RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A comparative study of the catalytic activity of nanosized oxides in the one-pot synthesis of highly substituted dihydropyridines

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Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A four-component reaction of aromatic aldehydes, ethyl cyanoacetate, arylamines, and dimethyl acetylenedicarboxylate has been achieved in the presence of nanosized oxides (ZnO NPs, CuO NPs, CeO_2 NPs, SnO NPs MgO NPs and CaO NPs) as highly effective heterogeneous catalysts to produce of polysubstituted dihydropyridines. Extraordinarily, the best results obtained in using CeO_2 nanoparticles as an efficient catalyst. This method provides several advantages including mild reaction condition, applicability to wide range of substrates, reusability of the catalyst and little catalyst loading.

1. Introduction

Dihydropyridines represent a common scaffold in numerous bioactive compounds and have a number of pharmacological properties. These compounds are used as calcium-channel-modulating agents, treatment of cardiovascular disease,[1] the high MDR-modulating activity,[2] HIV-1 protease inhibitors,[3] and DNA cutting activity.[4] Compounds with this ring system like tacrine-dihydropyridines have been designed for the treatment of Alzheimer's disease.[5] Some other examples of dihydropyridines such prominent drug molecules as nimodipine, nisoldipine, nitrendipine, amlodipine, nicardipine and nilvadipine utilize with superior bioavailability and a slower onset and prolonged effect. Dihydropyridines have been regarded as significant targets of organic synthesis. Therefore, looking for efficient and simple methods for the synthesis of dihydropyridines is an attractive challenge. Synthesis of bioactive compounds should be facile, flexible, rapid and useful in organic synthesis. Multi-component reactions (MCRs) are very flexible, atom economic in nature, convergent, simple and are usually considered for the development of environmentally benign synthetic methods. Thus, the synthesis polysubstituted dihydropyridines by the multicomponent reactions could enhance their efficiency from economic and ecological points of view. MCRs enhance the efficiency by combining several operational steps without isolation of intermediates or changing the reaction conditions. [6-10] Similarly, nanoparticles have received considerable attraction with the aim of finding significantly applications in organic reactions. In heterogeneous catalysis, the surface and structural understanding is important for the mechanism of the catalyst systems. Nanoparticles exhibit good catalytic activity due to their large surface area and active sites which are mainly responsible for their catalytic activity. Ideally, introducing neat processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions has received significant attention in recent years .[11-14]

Metal oxides represent a broad class of materials that have been researched extensively because of their unique properties and potential applications in diverse fields.[15] During the last decade, nanoparticle metal oxides have received significant attention as efficient catalysts in many organic reactions due to their high surface-to-volume ratio and coordination parts which provide a larger number of active sites per unit area in comparison with their heterogeneous counter sites. Nanocrystalline zinc oxide is one of the broadly used surface materials for many chemical transformations, such as photoactivity and flame-retardancy,[16] semiconductor[17] and antibacterial materials.[18] Tin and tin oxides are usually considered as promising potential anode materials for lithium-ion batteries due to their high theoretical reversible capacities, natural abundance and low cost.[19] Among the heterogeneous basic catalysts, magnesium oxide is a versatile material used as catalyst for several base-catalyzed organic transformations. Magnesium oxide (MgO) as a highly effective heterogeneous base catalyst used as an active catalyst in many reactions including the synthesis of tetrahydrobenzopyran and 3,4-dihydropyrano[c]chromenes[20] and 2-amino-4H-pyrans and 2-amino-5–oxo-5,6,7,8–tetrahydro-4H-chromenes.[21]

Nanocrystalline copper (II) oxides have been used as an efficient heterogeneous catalyst in various organic transformations such

as: C-arylation reactions,[22] cross-coupling reactions,[23] and polyhydroquinoline.[24] Recently, calcium oxide nanoparticles were used as an active catalyst in many chemical transformations including adsorption of Cr (VI) from aqueous solutions,[25] transesterification of sunflower oil,[26] and catalyzed synthesis of highly substituted pyridines.[27] CeO_2 has received much attention because of its many attractive characteristics, such as unique UV absorption ability,[28] ferromagnetism properties [29] and key component of catalyst formulation for the dehydrogenation of ethylbenzene to styrene.[30] Recently, cerium nanoparticles were used as a suitable catalyst in many reactions including synthesis of cyclic ureas,[31] polyhydroquinolines, [32] and 1,4-disubstituted-1,2,3-triazoles.[33] In the present research, CeO_2 nanoparticles were fabricated by a simple co-precipitation method. Compared with other techniques, the co-precipitation method is a simple and attractive procedure for preparation of the CeO_2 nanoparticles. Herein, we report the use of CeO_2 nanoparticles as an efficient catalyst for the preparation of 5-ethyl 2,3-dimethyl 6-amino-1-phenyl-1,4-dihydro-4-phenyl pyridine-2,3,5-tricarboxylate derivatives by four-component reaction of aromatic aldehydes, ethyl cyanoacetate, arylamines, and dimethyl acetylenedicarboxylate in ethanol at room temperature (Scheme 1). Meanwhile, we compare the catalytic activity of nanosized oxides (ZnO NPs, CuO NPs, SnO NPs MgO NPs and CaO NPs) in the one-pot synthesis of highly substituted dihydropyridines. The synthesis of 5-ethyl 2,3-dimethyl 6-amino-1-phenyl-1,4-dihydro-4-phenylpyridine-2,3,5- tricarboxylate derivatives has been reported using MCRs in the presence of catalysts including NaOH[34], Et_3N[35] and KF/Al_2O_3.[36]

