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An efficient synthesis of 3-indolyl-3-hydroxy oxindoles and 3,3-di(indolyl)indolin-2-ones catalyzed by sulfonated β -CD as a supramolecular catalyst in water



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ABSTRACT

Sulfonated- β -cyclodextrin (β -CD- SO_3H) promoted efficient and fast electrophilic substitution reaction of indoles with various isatins reflux in water is reported affording various 3-indolyl-3-hydroxy oxindoles and 3,3-di(indolyl)indolin-2-ones in good to excellent yields in short reaction time.

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Indole derivatives are important compounds that are widespread in nature as well as exhibit significant biological activities.¹ 3-Substituted 3-hydroxyoxindoles are encountered in a large variety of natural products with a wide spectrum of biological activities.² 3,3-di(indolyl)indolin-2-one derivatives were assessed as anticancer,³ anti-HIV,⁴ antiviral,⁵ anti-tumor,⁶ antifungal,^{7,8} anti-angiogenic,⁹ anticonvulsants,¹⁰ anti-Parkinson's disease therapeutic,¹¹ and effective SARS corona virus 3CL protease inhibitor.¹² Furthermore, a large number of bis (indolyl) methanes have been isolated from natural sources,¹³ and some of these natural products, for example, vibrindole have shown promising biological activity.¹⁴

Recently a number of methods for the synthesis of 3-substituted-3-hydroxyoxindoles and 3,3-di(indolyl)indolin-2-ones have been reported in the literature involving the use of K_2CO_3 ,^{15a} β -cyclodextrin,^{15b} triton-B,^{15c} ZnO nano-rods,^{15d} LiClO_4 ,^{15e} Sc/In (OTF),^{15f} cupreine,^{15g} ionic liquids,^{16a} bismuth(III) triflate,^{16b} indium(III) acetylacetonate,^{16c} silica sulfuric acid,^{16d} Bronsted acidic ionic liquid,^{16e} ruthenium,^{16f} ceric ammonium nitrate (CAN) under ultrasound irradiation,^{16g} iodine,^{16h} KSF,¹⁶ⁱ water-ethanol,^{16j} and water^{16k} at reflux temperature. These reported methodologies produce good results in many instances. However, some of the synthetic strategies suffer from metal catalyst, expensive reagents, long reaction time, environmentally hazardous, harsh reaction condition, tedious work-up procedure, unsatisfactory yield and

use of homogeneous catalyst which are difficult to separate from the reaction mixture and reuse.

Aqueous phase organic synthesis has attracted the attention of chemists as it overcomes the harmful effects associated with the organic solvents and is environmentally benign. These reactions become more sophisticated if they can be performed under supramolecular catalysis. In view of the above, the development of a generally applicable and environmentally benign methodology for the synthesis of 3-indolyl-3-hydroxy oxindoles and 3,3-di(indolyl)indolin-2-ones derivatives is highly desirable. We report, herein, an aqueous phase synthesis of 3-indolyl-3-hydroxy oxindoles and 3,3-di(indolyl)indolin-2-ones from isatins and indoles in the presence of sulfonated- β -cyclodextrin (β -CD- SO_3H) (Fig. 1 and Scheme 1).

Supramolecular catalysis is a discipline in chemistry which involves intermolecular interactions where covalent bonds are not established between the interacting species which can be molecules, ions or radicals.¹⁷ 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.¹⁸ The improvement of the reaction rate and selectivity with β -CD inclusion complexes has been reported in a number of organic reactions.¹⁹ β -cyclodextrin mediated reactions in water are very useful tool for economic as well as environmental points of view.^{20,21} Sulfonated- β -cyclodextrin shows good results over β -cyclodextrin in the synthesis of 2,3-dihydroquinazolin-4(1H)-one²² and 3,4-dihydropyrimidine-2(1H)-one.²³

