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Novel Aqueous Phase Supramolecular Synthesis of 3-Pyrrolyl-indolin-2-ones and Pyrrolylindeno[1,2-*b*]quinoxalines

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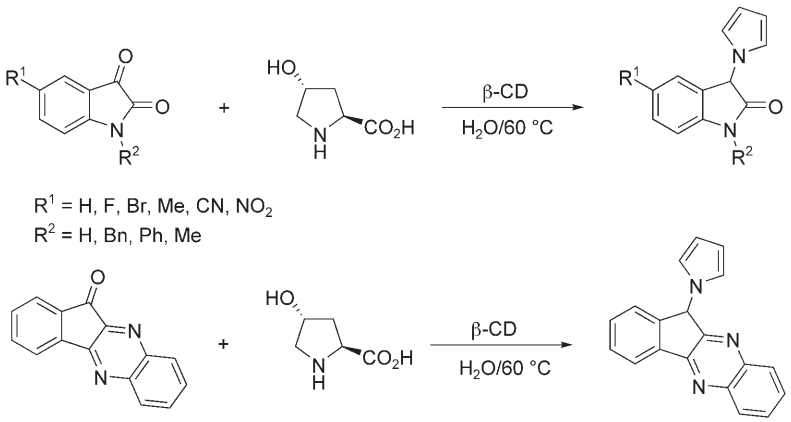
Abstract: Various 3-pyrrolylindolin-2-ones and pyrrolylindeno[1,2-*b*]quinoxaline were synthesized for the first time in high yields in water under neutral conditions by supramolecular catalysis involving β-cyclodextrin. The β-cyclodextrin can be recovered and reused a number of times without any loss of activity.

Keywords: β-cyclodextrin; *trans*-4-hydroxy-L-proline; indolinones; isatins; pyrroles; water

Pyrroles are an important class of compounds displaying remarkable pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antitumoral, and antioxidant activities.[1] Furthermore, they are useful intermediates in the synthesis of natural products and heterocycles[2] and are also widely used in materials science.[3] Various 3-substituted indoline-2-ones have been shown to exhibit tyrosine kinase inhibitory activity.[4] Receptor tyrosine kinases (RTKs) are important mediators of cellular signal transduction and are implicated in the transformation processes associated with human cancers.[5] In view of their high significance, many methodologies have been developed for the construction of the pyrrole skeleton.[6] The most frequently used methods include the classical Hantzsch procedure,[7] the cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal–Knorr synthesis)[8] and various cycloaddition strategies.[9] These approaches generally involve multistep synthetic operations limiting the scope of these reactions. Recently, a few syntheses of 3-pyrrolyl-2-indolinones by the condensation of *trans*-4-hydroxy-L-proline with various isatins have been described.[10] However, these methodologies also have limited scope due to the use of transition metal triflates, microwave irradiation, acidic conditions and hazardous solvents. As a consequence, the development of environmentally benign practical synthetic routes under neutral conditions in water for accessing these 3-pyrrolylindolin-2-ones still remains a major goal. Organic reactions in aqueous media have recently become the focus in organic synthesis since they overcome the



Scheme 1.

harmful effects of organic solvents and are environmentally benign.[10] Aqueous reactions can be made more sophisticated if they can be performed under supramolecular catalysis, for example, by β-cyclodextrins, overcoming many of the drawbacks observed in the previous methodologies.