<Scheme 1>

2. Results and discussion

In the beginning, we prepared nanosized oxides by simple techniques. The particle size diameter (D) of the nanoparticles has been calculated by the Debye–Scherrer equation ($D = K\lambda/\beta \cos\theta$), where β FWHM (full-width at half-maximum or half-width) is in radian and θ is the position of the maximum of the diffraction peak. K is the so-called shape factor, which usually takes a value of about 0.9, and λ is the X-ray wavelength (1.5406Å for CuKα). Fig.1 shows the XRD spectra of nanoparticles (see supplementary information). According to the Debye–Scherrer equation, the average particle sizes of the as-synthesized nanoparticles were calculatedand the results show that nanoparticles were obtained with an average diameter of 10-50 nm as confirmed by XRD analysis. The pattern agrees well with the reported pattern for nanosized oxides. In order to investigate the morphology and particle size of nanoparticles, SEM image of nanoparticles was presented in Fig.2 (see supplementary information). The SEM image shows particles with diameters in the range of nanometers. The results shown that the average particles size of CaO, ZnO, CuO, MgO, SnO and CeO_2 nanoparticles have been found to be 35 nm, 24 nm, 40 nm, 18 nm, 28 nm, 11nm respectively.

Initially, we carried out the MCR between 4-bromobenzaldehyde ethyl cyanoacetateat, dimethyl acetylenedicarboxylate and aniline at room temperature as a model reaction in the presence of different catalyst. Meanwhile, we observed the effect of different solvents on the progress of reaction. Ethanol was found to be the best solvent, in which the product was obtained in 90% yield. Unfortunately, when the model reaction was carried out in water, the desired product was only obtained in 33% yield. The model reaction was carried out in the presence of various nanocatalysts such CaO, ZnO, CuO, MgO, SnO and CeO_2 nanoparticles. When the reaction was carried out using CaO, MgO and CeO_2 nanoparticles as the catalyst, the product could be obtained in moderate to good yield of 65, 72 and 90%, respectively. Therefore, metal oxides show different yields due to kind of metal oxides. The chemical nature and the existing form of the catalyst play a vital importance for the reaction. From the results, it is obvious that CeO_2 nanoparticles is the best catalyst among those examined which were reported in Table 1. When 2, 4 and 6 mol% of CeO_2 nanoparticles were used; the yields were 85%, 90 % and 90 % respectively. Consequently, 4 mol% of CeO_2 NPs were expedient and excessive amount of CeO_2 nanoparticles did not change the yields, significantly. Size of prepared CeO_2 nanoparticles has been found to be 11nm. Perhaps, the increased surface area due to small particle size increased reactivity. The active sites of CeO_2 nanoparticles are responsible for the accessibility of the substrate molecules on the catalyst surface. Nanoparticle catalysts are highly active since most of the particle surfaces can be available to catalysis because chemical reactions take place mainly on the surface of the particles. The chemistry of rare earth differs from main group elements and transition metals due to the nature of the 4*f* orbitals, which are 'buried' inside the atom and are shielded from the atom's environment by the 4*d* and 5*p* electrons. Thus, the CeO_2 NPs may coordinate with the active groups further than other catalysts in the present reaction. These orbitals give rare earth inimitable catalytic, magnetic and electronic property.

<Table1 >

We also investigated recycling of nanosized oxides as catalyst under reflux conditions in ethanol. The results showed that CeO_2 NPs can be reused several times without noticeable loss of catalytic activity (Yields 90 to 89%) (Fig. 3). The extreme stability of the CeO_2 nanoparticles is mainspring of the continuous and high catalytic activity. The morphology of CeO_2 nanoparticle was investigated by scanning electron microscopy (SEM) before use and after reuse of five times with images shown in Fig. 4 (see supplementary information). Interestingly, the shape and size of the nanoparticles remained unchanged before and after reaction. We suppose that, this is also the possible reason for the extreme stability of the CeO_2 nanoparticles presented herein.

