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A flexible one-pot synthesis of pyrazolopyridines catalyzed by Fe_3O_4@SiO_2-SO_3H nanocatalyst under microwave irradiation

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KEYWORDS
Fe_3O_4@SiO_2-SO_3H;
Pyrazolopyridines;
Nanocatayst;
Multicomponent reaction.

Abstract. Fe_3O_4@SiO_2-SO_3H nanocatalyst has been used as an efficient catalyst for the preparation of pyrazolopyridines by a multi-component reaction of ethyl acetoacetate, aldehyde, hydrazine hydrate, and ammonium acetate under microwave irradiation. Atom economy, wide range of products, excellent yields in short times, use of microwave as green method, reusability of the catalyst, and little catalyst loading are some of the important features of this protocol.

1. Introduction

Pyrazolopyridines have a number of pharmacological properties such as antimicrobial [1,2], anti-diabetes [3], anti-herpesviruses [4], anti-leishmania [5], HIF-1αprolyl hydroxylase inhibitors [6], kinase inhibitors [7], and dopaminergic properties [8]. A rapid and experimentally simple synthesis of pyrazolopyridines under mild conditions is in high demand. Multi-component reaction is one of the most common methods that has been utilized for the synthesis of a variety of biologically active compounds [9-12]. The chemical synthesis productivity can be enhanced by nano-sized catalysts due to their small size and high surface-to-volume ratios [13-16]. Magnetic materials have emerged as a suitable group of heterogeneous catalysts owing to their numerous applications in synthesis and catalysis [17-19]. The surface functionalization of magnetic particles is an elegant way to bridge the gap between heterogeneous and homogeneous catalyses [20-22]. Therefore, the improvement of silica-coated magnetite nanoparticles as attractive potential in the search for supporting of catalysts is currently a subject of increasing interest in chemical process [23,24]. Sulfuric acid functionalized silica-coated magnetite nanoparticles as recyclable strong solid acid catalyst inaugurate a new avenue to introduce a stupendous and efficient system for facilitating catalyst recovery in synthetic chemistry [25-27]. Recently, carbonaceous materials (C-SO_3H) have attracted significant interest as catalyst in organic synthesis [28-30]. Herein, we reported the use of Fe_3O_4@SiO_2-SO_3H nano-catalyst as an efficient catalyst for the preparation of tetrahydropyrazolopyridines by a multi-component reaction of ethyl acetoacetate, an aldehyde, hydrazine hydrate, and ammonium acetate under microwave irradiation (Scheme 1). The synthesis of pyrazolopyridines has been reported in the presence of diverse catalysts such as carbonaceous material (C-SO_3H) [31], Ii-Proline [32], acetic acid [33], and *p*-TSA [34]. However, some of the reported methods tolerate disadvantages including long reaction times, harsh reaction conditions, and use of toxic and non-reusable catalyst. Therefore, to avoid these limitations, the exploration of an efficient

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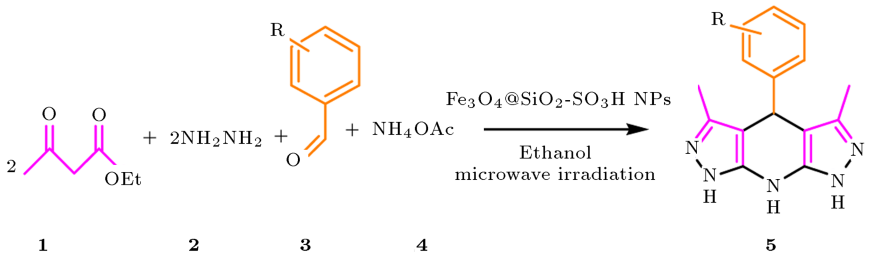


Scheme 1. Synthesis of tetrahydropyrazolo pyridines.

catalyst for the preparation of pyrazolopyridine is still favored.

2. Experimental section

2.1. Chemicals and apparatus

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 MHz spectrometer using DMSO-d_6 as solvent. The elemental analyses (C, H, and N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Fourier transform infrared (FTIR) spectra were recorded on WQF-510, spectrometer 550 Nicolet. The Energy-Dispersive X-ray Spectroscopy (EDS) measurements were performed by SAMX analyzer. Powder X-Ray Diffraction (XRD) measurements were carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ = 1.54056 nm). A TGAQ5 thermogravimetric analyzer was used to study the thermal properties of the compounds under an inert N_2 atmosphere at 20 mL min^{-1} and heating rate of 10°C min^{-1}. SEM images were taken by MIRA3-TESCAN. The magnetic properties of nanoparticles were measured by a vibrating sample magnetometer (VSMF, PPMS-9T) at 300 K Danesh Pajoh magnetic Co. in Science and Technology park, University of Kashan, Kashan, Iran.

