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ORIGINAL PAPER

Chemoselective synthesis of bis(indolyl)methanes using sulfonic acid-functionalized chitosan

Amit Kumar[1] · **Chetananda Patel**[1] · **Pooja Patil**[1] · **Shivam Vyas**[1] · **Abha Sharma**[1]

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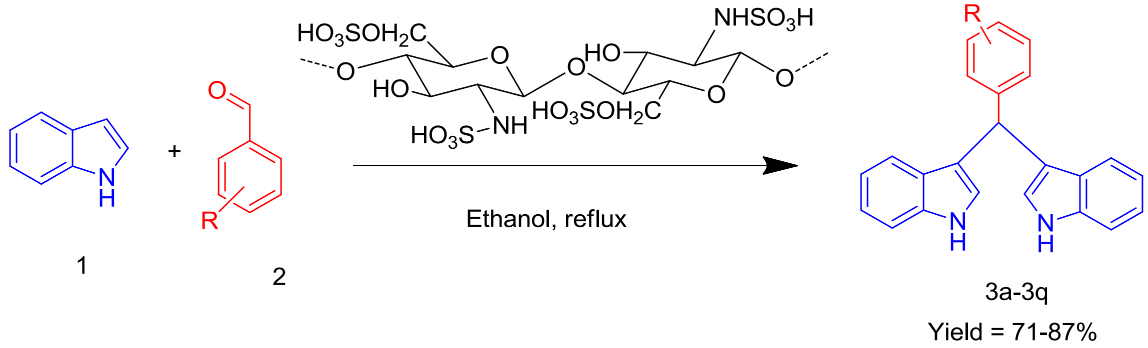
Abstract

Herein, we describe the electrophilic substitution reaction of indole with aldehydes and ketone using sulphonic acid functional group containing chitosan for the synthesis of bis(indolyl)methanes. The reaction is chemoselective affording a product from aldehydes and indole. The catalyst can be reused up to three times without great loss in yields. Hence, chitosan–SO_3H (CTSA) proved to be a heterogeneous, efficient, chemoselective, and reusable catalyst for the synthesis of bis(indolyl)methane derivatives.

Graphic abstract



Keywords Bis(indolyl)methanes · Chemoselective · CTSA · Recyclable

Introduction

A structurally diverse range of molecules has been isolated from plants and microorganisms which possess a wide range of biological activities (Bao et al. 2005; Casapullo et al. 2000; Garbe et al. 2000). Bis-indole alkaloids such as macrocarpamine, macralstonine acetate, villastonine, ramiflorine, deoxytopsentin, bromodeoxytopsentin have been isolated from plants and sponges (Oh et al. 2006; Tanaka et al. 2006; Wright et al. 1992; Wright and Phillipson 1990). Some novel bis- and tris-indole derivatives such as arundine, 1,1,3-tris(3-indolyl)butane, 3,3-bis(3-indolyl)butane-2-one, and 1,1,1-tris(3-indolyl)methane isolated from a bacteria *Vibrio parahaemolyticus* Bio249, reported by Veluri et al. (2003). Predominantly, bis(indolyl)methane (BIM) and their derivatives exhibit anti-bacterial(Kaur et al. 2015), anticancer (Ichite et al. 2009; Jamsheena et al. 2016), antioxidant (Simha et al. 2017) analgesic and anti-inflammatory activities (Sarva et al. 2016), acts as HIV-1 integrase inhibitor (Contractor et al. 2005), used in estrogen metabolism regulation in humans (Karthik et al. 2005), in the treatment of chronic fatigue, fibromyalgia, irritable

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✉ Abha Sharma
abha.sharma@niperraebareli.edu.in

[1] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Raebareli, India

bowel syndrome (Kamble et al. 2007), food industry (Shimoda and Shibamoto 1990), optics, and polymers (Lafzi et al. 2018; Shchepinov and Korshun 2003). It has also been developed as a molecular sensor for selective detection of copper and mercury ions (Liao et al. 2015; Martınez et al. 2008). Figure 1 shows the structure of some biologically important bis(indolyl)methane derivatives.

