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ORIGINAL PAPER

TiO_2 nanoparticles: an efficient heterogeneous catalyst for synthesis of bis(indolyl)methanes under solvent-free conditions

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Abstract Some bis(indolyl)methanes have been synthesized, in excellent yields, under solvent free conditions, by reaction of indoles with aromatic and aliphatic aldehydes in the presence of nano titanium(IV) oxide as an efficient, heterogeneous, reusable, and non-toxic catalyst.

Keywords Aldehydes · Bis(indolyl)methanes · Heterogeneous catalyst · Indoles · Nano-TiO_2

Introduction

Indole and its derivatives have been identified as an important class of heterocyclic compounds in medicinal chemistry. The reaction of indoles with aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. The azafulvenium salts can undergo further addition with a second molecule of indole to afford bis(indolyl)methanes [1]. Bis(indolyl)methanes are found widely distributed in the bioactive metabolites of terrestrial and marine organisms [2, 3]. Some compounds have potent pharmaceutical activity, for example as tranquilizers [4] or anticarcinogens [5, 6]. Because of their intriguing physiological activity, many synthetic procedures have been reported [7–9] in which development of environmentally benign aspects, by employing Lewis acid in ionic liquids [10, 11] or task-specific acidic ionic liquids [12], is of current interest in process chemistry. However, many of these methods still suffer from drawbacks, for example long reaction time, expensive reagents, low yields of products in some cases, high catalyst loading, corrosive reagents, and large amounts of solid supports which eventually result in the generation of large amounts of toxic waste. Recently, nanomaterials have been a topic of interest as heterogeneous catalysts, because they have extraordinary properties relative to bulk materials. Currently, nanometal oxides have attracted researchers' attention, because of their unusual physical and chemical catalytic properties [13–17].

Among the nanometal oxides employed, nano-TiO_2 has been proved to be a good catalyst because of its high activity, non-toxicity, easy availability, reusability, strong oxidizing power, and long-term stability [18–20]. Moreover, titanium dioxide is a prominent material for various kinds of industrial applications related to catalysis, e.g. in the selective reduction of nitrite or nitrate ions in stationary sources, photocatalysis for pollutant elimination or organic synthesis, and photovoltaic devices, sensors, and paints [21].

In this paper, nanoparticles of TiO_2 are introduced as a new and efficient low loading-catalyst for electrophilic condensation of indoles with aldehydes.

Results and discussion

Synthesis of different sizes of nano-TiO_2

Nanoparticles of TiO_2 were prepared by the sol–gel method by gradually adding titanium tetra-*n*-butoxide to a solution of deionized water in ethanol. The gel was prepared by aging the sol at room temperature for 24 h. The obtained gel was dried and calcined at 350, 450, or 550 °C to give nano-TiO_2 of different particle size.

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XRD diagrams of TiO_2 nanoparticles represent the (101) crystal face of anatase corresponding to a diffraction angle (2θ) of 25.25°, and the nanocrystalline anatase structure was confirmed by $2\theta = 37.82$ (004)°, 47.98 (200)°, 53.59 (106)°. The average crystalline size of TiO_2 was estimated by use of Scherrer's equation.

The intensity of the anatase peak increased and the width of (101) plane at $2\theta = 25.25°$ became narrower with increasing calcination temperature (from 350 to 550 °C), indicating the particles grew larger in size.

Figures 1, 2, 3 show transmission electron microscopy (TEM) photographs of different particles of nano-TiO_2. These particle sizes were in agreement with the calculated value of the crystallite size determined by XRD and using the Scherrer equation [22]. The particle size distribution was estimated to be 15, 30, and 50 nm.

Optimization of the reaction conditions

In order to determine the best reaction conditions, we studied the reaction of indole with benzaldehyde in the presence of different amounts of nano-TiO_2 at 80 °C under different conditions. As shown in Table 1, the best result was obtained with 10 mol% of nano-TiO_2 under solvent-free conditions (entry 2).

