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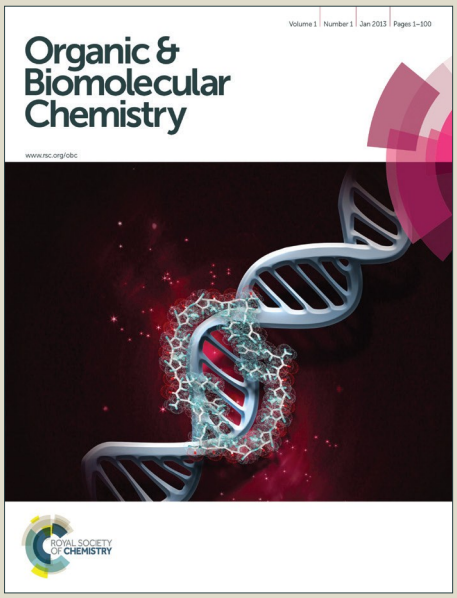

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An efficient iron-promoted synthesis of 6*H*-indolo[2,3-*b*]quinolines and neocryptolepine derivatives

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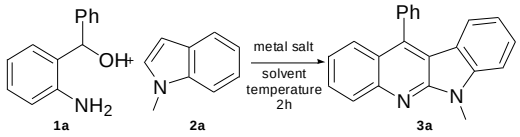
A facile and practical method for the preparation of 6*H*-indolo[2,3-*b*]quinolines and neocryptolepines was developed under the promotion of the easily available ferric trichloride, affording the desired products with moderate to good yields.

Indoloquinolines alkaloids are receiving considerable interest due to their striking biological activities.[1] For example, 6*H*-indolo[2,3-*b*]quinoline (norcryptotackieine) is a natural product isolated from the leaves of *Justicia betonica*[2] and shares many biological properties with 5-methyl-5*H*-indolo[2,3-*b*]quinoline.[3] The latter is isolated from *Cryptolepis sanguinolenta*[4-5] and usually used in traditional medicine against a variety of disorders.[6] 5*H*-indolo[2,3-*b*]quinolines and their analogues act as DNA topoisomerase II inhibitors.[7] Furthermore, these scaffolds witnessed the development of the design and synthesis for modern drugs.[8] Over the past decades, several synthetic methods were developed to prepare these polycyclic aromatic rings.[3] In 2011, for instance, Seidel group reported an extremely facile method for the synthesis of neocryptolepine derivatives.[9] Besides, other syntheses for the similar scaffolds were also developed and the neocryptolepines could be obtained easily by virtue of these scaffolds.[10] Subsequently, Parvatkar et al. also developed a microwave-assisted reductive cyclization to prepare 6*H*-indolo[2,3-*b*]quinoline alkaloids and the other two heterocyclic alkaloids in one step.[11] However, some of the synthetic routes were tedious, eco-unfriendly, or low atom efficiency. Therefore, developing more efficient and practical protocols for the preparation of indolo-fused quinolines is still highly desirable.

As an abundant, economical and environmentally benign element, iron has shown increasing promise in many organic syntheses.[12] Recently, iron catalyzed or mediated processes are still emerging and active.[13] In our group, great effort has been devoted to the Friedel-Crafts reaction,[14] iron catalysis,[15] and the synthesis of *N*-heterocyclic compounds.[16] Herein, we report a simple and efficient iron-mediated synthesis of indolo[2,3-*b*]quinolines and neocryptolepine derivatives.

Table 1. Optimization of reaction conditions [a]



Entry	Metal Salt	Solvent	Temp. (°C)	yield[b] (%)
1[c]	$FeCl_3$	DMA	80	16
2[d]	$FeCl_3$	DMA	80	37
3[e]	$FeCl_3$	DMA	80	47
4	$FeCl_3$	DMA	80	53
5	-	DMA	80	0
6	$FeCl_2$	DMA	80	0
7	$FeCl_3•6H_2O$	DMA	80	32
8	$Fe(ClO_4)_3•6H_2O$	DMA	80	Trace
9	$Cu(OAc)_2•H_2O$	DMA	80	0
10	$Fe_2(SO_4)_3$	DMA	80	Trace
11	$FeCl_3$	CH_3CN	80	23
12	$FeCl_3$	$ClCH_2CH_2Cl$	80	45
13	$FeCl_3$	DMF	80	49
14	$FeCl_3$	Toluene	80	Trace
15	$FeCl_3$	MeOH	80	83
16	$FeCl_3$	MeOH	65	58
17	$FeCl_3$	MeOH	r. t.	Trace
18	$FeCl_3$	MeOH	90	82

[a] Reaction conditions: **1a** (1.5 equiv, 0.3 mmol), **2a** (1.0 equiv, 0.2 mmol), metal salt (2.5 equiv) in solvent (0.5 mL). [b] Isolated yield. [c] 0.25 equiv of $FeCl_3$. [d] 1 equiv of $FeCl_3$. [e] 2.0 equiv of $FeCl_3$.