The most simple and straightforward approach for the synthesis of BIM is the brønsted acid-catalyzed electrophilic substitution reaction of indoles with aldehydes (Chakrabarty et al. 2006; Ke et al. 2005; Veisi et al. 2011). Other than acids, a variety of reagents such as iodine (Ji et al. 2004), modified zirconia (Nadkarni et al. 2008), $InCl_3$ and $In(OTf)_3$ (Nagarajan and Perumal 2002), tetramethyl guanidinium chlorosulfonate (Kalla et al. 2014), aluminum dodecatungstophosphate (Firouzabadi et al. 2006), silica-supported $AlCl_3$ (Boroujeni and Parvanak 2011), ionic liquids (Yadav et al. 2008; Ying et al. 2015), and $BF_3·OEt_2$ (Swetha et al. 2015) have also been used for the synthesis of BIM. The reported methodologies are associated with some drawbacks such as the use of costly, toxic reagent/solvents and tedious workup process; for example, there is a report of the synthesis of bis(indolyl)methane in the presence of iodine, the workup process of this protocol is not straightforward, and requires special treatment during the workup process (Ji et al. 2004). There are many reports of use of silica-supported catalyst; although product yield obtained was excellent, this protocol is not environmentally friendly (Boroujeni and Parvanak 2011). The other method of synthesis of BIM is the reaction of indole with benzyl alcohol and Bartoli indole reaction (Abe et al. 2013; Hikawa and Yokoyama 2013).

In recent years, the utilization of natural polymer-bound catalysts has been well explored owing to cost-effective, easy separation of catalysts and products (Bailey and Langer 1981; Dash et al. 2011; Xie et al. 2016). One such natural polymer is chitosan (CT, Fig. 2a) as it is a polysaccharide, biodegradable, biocompatible and can be chemically modified because of the presence of amine and hydroxyl groups. Chitosan can be made acidic by sulfonation, yielding chitosan–SO_3H (CTSA, Fig. 2b). Few reports show the utilization of biodegradable solid acid–chitosan as catalysts for an organic transformation (Khan and Siddiqui 2015; Mohammadi and Kassaee 2013; Reddy et al. 2013). Other modified forms of chitosan have been used in Suzuki cross-coupling (Martina et al. 2011), Ullmann reaction (Zeng et al. 2012), Michael addition reaction (Khalil et al. 2010), [3 + 2] Huisgen cycloaddition (Chtchigrovsky et al. 2009), Heck reaction (Calò et al. 2004), C–C bond formation (Kühbeck et al. 2012) and cycloaddition of CO_2 (Sun et al. 2012). Herein, we wish to report an efficient and practical synthesis of BIM catalyzed by CTSA (Scheme 1).

Fig. 1 Some biologically active bis(indolyl)methane derivatives

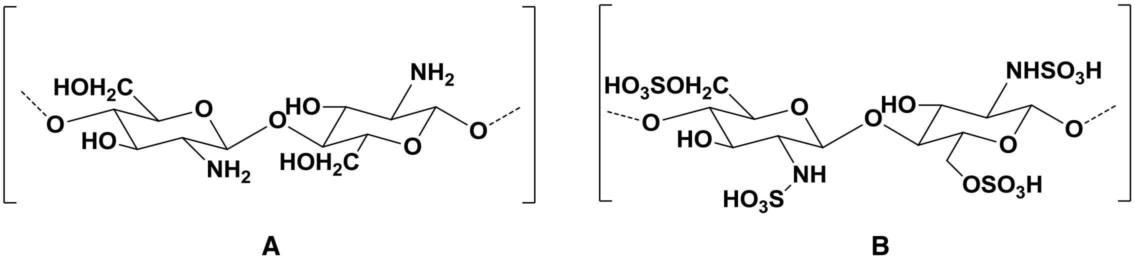
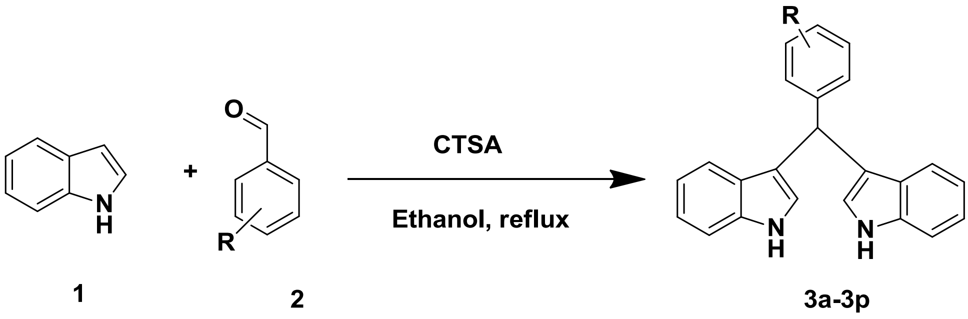


