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Uncapped SnO_2 quantum dot catalyzed cascade assembling of four components: a rapid and green approach to the pyrano[2,3-*c*] pyrazole and spiro-2-oxindole derivatives

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ABSTRACT

A new uncapped SnO_2 quantum dots (QDs) catalyzed strategy for the synthesis of substituted pyrano [2,3-*c*]pyrazole and spiro-2-oxindole derivatives has been developed via a multicomponent one pot approach in aqueous medium. The reactions can be performed at low catalyst loadings with excellent functional group tolerance. This communication also reports a comparative study of the efficiency related to the catalytic activity of uncapped SnO_2 QDs, oleic acid capped SnO_2 QDs, and SnO_2 nanoflower. Uncapped SnO_2 QDs, capped SnO_2 QDs, and SnO_2 nanoflower were prepared by simple solvothermal method and characterized by XRD, FESEM, and TEM images. The easy recovery of the catalyst and high yield of the products make the protocol attractive, sustainable, and economic. The catalyst was reused for six cycles with almost unaltered catalytic activity.

1. Introduction

One of the major areas of current research in the field of catalysis is the synthesis of metal or metal compound nanoparticles and their application in specific catalytic reactions.[1] Nanomaterials have been extensively employed in organic synthesis for their fundamental size and shape dependent properties. It is widely accepted that a smaller catalyst particle means higher activity.[2] As a result, both the activity and the stability of a solid catalyst suspended in a liquid media can benefit greatly from the use of small catalyst particles. Nano-catalysts mimic homogeneous (high surface area, easily accessible) as well as heterogeneous (stable, easy to handle) catalyst systems. Thus nano-catalysts make the system more efficient than conventional heterogeneous catalyst systems. All these render the catalyst cost-effective, making it promising for industrial applications.

Pyranopyrazoles are an important class of heterocyclic compounds. They exhibit a wide range of biological activities like antimicrobial,[3] anticancer,[4,5] anti-inflammatory[6] inhibitors of human Chk1 kinase[7] and also as biodegradable agrochemicals.[8] Furthermore, they play a significant role as crucial synthetic intermediates.[9] Again, substituted spiroindoline derivatives are much sought after class of heterocycles because of their potential applications in pharmaceutical field.[10] Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.[11] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[12–14] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[15–18] For example, spirotryprostatin B, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[16] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Fig. 1).[18]

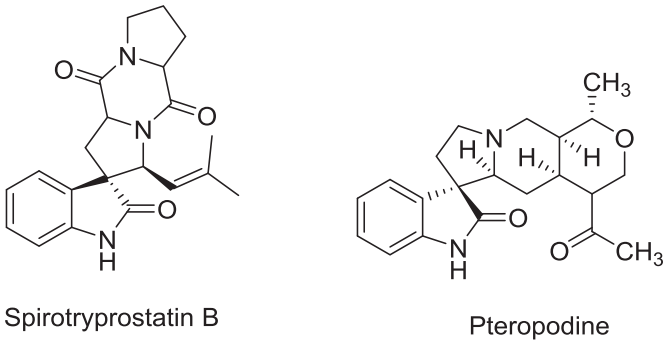

Fig. 1. Biologically active spirooxindole containing compounds.

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Synthetic approaches of substituted pyrano[2,3-*c*]pyrazoles and spirooxindole system have advanced a long way from the earlier reported multistep protocols[19,20] to the present day multicomponent reactions (MCRs). Conventional synthetic protocols though have a broad scope but generate copious extent of waste. As a result chemical industry is subjected to huge pressure to get rid of such waste. In this aspect, nano material-catalyzed multicomponent reactions have emerged as a valuable synthetic tool due to their efficiency, intrinsic atom economy, and structural diversity of resulting products, when compared to conventional multistep synthesis.

Synthesis of SnO_2 nanocrystals has attracted much attention from researchers owing to their potential applications based on gas sensing,[21] field-emission,[22] electrochemical,[23] photocatalytic,[24] and photovoltaic properties.[25,26] In continuation of our research program dedicated to synthesis and application of metaloxide nano-catalysts for design and synthesis of novel heterocyclic systems,[27] we have started our investigation with the objective of developing a clean, efficient, and straightforward methodology for the synthesis of pyrano[2,3-*c*]pyrazoles and spirooxindole systems utilizing a non-toxic and environmentally benign catalyst. Herein, we report a novel approach for the facile synthesis of pyrano[2,3-*c*] pyrazoles and spirooxindole derivatives by assembling the basic building blocks installing uncapped monodisperse SnO_2 quantum dots (QDs). Synthesis of SnO_2 nanoparticle, capped and uncapped monodisperse SnO_2 quantum dots (QDs),[28] and the fundamental difference of catalytic activity between these three types of nanoparticle have been demonstrated in this paper.

2. Results and discussion

The first step in the execution of this goal was the synthesis of SnO_2 nanoparticle. The catalyst was prepared by solvothermal method. SnO_2 nanoflower, capped and uncapped monodisperse SnO_2 quantum dots (QDs) were characterized by X-ray diffraction study, FESEM, and TEM images.