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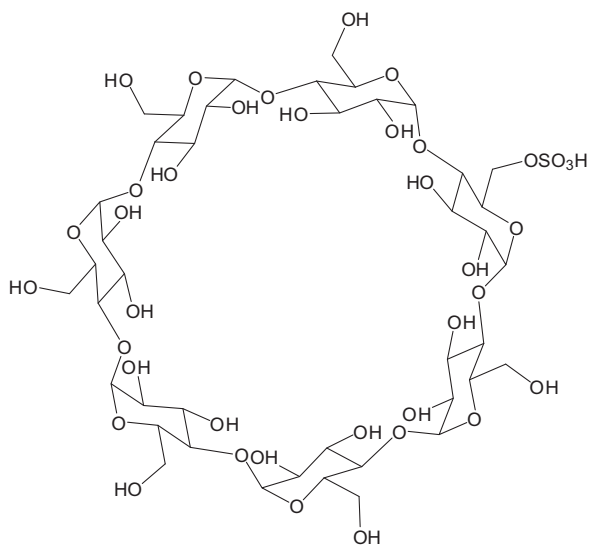


Figure 1. Chemical structure of β -CD-SO₃H.

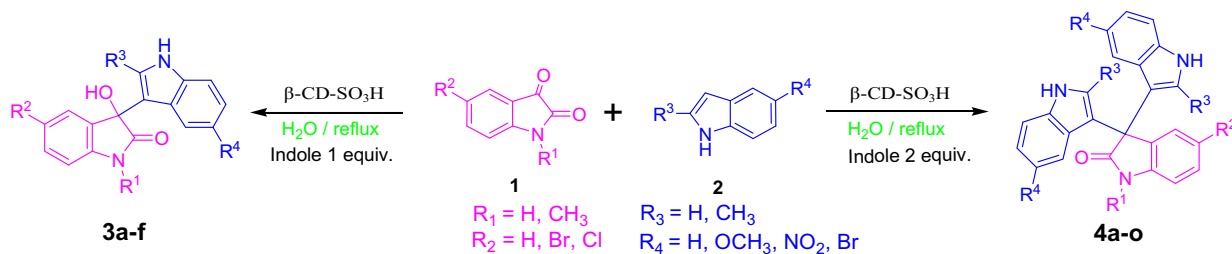
In continuation of our work on β -CD,²⁴ we envisioned β -CD-SO₃H as a supramolecular catalyst and study its application on the synthesis of 3-substituted 3-hydroxyoxindoles and 3,3-di(indolyl)indolin-2-ones to develop a simple and efficient method in aqueous media.

Initially, the β -CD-SO₃H was synthesized according to the method reported recently.^{22,23} The -SO₃H content obtained was in agreement with the proposed method, the value was 0.52 mequiv g⁻¹, and it matches with the literature report^{22,23}

confirmed the sulfonation of β -CD. The catalytic role β -CD-SO₃H for the synthesis of 3-substituted 3-hydroxyoxindoles and 3,3-di(indolyl)indolin-2-ones has been compared with various reported catalysts and found fast conversion within 5 min with yield up to 96% (Tables 1 and 2).

In order to optimize the reaction conditions and the performance of β -CD-SO₃H as a catalyst for the synthesis of 3-substituted 3-hydroxyoxindoles, we studied 5-methoxy indole with isatin as a model reaction. The reaction proceeds in the absence of β -CD-SO₃H to give lower yield (60%) with longer reaction time and in presence of 100 mol % β -CD and required 60 min to get 93% of yield.^{15b} The best result was obtained for 10 mol % of β -CD-SO₃H affording 96% of within 5 min (Tables 3 and 4). Encouraged by the initial success, we applied the optimal protocol to a variety of isatins and indoles (Table 5). Generally, the reactions were performed using 10 mol % of β -cyclodextrin-SO₃H in H₂O at reflux temperature for 5–15 min to give the desired products in good to excellent yields;²⁵ the results are summarized in Table 5.

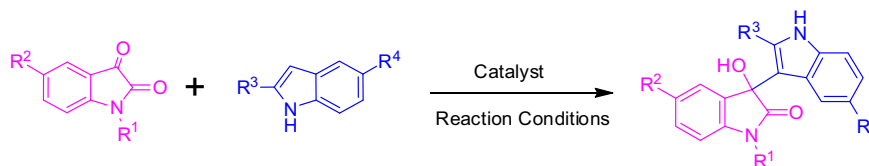
In order to optimize the reaction condition and the performance of β -CD-SO₃H as a catalyst for this 3,3-di(1*H*-indol-3-yl)indolin-2-one the reaction between simple isatin and 5-methoxy indole was selected as a model reaction by using different reaction parameters and various amounts of catalyst (Tables 3 and 4). The reaction proceeds in the absence of β -CD-SO₃H to give less yield (60%). The best result was obtained for 10 mmol % of β -CD-SO₃H (Table 6, entry 4c), affording 96% of 3,3-bis(5-methoxy-1*H*-indol-3-yl)indolin-2-one within 5 min. A further increase in the amount of catalyst has no significant effect on the yield and reaction time (Table 4, entries 4 and 5). The role of β -CD-SO₃H as the catalyst has been confirmed when a similar reaction was carried out in the absence of catalyst (Table 4, entry 1), giving only 60% yield with a longer reaction time 2 h. It indicates that β -CD-SO₃H not only improves the yield of the product but also accelerates the rate of reaction.



