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β-Cyclodextrin catalyzed synthesis of substituted indoles in aqueous medium

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ABSTRACT

β-Cyclodextrin catalyzed synthesis of indole derivatives from indole, aldehyde and *N*-methylaniline is reported. The β-cyclodextrin can be recovered and reused without significant loss of catalytic activity, and it is inexpensive, readily available when compared to other cyclodextrins (α, γ).

1. Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry and have offered many fascinating and challenging transformations in organic synthesis [1-7]. These multicomponent reactions are emerging as powerful tools for the synthesis of biologically important compounds [8-9]. 3-Substituted indole moieties are important as they are widely distributed in nature and reveal a broad range of biological activities [10]. Indoles with amino alkyl/aryl substituents at the 3-position are considered as potential pharmacophores [11] in drug discovery and are found in various natural products [12], useful in the treatment of migraine, breast cancer [13], and HIV-1 [14]. The immense potential of indole nucleus for development of drug candidates, prompted many synthetic chemists to explore different methodologies suitable for the synthesis of 3-substituted indoles.

In view of different biological activities associated with indole derivatives and in continuation of our interest in the use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various organic transformations [15-22], we here in report the synthesis of indole derivatives by the reaction of indole with different aldehydes and *N*-methylaniline under neutral conditions involving β-cyclodextrin in water medium.

2. Experimental

2.1. Instrumentation

All the products were characterized by their NMR and Mass spectra. ^{1}H NMR is recorded on Varian 200 spectrometer (200 MHz, in $CDCl_3$) and the chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. IR was recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer. Mass spectra were obtained using a VG Autospec mass spectrometer.

2.2. General procedure for the synthesis of N-((1H-indol-3-yl)(phenyl) methyl)-N-methylbenzenamine

All chemicals were purchased from Fluka and S. D. Fine Chemicals and directly used for the synthesis. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel $60F_{254}$ pre-coated plates. Visualization was accomplished with UV lamp or I_2 stain. All reactions were carried out without any special precautions in an atmosphere of air.

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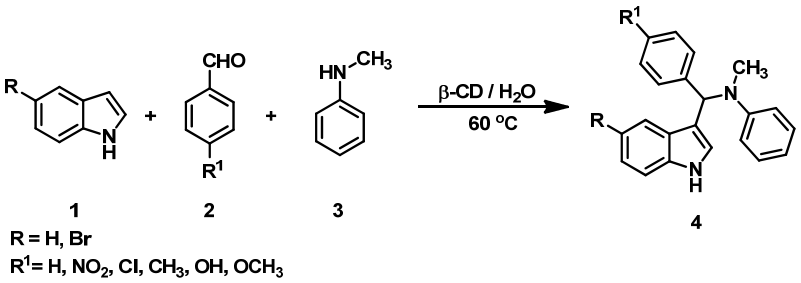

Scheme 1

Table 1. β-CD catalyzed synthesis of 3-substituted indoles [a].

Entry	R	R^1	Product	Time (h)	Yield (%) [b]
1	H	H	4a	4.0	86
2	H	4-Cl	4b	3.5	84
3	H	4-CH_3	4c	4.5	86
4	H	4-NO_2	4d	4.5	85
5	H	4-OCH_3	4e	4.5	83
6	H	4-OH	4f	4.5	81
7	Br	4-NO_2	4g	4.5	86
8	Br	4-OCH_3	4h	4.5	85
9	Br	4-Cl	4i	3.5	80
10	Br	4-CH_3	4j	4.5	85

[a] Reaction conditions: Aldehyde (1.0 mmol), *N*-methylaniline (1.0 mmol), indole (1.0 mmol), β-cyclodextrin (10 mol %), 60 °C.
[b] Isolated yield.

β-Cyclodextrin (1.135 g, 1 mmol) was dissolved in water (15 mL) by warming up to 60 °C until a clear solution was formed. To this clear solution, aldehyde (1.0 mmol) was added and stirred for 10 min, and then *N*-methylaniline (1.0 mmol) was added. After stirring for half an hour 1 equivalent of indole (1.0 mmol) was added. The reaction mixture was stirred until completion of the reaction as indicated by TLC. The reaction mixture was cooled and β-CD was filtered. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the organic layers were washed 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: hexane (2:8, *v*: *v*) as eluent to give the corresponding *N*-((1*H*-indol-3-yl) (phenyl) methyl)-*N*-methyl benzeneamine as pure product in good yield (Scheme 1).

