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Article

Nanocrystalline titanium dioxide catalyst for the synthesis of azlactones

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ABSTRACT

Titanium dioxide nanoparticles were prepared by an electrochemical reduction method using parameters such as current density, solvent polarity, distance between electrodes, and concentration of stabilizers to control the size of the nanoparticles. The nanoparticles were characterized by UV-Vis spectroscopy, X-ray diffraction, scanning electron microscopy and transmission electron microscopy, and their catalytic performance was tested for the synthesis of a series of 4-aryldiene-2-phenyl-5(4)-oxazolones from the cyclodehydration and condensation of the respective aldehyde, hippuric acid and acetic anhydride. Easy availability, reusability and eco-friendliness were some prominent features of the nanocrystalline titanium dioxide catalyst.

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1. Introduction

During the past few decades, many results were published in the area of the synthesis of heterocyclic molecules whose physical and chemical properties make them biologically important [1]. Among these, 2-oxazolin-5-ones (azlactones) are multifunctional compounds that are known to react at the C=C, C=N, C=O bonds, and so they are important for the synthesis of many natural products, synthetic intermediates and pharmaceuticals [2–4]. They are also useful precursors for the synthesis of unsaturated amino acids [5], peptides [6] and biosensors [7]. Substituted oxazole derivatives have been found to be useful for their biological activity such as antibacterial [8], antitubercular [9], anticancer [10] and antitumor [11] activity. Other application of oxazole derivatives includes their use as fluorescent whitening agents, lubricants, dyes and pigments [12–15].

The most common method for their preparation is the Erlemeyer-Plöchl reaction which proceeds by the cyclodehydration and condensation of the aldehyde and hippuric acid in dry

acetic anhydride catalyzed by sodium acetate [16]. The classical reaction has remained unchanged for the last century with only some modernization in the reagents and catalysts, such as the use of supported KF [17], Bi(OAc)₃ [18], Bi(OTf)₃ [19], [bmim]OH [20], Ca(OAc)₂ [21], ZnO NPs [22], alumina [23], KPO₄ [24] or a sonochemical reaction [25]. Each of these advances has its own merits, but they also suffer from drawbacks such as reaction at high temperature, unsatisfactory yields, harsh reaction conditions, and use of stoichiometric amounts of catalyst. Thus the development of a new synthesis strategy which can overcome these drawbacks using an easily accessible catalyst is still important.

Metal nanoparticles are promising materials as the heterogeneous catalyst in a variety of organic transformations [26–30]. Their catalytic properties are functions of their size and crystal lattice parameters and they show amazing levels of performance in terms of selectivity, activity and improved yield of products [31–33]. In particular, titanium dioxide nanoparticles exhibited many special properties because the band gap of the nanoparticles increased with the decrease in size. The

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use of TiO₂ nanoparticles has received considerable attention in green synthetic organic chemistry [34–38] and the photo-degradation of carcinogenic dyes [39] and pesticides [40].

The synthesis of transition metal nanoparticles by the electrochemical reduction method was originally reported by Reetz et al [41], who showed that it gave metal nanoparticles with a narrow size distribution. The cluster size was found to decrease with an increase in current density [42]. The solid product exhibited electronic, paramagnetic, optical and catalytic properties that were significantly better than those of the bulk material, which was due to its extremely small size and large surface area. In the present work, TiO₂ nanoparticles were prepared by the electrochemical reduction method and their catalytic activity was tested for the synthesis of azlactone.

2. Experimental

2.1. Catalyst preparation

All chemicals were purchased from Aldrich and S. D. Fine Chemicals Suppliers and used as received. The purity of the substrates and the reaction monitoring were determined by thin layer chromatography (TLC) and visualization under ultraviolet (UV) light. In the initial experiment we used a titanium metal sheet (1 cm × 1 cm) as anode and a platinum sheet (1 cm × 1 cm) as the cathode. The two electrodes were 1 cm apart. Tetrabutyl ammonium bromide (TBAB, 0.01 mol/L) in an acetonitrile and tetrahydrofuran solution (4:1) was the electrolyte. Upon applying a current density of 10 mA/cm², we obtained > 95% of the titanium dioxide clusters getting stabilized by TBAB. Electrolysis was carried out in nitrogen atmosphere. The titanium dioxide nanoparticles were white in color. Since the material was insoluble in the solvent used, the work up only needed simple decantation. The decanted solid product was washed with dry THF three to four times to remove excess tetrabutyl ammonium bromide and dried in a vacuum desiccator. The dried sample was calcined at 550 °C and stored in closed glass vials under ambient conditions.

