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Synthesis of pyrrolo[1,2-*a*]quinoxalines *via* an electrochemical C(sp^3)–H functionalization†

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An efficient iodine-mediated electrochemical C(sp^3)–H cyclization under mild conditions was developed. A variety of functionalized quinoxalines can be obtained with good to excellent yields by virtue of this method. The reaction was found to feature a broad substrate scope, regulation of product distribution, scalable preparation and high atom economy. The reaction mechanism was investigated in detail.

Pyrrolo[1,2-*a*]quinoxaline skeletons are widely present in pharmaceuticals and bioactive compounds.[1–7] For example, compounds **A** and **B**, which have strong anti-cancer and anti-malarial activities,[8,9] and compound **C**, shown to be a potent broad-spectrum enzyme inhibitor, each have this skeleton as shown in Fig. 1. In addition, some of them are also used as fluorescent probes of amyloid fibrils.[10] Owing to their biological significance and broad applicability across chemistry disciplines, the synthesis of pyrrolo[1,2-*a*]quinoxaline derivatives would be an intriguing pursuit for the synthetic chemistry community.

As shown in Scheme 1, several convenient and efficient methods for synthesizing pyrrolo[1,2-*a*]quinoxaline skeletons have been reported. For instance, an efficient, minimally toxic, and convenient Cu-catalyzed domino reaction of α-amino acids with 1-(2-halophenyl)-1*H*-pyrroles to synthesize pyrrolo[1,2-*a*]quinoxalines was reported.[11] Afterwards, a Cu-catalyzed tandem aerobic oxidative cyclization reaction was developed by using 2-arylanilines and 2-methylquinolines as the substrates.[12] These methods offer streamlined synthetic routes and improved atom economy by avoiding complex synthetic steps. However, the use of metal catalysts involves metal residues. Despite the advances made in this field, further investigation of more efficient and environmentally benign strategies that allow the preparation of this fused heterocyclic motif is in high demand.

Using electron transport to realize the redox process can effectively avoid the involvement of metals and oxidants, and has been widely applied in the construction of nitrogen-containing heterocycles.[13–15] Recently, a metal-free synthesis of [1,2-*a*]quinoxaline skeletons *via* a TEMPO-catalyzed electrochemical dehydrogenative cyclocondensation of *o*-aminophenol analogs was reported.[16] However, the electrochemical direct coupling of C(sp^3)–H/N–H bonds to construct nitrogen-containing heterocycles remains a challenge. 2-Methylquinoline contains an inert C(sp^3)–H bond. On the basis of our previous research,[17–21] herein we present a sustainable method for synthesizing pyrrolo[1,2-*a*]quinoxaline nitrogen heterocycles, using readily available materials, namely 2-methylquinoline **1a**, 2-(1*H*-pyrrol-1-yl)aniline **2a** and an iodine catalyst, under electrochemical conditions.

Initially, 2-methylquinoline **1a** and 2-(1*H*-pyrrol-1-yl)aniline **2a** were selected as the model substrates. The reaction was performed in an undivided cell at a constant current density of 10 mA cm^{-2} in the presence of NH_4I and $H_2C_2O_4$ in dimethyl sulfoxide (DMSO) at 100 °C for 12 h (Table 1). When the starting materials disappeared from the TLC, the desired product was obtained with 81% isolated yield (entry 1, Table 1). Subsequently, the effect of solvent was investigated, and DMSO was found to be the best solvent (entries 2 and 3, Table 1). Furthermore, various electrolytes were screened. The experimental results showed iodide ion to be necessary for the reaction and NH_4I to be the optimal electrolyte. And the yield decreased when acid was not included. The amount of NH_4I was next investigated, and 20 mol% of NH_4I favored this reaction (entries 4 and 5, Table 1). Changing the platinum electrode to a carbon anode or a carbon cathode led to a decrease

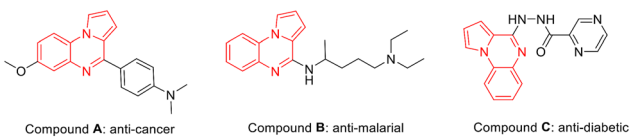

Fig. 1 Examples of biologically active pyrrolo[1,2-*a*]quinoxaline derivatives.

