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Short communication

A facile, efficacious and reusable Sm_2O_3/ZrO_2 catalyst for the novel synthesis of functionalized 1,4-dihydropyridine derivatives

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ABSTRACT

An efficient four component/one-pot protocol was developed for synthesis of novel functionalized 1,4-dihydropyridines at room temperature by a reaction of malononitrile, substituted aldehydes, dimethylacetylenedicarboxylate and 4-fluoroaniline in ethanol and using Sm_2O_3/ZrO_2 as catalyst. All reactions were completed in <20 min. The structures of all the new compounds were confirmed by different spectral analyses. The catalyst, Sm_2O_3/ZrO_2 was synthesized and characterized by various techniques including powder X-ray diffraction, N_2 adsorption/desorption, scanning electron microscopy, and transmission electron microscopy analysis. The key advantages of this process are good to high yields (87 to 96%), short reaction times, easy work-up, reusability and no chromatographic purification.

1. Introduction

Any improvement in an extensively used environmentally benign technique for synthesis of organics, will be a challenge for all researchers [1]. One of the effective tools used to merge fiscal and environmental benefits is the multicomponent reaction (MCR) strategy; which comprises two or more synthesis steps that are carried out without isolation of any intermediates, thus enhancing cost-effectiveness and energy savings [2,3]. MCRs have proved to be very powerful and efficient bond-forming techniques in heterocyclic and medicinal chemistry in the context of green approaches [4,5]. These protocols are also very flexible and atom economic in nature, and proceed through a sequence of reaction equilibria forming targeted products in high yields [6]. Among other reaction conditions, the nature of the catalyst is very important in determining yield, selectivity, solvents and general applicability [7]. Thus, the development of less expensive, mild, reusable, and specific catalysts for MCRs will remain a task and a matter of interest.

One of the promising green chemistry approaches is to replace conservative procedures which demand toxic and/or hazardous reagents, with atom-efficient benign alternatives [8]. Many of the conventional synthesis reactions are time consuming. Therefore catalysts are sought for to make them more efficient and to reduce the reaction times. Heterogeneous catalysts have also attracted a lot of attention in heterocyclic synthesis because of numerous advantages which include easy handling, environmental compatibility, non-corrosiveness, saving energy, and ease of product separation compared with typical hazardous and corrosive homogeneous counterparts [8–9]. The surface properties of a catalyst become crucial to enhance its effectiveness in selectivity [10].

Heterocyclic structures are commonly used vital templates for the design and improvement of potent and specific biologically active agents [11,12]. Pyridines and their derivatives, in particular form an important class of heterocyclic compounds, owing to their properties they are desired in many fields such as natural products, pharmaceuticals and functional materials [13]. They show a wide range of biological properties, such as antibacterial, antioxidant, antiviral, anticancer, anticonvulsant and antihypertension activity [14–19]. Pyridines are also known for their anti-inflammatory activity [20], as antagonists, inhibitors [21], and as herbicides and insecticidal agents [22,23]. Literature survey reveals that only four synthetic methods have been reported for different 1,4-dihydropyridine derivatives. While three protocols employed catalysts, triethylamine (TEA), sodium hydroxide and polyethylene glycol (PEG-600), the fourth used microwave irradiation [24–27]. These procedures demanded either costly reagents, tedious handling processes, high temperature and/or harsh reaction conditions. The product yields were <92%, while the reaction times ranged between 2 to 10 h. Thus, development of improved green protocols for organic synthesis and evaluation of the novel class of *N*-containing heterocyclic molecules were our focus. In continuation of our research toward the improvement of new green routes for the synthesis of heterocyclic compounds using green reaction methods with reusable catalysts [28–30],

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we have reported various heterocyclic molecules with biologically active potential [31–34].

Samarium salts are commonly used as catalysts and their effectiveness can be endorsed by their moderate to low toxicity, ease of handling, and low-cost. However, their use in stoichiometric amounts is often an impediment with economic and environmental aspects. Therefore, the use of a heterogenized version of samarium salts is a preferable choice for green organic transformations.

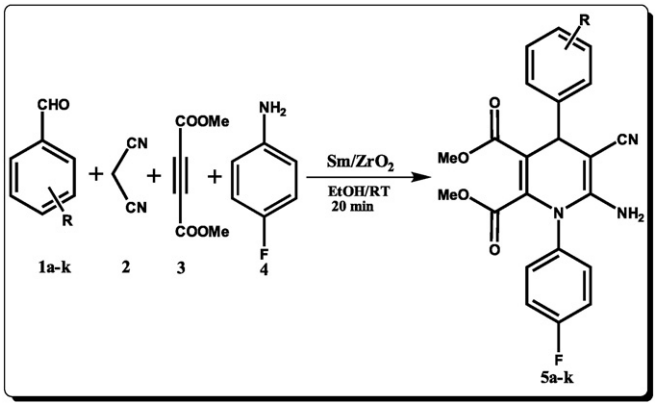
ZrO_2 is a fascinating support material and its phases (cubic, tetragonal, etc.) can be stabilized down at room temperature by the amount of dopant added, which can promote the activity of the supported metal catalysts. ZrO_2 has good redox and chemical stability across acid and alkaline pH, to be used as an acid-based bi-functional catalyst. Zirconia is extensively used as a support due to its high specific surface area and greater flexibility. Zirconia supported active species in a well-dispersed form provide a suitable environment for various applications [3].

