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Synthesis of pyrazolopyridines catalyzed by nano-$CdZr_4(PO_4)_6$ as a reusable catalyst

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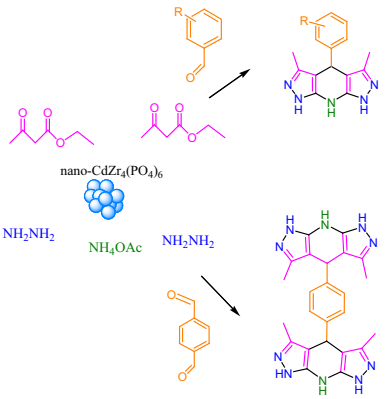
Abstract A simple and efficient method for the preparation of pyrazolopyridines by a multicomponent reaction of ethyl acetoacetate, an aldehyde, hydrazine and ammonium acetate using nano-$CdZr_4(PO_4)_6$ as an efficient catalyst is presented. The main advantages of this protocol include short reaction times, practical simplicity, high yields, recyclable catalysts and applicability to wide range of substrates.

Graphical Abstract



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Keywords Nano-$CdZr_4(PO_4)_6$ · Pyrazolopyridines · Nanocatalyst · Multicomponent reaction

Introduction

Pyrazolopyridines are attractive targets in organic and medicinal chemistry owing to their potency and wide spectrum of biological activities including antioxidant, antitumor and antimicrobial [1, 2], treatment of Type 2 diabetes mellitus [3], anti-virus [4], anti-Leishmania [5], protein kinase inhibitors [6] dopaminergic properties [7] and can also serve as synthetic intermediates for many kinds of pharmaceuticals or drug precursors [8–10]. Therefore, the development of simple methods for the synthesis of pyrazolopyridines is a major challenge and an interesting field in chemistry. The synthesis of pyrazolopyridine derivatives has been reported in the presence of diverse catalysts such as carbonaceous material (C-SO_3H) [11], L-Proline [12], acetic acid [13] and *p*-TSA [14]. However, some of the reported methods tolerate disadvantages including long reaction times, harsh reaction conditions and use of toxic and non-reusable catalyst. Therefore, to avoid these limitations, the exploration of an efficient, easily available catalyst with high catalytic activity and short reaction time for the preparation of pyrazolopyridine is still favored. Conventional step-by-step synthetic methods cannot actualize the requirements of modern synthetic chemistry, but multicomponent reactions (MCRs) have been developed as an efficient and powerful tool in modern synthetic organic chemistry [15–18]. The possibility of accomplishing multicomponent reactions under moderate conditions with a heterogeneous catalyst could improve their effectiveness from operating cost and ecological points of view. Nanoparticles have emerged as viable alternatives to conventional materials, as robust, high surface area heterogeneous catalysts and catalyst supports [19, 20]. $MZr_4(PO_4)_6$ structure ceramics have been interested because of their unique properties and potential applications in diverse fields [21, 22]. Herein we reported the use of nanocrystalline $CdZr_4(PO_4)_6$ ceramics as an efficient catalyst for the preparation of tetrahydropyrazolopyridines by a multicomponent reaction of ethyl acetoacetate, an aldehyde, hydrazine hydrate and ammonium acetate under reflux conditions in ethanol (Scheme 1).

Experimental

All organic materials were purchased commercially from Sigma–Aldrich and Merck and were used without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 200 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. All melting points are uncorrected and were determined in capillary tube on Boetius melting point

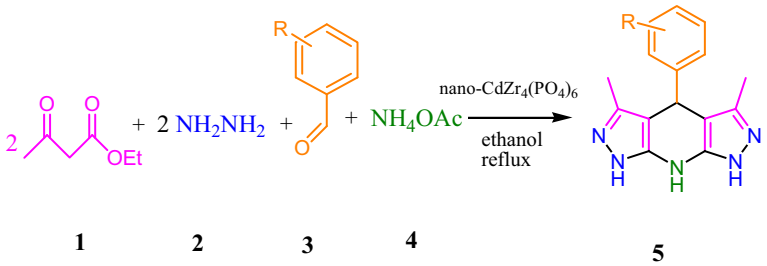
microscope. FT-IR spectra were recorded with KBr pellets using a Magna-IR, spectrometer 550 Nicolet. NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer with DMSO-d_6 as solvent and TMS as internal standard. CHN compositions were measured by Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Zr Kα radiation ($\lambda = 1.5406$ Å). In order to investigate the particle size and morphology of the synthesis structures nano-$CdZr_4(PO_4)_6$, FE-SEM images of the products visualized by a HITACHI S4160 Field Emission Scanning Electron Microscope.