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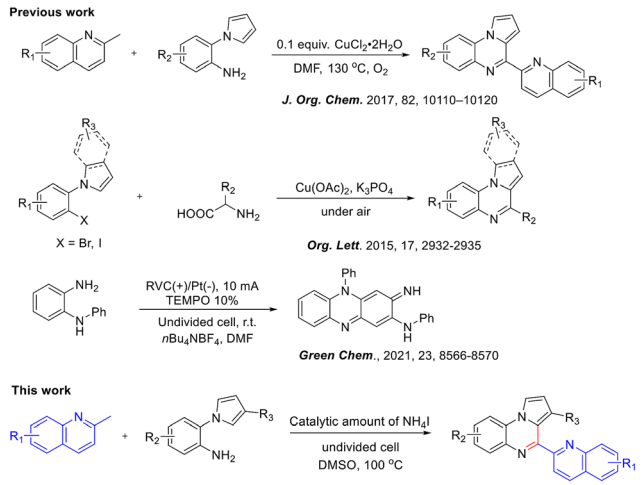
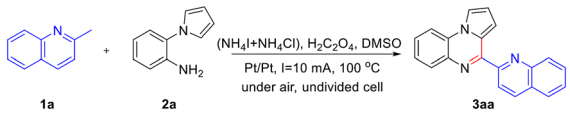


Scheme 1 Various protocols for synthesizing quinoxalines.

Table 1 Optimization of reaction conditions [a]



Entry	Variation from standard conditions	Yield [%]
1	None	81
2	DMF as the solvent	55
3	NMP as the solvent	Trace
4	Bu_4NI as the electrolyte instead of NH_4I	36
5	KI as the electrolyte instead of NH_4I	Trace
6	A graphite plate as cathode	64
7	A graphite plate as anode	Trace
8	7 mA, 15 mA instead of 10 mA	60, trace
9	90 °C, 110 °C instead of 100 °C	30, trace
10	NH_4Br, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ instead of NH_4Cl	69, 80
11	Without electricity	Trace

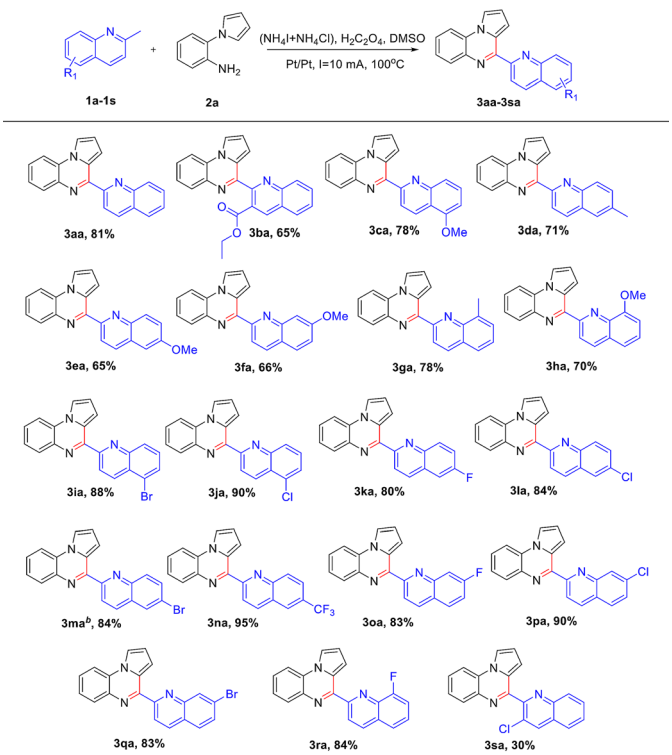
[a] Standard conditions: platinum plate (10 mm × 10 mm × 0.2 mm) as the anode, platinum plate (10 mm × 10 mm × 0.2 mm) as the cathode, undivided cell, **1a** (0.36 mmol), **2a** (0.3 mmol), $H_2C_2O_4$ (0.3 mmol), NH_4I (0.06 mmol), NH_4Cl (0.3 mmol) and DMSO (3 mL), air, 100 °C, 12 h.

in the yield (entries 6 and 7, Table 1). Then the current density and temperature were optimized: the highest yield was obtained at 100 °C with 10 mA current (entries 8 and 9, Table 1). Of the different auxiliary electrolytes tested, NH_4Cl proved to be the optimal one for the reaction (entry 10, Table 1). Almost the same yield of 80% was obtained when the reaction was conducted under a nitrogen atmosphere; however, a low yield of 40% was obtained when the reaction was carried out under an oxygen atmosphere, perhaps due to oxidization of the reactants and the generated molecular iodine. Further investigation showed use of electricity to be essential for having an efficient transformation (entry 11, Table 1). The optimal conditions are summarized in entry 1 of Table 1.

