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CeO_2/ZrO_2 as green catalyst for one-pot synthesis of new pyrano[2,3-*c*]-pyrazoles

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Abstract Ceria-doped zirconia (CeO_2/ZrO_2)-catalyzed synthesis of pyrano[2,3-*c*]-pyrazoles via four-component reaction of malononitrile, hydrazine hydrate, ethyl acetoacetate, and substituted aldehydes is described. The catalytic material CeO_2/ZrO_2 was prepared and characterized by different techniques including powder X-ray diffraction (P-XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and Brunauer–Emmett–Teller (BET) analysis. Twelve new pyrano[2,3-*c*]-pyrazole derivatives (**5a**–**k**) were synthesized in good to excellent yield (89–98%) and their structures established and confirmed by different spectroscopic methods, viz. ^{1}H, ^{13}C, and ^{15}N nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS). The environmental benefits of the process include excellent yield, short reaction time, simple work-up, elimination of toxic solvents, and avoidance of chromatographic separation. The CeO_2/ZrO_2 catalyst enables a facile synthesis procedure, is inexpensive, and has good reusability (at least six times).

Keywords Multicomponent reaction · Green synthesis · Pyrazoles · One-pot reaction · CeO_2

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Introduction

Multicomponent reactions (MCRs) are assimilation reactions in which three or more starting materials react with each other simultaneously to form a desired product [1]. This approach has been identified as a potent method for use in drug discovery due to the generation of essential target compounds [1–3]. MCR approaches have numerous significant benefits over classical, stepwise procedures, leading to formation of several bonds in a single step without the need for intermediate separations or purifications [4]. Thus, MCRs accomplish their goals in an efficient, fast, and environmentally benign manner with substantial time and cost savings [2, 3].

Development of heterogeneous catalysts for synthesis of heterocyclic compounds has become a key issue for researchers [5]. Heterogeneous materials as catalysts for green organic reactions offer both environmental and economic benefits. Many such materials are easy to recover and recycle, making their use appealing [6–8]. Such recyclable catalysts have numerous benefits such as being amenable to separation from the reaction without difficult work-up as well as offering long life, stability, recyclability, and high selectivity. This reduces waste production, whilst giving high product yields in short reaction times through green procedures [9].

Zirconia (ZrO_2) is an ecofriendly, widely available, and low-cost material [6]. It stands out amongst other metal oxides due to its excellent stability and mechanical properties, which can promote the activity of supported metal catalysts [9, 10]. It has been commonly used due to its substantial chemical and thermal stability, inertness, and high surface area [9–11]. Use of pure zirconia and its composites (with other metals) as catalysts for various organic transformations has been reported in literature [12, 13]. Cerium salts are generally used as dopants, offering advantages including ease of handling, low cost, high stability, and nonhazardous nature [14]. Cerium salts as dopant material are thus an appropriate choice for use in green organic conversions, playing a major role in green catalysis.

Heterocyclics play a vital role in drug discovery, pharmaceutical, agrochemical, and computational fields. Heterocyclic compounds are the main precursors in various clinical applications and play a pivotal role in generation of diverse biological activities [15, 16]. Pyranopyrazoles and their derivatives are important heterocyclic compounds, exhibiting remarkable biological properties including antibacterial, antifungal, antiviral, antitumor, anti-human immunodeficiency virus (HIV), anticonvulsant, antiinflammatory, and antioxidant actions [17–23]. Many pyranopyrazoles are also used as herbicidal and insecticidal agents [24]. Catalysts for synthesis of substituted pyranopyrazole derivatives reported in literature include [ChCl][$ZnCl_2$]$_2$ [25], Amberlyst $A_2$1 [26], per-6-ABCD [27], [$(CH_2)_4SO_3$-HMIM][HSO_4] [28], [DBU][Ac] [29], silicotungstic acid [30], NaOH/microwave [30], [Dsim]$AlCl_4$ [31], L-Proline [32], TEABr [33], and $FeNi_3/SiO_2$/HPGMNP [34], to mention a few. Many of these reports suffer from various limitations and weaknesses, such as use of severe reaction conditions, hazardous organic solvents, costly reagents and catalysts, nonreusability, long reaction time, or low product yield, limiting their scope for use in practical applications. Hence, development of

green protocols for heterocyclic synthesis involving facile and environmentally friendly methods (using green solvents in the reaction and/or work-up method) would be useful and desirable.

