Four-Component Fusion Protocol with NiO/ZrO₂ as a Robust Recyclable Catalyst for Novel 1,4-Dihydropyridines

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Supporting Information

ABSTRACT: Nickel oxide loaded on zirconia (NiO/ZrO₂) as an expedient catalyst is reported for the synthesis of 18 unsymmetrical 1,4-dihydropyridine derivatives. The Lewis acidic nature of the catalyst proved an excellent choice for the one-pot, four-component fusion reaction with excellent yields of 89–98% and a completion time of 20–45 min. Mechanistic studies show that enamine and imine functionalities are the two possible pathways for the formation of 1,4-dihydropyridines with high selectivity. Crystal structures of two novel compounds (5a, 5c) were reported. The catalyst demonstrated reusability up to six cycles. The reaction at room temperature and ethanol as a solvent make this protocol green and economical.

INTRODUCTION

Catalysts play a crucial role in facilitating product selectivity and decreasing the activation energy of the reactions.1 Although homogeneous catalysts show better efficiency in chemo- and regioselectivity and their reaction mechanisms are better understood, their recovery from the reaction mixture is often difficult and involves several neutralization procedures.2 To overcome these drawbacks, heterogeneous catalysts are more chosen in organic synthesis. Because of their surface-to-volume ratio, the amount of heterogeneous catalyst required for the transformation is reduced, enabling the transformation to become both efficient and economical, and it is easy to separate from the reaction medium.3 In this context, mixed metal oxides as heterogeneous catalysts contributed significantly to organic synthesis because of their tunable characteristics of the versatile surface sites.4 The synergy between active metal and support typically dictates the catalytic properties of the material.5 In this context, nickel has been used both as a homogeneous and heterogeneous catalyst in many organic transformations like C−C bond formations, reductive eliminations including C=N and C=O bond formation reactions, and cross-coupling reactions.6 Zirconia has attracted more interest than other support materials because of its higher tolerance toward corrosion and high temperatures,7 as demonstrated by the use of ZrO₂ in the heat shield of space shuttles. Moreover, zirconia gained importance as a catalyst due to its surface properties by possessing both acidic and basic sites. The surface properties can be modified by loading/doping with suitable metals.8,9 Based on these advantages, we prepared materials with different loadings of Ni on ZrO₂ support and investigated their efficacy as a reusable catalyst for selective organic transformation. Previous reports demonstrated the use of NiO/ZrO₂ as a catalyst for simple conversions such as oxidative dehydrogenation10 and C−S cross-coupling reactions.11 This is the first report of using NiO/ZrO₂ as a catalyst in a multicomponent, one-pot reaction system.

Multicomponent reactions (MCRs) are important synthetic tools with the ability to craft complex organic molecules with high atom economy. An MCR is an ecofriendly means to synthesize libraries of biologically important scaffolds.12 Among the heterocyclic compounds, N-heterocyclic scaffolds in general acquired more prominence in the medicinal and pharmaceutical chemistry. In particular, 1,4-dihydropyridines (1,4-DHPs) are scaffolds of biological importance as antimicrobial,13 anti-tubercular,14 anticancer,15 anticoagulant,16 neuroprotector,17 antioxidant,19 L/T-type calcium channel blocking,20 AChE inhibiting,21 and bone anabolic agents.22 1,4-DHPs were first reported by Hantzsch in 1882 via the multicomponent reaction of aromatic aldehyde, β-ketoester, and ammonia as nitrogen sources.23 Well-known commercial drugs like felodipine, diludine, and nifedipine constitute 1,4-DHPs as the core moiety (Figure 1).

Due to the vast biological and synthetic importance of 1,4-DHP derivatives, several protocols have been reported via a one-pot strategy and employing different catalysts like...
nano-tungsten trioxide-supported sulfonic acid (n-WSA), sulfated boric acid nanoparticles, chitosan-supported copper(II) sulfate, Fe₃O₄@SiO₂@Si-(CH₂)₃@melamine-picolineimine@SO₃H, sulfated polyborate, Fe₃O₄/KCC-1/BPAT, chitosan-supported vanadium oxo, magnetic guanidinylated chitosan, nano-ZrO₂-SO₃H (n-ZrSA), Gd(OTf)₃, nicotinic acid, γ-Fe₂O₃/Cu@cellulose, SBA-15@AMPD-Co, sulfamic acid, Fe₃O₄@D-NH-(CH₂)₄-SO₃H, Cu-adenine@boehmite, hydromagnesite, Cu(OTf)₂, ascorbic acid, NS-C₄(DABCO-SO₃H)₂·4Cl, CBr₄, and aminated CNTs. Many of these methods either suffer from usage of reflux conditions, lower yields, or long reaction times.

