ZnO nanoparticles: An efficient reagent, simple and One-Pot Procedure for Synthesis of Highly Functionalized Dihydropyridine Derivatives

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Abstract: A new and efficient one-pot synthesis of dihydropyridones derivatives by four-component reaction between cyanoacetamide, aryl aldehydes, and ethyl acetoacetate with ammonium acetate using nano ZnO is described. The reaction was performed in ethanol under reflux conditions and afforded good yields of products.

Keywords: Dihydropyridones derivatives, Ammonium acetate, Cyanoacetamide, Aryl aldehydes, Multi-component reaction, ZnO nanoparticles.

Introduction

Substituted dihydropyridones derivatives are important intermediates in the pharmaceutical, dye and photo industries.¹ pyridones are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products such as NAD nucleotides, pyridoxol (vitamin B₆), and pyridine alkaloids.² Due to their π-stacking ability, some pyridines are used in supramolecular chemistry.³ Some examples are used as pharmaceuticals (as antimalarial, vasodilator, anesthetic, anticonvulsant, and antiepileptic), dyes, additives (as antioxidant), agrochemicals (as fungicidal, pesticidal, and herbicidal), veterinary (as anthelmintic, antibacterial, and antiparasitic), and also in qualitative and quantitative analysis.⁴⁻⁷ So far, the most common synthetic methods for the preparation of pyridine ring systems involve: transformation of another ring, and cyclizations classified on the basis of the number of ring atoms in each of the components being cyclized: from six ring atoms by N–Cα, Cα–Cβ, or Cβ–Cγ bond
formation; by formation of two bonds, from [5+1], [4+2], or [3+3] atom fragments; by formation of three bonds, from [4+1+1], [3+2+1], or [2+2+2] atom fragments; and by formation of four bonds, from [3+1+1+1] or [2+2+1+1] atom fragments. Synthesis of 4-aryl-3-cyano-2,5-dihydro pyridin-2-one derivatives under solvent-Free conditions we reported.

Nanomaterials have attracted considerable interest in the last decade because of their unique properties in physics and chemistry as well as their potential industrial applications. Among these materials, ZnO is an important semiconductor material, having a wide range of properties. The size and morphology of ZnO nanoparticles have great influences on their performances. Recently, efforts have been made for the synthesis of ZnO particles with controlled morphologies. Wurtzite-type ZnO crystals are used for a wide variety of industrial applications, such as semiconductors, catalysts, room-temperature UV lasers, and sensors.

**Experimental**

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Islamic Azad University Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. \(^1\)H and \(^13\)C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. \(^1\)H and \(^13\)C NMR spectra were obtained on solution in CDCl\(_3\) using TMS as internal standard. Column chromatography was performed with Merck silica gel 60, 230–400 mesh. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

**General procedure**

In a typical experiment, a mixture of ZnO nanoparticles (10 mol%), aryl aldehydes 1 (1 mmol), and cyanoacetamide 2 (1 mmol) in ethanol (20 mL) was stirred at room temperature for 3h and was added to it a solution of ethyl acetoacetate (1 mmol) 3 and NH\(_4\)OAc (1 mmol) and was refluxed for 8h. After completion of the reaction, as indicated by TLC, the product was extracted with ethyl acetate (10 mL). The combined organic extracts were concentrated in vacuum and the resulting product was purified by column chromatography on silica gel with ethyl acetate and n-hexane (1:1) as eluent to afford the pure product.

**Ethyl 5-cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine 3-carboxylate (1A)**

White powder, (59 %), m.p. 143–145°C, IR (KBr) (\(\nu_{max}/\text{cm}^{-1}\)): 3411 (NH), 2234 (CN), 1709 (C=O) MS, m/z (%): 284 (M\(^+\), 5). Anal. Calcd for C\(_{16}\)H\(_{16}\)N\(_2\)O\(_3\): C, 67.59; H, 5.67; N, 9.85 %. Found: C, 67.43; H, 5.72; N, 9.75 %. \(^1\)H NMR (500.1 MHz, CDCl\(_3\)): \(\delta = 0.80(3\text{H, t, } 3J_{HH} = 7 \text{ Hz, CH}_3), 2.38 (3\text{H, s, CH}_3), 4.09 (2\text{H, q, } 3J_{HH} = 7 \text{ Hz, CH}_2), 4.16 (H, d, 3J_{HH} = 7.1 \text{ Hz, CH}, 4.47 (H, d, 3J_{HH} = 7.1 \text{ Hz, CH}), 7.26-7.61 (5\text{H, m, aromatic}), 13.38(1 \text{H, broad s, NH}). \(^13\)C NMR (125.7 MHz, CDCl\(_3\)): \(\delta = 14.50 \text{ and } 19.27 (2\text{CH}_3), 41.66 \text{ and } 41.97 (2\text{CH}), 61.23 (\text{CH}_2), 108.12 (\text{CN}), 114.62 \text{ and } 146.48 (C=C), 128.25, 128.95, 129.45, 136.47 \text{ (aromatic), 163.71 and 165.91 (2C=O).}

