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Nanocrystalline titania-based sulfonic acid (TiO₂-Pr-SO₃H) as a new, highly efficient, and recyclable solid acid catalyst for preparation of quinoxaline derivatives

Seyyed Vahid Atghia* and Somayeh Sarvi Beigbaghlou

Abstract

Nanocrystalline titania-based sulfonic acid (TiO₂-Pr-SO₃H) was used as an efficient and reusable catalyst for the synthesis of quinoxalines. The clean and mild acidity condition, quantitative yields of products, short reaction time, and low reaction temperature are attractive features of this method, making it suitable for heat- or acid-sensitive substrates, particularly in drug synthesis. In practice, this method affords an advantageous combination of satisfactory yields, easy product isolation, and purification.

Keywords: Nanocrystalline titania, 1,2-Dicarbonyls, Quinoxaline, Solid acid catalyst

Background

Among various classes of nitrogen-containing heterocyclic compounds, quinoxaline derivatives are important components of several pharmacologically active compounds [1,2]. These compounds are widely used as anticancer and anthelmintic agents [3], antiviral, and antibacterial [4]. Also, quinoxalines have been reported for their applications as dyes [5] and building blocks in the synthesis of organic semiconductors [6], and they also serve as useful rigid subunits in macrocyclic receptors or molecular recognition [7] and chemically controllable switches [8]. Therefore, the preparation of these compounds has gained considerable attention in recent years.

Improved methods have been reported for the synthesis of quinoxalines; some of the newly used reagents include alumina [9], montmorillonite K-10 [10], sulfated TiO₂ [11-13], clayzic [14], zirconium (IV)-modified silica gel [15], PEG-400 [16], heteropoly acid [17], ZrO₂/M_xO_y/MCM-41 [18], cellulose sulfuric acid [19], and Ga(OTf)₃ [20]. These procedures, although effective, have various drawbacks such as requirement of long reaction times (24 h [14]), potential



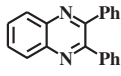

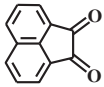
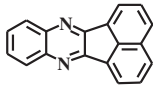

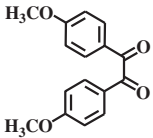
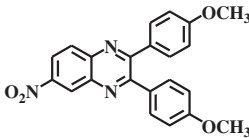
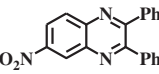

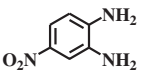
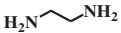




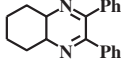
hazards, difficulty in catalyst preparation (e.g., preparation of ZrO₂/M_xO_y/MCM-41 involves a complex procedure and calcination at 500°C) and low yields. Hence, introduction of new methods to circumvent these problems is still in demand.

In recent years, there has been considerable growth of interest in the catalysis of organic reactions by solid acid catalysts. Solid acid catalysts provide numerous opportunities for recovering and recycling the catalysts from reaction mixtures. These features can lead to improved processing steps, better process economics, and environmentally friendly industrial manufacturing.