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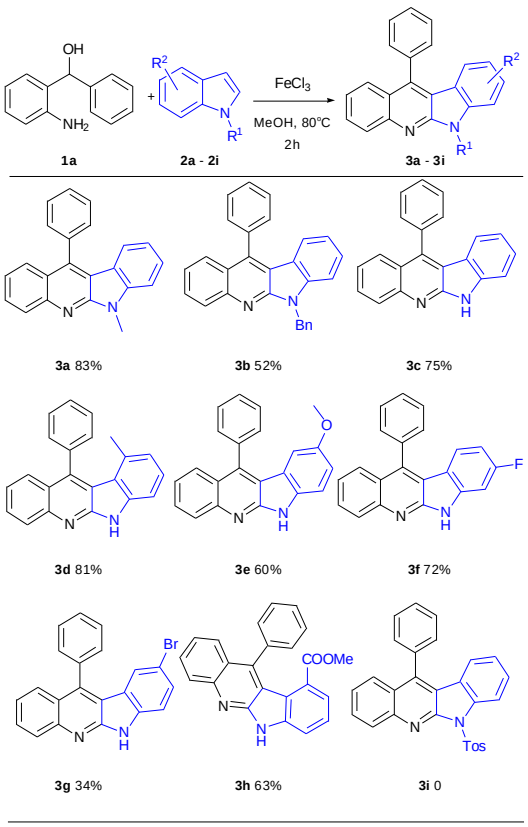
Table 2 The reaction of 2-amino-α-phenylbenzenemethanol with different indoles

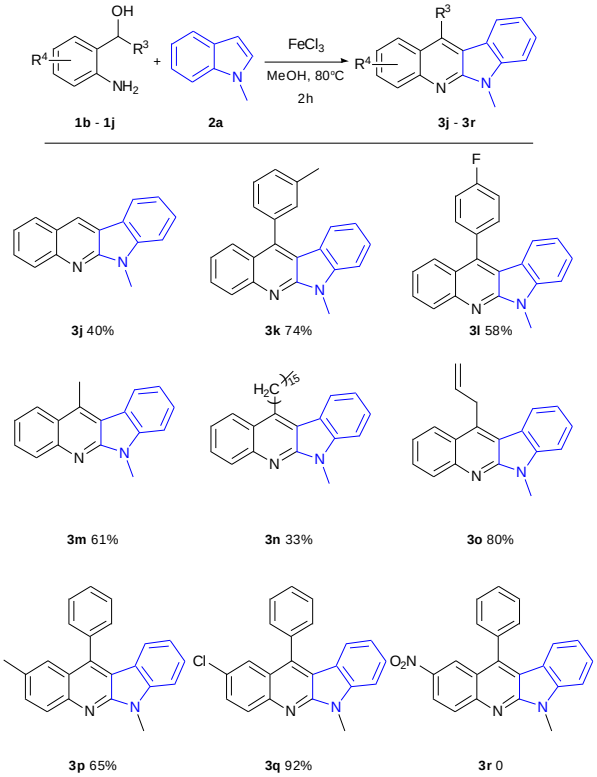


[a] Reaction conditions: **1a** (1.5 equiv, 0.3 mmol), **2** (1.0 equiv, 0.2 mmol), $FeCl_3$ (2.5 equiv) in methanol (0.5 mL).[b] Isolated yield.

