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Pseudo six-component process for the synthesis of tetrahydrodipyrazolo pyridines using Ionic liquid immobilized on $FeNi_3$ nanocatalyst

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A highly efficient method for the synthesis of tetrahydrodipyrazolopyridines by a multicomponent reaction of ethyl acetoacetate, an aldehyde, hydrazine and ammonium acetate using ionic liquid (ILs) supported on $FeNi_3$ nanocatalystis described. This method provides several advantages including mild reaction conditions, applicability to wide range of substrates, reusability of the catalyst and little catalyst loading.

1. Introduction

Pyrazolopyridines represent a common scaffold in numerous bioactive compounds and have a number of pharmacological properties. The pyrazolopyridines exhibit important biological properties such as anti-virus,[1] anti-Leishmania,[2] protein kinase inhibitors,[3] PDE4B inhibitors,[4] HIF 1-αprolyl hydroxylase inhibitors,[5] B-Raf^{V600E}inhibitors,[6] and dopaminergic properties.[7] The synthesis of pyrazolopyridines has been reported using MCRs in the presence of diverse catalysts including carbonaceous material (C-SO_3H),[8] *L*-Proline,[9] acetic acid,[10] and *p*-TSA.[11] Many methods for the synthesis of pyrazolopyridines are known, but some of these methods have certain drawbacks, including long reaction times, use of toxic and non-reusable catalyst and utilize of specific conditions. Therefore, looking for efficient and simple methods for the synthesis of pyrazolopyridines is an attractive challenge. For this reason, Multicomponent reactions (MCRs) are particularly well suited for diversity-oriented synthesis.[12-13] Thus; the synthesis pyrazolopyridines by the multicomponent reactions with a heterogeneous catalyst could enhance their efficiency from economic and ecological points of view. To overcome the separation problems of the nanocatalysts, magnetic materials have emerged as recoverable catalysts. Separation of magnetic nanoparticles is easy, convenient, economical and environmentally benign.[14-15] One of the most attractive alternatives to catalyst supports are magnetic nanoparticles (MNPs), which have witnessed increasing popularity due to their high surface areas and improved disperse ability in the reaction medium. In recent years, ionic liquids (ILs) as being environmental-friendly reaction media had attracted significant attention for their unique properties, such as high thermal stability, negligible vapor pressure, suitable solvents, high viscosity, and catalysis activities.[16-18] Although ILs possess some advantages but their useful applications have been limited by some difficulties in its recovery which lead to economical and environmental problems. These problems can be overcome by immobilization of ILs onto solid supports to obtain heterogeneous catalysts.[19] $FeNi_3$core–shell nanoparticles were used as a suitable catalyst in many reactions including synthesis of 1,3-thiazolidin-4-one, [20] Triazolo[1,2-a]indazole-triones,[21] and synthesis of 4H-benzo[b]pyrans.[22] Recently, immobilized functional ionic liquids as efficient, green, and reusable catalysts have been described by Yang *et al*. and the results are compared with those of traditional ILs.[23] Herein, we reported the use of ionic liquid (ILs) supported on $FeNi_3$ nanocatalystis as an efficient catalyst for the preparation of tetrahydrodipyrazolo pyridinesby multicomponent reaction of ethyl acetoacetate, aldehydes, hydrazine and ammonium acetate under reflux conditions in ethanol (Scheme 1).

<Scheme 1>

2. Results and discussion

At first $FeNi_3$ nanoparticles were prepared according to method reported in the literature with some modifications.[20,24] (Scheme 2). Nano-$FeNi_3$ was capped with SiO_2 generated from the hydrolyzation of tetraethyl orthosilicate (TEOS). After being coated with a SiO_2 and organic layer, the typical core–shell structure of the $FeNi_3$-ILs MNPs can be observed. The structural properties of synthesized $FeNi_3$-ILs MNPs were analyzed by X-ray power diffraction (XRD). As shown in Fig. 1.

<Scheme 2>

Fig. 1.

In order to investigate the morphology and particle size of nanoparticles, SEM image of nanoparticles was presented in Fig.2. The SEM image shows particles with diameters in the range of nanometers. The results show that $FeNi_3$-ILs MNPs were obtained with an average diameter of 30–35 nm as conformed by XRD analysis.

Fig. 2.

This structure was further supported by the FT-IR spectra. The FT-IR spectrum of $FeNi_3$-ILs MNPs showed the typical bands at 2920 and 2850 cm^{-1} attributed to C-H stretching vibrations of alkyl chains. Moreover, the broad peak at 1053 cm^{-1} belonged to S=O stretching vibrations in the sulphonate functional groups. Bands at 1628 and1506 cm^{-1} were related to N-H bending vibrations in the ammonium groups. These results indicated that IL was successfully immobilized on $FeNi_3$ MNPs (**Fig 3**).

Fig. 3.

The magnetic properties of the nanoparticles were characterized using a vibrating sample magnetometer (VSM). Magnetic measurement shows that $FeNi_3$, and $FeNi_3$-ILs MNPs have saturation magnetization values of 59.2, and 39.1 emu/g respectively (Fig 4).These results exhibit that catalyst can be easily separated and recovered by an external magnetic field.

Fig. 4.

Initially, we carried out the MCR between hydrazine hydrate, ethyl acetoacetate, 4-nitrobenzaldehyde and ammonium acetate under reflux condition in ethanol as a model reaction in the presence of different catalyst. Meanwhile, we observed the effect of different solvents on the progress of reaction. Ethanol was found to be the best solvent, in which the product was obtained in 92% yield. Unfortunately, when the model reaction was carried out in water, the desired product was only obtained in 58 % yield.

The model reaction was carried out in the presence of various nanocatalysts such as Et_3N, K_2CO_3, ZnO, CuO, $FeCl_3$, $FeNi_3$ NPs, ZnO-ILs and CuO-ILs NPs and $FeNi_3$-ILs MNPs. When the reaction was carried out using $FeNi_3$-ILsMNPs (0.002 gr) as the catalyst, the products were obtained in good to high yields.

