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Article

Electrochemical [4 + 1] Tandem sp^3(C−H) Double Amination for the Direct Synthesis of 3-Acyl-Functionalized Imidazo[1,5-*a*]pyridines

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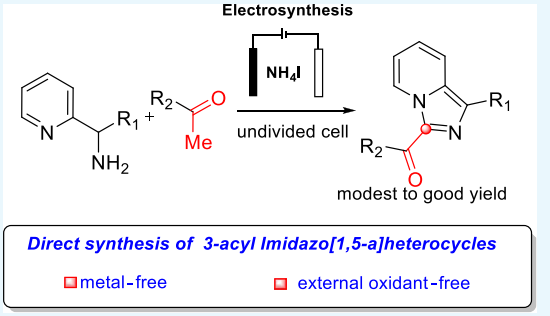
ABSTRACT: 3-Acyl imidazo[1,5-*a*]pyridines, featured pharmaceutical moieties that were prepared by a three-step reaction conventionally, could be obtained in one step by an electrochemical tandem sp^3 (C−H) double amination of acetophenones with pyridine ethylamines using ammonium iodide as a redox mediator.



INTRODUCTION

Imidazo[1,5-*a*]pyridines are featured fused N-heterocyclic compounds that have extensive applications in pharmaceutical chemistry for drug discovery.[1] In recent years, a number of synthetic methods have been developed for the construction of these compounds,[2] which greatly facilitates the research of the structure−activity relationship (SAR) for pharmaceutical chemists. However, these methods exhibit limitation in the synthesis of 3-acyl imidazo[1,5-*a*]pyridines. 3-Acyl imidazo-[1,5-*a*]pyridines, key pharmacophore that has been extensively employed in bioactive compounds, such as the cannabinoid receptor type 2 (CB_2) agonist (Scheme 1, **cmpd 1**) for inflammatory pain, monosodium iodoacetate for osteoarthritis pain,[3] the fibroblast growth factor receptor antagonist (Scheme 1, **cmpd 2**) for bladder cancer,[4] and the retinoic acid receptor-related orphan receptor gamma *c* agonist (Scheme 1, **cmpd 3**) for the treatment of autoimmune diseases.[5]

Researchers have been focused on tumor inhibitor research in the past years,[6] and we intended to make a systematic investigation on the SAR of 3-acyl imidazo[1,5-*a*]pyridine for its derivatives that revealed a potential antiproliferation effect on a variety of cancer cells in our primary study. However, the synthesis of this skeleton by conventional methods must be achieved through multistep reactions;[3] besides, using trichlorophosphate, a highly corrosive reagent, seems inevitable in the synthesis process (Scheme 2). Obviously, its efficiency is unsatisfactory and the process is environment-hazardous as well. More recently, nearly parallel but reported earlier than our report, Li's group focused on the aggregation-induced emission property of 3-acyl imidazo[1,5-*a*]pyridines and reported an iodine-mediated sp and sp^2 hydrocarbon activation for direct synthesis from phenylacetylenes (styrenes) and pyridin-2-phenyl(pyridin-2-yl)methanamines.[7] Because most of the substituted phenylacetylenes and styrenes are expensive and even commercially unavailable, direct sp^3 hydrocarbon functionalization-based efficient and green method for 3-acyl imidazo[1,5-*a*]pyridines is still undiscovered and desirable.

During the past decade, electrocatalysis, including direct electrocatalysis and indirect electrosynthesis, as a green synthetic strategy has provided an alternative synthesis method for organic synthesis,[8] and a series of elegant electro-organic reactions for the construction of C−C,[9] C−N,[10] C−O,[11] and C−S[12] bonds have been developed. In recent years, indirect electrosynthesis with mediators has attracted more attention for its reaction controllability and selectivity advantages.[8] Halogen ions, one of the most versatile and cost-efficient mediators, are always combined with irreversible halogenation in indirect electrosynthesis and can enhance the reaction efficiency and functional group compatibility.[13] Apparently, the indirect electrocatalytic functionalization of sp^3 hydrocarbons with a redox mediator as a green synthetic strategy improves the synthesis efficiency and shortens the synthesis steps via employing nonfunctionalized cheap starting materials.[14] In virtue of the formal achievements and the advantage of indirect electrosynthesis, herein, we report a chemoselective electrochemical tandem [4 + 1] sp^3 hydrocarbon double amination for the direct synthesis of 3-acyl imidazo[1,5-*a*]pyridines from pyridine ethylamines and acetophenones.