With the optimal electrolytic conditions in hand, various methyl N-hetero-aromatics were examined. To our delight, a wide range of methyl N-hetero-aromatics underwent the reaction efficiently to afford the desired products with good to excellent yields. As shown in Table 2, the electronic nature of the substituent on the quinoline ring had an influence on the reaction yield. When the quinoline ring bore electron-donating groups, the desired product was obtained with 65%–78% yields (**3ca–3ha**). The quinoline ring bearing electron-withdrawing substituents afforded the desired products with higher yields than those bearing electron-donating substituents (**3ia–3ra**). In particular, the strongly electron-withdrawing trifluoromethyl group was favorable for the reaction, with a yield of up to 95% (**3na**). In addition, steric hindrance from a substituent on the quinoline ring appeared to have a negative influence on the reaction, as substitution of ethoxycarbonyl onto the quinoline ring gave a slightly deceased yield (**3ba**). We tested 3-chloro-2-methylquinoline as the substrate and the desired product was obtained with 30% yield (**3sa**): the electronic effect apparently had a greater influence on the reaction than did the steric effect, as the electron-withdrawing group on substrate **1** was favorable for the reaction.

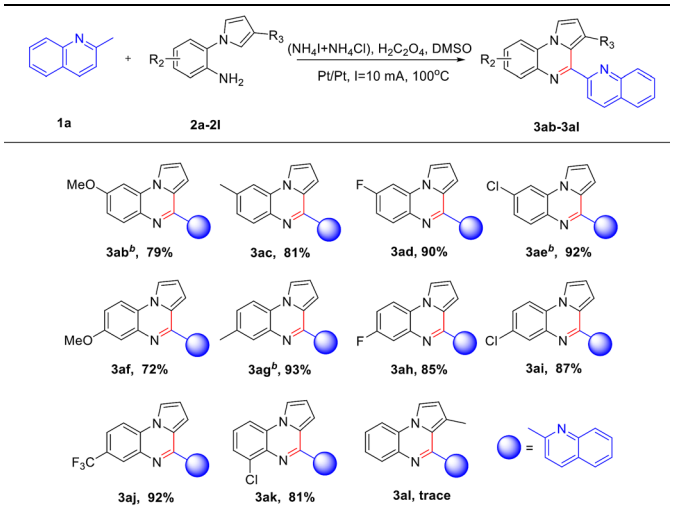
Various substituents on the phenyl ring of 2-(1*H*-pyrrol-1-yl) aniline were successfully utilized in the reaction, having delivered the corresponding products in good yields. As shown in

Table 2 Scope of methyl N-heteroaromatics[a]

