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Electrochemical synthesis of 1,2,4,5-tetrasubstituted imidazoles from enamines and benzylamines†

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An electrochemical method for synthesizing 1,2,4,5-tetrasubstituted imidazoles was developed under undivided electrolytic conditions. This synthesis was specifically realized based on electrochemical C(sp^3)–H amination *via* enamines and amines. Readily available starting materials were used, avoiding the use of both transition metals and oxidants. The practicability of the method lies in its broad substrate adaptability and in its ability to provide a simple green pathway for synthesizing $GABA_A$ receptor analogs.

Introduction

Imidazole is an important heterocyclic compound, and exists in many natural products and drugs (Fig. 1). Examples of imidazole with a substituent group attached to the nitrogen atom have been found to display anti-virus,[1] anti-inflammatory,[2] anticancer,[3] and antifungal activities as well as other pharmacological effects.[4] Furthermore, imidazole is also used as an environmentally friendly ionic solvent and carbene ligand.[5,6]

Traditional methods for synthesizing imidazole derivatives include the Bredereck synthesis, van Leusen reaction and Debus–Radziszewski reaction.[7] However, most of the existing methods show poor regioselectivity, give only 4,5-bisarylimidazoles, and many of these reaction conditions require the use of a strong base or high temperature or produce environmentally unfriendly byproducts. Currently, transition-metal-catalyzed methods are more commonly used to synthesize imidazole derivatives. However, relatively few metal-free syntheses of imidazoles have been reported.[8] C(sp^3)–H amination reactions have provided a new way to synthesize 1,2,4,5-tetrasubstituted imidazole.[9] In 2014, Devendra K. Agrawal and co-workers reported a concise route involving copper-mediated oxidative C–H functionalizations to synthesize highly substituted imidazoles from benzylamine and Enamine ester (Scheme 1a).[10] In 2019, Xia and co-workers reported reacting two enamine molecules with iodine under basic conditions to form 4-functionalized imidazolium salts (Scheme 1b).[11] Substitution in the conventional methods, the reaction conditions included transition metals, equivalent bases, or dangerous oxidizing agents, which have detrimental features.

Our group has been committed to conducting research on β-enamine esters.[12] As a simple and easily available substrate, it has multiple reaction sites, which provide a novel method for the construction of heterocycles. In 2021, our team reported examples of an electrochemical oxidative cyclization to synthesize polysubstituted pyrroles from enamines (Scheme 1c).[13] There have, however, been few reports of electrochemically performed intermolecular reactions involving β-enamine esters, and the apparent difficulty in achieving such intermolecular reactions might be due to competitive intramolecular oxygenation cyclization. In the current work, we developed a set of efficient electrochemical syntheses of tetrasubstituted imidazoles from β-enamine esters and amines (Scheme 1d).

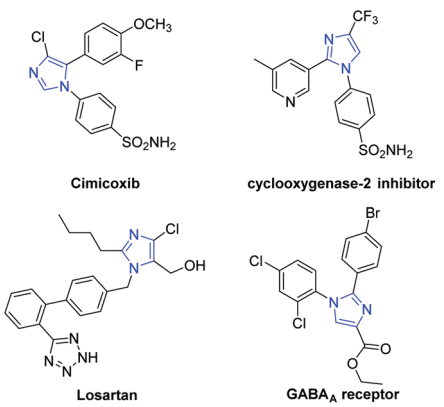

Fig. 1 Examples of useful imidazole-containing molecules.

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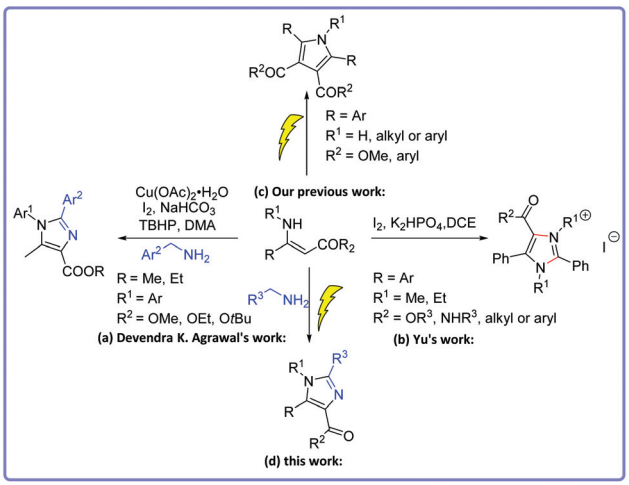