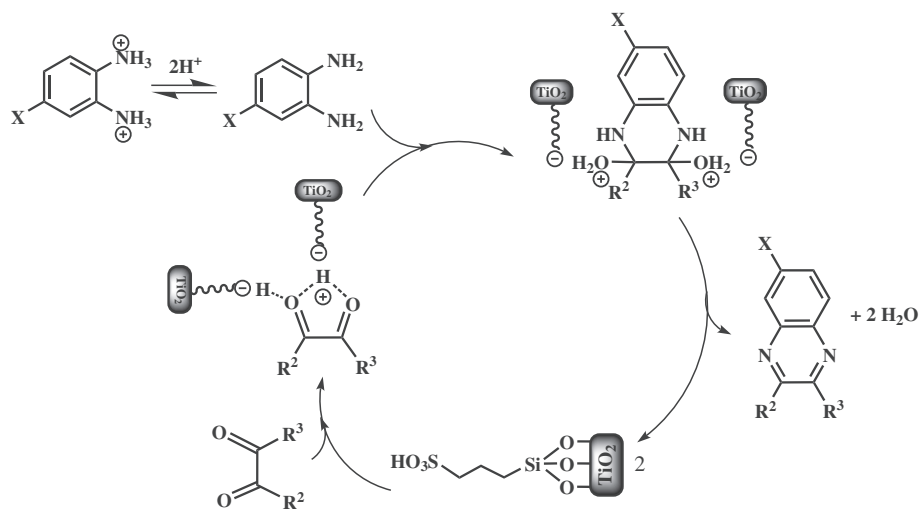
In the present study, the synthesis of chemically bound adsorbed sulfonic acid on TiO₂ (TiO₂-Pr-SO₃H) by the reaction of (3-mercaptopropyl) trimethoxysilane and TiO₂ and oxidation of the thiol groups with H₂O₂ is reported. The characterization of TiO₂-Pr-SO₃H was performed by means of various techniques such as Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and thermogravimetric analysis (TGA). The acidic property of the synthesized catalyst was evaluated by the calculation of Hammett acidity function. The assessment of the catalyst was carried out in the preparation of quinoxalines under mild conditions at room temperature (Scheme 1).

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Table 2 Synthesis of quinoxalines in the presence of TiO₂-Pr-SO₃H

Entry	Amine	Carbonyl compound	Time (min)	Yield ^a (%)	Product
1			10 (10, 14) ^b	95 (94, 90) ^b	
2			5	91	
3			4	96	
4			10	90	
5			25	85	
6 ^c			30	80	

^aIsolated yields; ^bTimes and yields in successive reusing runs 1 to 3; ^cIsolated as *cis*-/*trans*-mixture.



Scheme 2 Proposed mechanism.

Table 3 Comparison of the efficiency of TiO₂-Pr-SO₃H in the synthesis of 2,3-diphenylquinoxaline with other reported methods

Entry	Reagent	Solvent	Amount of catalyst (mg)	Time (min)	Yield (%) ^a
1	TiO ₂ -Pr-SO ₃ H (this work)	EtOH	10	10	95
2	Montmorillonite K-10 [10]	H ₂ O	21	150	100
3	Claycic [14]	H ₂ O-EtOH	100	24	89
5	Heteropoly acid [17]	Acetic acid	30	5	98
6	ZrO ₂ /M _x O _y /MCM-41 [18]	MeCN	40	120	97
7	Cellulose sulfuric acid [19]	EtOH	10	60	93
8	Cellulose sulfuric acid [19]	H ₂ O	10	150	80

^aIsolated yields.

the substrate and reaction monitoring were accompanied by thin-layer chromatography (TLC) on silica gel POLYGRAM SILG-UV₂₅₄ (Carl Roth GmbH, Karlsruhe, Germany) plates.

Instrumentation

Thermogravimetric analyses were conducted using a TGA PYRIS 1 (PerkinElmer Instruments, Waltham, MA, USA) thermoanalyzer instrument. Samples were heated from 25°C to 600°C at ramp 10°C/min under N₂ atmosphere. Wide-angle XRD measurements were performed at room temperature on a Siemens D-500 X-ray diffractometer (Munich, Germany), using Ni-filtered Cu-Kα radiation (λ = 0.15418 nm). IR and FT-IR spectra were obtained in KBr wafers on Shimadzu IR-470 (Kyoto, Japan) and PerkinElmer RX1 (Waltham, MA, USA) spectrophotometers respectively. TEM analysis was performed on a Philips model CM 10 (FEI Co., Hillsboro, OR, USA) instrument. Sample was prepared by sonicating a small amount of powder in methanol and then placing a drop of the mixture on a 3-mm TEM Cu grid having a lacey carbon support film. Scanning electron microphotographs were obtained on a LEO 1430VP instrument. The absorption spectra in