Fig. 2 Structures of **a** chitosan and **b** CTSA

Scheme 1 Synthesis of bis(indolyl)methane derivatives catalyzed by CTSA

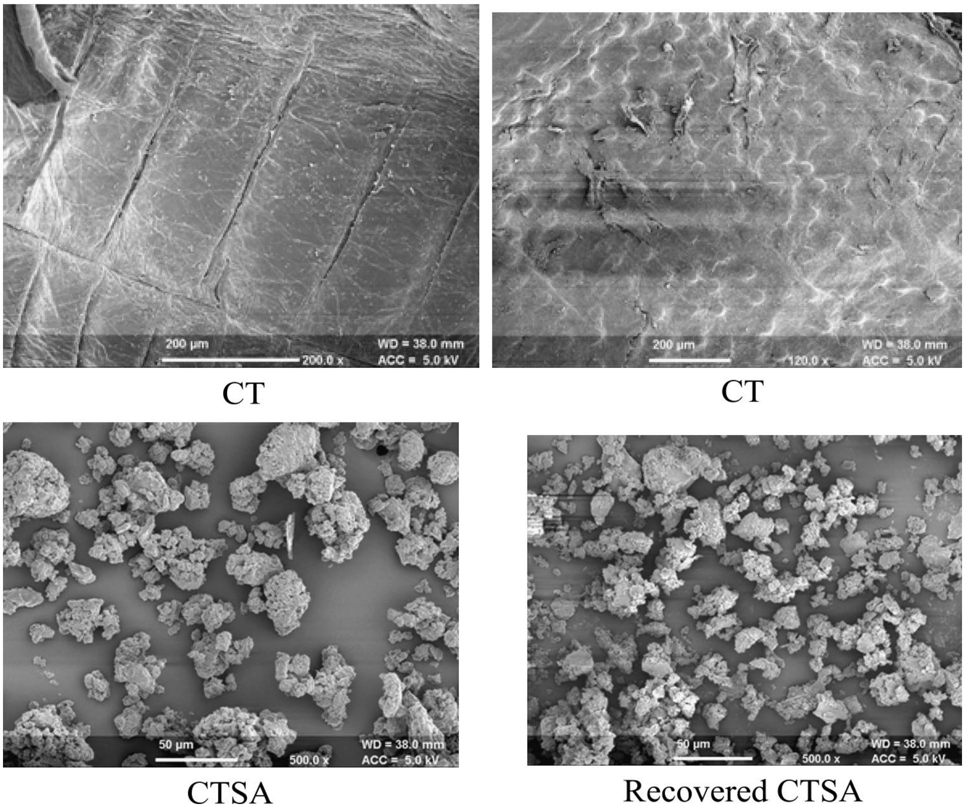


Results and discussion

Our study started with the modification of chitosan with chlorosulfonic acid led to the formation of CTSA (Fig. 2b). The functionalization of CT to CTSA was confirmed by analyzing FT-IR spectra. The IR spectrum of CTSA showed a broad band at 2400–3400 cm^{-1} due to stretching vibration of acidic OH bond. The sulphonic acid group is introduced at OH as well as NH_2 group of chitosan; its S=O stretching bands appeared at 1216 cm^{-1} and 1069 cm^{-1} for –O–SO_3H and –NH–SO_3H, respectively. The S–N bond stretching vibration in the –HN–SO_3H appeared at 669 cm^{-1}. The appearance of these bands confirmed the introduction of sulphonic acid groups in CTSA which are absent in CT (Fig. 2a). CTSA elemental analysis showed the carbon, nitrogen and sulfur content 28.43% 5.33% and 7.45%, respectively. The SEM micrograph of the CT, CTSA and recovered CTSA showed homogeneous nature of the material. The surface of CT appeared smooth and homogeneous. After modification of CT to CTSA, SEM image showed homogeneous nature of the material which remained as such for recovered CTSA. The surface of the CTSA and recovered CTSA appeared to be unaffected after modification. The SEM images of CT, CTSA and recovered CTSA are shown in Fig. 3.

