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# 1,3-Dibromo-5,5-dimethylhydantoin: a versatile catalyst for synthesis of 3,3-bis(indolyl)oxindoles

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## Abstract

A condensation of various isatins with indole derivatives has been carried out in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as catalyst at 50 °C in ethanol in order to form 3,3-bis(indolyl) oxindoles. The products were obtained within 20-90 min by 70-96% yields. The efficacy of the procedure has been confirmed by catalyzing the condensation reaction of pyrrole which was used as another sort of heterocycle with indole to obtain its corresponding 3,3-bis(2-pyrrolyl)oxinole. A plausible mechanism of the condensation based on DBDMH activating role has also been proposed. DBDMH is an effective, commercially available, insensitive to moisture and easily handling catalyst. Simple procedure, easy work-up, mild reaction conditions, high yields and short reaction times are the highlighted points of reported method.

**Keywords:** 1,3-Dibromo-5,5-dimethylhydantoin, isatin, indole, 3,3-bis(indolyl)oxindoles.

## Introduction

Isatin (1H-indole-2,3-dione) which would be identified as an endogenous compound in the human body has a range of biological properties including actions in the brain and offering protection against certain type of infections [1]. A numerous category of isatins is oxindoles which possess antibacterial, anti-inflammatory,antiprotozoal and mechanism-specific antiproliferative properties and also patented as PR (progestrone receptors) agonists [2]. Much attention has been devoted to the preparation of oxindole rings because their systems are the core structure of many pharmacological agents [3]. For

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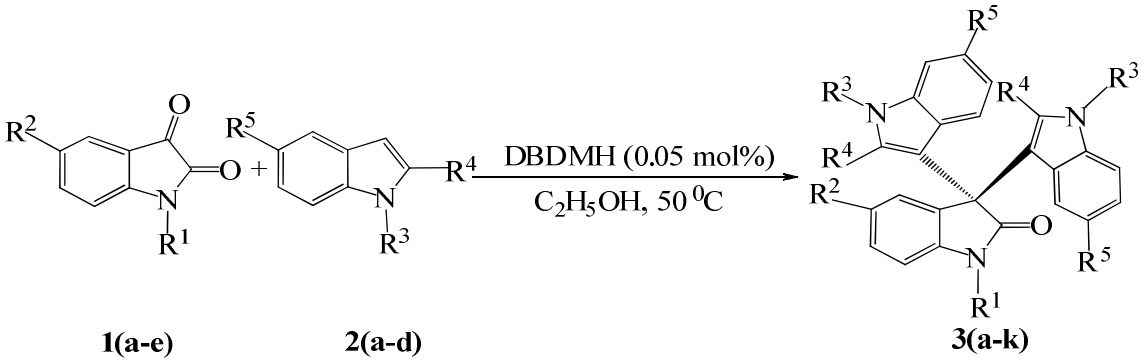
example, spiro[indole-thiazolidinones] possess antifungal activities against pathogens [4]. The synthesis of 3,3-bis(indolyl)oxindole (Scheme 1, 3a) was first reported by Seidel in 1950 [5]. 3,3-Bis(indolyl)oxindole(3,3-Bis(indolyl) indoline-2-ones) showed anti-cancer properties [6]. During recent years, some methods which have been reported for the condensation of some electron-rich heteroaromatics such as indoles and pyrroles with isatins consist of using catalysts such as silica sulfuric acid (SSA) [7], $KAl(SO_4)_2{\cdot}12H_2O$ [8], cerric ammonium nitrate (CAN) [9], Phosphotungstic acid ($H_6P_2W_{18}O_{62}$) [10], montmorillonite K10 clay [11], KSF [12], ionic liquids [13], $FeCl_3$ [6] and $I_2$ [14] to prepare the corresponding, 3,3-bis(3-indolyl) and 3,3-bis(2-pyrrolyl)oxindoles. 1,3-Dibromo-5,5 dimethylhydantoin (DBDMH) is a five-membered heterocycle which has been extensively used as a brominating agent [15-17], and oxidant [18-20] agent in organic synthesis. During the last decade, DBDMH has attracted special attention as an efficient homogeneous catalyst in organic transformation, it is so because this compound is relatively nontoxic, commercially available, inexpensive, and insensitive to air and moisture. Therefore, in continuation of previous works on indole/isatin heterocylces [21-25] and DBDMH [26-28], we wish to report a new usage of DBDMH as an impressive, inexpensive and easily handling Lewis acid catalyst for the synthesis of 3,3-bisoxindole derivatives *via* the condensation reaction of various isatins with indoles and pyrrole at 50 °C in ethanol (Scheme 1).




**1(a-e)** **2(a-d)** **3(a-k)**

**Scheme 1.** Synthesis of 3,3-bis(indolyl)oxindoles.

## Experimental

*General*

Isatins, indoles, pyrrole, DBDMH and solvents were purchased from Merck, Aldrich and Alfa Aesar and were used without further purification. *N*-Benzylisatin is synthesized from isatin according to the reported procedure [29]. Melting points were determined using a Stuart Scientific SMP2 capillary apparatus and are not corrected. IR spectra were recorded from KBr discs on Shimadzu IR-435. $^1$H NMR spectra were recorded with a Brucker drx 500 (500 MHz) machine. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. Preparative layer chromatography (PLC) was carried out on 20×20 cm$^2$ plates, coated with a 1 mm layer of Merck silica gel $PF_{254}$, prepared by applying the silica as slurry and drying in air.