Preparation of nano-$CdZr_4(PO_4)_6$

Nano-$CdZr_4(PO_4)_6$ was prepared according to the procedure reported in the literature [23]. $ZrOCl_2$ was used as zirconium source. Firstly 1 mmol (322 mg) of $ZrOCl_2{\cdot}8H_2O$ and 1 mmol (266 mg) of $Cd(OAC)_2{\cdot}2H_2O$ were added in 15 mL of $HO(CH_2)_2OH$ and sonicated at 30 W power to completely dissolution. Afterward 0.8 mL H_3PO_4 (85 %), 4 mmol of NH_4Cl and 1.4 mL of CH_3NH_2 water solution (25.0–30.0 %) were added consecutively and sonicated for 30 min. Then, the reaction mixture was transferred into a Teflon-lined autoclave under autogenous pressure at 200 °C for 5 days. When the reaction was completed, dispersed precipitate was obtained. The solid was filtered and washed with distilled water and ethanol several times. Subsequently product was dried at 50 °C for 5 h and calcined at 700 °C for 2 h. Afterward the solid was added in 20 mL of DMF and sonicated at 95 W power for 2 h. Finally the resulting product was filtered, washed with distilled water and absolute ethanol and dried at 150 °C for 2 h in vacuum to afford pure nano-$CdZr_4(PO_4)_6$ ceramics.

General procedure for the preparation of tetrahydrodipyrazolopyridines

A mixture of hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2 mmol) and nano-$CdZr_4(PO_4)_6$ (0.6 mol%) in EtOH (5 mL) was magnetically stirred at 25 °C followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol).



Scheme 1 Synthesis of tetrahydrodipyrazolo pyridines by nano-$CdZr_4(PO_4)_6$

The reaction mixture was heated at reflux for 30–40 min and then cooled to 25 °C. The formed precipitate was isolated by filtration. The product was dissolved in hot CH_3OH and the catalyst was filtered. After cooling, the crude products were precipitated. The precipitate was washed with EtOH to afford the pure product and then dried well under vacuum pump (note: Hydrazine solutions are hazardous because of their toxic, corrosive, flammable or explosive properties. Hydrazine solutions should always be handled with great care. Avoid inhaling the vapours from hydrazine solutions at all times and whenever possible use a reliable fume hood. Avoid skin contact with hydrazine at all times).

Spectral data

*3,5-Dimethyl-4-(4-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4′,3′-e] pyridine (**5a**)*

Cream solid; m.p. 295–297 °C; IR (KBr): ν_{max} 3329 (stretching, NH), 2963 (stretching, CH), 1603 (aromatic C=C), 1511 (stretching NO_2), 1348 (stretching NO_2), 846 (C–H out of plan bending, para-substituted) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 6H, $2CH_3$), 4.95 (s, 1H, CH), 7.34–7.36 (d, 2 H, $J = 8$ Hz, 2CH, ArH), 8.09–8.11 (d, 2 H, $J = 8$ Hz, 2CH, ArH), 11.25 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.75, 33.43, 103.62, 123.46, 129.25, 140.18, 146.09, 152.24, 161.34 ppm; Anal.Calcd. For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.14; H, 4.51; N, 27.14.

*3,5-Dimethyl-4-(4-methyl-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4′,3′-e] pyridine (**5b**)*

White solid; m.p. 243–245 °C; IR (KBr): ν_{max} 3300 (stretching, NH), 2924 (stretching, CH), 1602 (aromatic C=C), 1130 (stretching, C–N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H, $2CH_3$), 2.21 (s, 3H, CH_3), 4.74 (s, 1H, CH), 6.98–7.00 (m, 4H, 4 CH of aromatic), 11.24 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.84, 20.95, 32.84, 104.82, 127.81, 128.80, 134.68, 140.21, 140.72, 161.52 ppm; Anal.Calcd. For $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07; Found C, 68.72; H, 6.24; N, 25.14.

*3,5-Dimethyl-4-(3-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4′,3′-e] pyridine (**5c**)*

Cream solid; m.p. 286–288 °C; IR (KBr): ν_{max} 3200 (stretching, NH), 2963 (stretching, CH), 1599 (aromatic C=C), 1527 (stretching, NO_2), 1347 (stretching, NO_2), 1300 (stretching, C–N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 6H, $2CH_3$), 4.97 (s, 1H, CH), 7.52 (m, 2 H, 2CH, ArH), 7.93 (s, 1H, CH, ArH), 8.02 (d, 1 H, $J = 8$ Hz, CH, ArH), 11.25 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.74, 33.11, 103.74, 121.22, 122.32, 129.72, 135.20, 140.22, 146.26, 148.05,

161.3 ppm; Anal.Calcd. For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.17; H, 4.49; N, 27.15.

*3,5-Dimethyl-4-(4-methoxy-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4′,3′-e] pyridine (**5d**)*

Cream solid; m.p. 186–188 °C; IR (KBr): ν_{max} 3267 (stretching, NH), 2924 (stretching, CH), 1597 (aromatic C=C), 1239 (stretching, C–O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H, 2 CH_3), 3.69 (s, OCH_3), 4.74 (s, 1H, CH), 6.74–6.76 (d, 2 H, $J = 8$ Hz, 2CH, ArH), 6.99–7.01 (d, 2 H, $J = 8$ Hz, 2CH, ArH), 11.32 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.82, 32.40, 55.51, 104.92, 113.53, 128.82, 135.66, 140.12, 146.18, 157.68 ppm; Anal.Calcd. For $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71; Found C, 65.12; H, 5.89; N, 23.77.

