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Electrochemical Oxidative C3 Acyloxylation of Imidazo[1,2-*a*]pyridines with Hydrogen Evolution

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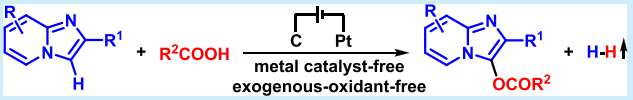
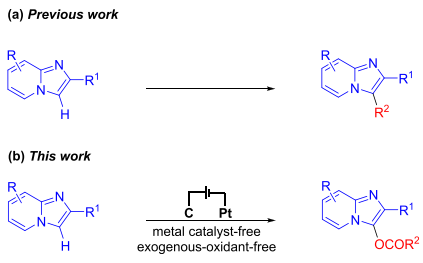
ABSTRACT: The C3-functionalized imidazo[1,2-*a*]pyridines are versatile nitrogen-fused heterocycles; however, the methods for the C3 acyloxylation of imidazo[1,2-*a*]pyridines have never been reported. Herein we demonstrate the electrochemical oxidative C3 acyloxylation of imidazo[1,2-*a*]pyridines for the first time. Notably, by using electricity, the electrochemical oxidative C3 acyloxylation of imidazo[1,2-*a*]pyridines was carried out under mild conditions. Moreover, in addition to aromatic carboxylic acids, alkyl carboxylic acids were also competent substrates.



The imidazo[1,2-*a*]pyridines, especially the C3-functionalized imidazo[1,2-*a*]pyridines, are versatile nitrogen-fused heterocycles that are not only significant structural components in many natural products and biologically active molecules[1] but also frequently found in many commercially available drugs,[2] such as miroprofen, GSK812397, olprinone, zolimidine, minodronic acid, and alpidem. Consequently, to find many more biologically active molecules, the further C3 functionalization of imidazo[1,2-*a*]pyridines is greatly desirable. Much effort has been dedicated to modifying imidazo[1,2-*a*]pyridines, and a variety of effective transformations for C3 arylation,[3] alkylation,[4] carbonylation,[5] halogenation,[6] amination,[7] phosphonation,[8] selenation,[9] and sulfenylation[10] have been established in the past decade (Scheme 1a).

Scheme 1. C3 Functionalization of Imidazo[1,2-*a*]pyridines



However, even though there has been great achievement in the C3 functionalization of imidazo[1,2-*a*]pyridines, the C3 acyloxylation of imidazo[1,2-*a*]pyridines still remains a standing challenge and has never been reported. Given that the C3-functionalized imidazo[1,2-*a*]pyridines frequently exhibit much better biological activity than imidazo[1,2-*a*]pyridines themselves, we would like to explore an efficient and practical method to realize the C3 acyloxylation of imidazo[1,2-*a*]pyridines.

Organic electrosynthesis has been recognized as an environmentally benign and powerful synthetic method.[11] By employing anodic oxidation or cathodic reduction, organic electrosynthesis can realize redox transformations under exogenous-oxidant-free or exogenous-reductant-free conditions.[12] Moreover, by modifying the operating current or voltage, organic electrosynthesis can provide a new opportunity for the reactions that do not easily occur with traditional chemical oxidants or reductants. As a part of our continuing research interest in the area of electrochemical oxidative cross-coupling with H_2 evolution reactions,[13] we herein report the C3 acyloxylation of imidazo[1,2-*a*]pyridines for the first time (Scheme 1b). Note that by using the strategy of electrochemical anodic oxidation, the C3 acyloxylation of imidazo[1,2-*a*]pyridines was conducted without the use of a metal catalyst or exogenous oxidant. Furthermore, by using the strategy of electrochemical oxidative C−H/O−H cross-coupling with H_2 evolution, this C−H acyloxylation reaction exhibits excellent atom economy and produces valuable H_2 as the sole byproduct.

Our investigation was commenced with *p*-toluic acid (**1a**) and 2-phenylimidazopyridine (**2a**) as model substrates, K_2CO_3 as an electrolyte and base, and a mixture of acetonitrile and water as a cosolvent. Encouragingly, when the electrolysis of *p*-toluic acid (**1a**) and 2-phenylimidazopyridine (**2a**) was performed under a controlled current of 8 mA for 4.5 h, the expected C3 acyloxylation reaction occurred smoothly and resulted in **3a** in 82% isolated yield (Table 1, entry 1). Control experiments indicated that the electric current and K_2CO_3 were necessary for obtaining C3 acyloxylation product **3a** (Table 1, entries 2 and 3). Using Na_2CO_3 or K_3PO_4, a slight