< Fig 3>

< Fig 4>

A series of aromatic aldehydes and amines were investigated (Table 2). The results were excellent in yields using aromatic aldehydes, either bearing electron-withdrawing substituents or electron-donating substituents.

All the products were well characterized by IR, ^{1}H NMR and ^{13}C NMR.

<Table 2 >

A plausible mechanism for the preparation of highly substituted dihydropyridines using CeO_2 NPs is shown in Scheme 2. Firstly, we assumed that the reaction occurs via a Knoevenagel condensation between ethyl cyanoacetate and aldehyde, to form the intermediate **I_1** on the active sites of CeO_2 NPs, and make aldehydes more electrophilic. Then, arylamine added to acetylenedicarboxylate to give the intermediate **I_2**. Michael addition of **I_2** to **I_1** yielded the adduct **I_3**. The migration of the hydrogen atom will provide the intermediate **I_4** and subsequent intramolecular addition of the amino group to the C≡N gave the cyclic intermediate **I_5**. In the end, the N-aryl dihydropyridine was formed by the tautomerization of the imino group to the amino group. The role of CeO_2 NPs probably would be activation of the nitrile to transform into amine.

<Scheme 2 >

3. Experimental

3.1. Chemicals and apparatus

The products were isolated and characterized by physical and spectral data. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the presence of tetramethylsilane as internal standard. The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. Melting points were determined on Electro thermal 9200, and are not corrected. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ= 1.5406 Å). Microscopic morphology of products was visualized by SEM (LEO 1455VP) and ((MIRA 3 TESCAN).

3.2. Preparation of CaO nanoparticles

Calcium oxide nanoparticles were prepared in accordance with the procedure reported by Tang et al.[37] NaOH (1 g) was added to a mixture of ethylene glycol (12 ml) and Ca $(NO_3)_2$. $4H_2O$ (6 g) and the solution stirred vigorously at room temperature for 10 min; the gel solution was kept about 5 h at static state. Afterwards, it was washed using water and dried under vacuum drying. Finally, the prepared CaO nanoparticles were calcinated at 700 °C for 3 h. The sample is characterised by X-ray diffraction (XRD) and scanning electron microscopy (SEM). The average crystallite size of CaO has been found to be 35 nm.

3.3.Preparation of ZnO nanoparticles

Zinc oxide nanoparticles were prepared according to the procedure reported by Shen et al. [38] In a typical procedure, zinc acetate (9.10 g, 0.05 mol) and oxalic acid (5.4 g, 0.06 mol) were combined by grinding in an agate mortar for 1 h at room temperature. Afterwards, the formed ZnC_2O_4. $2H_2O$ nanoparticles were calcinated at 450 °C for 30 min to produce ZnO nanoparticles under thermal decomposition conditions. Crystallite size of ZnO has been found to be 24 nm.

3.4. Preparation of CuO nanoparticles

Copper (II) oxide nanoparticles were prepared according to the procedure reported by Jang et al.[39] A solution of copper acetate (1.0 g) and acetic acid (1.0 mL) in 250 mL of distilled water was heated at 100 ^{o}C. Then 0.8 g of NaOH was added quickly under vigorous stirring. The reaction mixture being cooled to room temperature and the obtained black powders were separated by centrifugation. The collected precipitate then washed several times with distilled water, ethanol and dried at 100^{o}C for 10 h. The results show that spherical CuO nanoparticles were obtained with an average diameter of 40 nm as confirmed by XRD analysis.

3.5.Preparation of MgO nanoparticles

We prepared Magnesium oxide nanoparticles (NPs) in this study using ultrasound technique. A solution of 1 mol/L sodium hydroxide was added drop-wise to a solution prepared from dissolving 2 g of Mg $(NO_3)_2.6H_2O$ and 0.5 g polyvinyl pyrolydon (PVP) as surfactant. Then the reaction mixture was sonicated for 30 min ultrasonic power 90W. The prepared gel was centrifuged and washed several times with deionized water and ethanol, and finally calcined in a furnace at 600 ^{o}C for 2 h. The crystallite size diameter (D) of the MgO NPs has been calculated by Debye–Scherrer equation ($D = K\lambda/\beta\cos\theta$). The results show that hexagonal MgO NPs[40] were gained with an average diameter of 18 nm. Nano magnesium oxide has a network crystalline structure contain of Lewis basic and Lewis acid. All these factors cause that nano magnesium oxide employs as an efficient catalyst.