2.1.1. Preparation of Fe_3O_4 nanoparticles

Fe_3O_4 nanoparticles were synthesized by co-precipitation method. $FeCl_3.6H_2O$ (11.68 g) and $FeCl_2.4H_2O$ (4.30 g) were dissolved in 200 mL deionized water, and then 15 mL $NH_3.H_2O$ (25%) was added to the solution drop-wise under nitrogen atmosphere and vigorous stirring at 70-75°C. The magnetic nanoparticles were separated from the solution by using an external magnet and washed twice with deionized water.

2.1.2. Preparation of Fe_3O_4@SiO_2 nanoparticles

1 g of magnetic nanoparticles was dispersed in 20 mL ethanol in ultrasonic bath and sonicated for 30 min at room temperature. Then, 6 mL aqueous NH_3 (25%) and 2 ml tetraethyl orthosilicate (TEOS) were added to the solution. The resulting solution was stirred at 35-40°C for 24 h. The Fe_3O_4@SiO_2 NPs were separated from the solution by using an external magnet, washed with ethanol (3 × 15 mL), and dried at room temperature.

2.1.3. Preparation of Fe_3O_4@SiO_2-SO_3H nanoparticles

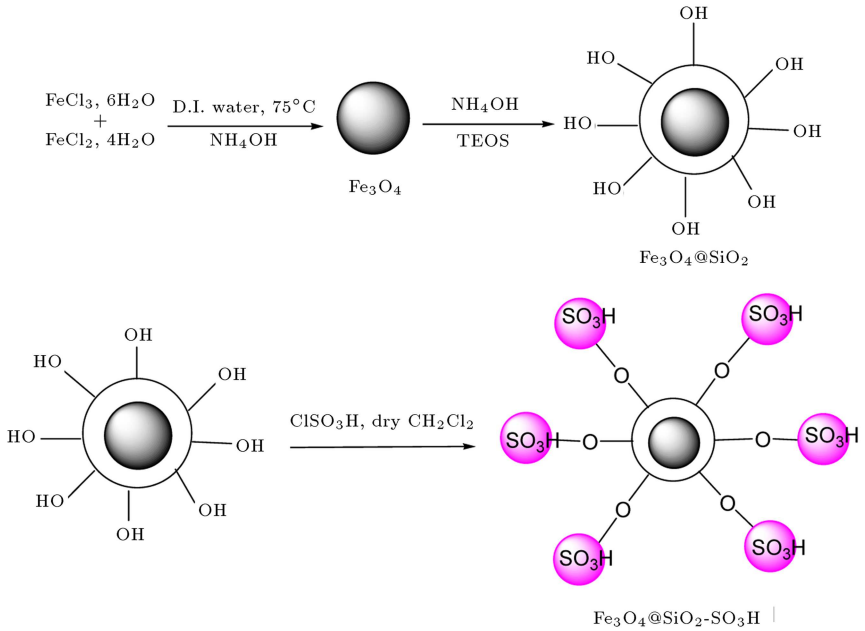
Firstly, 1 g of Fe_3O_4@SiO_2 was dispersed in dry CH_2Cl_2 (16 mL) and sonicated for 10 min. Then, chlorosulfonic acid (0.8 mL in dry CH_2Cl_2) was added drop-wise to a cooled (ice-bath) solution of Fe_3O_4@SiO_2 during a period of 30 min under vigorous stirring. The mixture was stirred for 60 min, while the residual HCl was removed by suction. The resulted MNPs were separated by using a magnet, washed several times with dried CH_2Cl_2 and methanol before being dried under vacuum at 60°C. The number of H^+ sites of Fe_3O_4@SiO_2-SO_3H NPs was determined by pH-ISE conductivity titration (Denver Instrument Model 270) and found to be 1.69 H^+ sites per 1 g of solid acid at 25°C. The overall schematic procedure used to synthesize the magnetic nanocatalysis is illustrated in Scheme 2.

2.1.4. General procedure for the preparation of tetrahydrodipyrazolopyridines

A mixture of hydrazine hydrate (2.0 mmol), ethyl acetoacetate (2 mmol), and nano-Fe_3O_4@SiO_2-SO_3H NPs (0.004 g) in EtOH (5 mL) was magnetically stirred at 25°C followed by the addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was irradiated inside microwave oven with the power level at 500 W. After the completion of the reaction monitored by TLC, 10 mL ethanol was added to the reaction mixture, and catalyst Fe_3O_4@SiO_2-SO_3H NPs was separated by external magnetic field. The precipitate was washed with EtOH to afford the pure product.