Based on the optimized reaction conditions, the procedure was applied to a variety of different aldehydes and indoles (Scheme 1). The results are summarized in Table 2.

This method is effective for aldehydes bearing both electron-withdrawing and electron-donating substituents on the aromatic ring. Aliphatic aldehydes also react satisfactorily under these conditions.

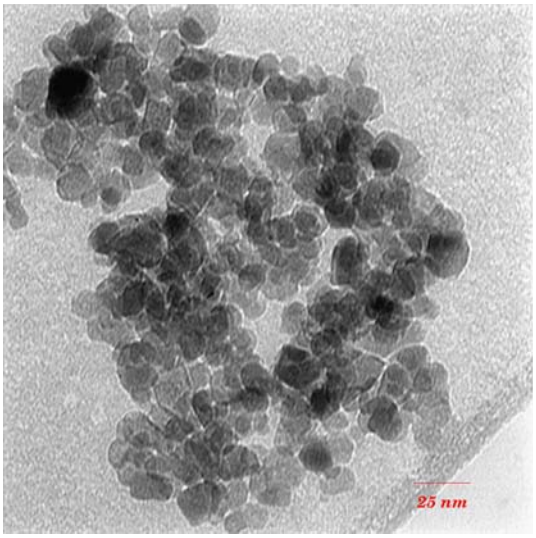

Fig. 1 TEM image of the TiO_2 nanoparticles prepared by calcination of the gel at 350 °C

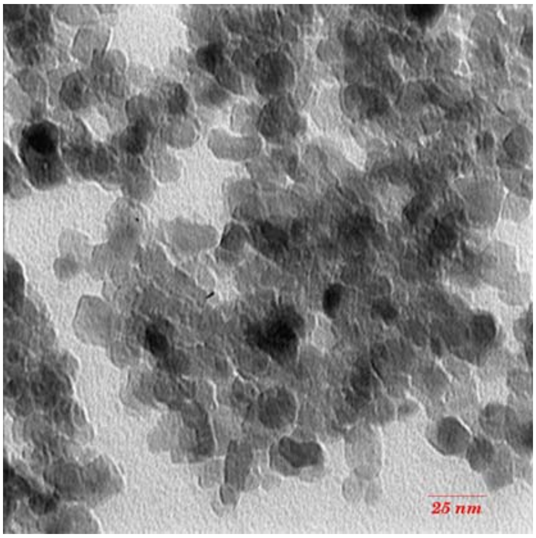

Fig. 2 TEM image of the TiO_2 nanoparticles prepared by calcination of the gel at 450 °C

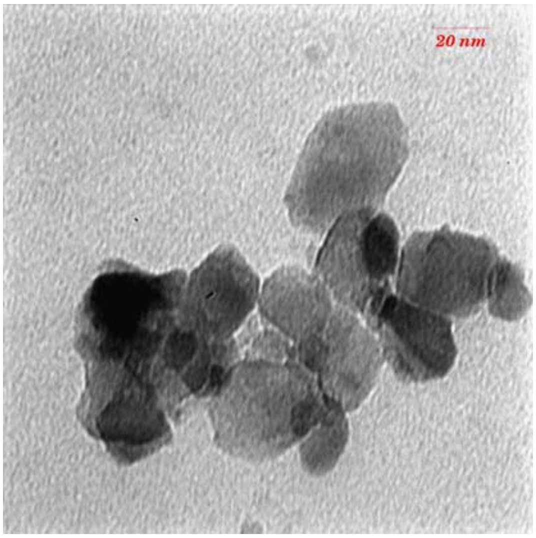

Fig. 3 TEM image of the TiO_2 nanoparticles prepared by calcination of the gel at 550 °C

Table 1 Determining the best reaction conditions for treatment of indole with benzaldehyde and different amounts of nano-TiO_2

Entry	Catalyst	Solvent	Time (min)	Yield (%)
1	5% nano-TiO_2	None	10	95
2	10% nano-TiO_2	None	3	95
3	20% nano-TiO_2	None	3	95
4	30% nano-TiO_2	None	3	95
5	10% nano-TiO_2	CH_2Cl_2	250	50
6	10% nano-TiO_2	CH_3CN	220	65
7	10% nano-TiO_2	MeOH	220	60