After the preparation and characterization of CTSA, we checked the possibility of CTSA to act as a catalyst for the synthesis of BIM. A reaction between indole (117 mg, 1 mmol) and benzaldehyde (53 mg, 0.5 mmol) in EtOH (2 mL) in the presence of CTSA (100 mg) was selected as a model reaction (78 °C). A promising result was obtained and

Fig. 3 SEM image of the CT and catalyst



CT

CT

CTSA

Recovered CTSA

Table 1 Screening of solvents for the synthesis of bis(indolyl)methanes on the model reaction

Entry	Solvents	Temperature	Time[a]	Yield[b]
1.	EtOH	Reflux	1 h 30 min	87
2.	MeOH	Reflux	2 h	82
3.	iPrOH	Reflux	2 h	80
4.	H_2O	Reflux	6 h	82
5.	PEG-200	80 °C	7 h	65
6.	PEG-400	80 °C	7 h	63
7.	PEG-600	80 °C	7 h	59
8.	EtOH[c]	Reflux	1 h	No reaction
9.	Neat	RT	1 h	Trace product

Indole (1 mmol), benzaldehyde (0.5 mmol), 100 mg CTSA and 2 mL solvent

[a] Reaction progress monitored by TLC

[b] Isolated yield

[d] Without a catalyst

Table 2 Optimization of temperature and amount of catalyst for the synthesis of bis(indolyl)methanes in EtOH

Entry	CTSA[a] (mg)	Temp °C	Time (h)	Yield (%)
1.	10	rt	24	33
2.	10	60	21	40
3.	20	60	17	45
4.	30	60	15	56
5.	40	60	12	60
6.	50	60	10	65
7.	60	60	9	73
8.	70	60	8	75
9.	80	60	7	76
10.	90	60	8	77
11.	100	60	8	78
12.	40	78	8	66
13.	50	78	4	72
14.	60	78	2 h 45 min	78
15.	70	78	2	80
16.	80	78	1 h 50 min	83
17.	90	78	1 h 40 min	87
18.	100	78	1 h 30 min	87
19.	120	78	1 h 45 min	85
20.	140	78	1 h 50 min	84

Indole (1 mmol), benzaldehyde (0.5 mmol), and 2 mL solvent

[b] Amount of CTSA groups

this encouraged us to study further. The study was directed further by taking different solvents such as methanol, ethanol, water, PEG200, PEG400 and PEG600, and the results are summarized in Table 1. We observed that the best solvent in terms of reaction time and yield was EtOH (Table 1, entry 1). In water (Table 1, entry 4) also yield was found near to EtOH but a drawback associated with this was the difficulty in recovery of the catalyst. The product obtained in water was in the precipitate form and catalyst was also not soluble. At the time of workup, first, we had to add EtOH to dissolve the product which was then filtered. In polyethylene gylcol (Table 1, entries 5–7), more time was required for the reaction and less yield of products was obtained, but in MeOH and *i*PrOH, i.e., in protic solvents (Table 1, entries 2–3), yield of the products was found to be good.

After finding out the best solvent for the reaction, a study has been done for optimization of reaction temperature and amount of catalyst. This was carried out with the reaction of indole (1a, 1 mmol), benzaldehyde (2a, 0.5 mmol) and 10 mg CTSA in EtOH (2 mL) at room temperature (rt). We observed that the reaction ended in 24 h with 33% yield (Table 2, entry 1). This study showed that it is effective as a catalyst. Now, to determine the best reaction condition, i.e., the amount of CTSA, temperature and reaction time, reaction was proceeded with the same amount of catalyst at 60 °C. It was found that at this temperature reaction completed in 21 h with 40% yield (Table 2, entry 2). Now at this temperature, we varied the amount of catalyst, 20 mg, and observed that reaction time decrease to 17 h with 45% yield (Table 2, entry 3) and carried out the reaction up to 100 mg of catalyst with 10 mg of difference in each reaction (Table 2, entries 4–7). After this, we increased the temperature to 100 °C and observed that optimum quantity of catalyst was found to be 100 mg and reaction ended in 1 h and 30 min (Table 2, entry 14). The result of the optimization of reaction conditions is listed in Table 2.

