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Efficient, Rapid, and Solvent-Free Synthesis of Substituted Bis(indolyl)methanes Using Sulfated Anatase Titania as a Solid Acid Catalyst

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Efficient, Rapid, and Solvent-Free Synthesis of Substituted Bis (indolyl)methanes Using Sulfated Anatase Titania as a Solid Acid Catalyst

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A rapid and solvent-free green synthesis of bis(indolyl)methanes using sulfated anatase titania ($TiO_2-SO_4^{2-}$) as solid acid catalyst under simple physical grinding has been developed. The advantage of this method is short reaction time with excellent yield and safety, inexpensive cost, and use of easily recyclable nanocatalytic material. Higher activity of sulfated titania over TiO_2 is found to be due to its increased Brønsted acidity.

Keywords: bis(indolyl)methanes, simple physical grinding, TiO₂-SO₄²⁻, green synthesis, reusability

Introduction

Bis(indolyl)methanes are potential candidates for screening by the medicinal chemists owing to their widespread medicinal applications.^[1–3] They have been isolated from plants and marine sources.^[4–7] Due to their vast biological activity associated with medicinal application^[8,9] there exists a continuing interest for a synthetic method using milder, selective, nonhazardous, inexpensive, recyclable, and eco-friendly catalyst. Various methods for synthesis of bis(indolyl)methanes have been reported using acid catalysts in the electrophilic substitution of indoles with various aldehydes.^[10–13] Other catalysts like $Ln(OTf)_3$,^[11] $LiClO_4$,^[12] $In(OTf)_3$,^[14] $Dy(OTf)_3$,^[15] $InCl_3$,^[16] InF_3 ,^[17] EAN,^[18] $SBA-15/SO_3H$,^[19] $CuBF_4\dot{c}SiO_2$,^[20] Ph-PMO-SO_3H,^[21] $H_6P_2W_{18}O_{62}$,^[22] [Bmim] BF₄, $[bmim]PF_6$,^[23] [acmim]Cl, and $[hmim]HSO_4$ ^[24] have also been reported for the synthesis of bis(indolyl)methanes. However most of these methods have several disadvantages such as the use of toxic metal ions, expensive solvents, longer reaction times, tedious work up, low yield, higher catalyst quantity, and the formation of waste. Additionally the main drawback of most of the existing methods is that the catalysts decompose during the aqueous workup and their recovery is often impossible. Anatase titania and their modified forms have gained increasing interest because of their enhanced activity in typically acid catalyzed reactions and they are

considered as solid "super acids." Super acidity of modified metal oxides is attributed mainly to Brönsted acidity.^[25] Significant progress has been made in the use of TiO_2 -SO₄²⁻ as solid acid catalyst in the synthesis of heterocyclic compounds as this catalyst is found to be highly cost effective, recoverable and reusable at room temperature when compared to other catalysts.^[26] In addition, TiO_2 -SO₄²⁻ is easier to handle than sulfuric acid and can be separated easily from the reaction mixture by simple filtration. It has also been reported that sulfate loading of TiO₂ using sulfuric acid increases Brönsted acidic sites much more than its Lewis acidic sites.^[27] In continuation of our interest in exploring novel synthetic methods for green chemical synthesis,^[26,28–30] of various heterocyclics using solid acid catalysts, we herein report a simple, rapid, and efficient method for synthesizing bis(indolyl) methanes under ambient and solvent free conditions (Scheme 1).

Experimental

Indole, benzaldehyde, substituted benzaldehyde, other aromatic aldehydes, ethylacetate (laboratory grade), and AnalaR grade titanium isopropoxide (Himedia 98.0%), 2propanol (Spectrochem 99.5%) were used as received. The sulfated titania TiO₂-SO₄²⁻ was prepared according to the procedure reported from our laboratory by sol-gel method and the results of characterization by FT-IR, XRD, SEM, EDS, HR-TEM, AFM, and BET surface area measurements were discussed in our earlier papers.^[26,29,30] All products were characterized by GC-MS analysis (see supplementary data, Figures S1–18) and some selected products were characterized by ¹H and ¹³C NMR spectra.

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Sch. 1. TiO_2 -SO₄²⁻ catalyzed synthesis of bis(indolyl)methanes.