*1,4,7,8-Tetrahydro-3,5-dimethyl-4-phenyldipyrazolo-[3,4-b:4′,3′-e]pyridine (**5e**)*

White solid; m.p. 240–242 °C; IR (KBr): ν_{max} 3181 (stretching, NH), 2924 (stretching, CH), 1600 (aromatic C=C), 1200 (stretching, C–N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H, 2CH_3), 4.79 (s, 1H, CH), 7.09–7.19 (m, 5 H, CH, ArH), 11.34 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.84, 33.24, 104.65, 125.84, 127.92, 128.16, 140.24, 143.82, 161.54 ppm; Anal.Calcd. For $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40; Found C, 67.97; H, 5.77; N, 26.49.

*3,5-Dimethyl-4-(2-methyl-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4′,3′-e] pyridine (**5f**)*

White solid; m.p. 290–292 °C; IR (KBr): ν_{max} 3300 (stretching, NH), 2923 (stretching, CH), 1602 (aromatic C=C), 1202 (stretching, C–N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.87 (s, 6H, 2CH_3), 2.09 (s, 3H, CH_3), 4.91 (s, 1H, CH), 7.03–7.17 (m, 4H, 4CH, ArH), 10.65 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.88, 20.73, 32.83, 104.80, 125.51, 127.80, 128.85, 129.34, 134.69, 140.24, 140.74, 161.69 ppm; Anal.Calcd. For $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07; Found C, 68.88; H, 6.10; N, 25.15.

*3,5-Dimethyl-4-(4-chloro-phenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b;4′,3′-e] pyridine (**5g**)*

White solid; m.p. 255–257 °C; IR (KBr): ν_{max} 3180 (stretching, NH), 2924 (stretching, CH), 1597 (aromatic C=C), 1091 (stretching, C–N), 607 (stretching, C–Cl) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 6H, 2CH_3), 4.79 (s, 1H, CH), 7.09–7.11 (d, $J = 8$ Hz, 2 H, 2 CH, ArH), 7.24–7.26 (d, $J = 8$ Hz, 2H, 2CH, ArH), 11.50 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.78, 32.67, 104.34, 128.06, 129.85, 130.49, 140.16, 142.78, 161.46 ppm; Anal.Calcd. For $C_{15}H_{14}ClN_5$: C, 60.10; H, 4.71; N, 23.36 Found C, 60.15; H, 4.78; N, 23.28.

*3,5-Dimethyl-4-(4-bromo-phenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b;4′,3′-e] pyridine (**5h**)*

Yellow solid; m.p. 165–167 °C; IR (KBr): ν_{max} 3100 (stretching, NH), 2924 (stretching, CH), 1598 (aromatic C=C), 1142 (stretching, C–N), 508 (stretching, C–Br) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 6H, $2CH_3$), 4.78 (s, 1H, CH), 7.03–7.05 (d, $J = 8$ Hz, 2 H, 2 CH, ArH), 7.39–7.41 (d, $J = 8$ Hz, 2H, 2 CH, ArH), 11.50 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.23, 32.43, 104.45, 118.30, 129.62, 130.34, 131.85, 142.66, 157.42 ppm; Anal.Calcd. For $C_{15}H_{14}BrN_5$: C, 52.34; H, 4.10; N, 20.35 Found C, 52.39; H, 4.15; N, 20.30.

*4-(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′ e]pyridin-4-yl)-N,N-dimethylaniline (**5i**)*

Cream solid; m.p. 240–242 °C; IR (KBr): ν_{max} 3200 (stretching, NH), 2950 (stretching, CH), 1598 (aromatic C=C), 1145 (stretching, C–N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H, $2CH_3$), 2.98 (s, 6 H, $N(CH_3)_2$), 4.64 (s, 1H, CH), 6.56–6.58 (d, $J = 8$ Hz, 2 H, 2CH, ArH), 6.90–6.92 (d, $J = 8$ Hz, 2H, 2CH, ArH), 11.28 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.84, 32.35, 40.92, 105.23, 112.73, 128.35, 131.64, 137.02, 149.05, 161.66 ppm; Anal.Calcd. For $C_{17}H_{20}N_6$: C, 66.21; H, 6.54; N, 27.25 Found C, 66.33; H, 6.59; N, 27.36.

*3,5-Dimethyl-4-(4-hydroxy-phenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b;4′,3′-e] pyridine (**5j**)*

White solid; m.p. 267–268 °C; IR (KBr): ν_{max} 3266–3300 (stretching, NH and OH), 2924 (stretching, CH), 1562 (aromatic C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 6H, $2CH_3$), 4.65 (s, 1H, CH), 6.56–6.58 (d, $J = 8$ Hz, 2 H, 2CH, ArH), 6.88–6.90 (d, $J = 8$ Hz, 2H, 2CH, ArH), 9.10 (s, OH), 11.50 (s, 3H, 3NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.32, 31.75, 104.5, 114.42, 128.23, 133.35, 139.76, 155.03, 161.04 ppm; Anal.Calcd. For $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90; Found C, 64.09; H, 5.30; N, 24.83.

