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Electrocatalytic intramolecular oxidative annulation of *N*-aryl enamines into substituted indoles mediated by iodides

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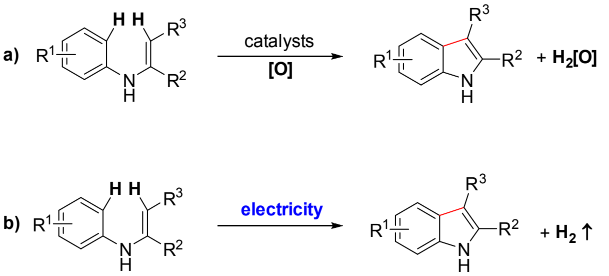
Shan Tang,‡[a] Xinlong Gao,‡[a] and Aiwen Lei*[a,b]

An electrocatalytic reaction protocol is developed for achieving intramolecular dehydrogenative annulation of *N*-aryl enamines. It offers a simple and efficient way for the synthesis of indoles in an undivied cell. Good to excellent yields are obtained under oxidant-free and transition-metal-free conditions. Moreover, imidazo[1,2–a]pyridines could also be produced when *N*-pyridyl enamines were used as the substrates.

Indoles are important structure moieties, which widely distributed in natural products, pharmaceuticals, agrochemicals and materials.[1] Continuous efforts have been devoted to developing efficient methods regarding their synthesis.[2] One of most straightforward strategies is the intramolecular oxidative cyclization of *N*-aryl enamines.[3] Such transformations have been previously accomplished by using stoichiometric or excess amount of oxidants such as Cu(II) salts,[4] hypervalent iodine reagents,[5] *N*-bromosuccinimide (NBS)[6] and oxygen[7] (Scheme 1a). From the viewpoint of atom-economic and sustainable chemistry, direct oxidative annulation of *N*-aryl enamines under oxidant-free conditions with hydrogen evolution is more appealing.[8]

Electrosynthesis is recognized as a versatile and environmentally friendly synthetic tool and attracted continuous interests.[9] Over the past decade, application of electrochemical anodic oxidation to replace chemical oxidants in dehydrogenative cross-coupling reactions has received increasing attention.[10] Moreover, redox mediators have been widely used to achieve indirect anodic oxidation processes.[11] Recently, our group was interested in iodine-catalysed oxidative annulation for the synthesis of heterocycles.[12] However, these reactions required the use of strong oxidants especially peroxides. Since iodide salts have been reported to act as redox mediators under electrochemical conditions,[13] we decided to study iodine-promoted oxidative annulation reactions under electrochemical conditions. In this work, we would like to communicate our development on an external chemical oxidant-free electrocatalytic oxidative annulation of *N*-aryl indoles for the synthesis of indoles (Scheme 1b).



Scheme 1. Intramolecular dehydrogenative C-H/C-H cross-coupling for the synthesis of indoles.

Ethyl 3-phenyl-3-(phenylamino)acrylate (**1a**) was used as the model substrate to test the reaction conditions. By using KI as the electrolyte under 7 mA constant current, the desired indole **2a** was obtained in 72% yield in an undivided four-necked bottle (Table 1, entry 1). Further optimization was carried out by adding co-solvents into the reaction system. Acetonitrile and 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) suppressed the oxidative annulation process (Table 1, entries 2 and 5). Alcohols such as methanol and isopropanol promoted the formation of indole (Table 1, entries 3 and 4) while water gave the best result, which afforded **2a** in an excellent yield (Table 1, entry 6). The effect of electrolyte was also explored. Iodide salts such as NaI and tetrabutylammonium iodide gave similar results with KI (Table 1, entries 7 and 8). Only 30% yield of **2a** could be obtained by using NaBr instead of KI (Table 1, entry 9) In this transformation, KI not only served as the electrolyte but also acted as redox mediator for this oxidative annulation (Table 1, entry 10). As was expected, no desired product could be obtained by using tetrafluoroborate or perchlorate as the electrolyte (Table 1, entries 10 and 11). Carbon anode and nickel cathode can be used for this

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[a] College of Chemistry and Molecular Sciences, Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, Hubei, China. E-mail: aiwenlei@whu.edu.cn
[b] National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, China

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‡ Shan Tang and Xinlong Gao contributed equally

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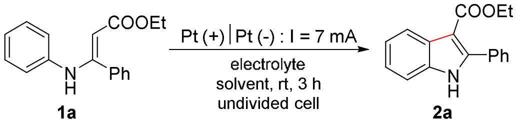
transformation while with decreased reaction efficiency (Table, entries 12 and 13).

Table 1. Condition optimization.



