Micelle Promoted Synthesis of Bis-(indolyl)methanes

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Abstract: Bis-(indolyl)methanes were synthesized by a simple, clean and highly efficient Tween-20 micelle promoted reaction of indole with aldehydes in water by the single step reaction. The absence of electrical double layer in the non-ionic surfactant micelles makes them as potential model adsorbent in the interfacial processes. This approach had explored the present synthesis of bis-(indolyl)methanes.

Keywords: Aldehydes, bis-indolylmethanes, green chemistry, indoles, non-ionic surfactants, tween-20.

INTRODUCTION

Indole moiety is a major constituent in a wide variety of pharmaceuticals [1]. Many bis-indole alkaloids are recognized as one of the major groups of sponge metabolites because of their broad spectrum of biological properties [2-7]. Bis-indolylmethanes are obtained by the reaction of indole with aldehydes through the azafulvanium salts as intermediate in their synthesis [8]. Several other methods are available for the preparation of bis-indolylmethanes using protic [9-15], and Lewis acids [16-20]. Also other reagents, such as P_2O_5 / SiO₂ [21], and heteropolyacids [22-24] were used for their synthesis. Ionic liquids in conjugation with In(OTf)₃ or FeCl₃.6H₂O [25] were acted as media for their synthesis. Recently oxalic acid [26, 27], as solid supported catalyst [28, 29] had also been successfully exploited for the preparation of bis-indolylmethanes. The Lewis and Brønsted acid surfactant catalyzed synthetic reactions are known for them [30]. But majority of the available methods suffer from several setbacks such as requirement of stoichiometric amount of the Lewis acids, generation harmful wastes, posing environmental problem and long reaction times associated with poor product yields.

As the use of environmentally friendly reaction medium is one of the fundamental principles of green chemistry. In reactions such water as a reaction solvent had received much attention in the synthesis of organic compounds, because it would be considerably safe, non-toxic, environmentally friendly, and cheap as compared to organic solvents [31]. However, water is rarely considered as a solvent for organic reactions based on the reason of limited solubility of most organic compounds in water. As the solubility is important for good reactivity, alternatives for improving the solubility of organic substrates in water will ultimately expand the scope of water-based organic synthesis [32]. Incorporation of surface-active agents (surfactants) in aqueous media has proved to enhance the reactivity of water mediated reactions *via* the formation of micelles or vesicular cavities. The use of micellar and vesicle forming surfactants as catalysts in water is widespread and has been studied for a number of different synthetic transformations/ multicomponent reactions in water [33]. Surfactant-type catalyzed organic reaction had motivated the organic synthesis in aqueous medium [33] like synthesis of benzylamino coumarins [34], Betti base [35]. Based on this back ground here in is reported a highly efficient green procedure for the preparation of bis-(indolyl)methane derivatives.

RESULTS AND DISCUSSION

The highly efficient green procedure for the preparation of bis-indolylmethane derivatives (3a-r) proceeds by the single step reaction of two moles of indole (1) with one mole of aldehyde (2) using non-ionic surfactant Tween-20 as catalyst in aqueous media (Scheme 1). The absence of electrical double layer in the non-ionic surfactant micelles makes them as potential model adsorbent in the interfacial processes [36]. This property of non-ionic surfactant was explored in the present synthesis of bis-indolylmethanes from the reaction of indole with aldehydes. Tween-20 is also commonly used non-ionic detergent in water as solubilizer with a wide range of applications in biological systems [37, 38]. Solubilization of lipid membranes triggered by Tween-20 as a well-described phenomenon to use as an emulsifier and complexing agent in both aqueous and non-aqueous media is well known.

In the selection of catalyst, several surfactants and boric acid catalysts in water medium were attempted for optimization of reaction between indole and benzaldehyde (Table 2, entry 1). The non-ionic surfactant catalysts like Triton CF-10, [benzyl-polyethylene glycol (1,1,3,3-tetra methylbutylphenyl) ether], Triton X-100 (*t*-octyl phenoxypolyethoxy-ethanol) and Tween-20 (*t*-octylphenoxypolyethoxyethanol) were found to be very effective promoters of the reaction, require a less reaction time and almost quantitative product yield of them Tween-20 drives the reaction very fast and affords the product in 98% yield.

