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ARTICLE

Electrochemically Initiated Intermolecular C-N Formation /Cyclization of Ketones with 2-Aminopyridines: an Efficient Method for the Synthesis of Imidazo[1,2-a]pyridines

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Electrochemical intermolecular C-N formation/cyclization of ketones with 2-aminopyridines using catalytic hydriodic acid as the redox mediator was developed, providing imidazo[1,2-a]pyridines under more environmentally benign conditions. The reaction proceeds in a simple undivided cell, using low toxic ethanol as the solvent, without external oxidants, and exhibits high atom economy. A variety of ketones including acetophenones, unsatruated and alkyl ketones are amenable to this reaction, affording the corresponding products in moderate to excellent yields. A three-component tandem reaction realizing C-N, C-S/C-Se bond formation can also be achieved under standard conditions.

Introduction

Electrosynthesis, which employs electrons as reagents, has been recognized as a green technology since it does not generate reagent waste[1]. It provides an alternative method to achieve C–H functionalization by electron transfer between an electrode (direct electrolysis) and a substrate or by using a redox catalyst (indirect electrolysis)[2]. During the past decade, the application of electrochemical anodic oxidation in synthetic organic chemistry has received increasing attention[3, 2c], and a series of elegant eletroorganic reactions for C-C[4], C-N[5], C-O[6], C-S[7] bond formations have been developed independently by several research groups.

N-heterocycles are widely found in biologically active natural products, pharmaceuticals, and functional materials[8]. Accordingly, efficient, green and sustainable strategies for the synthesis of important *N*-heterocycles are highly demanding. The development of modern organic electrosynthesis provides a new platform for the synthesis of *N*-heterocycles in a green way[9]. Various intramolecular electrochemically oxidative aminations of alkenes, alkynes, arenes and alkanes have been developed for the construction of *N*-heterocylces[10]. Despite the great progresses in electrosynthesis, only limited intermolecular amination to access *N*-heterocycles was reported[11]. To form *N*-heterocycles by intermolecular amination, each component needs two functional groups at least, one for C-N formation, and another for cyclization. How to control electrochemical oxidative conditions to realize C-N formation while not interfere with another functional group is challenging.

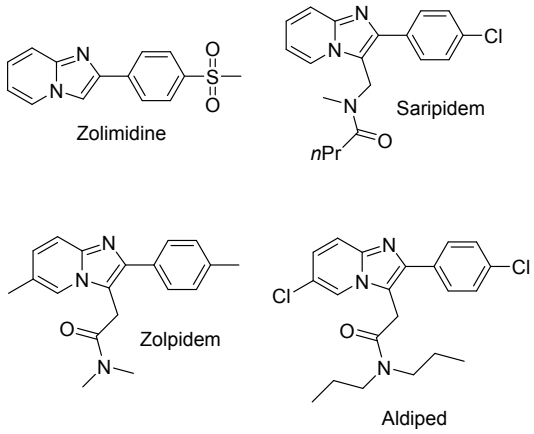

Fig.1 Commercial drugs containing imidazo[1,2-a]pyridine

Imidazo[1,2-a]pyridine is an important class of privileged structural motif and is recognized as a "drug prejudice" scaffold due to its wide range of applications in medicinal chemistry[12]. Imidazopyridines show a variety of activities such as antipyretic[13], antiviral[14], antibacterial[15], anticancer[16], antiulcer[17] and anti-inflammatory[18] properties (Fig. 1). Traditional methods starting from 2-aminopyridines and ketones usually involve stoichiometric amount of chemical oxidants or other toxic reagents and high temperature, optionally the use of metal reagents[19]. We aim to explore an efficient environmentally-friendly electrochemical method to

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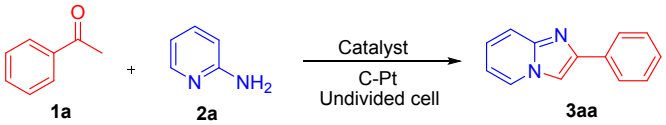
construct this important *N*-heterocyclic moiety. The challenge lies in controlling reaction conditions to realize selective oxidative amination of ketones with pyridines, while the labile amino not being oxidized or undergoing other side-reaction. Herein, we developed the first metal-free intermolecular electrochemical C-N formation cyclization for the construction of imidazopyridines from 2-aminopyridines and ketones. This reaction proceeds in a simple undivided cell in low toxic ethanol[20] in the presence of catalytic amount of hydriodic acid (HI), providing an environmentally benign access to prepare important *N*-heterocycles.