2.2. Spectral data of products

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°C; IR (KBr): ν_{max} 3402, 2964, 1605, 1514, 1347, 1178, 845 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 6H), 4.97 (s, 1H), 7.34-7.36 (d, 2H, J = 8 Hz), 8.09-8.11 (d, 2H, J = 8 Hz), 11.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.76, 33.42, 103.63, 123.45, 129.26, 140.19, 146.06, 152.24, 161.35 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, 4.52; N, 27.15.



Scheme 2. Preparation routes of Fe_3O_4@SiO_2-SO_3H nanoparticles.

3,5-Dimethyl-4-(4-methyl-phenyl)-1,4,7,8-tetrahydro di pyrazolo [3,4-b;4′,3′-e]pyridine (5b)
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 2.03 (s, 6H), 2.22 (s, 3H), 4.75 (s, 1H), 6.99-7.01 (m, 4 H), 11.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.85, 20.93, 32.85, 104.82, 127.82, 128.85, 134.69, 140.21, 140.73, 161.53 ppm; Anal.Calcd.For $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07; Found C, 68.75; H, 6.27; N, 25.15.

3,5-Dimethyl-4-(3-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b;4′,3′-e]pyridine (5c)
Cream solid; m.p. 286-288°C; IR (KBr): ν_{max} 3200, 2963, 2855, 1599, 1347 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 4.96 (s, 1H), 7.54 (m, 2H), 7.94 (s, 1H), 8.03 (d, 1 H, J = 8 Hz), 11.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.75, 33.13, 103.75, 121.25, 122.37, 129.73, 135.22, 140.23, 146.27, 148.06, 161.33 ppm; Anal.Calcd.For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.18; H, 4.48; N, 27.16.

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} 3266, 2923, 1597, 1512, 1347, 1235, 793 cm^{-1}; 1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 3.69 (s, OCH_3), 4.76 (s, 1H), 6.76-6.78 (d, 2H, J = 8 Hz), 6.98-7.00 (d, 2H, J = 8 Hz), 11.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.80, 32.42, 55.50, 104.93, 113.52, 128.81, 135.65, 140.13, 140.17, 157.67 ppm; Anal.Calcd.For $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71; Found C, 65.13; H, 5.85; N, 23.78.

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, 2925, 1602, 1525, 1488, 727 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 6H), 4.76 (s, 1H), 7.09-7.18 (m, 5 H), 11.37 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.85, 33.27, 104.66, 125.83, 127.95, 128.17, 140.28, 143.83, 161.55 ppm; Anal.Calcd.For $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40; Found C, 67.93; H, 5.74; N, 26.46.

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} 3302, 2926, 1603, 1526, 1449, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.88 (s, 6H), 2.08 (s, 3H), 4.92 (s, 1H), 7.05-7.18 (m, 4 H), 10.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.87, 20.75, 32.85, 104.82, 125.52, 127.82, 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, 68.89; H, 6.13; N, 25.15.

3,5-Dimethyl-4-(4-chloro-phenyl)-1,4,7,8-tetrahydro dipyrazolo [3,4-b;4′,3′-e]pyridine (5g)
White solid; m.p. 255-257°C; IR (KBr): ν_{max} 3184, 2926, 1596, 1487, 1143, 1092 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 6H), 4.78 (s, 1H), 7.010-7.12 (d, J = 8 Hz, 2H), 7.26-7.28 (d, J = 8 Hz, 2H), 11.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.78, 32.67, 104.34, 128.07, 129.86, 130.48, 140.17, 142.79, 161.45 ppm; Anal.Calcd.For $C_{15}H_{14}ClN_5$: C, 60.10; H, 4.71; N, 23.36 Found C, 60.15; H, 4.77; N, 23.26.

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} 3103, 2925, 1598, 1488, 1144, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 6H), 4.79 (s, 1H), 7.04-7.06 (d, J = 8 Hz, 2H), 7.40-7.42 (d, J = 8 Hz, 2H), 11.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.25, 32.44, 104.46, 118.32, 129.63, 130.35, 131.86, 142.67, 157.45 ppm; Anal.Calcd.For $C_{15}H_{14}BrN_5$: C, 52.34; H, 4.10; N, 20.35 Found C, 52.38; H, 4.15; N, 20.33.