Among the ionic surfactant catalysts the anionic surfactants Sodium dodecyl sulfate (SDS) and 4-dodecylben-

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Scheme 1. Synthesis of bis-indolylmethanes using Tween-20 surfactant in water.

Table 1.	Screening of	f various types of	f catal	lysts f	for t	he synt	hesi	is of	f b	ois-in	doly	lmet	hanes
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Entry	Catalyst ^a	Time (h)	Yield (%) ^b
1	Boric acid	5.5	40
2	SDS	4.0	60
3	SDBS	4.5	70
4	Triton X-100	4.5	90
5	Triton CF-10	4.2	84
6	Tween-20	4.0	98
7	СТАВ	5.0	20

^aReaction were carried out at 60-70 °C for 4-5.5 h with aldehyde (1.0 mmol) and Indole (2.0 mmol) in a solution of catalyst (5 mol %) and water (2 mL). ^bIsolated yield.

zenesulfonic acid (SDBS) were slightly less effective than the cationic surfactant cetyltrimethylammonium bromide (CTAB). The simple boric acid also catalyzes the reaction at a slow rate and affords the product in poor yield (Table 1). The necessity of catalyst in this reaction is proved by the fact that when the reaction is run without it, the starting materials are recovered even after running the reaction for a long time.

The aqueous reaction medium turns turbid during the reaction due to precipitation of reactants encapsulated in non-ionic surfactant micelles **4**. The amphiphilic surfactant molecule assemblies of the micelles **4** being sufficiently hydrophobic render the organic substances and reagents more soluble in the aqueous medium [39-42], bring them in close proximity and enhance chemical reaction between them. The boundary of the micelle **4** acts as a kind of one

way chemical membrane. This seems to protect water liable zwitterion intermediates **5** from hydrolytic decomposition. At the same time it allows transfer of water molecule formed during the reaction to the surrounding aqueous environment (Fig. **1**). This reaction situation acts favorably for the accelerated rate of electrophilic substitution of the carbonyl carbon of **2** on the C3 atom of Indole **1** regiospecifically leading to the coupling of two indole **1** moieties with a substituted methylene bridge.

EXPERIMENTAL

Chemicals were procured from Sigma-Aldrich and Merck, used without further purification. All solvents used for the spectroscopic and other physical studies were reagent



Fig. (1). Schematic representation of micelle promoted bis-indolylmethanes synthesis.

Table 2.	Synthesis of bis-indolylmethanes by using tween-20	

Fntry	Aldehyde	Time (h)	Vield (%)	Melting point (°C)			
Entry	machyac	Time (ii)	1 km (70)	Literature	Found		
3a	СНО	4	98	125-127	124-126 ^{24,26}		
3b	CI — CHO	5	96	102-104	104-106 ²⁶		
3c	СІ	5	93	72-74	73-75 ²⁶		
3d	O ₂ N — CHO	4	98	221-223	220-222 ²⁶		
3e	CHO NO ₂	4.5	93	264-226	265-266 ^{24,26}		
3f	Н ₃ С — СНО	6	91	97-99	96-98 ^{24,26}		
3g	H ₃ CO — CHO OCH ₃	6	95	191-193	191-193 ^{24,26}		
3h	СНО ОСН3	5.5	96	133-135	134-136 ²⁶		
3i	H ₃ CO H ₃ CO — CHO	5.5	91	195-197	197-199 ⁴⁴		
3j	Н ₃ СО НО — СНО	4.5	83	125-127	126-127 ⁹		
3k	СІ СНО	4	87	218-220			
31	Br CHO OH	4.25	90	228-230	228-230 ⁴		
3m	Cl — CHO	4	90	102-104	103-105 ²⁶		