In this communication, the scope of Sm_2O_3 supported on zirconia as a novel recyclable heterogeneous catalyst for efficient, convenient and facile green synthesis of novel highly functionalized 1,4-dihydropyridine derivatives through the one-pot reaction of malononitrile, substituted aldehydes, dimethyl acetylenedicarboxylate and 4-fluoroaniline at room temperature with ethanol as solvent was described. We are not aware of reports in literature on the use of samarium doped ZrO_2 as catalyst for the synthesis of functionalized 1,4-dihydropyridines.

2. Experimental section

2.1. General synthesis of functionalized 1,4-dihydropyridine derivatives (5a–5k)

Initially the mixture of substituted aldehyde (1.0 mmol), malononitrile (1.1 mmol) and samarium supported ZrO_2 catalyst (30 mg) in absolute ethanol (5 mL) solution was stirred at room temperature (RT) for 5 min. Subsequently, a solution of dimethylacetylenedicarboxylate (1.0 mmol) and 4-fluoroaniline (1.0 mmol) in absolute ethanol (5 mL) was added to this mixture and stirring continued at RT for another 15 min. The reaction progress was monitored by TLC. After completion of the reaction, the catalyst was filtered, and the solvent was evaporated to obtain the crude product. The crude was recrystallized by ethanol to obtain pure product (Scheme 1). The novel products obtained were characterized by using various spectral analyses. Catalyst preparation and details of catalyst characterization are included in the Supporting information (S1). The experimental section and target compound characterization data (5a–5k) are described in the Supporting information (S2).



Scheme 1. Synthesis of functionalized 1,4-dihydropyridine derivatives.

3. Results and discussion

3.1. Textural properties and chemical composition

The texture of the prepared catalysts was assessed by physisorption analysis. Fig. 1 shows an isotherm of 2% Sm_2O_3/ZrO_2 catalyst in an N_2 adsorption–desorption study and all synthesized samples exhibited type IV isotherms. The type IV isotherm is related to the mesoporous structure of the prepared catalysts and structural mesopores play a significant role on the supported metal dispersion and its activity. The 2% Sm_2O_3/ZrO_2 material showed a surface area of 145 $m^2\ g^{-1}$ with a pore volume of 0.24 $cm^3\ g^{-1}$. The elemental analysis showed the presence of an anticipated amount of samarium (1.98 wt.%) in the catalyst.

3.2. Scanning electron microscopy and transmission electron microscopy analysis

Fig. 2a displays a SEM image of the 2% Sm_2O_3/ZrO_2 catalyst. It illustrates randomly distributed spherical, oval and elongated stick or rod shaped metal oxide particles. Agglomeration of particles leading to formation of larger particles as a result was observed. The figure also reveals that the catalyst has a consistent morphology and clusters of metal particles on the support surface. The rod-like particles of Sm_2O_3 approximately 50–150 nm in length and <20 nm in width were observed on the zirconia surface. The SEM–EDX spectrum (Fig. 2d) shows the presence of Sm and Zr on the surface of the catalyst. For the 1% Sm_2O_3/ZrO_2 catalyst loading the particles are small and have a high surface area, but had less number of active sites relative to the 2% Sm_2O_3/ZrO_2. With the 4% Sm_2O_3/ZrO_2 loading, the samaria particles are visibly larger, hence had a smaller surface area, when compared to the 2% loading and thus slightly lower yield (Supporting information — S3).

TEM results showed the presence of differently shaped metal oxide particles (Fig. 3). This indicates all particles are well distributed throughout the sample. The TEM micrograph showed that the catalyst prepared on a ZrO_2 support has good dispersion of Sm_2O_3 with the average particle size distribution in the range of 20–40 nm.

3.3. X-ray diffraction study

An X-ray diffractogram of the prepared catalyst is depicted in Fig. 4. The XRD study reveals the presence of a crystalline ZrO_2 phase (JCPDS 37-1484) with an Sm_2O_3 phase (JCPDS 42-1461). The intense and sharp peak at ~28° corresponds to the (222) plane of Sm_2O_3 and also

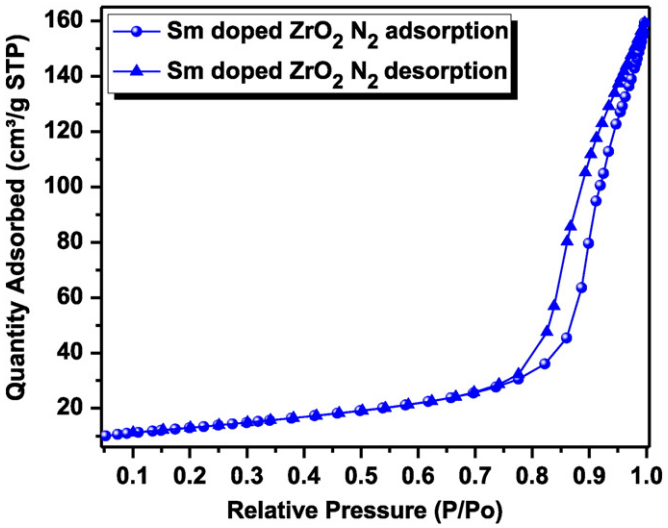


Fig. 1. N_2 adsorption–desorption isotherms of 2% Sm_2O_3/ZrO_2 catalyst.