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Synthesis of Cyclohepta[*b*]indoles and Furo[3,4-*b*]carbazoles from Indoles, Tertiary Propargylic Alcohols, and Activated Alkynes

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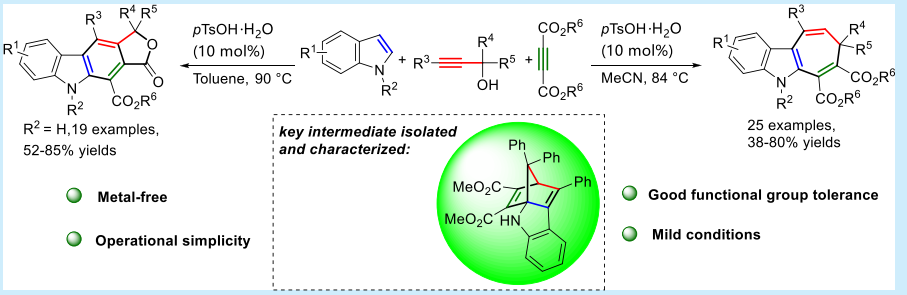
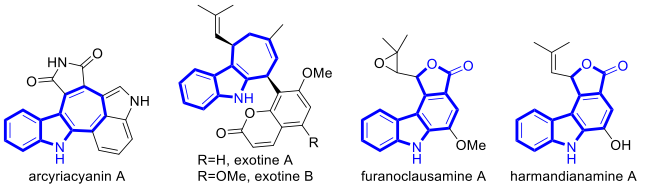


ABSTRACT: A robust metal-free and environmentally friendly approach to cyclohepta[*b*]indole and furo[3,4-*b*]carbazole frameworks via a three-component reaction from indoles, tertiary propargylic alcohols, and activated alkynes is described. A probable mechanism was proposed on the basis of the isolation and characterization of a key intermediate of the reaction. A gram-scale reaction and product derivatizations were also performed to demonstrate the practicality of the developed methodology.

Cyclohepta[*b*]indole structural motifs are abundant in natural products with various biologically activities.[1] For example, arcyriacyanin A, a cytotoxic compound that inhibits protein kinase C and protein tyrosine kinase, was isolated from *Arcyria nutans*.[2] Exotines A and B, exhibiting inhibitory effects on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in BV-2 microglial cells, were isolated from the roots of *Murraya exotica* (Scheme 1).[3] Furocarbazoles, a significant class of tetracyclic compounds among the numerous carbazole derivatives, exist in a variety of naturally occurring compounds and exhibit a rather impressive range of biological activities.[4] The first furocarbazoles were furostifoline and eustifoline D, isolated from the root bark of *Murraya euchrestifolia*.[5] Since then, more furocarbazole alkaloids have been isolated, such as furanoclausamine A[6] and antibacterial harmandianamine A[7] (Scheme 1). The wide range of applications makes these frameworks an attractive synthetic target, and many efforts have been devoted to their construction.[8]

Scheme 1. Naturally Occurring Cyclohepta[*b*]indole and Furo[3,4-*b*]carbazole Alkaloids



Constructing cyclohepta[*b*]indoles by means of Fischer indole synthesis is very common. Despite being a well-established transformation, this reaction possesses certain limitations.[9] This has triggered the invention of novel methodologies, which involve pericyclic reactions from indoles. Notably, most synthetic strategies for the construction of cyclohepta[*b*]indoles from indoles required substrates pre-functionalized on either the C2 or C3 position.[10] Until now, only a few examples for the synthesis of cyclohepta[*b*]indoles from 2,3-unsubstituted indoles have been reported. In 2009, a Brønsted-acid-catalyzed tandem double Friedel−Crafts reaction to synthesize cyclohepta[*b*]indoles using indoles and non-symmetrical divinyl ketones was developed by Carbery's group (Scheme 2a).[11] In 2011, a chiral thioamide- and gold(I)-catalyzed enantioselective synthesis of tetracyclic cyclohepta-[*b*]indoles via a sequential double Friedel−Crafts-type reaction of indoles and *ortho*-alkyne-substituted nitrostyrenes was developed by Enders' group (Scheme 2a).[12] In 2018, a ruthenium-catalyzed cascade annulation of indoles with propargyl alcohols for the construction of cyclohepta[*b*]indoles was reported by Haak's group (Scheme 2a).[13] In addition, gallium(III)-catalyzed three-component (4 + 3) cycloaddition