In our pursuit to develop efficient, environmentally benign, green approaches for synthesis of different heterocyclic compounds [35–37], we recently reported various synthetic methods for several biologically interesting products [38–42]. We report herein a new approach using CeO_2/ZrO_2 as highly efficient reusable catalyst for synthesis of a series of new pyranopyrazole derivatives by reaction of aromatic aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate at room temperature with ethanol as solvent.

Experimental

Catalyst preparation

A range of supported catalysts with CeO_2/ZrO_2 weight percentages of 1, 5, and 10 wt% were synthesized using the wet impregnation procedure [4, 6]. Each heterogeneous catalyst was prepared from a mixture of zirconia (ZrO_2, 3 g, catalyst support, Alfa Aesar) and an appropriate amount (wt%) of cerium nitrate [$Ce(NO_3)_3$-$6H_2O$ (Alfa Aesar)] in distilled water (50 mL). The reaction mixture was stirred at room temperature (R.T.) for 10 h. The resulting slurry was filtered under vacuum and dried in an oven at 110–120 °C for 5 h, then calcined in presence of air at 450 °C for 5 h to form 1, 5, and 10 wt% CeO_2/ZrO_2 catalysts.

General procedure for synthesis of pyranopyrazole derivatives

In a typical reaction, equimolar ratios of aldehydes (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), and ethyl acetoacetate (1 mmol) were dissolved in ethanol (10 mL) at R.T. followed by addition of CeO_2/ZrO_2 (50 mg) as catalyst. The reaction mixture was stirred continuously for 15 min at R.T. (Scheme 1) using a magnetic stirrer. The progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was then filtered, and the filtrate subsequently extracted with ethyl acetate and evaporated under reduced pressure to obtain crude product, which was then purified with ethanol to afford pure product **5a–k**. The reaction products were identified and validated by various spectral techniques (^1H, ^{15}N, and ^{13}C-NMR and HRMS). Spectral instrumentation details are incorporated in the Electronic Supplementary Material (SI-II), along with details on some of the compounds.

*6-Amino-4-(2,4,6-trimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5a**)* ^1H NMR (400 MHz, DMSO-d_6) $\delta = 1.79$ (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.12 (s, 1H, CH), 6.259 (s, 2H, ArH), 6.69 (s, 2H, NH_2), 12.29 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 9.66, 25.39, 51.50, 55.01, 55.42, 55.63, 91.07, 112.27, 154.35, 159.53, 160.57, 161.22; HRMS of $[C_{17}H_{18}N_4O_3 + H]^+$ (*m*/*z*): 343.1141; Calcd.: 343.1141.

*6-Amino-4-(2-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5b**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.76$ (s, 3H, CH_3), 5.06 (s, 1H, CH), 6.91 (s, 2H, NH_2), 7.05 (t, $J = 8$ Hz, 1H, ArH), 7.25–7.31 (m, 2H, ArH), 7.41 (dd, $J = 7.8$ Hz, 1.08 Hz, 1H, ArH) 12.11 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 161.12, 154.95, 152.15, 146.19, 137.29, 135.09, 123.98, 120.97, 120.72, 111.06, 97.75, 60.22, 56.66, 55.48, 30.32, 9.42; HRMS of $[C_{14}H_{11}ClN_4O_3 + H]^+$ (*m/z*): 287.1340; Calcd.: 287.1344.

