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Three-Component Ring-Expansion Reaction of Indoles Leading to Synthesis of Pyrrolo[2,3-*c*]quinolines

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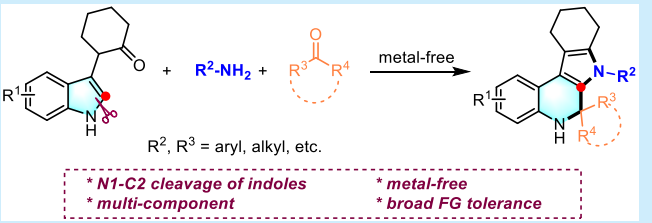
ABSTRACT: Herein, we have developed an atom- and step-economic three-component cascade reaction that enables a modular platform for the synthesis of pyrrolo[2,3-*c*]quinoline compounds through ring-expansion/cyclization by way of novel N1−C2 cleavage of indoles. The metal-free catalytic system exhibits a broad functional group tolerance.



Indoles are among the most widespread nitrogen-containing heterocycles in medicinal chemistry and natural products, thus representing an ideal substrate class for the construction of diverse and complex heterocycles and attracting extensive research interest.[1] In recent decades, the C−H/N−H functionalization and dearomatization of indole have proven to be quite fruitful.[2] Nevertheless, the methodology of building heterocycles through the ring expansion of the indole heteroaromatic core is rarely reported, which could in part be attributed to the fact that the indole ring is unstrained cyclic precursors. Recently, tremendous efforts have been devoted to the ring expansion of indole, which provides new synthetic methods for the rapid preparation of important heterocycles. Among the established protocols, ring-expanding reactions of indole through C2−C3 bond cleavage and reconstruction have played an important role in the construction of complex molecules and the synthesis of drug molecules.[3] Using this strategy, quinolines,[4] benzoxazines,[5] quinazolinones,[6] benzo[*b*]azepines,[7] and benztriazolines[8] have been successfully synthesized (Figure 1a). Very Recently, Morandi et al. developed a strategy for the insertion of a nitrogen atom into indoles affording the quinazolines, which achieved the late-stage modification of drug molecules with indole core structure.[9] However, to the best of our knowledge, there are only a few examples of indole ring expansion reactions via a N1−C2 bond cleavage.[10] In 2022, Shang et al. reported a novel Pd(II)-catalyzed ring expansion reaction of indole, proceeding through nucleophilic addition/N1−C2 cleavage/regioselective cyclization cascade, for the rapid assembly of seven-membered azaheterocycle (Figure 1b).[11] Therefore, it is conceivable that the ring expansion of indole via N1−C2 bond cleavage would develop a new synthetic method of structurally unique N-heterocycles, which will be substantially instructive for the reactivity discovery of indole compounds.

Pyrrolo[2,3-*c*]quinolines represent an important class of *N*-heterocycles and exhibit valuable bioactivities.[12] Particularly, marinoquinolines A-F, aplidiopsamine A, and trigonoine B have been demonstrated to possess potent antiplasmodial, antiproliferative, antibacterial, antifungal, phosphodiesterase, and AChE inhibitory activity (Figure 1c).[13] Therefore, the efficient synthesis of the privileged structure has attracted considerable attention. Nowadays, the synthesis methods of pyrrolo[2,3-*c*]quinolines have been widely reported, among which multistep processes from highly functionalized precursors were the primary strategy.[14] These reactions mainly involve the indole Fischer reaction, the Hemetsberger−Knittel cyclization, the Bartoli indolization, the Diels−Alder reactions, the Heck reactions, the Pd-catalyzed cross-coupling reactions, and the Brønsted acid-promoted arene-ynamide cyclization. Although numerous synthetic strategies have been developed to build such appealing tricyclic skeletons, one-step procedures are still limited.[15] Within our ongoing program on the construction of nitrogen-containing heterocycles,[16] herein, we report a concise synthesis of pyrrolo[2,3-*c*]quinoline compounds through ring-expansion/cyclization in the manner of novel N1−C2 cleavage of indoles (Figure 1d). The present protocol has significant advantages, including metal-free conditions, multicomponent assembly with high atom economy, and excellent functional group (FG) tolerance.

