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An efficient one-pot, four-component synthesis of a series of pyrazolo [3,4-*b*] pyridines in the presence of magnetic LDH as a nanocatalyst

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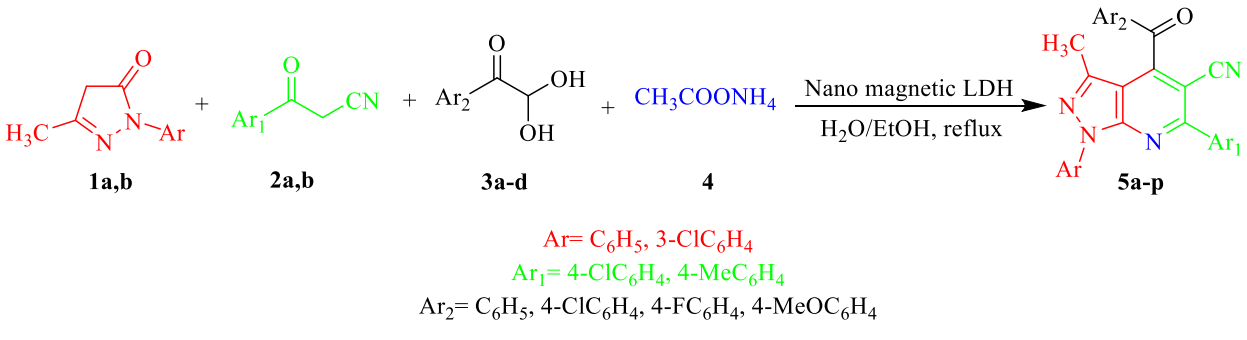
ABSTRACT

In this research study, one-pot, four-component reaction of 3-aryl-3-oxopropanenitriles, 1-aryl-3-methyl-1*H*-pyrazol-5 (4*H*) one, arylglyoxals and ammonium acetate using green solvent systems and different catalysts under the reflux conditions afforded a series of the corresponding 4-aroyl-3-methyl-1,6-diaryl-1*H*-pyrazolo [3,4-*b*] pyridine-5-carbonitrile derivatives. The best yields (70-85%) were obtained using the metal oxide silica based-matal bifunctional LDH (layered double hydroxide) as a magnet nanocatalyst in EtOH/H_2O (1:1) under the reflux conditions. This protocol provided mild reaction conditions, good yields, simple workup procedure, easy preparation of nanocatalyst and, products to structurally diverse bicyclic pyrazolo [3,4-*b*] pyridines, demonstrating biological and pharmacological activities.

Graphical Abstract



Introduction

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The green synthesis of the nitrogen-containing heterocycles *via* environmentally friendly procedures has attracted a great deal of attention due to their biological and pharmaceutical activities in organic and pharmaceutical chemistry [1–3]. Among these heterocycles, polycyclic heterocycles have received considerable attention because of various applications. Fused heterocyclic compounds such as pyrazolopyridines have biological and pharmacological activities including, antibacterial [4], antimicrobial [5, 6], antileishmanial [7, 8], antiproliferative agents [9], cytotoxicities, anti-biofilm and antioxidant [10], antimalarial [11], and anticancer [12] have classified as an important and vital structure.

Multicomponent reactions by multiple bond-making in green solvents at the presence of green catalysts would be a powerful tool in organic synthesis. MCRs offer benefits such as short time, with high atom-economy, high selectivity and environmentally friendly chemical process [13–16].

Nowadays, with the advancement of materials science and technology, organic synthesis have been able to reach the diverse procedures in the synthesis of complicated biological and bioactive scaffolds with the help of a creative role of nanocatalysts; which are among the principles of green chemistry. Nanocatalysts have altered to powerful and valuable tools in MCRs due to their unique and eminence physicochemical properties, which derives from the size control. The results of activity and application nonmagnetic-LDH were also studied in the multicomponent synthesis of various heterocyclic compounds. It was found that, these compounds have many advantages in chemical synthesis such as the great capacity for adsorption, functionalization, high stability of thermal and chemical, and their acid-base properties. LDHs could be synthesized using the simple and economic procedures. Recently, the combination of magnetic nanoparticles (MNPs) and LDH as magnetite-LDH has been provided to be applied in a wide range of synthetic methods since the nanoparticles possess a high surface to volume ratio, which increases their activity and selectivity. In addition, at the end of the reaction, they can be simply separated by a magnetic field [17–19].

In continuation of our interests in development of the synthetic strategies to obtain new heterocyclic compounds [20–24], we have very recently reported the one-pot, three-component synthesis of a new series of pyrazolo [3,4-*b*] pyridines in the presence of Al_2O_3 as a nanocatalyst [25]. Herein, we reported the one-pot, four-component synthesis of a series of 4-aroyl-3-methyl-1, 6-diaryl-1*H*-pyrazlo [3,4-*b*] pyridine-5-carbonitriles at the presence of different catalysts under the reflux conditions.

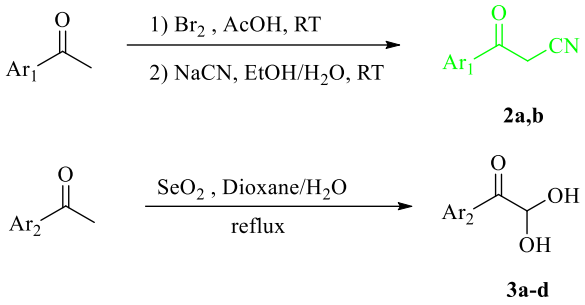
Experimental

Materials and methods

All the chemicals were purchased from the Acros and Merck companies and were used without purification. The melting points were recorded using a Philip Harris C4954718 apparatus and are uncorrected. FT-IR (KBR) spectra were recorded on a Thermo Nicolet (Nexus 670) spectrometer using KBr discs.^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in $CDCl_3$ using TMS as the internal standard. Progress of the reactions was monitored by the thin layer chromatography (TLC) using silica gel SIL G/UV254 plates. The scanning electron microscopy (SEM) images were obtained from JEOL JXA-840 Electron Microscopy Ltd. Japan. Elemental analysis was performed using a Leco Analyzer 932.