3.6. Preparation of SnO nanoparticles

Tin oxide nanoparticles were prepared according to the procedure reported in the literature.[41-42] A 100 ml aqueous solution of 10^{-2} M is prepared by dissolving 0.225 g of tin (II) chloride ($SnCl_2.2H_2O$) in dilute HCl. The solution was continuously stirred and diluted NH_4OH was added drop-wise to obtain a precipitate. The solution pH increased to 5. The precipitate was washed several times to remove excess ions. The precipitate dispersed in water kept under irradiation of microwave for 18

min. The sample is characterised by X-ray diffraction (XRD) and scanning electron microscopy (SEM). Size of prepared SnO nanoparticles in the presence of microwave was reduced until 28 nm.

3.7. Preparation of CeO_2 nanoparticles

Nano $CeO_2$was prepared according to the procedure reported in the literatures with some modification.[43] CeO_2 nanoparticles were prepared by a co-precipitation technique with post-annealing in air. Briefly, 3 g of highly pure $Ce(NO_3)_3.6H_2O$ was dissolved in the mixture of 50 ml deionised water and 20 ml alcohol. Then, the appropriate amount of aqueous ammonia solution (28 wt%) was added to the above solution till the pH value reached 8. Where after, the mixture was stirred for 4 h at room temperature and then dried at 80°C for 6 h. After, the solid was treated at 700°C for 2 h to obtain the CeO_2 nanoparticles. The pattern agrees well with the reported pattern for CeO_2 nanoparticles (JCPDS No. 43-1002). The crystalline size was calculated from FWHM using Scherrer's formula and was observed to be 11 nm.

3.8. General procedure for the preparation of 5-ethyl 2,3-dimethyl 6-amino-1-phenyl-1,4-dihydro-4-phenyl pyridine-2,3,5-tricarboxylate derivatives:

A mixture of aldehyde (2 mmol), ethyl cyanoacetate (2 mmol) and 4 mol% of CeO_2 NPs were stirred in 3 mL ethanol at room temperature for 30 minutes. Then, a solution of dimethyl acetylenedicarboxylate (2 mmol) and aromatic amine (2 mmol) in 2 mL ethanol was added to it. The whole solution was stirred at room temperature within 140-160 minutes (Table 2). The reaction was monitored by TLC. After completion of the reaction, the solvent was concentrated and the reaction mixture was diluted in $CHCl_3$; the catalyst was isolated by centrifuging and the heterogeneous catalyst was recovered. The $CHCl_3$ was evaporated and the solid separated out was filtered and was washed with ethanol to get pure product. The structures of the products were fully established on the basis of their ^{1}H NMR, ^{13}C NMR and FT-IR spectra.

3.9.Spectral data

5-ethyl 2,3-dimethyl 6-amino-1-(4-chlorophenyl)-1,4-dihydro-4-phenyl pyridine-2,3,5-tricarboxylate (*5a*) white solid; m.p. 185-186 °C; IR (KBr): ν_{max} 3380, 3269, 2953, 1745, 1712, 1653, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 6Hz, 3H, CH_3), 3.48 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.10 (q, *J*= 6Hz, 2H, CH_2,), 5.01 (s, 1H, CH), 6.17 (brs, 2H, NH_2), 7.20 (1H, ArH), 7.27 (5H, ArH), 7.47 (3H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.5, 166.1, 164.0, 150.9, 146.7, 141.0, 136.4, 134.0, 131.9, 130.1, 128.1, 127.8, 126.4, 108.2, 80.6, 59.5, 52.6, 51.9, 37.0, 14.4 ppm; Anal.Calcd.For $C_{24}H_{23}ClN_2O_6$: C, 61.21; H, 4.92; N, 5.95.Found C, 61.39; H, 4.82; N, 5.85.

5-ethyl 2,3-dimethyl 6-amino-4-(4-chlorophenyl)-1,4-dihydro-1-phenyl pyridine-2,3,5-tricarboxylate (5b)white solid; m.p. 129-130 °C; IR (KBr): ν_{max} 3426, 3278, 2951, 1749, 1714, 1657, 1597, 1503cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 6.8Hz, 3H, CH_3), 3.41 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 4.05 (q, *J* = 6.8Hz, 2H, CH_2), 4.98 (s, 1H, CH), 6.24 (brs, 2H, NH_2), 7.26 (m, 2H, ArH), 7.33-7.38 (m, 2H, ArH), 7.51 (m, 5H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.4, 166.0, 163.9, 151.2, 145.6, 141.5, 135.2, 131.8, 130.5, 130.4, 129.9, 129.3, 128.2, 107.2, 79.8, 59.4, 52.4, 51.9, 36.6, 14.5 ppm; Anal.Calcd.For $C_{24}H_{23}ClN_2O_6$: C, 61.21; H, 4.92; N, 5.95.Found C, 61.38; H, 4.85; N, 5.87.