Scheme 1. General scheme for the synthesis of 3-indolyl-3-hydroxy oxindoles and 3,3-di(indolyl)indolin-2-ones.

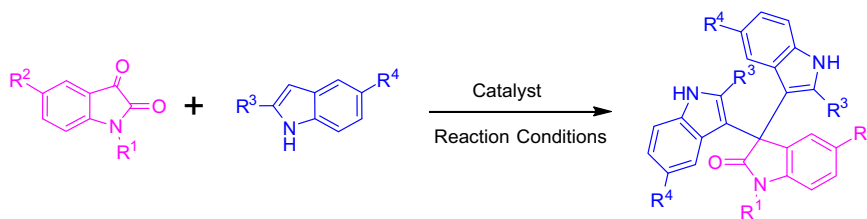
Table 1

Comparison for preparation methods of 3-substituted 3-hydroxyoxindoles with various reported catalysts



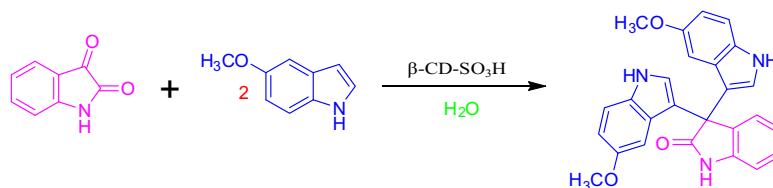
Entry	Catalyst	Reaction conditions	Time (h/min)	Yield (%)	Refs.
1	K ₂ CO ₃	20 mol %, rt, in water	1 h	91	15a
2	Triton-B	7 mol %, rt, in water	15 min	94	15c
3	ZnO nano-rods	10 mol %, 80 °C, in water	1.5 h	95	15d
4	LiClO ₄	10 mol %, 60 °C, in ethanol	4 h	93	15e
5	β -Cyclodextrin	100 mol %, 40 °C, in water	1 h	93	15b
6	β -CD-SO ₃ H	10 mol %, reflux in water	5 min	96	This work

Table 2
Comparison of preparative methods of 3,3-di(indolyl)indolin-2-ones with various reported catalysts



Entry	Catalyst	Reaction conditions	Time (h/min)	Yield (%)	Refs.
1	Ionic liquid	60 mol % of ([BMIM][BF ₄ LiCl]), rt	1 h	93	16a
2	Bismuth(III) Triflate	2 mol %, CH ₃ CN, rt	3 h	92	16b
3	Indium(III) acetylacetonate	10 mol %, (H ₂ O:CH ₃ CN 4:1), rt	2.5 h	92	16c
4	Silica sulfuric acid	0.2 g, CH ₂ Cl ₂ , rt	2 h	92	16d
5	Ruthenium trichloride	5 mol %, MeOH, 50 °C	2 h	75	16f
6	Ceric ammonium nitrate (CAN)	10 mol %, US, EtOH, rt	3 h	95	16g
7	I ₂ (Iodine)	10 mol %, CH ₂ Cl ₂ , rt	14 h	82	16h
8	KSF	0.1 g, reflux in EtOH	0.5 h	90	16i
9	β-CD-SO₃H	10 mol %, H₂O, reflux	5 min	96	This work

Table 3
Study of the effect of temperature on reaction time and yields for the synthesis of 3,3-bis(5-methoxy-1*H*-indol-3-yl)indolin-2-one^a