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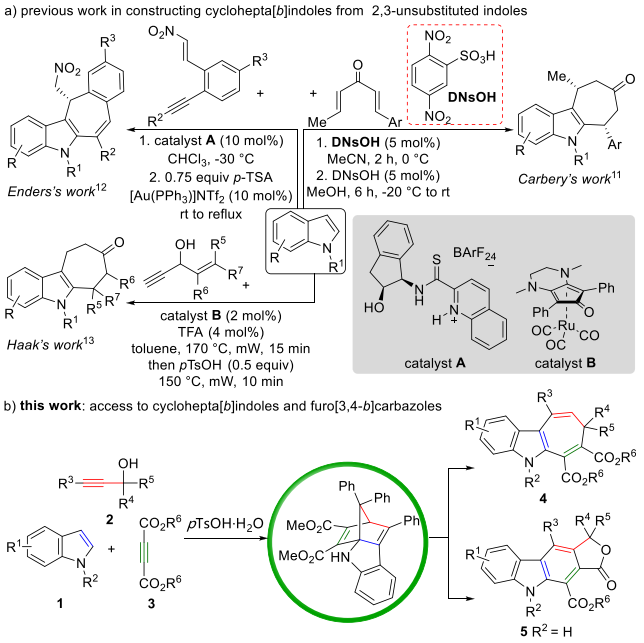
Scheme 2. Strategies for the Construction of Cyclohepta[*b*]indole Scaffolds

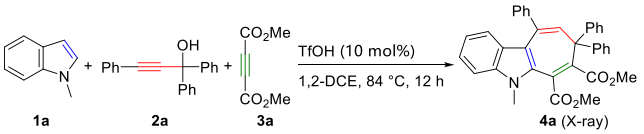


reactions[9b] and two gold(I)-catalyzed cascade reactions of indoles with skipped diynes (1,4-diynes)[14] and 1,6-conjugate addition of indoles with 2-alkynyl *p*-quinone methides[15] to afford this framework were also documented. However, current methods suffer from a limited substrate scope, complicated catalyst or noble metal catalyst systems, not easily accessible starting materials, and/or multi-step manipulations. Thus, the development of simple methods with wide product diversity is still highly desirable.

As part of our continuing efforts on heterocycle formation using readily available starting materials (propargylic alcohols) under mild conditions,[16] herein, we describe a general three-component approach to cyclohepta[*b*]indoles and furo[3,4-*b*]carbazoles from indoles, tertiary propargylic alcohols, and activated alkynes under mild metal-free conditions without the use of any expensive reagents (Scheme 2b).

Our initial studies commenced with the reaction of *N*-methylindole **1a**, propargylic alcohol **2a**, and dimethyl acetylenedicarboxylate (DMAD) **3a** in 1,2-dichloroethane (1,2-DCE) in the presence of trifluoromethanesulfonic acid (TfOH) at 84 °C for 12 h (Scheme 3). To our delight, product

