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SHORT COMMUNICATION

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A facile synthesis of pyrrolo[2,3-*j*]phenanthridines via the cascade reaction of indoleanilines and aldehydes

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Abstract

A facile method for the synthesis of pyrrolo[2,3-*j*]phenanthridines from indoleanilines and aldehydes in the presence of Brønsted acid catalyst and benzoquinone oxidant has been established. This approach features excellent yields, high efficiency and a wide range of substrate scope. Mechanism studies exhibited that this reaction was a cascade process including acid-catalyzed condensation of indoleanilines with aldehydes, cyclization and oxidative aromatization.

The construction of heterocyclic compounds has a pivotal impact in the areas of organic and medicinal chemistry [1]. Nitrogen-containing heterocyclic compounds are a prominent class of heterocyclic compounds and play an increasingly important role in modern life including drug development, materials science and agrochemistry [2]. Among the various types of nitrogen-containing heterocyclic compounds, phenanthridine was found to be a critical scaffold in pharmaceutical drugs, functional materials and natural products [3]. For example,

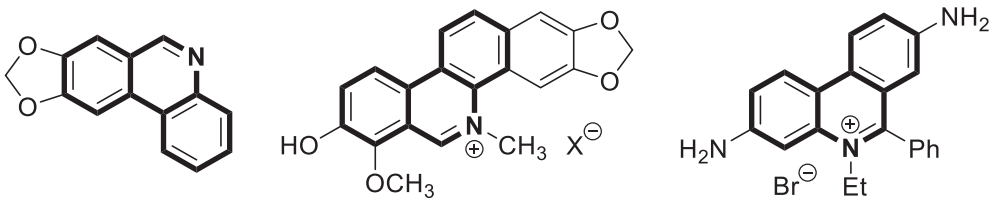


FIGURE 1 Bioactive phenanthridine derivatives

SCHEME 1 Synthesis of pyrrolo[2,3-*j*]phenanthridines via the cascade reactions

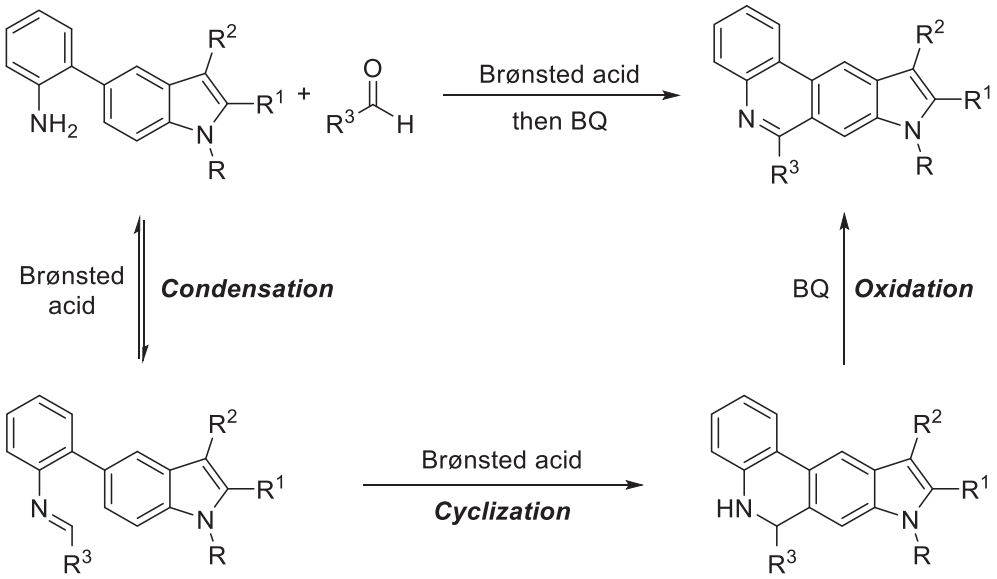
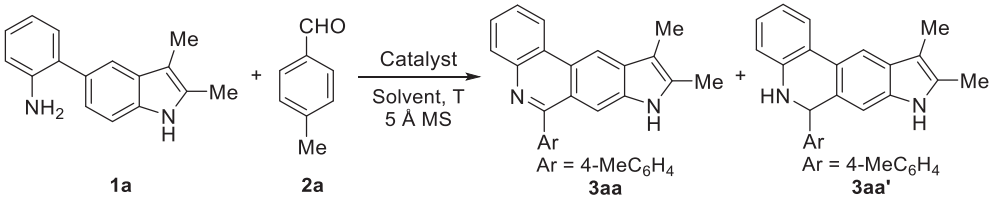


