



ZnO nanoparticles embedded in SBA-15 as an efficient heterogeneous catalyst for the synthesis of dihydropyrimidinones via Biginelli condensation reaction



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ABSTRACT

A new ZnO@SBA-15 nanocomposite material has been fabricated by an “in situ” generation of ZnO NPs on SBA-15 support. The as-synthesized nanocomposite material was fully characterized with various spectroscopic techniques and their catalytic activity was tested for the synthesis of a diverse range of dihydropyrimidinones (DHPMs) and thione derivatives via Biginelli condensation reaction. The catalytic efficiency of ZnO@SBA-15 nanocomposite was far superior with a remarkably lower catalyst loading and shorter reaction time compared to unsupported ZnO nanoparticles. The catalyst was recycled for minimum of four times without significant loss in its catalytic activity. Moreover, a tentative catalytic cycle for the reaction is also proposed.

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1. Introduction

Multicomponent reactions (MCRs) have become current research interest to the synthetic organic chemist owing to their synthetic efficiency, atom economy and procedural simplicity. The combinatorial chemistry of these reactions allows synthesizing large library of structurally related compounds. MCRs are also an important tool to the modern drug development research so as to achieve a synthetic target in an expeditious way. Furthermore, MCRs are environmentally benign processes and their one pot synthesis chemistry reduces the energy consumption and by-product formation [1]. Biginelli reaction is one of the most studied multicomponent reaction that used to synthesize dihydropyrimidinones (DHPMs), an important class of compounds that has diverse pharmacological properties [2]. This reaction attracted much attention after the discovery of calcium channel modulator drug nifedipine which features DHPM backbone, used in the treatment of cardiovascular diseases [3]. Monastrol, an anticancer agent that can specifically inhibit mitotic kinesin Eg5 [4]. DHPMs

compounds viz SQ 32547 and SWO2, are effective orally active antihypertensive agents [5]. Most notably, several alkaloids extracted from marine sources having DHPM as their core building blocks shows interesting biological properties. Batzelladine is one of such marine natural alkaloid have shown its activity as potent HIV gp-120-CD4 inhibitors [6]. Some ester, cyanide substituted DHPMs are reported to be promising antibacterial agents [7]. Several pyrimidinone-amide derivatives of DHPMs are tested as anti-malarial agents, a new class of Hsp70 modulators, could inhibit the replication of the pathogenic *P. falciparum* stages in human red blood cells [8]. A series of compounds 3-(4,6-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives showed significant anti-inflammatory activity [9]. The classical Biginelli reaction involves one pot condensation of an aldehyde, a β -ketoester (active methylene compound) and urea or thiourea under strongly acidic conditions [10]. The main drawbacks of this classical method is the harsh reaction conditions, longer reaction times, and lower yields when substituted aromatic and aliphatic aldehydes are used as substrates [11]. So the classical Biginelli reaction is not suitable for substrates having acid-sensitive functional groups. In order to increase the product yield, various homogenous [12] and heterogeneous [13] catalysts are used for the Biginelli reaction but both homogenous and heterogeneous catalysts have severe limitations. The high temperature, longer reaction

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time, high catalyst loading needed for homogenous catalysts whereas heterogeneous catalysts also had metal leaching problem apart from the same limitation as homogeneous catalysts.

Metal oxide is widely used as catalyst in many important organic transformations. The main features of the metal oxide is their stability, recyclability, non toxic, non-hygroscopic properties which make it an efficient catalyst [14–16]. Zinc Oxide (ZnO) is one of such metal oxide and it has previously demonstrated its catalytic activity for many organic transformations [15,16]. But unsupported ZnO NPs has one major drawback that it generally aggregated during the synthesis process which reduces its surface area and thereby reducing active catalytic sites for adsorption of reagents [16,17]. Due to this reasons, high catalyst loading and longer reaction time required for many ZnO catalysed reactions [17]. But this problem can be solve by increasing the dispersion of ZnO nanoparticles (NPs) on a high surface area support such as mesoporous SBA-15. SBA-15 is one of the most well studied mesoporous silica-based material having very high specific surface area, highly uniform 2D hexagonal array of pores, good thermal and hydrothermal stability [18]. It serves as a support for various metal and metal oxide NPs that are investigated for catalytic application [19,20]. Recently D. Bhuyan et al. demonstrated that catalytic activity of unsupported magnetic Fe_3O_4 NPs can be enhanced by supporting it on mesoporous SBA-15 for the A [3] coupling reaction [20c]. Moreover, PEG-4000 used in our synthesis method provided better distribution of uniform sized ZnO NPs over existing methods which often result aggregated ZnO NPs [21,26].

In the present work, we have synthesized ZnO NPs on SBA-15 support by a calcination process. The as-synthesized ZnO NPs have very narrow size distribution, well dispersed and very high surface area. Furthermore the as-synthesized ZnO NPs exhibited enhanced catalytic activity for Biginelli condensation reaction and a diverse range of DHPMs compounds were synthesized.