Results and discussion

Table 1. Optimization of reaction conditions [a]



1a 2a 3aa

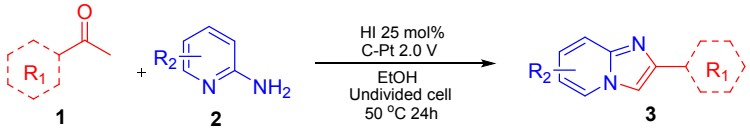
Entry	Equiv. of **2a**	Catalyst	I or E_{cell}	T(℃)	Yield[b]
1	1.5	-	2.0 V	50	N.D
2	1.5	NaI 25%	2.0V	50	7%
3	2	TBAI 20%, $BF_3{\cdot}Et_2O$ 20%	2.0V	50	39%
3	2	HI 1eq.	2.0V	50	62%
4[c]	2	HI 1eq.	2.0V	50	33%
5	2	HI 1eq.	5 mA	50	33%
6	2	HI 50%	2.0V	50	90%
7	2	HI 12%	2.0V	50	95%
8	1.5	HI 12%	2.0V	50	65%
9	1.5	HI 12%	2.0V	35	57%
10	**1.5**	**HI 25%**	**2.0V**	**50**	**99%**
11	1.2	HI 25%	2.0V	50	60%
12	1.2	HI 35%	2.0V	50	64%
13	1.2	HI 50%	2.0V	50	41%
14[d]	1.5	HI 25%	2.0V	50	30%

[a] Reaction conditions: **1a** (0.8 mmol), **2a**, nBu_4NBF_4 (0.1 M) as supporting electrolyte in EtOH (3 mL), undivided cell, carbon fell anode (1.5 cm^2), platinum cathode (1.5 cm^2). [b] Isolated yield. [c] under argon atmosphere. [d] Using water/ethanol (20:3) as the solvent.

2-aminopyridine (**1a**) and acetophenone (**2a**) were chosen to study reaction conditions for the oxidative amination/cyclization reaction. Initially, the reaction was carried out by the direct electrolysis of the mixture of **1a** and **2a** in ethanol. Various reaction conditions were tested, but no obvious product formation was observed (Table 1, entry 1). Then we turned our attention to indirect electrolysis. Using NaI as the redox catalyst, the reaction underwent, albeit in low efficiency (Entry 2). The addition of Lewis acid prompted the reaction as we expected (Entry 3). We were pleased to find that the addition of HI provided better results, affording the product in 62% yield. Further improvements were observed when the amount of HI was reduced to 12 mol%, which furnished the product in 95% yield (Entry 7 vs entries 3 and 6). After carefully screening the amount of HI and the ratio of substrates as well as other conditions, the optimized reaction conditions (Entry 10) were established, affording the product in 99% yield. Furthermore, the reaction also works using a mixture of water and ethanol as the solvent (water/ethanol: 20/3) (Entry 14).

With the optimized reaction conditions in hand, we examined the substrate scope of this transformation (Table 2). Both the electron-deficient and electron-rich acetophenones are found to be suitable substrates to provide the desired products in moderate to excellent yields (**3ba-3ia, 3ja and 3ka**). This reaction tolerates a variety of functional groups including nitro (**3ba**), trifluoromethyl (**3ca**), nitrile (**3da**), sulfonyl (**3ea**), ester (**3fa** and **3ka**), halides (**3ga**-**3ia**) and ether (**3ja**). Notably, this reaction is a highly efficient method towards Zolimidine (**3ea**), a gastroprotective drug used for peptic ulcer and gastroesophageal reflux disease. Interestingly, 2-hydroxy acetophenones, which are usually labile in an oxidation system, underwent this transformation smoothly, affording 2-hydroxyl aryl imidazopyridines in good yields (**3la, 3na, 3oa**). These compounds exhibit efficient ESIPT luminescence in the solid state[21]. This reaction was amenable to unsaturated ketones, affording monosubstituted alkenyl imidazopyridines exclusively (**3ta, 3ua**). To the best of our knowledge, metal-free synthesis of alkenyl imidazopyridines has not been reported[22]. Alkyl ketones, which usually have lower boiling points and are less active than aromatic ketones, underwent this transformation efficiently under modified conditions (**3va**-**3ya**). The scope of 2-aminopyridines was also studied. When alkyl or phenyl substituted 2-aminopyrides were subjected to this reaction, the corresponding products were isolated in good yields (**3ab-3ae**). 2-Aminoquinolin afforded the corresponding product in 20% isolated yield (**3af**). Electron-deficient halogenated 2-aminopyridines did not undergo such transformation, keeping intact during electrolysis (data not shown).