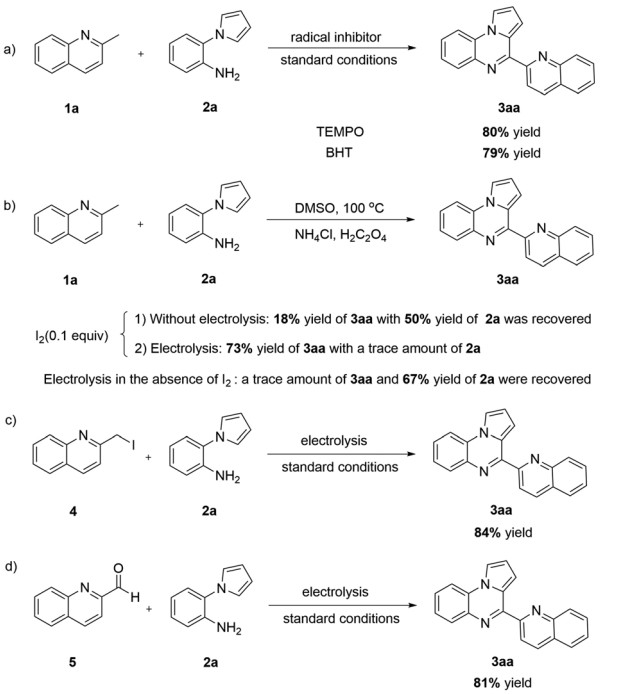


[a] Unless otherwise noted, all reactions were performed with **1a–1s** (0.36 mmol), **2a** (0.3 mmol), NH_4I (0.06 mmol), NH_4Cl (0.3 mmol), $H_2C_2O_4$ (0.3 mmol) and DMSO (3.0 mL) at 100 °C for 12 h. [b] $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ was deemed to be the optimal auxiliary electrolyte for the reaction. Isolated yields after column chromatography are shown.

Table 3 Scope of pyrrolo-heterocyclic anilines[a]



[a] Unless otherwise noted, all reactions were performed with **1a** (0.36 mmol), **2a–2l** (0.3 mmol), NH_4I (0.06 mmol), NH_4Cl (0.3 mmol), $H_2C_2O_4$ (0.3 mmol), and DMSO (3.0 mL) at 100 °C for 12 h. [b] $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ was deemed to be the optimal auxiliary electrolyte for the reaction. Isolated yields after column chromatography are shown.

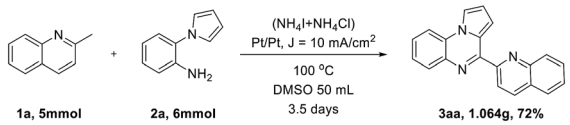


Scheme 3 Control experiments.

Table 3, reactions using both electron-rich and electron-poor substituents proceeded smoothly, affording the desired products with good to excellent yields (**3ab–3ak**). In addition, according to our results (**3ak**), steric hindrance from a substituent on the phenyl ring had little effect on the reaction. Note that the reaction yield dropped sharply when we installed a methyl group on the pyrrole ring of 2-(1*H*-pyrrol-1-yl)aniline (**3al**), perhaps due to steric hindrance.

To demonstrate the practicality and the scalability of this developed method, a gram-scale experiment was performed (Scheme 2). The desired product **3aa** was obtained smoothly in 72% yield.

Finally, control experiments were performed to investigate the mechanism (Scheme 3). Initially, the reaction proceeded well in the presence of free-radical trappers 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and butylated hydroxytoluene (BHT), suggestive of the reaction perhaps not proceeding through a radical process (Scheme 3a). Then, molecular iodine in the amount of 0.1 equiv. was added to the reaction mixture without electrolysis. However, only an 18% yield of the desired product was obtained while **2a** was recovered with a 50% yield. In contrast, when molecular iodine in the amount of 0.1 equiv. was added to reaction mixture and then electrolysis was conducted for 12 h, the desired product was obtained with 73% yield. The target product was not obtained without adding iodine molecules (Scheme 3b). These results indicated molecular iodine to be the active species and indicated electricity to be necessary. When we synthesized and then used 2-(iodomethyl)quinoline as the substrate in the reaction, the desired product was gratifyingly obtained with 84% yield, suggestive of 2-(iodomethyl)quinoline being an intermediate in the developed reaction. Furthermore, a small amount of quinoline-2-carbaldehyde was detected using GCMS in the absence of **1a** under standard conditions. However, there was no reaction without electricity. Therefore, we employed quinoline-2-carbaldehyde in this reaction, and the desired product was obtained with 81% yield. These results together were suggestive of quinoline-2-carbaldehyde being another intermediate in this reaction and were indicative of the need to use electricity.



Scheme 2 Gram-scale experiments.

Cyclic voltammetry (CV) experiments were also performed to gain insight into the reaction process. As shown in Fig. 2, in the range of 0–2.0 V *vs.* Ag/AgCl, no obvious oxidation wave of **1a** and **2a** was observed, perhaps due to the inertness of the C(sp^3)–H bond. In contrast, the CV curve of NH_4I showed two oxidation waves, at 0.76 V and at 1.02 V. This result was indicative of iodide anions being oxidized first, and of the following transformation being initiated from this oxidized iodide ion, with this ion serving as the intermediate of this reaction. The CV curve of 2-(iodomethyl)quinolone (**4**) showed two oxidation waves at 0.71 V and at 0.88 V *vs.* Ag/AgCl, respectively, indicative of intermediate **4** having become oxidized.