Preparation of starting materials

Preparation of the starting materials including 3-oxo-3-phenylpropanenitriles (**2a, b**) [27, 28], and arylglyoxal monohydrates (**3a-d**) [26], along with reaction conditions are shown in (Scheme 1).



Scheme 1. Preparation of starting materials

Catalyst preparation of nanocatalyst

Preparation of nanomagnetic Fe_3O_4

The Fe_3O_4 nanoparticles were prepared according to a previously reported method by chemical co-precipitation of chloride salts of Fe^{2+} and Fe^{3+} [29]. $FeCl_2.4H_2O$ (2.147 g, 0.0108 mol) and $FeCl_3.6H_2O$ (5.838 g, 0.0216 mol) were dissolved in distilled water (100 mL). The solution was stirred at 85 ˚C under the N_2 atmosphere for 10 min. Then, aqueous ammonia (25 wt. %, 10 mL) was added to the prepared solution at 85 °C and a black precipitate was immediately formed. The resulting mixture was heated up to 85 °C and kept for 30 min while stirred under the N_2 atmosphere followed by cooling to the room temperature. The precipitate was magnetically separated from the reaction mixture and washed twice with distilled water and solution of NaCl (0.02 M).

Preparation of Nano-Fe_3O_4@SiO_2

The silica was covered on the Fe_3O_4 core according to the reported method [30]. Magnetite (1.5 g) was dissolved in distilled water (20 mL) and it was added to 2-propanol (200 mL) and homogenized by ultrasonic (30 min). Under continuous mechanical stirring, PEG (5.36 g), distilled water (20 mL), aqueous NH_4OH (28 wt. %, 10 mL) and TEOS (2 mL) were respectively added into the suspension and stirring was continued for 24 h at room temperature. After completing the reaction, the product was collected by an external magnet and washed twice with ethanol and distilled water.

Preparation of Fe_3O_4@SiO_2@Ni-Zn-Fe LDH

The in-situ growth of the mesoporous Ni-Zn-Fe LDH on the surface of the Fe_3O_4@SiO_2 nanoparticles was carried out. Firstly, the Fe_3O_4@SiO_2 (0.25 g), NaOH (0.160 g, 0.004 mol) and Na_2CO_3 (1.060 g, 0.01 mol) were dissolved in 30 mL deionized water and, then the $Ni(NO_3)_2.6H_2O$ (2.617 g, 0.009 mol), $Zn(NO_3)_2.6H_2O$ (1.785 g, 0.006 mol) and $FeCl_3.6H_2O$ (1.352 g, 0.005 mol) were also dissolved in 30 mL deionized water. Then both the prepared solutions were sonicated for 30 min and subsequently were added drop wise with stirring vigorously to 30 mL distilled water. The pH of solution was set at 11 by adding carbonate/bicarbonate buffer during the process. The resulting slurry was stirred at room temperature for an additional of 30 min

and then it was aged for 20 h at 80 °C. Subsequently, the acquired sample was cooled to room temperature and filtered. The solid product dried at 150 °C and the obtained catalyst was named as Fe_3O_4@SiO_2@Ni-Zn-Fe LDH.

The morphology and size distribution of the synthesized materials was analyzed by SEM. The SEM images demonstrated that, the catalyst is roughly spherical and granule nanoparticles. The size distribution of the Fe_3O_4@SiO_2@Ni-Zn-Fe LDH ranged from 17 nm to 36 nm. The SEM approved the nanostructure of the catalyst [31].

General procedure for synthesis of new pyrazolopyridine derivatives

The 3-oxo-3-phenylpropanenitrile (1 mmol) was dissolved in H_2O/EtOH (1:1) (5 mL) and arylglyoxal hydrate (1 mmol), 1-aryl-3-methyl-1*H*-pyrazol-5 (4*H*) one (1 mmol), ammonium acetate with the nanomagnetic catalyst (10% mol) was then added to the reaction mixture. The reaction mixture refluxed for an appropriate time (approximately 2 h). After completion of the reaction (monitored by TLC, EtOAc/Hexane, 2:3), the magnetic nanocatalyst was separated by an external magnet. The precipitate was filtered and then washed with water and dried. Recrystallization from ethanol gave the desired product (**5a–p**) as white to yellow needles 70-85% yields as shown in (Scheme 1).

*6-(4-Chlorophenyl)-3-methyl-1-phenyl-4-(phenyl-carbonyl)-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4a**)*

White needles, mp 170−171 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3065, 2923, 2217, 1675, 1585, 1493, 1441, 1221, 1091, 780, 744, and 672. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (2H, d, *J*=8.1), 7.98–7.86 (4H, m), 7.77–7.66 (1H, m), 7.59–7.44 (6H, m), 7.34 (1H, t, *J*=7.5), 2.29 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.9, 161.3, 157.0, 149.2, 149.4, 145.1, 139.4, 137.0, 132.6, 131.9, 130.9, 129.8, 129.4, 129.3, 129.1, 124.9, 120.3, 115.1, 110.9, 95.7, 12.8. Anal. Calcd. for $C_{27}H_{17}ClN_4O$: C, 72.24; H, 3.82; N, 12.48; Found: C, 72.18; H, 3.62; N, 12.52.

