

Environmentally benign synthesis of bis(indolyl)methanes using sulfated mesoporous titania as a catalyst

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ABSTRACT

Bis(indolyl)methanes, and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry. An efficient and an environmentally benign route for the synthesis of bis(indol-3-yl)methane derivatives (3) has been achieved by one pot, two component condensation reaction of derivatives of aldehydes (1) with indole (2) in presence of sulfated titania. Modification by sulphate ion cause an increase in acidity of titania so as to make it an efficient, reusable, and cheap catalyst giving high yields of bis(indol-3-yl)methanes.

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KEYWORDS

Titania (T);
Sulfated Titania (ST);
Indole;
Bis(indolyl)methane (BIM).

INTRODUCTION

Bis (indolyl) methanes (BIMs) and their derivative belongs to an important group of biologically active metabolites that are phyto-chemically derived from Brassica vegetables^[1]. BIMs are known for their immense biological and pharmaceutical activity^[2,3]. BIMs are found in cruciferous plants and promote estrogen metabolism and also induces apoptosis in human cancer cells^[4]. They are reported to possess promising biological activities including anticancer, antimicrobial, antifungal, anti-inflammatory, analgesic, anthelmintic and cardiovascular activities. Therefore, the synthesis of these compounds have gained a special interest^[5]. It was Fischer^[6] in 1886 who prepared 3, 3-Bis (indolyl) methanes for the first time by employing merely an acid catalyzed Friedel-Crafts reaction between indole and carbo-

nyl compounds. After that several methods with different catalysts have been reported in literature for the preparation of BIMs from indole and carbonyl compounds^[7]. However, many of these methods still suffer from drawbacks of either involving expensive reagents, low yields of products in some cases or long reaction time or even high catalyst loading, thus generating large amounts of toxic waste.

In recent years, hazardous and polluting, liquid acids are getting replaced by solid acids to ease their separation from reacting mixture and allow regeneration. The ease of separation and their availability for reuse with easier work up render the process as green. Among the various solid catalysts, sulfated metal oxides^[8,9,10] are potential catalysts for many reactions. For example, solid acids like zeolites,^[11] montmorillonite K 10 clay,^[12] ammonium salts,^[13] silica sulfuric acid,^[14] molecular iodine,^[15]

have been recently reported as very active catalyst for the synthesis of BIMs. Alternatively, sulfated titania has shown to be a good solid acid catalyst for a large number of reactions like : esterification,^[16] isomerization,^[17] trans esterification of vegetable oils,^[18] alkylation,^[19] acylation of aromatics,^[20] decomposition of isopropanol,^[21] photocatalytic removal of toluene^[22]. The acid strength for the sulfated metal oxides is found to be even stronger than 100% sulfuric acid^[23-25]. Besides acidity properties, the physical properties^[26] like structural stability, porosity and the large specific surface area of the catalyst are also important. Bokhimi^[27] and coworkers have found that the sulfate ions tend to be less deformed and consequently more stable when anchored to anatase phase of titania at annealing temperatures of 400-600°C. The addition of sulfate induces the structural transformation from rutile phase to anatase phase^[28,29]. We report herein the synthesis of BIMs by one-pot two component reaction of an aldehyde and indole under solvent-free conditions using sulfated titania as an efficient catalyst as per Scheme 1.

The scope of application of the presented method is demonstrated by using various substituted aromatic, aliphatic and heterocyclic aldehydes to react with indole. The advantages of this protocol are mild reaction conditions, cheap catalyst, high conversion, easy handling, efficient and solvent free synthesis under low temperature conditions.

