

Electrochemically promoted synthesis of polysubstituted oxazoles from β -diketone derivatives and benzylamines under mild conditions†

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An efficient electrochemical synthesis of poly-substituted oxazoles from readily available β -diketone derivatives and benzylamines is described. This electrochemical procedure does not need hazardous oxidants and transition metal catalysts as well as molecular I_2 additives. Compared with the traditional thermo-chemical method, the present electrochemical method is greener and more efficient.

Many natural and synthetic compounds containing oxazole moieties exhibit promising antitumor, antibacterial, antiviral or antifungal activities.¹ For example, Leucamide A and its analogues composed of several oxazole moieties have been confirmed as significant antitumor agents.² Owing to their important applications, the synthesis of oxazole derivatives has attracted extensive attention in both academic and industrial fields. Some synthetic methods have been developed for the preparation of oxazoles, mainly including cyclization of acyclic precursors,³ the coupling of the prefunctionalized oxazoles with organometallic reagents,⁴ and oxidation of oxazolines.⁵ However, these methods still face some challenges such as starting materials not easily accessible, harsh reaction conditions and tedious synthetic procedures. Recently, the Wang group has reported a novel method for the synthesis of polysubstituted oxazoles from readily available materials (benzylamine with β -diketone derivatives) *via* a tandem oxidative cyclization.⁶ Unfortunately, the oxidative procedures require the use of a stoichiometric amount of hazardous oxidant TBHP (*t*-BuOOH) and molecular I_2 additive, and transition metal catalysts. From the viewpoint of green chemistry and synthetic methodology, it is still highly desirable to develop eco-friendly and more efficient method for the synthesis of polysubstituted oxazoles from benzylamine and β -diketone derivatives.

An electrochemical method is particularly attractive in organic synthesis because electrochemical processes can

decrease pollution and make the chemistry environmentally friendly.⁷ The advantage of an electrochemical method lies in the fact that electrons can act as green and safe “reagents” to replace hazardous redox chemicals to carry out oxidation or reduction reactions. On the other hand, the desired reactive species could be conveniently electrogenerated *in situ* through the transfer of electrons. Based on the green characteristic of an electrochemical method, we have been interested in developing new electrochemical process in organic synthesis.⁸ Herein, we report for the first time an efficient electrochemical synthesis of polysubstituted oxazoles from readily available benzylamine and β -diketone derivatives under mild conditions, without the use of hazardous or toxic oxidants and transition metal catalysts.

In our investigation, ethyl acetoacetate **1a** and benzylamine **2a** were chosen as model substrates. In order to obtain satisfactory results, some important factors (including supporting electrolytes, solvents and electrode materials) were carefully examined, as shown in Table 1. With NaI as the supporting electrolyte and DMF as the solvent, **1a** with **2a** could be smoothly transformed into the target product ethyl 5-methyl-2-phenyl-oxazole-4-carboxylate **3aa** in a 60% yield (Table 1, entry 1). However, the electrolysis with KI or *n*-Bu₄NI as the supporting electrolyte gave unsatisfactory results (Table 1, entries 2 and 3). Very pleasingly, the yield of **3aa** could be enhanced up to 91% when the supporting electrolyte was changed from NaI to NH₄I (Table 1, entry 4). With NH₄Br as supporting electrolyte, benzonitrile was the main product (64% yield), while the target product **3aa** was only obtained in a low yield (34%, Table 1, entry 5). With NH₄Cl as supporting electrolyte, **3aa** was not detected and some by-products such as benzonitrile and benzaldehyde were observed (Table 1, entry 6). These results indicate that supporting electrolytes have a great impact on the formation of oxazoles. NH₄I appears to be the most suitable supporting electrolyte for this electrochemical process. In the present electrochemical system with graphite as the inert anode, the supporting electrolyte could not only act as conducting salts but also take part in electrochemical reactions to

