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Iodine-Catalyzed Cascade Formal [3 + 3] Cycloaddition Reaction of Indolyl Alcohol Derivatives with Enaminones: Constructions of Functionalized Spirodihydrocarbolines

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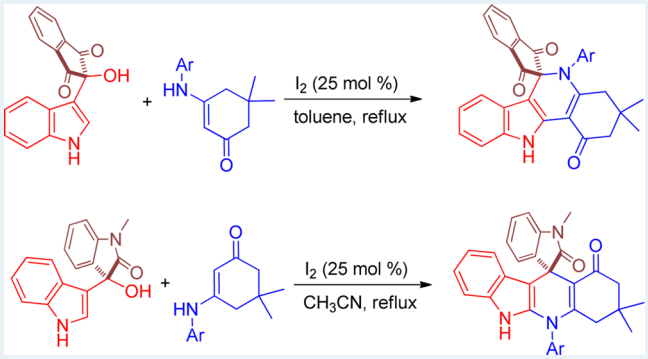
Supporting Information

ABSTRACT: A simple and practical method for the synthesis of spirodihydrocarboline derivatives from indolyl alcohol derivatives with enaminones via an iodine-catalyzed cascade formal [3 + 3] cycloaddition reaction has been developed. The reaction afforded the desired products under mild conditions in moderate to good yields with excellent regioselectivities.



KEYWORDS: *iodine, cascade reaction, formal [3 + 3] cycloaddition reaction, carbolines, indolyl alcohol*

Carboline derivatives are an important class of indole derivatives that are widespread in plants and animals.[1] Among of them, γ-carbolines have attracted special attention in organic synthesis for their versatile biological activities. Numerous γ-carboline medical agents have been designed and synthesized, many of which have shown specific effects on the human cardiovascular and nervous systems.[2,3] For example, SK5M (5-methyl-γ-carboline, **IV**) showed antibovine viral diarrhea virus (BVDV) activity;[4] Dimebon (**V**) is an antihistamine drug;[5] Flutroline (CP-36584) (**VI**) is a novel antipsychotic drug;[6] and compounds **VII** showed antagonist activities at human 5-HT$_6$ and H$_1$ receptors (Figure 1).[7] A literature survey indicates that several strategies have been applied to synthesis of γ-carboline derivatives, such as Fischer indole synthesis,[8] iso-Pictet−Spengler reaction of isotryptamine with aldehydes,[9] benzyne strategy from 2-fluorophenyl imines with LDA,[10] as well as Pd(OAc)$_2$/Cu(OAc)$_2$ or a hypervalent iodine reagent-promoted oxidative annulation strategy.[11] These methods suffer from harsh reaction conditions, long preparation steps, and expensive catalyst. Therefore, it is more desirable to develop new approaches to synthesize γ-carbolines.

Cascade reactions are very promising and are seen as an economical, energy-saving, and environmentally benign strategy for synthesis of complex molecules in an efficient way with undeniable advantages, such as only a single workup procedure and purification step without the isolation of the intermediates.[12] During past decades, cascade reactions have been well studied and applied in the construction of complex molecules as well as the total synthesis of natural products.[13] In recent

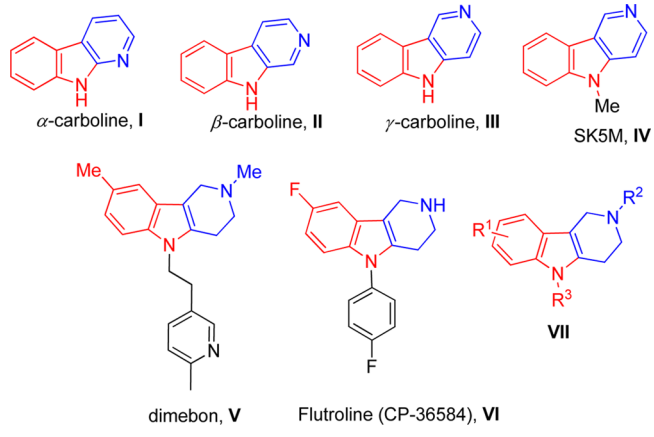


Figure 1. Representative examples of carbolines.

years, molecular iodine has been used for various organic transformations, such as esterification, acylation, and allylation as well as for Michael addition for its low toxic, readily available, and economic consideration.[14] In addition, iodine-catalyzed domino reactions have also been well explored for construction of complex molecules.[15] In the past several years, our group and others have demonstrated Lewis acids or iodine-catalyzed reactions of 3-indolylmethanols[16−18] with different nucleophiles