Scheme 3. Formation of Cyclohepta[*b*]indole 4a

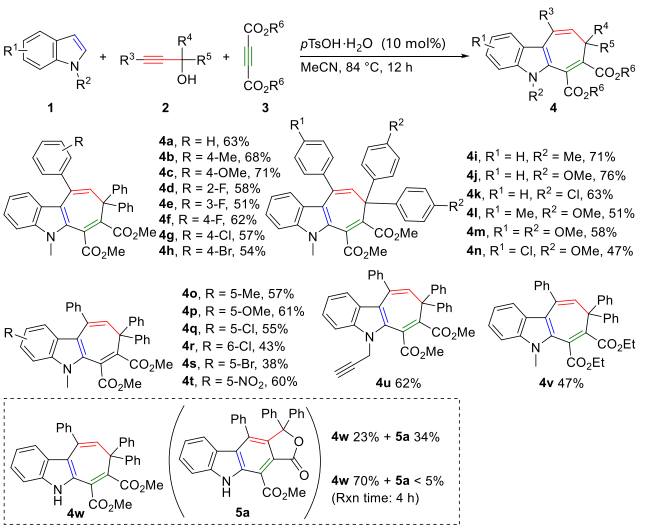


4a was isolated in 53% yield, and its structure was additionally confirmed by X-ray crystallographic analysis (for details, see the Supporting Information).

To improve the efficiency, different Lewis acid and Brønsted acid catalysts and solvents were screened (Table S1 of the Supporting Information). It turned out that *p*TsOH·H_2O was the most efficient catalyst, and MeCN was the best reaction medium for the formation of product **4a** (entry 13 in Table S1 of the Supporting Information).

With the optimized reaction conditions in hand, a series of propargylic alcohols **2** were reacted with *N*-methylindole **1a** and dimethyl acetylenedicarboxylate **3a** to examine the reaction scope with regard to the formation of cyclohepta[*b*]-indole **4**, and the related outcomes are summarized in Scheme 4. A variety of functional groups, including methoxy and

Scheme 4. Scope for the Synthesis of Cyclohepta[*b*]indole Derivatives 4[a,b]



[a]Reaction conditions: compound **1** (0.5 mmol, 1.0 equiv), compound **2** (0.5 mmol, 1.0 equiv), compound **3** (0.5 mmol, 1.0 equiv), *p*TsOH·H_2O (0.05 mmol), MeCN (5 mL), 84 °C, and 12 h. [b]The isolated yield refers to cyclohepta[*b*]indole.

halogen substituents, were found to be compatible with the optimized reaction conditions. In general, propargylic alcohols **2** bearing electron-donating substituents (**4b**, **4c**, **4i**, **4j**, **4l**, and **4m**; Scheme 4) on the R^3 group or the R^4 and R^5 groups provided higher yields than those with electron-withdrawing substituents (**4d**–**4h**, **4k**, and **4n**). Such a phenomenon suggests the intermediacy of carbocation species in this reaction. However, alkyl groups (R^1), such as methyl, *n*-butyl, trimethylsilyl, and cyclopropyl, were incompatible with the optimized conditions, which is a limitation of the current reaction system. In addition, the primary alcohol 3-phenylprop-2-yn-1-ol and the secondary propargylic alcohol 1,3-diphenylprop-2-yn-1-ol were tested, respectively, under the same reaction conditions for 24 h, but no desired products were detected, while a complex mixture of unidentified products was observed.

Subsequently, different substituted indoles were tested to examine the reaction scope with regard to the formation of cyclohepta[*b*]indole **4**. In general, desired products were obtainable regardless of the changes of the substituents on the benzene ring (R^1) or nitrogen atom (R^2) of the examined indoles (**4o**–**4t**). Moreover, *N*-propargyl indole and diethyl acetylenedicarboxylate were also suitable substrates for the reaction (**4u** and **4v**). However, other substrates, such as *N*-allylindole, *N*-benzylindole, methyl propiolate, methyl phenylpropiolate, and acetylenedicarboxylic acid, were incompatible with the optimized conditions. Notably, when *N*-unsubstituted indole **1b** was subjected to the reaction conditions, unexpected