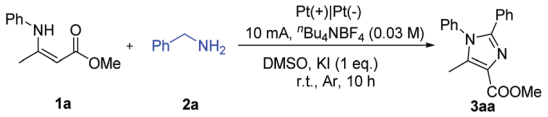
Scheme 1 Syntheses of various multi-substituted imidazoles including those of our previous work and current work.

Results and discussion

Initially, methyl (*Z*)-3-(phenylamino)but-2-enoate **1a** and benzylamine **2a** were selected as the model substrates to optimize the electrolysis conditions. The desired product 1,2,4,5-tetra-substituted imidazole **3aa** was obtained in 80% yield in an undivided cell containing two platinum electrodes. The best condition was found to be that employing KI (1 eq.) and $^{n}Bu_4NBF_4$ (0.03 M) in DMSO at room temperature under a constant current of 10 mA under argon conditions for 10 h (Table 1, entry 1). A series of control experiments validated the necessity of each reaction condition. Replacing the platinum electrode with a graphite electrode or nickel foam was associated with a decrease in the efficiency of the transformation (Table 1, entries 2–4). Including KI was found to be essential for the reaction (Table 1, entry 9), while other electrolytes such as TBAI, NH_4I, NH_4Br and NaI showed poor performances (Table 1, entries 5–8). Not including KI resulted in no formation of target product. When the amount of KI included was changed to 10 mol%, the yield decreased to 67% (Table 1, entry 10), demonstrating that the halide ion might act as a redox agent to promote the formation of products. When other solvents such as DMF, DMAc or MeOH were used instead of DMSO, a low or trace yield of **3aa** was observed (Table 1, entries 11–14). Either increasing or lowering the current was associated with a lower yield of the final product (Table 1, entries 15 and 16). Meanwhile, the reaction showed little sensitivity to oxygen and could be run under atmospheric conditions (Table 1, entry 17). Finally, no product was found when there was no electricity (Table 1, entry 19), indicating the crucial nature of including electricity.

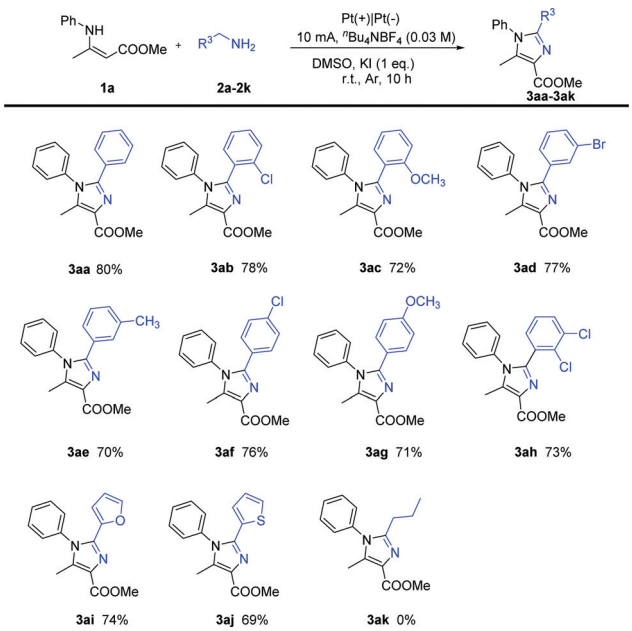
After establishing the optimal reaction conditions, the adaptability of the substrate was also investigated. As shown in Scheme 2, various kinds of benzylamines were examined, and all of them gave the corresponding products in good yields. Both the electron-donating groups (EDGs) and electron-with-

Table 1 Optimization of reaction conditions[a]



