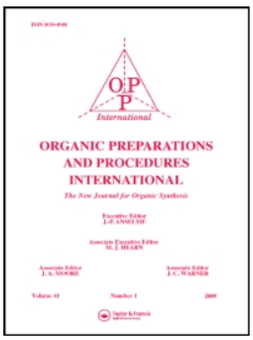

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ZnO Nanoparticle-Catalyzed Multicomponent Reaction for the Synthesis of 1,4-Diaryl Dihydropyridines

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Compounds in the 1,4-dihydropyridine (1,4-DHP) scaffold exhibit a wide range of pharmacological activities. The scaffold is the core of vasodilator, antitubercular, antiviral, antitumorous, antidiabetic, analgesic, anti-inflammatory, hypnotic and anticonvulsant agents.[1–5] Also, 1,4-DHPs are well known calcium channel blockers,[6] cocaine dependent regulators[7] and multidrug resistance (MDR) reversing agents.[8] Cardiovascular agents like amlodipine, nicardipine and nifedipine are effective antihypertensive drugs embracing the pyridine nucleus.[9,10] Pyridine based derivatives have broad applications in coordination chemistry, luminescent sensor materials, non-linear optical materials and also as ligands.[11–14] N-aryl substituted DHPs were found to be prominent sirtuin activators and inhibitors,[15] antidyslipidemic and antioxidant agents,[16] and potential inhibitors of the leishmania parasite.[17]

In view of the extensive biological profile of 1,4-DHPs, several synthetic methodologies have been reported in the literature. The classical Hantzsch synthesis is a multicomponent condensation of aldehydes with ethyl acetoacetate and ammonia.[18] However, this method requires long reaction times with low yields of products. Other commonly used methods include cycloaddition reactions, iminoannulation, ring closing metathesis (RCM), and coupling reactions of vinyl amides with alkenes or alkynes.[19–22] Certain improvements have been proposed to overcome the shortcomings of existing methods including use of ionic liquids;[23] silica supported acids,[24] metal triflates,[25] HY-zeolites,[26] boronic acids,[27] L-proline,[28] TMSCl/piperazine,[29] $InCl_3$,[30] and DBU,[31] were used as catalysts. The use of microwave,[32] ultrasound radiation,[33] and novel aqueous media[34] have also been reported.

Recently, Yan[35] and Liu[36] reported a multicomponent reaction (MCR) pathway for the synthesis of N-substituted DHPs (*Scheme 1, A* and *B*). The reaction required a long reaction time (about 4h or longer). In continuation of our own studies[37–41] it was thought worthwhile to develop cost effective, environmentally-benign nanoparticles to catalyze formation of

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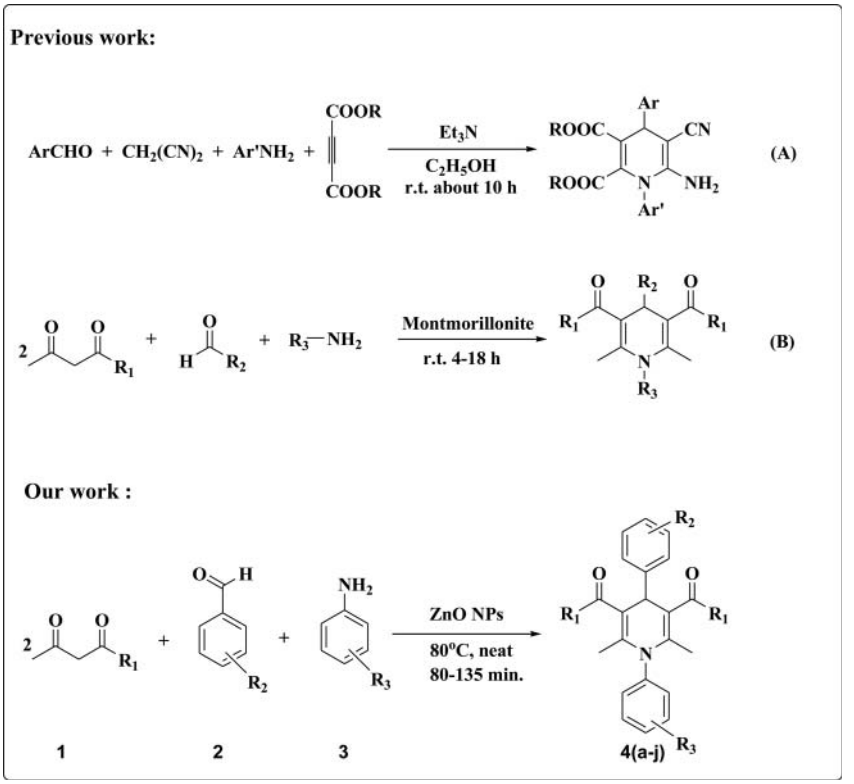
polysubstituted pyridines. We now report an efficient, convenient, and neat protocol for synthesizing 1,4-DHPs using zinc oxide nanoparticles (ZnO NPs) (*Scheme 1*, C) as the heterogenous support catalyst.