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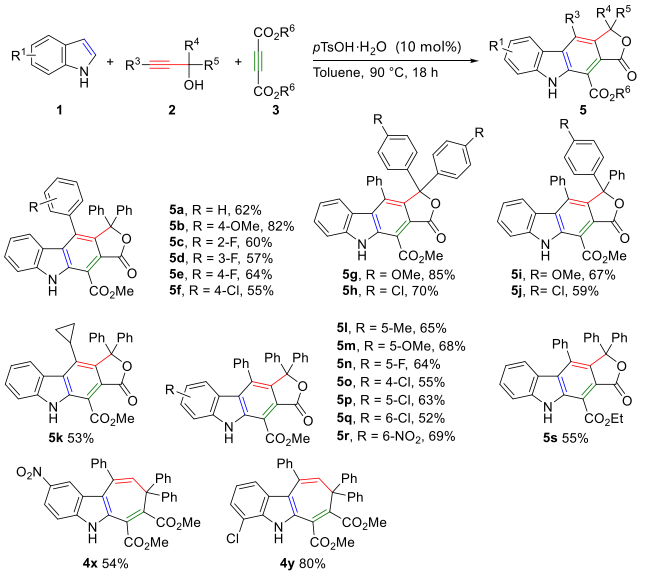
byproduct furo[3,4-*b*]carbazole **5a** was isolated in a 34% yield, besides the desired product **4w** in a 23% yield, and the yield of product **4w** could be improved to 70% with reduced formation of product **5a** when the reaction was shortened to 4 h. The structures of the products **4w** and **5a** were additionally confirmed by X-ray crystallographic analysis (for details, see the Supporting Information).

Considering the importance of the furo[3,4-*b*]carbazole structure of product **5a**, we undertook an extensive study on the selective formation of such a structure by tuning the reaction parameters in the model reaction of indole **1b**, propargylic alcohol **2a**, and dimethyl acetylenedicarboxylate **3a** (Table S2 of the Supporting Information). It is found that the reaction performed in toluene could exclusively provide the desired furo[3,4-*b*]carbazole **5a** in the yield of 62% (entry 11 in Table S2 of the Supporting Information), indicating that the reaction medium played a crucial role in the product selectivity process.

With the optimal reaction conditions being established, we then tested the substrate scope for the synthesis of furo[3,4-*b*]carbazole **5** (Scheme 5). Propargylic alcohols bearing

Scheme 5. Scope for the Synthesis of Furo[3,4-*b*]carbazole Derivatives 4[a,b]

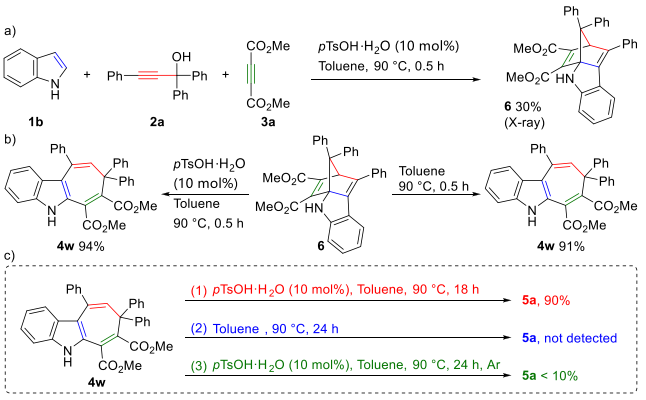


[a]Reaction conditions: compound **1b** (0.5 mmol, 1.0 equiv), compound **2** (0.5 mmol, 1.0 equiv), compound **3** (0.5 mmol, 1.0 equiv), *p*TsOH·H_2O (0.05 mmol), toluene (5 mL), 90 °C, and 18 h. [b]Isolated yields were reported.