*3,5-Dimethyl-4-(2-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4′,3′-e] pyridine (**5k**)*

Cream solid; m.p. 187–188 °C; IR (KBr): ν_{max} 3300 (stretching, NH), 2925 (stretching, CH), 1604 (aromatic C=C), 1525 (stretching, NO_2), 1360 (stretching, NO_2), 1177 (stretching, C–N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.90 (s, 6H, 2 CH_3), 5.43 (s, 1H, CH), 7.36–7.68 (m, 4 H, 4 CH, ArH), 10.95 (s, 3H, 3 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.02, 28.94, 101.94, 123.85, 127.12, 130.22, 131.64, 136.24, 138.62, 149.50, 160.54 ppm; Anal.Calcd. For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.15; H, 4.43; N, 27.13.

*1,4-Bis[(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)] benzene (**5l**)*

Orange solid, m.p. >300 °C; IR (KBr): ν_{max} 3200 (stretching, NH), 1591 (aromatic C=C), 1200 (stretching, C–N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 12H, $4CH_3$), 4.70 (s, 2H, 2CH), 6.94 (4 H, 4CH, ArH), 11.25 (s, 6H, 6NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.70, 33.20, 104.55, 129.34, 134.43, 139.50, 160.20 ppm; Anal.Calcd. For $C_{24}H_{24}N_{10}$: C, 63.70; H, 5.35; N, 30.95; Found C, 63.79; H, 5.44; N, 30.85; MS (EI, 70 eV): *m*/*z* 452 (M^+).

Results and discussion

$ZrOCl_2$ and $Cd(OAc)_2{\cdot}2H_2O$ were utilized as the starting materials for the preparation of nano-$CdZr_4(PO_4)_6$. In this technique, the ultrasonic irradiation was performed before and after solvothermal method. Sonication was used to speed dissolution, by breaking the interactions between particles. When the solution containing precursor is exposed via an ultrasound solvothermal route, extremely high pressures and temperatures are produced to generate $CdZr_4(PO_4)_6$ nuclei. At the beginning of the reaction, the reactant particles and the moleculars of methylamine disperse randomly in the glycol solution under ultrasound irradiation. The $CdZr_4(PO_4)_6$ form gradually around the methylamine moleculars. After calcined at a high temperature, methylamine decomposed into carbon dioxide, carbon monoxide and nitrogen oxide, thus the nano-$CdZr_4(PO_4)_6$ were finally obtained. The particle size diameter (D) of the nano-$CdZr_4(PO_4)_6$ 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. Figure 1 shows the XRD spectra of nano-$CdZr_4(PO_4)_6$. The pattern agrees well with the reported pattern for nano-$CdZr_4(PO_4)_6$ (JCPDS no. 45-0017). All the strong peaks appeared at 2θ = 19.92, 22.08, 24.30, 25.02, 28.85, 31.12, 35.14, 38.50, 41.05, 42.71, 46.50, 48.32, 51.37, 55.42, 60.21, 63.72, 67.02, 70.87, 74.52 are indexed to the highly crystalline monoclinic structure of nano-$CdZr_4(PO_4)_6$. According to the Debye–Scherrer equation, the average particle sizes of the as-synthesized nano-$CdZr_4(PO_4)_6$ were calculated and the results show that nano-$CdZr_4(PO_4)_6$ was obtained with an average diameter of 19–23 nm as confirmed by XRD analysis. In order to investigate the morphology and particle size of nano-$CdZr_4(PO_4)_6$, FE-SEM image of nano-$CdZr_4(PO_4)_6$ was presented in Fig. 2. The FE-SEM image shows particles with diameters in the range of nanometers.

Initially, we carried out the MCR between hydrazine hydrate, ethyl acetoacetate, 4-nitrobenzaldehyde and ammonium acetate 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 94 % yield. Unfortunately, when the model reaction was carried out in water, the desired product was only obtained in 62 % yield.