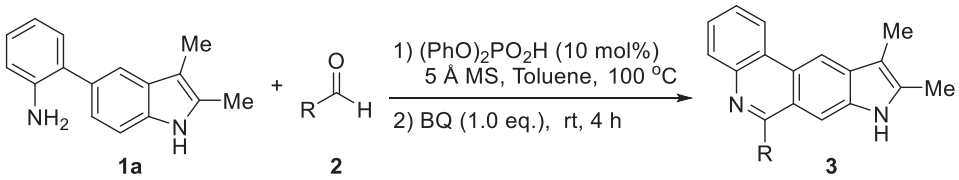
TABLE 1 Optimization of reaction parameters



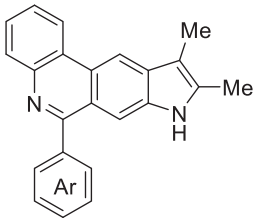
1a 2a 3aa 3aa'

Entry[a]	Solvent	Catalyst[b]	1a:2a	3aa yield (%)[b]	3aa′ yield (%)[b]
1	Toluene	$TsOH·H_2O$	1:1.5	18	42
2	Toluene	TfOH	1:1.5	16	35
3	Toluene	PhCOOH	1:1.5	6	24
4	Toluene	$Sc(OTf)_3$	1:1.5	36	18
5	Toluene	$(PhO)_2PO_2H$	1:1.5	48	23
6	DCE	$(PhO)_2PO_2H$	1:1.5	35	37
7	CH_3CN	$(PhO)_2PO_2H$	1:1.5	42	17
8	THF	$(PhO)_2PO_2H$	1:1.5	/	/
9[c]	Toluene	$(PhO)_2PO_2H$	1:1.5	51	23
10[d]	Toluene	$(PhO)_2PO_2H$	1:1.5	63	13
11[d]	Toluene	$(PhO)_2PO_2H$	1:1	71	16
12[d]	Toluene	$(PhO)_2PO_2H$	1.2:1	69	21
13[d,e]	Toluene	$(PhO)_2PO_2H$	1.2:1	70	22
14[d,f]	Toluene	$(PhO)_2PO_2H$	1.2:1	90 (91[g])	/

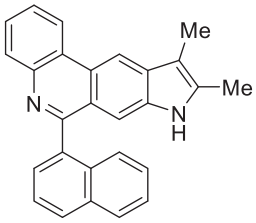
[a]Reactions were carried with **1a** (0.20 mmol), **2a** (0.30 mmol), catalyst (10 mol%), 5 Å MS (100 mg), solvent (2.0 mL), 60°C, 21 h, air atmosphere.
[b]Determined by NMR using CH_2Br_2 as internal standard.
[c]80°C.
[d]100°C.
[e]O_2 atmosphere.
[f]Then, BQ (0.20 mmol) was added and reacted at room temperature for 4 h.
[g]Isolated yield.



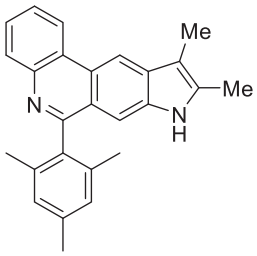
SCHEME 2 Substrate scope of aldehydes



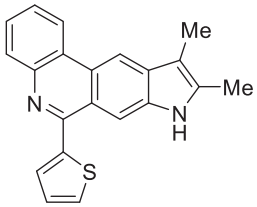
3aa Ar = 4-MeC$_6$H$_4$, 91% yield
3ab Ar = 3-MeC$_6$H$_4$, 95% yield
3ac Ar = 2-MeC$_6$H$_4$, 96% yield
3ad Ar = C$_6$H$_5$, 84% yield
3ae Ar = 4-FC$_6$H$_4$, 94% yield
3af Ar = 4-ClC$_6$H$_4$, 91% yield
3ag Ar = 4-BrC$_6$H$_4$, 88% yield
3ah Ar = 4-MeOC$_6$H$_4$, 79% yield
3ai Ar = 4-PhC$_6$H$_4$, 88% yield