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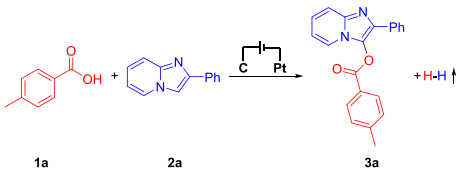
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

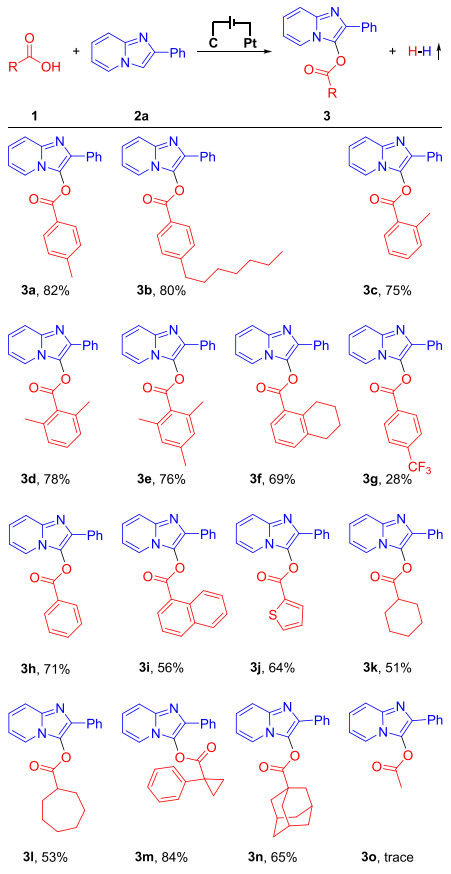
entry	variation(s) from the standard conditions	yield (%)
1	none	82
2	no electric current	0
3	no K_2CO_3 (0.1 mmol $^nBu_4NBF_4$ was added)	trace
4	Na_2CO_3 instead of K_2CO_3	78
5	K_3PO_4 instead of K_2CO_3	67
6	1.0 equiv of K_2CO_3	68
7	1.5 equiv of K_2CO_3	78
8	12 mA, 3 h	78
9	6 mA, 6 h	74
10	nickel plate as the cathode	37
11	stainless-steel plate as the cathode	56
12	carbon cloth as the anode	66
13	MeCN/H_2O 10.5:0.5	80
14	MeCN/H_2O 9:2	44

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), K_2CO_3 (1.2 equiv), MeCN (10 mL), H_2O (1 mL), 40 °C (oil bath), N_2, graphite plate anode, platinum plate cathode, 8 mA, 4.5 h, isolated yields.

loss of yield was observed (Table 1, entries 4 and 5). The amount of K_2CO_3 was next investigated. However, either increasing or decreasing the amount of K_2CO_3 led to a decreased C−H/O−H cross-coupling yield (Table 1, entries 6 and 7). Increasing the operating current to 12 mA furnished the C3 acyloxylation product in a slightly reduced yield (Table 1, entry 8), whereas when the electrolysis was conducted at a controlled current of 6 mA for 6 h, a 8% yield loss was observed (Table 1, entry 9). The combination of a graphite plate anode and a platinum plate cathode was important for obtaining the C3 acyloxylation product in high yield. Either replacing the platinum plate with a nickel plate or a stainless-steel plate or replacing the graphite plate with a carbon cloth led to the desired C−H/O−H cross-coupling product in low yield (Table 1, entries 10−12). Finally, the amount of water was also investigated. Performing the C−H/O−H cross-coupling reaction with 0.5 mL of H_2O as the cosolvent, the expected C3 acyloxylation product was isolated in 80% yield (Table 1, entry 13), whereas when the reaction was conducted with 2.0 mL of H_2O as the cosolvent, only a 44% yield of C−H/O−H cross-coupling product was obtained (Table 1, entry 14).

Having the optimized reaction conditions in hand, we set out to evaluate the substrate scope of this electrochemical oxidative C3 acyloxylation reaction. First, we explored the substrate scope with various carboxylic acids. As shown in Scheme 2, aromatic carboxylic acids bearing electron-donating groups led to the expected C3 acyloxylation products in good to high yields (Scheme 2, **3a**−**3f**), whereas when electron-poor 4-(trifluoromethyl)benzoic acid was used in the reaction, the corresponding cross-coupling product was isolated in low yield (Scheme 2, **3g**). Employing benzoic acid as the reaction partner, the electrolysis occurred smoothly with 2-phenylimidazopyridine (**2a**) and resulted in the desired C−H/O−H cross-coupling product in 71% yield (Scheme 2, **3h**). In addition to benzoic acid derivatives (Scheme 2, **3a**−**3h**), 1-