2.2. Catalyst characterization

The titanium dioxide nanoparticles were characterized by UV-Vis spectrophotometry, XRD, TEM, and SEM-EDS techniques. The wavelength of absorbance was determined by a UV-Vis spectrophotometer [JASCO 503] using a quartz cuvette and an acetonitrile/tetrahydrofuran solution as reference. The IR spectra were recorded on a FT-IR spectrometer [JASCO, FT-IR/4100, Japan] using dry KBr as the standard reference. The XRD patterns of the TiO₂ nanoparticles were recorded on a Bruker 8D advance X-ray diffractometer using Cu K α radiation of wavelength 0.154 056 nm. To study the morphology of TiO₂ nanoparticles, SEM analysis was carried out with a JEOL (JSM-6330 LA) equipment operated at 20.0 kV and 1.0 nA. The elemental compositions of the TiO₂ nanoparticles were examined using a energy dispersive spectrometer (EDS). The TEM analysis was carried out with a Philips Model CM200 equipment operated at 20–200 kV. ¹H NMR spectra were recorded

on an 400 MHz FT-NMR spectrometer with CDCl₃ as a solvent. The chemical shift values are recorded as δ (ppm units) relative to tetramethylsilane (Me₄Si) as an internal standard.

2.3. Typical reaction procedure

A mixture of an aromatic or heteroaromatic aldehyde (2 mmol), hippuric acid (2 mmol), acetic anhydride (6 mmol) and 100 mg of TiO₂ nanoparticles in 5 ml ethanol was heated with constant stirring at 120 °C. At first the mixture became almost solid and then with increase in temperature, it gradually turned into a deep yellow colored liquid. The progress of reaction was monitored by TLC. After completion of the reaction, 30 ml of hot ethanol was added to the flask to separate out the catalyst. After cooling, the yellow color product was filtered and washed with ice cold ethanol and then with hot water, and dried and recrystallized to afford pure crystals of the desired compound. The products (**3a–3m**) were confirmed by comparison with standard samples using the IR, ¹H NMR and ¹³C NMR spectra and melting points.

2.4. Spectral data of representative compounds

3a. Bright yellow needles. ¹H NMR (CDCl₃, ppm) δ = 8.22–8.17 (m, 4H, ArH), 7.55–7.61 (m, 3H, ArH), 7.22–7.39 (m, 3H, Ar-H and -CH=); ¹³C NMR (101 MHz, CDCl₃) δ = 110.0, 125.6, 128.4, 128.8, 128.9, 131.2, 131.8, 132.4, 133.3, 133.5, 163.6, 167.6; IR (KBr) ν = 3322, 2930, 1795, 1655, 1165 cm⁻¹.

3c. Yellow needles. ¹H NMR (CDCl₃, ppm) δ = 7.16 (s, 1H, -CH=), 7.40–7.64 (m, 5H, Ar-H), 7.85 (d, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 8.19 (d, 1H, Ar-H), 8.30 (s, 1H, Ar-H); ¹³C NMR (101 MHz, CDCl₃) δ = 125.39, 128.06, 128.58, 129.01, 129.87, 131.12, 131.25, 131.70, 134.02, 134.42, 135.84, 190.25; IR (KBr): ν = 3322, 2930, 1799, 1657, 1165 cm⁻¹.

