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One-pot access to indolylchromeno[2,3-*b*]indoles via iodine-mediated Friedel-Crafts alkylation/oxidative coupling reaction of indoles and salicylaldehydes

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ABSTRACT

An I_2-mediated Friedel-Crafts alkylation/oxidative coupling reaction of indoles and salicylaldehydes was developed. With the developed protocol, a series of indolylchromeno[2,3-*b*]indoles were obtained in good yields (up to 88%) under mild reaction conditions. Two possible reaction mechanisms were tentatively brought forward to account for the formation of the products in light of some control experiments.

1. Introduction

Chromeno[2,3-*b*]indoles are ubiquitous structural motifs in numerous natural or synthetic biologically active molecules.[1] For examples, Hyrtimomine **A** and **B** were isolated from a sponge Hyrtios sp. in 2013, and Hyrtimomine **A** exhibited cytotoxicity against KB and L1210 cells.[1d] Chromeno[2,3-*b*]indole derivative **C** also possesses biological activity, as shown by antimalarial agents (Fig. 1).[1a] It is noteworthy that these biologically active compounds not only contain a chromeno[2,3-*b*]indole framework core but also incorporate different groups on the C-11 position. Therefore, many efforts have been made to the development of efficient synthetic methods to access various chromeno[2,3-*b*]indole compounds, which are particularly characterized by a substitution installed at the C-11 position.[2] Certainly, installing different subsets at the C-11 position of the chromeno[2,3-*b*]indole scaffold should generate a new type of compounds, which probably have some potential biological activities and fuel ongoing investigations on the new drug discovery. On the other hand, the indole moiety is a privileged heterocyclic ring system featured in a large number of biologically interesting natural and unnatural compounds.[3] However, a comprehensive literature study reveals that the strategy for the synthesis of indolylchromeno[2,3-*b*]indoles, bearing a indole group at the C-11 position of chromeno[2,3-*b*]indole framework core, remains underdeveloped.[4] In particular, Lankalapalli and co-workers recently reported a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated intramolecular C–O bond formation method for the synthesis of indolylchromeno[2,3-*b*]indole compounds by 3,3′-diindolylmethanes as starting materials, and further evaluate their antibiotic activity.[4] Therefore, taking account of the potentially biological significance of indolylchromeno[2,3-*b*]indoles in medicinal chemistry research, the development of simple and efficient approaches for the synthesis of the structurally diverse indolylchromeno[2,3-*b*]indoles from readily available starting materials is highly in demand.

In recent years, iodine-catalyzed or iodine-mediated cascade reactions have attracted great attentions from organic chemists due

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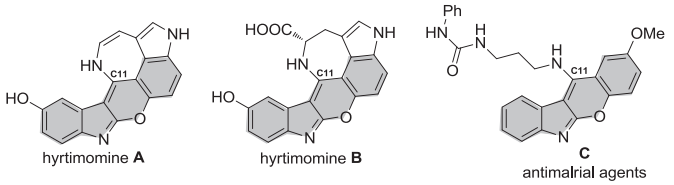


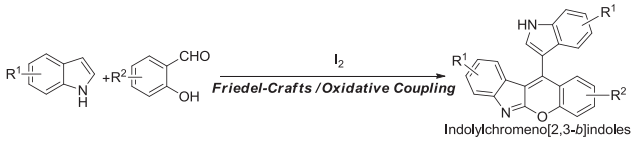
Fig. 1. Examples of biologically active compounds containing chromeno[2,3-*b*]indole scaffold.

to the inexpensive and eco-friendly of molecular iodine.[5] It is well known that iodine could be applied in oxidative coupling reaction based on its oxidizing ability.[6] Meanwhile, iodine also could serve as a mild Lewis acid for some transformations.[7] As part of our ongoing investigation aiming at developing new methodologies for the synthesis of diverse heterocycles,[8] recently, we have found that the reaction between indoles and salicylaldehydes could be realized via a Friedel-Crafts alkylation/oxidative coupling process in the presence of molecular iodine, affording a series of structurally diverse indolylchromeno[2,3-*b*]indole compounds (Scheme 1). Herein, we wish to report our research findings in this subject.