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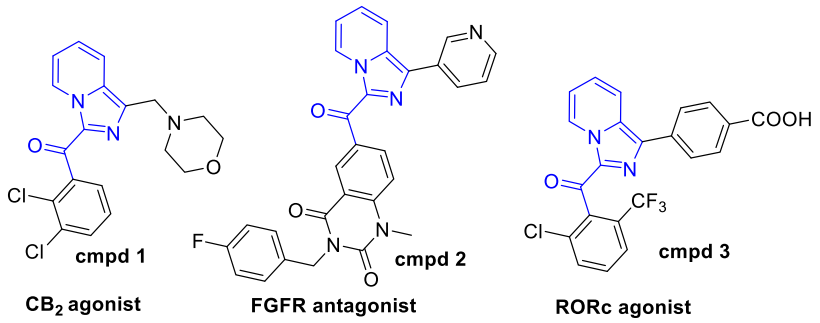
Scheme 1. Examples of Bioactive 3-Acyl Imidazo[1,5-*a*] Pyridines



Scheme 2. Strategies for the Construction of 3-Acyl Imidazo[1,5-*a*] Pyridines

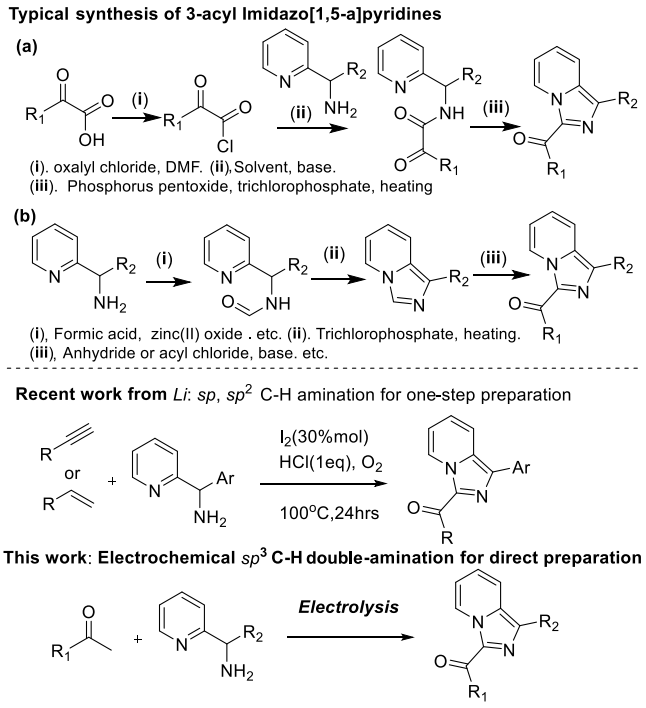
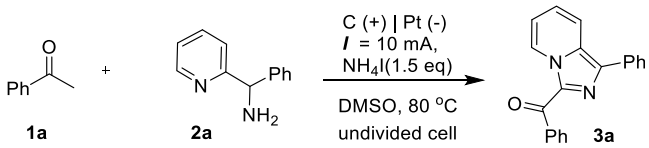


Table 1. Effects of Reaction Parameters[a]



entry	variation from the standard conditions	yield (%)
1	none	76
2	KI instead of NH_4I	46
3	NaI instead of NH_4I	38
4	$^nBu_4NI$ instead of NH_4I	21
5	NH_4Br instead of NH_4I	67
6	DMA instead of DMSO	73
7	DMF instead of DMSO	59
8	70 °C instead of 80 °C	53
9	90 °C instead of 80 °C	66
10	room temperature	n.d.
11	platinum plate anode	61
12	8 mA	53
13	12 mA	56
14	1.5 equiv I_2 instead of NH_4I and electric current	16
15	1.5 equiv I_2 instead of NH_4I and electric current, DMA as the solvent	trace

[a]Reaction conditions: graphite rod anode, platinum plate cathode, constant current = 10 mA, **1a** (0.2 mmol), **2a** (2 equiv, 0.4 mmol), NH_4I (1.5 equiv, 0.3 mmol), DMA (3 mL), 80 °C, 16 h. Isolated yields are shown. n.d. = not detected.

