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Supramolecular Synthesis of 3-Indolyl-3-hydroxy Oxindoles under Neutral Conditions in Water

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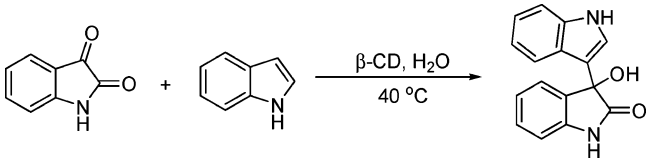
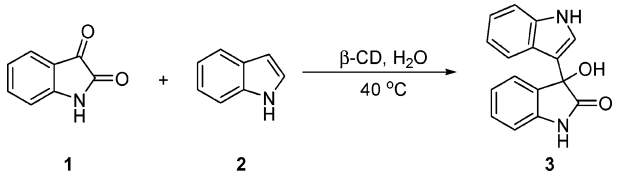


Various 3-indolyl-3-hydroxy oxindoles were prepared for the first time by supramolecular catalysis involving the reaction of β-CD:isatin complexes with indoles under neutral conditions in water. β-Cyclodextrin can be recovered and reused a number of times without loss of activity.

Supramolecular chemistry involves noncovalent intermolecular forces and has profound influence on the catalysis of a variety of organic reactions. It involves reversible formation of host−guest complexes by molecular recognition as seen in enzymes. Among various supramolecular hosts, cyclodextrins have excited much interest as enzyme models.[1] The most accessible β-cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of seven glucose units. The cavity size and the inner hydrophobicity are suitable for encapsulating a variety of guests such as aromatic compounds.[2] The improvement of the reaction rate and selectivity with β-CD inclusion complexes has been reported in a number of organic reactions.[3] The complex formation with β-CD could alter product distribution in the organic reactions. These characteristics arise from the geometrical constraint of the guest molecules on inclusion into β-CD. Herein, we demonstrate the molecular recognition ability and catalysis by cyclodextrins in the exclusive formation of 3-indolyl-3-hydroxy oxindoles from isatins and indoles under neutral conditions in water.

SCHEME 1



Isatins are familiar for their manifold biological activity and indole fragment is featured widely in a wide variety of biologically active compounds.[4] Some derivatives of isatin are key intermediates in the synthesis of natural products.[5] Isatin and its derivatives possess a reactive keto-carbonyl group that readily undergoes condensation reactions under mild conditions.[6] Different derivatives of isatin have been synthesized to study their bioactivity. Oxindoles are well-known among these compounds. Oxindoles are useful as antibacterial, anti-inflammatory,[7] laxative,[8] Growth hormone secretagogue,[9] and new targets for cancer chemotherapy.[10] These intermediates are also useful in the synthesis of chiral ligands to obtain high enantioselectivities in numerous catalytic reactions.[11]

In spite of different biological activities associated with various oxindole derivatives,[12] the synthesis of monosubstituted 3-indolyl-3-hydroxy oxindoles by Friedel−Crafts reaction of indoles with electron-deficient carbonyl compounds such as isatins will be one of the synthetically useful transformations since this reaction usually results in 3,3′-biindolyl oxindoles.[13] Thus, there is need to develop a generally applicable, mild and environmentally benign practical methodology for 3-indolyl-3-hydroxy oxindoles from isatin and indoles under neutral conditions with a recyclable catalyst especially in water for reasons of safety, economical and environmental concerns. This becomes further sophisticated if these reactions can be performed under supramolecular catalysis. We have attempted the

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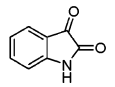
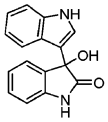
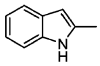
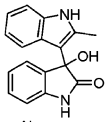
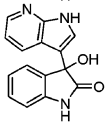
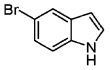
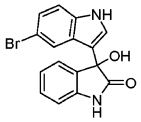
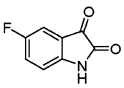
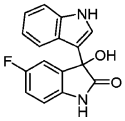
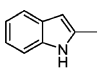
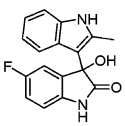
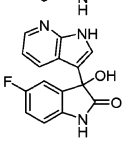
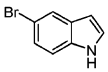
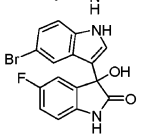
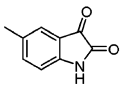
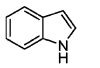
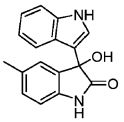
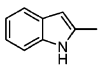
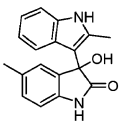
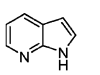
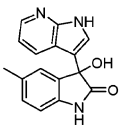
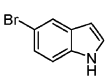
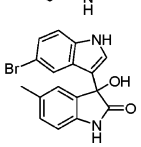
TABLE 1. Synthesis of 3-Hydroxy-3-indolylindolin-2-ones in the Presence of β-Cyclodextrin in Water

Entry	Isatin (**1**)	Indole (**2**)	Product (**3**)[a]	Time (min)	Yield (%)[b]
a				80	91
b				50	93
c				55	90
d				150	85
e				70	93
f				45	94
g				50	89
h				140	86
i				70	89
j				60	93
k				70	91
l				190	84

[a] All products were identified by IR, NMR, mass spectroscopy, and elemental analysis. [b] Yields of products isolated after column chromatography.

synthesis of 3-indolyl-3-hydroxy oxindoles from isatins and indoles by utilizing β-cyclodextrin in water under neutral conditions.