Initially, we utilized 2-(1H-indol-3-yl)cyclohexanone (**1a**), aniline (**2a**), and cyclohexanone (**3a**) as model substrates to

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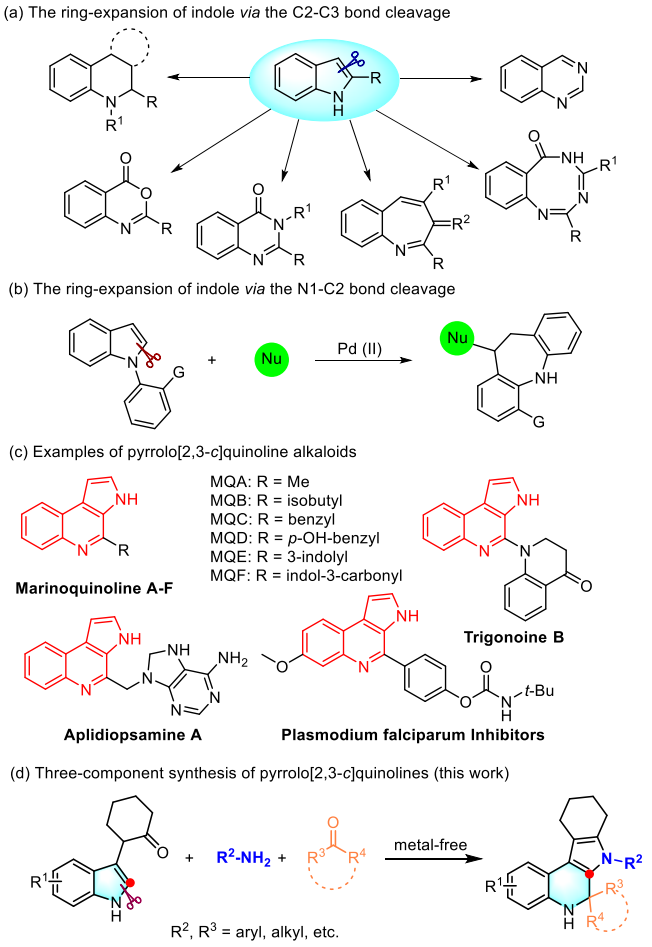
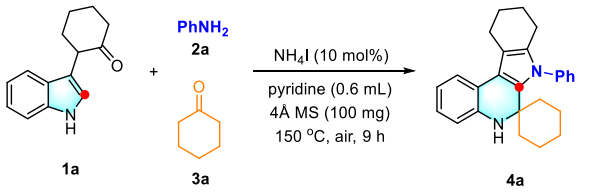


Figure 1. Ring-expansion reaction of indoles and examples of pyrrolo[2,3-*c*]quinoline alkaloids.

identify the optimal conditions for this three-component ring-expanding reaction. Upon extensive studies of the reaction conditions, a combination of NH_4I (10 mol %), 4 Å MS (100 mg), and pyridine (0.6 mL) solvent generated the desired 4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline product **4a** in 90% yield (Table 1, entry 1). The three-component assembly could be carried out in only 17% yield without catalyst (entry 2). Different iodine catalysts, such as elemental iodine, KI, and TBAI, were used instead of NH_4I. However, these alternatives resulted in lower efficiency with yields ranging from 45% to 74% (entry 3). Similarly, replacing the optimal catalyst with NH_4Br and NH_4OAc also led to decreased yields of 73% and 59%, respectively (entry 4). Moreover, reducing or increasing the amount of catalyst slightly decreased the yield (entries 5 and 6). When PhCl or DMF was used as the solvent, only trace amounts of **4a** were obtained (entry 7). Notably, removing the molecular sieves from the system resulted in a significant decrease in yield (entry 8), while lowering the reaction temperature to 140 °C reduced the yield to 76% (entry 9). Finally, control experiments showed that the reaction atmosphere did not affect the reaction (entry 10), indicating an oxidant-free aromatization process in the formation of **4a**.

Using the highly efficient NH_4I/pyridine system, the substrate scope was investigated for the novel generation of pyrrolo[2,3-*c*]quinolines via indole ring expansion reaction. It was discovered that the NH_4I-catalytic system can tolerate various types of amines (Figure 2a). The corresponding

Table 1. Screening Reaction Conditions[a]



entry	variation from standard conditions	yield (%)
1	none	90
2	without NH_4I	17
3	I_2, KI, TBAI instead of NH_4I	45, 74, 58
4	NH_4Br, NH_4OAc instead of NH_4I	73, 59
5	NH_4I (5 mol %)	72
6	NH_4I (20 mol %)	85
7	PhCl, DMF as solvent	trace
8	without 4 Å MS	57
9	140 °C instead of 150 °C	76
10	O_2, Ar instead of air	90, 88

[a]Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), NH_4I (0.02 mmol), pyridine (0.6 mL), 4 Å MS (100 mg), 150 °C, 9 h, the isolated yield is based on **1a**.

