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Synthesis of Bis(indolyl)methanes Using Recyclable PEG-Supported Sulfonic Acid as Catalyst

Shou-Ri Sheng · Qiu-Ying Wang · Yan Ding · Xiao-Ling Liu · Ming-Zhong Cai

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Abstract An operationally simple, efficient and environmentally benign synthetic method to bis(indolyl) methanes has been developed in good yields (80–96%) by electrophilic substitution reactions of indole with aldehydes or ketones in methanol in the presence of 5 mol% of poly (ethylene-glycol) (PEG) supported sulfonic acid with respect to indole under mild conditions. Recovery and recycling of the poly (ethylene-glycol)-supported catalyst were also described.

Keywords Bis(indolyl)methane · PEG-supported sulfonic acid · Indole · Carbonyl compound · Environmentally benign

1 Introduction

The importance of indoles and their derivatives owing to their biological activities is well recognized by synthetic as well as biological chemists [1]. Bis(indolyl)methanes, which contain two indole or substituted indole units in a molecule, feature widely in bioactive metabolites of terrestrial and marine origin [2–6]. Therefore, there is a great deal of interest in the synthesis of this class of compounds. Generally, these molecules are obtained from the condensation of indoles with aldehydes and ketones in the presence of traditional protic [7–9] or Lewis acids [10–13]. Additionally, montmorillonite clay K-10 [14], and other catalysts such as $InCl_3$, In $(OTf)_3$, $LnCl_3$, $Dy(OTf)_3$, $Ln(OTf)_3$, and Re $(PFO)_3$ were also found to catalyze these reactions [15–18]. However, many of these Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required [19]. These problems can be solved to some extent by using expensive lithium perchlorate. But this catalyst requires longer reaction time for nitro-substituted aromatic aldehydes, giving the corresponding bis(indolyl)methanes in moderate yields [20]. In addition, $PPh_3{\cdot}HClO_4$, $NaHSO_4$–SiO_2, I_2 and NBS [21–25], or ionic liquids [26, 27] have been used for such organic synthesis [26]. Recently, the use of protic solvent has been successfully developed to synthesis of bis(indolyl)methanes efficiently [28]. Although methods for preparation of bis(indolyl)methanes are well documented, some of the reported protocols suffered from the usage of expensive reagents, prolonged reaction times, low product yields, complicated manipulations along with the involving of environmentally toxic media, or use of an additional microwave or ultrasound irradiation. So, the development of simple, convenient and environmentally friendly approaches for the preparation of these pharmaceutically important compounds is still demanding. In the past years soluble polymers have gained attraction due to practically homogeneous reaction conditions [29–31], and a number of reviews have appeared on the use of soluble polymer-supported catalysts and reagents [32–34]. We now introduce here a novel facile method for the synthesis of bis(indolyl)methanes by condensation of indole with aldehydes or ketones using PEG-bound sulfonic acid as an efficient and recyclable catalyst under mild conditions.

S.-R. Sheng (✉) · Q.-Y. Wang · Y. Ding · X.-L. Liu · M.-Z. Cai
College of Chemistry and Chemical Engineering, Jiangxi Normal University, 330022 Nanchang, People's Republic of China
e-mail: shengsr@jxnu.edu.cn

2 Experimental

2.1 Materials and Methods

Melting points were uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. FT–IR spectra were taken on a Perkin–Elmer SP One FT–IR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer. The other reagents were purchased from commercial sources and were used without further purification.

2.2 Synthesis of PEG-Supported Sulfonic Acid (3)

PEG 4000 (10.0 g, 2.5 mmol) (**1**) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Methanesulfonylchloride (2.0 mL, 25.0 mmol) and triethylamine (1.5 mL) was then added dropwise. The reaction mixture was stirred at rt. overnight and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (100 mL) and added dropwise with vigorous stirring to diethyl ether (1.0 L). The resulting precipitate was collected by filtration, washed with diethyl ether (3 × 30 mL) and then dried under high vacuum to give the desired PEG 4000 dimesylate as a white solid (9.76 g, 94% based on polymer recovery). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.50–3.66 (m, PEG CH2), 3.06 (s, 6 H, SO_2CH_3).