Table 2. Substrate scope of various ketones and 2-aminopyridines [a]



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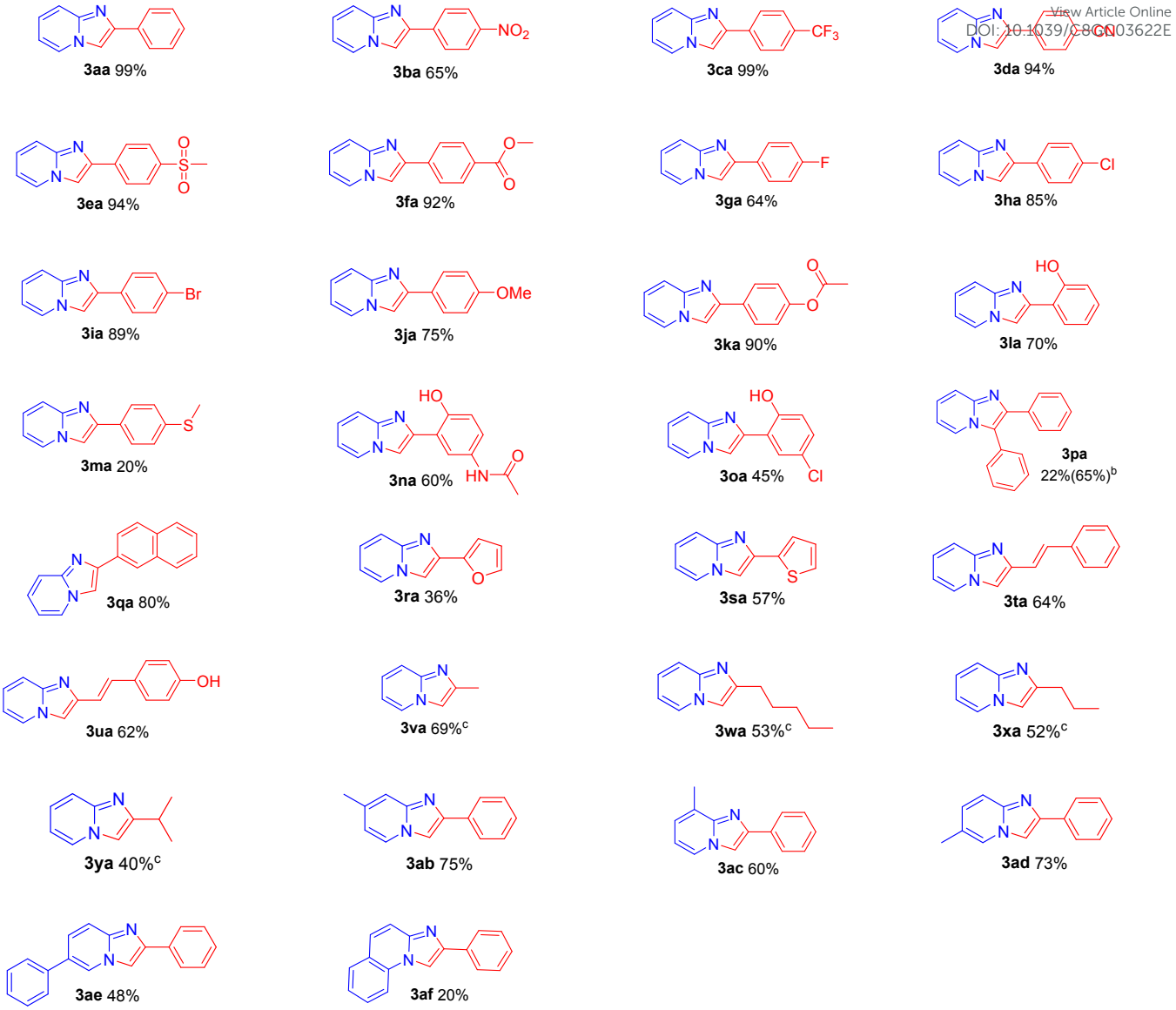
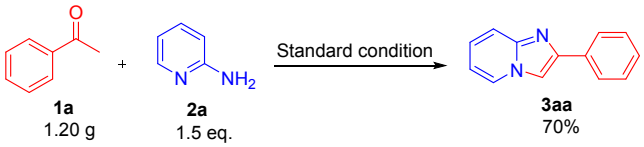
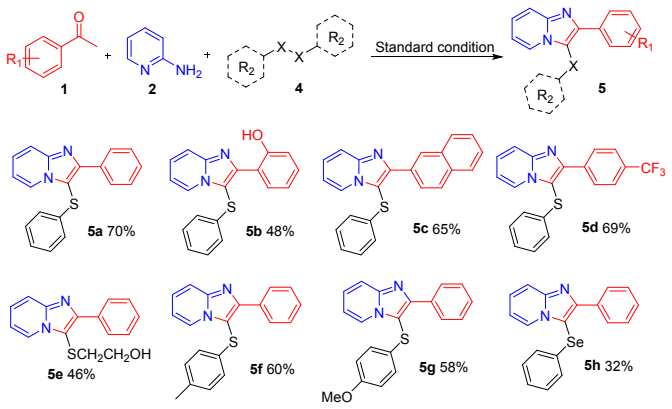