(Table 1) Contd	

Fntry	Aldehyde	Time (h)	Vield (%)	Melting point (°C)			
Entry	Antellyut	Time (II)	1 km (70)	Literature	Found		
3n	СІ — СНО	4	88	152-154	153-154 ⁴⁴		
30	N — CHO	5	92	208-210	210-212 ²⁶		
3р	CHO OCH ₂ C ₆ H ₅	4.5	93	264-266			
3q	СНО	5	95	96-98	98-100 ^{21,26}		
3r	CHO NO ₂	4.5	96	150-152			

^aIsolated yield.

grade and further purified by literature methods [43]. The melting points (mp) were determined in open capillary tubes on a Mel-Temp apparatus (Tempo Instruments and Equip Pvt. Ltd., Mumbai, India), expressed in degrees centigrade (°C) and were uncorrected. Infrared (IR) Spectra were obtained on a Nicolet (San Diego, CA, USA) 380 Fourier transform infrared (FT-IR) spectrophotometer at the Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati, India and samples were analyzed as potassium bromide (KBr) disks and absorptions (v_{max}) were reported in wave numbers (cm⁻¹). The ¹H, ¹³C, and ³¹P-NMR spectra were recorded on a Bruker (Ettlingen, Germany) ÂMX 400 MHz nuclear magnetic resonance (NMR) spectrometer operating at 400 MHz for ¹H-NMR, 100.57 MHz for ¹³C-NMR, and 161.9 MHz for ³¹P-NMR respectively and expressed in parts per million (ppm). All compounds were dissolved in DMSO- d_6 and chemical shifts were referenced to TMS in ¹H-NMR and ¹³C-NMR and 85% H₃PO₄ in ³¹P NMR. Mass spectra were recorded on a Jeol SX 102DA/600 (Tokyo, Japan) mass spectrometer using argon/xenon (6 keV, 10 mA) as the FAB gas. Microanalysis was performed with a Thermo Finnigan (Courtaboeuf, France) Flash EA 1112 I instrument at University of Hyderabad, Hyderabad, India. The purity of all the products was accomplished by TLC on silica gel polygram SIL G/UV 254 plates.

General Experimental Procedure for the Synthesis of Bis-(indolyl)methanes

The aldehyde (1 mmol) and indole (2 mmol) were added to a solution of Tween-20 (5 mol %) and water (2 mL) in a round bottomed flask. The reaction mixture was continuously stirred at 70-80 °C. After completion of the reaction as indicated by TLC, the reaction mixture was extracted thrice with ethyl acetate (3 X10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was further purified by silica gel column chromatography using hexane/ethylacetate mixture as an eluent.

The same experimental procedure was adopted for the synthesis of all the Bis-(indolyl)methanes **3a-r** and their structural moieties are tabulated in Table **2** above. The spectral data of some of the representative compounds are given below.

Spectral Data of the Selected Compounds

3,3'-(phenylmethylene)bis(1H-indole) (3a)

Solid; mp 124-126 °C; IR (KBr, cm⁻¹): 3415 (NH), 3055, 1620, 1600, 1455, 1095, 750; ¹H NMR (400 MHz, DMSO-d₆): δ 7.95 (br s, 2H, NH), 7.35 (m, 6H), 7.30 (m, 2H), 7.22 (m, 3H), 7.00 (t, 2H, J= 7.0), 6.65 (s, 2H), 5.90 (s, IH, Ar-CH); Anal. Calc. for C₂₃H₁₈N₂ (322.14): C, 85.7; H, 5.6; N, 8.7 %; Found: C, 85.8; H, 5.5; N, 8.6 %.

3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (3b)

Solid; mp 104-106 °C; IR (KBr, cm⁻¹): 3415 (NH), 3055, 1490, 1450, 1090; ¹H NMR (400 MHz, DMSO-d₆): δ 7.95 (br s, 2H, NH), 7.35-7.25 (m, 8H), 7.15 (t, 2H, J= 7.9), 7.05 (t, 2H, J= 8.3), 6.65 (s, 2H), 5.80 (s, I H, Ar-CH).