Table1

Table 1 shows the influence of particles size on the activity of $FeNi_3$-ILs MNPs in the synthesis of tetrahydrodi pyrazolopyridines. However, the activity of catalysts is influenced by the acid– base properties and many other factors such as size, surface area, geometric structure (particularly pore structure), the distribution of sites and the polarity of the surface sites.[25] In this work, we evaluates an example in solid-based heterogeneous catalytic systems that have been developed with the aid of ILs. $FeNi_3$-SO_3^- $^+NH_3$-CH_2CH_2-OH composed of $FeNi_3$-SO_3^- as anion and $^+NH_3$-CH_2CH_2-OH as cation.

We also investigated recycling of $FeNi_3$-ILsMNPs as catalyst under reflux conditions in ethanol. After completion of the reaction, the catalyst was separated using an external magnet, washed with methanol and dried with a vacuum pump. The catalyst could be reused for eight times with a minimal loss of activity. Perhaps, activity of $FeNi_3$-ILsMNPs is decreased by the number of the regeneration (Yields 92 to 89%) (Fig. 5).

Fig. 5.

The extreme stability of the $FeNi_3$-ILsMNPs is mainspring of the continuous and high catalytic activity. The morphology of $FeNi_3$-ILsMNPs was investigated by scanning electron microscopy (SEM) before use and after reuse of seven times with images shown in Fig. 6. Interestingly, the shape and size of the nanoparticles remained unchanged before and after reaction. We suppose that, this is also the possible reason for the extreme stability of the$FeNi_3$-ILsMNPs presented herein.

Fig. 6.

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

Table 2

Scheme 3

A plausible mechanism for the preparation of tetrahydrodipyrazolo pyridines using $FeNi_3$-ILsMNPs is shown in Scheme 4. The mechanism involves the initial nucleophilic attack of hydrazine on the ethyl acetoacetate and subsequent cyclization to form the pyrazolone and then, the reaction of pyrazolone with an aldehyde to give intermediate **II**. In the next step, the reaction can be followed by attack of the second pyrazolone ring that leads to the formation of **III**. Finally, nucleophilic attack of ammonia on intermediate **III** followed by intramolecular

cyclization leads to product **5**. The $FeNi_3$-ILs MNPs has the active sites of NH_3^+ as cation and $FeNi_3$-SO_3^- as anion.

Scheme 4

3. Experimental

3.1. Chemicals and apparatus

The products were isolated and characterized by physical and spectral data. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the presence of tetramethylsilane as internal standard. The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. Melting points were determined on Electro thermal 9200, and are not corrected. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. $FeNi_3$ and $FeNi_3$-ILsMNPs have been measured with a vibrating sample magnetometer (VSM, PPMS-9T) at 300 K in Iran (Kashan university). Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ= 1.5406 Å). Microscopic morphology of products was visualized by SEM (ZEISS).

3.2. Preparation of $FeNi_3$nanoparticles

$FeCl_2{\cdot}4H_2O$ and $NiCl_2{\cdot}6H_2O$ (the total amount of Fe^2+ and Ni^2+ was 0.04 mol) were dissolved into 200 ml deionized water to form a preliminary reaction solution. Certain amounts of sodium hydroxide (NaOH) solution were added into the former solution with moderate stirring. Adjust the amount of added NaOH solution carefully so that the pH value was in the range 10≤pH≤13. At this moment, a dark brown suspension was formed. 0.16 mol aqueous hydrazine ($N_2H_4{\cdot}H_2O$, 80% concentration) was then added into the above suspension. This reaction was continued for about 24 h. During this period, the pH value was kept in the range 10≤pH≤13 by adding NaOH. Final resulting particles were separated magnetically and washed repeatedly until the pH value was 7. The suspension was repeatedly washed, filtered for several times and dried at 100 ºC in the air.

3.3. General procedure for the preparation of $FeNi_3/SiO_2$nanoparticles

$FeNi_3$-ILs MNPs was prepared according to the procedure reported in the literature with some modification.[20] Firstly, a mixture of ethanol (100 mL) and distilled water (20 mL) was added to magnetic nanoparticles ($FeNi_3$ NPs) (1 g), and the resulting dispersion was sonicated for 15 min. After adding ammonia water (3 mL), tetraethyl orthosilicate (TEOS, 2.2 mL) was added to the reaction solution. The resulting dispersion was under mechanically stirred continuously for 20 h at room temperature. The magnetic $FeNi_3/SiO_2$ nanoparticles were collected by magnetic separation and washed with ethanol and deionized water in sequence.

3.4. General procedure for the preparation of $FeNi_3/SiO_2/SO_3H$ nanoparticles

To a round-bottomed flask (100 mL) $FeNi_3/SiO_2$ MNPs (0.40 g) in CH_2Cl_2 (50 mL), was added chlorosulfonic acid (12 mmol) dropwise over a period of 20 min at room temperature (Fig. 1). After vigorous stirring for 24 h, the magnetic $FeNi_3/SiO_2/SO_3H$ nanoparticles were collected by magnetic separation and washed with ethanol and deionized water in sequence.

3.5. General procedure for the preparation of $FeNi_3$-ILs nanoparticles

Ethanolamine (5 mmol) was dispersed in dry CH_2Cl_2 (20 mL) and $FeNi_3/SiO_2/SO_3H$ (0.1 g) nanoparticles were added. Then the mixture was heated to 60 °C for 15 h under nitrogen atmosphere. The resulting solid was separated by an external magnet and washed 4 times with CH_2Cl_2, ethanol and H_2O. After drying at room temperature in vacuum, $FeNi_3$-ILs was obtained as reddish-brown powder**.**

3.6. General procedure for the preparation of tetrahydrodipyrazolopyridines*:*

A mixture of hydrazine hydrate 80% (2.0 mmol) and ethyl acetoacetate (2.0 mmol) and $FeNi_3$-ILs MNPs (0.002 gr) in EtOH (5 mL) was magnetically stirred at 25 °C followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was heated at reflux for 40-50 min and then cooled to 25 °C. After completion of the reaction monitored by TLC, 10 mL ethanol was added to the reaction mixture and the catalyst $FeNi_3$-ILs MNPs was separated by external magnetic field. The precipitate was washed with EtOH to afford the pure product and then dried well under vacuum pump.