pyrrolo[2,3-*c*]quinolines were generated in moderate to good yields (**4a**–**4s**, 35%–90% yield), even when using substituted anilines containing halogen groups (**4g**–**4i**, **4l**), bulky disubstituents (**4o**–**4q**), and trisubstituents (**4r**). Notably, in the gram-scale reaction, the product **4a** was afforded in 83% yield. Furthermore, diamines with an *N*-phenyl and piperidine moiety also worked smoothly, leading to the formation of amino products (**4k** and **4s**). One free amino group could remain when benzene-1,4-diamine (**4w**, 52% yield) and naphthalene-1,5-diamine (**4x**, 72% yield) were employed even with excess **1a** and **3a**. The current system was also found to accommodate polycyclic aromatic amines that contained naphthyl and benzothiazolyl moieties (**4t**–**4v**, 44%–65% yield). Additionally, benzylamines and 2-phenylethanamines were discovered to be productive to a satisfactory extent (**4y**–**4ad**, **4af**–**4ai**, 57%–91% yield). 2-Thiophenemethylamine and tryptamine gave the target pyrrolo[2,3-*c*]quinoline products **4ae** and **4aj** in 51% and 58% yields, respectively. Other aliphatic amines, including branched and linear amines, generated the ring expansion products in moderate to excellent yields (**4ak**–**4aq**, 32%–84% yield). It is worth mentioning that the presence of a hydroxyl group did not impact the yield of the resulting pyrrolo[2,3-*c*]quinoline product (**4ar**, 73% yield) for the hydroxy-containing amine reactant. Besides, other anilines attached with a range of bioactive molecules, including Ketoprofen (**4as**), Loxoprofen (**4at**), and Naproxen (**4au**), were all tolerated to furnish the desired pyrrolo[2,3-*c*]quinoline products.

Subsequently, the substrate scope, with respect to the ketone component, was probed (Figure 2b). First, a number of substituted cyclohexanone derivatives were employed for this system, and the corresponding products were afforded in moderate to good yields (**5a**–**5m**). The ester groups were well tolerated to give the corresponding products in good yields (**5h** and **5i**). Besides cyclohexanones, other cyclic ketones such as cycloheptanone also successfully participated in the reaction (**5n**, 36% yield). 6,7-Dihydro-4-benzo[*b*]thiophenone and 2-indanone showed very low reactivity (**5o** and **5p**, 19% and 17% yield, respectively), which may be attributed to the increase of

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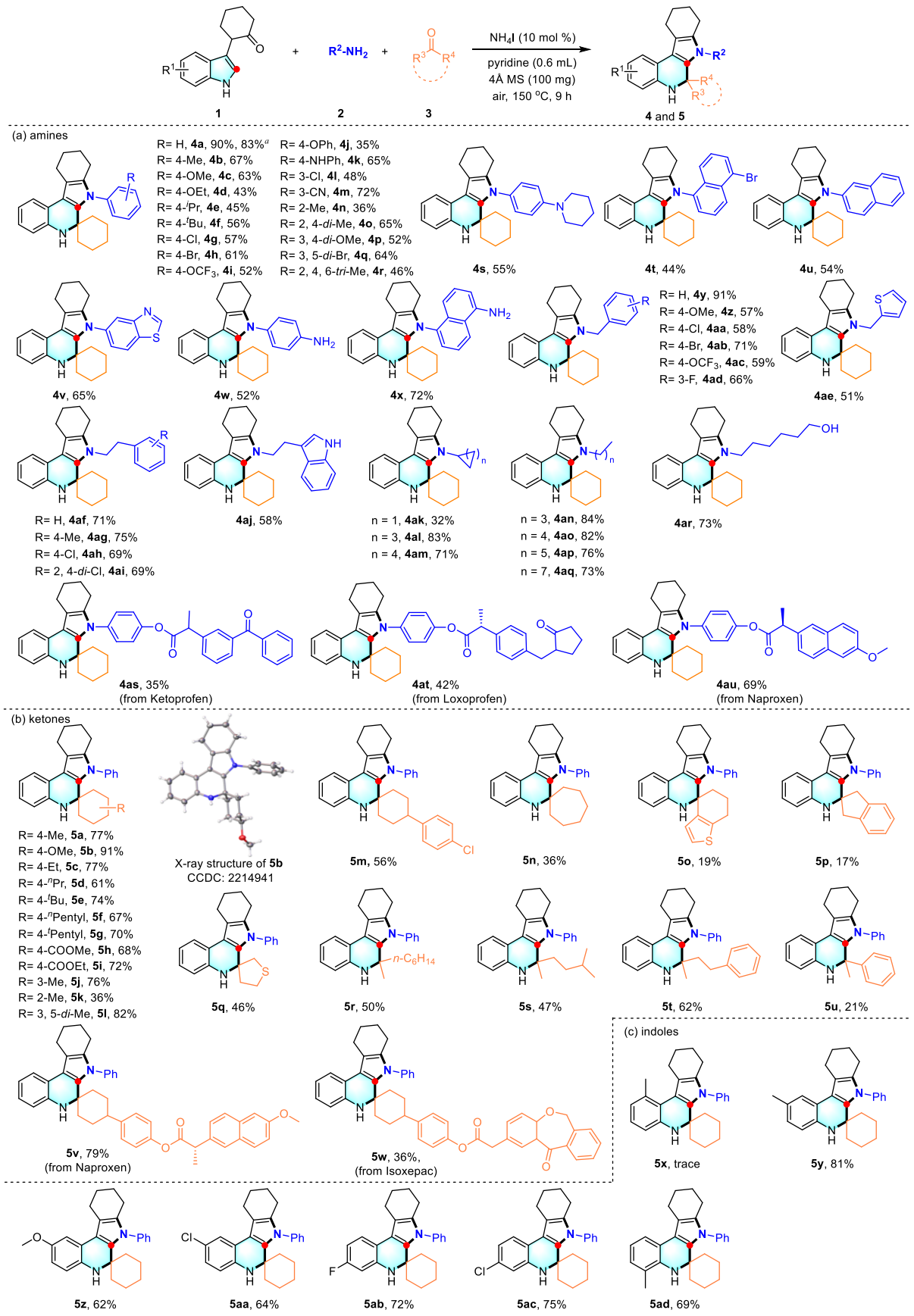