RESULTS AND DISCUSSION

As shown in Table 1, the optimized condition under which the electrosynthesis of acetophenone (**1a**), pyridin-2-phenyl-(pyridin-2-yl)methanamine (**2a**), and NH_4I was performed at a 10 mA constant current for 16 h in an undivided cell, product **3a** was obtained with 76% yield (Table 1, entry 1). In the optimization process, reaction parameters such as the redox mediator, solvent, temperature, and so forth were investigated. As for the other redox mediator, KI, NaI, and $^nBu_4NI$ all gave lower yields (Table 1, entries 2−4), and NH_4Br only gave a trace amount of **3a** (Table 1, entry 5). As for the reaction solvent, dimethylacetamide (DMA) as the solvent provided 73% yield (Table 1, entry 6), while dimethylformamide (DMF) as the solvent only provided 59% yield (Table 1, entry 7). As for the reaction temperature, decreasing the temperature to 70 °C and increasing to 90 °C both failed to increase the yield (Table 1, entries 8 and 9), and **3a** was not detected after electrolysis at room temperature (Table 1, entry 10). Replacing the graphite rod anode by a platinum plate anode also gave lower yields (Table 1, entry 11); decreasing the current to 8 mA and increasing to 12 mA both provided lower yields (Table 1, entries 12 and 13). Employing an equivalent amount of I_2 instead of NH_4I and the electrolysis only gave 18% yield of **3a** (Table 1, entry 14), and the same reaction in DMA failed and produced a trace amount of **3a** (Table 1, entry 15), indicating that anodic oxidative dehydrogenation was a critical factor to this transformation.

With the optimized conditions in hand, the substrate scope of the reaction was investigated (Table 2). First, a variety of acetophenones were investigated (R_1 group). It was found that the solvent effect greatly affected the transformation. Selecting DMA as the solvent for electron-deficient acetophenones could avoid the unexpected side reactions that happened in the dimethyl sulfoxide (DMSO) solvent; besides, less reaction time was needed for electron-deficient acetophenones. Specifically, the electron-withdrawing group chloride provided higher yields than the electron-donating group methyl (**3b−3d** vs **3e−3g**) and needed less reaction time, and similar electronic effects were found in other acetophenones (**3h−3o**). Also, this electrolysis system exhibited good functional-group tolerance, including methoxyl (**3h**), hydroxyl (**3i**),

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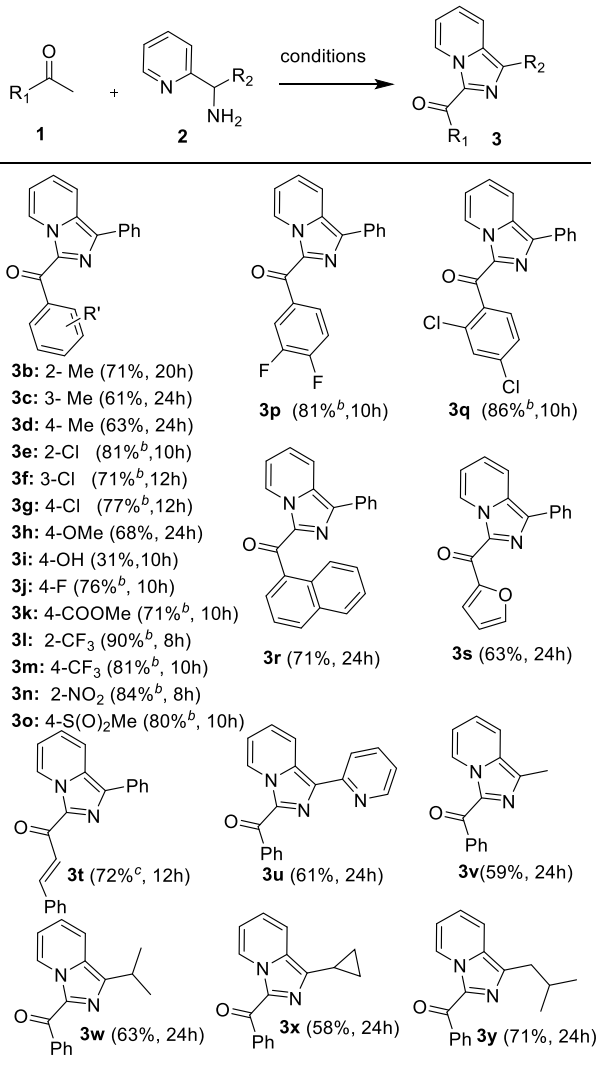
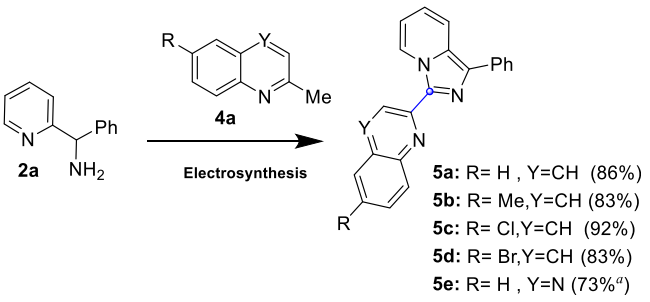
Table 2. Investigation on Various Ketones[a]