We report for the first time NiO/ZrO₂ as a reusable catalyst in a one-pot four-component fusion reaction for the synthesis of novel 1,4-dihydropyridine derivatives at room temperature. We also report significant advances into the proposed mechanism based on the reaction intermediates, including a single-crystal structure.

RESULTS AND DISCUSSION

X-ray Diffraction (XRD) Analysis. Figure 2 shows the X-ray diffraction pattern of 2.5 wt % NiO–ZrO₂ and the diffraction peaks (2 theta) from 0 to 80°. The major diffraction peaks at 2θ of 24.5, 27.8, 31.3, 35.4, 40.5, 50.3, 54.4, 55.6, 57.8, 59.9, 65.4, and 71.2° for ZrO₂ are correlated with the international standard file (JCPDS 37-1484). The NiO peaks are displayed in the XRD diffractogram at 2θ = 37.2, 45.3, 62.8, 71.3, and 75.5° were further matched with the standard file (JCPDS 47-1049). The diffraction pattern revealed the polycrystalline nature of the prepared catalytic material.

Transmission Electron Microscopy (TEM) Analysis. The TEM investigation was performed to explore the catalyst morphology. Figure 3 illustrates a distinctive TEM image NiO/ZrO₂ (2.5 wt %). The image indicated an irregular cubic structure.
morphology with nominal agglomeration of NiO. It was further observed that the black irregular-shaped nickel oxide particles are evenly distributed on the surface of oval-shaped zirconia particles, which may improve catalytic activity.

**Scanning Electron Microscope (SEM) Analysis.** The surface morphology of 2.5 wt % NiO/ZrO₂ was assessed by SEM, which is shown in Figure 4. Figure 4a shows the irregular-round particles aggregated on the surface of ZrO₂. The surface was further analyzed by mapping and energy-dispersive X-ray spectroscopy (EDS) (Figure 4b,c), which show the even distribution of Ni on the surface of zirconia.

**Brunauer−Emmett−Teller Surface Area Analysis.** The 2.5 wt % NiO/ZrO₂ N₂ adsorption−desorption isotherm illustrated in Figure 5 shows a type-IV adsorption isotherm with a hysteresis loop of H₂, which is a characteristic of a mesoporous material (p/p₀ range of 0.67−0.98). The surface area is 76.35 m² g⁻¹ with a pore volume of 0.29 cm³ g⁻¹ and a pore size 12.14 nm.

**Pyridine IR.** The nature of the surface active sites was examined by ex-Pyridine IR. Pyridine is widely used as a probe to characterize the surface acidity of the materials.

**Table 1. Effect of Different Catalysts on the Synthesis of 5a**

| entry | catalyst solvent | condition | time (h) | yield (%) |
|-------|------------------|-----------|----------|-----------|
| 1     | −                | −         | RT       | 8         | 12        |
| 2     | −                | −         | reflux   | 8         | 17        |
| 3     | TEA             | EtOH      | RT       | 5.0       | 30        |
| 4     | pyridine        | EtOH      | RT       | 7.0       | 27        |
| 5     | DABCO           | EtOH      | RT       | 5.0       | 25        |
| 6     | NaOH            | EtOH      | RT       | 6.0       | 33        |
| 7     | K₂CO₃          | EtOH      | RT       | 6.0       | 29        |
| 8     | AcOH            | EtOH      | RT       | 3.5       | 36        |
| 9     | FeCl₃           | EtOH      | RT       | 5.0       | 38        |
| 10    | PTSA           | EtOH      | RT       | 6.0       | 45        |
| 11    | TFA            | EtOH      | RT       | 4.0       | 40        |
| 12    | SiO₂            | EtOH      | RT       | 4.0       | 53        |
| 13    | ZrO₂            | EtOH      | RT       | 2.0       | 68        |
| 14    | Al₂O₃          | EtOH      | RT       | 3.5       | 60        |
| 15    | NiO             | EtOH      | RT       | 2.5       | 65        |
| 16    | 2.5% CaO/ZrO₂  | EtOH      | RT       | 1.0       | 73        |
| 17    | 2.5% CeO₂/ZrO₂ | EtOH      | RT       | 0.75      | 81        |
| 18    | 2.5% NiO/ZrO₂  | EtOH      | RT       | 0.33      | 98        |
| 19    | 1% NiO/ZrO₂    | EtOH      | RT       | 0.50      | 91        |
| 20    | 5% NiO/ZrO₂    | EtOH      | RT       | 0.41      | 94        |