5-ethyl 2,3-dimethyl 6-amino-4-(4-chlorophenyl)-1,4-dihydro-1-m-tolylpyridine-2,3,5-tricarboxylate (5c)white solid; m.p. 152-153 °C; IR (KBr): ν_{max} 3453, 3275, 2978, 2947, 1734, 1710, 1664, 1596, 1500cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 6.6Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.43 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 4.06 (q, *J* = 6.6Hz, 2H, CH_2), 4.97 (s, 1H, CH), 6.25 (brs, 2H, NH_2), 7.26-7.33 (m, 8H, ArH)ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.4, 166.1, 163.8, 151.3, 145.7, 141.6, 140.2, 135.1, 131.8, 131.1, 130.9, 129.6, 129.3, 128.2, 127.3, 107.1, 79.2, 59.4, 52.4, 61.8, 36.7, 21.2, 14.4 ppm; Anal.Calcd.For $C_{25}H_{25}ClN_2O_6$: C, 61.92; H, 5.20; N, 5.78.Found C, 61.88; H, 5.16; N, 5.81.

5-ethyl 2,3-dimethyl 6-amino-1,4-dihydro-1,4-diphenyl pyridine-2,3,5-tricarboxylate (5d)white solid; m.p. 136-140 °C; IR (KBr): ν_{max}3378, 3269, 2955, 1744, 1713, 1656, 1595, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J*= 6Hz, 3H, CH_3), 3.43 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 4.06 (q, *J* = 6Hz, 2H, CH_2), 5.02 (s, 1H, CH), 6.23 (brs, 2H, NH_2), 7.19 (m, 1H, ArH), 7.29(m, 3H, Ar), 7.42(m, 3H, ArH), 7.52(m, 3H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.6, 166.3, 164.1, 151.3, 147.0, 141.4, 135.4, 130.5, 130.3, 129.8, 128.1, 127.8, 126.3, 107.7, 80.3, 59.4, 52.4, 51.8, 37.1, 14.4 ppm; Anal.Calcd.For $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42.Found C, 66.12; H, 5.47; N, 6.51.

5-ethyl 2,3-dimethyl 6-amino-4-(4-bromophenyl)-1,4-dihydro-1-phenylpyridine-2,3,5-tricarboxylate (5e) white solid; m.p. 138-141°C; IR (KBr): ν_{max} 3490, 3292, 2951, 1739, 1712, 1662, 1602, 1497cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J= 6.8Hz, 3H, CH_3), 3.41 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.08 (q, J = 6.8Hz, 2H, CH_2), 4.98 (s, 1H, CH), 6.24 (brs, 2H, NH_2), 7.29 (m , 2H, ArH), 7.41 (m, 4H, ArH), 7.51 (m, 3H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.4, 165.9, 163.9, 150.9, 145.9, 141.3, 136.7, 133.8, 131.9, 131.2, 130.3, 129.6, 120.2, 107.6, 80.2, 59.6, 52.6, 52.0, 36.7, 14.4 ppm; Anal.Calcd.For $C_{24}H_{23}BrN_2O_6$: C, 55.93; H, 4.50; N, 5.44.Found C, 55.82; H, 4.41; N, 5.50.

5-ethyl 2,3-dimethyl 6-amino-1-(4-chlorophenyl)-1,4-dihydro-4-(4-methoxy phenyl)pyridine-2,3,5-tricarboxylate (5f) white solid; m.p. 181-182 °C; IR (KBr): ν_{max} 3390, 3274, 2950, 1742, 1712, 1655, 1608, 1500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 6.8Hz, 3H, CH_3), 3.46 (s, 3H, OCH_3), 3.63 (s, 3H,

OCH_3), 3.73 (s, 3H, OCH_3), 4.07 (q, J = 6.8Hz, 2H, CH_2), 4.94 (s, 1H, CH), 6.14 (brs, 2H, NH_2), 6.83 (d, 2H, ArH), 7.25 (m, 4H, ArH), 7.45 (d, J=8 , 2H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ ppm; 169.5, 166.2, 164.0, 158.1, 150.8, 140.8, 139.2, 136.4, 134.0, 131.9, 130.1, 128.7, 113.5, 108.4, 80.8, 59.4, 55.2, 52.6, 51.9, 36.1, 14.4; Anal.Calcd.For $C_{25}H_{25}ClN_2O_7$: C, 59.94; H, 5.03; N, 5.59.Found C, 59.83; H, 5.09; N, 5.49.