3.7. Spectral data

3,5-Dimethyl-4-(4-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4',3'-e]pyridine (5a) cream solid; m.p. 295-297 ºC; IR (KBr): ν_{max} 3400, 2963, 1603, 1511, 1348, 1177, 846 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 6H), 4.95 (s, 1H), 7.34-7.36 (d, 2 H, J = 8 Hz), 8.09-8.11 (d, 2 H, J = 8 Hz), 11.25 (s, 3H)ppm;^{13}C NMR (100 MHz, DMSO-d_6) δ 10.75, 33.43, 103.62,123.46, 129.25, 140.18, 146.09, 152.24, 161.34 ppm; Anal.Calcd.For$C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; FoundC, 58.12; H, 4.50; N, 27.15;

3,5-Dimethyl-4-(3-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4',3'-e]pyridine (5b) cream solid; m.p. 286-288ºC; IR (KBr): ν_{max} 3200, 2963, 2855, 1599, 1347 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 6H), 4.97 (s, 1H), 7.52 (m, 2 H), 7.93 (s, 1H), 8.02 (d, 1 H, J = 8 Hz), 11.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.74, 33.11, 103.74, 121.22, 122.32, 129.72, 135.20, 140.22, 146.26, 148.05, 161.3 ppm; Anal.Calcd.For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.16; H, 4.48; N, 27.14;

3,5-Dimethyl-4-(4-methyl-phenyl)-1,4,7,8-tetrahydro dipyrazolo[3,4-b;4',3'-e]pyridine (5c): white solid; m.p. 243-245 °C; IR (KBr): ν_{max} 3300, 2924, 1602, 1512 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 2.21 (s, 3H), 4.74 (s, 1H), 6.98-7.00 (m, 4 H), 11.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.84, 20.95, 32.84, 104.82, 127.81, 128.80, 134.68, 140.21, 140.72, 161.52 ppm; Anal.Calcd.For$C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07; Found C, 68.71; H, 6.22; N, 25.12;

3,5-Dimethyl-4-(4-methoxy-phenyl)-1,4,7,8-tetrahydro dipyrazolo [3,4-b;4',3'-e]pyridine (5d):cream solid; m.p. 186-188 °C; IR (KBr): ν_{max} 3267, 2924, 1597, 1510, 1348, 1239, 792 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 3.69 (s, OCH_3), 4.74 (s, 1H), 6.74-6.76 (d, 2 H, J = 8 Hz), 6.99-7.01 (d, 2 H, J = 8 Hz), 11.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.82, 32.40, 55.51, 104.92, 113.53, 128.82, 135.66,140.12, 140.18, 157.68 ppm; Anal.Calcd.For $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71; Found C, 65.12; H, 5.89; N, 23.75;

1,4,7,8-Tetrahydro-3,5-dimethyl-4-phenyldipyrazolo-[3,4-b:4',3'-e]pyridine (5e):white solid; m.p. 240-242 °C; IR (KBr): ν_{max} 3181, 2924, 1600, 1523, 1484, 725 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 4.79 (s, 1H), 7.09-7.19 (m, 5 H), 11.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.84, 33.24, 104.65, 125.84, 127.92, 128.16,140.24, 143.82, 161.54 ppm; Anal.Calcd.For $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40; Found C, 67.95; H, 5.76; N, 26.49.

3,5-Dimethyl-4-(2-methyl-phenyl)-1,4,7,8-tetrahydro dipyrazolo [3,4-b;4',3'-e]pyridine (5f) White solid**;** m.p. 290-292 °C; IR (KBr): ν_{max} 3300, 2923, 1602, 1527, 1448, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.87 (s, 6H), 2.09 (s, 3H), 4.91 (s, 1H), 7.03-7.17 (m, 4 H), 10.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.88, 20.73, 32.83, 104.80, 125.51, 127.80, 128.85, 129.34, 134.69, 140.24, 140.74, 161.69 ppm; Anal.Calcd.For $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07; Found C, 68.88; H, 6.10; N, 25.17**;**

3,5-Dimethyl-4-(4-chloro-phenyl)-1,4,7,8-tetrahydro di pyrazolo [3,4-b;4',3'-e]pyridine (5g): white solid; m.p. 255-257°C; IR (KBr): ν_{max} 3180, 2924, 1597, 1487, 1142, 1091 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 6H), 4.79 (s, 1H), 7.09-7.11 (d, J= 8 Hz, 2 H), 7.24-7.26 (d, J= 8 Hz, 2H), 11.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.78,32.67, 104.34, 128.06, 129.85, 130.49, 140.16, 142.78, 161.46ppm; Anal.Calcd.For$C_{15}H_{14}ClN_5$: C, 60.10; H, 4.71; N, 23.36 Found C, 60.15; H, 4.78; N, 23.29.

3,5-Dimethyl-4-(4-bromo-phenyl)-1,4,7,8-tetrahydro di pyrazolo [3,4-b;4',3'-e]pyridine (5h):yellow solid; m.p. 165-167 °C; IR (KBr): ν_{max} 3100, 2924, 1598, 1487, 1142, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 6H), 4.78 (s, 1H), 7.03-7.05 (d, J= 8 Hz, 2 H), 7.39-7.41 (d, J= 8 Hz, 2H), 11.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.23, 32.43, 104.45,118.30, 129.62, 130.34, 131.85, 142.66, 157.42 ppm; Anal.Calcd.For$C_{15}H_{14}BrN_5$: C, 52.34; H, 4.10; N, 20.35 Found C, 52.39; H, 4.15; N, 20.31.