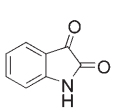
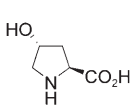
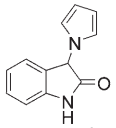
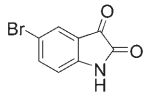
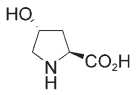
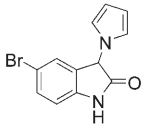
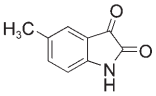
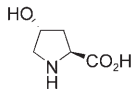
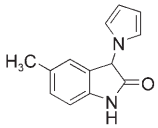
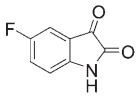
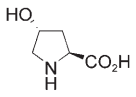
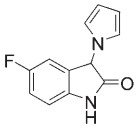
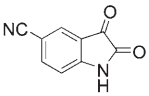
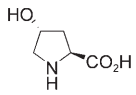
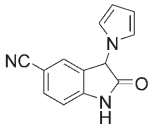
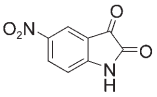
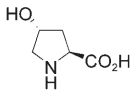
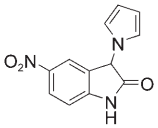
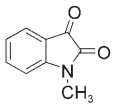
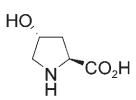
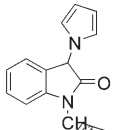
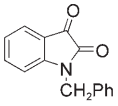
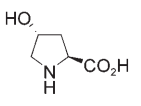
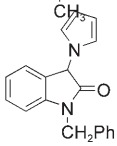
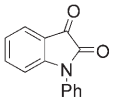
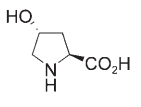
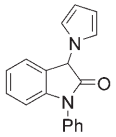
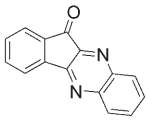
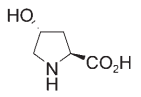
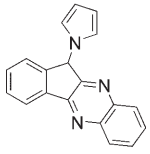
Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by a supramolecular process involving reversible formation of host-guest complexes through non-covalent bonding as seen in enzymes.

In continuation of our interest in the β-cyclodextrin-catalyzed biomimetic synthesis of heterocyclic compounds in the aqueous phase,[12] we have explored, the aqueous phase synthesis of 3-pyrrolylindolin-2-ones by condensation of *trans*-4-hydroxy-L-proline with isatin derivatives under neutral conditions and demonstrated the remarkable catalytic activity of β-cyclodextrin (Scheme 1).

In general, the reactions were carried out by forming *in situ* the β-CD complex of the isatin in water, followed by the addition of *trans*-4-hydroxy-L-proline and stirring at 60 °C. The corresponding 3-(1*H*-pyrrol-1-yl)-indolin-2-one compounds were obtained in impressive yields (90–96%) after 75–95 min. This methodology is compatible with various substituted isatins having different functionalities such as bromo, fluoro, methyl, cyano, nitro and with 1-methyl-, 1-phenyl- and 1-benzylisatins (Table 1, entrries a–i). It was also found that 11*H*-indeno[1,2-*b*]quinoxalin-11-ones (Table 1, entry j) underwent condensation with *trans*-4-hydroxy-L-proline to give 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalines in 87% yield under similar conditions. These reactions proceeded efficiently under neutral conditions. No by-product formation was observed. β-Cyclodextrin can be easily recovered and reused.

The ^{1}H NMR spectra (D_2O) of β-CD, the β-CD:isatin complex and a freeze-dried reaction mixture of the β-CD:isatin complex with the *trans*-4-hydroxy-L-proline were studied. It was observed from Figure 1 that there was an upfield shift of the 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.[13] In the spectra of the reaction mixture of the β-CD:isatin complex with *trans*-4-hydroxy-L-proline at 50 min we also observed an upfield shift of the CD H_6 proton by 0.045 ppm. This indicated that the reaction proceeded by complexation of *trans*-4-hydroxy-L-proline from the primary side of cyclodextrin (Figure 1). This clearly demonstrates that the isatin is ideally located for the condensation with the *trans*-4-hydroxy-L-proline in the hydrophobic microenvironment of β-cyclodextrin cavity (Figure 2).

Table 1. β-CD-catalyzed synthesis of 3-(1*H*-pyrrol-1-yl)indolin-2-ones and 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline.

Entry	Isatin (**1**)	*trans*-4-hydroxy-L-proline (**2**)	Product **3**[a]	Time [min]	Yield [%][b]
a				90	94
b				90	95
c				80	96
d				90	94
e				75	92
f				75	95
g				90	93
h				90	92
i				90	90
j				95	87

[a] All products were identified by IR, NMR, mass spectroscopy and elemental analysis.

[b] Yields of products isolated after column chromatography.