It is known that the surface of metal oxides possess both Lewis acid and base sites.[42] ZnO is certainly one of the most powerful metal oxides.[43–45]



Scheme 1 Multicomponent (MCR) synthesis of substituted-1,4-DHPs.

We prepared a number of substituted-1,4-DHP derivatives. This was achieved through a one pot three-component reaction among aldehydes, β-dicarbonyl compounds and substituted aromatic amines in a solvent free medium.

Characterization of the synthesized ZnO nanoparticles was performed by XRD, SEM, TEM, high resolution transmission electron microscopy (HRTEM), EDX, UV-visible spectroscopy and FTIR spectroscopy. *Figure 1* shows the XRD pattern of the ZnO NPs. An X-ray diffractogram depicted broadened peaks centered at 31.7°, 34.4°, 36.2°, 47.5°, 56.6°, 62.9°, 66.4°, 67.9°, 69.1°, 76.9° which were attributed to the presence of (100), (002), (101), (102), (110), (013), (200), (112), (201), (202) indices, respectively. All the diffraction peaks were indexed to the pure zincite hexagonal phase of ZnO (space group $P6_3mc$), having lattice parameters a = 3.25 and c = 5.21Å which are in accord with the standard JCPDS card no. 96-900-4180. No characterization peaks for any other phases of ZnO were observed, confirming the phase purity of the synthesized material. The sharpness of the peaks indicated the crystalline nature of the catalyst. The average crystallite size has been calculated using the Scherrer equation,

$$D = K\lambda/\beta \mathrm{Cos}\theta$$

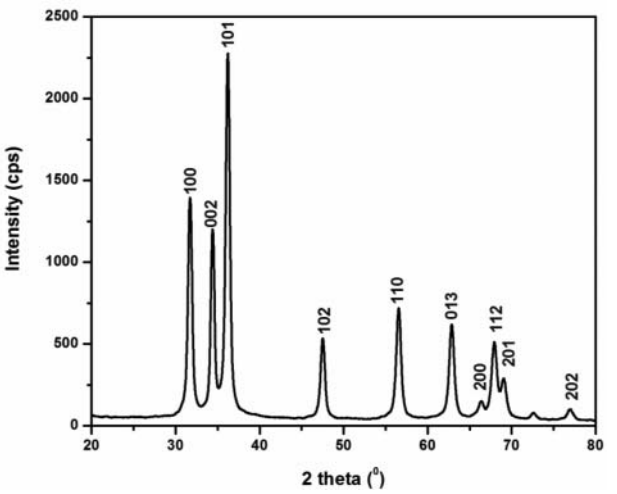


Figure 1 XRD pattern of Zinc oxide nano particles.

where D is the crystallite size, K is the particle shape factor whose value is 0.9, λ is wavelength of Cu Kα radiations (1.54 Å), β is the full width at half maximum (FWHM) of selected peak and θ is the Bragg's angle. The average crystallite size determined by the equation was found to be 21.3 nm.

The morphology of the catalyst was further determined by SEM and TEM analysis (*Figures 2 and 3*). SEM images of the catalyst resulted in flower like structures. The crystalline nature of the zinc oxide flowers was authenticated by

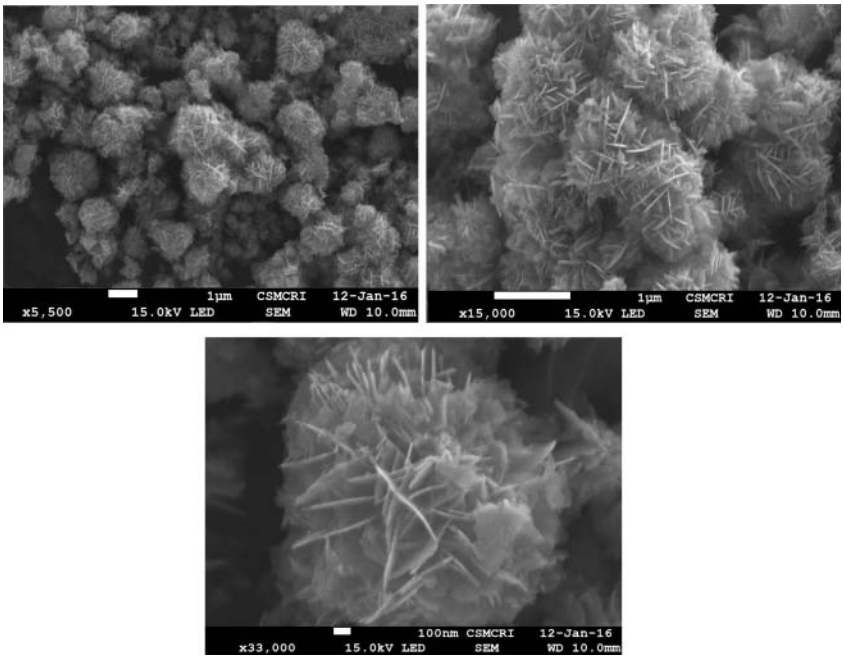


Figure 2 SEM images showing growth of flowerlike structure.

