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PEG-SO₃H as a Catalyst for the Preparation of Bis-Indolyl and Tris-Indolyl Methanes in Aqueous Media

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PEG-SO₃H AS A CATALYST FOR THE PREPARATION OF BIS-INDOLYL AND TRIS-INDOLYL METHANES IN AQUEOUS MEDIA

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GRAPHICAL ABSTRACT



Abstract A facile, efficient, and green synthesis of bis-indolyl and tris-indolyl methanes has been developed by one-pot condensation of indole with structurally diverse aldehydes and ketones in the presence of poly(ethylene glycol)–bound sulfonic acid as catalyst at room temperature.

Keywords Aqueous medium; green synthesis; indoles

INTRODUCTION

Indoles are privileged heterocyclic rings, and many biologically active and natural products are 3-substituted indoles.^[1] Indole forms an integral part of many natural products of therapeutic importance and possesses potentially reactive sites for a variety of chemical reactions to generate molecular diversity. Several bis-(indo)alkaloids exhibit biological activity, antibacterial activity, potent carcinogenic properties,^[2] genotoxicity and DNA-damaging activites,^[3] and antitumorigenic activity.^[4] Synthetically, these compounds are obtained by the condensation of indoles with aldehydes/ketones in the presence of several Brønsted and Lewis acid catalysts such as In(OTf)₃,^[5] Dy(OTf)₃,^[6] Sc(OTf)₃,^[7,8] ceric ammonium nitrate (CAN),^[9] ZrOCl₂,^[10] InCl₃,^[11] AIPW₁₂O₄₀,^[12] ionic liquids,^[13] trichloro-1,3,5 triazine,^[14] potassium hydrogen sulfate,^[15] sodium dodecyl sulfate,^[16] lanthanide triflates,^[17] silica chloride,^[18] P₂O₅/SiO₂,^[19] trityl chloride,^[20] [Cu(3,4-tmtppa)] (MeSO₄)₄,^[21] and magnesium sulfate.^[22]

Soluble polymer and insoluble polymer are two main classes of polymersupported compounds. A functionalized polymer plays a dual role in the progress of a reaction, as a catalyst and solvent.^[23] Recently it has been shown that poly

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(ethylene glycol) (PEG)-bound sulfonic acid is an efficient Lewis acid catalyst for 3,4-dihydropyrimidone^[24] synthesis, and at the same time products are obtained by a simple operational procedure.

We report here an efficient and green method for the synthesis of bis(indolyl) methanes with PEG-6000 SO₃H in water medium with good to excellent yields with shorter reactions times. In addition, to the best of our knowledge, there are no reports on the use of PEG-6000 bound sulfonic acid as a catalyst for this conversion. This fact has prompted us to investigate PEG-SO₃H for the electrophilic substitution of indole with various aldehydes and ketones in a facile and practical manner.

RESULTS AND DISCUSSION

In our initial experiments, the condensation of benzaldehyde and indole (1:2) was performed in the presence of PEG-SO₃H. This facilitated the formation of bis-(indolyl)methanes in good yields but requires comparatively more time. Then the reaction was carried in water medium and proceeded smoothly with shorter reaction time in good yields. The results show that in water (10 mL) the catalytic activity of PEG-SO₃H was increased in all the cases (Table 1), probably because of the increase in solubility.

Encouraged by the result acquired from benzaldehyde, we examined a number of structurally diverse aldehydes and ketones to furnish bis-(indolyl)methanes in good to excellent yields in short reaction times under the present catalytic condition. The results are displayed in Table 1. A variety of carbonyl compounds reacted smoothly with indoles under the present reaction condition. Electron deficiency and the nature of substituents on the ring of aldehydes did not show any obvious effects on this conversion. Electron-rich as well as electron deficient aldehydes reacted with indoles with equal ease to give the products in excellent yields (Table 1, entries 2–14). We found that a number of aromatic, α , β -unsaturated, and heteroaromatic aldehydes (Table 1, entries 1–14) afforded the corresponding bis(indolyl)methanes in good yields. It is also worth mentioning that the reaction is general and is also applicable to various aliphatic and aromatic ketones (Table 1, entries 15 and 16) to afford the corresponding bis(indolyl)methanes in good yields, although the reaction time slightly increased for their conversion.

To explore further the potential of this protocol for bis-(indole)synthesis, we have investigated the reaction of terephthaldialdehyde and indole aldehydes with indole. Tris-indolyl and di(bis-indolyl methanes) were obtained in excellent yields (Scheme 1). The method is better than the previously reported synthesis of tris-indolyl methanes.^[25] Unfortunately, the use of recycled PEG-SO₃H resulted in a significant loss of its activity as the yield of **3a** dropped.