Then the optimized protocol was extended to the reaction of indole with different aromatic aldehydes and ketones. The result showed that this method applicable to a wide range of aromatic aldehydes gave the corresponding products in good to very good yield in 30 min–3 h. Unsubstituted aromatic benzaldehyde furnished the product in 1 h and 30 min with 87% yield. The various substituted aromatic aldehydes bearing electron-donating and -withdrawing groups produced derivatives with the yield from 71 to 87% (Table 3). Further, rate of reaction was influenced by the nature of substituent present on aromatic aldehyde. We found slow rate with electron-withdrawing group-bearing aromatic aldehydes. On the other hand, we found the difference in the yield of product with the position of substituent on the aromatic aldehydes. Slightly greater yield was found for indole reaction with para-substituted aromatic aldehydes. All the prepared products were characterized by ^{1}H-NMR and ^{13}C-NMR. The ^{1}H NMR spectrum of novel compound 3q showed multiplets in the range of δ 7.57–6.81 for all the aromatic protons. The two NH protons have appeared at δ 7.84 and singlet for two protons appeared at δ 6.56 which is for indole 'pyrrole' ring. The peak at δ 6.25 appeared as singlet for CH proton. The

Table 3 Synthesis of bis(indolyl)methanes derivatives catalyzed by CTSA

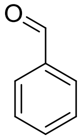
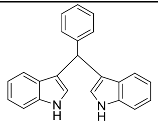
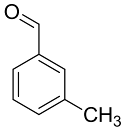
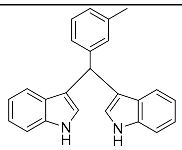
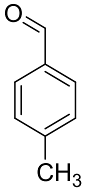
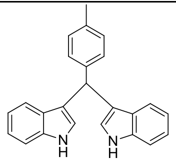
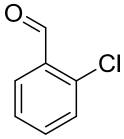
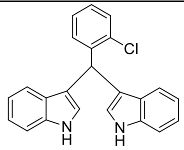
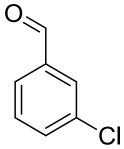
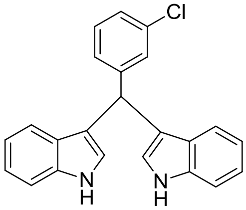
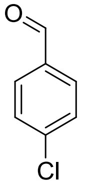
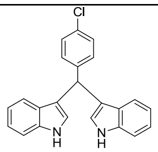
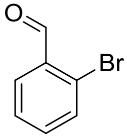
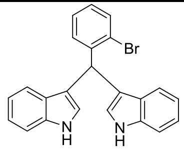
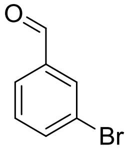
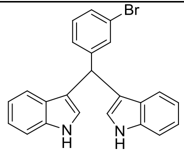
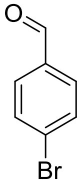
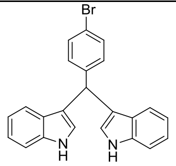
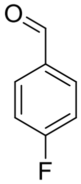
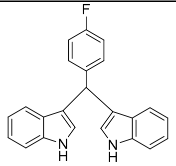
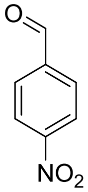
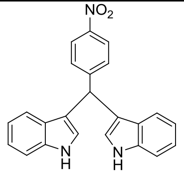
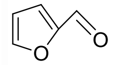
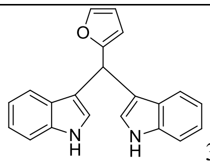
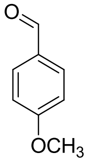
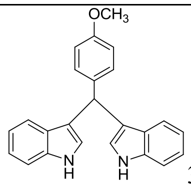
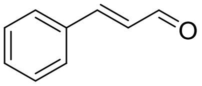
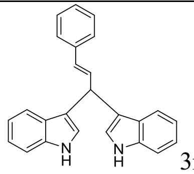
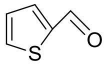
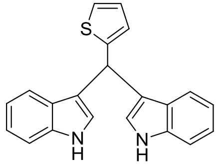
Entry	Aldehyde	Product[a]	Time	Yield (%)
1.		 3a	1 h 30 min	87
2.		 3b	1h	81
3.		 3c	1h	85
4.		 3d	2 h	78
5.		 3e	2h	79
6.		 3f	1 h	81
7.		 3g	2 h	72
8.		 3h	2 h	74