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generate reactive species. According to the Wang group's work,⁶ the molecular I₂ additive was utilized to effectively improve the reaction efficiency of ethyl acetoacetate **1a** with benzylamine **2a**. In the present case, we deduce that the I₂ electrogenerated *in situ* at the graphite anode ($2\text{I}^- \rightarrow \text{I}_2 + 2\text{e}^-$) could play the same important role in this transformation. Electrolytic medium (solvent) is another key factor. When DMF was replaced with MeCN or H₂O as the solvent, the yield of **3aa** was less than 5% (Table 1, entries 8 and 11), and the substrates were almost quantitatively recovered. When THF or MeOH was employed as the solvent, **3aa** was obtained in a low yield of 36% and 16%, respectively (Table 1, entries 7 and 9). In DMSO solvent, the yield is much lower than in DMF (Table 1, entries 10 and 4). Among the tested solvents, DMF seems to be the most appropriate solvent for this transformation. Subsequently, several cathode materials including Zn, Al and Cu were used to carry out the transformation under the same conditions. These electrode materials give quite satisfactory results (Table 1, entries 12–14). According to the experimental result of entry 4 (Table 1), the optimized electrolytic system should consist of NH₄I as supporting electrolyte, DMF as solvent, a graphite anode and a Ni cathode.

To test the scope of this electrochemical methodology, our investigation was extended to different 1,3-dicarbonyl compounds and benzylamines. All the electrosyntheses were carried out under the optimized conditions (Table 1, entry 4) and the results are listed in Table 2. Pleasingly, the β -keto esters with different alkyl substituents, regardless of their electronic or steric properties, could provide the corresponding products with satisfactory yields (Table 2, **3aa–3ea**). Moreover, when 1,3-diketones were used as the substrate, the reactions with

benzylamine **2a** could be performed smoothly to give the corresponding products in 77–81% yields (Table 2, **3fa–3ga**). With β -keto amides, good yields were obtained as well (Table 2, **3ha** and **3ia**). For the benzylamine derivatives, an electron-donating group on the aromatic ring gave somewhat lower yields of oxazoles (Table 2, compare **3aa** (85%) with **3ab–3ae** (68–74%)), while an electron-withdrawing substituent had little influence (Table 2, compare **3aa** with **3ah** (85%)). The position of the OCH₃ group on the benzylamine (*para*, *meta*, and *ortho* positions) has very little influence on the reaction yield (Table 2, **3ac–3ae**). In the heterocyclic amine case, the corresponding products could be obtained in moderate to high yields (Table 2, **3ai–3ak**). However, the desired product was not formed with *n*-BuNH₂ as the substrate (Table 2, **3al**). This probably means that it is necessary to have a weak C–H bond to be adjacent to the amino group for this transformation.⁶

In order to probe the reaction process, several control experiments were carried out. In the absence of benzylamine (**2a**), ethyl-2-iodo-3-oxobutanoate (**A**) was observed (Scheme 1, eqn (1)). Although the yield of **A** was low (only 21%), this result indicates that **A** could be formed under the electrochemical conditions. Further investigation revealed that **A** with benzylamine (**2a**) could be electrochemically converted into the target product **3aa** in a 61% yield (Scheme 1, eqn (2)). However, **3aa** was not formed at all if no electric current was passed through the electrolytic cell (Scheme 1, eqn (3)). This means that electrochemical oxidation or activation is necessary for the formation of **3aa**.

Based on our experimental results and the previous reports,^{6,9,10} a possible reaction mechanism is outlined in Scheme 2. I₂ generated *in situ* at the anode ($2\text{I}^- \rightarrow \text{I}_2 + 2\text{e}^-$)

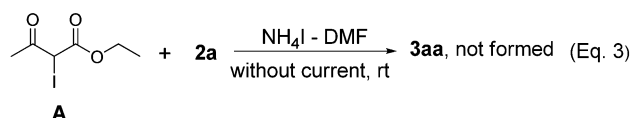
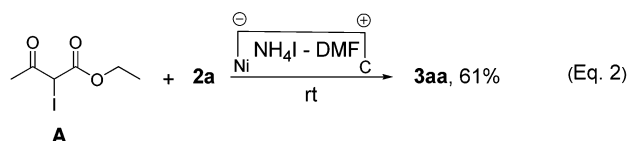
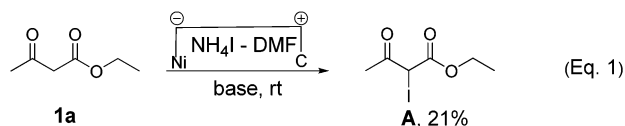
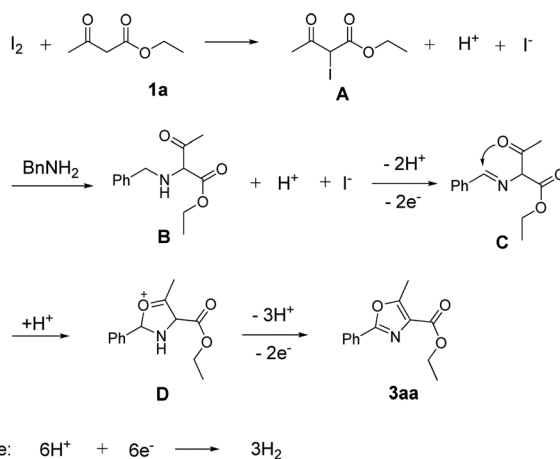
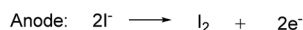
Table 1 Optimization of electrolytic conditions^a