PEG 4000 dimesylate (10.0 g, 2.40 mmol) in acetone (50 mL), and lithium bromide (1.47 g, 16.9 mmol) were heated at reflux for18 h. The solution was cooled and a white solid removed by filtration. The filtrate was evaporated in vacuo, the crude product dissolved in hot propan-2-ol (50 mL), then cooled to 5 °C. The precipitate formed was collected by filtration, washed with propan-2-ol (10 mL), and Et_2O (2 × 25 mL), and dried in vacuo to afford PEG 4000 dibromide (**2**) as a colourless solid (9.90 g, 100%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.40–3.86 (m, PEG CH2), 3.45 (t, J = 6.3 Hz, CH_2Br).

To a solution of **2** (8.25 g, 2.0 mmol) in propan-2-ol/water (1:1, 100 mL), was added 4-hydroxybenzenesulfonic acid (mono sodium salt) (4.65 g, 20.0 mmol), and sodium hydroxide (800 mg, 20.0 mmol). The reaction mixture was heated at reflux for 24 h. The solvent was removed in vacuo, and the crude product dissolved in hot propan-2-ol (100 mL), from which an insoluble white solid was removed by filtration. The filtrate was cooled to 5 °C, and the precipitate, which formed collected by filtration. This was washed with propan-2-ol (10 mL), Et_2O (2 × 25 mL) and dried in vacuo to afford PEG 4000 disulfonic acid sodium salt as a white solid (8.10 g, 93%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.41–3.84 (m, PEG CH_2), 4.15 (t, J = 5.1 Hz, 4 H, CH_2OAr), 6.84 (d, J = 8.7 Hz, 4 H, Ar–H), 7.85 (d, J = 8.7 Hz, 4 H, Ar–H).

To a solution of PEG 4000 disulfonic acid sodium salt (21.8 g, 5.0 mmol), in propan-2-ol/water (1:1, 100 mL), was added concd. HCl (2.5 mL) and stirred for 5 h at rt. The solvent was removed in vacuo and the crude product dissolved in hot propan-2-ol (100 mL). The solution was cooled to 0 °C, and the precipitate formed collected by filtration. The precipitation step was repeated, the combined precipitates washed with propan-2-ol (10 mL), and Et_2O (2 × 25 mL), and then dried in vacuo to afford PEG 4000 disulfonic acid (**3**) (0.22 mmol SO_3H/g, the loading of functional was analyzed by analysis of elementary sulfur) as a white solid (20.3 g, 94%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.38–3.88 (m, PEG CH2), 4.22 (t, J = 4.6 Hz, 4 H, CH2OAr), 7.05 (d, J = 9.0 Hz, 4 H, Ar–H), 7.94 (d, J = 9.0 Hz, 4 H, Ar–H), 11.26 (s, 2 H).

2.3 General Procedure for the Preparation of Bis(indolyl)methanes

To a solution of indole (2.0 mmol) and carbonyl compound (1.0 mmol) in methanol (10.0 mL) was added PEG 4000 disulfonic acid (0.1 mmol, 0.45 g) and the reaction mixture was shaken at room temperature for the given time in Table 1. After completion of the reaction as monitored by TLC, the solvent was removed in vacuum and the mixture was cooled to 0 °C and then diethyl ether (100 mL) was added with vigorous stirring. For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The resulting PEG-bound sulfonic acid was then collected by filtration, washed with cold diethyl ether (2 × 20 mL) for the next run. The diethyl ether of the filtrate was evaporated and the crude product was purified by column chromatography and eluted with ethyl acetate/petroleum ether mixture to afford the pure product. All the products obtained were characterized by ^{1}H NMR, IR and microanalysis and also by comparison of the spectral data with that reported.

2.4 Selected Spectroscopic Data

Compound 6a: Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (brs, 2H), 7.40–7.34 (m, 6 H), 7.30–7.16 (m, 7 H), 6.55 (s, 2H), 5.90 (s, 1H). IR (KBr): ν 3415, 3025, 1620, 1600, 1220, 1095, 965, 745 cm^{-1}. Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69; Found: C, 85.76; H, 5.58; N, 8.59.

Compound 6k: Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 2 H), 7.50–7.05 (m, 11 H), 6.91 (s, 2 H), 5.92 (s, 1 H). IR (KBr): ν 3411, 1710, 1450, 1262 cm^{-1}. Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; Found: C, 80.84; H, 5.24; N, 9.05.

