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Electrochemical Desulfurative Cyclization Accessing Oxazol-2-amine Derivatives via Intermolecular C−N/C−O Bond Formation

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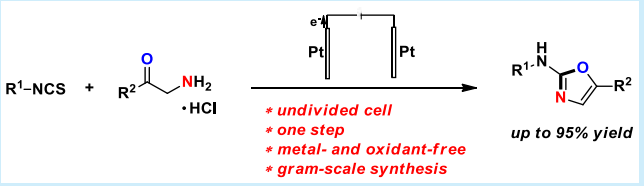
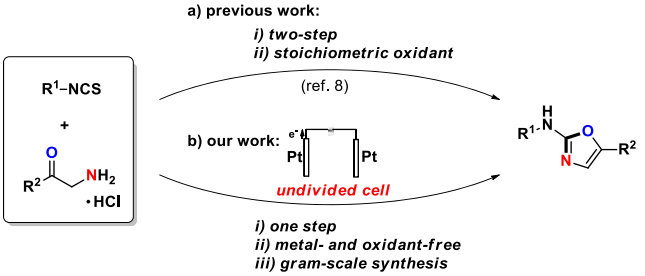
ABSTRACT: A practical protocol has been established to access diverse oxazol-2-amine derivatives in one step via the electrochemical desulfurative cyclization of isothiocyanates and α-amino ketones. On the basis of the cycle of in situ generation of iodine/desulfurative cyclization/iodide anion regeneration, the reaction is performed under metal-free and external-oxidant-free electrolytic conditions to achieve the formation of intermolecular C−O and C−N bonds, providing oxazol-2-amines in moderate to excellent yields.



Oxazoles contain O and N heteroatoms that have attracted long-term attention due to their widespread presence in natural products, pharmaceuticals,[1] catalysts, and functional materials. Among them, many molecules with an oxazol-2-amine motif have shown pharmaceutical and therapeutic activities, such as antituberculosis, antiviral, and analgesic activities.[2,3] Although many efforts have been made for oxazole synthesis,[4−8] the synthesis of valuable oxazol-2-amine derivatives is still rare. Among transition-metal-catalyzed methods, the Buchwald−Hartwig reaction[5] is considered effective for oxazol-2-amine preparation, which is achieved by the Pd-catalyzed arylation of amines under a strong base. Additionally, the Au-catalyzed heterocyclization of alkynes and nitriles has also been developed for preparing oxazol-2-amines.[6] Despite the high efficiency, the use of noble-metal catalysts still has problems such as high cost and residues in drug production. In recent years, the metal-free synthesis of oxazol-2-amines has received great attention, and some strategies have been implemented, including the multistep conversion of isocyanide dichlorides[7] and PPh_3-mediated cyclization reactions.[3] Among them, the PPh_3-mediated cyclization between β-ketoazides and isothiocyanates often occurs during the synthesis of oxazol-2-amine active molecules. Recently, a two-step synthesis method of 2-amino-substituted oxazoles with stoichiometric I_2 as an oxidant was described (Scheme 1a).[8] To reduce the use of stoichiometric oxidants, it is necessary to develop a facile and sustainable catalytic system to achieve the efficient synthesis of oxazol-2-amines.

Carbon−heteroatom bonds, including C−O and C−N bonds, are important moieties that exist in a variety of functional heterocycles.[9] With the development of electrochemical synthesis, tremendous progress has been made in the formation of carbon−heteroatom bonds.[10] Electrochemical technology can be used for heterocyclic synthesis by replacing the use of stoichiometric oxidants with anodic oxidation. For iodine-requiring heterocyclic synthesis reactions, the anodic oxidation can convert the iodide ion to an iodine radical or cation in situ,

Scheme 1. Synthesis of Oxazol-2-amine Derivatives *via* Electrochemical Desulfurative Cyclization



which will be regenerated at the anode after undergoing the reaction cycle. Therefore, a smaller amount of iodide salt is required in the electrochemical system. For example, Tang et al. have synthesized various thiadiazoles using a catalytic amount of iodine salts under electrolysis conditions.[11] For the development of environmentally friendly methods for oxazol-2-amines synthesis, we propose a metal-free and external-oxidant-free electrochemical strategy for the one-pot synthesis of oxazol-2-amine derivatives from isothiocyanates and α-amino ketones via desulfurative cyclization using $^nBu_4NI$ as an electrolyte (Scheme 1b).