3,3'-((2-chlorophenyl)methylene)bis(1H-indole) (3c)

Solid; mp 73-75 °C; IR (KBr, cm⁻¹): 3410 (NH), 3050, 1620, 1455, 1415, 1340, 1095, 1045, 1015; ¹H NMR (400 MHz, DMSO-d₆): δ 7.97 (brs, 2H, NH), 7.41-7.35 (m, 4H), 7.20-7.10 (m, 6H), 7.05 (t, 2H), 6.70 (s, 2H), 6.30 (s, 1H, Ar-CH).

3,3'-((4-nitrophenyl)methylene)bis(1H-indole) (3d)

Solid; rnp 220-222 °C; IR (KBr, cm⁻¹): 3420 (NH), 3050, 1595, 1510, 1455, 1340; ¹H NMR (400 MHz, DMSO-d₆): δ 8.15 (d, 2H, J= 8.8). 8.05 (brs, 2H, NH), 7.50 (d, 2H, J= 8.8), 7.40 (d, 2H, J= 8.2), 7.35 (d, 3H, J= 8.0), 7.05-7.00 (m, 3H), 6.70 (s, 2H), 5.98 (s, IH, Ar-CH); Anal. Calc. for C₂₃H₁₇N₃O₂ (367.40): C, 75.2; H, 4.7; N, 11.4 %; Found: C, 75.3; H, 4.5; N, 11.6 %.

3,3'-(p-tolylmethylene)bis(1H-indole) (3f)

Solid; mp 96-98 °C; IR (KBr, cm⁻¹): 3415 (NH), 3040, 2930, 1610, 1515, 1220, 1055, 775; ¹H NMR (400 MHz, DMSO-d₆): δ 7.98 (brs, 2H, NH), 7.5 (d, 17.6, 2H), 7.29-7.25 (rn, 6H), 7.1 (d, 2H, J= 7.6), 7.05 (t, 2H, J= 7.2), 6.70 (s, 2H), 5.85 (s, 1H, Ar-CH), 2.35 (s, 3H, Ar-CH₃); Anal. Calc. for C₂₄H₂₀N₂ (349.45): C, 85.7; H, 6.0; N, 8.3 %; Found: C, 85.4; H, 5.9; N, 8.0 %.

3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) (3g)

Solid; mp 191-193 °C; IR (KBr, cm⁻¹): 3415 (NH), 2930, 1610, 1505, 1455, 1240, 1220; ¹H NMR (400 MHz, DMSO-d₆): δ 3.75 (s, 3H, CH₃), 5.80 (s, 1H, Ar-CH), 6.65 (s, 2H), 6.80 (d, 2H, J= 8.2), 7.05 (t, 2H, J= 7.2), 7.15 (t, 2H, J= 7.2), 7.20 (s, 2H), 7.35-7.40 (m, 4H), 7.98 (brs, 2H, NH). Anal. Calc. for C₂₄H₂₀N₂O (352.43): C, 81.8; H, 5.7; N 8.0 %; Found: C, 81.7; H, 5.8; N, 8.0 %.

3,3'-((3,4-dimethoxyphenyl)methylene)bis(1H-indole) (3i)

Solid; mp 197-199 °C; IR (KBr, cm⁻¹): 3445 (NH), 3060, 2980, 1620, 1495, 1235, 1005, 765; ¹H NMR (400 MHz, DMSO-d₆): δ 10.45 (br s, 2H, NH), 7.35 (t, 4H, J= 8.2), 7.05 (t, 2H, J= 8.0), 6.90 (d, 2H, J= 8.2), 6.85 (s, 1H), 3.75 (s, 3H), 6.80 (d, 2H, J= 8.2), 6.72 (d, 2H, J= 2.4), 5.75 (s, 1H), 3.82 (s, 3H).