“Reaction conditions: 2,3,4-trimethoxybenzaldehyde (1 mmol) (1), ethyl acetoacetate (1 mmol) (2), 1,3-cyclohexadione (1 mmol) (3), and ammonium acetate (1 mmol) (4); 5 mL of solvent; and stirring at RT. Isolated yields. †100 mg of catalyst. ‡60 mg of catalyst. §30 mg of catalyst. "No catalyst.

**Table 2. Role of Different Solvent in the Synthesis of 5a**

| entry | solvent | time (h) | yield (%) |
|-------|---------|----------|-----------|
| 1     | n-hexane | 4.0      | −         |
| 2     | toluene  | 4.0      | −         |
| 3     | DMF      | 1.3      | 19        |
| 4     | THF      | 1.1      | 24        |
| 5     | MeCN     | 1.0      | 31        |
| 6     | CH₃OH    | 0.75     | 76        |
| 7     | C₂H₅OH   | 0.33     | 98        |

“Reaction conditions: 2,3,4-trimethoxybenzaldehyde (1 mmol) (1), ethyl acetoacetate (1 mmol) (2), 1,3-cyclohexadione (1 mmol) (3), and ammonium acetate (1 mmol) (4); 5 mL of solvent; and stirring at RT. No product.

**Table 3. Optimization of the Amount of 2.5% NiO/ZrO₂ Catalyst for the Synthesis of 5a**

| entry | catalyst (mg) | time (h) | yield (%) |
|-------|---------------|----------|-----------|
| 1     | 10            | 0.83     | 74        |
| 2     | 20            | 0.5      | 85        |
| 3     | 30            | 0.33     | 98        |
| 4     | 40            | 0.33     | 98        |
| 5     | 50            | 0.33     | 97        |
| 6     | 60            | 0.33     | 97        |

“Reaction conditions: 2,3,4-trimethoxybenzaldehyde (1 mmol) (1), ethyl acetoacetate (1 mmol) (2), 1,3-cyclohexadione (1 mmol) (3), and ammonium acetate (1 mmol) (4); 5 mL of EtOH; and stirring at RT.
Pyridine as a base interacts with Brønsted acid sites and through H⁺ transfer lead to the formation of pyridinium ion. Pyridine can act as a Lewis base, and it is capable to donate a pair of electrons toward the electrophilic Lewis acidic sites. Such characteristic bands are perceived in the range of 1550−1400 cm⁻¹. Based on this, the characteristic peak at 1448 cm⁻¹ corresponds to the Lewis acidic sites with bands at 1481 and 1531 cm⁻¹ that correspond to the Lewis + Brønsted and Brønsted acidic sites, respectively. Figure 6 confirms that the catalyst possesses prominent Lewis acidic sites, which could facilitate its catalytic activity.

**Reaction Optimization.** The catalytic efficiency of prepared NiO/ZrO₂ toward the title multicomponent reaction was evaluated. The reaction was performed by taking four components, 2,3,4-OMe benzaldehyde (1a), ethyl acetoacetate (1 mmol) (2), 1,3-cyclohexadiene/5,5-dimethyl-1,3-cyclohexanedione (1 mmol) (3), and ammonium acetate (1 mmol) (4); 5 mL of ethanol; 2.5% NiO/ZrO₂ (30 mg) catalyst; and stirring at RT; melting point (m.p.) in °C.