[a]Reaction conditions: graphite rod anode, platinum plate cathode, constant current = 10 mA, **1** (0.2 mmol), **2** (2 equiv, 0.4 mmol), NH_4I (1.5 equiv, 0.3 mmol), DMSO (3 mL), 80 °C. Isolated yield. [b]DMA (3 mL) as the solvent, **2a** (1.5 equiv, 0.3 mmol). [c]**2a** (1.2 equiv, 0.24 mmol).

fluorine (**3j**), ester (**3k**), trifluoromethyl (**3l** and **3m**), nitrile (**3n**), and sulfonyl (**3o**). Also, multisubstituted acetophenone still provided the target products (**3p**–**3q**). Besides, heteroaromatic ketone, condensed aromatic ketone, and unsaturated ketone were also applicable to this reaction (**3r**, **3s**, and **3t**). As for the other substrate amines (R_2 group), both heteroaryl and alkyl-substituted pyridinethylamines could react with acetophenone successfully and give the corresponding target products (**3u** and **3v**–**3y**) with a modest yield. The above results demonstrated that this method was applicable to many kinds of ketones and pyridinethylamines and exhibited good substrate applicability. Moreover, this method could be extended to other active methyl compounds for large π-system construction. The results showed that under the standard reaction conditions, 2-methylquinolines and 2-methylquinoxaline were all applicable in this electrolytic reaction, and the corresponding products were obtained with a satisfactory yield (Scheme 3, **5a**–**5e**). In virtue of this transformation, large π-systems with potential fluorescence properties could be effectively constructed.

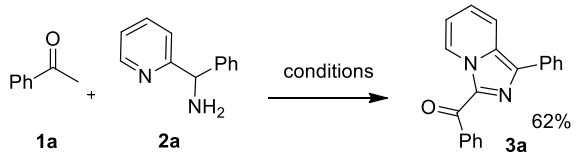
Scheme 3. Investigations on Other Active Methyls[a]



[a]Reaction conditions: graphite rod anode, platinum plate cathode, constant current = 10 mA, **1a** (0.2 mmol), **2a** (2 equiv, 0.4 mmol), NH_4I (1.5 equiv, 0.3 mmol), DMA (3 mL), 80 °C, 16 h. Isolated yields are shown. [a]Reacted at 100 °C.

The electrochemical method was then evaluated by performing a 10 mmol-scale reaction. Using a 25 mA constant current and reaction for 20 h, 62% yield of **3a** could be obtained (Scheme 4). The result indicated the potential of this electrochemical synthesis for imidazo[1,5-*a*]pyridines.

Scheme 4. Gram-Scale Synthesis[a]



[a]Reaction conditions: graphite rod anode, platinum plate cathode, constant current = 25 mA, **1a** (10 mmol), **2a** (20 mmol), NH_4I (15 mmol), DMSO (50 mL), 80 °C, 20 h.

To investigate the mechanism of the reaction, a set of control experiments were performed (Scheme 5, **A**, **B**, **C**, and **D**). First, using 2-iodo-1-phenylethanone (**1aa**) 2-oxo-2-and phenylacetaldehyde (**1ab**) reacted with **2a** under the standard condition could provide **3a** with 83 and 67% yield, respectively, indicating that **1aa** and **1ab** were possible intermediates. Besides, a radical trap experiment was performed; 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) (0.4 mmol) was added to the reaction system in the **3a** synthesis, and the result showed that the addition of TEMPO did not have an apparent influence on the yield of **3a** (63%), indicating that this reaction might not experience radical process. Moreover, an oxygen-free experiment under the N_2 protection was also performed in the synthesis of **3a**, and 78% yield of **3a** also indicated that the oxidative dehydrogenation process was not promoted by oxygen.

Based on the information obtained above and the literature,[13] a plausible mechanism is proposed in Scheme 6. The anodic oxidation of NH_4I generates molecular iodine, which reacts with ketone and forms α-iodoketone **1aa**. The nucleophilic substitution of α-iodoketone with amine forms intermediate **I**; intermediate **I** experiences anodic oxidative dehydrogenation to form intermediate **II**, and intramolecular nucleophilic attack followed by anodic oxidative dehydrogenation and gives product **3a**.