3f. Bright yellow solid. ¹H NMR (CDCl₃, ppm) δ = 8.19–8.16 (m, 2H), 8.10 (d, J = 8.1 Hz, 2H), 7.62–7.52 (dd, J = 10.5 Hz, 4.6, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 2.42 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 21.3, 125.6, 128.6, 128.9, 129.6, 132.1, 132.3, 133.1, 133.3, 133.6, 139.0, 163.5, 167.7; IR (KBr) ν = 3432, 2922, 1791, 1654, 1160 cm⁻¹.

3h. Orange solid. ¹H NMR (CDCl₃, ppm) δ = 3.87 (s, 3H, CH₃), 7.12 (d, 2H, J = 8.4 Hz, ArH), 7.35 (s, 1H, -CH=), 7.62–7.74 (m, 3H, ArH), 8.12 (d, 2H, J = 8.4 Hz, ArH), 8.32 (d, 2H, J = 8.4 Hz, ArH); IR (KBr) ν = 3432, 2938, 1789, 1654, 1162 cm⁻¹.

3g. Yellow needles. ¹H NMR (CDCl₃, ppm) δ = 7.39 (d, 1H, J = 7.6 Hz, ArH), 7.48 (s, 1H, -CH=), 7.53–7.66 (m, 4H, ArH), 8.17 (d, 2H, J = 7.6 Hz, ArH), 8.90 (d, 1H, J = 8.4 Hz, ArH); IR (KBr) ν = 3448, 3088, 1798, 1658, 1170 cm⁻¹.

3. Results and discussion

3.1. SEM-EDS results

SEM analysis was carried out to study the morphology of the TiO₂ nanoparticles. It can be seen from Fig. 1(a) that the TiO₂ powders have a uniform size and can be classified as nanoparticles. The EDS spectrum was used to analyze the composition

Fig. 1. (a) SEM and (b) EDS characterization of the TiO₂ nanoparticles.

of the TiO₂ nanoparticles. The result is shown in Fig. 1(b). The Ti and O peaks were clearly present in the spectrum and there was no other peak, which indicated that TiO₂ particles were successfully synthesized by the electrochemical reduction method.

3.2. UV-Vis spectra

As the electrochemical reduction proceeded, the change in colour of the reaction mixture with time was monitored. It was seen that between 15 to 20 min a change in color took place. The spectra were recorded after every 30 min reaction. In Fig. 2, the UV-Vis absorbance spectra showed that the intensity of the characteristic band at 344 nm increased with time, which indicated the formation of titanium dioxide nanoparticles with the anatase phase.

Fig. 2. UV-vis spectra of the TiO₂ nanoparticles.

Fig. 3. SAED pattern (a) and TEM image (b) of the TiO₂ nanoparticles.

3.3. TEM characterization

TEM analysis was carried to examine the particle size, crystallinity and morphology of the sample. The sample for TEM analysis was prepared by the evaporation of very dilute alcoholic suspensions onto carbon-coated copper grids. The magnified image in Fig. 3 showed that the particles were well dispersed and no aggregation was observed. The particles have a tetragonal shape with sizes of 25–30 nm.

3.4. XRD characterization

In Fig. 4, the peaks corresponding to the (101), (004), (200), (105), (204), (220), and (215) planes with the lattice parameters $a = b = 3.780$ and $c = 9.513$ indicated the formation of TiO₂ nanoparticles with the anatase phase. All the peaks were in

Fig. 4. XRD pattern of the TiO₂ nanoparticles.

Scheme 1. Synthesis of 4-aryldiene-2-phenyl-5(4)-oxazolones derivatives catalyzed by TiO₂ NPs.

good agreement with JCPDS card no. 86-1156. The TiO₂ had a pure tetragonal crystal phase structure. The particle size was calculated from the X-ray line broadening and full width at half maximum (FWHM) using the Debye-Scherrer equation $D = 0.94\lambda/\beta\cos\theta$, where D is particle size, λ is wavelength, θ is diffraction angles, and β is FWHM. The average particle size was found to be 25.63 nm.