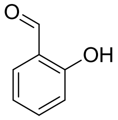
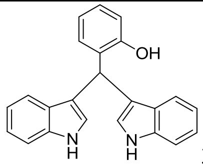
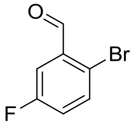
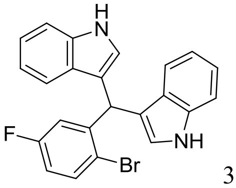
Table 3 (continued)

Entry	Aldehyde	Product[a]	Time	Yield (%)
9.		 3i	2 h 30 min	79
10.		 3j	1 h 20 min	72
11.		 3k	3 h	77
12.		 3l	50 min	71
13.		 3m	1h 15 min	75
14.		 3n	30 min	81
15.		 3o	45min	78

^{13}C NMR spectrum showed signals at δ 163.9 for carbon-bearing fluoro group and at δ 145.7 for carbon attached to bromo substituent. The signal at δ 39.9 was for sp^3-hybridized carbon in 3q derivative.

The various reported catalysts used for the synthesis of bis(indolyl)methane are tabulated in Table 4. The present protocol is recyclable, eco-friendly and in some aspects superior to some reported methods.

Table 3 (continued)

Entry	Aldehyde	Product^a	Time	Yield (%)
16.		 3p	1 h 10 min	74
17.		 3q	1 h 30 min	75

^{a}Products were identified by ^{1}H and ^{13}C NMR, and known products were matched with the literature data (Swetha et al. 2015; Khalil et al. 2010; Chtchigrovsky et al. 2009)

Table 4 Efficiency of reported catalyst used for the synthesis of 3,3′-(phenylmethylene)bis(1H-indole)

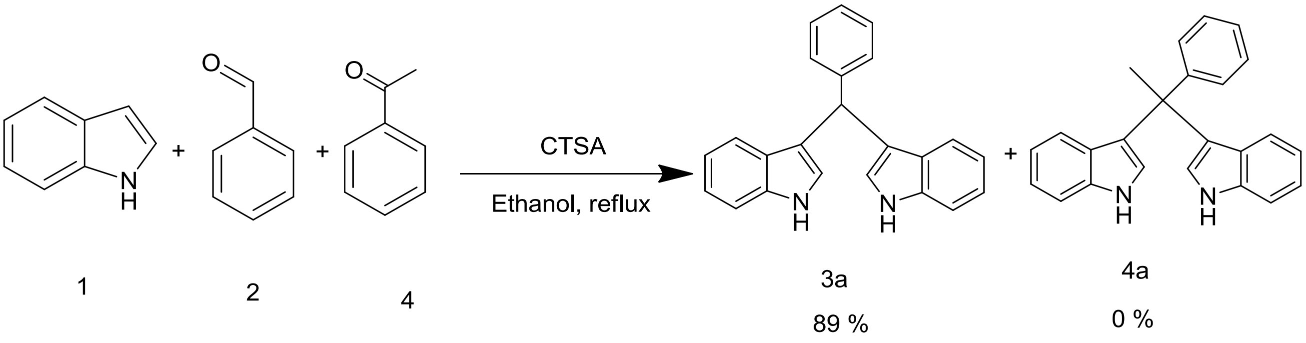
Catalysts	Time (h)	Yield (%)	References
Ln(OTf)$_3$	12	95	Chen et al. (1996)
LiClO$_4$	2.5	90	Yadav et al. (2001)
I$_2$	0.16	76	Ji et al. (2004)
SiO$_2$–H$_2$SO$_4$	0.75	92	Pore et al. (2006)
SiO$_2$–NaHSO$_4$	2.5	89	Ramesh et al. (2003)
Heteropolyacid	2	84	Azizi et al. (2007)
Zeolite	2	80	Karthik et al. (2004)
Zeokarb-225	7.5	95	Magesh et al. (2004)
In(OTf)$_3$	0.41	71	Nagarajan and Perumal (2002)
SbCl$_3$	1.15	94	Srinivasa et al. (2008)

After testing various aromatic aldehydes, protocol extended for the reaction of a ketone with indole, no product was observed. This observation prompted us to perform the reaction with benzaldehyde, acetophenone and indole (Scheme 2). The result of this reaction indicated that the formation of '3a' alone suggests that the reaction is chemoselective.