4-(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo [3,4-b:4′,3′e]pyridin-4-yl)-N,N-dimethyl aniline (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 2.05 (s, 6H), 2.97 (s, 6 H), 4.63 (s, 1H), 6.55-6.57 (d, J = 8 Hz, 2H), 6.92-6.94 (d, J = 8 Hz, 2H), 11.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.85, 32.36, 40.93, 105.24, 112.75, 128.36, 131.64, 137.03, 149.03, 161.67 ppm; Anal.Calcd.For $C_{17}H_20N_6$: C, 66.21; H, 6.54; N, 27.25 Found C, 66.35; H, 6.59; N, 27.38.

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, 2926, 1562, 1467, 1142, 858 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 6H), 4.66 (s, 1H), 6.56-6.58 (d, J = 8 Hz, 2H), 6.88-6.90 (d, J = 8 Hz, 2H), 9.11 (s, OH), 11.52 (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, 64.07; H, 5.31; N, 24.87.

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} 3303, 2927, 1604, 1553, 1348, 1178, 849 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.92 (s, 6H), 5.44 (s, 1H), 7.37-7.67 (m, 4 H), 10.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.03, 28.95, 101.95, 123.84, 127.17, 130.25, 131.64, 136.26, 138.62, 149.50, 160.55 ppm; Anal.Calcd. For $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; Found C, 58.15; H, 4.45; N, 27.14.

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} 3185, 1592, 1507, 1204, 783, 605 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 12H), 4.71 (s, 2H), 6.93 (4 H), 11.20 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.70, 33.22, 104.56, 129.35, 134.44, 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, 63.75; H, 5.42; N, 30.86; MS (EI, 70 eV): m/z 452 (M^+).

3. Results and discussion

The morphology and particle size of Fe_3O_4@SiO_2-SO_3H nanoparticles were investigated by Scanning Electron Microscopy (SEM), as shown in Figure 1. It is observed that average size of Fe_3O_4@SiO_2-SO_3H is about 20-33 nm.

XRD patterns of Fe_3O_4 and Fe_3O_4@SiO_2-SO_3H are shown in Figure 2. The characteristic peaks in both spectra are in agreement with the standard XRD pattern of iron oxide (cubic phase). A broad peak in 2θ range of 19° to 27° is related to the silica shell coated on Fe_3O_4 NPs.

Figure 3 illustrates room temperature specific magnetization (M) versus applied magnetic field (H) curve measurements for Fe_3O_4, Fe_3O_4@SiO_2, and Fe_3O_4@SiO_2-SO_3H. As illustrated in Figure 3, the amounts of saturation magnetization for Fe_3O_4@SiO_2NPs and Fe_3O_4@SiO_2-SO_3H are 39.7 and 10.43, respectively. The lower saturation magnetization of Fe_3O_4@SiO_2-SO_3H than that of

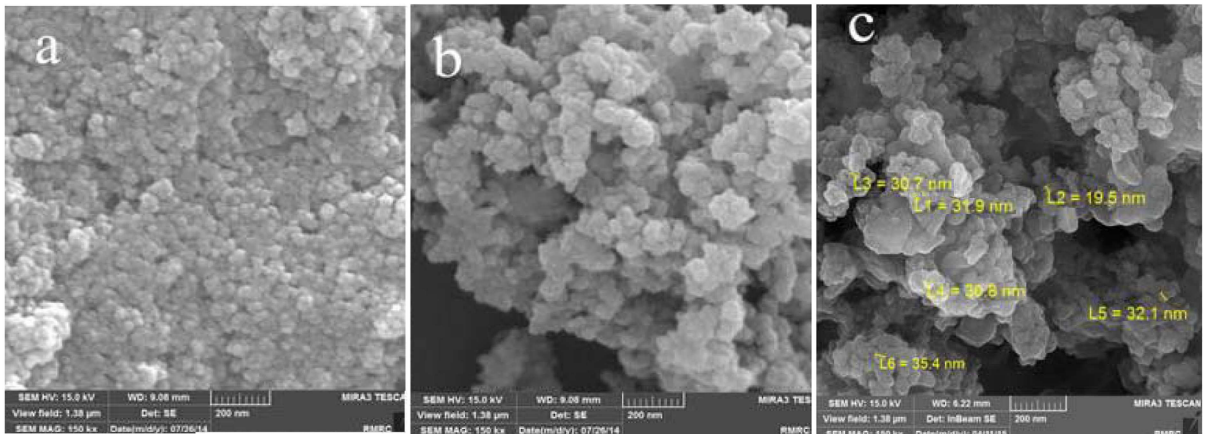


Figure 1. SEM images of (a) Fe_3O_4 NPs, (b) Fe_3O_4@SiO_2 NPs, and (c) Fe_3O_4@SiO_2-SO_3H.