*6-(4-Chlorophenyl)-4-[(4-fluorophenyl) carbonyl]-3-methyl-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carbo- nitrile (**4b**)*

Yellow needles, mp 176–178 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3069, 2223, 1676, 1590, 1494, 1416, 1387, 1228, 1094, 755, and 681. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36–8.24 (2H, m), 8.06–7.92 (4H, m), 7.61–7.50 (4H, m), 7.45–7.28 (3H, m), 2.32 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 169.9, 159.3, 152.4, 149.9, 143.5, 141.4, 138.3, 135.9, 134.9, 134.1, 131.8, 130.7, 130.3, 128.2, 128.1, 125.7, 125.3, 121.0, 117.8, 114.1, 98.9, 14.8, 12.3. Anal. Calcd. for $C_{27}H_{16}ClFN_4O$: C, 69.46; H, 3.45; N, 12.00; Found: C, 69.36; H, 3.65; N, 12.49.

*6-(4-Chlorophenyl)-4-[(4-methoxyphenyl)carbonyl]-3-methyl-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4c**)*

White needles, mp 207–208 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3060, 2222, 1658, 1585, 1501, 1430, 1266, 1174, 1020, 846, and 756. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (2H, d, *J*=7.8), 7.97 (2H, d, *J*=8.4), 7.86 (2H, d, *J*=8.1), 7.48–7.55 (4H, m), 7.34 (1H, t, *J*=7.5), 7.00 (2H, d, *J*=8.7), 3.90 (3H, s), 2.30 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190, 164.5, 157.0, 150.2, 149.8, 144.2, 140.5, 139.9, 137.6, 133.7, 131.9, 129.3, 129.5, 128.7, 127.8, 122.5, 121.8, 117.2, 115.8, 112.9, 56.8, 13.8. Anal. Calcd. for $C_{28}H_{19}ClN_4O$: C, 70.22; H, 4.00; N, 11.70; Found: C, 70.11; H, 3.86; N, 11.51.

*6-(4-Chlorophenyl)-4-[(4-chlorophenyl) carbonyl]-3-methyl-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4d**)*

Yellow needles, mp 170–172 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3075, 2923, 2217, 1677, 1580, 1492, 1440, 1223, 1090, 783, 745, and 674. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (2H, d, *J*=7.8), 8.01 (2H, d, *J*=8.1), 7.89 (2H, d, *J*=8.4), 7.62–7.51 (6H, m), 7.41 (1H, t, *J*=7.2,), 2.35 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 158.0, 150.2, 146.6, 143.9, 142.5, 140.4, 138.1, 134.4, 132.3, 131.3, 130.1, 129.5, 129.0, 128.2, 128.1, 128.0, 126.2, 120.3, 115.0, 13.1. Anal. Calcd. for $C_{27}H_{16}Cl_2N_4O$: C, 67.09; H, 3.34; N, 11.59; Found: C, 66.81; H, 3.25; N, 11.61.

*3-Methyl-6-(4-methylphenyl)-1-phenyl-4-phenylcarbonyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4e**)*

Pale-yellow needles, mp 174–175 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3064, 2920, 2217, 1675, 1591, 1496, 1429, 1383, 1213, 1020, 743, and 680. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37–8.30 (2H, m), 8.01–7.89 (3H, m), 7.74 (1H, t, *J*=7.2), 7.67–7.47 (4H, m), 7.45–7.27 (4H, m), 2.72 (3H, s), 2.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 164.3, 162.8, 154.4, 143.5, 139.8, 137.2, 136.5, 135.8, 135.7, 131.1, 129.8, 129.5, 129.0 (2C), 127.6, 122.2, 117.4, 115.8, 102.6, 20.5, 13.5. Anal. Calcd. for $C_{28}H_{20}N_4O$: C, 78.49; H, 4.70; N, 13.08; Found: C, 78.23; H, 4.59; N, 13.20.

*4-[(4-Fluorophenyl)carbonyl]-3-methyl-6-(4-methyl-phenyl)-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4f**)*

Pale-yellow needles, mp 204–206 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3070, 2920, 2220, 1673, 1587, 1481, 1423, 1383, 1231, 1087, and 773. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34–8.22 (2H, m), 8.05–7.83 (3H, m), 7.57–7.42 (3H, m), 7.40–7.28 (3H, m), 7.28–7.15 (2H, m), 2.44 (3H, s), 2.28 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 163.4, 160.0, 142.2, 138.0, 134.9, 134.3, 133.0, 132.6, 128.5, 128.4, 128.3, 128.2 (2C), 126.1, 126.0, 120.8, 117.9, 115.3, 112.7, 99.5, 95.6, 20.5, 13.7. Anal. Calcd. for $C_{28}H_{19}FN_4O$: C, 75.32; H, 4.29; N, 12.55; Found: C, 75.28; H, 4.15; N, 12.65.

*4-[(4-Methoxyphenyl)carbonyl]-3-methyl-6-(4-methyl-phenyl)-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4g**)*

White needles, mp 183–184 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3060, 2926, 2221, 1675, 1594, 1503, 1428, 1389, 1259, 1176, 1024, 783, and 678. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (2H, d, *J*=7.8), 8.05–7.89 (4H, m), 7.62–7.48 (4H, m), 7.45–7.33 (3H, m), 3.95 (3H, s), 2.50 (3H, s), 2.35 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.3, 164.1, 160.3, 158.2, 141.5, 137.2, 136.1, 134.1, 132.0, 128.1, 128.4, 128.3, 128.2, 127.5, 126.6, 126.0, 120.9, 117.9, 115.5, 113.7, 100.1, 56.8, 20.5, 13.9. Anal. Calcd. for $C_{29}H_{22}N_4O_2$: C, 75.97; H, 4.84; N, 12.22; Found: C, 75.88; H, 4.95; N, 12.21.