3.5. Catalytic activity

Our literature survey showed that the Erlenmeyer reaction is affected by the acid as well as the base and only scant literatures are available for this reaction. Thus we would like to report the present protocol of the use of TiO₂ nanoparticles for the synthesis of 4-aryldiene-2-phenyl-5(4)-oxazolones by reacting aldehyde **1**, hippuric acid **2**, acetic anhydride in 5 ml of ethanol with constant stirring and heating at 120 °C as shown in Scheme 1. Both aromatic aldehydes with an electron-donating or electron-withdrawing group as well as a heterocyclic system such as Furan-2-carboxyaldehyde reacted smoothly to produce high yields of the products. The results with different aromatic aldehydes are summarized in Table 1.

We also evaluated the amount of catalyst required for the reaction. We found that the yields were obviously affected by the amount of catalyst loading. We investigated the model reaction of benzaldehyde, hippuric acid and acetic anhydride using

Table 1

Synthesis of 4-aryldiene-2-phenyl-5(4)-oxazolones derivatives catalyzed by TiO₂ NPs.

Product ^a	R	Time (min)	Yield (%)	Melting point (°C)	
				Found	Reported
3a	C ₆ H ₅	30	95	169–170	170–172 [20]
3b	4-ClC ₆ H ₄	25	96	185–187	187–188 [20]
3c	3-ClC ₆ H ₄	35	95	155–156	156–157 [19]
3d	4-NO ₂ C ₆ H ₄	30	94	242–243	240–241 [23]
3e	3-NO ₂ C ₆ H ₄	25	96	163–164	166–167 [20]
3f	4-CH ₃ C ₆ H ₄	35	95	144–145	141–143 [23]
3g	2,4-Cl ₂ C ₆ H ₃	40	92	159–160	160–162 [19]
3h	4-OMeC ₆ H ₄	45	93	155–156	155–157 [23]
3i	C ₆ H ₅ COCH ₃	40	94	104–106	105–106 [23]
3j	2-furfural	50	93	169–170	170–171 [20]
3k	4-FC ₆ H ₄	35	95	170–171	169–170 [20]
3l	4-BrC ₆ H ₄	40	92	196–197	195–196 [18]
3m	C ₆ H ₅ CH=CH	40	93	128–129	130–131 [20]

^a Reaction conditions: aldehyde (2 mmol), hippuric acid (2 mmol), acetic anhydride (6 mmol) and 100 mg of TiO₂ nanoparticles in 5 ml ethanol stirred at 120 °C.

Table 2

Screening of catalyst (TiO₂ NPs) concentration for the synthesis of **4a**.

Entry	Catalyst amount (mg)	Time (min)	Yield (%) ^a
1	50	120	35
2	70	120	67
3	90	90	89
4	100	30	95
5	120	30	96

Table 3

Recycle of TiO₂ NPs in the synthesis of **4a**.

Run	Fresh	1	2	3
Yield (%)	95	95	94	92

different amounts of catalyst from 50 to 120 mg. The best yield was obtained using 100 mg catalyst. With even more catalyst, the yield of the desired product was found to be constant. We also carried out the reaction without any catalyst, but the product was isolated in poor yield (10%) and the starting material was recovered. Therefore, the catalyst plays a crucial role in the success of the reaction in term of the yields of the product. The results obtained are summarized in Table 2.

In this study, the catalyst was recovered and reused. The catalyst was recovered by a simple work-up using centrifugation, and then it was washed with ethanol and reused. This was done for three successive runs, which gave yields of the product that were almost the same as that in the first run. This is shown in Table 3.

4. Conclusions

We demonstrated a mild, simple and green procedure for the synthesis of 4-aryldiene-2-phenyl-5(4)-oxazolones using recyclable TiO₂ nanoparticles. The catalyst promoted the yields and shortened the reaction time. The catalyst showed excellent stable activity during three recycle runs. The ease of work-up and the clean procedure will make the present method a useful and important method for the synthesis of azlactones.

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Graphical Abstract

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Size controlled synthesis of TiO₂ by electrochemical reduction gave nanoparticles for the synthesis of 4-aryldiene-2-phenyl-5(4)-oxazolones. The smaller size catalyst has promising features for the reaction.

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