In a preliminary study, we selected phenyl isothiocyanate (**1a**) and 2-aminoacetophenone hydrochloride (**2a**) as model substrates to optimize the conditions (Table 1). To prevent the intermediate from being hydrolyzed, electrolysis was

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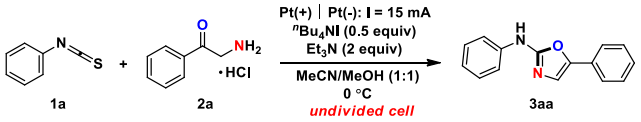
Table 1. Optimization of the Reaction Conditions[a,b]



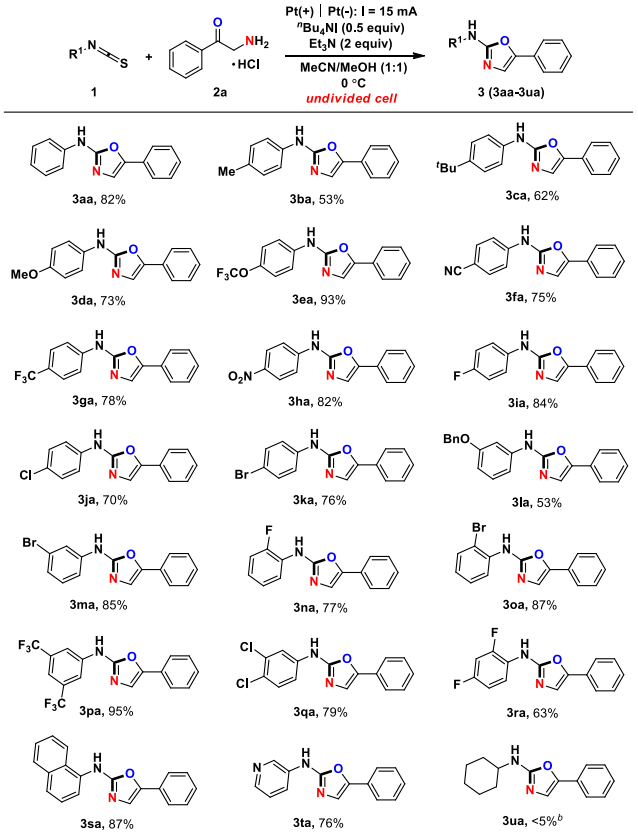
entry	variation from standard conditions	yield (%)
1	**none**	**86**
2	MeCN or MeOH as solvent	35, 32
3	MeCN/MeOH (5:1, 2:1, or 1:2) as solvent	68, 77, 36
4	K_2CO_3 (2 equiv) instead of Et_3N	trace
5	KO^{t}Bu (2 equiv) instead of Et_3N	trace
6	DABCO (1 equiv) instead of Et_3N	21
7	DBU (2 equiv) instead of Et_3N	8
8	with E_3N (1 or 0 equiv)	76, 0
9	with ^{n}Bu$_4$NI (0.2 or 0 equiv)	39, 0
10	with ^{n}Bu$_4$NI (0.2 equiv) and ^{n}Bu$_4$NPF$_6$ (0.3 equiv)	32
11	^{n}Bu$_4$NBr or ^{n}Bu$_4$NPF$_6$ instead of ^{n}Bu$_4$NI	trace, 0
12	NH_4I or KI instead of ^{n}Bu$_4$NI	55, 38
13	graphite rod as anode	13
14	10 mA, 3 h or 20 mA, 1.5 h	69, 84
15	no electricity	0

