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V_2O_5/ZrO_2 as an efficient reusable catalyst for the facile, green, one-pot synthesis of novel functionalized 1,4-dihydropyridine derivatives

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ABSTRACT

A practical method is designated for the one-pot, multicomponent synthesis of 1,4-dihydropyridine derivatives by cyclo-condensation of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, acetoacetanilide and ammonium acetate. Using ethanol as solvent and V_2O_5/ZrO_2 as heterogeneous catalyst, ten novel 1,4-dihydropyridines were synthesized at room temperature (Reaction time < 20 min). XRD, TEM, SEM and BET analysis were used to characterize the catalyst materials. Simple work-up, green solvent, short reaction times, moderate reaction conditions and excellent yields (90–96%) are the attractive features of this novel approach. With no need of chromatographic separation, the reaction product is easily separable in pure form.

1. Introduction

In recent years, mixed oxides and bimetallic compounds were most extensively explored class of solid catalyst materials, either as active phases or as supports [1–3]. The presence of two or more metal cations in mixed oxides provide an opportunity to control and design the morphologies and properties of the materials [4,5]. In general, the mixed oxides are crystalline [6,7], but the nature depends on calcination temperatures as at moderate calcination, some phases may remain amorphous [8]. Due to their varied characteristics and composition, the benefits accrued from the crystalline mixed oxides are many [9]. Literature shows the use of numerous mixed oxides and bimetallic materials in various applications, as adsorbents, catalysts or photocatalysts in water treatment and as catalysts in value added conversions [10–15]. In the recent past, zirconium oxide (ZrO_2) received significant attention due to its amphoteric nature, as it can act as bi-functional material [16]. High specific surface area, better flexibility, active metal centre, thermal satiability and cost-effectiveness make it appropriate choice over wide-ranging temperatures [17]. Literature reports show its usage both as active material and support of mixed catalysts in synthetic chemistry [18]. Zirconia as catalyst has been employed in many organic shift reactions, such as epoxidation [19], isomerization [20], alkylation [21], C-C bond formation [22], to mention a few. The scope for dispersion of active material as nanoparticles on zirconia makes it ideal support material for various applications. Vanadia is well known material as catalyst, alone or doped on different supports. It is used in variety reactions including oxidations, reductions, and many synthetic transformation reactions [23]. In the current study, the synergic properties of Zr plus V as catalyst are explored and its activity as bimetallic catalyst is optimized.

Classical organic chemistry is in pursuit of opt environmentally friendly synthetic methodologies for chemical, pharmaceutical industries [24]. Main principles of green chemistry are to create environmentally benign products with high atom efficiency, prevention of waste, use of nontoxic materials and use of catalysts rather than stoichiometric reagents [25]. In order to fulfil the green chemistry principles, carrying a reaction in heterogeneous environment makes the route more economical and eco-friendly [26], as recovery and reusability of heterogeneous catalysts is simple [27]. In contrast to multi-step reactions, multicomponent reactions (MCRs) can synthesize complex molecules in one-pot with good atom-economy, selectivity and in high yields [28], providing a quick access to new organic molecules [28–30]. The combination of MCR approach with use heterogeneous catalyst is most effective option in synthetic chemistry [31,32].

Heterocyclic compounds are key moieties in many bioactive pharmaceuticals, medicinal, computational and natural products, which inspire synthetic chemist towards the synthesis of larger and novel molecules. The 1,4-dihydropyridine nucleus is one of the most attractive heterocyclic framework that is present in many drugs and pharmaceuticals. The dihydropyridine scaffold has received greater attention due to its breadth of biological activities, ranging from cardiovascular disease [33], anti-cancer [34], anti-microbial [35], anti-oxidant [36], anti-coagulant [37], anti-leishmanial and anti-trypanosomal [38], anti-tubercular agents [39], HIV-1 protease inhibitors [40] to antioxidant activities [41]. Due their pecuniary and scientific relevance, many synthetic methods were described in literature for

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production of different dihydropyridines. The Hantzsch synthesis is the well-known technique for the preparation of 1,4-dihydropyridines [42]. Some of such methods employed I_2 [43], TMSI [44], Et_3N [45], polyethylene glycol (PEG-600) [46] nano-γ-Fe_2O_3-SO3H [47], [PVPH]ClO_4 [48], L-proline [49], NaOH [50] etc., as catalysts. Many those reactions either demand high energy and expensive reagents or punitive reaction conditions and long reaction times or give low yields. Consequently, continued pursuit for improved and greener approaches for the synthesis of dihydropyridine derivatives is paramount. To the best of our knowledge, there are no reports on the use of vanadia loaded zirconia as a catalyst for the synthesis of dihydropyridines via multi-component reactions.

Encouraged by the promising results in developing synthetic methods for varied heterocyclic molecules [51–58], we recently, we have reported different approaches for preparation of various medicinally interesting heterocyclic protocols [59–64]. In this communication, we report the synthesis and characterization of vanadia doped zirconia and its versatility as catalyst in one-pot synthesis of novel functionalized dihydropyridine derivatives using four-component reaction and ethanol as solvent at room temperature.