The catalytic activity of cyclodextrins for these reactions is established by the fact that no reaction was

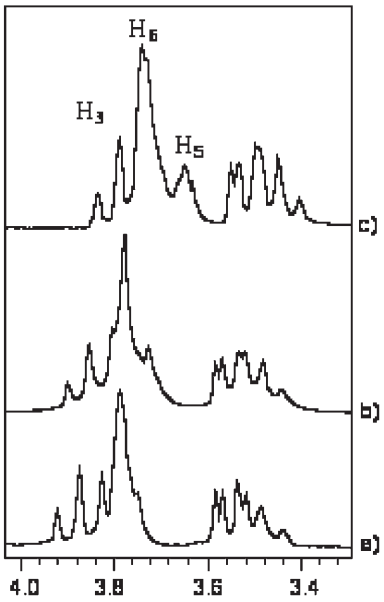


Figure 1. ^{1}H NMR spectra of a) β-CD, b) β-CD:isatin complex and c) reaction mixture after 50 min. The spectra were recorded in D_2O at 25 °C.

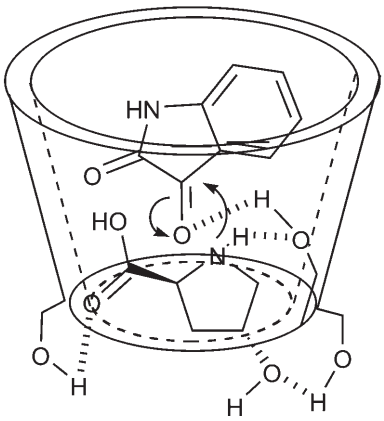


Figure 2.

observed in the absence of cyclodextrin. The complexation with β-CD increases the reactivity of both the keto and amino groups of isatin and *trans*-4-hydroxy-L-proline due to intermolecular hydrogen bonding with the CD hydroxy groups facilitating the established sequence of reactions such as condensation, decarboxylation, dehydration, and aromatization of the product.[10] Here, β-CD not only forms the inclusion complex with isatin and *trans*-4-hydroxy-L-proline but is also involved in the intermolecular hydrogen bonding with the guests promoting the condensation and dehydration reactions.

In conclusion, we have presented the first neutral aqueous phase synthesis of functionalized pyrroles, 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline and 3-(1*H*-pyrrol-1-yl)indolin-2-one compounds by the condensation of *trans*-4-hydroxy-L-proline with 11*H*indeno[1,2-*b*]quinoxalin-11-one or isatin derivatives under biomimetic conditions in the presence of β-cyclodextrin. This straightforward, environmentally benign methodology may find widespread applications in organic and medicinal chemistry.

Experimental Section

General Information

^{1}H NMR spectra were recorded on Gemini-200 MHz or Avance-300 MHz spectrometers in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. IR spectra were recorded on Nicolet FT-IR. spectrometer. Melting points were recorded on Büchi R-535 apparatus and are uncorrected.

General Procedure for the Synthesis of 3-(1*H*-Pyrrol-1-yl)-indolin-2-ones

β-CD (1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed. Then, isatin (1 mmol) was added portionwise followed by *trans*-4-hydroxy-L-proline (1 mmol) and the mixture was stirred at 60 °C until the reaction was complete (as monitored by TLC) (Table 1). However in the case of indenoquinoxalinone (entry j, Table 1), this compound was dissolved in methanol (0.5 mL methanol/mmol) and added dropwise to the aqueous solution of cyclodextrin. It is observed that isatin forms a clear solution in water at 60 °C whereas indenoquinoxalinone is insoluble in water at this temperature necessitating its dissolution in methanol before the addition. After completion of the reaction, 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. This β-CD was recycled for five times without any loss of activity and change in the yield in the cases of **3a** and **3c**. All the compounds were characterized by ^{1}H NMR, IR, MS analyses and compared with the authentic compounds.[10]

Preparation of β-CD:Isatin Inclusion Complex

β-CD (1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed, and then isatin (1 mmol) was added portionwise and the mixture was allowed to cool to room temperature. It was cooled to 5 °C for 12 h and the orange precipitate was filtered and dried.

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