[a]Reaction conditions: undivided cell, **1a** (0.2 mmol), **2a** (0.24 mmol), Pt plates (1 cm × 1 cm) as anode and cathode, constant current = 15 mA, ^{n}Bu$_4$NI (0.5 equiv), Et_3N (2 equiv), MeCN/MeOH (1/1 v/v, 2 mL), air, 0 °C, 2 h, Q = 5.6 F mol^{-1}. [b]Yield is determined by ^{1}H NMR analysis with CH_2Br_2 as the internal standard.

performed in an ice bath at 0 °C. Initially, the reaction was electrolyzed in an undivided cell equipped with Pt plates as the anode and cathode using ^{n}Bu$_4$NI as an electrolyte and Et_3N as a base in the solvent mixture MeCN/MeOH (1:1) under a constant current of 15 mA. Satisfyingly, the desired product (**3aa**) was detected in 86% yield after the reaction was performed for 2 h (entry 1). In the process of condition optimization, we found that using MeCN or MeOH as a solvent could dramatically lower the yield of **3aa** (entry 2). Because slightly changing the ratio of MeCN and MeOH to 5:1, 2:1, or 1:2 led to a slight decrease in yield (entry 3), the use of the solvent mixture MeCN/MeOH (1:1) was considered the best chose. Subsequently, several bases were examined. Some inorganic salts, including K_2CO_3 and KO^{t}Bu, were not suitable for this electrochemical reaction due to their lower solubility under low-temperature conditions (entries 4 and 5). Replacing Et_3N with a stronger organic base such as DABCO or DBU also reduced the reaction efficiency (entries 6 and 7). Reducing the amount of Et_3N resulted in a slight decrease in yield, and no **3aa** was produced without the addition of Et_3N (entry 8). A lower yield was given when the amount of ^{n}Bu$_4$NI was decreased to 0.2 equiv, and no desired product was detected without the addition of ^{n}Bu$_4$NI, which was probably affected by the electrolyte concentration (entry 9). The addition of ^{n}Bu$_4$NPF$_6$ (0.3 equiv) as a supporting electrolyte did not increase the yield (entry 10), and other electrolytes such as ^{n}Bu$_4$NBr and ^{n}Bu$_4$NPF$_6$ were proved to be ineffective (entry 11). These results indicated that the concentration of iodide ions would affect the yield. Other iodide salts could also be used for electrolysis to obtain the desired product in moderate yields (entry 12). Electrode examination showed that using a graphite rod as an anode could seriously reduce the cyclization efficiency (entry 13). Neither reducing nor increasing the current could increase the reaction yield (entry 14). No product (**3aa**) was detected when the reaction was performed without electricity (entry 15). On the basis of the above results, the optimized reaction conditions were 0.5 equiv of ^{n}Bu$_4$NI and 2 equiv of Et_3N in MeCN/MeOH (1:1) under a constant current of 15 mA at 0 °C.

Under the optimized electrolysis conditions, we subsequently investigated the substrate scope of thiocyanates for this electrochemical desulfurative cyclization (Scheme 2). Gratifyingly, substrates with electron-rich substituents (methyl-, ^{t}butyl-, methoxy-, and trifluoromethoxy-) were well compatible with the system, and the target products (**3ba**−**3ea**) were given in moderate to excellent yields. Among them, the reaction of thiocyanate containing a trifluoromethoxy proceeded smoothly to give the oxazol-2-amine products (**3ea**) in a higher yield of 93%. Furthermore, thiocyanates with valuable substituents (cyano-, trifluoromethyl-, and nitro-) or halogens (F, Cl, and Br) underwent the reaction smoothly, and the corresponding products (**3fa**−**3ka**) were delivered in good to excellent yields. The reaction of benzyloxy-containing thiocyanate with 2-aminoacetophenone hydrochloride gave **3la** in a moderate yield, probably due to the low solubility of the intermediate in the system. The use of meta- or ortho-brominated phenyl isothiocyanate produced the corresponding products (**3ma** and **3oa**) in 85 and 87% yield, respectively, indicating that the steric position of substituents had no significant effect on this conversion. 2-Fluorophenyl isothiocyanate was also suitable for electrolysis, and the desired product (**3na**) was obtained in 77% yield. Notably, disubstituted phenyl isothiocyanates were

Scheme 2. Substrate Scope of Thiocyanates[a]



[a]Reaction conditions: undivided cell, **1** (0.5 mmol), **2a** (0.6 mmol), Pt plates (1 cm × 1 cm) as anode and cathode, constant current = 15 mA, ^{n}Bu$_4$NI (0.5 equiv), Et_3N (2 equiv), MeCN/MeOH (1/1 v/v, 5 mL), air, 0 °C, 5 h, Q = 5.6 F mol^{-1}. Isolated yields. [b]Yield determined by GC analysis with *n*-dodecane as the internal standard.