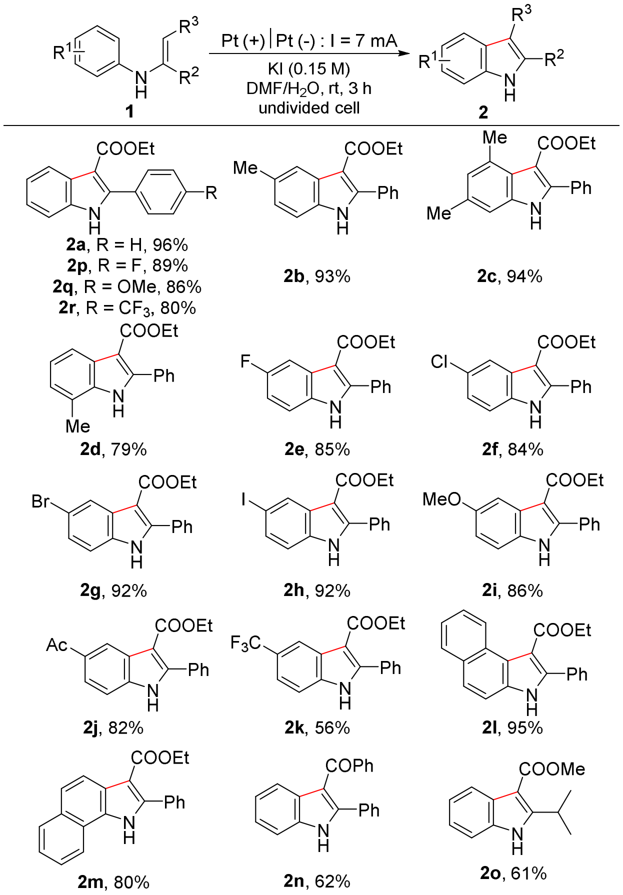
1a **2a**

Entry	Solvent	Electrolyte	Yield (%)	Current efficiency (%)
1	DMF	KI	72	18
2	DMF/CH_3CN	KI	20	5
3	DMF/MeOH	KI	89	23
4	DMF/^{i}PrOH	KI	93	24
5	DMF/HFIP	KI	n.d.	-
6	DMF/H_2O	KI	99	25
7	DMF/H_2O	NaI	97	25
8	DMF/H_2O	^{n}Bu$_4$NI	90	23
9	DMF/H_2O	NaBr	30	8
10	DMF/H_2O	^{n}Bu$_4$NBF$_4$	n.d.	-
11	DMF/H_2O	$LiClO_4$	n.d.	-
12[c]	DMF/H_2O	KI	60	15
13[d]	DMF/H_2O	KI	52	13

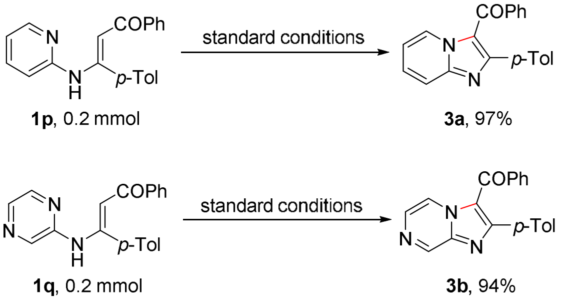
[a] Reaction conditions: Pt plate anode, Pt plate cathode, constant current = 7 mA (J_{anode} = 12 mA/cm^2), **1a** (0.20 mmol), KI (0.15 M), DMF (10.0 mL), co-solvent (0.2 mL), room temperature, 3 h (3.9 F). [b] Yields of **2a**were determined by GC analysis with biphenyl as the internal standard, n.d. = not detected. [c] Graphite rod anode was used instead of Pt anode. [d] Nickel plate cathode was used instead of Pt plate cathode.

With the optimized condition in hand, we then turned to explore the functional group tolerance for the synthesis of indoles (Table 2). Electron neutral *N*-phenyl enamines showed excellent reactivity in the synthesis of indoles (**2a-2h**). Methyl groups at the para or *ortho* position did not affect the reaction efficiency (**2b** and **2c** while *ortho*-methyl substituent led to a slightly decreased reaction efficiency (**2d**). Halide substituents including F, Cl, Br and even I were all well tolerated under the electrochemical conditions (**2e-2h**). Both strong electron-rich and electron-deficient *N*-phenyl enamines were all able to furnish corresponding indoles (**2i-2k**). Besides *N*-phenyl enamines, *N*-naphthyl and *N*-pyridyl enamines were also suitable in this transformation which afforded the desired indole in good yields (**2l** and **2m**). Replacement of carboxylic ester by ketone led to decreased reaction efficiency (**2n**). N-Phenyl enamines bearing either electron-donating or electron-withdrawing substituents on the C-2 aryl group all demonstrated good reactivity for the synthesis of indoles (**2o-2r**). Changing the C-2 substituent from phenyl group to isopropyl group also gave a decreased reaction yield (**2o**). Importantly, imidazo[1,2-a]pyridine could be synthesized when *N*-pyridyl enamines were applied as the substrates (Scheme 2).

