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Anchored sulfonic acid on silica-layered NiFe₂O₄: a magnetically reusable nanocatalyst for Hantzsch synthesis of 1,4-dihydropyridines

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Abstract: In this study, the immobilization of sulfonic acid on silica-layered nickel ferrite, NiFe₂O₄@SiO₂@SO₃H, was investigated. The sulfonated Ni-nanocatalyst was then characterized using FT-IR, SEM, EDX, XRD and VSM analyses. Catalytic activity of the Ni-nanocomposite was also studied towards Hantzsch synthesis of 1,4-dihydropyridines via one-pot condensation reaction of 1,3-diketones (ethyl acetoacetate or 4-hydroxycoumarin), aromatic aldehydes and aqueous ammonia in H₂O (70 °C) as a green solvent. All reactions were carried out within 10–100 min to afford the products in high to excellent yields. The green aspect of this synthetic protocol was more studied by examining the reusability of NiFe₂O₄@SiO₂@SO₃H MNPs for seven consecutive cycles without the significant loss of catalytic activity. The current method represents remarkable advantages in terms of mild reaction conditions, using H₂O as an environmental-friendly solvent, stability and easy separation of the magnetic nanocatalyst, high yield of products, wide tolerance of starting materials and the perfect reusability of the applied Ni-nanocatalyst.

Keywords: Ethyl acetoacetate; Hantzsch 1,4-dihydropyridines; 4-hydroxycoumarin; NiFe₂O₄; sulfonic acid

1. Introduction

Catalysis is one of the essential aspects of chemical reactions which is offering selectivity and high yield of the products as well as faster reaction rates. In this context, acids are used frequently as catalysts in various laboratory and industrial reactions [1–4]. Strong acids such as sulfuric, phosphoric and hydrochloric acids are used as homogeneous acid catalysts in various organic reactions, such as alkylation, hydration, dehydration, rearrangement, carbonyl and condensation reactions. Nevertheless, sulfuric acid is not considered as a reusable and benign catalyst. It has several drawbacks in terms of corrosiveness, insufficient isolation and tedious workup procedure. In spite of these, the need for sulfuric acid in chemical reactions is crucial [5]. The literature review shows that numerous efforts have been realized for modifying homogeneous catalysts to heterogeneous one. In this area, the immobilization of homogeneous catalysts on the surface of solid supports such as metal oxide [6–8], polymer matrix [9–12], carbon materials [13–17], porous silica [5, 18–21] and zeolites [22–24] has gained the considerable interest.

Nowadays, the application of magnetic nanoparticles (MNPs) of transition metal oxides as solid supports has been frequently studied. They are easily prepared and because of the extreme surface area of nanoparticles, stability, magnetic property and the inherent electronic influence of transition metal constituents are the suitable candidates to immobilize various homogeneous catalysts. In this area, the application of cubic spinel nickel ferrite (NiFe₂O₄) has been more investigated. This magnetic material has high thermal stability (up to 900 °C) and super paramagnetic property for easy separation from the reaction mixture [25–30]. In spite of the great capabilities of nano ferrites, however, they have a strong tendency for agglomeration. Encapsulation of nano ferrites nucleus with silica layer is an easy way to overcome the mentioned shortcoming. It is also reported that the suitable deposition of silica layer on the surface of magnetic nucleus improves their chemical stability [31–34].

Recently, a considerable impact has been paid to the synthesis of acidic functional groups anchored on the surface of magnetic nanoparticles towards the promotion of various organic reactions. As well, they have good the magnetic property, high stability and clean reaction products without possessing disadvantages of homogeneous acid-catalysts [35–42].

Among *N*-containing heterocycles, 1,4-dihydropyridines (1,4-DHPs) are too important materials and received much attention due widespread biological activities such as anti-cancer, vasodilator, cytotoxic, antidiabetic, antitumor, antimicrobial, antialzheimer and hepatoprotective agents [43–50]. 1,4-DHPs are

also served as L-type Ca²⁺ channel blockers to treat hypertension and angina diseases [51–54]. These characteristics clearly represent the considerable impact of 1,4-DHPs as the source of valuable drugs. The literature review shows that using alginic acid [55], AlCl₃·6H₂O [56], MgAl₂-hydrotalcite [57], MgO NPs [58], TiO₂ NPs [59], montmorillonite K10 [60], chitosan supported copper sulfate [61], cellulose sulfuric acid [62], CeO₂ [63], acidic ionic liquid on polymer [PS-IM(CH₂)₄SO₃H][HSO₄] [64], PPh₃ [65], Fe₃O₄ NPs [66], trifluro-ethanol [67] and tetra-*n*-butylammonium bromide/microwave [68] for synthesis of diester 1,4-DHPs as well Fe₃O₄@SiO₂ [69], guanidinium-based sulfonic acid [70], silica gel or acidic alumina/microwave [71] and lactic acid [72] for synthesis of coumarin-based 1,4-DHPs has been successfully reported. Although the reported method have the own merits and shortcomings, however, the development of simple, efficient and environmental benign protocols for synthesis of 1,4-DHPs using reusable heterogeneous solid acid catalyst is highly demanded. Figure 1 shows the structure of some pharmacological active 1,4-DHPs.