Typical Procedure for the Preparation of 3,3'-(*phenylmethylene*)*bis*(1*H-indole*), 3*a*

A mixture of 1 mmol of benzaldehyde and 2 mmol of indole with 100 mg of TiO_2 -SO₄²⁻ were mixed and ground in a pestle and mortar at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate was added to the mixture and agitated. The catalyst was filtered off and washed with ethylacetate and the washings were combined. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. Product was obtained as thick viscous oil, which on standing solidified as pink solid. The structure of product obtained was confirmed by ¹H NMR, ¹³C NMR, and GC-MS analysis.

3,3'-(Phenylmethylene)bis(1H-indole), 3a. Pink solid; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (bs, 2H, NH), 7.34–7.41 (m, 6H), 7.28–7.29 (m, 2H), 7.21–7.22 (m, 3H), 6.98–7.02

(t, 2H), 6.66 (s, 2H), 5.89 (s, 1H, Ar–CH); ¹³C NMR (100 MHz, CDCl₃): δ 144.0, 136.7, 128.3, 127.1, 126.2, 124.1, 123.6, 122.0, 120.8, 119.8, 119.3, 111.0, 40.2; GC-MS (*m*/*z*): 322 (M⁺).

- 3,3'-(2-Chlorophenylmethylene)bis(1H-indole), 3c. Pink solid; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (bs, 2H, NH), 7.35– 7.43 (m, 4H), 7.08–7.23 (m, 6H), 6.99–7.04 (t, 2H), 6.63 (s, 2H), 6.34 (s, 1H, Ar–CH); ¹³C NMR (100 MHz, CDCl₃): δ 141.3, 136.7, 133.9, 130.4, 129.5, 127.5, 127.0, 126.7, 123.8, 122.1, 120.8, 119.9, 119.3, 118.4, 111.1, 36.7; GC-MS (m/z) = 322 (M⁺).
- 3,3'-(2-Methylphenylmethylene)bis(1H-indole),3n. Pink solid;
 ¹H NMR (400 MHz, CDCl₃): δ 7.82 (bs, 2H, NH), 7.33–7.39 (m, 4H), 7.10–7.24 (m, 6H), 6.98–7.05 (t, 2H), 6.53–6.55 (s, 2H), 6.01 (s, 1H), 2.38 (s, 3H, CH₃);
 ¹³C NMR (100 MHz, CDCl₃): δ 142.08, 136.74, 136.10, 130.21, 128.42, 127.21, 126.11, 125.87, 124.17, 123.91, 122.02, 120.77, 119.83, 119.23, 111.07, 36.22, 19.59; GC-MS (*m*/*z*): 336 (M⁺).



Sch. 2. Plausible reaction mechanism for synthesis of bis(indolyl)methane using TiO_2 -SO₄²⁻.

Sulfated titania was characterized by FT-IR, XRD, SEM, EDS, HR-TEM, AFM, and BET surface area measurements and reported from our laboratory. XRD peaks exactly match with the anatase phase of TiO₂, and sulfate modification does not change the phase. $TiO_2-SO_4^{2-}$ has similar 2θ values to TiO₂ but the peak intensities differ. The FWHM of TiO_2 -SO₄²⁻ peaks are higher than TiO_2 and this broadening of peaks implies the decrease in crystalline size of TiO₂. Both size reduction and retardation of aggregation result in increase in surface area of the cat-

alyst. HR-TEM and AFM analyses reveal a globular structure of the catalyst and a slight corrosion of TiO_2 by sulfate. TiO_2 -SO₄²⁻ has a higher surface area (142.8 m² g^{-1}) than bare TiO₂ (86.0 m² g⁻¹). The XPS survey spectrum of the TiO_2 -SO₄²⁻, shown in Figure 1a, indicates the peaks of elements Ti, O, and S. Binding energy peaks of Ti2p occur at 458.6 and 463.6 eV (Figure 1b). Normally the Ti2p line in the case of pure TiO₂ samples is observed at 458.5 eV.^[28] The BE peaks are shifted upward by the presence of sulfate in the catalyst. The O1s (Figure 1c) show two contributions at 530.4 and 532.2 eV. The main peak at 530.4 eV could be ascribed to lattice oxygen in TiO₂, while the signal at 532.2 eV could be associated oxygen in sulfate. The binding energy peaks of the S2p (Figure 1d) are observed at 168.8 and 170.2 eV.