2. Experimental

2.1. Catalyst preparation

Using simple wet-impregnation technique, materials with different loading of vanadia on zirconia (1, 2.5, & 5 wt% of V on Zr) were prepared by [65–67]. To prepare the materials, a mixture of zirconia, ZrO_2 (3 g), (Alfa Aesar) and appropriate amount (wt%) of vanadium (V) oxide, 99.9% [V_2O_5 (Alfa Aesar)] in distilled water (100–150 mL) were used. The reaction mixture was stirred at room temperature (RT) for 6 h, followed by filtering the resultant slurry under vacuum. The material was dried for 5 h in an oven at 120–150 °C and calcined at 450 °C for 5 h in the presence of air, to obtain different wt% of V_2O_5/ZrO_2 catalysts.

2.2. General procedure for the synthesis of dihydropyridine derivatives

In initial study, equimolar mixture of 2-methoxy benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), acetoacetanilide (1 mmol) and ammonium acetate (1 mmol) were stirred at room temperature in a 5 mL of ethanol as a green reaction medium followed by addition of catalyst (60 mg). Under continuous stirred conditions at RT (15 min), TLC monitored the reaction progress (Scheme 1). After the completion of the reaction, catalyst was filtered and the crude product was extracted by solvent extraction using ethyl acetate, followed by evaporation of solvent under vacuum to recover the product. Ethanol was used to dissolve the crude product and to obtain pure compounds (**5a-j**). Reaction products from every reaction were characterized by analysis using ^1H NMR, ^{15}N NMR, ^{13}C NMR, HRMS and FT-IR. The related details and spectra are assimilated to the supplementary information file.

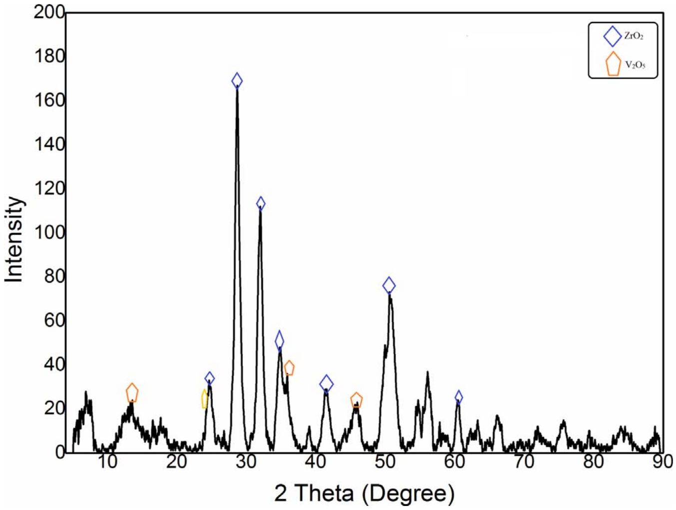


Fig. 1. Powder X-ray diffractogram of 2.5% V_2O_5/ZrO_2 catalyst.

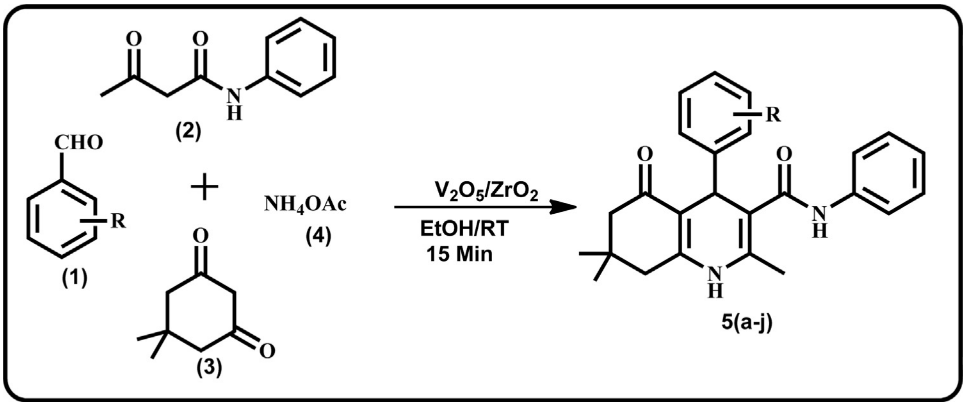
3. Results and discussion

3.1. Powder X-ray diffractogram (XRD)

The phase and crystallinity of the prepared catalyst was analyzed by X-ray diffraction studies. XRD patterns of calcinated 2.5% V_2O_5/ZrO_2 catalyst is shown in Fig. 1. The distinctive X-ray diffraction patterns at 2θ = 24.8°, 28.6°, 31.9°, 34.7°, 41.3°, 50.8° and 60.4° of ZrO_2 (JCPDS 37-1484) recognized by an assessment with literature records and approve that the particles are polycrystalline structure [68]. As can be perceived from the image, intensive peaks of V_2O_5, the diffractions at 2θ = 17.29°, 26.48°, 36.17°, and 49.79° (JCPDS41-1426) [69]. The average crystallite size of the sample was calculated by using Scherrer equation. It was about 7.6 nm, based on maximum intensity diffraction peak of V_2O_5/ZrO_2.

3.2. SEM and TEM analysis

Fig. 2a reveals a distinctive SEM surface morphology micrograph of the catalytic sample vanadia loaded on zirconia material. On keen examination of SEM micrograph the catalyst material displayed and settled as a large irregular shapes. It demonstrates that the agglomeration state of the zirconia units with vanadia due to its homogenous dispersion. The micrographs of SEM–EDX approved the similar dis-



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