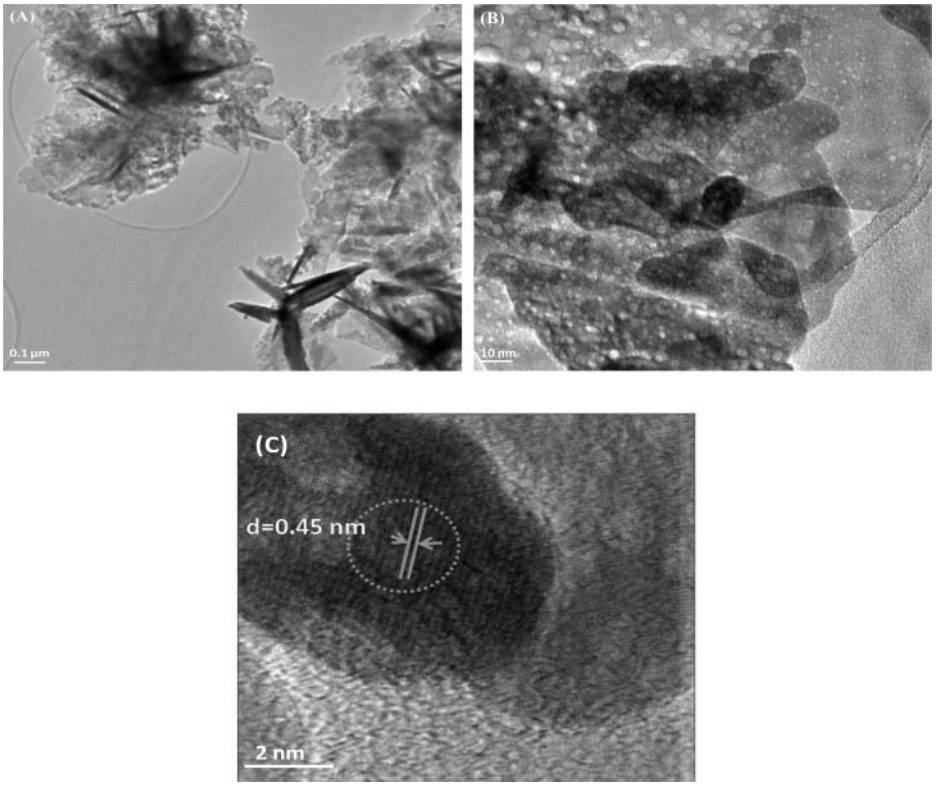


Figure 3 TEM and HRTEM images of ZnO NPs; (A,B) Growth of flowerlike structure (C) HRTEM showing interplanar spacing of 0.45 nm.

the XRD pattern. The diameter of the flower like structure is found to be in the range of 1–2 μm.

TEM images represent the growth of the flower like structure (*Fig. 3A and 3B*). The HRTEM image displayed clear lattice fringes and reveal the single crystalline nature of the sample. The measured lattice spacing is about 0.45 nm (Fig. 3C).

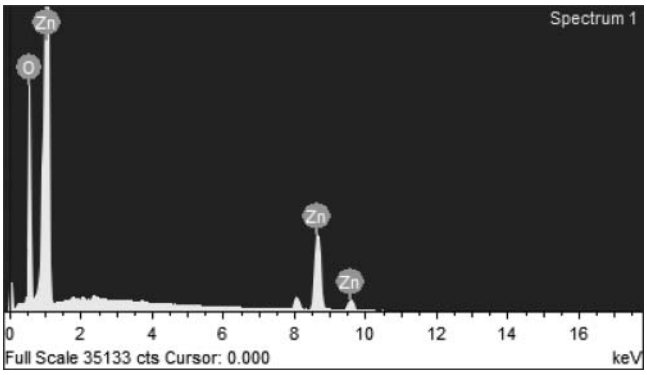


Figure 4 EDX spectrum of Zinc oxide nanoparticles.

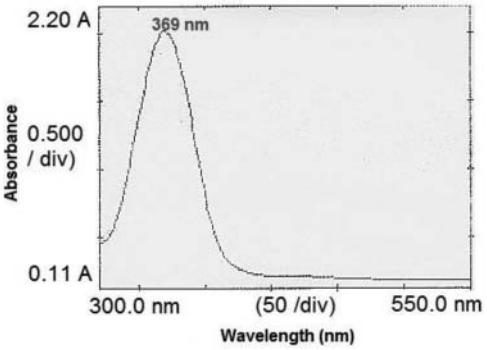


Figure 5 UV-visible spectrum of Zinc oxide nanoparticles.

The chemical purity of the samples was tested by EDX studies. The EDX spectra (*Figure 4*) ascertained the presence of zinc and oxygen as the only elements.

The UV-vis spectrum of the obtained nano-particles is depicted in *Figure 5*. Absorption at 369 nm was observed for the prepared ZnO NPs in 0.01M ethanolic solution. The band gap energy for this wavelength was 3.36 eV. The observed value is close to the electronic transition from the valence band to the conduction band ($O_{2p} \rightarrow Zn_{3d}$) of ZnO (band gap of 3.3 eV).[46]

The presence of a prominent peak at 364.07 cm^{-1} in the FTIR spectrum (*Figure 6*) showed the presence of Zn-O stretching vibration in the obtained ZnO NPs. The absence of any other IR peak confirms the structural purity of the prepared sample.