electron-donating substituents (**5b**, **5g**, and **5i**) provided higher yields than those with electron-withdrawing substituents (**5c**−**5f**, **5h**, and **5j**). Particularly, corresponding products (**5c**−**5e**) could be obtained in comparable yields, irrespective of the positions of the F substituent on the benzene ring (R^3). Notably, the cyclopropyl group has a wide range of applications in drug molecular design,[17] and the propargylic alcohol bearing a cyclopropyl group was tolerated in the reaction to generate the desired product **5k** in 53% yield. However, other alkyl groups (R^1), such as methyl, *n*-butyl, and trimethylsilyl, were incompatible with the optimized conditions. Furthermore, desired products were obtainable, despite the changes in the substituents and substituent positions on the benzene ring (R^1) of the examined indoles (**5l**−**5r**). Diethyl acetylenedicarboxylate was also suitable for the reaction. It was noteworthy that the reactions with 5-nitroindole and 7-chloroindole culminated in the formation of cyclohepta[*b*]indoles (**4x** and **4y**), which were hardly converted to furo[3,4-*b*]carbazoles.

To gain some insight into the mechanism of this cascade sequence, some control experiments were conducted. Terminating the reaction of compounds **1b**, **2a**, and **3a** under the standard reaction conditions at an early stage (0.5 h) gave the compound **6** in 30% yield (Scheme 6a). Intermediate **6** could

Scheme 6. Controlled Experiments



be transformed into product **4w** in 94% yield after 0.5 h (Scheme 6b) and also generated product **4w** in 91% yield without *p*TsOH·H_2O, suggesting that compound **6** was a key intermediate in the transformation and *p*TsOH·H_2O was not indispensable for the conversion of compound **6** to product **4w**. Furthermore, product **4w** could be transformed into furo[3,4-*b*]carbazole **5a** in 90% yield under the standard reaction conditions (reaction 1 in Scheme 6c); however, product **5a** was not detected, and the staring material was recovered in 90% yield without *p*TsOH·H_2O (reaction 2 in Scheme 6c), indicating that *p*TsOH·H_2O was necessary for the conversion of compound **4w** to product **5a**. Note that product **5a** was obtained in less than a 10% yield and the staring material was recovered in a 82% yield under an argon atmosphere (reaction 3 in Scheme 6c), demonstrating that oxygen was essential in the transformation of compound **4w** to product **5a** as well. The structure of product **6** was additionally confirmed by X-ray crystallographic analysis (for details, see the Supporting Information).

On the basis of our experimental results, a plausible reaction pathway is postulated in Scheme 7. In the presence of the *p*TsOH·H_2O catalyst, indole **1b** and propargylic alcohol **2a** form 3,4-dihydrocyclopenta[*b*]indole **A**,[18] which would then undergo a Diels−Alder reaction with compound **3a** to form intermediate **6**. The isolation of compound **6** in Scheme 6a is in support of this assumption. Then, the intermediate **6** would be transformed to intermediate **B** via a [1,3]-alkyl shift, followed by retro-6π-eletrocyclization to provide product **4w**.[19] Next, intermediate **B** would be trapped by oxygen and would undergo an oxidative radical ring-opening reaction to deliver radical **C** and a hydroperoxy radical.[20] Then, radical **C** would undergo radical addition with a hydroperoxy radical, followed by the loss of half of an oxygen molecule, and subsequent transesterification would deliver product **5a** with the extrusion of one molecule of methanol.