### General procedure for the synthesis of 3,3-bis(indolyl)oxindoles

To the solution of isatins 1a-e (1 mmol) and indoles 2a-d or pyrrole (2.1 mmol) in $C_2H_5OH$ (5 mL), DBDMH (0.05 mmol) was added. The mixture was stirred at 50 °C. The progress of the reaction was monitored by TLC. After completion (20-90 min), the solvent was evaporated and the resulting crude residue was purified by chromatography on silica gel (eluent: *n*-hexane-ethyl acetate, 1:1) to afford the pure products (70-96%). All the products were characterized by comparison of their spectroscopic data (IR, $^1$HNMR and Mass spectra) with those of the authentic samples in literature. The spectral data of a selected compound (3l) is given below.

**3,3-Bis(2-pyrrolyl)-oxindole (3l) [9].** Pale yellow solid, mp 173-175 °C; IR (KBr): υ= 3351 (NH), 3261 (NH), 1710 (C=O), 1618, 1462, 1078, 738 (N-H) Cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ= 6.02 (br s, 2H), 6.13-6.14 (m, 2H), 6.75 (s, 2H), 6.94 (d, *J*= 7.74 Hz, 1H), 7.14 (t, *J*= 7.56 Hz, 1H), 7.28 (br s, 1H, NH), 7.29 (t, *J*= 7.88 Hz, 1H), 7.49 (d, *J*= 7.45 Hz, 1H), 8.67 (br s, 2H, $NH_2$) ppm. EI-MS m/z (%) 263 [$M^+$, 53] (18), 220 [$M^+$-CO, -NH] (25), 153 [$M^+$-HCO, -NH-, -pyrroyl] (17), 65 [pyrolyl$^+$] (100).

## Results and discussion

To investigate the solvent nature and DBDMH amount on reaction rate, the model condensation of indole and isatin was performed in various solvents, mole ratio of catalyst and also different thermal conditions. The results are summarized in Table 1. According to the data, among different polar and non-polar solvents, EtOH led the best

results (Entries 1, 2, 4, 5 and 7). Optimizing the temperature effect confirmed that 50 °C is appropriate (Entries 5, 6 and 8). The 0.05 mmol of DBDMH is the enough amount of the catalyst (Entries 6, 9 and 10). Therefore, performing the reaction in ethanol at 50 °C has been chosen as the best condition for this purpose. Under this optimum media, the model reaction has been accomplished with different amounts of isatin and indole. The best results were obtained with the use of indole (2.1 mmol) and isatin (1 mmol). Under optimized reaction conditions, the reactions of various isatins 1(a-e) with indoles 2(**a-d**) were carried out until maximum progression of the reactions (Scheme 1). The results are given in Table 2.

In the next step, our aim was to confirm the efficacy of catalyst; we used pyrrole as another sort of *N*-bearing heterocycle which underwent condensation reaction with isatin. It is worth mentioning that the corresponding 3,3-bis(2-pyrrolyl)oxindole was obtained in good yield (Scheme 2). The result revealed the efficacy of the catalyst, as it could condense other heterocycles rather than indoles with isatin.

**Table 1.** Optimizing the condensation reaction of indole (2.1 mmol) and isatin (1 mmol) for the synthesis of 3,3-bis(indolyl)oxindole (3a) by DBDMH

| Entry | Condition | Temperature (°C) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | DBDMH (0.05 mmol)/ *n*-hexane | rt | 240 | 10 |
| 2 | DBDMH (0.05 mmol)/ $H_2O$ | rt | 60 | -[b] |
| 3 | DBDMH (0.05 mmol)/ solvent-free | rt | 60 | -[b] |
| 4 | DBDMH (0.05 mmol)/ $CH_3CN$ | 50 | 60 | 40 |
| 5 | DBDMH (0.05 mmol)/ EtOH | rt | 240 | 88 |
| 6 | DBDMH (0.05 mmol)/ EtOH | 50 | 60 | 90 |
| 7 | DBDMH (0.05 mmol)/ MeOH | 50 | 60 | 90 |
| 8 | DBDMH (0.05 mmol)/ EtOH | 80 | 60 | 92 |
| 9 | DBDMH (0.03 mmol)/ EtOH | 50 | 60 | 70 |
| 10 | DBDMH (0.07 mmol)/ EtOH | 50 | 60 | 90 |

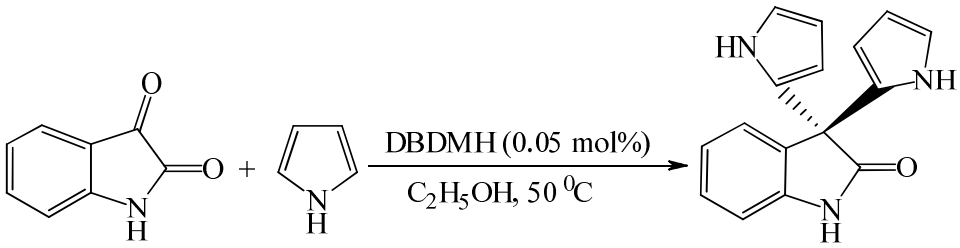
[a]Isolated yields.
[b]Different products were obtained