*6-Amino-4-(2-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5c**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.79$ (s, 3H, CH_3), 4.86 (s, 1H, CH), 6.90 (s, 2H, NH_2), 6.90–7.29 (m, 4H, ArH), 12.10 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.35, 30.02, 55.53, 96.59, 115.37, 120.53, 124.69, 128.87, 129.76, 130.76, 135.72, 154.87, 158.69, 161.28; HRMS of $[C_{14}H_{11}FN_4O_3 + H]^+$ (*m/z*): 271.0623; Calcd.: 271.0626.

*6-Amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5d**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.81$ (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.49 (s, 1H, CH), 6.55 (dd, $J = 8.12$ Hz, 1.84 Hz, 1H, ArH), 6.71 (t, $J = 108.8$ Hz, 2H, ArH), 6.76 (s, 2H, NH_2), 8.82 (s, 1H, OH), 12.03 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.79, 35.79, 55.41, 57.42, 97.67, 111.19, 111.72, 119.46, 120.81, 135.63, 136.86, 147.53, 148.51, 154.68, 160.72; HRMS of $[C_{15}H_{14}N_4O_3 + H]^+$ (*m/z*): 299.0786; Calcd.: 299.0800.

*6-Amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5e**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.80$ (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.42 (s, 1H, CH), 6.52 (s, 1H, ArH), 6.58–6.60 (m, 1H ArH), 6.76 (s, 2H, NH_2), 6.82 (d, $J = 8.2$ Hz, 1H, ArH), 8.88 (s, 1H, OH), 12.04 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.70, 35.63, 57.70, 97.70, 111.80, 114.45, 118.05, 120.80, 135.54, 137.08, 146.45, 154.71, 160.60; HRMS of $[C_{15}H_{14}N_4O_3 + H]^+$ (*m/z*): 299.0732; Calcd.: 299.0732.

*6-Amino-4-(4-ethylphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5f**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.16$ (t, $J = 7.6$ Hz, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.58 (dd, $J = 15.24$ Hz, 7.56 Hz, 2H, CH_2), 4.54 (s, 1H, CH), 6.59 (dd, $J = 7.52$ Hz, 1.28 Hz, 1H, ArH), 6.80 (s, 2H, NH_2), 6.89 (d, $J = 6.8$ Hz, 1H, ArH), 6.99 (t, $J = 7.96$ Hz, 1H, ArH), 11.99 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.73, 15.39, 27.68, 35.81, 57.33, 97.72, 120.82, 127.05, 127.31, 127.73, 128.31, 128.38, 135.50, 141.72, 141.96, 154.72, 160.78; HRMS of $[C_{16}H_{16}N_4O + H]^+$ (*m/z*): 281.1040; Calcd.: 281.1039.

*6-Amino-4-(4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5g**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.78$ (s, 3H, CH_3), 4.62 (s, 1H, CH), 6.86 (s, 2H, NH_2), 7.13–7.19 (m, 4H, ArH), 12.10 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.67, 35.41, 57.10, 97.46, 115.01, 115.22, 129.25, 129.33, 135.59, 160.79; HRMS of $[C_{14}H_{11}FN_4O + H]^+$ (*m/z*): 271.0835; Calcd.: 271.0839.

*6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5h**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.78$ (s, 3H, CH_3), 4.46 (s, 1H,

CH), 6.68 (d, $J = 8.4$ Hz, 2H, ArH), 6.74 (s, 2H, NH_2), 6.94 (d, $J = 8.4$ Hz, 2H, ArH), 9.26 (s, 1H, OH), 12.02 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.70, 35.45, 57.81, 98.03, 115.07, 120.84, 128.38, 134.72, 135.49, 154.72, 155.97, 160.59; HRMS of $[C_{14}H_{12}N_4O_2 + H]^+$ (*m*/*z*): 269.0835; Calcd.: 269.0839.

*6-Amino-4-(4-(dimethylamino)phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5i**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.78$ (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$), 4.45 (s, 1H, CH), 6.65 (d, $J = 8.56$ Hz, 2H, ArH), 6.73 (s, 2H, NH_2), 6.96 (d, $J = 8.56$ Hz, 2H, ArH), 12.02 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.74, 35.34, 57.98, 98.15, 112.28, 120.92, 127.98, 129.45, 132.01, 135.44, 149.19, 154.76, 160.52.