The role of ZnO NPs was explored as the catalytic support under solvent free conditions to synthesize our N-substituted-1,4-dihydropyridine derivatives. Optimization studies were carried out by reacting together benzaldehyde, ethyl acetoacetate and 4-bromo aniline in the presence of a variable catalytic amount of ZnO (5 mol% to 20 mol%).

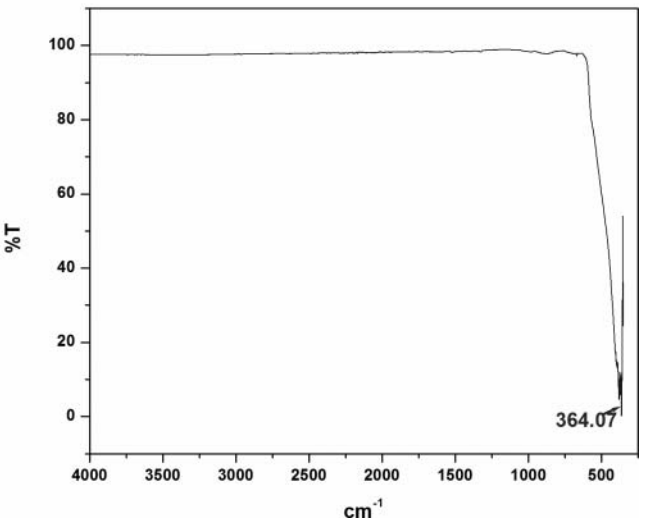


Figure 6 FTIR spectrum of Zinc oxide nanoparticles.

Table 1
Optimization of Catalyst Concentration for the Model Reaction[a]

Entry	Catalyst (mol%)	Time[b] (min.)	Yield[c] (%)
1.	ZnO NPs (5)	100	70
2.	ZnO NPs (10)	90	83
3.	ZnO NPs (15)	90	92
4.	ZnO NPs (20)	90	90
5.	ZnO bulk (15)	180	66
6.	ZnO bulk (20)	180	65

[a]Reaction condition: The mixture of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), and 4-bromo aniline (1 mmol) with different concentration of catalyst was heated at 80°C.
[b]All the reactions were monitored by TLC.
[c]Isolated yield.

Initially the reaction was carried out under ambient conditions using 5 mol% of catalyst loading in solvent free media. It was observed that a very poor yield was obtained even after the elapse of 6 hrs reaction time; no remarkable change took place on increasing the reaction time up to 8 hrs. To our surprise, the use of 15 mol% of ZnO at 80°C was found to afford the corresponding diethyl-1-(4-bromophenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5- dicarboxylate (*Table 1*, Entry 3) in 92% yield. The use of ZnO NPs in comparison to bulk ZnO reduces the reaction time by a factor of two with higher yields (*Table 1*, Entries 3 and 5). This may be attributed to the nanosize of the catalyst particles with enhancement in the surface area.

In order to investigate the effect of solvent media we have carried out the reaction in different solvents, including water (H_2O), methanol, acetonitrile (ACN) and dimethyl

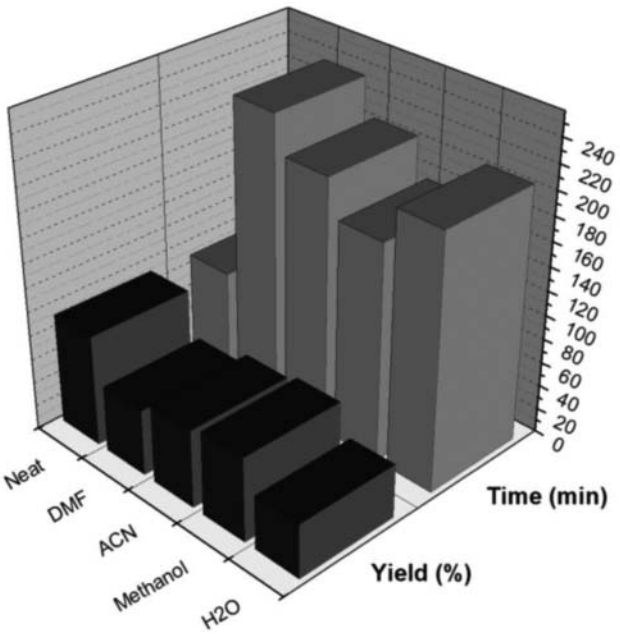
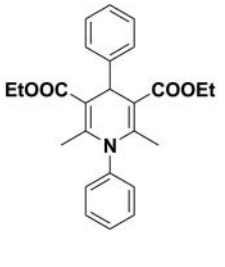


Figure 7 Graphical representation of solvent effect.

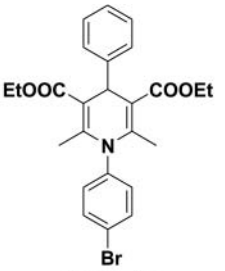
formamide (DMF). It was observed that this three-component one pot reaction resulted in the best outcome under neat reaction conditions (*Figure 7*).

