Aqueous phase supramoleculer synthesis of 3,2- and 3,3-dihetero-aromatic oxindoles catalysed by β-cyclodextrin

Subhendu Naskar, Pritam Saha, Rupankar Paira, Priyankar Paira, Abhijit Hazra, Krishnendu B.Sahu, Sukdeb Banerjee and Nirup B. Mondal*

Department of Chemistry, Indian Institute of Chemical Biology, Council of Scientific and Industrial Research, 4 Raja S C Mullick Road, Jadavpur, Kolkata- 700032, India

A high yielding green protocol is described for the synthesis of 3,2 and 3,3-diheteroaromatic oxindole involving the condensation of isatin with indole or pyrrole in an aqueous medium under neutral conditions by supramoleculer catalysis by β-cyclodextrin. The β-cyclodextrin can be easily recovered and reused without any loss of activity.

Keywords: Oxindole, β-cyclodextrin, supramoleculer synthesis, water

In recent years the notion of 'green chemistry' has encouraged synthetic organic chemists to perform organic reactions in water because in comparison with organic solvents this reaction medium offers several advantages. It is cheap, non-toxic, non-inflammable and safe, and the unique physical and chemical properties of water often increases the reactivity or selectivity compared to organic solvents.[1] The products can be easily isolated by simple filtration or recrystallisation. However the basic problem in performing reactions in water is that many organic compounds are hydrophobic and are insoluble in water. This limitation can easily be overcome by using a supramoleculer catalyst such as β-cyclodextrin. Cyclodextrins (CDs) are torus-shaped cyclic oligosaccharides consisting of D-glucopyranosyl units connected by α (1→4) glycosidic linkages. The natural CDs, which consist of six, seven, or eight glucose units, are known as α-, β-, and γ-CD, respectively.[2] CDs have hydrophobic cavities, which bind substrates selectively and catalyse chemical reactions by a supramoleculer interaction involving reversible formation of host–guest complexes through non-covalent bonding as seen in enzyme complexation processes.[3] Because of these unique structural properties CDs have been widely used in food and cosmetics, as well as pharmaceutical, and industrial chemistry.[4-7]

For over a decade we have been examining the preparation of bioactive molecules[8-10] from indoles. Intrigued by the unique characteristics of cyclodextrins we have used them as catalysts for the synthesis of potentially bio-active oxindoles.[11,12] 3,3-Diaryloxindoles, derived from indole-2,3-dione (isatin), posses antibacterial, antiprotozoal and anti-inflammatory activities[13-17] and are also used as laxatives.[18] The naturally occurring oxindole derivative, convolutamydine, has potent activity in the differentiation of HL-60 human plomyelocytic leukaemia cells.[19] The varied biological activities of oxindole derivatives have attracted the attention and a number of synthetic methodologies have been developed for the preparation of 3,3-diaryl oxindole derivatives.[20-22] Most of the strategies are based on the acid catalysed condensation of arenes with isatin. Recently, several reports have appeared in the literature regarding condensation of isatin with heteroaromatics.[23-27] Despite the availability of different methodologies, there is scope for the development of green protocol with a greater efficiency and simpler operation. We report here a green protocol for the synthesis of 3,2- and 3,3-diheteroaromatic oxindoles in water from the reaction of isatin and substituted indoles catalysed by β-cyclodextrin.

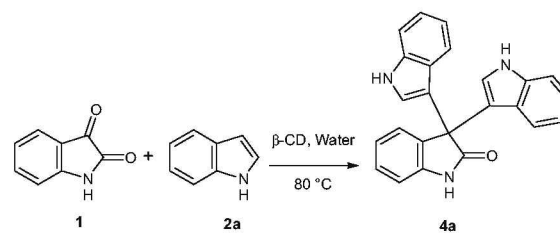
Results and discussion

The condensation of isatin (**1**) with indole (**2a**) was attempted first in order to optimise the conditions by varying the conditions, the amount of reactants, catalyst and time period (Table 1). The reaction was carried out *in situ* by forming the β-cyclodextrin complex of isatin (**1**) in water at 60 °C, followed by addition of indole (**2a**) with constant stirring at 80 °C (Scheme 1). After several attempts of varying the time period and the catalyst loading, it was found that the reaction gave a maximum yield of 3,3-bis (1*H*-indol-3-yl) indolin-2-one (**4a**) within 20 minutes with the mole ratio 1 : 1 : 2 of β-cyclodextrin, isatin and indole (Table 1, entry 6). With a smaller amount of catalyst, the yield was lower, but a higher yield was not obtained when more catalyst was employed even after a longer reaction time (Table 1, entry 9). In the absence of β-cyclodextrin, the reaction gave very low yield of the product and even after a long time. Recently, Srihari and Murthy have reported a similar observation.[28] Encouraged by the results obtained with the above optimum reaction conditions, we used various indole derivatives (**2b–h**) and also pyrrole (**3**) in order to establish the generality and scope of this new methodology. The results are summarised in Table 2. Most of the reactions proceeded very cleanly at the optimum temperature and no undesirable side products were obtained, although the yields varied with the individual substrates. For instance, in the case of indole derivatives having electron-withdrawing groups at the 2 or 3 positions (**4f**, **4h**) lower yields were obtained even after longer reaction times (1–2 h). The possibility of recycling the β-cyclodextrin was studied with the reaction of isatin and indole at 80 °C in water. After the reaction was complete the product was isolated