*6-Amino-4-(2,3-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5j**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.76$ (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.82 (s, 1H, CH), 6.59 (dd, $J = 7.52$ Hz, 1.28 Hz, 1H, ArH), 6.80 (s, 2H, NH_2), 6.89 (d, $J = 6.8$ Hz, 1H, ArH), 6.99 (t, $J = 7.96$ Hz, 1H, ArH), 11.99 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.42, 30.32, 55.48, 56.66, 60.22, 97.75, 111.06, 120.97, 123.98, 135.09, 137.29, 146.19, 152.15, 154.95, 161.12.

*6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5k**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.82$ (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.54 (s, 1H, CH), 6.69 (dd, $J = 7.52$ Hz, 1.96 Hz, 1H, ArH), 6.75 (d, $J = 1.96$ Hz, 1H, ArH), 6.80 (s, 1H, NH_2), 6.88 (d, $J = 8.28$ Hz, 1H, ArH), 12.07 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 9.79, 35.79, 55.41, 57.42, 97.67, 111.19, 111.72, 119.46, 120.81, 135.86, 147.53, 148.51, 154.68, 160.72; HRMS of $[C_{16}H_{16}N_4O_3 + H]^+$ (*m*/*z*): 313.0952; Calcd.: 313.0957.

*6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5l**)* ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.77$ (s, 3H, CH_3), 4.58 (s, 1H, CH), 6.84 (s, 2H, NH_2), 7.15–7.23 (m, 5H, ArH), 12.09 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): 9.69, 36.22, 57.22, 97.61, 126.69, 127.42, 127.65, 128.39, 135.57, 144.40, 154.73, 160.84; HRMS of $[C_{14}H_{14}N_4O + H]^+$ (*m*/*z*): 253.0953; Calcd.: 299.0953.

Results and discussion

BET surface area and elemental (ICP) analysis

The porosity of the synthesized catalyst was determined by N_2 adsorption–desorption analysis. The N_2 physisorption isotherms were determined for the 5% ceria supported on zirconia catalyst. The N_2 adsorption–desorption isotherms showed a characteristic hysteresis loop of a type IV adsorption isotherm, indicating mesoporous nature of the catalyst (Fig. 1). The mesoporous structure was confirmed by the pore size values in the mesoporous region for the samples (3 nm < pore size < 50 nm) and the p/p^0 isotherm range of 0.76–0.94. The prepared catalyst showed specific surface area of 56 m^2 g^{-1} with pore volume of 0.212 cc g^{-1}.

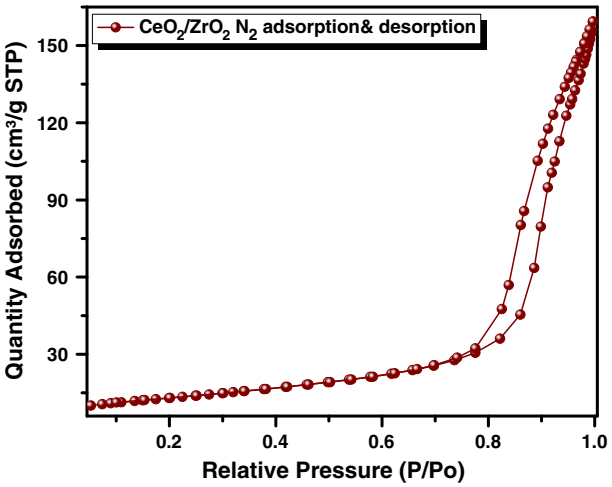

Fig. 1 BET surface area results for 5% CeO_2/ZrO_2 catalyst

Inductively coupled plasma (ICP) analysis results confirmed the presence of the anticipated amount of CeO_2 in the catalyst (4.96 mol%).