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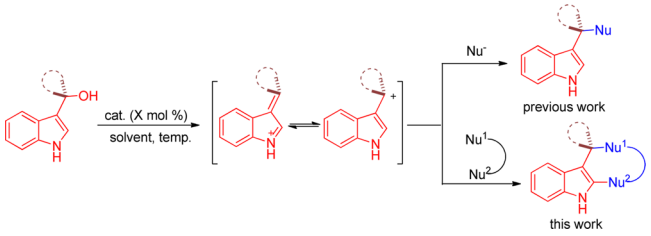
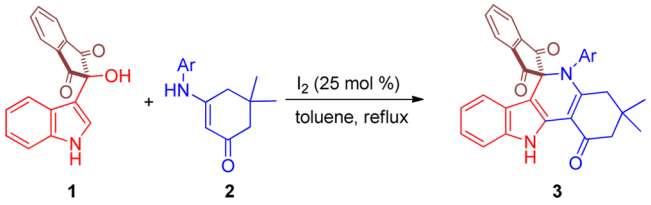
with one nucleophilic center through the transient vinyliminium or carbocation intermediates, providing substituted indole derivatives (Scheme 1). As a continuation of our work

Scheme 1. The Reaction of 3-Indolylmethanol Derivatives with Nucleophiles



on this project,[18] we planned to employ 3-indolylmethanol derivatives to study nucleophiles with two nucleophilic centers, such as enaminones with 1,3-bis-nucleophilic centers, yielding substituted fused indoles through C2 functionalization of the indole framework. Herein, we would like to report this work. These cascade reactions between 2-hydroxy-2-(1*H*-indol-3-yl)-1*H*-indene-1,3(2*H*)-diones **1** and enaminones **2** as a dinucleophile were conducted for the regioselective construction of a spiro-substituted carboline framework through iodine-catalyzed formal [3 + 3] cycloaddition reaction, which involved a sp^2–sp^2 C–C coupling process (Scheme 2). The present work represents the first example for construction of these special types of tetracyclic spiro-substituted carbolines with high regioselectivity.

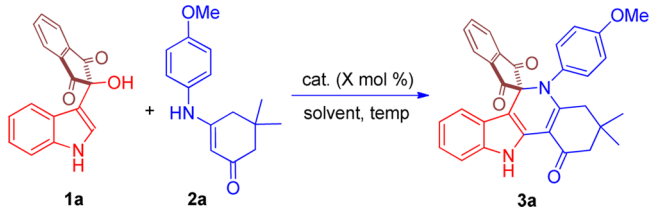
Scheme 2. The Regioselective Construction of Spiro-Substituted Carbolines



We began our investigation by examining the formal [3 + 3] cycloaddition reaction of 2-hydroxy-2-(1*H*-indol-3-yl)-1*H*-indene-1,3(2*H*)-dione **1a** with 3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-enone **2a** (Table 1). Significantly, it was found that iodine was crucial for this reaction; no reaction or very low conversion resulted when the reaction was catalyzed by another Brønsted acid (entry 2) or Lewis acid (entry 3) or without catalyst (entry 1). Then, it was quickly discovered that 25 mol % iodine in toluene under reflux conditions was the optimal reaction condition by screening the reaction solvent, catalyst loading, and reaction temperature. The formal [3 + 3] cycloaddition product was further confirmed by single-crystal X-ray analysis (Figure 2).

Under the optimized reaction conditions, a variety of 3-arylamino-5,5-dimethylcyclohex-2-enone could be reacted with 2-hydroxy-2-(1*H*-indol-3-yl)-1*H*-indene-1,3(2*H*)-dione to furnish the desired cyclized products (Table 2). In particular, the reactants can be not only phenyl groups bearing either electron-withdrawing substituents, such as nitro, fluoro, chloro, bromo, iodo, and cyano groups, but also having electron-donating substituents, such as methoxy, methyl, ethyl, ethyoxyl, *t*-butyl, or benzyloxy groups on the enaminone ring, were well tolerated

Table 1. Optimization of Reaction of 1a and 2a



entry	cat. (mol %)	solvent	temp (°C)	yield (%)[a]
1		CH_3CN	reflux	trace
2	*p*-TsOH (10)	CH_3CN	reflux	5
3	$InCl_3$ (10)	CH_3CN	reflux	8
4	I_2 (10)	CH_3CN	reflux	61
5	I_2 (10)	DMF	150	49
6	I_2 (10)	DMSO	150	trace
7	I_2 (10)	CH_3OH	reflux	47
8	I_2 (10)	EtOH	reflux	57
9	I_2 (10)	THF	reflux	trace
10	I_2 (10)	CH_2Cl_2	reflux	trace
11	I_2 (10)	1,4-dioxane	reflux	41
12	I_2 (10)	toluene	reflux	70
13	I_2 (5)	toluene	reflux	66
14	I_2 (15)	toluene	reflux	73
15	I_2 (25)	toluene	reflux	78
16	I_2 (30)	toluene	reflux	72
17	I_2 (25)	toluene	100	74
18	I_2 (25)	toluene	80	65

[a]Yields were determined by HPLC–MS.