4-(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4',3' e]pyridin-4-yl)-N,N-dimethylaniline (5i):cream solid; m.p. 240-242 °C; IR (KBr): ν_{max} 3200, 2950, 1598, 1470, 1145, 751 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 2.98 (s, 6 H), 4.64 (s, 1H), 6.56-6.58 (d, J= 8 Hz, 2 H), 6.90-6.92 (d, J= 8 Hz, 2H), 11.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.84, 32.35, 40.92, 105.23, 112.73, 128.35, 131.64, 137.02, 149.05,161.66 ppm; Anal.Calcd. For $C_{17}H_{20}N_6$: C, 66.21; H, 6.54; N, 27.25 Found C, 66.33; H, 6.59; N, 27.37.

3,5-Dimethyl-4-(4-hydroxy-phenyl)-1,4,7,8-tetrahydro di pyrazolo [3,4-b;4',3'-e]pyridine (5j):White solid,; m.p. 267-268 °C; IR (KBr): ν_{max} 3266, 2924, 1562, 1465, 1142, 859 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 6H), 4.65 (s, 1H), 6.56-6.58 (d, J= 8 Hz, 2 H), 6.88-6.90 (d, J= 8 Hz, 2H), 9.10 (s, OH), 11.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.32,31.75, 104.5, 114.42, 128.23, 133.35, 139.76, 155.03, 161.04 ppm; Anal.Calcd.For$C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90; Found C, 64.09; H, 5.30; N, 24.82;

3,5-Dimethyl-4-(2-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b;4',3'-e]pyridine (5k):cream solid; m.p. 187-188 °C; IR (KBr): ν_{max} 3300, 2925, 1604, 1550, 1348, 1177, 846 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.90 (s, 6H), 5.43 (s, 1H), 7.36-7.68 (m, 4 H), 10.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.02, 28.94, 101.94, 123.85, 127.12, 130.22,131.64, 136.24, 138.62, 149.50, 160.54ppm; Anal.Calcd.For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.15; H, 4.43; N, 27.12;

1,4-Bis[(1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)] benzene (5l):Orange solid, m.p. >300°C; IR (KBr): ν_{max} 3186, 1591, 1508, 1200, 785, 608 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 12H), 4.70 (s, 2H), 6.94 (4 H), 11.25 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.70, 33.20, 104.55, 129.34, 134.43, 139.50, 160.20 ppm; Anal.Calcd.For$C_{24}H_{24}N_{10}$: C, 63.70; H, 5.35; N, 30.95; Found C, 63.79; H, 5.44; N, 30.86; MS (EI, 70 eV): m/z 452 (M^+).

4. Conclusions

In conclusion, we have developed a straightforward and efficient approach to synthesis of tetrahydrodipyrazolopyridines by a simple one-pot pseudo six-component reaction of hydrazine hydrate, ethyl acetoacetate, aldehydes and ammonium acetate in the presence of $FeNi_3$-ILs nanoparticles as catalyst.

The procedure offers several advantages including short reaction times, a simple procedure, high atom economy; excellent yields, reusability of the catalyst and little catalyst loading. This green nanocatalyst could be used for other significant organic reactions and transformations. Further explorations of similar protocols are underway in our laboratory. Meanwhile, this recoverable catalyst will provide a regular platform for heterogeneous catalysis, green chemistry, and environmentally benign protocols in the near future. We hope that this article will serve to stimulate research in this fascinating and very useful area of organic synthesis.

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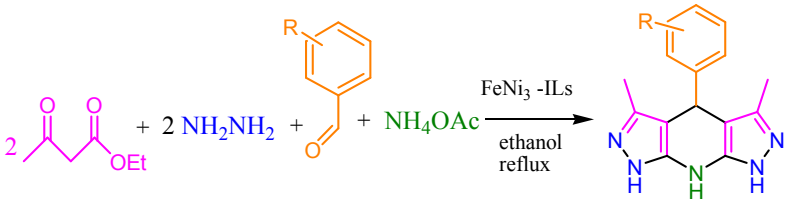
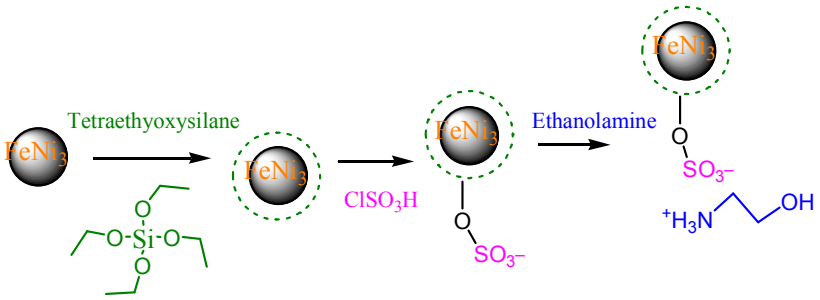
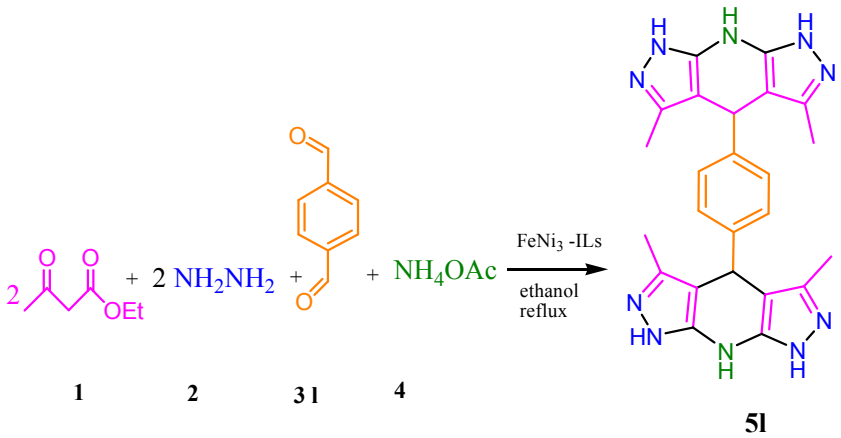