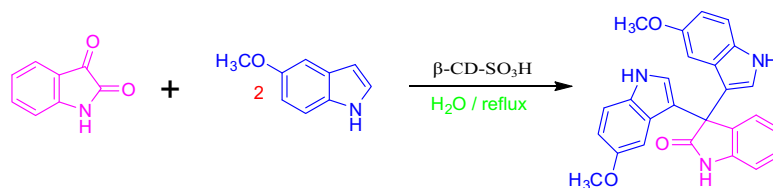


Entry	Temp (°C)	Time (min)	Yield ^b (%)
1	Rt	300	40
2	40	240	60
3	60	120	80
4	80	30	84
5	100	5	96

^a Reaction condition: isatin (1.0 mmol), 5-methoxy indole (2.0 mmol), β-CD-SO₃H (0.1 mmol) and water (2 mL).

^b Isolated yield.

Table 4
Formation of 3,3-bis(5-methoxy-1*H*-indol-3-yl)indolin-2-one using different amounts of catalyst at reflux in aqueous media^a



Entry	Catalyst (mmol)	Time (min)	Yield ^b (%)
1	β-CD-SO ₃ H (0.00)	120	60
2	β-CD-SO ₃ H (0.05)	20	90
3	β-CD-SO₃H (0.10)	5	96
4	β-CD-SO ₃ H (0.20)	5	94
5	β-CD-SO ₃ H (0.30)	5	94

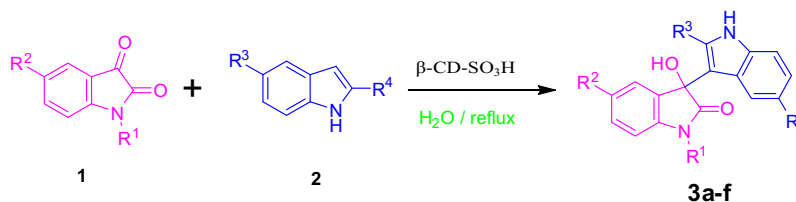
^a Reaction condition: isatin (1.0 mmol), 5-methoxy indole (2.0 mmol), water (2 mL), refluxed.

^b Isolated yield.

The significant presence of β-CD-SO₃H has a great influence on the reaction time as well as the yield (Table 4, entry 3). Temperature plays an important role, as at low temperature there is only a trace

amount of product formed and required longer reaction time and as the temperature increases from 40 °C to reflux the yields also increase with decrease in reaction time (Table 3).

Table 5
Synthesis of 3-hydroxy-3-indolyindoline-2-ones in the presence of β -CD-SO₃H in water at reflux temp^a



Sr. No.	Isatin	Indole	Product	Time (min)	Yield ^b (%)
3a				5	86
3b				5	92
3c				15	88
3d				5	96
3e				10	86
3f				5	88

^a Reaction condition: isatin (1.0 mmol), indole (1.0 mmol), β -CD-SO₃H (0.1 mmol), water (2 mL).

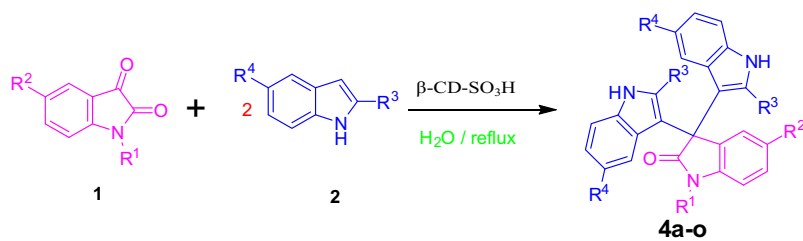
^b Isolated yield.

A variety of structurally divergent isatins possessing different substituents were selected to understand the scope and generality of the β -CD-SO₃H promoted reaction to form 3,3-di(indolyl)indolin-2-ones.²⁶ The results obtained are summarized in Table 6. For all the entries water was used as the solvent and the reaction was conducted under reflux condition. In all cases, the conversion was completed within 5–45 min with good to excellent yields except for 5-nitroindole (Table 6 entry 4e, 80% and entry 4i, 91%). A further increase in reaction time had no significant effect on the yields. In addition, the substituent on the aromatic indoles showed slightly different effects on the yields, reactions of aromatic indoles with electron-donating groups afforded little better yields of products than those with the electron-withdrawing groups (Table 6 entry 4e, 80% and entry 4i, 91%).