Entry	Variation from standard conditions	Yield[b] (%)
1	None	80
2	Graphite as anode	71
3	Graphite as cathode	63
4	Ni foam as cathode	72
5	$^{n}Bu_4NI$ instead of KI	34
6	NH_4I instead of KI	44
7	NaI instead of KI	37
8	NH_4Br instead of KI	22
9	No KI	0
10	10 mol% KI instead of 1 equiv. KI	67
11	MeCN instead of DMSO	56
12	DMAc instead of DMSO	46
13	DMF instead of DMSO	50
14	MeOH instead of DMSO	Trace
15	15 mA instead of 10 mA	75
16	5 mA instead of 10 mA	69
17	Under air	77
18	No $^{n}Bu_4NBF_4$	76
19	No electricity	0

[a] Reaction conditions: **1a** (0.5 mmol, 95.5 mg), **2a** (1.5 mmol, 160 mg), KI (0.5 mmol, 83 mg), $^{n}Bu_4NBF_4$ (0.03 M), dimethyl sulfoxide (DMSO, 5 mL) in an undivided cell with a platinum plate anode (20 mm × 15 mm) and a platinum plate cathode (20 mm × 15 mm), constant current = 10.0 mA, argon, rt, 10 h. Isolated yields. [b] Isolated yields after column chromatography.



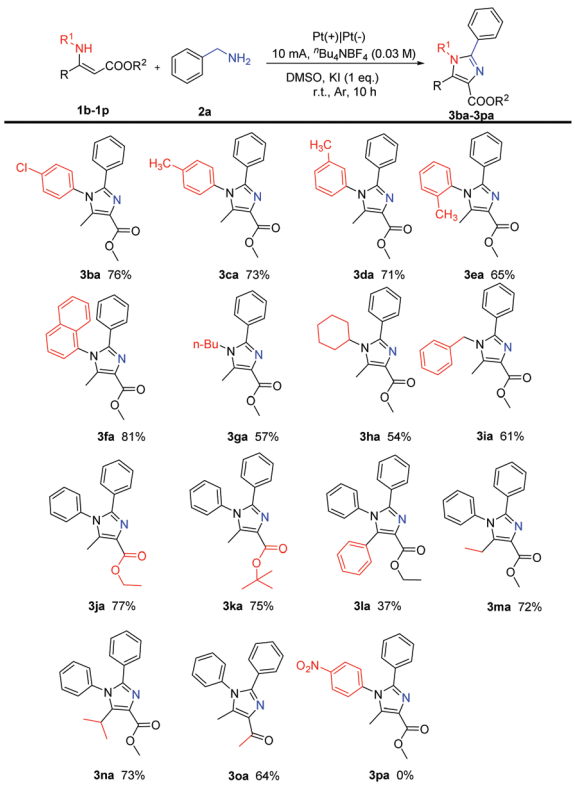
Scheme 2 Benzylamine scope. Reaction conditions: **1a** (0.5 mmol, 95.5 mg), **2a–2k** (1.5 mmol, 160 mg), KI (0.5 mmol, 83 mg), $^{n}Bu_4NBF_4$ (0.03 M), dimethyl sulfoxide (DMSO, 5 mL) in an undivided cell with a platinum plate anode (20 mm × 15 mm) and a platinum plate cathode (20 mm × 15 mm), constant current = 10.0 mA, argon, rt, 10 h. Isolated yields.

drawing groups (EWGs) on the benzylamine were compatible with the reaction, but the yield of benzylamine with electron-withdrawing substituents (**3ab**, **3ad**, **3af**) was better than that with electron-donating substituents (**3ac**, **3ae**, **3ag**). When a polysubstituted benzylamine was used as a substrate, the yield of the corresponding product (**3ah**) was 73%. In addition, furan-2-ylmethanamine (**3ai**) and thiophen-2-ylmethanamine (**3aj**) were smoothly synthesized in 74% and 69% yields, respectively. However, for aliphatic amines with long chains, no target product was obtained. This meant that the weak C–H bond adjacent to the amino group was essential for the smooth progress of the reaction.