1 **2** **3** **4** **5**

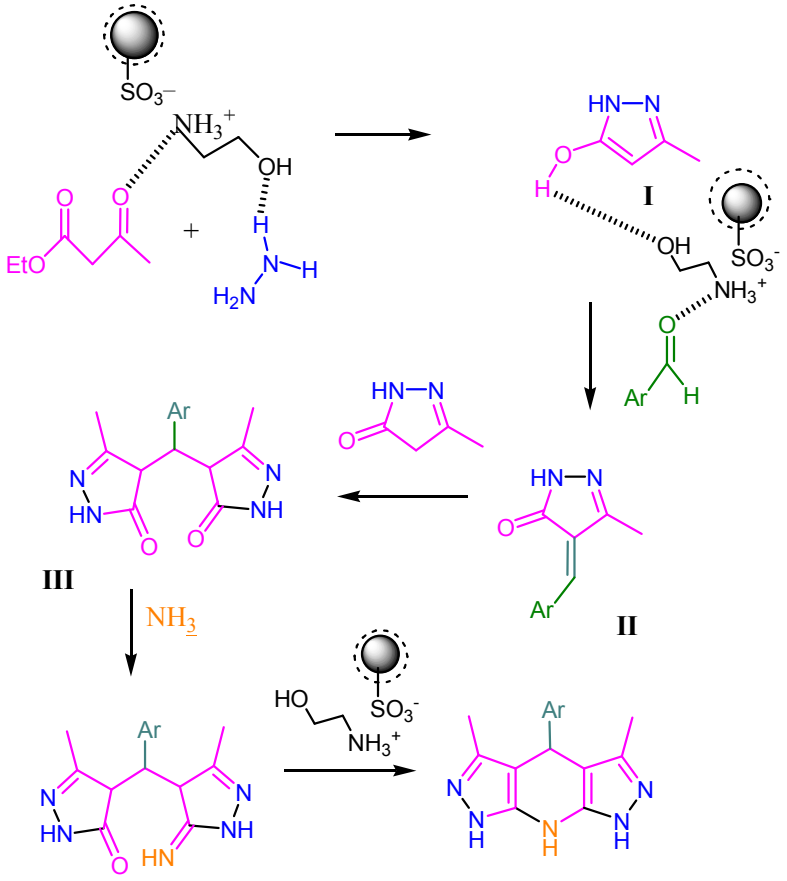
Scheme 1.Synthesis oftetrahydrodipyrazolo pyridines by $FeNi_3$-ILs nanocatalyst



Scheme 2. Schematic illustration of the synthesis for $FeNi_3$-ILs MNPs



Scheme 3.Synthesis of 1,4-Bis[(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)] benzene by $FeNi_3$-ILsnanocatalyst