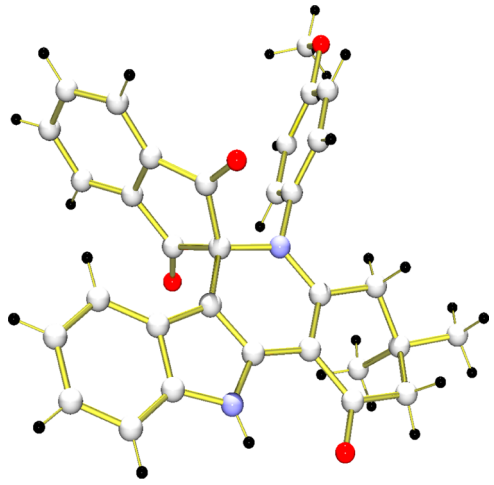


Figure 2. Crystal structure of **3a**.

under the reaction conditions, leading to the final products in moderate to good yield (**3a**–**3l**). The 6,6-dimethyl-3-(*p*-tolylamino)cyclohex-2-enone was converted into the corresponding spirodihydro-carboline **3q** in 62% yield. In addition, methyl and methoxy substituents on the indole ring were also found to be suitable for the present cascade reactions to afford the expected indene-spiro dihydrocarbolines **3m**, **3n**, **3o**, and **3p** in 60%, 64%, 67%, and 59% yields, respectively. The structure of compound **3g** was also confirmed by X-ray analysis (Figure 3). *N*-Substituted 3-aminocyclohex-2-enone was also suitable for the reaction and gave the desired products **3r** and **3s** in 53% and 41% yields.

Subsequently, we investigated the substrate scope with respect to 3-hydroxy-3-(1*H*-indol-3-yl)-1-methylindolin-2-one

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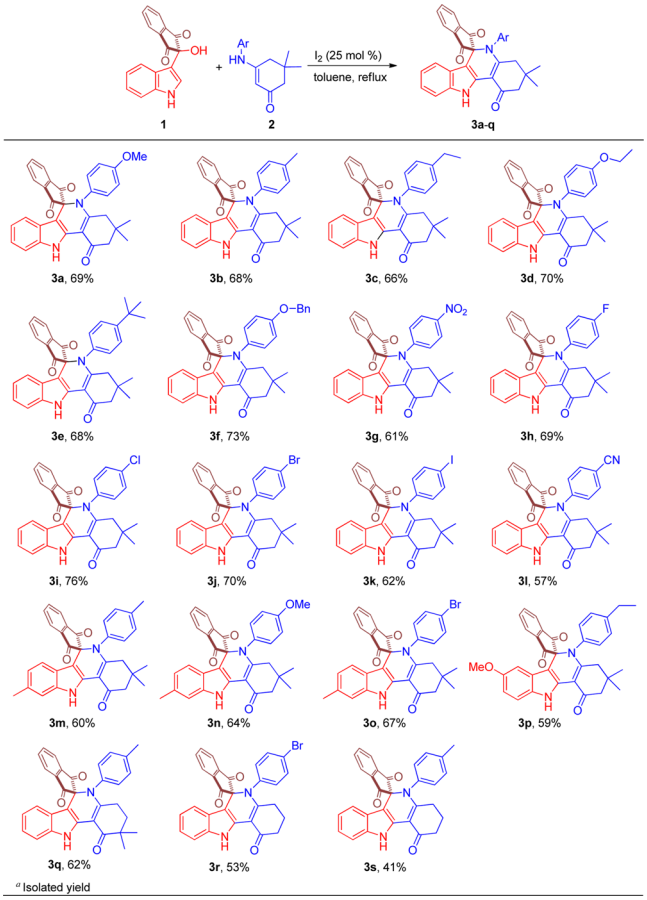
Table 2. The Reaction of 1 and 2



[a]Isolated yield.