Table 1 Optimisation of catalysis content and reaction time

Entry	β-CD/mmol	T/°C	Time/min	Yields/%[a]
1	0.25	80	120	42
2	0.25	80	240	48
3	0.5	80	80	53
4	0.5	80	160	65
5	0.75	80	60	70
6	1	80	20	98
7	1	80	40	98
8	1.5	80	20	98
9	1.5	100	40	98

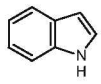
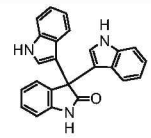
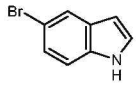
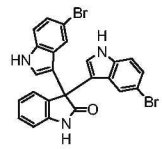
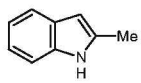
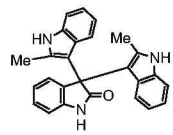
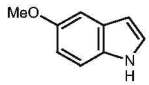
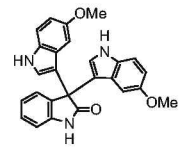
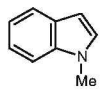
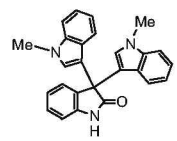
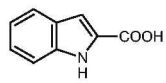
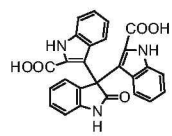
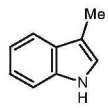
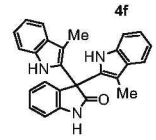
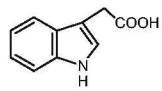
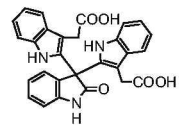
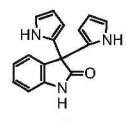
[a]Isolated yields of pure products.



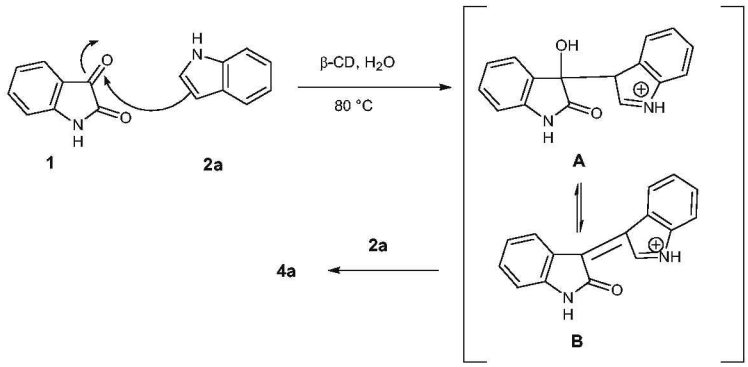
Scheme 1 β-cyclodextrin catalysed synthesis of **4a** in water.

* Correspondent. E-mail: nirup@iicb.res.in

Table 2 Synthesis of oxindoles by condensation of isatin with indoles or pyrrole catalysed by β-cyclodextrin

Entry	Indoles/pyrrole	Products[a]	Time/min	Yields/%[b]
1	 **2a**	 **4a**	20	98
2	 **2b**	 **4b**	20	95
3	 **2c**	 **4c**	20	96
4	 **2d**	 **4d**	20	96
5	 **2e**	 **4e**	20	95
6	 **2f**	 **4f**	100	75
7	 **2g**	 **4g**	20	90
8	 **2h**	 **4h**	120	65
9	 **3**	 **5**	20	96

[a]All products are characterised by IR, NMR and mass spectroscopy.
[b]Isolated yield of pure products.



Scheme 2 Schematic representation for the formation of **4a**.

by filtration and the aqueous filtrate was cooled to 5 °C. β-Cyclodextrin crystallised out and was recovered by filtration. This β-cyclodextrin was recycled for five times without any loss of activity and also without noticeable change in the yield in the case of **4a**.