With the optimized reaction conditions for the model system in hand, the scope and limitations of the protocol were explored for reactions of structurally diverse substrates (*Table 2*). The reaction can tolerate a variety of substituted aldehydes and anilines with both electron-withdrawing and electron-donating groups. Steric hindrance exerted an impact on the reaction time and yields. Among all the examined substituted anilines, para

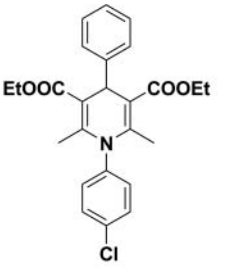
Table 2
Synthesis of Substituted 1,4-dihydropyridines Using Zinc Oxide Nanoparticles[a,b]



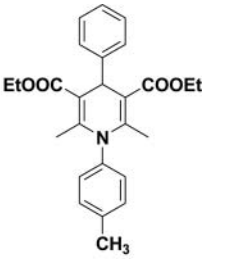
4a, Time 120
Yield 82 %



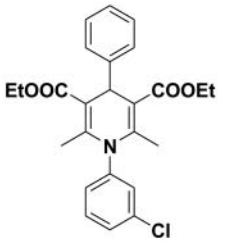
4b, Time 90
Yield 92 %



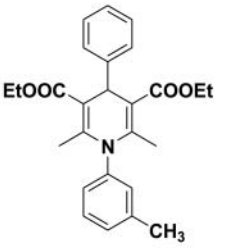
4c, Time 80
Yield 90 %



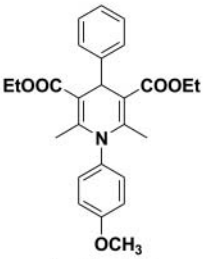
4d, Time 110
Yield 88 %



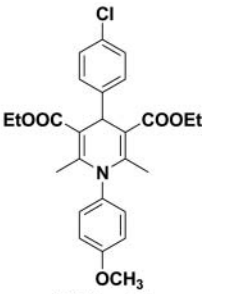
4e, Time 120
Yield 86 %



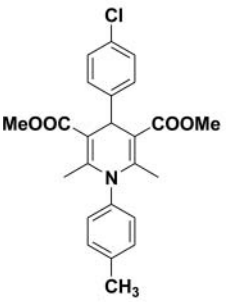
4f, Time 135
Yield 85 %



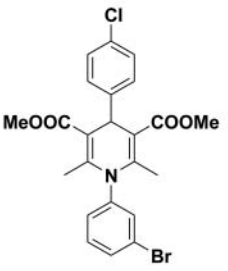
4g, Time 100
Yield 87 %



4h, Time 120
Yield 89 %



4i, Time 105
Yield 88 %

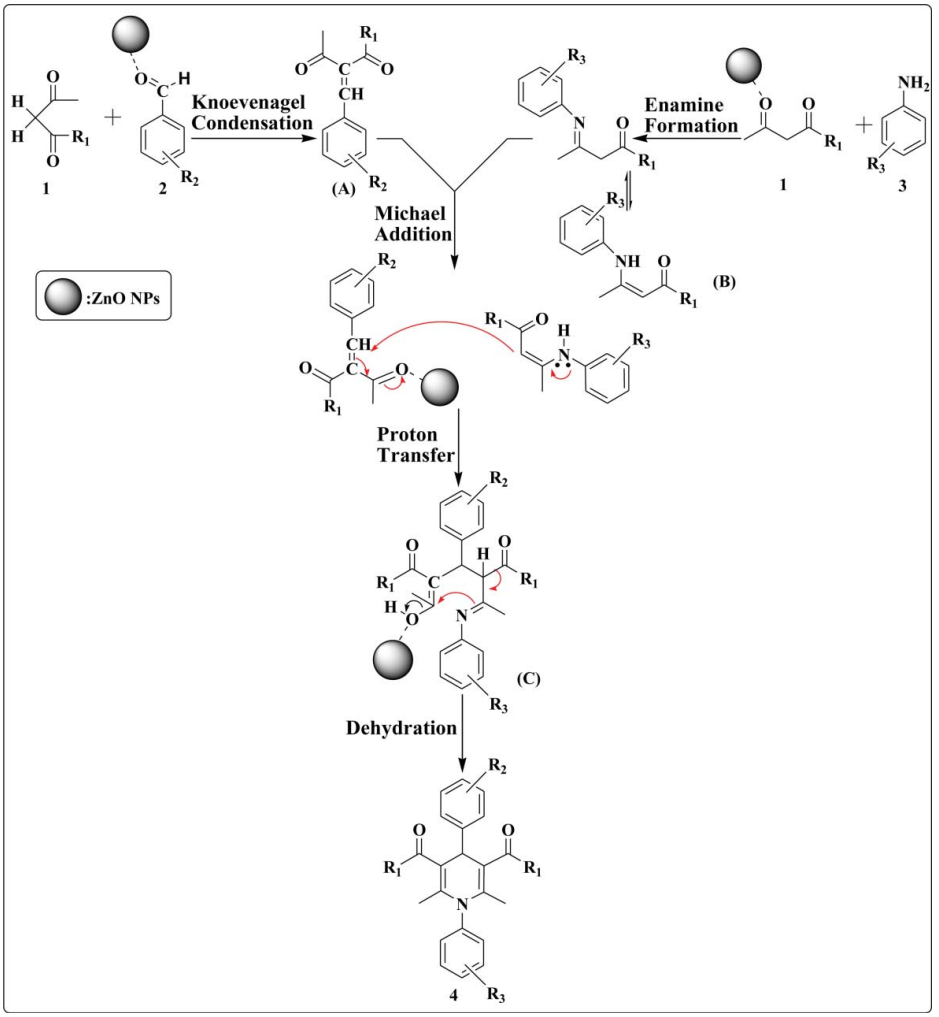


4j, Time 100
Yield 87 %

[a]Reaction conditions: The mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), and aniline (1 mmol) with 15 mol% catalyst was heated at 80°C.
[b]Isolated yield.

substituted compounds gave better yields in comparison to the meta substituted ones (*Table 2*, Entries 4c-4f).

A plausible mechanistic pathway for the formation of final product **4** is depicted in *Scheme 2*. The reaction may proceed through the formation of **A** by Knoevenagel condensation between **1** and **2**, which further undergoes Michael addition with enamine (**B**) (formed by reacting together **1** and **3**). In this mechanism the Lewis acid sites of the catalyst (Zn^{2+}) coordinate to the oxygen of carbonyl groups and Lewis basic sites (O^{2-}) help



Scheme 2 A plausible mechanistic pathway to the synthesis of 1,4-dihydropyridine (1,4-DHP).

in deprotonation of active methylene compounds. The Michael adduct **(C)** thus formed undergoes dehydration and affords the final 1,4-DHP **4**.

Recyclability and reusability of ZnO NPs were examined. After completion of the reaction, the catalyst was filtered, washed with distilled water and methanol, dried and activated at 150°C for 4 h, and reused for subsequent experiments (up to four cycles)

Table 3
Recyclability of the Zinc Oxide Nanocatalyst for the Synthesis of Diethyl-1-(4-bromophenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5- dicarboxylate **4b**

Entry	Cycle	Yield[a] (%)
1.	Cycle 1	92
2.	Cycle 2	89
3.	Cycle 3	87
4.	Cycle 4	84

[a]Isolated Yield.

under similar reaction conditions. It was noticed that there was only a minor variation in the yields of the product in these experiments (*Table 3*).

