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A facile, aqueous phase green synthetic protocol for the synthesis of 5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiols

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ABSTRACT

5,9b-Dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiols were synthesized for the first time in water under neutral conditions by using isatin, semicarbazide/thiosemicarbazide, mediated by β-cyclodextrin in excellent yields. β-Cyclodextrin has been recovered and reused without any loss of catalytic activity.

Over the years synthetic heterocyclic chemistry is providing impetus to the development of new drug scaffolds through iterative manipulation of functional groups around the rudimentary skeletal systems. Among these, heterocyclic compounds have been given special emphasis due to a wide variety of medicinal and biological properties associated with them[1] (Fig. 1).[2] In view of this, globally researchers started exploring simple and novel one-pot procedures to obtain potential new molecular entities,[3] belonging to a broad range of heterocyclic systems. 5,9b-Dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiols and their analogues exhibit varied biological activities/medicinal applications such as antimicrobial,[4–8] antiviral,[9] antihypertensive,[9,10] blood-platelet aggregation inhibitory,[10,11] and analgesic[12] activities. In addition, 3-arylidene-and 3-alditol-1-ylidenehydrazino-1,2,4-triazino[5,6-*b*]indoles showed antitumor activity against P388 lymphocytic leukemia in mice[13] and antibacterial activity.[14,15] Recently Ivachtchenko et al., reported the synthesis of 5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol by using isatin, and thiosemicarbazide mediated by base followed by acid.[16]

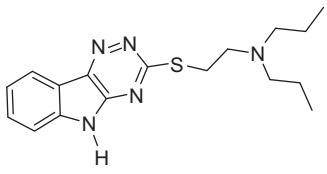

Figure 1. Polycyclic fused heteroaromatic skeleton with good biological activities.

In view of different biological activities associated with various 5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol derivatives and in continuation of our interest in the use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various transformations,[17] we have attempted a novel aqueous phase synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-thiols by the reaction of isatin derivatives with semicarbazide/thiosemicarbazide under neutral conditions involving supramolecular catalysis using β-cyclodextrin. Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding as seen in enzymes. We describe, herein, the first aqueous phase synthesis of a 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-thiol derivatives demonstrating the remarkable catalytic activity of β-cyclodextrin (Schemes 1 and 2). In general, the reaction was carried out by the in situ formation of β-CD complex of isatin in water followed by the addition of semicarbazide/thiosemicarbazide and stirring at 50–55 °C to give the corresponding a 5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-thiols in high yields (80–90%). These reactions

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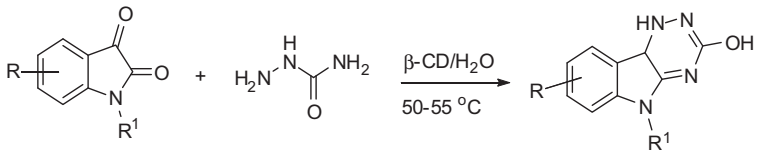
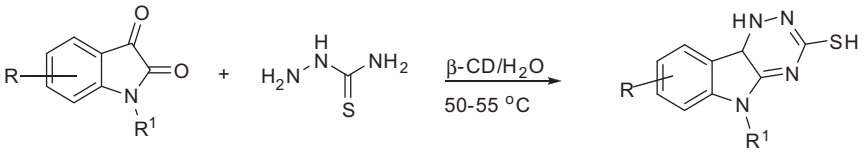


R = -H, -F, -Br, -Cl, -CH3, -OCH3, -NO2. R1 = -H, -CH3, -C6H5, -CH2C6H5.

Scheme 1. Synthesis of 5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols.



R = -H, -F, -Br, -Cl, -CH3, -OCH3, -NO2. R1 = -H, -CH3, -CH2C6H5.

Scheme 2. Synthesis of 5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3thiols.