β -CD-SO₃H was chosen as the catalyst since it is recyclable, environmentally benign, easily accessible and due to presence of the –SO₃H group it possesses greater solubility than β -CD in water which enhances the rate of reaction greater than β -CD and shows good results over β -CD. The supramolecular β -CD have tendency to form inclusion complex with isatin which is reported by Rama Rao^{15b} similarly due to presence of the –SO₃H group in β -CD-SO₃H it possesses greater solubility than β -CD and also forms inclusion complex more effectively with isatin to enhance the rate of reaction.

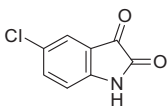
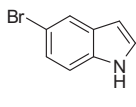
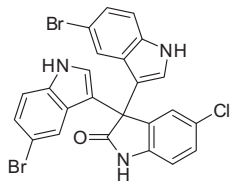
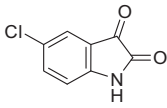
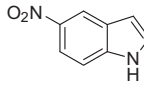
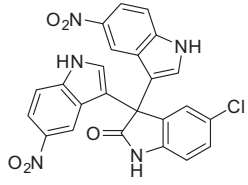
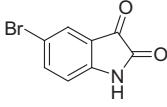
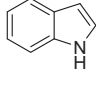
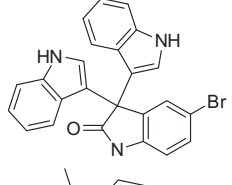
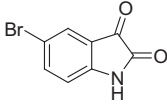
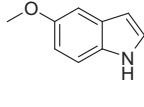
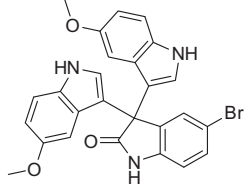
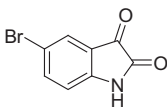
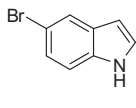
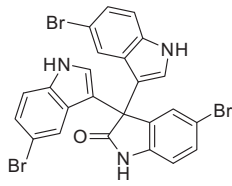
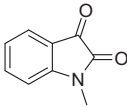
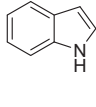
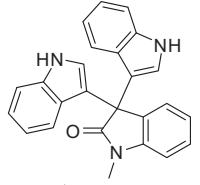
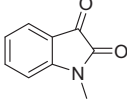
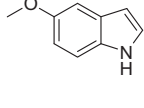
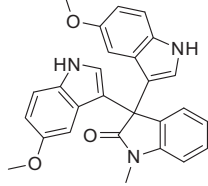
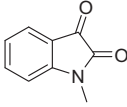
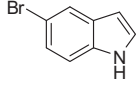
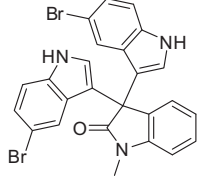
The catalyst recovery and reusability²⁷ were studied by three cycles including the use of fresh catalyst for the synthesis of 3,3-bis(5-methoxy-1H-indol-3-yl)indolin-2-one (Table 6, entry 4c). In every cycle, the catalyst was almost quantitatively recovered and after second and third use of catalyst decrease in yield is not much more significant which is shown in Figure 2. The FTIR spectra

Table 6
 β -CD-SO₃H catalyzed synthesis of 3,3-di(indolyl)indolin-2-ones^a



Sr. No.	Isatin	Indole	Product	Time (min)	Yield ^b (%)
4a				10	95
4b				15	95
4c				5	96 ^c , 94 ^d , 92 ^e
4d				45	94
4e				130	80
4f				30	91
4g				15	93

Table 6 (continued)

Sr. No.	Isatin	Indole	Product	Time (min)	Yield ^b (%)
4h				30	93
4i				130	91
4j				30	85
4k				30	88
4l				45	87
4m				15	94
4n				10	95
4o				45	90

^a Reaction condition: isatin (1.0 mmol), indole (1.0 mmol), β -CD-SO₃H (0.1 mmol), water (2 mL).

^b Isolated yield.

^{c,d,e} Yield after I, II, and III recycle of catalyst.

(Fig. 3) of fresh and recovered β -CD-SO₃H were also measured and no change was found in the functional group as well as in fingerprint region, indicating that no reaction occurs with β -CD-SO₃H.