Scheme 4.Proposed Mechanism for the pseudo six-component process

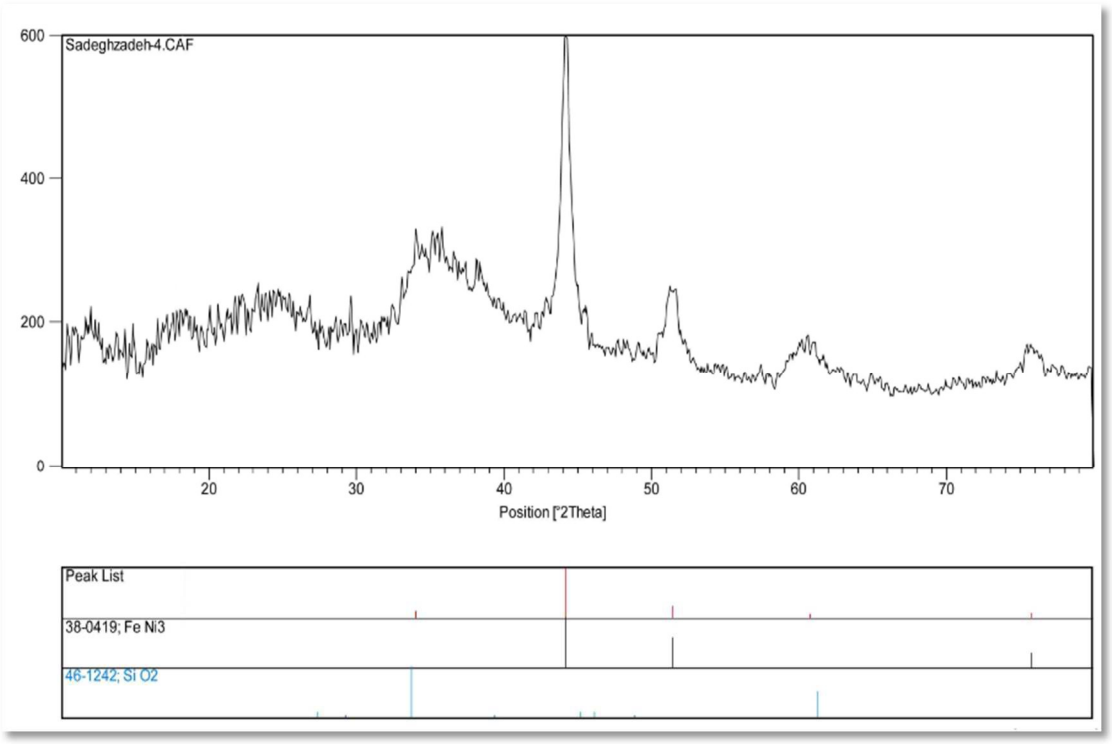


Fig 1. XRD analysis of $FeNi_3$-ILsMNPs

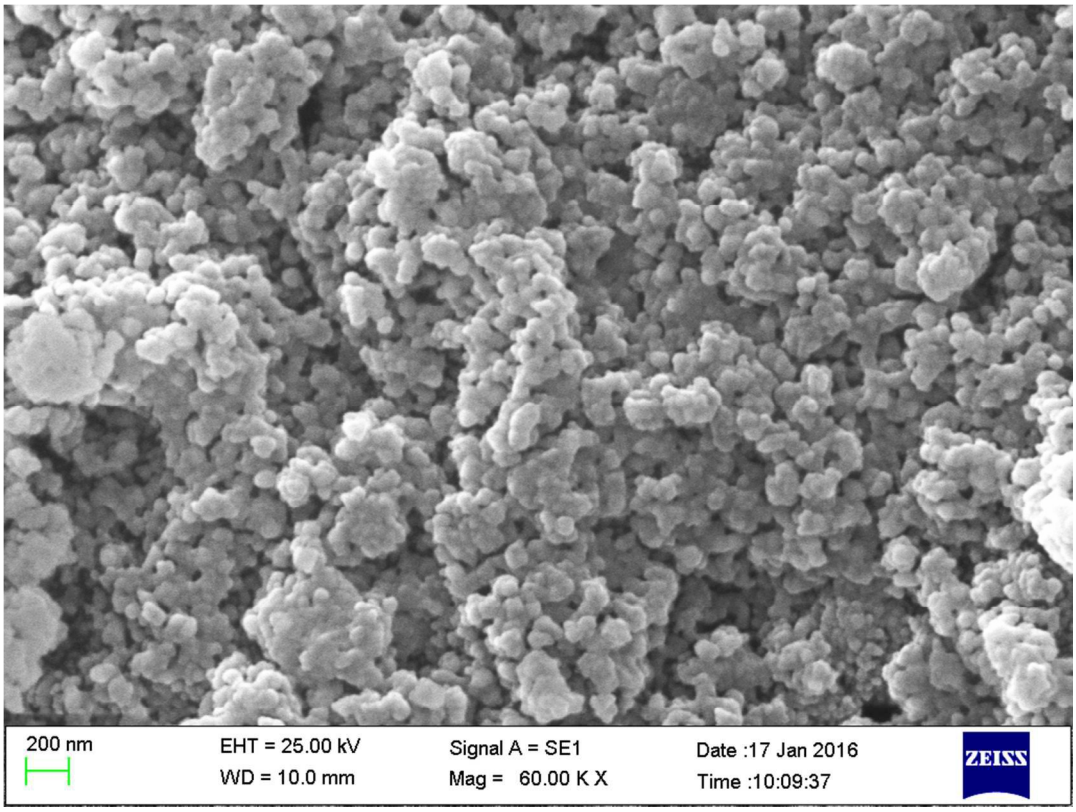


Fig. 2. SEM images of $FeNi_3$-ILs MNPs

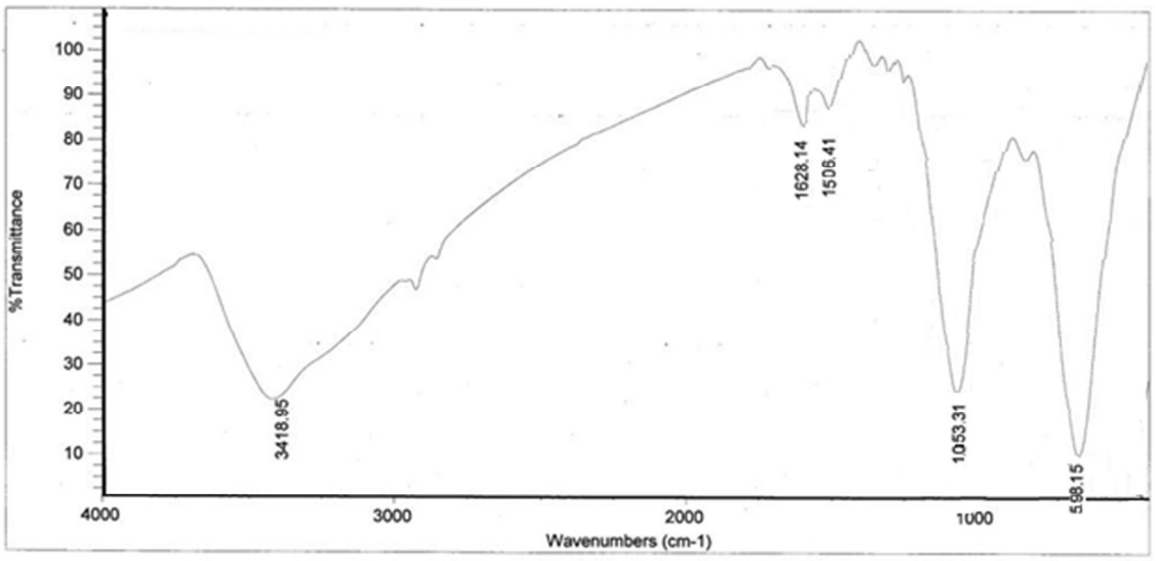


Fig 3.FTIR spectra of $FeNi_3$-ILs MNPs

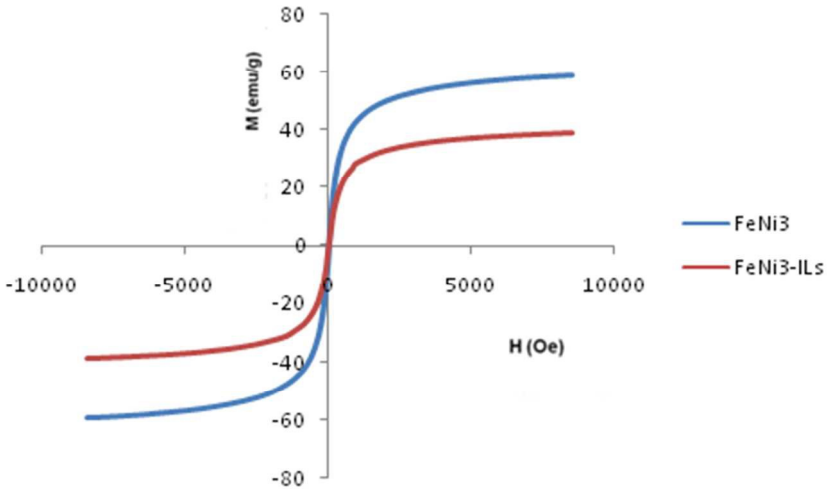


Fig. 4. Room-temperature magnetization curves of the nanocatalysis

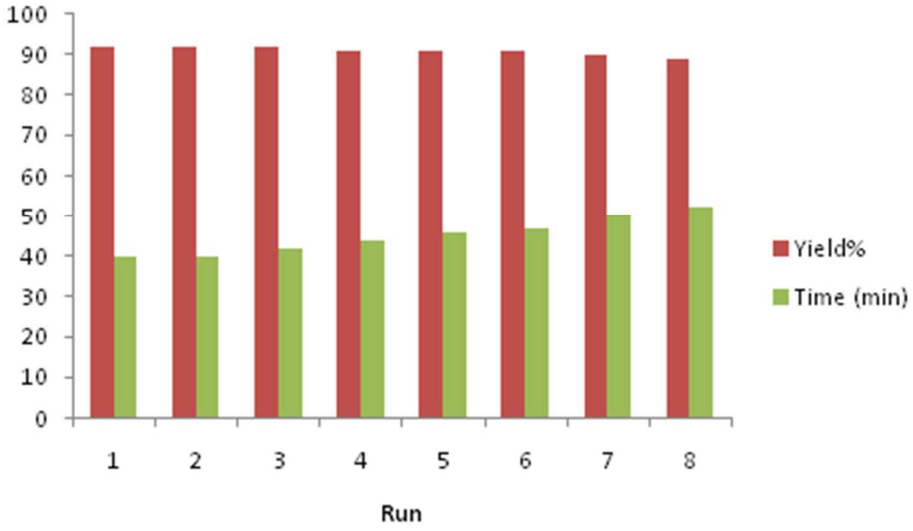


Fig 5. Reusability of $FeNi_3$-ILs MNPs as catalyst for the synthesis of **5a**

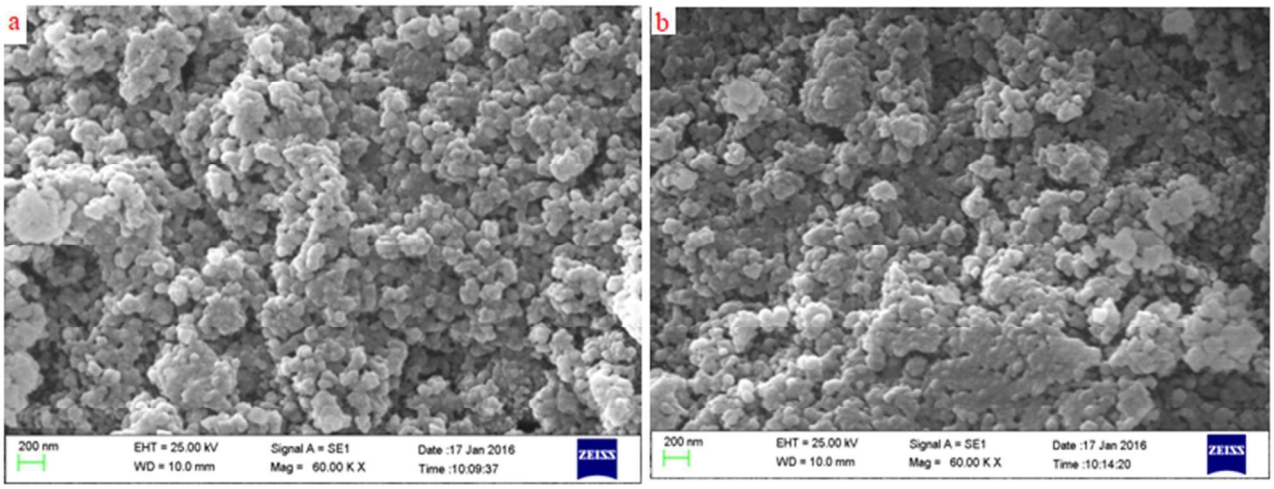