proceeded efficiently without the need of any metal or acid catalyst. The reaction goes to completion in a short time (4–5 h). This methodology is also compatible with various substituted isatins. Even though these reactions take place with α-CD, γ-CD also effects this reaction *albeit* in lower yield. Therefore β-CD has been chosen as the mediator as it is inexpensive and easily accessible. Several examples illustrating this simple and practical methodology are summarized in Tables 3 and 4. No byproduct formation was observed. β-Cyclodextrin can be easily recovered and reused. All the compounds were characterized by ^{1}H NMR, IR, and mass spectrometry.[18,19] The catalytic activity of cyclodextrins for these reactions is established by the fact that no reaction was observed in the absence of cyclodextrin. Evidence for the complexation between isatin and cyclodextrin is obtained by ^{1}H NMR studies. Comparative ^{1}H NMR studies of β-CD, β-CD/isatin complex indicated an upfield shift of H3 (0.02 ppm) and H5 (0.02 ppm) protons of cyclodextrin in the β-CD: isatin complex as compared to β-CD, confirming the formation of an inclusion complex of isatin with β-CD.[17a] The complexation with β-CD increases the reactivity of the keto group of isatin due to intermolecular hydrogen bonding with the CD-hydroxyl groups facilitating the reaction with semicarbazide. Here, β-CD not only forms an inclusion complex with isatin but is also involved in the intermolecular hydrogen bonding with the guest to promote the reaction. β-CD was recovered and reused. After the reaction, the reaction mass was cooled to room temperature, β-CD was filtered, washed with ice-cold water and dried. The recovered β-CD was further used with the same substrate as a catalyst and checked for the yields and catalytic activity of recovered catalyst (β-CD). As shown in Table 1, the yields of 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-ols (Entry 1, Table 1) after two to three recycles were almost same.

Table 1
Recyclability of β-CD[a]

Cycles	Yield [%]	Catalyst recovered[b] [%]
Native	89	88
1	86	84
2	85	83
3	81	80

[a] All reactions was carried out using isatin (1.0 mmol), semicarbazide (1.0 mmol), and β-CD (1.0 mmol).
[b] Isolated yield.

In this study, a model reaction was conducted by reacting isatin and semicarbazide in water at 50–55 °C to obtain the corresponding 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-ol in low yields (18%). Because of poor solubility of isatin in water, reaction at elevated temperature also resulted in the formation of undesired products. When the same reaction was conducted using β-CD at room temperature the product was obtained in moderate yield (55%). However in a controlled experiment using β-CD as a supramolecular catalyst at 50–55 °C, the product was obtained in excellent yield (89%) (Scheme 1). In due course of the methodology development, for the first time various cyclodextrins such as α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin were examined

Table 2
Optimization of reaction conditions using different catalysts[a]

Entry	Catalyst	Yield [%][b]
1	Water (without catalyst)	18
2	α-Cyclodextrin	38
3	β-Cyclodextrin	89
4	γ-Cyclodextrin	58

[a] All reactions was carried out using isatin (1.0 mmol), semicarbazide (1.0 mmol), and β-CD (1.0 mmol).
[b] Isolated yield.

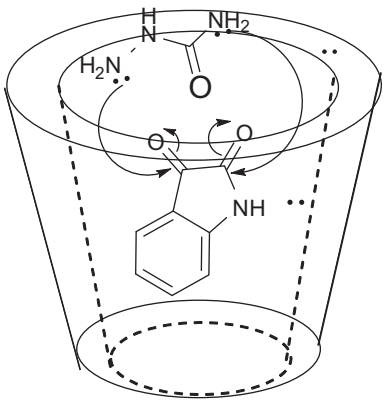
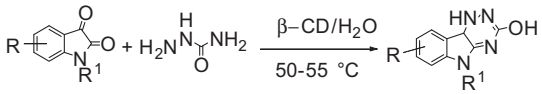
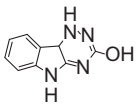
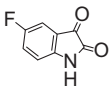
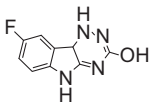
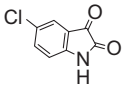
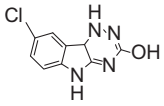
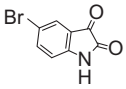
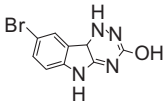
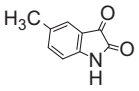
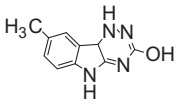
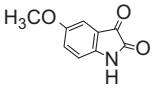
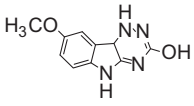
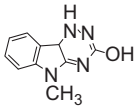
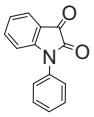
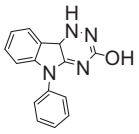
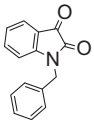
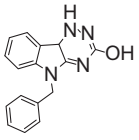
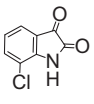
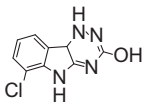
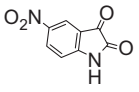
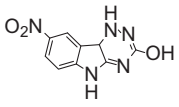


Figure 2. Possible mechanistic pathway for the formation of 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-ol using β-cyclodextrin.

Table 3
Synthesis of 5,9b-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole-3-ols[a]



Entry	Isatin	Product	Yield (%)[b]
1			89
2			90
3			88
4			87
5			85
6			83
7			84
8			86
9			85
10			87
11			90

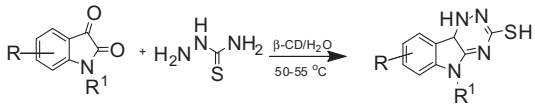
[a] Reaction conditions: isatin (1.0 mmol), semicarbazide (1.0 mmol), β-CD (1.0 mmol), and water (10 mL).
[b] Isolated yield.

for their efficiency as promoters in carrying out the reaction under supramolecular catalysis (Table 2).