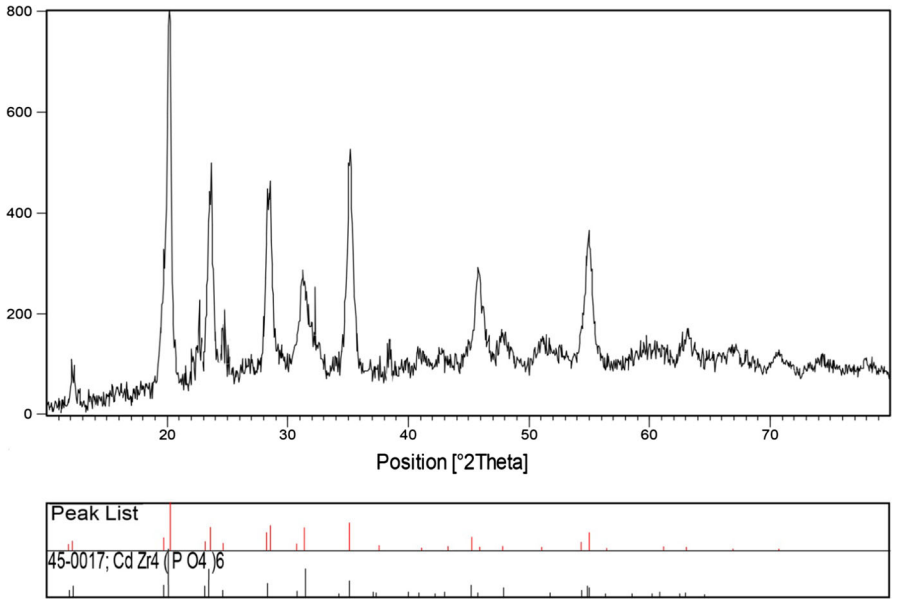


Fig. 1 XRD pattern of nano-$CdZr_4(PO_4)_6$

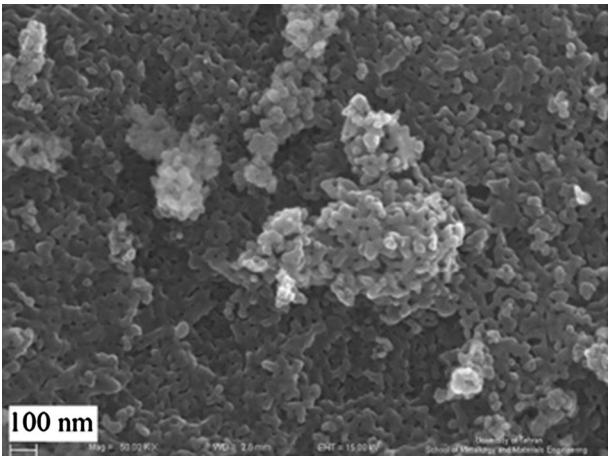


Fig. 2 SEM images of nano-$CdZr_4(PO_4)_6$

The model reaction was carried out in the presence of various catalysts such Et_3N, ZnS, nano-ZrO_2, nano-CeO_2, nano-$CdZr_4(PO_4)_6$. When the reaction was carried out using (0.6 mol%) nano-$CdZr_4(PO_4)_6$ as the catalyst, the product could be obtained in good yield (Table 1).

The recycling of nano-$CdZr_4(PO_4)_6$ catalyst was checked and the results are summarized in Fig. 3. The possibility of recycling of the catalyst is a significant

Table 1 Optimization of reaction conditions

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)[a]
1	–	EtOH	300	53
2	Et_3N (20)	EtOH	400	58
3	ZnS NPs (4)	EtOH	200	62
4	Nano-ZrO_2 (4)	EtOH	100	68
5	Nano-CeO_2 (3)	EtOH	100	64
6	Nano-$CdZr_4(PO_4)_6$ (0.4)	EtOH	40	90
7	Nano-$CdZr_4(PO_4)_6$ (0.6)	EtOH	40	94
8	Nano-$CdZr_4(PO_4)_6$ (0.8)	EtOH	40	94
9	Nano-$CdZr_4(PO_4)_6$ (0.6)	H_2O	110	62
10	Nano-$CdZr_4(PO_4)_6$ (0.6)	CH_3CN	80	74
11	Nano-$CdZr_4(PO_4)_6$ (0.6)	DMF	80	70

Hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), 4-nitrobenzaldehyde (1 mmol) and ammonium acetate (4 mmol)

[a] Isolated yield

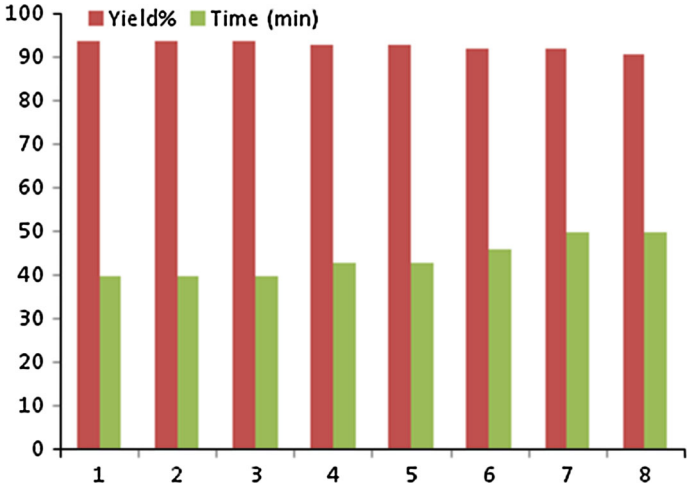


Fig. 3 Reusability of nano-$CdZr_4(PO_4)_6$ as catalyst for the synthesis of **5a**

process from different aspects such as environmental concerns, and commercial applicable processes. In the recycling procedure of nanocrystalline $CdZr_4(PO_4)_6$ ceramics, hot CH_3OH was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by filtering. The reusability of the catalyst was tested for eight runs, providing almost similar yields of the desired product.