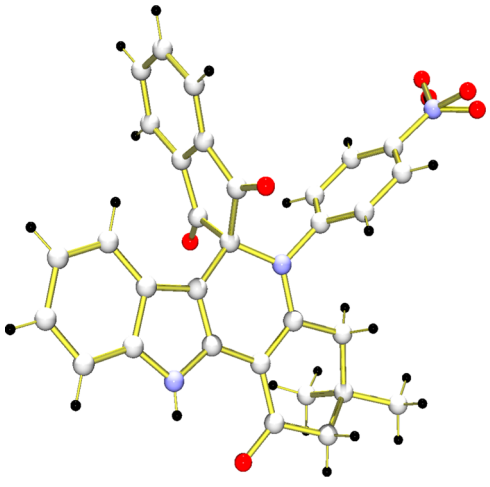
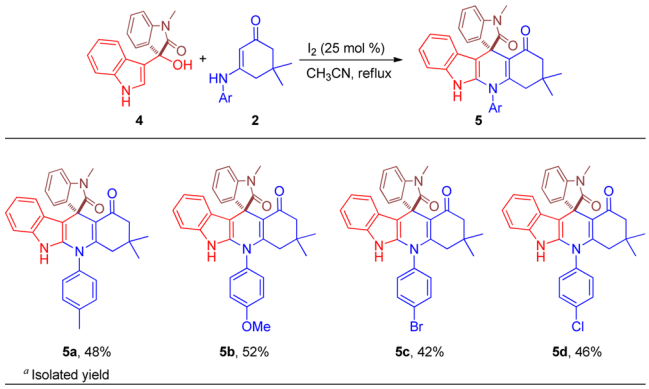


Figure 3. Crystal structure of **3g**.

4, which could be easily prepared from indole with **N**-methyl isatin. The target γ-carboline product was not obtained in toluene. To our surprise, α-carboline derivatives **5** were obtained in moderate yields in CH_3CN instead of γ-carboline products when 3-hydroxy-3-(1*H*-indol-3-yl)-1-methylindolin-2-one was subjected to the reaction with enaminones as a dinucleophile under the identical reaction conditions (Table 3). The results indicated that the difference in the functionalized indolyl alcohol derivatives determined the reactions with different regioselectivities. Importantly, there is no literature

Table 3. The Reaction of 4 and 2

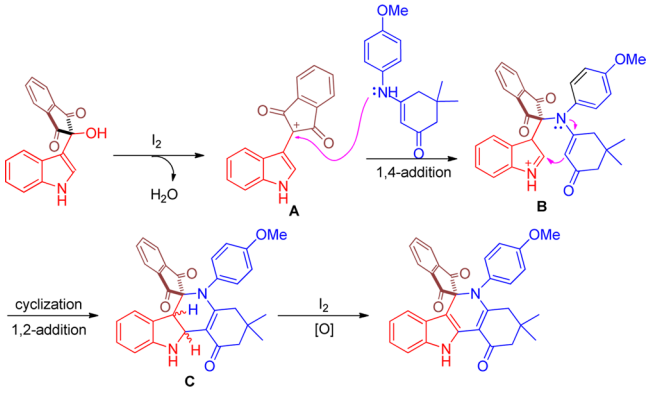


[a]Isolated yield.

dealing with the iodine-catalyzed formal [3 + 3] cycloaddition reaction for the construction of α-carboline derivatives through C2 N-arylation of the indole unit in a simple one-step operation.

On the basis of the previous results and the literature reports, a plausible mechanism has been proposed, as shown in Scheme 3. First, the carbocation intermediate **A** could be easily formed

Scheme 3. Plausible Mechanism



from indolyl alcohols in the presence of a catalytic amount of iodine.[19] Subsequently, the lone pair electrons on enaminone attack the carbocation to give 1,4-addition intermediate **B**, followed by a cascade intramolecular 1,2-addtion of enamine to iminium to afford the [3 + 3] cyclization tetrahydrogen carboline intermediate **C**. The compound **C** could be easily oxidized to give the desired dihydrogen carboline product under the reaction conditions. As the [3 + 3] cyclization of 3-hydroxy-3-(1*H*-indol-3-yl)-1-methylindolin-2-one with enaminones, the different reaction activity between the carbocation intermediate with enaminones may furnish the different regioselective products.

In conclusion, we have developed an iodine-catalyzed method for the regioselective formal [3 + 3] cycloaddition reaction of indolyl alcohol derivatives with enaminones. This protocol provides a simple and practical strategy for the synthesis of spirodihydrocarboline derivatives, especially the spirodihydro-γ-carboline derivatives. Because of the potential high activities of γ-carboline derivatives, we believe this study will find applications in synthetic chemistry and medicinal chemistry as well as bioorganic chemistry.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds and CIF files for **3a** and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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