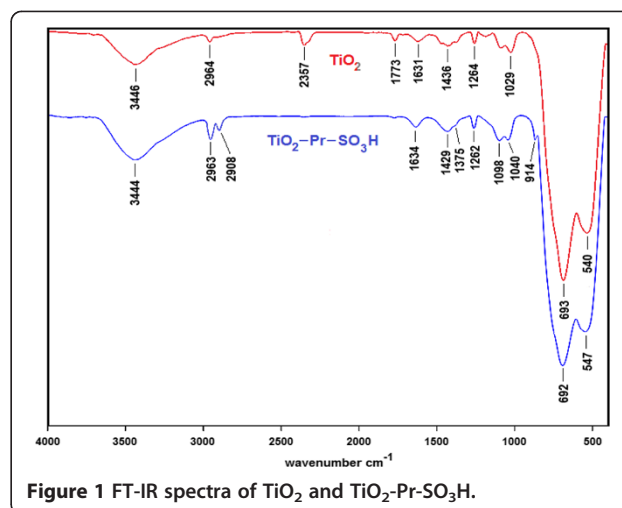


Figure 1 FT-IR spectra of TiO₂ and TiO₂-Pr-SO₃H.

the UV-visible regions were recorded by a PerkinElmer LAMBDA 25 recording spectrophotometer. ¹H and ¹³C NMR spectra were measured in CDCl₃ with a Bruker DRX-400AVANCE (Karlsruhe, Germany) spectrometer at 400 and 100 MHz, respectively.

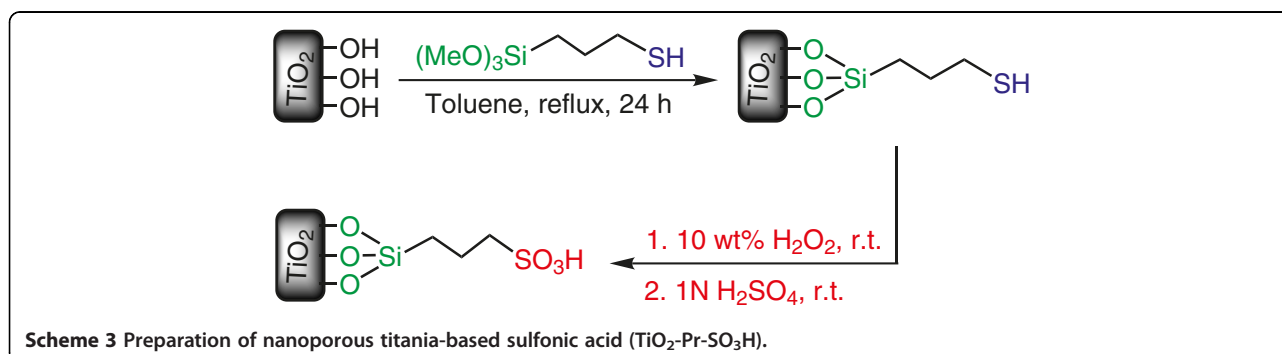
Catalyst preparation

Synthesis of 3-mercaptopropyltitania

To 20 g of TiO₂ (anatase, from Sigma-Aldrich) in dry toluene, 25 mL of (3-mercaptopropyl) trimethoxysilane was added, and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropyltitania (MPT), which was washed with acetone and dried.

Oxidation of 3-mercaptopropyltitania

MPT was oxidized with 10 wt.% H₂O₂ in methanol (20 mL) for 24 h at room temperature. The prepared sample was then treated with 1 N H₂SO₄ at ambient temperature for complete protonation, and then the mixture was filtered and washed with H₂O and acetone to obtain TiO₂-Pr-SO₃H catalyst (Scheme 3).



Scheme 3 Preparation of nanoporous titania-based sulfonic acid (TiO₂-Pr-SO₃H).