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all suitable substrates for this electrolysis (**3pa**–**3ra**). Among them, the reaction provided oxazol-2-amine product (**3pa**) in a yield of up to 95% when 3,5-ditrifluoromethyl phenyl isothiocyanate was used as the substrate. Furthermore, naphthalene ring and pyridine groups were also compatible with the electrolysis conditions, and the corresponding products (**3sa** and **3ta**) were delivered in 87 and 76% yields, respectively. However, only a trace of oxazol-2-amine product (**3ua**) was detected when alkyl isothiocyanate was used as the substrate, probably due to the poor stability of the corresponding intermediate.

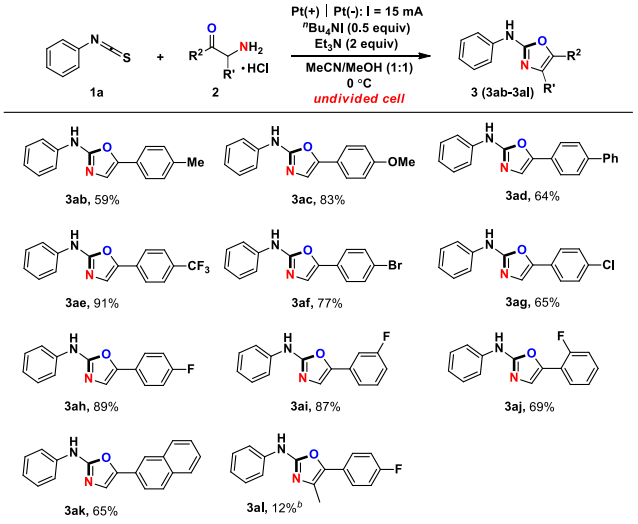
Next, we turned our attention to investigate the substrate scope of substituted 2-aminoacetophenone hydrochloride (Scheme 3). Different substituents, including methyl-, methoxy-, phenyl-, trifluoromethyl- and halo-, could be tolerated in the electrochemical desulfurative cyclization. The reaction of the *para*-methoxy-containing substrate exhibited a good yield of 83% (**3ac**), whereas the reaction of the *para*-methyl-containing substrate gave **3ab** in a moderate yield. The substrate with a large conjugated group (Ph) was converted in moderate yield (**3ad**) due to the low solubility of the intermediate. With the substrate containing a trifluoromethyl substituent at the para position, the reaction produced **3ae** in up to 91% yield. When a halogen atom was contained at the para position of the benzene ring, the target products were isolated in moderate to good yields (**3af**–**3ah**). Substrates containing a fluorine atom in the para or meta position (**3ah** and **3ai**) seemed to react better than those containing a fluorine atom in the ortho position (**3aj**). The naphthalene substrate (**2k**) could also be applied for electrochemical desulfurative cyclization and was converted to **3ak** in 65% yield. In addition, when 2-amino-1-(4-fluorophenyl)-propan-1-one was employed to react with phenyl isothiocyanate, the desired product (**3la**) was detected in 12% yield.

The scale-up experiment was subsequently conducted to demonstrate the practical utility of the electrochemical desulfurative cyclization (Scheme 4). When the reaction was performed on a 5 mmol scale, the desired products **3aa** was obtained in an isolated yield of 73%. Although the yield decreased slightly in the scale-up experiment, the experimental result still exhibited the application value of electrochemical strategies in the synthesis of heterocycles.