*4-[(4-Chlorophenyl) carbonyl]-3-methyl-6-(4-methyl-phenyl)-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4h**)*

Pale-yellow needles, mp 170–171 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3053, 2920, 2219, 1671, 1581, 1465, 1420, 1387, 1215, 1088, 1015, 747, and 676. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (2H, d, *J*=7.2), 7.93 (2H, d, *J*=6.9), 7.60–7.48 (5H, m), 7.41–7.32 (4H, m), 2.68 (3H, s), 2.30 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 160.8, 150.7, 148.7, 143.8, 137.9, 137.5, 135.7, 133.2, 132.4, 131.4, 129.3, 129.1, 129.0, 128.0, 125.7, 125.3, 115.3, 97.2, 21.5, 13.7. Anal. Calcd. for $C_{28}H_{19}ClN_4O$: C, 72.65; H, 4.14; N, 12.10; Found: C, 72.56; H, 4.08; N, 11.90.

*1-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-4-phenylcarbonyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4i**)*

White needles, mp 178–179 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3072, 2935, 2219, 1663, 1584,

1486, 1263, 1161, 1095, 1015, 835, and 774. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (1H, s), 8.27 (1H, d, *J*=8.4), 7.98 (2H, d, *J*=8.1), 7.90 (2H, d, *J*=7.8), 7.73 (1H, t, *J*=7.2), 7.63–7.50 (4H, m), 7.43 (1H, t, *J*=7.8), 7.30 (1H, d, *J*=7.8), 2.27 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 160.3, 151.4, 148.5, 142.6, 139.0, 137.8, 135.7, 136.3, 135.9 (2C), 131.0, 130.7, 130.2, 130.0, 129.5, 129.0, 127.7, 126.3, 121.2, 117.5, 115.2, 13.7. Anal. Calcd. for $C_{27}H_{16}Cl_2N_4O$: C, 67.09; H, 3.34; N, 11.59: Found: C, 66.97; H, 3.40; N, 11.69.

*1-(3-Chlorophenyl)-6-(4-chlorophenyl)-4-[(4-fluoro-phenyl)carbonyl]-3-methyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4j**)*

White needles, mp 207–209 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3094, 2942, 2220, 1664, 1584, 1488, 1425, 1229, 1090, 1012, 840, 761, 675, and 613. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (1H, s), 8.32 (1H, d, *J*=7.8), 8.11–7.94 (4H, m), 7.60 (2H, d, *J*=8.4), 7.51 (1H, t, *J*=8.1), 7.38–7.29 (3H, m), 2.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 166.9, 158.3, 150.4, 146.9, 142.5, 139.4, 135.3, 134.2, 134.9, 132.0, 130.1, 129.7, 129.3, 129.0, 128.1, 125.7, 125.3, 120.1, 115.9, 112.1, 96.9, 13.9. Anal. Calcd. for $C_{27}H_{15}Cl_2FN_4O$: C, 64.69; H, 3.02; N, 11.18: Found: C, 64.61; H, 3.10; N, 11.08.

*1-(3-Chlorophenyl)-6-(4-chlorophenyl)-4-[(4-methoxy-phenyl)carbonyl)]-3-methyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4k**)*

Orange needles, mp 177–178 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3079, 2935, 2224, 1664, 1587, 1491, 1441, 1263, 1174, 1096, 1020, 839, 774, and 670. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, s), 8.29 (1H, d, *J*=8.1), 8.01 (2H, d, *J*=6.9), 7.90 (2H, d, *J*=5.7), 7.58–7.43 (4H, m), 7.04 (2H, d, *J*=8.1), 3.89 (3H, s), 2.33 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 167.5, 151.4, 150.9, 144.8, 139.0, 137.2, 135.1, 134.7, 132.5, 130.6, 130.2, 129.2, 129.0, 128.0, 126.2, 126.0, 120.9, 117.8, 116.4, 111.2, 54.8, 13.8. Anal. Calcd. for $C_{28}H_{18}Cl_2N_4O_2$: C, 65.51; H, 3.53; N, 10.91: Found: C, 65.42; H, 3.40; N, 10.84.

*1-(3-Chlorophenyl)-6-(4-chlorophenyl)-4-[(4-chloro-phenyl)carbonyl]-3-methyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4l**)*

Light-orange needles, mp 192–194 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3084, 2935, 2221, 1675, 1581, 1491, 1486, 1222, 1091, 1007, 903, 773, and 674. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (1H, s), 8.30 (1H, d, *J*=8.1), 8.00 (2H, d, *J*=8.4), 7.87 (1H, d, *J*=8.1), 7.61–7.51 (4H, m), 7.52–7.42 (2H, m), 7.34 (1H, d, *J*=8.7), 2.32 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 158.8, 151.4, 148.6, 144.4, 142.9, 140.4, 138.3, 136.2, 133.9, 131.8, 130.7, 130.2, 129.4, 129.1, 129.0, 126.5, 126.3, 118.1, 116.8, 112.5, 98.0, 13.8. Anal. Calcd. for $C_{27}H_{15}Cl_3N_4O$: C, 62.63; H, 2.92; N, 10.82; Found: C, 62.55; H, 3.14; N, 10.89.