In conclusion, we have developed a simple, efficient and environmentally-benign MCR methodology. ZnO NPs have been used as the heterogenous catalyst for the synthesis of desired 1,4-diaryl dihydropyridines by reacting together aldehydes, β-dicarbonyl compounds and a number of substituted anilines. This one pot synthesis of 1,4-DHPs offer easy recovery and reusability of the catalyst. Furthermore, neat conditions, short reaction time, high yields and easy work up are among the noteworthy advantages.

Experimental Section

All chemicals were purchased from Sigma Aldrich and Merck India, and used without further purification. The reactions were performed in an aerobic atmosphere without any specific precautions. UV-visible spectrum was recorded on Schimadzu UV-visible spectrophotometer in a wavelength range of 300–550 nm. Fourier Transform Infra Red (FT-IR) spectra were recorded as ATR spectra and KBr pellets within the range of 4000–350 cm^{-1} using Frontier Perkin-Elmer FTIR SP 10 STD. The ^{1}H and ^{13}C NMR spectra of the synthesized compounds were recorded at 400 MHz using Bruker Avance II 400 NMR spectrometer in chloroform ($CDCl_3$) solvent, and the chemical shifts were expressed in parts per million. Mass analysis was performed on quadrupole-time-of-flight (Q-TOF) mass spectrometer (MICROMASS) using electrospray ionization (ESI) in positive mode. The XRD measurements were carried out on Bruker D8 Advance X-ray diffractometer using Cu K-alpha radiations of 0.154 nm. Transmission Electron Microscopic (TEM) images were recorded using Jeol (Jem-2100) electron microscope operated at an acceleration voltage of 200 kV. Scanning Electron Microscopic (SEM) images and their corresponding Electron Dispersive X-ray analysis (EDX) data were recorded by Jeol microscope (JSM7100F). Elemental analyses were performed on Thermo Scientific (Flash 2000) CHN Elemental Analyzer. Thin-layer chromatography (TLC) was performed using precoated aluminium sheets with silica gel 60 F254.

Synthesis of Catalyst

Catalyst synthesis was achieved by the hydrothermal chemical precipitation method with slight modifications.[47] A 25 ml aqueous solution of zinc acetate di-hydrate (0.5 M) was prepared at room temperature under constant stirring for 15 min. In another round bottomed flask, a homogenous solution was prepared by dissolving 1.25 M of sodium hydroxide in 25 ml of deionized (DI) water using a magnetic stirrer at room temperature

for 15 min. Afterwards the zinc acetate solution was added dropwise to the sodium hydroxide solution under constant and vigorous stirring for approximately 10 min. The solution was left under continuous stirring at room temperature for two hours; this yielded $Zn(OH)_2$ in the form of a white precipitate. The precipitate was filtered and washed with DI water and ethanol. The precipitate was dried at about 80°C in air followed by manual grinding to a fine powder. Finally, the product was calcined in a muffle furnace at 300°C for 12 h. The yield obtained was 1.5g.

