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Highly efficient synthesis of 3-indolyl-substituted phthalides via Friedel–Crafts reactions in water

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ABSTRACT

An efficient and simple method for the synthesis of 3-indolyl-substituted phthalides via Friedel–Crafts reaction of indoles with 2-formylbenzoic acids in pure water has been developed. The reaction affords a wide range of 3-indolyl-substituted phthalides in good to excellent yields.

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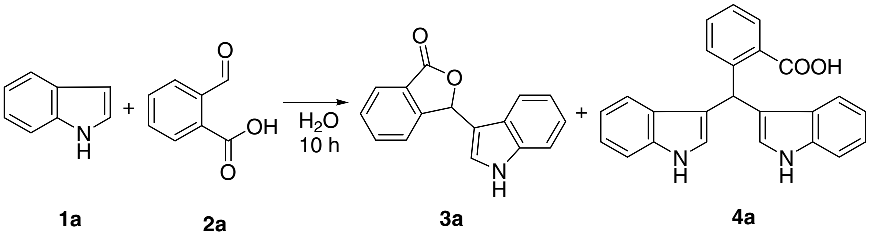
The indole ring is widely present in a variety of biologically active compounds and has become an important structural component in many pharmaceutical agents owing to the great structural diversity of biologically active indoles.[1] Substituted indoles have been referred to as 'privileged structures' for drug development and 3-substituted indole is one important class of indole derivatives. [2] Phthalides occur as structural subunits in numerous natural products that exhibit a wide range of biological activity.[3] Accordingly, the incorporation of indole into phthalide may potentially provide a class of novel drug candidates with unusual biological activities. However, despite the potential utility of 3-indolyl-substituted phthalides in new drug discovery, their synthesis has been rarely studied.[4] Developing new and environmentally benign synthetic methods is important in organic synthesis. In recent years, organic reactions that can proceed in aqueous media have attracted great interest because of significant environmental and economical advantages over those occurring in organic solvents.[5] Thus, it is of interest to develop a practical and general method for the synthesis of 3-indolyl-phthalide under neutral conditions in water in view of economical and environmental concerns. Following our interest in green chemistry and medicinal chemistry, we herein present a straightforward and mild route to synthesize 3-indolyl-phthalide in pure water.

We first examined the reaction between indole **1a** and 2-formylbenzoic acid **2a** in pure water (Scheme 1). Reaction of indole **1a** with 1.5 equiv of **2a** gave the desired product **3a** in 83% yield with a trace amount of bisindole by-product **4a** in water at room temperature (Table 1, entry 1). When we increased the reaction temperature

Table 1
Screening and optimization of the reaction conditions[a]

Entry	**1a**:**2a**	Temp. (°C)	Yield of **3a**[b] (%)
1	1:1.5	25	83
2	1:1.5	40	97
3	1:1.2	40	91
4	1:1	40	86

[a] Reactions were carried out with 0.3 mmol of indole **1a**, 0.45 mmol of 2-formylbenzoic acid **2a** in 1 mL of H_2O at the indicated temperature.
[b] Isolated yield after chromatographic purification.



Scheme 1. Synthesis of 3-indolyl substituted phthalides **3a**.

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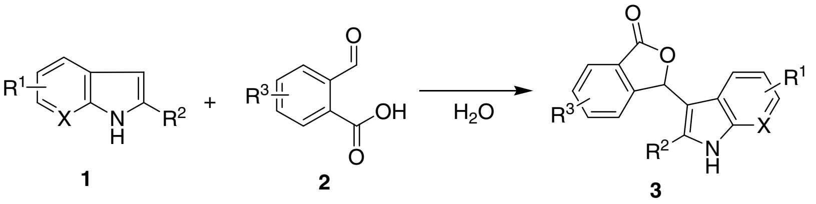
Table 2
Synthesis of 3-indolyl-substituted phthalides in water[a]