3,3'-((5-chloro-2-hydroxyphenyl)methylene)bis(1H-indole) (3k)

Solid; mp 218-220 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 10.80 (brs, 2H, NH), 9.60 (s, 1H, OH), 7.50-6.70 (m, 13H, Ar-H), 6.25 (s, 1H, Ar-CH), 5.14 (s, 2H, O-CH₂); ¹³C NMR (125 MHz, DMSO-d₆): δ 157.2, 139.4, 134.2, 131.5, 129.5, 127.5, 126.6, 125.3, 124.6, 120.2, 119.8, 118.2, 112.7, 111.8, 43.4; Anal. Calc. for C₂₃H₁₇ClN₂O: C, 74.09; H, 4.60; N, 7.51; Found: C, 73.96; H, 4.56; N, 7.45; LCMS m/z: 373.

3,3'-((3,4-dichlorophenyl)methylene)bis(1H-indole) (3n)

Solid; mp; 153154 °C; IR (KBr, cm⁻¹): 3450 (NH), 3050, 2975, 1610, 1475, 1250, 1015, 775; ¹H NMR (500 MHz, DMSO-d₆): δ 7.92 (brs, 2H, NH), 7.40 (d, 1H), 7.25 (t, 2H, J= 8.2), 7.2 (s, 1H), 7.02-6.92 (m, 4H), 6.95 (m, 2H), 6.87 (rn, IH), 6.75 (d, 2H, 12.4), 5.83 (s, IH), LCMS m/z: 391 (M⁺).

3,3'-((2-(benzyloxy)phenyl)methylene)bis(1H-indole) (3p)

Solid; mp 264-266 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 10.78 (brs, 2H, NH), 7.37-6.77 (m, 19H, Ar-H), 6.31 (s, 1H, Ar-CH), 5.14 (s, 2H, O-CH₂); ¹³C NMR (125 MHz, DMSO-d₆): δ 155.7, 137.8, 137.0, 133.7, 129.5, 128.6, 127.9, 127.5, 127.4, 127.2, 124.1, 121.2, 120.7, 119.3, 118.5, 118.2, 112.8, 111.8, 69.7, 32.3; LCMS m/z: 429 (+ve), 427 (-ve).

3,3'-(3-phenylprop-2-ene-1,1-diyl)bis(1H-indole) (3q)

Semisolid; IR (KBr, cm⁻¹): 3450 (NH), 3110, 2960, 1595, 1475, 1050, 990, 765; ¹H NMR (500 MHz, DMSO-d₆): 7.95 (br s, 2H, NH), 7.75 (d, 1H, J= 16.0), 7.55 (m, 2H), 7.40 (m, 3H), 7.30 (m, 4H), 7.15 (t, 2H, J= 8.0), 7.05 (t, 2H, J= 8.0), 6.65 (d, 2H, J= 2.2), 6.42 (d, 1H, J= 16.0), 5.95 (s, 1H); LCMS m/z: 346 (M⁺).

3,3'-(3-(2-nitrophenyl)prop-2-ene-1,1-diyl)bis(1H-indole) (3r)

Solid; mp 150-152 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.02 (brs, 2H, NH), 7.91 (dd, 1H, J= 8 & 1.5 Hz,), 7.66-7.00 (m, 14H, Ar-H & one =CH), 6.77 (dd, J= 15.5 & 7.5 Hz, 1H, =CH-C), 5.48 (d, 1H, J= 7.5 Hz, Ar-CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 147.7, 137.7, 136.7, 133.7, 132.9, 129.0, 127.5, 126.8, 125.8, 124.4, 122.7, 122.0, 119.8, 119.3, 117.6, 111.1, 37.7; Anal. Calcd. for C₁₅H₂₀NO₇P: C, 50.42; H, 5.60; N, 3.92 %. Found: C, 50.38; H, 5.67; N, 3.99%; LCMS m/z: 394.

CONCLUSION

In summary, a simple, highly efficient and eco-friendly Tween-20 micelle promoted procedure for the preparation of bis-(indolyl)methanes by the reaction of indoles with aldehydes in aqueous medium is reported. The significance is that it serves as a versatile method for coupling two indole moieties at their C3-position with a substituted methylene bridge.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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