EXPERIMENTAL

All chemicals were purchased from Merck and Sigma-Aldrich chemical companies and used without purification. All the reactions were monitored and R_f values were determined using thin layer chromatography (TLC) using silica gel 60F₂₅₄ pre coated plates from Merck. Melting points were determined using Melting point apparatus. FT-IR spectra were

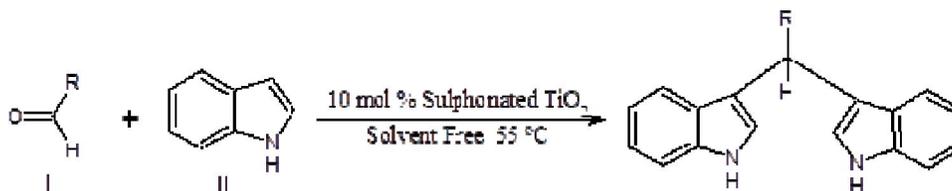
recorded from spectral grade KBr disc for solid samples using Perkin Elmer, G-FTIR spectrophotometer. The recording was performed at 4000-400 cm^{-1} wave number range. ^1H NMR spectra were recorded on a Bruker, Avance II (500MHz) using CDCl_3 solvent system.

Synthesis of Mesoporous titania (MT)

MT was synthesized by solution combustion method involving the combustion of stoichiometric amount of titanyl nitrate with hydroxyl cellulose as a fuel at 425°C in a muffle furnace. Titanyl nitrate was prepared as per the method in literature with little modification. 1 ml Titanium iso-propoxide was hydrolysed with 8.0 ml IPA (isopropyl alcohol) keeping the temperature constant at 273°K and later 0.37 ml of deionised water was added to it, to get a thick white precipitate of titanium oxyhydroxide. The precipitate was then washed to remove excess alcohol. Later the precipitate was re dispersed in water containing nitric acid to get an $\text{H}^+ : \text{Ti}^{4+}$ ratio of 0.5. The peptized solution was kept for 12 hours at 70°C to get a clear light blue color sol. The sol was dried to get white titanyl nitrate powder. The titanyl nitrate in solution form was mixed with stoichiometric amount of hydroxyl cellulose (x is unity) to form a precursor solution for combustion synthesis reaction. This precursor solution was placed on a preheated hot plate (150°C), in order to ensure homogeneous mixing and onset of dehydration of the aqueous mixture. Once the solution becomes viscous it was transferred to a preheated furnace (350°C), where the reaction was accompanied by release of a large amount of gases to give dry foamy, white to yellow product. The powder thus obtained was further calcined at 425 °C to get mesoporous titania

General method of synthesis of BIMs

A mixture of indole (2 mmol) and aromatic aldehyde (1 mmol) were added along with ST (10



Scheme 1 : General scheme for the synthesis of BIMs using Mesoporous Sulfated Titania catalyst

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mol%) to a test tube, heated and stirred well in an oil bath at 80°C for required time to get a solid product. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was washed with diethyl ether in order to remove excess indole and aldehyde. The obtained solid was extracted with hot ethyl acetate and the catalyst was filtered. Evaporation of the solvent under vacuum afforded a pink colored solid which was again washed with diethyl ether. The product BIMs, thus obtained was recrystallized twice. Good yield (80–98%) of BIMs was finally obtained after drying in air. The results are summarized in (TABLE 2). The catalyst was recycled and reused five times with reproducible yields. The formation of the desirable BIMs was detected by their melting points and by IR, ¹H NMR, ¹³C NMR spectroscopic methods.

RESULTS AND DISCUSSION

Benzaldehyde (1) was chosen as a model for reaction with indole (2) which afforded bis(indolyl)methanes (BIMs) as a product (3). Benzaldehyde was reacted with 2 m mol of indole under different reaction conditions using variable amount of titania (T)/ sulfated titania (ST)^[38] as per TABLE 1.

On considering the reaction time and yield of product, it was found that 10% ST is sufficient for the best results.