To investigate the mechanism involved in the electrochemical intermolecular C–O and C–N formation in the synthesis of oxazol-2-amines, several control experiments were then conducted (Scheme 5). First, because of the observation of the released elemental sulfur, we speculated that the reaction required a desulfurization process. Subsequently, phenyl isothiocyanate was replaced with 4-tolyl isocyanate as the substrate for electrolysis under optimal conditions, and no desired product **3ba** was detected, except for a large amount of methyl 4-methylbenzoate (eq a). Subsequently, **1a** and **2a** were mixed in the presence of Et_3N to form the thiourea intermediate **4aa**, and the desired product **3aa** was delivered in a 74% yield after electrolysis, where the thiourea intermediate **4aa** ($[M + H]^+$ = 271.0905) was confirmed by HRMS analysis (eq b). These results proved that desulfurization cyclization was the key step during the electrolysis process. We next added 1.5 equiv of free-radical scavenger (BHT or TEMPO) to the optimal electrolytic system, and the reaction gave **3aa** in a yield of 68 or 73%, respectively (eqs c and d). When the amount of TEMPO was increased to 4 equiv, the yield of **3aa** decreased slightly, probably because the TEMPO anion could form adduct **5** with **1a** through nucleophilic addition and desulfurization processes, wherein adduct **5** ($[M + H]^+$ = 277.1910) was further confirmed by the high-resolution mass spectrometry (HRMS) analysis (eq d). Therefore, our electrochemical desulfurization cyclization may not undergo a free-radical process.

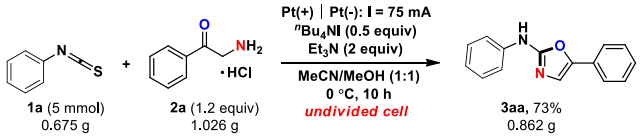
To further investigate the reaction mechanism, cyclic voltammetry (CV) experiments were also implemented, and the results are recorded in Figure 1. Within the scanning window (0–2 V), the CV of $^nBu_4NI$ (curve b) showed two oxidation signals at 0.78 and 1.17 V vs Ag/AgCl, responding to the oxidation process of iodide ions in electrolysis. After the addition

Scheme 3. Substrate Scope of Substituted 2-Aminoacetophenone Hydrochloride[a]

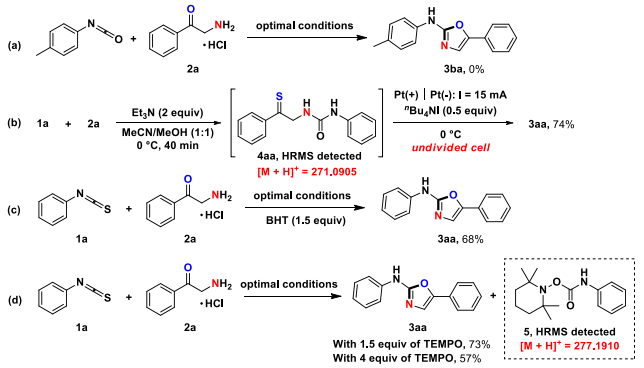


[a]Reaction conditions: undivided cell, **1a** (0.5 mmol), **2** (0.6 mmol), Pt plates (1 cm × 1 cm) as anode and cathode, constant current = 15 mA, $^nBu_4NI$ (0.5 equiv), Et_3N (2 equiv), MeCN/MeOH (1/1 v/v, 5 mL), air, 0 °C, 5 h, Q = 5.6 F mol^{-1}. Isolated yields. [b]Yield determined by GC analysis with *n*-dodecane as the internal standard.