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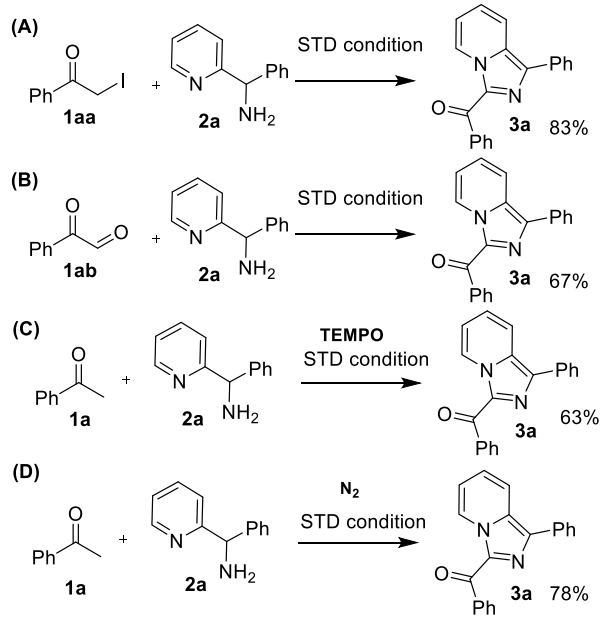
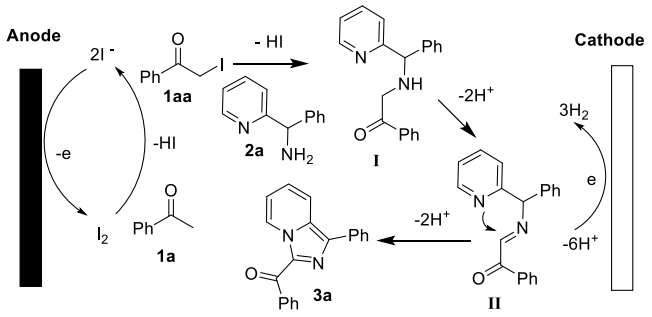
Scheme 5. Control Experiments



Scheme 6. Plausible Mechanism of the Reaction



CONCLUSIONS

In conclusion, we have developed an efficient electrochemical method for 3-acyl imidazo[1,5-*a*]pyridine synthesis, in which double amination of sp^3 hydrocarbons of inexpensive ketone methyls well avoids the conventional multistep reaction for 3-acyl imidazo[1,5-*a*]pyridine synthesis. This transformation exhibits a good substrate scope and functional-group tolerance and gives modest-to-good yield. Also, the application of this method can be extended to other active methyl groups for large π-system preparation. Direct synthesis, inexpensive materials, simple metal-free system with no external electrolyte and oxidant, and scalability make this method a practical and green method for 3-acyl imidazo[1,5-*a*]pyridine and large π-system preparation.

EXPERIMENTAL SECTION

Experimental Reagents and Instruments. Unless otherwise noted, all reactions were carried out under the air atmosphere; commercial materials and solvents were used without further purification. ^{1}H NMR (400 MHz, 500 MHz, or 600 MHz) and ^{13}C NMR (101 MHz, 126 MHz, or 151 MHz) spectra were measured using $CDCl_3$ or DMSO-d_6 as the solvent at room temperature. High-resolution mass spectra were recorded on a Bruker VPEXII spectrometer with the ESI mode. Flash column chromatography was performed on silica gel with 200−300 mesh.

General Procedure for the Electrosynthesis. *General Procedure.* Ketones or active methyl compounds (0.2 mmol, 1 equiv), pyridine ethylamines (0.4 mmol, 2 equiv), NH_4I (0.3 mmol), and the solvent (DMSO or DMA, 3 mL) were added to a 20 mL tube equipped with a graphite rod anode (diameter = 0.6 cm) and a platinum cathode (1.0 cm^2). The electrosynthesis was carried out at 80 °C at a constant current of 10 mA for a specified time; the reaction progress was monitored by thin-layer chromatography (TLC). Then, water (10 mL) was added, and the aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed through silica gel and eluted with ethyl acetate/hexanes to give the product.

Gram-Scale Reaction Procedure. Acetophenone (**1a**, 10 mmol), phenyl(pyridin-2-yl)methanamine (**2a**, 20 mmol), NH_4I (30 mmol), and DMSO (50 mL) were added to a 100 mL tube equipped with a graphite rod anode (diameter = 0.6 cm) and a platinum cathode (1.0 cm^2). The electrosynthesis was carried out at 80 °C at a constant current of 25 mA for 20 h; the reaction progress was monitored by TLC. The system was poured into water (100 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic phase was washed with saturated brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed through silica gel and eluted with ethyl acetate/hexanes (5:1) to give product **3a** (62%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06029.

Details of characterization data and NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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