In order to study the generality of this procedure, various derivatives of bis (indolyl) methanes were synthesized TABLE 2. Several aryl aldehydes

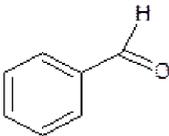
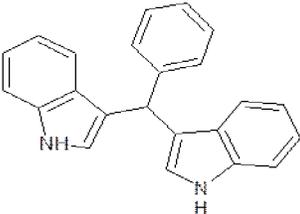
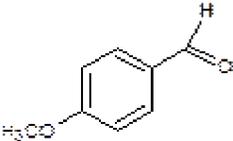
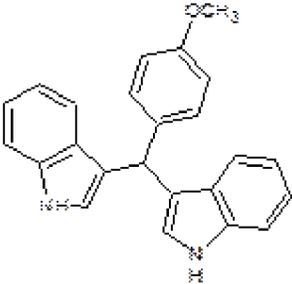
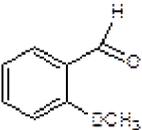
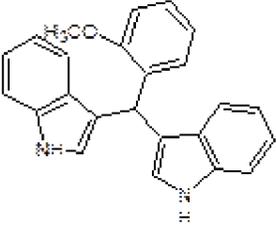
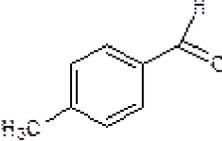
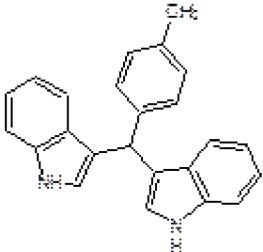
with electron withdrawing and releasing functional groups undergo efficient formation of BIMs within short duration. The electronic nature of the substituents in the aromatic ring did not show any noticeable effect on this conversion. Excellent yield was obtained in the reaction of indole with heterocyclic aldehydes. Aliphatic aldehydes took some what longer time than their aromatic counterparts. It was found that ketones did not react at all with indole 1 under the similar reaction conditions, demonstrating the chemo selective nature of the methodology. The reusability of the catalyst was examined for the reaction of 4-methoxy benzaldehyde (entry 1b) and indole as model substrate as per Scheme 1. The result showed that the solid catalyst, ST, could be reused for at least five times without showing any reduction in the catalytic property. A plausible mechanism for the reaction is shown in Scheme 2. TiO₂ has both Lewis acid as well as Lewis base type sites for ex Ti⁴⁺ site, is of Lewis-acid type and O²⁻ site is of Lewis-base type. Apart from this it has surface –OH groups^[39]. Titania is a weak acid but the strong acidity of titania on sulphate modification is attributed to the presence of electron withdrawing sulphate ions on metallic cation, which gives rise to an electron deficient metal centre^[40] that can behave as a strong Lewis acidic site^[41]. In the sulfated metal oxide there may be as many Lewis acid sites as Bronsted acid. The strong acidity of sulfated titania is attributed to Bronsted acid sites which are either already existing or are created by the neighboring Lewis acid sites. Some of the other basic sites due to surface hydroxyl groups, on modification with sulfate ions are converted to acid sites via anion

TABLE 1 : Determining the best reaction conditions for treatment of benzaldehyde (1) with indole

Entry	Catalyst	Solvent	Time (h)	Yield(%) ^b
1	2% T	None	5.0	87
2	5% T	None	3.0	91
3	10% T	None	1.5	94
4	10% ST	None	0.5	95
5	10% ST	CH ₃ CN	4	15
6	10% T	CH ₃ CN	6	10
7	5% T	CH ₂ Cl ₂	5	50
8	5% T	CH ₃ OH	3.5	55

a Reaction conditions 1(1mmol), 2(2mmol), T/ ST (10mol%), 50°C b Isolated Yield

TABLE 2 : MST catalysed synthesis of BIMs (3) by reaction of benzaldehyde (1) with indole

Entry	Aldehyde (1a-u)	Product (3a-u)	Time (h)	Yield %	M.p. (°C)
1	 1a	 3a	0.5	98	122-124
2	 1b	 3b	1.5	96	187-189
3	 1c	 3c	2	96	127-129
4	 1d	 3d	1	91	90-94

exchange^[42] between SO_4^{2-} and OH^- . As per Scheme 2, the Lewis acid moiety (Ti^{4+}) activates the carbonyl through hydrogen bonding^[43] to give intermediate II. The intermediate II on losing water affords III. The condensation of both indole molecules was confirmed from the disappearance of stretching frequency of carbonyl group at 1690 cm^{-1} in IR spectrum of various derivatives of BIMs. The product obtained are well known compounds and were characterized by comparison of their physical and spectroscopic data with those of reported ones.