Compound 6m: Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (br s, 2 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.36

Table 1 Preparation of bis(indolyl)methane derivatives (**6a–6o**)

Entry	R^1	R^2	Time (h)	Comp.	Yield (%)[a]	M.p. (L) (°C)
1	C_6H_5	H	2.5	**6a**	95[b]	124–125 (124–126) [37]
2	C_6H_5	H	2.5	**6a**	94[c]	
3	C_6H_5	H	2.8	**6a**	92[d]	
4	C_6H_5	H	3.0	**6a**	90[e]	
5	4-$CH_3C_6H_4$	H	2.0	**6b**	96	96–97 (94–96) [24]
6	4-$CH_3OC_6H_4$	H	2.0	**6c**	90	187–188 (185–187) [38]
7	3,4-$(MeO)_2C_6H_3$	H	2.5	**6d**	90	198–199 (198–200) [20]
8	4-$NO_2C_6H_4$	H	8.0	**6e**	86	216–218 (217–220) [38]
9	3-$NO_2C_6H_4$	H	9.0	**6f**	85	260–261 (260) [37]
10	4-ClC_6H_4	H	3.5	**6g**	90	77–78 (76–77) [38]
11	2-ClC_6H_4	H	3.0	**6h**	85	72–73 (70–71) [38]
12	3,4-$Cl_2C_6H_3$	H	2.0	**6i**	91	155–156 (154–156) [20]
13	4-(OH)–3-$MeOC_6H_3$	H	3.5	**6j**	93	98–100 (99–101) [16]
14	2-furyl	H	3.0	**6k**	89	322–323 (325) [38]
15	Cyclohexyl	H	4.5	**6l**	80	136–137 (138–140) [20]
16	$CH_3(CH_2)_4$	H	4.0	**6m**	85	70–71 (68–70) [20]
17	$(CH_2)_5$		5.5	**6n**	88	118–119 (118–120) [20]
18	$(CH_2)_4$		6.0	**6o**	83	73–74 (72–74) [20]

[a] Yields refer to the isolated pure products
[b] With the fresh resin
[c] With the first regenerated resin
[d] With the second regenerated resin
[e] With the third regenerated resin

(d, J = 8.0 Hz, 2 H), 7.18 (t, J = 8.0 Hz, 2 H), 7.02 (t, J = 8.0 Hz, 2 H), 6.84 (d, J = 2.5 Hz, 2 H), 4.60 (t, J = 6.7 Hz, 1 H), 2.26–4.24 (m, 2 H), 1.27–1.24 (m, 6 H), 0.8 (t, J = 6.7 Hz, 3 H). IR (KBr): ν 3500, 3065, 3028, 2950, 1615, 1585, 1250, 1062, 773 cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85; Found: C, 83.58; H, 7.71; N, 8.90.

Compound **6n**: Colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (br s, 2 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.26 (d, J = 8.0 Hz, 2 H), 7.06–7.04 (m, 4 H), 6.80 (t, J = 8.0 Hz, 2 H), 2.56–2.54 (m, 4 H), 1.80–1.77 (m, 6 H). IR (KBr): ν 3465, 3028, 2950, 1618, 1580, 1495, 1230, 1009, 782 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91; Found: C, 84.12; H, 7.12; N, 8.99.

2.5 Recycling of the Catalyst

After finishing the above condensation reaction, methanol was evaporated and the PEG-bound sulfonic acid was readily recovered by precipitation with cold diethyl ether followed by filtration and washing with diethyl ether (average recovery yields ranged from 92 to 95%) for the next run directly without any activation. The recycled catalyst was used for four consecutive condensation reactions without observation of appreciable loss in its catalytic activities.