**Figure 7.** Library synthesis of novel unsymmetrical 1,4-dihydropyridine derivatives. Reaction conditions: substituted aldehydes (1 mmol) (1), ethyl acetoacetate (1 mmol) (2), 1,3-cyclohexadiene/5,5-dimethyl-1,3-cyclohexanedione (1 mmol) (3), and ammonium acetate (1 mmol) (4); 5 mL of ethanol; 2.5% NiO/ZrO₂ (30 mg) catalyst; and stirring at RT; melting point (m.p.) in °C.
same reaction conditions. SiO \textsubscript{2} gave 53% yield, Al\textsubscript{2}O\textsubscript{3} gave 60% in 3.5–4 h time, ZrO \textsubscript{2} gave a higher yield of 68% in 2 h time, and NiO gave 65% in 2.5 h time (Table 1, entries 12–15). Considering the interesting results from NiO and ZrO \textsubscript{2}, we identified the efficient catalyst, the scope of various ZrO \textsubscript{2}-based mixed oxide catalysts, 2.5 wt % CuO/ZrO \textsubscript{2}, CeO\textsubscript{2}/ZrO \textsubscript{2}, and NiO/ZrO \textsubscript{2} (Table 1, entries 16–18) were investigated. An impressive yield of 98% was observed with 2.5% NiO/ZrO \textsubscript{2} in a relatively short time of 20 min compared to 73% in 60 min with 2.5% CuO/ZrO \textsubscript{2} (Table 1, entry 16) and 81% yield in 45 min (Table 1, entry 17) with 2.5% CeO\textsubscript{2}/ZrO \textsubscript{2}. While using 1% NiO/ZrO \textsubscript{2} catalyst yielded 91% product in 30 min under similar conditions (Table 1, entry 19), 5% NiO/ZrO \textsubscript{2} led to a slight decreased yield (94%) in 25 min (Table 1, entry 20). Therefore, 2.5% NiO/ZrO \textsubscript{2} was the preferred catalyst for further studies. The higher catalytic activity may be due to the even distribution of the active material on the surface of the support and availability of more optimally active NiO sites in combination with ZrO \textsubscript{2}, which help in speeding up the rate of reaction selectively compared to 1 and 5% catalyst. For the 1% NiO/ZrO \textsubscript{2} catalyst loading, the particles are small and have a high surface area but less number of active sites compared to the 2.5% NiO/ZrO \textsubscript{2}, whereas for 5% NiO/ZrO \textsubscript{2} loading, the nickel particles are visibly larger and hence have a smaller surface area, thus slightly lower yield when compared to the 2.5% NiO/ZrO \textsubscript{2}. Hence, 2.5% NiO/ZrO \textsubscript{2} acts as a good promoter for the present transformation.

To further optimize the conditions, we examined the role of the solvent in the organic conversion employing different nonpolar and polar solvents (Table 2). In the presence of nonpolar solvents like n-hexane and toluene at RT, no product was identified even after 4 h possibly due to the poor solubility of the reactants. Among the polar solvents such as DMF, THF, MeCN, EtOH, and MeOH, the highest yields were observed employing the optimized conditions, of which 12 were novel derivatives. All of the 18 derivatives gave excellent yields in a relatively short time of 10 min (Figure 11). Characterization relied on liquid chromatography–mass spectrometry (LC–MS) studies and was based on peaks identified at 112 and 130 corresponding to the presence of enamine, the peak at 309 corresponding to imine, and the peak at 291 to the existence of a Knoevenagel condensation transient intermediate. Based on experimental observations, the generation of the final product is proposed to occur through two pathways: (i) by enamine and (ii) by imine, which is supported by the literature reports.45,46 In the proposed scheme, the key intermediates in the reaction are designated as (6), (7), (8), and (9). It is assumed that for the formation of a knoevenagel intermediate\textsuperscript{47} between 2,3,4-OMe benzaldehyde (1) and 1,3-cyclohexanedione (2), Lewis acidic sites present on the surface plays a key role, which can activate the carbonyl group of aldehyde and make it electrophilic to form an intermediate (a) and then react with nucleophilic 1,3-cyclohexanedione (2), which further will dissociate from the catalyst surface by taking a proton from the solvent ethanol to give the intermediate (b) and to give (6) upon further dehydration. Similarly, (7) is also formed by the same procedure with the reaction of ethyl acetoacetate through the intermediate (c).

At $\delta = 18.04, 26.29, 110.54, 103.90, 143.42, 167.28,$ and 194.25. The HRMS showed the m/z = 400.1770 [C\textsubscript{23}H\textsubscript{27}NO\textsubscript{6}-H\textsuperscript{+}], which corresponds well with the theoretical value for 5a.

