tetramethylpiperidine **38**.[12] The latter has been detected by high resolution mass spectrometry (HRMS). Intermediate **37** undergoes proton loss to afford the final oxazolone **3**. For substrates that do not contain a propargylic proton, reaction of the iminium intermediate with $H_2O$ affords a hydration product (e.g. **23**).

**Scheme 4** Proposed mechanism




## Conclusions

In summary, we have developed a TEMPO-mediated electrochemical synthesis of functionalized oxazol-2-ones and imidazol-2-ones through oxidative cyclization of propargylic carbamates and ureas. In these reactions, TEMPO serves as both a redox mediator to produce amidyl radicals and an oxygen-atom donor.

## Experimental

**General procedures for the electrosynthesis:** A 10 mL three-necked round-bottomed flask (Figure S1) was charged with TEMPO (0.3 mmol, 1.5 equiv), the substrate (0.2 mmol, 1.0 equiv), $n$Bu$_4$NBF$_4$ (0.1 mmol, 0.5 equiv), and $CF_3COONa$ or $K_2CO_3$ (0.4 mmol, 2.0 equiv). The flask was equipped with a reticulated vitreous carbon (100 PPI, 1 cm x 1 cm x 1.2 cm) anode and a platinum plate (1 cm x 1 cm) cathode and then flushed with argon. MeCN (5.5 mL) and $H_2O$ (0.5 mL) were added. The electrolysis was carried out at room temperature using a constant current of 5 mA or 10 mA until complete consumption of the substrate (monitored by TLC or $^1$H NMR). The reaction mixture was concentrated under reduced pressure and the residue was chromatographed through silica gel eluting with ethyl acetate/hexane to give the desired product.

## Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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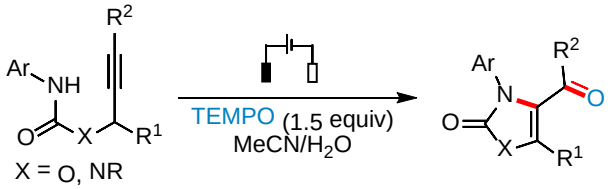


An electrochemical synthesis of oxazol-2-ones and imidazol-2-ones has been developed via 5-*exo-dig* cyclization of amidyl radicals. The electrosynthesis relies on the dual functional of TEMPO as a redox mediator for amidyl radical formation and an oxygen atom donor.

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