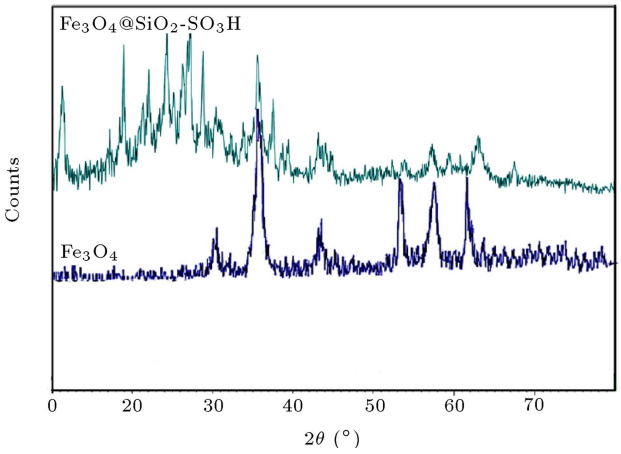


Figure 2. The XRD pattern of Fe_3O_4@SiO_2-SO_3H and XRD pattern of Fe_3O_4.

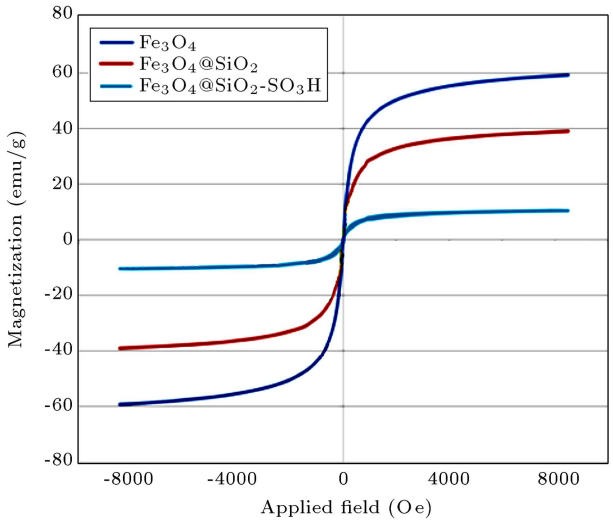


Figure 3. The VSM curves of Fe_3O_4, Fe_3O_4@SiO_2, and Fe_3O_4@SiO_2-SO_3H.

Fe_3O_4@SiO_2NPs is attributed to the extra layer coated onto MNPs.

The FT-IR spectra of sulfuric acid-functionalized Fe_3O_4@SiO_2, Fe_3O_4@SiO_2, and Fe_3O_4 NPs are shown in Figure 4. The peak appeared at 580-600 cm^{-1} in all the three spectra is related to characteristic absorption of Fe-O vibrations. The intense peaks appeared at around 1040-1080 cm^{-1} are attributed to asymmetric and symmetric stretching vibrations of Si-O-Si bonds. These basic characteristic peaks verified that SiO_2 was coated on the surface of Fe_3O_4 NPs. In the spectrum of Fe_3O_4@SiO_2-SO_3H, the presence of acid group is confirmed by the strong and broad peak at 3199 cm^{-1} which could be attributed to OH stretching vibration. The presence of sulfonyl group is also verified by the peaks appeared at 1215 and 1120 cm^{-1}. The peak at 1120 cm^{-1} was covered with a stronger absorption peak of Si-O bond at 1076 cm^{-1}.

Figure 5(a) shows the EDS spectra of Fe_3O_4

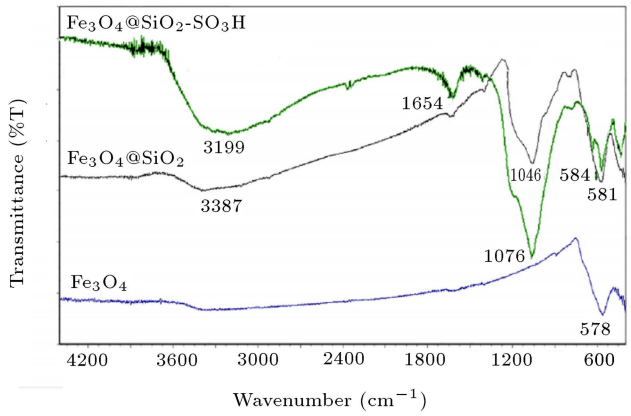


Figure 4. FT-IR spectra of Fe_3O_4, Fe_3O_4@SiO_2 and Fe_3O_4@SiO_2-SO_3H NPs.

