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Water-Promoted Synthesis of 3,3'-Di(indolyl)oxindoles

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Water-Promoted Synthesis of 3,3'-Di(indolyl)oxindoles

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Abstract: The reaction of isatin and indoles in refluxing water/ethanol (7:3) affords 3,3'-di(indolyl)oxindoles in excellent yields.

Keywords: 3,3'-Di(indolyl)oxindoles, indole, isatin, water-promoted reaction

The importance of indole and its derivatives is well recognized by synthetic as well as biological chemists.^[1] Therefore, considerable efforts have been made to synthesize analogs of 3,3'-di(indolyl)oxindoles, which were prepared from the reaction of isatin and indoles using a broad range of acidic catalysts such as protic acid,^[2] ceric ammonium nitrate (CAN)/ultrasound,^[3] KAl(SO₄)₂,^[4] silica sulfuric acid,^[5] and Bi(OTf)₃.^[6]

Continuing our interest in indoles and the development of green procedures for the synthesis of diverse heterocyclic compounds of biological significance,^[7] we report a simple and efficient method for 3,3'-di(indolyl)oxindoles by the reaction of isatin and indoles in H₂O–EtOH (Scheme 1).

One equivalent of isatin 1a and 2 equiv. of indole 2a in a water– ethanol mixture (7:3) were heated under reflux for 7 min to afford 3,3'di(indolyl)oxindole 3a in 85% yield. The structure of the compound was supported by the spectroscopic data, elemental analysis, and comparison with the sample prepared by the literature procedure.^[3,5]

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Scheme 1. Synthesis of 3,3'-di(indolyl)oxindoles.

We have synthesized a series of compounds 3b-n by utilizing isatin derivatives (1a-d) and indole derivative (2a-e) under similar conditions (Table 1). It is interesting to note that 5-methyl indole had the greatest reactivity, but 3-methyl indole did not react.

We also studied the reaction in various solvents such as dichloromethane, acetonitrile, toluene, and tetrahydrofuran (THF) under refluxing conditions in the absence of a catalyst. However, we could not get satisfactory results. When methanol/ethanol was used as the reaction medium, it gave a good yield of the product, but when we used aqueous methanol or ethanol, it greatly increased the yield and reduced the reaction time. However, because of the toxicity of methanol, reactions were carried out using only $EtOH/H_2O$.

In conclusion, we report a very simple and efficient method for the synthesis of 3,3'-di(indolyl)oxindoles from the reaction of isatins and

Product	R	\mathbf{R}^1	\mathbb{R}^2	R ³	Time (min)	Yield (%) ^a
3a	Н	Н	Н	Н	7	85
3b	Н	Н	CH_3	Н	10	75
3c	Н	Н	Н	CH_3	5	86
3d	Н	CH_3	Н	Н	10	80
3e	Н	Н	Н	Br	38	55
3f	CH_3	Н	Н	Н	8	82
3g	CH_3	Н	CH_3	Н	12	70
3h	CH ₃	Н	Н	CH_3	5	83
3i	CH ₃	CH_3	Н	Н	8	74
3j	Ts	Н	Н	Н	10	78
3k	Ts	Н	CH_3	Н	12	77
31	Ts	Н	Н	CH_3	8	80
3m	Allyl	Н	Н	Н	10	75
3n	Allyl	Н	CH_3	Н	12	75

Table 1. Reaction of isatin 1 with various indoles 2

^aIsolated yields.

indoles, in the absence of any added catalyst. As far as possible, the reactions were carried out in an environmentally friendly by using water as a major part of the solvent system, thereby reducing the use of organic solvents. The products were obtained in excellent yields in a short reaction time. A suitable mechanism is put forward for the reaction where the solvent itself promotes the reaction. Undoubtedly it will be a valuable addition to the chemistry of indoles.

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