*1-(3-Chlorophenyl)-3-methyl-6-(4-methylphenyl)-4-phenylcarbonyl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4m**)*

Pale-yellow needles, mp 200–202 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3060, 2921, 2218, 1669, 1589, 1481, 1382, 1023, 775, and 741. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (1H, s), 8.29 (1H, d, *J*=8.1), 7.99–7.86 (4H, m), 7.61–7.52 (1H, m), 7.42–7.31 (4H, m), 7.28–7.19 (2H, m), 2.44 (3H, s), 2.24 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 159.5, 151.5, 142.9, 144.5, 141.9, 139.0, 136.2, 134.4, 134.5, 131.0, 130.6, 129.1, 128.5, 128.0, 125.5, 121.0, 120.4, 118.8, 115.2, 100.9, 98.5, 21.7, 13.8. Anal. Calcd. for $C_{28}H_{19}ClN_4O$: C, 72.65; H, 4.14; N, 12.10; Found: C, 72.61; H, 4.16; N, 12.18.

*1-(3-Chlorophenyl)-4-[(4-fluorophenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4n**)*

Yellow needles, mp 184–185 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3070, 2920, 2219, 1672, 1591, 1480, 1381, 1229, 1090, 1031, 772, 741. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (1H, s), 8.44–8.34 (1H, m), 8.05–7.95 (4H, m), 7.56–7.39 (4H, m), 7.41 (2H, m), 2.52 (3H, s), 2.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2, 164.4, 160.9, 151.6, 148.9, 142.9, 141.3, 139.1, 134.2, 134.1, 132.0, 131.6, 131.2, 129.6, 127.5, 126.0, 121.6, 118.2, 116.1, 115.0, 99.9, 97.0, 20.5, 13.9. Anal. Calcd. for $C_{28}H_{18}ClFN_4O$: C, 69.93; H, 3.77; N, 11.65; Found: C, 69.80; H, 3.85; N, 11.72.

*1-(3-Chlorophenyl)-4-[(4-methoxyphenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4o**)*

Pale-yellow needles, mp. 204–205 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3064, 2925, 2222, 1653, 1595, 1485, 1386, 1264, 1176, 1091, 1026, 907, 776, 739. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (1H, s), 8.35 (1H, d, *J*=8.1), 7.96 (2H, d, *J*=7.8), 7.51–7.36 (5H, m), 7.30 (1H, t, *J*=7.2), 7.01 (2H, d, *J*=7.8), 3.94 (3H, s), 2.70 (3H, s), 2.50 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9, 160.9, 151.6, 145.9, 141.9, 139.9, 137.0, 136.9, 134.2, 134.0, 131.1, 129.9, 129.7, 129.2, 128.5, 126.5, 121.6, 120.5, 117.6, 117.4, 1165.0, 100.1, 21.4, 13.7. Anal. Calcd. for $C_{29}H_{21}ClN_4O_2$: C, 70.66; H, 4.29; N, 11.37; Found: C, 70.55; H, 4.19; N, 11.40.

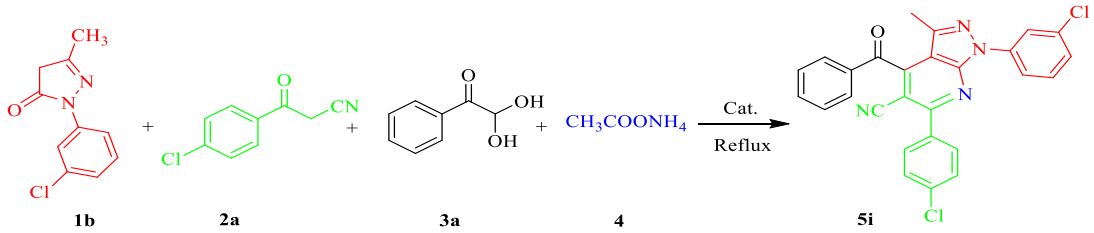
*1-(3-Chlorophenyl)-4-[(4-chlorophenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile (**4p**)*

Yellow needles, mp 194–195 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3060, 2920, 2220, 1673, 1584, 1481, 1383, 1224, 1086, 1010, 905, 775, 726. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (1H, s), 8.44 (1H, d, *J*=7.8), 8.37–8.28 (1H, m), 7.94 (2H, d, *J*=8.4), 7.85 (2H, d, *J*=8.4), 7.54 (2H, d, *J*=8.4), 7.38 (2H, d, *J*=8.4), 7.36–7.20 (1H, m), 2.47 (3H, s), 2.30 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.8, 161.6, 149.6, 144.3, 142.3, 140.9, 139.6, 135.9, 134.5, 133.8, 131.9, 130.2, 129.9, 129.5, 129.4, 129.2, 129.0, 126.0, 124.8, 117.1, 115.0, 100.1, 22.5, 13.8. Anal. Calcd. for $C_{28}H_{18}Cl_2N_4O$: C, 67.62; H, 3.65; N, 11.26; Found: C, 67.50; H, 3.57; N, 11.19.

Results and Discussion

In our initial studies, the reaction of 1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**1b**), 3-(4-chlorophenyl)-3-oxo propanenitrile (**2a**), phenylglyoxal hydrate (**3a**) and ammonium acetate (**4**) was chosen as a trial reaction (Table 1). By refluxing the reaction mixture using various catalysts and solvent systems (Table 1), a solid precipitate was isolated in 40-84% yields, which was characterized by its spectral data to be the desired substituted pyrazolo[3,4-*b*]pyridine (**5i**). The best result was obtained in terms of yield (84%) and reaction time (2 h) when the reaction was performed using 10% mol of magnetic LDH as a nanocatalyst in H_2O/EtOH (1:1) (Table 1, entry 8). To study the effect of the amount of catalyst, the reaction was carried out in the presence of various amounts of nano LDH ranging from 5 to 15% mol and the best condition was using 10% mol of catalyst in H_2O/EtOH (1:1). As reaction time increased, there was no significant change in the yield of the reaction (Table 1, entry 9). Increasing the amount of catalyst improved the yield of the reaction. To find the best solvent for this reaction, we carried out the trial reaction using various green solvent systems including, EtOH, EtOH/H_2O (1:1), and H_2O (as demonstrated in Table 1). Among all these solvents, EtOH/H_2O (1:1) was proved the best solvent for this reaction in terms of yield (Table 1, entry 8). The catalyst with acidic nature such as *p*-TSA, and *L*-proline as an amino acid provided lower yields (Table 1).