[a] Reaction conditions: ketone **1** (0.8 mmol), 2-aminopyridine **2** (1.5 equiv.), HI (25 mol%), nBu_4NBF_4 (0.1 M) in EtOH (3 mL), undivided cell, carbon fell anode (1.5 cm^2), platinum cathode (1.5 cm^2), 50 °C. [b] Yield based on conversion. [c] Using ketone/ethanol (1:2) as the solvent.



Scheme 1 Gram-scale synthesis of **3aa**. Reaction conditions: **1a** (10 mmol), **2a** (15 mmol), HI (25 mol%), carbon felt anode (6.0 cm^2), platinum cathode (1.5 cm^2), constant potential (E_{cell}=1.5 V), undivided cell, air, 50 °C, 48 h. Isolated yield.

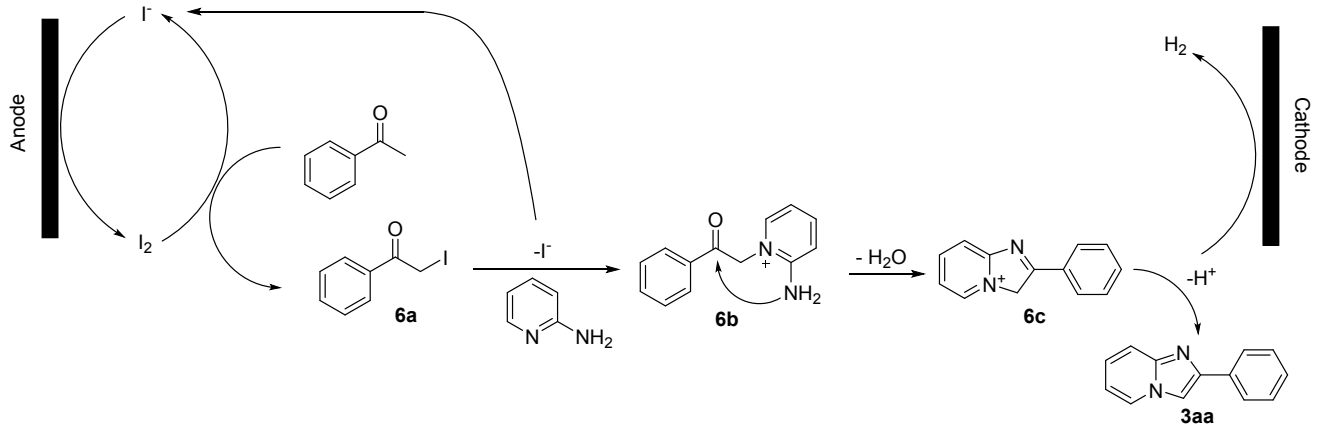
A gram-scale reaction using 10 mmol of **1a** (1.20 g) was conducted to assess the scalability of this electrochemical tandem cyclization under the standard condition (Scheme 1). This transformation proceeded smoothly and imidazo[1,2-a]pyridine **3aa** was obtained in 70% isolated yield with 26% recovery of **1a**.



Scheme 2 Three-component reaction of 2-aminopyridine, acetophenones and sulfide/selenide derivatives under standard conditions.