At the outset of our investigations, 2-amino-α-phenylbenzenemethanol (**1a**) and 1-methylindole (**2a**) were chosen as model substrates to investigate the reaction. The results were summarized in Table 1. Firstly, the reaction of 1.5 equiv of **1a** and 1 equiv of **2a** offered 16% yield of the expected product 6-Methyl-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (**3a**) in the presence of 0.25 equiv $FeCl_3$ in DMA at 80 °C for 2 h (Table 1, entry 1). It was found that the loading of metal salt had an important influence on the reaction (Table 1, entries 2-4). When 2.5 equiv of $FeCl_3$ was added in the reaction, 53% yield of the product was obtained (Table 1, entry 4). When the metal salt was raplaced with $FeCl_2$ or absent, we could not get the desired products (Table 1, entry 5 and 6). It indicated that $FeCl_3$ played a role of oxidant in the process of reaction other than the function of catalysis. Then the different Lewis acids were screened, and we found that $FeCl_3$ was the best (Table 1, entries 7-10). Subsequently, different solvents were optimized. The result illustrated that methanol offered the product in 83% yield, while CH_3CN, DMF and $ClCH_2CH_2Cl$ provided relatively low yields (Table 1, entries 11-15). Thus methanol was the best solvent. On the other hand, the reaction temperature had a great influence on the reaction. With the decrease of the temperature, the reaction yield was reduced (Table 1, entry 16). When the reaction was carried out at room temperature, only trace amount of product was isolated (Table 1, entry 17). Nevertheless, when the reaction temperature was beyond 80°C, the reaction yield was slightly decreased (Table 1, entry 18). Therefore, the optimal reaction condition was selected as listed in entry 15.

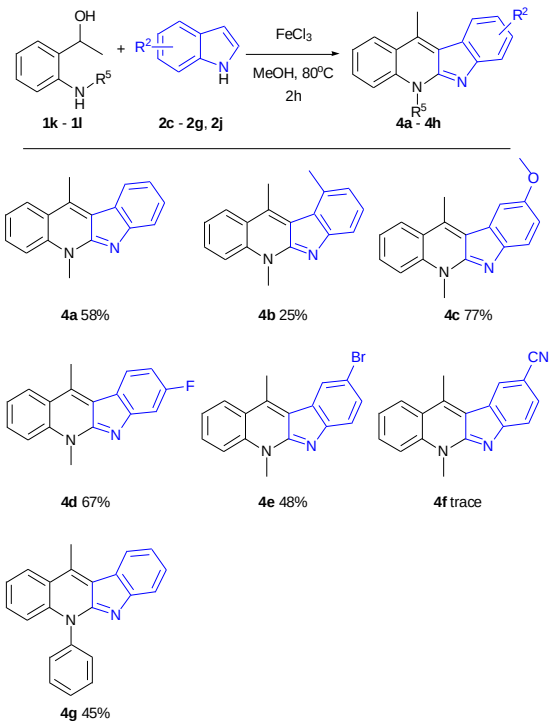
With the optimized conditions in hand, we explored the scope of different substrates. Firstly, several substituted indoles were examined, and the results were listed in Table 2. Generally, both *N*-substituted and *N*-unsubstituted indoles could be converted to the corresponding products in moderate to good yields (Table 2, **3a**-**3h**). The electron-withdrawing groups seemed to less efficient than the electron-donating groups in this reaction (Table 2, **3g**-**3h**). For example, 5-bromo-1*H*-indole could only afford the product with 34% yield (Table 2, **3g**) while 4-methyl-1*H*-indole could be a good substrate to give the product with a high yield of 81% (Table 2, **3d**). Moreover, no reaction was observed in the case of the 1-tosyl indole (Table 2, **3i**), perhaps due to the strong electron-withdrawing effect. Subsequently, the reactions of 1-methylindole with different (2-aminophenyl)methanol derivatives were also investigated (Table 3, **3j**-**3r**). Regardless of that R^3 was alkyl or aryl groups, the corresponding products could be obtained in moderate to good yields (Table 3, **3j**-**3q**). It was noticed that allyl group was tolerated in the reaction (Table 3, **3o**). As for the 2-aminobenzyl alcohol, which had no any substitution on the benzyl position of the 2-aminobenzyl alcohol, the corresponding reaction yield was decreased to 40%. It was possibly due to the lack of electron-rich substituent R^3 (Table 3, **3j**). And these different R^4 substituent groups implied that electron-rich substituent favored the reaction. No reaction occurred when the R^4 was nitro-group (Table 3, **3r**).