Scheme 2. Substrate Scope for Electrochemical Oxidative C−H/O−H Cross-Coupling with Different Carboxylic Acids[a]



[a]Reaction conditions: graphite plate anode, platinum plate cathode, constant current = 8 mA, **1** (0.3 mmol), **2a** (0.6 mmol), K_2CO_3 (1.2 equiv), MeCN (10 mL), H_2O (1 mL), 40 °C (oil bath), N_2, 4.5 h, isolated yields.

naphthoic acid and thiophene-2-carboxylic acid were also competent substrates, generating the corresponding C3 acyloxylation products in 56 and 64% yield (Scheme 2, **3i**−**3j**), respectively. It is noteworthy that alkyl carboxylic acids could also react with 2-phenylimidazopyridine (**2a**) under standard electrochemistry conditions (Scheme 2, **3k**−**3n**). For example, when cyclohexanecarboxylic acid or cycloheptanecarboxylic acid was used as the acyloxylation reagent, 51 and 53% yields of C−H/O−H cross-coupling products were isolated (Scheme 2, **3k**,**3l**), whereas when 1-phenyl-1-cyclopropanecarboxylic acid was treatment with 2-phenylimidazopyridine (**2a**), the expected C3 acyloxylation reaction smoothly occurred and afforded the corresponding C−H/O−H cross-coupling product in high yield (Scheme 2, **3m**). Interestingly, the electrochemical oxidative C3 acyloxylation reaction was also compatible with the 1-adamantane carboxylic acid, and the expected C3 acyloxylation product was obtained in 65% yield (Scheme 2, **3n**).

Next, we explored the scope of imidazo[1,2-*a*]pyridines. As shown in Scheme 3, 2-phenylimidazo[1,2-*a*]pyridines bearing electron-donating substituents at the 2-phenyl moiety resulted in the desired C3 acyloxylation products in 68−71% yields (Scheme 3, **4a**−**4c**). In contrast, 2-phenylimidazopyridines with electron-withdrawing groups at the 2-phenyl moiety delivered the corresponding C3 acyloxylation products in

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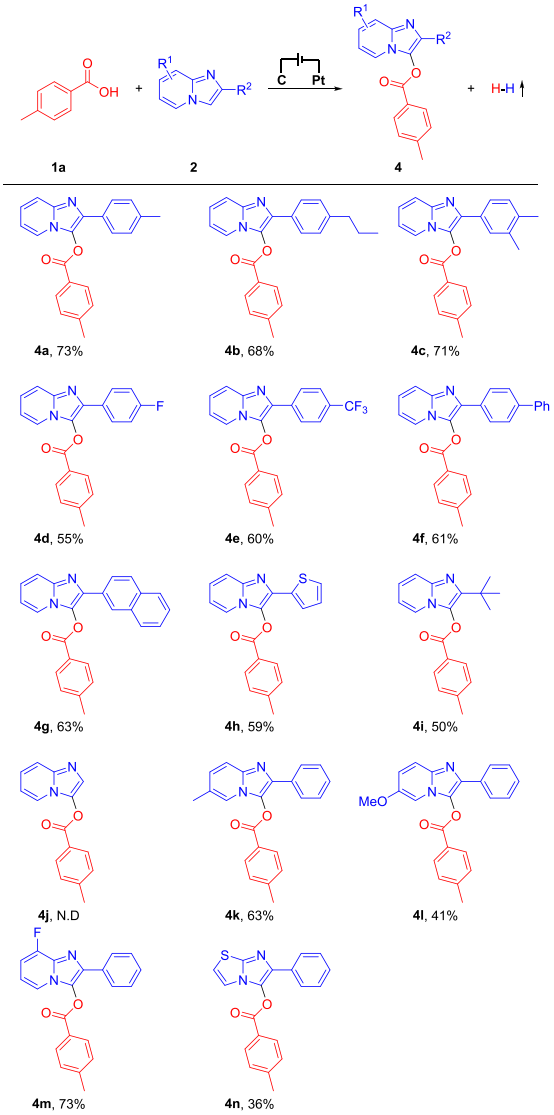
Scheme 3. Substrate Scope for Electrochemical Oxidative C−H/O−H Cross-Coupling with Different Imidazo[1,2-*a*]pyridines[a]