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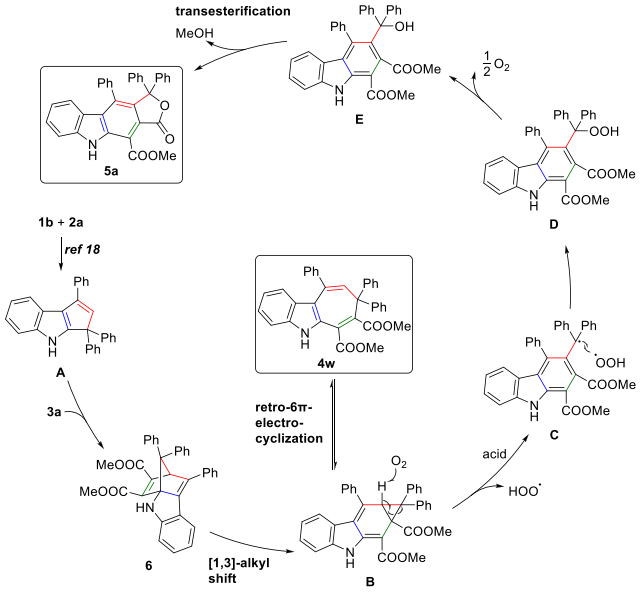
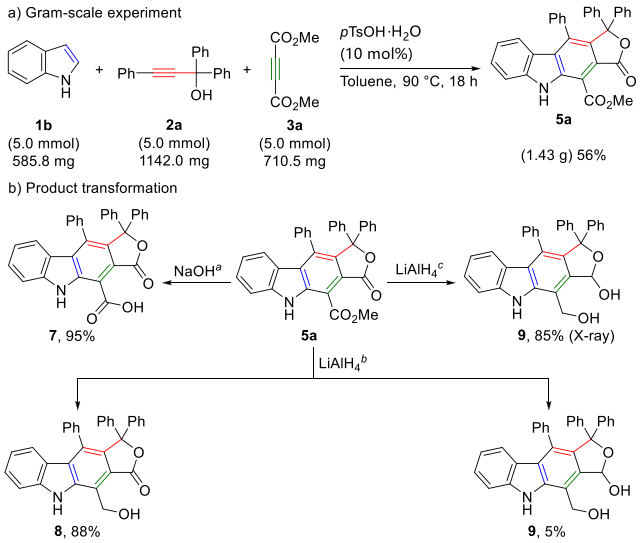
Scheme 7. Possible Mechanisms for the Formation of Products 4w and 5a



A gram-scale synthesis of product **5a** was successfully achieved under the optimized conditions (Scheme 8a),

Scheme 8. Scale-up Reaction and Product Transformations



[a]Compound **5a** (0.3 mmol, 152.9 mg), NaOH (6 mmol, 240.0 mg), EtOH (4 mL)/H_2O (1 mL), 25 °C, and 2 h, under air. [b]Compound **5a** (0.3 mmol, 152.9 mg), $LiAlH_4$ (1.5 mmol, 56.9 mg), tetrahydrofuran (THF, 5 mL), 25 °C, and 3 min, under air. [c]Compound **5a** (0.3 mmol, 152.9 mg), $LiAlH_4$ (9 mmol, 341.6 mg), THF (5 mL), 0 °C −25 °C, and 2 h, under air.

resulting in a slightly lower yield of 56% compared to the small-scale reaction (**5a**, 62%; Scheme 5). Moreover, the ester group of product **5a** could be easily hydrolyzed by NaOH to give the free carboxylic acid **7** or be reduced to alcohol **8** by $LiAlH_4$, with lactone being unaffected. Lactone **5a** could be reduced to product **9** in the presence of an excess of $LiAlH_4$ (Scheme 8b). The structure of product **9** was additionally confirmed by X-ray crystallographic analysis (for details, see the Supporting Information).

In summary, a novel metal-free and environmentally friendly three-component approach to useful cyclohepta[*b*]indole and furo[3,4-*b*]carbazole scaffolds was developed. Tunable chemoselectivity, simple operation, and mild conditions are the main advantages of this strategy. Efforts toward the utilization of readily available propargylic alcohols to the synthesis of other useful cyclic compounds are underway in our laboratories.

■ 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.3c00885.

Experimental procedures, characterization data, and crystallography data (PDF)

^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2215343−2215347 contain 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

Haiting Yin conducted most of the synthetic experiments. Yifan Jiang conducted a part of the synthesis of furo[3,4-

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b]carbazoles. Yunjun Wu, Meifang Wang, and Shaoyin Wang directed the projects and wrote the manuscript. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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