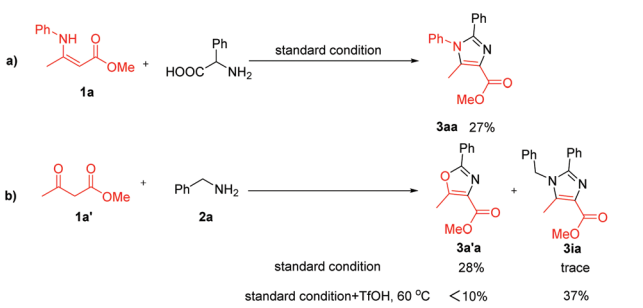
In addition, a range of alkenamine substrates was investigated (Scheme 3). First, we examined the effect of the substituent group on the benzene ring on the reaction, the substituted groups of halogen, methyl were chosen, including the benzene ring substituted at the *o*-position (**3ea**), the *m*-position (**3da**) and the *p*-position (**3ba**, **3ca**). The results showed that these were good substrates for the reaction, and the yields were in the range 65%–76%. The yields of the alkenamine compounds with substituents attached to the *para*-position were higher than for those with substituents attached to the *ortho*-position. This difference was attributed to the *para*-position not being involved in steric clashes. And the yields resulting from the use of the electron-withdrawing groups in the same position were slightly higher than those resulting from the use of electron-donating groups. The highest yield of 81% was obtained when a thick ring was on *N*. The substrate with the strong electron-withdrawing group NO_2 on the *N*-phenylene ring (**3pa**) was tested but unfortunately did not react. We went on to test some other non-aromatic substituents on *N*. Happily, under the standard conditions of the reaction, even if the substituent on the *N* was a non-aromatic group such as ^{n}butyl (**3ga**), cyclohexyl (**3ha**), or benzyl (**3ia**), corresponding multisubstituted imidazoles containing $COOR^2$ were successfully synthesized in the medium. Also, the replacement of methyl ester with ethyl or *tert*-butyl ester did not result in a significant decrease in the reaction yield (**3ja**, **3ka**). When the R group was a benzene ring (**3la**), only a 37% yield of the intended target was obtained; and a by-product was obtained, namely an indole resulting from an oxidative cyclization of the substrate.[14] When R was an ethyl group (**3ma**) or isopropyl group (**3na**), the corresponding polysubstituted imidazole was still obtained in good yield (72%, 73%). When use of methylenimine ketone (**3oa**) was involved in the reaction, a product yield of 64% was still obtained.

Amino acids have also been tested due to their low costs and easy availability. In particular, the same product **3aa** was obtained in 27% yield when using the amino acid 2-amino-2-phenylacetic acid instead of benzylamine (Scheme 4a). The ability to use an amino acid improved the applicability of the reaction. The general synthesis of enamine compounds was achieved by carrying out dehydration condensations of 1,3-dicarbonyl compounds with amines. To make the reaction substrate and operation simpler, we also performed a one-pot tandem reaction with methyl acetoacetate and benzylamine as substrates under standard conditions; this reaction did not yield the target product, but rather a polysubstituted oxazole. Based on the preparation of enamine requiring acid catalysis, we conducted a simple screening of acids and temperature. A 37% yield was achieved by adding trifluoromethanesulfonic acid and adjusting the temperature to 60 °C (Scheme 4b).

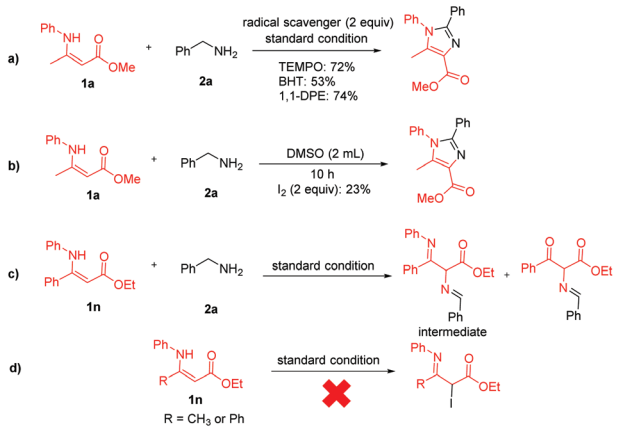
Finally, to understand the mechanism of the reaction, we performed the control experiments shown in Scheme 5. The addition of 2 equiv. of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and 1,1-diphenylethylene (1,1-DPE) to the reaction solution under standard reaction conditions gave 72%, 53%, and 74% yields,