Table 1. Optimization of the reaction conditions



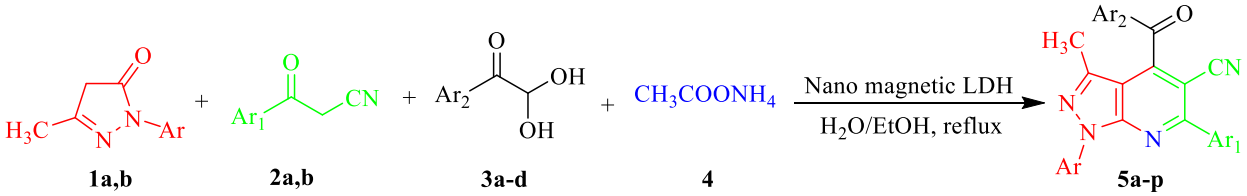
1b 2a 3a 4 5i

Entry	Solvents	Temp (°C)	Catalyst (%)	Time (h)	Yields (%)
1	EtOH	Reflux	CH_3COONH_4 (20)	7	43
2	EtOH/H_2O (1:1)	Reflux	CH_3COONH_4 (20)	7	40
3	EtOH/H_2O (1:1)	Reflux	*L*-proline (20)	7	52
4	EtOH	Reflux	*L*-proline (20)	7	58
5	EtOH	Reflux	*p*-TSA (20)	7	50
6	EtOH/H_2O (1:1)	Reflux	*p*-TSA (20)	7	47
7	EtOH/H_2O (1:1)	Reflux	Nano LDH(5)	2	71
8	EtOH/H_2O (1:1)	Reflux	Nano LDH(10)	2	84
9	EtOH/H_2O (1:1)	Reflux	Nano LDH(10)	3	85
10	EtOH/H_2O (1:1)	Reflux	Nano LDH(15)	2	82
11	EtOH	Reflux	Nano LDH(10)	2	80
12	EtOH/H_2O (1:2)	Reflux	Nano LDH(10)	2	79
13	H_2O	Reflux	Nano LDH(10)	24	-

After optimizing the reaction condition (Scheme 2), we next verify the scope of this reaction with 1-aryl-3-methyl-1*H*-pyrazol-5(4*H*)one (**1a, b**), 3-aryl-3-oxopropanenitriles (**2a, b**), different arylglyoxals (**3a–d**), and ammonium acetate (**4**), to obtain our desired pyrazolopyridine derivatives (**5a–p**) (Table 2).

Reusability of Fe_3O_4@SiO_2@Ni-Zn-Fe LDH

After completion of the reaction, the nanocatalyst easily separated from the reaction mixture by an external magnetic field, washed with $CHCl_3$, dried at room temperature and reused for six consecutive runs without considerable loss of activity (Figure 1).



1a,b 2a,b 3a-d 4 5a-p

Ar= C_6H_5, 3-ClC_6H_4
Ar_1= 4-ClC_6H_4, 4-MeC_6H_4
Ar_2= C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$

Scheme 2. One-pot four-component synthesis of substituted pyrazolo[3,4-*b*]pyridine derivatives

Table 2. Substituted pyrazolo[3,4-*b*]pyridines

Entry	Product	Ar	Ar_1	Ar_2	Time (h)	Yield (%)*	Mp(obsd) (°C)	Mp(Lit.) (°C) [21]

1	**5a**	C_6H_5	4-ClC_6H_4	C_6H_5	1	85	170-171	171-173
2	**5b**	C_6H_5	4-ClC_6H_4	4-FC_6H_4	1	81	176-178	178-179
3	**5c**	C_6H_5	4-ClC_6H_4	4-$MeOC_6H_4$	2	70	207-208	206-207
4	**5d**	C_6H_5	4-ClC_6H_4	4-ClC_6H_4	2	76	170-172	170-172
5	**5e**	C_6H_5	4-MeC_6H_4	C_6H_5	2	79	174-175	175-176
6	**5f**	C_6H_5	4-MeC_6H_4	4-FC_6H_4	2	75	204-206	204-205
7	**5g**	C_6H_5	4-MeC_6H_4	4-$MeOC_6H_4$	3	71	183-184	184-186
8	**5h**	C_6H_5	4-MeC_6H_4	4-ClC_6H_4	2	72	170-171	169-170
9	**5i**	3-ClC_6H_4	4-ClC_6H_4	C_6H_5	1	84	178-179	178-179
10	**5j**	3-ClC_6H_4	4-ClC_6H_4	4-FC_6H_4	2	74	207-209	208-209
11	**5k**	3-ClC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	2	72	177-178	176-178
12	**5l**	3-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4	1	81	192-194	191-193
13	**5m**	3-ClC_6H_4	4-MeC_6H_4	C_6H_5	2	78	200-202	201-202
14	**5n**	3-ClC_6H_4	4-MeC_6H_4	4-FC_6H_4	2	79	184-185	185-187
15	**5o**	3-ClC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	2	72	204-205	205-206
16	**5p**	3-ClC_6H_4	4-MeC_6H_4	4-ClC_6H_4	2	78	194-195	193-195