A plausible mechanism for the formation of **4a** in water using β-cyclodextrin, as catalyst, is depicted in Scheme 2. It is presumed that isatin was dissolved in water by forming an inclusion complex with β-cyclodextrin from the secondary side of β-cyclodextrin.[29] On the other hand, indole also formed an inclusion complex with β-cyclodextrin by forming a hydrogen bond between *N*-1 hydrogen of indole with one of the hydroxyl groups surrounding the edge of β-cyclodextrin cavity.[30] Thus both isatin and indole are in close proximity in the β-cyclodextrin cavity facilitating the nucleophilic attack of one indole molecule on the carbonyl carbon of isatin, resulting the formation of intermediate **A** which is in equilibrium with intermediate **B**. Next a Michael type addition may occur by another indole molecule, leading to the formation of **4a**.

In conclusion, we have developed a simple, efficient and green protocol for the synthesis of 3,2- and 3,3-diheteroaromatic oxindole in an aqueous medium under neutral conditions with supramoleculer catalysis involving β-cyclodextrin. The green reaction conditions, ease of product separation and excellent yield of products, make this protocol a useful one for the preparation of 3,2- and 3,3-diheteroaromatic oxindoles.

Experimental

Melting points were determined with a capillary melting point apparatus. IR spectra were recorded on a JASCO FTIR (model 410) in KBr pellets. ESI-MS (positive) was conducted using LC-ESI-Q-TOF micro Mass spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker 300 MHz DPX spectrometer at 300 and 74.99 MHz respectively, with tetramethylsilane as internal standard. The chemical shifts are reported in δ units. Isatin, β-cyclodextrin, indoles derivatives and pyrrole were purchased from Aldrich Chemicals Ltd (USA). TLC was performed on pre-coated silica gel 60 F_{254} aluminium sheets (E. Merck, Germany) using the solvent system 1–6% MeOH in $CHCl_3$ and spots were developed using the Liebermann–Burchard reagent.

General experimental procedure for the synthesis of 3,3-bis (1H-indol-3-yl) indolin-2-one (**4a**)

β-Cyclodextrin (1 mmole) was dissolved in water (20 mL) by warming to 60 °C until a clear solution was formed. Then isatin (1 mmole) was added in portions with constant stirring followed by indole (2 mmole). The mixture was stirred at 80 °C until the reaction was complete (monitored by TLC). After completion of the reaction, the product was filtered as white solid and purified by recrystallisation (methanol–chloroform). The same experimental procedure was followed for synthesis of other oxindole derivatives (**4b–h** and **5**). All the products were characterised by IR, NMR and mass spectroscopy. The physical and spectroscopic data of the compounds **4a–5** are as follows.

3,3-Bis(1H-indol-3-yl)indolin-2-one (**4a**): Colourless needles, m.p. 310–311 °C; (lit.[23] 311–313 °C). IR: 3391, 3312, 1706, 746 cm^{-1}. NMR (pyridine-d_5): δ_H 7.00 (d, 2H, J = 7.2 Hz), 7.06 (t, 1H, J = 7.5 Hz), 7.21 (m, 1H), 7.28 (d, 1H, J = 6.3 Hz), 7.32 (d, 2H, J = 7.2 Hz), 7.53–7.59 (m, 4H), 7.66 (d, 2H, J = 7.2 Hz), 8.13 (d, 1H, J = 8.1 Hz), 12.09 (s, 2H, N*H*-indole), 12.13 (s, 1H, –N*H*CO); δ_C 54.08 (C), 110.0 (CH), 112.1 (CH), 116.1 (CH), 119.2 (CH), 121.8 (CH), 122.0 (CH), 122.1 (CH), 125.5 (CH), 126.0 (CH), 127.2 (C), 128.2 (CH), 136.0 (C), 138.5 (C), 142.7 (C), 180.4 (C, NHCO). ESI-MS: *m/z* 386 [M + Na]$^+$.

3,3-Bis(5-bromo-1H-indol-3-yl)indolin-2-one (**4b**): Colourless prisms, m.p. 317–318 °C (lit.[28] 318–319 °C). IR: 3386, 3302, 1716, 735 cm^{-1} NMR (pyridine-d_5): δ_H 6.97–7.02 (m, 1H), 7.22 (d, 1H, J = 7.2 Hz), 7.28 (d, 2H, J = 7.5 Hz), 7.39 (s, 1H), 7.42 (s, 1H), 7.51–7.59 (m, 4H), 8.38 (s, 2H), 12.21 (s, 1H, N*H*-CO), 12.43 (s, 2H, N*H*-indole); δ_C 53.9 (C), 110.5 (CH), 112.9 (C), 114.2 (CH), 115.9 (C), 122.5 (CH), 124.5 (CH), 124.9 (CH), 126.1 (CH), 127.2 (CH), 128.9 (CH), 129.0 (C), 135.3 (C), 137.4 (C), 142.8 (C), 180.2 (C, NHCO). ESI-MS: *m/z* 544 [M + Na]$^+$.