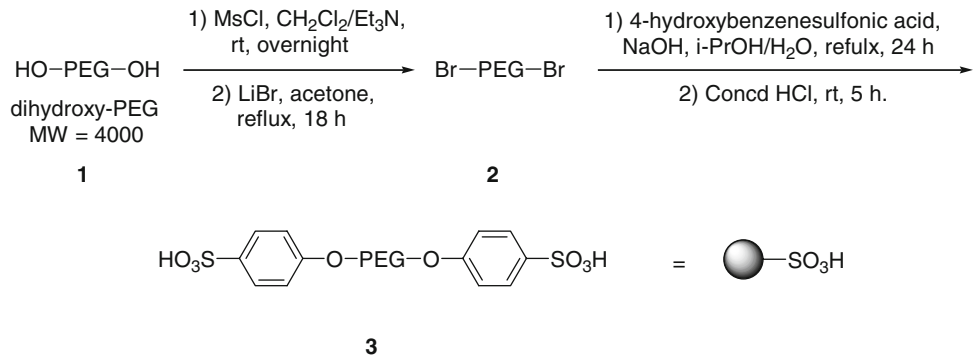
3 Results and Discussion

As shown in Scheme 1, the dimesylation of PEG 4000 was carried out as previously reported and then conversion to the corresponding dibromide achieved under standard conditions [35, 36]. Reaction with 4-hydroxybenzenesulfonic acid and sodium hydroxide followed by acidification with concd HCl gave the difunctionalised PEG-supported sulfonic acid (**3**). In our hands, an attempt was carried out for the conversion the dimesylation of PEG 4000 to **3** directly. However, the obtained yield of **3** was low (55%). Therefore, we adopted a four-step approach to **3** via the intermediate PEG 4000 dibromide, with the overall yield being 82% based on PEG 4000.

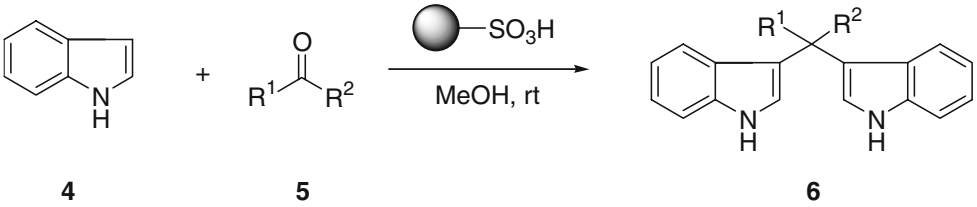
With PEG-supported sulfonic acid (**3**) in hand, we optimized the reaction conditions for the synthesis of target compounds **6** (Scheme 2). First of all, the condensation reaction of indole (**4**) with benzaldehyde (**5a**) to the corresponding 3,3′-bis-indolyl-phenylmethane (**6a**) in the presence of the catalyst (**3**) at room temperature in various solvents like dichloromethane (60%), diethyl ether (71%) or acetonitrile (80%) was investigated. Interestingly, after a series of experiments, 95% yield of **6a** was obtained when **4** and **5a** was allowed to react with stirring at room temperature for 2.5 h using methanol as a solvent and in the presence of 5 mol% of PEG-supported sulfonic acid with respect to indole (Table 1, entry **1**). Similarly, the electrophilic substitution reactions of indole (**4**) with other aldehydes (**5b–5m**) or ketones (**5n–5o**) proceeded smoothly at room temperature to afford the corresponding bis(indole) derivatives (**6b–6o**) with good yields in a short reaction time (Table 1).

As seen from Table 1, the effect of electron deficiency and the nature of the substituents on the aromatic ring showed some effect on this conversion. The nitro-substituted

Scheme 1



Scheme 2



aryl aldehydes (Table 1, entries **8** and **9**) required longer reaction times to produce comparable yields than those of their simple and electron-rich counterparts. Electron-rich aldehydes like anisaldehyde (Table 1, entry **6**), veratraldehyde (Table 1, entry **7**) and so forth, reacted rapidly with indole, whereas aliphatic aldehydes such as cyclohexane carboxaldehyde (Table 1, entry **15**) and hexanal (Table 1, entry **16**) afforded good yields of products in 4–5 h of reaction time. Furthermore, the reaction of indole with ketones such as cyclohexanone (Table 1, entry **17**) and cyclopentanone (Table 1, entry **18**) gave the products in good yields but with longer reaction times compared to electron-rich aldehydes. In addition, the acid sensitive substrate furfural is also converted easily to the corresponding bis(indolyl)methane in good yield (Table 1, entry **14**).

The reusability of the catalyst was also examined by treating indole (**4**) and benzaldehyde (**5a**) in the presence of 5 mol% of the catalyst under above similar conditions. The results indicated that the recovered PEG-bound sulfonic acid can be reused directly for four consecutive reactions to afford **6a** in 95, 94, 92, 90% yields with a few increase in reaction time, respectively, as shown in Table 1 (entries **1–4**). It must be noted that, when the catalytic activity of polymeric sulfonic acid decreased, the resin could be treated with concd HCl again for keeping its catalytic activity.

4 Conclusion

In summary, we have demonstrated a novel, efficient and environmentally benign protocol for the preparation of bis(indolyl)methanes through the electrophilic substitution reactions of indole with various aldehydes or ketones in the presence of catalytic amount of PEG-supported sulfonic acid. This method offers good advantages such as mild reaction conditions, short reaction times, high yields, readily availability of cheap and recyclable catalyst, and with a facile work-up procedure.

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