The reaction between indole and benzaldehyde was carried out with different catalyst loading to determine the optimal conditions for the synthesis of bis(indolyl)methanes. 2 mmol of indole and 1 mmol of benzaldehyde with 50 mg of sulfated titania catalyst under simple grinding resulted 90% product yield in 10 min. By increasing the catalyst loading to 100 mg/mmol of benzaldehyde, the reaction was very quick with total conversion of benzaldehyde giving 99% product in 3 min. However, increase in the amount of catalyst beyond 100 mg/mmol of benzaldehyde did not result in any improvement in reaction yield

(170.2) (168.8)

S2p

200

53

532

01s

(a)

C

(c)

O1s

528

164 160 172 168 Binding energy (eV) Fig. 1. X-Ray photoelectron spectra of TiO_2 -SO₄²⁻: (a) survey spectrum, (b) Ti2p peak, (c) O1s peak, and (d) S2p peak.



Entry	Aldehyde	Product	Grinding time (min)	Yield ^a (%)	Observed mass – M ⁺
1			3	99	322
	la H,O				
2			3	90	356
3			3	90	356
4	H O Br 1d	Br	3	80	402
5	H O Br 1e		3	80	402
6	D Br		3	80	402
7	l 1g	3f	3	60	448
8	I h		3	60	448
		∽ ∏ ∏ ∽ 3h			(Continued on next page)

Entry	Aldehyde	Product	Grinding time (min)	Yield ^a (%)	Observed mass - M ⁺
9		NO ₂ NO ₂ NO ₂ J	2	92	367
10			30	82	432
11			6	83	372
12	11 0		6	60	372
13	©∕∽⊙ 1m	N H H M	5	99	312
14	H O Me 1n		4	99	336
15	H OMe 10	OMe H N 30	2	99	352
16	H O OMe	OMe	2	99	352

 Table 1. Percentage yields of bis(indolyl)methanes from various aldehydes (Continued)

(Continued on next page)

1p

Table 1. Percentage yields of bis(indolyl)methanes from various aldehydes (Continued)

Entry	Aldehyde	Product	Grinding time (min)	Yield ^a (%)	Observed mass – M ⁺	
17	∑ ^S ∕⊂0 1q	S S S S S S S S S S S S S S S S S S S	5	99	328	
18	OH 1r	OH OH H 3q	30	36	338	

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Reaction conditions: Indole = 2 mmol, aldehyde = 1 mmol, TiO_2 -SO₄²⁻ = 0.1 g, room temperature, grinding.

^aYield are with respect to aldehyde.

and time. When reaction was carried out with bare TiO_2 at room temperature under grinding for 30 min the yield was only 65%. No reaction occurred without catalyst. To validate the scope of this method, this reaction was carried out with various substituted aromatic aldehydes 1a-1r, indole 2, and TiO_2 -SO₄²⁻ under the optimized conditions by simple grinding to produce corresponding bis (indolyl)methanes 3a-3r (Table 1, entries 2-18). There is no significant change in yield with the electronic nature of the substituents as the yields are more than 90% with p- NO_2 and p-OCH₃ benzaldehyde (Table 1, entries 9 and 15), but the size of the substituent has some effect on the reaction time and yield. Thus chlorobenzaldehyde gave higher yield than bromo- and iodobenzaldehydes (Table 1, entries 2-8). In case of 4-fluoro-3-phenoxybenzaldehyde (Table 1, entry 10) the yield was 82% in 30 min grinding. The longer reaction time is due to the steric effect of phenoxy group. However there is a marked decrease in reactivity with 4-hydroxybenzaldehyde (Table 1, entry 18). As reported previously the catalytic activity of TiO_2 is decreased by the strong interaction of surface OH groups of TiO₂ with phenolic compounds (Ph–OH) to form a linkage of \equiv Ti–O–Ph.^{31,32} 3-Naphthaldehydes react slower than benzaldehydes, which could be due to steric effect. Furan-2-aldehyde and thiophene-2-aldehyde gave good yield.