Scheme 4. Scale-up Experiment



Scheme 5. Control Experiments



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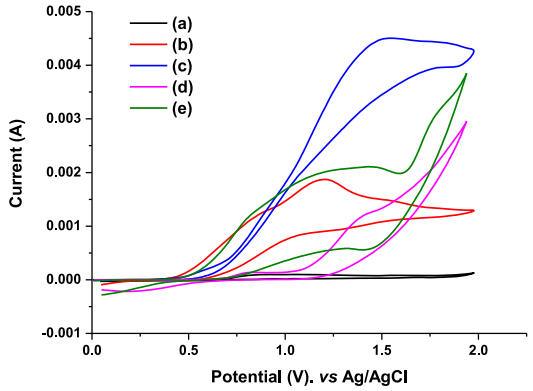
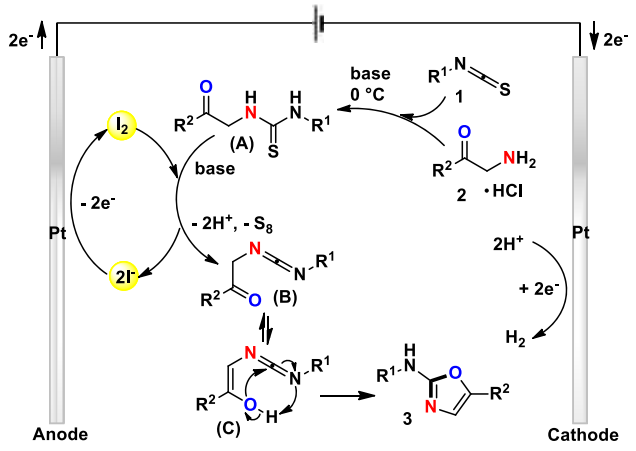


Figure 1. Cyclic voltammograms of reactants and their mixtures in 0.05 M $^{n}Bu_4NPF_6$ solution in MeCN/MeOH (1:1): (a) background, (b) $^{n}Bu_4NI$ (0.05 M), (c) $^{n}Bu_4NI$ (0.05 M) + Et_3N (0.2 M), (d) **1a** (0.1 M) + **2a** (0.1 M), and (e) **1a** (0.1 M) + **2a** (0.1 M) + $^{n}Bu_4NI$ (0.05 M). The voltammogram was obtained at a scan rate of 0.2 V/s with the Pt electrode as a counter electrode, Ag/AgCl (saturated KCl) as a reference electrode, and glassy carbon electrode as a working electrode.

of Et_3N, an oxidation peak appeared at 1.51 V vs Ag/AgCl in curve c. The mixture of isothiocyanate (**1a**) and 2-amino-acetophenone hydrochloride (**2a**) displayed no significant oxidative peak (curve d). Different from curve d, the oxidation peak was observed at 1.29 V vs Ag/AgCl in curve e due to the addition of $^{n}Bu_4NI$. On the basis of the cyclic voltammetry curves, we speculated that $^{n}Bu_4NI$ could promote the desulfurative cyclization through the in situ formation of iodine through anodization.

On the basis of the above experimental results, a plausible mechanism is proposed in Scheme 6. Initially, thiourea

Scheme 6. Proposed Mechanism



intermediate (**A**) is generated through the nucleophilic addition of α-amino ketone (**2**) to isothiocyanate (**1**) at 0 °C in the presence of a base. Meanwhile, an iodine molecule is formed on a platinum electrode through the anodic oxidation of iodide anions. Subsequently, the thiourea intermediate (**A**) undergoes desulfurization under the promotion of an iodine molecule and a base to form a carbodiimide intermediate (**B**)[12] and release two protons while regenerating the iodine anion. The isomerization of carbodiimide intermediate (**B**) forms the enol intermediate (**C**) followed by intramolecular cyclization to form the oxazol-2-amine product (**3**). In addition, the released protons are reduced to hydrogen on the platinum cathode.

In conclusion, a novel synthesis of oxazol-2-amine derivatives through the electrochemical desulfurative cyclization of isothiocyanates and α-amino ketones has been established. A series of substituted oxazol-2-amines are provided in moderate to excellent yields under metal-free and external-oxidant-free electrolytic conditions. The reaction is achieved through the formation of intermolecular C−O and C−N bonds at low temperatures based on the cycle of in situ generation of iodine/desulfurative cyclization/iodide anion regeneration. Furthermore, the protocol is practical and environmentally friendly and is characterized by simple electrolytic conditions and readily available substrates. Further efforts are currently underway to further expand the synthetic applications of oxazol-2-amine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04218.

Details of complete experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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