**Insight into the Mechanism.** To examine the mechanism of the present reaction, an attempt was made to identify the reaction intermediates by analyzing the reaction mixture after 10 min (Figure 11). Characterization relied on liquid chromatography–mass spectrometry (LC–MS) studies and was based on peaks identified at 112 and 130 corresponding to the presence of enamine, the peak at 309 corresponding to imine, and the peak at 291 to the existence of a Knoevenagel condensation transient intermediate. Based on experimental observations, the generation of the final product is proposed to occur through two pathways: (i) by enamine and (ii) by imine, which is supported by the literature reports.45,46 In the proposed scheme, the key intermediates in the reaction are designated as (6), (7), (8), and (9). It is assumed that for the formation of a knoevenagel intermediate\textsuperscript{47} between 2,3,4-OMe benzaldehyde (1) and 1,3-cyclohexanedione (2), Lewis acidic sites present on the surface plays a key role, which can activate the carbonyl group of aldehyde and make it electrophilic to form an intermediate (a) and then react with nucleophilic 1,3-cyclohexanedione (2), which further will dissociate from the catalyst surface by taking a proton from the solvent ethanol to give the intermediate (b) and to give (6) upon further dehydration. Similarly, (7) is also formed by the same procedure with the reaction of ethyl acetoacetate through the intermediate (c).
Furthermore, ammonium acetate (4) acts as a nitrogen source to further dissociate to ammonia (4a). The enamine intermediates (8) and (9) are formed by the reaction of ammonia (4a) with (2) and (3) on the catalyst surface. Enamine (8) possibly reacts with (7) and undergoes Michael addition to give the key structure (11). The ring closure of (11) leads to the formation intermediate (12), which undergoes dehydration, finally yielding the stable product, 5a. Similarly, the enamine (9) upon reaction with (6) gives (13) via Michael addition and subsequent ring closure generates intermediate (14), which upon dehydration offers 5a. The enamine (9) reacts with (1) to give an imine intermediate (10), which further reacts with (2) to give (13). Further ring closure provides the intermediate (14) followed by dehydration, which gives 5a (Scheme 2). The comparative catalytic efficiency of the 2.5% NiO/ZrO2 with other reported catalysts is given in Table 5.

Moreover, green metrics calculations for a series of synthesized 1,4-dihydropyridine derivatives were performed.

### Table 4. Single-Crystal Data of 5a and 5c

| Identification code | 5a       | 5c       |
|---------------------|----------|----------|
| Empirical Formula   | C_{22}H_{27}NO_{6} | C_{20}H_{23}NO_{3} |
| Formula Weight      | 401.44   | 325.39   |
| Temperature (K)     | 100.0    | 100.0    |
| Crystal System      | orthorhombic | triclinic |
| Space Group         | Pna2_1   | P-1      |
| a (Å)               | 14.6636(6) | 7.2992(10) |
| b (Å)               | 8.4477(3)  | 9.5818(10) |
| c (Å)               | 15.5290(6) | 12.3976(2) |
| α (°)               | 90       | 83.9450(10) |
| β (°)               | 90       | 86.8650(10) |
| γ (°)               | 90       | 71.9730(10) |
| Volume (Å³)         | 1926.26(13) | 819.69(2)  |
| Z                   | 4        | 2        |
| Dcalc (g/cm³)       | 1.384    | 1.318    |
| μ (mm⁻¹)            | 0.101    | 0.088    |
| Crystal size (mm³)  | 0.38 × 0.24 × 0.16 | 0.31 × 0.23 × 0.12 |
| Radiation           | Mo Kα (λ = 0.71073) | Mo Kα (λ = 0.71073) |
| 2θ range for data collection (°) | 5.246–56.7 | 3.304–57.038 |
| Index ranges        | −19 ≤ h ≤ 15, −11 ≤ k ≤ 11, −20 ≤ l ≤ 20 | −9 ≤ h ≤ 9, −12 ≤ k ≤ 12, −16 ≤ l ≤ 16 |
| Independent reflections | 4622 [R_{int} = 0.0196, R_{sym} = 0.0237] | 4083 [R_{int} = 0.0179, R_{sym} = 0.0131] |
| Data/restraints/parameters | 4622/1/267 | 4083/0/220 |
| Goodness-of-fit on F² | 1.024 | 1.048 |
| Final R indexes [I ≥ 2σ(I)] | R₁ = 0.0312, wR₂ = 0.0772 | R₁ = 0.0365, wR₂ = 0.0972 |
| Final R indexes [all data] | R₁ = 0.0345, wR₂ = 0.0796 | R₁ = 0.0408, wR₂ = 0.1008 |
| Largest diff. peak/hole (e Å⁻³) | 0.29/−0.21 | 0.40/−0.19 |

Figure 10. ¹³C chemical shifts and selected HMBC interactions of −CH and −NH protons of 5a.

Figure 11. LC–MS spectra of the reaction mixture with compound 5a.
For the proposed method, the calculated atom economy and atom efficiency ranges from 74.1 to 83.2%, which are below 100% due to the loss of three H₂O molecules and one acetate ion as byproducts, and E factors ranging from 0.26 to 0.44 g/g are also validated and indicate the good green credential of the present protocol. The other green metrics are shown in Table S1, page S50 (Supporting Information).