***** Isolated yield.

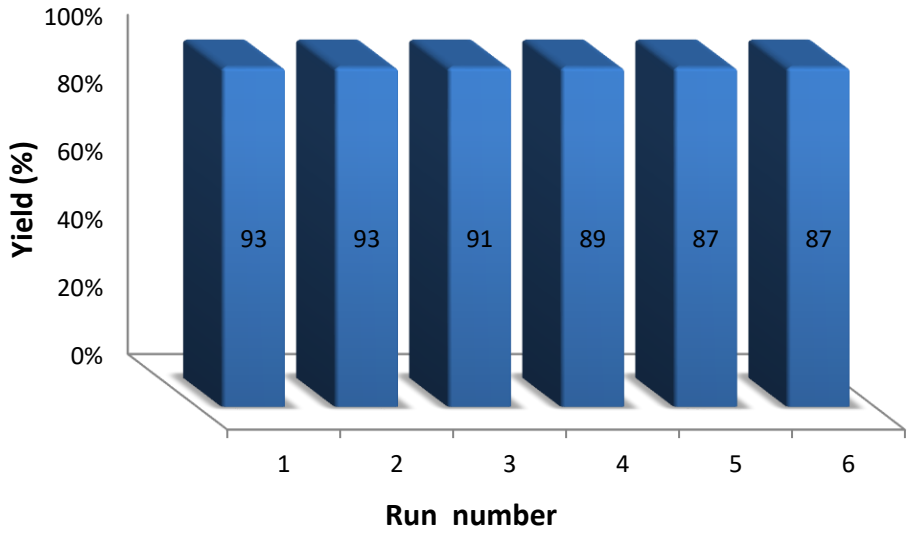


Figure 1. Reusability of Fe_3O_4@SiO_2@Ni-Zn-Fe LDH in the model reactions

Morphology

The morphology and size distribution of the synthesized nanocatalyst was determined using the scanning electron microscopy (SEM). The SEM images of the Fe_3O_4@SiO_2@Ni–Zn–Fe LDH revealed that, the catalyst was constructed from roughly spherical and granular nanoparticles in Figure 2. The distribution size of nanoparticles in Fe_3O_4@SiO_2@Ni–Zn–Fe LDH were at the range of 17-36 nm. Therefore, the mesoporous structure of nanocatalyst was approved [31].