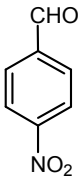
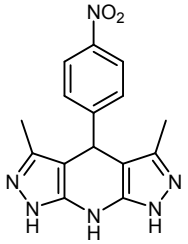
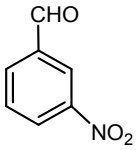
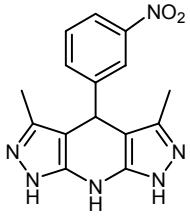
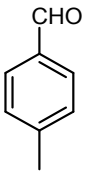
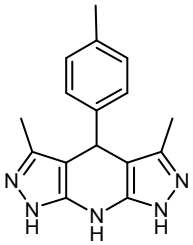
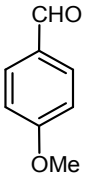
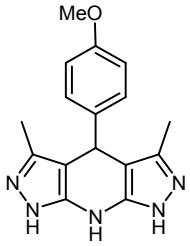
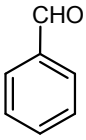
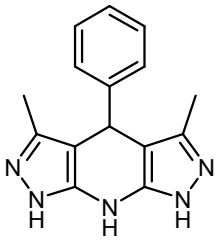
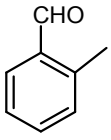
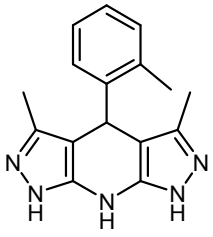
Fig 6. SEM of $FeNi_3$-ILs MNPs **(a)** before use **(b)** after reuse of seven times