**Reusability of the Catalyst.** To examine the catalyst stability, recyclability experiments were conducted. After every run, the catalyst was recovered from the reaction mixture, washed with ethanol, and dried at 120 °C for 2 h. For the first six cycles, the catalyst proved efficient and the activity was retained with no loss. Afterward, the material catalytic activity decreased in the seventh cycle (Figure 12). To examine the heterogeneity of the used 2.5% NiO/ZrO₂ catalyst, a hot filtration method was employed for the synthesis of 5a. Ten minutes after the start of the reaction, the catalyst was removed from the reaction mixture through centrifugation and the remaining reaction mixture was kept under the same stirred condition to monitor the reaction progress. Even after 60 min, no reaction or increase in the product yield was observed (Figure 13). From the above result, it shows that the catalyst...
leaching is very low. Furthermore, the catalyst after the reaction was analyzed by XRD and TEM incorporated (Figure S1). The XRD pattern of the reused material is much similar to that of the fresh one; furthermore, from the TEM image of the reused catalyst, there is as much similar to that of the fresh one, which indicates that there is no such erosion of the active material from the support, which shows the presence of the heterogeneous nature of material.

![Figure 12. Recycling study of 2.5% NiO/ZrO2 catalyst for the synthesis of 1,4-dihydropyridine 5a.](image)

**CONCLUSIONS**

We introduced NiO/ZrO2 as an efficient and cost-effective catalyst for the synthesis of 12 novel 1,4-dihydropyridine derivatives in a four-component, one-pot strategy. This method proved effective toward the reaction of aromatic, heteroaromatic, and aliphatic aldehydes obtained with high yields. ESI-MS/MS studies are conducted, and insights into the mechanism of the reaction are proposed, which revealed that 1,4-DHPs mainly follow the enamine and imine pathways.

![Figure 13. Hot filtration test results of 2.5% NiO/ZrO2 catalyst for 5a. Reaction conditions: 2,3,4-trimethoxybenzaldehyde (1 mmol) (1), ethyl acetoacetate (1 mmol) (2), 1,3-cyclohexadiene (1 mmol) (3), and ammonium acetate (1 mmol) (4); 5 mL of EtOH; and stirring at RT.](image)

We anticipate that this catalytic system will find further applications in both academic and industrial fields, and the prepared series of 1,4-DHPs may provide potential biological activity in the area of pharmaceutical sector.

**EXPERIMENTAL SECTION**

**Catalyst Preparation.** A series of nickel oxide-loaded zirconia (NiO/ZrO2) catalysts with different weight percentages (1, 2.5, and 5 wt %) of Ni were prepared by the wet impregnation method. A mixture of zirconium oxide (ZrO2, 2 g, Alfa Aesar) and appropriate amount (wt %) of nickel sulfate (NiSO4·6H2O, Alfa Aesar) in 60 mL of deionized water was stirred for 7 h at room temperature. The resultant slurry was filtered under vacuum and dried at 100 °C for 6 h, followed by calcination at 450 °C for 6 h in the presence of air, to obtain...
different weight percents of NiO/ZrO₂. Instrumentation details are included in the Supporting Information (page S2).

General Method for the Synthesis of Series of 1,4-Dihydropyridine Derivatives (5a−r). For the synthesis of a series of 1,4-dihydropyridine derivatives, the reaction was performed in a 25 mL round-bottom flask containing 5 mL of EtOH as a solvent. To these equimolar quantities of substituted aldehyde, ethyl acetooacetate, ammonium acetate, and 1,3-cyclohexadiene, was added 30 mg of NiO/ZrO₂ and stirred at room temperature (RT) (Scheme 3). TLC was used to monitor the progress of the reaction at regular time intervals. After completion of the reaction, the catalyst was filtered by adding excess ethanol. The solvent was then evaporated, and the pure product was afforded by recrystallization from EtOH. The details and spectra are given in the Supplementary Information (pages S5–S12 and S13–S49).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b02608.

CIF file for compound 5a (CIF)
CIF file for compound 5c (CIF)
Catalyst instrumentation details; XRD and TEM images; ¹H NMR spectra; ¹⁵N NMR spectra; ¹³C NMR spectra; HMBC spectra; HRMS spectra; and green metrixes (PDF)

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Notes

The authors declare no competing financial interest.

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