In conclusion, we report β -CD-SO₃H as a highly efficient, reusable, environmentally benign catalyst for the synthesis of 3-substituted 3-hydroxyoxindoles and 3,3-di(indolyl)indolin-2-

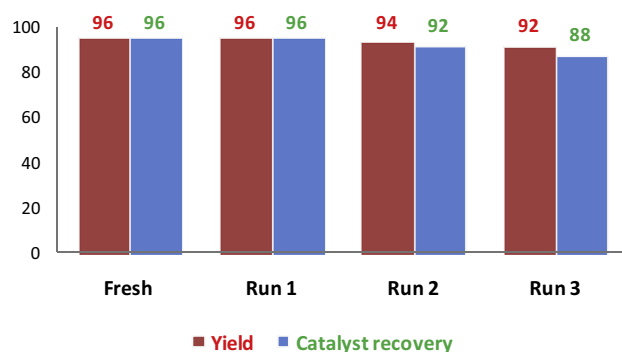


Figure 2. Catalyst β -CD-SO₃H recyclability data (for Table 6, entry 4c).

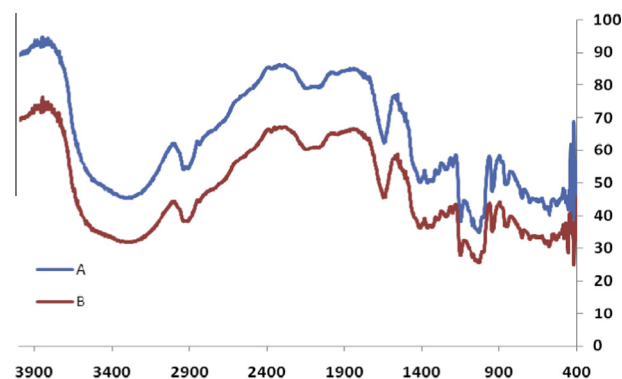


Figure 3. FTIR of (a) fresh β -CD-SO₃H and (b) recovered β -CD-SO₃H (for Table 6, entry 4c).

ones. The advantages of this catalyst are good to excellent yields of product, short reaction times, simple and clean work-up of the desired product without column chromatography, easy recovery and reuse of the catalyst.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.12.012>.

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- General procedure for preparation of sulfonated β -cyclodextrin: To a magnetically stirred mixture of β -cyclodextrin (5.107 g, 4.5 mmol) in CH₂Cl₂ (20 mL), chlorosulfonic acid (1.048 g, 9 mmol) was added slowly drop by drop at 20 °C during 3 h. After completion of addition, the mixture was stirred for 2 h to remove HCl from reaction vessel. Then, the mixture was filtered and washed with methanol (30 mL) and dried at room temperature to obtain sulfonated β -cyclodextrin as white powder (5.28 g). The -SO₃H content was measured by titration method and showed 0.52 mequiv g⁻¹.
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 - General procedure for the preparation of 3-indolyl-3-hydroxy oxindoles (**3a–f**): To the reaction mixture containing isatin (1 mmol) and indole (1 mmol) in water (2 mL), catalytic amount of β -CD-SO₃H (10 mol%) was added and stirred at reflux temperature for appropriate time and monitored through the TLC. After completion of reaction, it was cool at room temperature and filter to get the precipitate. The crude product was recrystallized from aqueous ethanol (60:40) giving pure 3-indolyl-3-hydroxy oxindoles.

26. *General procedure for the preparation of 3,3-di(indolyl)indolin-2-ones (4a–o):* Sulfonated- β -cyclodextrin (β -CD-SO₃H) (0.1 mmol) was dissolved in water (2 mL) at room temperature by stirring to get the clear solution. Then the reaction was shifted to reflux with addition of isatin (1 mmol) and indole (2 mmol) with constant stirring. The progress of the reaction was monitored by TLC. After completion of reaction, it was cooled to room temperature and filtered, to get the solid. The crude product was recrystallized from aqueous ethanol (60:40) giving pure 3,3-di(indolyl)indolin-2-ones.
27. *Catalyst recovery and reuse:* The catalyst recovery is convenient and easy to perform. The filtered aqueous layer was evaporated under vacuum and the crude catalyst was collected. The recovered crude catalyst was washed with diethyl ether to obtain pure catalyst, dried it and reused for next reaction.