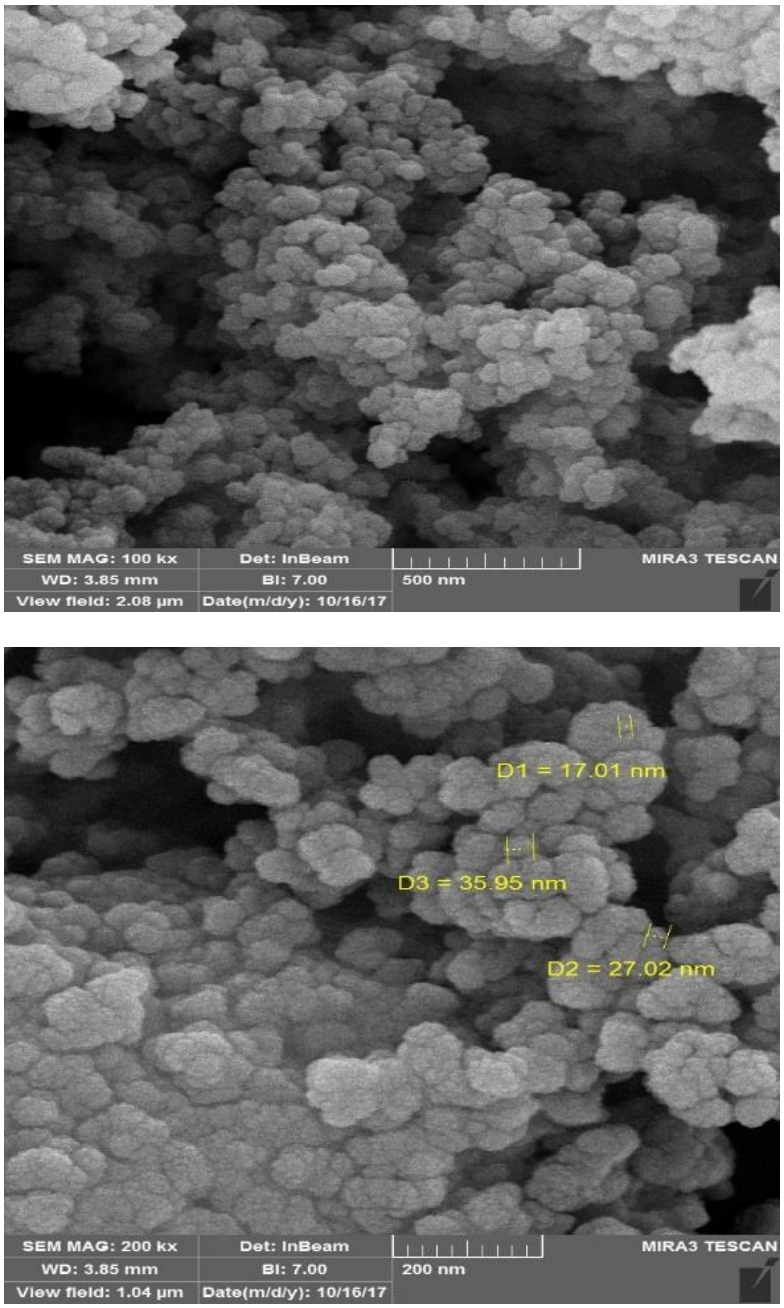
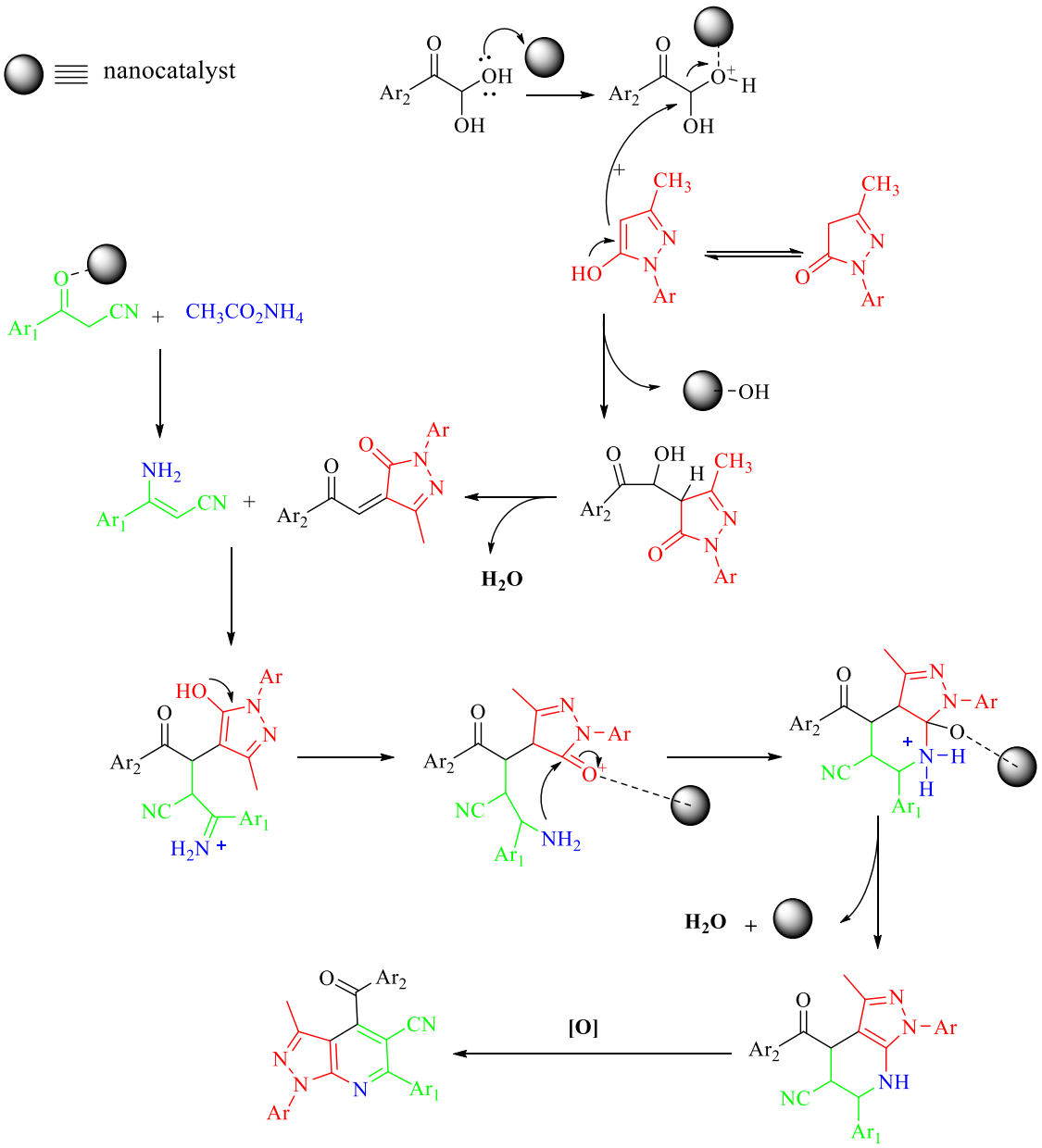


Figure 2. The SEM image of desired nanocatalyst

Mechanistically, the formation of products (**5a–p)** was achieved by a sequence of reactions involving activation of the carbonyl group (arylglyoxal) with nanocatalyst as a Bronsted acidic catalyst. The initial condensation of arylglyoxals with 5-amino-1-aryl-3-methylpyrazoles, followed by the second condensation of the intermediate with 3-aryl-3-oxopropanenitriles, providing the corresponding dihydro-1*H*-pyrazolo [3,4-*b*] pyridines through intramolecular heterocyclization. Finally, subsequent tautomerization, which was to the desired 4-aroyl-1, 6-diaryl-3-methyl-1*H*-pyrazolo [3,4-*b*]-pyridine-5-carbonitriles via autoxidation (Scheme 3).



Scheme 3. The proposed mechanism for synthesis of substituted pyrazolo [3,4-*b*] pyridines catalyzed by magnetic LDH as a nanocatalyst

Conclusions

In this work, we reported one-pot, four-component synthesis of a series of pyrazolo[3,4-*b*]pyridine derivatives in the presence of Fe_3O_4@SiO_2@Ni-Zn-Fe LDH as a nanocatalyst. Surprisingly, the application of metal oxide-metal multifunctional heterogeneous nanocatalysts in organic synthesis had been noticeable increased. Among these, the use of magnetic nanocatalysts was found to be highly worthwhile. This new pyrazolo[3,4-*b*]pyridine may have biological and pharmaceutical applications, and they could also serve as intermediates for new planar polycyclic heterocycles. The simplicity, ease of product and catalyst isolations, mild

reaction conditions, using green solvents and good yields were found to be the main advantages of this method.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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