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An efficient synthesis of bis(indol-3-yl)methane derivatives using montmorillonite k10 as solid acid catalyst in green solvent

Sunil S Choudhare, Manojkumar U Chopade, Gopinath S Khansole, Ashok R Karad, Navanand B Wadwale and Vijay N Bhosale

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Abstract

An efficient solvent-free synthesis of bis(indol-3-yl)methane derivatives was developed using montmorillonite K10 as a reusable solid catalyst. The reactions were performed by simple grinding of the reactants in a mortar at room temperature. This clay-supported method produced the desired products in good to excellent yields. Various reaction parameters, including molar ratio, catalyst loading, reaction time, and temperature, were systematically studied for their impact on the yield. The structures of all newly synthesized compounds were confirmed through spectroscopic analysis. This green synthetic approach offers notable advantages such as high product yields, reduced reaction times, ease of product isolation, and the use of an environmentally friendly, recyclable catalyst.

Keywords: Montmorillonite k-10, bisindolylmethane, environmentally, green synthesis

1. Introduction

Indole is an interesting structural motif present in more than 3000 isolated natural products and entrenched in many organic systems [1, 2, 3]. Its derivatives have been identified as an important class of heterocyclic compounds in pharmacology, medicinal and biochemistry [4, 5]. Bis-indolylmethanes which are found in marine sponges [6, 7] are effective in the prevention of cancer due to their abilities to modulate cancer causing estrogen metabolites [8]. Indole serves as a key pharmacophore in bis(indolyl)methane (BIM) derivatives, many of which have been isolated from marine natural sources [9, 10]. These compounds represent a significant class of indole-based molecules known for their diverse and potent biological activities, including antibacterial, antifungal, antimicrobial, and anti-inflammatory properties [11]. Owing to the high reactivity at the C3 position of the indole ring, most reported BIMs are of the 3,3'-substituted type. Consequently, a wide variety of synthetic approaches have been developed for the preparation of bis(indol-3-yl)methanes (BIMs), utilizing Lewis acids, Brønsted acids, solid-supported catalysts, and even superacidic systems. Numerous catalysts have been reported in the literature for this purpose, including $In(OTf)_3$ [14], poly(vinyl sulfonic acid) [15], FeF_3 [16], $ZrCl_4$ [17], $[bimim][MeSO_4]$ [18], $InCl_3$ [19], SiO_2-$AlCl_3$ [20], $Cu_{1.5}PMo_{12}O_{40}$ [21], NH_4Cl [22], cellulose sulfuric acid [23], $Zn(OTf)_2$ [24], ultrasound-assisted methods [25], and supported-SO_3H catalysts [26], among others. Some studies have also explored the synthesis of BIMs in aqueous media [27], highlighting the increasing emphasis on environmentally friendly protocols. More recently, novel β-lactam compounds incorporating a bis(indolyl) framework have also been synthesized, expanding the structural diversity and potential biological applications of this important class of compound [28]. bis(indolyl)methanes (BIMs) and related compounds show a antitumor and antileishmanial properties [29]. 3,3'-Diindolylmethane(DIM) [1], is a powerful substance found naturally in cruciferous vegetables, which promotes beneficial metabolism of estrogen in women and men (Figure1a) [30]. Trisindoline [2] was isolated from marine bacterium *Vibrio* sp. (Figure 1a) [31]. Malassezin **[3]** which was obtained from the yeast Malassezia furfur and 6-formylindolo[3,2-*b*]carbazole (FICZ) [4] and indolo[3,2-*b*]carbazole (ICZ) [5] are an agonist of the arylhydrocarbon (AhR) receptor (Figure 1) [32]. These methods however involve expensive metal precursors, high temperature, harsh reaction conditions, longer reaction times, catalyst harmful to environment, and low yields. Therefore, the development of simple and efficient methods for the synthesis of bis(indol-3-yl)methane derivatives is an active area of research and there is scope for further improvement involving milder reaction conditions and higher product yields.

Sunil S Choudhare
Department of Chemistry,
Sant. Dnyaneshwar.
Mahavidyalaya, Soegaon,
Aurangabad, Maharashtra, India

Manojkumar U Chopade
Department of Chemistry,
Sant Dnyaneshwar
Mahavidyalaya, Soegaon,
Aurangabad, Maharashtra, India

Gopinath S. Khansole
Department of Chemistry,
DABN College, Chikhali, Sangli,
Maharashtra, India

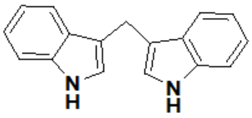
Ashok R Karad
Department of Chemistry, MGM
Ahmedpur, Latur, Maharashtra,
India

Navanand B Wadwale
Department of Chemistry,
MSG College Malegaon, Nashik,
Maharashtra, India