N-((1*H*-Indol-3-yl) (phenyl) methyl)-*N*-methylbenzenamine (Table 1, entry 1): Yield: 86%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.00 (s, 1H, NH, Pyr), 7.84 (s, 1H, CH, Pyr.), 7.15-7.36 (m, 8H, Ar-H), 7.0-7.12 (m, 3H, Ar-H), 6.47-6.60 (d, *J* = 9.06 Hz, 3H, Ar-H), 5.57 (s, 1H, CH), 2.82 (s, 3H, CH_3). MS (ESI, *m/z*): 313 $[M+H]^+$.

N-((4-Chlorophenyl) (1*H*-indol-3-yl) methyl)-*N*-methyl benzeneamine (Table 1, entry 2): Yield: 84%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.01(s, 1H, NH, Pyr), 7.96 (s, 1H, CH, Pyr.), 7.04-7.26 (m, 7H, Ar-H), 6.91-7.02 (d, *J* = 8.49 Hz, 2H, Ar-H), 6.39-6.53 (m, 4H, Ar-H), 5.48 (s, 1H, CH), 2.72 (s, 3H, CH_3). MS (ESI, *m/z*): 347 $[M+H]^+$.

N-((1*H*-Indol-3-yl) (p-tolyl) methyl)-*N*-methylbenzenamine (Table 1, entry 3): Yield: 86%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.00 (s, 1H, NH, Pyr), 7.90 (s, 1H, CH, Pyr.), 7.36-7.39 (d, 2H, *J* = 8.49 Hz, Ar-H), 7.19-7.23 (m, 3H, Ar-H), 6.93-7.16 (m, 5H, Ar-H), 6.49-6.52 (d, *J* = 7.52 Hz, 3H, Ar-H), 5.51 (s, 1H, CH), 2.77 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). MS (ESI, *m/z*): 327 $[M+H]^+$.

N-((1*H*-Indol-3-yl) (4-nitrophenyl) methyl)-*N*-methyl benzeneamine (Table 1, entry 4): Yield: 85%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.30 (s, 1H, NH, Pyr), 8.25 (s, 1H, CH, Pyr.), 7.23-7.35 (m, 5H, Ar-H) 7.09-7.15 (m, 2H, Ar-H), 6.91-6.99 (d, *J*=8.1 Hz, 3H, Ar-H), 6.44-6.55 (d, *J*=6.79 Hz, 3H, Ar-H), 5.58 (s, 1H, CH), 2.78 (s, 3H, CH_3). MS (ESI, *m/z*): 380 $[M+Na]^+$.

N-((1*H*-Indol-3-yl) (4-methoxyphenyl) methyl)-*N*-methyl benzenamine (Table 1, entry 5): Yield: 83%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.01 (s, 1H, NH, Pyr), 7.89 (s, 1H, CH, Pyr.), 7.47-7.60 (m, 4H, Ar-H), 6.94-7.18 (m, 5H, Ar-H), 6.47-6.52 (d, *J* = 8.30 Hz, 4H, Ar-H), 5.54 (s, 1H, CH), 3.80 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3). MS (ESI, *m/z*): 343 $[M+H]^+$.

4-((*1H*-Indol-3-yl) (methyl (phenyl) amino) methyl) phenol (Table 1, entry 6): Yield: 81%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.01 (s, 1H, NH, Pyr), 7.71 (s, 1H, CH, Pyr.), 7.31-7.36 (d, *J* = 7.55 Hz, 2H, Ar-H), 7.20-7.26 (d, *J* = 8.30 Hz, 3H, Ar-H), 6.91-7.15 (m, 6H, Ar-H), 6.60-6.65(d, *J*=9.01 Hz, 2H, Ar-H), 5.47 (s, 1H, CH), 5.37 (s, 1H, OH), 2.16 (s, 3H, CH_3). MS (ESI, *m/z*): 329 $[M+H]^+$.

N-((5-Bromo-1*H*-indol-3-yl) (4-nitrophenyl) methyl)-*N*-methylbenzenamine (Table 1, entry 7): Yield: 86%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.92 (s, 1H, NH, Pyr), 8.84 (s, 1H, CH, Pyr.), 8.09-8.23 (m, 6H, Ar-H), 7.30-7.35 (t, *J* = 8.30 Hz, 3H, Ar-H), 6.93(s, 1H, Ar-H), 6.49-6.59(d, *J* = 8.32 Hz, 2H, Ar-H), 5.56 (s, 1H, CH), 2.83 (s, 3H, CH_3). MS (ESI, *m/z*): 459 $[M+Na]^+$.