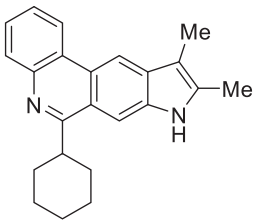
3aj 91% yield



3ak 69% yield



3al 81% yield



3am 32% yield

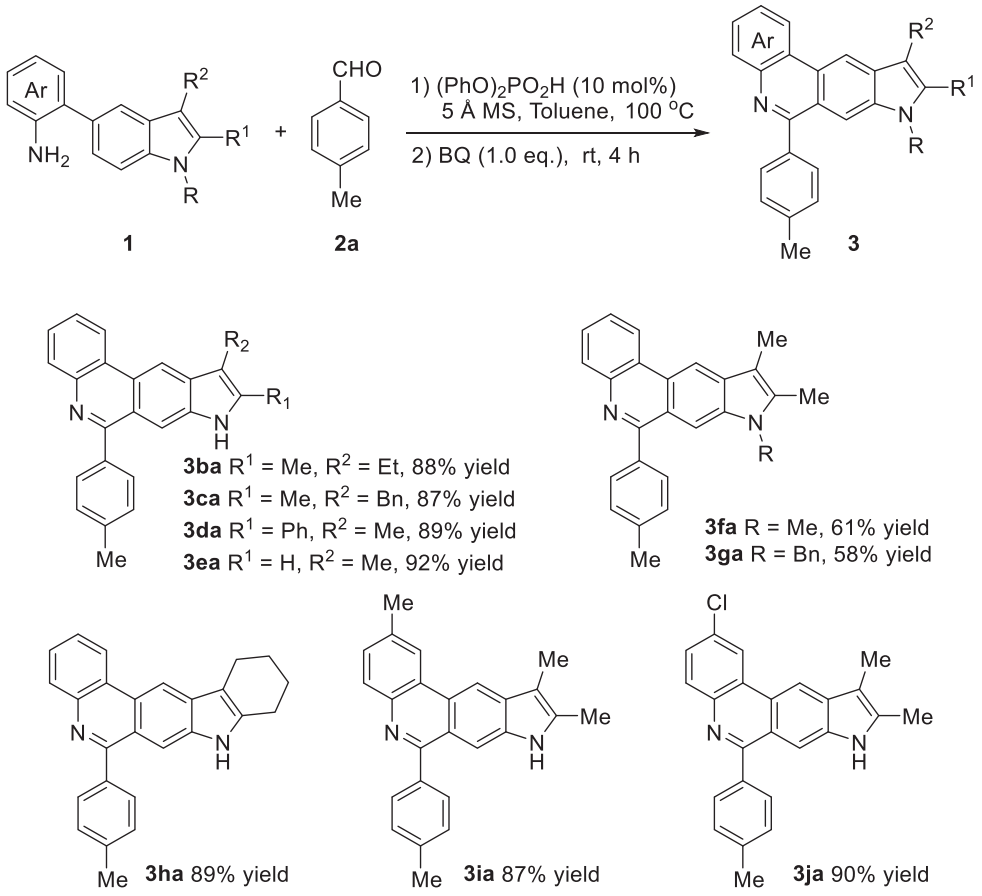
Reactions were carried with **1a** (0.24 mmol), **2** (0.20 mmol), (PhO)$_2$PO$_2$H (10 mol%), 5 Å MS (100 mg), toluene (2.0 mL), 100 °C. Then 1,4-benzoquinone (0.20 mmol) was added and reacted at room temperature for 4 h.

trispheridine showed anticancer properties [4], fagaridine exhibited antitumor properties [5] and ethidium bromide can be used as DNA intercalating agent and trypanocidal drugs [6] (Figure 1).

Due to the remarkable significance and a broad spectrum of biological activities of phenanthridine derivatives, their synthesis has been raised by great interests and numerous methodologies have been developed [7–15]. Pictet and Ankersmit firstly synthesized the phenanthridine by pyrolyzing the condensation product of benzaldehyde and aniline in 1889 [8]. Except for the classic Pictet–Hubert reaction [9], several efficient synthetic methods have also been exploited to obtain phenanthridine derivatives. The methods mainly include metal-mediated cascade reactions [10], oxidative cyclization of 2-isocyanobiaryls [11], photocatalytic radical addition cyclization reactions [12], *aza*-Wittig cyclizations [13], anionic ring closure reactions [14], microwave-mediated cyclizations [15] and so on [7,16]. Despite the considerable progress that has been achieved, these strategies are typically limited to specific substrates. Thus, the development of effective versatile methods for the preparation of phenanthridine derivatives remains a constant pursuit of organic chemists.