Suggested Mechanism for Catalytic Action

The reaction of indole with aldehydes proceeded through the successive intermediates of related carbinols. The sulfonic acid groups on the PEG are involved in salt formation with indolylcarbinols (Scheme 2). Because of their instability in acidic conditions, the indolylcarbinols lose water, generating the salts of

| | | Carbonal | | т: | V:-14 | Mp $(^{\circ}C)^{b}$ | |
|-------|--------|-------------------|---------|-------|----------|----------------------|-------------------------|
| Entry | Indole | compound | Product | (min) | $(\%)^a$ | Found | Reported |
| 1 | | СНО | 3a | 5 | 97 | 141–143 | 140–142 ^[19] |
| 2 | | сі- | 3b | 9 | 95 | 78–79 | 78-80 ^[19] |
| 3 | | ОН | 3c | 9 | 95 | 120–122 | 119-121 ^[28] |
| 4 | | СІ-СНО | 3d | 10 | 91 | 155–157 | 155–156 ^[26] |
| 5 | | но-Сно | 3e | 6 | 96 | 155–157 | |
| 6 | | МеО СНО | 3f | 12 | 93 | 99–100 | 98-100 ^[26] |
| 7 | | Вг | 3g | 16 | 96 | 126–128 | |
| 8 | | | 3h | 18 | 94 | 161–163 | |
| 9 | | N N N | 3i | 12 | 95 | 139–141 | 138-140 ^[27] |
| 10 | | √° | 3j | 11 | 90 | 150–153 | 147–149 ^[19] |
| 11 | | | 3k | 8 | 94 | 322–323 | 316–318 ^[19] |
| 12 | | 0 ₂ N- | 31 | 5 | 96 | 218–219 | 217–219 ^[19] |
| 13 | | °2N | 3m | 8 | 86 | 221–222 | 220–223 ^[19] |

 Table 1. Preparation of bis(indolyl) alkanes derivatives catalyzed by PEG-SO₃H

(Continued)

| Entry | Indole | Carbonyl compound | Product | Time (min) | Yield (%) ^a | $Mp (^{\circ}C)^{b}$ | |
|-------|------------------------|--|------------|---------------|---------------------------|----------------------|-------------------------|
| | | | | | | Found | Reported |
| 14 | | СНО | 3n | 13 | 89 | 102–104 | 100–102 ^[19] |
| 15 | |) N | 30 | 10 | 92 | 160–162 | 162 ^[29] |
| 16 | | $\bigcirc \vdash \!$ | 3p | 10 | 92 | 165–166 | 165–167 ^[19] |
| 17 | | | 3q | 13 | _ | | |
| 18 | | онс-С-Сно | 4 a | 5 | 97 | 256–258 | 257 ^[19] |
| 19 | Br | CHO | 5a | 5 | 97 | 185–187 | |
| 20 | | СНО | 5b | 9 | 95 | 160–162 | 160 ^[28] |
| 21 | $\bigcup_{\mathbb{H}}$ | СНО | 5c | 10 | 91 | 169–171 | 170 ^[25] |
| 22 | | СНО | 5d | 6 | 96 | 174–176 | |
| 23 | | онс-Сно | 6a | 5 | 97 | 193–195 | 194 ^[19] |
| 24 | Br | онс-Сно | 6b | 9 | 95 | 178–180 | |
| 25 | | онс-С-сно | 6c | 10 | 91 | 188–190 | |
| 26 | | онс | 6d | 6 | 96 | 266–268 | |

Table 1. Continued

^aIsolated yield.

^bAll compounds were identified by comparison of their melting points with the authentic samples and/ or IR as well as ¹H and ¹³C NMR data. Analytical data of compound **5a** were identical to those described in Ref.^[28]



Scheme 1. Synthetic route of bis-indolyl and tris-indolyl methanes.

indoleninium species, which act as electrophiles toward a second molecule of indole, giving the corresponding bis-indolyl methanes or tris-indolyl methanes respectively.

CONCLUSION

In conclusion, we have developed an efficient, one-pot, and environmentally friendly protocol for the synthesis of bis(indolyl) methanes, tris-indolyl, and di(bisindolyl methanes). Prominent advantages of this method are operational simplicity, good yields of products in short reaction times, high purity, and easy workup procedures.

EXPERIMENTAL

Materials and Methods

All chemicals were obtained from Sigma-Aldrich, Merck, and Lancaster and used as such without further purification. Melting points were determined using a calibrated thermometer by Guna digital melting-point apparatus and are uncorrected.