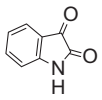
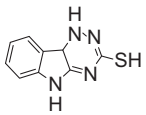
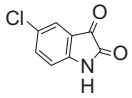
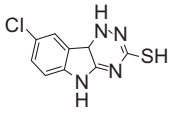
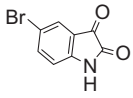
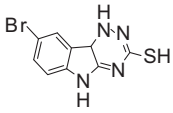
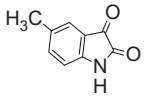
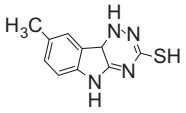
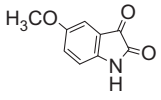
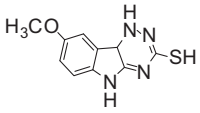
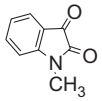
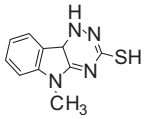
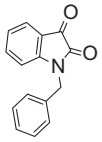
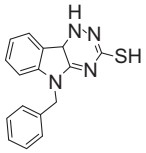
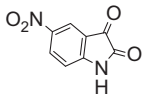
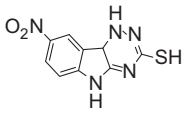
Cyclodextrin forms an inclusion complex with isatin, which further reacts with semicarbazide/thiosemicarbazide leading to the desired product as indicated in Figure 2.

In summary, we have developed an eco-friendly protocol for the synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-ols/5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-thiols in excellent

Table 4
Synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-*b*]indole-3-thiols[a]



R = -H, -F, -Br. -Cl, R_1 = -H, $-CH_3$, $-CH_2C_6H_5$.
$-CH_3$, $-OCH_3$, $-NO_2$.

Entry	Isatin	Product	Yield (%)[b]
1			83
2			84
3			83
4			81
5			80
6			80
7			82
8			85

[a] Reaction conditions: isatin (1.0 mmol), thiosemicarbazide (1.0 mmol), β-CD (1.0 mmol), and water (10 mL).
[b] Isolated yield.

yields under neutral conditions in one pot involving supramolecular catalysis by β-cyclodextrin in water. This simple and facile method will be a useful addition to green chemistry with an advantage that the reaction excludes highly flammable organic solvents, moisture sensitive or hazardous catalysts and elevated reaction temperatures.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.098.

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18. *General experimental procedure for the synthesis of 5,9b-dihydro-1H-[1,2,4]-triazino[5,6-b]indole-3-ol: (*Table 3*, Entry 1):* β-Cyclodextrin (1.0 mmol) was dissolved in water (10 mL) by warming to 50–55 °C until a clear solution was formed. Then, isatin (1.0 mmol) dissolved in methanol (0.5 mL) was added followed by semicarbazide (1.0 mmol) and the mixture was stirred at 50–55 °C until the reaction was complete (as monitored by TLC). After completion of the reaction, mixture was cooled to room temperature and β-cyclodextrin was filtered. The aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were extracted with water, saturated brine solution and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane (4:6) as eluent. The aqueous layer was cooled to 5 °C to recover β-CD (Table 1). The product was confirmed by IR, ^1H & ^{13}C NMR, mass spectra.
19. *Data for the representative examples of synthesized compounds:* 5,9b-dihydro-1H-[1,2,4]triazino[5,6-*b*]indol-3-ol (Table 3, Entry 1); Light yellow solid. M.p. 244–246 °C; IR ν_{max} (KBr): 3467, 3302, 3234, 3131, 2924, 2822, 1708, 1621, 1573, 1465, 1390, 1348, 1303, 1211 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$+DMSO,TMS) δ = 10.34 (s, 1H, –OH), 7.27–7.19 (m, 1H), 7.00 (d, 1H, *J* = 7.3 Hz), 6.69 (s, 1H), 6.45 (t, 1H), 6.35 (d, 1H, *J* = 7.7 Hz), 6.1 (s, 2H); ^{13}C NMR (75 MHz, DMSO,TMS) δ = 162.70, 154.96, 141.68, 131.04, 130.26, 122.03, 120.31, 120.08, 110.83; Mass (ESI-MS): *m/z* 189 $(M+H)^+$; Anal. Calcd for: ($C_9H_8N_4O$) C: 57.44, H: 4.28, N: 29.77; found C: 57.39, H: 4.22, N: 29.71.