3,3-Bis(2-methyl-1H-indol-3-yl)indolin-2-one (**4c**): Colourless needles, m.p. 298–299 °C (lit.[23] 300–301 °C). IR: 3410, 3332, 1708, 747 cm^{-1} NMR (pyridine-d_5): δ_H 2.49 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.90–6.99 (m, 3H), 7.11–7.23 (m, 4H), 7.31 (t, 1H, J = 7.5 Hz), 7.49–7.60 (m, 3H), 7.75 (d, 1H, J = 7.5 Hz), 11.86 (s, 1H, N*H*-indole), 11.92 (s, 1H, N*H*-indole), 11.95 (s, 1H, N*H*CO); δ_C 15.4 (CH_3), 15.8 (CH_3), 55.7 (C), 111.6 (CH), 112.6 (CH), 112.7 (CH), 112.8 (CH), 120.8 (CH), 122.1 (CH), 122.3 (CH), 122.4 (CH), 122.6 (CH), 123.6 (CH), 128.5 (CH), 130.0 (CH), 130.3 (C), 131.2 (C), 134.4 (C), 138.2 (C), 138.8 (C), 144.3 (C), 182.8 (C, NHCO). ESI- MS: *m/z* 414 [M + Na]$^+$.

3,3-Bis(5-methoxy-1H-indol-3-yl)indolin-2-one (**4d**):[26] Colourless needles, m.p. 240–241 °C. IR: 3368, 3191, 1709, 743 cm^{-1} NMR (pyridine-d_5): δ_H 3.54 (s, 6H, OMe), 6.98–7.02 (m, 1H), 7.04 (s, 2H), 7.26 (m, 1H), 7.28–7.33 (m, 1H), 7.48 (d, 4H, J = 8.7 Hz), 7.63–7.65 (m, 1H), 7.67 (s, 2H), 11.99 (s, 2H, N*H*-indole), 12.06 (s, 1H, N*H*CO); δ_C 55.5 (C), 56.7 (CH_3, OMe), 105.7 (CH), 111.2 (CH), 113.4 (CH), 114.0 (CH), 117.0 (C), 123.4 (CH), 127.5 (CH), 127.8 (CH), 129.0 (C), 129.6 (CH), 135.1 (C), 136.5 (C), 144.2 (C), 155.4 (C), 181.8 (C, NHCO). HRMS Calcd for $C_{26}H_{21}N_3O_3$: 446.1481. Found: 446.1485 [M + Na]$^+$.

3,3-Bis(1-methyl-1H-indol-3-yl)indolin-2-one (**4e**): Colourless prisms, m.p. 330–331 °C; (lit.[25] >300 °C). IR: 3314, 3055, 1616, 1450, 1244, 1204 cm^{-1}. NMR (DMSO-d_6): δ_H 3.38 (s, 3H, N-Me), 3.70 (s, 3H, N-Me), 6.82–6.87 (m, 8H), 6.89 (s, 2H), 6.93–7.01 (m, 1H), 7.10 (t, 1H, J = 7.5 Hz), 7.21–7.26 (m, 1H), 7.37 (d, 1H, J = 8.4 Hz), 10.63 (s, 1H, –N*H*CO); δ_C 33.2 (CH_3, N-Me), 53.3 (C), 110.5 (CH), 110.6 (CH), 114.3 (C), 119.3 (CH), 121.8 (CH), 121.9 (CH), 122.4 (CH), 125.8 (CH), 126.9 (C), 128.8 (CH), 129.3 (CH), 135.4 (C), 138.2 (C), 142.1 (C), 179.4 (C, NHCO). ESI-MS: *m/z* 414 [M + Na]$^+$.