5-ethyl 2,3-dimethyl 6-amino-1-(4-chlorophenyl)-1,4-dihydro-4-(3-nitrophenyl)pyridine-2,3,5-tricarboxylate (5g) light yellow solid; m.p. 186-187 ^oC; IR (KBr): ν_{max} 3437, 3223, 3108, 2987, 2954, 1751, 1710, 1663, 1603, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 3H, CH_3), 3.49 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.09 (m, 2H, CH_2), 5.11 (s, 1H, CH), 6.26 (brs, 2H, NH_2), 7.40 (d ,J = 7.5 Hz, 2H, ArH), 7.47 (td, J=8.4Hz, J= 2Hz, 1H, ArH), 7.51 (d, J=7.5 Hz, 2H, ArH), 7.72 (d, J=7.2Hz, 1H, ArH), 8.06(d, J=7.5Hz, 1H, ArH), 8.32(1H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.0, 165.6, 163.5, 151.2, 149.0, 148.3, 141.8, 136.8, 134.0, 133.4, 131.8, 130.3, 128.9, 122.9, 121.5, 107.0, 79.7, 59.7, 52.7, 52.1, 37.2, 14.4 ppm; Anal.Calcd.For $C_{24}H_{22}ClN_3O_8$: C, 55.87; H, 4.30; N, 8.15.Found C, 55.83; H, 4.19; N, 8.26.

5-ethyl 2,3-dimethyl 6-amino-1-(4-chlorophenyl)-1,4-dihydro-4-*p*-tolylpyridine-2,3,5-tricarboxylate (5h) white solid; m.p. 191-192^oC; IR (KBr): ν_{max} 3389, 3274, 2950, 1742, 1712, 1654, 1607, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 6.6Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.09 (q, J = 6.6Hz, 2H, CH_2), 4.97 (s, 1H, CH), 6.16 (brs, 2H, NH_2), 7.10 (d, J = 7.2Hz, 2H, ArH),7.28 (d, J = 7.2Hz, 2H, ArH), 7.33 (d, J = 7.8Hz, 2H, ArH), 7.47 (d, J = 7.8Hz, 2H, ArH) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.5, 166.2, 164.0, 150.9, 143.8, 140.9, 136.4, 135.8, 134.1, 131.9, 130.1, 128.9, 127.6, 108.4, 80.8, 59.5, 52.6, 51.9, 36.5, 21.1, 14.4 ppm; Anal.Calcd.For $C_{25}H_{25}ClN_2O_6$: C, 61.92; H, 5.20; N, 5.78.Found C, 61.81; H, 5.15; N, 5.82.

5-ethyl 2,3-dimethyl 6-amino-1,4-dihydro-4-(4-isopropyl phenyl)-1-phenylpyridine-2,3,5-tricarboxylate (5i) white solid; m.p. 142-144^oC; IR (KBr): ν_{max} 3391, 2956, 1747, 1709, 1657, 1597, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (m, 3H, CH_3), 1.30-1.58 (6H, CH_3), 2.89 (m,1H, CH), 3.43 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 4.10 (q, J = 6 Hz, 2H, CH_2), 5.00 (s, 1H, CH), 6.25 (brs, 2H, NH_2), 7.17(m, 2H,ArH), 7.28 (d, J= 6Hz, 2H, ArH), 7.33 (d, 2H, J=5.9Hz, ArH), 7.42(m, 1H,ArH), 7.51(m, 2H, ArH)ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.6, 166.3, 164.1, 151.3, 147.0, 141.4, 135.4, 130.5, 130.3, 129.8, 128.1, 127.8, 126.3, 107.7, 80.3, 59.4, 52.4, 51.8, 37.1, 33.6, 24.3, 14.4 ppm; Anal.Calcd.For $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85.Found C, 67.81; H, 6.15; N, 5.79.

4. Conclusions

In conclusion, we compare the catalytic activity of nanosized oxides in the one-pot synthesis of highly substituted dihydropyridines. An efficient, environmentally benign, atom economical and simple methodology for the preparation of polysubstituted dihydropyridines in the presence of CeO_2 nanoparticles is reported. The procedure offers several advantages including cleaner reaction profiles, use of easily available, cheap, high yields, shorter reaction time and simple experimental, reusability of the catalyst and little catalyst loading.This green nanocatalyst could be used for other significant organic reactions and transformations. Further explorations of similar protocols are underway in our laboratory. Meanwhile, this recoverable catalyst will provide a regular platform for heterogeneous catalysis, green chemistry, and environmentally benign protocols in the near future.

Acknowledgments

The authors acknowledge a reviewer who provided helpful insights. The authors are grateful to University of Kashan for supporting this work by Grant NO: 159196/XXI.

Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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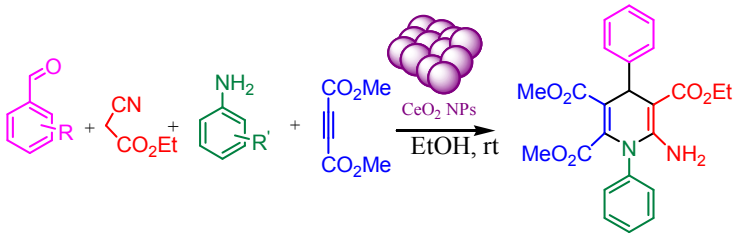
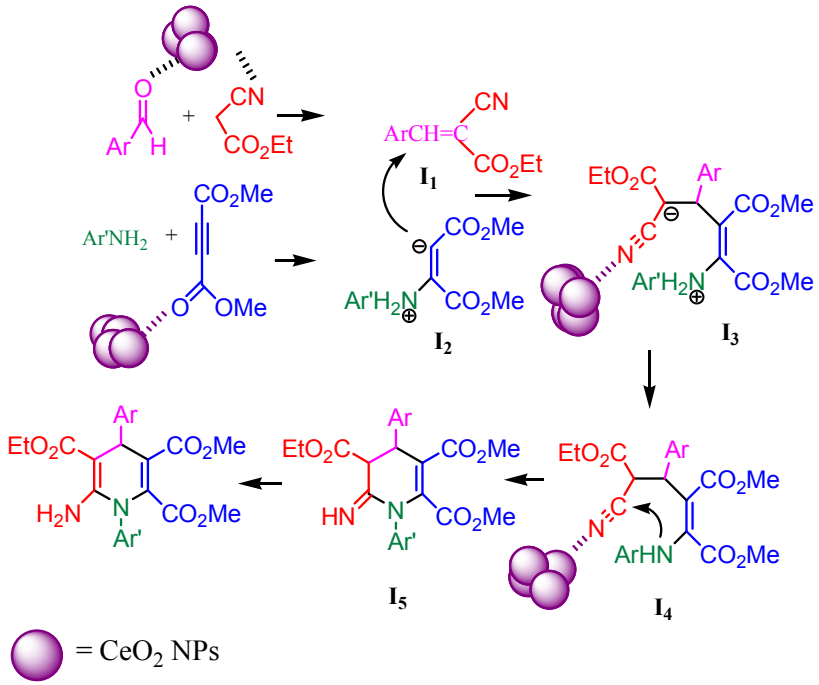


1 **2** **3** **4** **5 a-i**

Scheme 1.Synthesis of highly substituted dihydropyridines



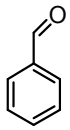
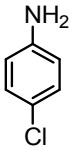
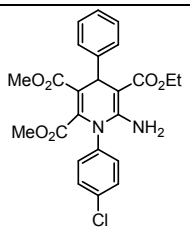
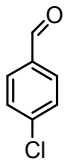
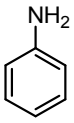
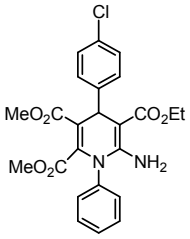
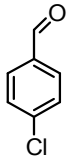
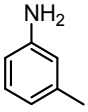
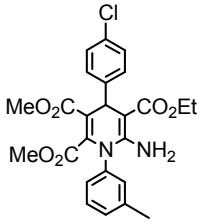
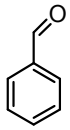
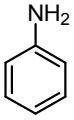
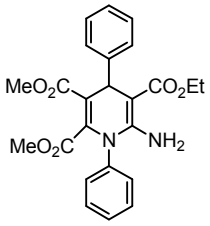
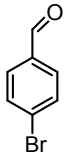
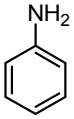
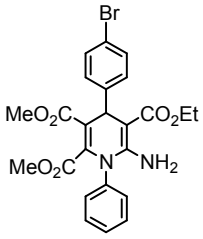
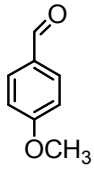
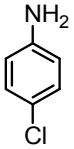
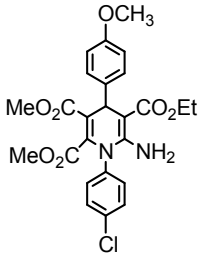
Scheme 2.Proposed Mechanism for the Four-Component Reaction

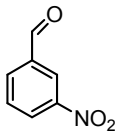
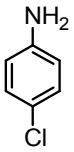
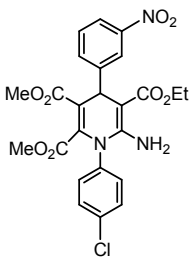
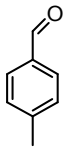
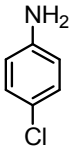
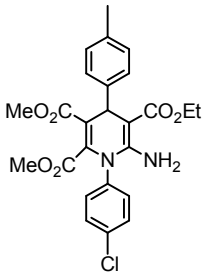
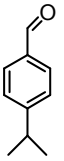
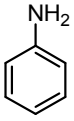
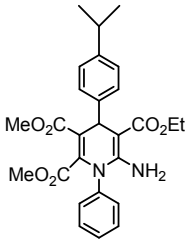
Table1. Optimization of reaction conditions using different catalysts [a]