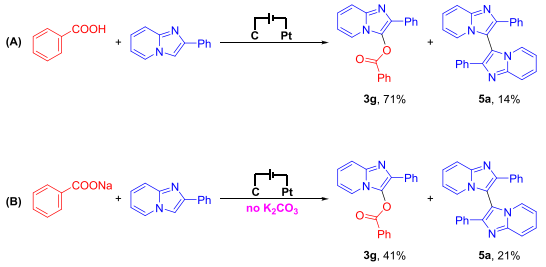


[a]Reaction conditions: graphite plate anode, platinum plate cathode, constant current = 8 mA, **1** (0.3 mmol), **2a** (0.6 mmol), K_2CO_3 (1.2 equiv), MeCN (10 mL), H_2O (1 mL), 40 °C (oil bath), N_2, 4.5 h, isolated yields.

moderate yields (Scheme 3, **4d**,**4e**). It is worth noting that in addition to 2-phenylimidazo[1,2-*a*]pyridines, 2-biphenylimidazo-[1,2-*a*]pyridine, 2-naphthylimidazo-[1,2-*a*]pyridine, 2-thienylimidazo-[1,2-*a*]pyridine, and even 2-*tert*-butylimidazo-[1,2-*a*]pyridine were also compatible cross-coupling partners, delivering the corresponding C3 acyloxylation products in moderate to good yields (Scheme 3, **4f**−**4i**). However, when C-2 unsubstituted imidazo[1,2-*a*]pyridine was employed in the reaction, the corresponding C−H/O−H cross-coupling product was not obtained (Scheme 3, **4j**). The reason for this may be because the corresponding radical cation intermediate is not stable. The effect of different substituents on the pyridine ring of imidazo[1,2-*a*]pyridines was also explored. To our delight, when 6-Me-, 6-OMe-, and 8-F-substituted imidazo[1,2-*a*]pyridines were employed, the corresponding C3 acyloxylation products could be obtained in moderate to high yields (Scheme 3, **4k**−**4m**). Interestingly, we note that 6-phenylimidazo[2,1-*b*]thiazole could also be employed as the reaction partner (Scheme 3, **4n**).

To shed light on the mechanism of this electrochemical oxidative C3 acyloxylation reaction, cyclic voltammetry (CV) experiments were first performed. (For details see the SI, Figure S1.) The oxidation peak of substrate **2a** was observed at 1.58 V. The mixture of **1a** and K_2CO_3 showed an oxidation peak at 1.88 V, whereas no obvious oxidation peak of **1a** was observed at 0−2.5 V. These results indicated that imidazo[1,2-*a*]pyridines are more readily oxidized than carboxylic acids and its conjugate bases. Second, two control experiments were conducted (Scheme 4). When the electrolysis of benzoic acid

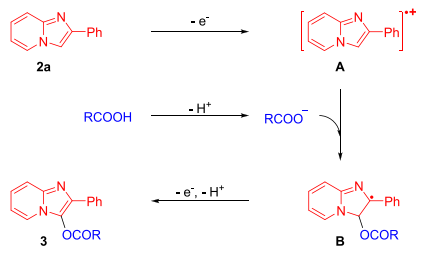
Scheme 4. Control Experiments



with 2-phenylimidazopyridine (**2a**) was performed under standard conditions, in addition to the 71% yield of C−H/O−H cross-coupling product **3g**, a 14% yield of homocoupling product **5a** was also isolated (Scheme 4a), indicating that imidazo[1,2-*a*]pyridines could be converted into the corresponding radical cation intermediate under the current electrochemical conditions. Using sodium benzoate as the acyloxylation reagent to react with 2-phenylimidazopyridine (**2a**) in the absence of K_2CO_3 resulted in a 41% yield of C3 acyloxylation product **3g** (Scheme 4b), suggesting that the role of K_2CO_3 may be to remove the proton of carboxylic acid to generate the corresponding carboxylate anion.

On the basis of our mechanistic studies and previous reports,[13c] a plausible mechanism for this electrochemical oxidative C3 acyloxylation reaction is presented in Scheme 5.

Scheme 5. Proposed Mechanism



The anodic oxidation of 2-phenylimidazopyridine (**2a**) generates the corresponding radical cation intermediate **A**. With the help of base, the deprotonation of carboxylic acid leads to the generation of $RCOO^-$. Next, $RCOO^-$ attacks the intermediate **A** to access the radical intermediate **B**. Following anodic oxidation and deprotonation, the desired C3 acyloxylation product **3** is finally produced. At the cathode, H_2O is reduced to generate OH^- and H_2.

In conclusion, the electrochemical oxidative C3 acyloxylation of imidazo[1,2-*a*]pyridines was developed for the first

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time. By using electricity, the oxidative C3 acyloxylation of imidazo[1,2-*a*]pyridines was performed under mild conditions. Moreover, in addition to aromatic carboxylic acids, alkyl carboxylic acids were also competent substrates, generating the corresponding C3 acyloxylation products in moderate to high yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02032.

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all of the compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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