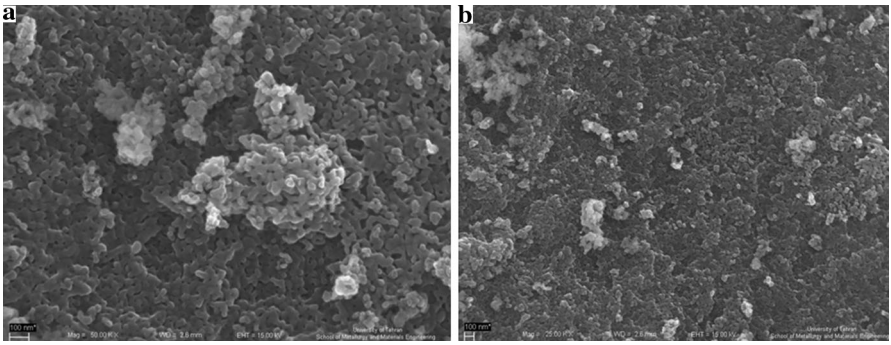


Fig. 4 SEM images of nano-$CdZr_4(PO_4)_6$ before use (**a**) and after reuse of eight times (**b**)

The morphology of nano-$CdZr_4(PO_4)_6$ was investigated by scanning electron microscopy (SEM) before use and after reuse of eight times with images shown in Fig. 4. The morphology of the nanoparticles remained almost unchanged before and after reaction. We believe that, this is also the possible reason for the extreme stability of the nano-$CdZr_4(PO_4)_6$ presented herein. The extreme stability of the nano-$CdZr_4(PO_4)_6$ is mainspring of the continuous and high catalytic activity.

With these encouraging results in hand, we turned to explore the scope of the reaction using different aromatic aldehydes as substrates under the optimized reaction conditions (Table 2). In general the reactions are clean and high-yielding. Several functional groups, such as Br, OH, Cl, NO_2, OMe, $N(CH_3)_2$, and CH_3, are compatible under the reaction conditions. Interestingly, a variety of aromatic aldehydes, including ortho, meta and para-substituted aryl aldehydes, participated well in this reaction and gave the corresponding products in a good to excellent yield (Table 2). The influence of electron-withdrawing and electron-donating substituents on the aromatic ring of aldehydes upon the reaction yields was investigated. It was shown that aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-releasing groups. Meanwhile, the practicable synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde, hydrazine hydrate, and ammonium acetate and ethyl acetoacetate to give 1,4-Bis[(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)] benzene (Scheme 2).

A plausible mechanism for the preparation of tetrahydrodipyrazolo pyridines using nano-$CdZr_4(PO_4)_6$ is shown in Scheme 3. The mechanism involves the initial nucleophilic attack of hydrazine on the ethyl acetoacetate and subsequent cyclization to form the pyrazolone and then, the reaction of pyrazolone with an aldehyde to give intermediate **II**. In the next step, the reaction can be followed by attack of the second pyrazolone ring that leads to the formation of **III**. Finally, nucleophilic attack of ammonia on intermediate **III** followed by intramolecular cyclization leads to product **5**. In this mechanism, the surface atoms of nano-$CdZr_4(PO_4)_6$ activate the C=O groups for better reaction with nucleophiles. These surface atoms behave as the centers where chemical reactions could be catalytically stimulated.

Table 2 Synthesis of tetrahydrodipyrazolo pyridines

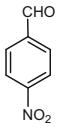
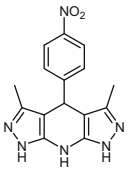
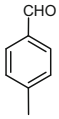
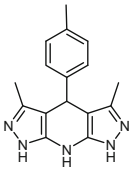
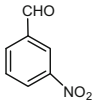
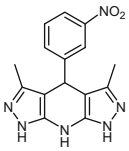
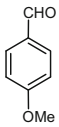
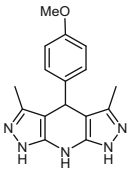
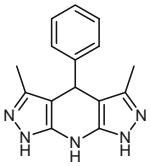
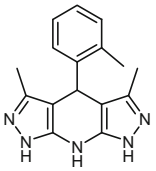
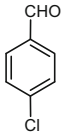
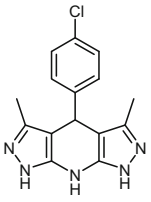
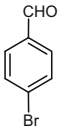
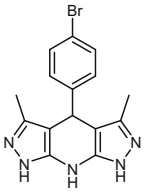
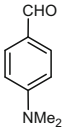
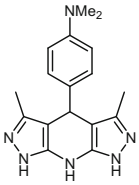
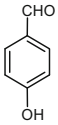
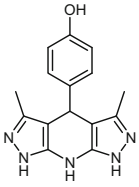
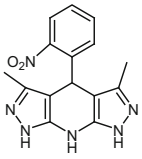
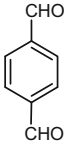
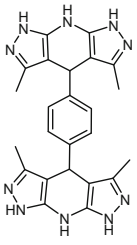
Entry	5a–5l	Aldehyde	Product	Time (min)	Yield (%)[a]	Melting points (°C)	
						Reported [References]	Found
1	**5a**			40	94	>300 [24]	295–297
2	**5b**			45	86	244–246 [24]	243–245
3	**5c**			42	90	286–288 [24]	286–288
4	**5d**			48	84	185–187 [24]	186–188
5	**5e**			43	88	240–242 [24]	240–242
6	**5f**			48	83	–	290–292
7	**5g**			40	92	254–256 [24]	255–257