¹H and ¹³C NMR spectra were recorded as solutions in dimethylsulfoxide(DMSO- d_6) on a Bruker AMX 400-MHz spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C with tetramethylsilane (TMS) as internal reference. Liquid chromatography (LC) mass spectra were recorded on a LCMS 2010A Shimadzu instrument.

Preparation of Catalyst^[24]

A solution of chlorosulfonic acid (10 mmol) was added to a stirring solution of PEG-6000 (1 mmol) in CH₂Cl₂ at 0 °C temperature. Then the resulting solution was stirred at room temperature overnight, and the solution was concentrated under vaccum. Appropriate ether was added, and the precipitate was filtered and washed with ether three times to afford the PEG-SO₃H. ¹H NMR (400 MHz, CDCl₃): δ 12.85 (s, 1H, SO₃H), 4.23 (s, 2H, CH₂SO₃H), 3.49–3.66 (m, PEG).

Typical Procedure for the Preparation of Bis-Indolyl Methanes

A mixture of aldehydes or ketones (1 mmol) and indole (2 mmol) in H_2O (10 ml) was stirred at room temperature in the presence of a catalytic amount of

PEG-SO₃H (0.05 mmol) for an appropriate time (Table 1). After completion of the reaction, as indicated by thin-layer chromatography (TLC), the reaction mixture was diluted with H₂O (20 ml). The solid was separated by filtration and washed with water $(3 \times 150 \text{ mL})$. The isolated solid product was dried under reduced pressure to obtain the pure products.

Typical Procedure for the Preparation of Tris-Indolyl Methanes

A solution of indolealdehydes (1 mmol) and indole (2 mmol) in H₂O (10 ml) was stirred at room temperature in the presence of a catalytic amount of PEG-SO₃H (0.05 mmol) for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with H₂O (20 ml), and the catalyst was totally dissolved in water. The solid was separated by filtration and washed with water (3×150 mL). The isolated solid product was dried under reduced pressure to obtain the pure products.

Typical Procedure for the Preparation Di(bis-Indolyl Methanes)

A solution of terephthalaldehyde (1 mmol) and indole (4 mmol) in H_2O (10 ml) was stirred at room temperature in the presence of a catalytic amount of PEG-SO₃H (0.05 mmol) for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with H_2O (20 ml). The solid was separated by filtration and washed with water (3×150 mL). The isolated solid product was dried under reduced pressure to obtain the pure products.

Characterization Data

4-(Di(1*H***-indol-3-yl)methyl)-2-ethoxyphenol (3e).** Mp: $155-157 \,^{\circ}$ C, ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 1.22 (t, 3H, J = 6.3 Hz), 4.10 (q, 2H), 5.88 (1H, s, ArCH), 6.65 (2H, s), 7.16 (2H, t, J = 6.9 Hz), 7.18–7.26 (3H, m), 7.32–7.36 (2H, m), 7.39–7.44 (4H, m), 7.98 (2H, br, NH), 10.21 (s, 1H); ¹³C NMR (DMSO-*d*₆): δ (ppm): 18.2, 55.1, 68.5, 111.4, 113.4, 114.5, 116.2, 118.2, 119.9, 122.8, 123.2, 123.9, 128.6, 132.4, 137.6, 146.2, 148.8; LCMS (m/z): 383 [M + H]⁺. Anal. calcd. for C₂₅H₂₂N₂O₂: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.44; H, 5.76; N, 7.27.

3-Bromo-2-(di(1*H***-indol-3-yl)methyl)phenol (3g).** Mp: $126-128 \,^{\circ}$ C; ¹H NMR (300 MHz, DMSO- d_6), δ : 5.92 (1H, s, ArCH), 6.65 (2H, s), 7.16 (2H, t, $J = 6.9 \,\text{Hz}$), 7.18–7.26 (3H, m), 7.32–7.36 (2H, m), 7.39–7.44 (4H, m), 7.98 (2H, br, NH), 10.23 (s, 1H); ¹³C NMR (DMSO- d_6): δ 31.8, 111.8, 114.1, 119.4, 120.2, 122.3, 126.1, 126.7, 128.2, 129.2, 130.3, 38.0, 145.2; LCMS (m/z): 417 [M + H]⁺. Anal. calcd. for C₂₃H₁₇BrN₂O: C, 66.20; H, 4.11; N, 6.71. Found: C, 66.14; H, 4.08; N, 6.67.