Indoles are privileged building blocks due to their remarkable significance in the natural world and biologically active molecules [17]. Indoles display versatile reaction positions. Therefore, the C–H functionalization of indoles has been efficient access for the construction of indole derivatives and gained tremendous attention [18]. Recently, the direct C6 functionalization of indoles has achieved progress and a series of protocols have been developed [19]. As our efforts in the exploring of C6 functionalization of indoles [19g], we expected to employ C6 functionalization of indoles in the synthesis of phenanthridine derivatives. Considering that amines could condense with aldehydes to provide imine using the acid catalyst and acid-catalyzed C6 functionalization of indoles with imine could take place, we envisioned designing and synthesizing 2-(1*H*-indol-5-yl)anilines, and utilizing them in the cascade reactions with aldehydes to prepare phenanthridine derivatives. Herein, we reported the synthesis of pyrrolo[2,3-*j*]phenanthridine derivatives via a cascade reaction of 2-(1*H*-indol-5-yl)anilines and aldehydes in the presence of Brønsted acid catalyst and benzoquinone oxidant, including acid-catalyzed condensation of indoleanilines with aldehydes, cyclization and oxidative aromatization (Scheme 1).

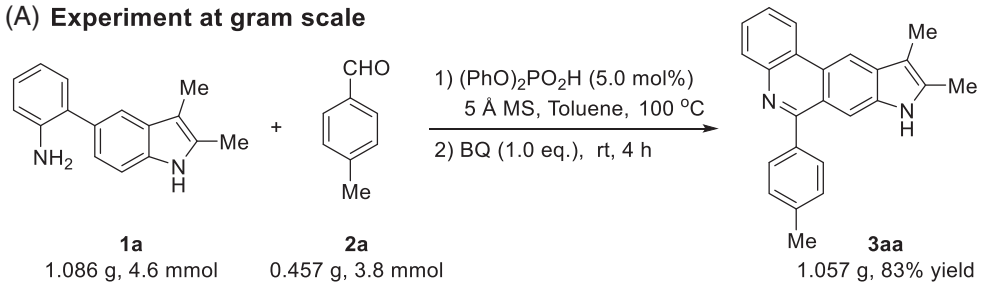
SCHEME 3 Substrate scope of 2-(1*H*-indol-5-yl)anilines



Reactions were carried with **1a** (0.24 mmol), **2a** (0.20 mmol), $(PhO)_2PO_2H$ (10 mol%), 5 Å MS (100 mg), toluene (2.0 mL), 100 °C. Then 1,4-benzoquinone (0.20 mmol) was added and reacted at room temperature for 4 h.

Initially, we synthesized 2-(1*H*-indol-5-yl)anilines through Suzuki cross-coupling from commercially available 5-bromoindoles and (2-aminophenyl) boronic acid or 2-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)anilines. Then, we started our studies using 2-(1*H*-indol-5-yl) aniline **1a** and *p*-tolualdehyde **2a** as model substrates, and the reaction was performed in toluene with *p*-toluenesulfonic acid as the catalyst at 60°C (Table 1, entry 1). It was exciting that we obtained the target product **3aa** in 18% yield and the undehydrogenated product **3aa′** in 42% yield. Encouraged by this result, we further optimized the reaction conditions. A series of catalysts were first examined (entries 1–5). It was observed that trifluoro-methanesulfonic acid and benzoic acid both slightly depressed the yield. Scandium trifluoromethanesulfonate was used as a catalyst, the yield of **3aa** was increased to 36%. When diphenyl phosphate was used as a catalyst, the yield of **3aa** was improved, and the yield of **3aa′** was reduced (entry 5). Different types of solvents were also screened, while the yield of **3aa** could not be further enhanced (entries 5–8), and no desired product was observed with tetrahydrofuran as the solvent. Therefore, toluene was the best solvent. Elevating the temperature to 100°C, the yield of **3aa** could be improved to 63% (entry 10). To further improve the reactivity, the ratio of indoleanilines **1a** and *p*-tolualdehyde **2a** was adjusted (entries 10–12). We found that the yields of **3aa** and **3aa′** were both improved when the amount of **1a** was increased (entry 12). Subsequently, the oxidants were examined. The yield of **3aa** was not significantly increased under the oxygen atmosphere (entry 13). Finally, 1,4-benzoquinone (BQ) was added to the reaction and served as an oxidant to realize the oxidative aromatization, giving the desired product **3aa** in 91% yield.