In line with the outlined strategies and continuation of our research program towards synthetic usefulness of magnetically nanocatalyst systems [73–76], herein, we wish to introduce sulfonic acid immobilized on silica-layered nickel ferrite, NiFe₂O₄@SiO₂@SO₃H as an efficient magnetic and reusable solid acid catalyst for the one-pot and three-component condensation reaction of aromatic aldehydes (1), ethyl acetoacetate (2)/4-hydroxycoumarin (3) and ammonia (4) in H₂O giving 1,4-dihydropyridines 5(a-l) and 6(a-l) in high yields (Figure 2).



Figure 2. Synthesis of 1,4-DHPs catalyzed by NiFe₂O₄@SiO₂@SO₃H MNPs

2. Experimental

2.1. Instruments and reagents

All chemicals were purchased from chemical companies with the best quality and they were used without further purification. ¹H, ¹³C NMR and FT-IR spectra were recorded on 300 MHz Bruker Avance and Thermo Nicolet Nexus 670 spectrometers. X-ray diffraction (XRD) measurements were carried out on a X'PertPro Panalytical, Holland diffractometer in 40 kV and 30 mA with a CuK α radiation (λ =1.5418 Å). Signal data were recorded in 2 θ = 10°–80° with a step interval of 0.05°. Morphology and size distribution of nanoparticles were examined by scanning electron microscopy (SEM) using FESEM-TESCAN MIRA3 instrument. The chemical composition of the prepared nanocomposites was determined by energy-dispersive X-ray (EDX) spectroscopy. Magnetic property of the nanocatalysts was measured using vibration sample magnetometer (VSM, Meghnatis Daghigh Kavir Co., Iran) analysis under an external magnetic field up to 20 kOe. Melting points were recorded on Electrothermal 9100 melting point apparatus and uncorrected. TLC was applied for monitoring of the reactions over silica gel 60 F254 aluminum sheet. Spectral data for compounds **5(a-I)** and **6(a-I)** were added in supplementary information.

2.2. Synthesis of NiFe₂O₄ MNPs

A desired amount of Ni(OAc)₂·4H₂O, Fe(NO₃)₃·9H₂O, NaOH and NaCl in a molar ratio of 1:2:8:2, respectively, were mixed in a mortar and grinded for 50 min at room temperature. After that, the mixture was washed with deionized water for several times and dried at 80 °C for 10 h. The resulting product was calcinated at 700 or 900 °C for 2 h to afford magnetically nanoparticles of NiFe₂O₄ [76].

2.3. Synthesis of NiFe₂O₄@SiO₂ MNPs

A mixture of NiFe₂O₄ (1.5 g) MNPs in *i*-PrOH (200 mL) and deionized water (20 mL) was prepared. The resulting mixture was then irradiated by ultrasound for 30 min. PEG-400 (5.36 g), deionized water (20 mL), aqueous ammonia 28% (10 mL) and tetraethyl orthosilicate (TEOS, 2 mL) was then added and the resulting mixture was stirred at room temperature for 28 h. After that, magnetically nanoparticles of NiFe₂O₄@SiO₂ were separated by an external magnetic field. The nanoparticles were then washed with ethanol and

deionized water followed by drying under air atmosphere for 12 h.

2.4. Synthesis of NiFe₂O₄@SiO₂@SO₃H MNPs

A suspension of NiFe₂O₄@SiO₂ (2 g) MNPs in CHCl₃ (15 mL) and under ice-bath condition (0–5 °C) was prepared. While the mixture was stirred, CISO₃H (0.5 g, 9 mmol) was added within 50 min in drop wise manner. The resulting mixture was continued to stirring for 2 h at room temperature for the complete releasing of HCl from the mixture. The mixture was then filtered and the solid residue was washed with MeOH (20 mL) and dried at room temperature for 12 h giving NiFe₂O₄@SiO₂@SO₃H as the black powder. Through the acid-base titration, the amount of sulfonic acid moiety (H⁺ sites) in the nanocatalyst was determined 0.33 mmol·g⁻¹.

