

TsOH·H₂O-Catalyzed Friedel-Crafts of Indoles of 3-Hydroxyisobenzofuran-1(3H)-One with Indoles: Highly Synthesis of 3-Indolyl-Substituted Phthalides

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ABSTRACT

An efficient and facile method for the synthesis of 3-indolyl-substituted phthalides by Friedel-Crafts alkylation of indoles with 3-hydroxyisobenzofuran-1(3H)-one has been developed. Using only 2 mol-% TsOH·H₂O as the catalyst, various substituted indoles can react smoothly at room temperature to give the corresponding phthalides products in good to excellent yields (up to 96%).

Keywords: Synthesis; 3-Indolyl-Substituted Phthalides; Friedel-Crafts Alkylation; 3-Hydroxyisobenzofuran-1(3H)-One; Indole

1. Introduction

Currently, the chemistry of phthalides has attracted much attention from many research groups, as they are the key skeleton for a number of synthetic and naturally occurring bioactive molecules [1-5]. In particular, 3-substituted phthalide moieties are embodied in numerous natural products. For examples, (-)-Alcyopterosin E which contains phthalides bone shows mild cytotoxicity toward Hep-2 (human larynx carcinoma) cell line [6]; 3-Butylphthalides isolated from the basidiomycete *Phanerochaete velutina* CL6387 appear to be specific for *Helicobacter pylori* [7]; and Cytosporone E has antifungal activities [8]; Fuscinarin isolated from soil fungus was found to compete effectively with macrophage inflammatory protein (MIP)-1 α for binding to human CCR5, an important anti HIV-1 target that interferes with HIV entry into cells [9]. On the other hand, the indole framework is a privileged structure motif in a large number of natural products and therapeutic agents [10,11]. The history of researches in indole and its derivatives has been more than 100 years, and this domain has become one of the hot research spot. And with the fresh and rapid development of life sciences, this research of indoles has drawn increasing attention from organic chemists [12-15]. Furthermore, it is well known that there are more than 3000 kinds of indole derivatives in the nature. Among them, more than 40 kinds are treatment medicines [11]. The potential biological activities of phthalides and indoles promoted us to

develop a synthesis of an interesting type of heterocyclic compounds via their combination. And it probably offers great opportunities for the lead compound discovery. However, due to the phthalides' specific structure feature containing the activity lactone motif, the methodology for the synthesis of 3-indolylsubstituted phthalides has been rarely explored. Up to date, the synthesis of this type compounds is mainly restricted to the reaction of indoles with 2-forylbenzoic acids either at high temperature ($T > 100^{\circ}\text{C}$) [16-18] or in the presence of an acidic cation exchange resin Amberlyst 15 [19]. The main drawbacks associated with these previously reported procedures are the unavailability of the common starting materials, 2-forylbenzoic acids, and in some cases, harsh reaction conditions [20-23]. Therefore, the development of simple, highly efficient alternative approach for the synthesis of 3-indolyl substituted phthalides is highly desirable. Herein, we report an efficient substitution reaction of 3-hydroxyisobenzofuran-1(3H)-one [24-26], which can be easily prepared via the reduction of readily available phthalic anhydride, and indoles using the TsOH·H₂O as a catalyst at room temperature for the synthesis of 3-indolyl substituted phthalides with high yields.

2. Experimental

2.1. General Information

¹H and ¹³C NMR spectra were recorded in CDCl₃ or DMSO on a Bruker AMX-300 or Varian 400 MHz instrumental using TMS as an internal standard. Elemental

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analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined on a T-4 melting point apparatus. All temperatures were uncorrected.

All solvents and chemicals were commercially available and used without further purification unless otherwise stated.

3-Hydroxyisobenzofuran-1(3H)-One

According to the literature [26,27], the solution of isobenzofuran-1(3H)-one [25] 1.34 g (1 mmol), NBS 2.71 g (1.2 mmol), AIBN 0.03 g (0.2 mmol) in 15 mL CCl₄ was heated to reflux until isobenzofuran-1(3H)-one disappeared (monitored by TLC). After removal of the solvent, the residue was purified by column chromatography on silica gel (200 - 300 mesh, gradient elution with petroleum ether/ethyl acetate = 6/1) to afford 3-bromoisobenzofuran-1(3H)-one 1.81 g, (85%). 3-bromoisobenzofuran-1(3H)-one was heated to reflux in water for 2 h, then the mixture was cooled to room temperature, a white crystal was separated out, after filtration, the product 3-hydroxyisobenzofuran-1(3H)-one was got, 1.13 g (88%), mp. 98°C.

2.2. General Procedure for the Synthesis of 3-Indolyl-Substituted Phthalides Catalyzed by TsOH·H₂O

The solution of TsOH·H₂O (0.02 mmol), 3-hydroxyisobenzofuran-1(3H)-one (1.00 mmol), and indoles (1.20 mmol) in CHCl₃ (2 mL) was stirred at ambient temperature until the raw material disappeared (monitored by TLC). After removal of the solvent, the residue was purified by column chromatography on silica gel (200 - 300 mesh, gradient elution with petroleum ether/ethyl acetate = 3/1) to afford the product.