In general, the reactions were carried out by the in situ formation of 1:1 β-CD complex with isatin (**1**) in water followed by the addition of indole (**2**) and stirring for 1−3 h at 40 °C to give the corresponding products (**3**) (Scheme 1). The reaction proceeds smoothly with a high degree of conversion without the formation of any byproducts. This methodology is also compatible with various substituted isatins and indoles. No asymmetric induction was observed in these reactions. Several examples illustrating this simple and practical methodology are summarized in Table 1. However, this reaction did not proceed when the nitro group was present in the 5-position of the indole ring. All the products were characterized by ^{1}H NMR, IR, mass spectroscopy, and elemental analysis. The catalyst β-CD can be easily recovered and reused.

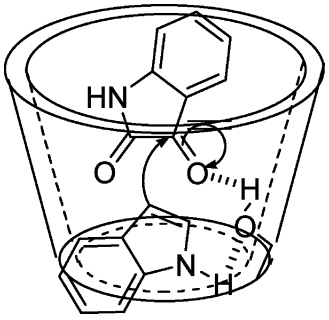


FIGURE 1. Supramolecular synthesis of 3-indolyl-3-hydroxy oxindoles.

The reaction also occurs at room temperature, but longer reaction times (>50 h) are required and the isolated yields of products are also low (15−25%). The substantial role of β-CD is illustrated by performing the reaction in water without using β-CD at 40 °C, where the formation of biindolyl products was identified. Use of a catalytic amount of β-CD (0.1 mmol per mole of the substrate) at 40 °C also has no impact and only gives biindolyl products. These experiments clearly demonstrate the significance of 1:1 complexation of β-CD with isatin in the catalysis of the reaction.

We propose a supramolecular catalysis for the formation of monosubstituted product by rigid complex formation between isatin and β-CD (Figure 1). The formation of complex can be explained by ^{1}H NMR studies. NMR spectroscopy is one of the most important techniques used for characterization of inclusion complexes. The formation of inclusion complex results in the shift changes in the resonances of the host cyclodextrin and the guest protons.[14]

A comparison of the ^{1}H NMR spectra (D_2O) of β-CD, β-CD:isatin complex, and freeze-dried reaction mixture of β-CD:isatin complex with the indole was studied. It is observed from Figure 2 that there is an upfield shift of H_3 (0.02 ppm) and H_5 (0.02 ppm) protons of cyclodextrin in the β-CD:isatin complex as compared to β-CD, indicating the formation of an inclusion complex of isatin with β-CD from the secondary side of cyclodextrin. It is further observed from the spectra of the reaction mixture of β-CD:isatin complex with the indole at 30 min that there is also an upfield shift of H_6 proton by 0.07 ppm. This indicates the complexation of the indole from the primary side of cyclodextrin for the reaction to proceed (Figure 2). This clearly demonstrates that the isatin is elegantly set for the

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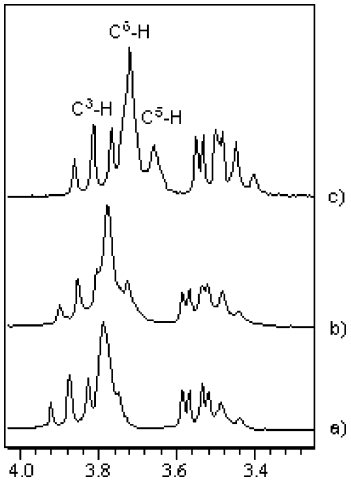

FIGURE 2. ^{1}H NMR spectra (200 MHz) of (a) β-CD, (b) β-CD:isatin complex, and (c) reaction mixture after 30 min. The spectra were obtained in D_2O at 25 °C.

addition reaction with the indole in the hydrophobic microenvironment of β-cyclodextrin cavity.

Thus, we have demonstrated, for the first time, an operationally simple and efficient aqueous phase synthesis of 3-indolyl-3-hydroxy oxindoles by using β-cyclodextrin under neutral conditions. β-Cyclodextrin, apart from being nontoxic, is also considered as metabolically safe.[15] This method is very simple, high yielding. and environmentally friendly. Further potential applications of this reaction are under study.

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Experimental Section

General Procedure for the Synthesis of 3-Indolyl-3-hydroxy Oxindoles. β-CD (1mmol) was dissolved in water (15 mL) by warming to 50 °C until a clear solution was formed. Then, isatin (1 mmol) dissolved in methanol (0.5 mL) was added dropwise followed by indole (1 mmol) and the mixture was stirred at 40 °C until the reaction was complete (as monitored by TLC) (Table 1). The mixture was extracted with ethyl acetate, and the extract was filtered. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the resulting product was further purified by column chromatography. The aqueous layer was cooled to 5 °C to recover β-CD by filtration. The recovered β-CD was reused for five consecutive runs in this reaction without any change in the yield and purity.

Preparation of β-CD:Isatin Inclusion Complex. β-CD (1 mmol) was dissolved in water (15 mL) by warming to 50 °C until a clear solution was formed, and then isatin (1 mmol) dissolved in methanol (1.0 mL) was added dropwise and the solution was allowed to come to room temperature. It was cooled to 5 °C for 12 h and the white precipitate was filtered and dried.

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Supporting Information Available: Characterization data for all compounds including ^{1}H NMR spectra and IR. This material is available free of charge via the Internet at http://pubs.acs.org.

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