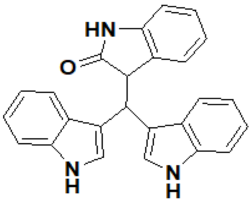
Vijay N Bhosale
Department of Chemistry,
Yeshwant Mahavidyalaya,
Nanded, Maharashtra, India

Corresponding Author:
Vijay N Bhosale
Department of Chemistry,
Yeshwant Mahavidyalaya,
Nanded, Maharashtra, India

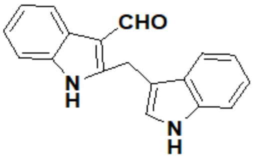
Montmorillonite K10 known for their Lewis acid activity, have many advantages such as ease of handling, commercial availability, non-corrosiveness, low cost and regeneration, have acquired important place in organic transformations over two decades [33]. It is the most widely studied in protection, deprotection reactions and MCRs under liquid phase as well as solvent free conditions [34]. It is a member of phyllosilicate mineral group which has two tetrahedral sheets sandwiching one octahedral sheet. Silicon is substituted by aluminium in octahedral structure caused an excess of negative charge in the structure which is balanced by other cations (Na^+, K^+, Mg^+, Ca^{++}) in the interlayer space. These ions can be exchanged by other cations; it makes montmorllonite become a useful catalyst [35-37]. Acid activated montmorillonite are widely used in various fields for example, solid acid catalyst and solid support in chemical industry [38-40]. In addition, this catalytic property is also improved with acid modification [41]. To overcome the limitations involved in the synthesis of symmetrical bis(indol-3-yl)methane derivatives we introduce an efficient, rapid and clean procedure for the synthesis of bis(indol-3-yl)methane derivatives using Montmorillonite K10 as solid acid catalyst.



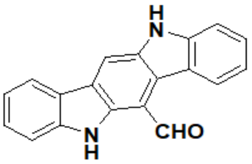
DIM(1)
AhR Agonist



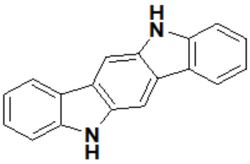
Trisindoline(2)



Malasszin (3) natural AhR Agonis



FICZ(4)



ICZ (5)

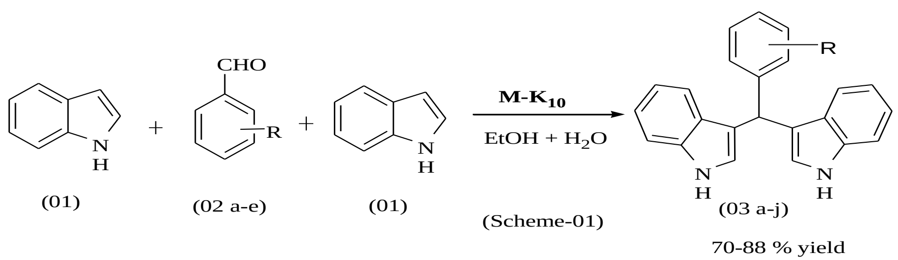
2. Experimental

All chemicals were of analytical grade, obtained commercially, and used without further purification. Reactions were conducted in dried glassware and monitored by TLC on silica gel plates (Merck Kieselgel 60 F254), visualized under UV light or with staining reagents. Melting points were determined using open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer (KBr). Mass spectra were obtained using a Shimadzu LC-MS 2010EV with an ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD (500 MHz) using $CDCl_3$ or DMSO-d_6 as solvents.

2.1 General procedure for the synthesis of of bis(indol-3-yl)methane Derivatives (03a-e)

A mixture of two moles of indole and one mole of substituted Aromatic aldehydes and Montmorillonite K10 as solid acid catalyst (10 Mole%)) was added and the mixture was ground in a mortar at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ethyl alcohol (10 ml) and the catalyst was filtered off and washed with ethyl alcohol (5-10 ml) and the filtrate was concentrated on a rotary evaporator under reduced pressure to afford crude product as a green catalyst for period of time to afford the respective products. Whenever required, the products were purified by column chromatography on silica gel (EtOAc: n-hexane, 1:9) so as to afford the pure bis-indolylmethanes to give (03a-j). The yield of products is between 75-90%. The reaction was monitored by TLC. These synthesized compounds were completely characterized from IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic technique and also elemental analysis.

2.2 Results and Discussion



(Scheme-01)

The reaction conditions were first optimized using a model reaction between two moles of indole and a substituted aromatic aldehyde, ground in a mortar at room temperature with montmorillonite K10 (10 mol%) in an ethanol-water mixture. Solvent screening revealed ethanol-water as the most effective medium, offering fast reaction rates and high yields (Table 1, entry 6). Other polar protic solvents gave moderate yields (Table 1, entry 5), while aprotic solvents like AcCN, THF, DMF, and DCM showed slower reactions and lower yields (Table 1, entries 1-4). Catalyst loading studies (Table 2) confirmed that 10 mol% montmorillonite K10 gave the best yield (Table 2, entry 6).