3a-3h, 3j, 3l and **3n** are known products according to the literatures [16,18,19].

2.2.1. 3-(5-Hydroxy-1H-indol-3-yl)isobenzofuran-1(3H)-One (3i)

White solid, yield: 89%, mp. 213.4°C - 215.1°C. ¹H NMR (DMSO-d₆, 400 MHz) δ:5.07 (s, OH), 6.56 (d, *J* = 8.0 Hz, 1 H), 6.78 (s, 1 H), 6.88 - 6.90 (m, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.62 (t, *J* = 7.2 Hz, 1 H), 7.80 (t, *J* = 7.2 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 10.18 (s, NH); ¹³C NMR (DMSO-d₆, 100 MHz) δ: 171.2, 154.6, 150.2, 135.9, 132.3, 131.5, 129.8, 129.3, 128.0, 127.5, 124.5, 120.2, 114.3, 112.9, 105.5, 78.5; C₁₆H₁₁NO₃ (265.07): calcd. C 72.45, H 4.18, N 5.28; found C 72.70, H 3.99, N 5.16.

2.2.2. 3-(6-(Benzyloxy)-1H-indol-3-yl)isobenzofuran-1(3H)-One (3k)

White solid, yield: 89%, mp. 194.5°C - 195.7°C. ¹H

NMR (CDCl₃, 400 MHz), δ:5.19 (d, *J* = 3.2 Hz, 2H, CH₂), 6.60 - 6.68 (m, 2 H), 6.84 (s, 1 H), 6.92 (d, *J* = 2.8 Hz, 1 H), 7.26 - 7.98 (m, 9 H), 8.00 (d, *J* = 8.8 Hz, 1 H), 10.24 (b, NH). ¹³C NMR (CDCl₃, 100 MHz), δ:170.6, 154.3, 149.4, 137.7, 135.0, 132.3, 129.5, 128.6, 127.9, 127.6, 126.6, 126.1, 125.8, 125.3, 123.3, 122.9, 119.0, 113.0, 108.6, 82.5, 70.4; C₂₃H₁₇NO₃ (355.12): calcd. C 77.73, H 4.82, N 3.94; found C 77.57, H 4.99, N 3.98.

2.2.3. 3-(6-Chloro-1H-indol-3-yl)isobenzofuran-1(3H)-One (3m)

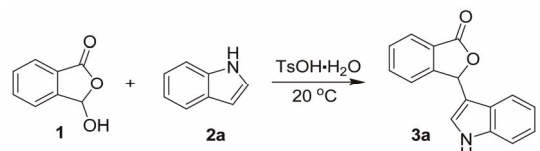
White solid, yield: 88%, mp. 139.1°C - 140.6°C. ¹H NMR (DMSO-d₆, 400 MHz), δ:6.77 (d, *J* = 3.6 Hz, 1 H), 6.91 (s, 1H), 7.04 (dd, *J* = 2.8 Hz, 9.2 Hz, 1 H), 7.52-7.68 (m, 5H), 7.96 (d, *J* = 9.6 Hz, 1H), 8.83 (s, 1 H); ¹³C NMR (DMSO-d₆, 100 MHz) δ:170.9, 150.7, 137.7, 135.6, 130.3, 128.7, 128.2, 127.4, 125.9, 124.4, 123.6, 119.4, 114.5, 111.9, 78.6; C₁₆H₁₀ClNO₂ (283.04): calcd. C 67.74, H 3.55, N 4.94; found C 67.84, H 3.56, N 4.86.

3. Results and Discussion

In our initial studies, all kinds of experimental parameters, such as solvents, molar ratios of the two substrates and catalyst loadings, were thoroughly investigated in the model Friedel-Crafts alkylation of indole (2a) with 3-hydroxyisobenzofuran-1(3H)-one (1) employing the TsOH·H₂O as the catalyst. And the results are listed in **Table 1**.

Solvent evaluation revealed that chloroalkanes (CH₂Cl₂ and CHCl₃) favored this transformation in terms of high yield (**Table 1**, Entries 1 and 2), and CH₂Cl₂ is

Table 1. Optimization of the reaction conditions^a.