**Table 2.** Synthesis of 3,3-bis(indolyl)oxindoles (3a-k) by DBDMH

| Product[a] | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Time (min) | Yield[b] (%) | Mp (°C) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Found | Reported |
| **3a** | H | H | H | H | H | 60 | 90 | 313-315 | 312-314[30] |
| **3b** | H | H | $CH_3$ | H | H | 45 | 80 | 329-331 | 330-332[30] |
| **3c** | H | H | H | $CH_3$ | H | 20 | 96 | 295-297 | 300-303[13a] |
| **3d** | H | H | H | H | Br | 60 | 80 | 300-302 | 298-300[12] |
| **3e** | $CH_3$ | H | H | H | H | 65 | 95 | 287-289 | 291-293[10] |
| **3f** | $CH_3$ | H | H | $CH_3$ | H | 65 | 80 | 266-268 | 271-273[13a] |
| **3g** | $PhCH_2$ | H | H | H | H | 50 | 87 | 282-284 | 288-289[10] |
| **3h** | $PhCH_2$ | H | H | $CH_3$ | H | 30 | 95 | 208-210 | 211-213[10] |
| **3i** | H | Br | H | H | H | 90 | 90 | 312-314 | 310-311[7] |
| **3j** | H | $NO_2$ | H | H | H | 90 | 90 | 300-301 | 298-299[8] |
| **3k** | H | $NO_2$ | $CH_3$ | H | H | 50 | 70 | 312-314 | >300[13b] |

[a]All products were characterized by comparison of their spectroscopic data (IR, $^1$HNMR) with those reported in literature.

[b]Yield of isolated product

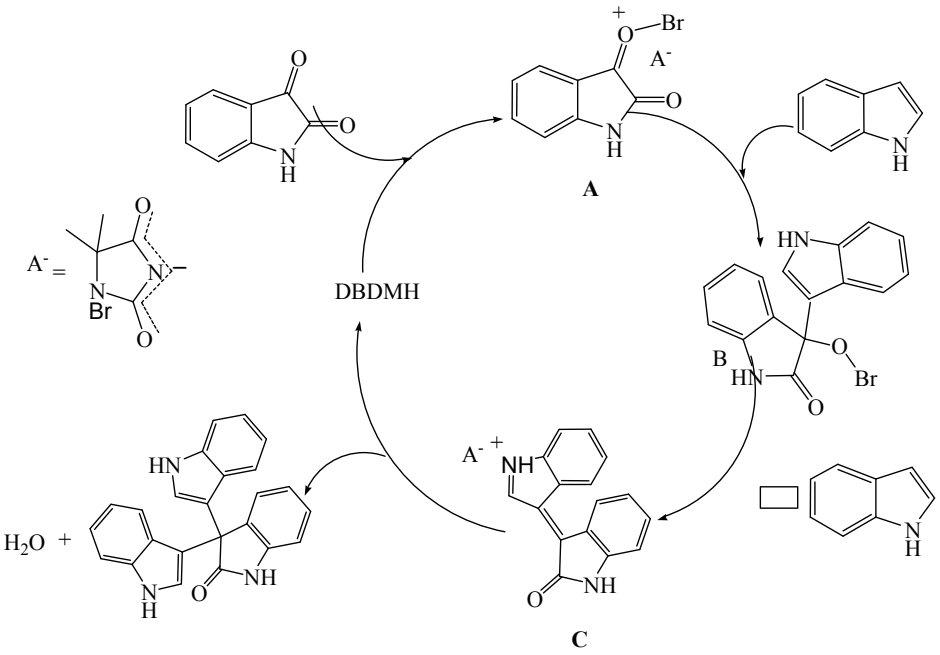



**3l** (60 min, 90 %)

**Scheme 2.** Synthesis of 3,3-bis(2-pyrrolyl)oxindole.

On the basis of forgoing results, we reported a proposed mechanism for this condensation. DDBDMH releases a bromonium ion which activates the 3-position carbonyl group of isatin form A. Nucleophilic attack of indole to this structure gave the

intermediate B that dehydrated to C. Subsequent nucleophilic addition of another indole to C form the 3,3-bis(indolyl)oxindole as the main product. The bromonium ion goes to the cycle as DBDMH (Scheme 3).




**Scheme 3.** The plausible mechanism of condensation

## Conclusion

In this paper, we have demonstrated the application of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as very effective, eco-friendly and inexpensive commercial-available catalyst in the synthesis of symmetrical 3,3-bis(heteroaryl)oxindoles under mild reaction conditions. The plausible mechanism confirmed the key role of DBDMH in catalyzing the condensation reaction. Simple experimental procedure associated with high yield and short reaction times make this protocol interesting for organic chemists.

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