**Ethyl 5-cyano-2-methyl-6-oxo-4-(4-chlorophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (2A)**

White powder, (58 %), m.p. 162–164°C, IR (KBr) (\(\nu_{max}/\text{cm}^{-1}\)): 3403 (NH), 2273 (CN), 1706 (C=O) MS, m/z (%): 318 (M\(^+\), 10). Anal. Calcd for C\(_{16}\)H\(_{15}\)ClN\(_2\)O\(_3\): C, 60.29; H, 4.74; N,
8.79%. Found: C, 60.20; H, 4.87; N, 8.63%. ¹H NMR (500.1 MHz, CDCl₃): 1H₂O 182.49 (NCH₂), 165.97 and 166.92 (C=O). ¹H NMR (125.7 MHz, CDCl₃): 1H₂O 182.49 (NCH₂), 165.97 and 166.92 (C=O). 

**Ethyl 5-cyano-2-methyl-6-oxo-4-(4-bromophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (3A)**

White powder, (61 %), m.p. 175–177°C, IR (KBr) (vmax/cm⁻¹): 3414 (NH), 2210 (CN), 1697 (C=O) MS, m/z (%): 363 (M⁺, 8). Anal. Calcd for C₁₈H₁₄BrN₂O₃: C, 52.91; H, 4.16; N, 7.71%. Found: C, 52.60; H, 4.25; N, 7.61%. ¹H NMR (500.1 MHz, CDCl₃): 1H₂O 182.49 (NCH₂), 165.97 and 166.92 (C=O). 

**Ethyl 5-cyano-2-methyl-6-oxo-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (4A)**

White powder, (57 %), m.p. 134–136°C, IR (KBr) (vmax/cm⁻¹): 3415 (NH), 2220 (CN), 1705 (C=O) MS, m/z (%): 314 (M⁺, 12). Anal. Calcd for C₁₇H₁₃BrN₂O₃: C, 64.96; H, 5.77; N, 8.91%. Found: C, 64.88; H, 5.70; N, 8.95%. ¹H NMR (500.1 MHz, CDCl₃): 1H₂O 182.49 (NCH₂), 165.97 and 166.92 (C=O). 

**Ethyl 5-cyano-2-methyl-6-oxo-4-(2-nitrophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (5A)**

White powder, (54 %), m.p. 166–168 °C, IR (KBr) (vmax/cm⁻¹): 3400 (NH), 2250 (CN), 1704 (C=O), 1346 and 1523 (NO₂). ¹H NMR (500.1 MHz, CDCl₃): 1H₂O 182.49 (NCH₂), 165.97 and 166.92 (C=O). 

**Ethyl 5-cyano-2-methyl-6-oxo-4-(3-nitrophenyl)-1,4,5,6-tetrahydropyridine 3-carboxylate (6A)**

White powder, (68 %), m.p. 190–192 °C, IR (KBr) (vmax/cm⁻¹): 3401 (NH), 2223 (CN), 1707 (C=O), 1319 and 1525 (NO₂). ¹H NMR (500.1 MHz, CDCl₃): 1H₂O 182.49 (NCH₂), 165.97 and 166.92 (C=O).
White powder, (63 %), m.p. 183–185 °C, IR (KBr) (ν_max/cm⁻¹): 3407 (NH), 2255 (CN), 1715 (C=O), 1345 and 1515 (NO₂). MS, m/z (%): 329 (M⁺, 10). Anal. Calcd for C₁₈H₁₃N₃O₅: C, 58.36; H, 4.59; N, 12.76%. Found: C, 58.50; H, 4.71; N, 12.53%. ¹H NMR (500.1 MHz, CDCl₃): δ = 1.06 (3H, t, J_HH = 7 Hz, CH₃), 2.31 (3H, s, CH₃), 3.98 (2H, q, J_HH = 7 Hz, CH₂), 4.13 (H, d, J_HH = 7.1Hz, CH), 4.18 (H, d, J_HH = 7.1Hz, CH), 7.31 -8.06 (4H, m, aromatic), 10.28 (1H, broad s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ = 14.48 and 19.00 (2CH₃), 41.01 and 41.71 (2CH), 61.01 (CH₂), 105.54 (CN), 114.59 and 144.77 (C=C), 124.42, 129.40, 148.12, 149.04, 159.33, 162.47 (aromatic and olefinic), 164.57 and 165.48 (2C=O).

**Ethyl 5-cyano-2-methyl-6-oxo-4-(4-nitrophenyl)-1,6-dihydropyridine 3-carboxylate (7B)**

White powder, (37 %), m.p. 198–200°C, IR (KBr) (ν_max/cm⁻¹): 3395 (NH), 2225 (CN), 1721 (C=O), 1348 and 1593 (NO₂). MS, m/z (%): 327 (M⁺, 3). Anal. Calcd for C₁₈H₁₃N₃O₅: C, 58.72; H, 4.00; N, 12.84%. Found: C, 58.55; H, 4.15; N, 12.99%. ¹H NMR (500.1 MHz, CDCl₃): δ = 0.88 (3H, t, J_HH = 7 Hz, CH₃), 2.66 (3H, s, CH₃), 3.96 (2H, q, J_HH = 7 Hz, CH₂), 7.25 -8.37 (4H, m, aromatic), 13.54 (1H, broad s, NH). ¹³C NMR (125.7 MHz, CDCl₃): δ = 13.96 and 18.87 (2CH₃), 62.46 (CH₂), 105.12 (CN), 114.18, 124.40, 129.01, 142.17, 149.04, 154.22, 159.33, 162.47 (aromatic and olefinic), 164.57 and 165.48 (2C=O).