TEM analysis

TEM analysis provided more structural information on the catalyst. Figure 2 shows a distinctive TEM image of CeO_2 supported on ZrO_2, showing black ceria particles with irregular cube-like shape and particle dimension ranging between 20 and 28 nm, and zirconia as white globular-shape particles. No drastic change in the morphology of the catalyst was noticed after use.

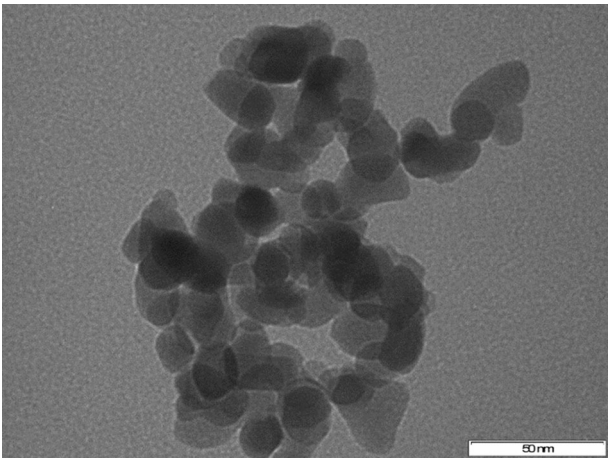

Fig. 2 TEM micrograph of 5% CeO_2/ZrO_2 catalyst

SEM analysis

Figure 3a exhibits a representative SEM surface morphology micrograph of the sample of CeO_2 on ZrO_2. A few large cubic sheet asymmetrical silhouettes are observed in the SEM image of CeO_2/ZrO_2, revealing the aggregated state of the zirconia particles with ceria. The SEM-EDX analysis confirmed uniform distribution of ceria on the zirconia surface (Fig. 3b). The SEM-EDX results agreed well with the data from ICP elemental analysis. Furthermore, the morphology of the catalyst on SEM images highlighted the crystallinity and homogeneity of the sample.

Powder X-ray diffraction (XRD) analysis

The powder XRD patterns of calcined ceria-doped zirconia are shown in Fig. 4. The diffraction peaks at 2θ values of 28.7°, 33.2°, 47.5°, 56.3°, 59.3°, 69.8°, 76.6°, and

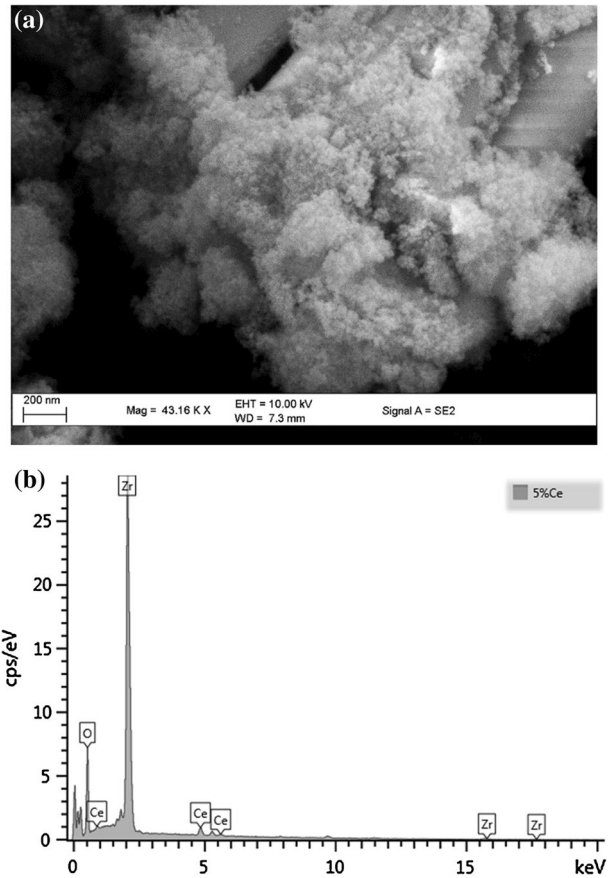

Fig. 3 **a** SEM micrograph and **b** SEM-EDX micrograph of 5% CeO_2/ZrO_2 catalyst