Entry	Anode–cathode	Supporting electrolyte	Solvent	Yield ^b (%)	η^c (%)
1	C–Ni	NaI	DMF	62	42
2	C–Ni	KI	DMF	40	27
3	C–Ni	<i>n</i> -Bu ₄ NI	DMF	18	12
4	C–Ni	NH ₄ I	DMF	91	62
5	C–Ni	NH ₄ Br	DMF	34	23
6	C–Ni	NH ₄ Cl	DMF	0	0
7	C–Ni	NH ₄ I	THF	36	24
8	C–Ni	NH ₄ I	MeCN	<5	<3
9	C–Ni	NH ₄ I	EtOH	16	11
10	C–Ni	NH ₄ I	DMSO	60	40
11	C–Ni	NH ₄ I	H ₂ O	<5	<3
12	C–Zn	NH ₄ I	DMF	89	60
13	C–Al	NH ₄ I	DMF	84	56
14	C–Cu	NH ₄ I	DMF	81	54

^a Electrolytic conditions: **1a** (2.0 mmol), **2a** (2.0 mmol), solvent (10 mL), supporting electrolyte (0.4 mol L^{−1}), undivided cell, current density 12 mA cm^{−2}, 8 h and rt. ^b Determined by GC. ^c Current yield.

Table 2 Electrosynthesis of polysubstituted oxazoles from 1,3-dicarbonyl compounds and benzylamine derivatives^a

1a-m	2a-k	electrolysis rt	3
3aa, 85%	3ba, 75%	3ca, 78%	3da, 73%
3ea, 87%	3fa, 81%	3ga, 77%	3ha, 72%
3ia, 54%	3ja, 75%	3ka, 68%	3la, 67%
3ab, 74%	3ac, 68%	3ad, 70%	3ae, 70%
3af, 57%	3ag, 81%	3ah, 85%	3ai, 42%
3aj, 56%	3ak, 78%	3al, 0%	

^a Isolated yield (electrolytic conditions as shown in Table 1, entry 4).**Scheme 1** Control experiments.**Scheme 2** Proposed reaction mechanism.

could react with **1a** to form **A**. Then **A** with BnNH₂ (**2a**) is converted to **B**. Subsequently, the electrooxidation of **B** generates **C**, which undergoes an intramolecular cyclization to give the intermediate **D** in a tandem process. Finally, **D** is transformed into the product (**3aa**) by deprotonation and electrochemical oxidation. It is worthy to note that I[−] ions are regenerated during the electrolysis. The formation of **3aa** consumes electrons only.

In conclusion, an efficient synthesis of polysubstituted oxazoles derivatives *via* an electrochemical route from readily available benzylamine and β-diketone derivatives was demonstrated. The molecular I₂ electrogenerated *in situ* at the anode and electrochemical oxidation play a key role in the formation of polysubstituted oxazoles. It is noteworthy that the present electrochemical procedure gives the oxazoles in good to excellent yields, under mild conditions, and does not involve hazardous oxidants, transition metal catalysts, and molecular I₂ additive. Furthermore, it is accessible to any synthetic organic laboratory and it can be easily scaled up because no sophisticated and expensive electrochemical instruments (such as a potentiostat) are required. Therefore, compared with the reported thermo-chemical method,⁶ the present electrochemical method appears to be more eco-friendly and more attractive.

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