Table 3 The reaction of various (2-aminophenyl)methanol derivatives with 1-methylindole [a]



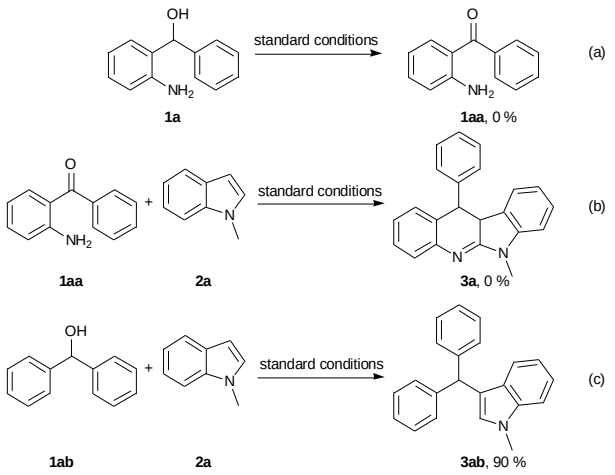
[a] Reaction conditions: **1** (1.5 equiv, 0.3 mmol), **2a** (1.0 equiv, 0.2 mmol), $FeCl_3$ (2.5 equiv) in methanol (0.5 mL). [b] Isolated yield.

Table 4 The synthesis of neocryptolepine derivatives [a]

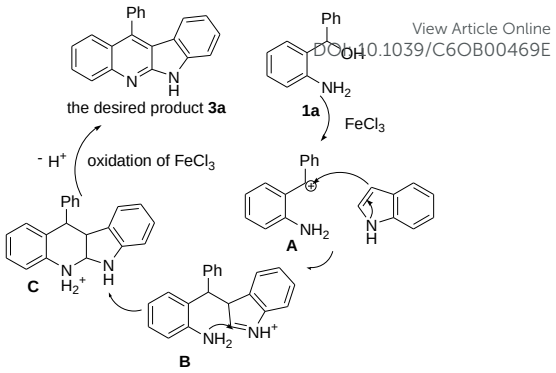


[a] Reaction conditions: **1** (1.5 equiv, 0.3 mmol), **2** (1.0 equiv, 0.2 mmol), $FeCl_3$ (2.5 equiv) in methanol (0.5 mL). [b] Isolated yield.

Knowing the importance of the neocryptolepines as biologically active molecules, α-methyl-2-(methylamino)-benzenemethanol was employed as the substrate to access the relevant product. To our delight, 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (11-methyl neocryptolepine, **4a**) and its derivatives can be obtained in one-step with moderate yields (Table 4, **4a** - **4e**). The yield was decreased a lot while there was a strong electron-withdrawing group (Table 4, **4f**). α-Phenyl-2-(methylamino)-benzenemethanol was also chosen as the substrates to access the relevant product in 45% yield (Table 4, **4g**). Although the yields needed to be optimized further, this provided a viable and facile access to neocryptolepine derivatives.



Scheme 1 Controlled experiments for mechanistic investigations



Scheme 2 Postulated reaction pathway for the construction of indolo[2,3-*b*]quinolines.

To get an insight into the mechanism of this process, several controlled experiments were conducted. First, only 2-amino-α-phenylbenzenemethanol (**1a**) was employed under the standard conditions, and no 2-aminobenzophenone (**1aa**) was detected (Scheme 1a). Subsequently, using 2-aminobenzophenone (**1aa**) and 1-methylindole (**2a**) as the reagent under the standard conditions had no reaction, suggesting that **1aa** might not be an intermediate in this reaction (Scheme 1b). Furthermore, 3-(1,1-Diphenylmethyl)-1-methyl-1*H*-indole (**3ab**) could be isolated from the reaction of diphenylmethanol (**1ab**) with **2a** in a 90% yield (Scheme 1c). This indicates that there may be a Friedel-Crafts progress during this reaction.

Based on the experimental results and previous literature[9, 15(a)], a possible reaction pathway is proposed as shown in Scheme 2. Firstly, $FeCl_3$ as a strong Lewis acid may activate 2-amino-α-phenylbenzenemethanol (**1a**) to generate intermediate **A**, which undergoes the Friedel-Crafts reaction to generate intermediate **B**. Then intramolecular cyclization is proceeded to yield intermediate **C,** **C** subsequently undergoes a deprotonation and oxidation by $FeCl_3$ to give the desired product **3a**[17].

In summary, an efficient and simple protocol for the synthesis of indolo[2,3-*b*]quinolines and neocryptolepines by reactions of aminophenyl alcohols and indoles was described under the promotion of iron trichloride. This procedure features mild reaction conditions, operational simplicity, and environmentally friendly reagent. Moreover, 11-methyl neocryptolepine and its derivatives were synthesized through this procedure. Further applications and detailed mechanism of this reaction are in progress in our laboratory.

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