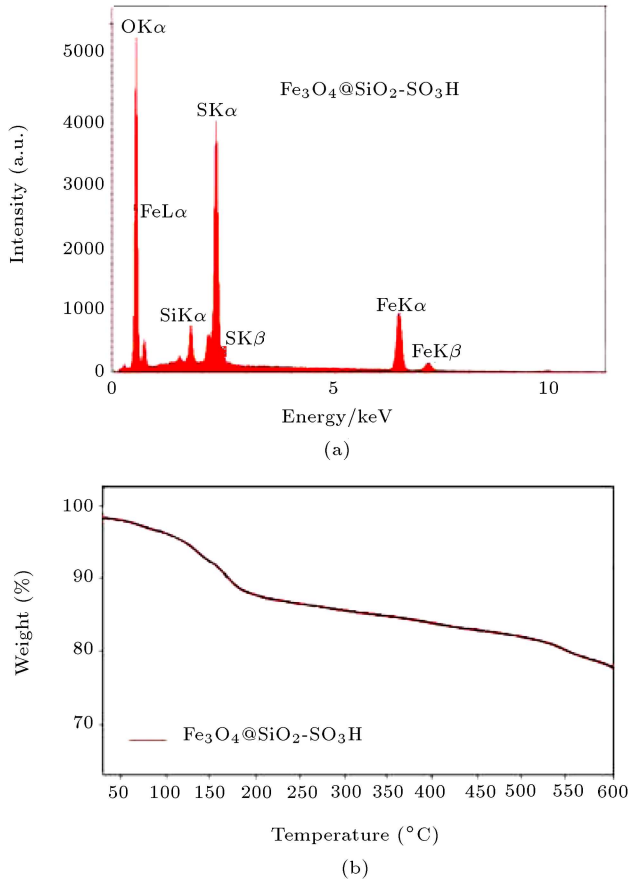


Figure 5. (a) EDS spectrum of Fe_3O_4@SiO_2-SO_3H NPs. (b) TGA curve of Fe_3O_4@SiO_2-SO_3H.

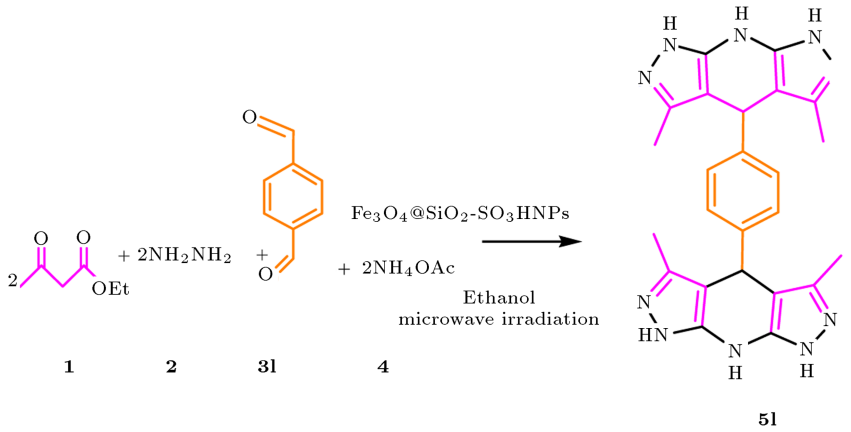
@SiO_2-SO_3H. The presence of elements, such as oxygen, iron, silicon, and sulfur, was confirmed in the EDS spectrum of Fe_3O_4@SiO_2-SO_3H NPs and their weight percentages were about 58.14, 22.77, 2.23, and 16.86, respectively. Thermal behavior of the prepared catalysts was studied by TGA; the related curves are shown in Figure 5(b). In the both curves, the small weight loss at temperatures between 30 to 250°C is attributed to the removal of surface hydroxyl groups

and physically adsorbed solvent molecules trapped in SiO_2 layer. The weight loss observed at 250-450°C in TGA curve of Fe_3O_4@SiO_2-SO_3H NPs is mainly related to the decomposition of SO_3H groups grafted to the silica surface.

Initially, we carried out the MCR between hydrazine hydrate, ethyl acetoacetate, 4-nitrobenzaldehyde, and ammonium acetate under microwave irradiation in ethanol as a model reaction in the presence of different catalyst. Meanwhile, we observed the effects of different solvents on the progress of reaction. Ethanol was found to be the best solvent, in which the product was obtained in 97% yield under microwave irradiation (500 W). When the reaction was carried out using (0.004 g) Fe_3O_4@SiO_2-SO_3H NPs as the catalyst, the product could be obtained in good yield (Table 1).

The above results obviously show that the present catalytic procedure is extendable to a wide variety of substrates to construct a diversity-oriented library of pyrazolopyridines (Table 2). Meanwhile, the practicable synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde, hydrazine hydrate, ammonium acetate, and ethyl acetoacetate to give 1,4-Bis[(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e] pyridin-4-yl)] benzene (Scheme 3).