3,3-Bis(2-carboxy-1H-indol-3-yl)indolin-2-one (**4f**): Colourless needles, m.p. 287–288 °C. IR: 3426, 3326, 1698, 749 cm^{-1} NMR (pyridine-d_5): δ_H 6.82–6.87 (m, 1H), 7.03–7.11 (m, 2H), 7.24 (d, 1H, J = 7.5 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.42 (t, 2H, J = 7.8 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.80 (d, 2H, J = 8.1 Hz), 7.88 (d, 1H, J = 7.8 Hz), 13.11 (s, 1H, N*H*CO), 13.23 (s, 2H, N*H*-indole), 13.59 (s, 2H, COO*H*); δ_C 56.1 (C), 111.1 (CH), 112.9 (CH), 113.0 (CH), 113.1 (CH), 120.4 (CH), 120.6 (CH), 122.3 (CH), 122.8 (CH), 122.9 (CH), 124.3 (CH), 124.4 (CH), 124.7 (C), 126.6 (C), 126.9 (C), 128.3 (C), 129.2 (CH), 136.6 (C), 137.4 (C), 143.5 (C), 163.4 (C, COOH), 164.5 (C, COOH), 186.0 (C, NHCO). HRMS Calcd for $C_{26}H_{17}N_3O_5$: 474.1066. Found: 474.1069 [M + Na]$^+$.

3,3-Bis(3-methyl-1H-indol-2-yl)indolin-2-one (**4g**): Colourless prisms; m.p. 302–303 °C; IR: 3421, 1715, 1465, 745 cm^{-1}. NMR (pyridine-d_5): δ_H 2.32 (s, 6H, CH_3), 6.92 (t, 1H, J = 7.5 Hz), 7.00 (d, 1H, J = 7.5 Hz), 7.12 (d, 2H, J = 6.9 Hz), 7.16–7.17 (m, 1H), 7.19–7.23 (m, 4H), 7.46 (d, 1H, J = 8.7 Hz), 7.62 (d, 2H, J = 7.5 Hz), 11.75 (s, 2H, N*H*-3Me indole), 12.19 (s, 1H, N*H*CO); δ_C 9.54 (CH_3), 55.9 (C), 110.2 (CH), 111.5 (CH), 118.7 (CH), 119.0 (CH), 121.7 (CH), 122.6 (CH), 126.4 (CH), 129.1 (C), 130.4 (C), 132.5 (C), 132.8 (C), 136.4 (C), 142.7 (C), 177.5 (C, NHCO). HRMS Calcd for $C_{26}H_{21}N_3O$: 414.1582. Found: 414.1587 $[M + Na]^+$.

3,3-Bis(3-carboxymethyl-1H-indol-2-yl)indolin-2-one (**4h**): Colourless needles, m.p. 208–209 °C. IR: 3349, 3312, 1714, 748 cm^{-1} NMR (pyridine-d_5): δ_H 4.17 (s, 4H), 6.90–6.95 (m, 1H), 7.04–7.1 (m, 1H), 7.14–7.18 (m, 1H), 7.38–7.41 (m, 4H), 7.89–7.91 (m, 4H), 7.99 (d, 1H, J = 7.2 Hz), 11.87 (s, 4H, 2N*H*, 2COO*H*), 12.43 (s, 1H, N*H*CO); δ_C 32.9 (CH_2), 57.6 (C), 109.7 (C), 111.8 (CH), 113.2 (CH), 120.8 (CH), 120.9 (CH), 123.4 (CH), 124.1 (CH), 128.5 (CH), 130.6 (CH), 131.6 (C), 133.4 (C), 135.1 (C), 138.0 (C), 144.3 (C), 175.8 (C, COOH), 179.0 (C, NHCO). HRMS Calcd for $C_{28}H_{21}N_3O_5$: 502.1379. Found: 502.1376 $[M + Na]^+$.

3,3-Bis(1H-pyrrol-2-yl)indolin-2-one (**5**): Brown needles, m.p. 263–264 °C (lit.[28] 265–266 °C). IR: 3435, 2930, 1716, 764 cm^{-1}. NMR (pyridine-d_5): δ_H 6.30 (dd, 2H, J = 2.7 Hz and 5.7 Hz), 6.39–6.42 (m, 2H), 6.93 (d, 1H, J = 7.8 Hz), 7.02–7.07 (m, 3H), 7.21 (t, 1H, J = 7.8 Hz), 7.75 (d, 1H, J = 7.5 Hz), 11.77 (s, 2H, N*H*-pyrrole), 11.94 (s, 1H, N*H*CO); δ_C 56.1 (C), 109.5 (CH), 109.8 (CH), 112.0 (CH), 121.0 (CH), 123.9 (CH), 127.8 (CH), 130.3 (CH), 132.5 (C), 135.6 (C), 144.4 (C), 180.4 (C, NHCO). ESI-MS: *m/z* 286 $[M + Na]^+$.

We are extremely grateful to the Council of Scientific and Industrial Research (CSIR) for awarding fellowship to P.P., A.H., K.B.S. and S.N.

Received 24 October 2008; accepted 10 December 2008
Paper 08/0261 *doi: 10.3184/030823409X401763*
Published online: 6 April 2009

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