N-((5-Bromo-1*H*-indol-3-yl) (4-methoxyphenyl)methyl)-*N*-methylbenzenamine (Table1, entry 8): Yield: 85%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.00 (s, 1H, NH, Pyr), 7.30 (s, 1H, CH, Pyrro), 7.10-7.71 (m, 6H, Ar-H), 6.98-7.05 (d, *J*=9.16 Hz, 2H, Ar-H), 6.71-6.75 (d, *J* = 8.25 Hz, 2H, Ar-H), 6.44-6.49 (d, *J* = 8.24 Hz, 2H, Ar-H), 5.40 (s, 1H, CH), 3.71 (s, 3H, OCH_3), 2.76 (s, 3H, CH_3). MS (ESI, *m/z*): 422 $[M+H]^+$.

N-((5-bromo-1*H*-indol-3-yl) (4-chlorophenyl)methyl)-*N*-methylbenzenamine (Table 1, entry 9): Yield: 80%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.10 (s, 1H, NH, Pyr), 8.00 (s, 1H, CH, Pyr.), 7.05-7.32 (m, 6H, Ar-H), 6.92-6.94 (d, *J*=8.30 Hz, 2H, Ar-H), 6.47-6.53 (d, *J* = 8.30 Hz, 4H, Ar-H), 5.42 (s, 1H, CH), 2.75 (s, 3H, CH_3). MS (ESI, *m/z*): 426 $[M+H]^+$.

N-((5-bromo-1*H*-indol-3-yl) (*p*-tolyl) methyl)-*N*-methyl aniline (Table 1, entry 10): Yield: 85%. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 8.00 (s, 1H, NH, Pyr), 7.95 (s, 1H, CH, Pyr.), 7.36 (s, 1H, Ar-H), 7.17-7.25 (m, 2H, Ar-H), 7.05 (s, 3H, Ar-H), 6.95-6.99 (d, *J* = 8.30 Hz, 3H, Ar-H), 6.49-6.53 (d, *J* = 8.30 Hz, 3H, Ar-H), 5.44 (s, 1H, CH), 2.81 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). MS (ESI, *m/z*): 406 $[M+H]^+$.

3. Results and discussion

Cyclodextrins are cyclic oligosaccharides with hydrophobic cavities, and can bind substrates selectively and catalyze

chemical reactions by supramolecular catalysis involving reversible host-guest complexation. We describe herein, the aqueous phase synthesis of indole derivatives demonstrating the remarkable catalytic activity of β-cyclodextrin (Scheme 1). In general, the reaction was carried out by the in situ formation of the β-CD complex of aldehyde in water followed by the addition of 1 equivalent of *N*-methylaniline and 1 equivalent of indole followed by subsequent stirring at 60 °C to give the corresponding *N*-((1*H*-indol-3-yl)(phenyl)methyl)-*N*-methyl benzenamine in high yields.

The reaction goes to the completion in a short time (3.5-4.5 h). Several examples illustrating this simple and practical methodology are summarized in Table 1. No byproduct formation was observed. β-Cyclodextrin can be easily recovered and reused. All the compounds were characterized by ^{1}H NMR, and mass spectrometry. The catalytic activity of cyclodextrin in these reactions was established by the fact that no reaction was observed in the absence of cyclodextrin. Evidence for the complexation between aldehyde and cyclodextrin is supported by ^{1}H NMR spectroscopy. The complexation with β-CD increases the reactivity of aldehyde functional group due to the intermolecular hydrogen bonding with the CD-hydroxyl groups facilitating the addition of *N*-methylaniline. Here, β-CD not only forms the inclusion complex with aldehyde but is also involved in the intermolecular hydrogen bonding with the guest to promote the reaction.

4. Conclusion

A neutral aqueous phase synthesis of substituted indoles was developed by the reaction of the corresponding aldehyde with *N*-methylaniline and indole promoted by β-cyclodextrin. These cyclodextrin-mediated aqueous phase reactions are very useful both from economical and environmental perspective. This straightforward and environmentally benign methodology may find wide spread application in organic and medicinal chemistry.

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