Heterogeneous catalyst was recovered and its efficiency again for the synthesis of 4a was checked for three subsequent runs (Fig. 4). The catalyst was easily recovered by filtering the reaction mixture followed by washing with ethanol, acetone and kept for air drying. There was some decrease in catalytic activity of CTSA in the third run of reaction. In the present protocol, we utilized natural product-modified catalyst which is a biodegradable and reusable catalyst, therefore, fulfilling some aspects of green chemistry principle.

Conclusion

In conclusion, the CTSA proved to be an effective, chemoselective, heterogeneous and recyclable catalyst for the synthesis of bis(indolyl)methane derivatives thus making methodology clean and simple for its synthesis.



Scheme 2 Chemoselective synthesis of bis(indolyl)methane (3a)

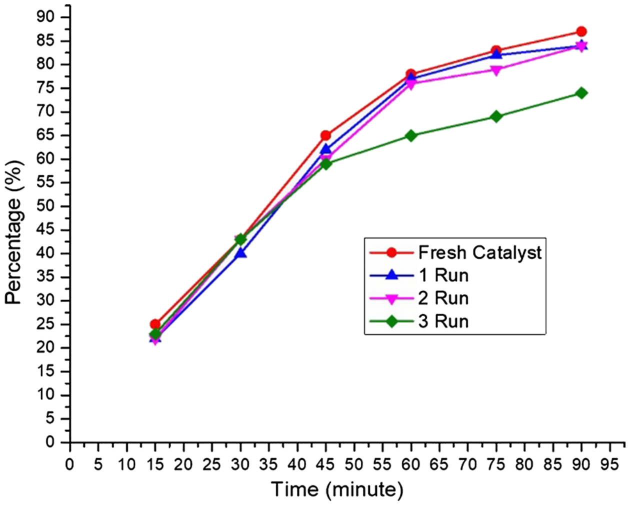


Fig. 4 Percentage conversion with time

Experimental

Methods and materials

All reagents and solvents used in this work are available commercially and used as such without further purification. Reaction progress was monitored by TLC aluminum sheet and silica gel 60 F_{254}.^{1}H NMR and ^{13}C NMR spectra were recorded on 300 and 100 MHz Brucker instrument, respectively, using $CDCl_3$ as solvent and Me_4Si as an internal standard.

Modification of CT to CTSA

CTSA was synthesized by the reported method (Khan and Siddiqui 2015). In round-bottom flask, 2.00 g of chitosan was taken in 20 mL of dry dichloromethane and then 4 mL chlorosulfonic acid was added dropwise at 0 °C in 2 h. After its whole addition, the mixture was stirred for another 4 h at room temperature until HCl was removed from the reaction vessel. Then the mixture was filtered and washed many times with methanol until a neutral pH level was accomplished. Then the product was dried at room temperature to obtain a white powder of CTSA.

General procedure for the synthesis of bis(indolyl) methanes

For the synthesis of bis(indolyl) methane derivatives, indole (1 mmol) and different aldehydes (0.5 mmol) were taken in 2.0 mL of EtOH in a 25-mL round-bottom flask containing a magnetic stir bar. Then 100 mg of the CTSA was added to the reaction mixture and the reaction mixture was refluxed. After the completion of the reaction, the reaction mixture was filtered to separate the catalyst. The filtrate was concentrated and after addition of water, the solid product was obtained.