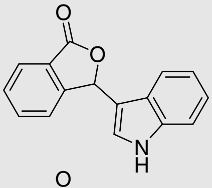
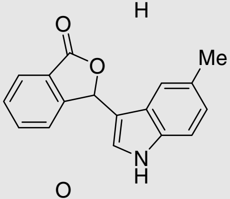
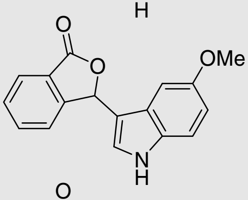
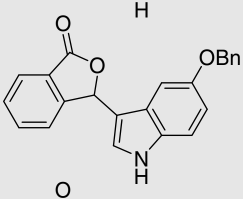
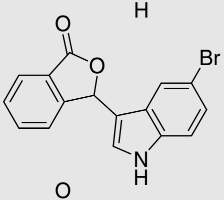
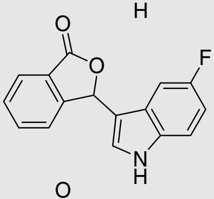
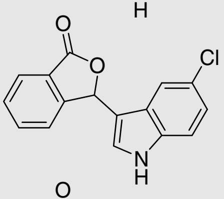
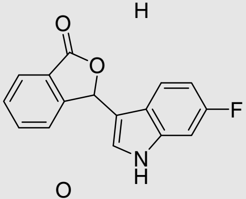
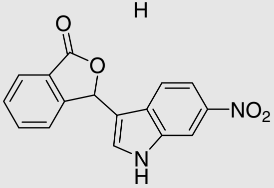
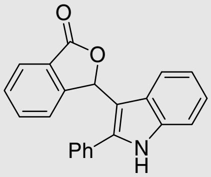
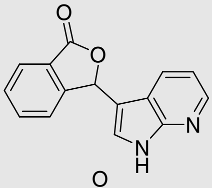
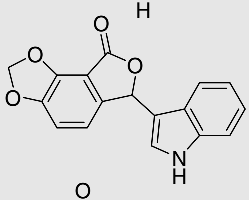
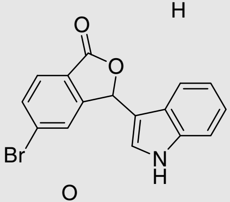
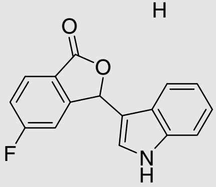
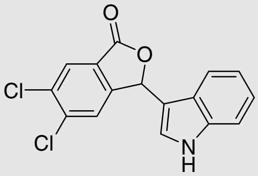
Entry	1	2	Phthalide	Temp. (°C)	Time (h)	Yield of **3**[b] (%)
1	$R^1 = R^2 = H$, X = CH **1a**	$R^3 = H$ **2a**		40	10	**3a** (97)
2	R^1 = 5-Me, R^2 = H, X = CH **1b**	$R^3 = H$ **2a**		15	24	**3b** (71)
3	R^1 = 5-OMe, R^2 = H, X = CH **1c**	$R^3 = H$ **2a**		15	24	**3c** (76)
4	R^1 = 5-OBn, R^2 = H, X = CH **1d**	$R^3 = H$ **2a**		60	24	**3d** (73)
5	R^1 = 5-Br, R^2 = H, X = CH **1e**	$R^3 = H$ **2a**		40	10	**3e** (99)
6	R^1 = 5-F, R^2 = H, X = CH **1f**	$R^3 = H$ **2a**		40	10	**3f** (95)
7	R^1 = 5-Cl, R^2 = H, X = CH **1g**	$R^3 = H$ **2a**		40	10	**3g** (91)
8	R^1 = 6-F, R^2 = H, X = CH **1h**	$R^3 = H$ **2a**		40	10	**3h** (94)
9	R^1 = 6-NO_2, R^2 = H, X = CH **1i**	$R^3 = H$ **2a**		80	24	**3i** (93)

Table 2 (*continued*)

Entry	1	2	Phthalide	Temp. (°C)	Time (h)	Yield of **3**[b] (%)
10	R^1 = H, R^2 = Ph, X = CH **1k**	R^3 = H **2a**		40	24	**3j** (86)
11	R^1 = R^2 = H, X = N **1l**	R^3 = H **2a**		60	24	**3k** (83)
12	R^1 = R^2 = H, X = CH **1a**	R^3 = 3′,4-(O-CH_2-O)- **2b**		60	24	**3l** (80)
13	R^1 = R^2 = H, X = CH **1a**	R^3 = 5-Br **2c**		60	24	**3m** (82)
14	R^1 = R^2 = H, X = CH **1a**	R^3 = 5-F **2d**		60	24	**3n** (87)
15	R^1 = R^2 = H, X = CH **1a**	R^3 = 4,5-Cl_2 **2e**		40	10	**3o** (80)

[a] Reactions were carried out with 0.3 mmol of indole **1**, 0.45 mmol of 2-formylbenzoic acid **2** in 1 mL of H_2O at the indicated temperature.

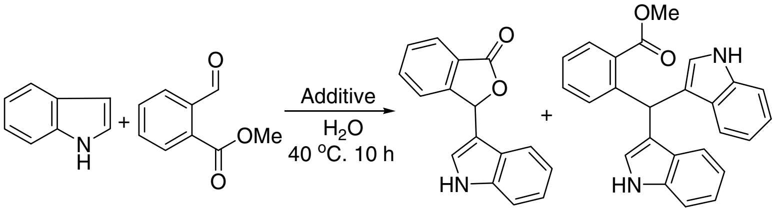
[b] Isolated yield after chromatographic purification.

to 40 °C, the reaction proceeded in nearly quantitative yield while no bisindole by-product **4a** was observed (Table 1, entry 2).

In general, decreasing the amount of 2-formylbenzoic acid **2a** resulted in a slightly lower yield and the emergence of bisindole by-product (Table 1, entries 3 and 4).