2-(Di(1*H***-indol-3-yl)methyl)-5-(diethylamino)phenol (3h).** Mp: 161–163 °C, ¹H NMR (300 MHz, DMSO- d_6), δ (ppm): 1.12 (t, 6H, J = 6.2 Hz), 3.42 (q, 4H), 5.52 (1H, s, ArCH), 6.65 (2H, s), 7.18–7.26 (3H, m), 7.32–7.36 (2H, m), 7.39–7.44 (6H, m), 8.26 (2H, br, NH), 9.56 (s, 1H); ¹³C NMR (DMSO- d_6), δ (ppm): 14.2, 38.2, 44.5, 98.5, 105.6, 112.2, 111.4, 114.5, 118.8, 119.5, 120.2, 122.2, 123.4, 128.4,

136.5, 148.4, 156.9; LCMS (m/z): 410 $[M + H]^+$. Anal. calcd. for $C_{27}H_{27}N_3O$: C, 79.19; H, 6.65; N, 10.26. Found C, 79.12; H, 6.59; N, 10.21.

3,3'-((1*H***-Indol-3-yl)methylene)bis(5-methyl-1***H***-indole) (5d). Mp: 174–176 °C, IR (KBr): \nu_{max} = 3298, 3010, 2956, 1622 cm⁻¹. ¹H NMR (300 MHz, DMSO-***d***₆) \delta: 2.68 (s, 6H), 5.72 (s, 1H, Ar-CH), 6.21 (s, 3H), 6.82 (s, 3H), 7.24–7.35 (m, 2H), 7.42–7.56 (m, 5H), 10.73 (s, 3H, –NH); LCMS: m/z 390 [M + H]⁺; ¹³C NMR (DMSO-***d***₆): \delta 22.4, 54.6, 111.1, 111.8, 112.6, 118.0, 118.8, 119.8, 120.8, 121.7, 123.2, 127.4, 128.5, 128.8, 134.5, 136.5. Anal. calcd. for. C₂₇H₂₃N₃: C, 83.26; H, 5.95; N, 10.79. Found: C, 83.18; H, 5.90; N, 10.75.**

1,4-Bis(bis(5-bromo-1H-indol-3-yl)methyl)benzene (6b). Mp: 178–180 °C, IR (KBr): $\nu_{max} = 3328$, 3025, 1632. ¹H NMR (300 MHz, DMSO- d_6), δ (ppm): 5.83 (s, 2H, Ar-CH), 6.55 (s, 4H), 7.21–%32 (m, 4H), 7.26–7.43 (m, 12H), 9.52 (br, s, 4H, NH); ¹³C NMR (DMSO- d_6): δ (ppm): 54.6, 111.4, 113.6, 116.8, 122.0, 123.5, 124.9, 128.8, 129.7, 134.8, 135.7. Anal. calcd. for C₄₀H₂₆Br₄N₄: C, 54.45; H, 2.97; N, 6.35. Found: C, 54.39; H, 2.94; N, 6.30.

1,4-Bis(bis(2-methyl-1H-indol-3-yl)methyl)benzene (6c). Mp 188–190 °C, IR (KBr): $\nu_{max} = 3342$, 2975, 1626. ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.52 (s, 12H), 5.74 (s, 2H, Ar-CH), 6.35 (s, 4H), 7.32–7.39 (m, 4H), 7.45–7.63 (m, 12H), 10.21 (br, s, 4H, NH); ¹³C NMR (DMSO-*d*₆): δ 14.2, 50.6, 112.4, 113.5, 119.2, 120.8, 121.7, 126.3, 128.9, 132.1, 136.5, 137.3. LCMS (m/z): 623 [M+H]⁺. Anal. calcd. for C₄₄H₃₈N₄: C, 84.85; H, 6.15; N, 9.00. Found: C, 84.74; H, 6.08; N, 8.91.

1,4-Bis(bis(5-methyl-1H-indol-3-yl)methyl)benzene (6d). Mp 226–228 °C, IR (KBr): $\nu_{max} = 3328$, 2986, 1638. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm): 2.56 (s, 12H), 5.72 (s, 2H, Ar-CH), 6.28 (s, 4H), 7.26–7.38 (m, 4H), 7.41–7.66 (m, 12H), 9.18 (br, s, 4H, NH). ¹³C NMR (DMSO-*d*₆): δ 14.1, 51.4, 111.6, 112.8, 117.4, 119.9, 121.2, 126.0, 128.5, 131.4, 135.4, 137.0. LCMS (m/z): 623 [M+H]⁺. Anal. calcd. for C₄₄H₃₈N₄; C, 84.85; H, 6.15; N, 9.00. Found: C, 84.73; H, 6.09; N, 8.94.

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