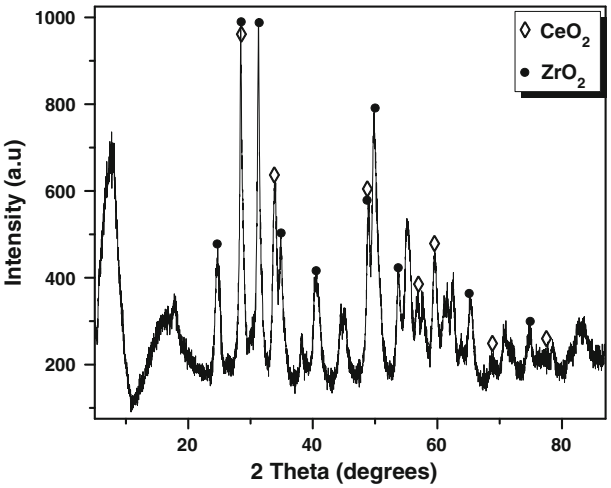

Fig. 4 Powder X-ray diffractogram of 5% CeO_2/ZrO_2 catalyst

79.4° were assigned to ceria. All these diffraction peaks agree with International Centre for Diffraction Data data [Joint Committee on Powder Diffraction Standards (JCPDS) file no. 43-1002]. The 5% CeO_2/ZrO_2 sample exhibited diffraction peaks at 2θ values of 24.7°, 28.8°, 31.8°, 34.6°, 41.4°, 50.9°, and 60.5°, corresponding to ZrO_2 (JCPDS file no. 01-089-9066). The peaks identified in the diffractogram confirm the polycrystalline nature of the material. The average crystallite size of the sample was about 6.9 nm, as obtained from the highest-intensity diffraction peaks of CeO_2/ZrO_2 using the Scherrer equation.

Optimization procedure

A model reaction with benzaldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1.2 mmol), and ethyl acetoacetate (1 mmol) as reactants was investigated in detail under varied conditions, i.e., absence and presence of different catalysts and using various solvents and temperature conditions. First, the reaction was studied without catalyst or solvent at both R.T. and reflux conditions, showing no reaction even after 10 h (Table 1, entries 1 and 2). When the reaction was carried out with various basic catalysts such as triethylamine (TEA), Na_2CO_3, pyridine, and Na_2S and with ethanol as solvent, yield of product was low, even after 6 h (Table 1, entries 3–6). Then, the reaction was examined in ethanol condition at R.T. and in the presence of different acidic catalysts such as AcOH, trifluoroacetic acid (TFA), and *p*-toluenesulfonic acid (PTSA), but even after 6 h afforded very low product yield (Table 1, entries 7–9). Next, the reaction was tried in presence of ionic liquids, L-proline or $(Bmim)BF_4$, with moderate product yield at R.T. conditions (Table 1, entries 10 and 11). Further, when pure oxide catalysts, such as Al_2O_3, SiO_2, and ZrO_2, were employed using the same solvent at R.T., the reaction revealed moderate to good yield after 1.5–3.0 h reaction time (Table 1, entries 12–14). Noting the encouraging result with ZrO_2, to enhance the reaction efficiency it was used as

Table 1 Optimization of conditions for model reaction[a]

Entry	Catalyst	Temperature	Time (h)	Yield (%)[b]
1	–	R.T.	10	–
2	–	Reflux	10	–
3	TEA	R.T.	8.0	19
4	Na_2CO_3	R.T.	6.0	27
5	Pyridine	R.T.	7.0	23
6	Na_2S	R.T.	7.5	20
7	AcOH	R.T.	6.5	09
8	TFA	R.T.	7.0	12
9	PTSA	R.T.	7.5	14
10	L-Proline	R.T.	4.5	39
11	$(Bmim)BF_4$	R.T.	5.0	48
12	Al_2O_3	R.T.	3.0	51
13	SiO_2	R.T.	2.5	59
14	ZrO_2	R.T.	1.5	70
15	5% Fe_2O_3/ZrO_2	R.T.	0.75	84
16	5% V_2O_5/ZrO_2	R.T.	0.50	89
17	5% CeO_2/ZrO_2	R.T.	0.25	98
18	1% CeO_2/ZrO_2	R.T.	0.35	90
19	10% CeO_2/ZrO_2	R.T.	0.25	97