Entry	Catalyst (mol-%)	Solvent	Molar ration (1:2)	Time (h)	Yield (%) ^b
1	2	CHCl ₃	1:1.2	3	90
2	2	CH ₂ Cl ₂	1:1.2	3	95
3	2	THF	1:1.2	3	81
4	2	EA	1:1.2	3	72
5	2	CH ₃ OH	1:1.2	5	61
6	2	EtOH	1:1.2	5	61
7	1	CH ₂ Cl ₂	1:1.2	12	78
8	5	CH ₂ Cl ₂	1:1.2	2	94
9	2	CH ₂ Cl ₂	1.2:1	3	83
10	2	CH ₂ Cl ₂	1:1	3	87
11	2	CH ₂ Cl ₂	1:1.5	3	92

^aReactions were performed on a 1 mmol scale of **1** (3-hydroxyisobenzofuran-1(3H)-one) with a concentration of 0.5 mol·L⁻¹; ^bIsolated yield.

the optimal solvent providing the corresponding Friedel-Crafts alkylation product with the highest yield of 95% (**Table 1**, Entry 2, 95%). Marked decrease in yields was observed in this reaction when using other solvents, such as THF, methanol, ethanol and ethyl acetate (**Table 1**, Entries 3-6). Moreover, it was found that a ring-opened product was obtained in the case of the methanol or ethanol as the solvent. In addition, the adjustment of the catalyst loading also brought out some influence both on the reaction rate and chemical yield. For example, using the great amount of catalyst, we could obtain the alkylation product **3a** in quite shorter time with almost the same high level yield (**Table 1**, Entry 8). Reducing the catalyst loading from 2 mol-% to 1 mol-% led to an obvious decrease both on reaction rate and yield. Furthermore, the molar ratio of the two reactants was found to be an essential factor to the yield of the reaction. As shown in **Table 1**, the yield of **3a** was enhanced with the decrease in the molar ratio of **1** to **2a**, and the maximal yield of 95% was obtained when the molar ratio reached 1:1.2 (**Table 1**, Entry 2). Further decreased the molar ratio to 1:1.5 resulted in a lower yield of **3a** (**Table 1**, Entry 10).

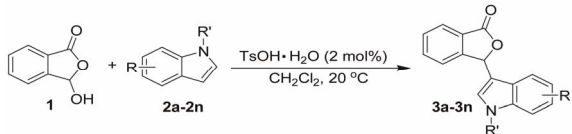
On the basis of the optimal reaction conditions of indole **2a** (2 mol-% TsOH·H₂O as the catalyst, substrates molar ratio (**1:2a** = 1:1.2), 0.5 M 3-hydroxyisobenzofuran-1(3*H*)-one **1**, at 20°C in CH₂Cl₂), a plethora of indoles **2** were evaluated for the reaction with 3-hydroxyisobenzofuran-1(3*H*)-one **1**, and the results are summarized in **Table 2**.

As shown in **Table 2**, the reaction has broad applicability with respect to the indoles. A wide range of indoles bearing either an electron-withdrawing or electron-donating substituent at various positions on the indole ring were included as the reaction partners, leading to the formation of the desired products in good to excellent yields (**Table 2**, Entries 2-14, in most cases, over 90% yields were obtained). Generally, electron-rich indoles exhibited a higher reactivity than those of electron-poor ones. It is worth noting that the most electron-deficient nitro-substituted indole **2n** also worked well to affording the corresponding alkylation product **3n** with satisfactory yield (**Table 2**, Entry 14). Subsequently, the reaction between indole (**2a**) and 3-ethyl-3-hydroxyisobenzofuran-1(3*H*)-one [23,27], an interesting reaction partner, since an oxygen-containing quaternary carbon will be created in the Friedel-Crafts alkylation reaction, was also investigated. Unfortunately, no reaction occurred even at elevated reaction temperature (60°C).

4. Conclusion

In summary, we have developed an efficient and facile method for the synthesis of 3-indolyl-substituted phthalides by Friedel-Crafts alkylation of indoles with

Table 2. The synthesis of 3-indolyl-substituted phthalides between 3-hydroxyisobenzofuran-1(3*H*)-one and indoles catalyzed by TsOH·H₂O^a.



Entry	Product	R	R'	Time (h)	Yield (%) ^b
1	3a ^c	H	H	3	95
2	3b ^c	H	CH ₃	3	93
3	3c ^c	2-CH ₃	H	3	96
4	3d ^c	2-Ph	H	3	88
5	3e ^c	5-OCH ₃	H	3	96
6	3f ^c	5-OBn	H	12	92
7	3g ^c	5-F	H	24	91
8	3h ^c	5-Cl	H	24	92
9	3i	5-OH	H	24	89
10	3j ^c	5-Br	H	24	94
11	3k	6-OBn	H	12	89
12	3l ^c	6-F	H	5	89
13	3m	6-Cl	H	24	88
14	3n ^c	6-NO ₂	H	24	77

^aReactions were performed on a 1 mmol scale of **1** with a concentration of 0.5 mol·L⁻¹; ^bisolated yield; ^cAccording to the literatures [16,18,19].

3-hydroxyisobenzofuran-1(3*H*)-one. Compared to the limited literature reports, this method is more attractive because of its high efficiency, mild reaction conditions, readily available starting materials as well as the cheap catalyst. Various substituted indoles can react smoothly to give the corresponding phthalides in good to excellent yield. Attempts toward the asymmetric version of this alkylation reaction are underway in our laboratory at present.

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