Scheme 1

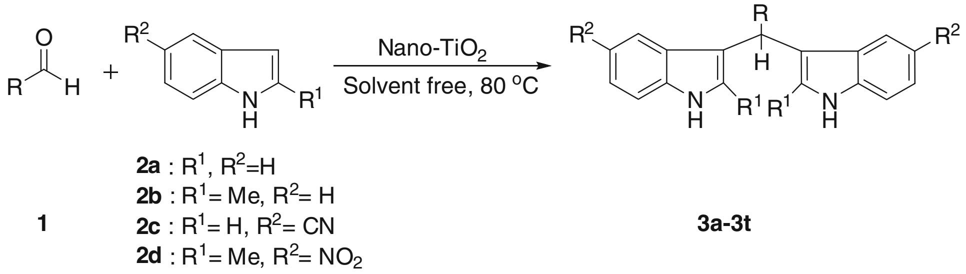

Table 2 Synthesis of BIMs by reaction of indoles and aldehydes in the presence of nano-TiO_2 under solvent free conditions

Entry	Aldehyde/R	Indole	Product	Time (min)	Yield (%)	M.p. (°C)
1	C_6H_5	**2a**	**3a**	3	95	124–127 (Ref. [23] 124–126)
2	$4\text{-}OMeC_6H_4$	**2a**	**3b**	3	90	192–194 (Ref. [23] 194)
3	$4\text{-}ClC_6H_4$	**2a**	**3c**	5	80	79–81 (Ref. [24] 76–78)
4	$4\text{-}MeC_6H_4$	**2a**	**3d**	5	85	95–97 (Ref. [23] 96–98)
5	$4\text{-}NO_2C_6H_4$	**2a**	**3e**	3	90	241–243 (Ref. [23] 245–246)
6	$4\text{-}OHC_6H_4$	**2a**	**3f**	3	91	120–123 (Ref. [23] 119–121)
7	$2\text{-}OMeC_6H_4$	**2a**	**3g**	5	93	129–132 (Ref. [23] 131–133)
8	$3\text{-}NO_2C_6H_4$	**2a**	**3h**	5	91	267–269 (Ref. [23] 261–263)
9	C_6H_5	**2b**	**3i**	5	93	247–248 (Ref. [24] 244–246)
10	$CH_3(CH_2)_6$	**2b**	**3j**	35	70	Oily Liquid (Ref. [25])
11	$4\text{-}MeC_6H_4$	**2b**	**3k**	5	85	175–177 (Ref. [24] 175–177)
12	$4\text{-}NO_2C_6H_4$	**2b**	**3l**	5	95	239–241 (Ref. [24] 241–243)
13	C_6H_5	**2c**	**3m**	5	94	241–243 (Ref. [23] 240–242)
14	$4\text{-}OMeC_6H_4$	**2c**	**3n**	5	87	245–248 (Ref. [23] 245)
15	$4\text{-}NO_2C_6H_4$	**2c**	**3o**	5	90	157–159 (Ref. [23] 158–159)
16	$4\text{-}NO_2C_6H_4$	**2d**	**3p**	15	85	171–173 (Ref. [25] 170–172)
17	$1\text{-}C_{10}H_7$	**2d**	**3q**	20	80	156–159 (Ref. [25] 156–159)
18	$3\text{-}OHC_6H_4$	**2d**	**3r**	20	85	139–140 (Ref. [25] 138–140)
19	$4\text{-}ClC_6H_4$	**2d**	**3s**	20	77	148 (Ref. [25] 145–147)
20	$2\text{-}OHC_6H_4$	**2d**	**3t**	25	80	135–137 (Ref. [25] 135–137)

The products were characterized by comparison of their spectroscopic and physical data with those from authentic samples synthesized by the procedures given in the references

To demonstrate the reusability of the catalyst, it was recovered from the reaction of indole with benzaldehyde by centrifugation and washed with 2 × 3 cm^3 ethyl acetate. It was then used without further purification for the next reaction. There were no significant decreases in efficiency of the recovered catalyst compared to the fresh material. The catalyst was reusable at least up to four times.