A plausible mechanism is proposed in Scheme 2 for the synthesis of bis(indolyl)methanes. This involves the following steps: (a) protonation of carbonyl group of aldehyde by acidic $\text{TiO}_2\text{-}\text{SO}_4^{2-}$ producing intermediate **a**, (b) nucleophilic addition of indole molecule to electron deficient carbonyl group of protonated aldehyde followed by dehydration to give intermediate **b**, (c) intermediate **b** is protonated by sulfated titania to form N-protonated intermediate **c**, and (d) addition of another molecule of indole

with intermediate **c** and deprotonation give bis(indolyl) methane product. Solid acid catalyst TiO_2 - SO_4^{2-} promotes protonation, dehydration, and deprotonation.

Reusability of the catalyst was examined for five runs (Table 2). The catalyst was separated from the reaction mixture by filtration and dried at 100°C for 1 h. The percentage of the recovered catalyst was more than 95% after each run. This recovered catalyst was used for further runs. The yield of the product was more than 95% even at the fifth run. To show the advantage of this solid acid catalyst, a comparison of efficiency of TiO_2 -SO₄²⁻ over other catalysts reported for the synthesis of bis(indolyl)methanes is given in Table 3. Other catalysts required longer reaction time and gave lesser yield than the TiO_2 -SO₄²⁻ catalyst. When compared to bare TiO₂ (65% yield in 30 min), the increase in yield with $TiO_2-SO_4^{2-}$ (99% in 3 min) is many fold. It is reported that the Brønsted acidity of bare TiO_2 and 5 wt% TiO_2 -SO₄²⁻ are 0.77 and 5.17, respectively.²⁷ The increase in Brønsted acidity of TiO_2 -SO₄²⁻ is about 7 times more than bare TiO₂. Hence the higher catalytic activity is due to increased Brønsted acidic sites in sulfated titania, which promote protonation of carbonyl groups, followed by dehydration and deprotonation in the synthesis of bis(indolyl)methanes.

Table 2. TiO_2 -SO₄²⁻ catalyst recovery and reusability

Run	1	2	3	4	5
Yield ^a (%)	>99	>99	>97	>95	>95
Catalyst recovery (%)	>98	>97	>97	>96	>96

Reaction conditions: Indole = 2 mmol, benzaldehyde = 1 mmol, TiO₂- $SO_4^{2-} = 0.1$ g, room temperature, grinding.

^aYield based on benzaldehyde.

Table 3. Efficiencies of various acid catalysts in the synthesis of bis(indolyl)methanes from benzaldehyde and indole

Entry	Reaction condition	Reaction time (min)	Catalyst	Yield ^a (%)
1	TiO ₂ -SO ₄ ²⁻ , RT, physical grinding	3	TiO ₂ -SO ₄ ²⁻	99 (present work)
2	EAN, RT	3	EAN	93 ^[18]
3	Microwave oven, 450 W	5	[bmim][HSO ₄]	93 ^[24]
4	Dy(OTf) ₃ /ionic liquid	60	Dy(OTf) ₃	98 ^[15]
5	FeCl ₃ based IL, 60 °C, [BTBAC]Cl-FeCl ₃	10	[BTBAC]Cl-FeCl ₃	98 ^[33]
6	Ionic liquid, RT	90	FeCl ₃ ċ6H ₂ O	98 ^[34]
7	Ionic liquid, RT	15	In(OTf) ₃	90 ^[14]
8	HY-zeolite/CH ₂ Cl ₂	60	HY-zeolite	85 ^[35]

RT = Room temperature, EAN = ethylammonium nitrate, $[bmim][HSO_4] = 1$ -butyl-3-methylimidazolium hydrogen sulfate, $Dy(OTf)_3 =$ dysprosium(III) triflate, $[BTBAC]Cl-FeCl_3 =$ benzyltributylammonium chloride-ferric chloride, $In(OTf)_3 =$ indium triflate, HY-zeolite = dealuminated zeolite from PQ corporation, USA.

^aYield with respect to aldehyde.

Conclusions

In this communication, we report a green and efficient TiO₂-SO₄²⁻ catalyst for the synthesis of biologically and pharmacologically important bis(indolyl)methanes from indole and various substituted benzaldehydes. The advantages of this novel and practical method include shorter reaction time, excellent product yield, solvent-free condition and simple physical grinding with easy workup. Easy recovery and reusability of this catalyst makes this as a green process. This method will be very useful for the large-scale production of bis(indolyl)methanes using commercially available grinding equipments.

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Supplementary Material

Supplemental data for this article can be accessed at the publisher's website.

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