Based on the above experimental results and the previous reports, a plausible reaction mechanism was proposed, as

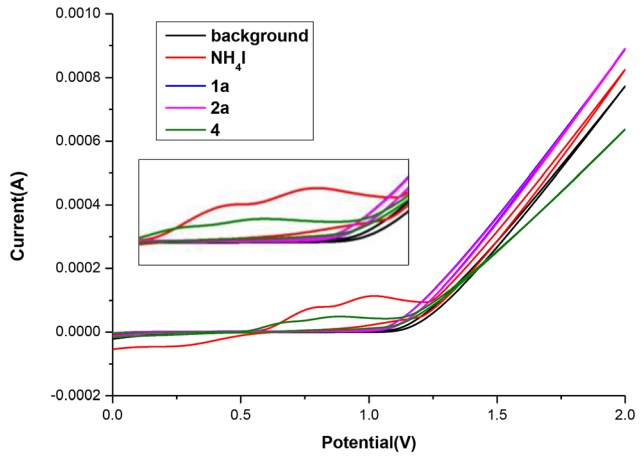
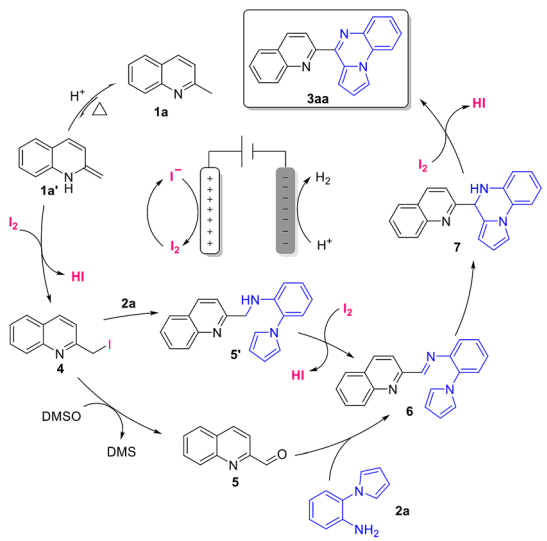


Fig. 2 Cyclic voltammetry experiments. Cyclic voltammograms of **1a**, **2a**, NH_4I and **4** in 0.1 M NH_4Cl/DMSO using a Pt disk as the working electrode, and Pt wire and Ag/AgCl as the counter and reference electrodes, respectively, at a scan rate of 100 mV s^{-1}: background, NH_4I (2 mmol L^{-1}), **1a** (5 mmol L^{-1}), **2a** (5 mmol L^{-1}) and **4** (5 mmol L^{-1}).

shown in Scheme 4. According to this mechanism, initially an iodide anion is oxidized to molecular iodine on the anode surface. Then molecular iodine reacts with the isomer 2-methylquinoline (**1a′**) to generate 2-(iodomethyl)quinoline (**4**), which could be oxidized by DMSO to form the intermediate quinoline-2-carbaldehyde (**5**). This intermediate reacts with **2a** to give intermediate **6**. At the same time, 2-(iodomethyl)quinoline (**4**) can be easily nucleophilically attacked by **2a** to form intermediate **5′**. Furthermore, intermediate **5′** is oxidized by molecular iodine to give imine intermediate **6**. Finally, nucleophilic cyclization of intermediate **6** generates **7**, which is further oxidized to produce the desired product **3aa**. Meanwhile, protons are reduced at the cathode to form molecular hydrogen.



Scheme 4 Proposed possible reaction mechanism.

Conclusions

In summary, we developed a practical and efficient approach for the construction of pyrrolo[1,2-*a*]quinoxaline N-heterocycles from readily available 2-(1*H*-pyrrol-1-yl)aniline and 2-methylquinoline under metal-free and chemical-oxidant-free conditions. The reaction featured a broad substrate scope, high atom economy, and environmental friendliness. The developed approach further demonstrated good scalability and diverse transformations of the electrolysis product in one pot.

Author contributions

Z. Wang conceived the idea and wrote the manuscript. S. Peng, T. Li, K. Li and Q. Sun analysed the data and participated in preparation of the manuscript.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request. The data include experimental procedures and compound characterizations, including HRMS and NMR analyses.

Conflicts of interest

There are no conflicts to declare.

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