To further explore the reaction scope, bis(indolyl)methane derivatives (03a-03j) were synthesized by grinding indole (01) with various substituted aromatic aldehydes (02a-02j) in an ethanol-water mixture using montmorillonite K10 as a solid acid catalyst. The results are summarized in Table 3. Substituents on the aromatic ring influenced the reaction: both electron-rich and electron-poor aldehydes gave good yields (Table 3, entries 1-5), though nitro-substituted aldehydes required longer reaction times. All products (03a-03j) were obtained in excellent yields and were characterized from IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic technique and elemental analysis.

Table 1: Optimization of the reaction conditions using different solvents[a]

Entry	Solvent	Reaction Time (min)	Yield (%)[b]
1	AcCN	70	45
2	THF	65	48
3	DMF	50	55
4	DCM	45	60
5	Ethylene glycol	40	60
6	Ethanol-water	30	88

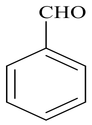
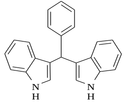
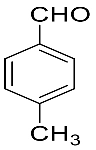
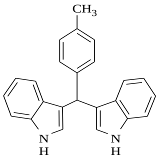
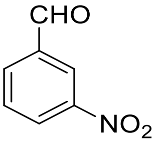
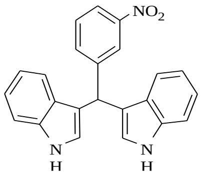
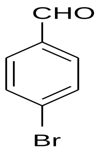
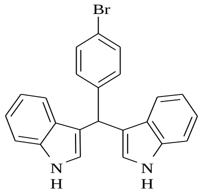
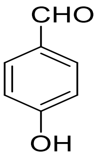
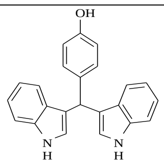
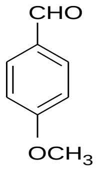
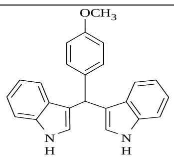
[a]Reaction conditions: Indole (10 mmol) and Aromatic aldehyde (10 mmol) was ground in a mortar at room temperature.
[b] Isolated yields.

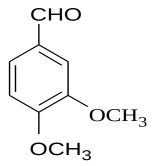
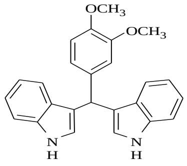
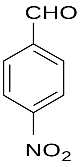
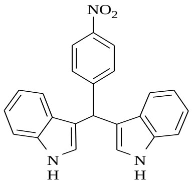
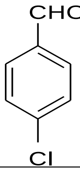
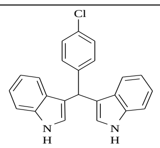
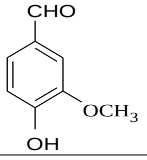
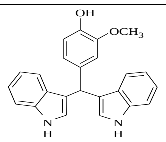
Table 2: Optimization study for the amount Montmorillonite K10 [a]

Entry	Catalyst (Mole%)	Temperature (°C)	Reaction Time (h)	Yield%[b]
1	01	R.T	60	45
2	02	R.T	60	50
3	05	R.T	60	55
4	08	R.T	50	60
5	10	R.T	30	88
6	15	R.T	30	90
7	20	R.T	30	90

[a]Reaction conditions: Indole (10 mmol) and Aromatic aldehyde (10 mmol) was ground in a mortar at room temperature.
[b] Isolated yiel.

Table 3: Reaction of *Indole* and Aromatic aldehyde for the synthesis of (03a-j) [a]

Entry	Aldehyde (02a-j)	Products (03 a-j)	Time (min)	Yield (%)[b]	M.P. (°C)
1		 3a	30	80	125-127
2		 3b	18	75	99-101
3		 3c	45	84	265-267
4		 3d	20	80	160-162
5		 3e	18	72	125-127
6		 3f	20	74	190-192

7		 3g	24	76	196-198
8		 3h	50	88	222-224
9		 3i	35	82	122-124
10		 3j	22	75	110-112

[a]*Reaction conditions:* (01) (10 mmol), (02) (10 mmol) and ethanol+water in Montmorillonite K10 10 mole% were ground in a mortar at room temperature
[b] Isolated yield.