Comparing nano-TiO_2 with some reported methods

In order to assess the capability of this method compared with reported methods for the preparation of bis(indolyl)methanes from indoles and carbonyl compounds, the synthesis of compound **3a** was compared with reported methods. As can be seen from Table 3, the nano-TiO_2 method is more efficient than some others. Comparing the nano-TiO_2 catalyst with bulk TiO_2 catalyst under the same condition proves that using the nanoparticles substantially reduces the reaction time.

In conclusion, we have developed a new method for the synthesis of bis(indolyl)methanes from aldehydes and indoles using nano-TiO_2 as a very efficient, practical, heterogeneous, and reusable catalyst.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting-point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. The ^1H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants J are given in Hertz. The mass spectra were scanned on a

Table 3 Comparison of our results for condensation of indole with benzaldehyde with results obtained by other groups

Entry	Reagent and conditions	Time (min)	Yield[a] (%)	Ref.
1	Nano-TiO_2, Solvent-free, 80 °C	3	95	–[b]
2	TiO_2, Solvent-free, 80 °C	180	98	[26]
3	P_2O_5/SiO_2, Solvent-free, rt	30	94	[24]
4	$Zn(HSO_4)_2$	180	91	[28]
5	$PPh_3{\cdot}HClO_4/CH_3CN$	30	61	[29]
6	$Ln(OTf)_3/EtOH.H_2O$	720	95	[30]
7	$ZrOCl_2.8H_2O$, Solvent-free, 50 °C	40	84	[31]
8	$In(OTf)_3/CH_3CN$	25	71	[32]
9	Zeokarb-255/CH_3CN	450	95	[33]
10	$La(PFO)_3/EtOH$	30	90	[34]
11	$AlPW_{12}O_{40}$,CH_3CN, rt	15	92	[35]

[a] Isolated yield

[b] Current method

Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

2-Methyl-5-nitroindole was prepared according to a published method [27]. Other reagents were commercially available from Merck and Aldrich.

Synthesis of TiO_2 nanoparticles

TiO_2 nanoparticles were prepared by the sol–gel method using deionized water–ethanol mixed solution as the starting materials. Titanium tetra-*n*-butoxide (4.6 g, 13.5 mmol) was gradually added to 25 cm^3 30% ethanol solution. The mixture was stirred for 4 h. The gel was prepared by aging the sol for 24 h at room temperature. The obtained gel was dried at 70 °C for 12 h, and was calcined at 350, 450, or 550 °C for 2 h to obtain TiO_2 nanoparticles of different sizes.

Catalyst characterization

XRD patterns of the TiO_2 nanoparticles were obtained using a HZG 4A powder diffractometer (Carl Zeiss, Jena) with Co K_α irradiation (Mn filter). The particle size was calculated using the Scherrer equation and confirmed by transmission electron microscopy (TEM), which was performed on a Zeiss Leo 912 AB electron microscope.

TEM images were prepared by dropping TiO_2 ethanolic suspension on to a copper grid coated with a thin layer of carbon. The surface area of the samples was measured by N_2 adsorption at 77 K using a dynamic BET method using a Quanta Chrome Autosorb 1 surface area analyzer. The samples were purged in He atmosphere at 423 K for 12 h prior to adsorption.

*General procedure for preparation of BIMs **3a–3t***

In a typical reaction, a mixture of 1.5 g 4-nitrobenzaldehyde (10 mmol), 3.6 g 2-methyl-5-nitroindole (20 mmol), and 0.08 g nano-TiO_2 (1 mmol) were added to a test tube and heated in an oil bath at 80 °C for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the catalyst was filtered, followed by washing with 3 × 50 cm^3 ethyl acetate. The volume was concentrated under reduced pressure. After drying in air, practically pure product was obtained.