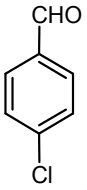
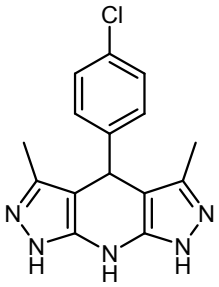
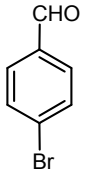
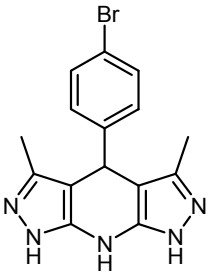
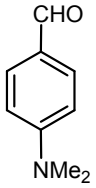
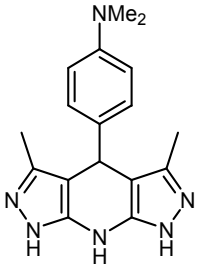
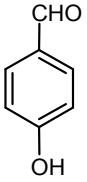
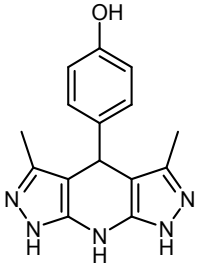
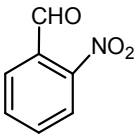
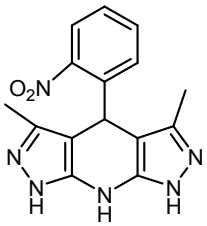
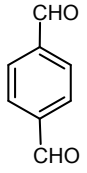
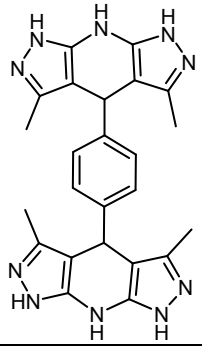
Table 1. Optimization of reaction conditions using different catalysts[a]

Entry	Catalyst	Solvent (reflux)	Time (min)	Yield%[b]
1	---------	EtOH	300	53
2	---------	H_2O	360	35
3	Et_3N (10 mol%)	EtOH	600	58
4	K_2CO_3 (5 mo1%)	EtOH	600	62
5	ZnO NPs (3 mol%)	EtOH	480	65
6	CuO NPs (3 mo1%)	EtOH	480	62
7	$FeCl_3$ (5 mol%)	EtOH	250	65
8	$FeNi_3$ NPs (2 mol%)	EtOH	280	74
9	ZnO-ILs NPs (0.003 gr)	EtOH	50	85
10	CuO-ILs NPs (0.003 gr)	EtOH	50	80
11	$FeNi_3$-ILs MNPs ≈ 30-35 nm (0.001 gr)	EtOH	50	87
12	$FeNi_3$-ILs MNPs ≈30-35 nm (0.002 gr)	EtOH	40	92
13	$FeNi_3$-ILs MNPs ≈50-55 nm (0.002 gr)	EtOH	40	88
14	$FeNi_3$-ILs MNPs ≈30-35 nm (0.003 gr)	EtOH	40	92
15	$FeNi_3$-ILs MNPs ≈30-35 nm (0.002 gr)	H_2O	70	58
16	$FeNi_3$-ILs MNPs ≈30-35 nm (0.002 gr)	CH_3CN	60	72
17	$FeNi_3$-ILs MNPs ≈30-35 nm (0.002 gr)	DMF	60	63
18	$HO\text{-}CH_2\text{-}CH_2\text{-}NH_3^+ \ ^-OOCH$ (20 mol%)	EtOH	80	68
19	$HO\text{-}CH_2\text{-}CH_2\text{-}NH_3^+ \ ^-OOCH$ (30 mol%)	solvent-free	80	73
20	$HO\text{-}CH_2\text{-}CH_2\text{-}NH_3^+ \ ^-OOCH_3$ (30 mol%)	solvent-free	80	78
21	$[HO_3SO\text{-}CH_2\text{-}CH_2\text{-}NH_2^+\text{-}SO_3H]HSO_4^-$ (30 mol%)	solvent-free	80	84

[a] hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), 4-nitrobenzaldehyde (1mmol) and ammonium acetate(4mmol)
[b]Isolated yield

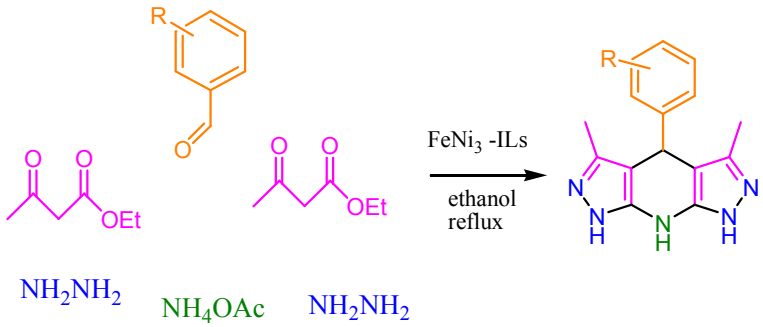
Table 2. Synthesis of tetrahydrodipyrazolo pyridines by $FeNi_3$-ILs nanocatalyst

Entry	5a-5l	aldehyde	product	Time (min)	Yield%	m.p (ref.)
1	5a			40	92	> 300 (26)
2	5b			45	84	286-288 (26)
3	5c			52	78	244-246 (26,28)
4	5d			50	80	185-187 (26)
5	5e			48	86	240-242 (26)
6	5f			54	82	290-292

7	**5g**			44	90	254-256 (26,28)
8	**5h**			47	88	165-167 (27)
9	**5i**			43	85	240-242 (26)
10	**5g**			50	82	267-268 (27)
11	**5k**			53	84	187-188 (27)
12	**5l**			55	89	>300

[a]Isolated yield

Graphical abstract



A flexible and highly efficient protocol for the synthesis of tetrahydrodipyrazolo pyridines using $FeNi_3$-ILs MNPs has been developed.