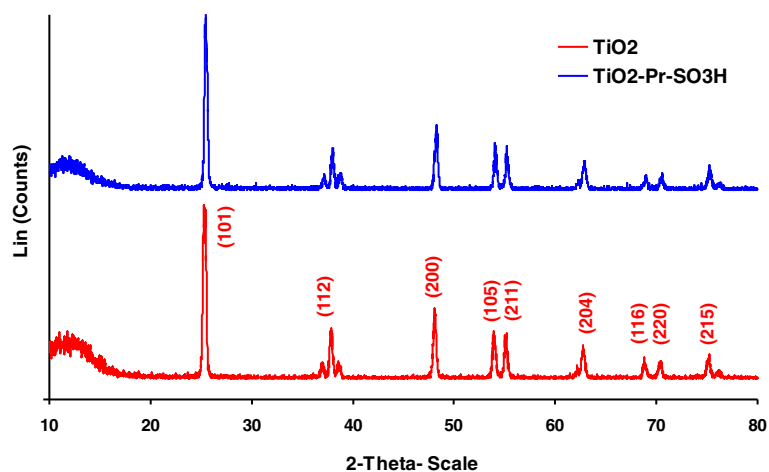


Figure 2 XRD patterns of TiO₂ and TiO₂-Pr-SO₃H.

Catalyst characterization

FT-IR analysis

FT-IR spectra for the pure TiO₂ and TiO₂-Pr-SO₃H samples are shown in Figure 1. In the case of TiO₂, the peaks at 3,446 and 1,773 cm⁻¹ correspond to the -OH stretching and bending vibrations of the adsorbed water, respectively. The spectrum of functionalized TiO₂ by sulfonic acid displays almost the same pattern as that of pristine TiO₂, but

the band at 3,000 to 3,600 cm⁻¹ that centered at 3,444 cm⁻¹ is flattened in sulfonated TiO₂ which can be attributed to the modification of TiO₂. Also, CH stretching vibrations of silylating agent was observed at 2,963 and 2,908 cm⁻¹, and the bands at 1,040 and 914 cm⁻¹ can be collectively attributed to Si-O stretching vibrations. Furthermore, the band at 1,375 cm⁻¹ corresponds to the stretching frequency of S = O in SO₃H.

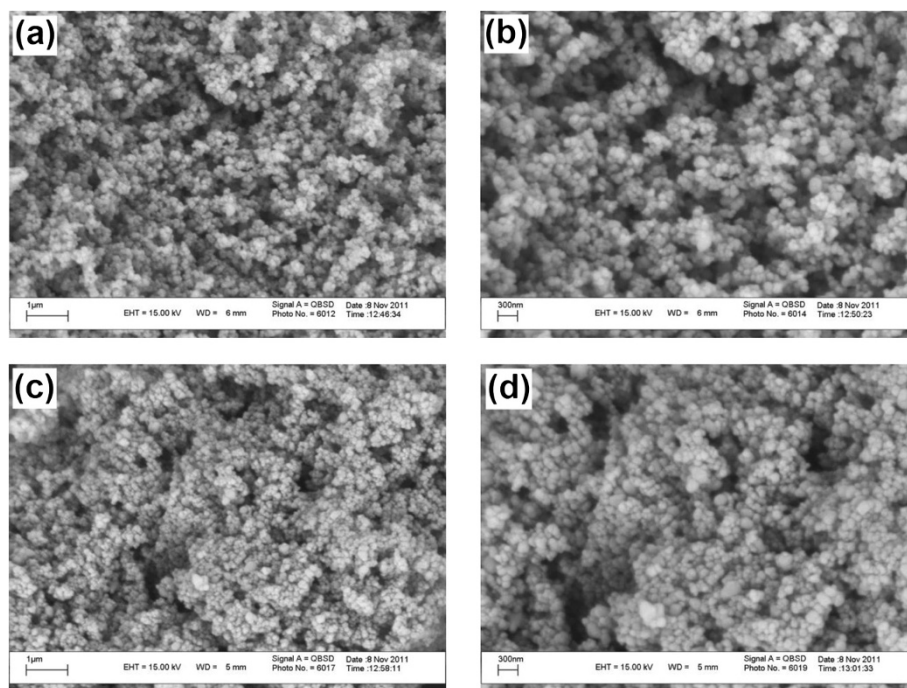


Figure 3 SEM images of TiO₂ and TiO₂-Pr-SO₃H. TiO₂ (a) $\times 30,000$ and (b) $\times 50,000$ magnifications and TiO₂-Pr-SO₃H (c) $\times 30,000$ and (d) $\times 50,000$ magnifications.