With the optimized conditions in hand, the substrate scope of aldehydes was explored. As shown in Scheme 2, in general, the cascade reaction of 2-(1*H*-indol-5-yl)aniline **1a** and aldehydes **2** performed smoothly. A series of aromatic aldehydes bearing a substituent at the *para*- (**2a**, **2e-i**), *meta*- (**2b**) or *ortho*- (**2c**) position were applicable, producing the corresponding phenanthridine derivatives in moderate to high yields. Notably, the substrates bearing electron-withdrawing or weak electron-donating substituents at the *para*-position proceeded well,



SCHEME 4 Gram scale experiment and synthetic transformations

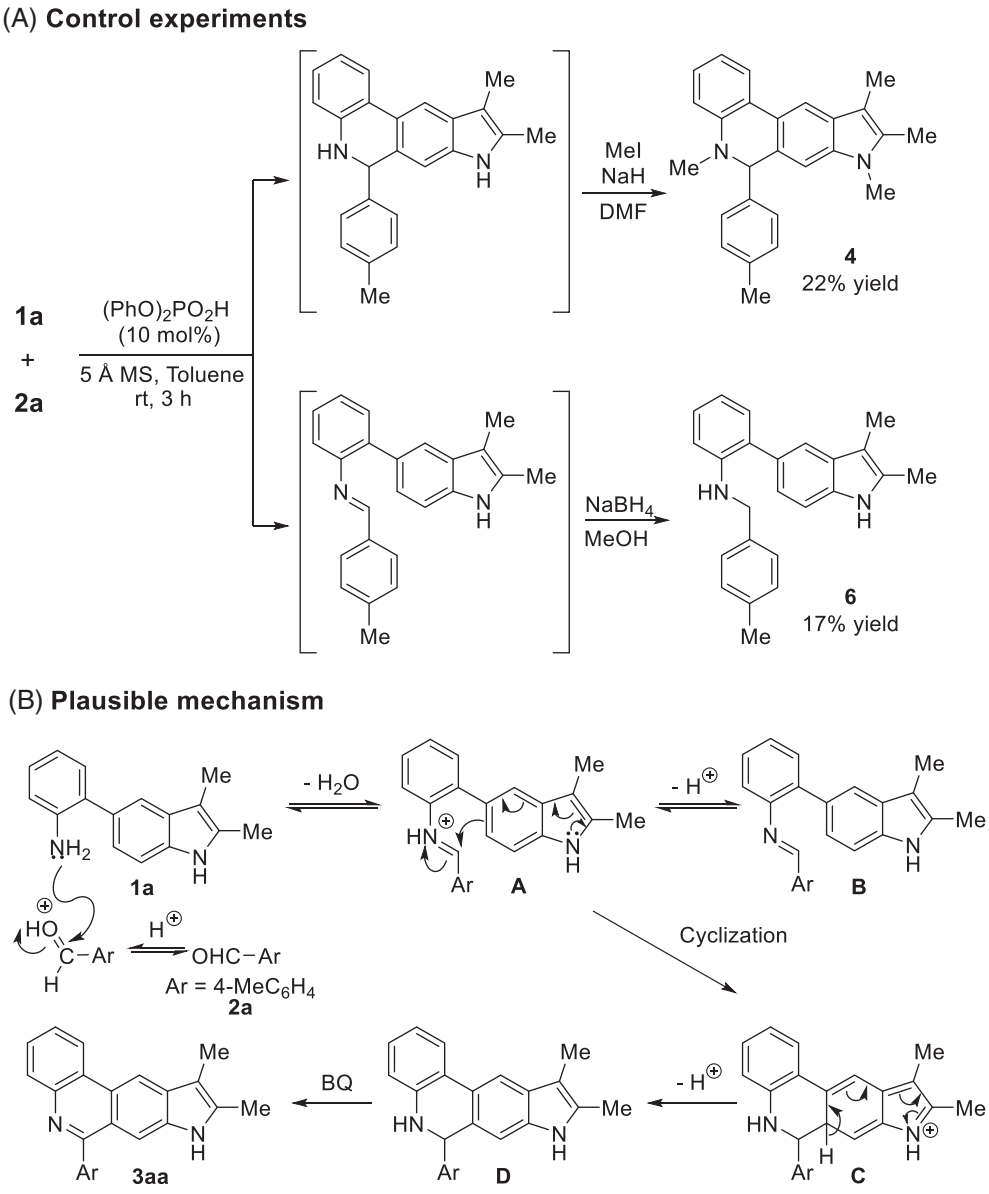
affording the desired products in good yields (**3aa**, **3ae**-**3ag**). For the substrates containing electron-donating groups involving methoxy (**2h**) and phenyl (**2i**), slightly diminished yields were obtained. Other aromatic aldehydes, such as 1-naphthaldehyde (**2j**), mesitaldehyde (**2k**) and heteroaromatic aldehyde (**2l**) could also be well tolerated for the reaction with moderate to high yields. For alkyl aldehydes, the reactivity decreased dramatically. Moderate 32% yield was achieved with cyclohexanecarboxaldehyde (**2m**), and the reaction shut down with formaldehyde.