Table 2. Synthesis of indoles.[a]



[a] Standard conditions: Pt plate anode, Pt plate cathode, constant current = 7 mA (J_{anode} = 12 mA/cm^2), **1a** (0.20 mmol), KI (1.5 mmol), DMF (10.0 mL), H_2O (1.0 mL), room temperature, 3 h (3.9 F).



Scheme 2. Synthesis of imidazo[1,2‑a]pyridine.

Since the method had been established, efforts were paid to get some insights into the reaction mechanism. Since iodide was able to be oxidized under electrochemical conditions, control experiments were conducted by using 2 equiv of iodine or *N*-iodosuccinimide (NIS) as oxidant directly in the reaction of **1a**. Without electricity, no desired cyclization product could be observed by using iodine as the oxidant (Scheme 3a) while a high reaction yield of indole **2a** could be obtained by using NIS as the oxidant (Scheme 3b). In the next step, radical inhibition experiments were carried out to probe whether the reaction went through a radical reaction pathway. By adding 1 equiv. of 2,2,6,6-tetramethylpiperidin-1-yl oxyl (TEMPO) or

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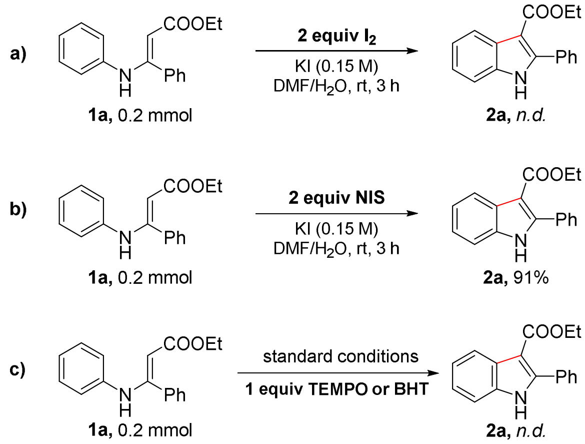
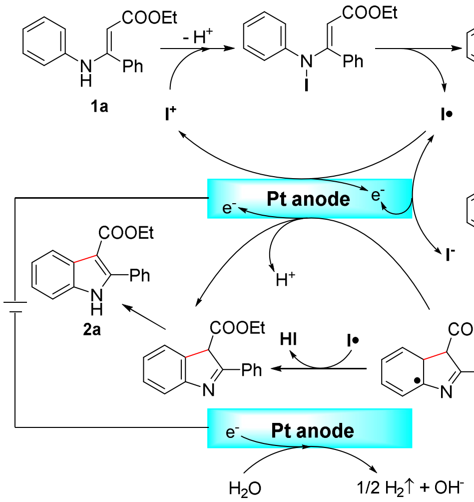
butylated hydroxytoluene (BHT) into the reaction system, no desired product could be observed in both cases (Scheme 3c).



Scheme 3. Mechanistic experiments.

Based on the above experimental results and previous reports,[6] a plausible mechanism was put forward in Scheme 4. In the first step, hyperiodide intermediate (I^+) can be generated from iodide ion through twice anodic oxidation. Then *N*-aryl enamine **1a** reacts with *in situ* generated I^+ to form an *N*-iodo intermediate. Homolysis of the N-I bond will initiate the cyclization process. Intramolecular radical addition, oxidation and deprotonation lead to the formation of indole **2a**. Meanwhile, the generated iodine radical can be either oxidized by anode to regenerate the hyperiodide intermediate. At the same time, concomitant cathodic reduction of water releases hydrogen gas during the reaction.



Scheme 4. Proposed mechanism.

Conclusions

In conclusion, an electrocatalytic intramolecular dehydrogenative annulation of *N*-aryl enamines was developed for the first time. It provided an environmentally friendly way for the synthesis of indoles. Moreover, imidazo[1,2‑a]pyridines could also be produced when *N*-pyridyl enamines were used as the substrates. The reactions proceed in high efficiency and good functional group tolerance by using KI as the electrolyte under external oxidant-free conditions. Mechanistically, KI not only acts as the electrolyte but also participates in the redox processes of the oxidative annulation.

Acknowledgements

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