2. Results and discussion

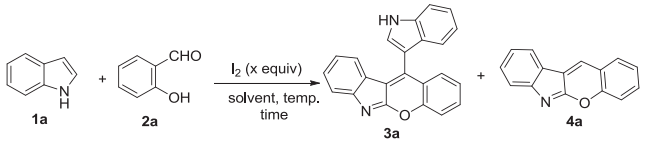
We initiated our investigation with the reaction of indole **1a** and salicylaldehyde **2a** in the presence of an equivalent of molecular iodine in methanol at reflux temperature. The reaction could proceed to completion within 2 h and furnish the desired 11-(1*H*-indol-3-yl)chromeno[2,3-*b*]indole **3a** in 41% yield and co-product **4a** in 18% yield (Table 1, entry 1). Lowering the amount of iodine to 0.5 equivalent, product **3a** was obtained only in 13% yield (Table 1, entry 2). To our delight, increasing the amount of iodine to 2.0 equivalents, an improved yield was achieved (Table 1, entry 3). Further enhancing the amount of iodine to 3.0 equivalents, no further improvement in the yield was obtained (Table 1, entry 4). Afterwards, the screening of various solvents was performed in the presence of 2.0 equivalent of molecular iodine (Table 1, entries 5–12). It was observed that the reaction only occurred in protonic solvents and ethanol turned out to be the best choice for the reaction in light of the yield (Table 1, entry 5 vs entries 6–12). When the reaction was carried out at room temperature, product **3a** and co-product **4a** were obtained in 42% and 43% yield, respectively (Table 1, entry 13). Ultimately, the ratio of **1a** to **2a** was investigated. Excellent yield (89%) could be achieved when the ratio of **1a** to **2a** was elevated from 2:1 to 3:1 (Table 1, entry 14 vs entry 15). It's worth noting that the reaction could conduct in air and it has almost no influence on the reactivity and yield (Table 1, entry 16).

With the optimized reaction conditions in hand, the substrate scope of the Friedel-Crafts alkylation/oxidative coupling reaction was explored. Firstly, various indoles were tested by reacting with salicylaldehyde **2a**. As summarized in Scheme 2, the position and electronic nature of the substituents on the indoles generally had slight effect on the reactivities. As to the substrates with either electron-withdrawing or electron-donating substituents at the C5-position of indoles, their reactions with **2a** could proceed smoothly,



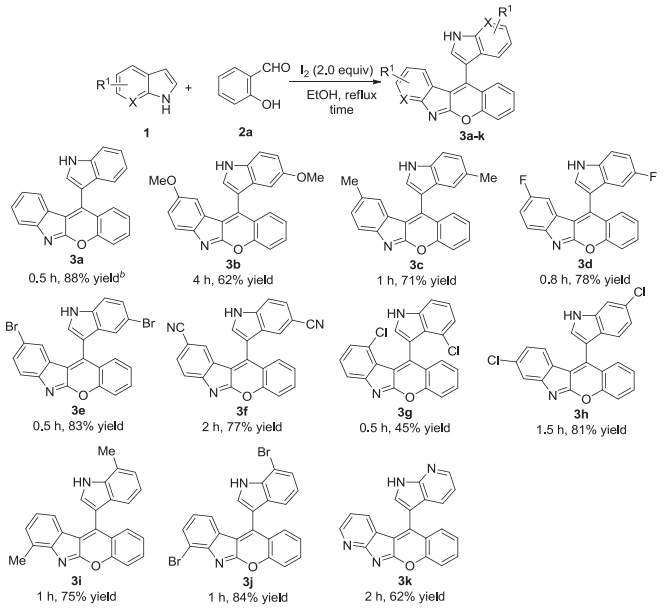
Scheme 1. The strategies for the synthesis of indolylchromeno[2,3-*b*]indole compounds.

Table 1
Optimization of reaction conditions.[a]



Entry	x	Solvent	Temp. (°C)	Time (h)	**3a**/yield (%)[b]	**4a**/yield (%)[b]
1	1.0	MeOH	reflux	2	41	18
2	0.5	MeOH	reflux	2	13	–
3	2.0	MeOH	reflux	2	51	28
4	3.0	MeOH	reflux	2	50	44
5	2.0	EtOH	reflux	2	54	27
6	2.0	H_2O	80	2	11	12
7	2.0	DMSO	80	2	–	–
8	2.0	DMF	80	2	–	–
9	2.0	CH_3CN	80	2	–	–
10	2.0	EtOAc	reflux	2	–	–
11	2.0	Toluene	80	2	–	–
12	2.0	DCE	80	2	–	–
13	2.0	EtOH	rt	2	42	43
14[c]	2.0	EtOH	reflux	2	62	23
15[d]	2.0	EtOH	reflux	0.5	89	–
16[d,e]	2.0	EtOH	reflux	0.5	88	–

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.5 mmol), **2a** (0.5 mmol) and I_2 in 5.0 mL of solvent at specified temperature for the specified reaction time under Ar.
[b] Isolated yield.
[c] 1.0 mmol of **1a** was used.
[d] 1.5 mmol of **1a** was used.
[e] The reaction was run in air.



[a]Unless otherwise noted, all reactions were carried out with **1** (1.5 mmol), **2a** (0.5 mmol) and I_2 (2.0 equiv) in 5.0 mL of EtOH at reflux temperature for the specified reaction time.
[b]Isolated yield

Scheme 2. Scope of I_2-mediated reaction of various indoles with salicylaldehyde.

and furnished the corresponding products **3b-f** in 62–83% yields. Moreover, the substrates with different substituent in the C4-, C6-, and C7-position also could react with **2a** and delivered the desired products in good results (products **3h-j**). However, 4-Cl substituted indole **1f** reacting with **2a** furnished the product **3g** only in 45%