References

1. Remers W (1972) Chem Heterocycl Compd 25:1
2. Porter JK, Bacon CW, Robins JD, Himmelsbach DS, Higman HC (1977) J Agric Food Chem 25:88
3. Osawa T, Namiki M (1983) Tetrahedron Lett 24:4719
4. Povszasz J, Katakin GP, Foleat S, Malkovies B (1996) Acta Phys Acad Sci Hung 29:299
5. Hong C, Firestone GL, Bjeldanes LF (2002) Biochem Pharmacol 63:1085
6. Carter TH, Liu CK, Ralph W Jr, Chen D, Qi M, Fan S, Yuan E, Rosen EM, Auborn KJ (2002) J Nutr 132:3314
7. Nagarajan R, Perumal PT (2004) Chem Lett 33:288
8. Chakrabarty M, Mukherji A, Karmakar S, Arims S, Harigaya Y (2006) Heterocycles 68:331
9. Chakrabarty M, Mukherjee R, Mukherji A, Arims S, Harigaya Y (2006) Heterocycles 68:1659 and earlier references cited in these references
10. Ji SJ, Zhou MF, Gu DG, Wang SY, Loh TP (2003) Synlett 13:2077
11. Ji SJ, Zhou MF, Gu DG, Jiang ZQ, Loh TP (2004) Eur J Org Chem 7:1584
12. Gu DG, Ji SJ, Jiang ZQ, Zhou MF, Loh TP (2005) Synlett 6:959
13. Itoh H, Utamapanya S, Stark JV, Klabunde KJ, Schlup JR (1993) Chem Mater 5:71
14. Jiang Y, Decker C, Mohs C, Klabunde KJ (1998) J Catal 180:24
15. Guzman J, Gates BC (2001) Nano Lett 1:689
16. Choudary BM, Mulukutla RS, Klabunde KJ (2003) J Am Chem Soc 125:2020
17. Choudary BM, Kantam ML, Ranganath KVS, Mahender K, Sreedhar B (2004) J Am Chem Soc 126:3396
18. Yamazaki S (1996) Bull Chem Soc Jpn 69:2955
19. Reich HJ, Chow F, Peake SL (1978) Synthesis 2:299
20. Bortolini O, Di Furia F, Modena G, Seraglia R (1985) J Org Chem 50:2688
21. Klyachko NL, Klibanov AM (1992) Appl Biochem Biotechnol 37:53
22. Rajabzadeh G, Jalalian A (2007) In: Proceedings of the 14th international sol–gel conference. Montpellier, France
23. Heravi MM, Bakhtiari K, Fatehi A, Bamoharram FF (2008) Cat Comm 9:289
24. Hasaninejad A, Zare A, Sharghi H, Niknam K, Shekouhy M (2007) Arkivoc 14:39
25. Rahimizadeh M, Eshghi H, Bakhtiarpoor Z, Pordel M (2009) J Chem Res 5:269
26. Hosseini-Sarvari M (2007) Acta Chim Slov 54:354
27. Brown K, Katritzky AR (1964) Tetrahedron Lett 5:803
28. Niknam K, Zolfigol MA, Sadabadi T, Nejati A (2006) J Iran Chem Soc 4:318

29. Nagarajan R, Perumal PT (2002) Synth Commun 32:105
30. Chen D, Yu L, Wang PG (1996) Tetrahedron Lett 37:4467
31. Firouzabadi H, Iranpoor N, Jafarpour M, Ghaderi A (2006) J Mol Cat A Chem 253:249
32. Nagarajan R, Perumal PT (2002) Tetrahedron 58:1229
33. Magesh CJ, Nagarajan R, Karthik M, Perumal PT (2004) Appl Catal A Gen 266:1
34. Wang L, Han JH, Sheng T, Fan JZ, Tang X (2005) Synlett 2:337
35. Firouzabadi H, Iranpoor N, Jafari AA (2006) J Mol Catal A Chem 244:168