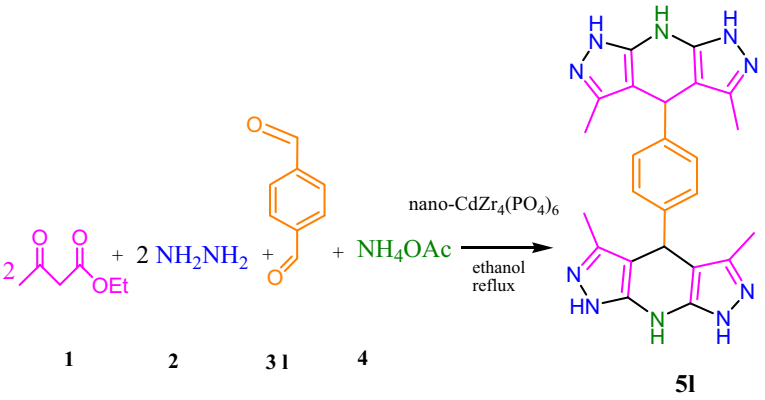
Table 2 continued

Entry	5a–5l	Aldehyde	Product	Time (min)	Yield (%)[a]	Melting points (°C)	
						Reported [References]	Found
8	**5h**			40	91	165–167 [25]	165–167
9	**5i**			50	82	240–242 [24]	240–242
10	**5g**			50	80	267–268 [25]	267–268
11	**5k**			40	91	187–188 [25]	187–188
12	**5l**			45	85	–	>300

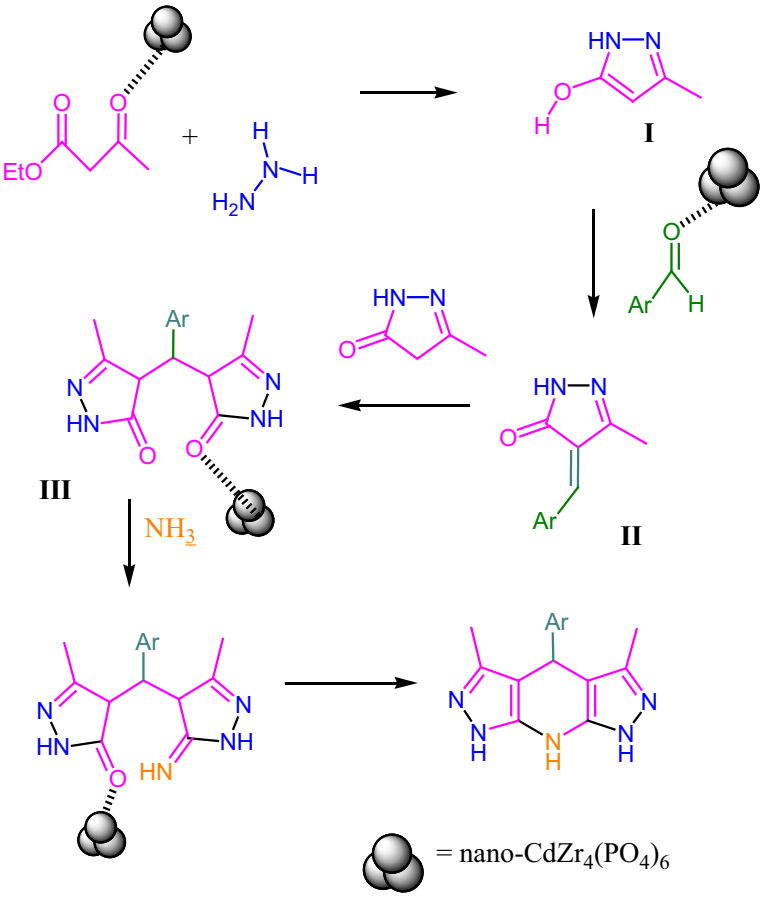
[a] Isolated yield

Conclusion

In conclusion, we have developed a straightforward and efficient approach to synthesis of tetrahydrodipyrazolopyridines by a simple one-pot pseudo six-component reaction of hydrazine hydrate, ethyl acetoacetate, aldehydes and ammonium acetate in the presence of nano-$CdZr_4(PO_4)_6$ as catalyst. The method



Scheme 2 Synthesis of 1,4-Bis[(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)] benzene by nano-$CdZr_4(PO_4)_6$



Scheme 3 Proposed mechanism for the pseudo six-component process

offers several advantages including rapid assembly of medicinally privileged heterocyclic molecules, cleaner reaction profiles, use of easily available, high yields, shorter reaction time and simple experimental and reusability of the catalyst. This green nanocatalyst could be used for other significant organic reactions and transformations. We hope that this article will serve to stimulate research in this fascinating and very useful area of organic synthesis.