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield % [Ref]
1	none	EtOH	24[h]	0
2	NaOH (10)	EtOH	480	85 (ref. 34)
3	Et_3N (30)	EtOH	600	86 (ref 35)
4	CaO NPs (10)	EtOH	250	65
5	ZnO NPs (10)	EtOH	275	59
6	CuO NPs (15)	EtOH	250	52
7	MgO NPs (6)	EtOH	210	72
8	SnO NPs (8)	EtOH	250	54
9	MgO NPs (6)	CH_3CN	220	63
10	CeO_2 NPs (4)	H_2O	290	33
11	CeO_2 NPs (4)	DMF	180	60
12	CeO_2 NPs (4)	CH_3CN	160	75
13	CeO_2 NPs (2)	EtOH	160	85
14	**CeO_2 NPs (4)**	**EtOH**	**140**	**90**
15	CeO_2 NPs (6)	EtOH	137	90
16	MgO NPs (4)	EtOH	140	61
17	SnO NPs (4)	EtOH	140	38
18	CuO NPs (4)	EtOH	140	35
19	ZnO NPs (4)	EtOH	140	40
20	CaO NPs (4)	EtOH	140	47

[a] 4-bromobenzaldehyde (2 mmol), ethyl cyanoacetate (2 mmol), dimethyl acetylenedicarboxylate (2 mmol) and aniline (2 mmol), [b]Isolated yield

Table 2. Synthesis of 5-ethyl 2,3-dimethyl 6-amino-1-phenyl-1,4-dihydro-4-phenylpyridine-2,3,5-tricarboxylate derivatives using CeO_2NPs[a]

Entry	5a-i	R	R´	Product	Time (min)	Yield (%)[a]	M.P ºC, (ref)
1	**5a**				151	85	185-186 (ref.35)
2	**5b**				142	88	129-130 (ref. 35)
3	**5c**				146	84	152-153 (ref. 35)
4	**5d**				143	87	136-140
5	**5e**				140	90	138-141
6	**5f**				153	81	181-182 (ref. 35)

7	**5g**				148	85	186-187 (ref. 35)
8	**5h**				150	84	191-192 (ref. 35)
9	**5i**				144	85	142-144

[a] aromatic aldehydes (2 mmol), ethyl cyanoacetate (2 mmol), dimethyl acetylenedicarboxylate (2 mmol), aromatic amine (2 mmol)
[b] Isolated yield

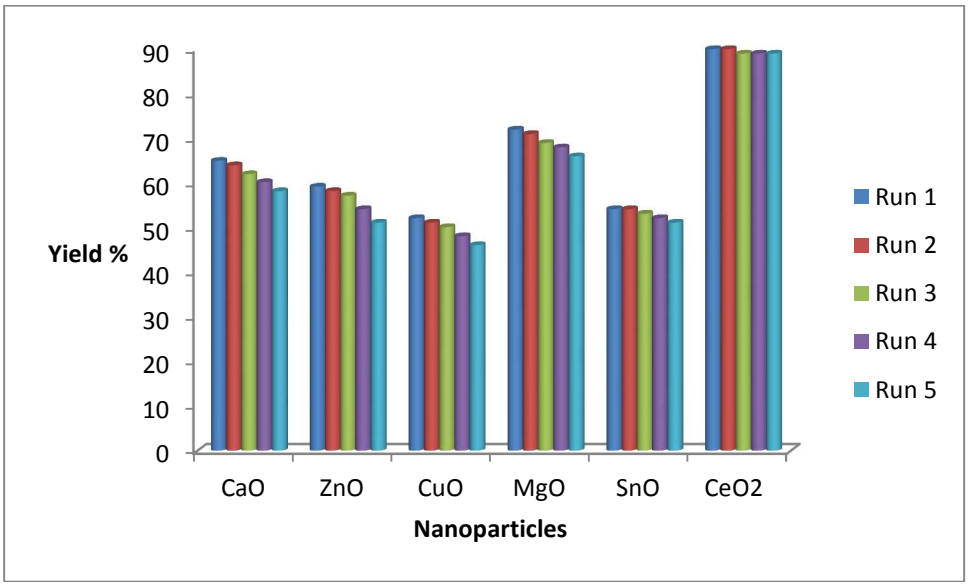


Figure 3. Recycling of nanosized oxides as catalyst

Graphical abstract

A flexible and highly efficient protocol for the synthesis of highly substituted dihydropyridinesusing nano CeO_2 has been developed.