3. Spectral Analysis

3, 3’-Bis(indolyl) phenylmethane (03a)

Yield 80%; M.P. 125-127^{0}C IR (KBr, *ν*max,) 3414, 3060, 1630, 1385, 730 cm^{-1}.; ^{1}H NMR (500MHz, DMSO-d$_6$, ppm) δ 5.95 (s, 1 CH), 6.70 (s, 2H, Ar), 7.10 (t, Ar, 2 H), 7.15-7.25 (m, 3H), 7.30-7.60 (m, Ar 8 H), 7.90 (bs, 2 H, NH).; ^{13}C NMR (125 MHz, DMSO-d$_6$, ppm): *δ* 142.4, 140.2, 138.2, 130.4, 129.7, 128.2, 127.2,124.2, 122.5, 120.2, 114.5, 110.4, 44.9. ; EI-MS (m/z: RA%): 322 (M$^{+\cdot}$, 100%).

3,3’-Bis(indolyl)-4-methylphenylmethane (03b):
Yield 75%; M.P. 99-101°C; IR (KBr, νmax, cm^{-1}) 3470, 3020, 1610, 1417, 1215, 1091, 759, 670 cm^{-1}.; ^{1}H NMR (500MHz, DMSO-d$_6$, ppm) 2.30 (s, 3H), 5.86 (s, 1H,), 6.60 (s, 2H), 6.80-7.44 (m, 12H), 7.96 (bs, 2H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$, ppm): 136.4, 134.4, 130.2, 126.2, 124.6, 122.7, 118.2, 116.4, 114.4, 110.4, 44.9, 22.4.; EI-MS (m/z: RA%): 336(M$^{+\cdot}$, 100%).

3,3’-Bis(indolyl)-4-methoxyphenylmethane (03f)
Yield 74%; M.P. 190-192°C; IR (KBr, νmax, cm^{-1}) 3472, 3016, 1618, 1420, 1218, 1094, 760, 674 cm^{-1}.; ^{1}H NMR (500MHz, DMSO-d$_6$, ppm) 3.80 (s, 3H), 5.88 (s, 1H,), 6.64 (2H, d), 6.86 (2H, d), 7.04 (2H, t),7.2 (2H, t); 7.30-7.46 (6H, m), 7.90 (2H, bs, NH); ^{13}C NMR (125, MHz, DMSO-d$_6$, ppm): 156.2, 142.6, 140.2, 138.4, 130.2, 129.6, 128.4, 127.2,124.2, 122.8, 120.7, 115.5, 112.7,64.2, 44.9; EI-MS (m/z: RA%): 352 (M$^{+\cdot}$, 100%).

3,3’-Bis(indolyl)-3,4-dimethoxyphenylmethane (03g)
Yield 76; M.P. 196-198^{0}C; IR (KBr, νmax, cm^{-1}) 3478, 3020, 1620, 1512, 14525, 1418, 1216, 1090, 1030, 759 cm^{-1}.; ^{1}H NMR (500MHz, DMSO-d$_6$, ppm) 3.80 (3H, s), 3.85 (3H, s), 5.83 (1H, s), 6.65(2H, d), 6.78 (2H, d), 7.20 (3H, t), 7.18 (2H, t), 7.30-7.45 (4H, m), 7.90 (2H, bs, NH)); ^{13}C NMR (125 MHz, DMSO-d$_6$, ppm): 150.2, 149.8, 140.2, 138.4, 130.2, 129.6, 128.4, 127.2,124.2, 122.8, 120.7, 115.5, 112.7, 60.2, 60.0, 44.9; EI-MS (m/z: RA%): 382 (M$^{+\cdot}$, 100%).

3,3’-Bis(indolyl)-4-nitro phenylmethane (03h)
Yield 88%; M.P. 222-224°C; IR (KBr, νmax, cm^{-1}) 3480, 3040, 1625, 1440, 1230, 1098, 780, 684 cm^{-1}.; ^{1}H NMR (500MHz, DMSO-d$_6$, ppm) 5.55 (s, 1H,), 6.80 (2H, d), 6.98 (2H, d), 7.22 (2H, t),7.32 (2H, t); 7.41-7.54 (6H, m), 7.98 (2H, bs, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$, ppm): 165.4, 150.6, 144.3, 140.2, 136.4, 120.6, 128.4, 126.2,124.4, 122.6, 120.7, 114.5, 111.9, 44.9; EI-MS (m/z: RA%): 367 (M$^{+\cdot}$, 100%).

4. Conclusion

We report a novel, eco-friendly, and solvent-free synthesis of bis(indol-3-yl) methane derivatives catalyzed by montmorillonite K10. This protocol offers notable advantages, including mild heterogeneous conditions, reduced reaction times, straightforward work-up, and excellent yields. The catalyst's low cost, ready availability, recyclability, and reusability make this method a sustainable and efficient alternative to existing synthetic approaches.

5. Acknowledgments

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