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References

1. M.A. El-Borai, H.F. Rizk, D.M. Beltagy, I.Y. El-Deeb, Eur. J. Med. Chem. **66**, 415 (2013)
2. S. Abu-Melha, Arch. Pharm. Chem. Life Sci. **346**, 912 (2013)
3. J.A. Pfefferkorn, M. Tu, K.J. Filipski, A. Guzman-Perez, J. Bian, G.E. Aspnes, M.F. Sammons, W. Song, J.C. Li, C.S. Jones, L. Patel, T. Rasmusson, D. Zeng, K. Karki, M. Hamilton, R. Hank, K. Atkinson, J. Litchfield, R. Aiello, L. Baker, N. Barucci, P. Bourassa, F. Bourbounais, T. D'Aquila, D.R. Derksen, M. MacDougall, A. Robertson, Bioorg. Med. Chem. Lett. **22**, 7100 (2012)
4. K.S. Gudmundsson, B.N. Johns, S.H. Allen, Bioorg. Med. Chem. Lett. **18**, 1157 (2008)
5. H.D. Mello, A. Echevarria, A.M. Bernardino, M. Canto-Cavalheiro, L.L. Leon, J. Med. Chem. **47**, 5427 (2004)
6. M. Chioua, A. Samadi, E. Soriano, O. Lozach, L. Meijer, J. Marco-Contelles, Bioorg. Med. Chem. Lett. **19**, 4566 (2009)
7. N. Tschammer, J. Elsner, A. Goetz, K. Ehrlich, S. Schuster, M. Ruberg, J. Kuhhorn, D. Thompson, J. Whistler, H. Hubner, P. Gmeiner, J. Med. Chem. **54**, 2477 (2011)
8. C.J. Mitchell, S.P. Ballantine, D.M. Coe, C.M. Cook, C.J. Delves, M.D. Dowle, C.D. Edlin, J.N. Hamblin, S. Holman, M.R. Johnson, P.S. Jones, S.E. Keeling, M. Kranz, M. Lindvall, F.S. Lucas, M. Neu, Y.E. Solanke, D.O. Somers, N.A. Trivedi, J.O. Wiseman, Bioorg. Med. Chem. Lett. **20**, 5803 (2010)
9. N.C. Warshakoon, S. Wu, A. Boyer, R. Kawamoto, S. Renock, K. Xu, M. Pokross, A.G. Evdokimov, S. Zhou, C. Winter, R. Walter, M. Mekel, Bioorg. Med. Chem. Lett. **16**, 5687 (2006)
10. S. Wenglowsky, D. Moreno, J. Rudolph, Y. Ran, K.A. Ahrendt, A. Arrigo, B. Colson, S.L. Gloor, G. Hastings, Bioorg. Med. Chem. Lett. **22**, 912 (2012)
11. Z. Chen, X. Shi, Q. Shen, H. Xu, F. Zhang, Tetrahedron Lett. **56**, 4749 (2015)
12. P. Gunasekaran, P. Prasanna, S. Perumal, Tetrahedron Lett. **55**, 329 (2014)
13. A. Ghaedi, G.R. Bardajee, A. Mirshokrayi, M. Mahdavi, A. Shafiee, T. Akbarzadeh, RSC Adv. **5**, 89652 (2015)
14. H.S. Sohal, M. Kaur, R. Khare, K. Singh, Am. J. Org. Chem. **4**, 21 (2014)
15. J. Safaei-Ghomi, M. Asgari-Keirabadi, B. Khojastehbakht-Koopaei, H. Shahbazi-Alavi, Res. Chem. Intermed. **42**, 827 (2016)
16. J. Safaei-Ghomi, H. Shahbazi-Alavi, E. Heidari-Baghbahadorani, RSC Adv. **4**, 50668 (2014)
17. A.K. Arya, M. Kumar, Green Chem. **13**, 1332 (2011)
18. B. Liu, E. Wei, S. Lin, B. Zhao, F. Liang, Chem. Commun. **50**, 6995 (2014)
19. V. Polshettiwar, R.S. Varma, Green Chem. **12**, 743 (2010)
20. D.Q. Dong, H. Zhang, Z.L. Wang, Res. Chem. Intermed. (2016). doi:10.1007/s11164-016-2457-3
21. N. Gorodylova, V. Kosinova, Z. Dohnalova, P. Belina, P. Sulcova, Dyes Pigments **98**, 393 (2013)
22. D.M. Liu, Mater. Chem. Phys. **36**, 350 (1994)
23. J. Safaei-Ghomi, M. Navvab, H. Shahbazi-Alavi, Ultrason. Sonochem. **31**, 102 (2016)
24. K. Zhao, M. Lei, L. Hu, Monatsh. Chem. **142**, 1169 (2011)
25. N.G. Shabalala, R. Pagadala, S.B. Jonnalagadda, Ultrason. Sonochem. **27**, 423 (2015)