General Procedure for the Synthesis of Compounds 4a-j: Diethyl 2,6-dimethyl-1, 4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

In a 50 ml round bottomed flask ethyl acetoacetate (0.25 ml, 2 mmol) **1a**, benzaldehyde (0.1 ml, 1 mmol) **2a** and a catalytic amount (15 mol%) of ZnO NPs were taken, followed by the addition of aniline (0.09 ml, 1mmol) **3a** at room temperature with stirring and heating at 80°C. The reaction progress was monitored by TLC (on aluminium sheets precoated with silica) using n-hexane/ethyl acetate (4:1) as the eluting system. After the completion of the reaction the mixture was cooled to room temperature and dissolved in 5 ml of methanol. The catalyst was separated out by filtration and the solvent was removed by rotary evaporator. Further purification of the product was achieved by column chromatography over silica gel using n-hexane/EtOAc (8:2, v/v) as the eluting system, yielding the pure product **4a**. Reddish brown semi solid; IR ($\bar{\upsilon}$, cm^{-1}) 3052, 2951, 2853, 1710, 1589, 1493, 1437, 1279, 1211, 1075, 750, 692; ^{1}H NMR (400 MHz, $CDCl_3$)δ: 1.28 (t, J = 7.2 Hz, 6H), 1.81 (s, 6H), 4.18 (q, J=7.2 Hz, 4H), 4.92 (s, 1H), 7.31–7.22 (m, 5H), 7.48–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 13.7, 14.5, 44.2, 59.8, 102.1, 115.8, 120.4, 126.3, 128.8, 129.1, 129.9, 142.3, 144.8, 155.2, 167.4; ESI MS, m/z $[M+H]^+$ 406.120.

Anal. Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found C, 73.93; H, 6.62; N: 3.51.

Diethyl 1-(4-bromophenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4b)

Yellowish brown semi solid; IR ($\bar{\upsilon}$, cm^{-1}): 3060, 2962, 2856, 1712, 1587, 1488, 1452, 1267, 1202, 1069, 823, 758, 659; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.7 Hz, 6H), 2.06 (s, 6H) 4.21 (q, J=7.7 Hz, 4H) 5.27 (s, 1H), 7.18 (d, J=8.2 Hz, 2H), 7.34–7.23 (m, 5H), 7.49 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.92, 18.4, 42.6, 59.8, 106.0, 116.4, 121.3, 126.1, 128.6, 132.5, 140.7, 146.1, 156.5, 167.7; ESI MS m/z $[M+H]^+$ 485.233.

Anal. Calcd. for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41; N, 2.89. Found C, 61.89; H, 5.32; N, 3.02.

Diethyl 1-(4-chlorophenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4c)

Reddish brown oil; IR ($\bar{\upsilon}$, cm^{-1}) 3073, 2955, 2849, 1708, 1592, 1484, 1440, 1275, 1210, 1076, 749, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 6H), 1.82 (s, 6H), 4.19 (q, J=7.2 Hz, 4H), 5.05 (s, 1H), 7.18 (d, J=8.2 Hz, 2H), 7.38–7.24 (m, 5H), 7.58 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 14.2, 42.8, 59.5, 103.4, 118.4, 124.2, 125.1, 128.5, 129.2, 129.9, 140.3, 143.9, 154.2, 165.2; ESI MS m/z $[M+H]^+$ 440.156.

Anal. Calcd. for $C_{25}H_{26}ClNO_4$: C, 68.25; H, 5.96; N, 3.18. Found C, 68.14; H, 5.82; N, 3.06.

Diethyl 2,6-dimethyl-4-phenyl-1-p-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (4d)
Dark brown semi solid; IR ($\bar{\upsilon}$, cm^{-1}) 3048, 2950, 2847, 1709, 1586, 1498, 1443, 1336, 1278, 1209, 1079, 729, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.6 Hz, 6H), 1.81 (s, 6H), 2.36 (s, 3H), 4.17 (q, J=7.6 Hz, 4H), 5.10 (s, 1H), 6.92 (d, J=8.4 Hz, 2H), 7.01 (d, J=8.4 Hz, 2H), 7.32–7.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.5, 24.2, 61.2, 106.2, 116.2, 126.2, 128.1, 128.8, 129.0, 130.0, 140.8, 146.7, 156.6, 167.9; ESI MS m/z $[M+H]^+$ 419.338.

Anal. Calcd. for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found C, 74.31; H, 6.82; N, 3.48.

Diethyl 1-(3-chlorophenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4e)
Reddish brown oil; IR ($\bar{\upsilon}$, cm^{-1}) 3069, 2953, 2847, 1710, 1590, 1481, 1441, 1276, 1208, 1074, 746, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=7.1 Hz, 6H), 1.79 (s, 6H), 4.16 (q, J=7.1 Hz, 4H), 5.09 (s, 1H), 7.20–7.06 (m, 4H), 7.40–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 13.9, 44.2, 61.1, 100.3, 101.9, 105.5, 109.4, 125.9, 128.6, 129.2, 131.4, 142.9, 153.8, 162.3, 165.8; ESI MS m/z $[M+H]^+$ 440.156.