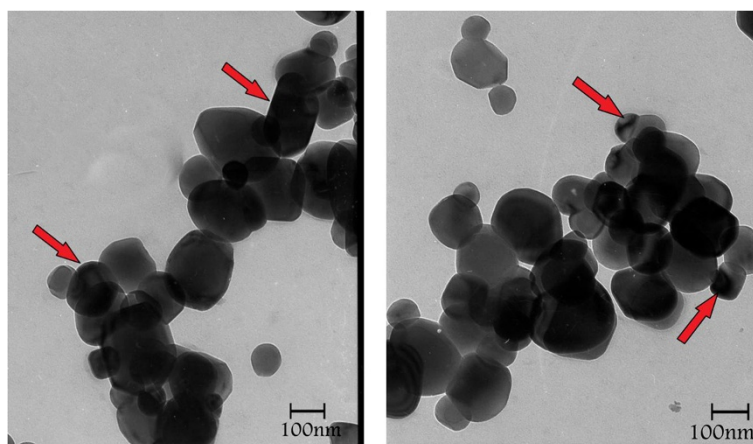


Figure 4 TEM images of $\text{TiO}_2\text{-Pr-SO}_3\text{H}$. Red arrow, corroded.

Wide-angle X-ray diffraction

XRD patterns of TiO_2 and $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ are given in Figure 2. XRD patterns clearly show anatase lines. It seems that the peak intensities of $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ are almost the same as those of TiO_2 , and the sulfate modification does not change the phase of TiO_2 . The average crystallite sizes of TiO_2 and $\text{TiO}_2\text{-Pr-SO}_3\text{H}$, determined using Debye-Scherrer equation, are 15.3 and 20 nm, respectively, which demonstrated that sulfate modification increases the size of TiO_2 .

SEM analysis

The representative SEM images of TiO_2 and $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ are shown in Figure 3a,b,c,d with $\times 30,000$ and $\times 50,000$ magnifications. All of the SEM images exhibit a cloud-like structure and small spherical-shaped particles. In $\text{TiO}_2\text{-Pr-SO}_3\text{H}$, aggregation of TiO_2 nanoparticles was clearly seen. However, the SEM micrographs of the catalyst show some modifications with respect to TiO_2 such that the primary surface structure of TiO_2 has changed.

TEM analysis

TEM images of $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ are shown in Figure 4. $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ particles are seen in different sizes ranging from 20 to 100 nm, and the average crystallite size of $\text{TiO}_2\text{-Pr-SO}_3\text{H}$, determined using XRD, was 20 nm. As can be seen in Figure 4, the particles are slightly corroded in the modification path. This is indicated in the figure by the arrow.

Thermal analysis

TGA was performed for the characterization of $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ in comparison with TiO_2 (Figure 5). The TGA curve of TiO_2 displays a weight loss (4 wt.%) below 100°C which corresponds to the loss of the physically adsorbed water. Also, there is a slight weight loss (3 wt.%) in the range of 100°C to 600°C , which possibly corresponds to the dehydroxylation of TiO_2 .

TGA of the catalyst shows an initial weight loss (4 wt.%) due to the desorption of water below 100°C . This is followed by a second weight loss that started

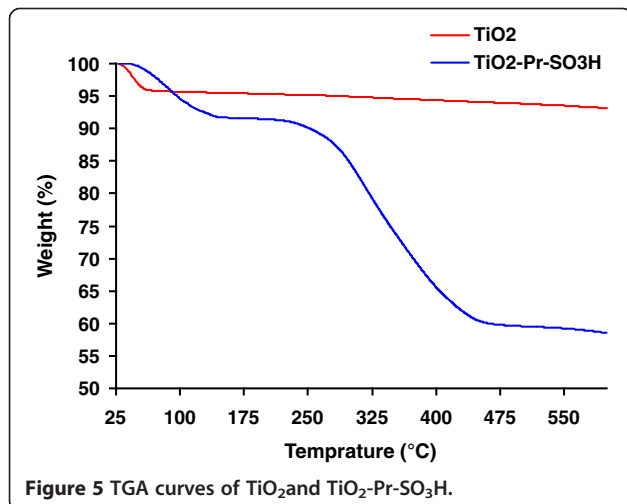


Figure 5 TGA curves of TiO_2 and $\text{TiO}_2\text{-Pr-SO}_3\text{H}$.