After completion of the reaction, the nanocatalyst was easily separated using an external magnet. The recovered magnetic nanoparticles were washed several times with acetone, and then dried at room temperature. Table 3 indicates that the catalyst could be reused for eight times with a minimal loss of activity for the synthesis of 5a.



Scheme 3. Synthesis of 1,4-Bis[(1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-y l)] benzene.

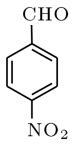
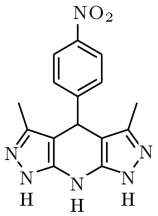
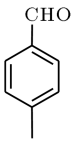
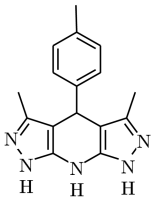
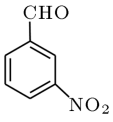
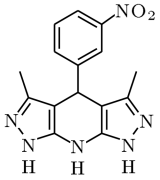
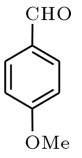
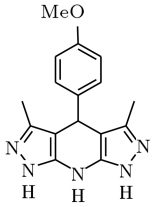
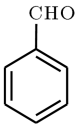
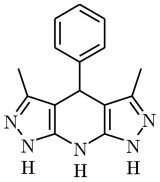
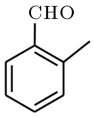
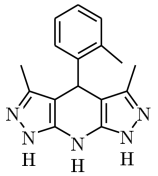
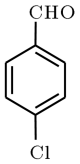
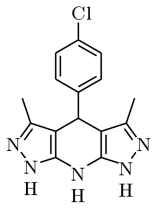
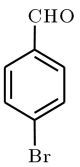
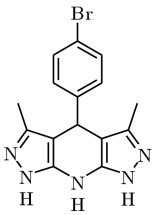
Table 1. Optimization of reaction conditions using different catalysts[a].

Entry	Catalyst	Solvent (under microwave irradiation)	Time (min)	Yield%[b]
1	Morpholine (10 mol%)	EtOH (500 W)	20	45
2	ZnO NPs (0.08 g)	EtOH (500 W)	20	52
3	SiO_2 NPs (0.08 g)	EtOH (500 W)	20	56
4	Fe_3O_4 NPs (0.06 g)	EtOH (500 W)	20	60
5	Fe_3O_4@SiO_2 NPs (0.06 g)	EtOH (500 W)	15	66
6	Fe_3O_4@SiO_2-SO_3H NPs (0.004 g)	H_2O (500 W)	25	70
7	Fe_3O_4@SiO_2-SO_3H NPs (0.004 g)	CH_3CN (500 W)	15	80
8	Fe_3O_4@SiO_2-SO_3H NPs (0.004 g)	EtOH (400 W)	15	94
9	Fe_3O_4@SiO_2-SO_3H NPs (0.002 g)	EtOH (500 W)	15	92
10	Fe_3O_4@SiO_2-SO_3H NPs (0.004 g)	EtOH (500 W)	15	97
11	Fe_3O_4@SiO_2-SO_3H NPs (0.006 g)	EtOH (500 W)	15	97
12	Fe_3O_4@SiO_2-SO_3H NPs (0.004 g)	EtOH (600 W)	15	95

[a]: Hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), 4-nitrobenzaldehyde (1 mmol) and ammonium acetate (4 mmol);

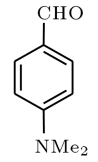
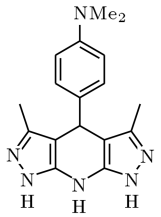
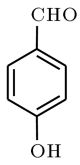
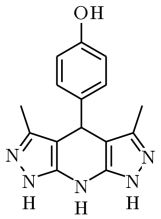
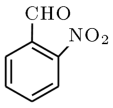
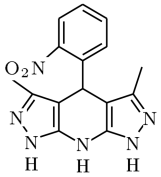
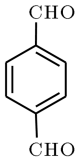
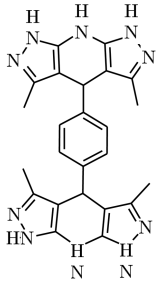
[b]: Isolated yield.

Table 2. Synthesis of pyrazolopyridines.

Entry	5a-5l	Aldehyde	Product	Time (min)	Yield%[a]	m.p [ref.]
1	5a			15	97	> 300 [35]
2	5b			20	90	244-246 [35]
3	5c			15	94	286-288 [35]
4	5d			20	88	185-187 [35]
5	5e			15	92	240-242 [35]
6	5f			20	90	290-292
7	5g			15	95	254-256 [35]
8	5h			15	94	165-167 [36]

[a]: Isolated yield.