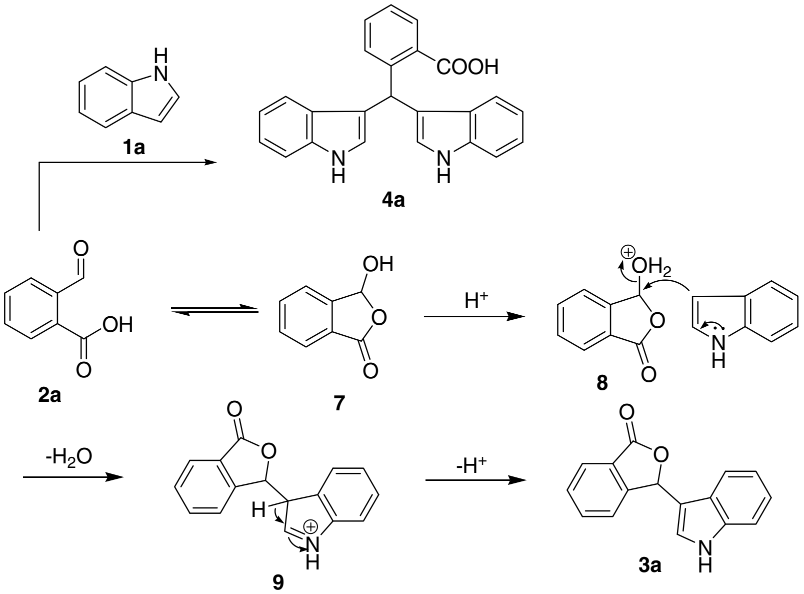
Under the optimized conditions (1 equiv of indoles and 1.5 equiv of 2-formylbenzoic acid), we tested a wide range of substituted indoles and substituted 2-formylbenzoic acids to investigate the scope of this reaction. The results are summarized in Table 2.[6]

Table 3
A comparison reaction between **1a** and **5**



1a **5** **3a** **6**

Entry	**1a**:**5**	Additive	Yield of **3a** (%)	Yield of **6** (%)
1	1:1.5	None	0	0
2	1:1.5	1.5 equiv Benzoic acid	0	88



Scheme 2. Possible reaction mechanism for the generation of 3-indolyl-phthalides.

As shown in Table 2, the process was found to be general with indoles bearing different substituents. A number of substituted indoles **1a–l**, containing either electron-donating or electron-withdrawing groups, even N-hetero-indole, have been tested in the reaction with 2-formylbenzoic acid **2a** to give the corresponding products in good to excellent yields. To our delight, even the indoles with strong electron-withdrawing group, NO_2, can react with 2-formylbenzoic acids smoothly in high yield (Table 2, entry 9). Subsequently, we examined substituted 2-formylbenzoic acids. For the substrates with either electron-donating group such as **2b** (Table 2, entry 12) or electron-withdrawing group such as **2c**, **2d**, and **2e** (Table 2, entries 13–15), the reactions went smoothly, affording the corresponding 3-indolyl-phthalides in high yields.

For elucidation of the reaction mechanism, a comparison reaction between indole **1a** and methyl 2-formylbenzoate **5** was carried out. The results are summarized in Table 3. Not surprisingly, we did not detect the corresponding adduct **3a** or bisindole product **6** (Table 3, entry 1). However, the reaction of **1a** and **5** led to **6** in 88% isolated yield in the presence of 1.5 equiv of benzoic acid (Table 3, entry 2). The 2-formylbenzoic acid is known to exist partially in the 3-hydroxy phthalide form **7**.[7] These indicated that the generation of 3-indolyl-phthalides may proceed through the *O*,*O*-acetals pathway catalyzed by **2a** itself via Friedel–Crafts reaction of indoles with **7** as shown in Scheme 2. The reaction of indole and protonated 3-hydroxy phthalide **8** could afford intermediate **9**. The product **3a** was obtained as a result of re-aromatization of **9** subsequently. As for bisindol product **4a**, it could be formed by second Friedel–Crafts reaction of another equivalent of **1a** with **3a** catalyzed by 2-formylbenzoic acid.

In summary, we have developed an efficient and simple method for the synthesis of 3-indolyl-substituted phthalides by Friedel–Crafts reaction of indoles with 2-formylbenzoic acids in pure water. This reaction is attractive because of its high efficiency, environmental friendliness, and no need of any other catalyst. Various substituted indoles and substituted 2-formylbenzoic acids can react smoothly to give corresponding phthalides in a green way. Attempts toward the asymmetric version of the reaction as well as the application of this method are underway in our laboratory currently.

Acknowledgements

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6. *General procedure for the preparation of 3-indolyl-phthalide* **3a**–**o**: A mixture of indole (0.3 mmol) and 2-formylbenzoic acid (0.45 mmol) in pure water (1 mL) was stirred at the indicated temperature. When the reaction is complete, 200 mL of dichloromethane was added. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (15 mL × 2), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel to give 3-indolyl-phthalide.
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