2. Experimental section

2.1. Chemicals

Tetraethyl orthosilicate (TEOS), Pluronic P123 triblock copolymer ($\text{EO}_{20}\text{PO}_{70}\text{EO}_{20}$, average molecular weight = 5800) were procured from Sigma-Aldrich. HCl (Merck), Zinc acetate dihydrate (Alfa Aesar), ZnO nanopowder (<50 nm average particle size, Sigma-Aldrich) and Polyethylene glycol-4000 (SRL) were procured from the mentioned chemical companies. All chemicals are analytical grade and used as received without further purification.

2.2. Characterization

Low angle X-ray diffraction patterns were recorded on a Philips X'Pert Pro diffractometer in the 2θ range from 0.5 to 5° using $\text{Cu K}\alpha$ radiation. Wide angle X-ray diffraction measurement were performed on a Rigaku, Ultima IV X-ray diffractometer in the 2θ range of 10 – 90° using $\text{Cu K}\alpha$ source ($\lambda = 1.54 \text{ \AA}$). The N_2 adsorption-desorption isotherm measurement was carried out on Autosorb-1 (Quantachrome, USA). Prior to analysis, the samples were degassed at 250°C for 3 h under high vacuum conditions. Brunauer–Emmett–Teller (BET) calculation was used to determine the specific surface areas of the samples. Pore size distributions were derived from desorption isotherms using the Barrett–Joyner–Halenda (BJH) method. The Transmission electron microscopy (TEM) images of the samples were recorded on a JEOL JEM-2011 transmission electron microscope operated at 200 kV. Field emission scanning electron microscopy (FESEM) images were obtained from a Carl Zeiss Sigma FESEM instrument. Energy dispersive X-ray spectroscopy (EDS) pattern and elemental

mapping analysis was recorded on Oxford X Max 20 equipment. FT-IR spectra (4000 – 400 cm^{-1}) were recorded as KBr pellets in a Shimadzu IR affinity-1 spectrophotometer. The absorbance spectra was recorded at room temperature using a UV-visible spectrophotometer (Model Shimadzu 1601 pc) as aqueous dispersion. The Atomic absorption spectroscopy (AAS) measurement was carried out using PerkinElmer (Model AAnalyst-700) spectrometer. Prior to AAS analysis, the sample was digested in aqua regia. ^1H and ^{13}C NMR data of the products were recorded at room temperature in a Bruker DPX-300 NMR spectrometer using DMSO-d_6 as the solvent. Melting point data of the samples were obtained from a Büchi melting point apparatus (Model M560).

2.3. Synthesis of SBA-15 material

SBA-15 was synthesized according to the reported literature by D. Zhao et al. using tetraethyl orthosilicate (TEOS) as the silica source, Pluronic P123 triblock copolymer as the template and HCl as the pH controlling agent [18a,20c].

2.4. Synthesis of ZnO NPs supported on mesoporous SBA-15

Zinc acetate dihydrate (0.1 g) and PEG-4000 (0.1 g) were dissolved in 50 mL double distilled water by vigorous stirring. After that, NH_3 solution was added to the mixture until the pH of the solution became 9.7. Then the resulting solution was heated at 80°C for 8 h and cool down naturally. Thereafter calcined SBA-15 (1 g) was added to the solution and sonicated for 30 min. The precipitate then filtered off and dried in vacuum desiccator. Finally, the precipitate was calcined at 450°C for 12 h at the heating rate of $3^\circ\text{C}/\text{min}$ and cool to room temperature naturally. The as-synthesized material is designated as ZnO@SBA-15 nanocomposite.

General procedure for the synthesis of DHPMs by Biginelli condensation reaction.

A mixture of the aldehyde (1 mmol), ethyl or methyl-acetoacetate (1 mmol), urea or thiourea (1.4 mmol), ethanol (2 mL) and 20 mg ZnO@SBA-15 catalyst (3.12 wt% ZnO) was stirred in a glass tube at 65°C . The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by filtration and the solvent was evaporated under reduced pressure to obtain a solid product. Then ethyl acetate (20 mL) was added to the solid product. The resulting organic layer was washed with 10% NaHCO_3 and brine solution, dried over anhydrous Na_2SO_4 and evaporated to give the desired product. The solid product was further purified by re-crystallization from ethanol. The re-crystallized pure products was characterized by ^1H NMR, ^{13}C NMR, melting point measurement respectively and compared with the reported data.

3. Result and discussion

Fig. 1(a) shows the low angle XRD patterns of as-synthesized SBA-15 materials which displayed three well resolved peaks indexed to the (100), (110) and (200) planes. These planes corresponds to the 2D hexagonal symmetry and long range mesoporous ordering, characteristic for SBA-15 [18]. The retention of aforementioned peaks in case of ZnO@SBA-15 nanocomposite confirmed that calcination process did not change mesoscopic ordering of SBA-15 support [21]. However, the observed shift in 2θ values as well as decrease in intensity of the planes for ZnO@SBA-15 is due to the presence of ZnO NPs which may partly block the pores so as to decrease the mesoscopic ordering a little [22]. Wide angle XRD patterns [Fig. 1 (b)] shows a broad band in between 2θ angle value of 15 and 35° which is the characteristic band of amorphous SBA-15 [23]. For ZnO@SBA-15 nanocomposite, in addition to the broad

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