Fig. 2a shows the XRD patterns of the as-synthesized uncapped SnO_2 QDs. All the diffraction peaks matched well to the standard diffraction data for rutile SnO_2 (JCPDS card no. 41-1445) while no traces of other phases or impurities are found. The gradual widening of peaks indicates large decrease in dimension. The average sizes of the uncapped SnO_2 QDs calculated by Debye–Scherrer formula considering the instrumental broadening and strain broadening using the (110) peak of the XRD pattern are 3.9 nm.

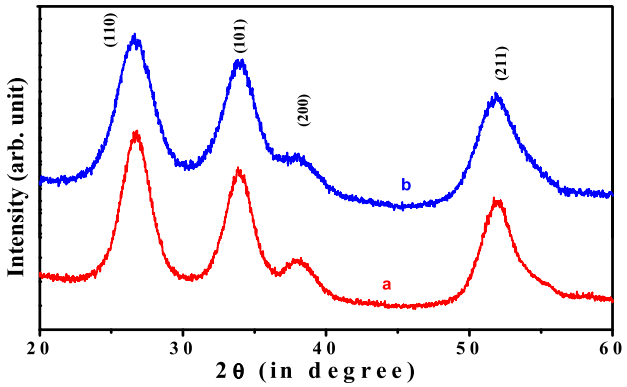

Fig. 2. (a) XRD patterns of the SnO_2 QDs and (b) XRD patterns of six times reused the SnO_2 QDs.

From the low-resolution TEM image of the uncapped SnO_2 QDs as displayed in Fig. 3(a), the size of the QDs is 4 nm±10%. The HRTEM image of uncapped SnO_2 QDs shown in Fig. 3(b) indicates 0.32 nm spacing between two adjacent lattice planes of a QD corresponding to the (110) lattice planes of SnO_2. The low-resolution TEM image as shown in Fig. 4 of the OA capped SnO_2 QDs gives nearly monodisperse QDs of size 2.7 nm±10%. Moreover the calculated sizes of the QDs are in good agreement with that obtained from XRD.

Fig. 5a shows the low-resolution FESEM image of beautifully grown nanoflower structures. The upper and lower insets of the figure show the front view and side view of a single nanoflower, respectively. The front view indicates that each SnO_2 nanoflower is 400 nm in diameter with four almost symmetrical nanopetals of width 100 nm and the side view shows that the nanoflower consists of multiple layers. Fig. 5b shows the low-resolution TEM image of the four flowers, two show side views and another two give front views.

This SnO_2 nanoparticles were then explored as a heterogeneous catalyst for the synthesis of fully substituted pyrano[2,3-*c*]pyrazole derivatives via four-component reaction (Scheme 1).

In order to find the best reaction conditions for the synthesis of pyrano[2,3-*c*]pyrazole derivatives, our introductory explorations focused on the search for a suitable catalyst. Initially, the one pot four-component reaction of phenyl hydrazine (1) (1.0 mmol), ethyl acetoacetate (2) (1.0 mmol), benzaldehyde (3) (1.0 mmol), and malononitrile (4) (1.0 mmol) as the substrates for the model reaction was investigated to establish the feasibility of the strategy and optimize the reaction conditions. The catalytic activities of various nano-metal oxides, nano-ZnO, Fe_3O_4, CuO, SiO_2, Al_2O_3, $ZnFe_2O_4$, SnO_2 were evaluated for this model reaction (Table 1, entries 2–8). From Table 1, it was evident that these nanosized particles successfully promoted this four-component reaction with high yields. Among the catalysts assessed, uncapped SnO_2 QDs showed superior catalytic activity and produced the best yield of the targeted pyrano[2,3-*c*]pyrazole derivative (**5a**). It was also noteworthy to mention that in absence of any catalyst the reaction was unable to proceed to give the expected product even after stirring the reaction mixture for about 12 h (Table 1, entry 1) in aqueous medium at room temperature.

In an effort to enhance the capacity of the chosen catalyst candidate we next sought to find the effect of different solvents (H_2O, dioxane, DMSO, CH_3CN, Toluene, and DMF) for the four-component coupling protocol (Table 1, entries 8–13). The best results in terms of yields were obtained using water as reaction medium compared to these conventional organic solvents. We next made a study on the effect of the catalyst loading in model reaction. We found that the yields were obviously affected by the amount of nano-SnO_2 loaded. It was found that 8 mol % of nano-SnO_2 was sufficient enough to afford **5a** with 93% isolated yield (Table 1, entry 15). The yield remained unaffected when the catalyst loading was increased to 10 mol % (Table 1, entry 8). However, the yield was decreased when the catalyst loading was reduced (Table 1, entry 14).

Our continuing investigations showed that among the three different types of screened SnO_2 nanoparticles (uncapped SnO_2 QDs, OA capped SnO_2 QDs, SnO_2 nanoflower) uncapped SnO_2 QDs showed maximum catalytic activity for the synthesis of pyrano[2,3-*c*]pyrazole, **5a** (Table 2). The 3.9 nm-sized catalyst (uncapped SnO_2 QDs) displayed maximum Lewis acidic character of Sn^{4+} because of its high surface area and, which in turn caused a large access of Sn^{4+} for the four-component coupling reaction. In case of OA capped SnO_2 QDs, the active metal ion of the catalyst (Sn^{4+}) could not approach to the reaction center due to the presence of oleic acid capping at the surface of SnO_2. The higher catalytic activity of SnO_2 nanoflower was probably due to its flower like morphology (causing higher surface area). These observations indirectly attest that Sn^{4+} was the active species of the catalyst.