Table 2. Synthesis of pyrazolopyridines (Continued).

Entry	5a-5l	Aldehyde	Product	Time (min)	Yield%[a]	m.p [ref.]
9	**5i**			20	87	240-242 [35]
10	**5g**			20	89	267-268 [37]
11	**5k**			15	95	187-188 [36]
12	**5l**			15	88	> 300

[a]: Isolated yield.

Table 3. Reusability of Fe_3O_4@SiO_2-SO_3H NPs (0.004 g) catalyst for the preparation of **5a**[a].

Run	1	2	3	4	5	6	7	8
Time (min)	15	15	15	15	15	15	20	20
Yield%[a]	97	97	96	96	95	95	94	92

[a]: Isolated yield.

A plausible mechanism for the preparation of tetrahydrodipyrazolo pyridines using Fe_3O_4@SiO_2-SO_3H NPs is shown in Scheme 4. The mechanism involves the initial nucleophilic attack of hydrazine on the ethyl acetoacetate, 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 the final product. In this mechanism, the surface atoms of Fe_3O_4@SiO_2-SO_3H NPs activate the C=O groups for better reaction with nucleophiles. These surface atoms act as the centers where chemical reactions could be catalytically spurred. This proposed mechanism was supported by findings of the literatures [34,38].

4. Conclusions

In conclusion, we have developed a straightforward and efficient approach to the synthesis of pyrazolopyridinesusing Fe_3O_4@SiO_2-SO_3H NPs as a catalyst. The method offers several advantages including rapid assembly of medicinally privileged heterocyclic molecules, accessibility, high yields, shorter reaction times, use of microwave as green method, the reusability of the catalyst, and low amount of catalyst.

Acknowledgement

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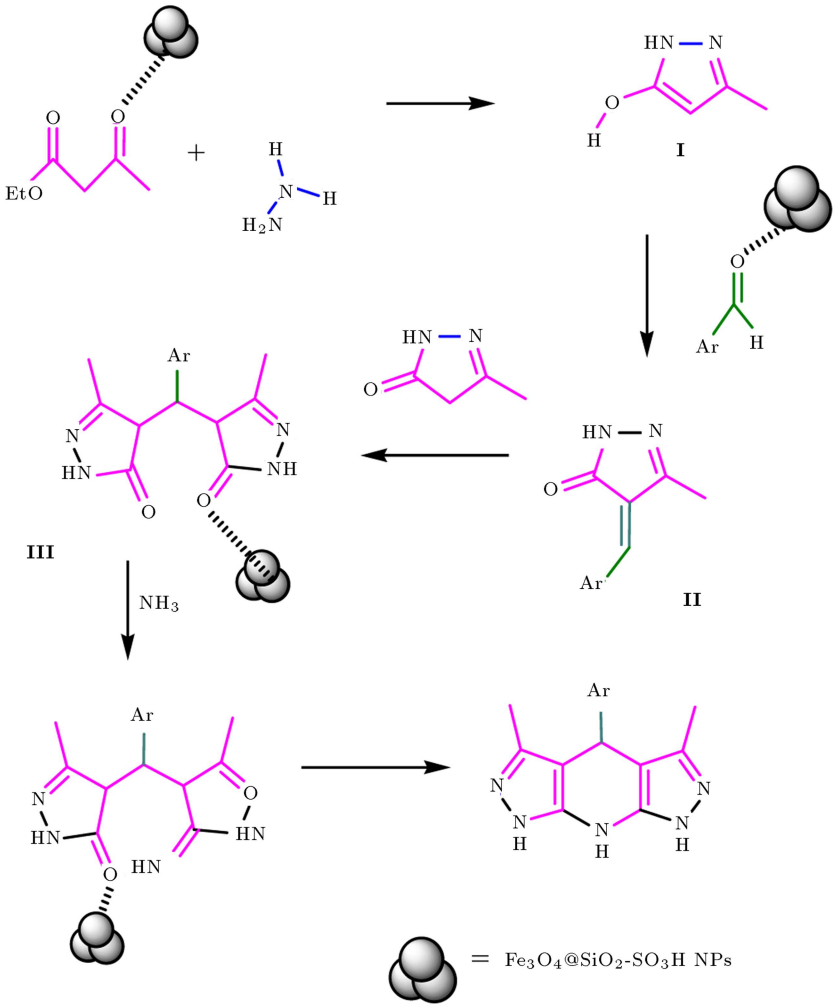

Scheme 4. The proposed mechanism for the pseudo six-component process.

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