Figure 2. Substrate scope. (ᵃYield of 3 mmol-scale reaction.)

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steric hindrance and ring rigidity caused by aromatic rings. Notably, a heterocyclic ketone like tetrahydrothiophen-3-one also could smoothly react with **1a** and aniline to give the pyrrolo[2,3-*c*]quinoline **5q** in 46% yield. 2-Octanone, 5-methylhexan-2-one, and benzylacetone as acyclic aliphatic ketones were compatible as well (**5r**−**5t**). Surprisingly, acetophenone, the simplest aromatic ketone, was smoothly enabled to generate the heterocycle product **5u**, albeit in a lower yield (21%), whereas benzophenone did not work in the current system. To illustrate the method's potential in pharmaceutical chemistry, cyclohexanones attached with commercially available drug molecules were also employed as substrates (**5v** and **5w**). The low yields of some products may be attributed to the easy decomposition of substrates in pyridine at high temperature.

Finally, indolylcyclohexanones bearing functional groups at the indole moiety were utilized (Figure 2c). It was observed that the C4 methyl substrate demonstrated extremely low reactivity, possibly due to steric hindrance effects (**5x**). To our delight, the reactants with C5−C7 substituents were effective compounds under the current system (**5y**−**5ad**, 62%−81% yield). For example, C5 methyl substrate **1y** reacted successfully to provide pyrrolo[2,3-*c*]quinoline **5y** in 81% yield. We also tried some other ketone-attached indole substrates, such as 2-(1H-indol-3-yl)cyclopentan-1-one and 3-(1H-indol-3-yl)butan-2-one. Unfortunately, no target products were detected when these indole substrates were used as raw materials under the optimized conditions.

Based on previous works and related literature,[11,17] we propose a plausible mechanistic reaction pathway to account for the product formation (Figure 3). The initial step involves

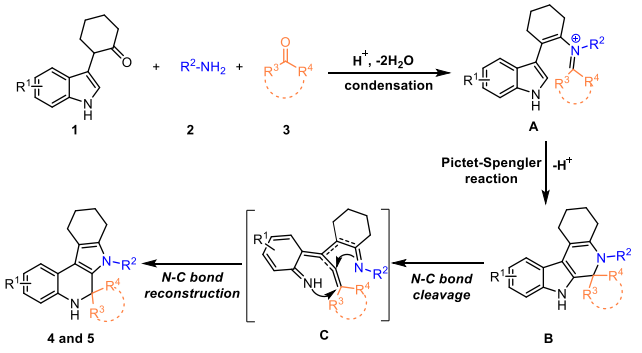

Figure 3. Possible mechanistic reaction pathway.

a condensation of 2-(1*H*-indol-3-yl)cyclohexanones (**1**) with amines (**2**) and ketones (**3**) to generate an imine intermediate **A**, which undergoes a Pictet−Spengler cyclization to form intermediate **B**. Then, intermediate **B** suffers an N1−C2 bond cleavage of indoles with further reconstruction to produce the desired products.

In summary, we developed a novel ring expansion reaction of indoles with amines and ketones. The facile procedure provides an uncomplicated and flexible approach to pyrrolo-[2,3-*c*]quinoline derivatives, commonly known as Marinoquinoline analogues. The NH_4I-based catalytic system exhibited remarkable efficiency in this indole ring expansion reaction and significant tolerance toward various functional groups. This protocol presents a practical approach and informative mechanistic for the synthesis of pyrrolo[2,3-*c*]quinoline through a novel N1−C2 cleavage of indoles.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02581.

Experimental procedures, characterization data, computational details, and ^{1}H NMR and ^{13}C NMR spectra for all products (PDF)

Accession Codes

CCDC 2214941 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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