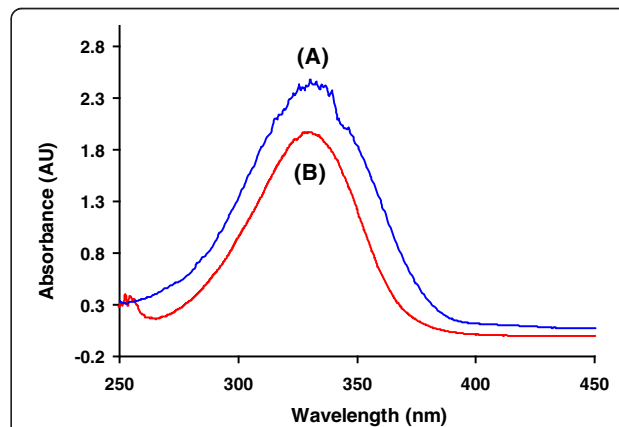


Figure 6 Absorption spectra of 4-nitroaniline (indicator; curve A) and $\text{TiO}_2\text{-Pr-SO}_3\text{H}$ (catalyst; curve B) in CCl_4 .

Table 4 Calculation of Hammett acidity function (H₀) of TiO₂-Pr-SO₃H

Entry	Catalyst	A _{max}	[I] _s (%)	[IH ⁺] _s (%)	H ₀
1	-	2.4113	100	0	-
2	TiO ₂ -Pr-SO ₃ H	1.1862	49.19	50.80	0.98

Condition for UV-visible spectrum measurement: solvent, CCl₄; indicator, 4-nitroaniline (pK(I)_{aq} = 0.99), 1.44 × 10⁻⁴ mol/L; catalyst, TiO₂-HClO₄, 20 mg, 25°C.

at 245°C, corresponding to the loss of the covalently bound organic group. From this weight loss, it is calculated that the loading of the organic group bound to the titania surface was 2.52 mmol g⁻¹. Also, from the TGA, we understood that TiO₂-Pr-SO₃H has a greater thermal stability (until 245°C) relative to TiO₂.

Surface acidity studies

The Hammett acidity function (H₀) can effectively express the acidity strength of an acid in organic solvents. It can be calculated using the following equation:

$$H_0 = pK(I)_{aq} + \log\left(\frac{[I]_s}{[IH^+]_s}\right),$$

Here, 'I' represents the indicator base (mainly substituted dinitroanilines), and [IH⁺]_s and [I]_s are respectively the molar concentrations of the protonated and unprotonated forms of the indicator. The pK(I)_{aq} values are already known (for example the pK(I)_{aq} value of 4-nitroaniline is 0.99) and can be obtained from many references. According to the Lambert-Beerlaw, the value of [I]_s/[IH⁺]_s can be determined and calculated using the UV-visible spectrum.

In our experiment, 4-nitroaniline was chosen as the basic indicator, and CCl₄ was chosen as the solvent because it is aprotic. The maximal absorbance of the unprotonated form of 4-nitroaniline was observed at 329 nm in CCl₄. As Figure 6 shows, the absorbance of the unprotonated form of the indicator in TiO₂-Pr-SO₃H was weak as compared to the sample of the indicator in CCl₄, which indicated that the indicator was partially in the form of [IH⁺]. The results obtained are listed in Table 4, which shows the acidity strength of TiO₂-Pr-SO₃H.

General procedure

To a mixture of a substituted 1,2-diketone (1 mmol) and 1,2-diamine (1 mmol) in ethanol (5 mL), TiO₂-Pr-SO₃H (10 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction mixture was heated for a few minutes. The catalyst was removed by filtration, the filtrate was concentrated, and the solid residue was recrystallized from ethanol to give the pure product.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Both authors - SVA and SSB - contributed equally in this article. Both authors read and approved the final manuscript.

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