Next, a series of 2-(1*H*-indol-5-yl)anilines **1** were tested (Scheme 3). A plethora of indole derivatives were suitable reaction partners, giving the desired products moderate to good yields. 3-Ethyl-substituted (**1b**), 3-benzyl-substituted (**1c**) and 2-phenyl-substituted indoles (**1d**) were applicable to the protocol with excellent yields. 2-Unsubstituted indole (**1e**) afforded the desired product in 92% yield. For *N*-protected indoles (**1e**, **1f**), moderate yields were achieved. Moreover, the ring-fused indole (**1g**) could also exhibit pleasing results with excellent yield. Indoles with an electron-donating group (**1h**) and electron-withdrawing group (**1i**) on the aniline ring of indole derivatives, conducted well with *p*-tolualdehyde, providing the products with elegant yields.

To demonstrate the potential synthetic application of this reaction, the gram scale experiment of **1a** (1.089 g) and **2a** (0.457 g) was conducted in the presence of a 5 mol% acid catalyst (Scheme 4A). The desired product **3aa** was obtained in 83% yield without the obvious loss of yield. To further illustrate the utility of this methodology, the transformations of phenanthridine derivative **3aa** were performed. Gratifyingly, the pyridine ring of **3aa** was reduced by tin powder and then protected with iodomethane to give *N*-protected product **4** in 78% yield (Scheme 4B). Additionally, the indole ring of **3aa** was successfully opened via Witkop oxidation using the oxone-halide system [20] to obtain the amide derivative **5** in 61% yield (Scheme 4C).

To shed some light on the mechanism of the reaction, the control experiments were carried out. The reaction of **1a** and **2a** was stirred in the presence of Brønsted acid catalyst at room temperature, followed by the protection of iodomethane. The *N*-protected dihydrophenanthridine product **4** was obtained in a 22% yield, indicating that dihydrophenanthridine derivative was the intermediate

SCHEME 5 Control experiments and plausible mechanisms



of this cascade reaction (Scheme 5A). The subjection of **1a** and **2a** to the acidic conditions, then reduction with sodium borohydride, secondary amine **6** was delivered in 17% yield, suggesting that this reaction involved the condensation of an aldehyde with an amine using acid catalyst to provide imine intermediate (Scheme 5A).

Based on the aforementioned experiments and previous reports [21], a plausible mechanism was proposed in Scheme 5B. Firstly, the carbonyl of **2a** was protonated. Then, the protonated carbonyl could serve as electrophile and was attacked by indoleaniline **1a**, subsequently, released one molecule of water to obtain the iminium ion **A**. The deprotonation of iminium ion **A** furnished imine intermediate **B**. Due to the nucleophilic activity of the C6 position of indoles, the cyclization reaction of iminium ion **A** occurred to generate cyclization intermediate **C**, followed by deprotonation to deliver dihydrophenanthridine derivative **D**. Finally, intermediate **D** was oxidized by 1,4-benzoquinone to afford the target pyrrolo[2,3-*j*] phenanthridine products **3aa**.

In conclusion, we have successfully developed a facile method for preparing pyrrolo[2,3-*j*]phenanthridine derivatives from indoleanilines and aldehydes with Brønsted acid catalyst and benzoquinone oxidant. The attractive advantages of this approach were easy operation, high efficiency, excellent yields and broad substrate scope. The mechanistic investigations suggested that this reaction was a cascade procedure involving acid-catalyzed condensation of indoleanilines and aldehydes, cyclization and oxidative aromatization. The establishment of this protocol provides convenient synthetic access for phenanthridine derivatives.

ACKNOWLEDGMENTS

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are openly available in the supplementary material of this short communication.

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