Anal. Calcd. for $C_{25}H_{26}ClNO_4$: C, 68.25; H, 5.96; N, 3.18. Found C, 68.13; H, 5.82; N, 3.28.

Diethyl 2,6-dimethyl-4-phenyl-1-m-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (4f)
Reddish brown viscous oil; IR ($\bar{\upsilon}$, cm^{-1}) 3053, 2954, 2847, 1707, 1588, 1497, 1439, 1337, 1277, 1207, 1074, 732, 706; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24(t, J=7.2 Hz, 6H), 1.79(s, 6H), 2.38 (s, 3H), 4.15 (q, J=7.2 Hz, 4H), 4.99 (s, 1H), 6.89–6.80 (m, 4H), 7.30–7.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 14.1, 23.7, 44.2, 61.5, 102.5, 116.3, 120.4, 125.9, 128.4, 129.1, 138.9, 141.5, 142.9, 154.6, 167.2; ESI MS m/z $[M+H]^+$ 420.214.

Anal. Calcd. for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found C, 74.34; H, 6.85; N, 3.26.

Diethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5 dicarboxylate (4g)[36]
Dark yellow oil; IR ($\bar{\upsilon}$, cm^{-1}) 3389, 3059, 2936, 2845, 1710, 1591, 1491, 1435, 1219, 1062, 832, 740; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.1 Hz, 6H), 1.91 (s, 6H), 3.84 (s, 3H), 4.16 (q, J=7.1 Hz, 4H), 5.12 (s, 1H), 6.89 (d, J=8.6 Hz, 2H), 6.99 (d, J=8.6 Hz, 2H), 7.39–7.21 (m, 5H); ^{13}C NMR (100 MHz, CCl_3): δ 13.5, 14.2, 43.6, 55.6, 61.0, 102.9, 116.2, 117.5, 126.1, 128.5, 129.4, 133.6, 144.1, 148.2, 154.9, 167.5; ESI MS m/z $[M+H]^+$ 436.211.

Anal. Calcd. for $C_{23}H_{23}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found C, 71.58; H, 6.65; N, 3.39.

Diethyl 4-(4-chlorophenyl)-1-(4-methoxyphenyl-)2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h)[36]
Dark yellow oil; IR ($\bar{\upsilon}$, cm^{-1}): 3063, 2947, 2836, 1708, 1598, 1501, 1454, 1254, 1088, 760, 697. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=7.1 Hz, 6H), 1.69 (s, 6H), 3.87 (s, 3H), 4.14 (q, J=7.1 Hz, 4H), 5.08 (s, 1H), 6.75 (d, J=8.7 Hz, 2H), 6.92 (d, J=8.7 Hz, 2H), 7.52 (d, J=8.8 Hz, 2H), 8.12 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

13.9, 14.4, 42.2, 55.5, 61.2, 104.5, 115.3, 120.5, 128.3, 130.8, 131.4, 133.4, 144.3, 153.2, 158.9, 167.4; ESI MS m/z $[M+H]^+$ 470.129.

Anal. Calcd. for $C_{24}H_{24}ClNO_4$: C, 66.45; H, 6.01; N, 2.98. Found C, 66.30; H, 5.96; N, 3.10.

Dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-1-p-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (4i)

Orange red semi solid; IR ($\bar{\upsilon}$, cm^{-1}) 3061, 2979, 2946, 2839, 1711, 1594, 1499, 1451, 1339, 1221, 1084, 745, 693; ^{1}H NMR (400 MHz, CDCl3): δ 1.75 (s, 6H), 2.34 (s, 6H), 3.70 (s, 3H), 5.12 (s, 1H), 6.99 (d, J=8.4 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.8 Hz, 2H), 8.08 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 14.1, 23.8, 41.9, 51.8, 104.2, 117.7, 128.6, 129.7, 130.4, 131.6, 137.6, 141.2, 144.8, 153.5, 167.7; ESI MS m/z $[M+H]^+$ 426.141.

Anal. Calcd. for $C_{24}H_{24}ClNO_4$: C, 67.68; H, 5.68; N, 3.29. Found C, 67.55; H, 5.72; N, 3.35.

Dimethyl 1-(3-bromophenyl)-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j)

Reddish Brown semi solid; IR ($\bar{\upsilon}$, cm^{-1}) 3076, 2956, 2848, 1710, 1589, 1486, 1439, 1272, 1211, 1079, 782, 732, 670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (s, 6H), 3.72 (s, 6H), 5.18 (s, 1H), 7.16–7.02 (m, 4H), 7.49 (d, J=8.8 Hz, 2H), 8.10 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 42.9, 52.4, 104.4, 115.5, 116.1, 120.9, 124.3, 127.6, 130.2, 131.2, 131.9, 139.8, 143.9, 152.6, 165.9; ESI MS m/z $[M+H]^+$ 491.033.

Anal. Calcd. for $C_{23}H_{21}BrClNO_4$: C, 56.29; H, 4.31; N, 2.85. Found C, 56.12; H, 4.23; N, 2.94.

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