[a] All products characterized by ^1H, ^{13}C, and ^{15}N NMR and HRMS spectral analysis

[b] Isolated yield

– No reaction

support for different metal oxides. As such, Fe_2O_3/ZrO_2, V/ZrO_2, and CeO_2/ZrO_2 composites were prepared and screened for activity. The mixed oxide catalytic reactions afforded very good to excellent yield (84–98%) within 45 min in ethanol at R.T. (Table 1, entries 15–17). In particular, CeO_2/ZrO_2 as catalyst recorded excellent yield (98%) of pyranopyrazoles in 15 min. Furthermore, use of 1% CeO_2/ZrO_2 catalyst yielded 90% product in 35 min in ethanol solvent (Table 1, entry 18). A further increase of the metal loading (10%) led to slightly decreased yield (97%) (Table 1, entry 19). Given these impressive results, CeO_2/ZrO_2 was chosen as the ideal catalyst for further study.

Next, to evaluate the influence of the quantity of catalyst on the synthesis of pyrano [2,3-*c*]pyrazoles, the reaction of hydrazine hydrate, malononitrile, ethyl acetoacetate, and benzaldehyde was studied using different amounts (10, 30, 50, 70, 90 mg) of CeO_2/ZrO_2. The 50 mg amount of catalyst proved optimal to complete the reaction in terms of yield and reaction time. Increased amount of catalyst did not improve either the yield or reaction time (Table 2). However, decrease in the quantity of catalyst to <50 mg affected the product yield, reducing it to 88% (Table 2). Thus, 50 mg of CeO_2/ZrO_2 at R.T. with ethanol as solvent was identified as the optimum reaction condition.

When the efficiency using different polar and nonpolar solvents was investigated, ethanol as solvent was found to be crucial for the reaction (Table 3). Under otherwise comparable conditions, the CeO_2/ZrO_2-catalyzed reaction in presence of relatively nonpolar solvents such as *n*-hexane, 1,4-dioxane, and toluene gave trivial

Table 2 Optimization of amount of 5% CeO_2/ZrO_2 as catalyst in model reaction[a]

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	10	45	88
2	30	35	92
3	50	15	98
4	70	20	97
5	90	15	94

[a] Reaction conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1.1 mmol), benzaldehyde (1 mmol), catalyst, and ethanol (10 mL) as solvent, stirred at room temperature

Table 3 Optimization of solvent for synthesis of pyrano[2,3-*c*]pyrazole derivatives using 5% CeO_2/ZrO_2 catalyst

Entry	Solvent	Yield (%)
1	*n*-Hexane	9
2	Toluene	13
3	1,4-Dioxane	10
4	CH_3CN	34
5	DMF	37
6	Ethanol	78
7	Methanol	69
8	Isopropanol	71

[a] Reaction conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1.1 mmol), benzaldehyde (1 mmol), catalyst (50 mg), and solvent (10 mL), stirred at room temperature

yields even after protracted reaction time (Table 3, entries 1–3). Even with polar aprotic solvents such as CH_3CN and dimethylformamide (DMF), the reaction yield was low (Table 3, entries 4 and 5). Although good results were also obtained when polar solvents CH_3OH, C_2H_5OH, and isopropanol were used (Table 3, entries 6–8), based on criteria such as reaction time, green nature, cost-effectiveness, and excellent yield, ethanol proved to be superior and the best solvent for the reaction.