Scheme 3 Enamine scope. [a] Reaction conditions: **1b–1k** (0.5 mmol, 95.5 mg), **2a** (1.5 mmol, 160 mg), KI (0.5 mmol, 83 mg), ^{n}Bu$_4$NBF$_4$ (0.03 M), dimethyl sulfoxide (DMSO, 5 mL) in an undivided cell with a platinum plate anode (20 mm × 15 mm) and a platinum plate cathode (20 mm × 15 mm), constant current = 10.0 mA, argon, rt, 10 h. [b] Isolated yields.



Scheme 4 One-pot tandem reaction method.

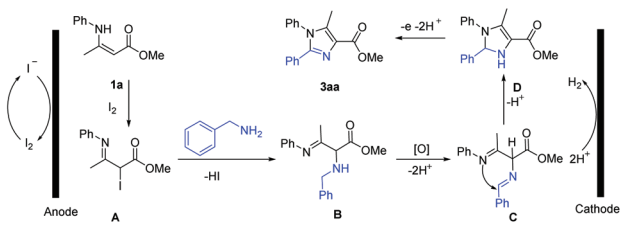


Scheme 5 Control experiments.

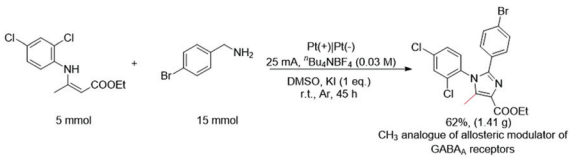
respectively, which indicated that the main step of the reaction did not involve a free radical mechanism. When molecular iodine was employed as an oxidant, the desired product was obtained with a yield of 23%. These results suggested that *in situ*-electrogenerated molecular iodine is the active species in the reaction. The intermediates were not separated under standard conditions, but the possible intermediates as well as the hydrolysis products of the intermediates were captured by performing high-resolution mass spectrometry. The intermediate structure was found to not be in the form of an enamine, but in the form of an imine. Finally, control experiments on enaminates under standard conditions unfortunately did not capture the possible intermediates, which may have been due to the instability of the iodine intermediates.

Based on the experimental results and previous reports,[10,15] a possible reaction pathway for the formation of **3aa** was proposed (Scheme 6). Initially, according to this proposal, molecular iodine was generated *in situ* on the anode, and this iodine reacted with β-enamine esters **1a** to generate the iodinated intermediate **A**. Then, the intermediate **B** was obtained as a result of nucleophilic substitution of benzylamine. Subsequently, the electrochemical oxidation of **B** generated **C**, and **C** underwent intramolecular cyclization to form intermediate **D**. Finally, according to the proposed mechanism, the target product was formed as a result of deprotonation and electrochemical oxidation.

The bioactive molecule ethyl 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-imidazolecarboxylate has been shown to



Scheme 6 Plausible mechanism.



Scheme 7 Gram-scale and synthetic applications.

display great potency as a specific allosteric modulator of the $GABA_A$ receptor.[16] Using the scheme reported herein, a gram-scale reaction of enaminyl esters and benzylamine was carried out at 5 mmol scale (Scheme 7), and the CH_3 analogue of the above bioactive molecule was obtained in 62% yield when the current was increased to 25 mA and the reaction time was extended to 45 h, demonstrating the potential utility of the reaction.

Conclusions

In summary, we have developed a green and facile electrochemical approach for synthesizing 1,2,4,5-tetrasubstituted imidazoles. Notably, the synthetic method exhibited a wide functional group tolerance, and did so without the use of an external oxidant or transition-metal catalyst. The reaction could be scaled up to a 5 mmol scale and was successfully used to construct a $GABA_A$ receptor analogue. The electrochemical reaction of enamines is being further investigated in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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