Selected spectroscopic data

3,3′-(Phenylmethylene)bis(1H-indole) (3a) Red solid; mp = 149-152 °C (Ref; 148–152 °C); yield: 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.38–7.12 (m, 11H), 6.98 (t, $J = 7.5$ Hz, 2H), 6.60 (s, 2H), 5.86 (s, 1H)). ^{13}C NMR ($CDCl_3$, 100 MHz): 144.7, 136.8, 129.6, 128.8, 126.7, 126.4, 125.8, 123.8, 122.1, 121.2, 119.3, 111.3, 40.6. MS-ESI: 322 $[M]^+$.

3,3′-((2-Chlorophenyl)methylene)bis(1*H*-indole) (3b) ^{1}H NMR (300 MHz, DMSO) δ 10.78 (s, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 7.9$ Hz, 2H), 7.19 (s, 1H), 7.16–7.13 (m, 2H), 7.06–6.96 (m, 3H), 6.90–6.84 (m, 2H), 6.82 (dd, $J = 4.8$, 1.4 Hz, 2H), 5.78 (s, 1H), 2.24 (s, 2H), MS-ESI: 336.1 $[M]^+$.

3,3′-(*p*-Tolylmethylene)bis(1H-indole) (3c) Pink solid; mp = 103-105 °C (Lit. 103-104 °C); yield: 85%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 2H), 7.39 (d, $J = 9$ Hz, 2H), 7.32 (d, $J = 9$ Hz, 2H), 7.22–6.96 (m, 8 H), 6.60 (s, 2H), 5.83 (s, 1H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 141.3, 136.3, 135.7, 129.3, 128.5, 126.7, 122.8, 122.2, 121.5, 120.2, 119.2, 110.3, 39.8, 21.5. MS-ESI: 336.1 $[M]^+$.

3,3′-((2-Chlorophenyl)methylene)bis(1*H*-indole) (3d) ^{1}H NMR (300 MHz, DMSO): δ 10.86 (s, 2H), 7.50–7.43 (m, 1H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.25 (m, 6H), 7.10–7.00 (m, 2H), 6.93–6.84 (m, 2H), 6.76 (d, $J = 1.9$ Hz, 2H), 6.22 (s, 1H). MS-ESI: 322.41 $[M]^+$.

3,3′-((4-Bromophenyl)methylene)bis(1*H*-indole) (3i) ^{1}H NMR (300 MHz, DMSO): δ 10.83 (s, 2H), 7.48–7.42 (m, 2H), 7.37–7.24 (m, 6H), 7.08–7.00 (m, 2H), 6.91–6.81 (m, 4H), 5.83 (s, 1H), MS-ESI: 401.31 $[M]^+$.

3,3′-((4-Fluorophenyl)methylene)bis(1*H*-indole) (3j) ^{1}H NMR (300 MHz, DMSO): δ 10.82 (s, 2H), 7.40–7.32 (m, 4H), 7.27 (d, $J = 7.8$ Hz, 2H), 7.12–6.99 (m, 4H), 6.90–6.80 (m, 4H), 5.85 (s, 1H), MS-ESI: 340.14 $[M]^+$.

3,3′-(Thiophene-2-ylmethylene)bis(1*H*-indole) (3o) ^{1}H NMR (300 MHz, DMSO): δ 10.84 (s, 2H), 7.35 (dd, $J = 11.3$, 4.2 Hz, 4H), 7.30 (dd, $J = 4.4$, 2.0 Hz, 1H), 7.07–6.99 (m, 4H), 6.94–6.84 (m, 4H), 6.13 (s, 1H), MS-ESI: 328.10 $[M]^+$.

3,3′-((2-Bromo-5-fluorophenyl)methylene)bis(1H-indole) (3q) Pink solid; mp = 135-136 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (s, 2H); 7.57-7.53 (1H, m); 7.40–7.35 (4H, m); 7.18 (t, $J = 7.5$ Hz, 2H); 7.03 (t, $J = 7.5$ Hz, 2H); 6.93 (dd, $J = 6$ Hz, 1H); 6.81 (1H, m); 6.56 (s, 2H), 6.25 (1H,s). ^{13}C NMR (CDCl$_3$, 100 MHz): 163.9 (C–F), 160.68(C–F), 145.7, 136.9 134.0 123.9, 122.4, 119.9, 119.6, 118.0, 117.5 39.9. ^{19}F-NMR (CD$_3$OD, 282 MHz): -116.97; MS–ESI: 418.04[M]$^+$.

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