An Efficient and Green Method for the Synthesis of Oxindole Derivatives in Water

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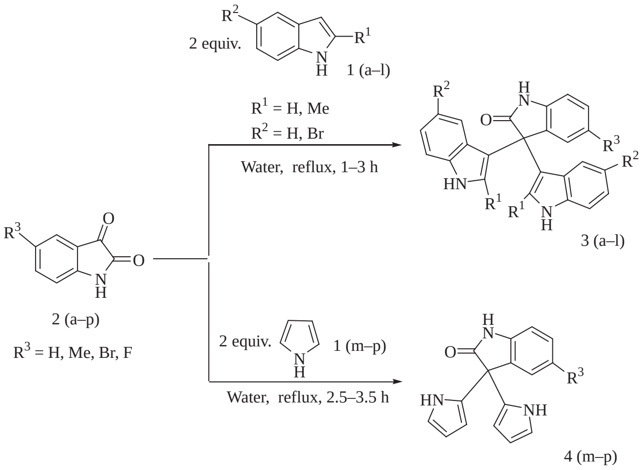
An environmentally benign method for the synthesis of 3,3-di(3-indolyl)- and 3,3-di(2-pyrrolyl)oxindoles by using various isatins, indoles, and pyrrole in water in excellent yields and high regioselectivity without using any catalyst.

Oxindole derivatives represent an important class of naturally occurring substances characterized by highly pronounced biological properties. Oxindole derivatives are found to be potent aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol,[1] and they possess different biological activities such as antibacterial, antiprotozoal, and anti-inflammatory activities.[2] Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds.[3] Furthermore, these heterocyclic compounds isolated recently from the marine bryozoan *Amathia convoluta* were found to show potent activity in the differentiation of HL-60 human promyelocytic leukenie cells.[4] Oxindole derivatives are precursors of some alkaloids.[5]

The syntheses of 3,3-diaryl, and dibarbiturates of oxindoles were reported by various mehods.[6] Recently, these 3,3-disubstituted oxindole derivatives were reported to be synthesized by using various catalysts such as silica sulfuric acid,[7] bismuth(III) triflate,[8] ceric ammonium nitrate (CAN),[9] and other routes.[10] However, these reactions were typically performed in organic solvents such as CH_3CN, CH_2Cl_2, EtOH, and workup procedures are typical.

To avoid the usage of these hazardous organic solvents and catalysts, we attempted the synthesis of 3,3-di(3-indolyl)- and 3,3-di(2-pyrrolyl)oxindoles in water in excellent yields without using any catalyst. To the best of our knowledge this reaction is not reported in water without using catalyst.

Nowadays, the development of environmentally friendly techniques is one of the priority goals of chemical research. Water as a solvent is not only inexpensive and environmentally benign, but also gives completely new reactivity. Water is a preferred solvent in organic reactions, offering a series of advantages over organic solvents such as safety, convenience, economics, environmental benign, etc. Organic reactions in water have attracted much attention.[11]



Scheme 1.

Table 1. Condensation of isatins with indoles

Entry	Indole **1**	Isatin **2**	Product[a] **3**	Time /h	Yield[b] /%
a	$R^1 = H, R^2 = H$	$R^3 = H$	**3a**	1.0	87
b	$R^1 = Me, R^2 = H$	$R^3 = H$	**3b**	1.0	85
c	$R^1 = H, R^2 = Br$	$R^3 = H$	**3c**	2.0	86
d	$R^1 = H, R^2 = H$	$R^3 = Me$	**3d**	1.0	93
e	$R^1 = Me, R^2 = H$	$R^3 = Me$	**3e**	1.0	84
f	$R^1 = H, R^2 = Br$	$R^3 = Me$	**3f**	3.0	85
g	$R^1 = H, R^2 = H$	$R^3 = Br$	**3g**	1.0	82
h	$R^1 = Me, R^2 = H$	$R^3 = Br$	**3h**	1.5	84
i	$R^1 = H, R^2 = Br$	$R^3 = Br$	**3i**	3.0	80
j	$R^1 = H, R^2 = H$	$R^3 = F$	**3j**	1.0	84
k	$R^1 = Me, R^2 = H$	$R^3 = F$	**3k**	1.0	82
l	$R^1 = H, R^2 = Br$	$R^3 = F$	**3l**	2.5	81

In general the reaction has been carried out by taking the two components isatins and indoles/pyrrole in deionized water and the mixture was refluxed for about 1.0–3.5 h (Scheme 1), which afforded the corresponding oxindole derivatives in excellent yields (93–65%).[12]

Entry d (Table 1) was taken as a representative example for comparing reaction rate in various organic solvents such as CH_2Cl_2, CH_3CN, DMF, MeOH, and DMSO. In DMSO and MeOH, only 10% product formation was observed after 16–18 h in reflux condition, whereas no product formation observed in CH_2Cl_2, CH_3CN, and DMF. After optimizing the condition, we next applied the generality of the condensation of various isatins with different indoles/pyrrole and the results obtained are listed in Tables 1 and 2.

Electron-withdrawing and -donating groups on isatin have not showed considerable effect on the product formation. But in the case of indole substituents showed prominent effect on

Table 2. Condensation of isatins with pyrrole

Entry	Pyrrole **1**	Isatin **2**	Product[a] **4**	Time /h	Yield[b] /%
m	Pyrrole	$R^3 = H$	**4m**	3.0	66
n	Pyrrole	$R^3 = Me$	**4n**	2.5	68
o	Pyrrole	$R^3 = Br$	**4o**	3.5	69
p	Pyrrole	$R^3 = F$	**4p**	3.5	65

[a] All products were characterized by IR, ^1H NMR and mass spectroscopy. [b] Unoptimized, isolated yields.

the product formation. The condensation of 5-bromoindole (Entries c, f, i, and l) with various isatins took longer times compared to the simple indoles. The reaction of pyrrole with isatin provides moderate yields, since there is probability for further reaction of another active 2-position of pyrrole with isatins. In all these reactions, electrophilic activation occurred only at the 3-position of the carbonyl of isatins. The carbonyl at the 2-position is unreactive and this may be due to stabilization by the indole nitrogen atom. The products were confirmed by spectroscopy (IR, ^{1}H NMR, and MS) or otherwise compared with known compounds. The procedure described in this paper was found to be much more effective than those described in earlier reports.

In conclusion, we have described a new and green protocol for the preparation of 3,3-di(3-indolyl)- and 3,3-di(2-pyrrolyl)-oxindoles. This green and environmentally benign method offers mild reaction conditions, short reaction times, high conversions, and easy experimental procedure. All the reactions reported by this method were proceeded smoothly without the formation of by-products. This method appears to be suited for large-scale operations.

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12 General procedure for synthesis of oxindole derivatives: A mixture of isatins (1 mmol) and indoles/pyrrole (2 mmol) taken in deionized water (2 mL) was refluxed for the appropriate time as mentioned in the Tables 1 and 2. The reaction was monitored by TLC. The product was filtered and the crude product was crystallized from ethanol.