X-ray diffraction patterns of the Titania (T) and Sulfated Titania (ST)

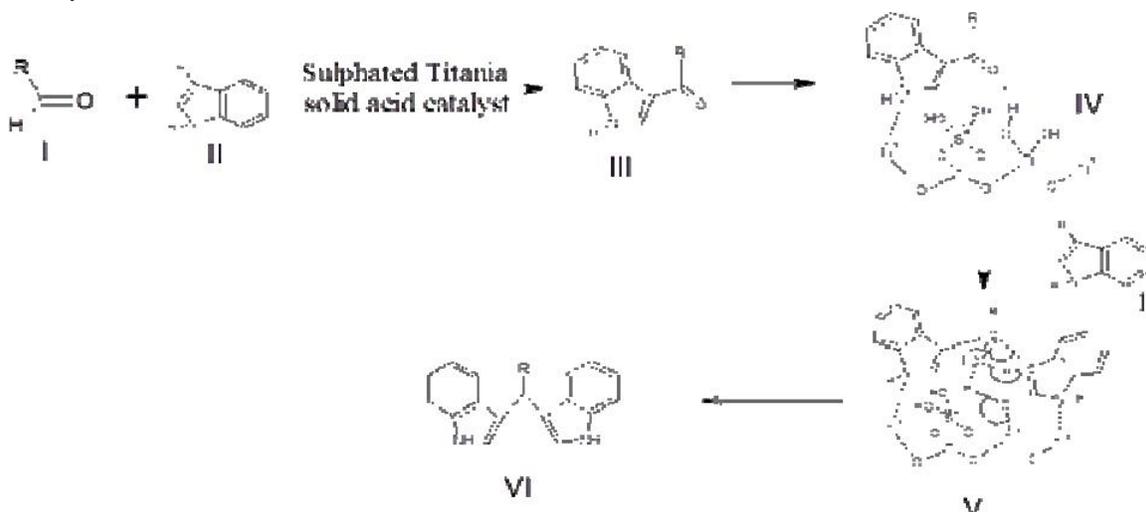
Figure 1. shows the XRD profiles of the T and

ST after calcination at 500°C . Sample ST shows three main peaks at $2\theta=25.48$ and 38.1 and 48.1 , corresponding to (101), (004) and (200) reflections of anatase phase whereas T shows two main peaks at $2\theta=27.3^\circ$, 36.2° corresponding to rutile phase. XRD profile of ST shows the absence of the peak corresponding to rutile phase, indicating that sulfation retards the transformation from anatase phase to rutile phase. The addition of sulfate caused a significant loss in the rutile phase.

SPECTROSCOPIC DATA

Formation of BIMs from aldehyde (TABLE 2)

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Scheme 2 : Plausible mechanism of the reaction for the synthesis of Bis(indolyl)methanes