Polyfunctional S- and Se-containing *N*-heterocyclic derivatives are widely found in molecules with biochemical and pharmacological properties[23]. Yet, highly efficient and selective formation of C–N and C–S/C-Se bonds simultaneously in one-pot through C–H bond functionalization is still an interesting challenge[24,19f,19h-19i]. On the basis of the oxidant-free electrochemical amination reaction that we have developed, a three-component approach towards 3-sulfenylimidazo[1,2-a]pyridines was performed under standard conditions in the presence of diphenyl disulfides. The aim products were obtained in moderate to good yields (Scheme 2, **5a**-**5g**). Interestingly, **5b** exhibits solid-state fluorescence and AIE properties (see the Supporting Information). Diphenyl diselenium can be applied to the same procedure to afford 3-selanylimidazopyridine in 32% yield (Scheme 2, **5h**). Based on the results of control experiments (see the Supporting information) and literature[25], this sulfenylation or selenation may proceed by the electrochemical formation of PhSI or PhSeI electrophilic species and subsequent electrophilic attack to the generated imdazo[1,2-a]pyridines **3**.

Imine formation was usually the first step in metal-catalyzed C-H functionalization for the synthesis of imidazo[1,2-a]pyridines[19a]. However, no obvious imine formation was observed by running this reaction under standard reaction conditions without electrifying. Therefore, we speculated that C-N formation between a pyridine and a ketone should occur before the imine formation. Liquid chromatograph-mass spectrometer analysis was used to monitor the reaction (See the supporting information). Other than the reactants and the product, which were assigned by comparison with authentic samples, new specie appeared (0.343 min) during the electrolysis, giving two signals m/z 213 and m/z 195. The two signals correspond to intermediates **6b** and **6c** respectively.



Scheme. 3 The proposed reaction mechanism

On the basis of the observations described above and literature[26], a possible mechanism is outlined in Scheme 3. The reaction begins with the anodic oxidation of iodide to generate molecular iodine[27], which reacts with the ketone to form α-iodo ketone **6a**. The nucleophilic substitution between 2-aminopyridine and intermediate **6a** gives intermediate **6b**, which subsequently undergoes an intramolecular cyclization to afford intermediate **6c**. The deprotonation of **6c** provides the desired product **3aa**.

Conclusions

In conclusion, we have developed an environmentally-friendly electrochemical intermolecular C-N formation/cyclization reaction for the synthesis of imidazo[1,2-a]pyridines. The electrolysis was performed under constant voltage in a simple undivided cell using catalytic amount of hydriodic acid as the redox mediator and low-toxic ethanol as the solvent. A variety of ketones including acetophenones, unsaturated ketones and alkyl ketones are amenable to the reaction, affording the corresponding products in moderate to excellent yields. This reaction was found to tolerate a variety of functional groups, including hydroxyl, nitro, cyanogen, ether, ester, halides and sulfonyl. We have also reported an electrochemical three-component tandem reaction for the synthesis of 3-sulfenylimidazopyridines. No external oxidants, lower temperature and lower equivalence of pyridine substrates are beneficial to actual industrial production.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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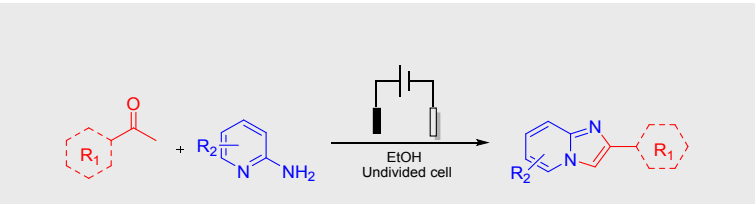

Electrochemical intermolecular C-N formation for the construction of N-heterocycles: A metal- and oxidant-free, electrochemical intermolecular C-N formation cyclization of ketones with 2-aminopyridines was developed, providing a series of imidazo[1,2-a]pyridines under more environmentally benign conditions. The reaction exhibits high atom economy and good functional-group tolerance. A three-component reaction towards 3-sulfenylimidazo[1,2-a]pyridines can also be achieved under standard conditions.

Key words: Electrochemistry, electrochemical oxidation, C-N formation, N-heterocycles, imidazo[1,2-a]pyridine

Electrochemically Initiated Intermolecular C-N Formation/Cyclization of Ketones with 2-Aminopyridines: an Efficient Method for the Synthesis of Imidazo[1,2-a]pyridines

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