CeO_2/ZrO_2 could catalyze synthesis of pyrano[2,3-*c*]pyrazole derivatives by facile one-pot reaction with excellent yields. Under the optimal reaction conditions, the flexibility and applicability of the protocol were confirmed by using a variety of other aromatic aldehydes instead of benzaldehyde. Convincingly, irrespective of use of aldehydes possessing different electron-withdrawing or electron-releasing substituents in *ortho*, *meta*, and/or *para* positions on the aryl ring, all the reactions gave impressive results, providing respective pyrano[2,3-*c*]pyrazole derivatives in very good to excellent yield (Table 4). All reaction products were characterized and their structures confirmed by ^{1}H, ^{15}N, and ^{13}C NMR and HRMS spectral data (Electronic Supplementary Material).

Table 4 Synthesis of pyrano[2,3-*c*]pyrazoles using 5% CeO_2/ZrO_2 catalyst

Entry	R	Product	Yield (%)	M.p. (°C)	Lit. m.p. (°C)
1	2,4,6-$(OMe)_3$	**5a**	92	227–228	–
2	2-Cl	**5e**	90	145–147	145–146 [27]
3	2-F	**5f**	91	258–260	–
4	3-OMe, 4-OH	**5d**	90	236–237	–
5	3-OH, 4-OMe	**5e**	93	209–211	–
6	4-Et	**5f**	95	241–243	–
7	4-F	**5g**	89	171–172	–
8	4-OH	**5h**	92	210–212	210–211 [27]
9	NN-$(Me)_2$	**5i**	89	162–165	–
10	2,3-$(OMe)_2$	**5j**	94	215–216	–
11	3,4-$(OMe)_2$	**5k**	92	192–193	–
12	H	**5l**	98	167–168	167–169 [27]

– New compounds/no literature available

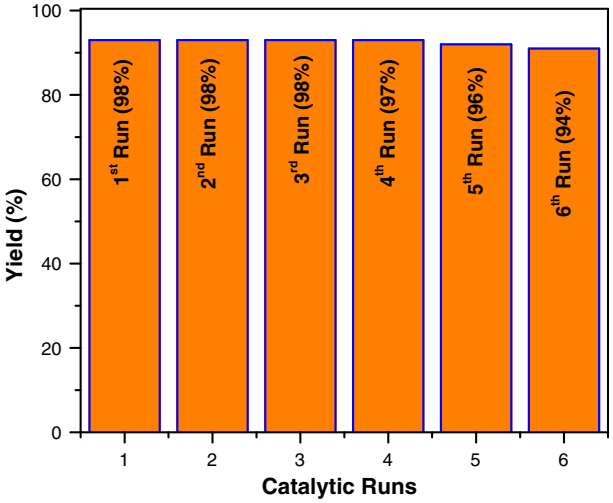

Fig. 5 Recyclability of CeO_2/ZrO_2 catalyst

Reusability of catalyst

Reusability of the synthesized heterogeneous catalyst is an important requirement from the environmental and economic points of view. In heterogeneous catalysis, poisoning of the catalyst and leaching of metal are the main limitations, impacting on the activity of catalyst in further use. To examine the stability of the catalyst, recycling experiments were performed. After each run, the catalyst was separated by filtration. The recovered catalyst was subjected to washing with dichloromethane, dried, and then reused for up to six cycles. No significant loss was observed in the

first five cycles. The catalytic activity of the CeO_2/ZrO_2 decreased by 4% when the recovered catalyst was reused in the sixth cycle (Fig. 5).

Conclusions

We present a simple, robust, efficient, and green multicomponent one-pot method for synthesis of pyrano[2,3-*c*]pyrazole derivatives in good to excellent yield using CeO_2/ZrO_2 as catalyst at R.T. The catalyst proved effective and recyclable for the MCR protocol. The advantages of the approach are excellent yield, cost-effectiveness, easy work-up, environmentally friendly reaction conditions, short reaction time, green solvent, and reusable catalyst. This procedure is promising for diversity-oriented synthesis of potentially bioactive heterocycles.

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