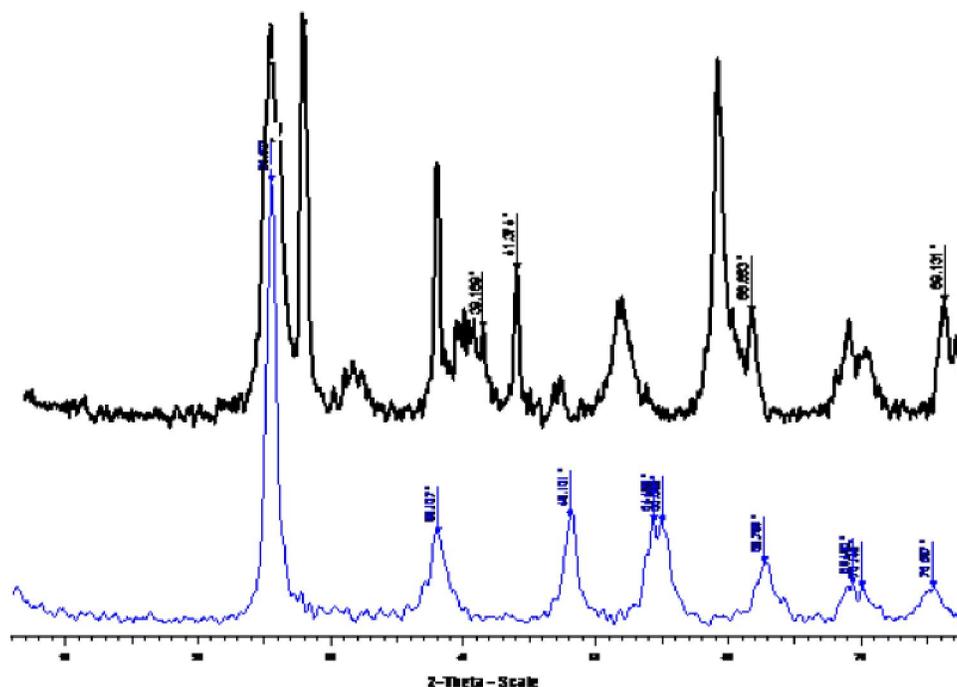


Figure 1 : XRD profiles of the T and ST after calcination at 500°C

gave a pink colored solid that showed IR stretching band for N-H at 3360 cm^{-1} . ^1H NMR spectrum, showed aldehyde proton at δ 9.8 disappeared while a singlet for methine proton shows upfield shift at δ 5.8 due to vicinity of nitrogen atom from indole. The aromatic protons gave complex multiplet at δ 6.6 to 7.7 representing twelve protons and NH protons of each indole molecule appeared at a downfield shift in between δ 6.0-8.0. The structure elucidation of the compounds has been explained from its ^{13}C NMR spectral data. Only one methine carbon signal was observed at δ 38 whereas aromatic carbons of in-

dole and benzene ring were observed in the range of δ 110 to 150.

2,2' (Phenylmethylene)bis(indole) (3a): Yield: 98%. M.p.: 122-125 °C. FT IR (KBr, ν , cm^{-1}): 3406, 2950, 1610, 1455, 800, 746. ^1H NMR (200 MHz, CDCl_3 , δ , ppm): 5.88 (s, 1H, Ar CH), 6.65 (s, 2H, Ar H), 6.99-7.34 (m, 13H, Ar H), 7.92 (br, s, 2H, NH). ^{13}C NMR (75 MHz, CDCl_3 , δ , ppm): 40.17, 110.94, 119.25, 119.69, 119.94, 121.88, 123.45, 126.09, 127.07, 128.14, 128.71,

136.67, 143.98. MS (ESIMS/MS, m/z): 321 (M⁺H).

2,2' ((4 Methoxyphenyl)methylene)bis(indole) (3b): Yield:96 %. M.p.: 186 190 °C. FT IR (KBr, ν , cm^{-1}): 3410, 2942, 1602, 1440, 1244, 1098, 750. ^1H NMR (200 MHz, CDCl_3 , δ , ppm): 3.78 (s, 2H, OCH_3), 5.83 (s, 1H, Ar CH), 6.62 (s, 2H, Ar H), 6.79 (t, 2H, Ar H), 6.82 (t, 2H, Ar H), 6.96 7.34 (m, 8H, Ar H), 7.92 (br, s, 2H, NH). ^{13}C NMR (75 MHz, CDCl_3 , δ , ppm): 39.35, 54.94, 110.85, 113.53, 119.28, 120.04, 120.11, 121.93, 121.32, 127.08, 129.57, 136.09, 136.71, 157.91. MS (ESI MS/MS, m/z): 351 (MH).

CONCLUSION

Pure titania shows only low acidity and sulfation increases its acidity. Sulfated titania is found to be a mild and efficient catalyst for the electrophilic substitution reaction of indole with various aldehydes including aromatic, aliphatic and heterocyclic substrates affording corresponding bis(indolyl)methanes in excellent yields. The catalyst used is cheap and the methodology applied is quite greener.

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