**Results and Discussion**

Herein we report a new and efficient one-pot synthesis of polysubstituted dihydropyridones derivatives by four-component reaction between cyanoacetamide, aryl aldehydes and ethyl acetoacetate with ammonium acetate using nano ZnO. The reaction was performed in ethanol under reflux conditions and afforded good yields of products. (Figure 1).

![Figure 1](image)

| Entry | Ar       | 8 yield (A/B) |
|-------|----------|--------------|
| 1     | C₆H₅     | 59 (Only A)  |
| 2     | 4-Cl C₆H₄ | 58 (Only A)  |
| 3     | 4-Br C₆H₄ | 61(Only A)   |
| 4     | 3-MeO C₆H₄ | 57 (Only A) |
| 5     | 2-NO₂C₆H₄ | 54 (Only A)  |
| 6     | 3-NO₂C₆H₄ | 68 (Only A)  |
| 7     | 4-NO₂C₆H₄ | 63/37        |

*Isolated yield*

The reaction course without ammonium acetate in the absence of zinc oxide a complex mixture was obtained from which no product was isolated. The reaction course in the presence of ammonium acetate without zinc oxide afforded the product in lower yield and longer reaction time. Using nano ZnO afforded the product in higher yield and shorter
reaction time. The structure of compounds A and B was deduced from their elemental analyses and their IR, $^1$H, and $^{13}$CNMR spectra data. The mass spectrum of compound 7A displayed the molecular ion peak at $m/z = 329$ as the base peak. The 500 MHz $^1$H NMR spectrum of compound 7A exhibited a D$_2$O-exchangable broad signal at 10.28 ppm for NH proton, and displays one sharp line ($\delta = 2.31$ ppm ) for the methyl group. Ethyl protons were observed as a triplet ($^3J_{HH} = 7$ Hz) at 1.06 ppm and a quartet at 3.98 ppm. Two doublet were observed respectively at 4.13 and 4.18 ppm for methine protons. ($^3J_{HH} = 7.1$ Hz). Aromatic protons resonated between 7.31 and 8.06 ppm as multiplets. The $^{13}$C NMR spectrum of compound 7A showed 14 distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 3407 cm$^{-1}$ for NH group. The carbonyl stretching vibrations observed as strong absorption bonds at 1715 cm$^{-1}$. The nitrile stretching vibrations observed absorption bond at 2255 cm$^{-1}$. The nitro stretching vibrations observed absorption bonds at 1345 and 1515 cm$^{-1}$.The mass spectrum of compound 7B displayed the molecular ion peak at $m/z = 327$ as the base peak. The 500 MHz $^1$H NMR spectrum of compound 7B exhibited a D$_2$O-exchangable broad signal at 10.28 ppm for NH proton, and displays one sharp line ($\delta = 2.66$ ppm ) for the methyl group. Ethyl protons were observed as a triplet ($^3J_{HH} = 7$ Hz) at 0.88 ppm and a quartet at 3.96 ppm. Aromatic protons resonated between 7.25 and 8.37 ppm as multiplets. The $^{13}$C NMR spectrum of compound 7B showed 14 distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 3395 cm$^{-1}$ for NH group. The carbonyl stretching vibrations observed as strong absorption bonds at 1721 cm$^{-1}$. The nitrile stretching vibrations observed absorption bond at 2225 cm$^{-1}$. The nitro stretching vibrations observed absorption bonds at 1348 and 1593 cm$^{-1}$. Although the mechanistic details of the above reaction are not known, a plausible mechanism may be advanced to rationalize product formation.

Resumably a intermediate 3 formed from michael addition of product 1 the addition of cyanoacetamide with aryl aldehydes using nano ZnO and product 2 the addition of ethyl acetoacetate with ammonium acetate which could undergo stepwise cyclization to produce A by elimination of NH$_3$. The amide tautomer is considerably more stable. Admittedly the exchangeable peak in the 1H NMR spectrum is very high for a NH peak, and would appear to be more consistent with a OH peak. The A product is finally converted to B by oxidation (Figure 2).

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**Figure 2.** Suggested mechanism for formation of compound A and B.
Conclusion
In summary, here we reported a four-component reaction between cyanoacetamide, aryl aldehydes and ethyl acetoacetate with ammonium acetate using nano ZnO. The reaction was performed in ethanol under reflux conditions and afforded good yields of products. The present method carries the advantage that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification. nano ZnO was prepared as previously described in the literature.16

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