2.5. A general procedure for Hantzsch synthesis of 1,4-DHPs catalyzed by NiFe₂O₄@SiO₂@SO₃H MNPs

In a round-bottom flask (10 mL) equipped with a magnetic stirrer, a mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate or 4-hydroxycoumarin (2 mmol) and aqueous ammonia 28% (2 mmol) in H₂O (2 mL) was prepared. NiFe₂O₄@SiO₂@SO₃H MNPs (20 mg) was then added and the resulting mixture was stirred at 70 °C for an appropriate time (Table 2 and 3). Progress of the reaction was monitored by TLC (eluent, *n*-hexane /EtOAc: 10/4). After completion of the reaction, EtOAc (3 mL) was added and the mixture was stirred for 5 min followed by magnetic separation of the Ni-nanocatalyst. At the next, the organic layer was separated from the aqueous solution and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave the corresponding 1,4-DHP product in high yield. Further purification could be carried out by recrystallization from hot EtOH.

3. Results and Discussion

3.1. Synthesis and characterization of NiFe2O4@SiO2@SO3H MNPs

The synthesis of sulfonated silica-layered NiFe₂O₄ (NiFe₂O₄@SiO₂@SO₃H) MNPs was carried out in a threestep procedure: i) synthesis of NiFe₂O₄ MNPs by solid state grinding of Ni(OAc)₂·4H₂O and Fe(NO₃)₃·9H₂O in the presence of NaOH followed by calcination at 700 or 900 °C, ii) layering of SiO₂ by tetraethyl orthosilicate (TEOS) on nano nucleus of NiFe₂O₄ and iii) immobilization of sulfonic acid moiety on the surface of NiFe₂O₄@ SiO₂ MNPs via the simple reaction of silica-layered nickel ferrite with ClSO₃H at 0–5 °C (Figure 3).



Figure 3. Preparation of NiFe₂O₄@SiO₂@SO₃H MNPs

3.2. Characterization of NiFe₂O₄@SiO₂@SO₃H MNPs

After the successful synthesis of sulfonated silica-layered nickel ferrite, the structure of nanocatalyst was elucidated using FT-IR, SEM, EDX, and VSM analyses.

3.2.1. FT-IR analysis

Fourier transform Infrared spectroscopy is a straightforward method for elucidation of structure as well as functional groups in a material. In this context, FT-IR spectra of NiFe₂O₄, NiFe₂O₄@SiO₂ and NiFe₂O₄@SiO₂ @SO₃H MNPs are illustrated in Figure 4. In the case of NiFe₂O₄ (Figure 4a), two main metal-oxygen bands at 598 and 432 cm⁻¹ are attributed to the tetrahedral and octahedral frameworks of iron or nickel ions [77–80]. The band around 3700 cm⁻¹ is also attributed to hydroxyl groups bonded to metal ions, and the absorption bands at 3437 and 1640 cm⁻¹ to H-O-H stretching and bending vibrations of physically adsorbed water, respectively. FT-IR spectrum of silica-layered nickel ferrite (Figure 4b) shows the stretching absorption bands corresponding to Si-O-Si at the range of 1000–1200 cm⁻¹. In the case of NiFe₂O₄@SiO₂@SiO₂@SO₃H (Figure 4c) and due overlapping of Si-O-Si, Fe-O-Si and O-S-O stretching bands at 1086 cm⁻¹, the presence of SO₃H groups on the surface of NiFe₂O₄@SiO₂ MNPs is demonstrated. As well, the absorption band at 3431 cm⁻¹ is attributed to stretching vibration band of OH in sulfonic acid moiety on the surface of silica-layered nickel ferrite synthesis of NiFe₂O₄@SiO₂@SO₃H MNPs.



3.2.2. SEM and EDX analysis

The morphology and elemental composition of the prepared NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H MNPs were determined by SEM and EDX analyses. SEM images of the prepared samples of NiFe₂O₄ at 700 °C (Figure 5a and b) and 900 °C (Figure 5c and d) show that the prepared one at 700 °C was agglomerated and constructed from roughly particles. Accordingly, the prepared NiFe₂O₄ at 900 °C was constructed from regular-shape particles with the uniform distribution. These results represent that the influence of calcination-temperature on morphology and size distribution of nanoparticles is noteworthy. Therefore, it is concluded that calcination of NiFe₂O₄ at 900 °C gives the best crystallinity structure with size distribution of nanoparticles in the range of 55–72 nm. In this context, SEM images of NiFe₂O₄@SiO₂@SO₃H MNPs (Figure 6a-c) show that the sulfonated nanocomposite was constructed from regular and spherical

nanoparticles with uniform distribution. It's seen that due layering of SiO₂@SO₃H moiety on the surface of NiFe₂O₄, the size of nanoparticles in NiFe₂O₄@SiO₂@SO₃H MNPs is bigger than that of NiFe₂O₄. As well, the nanoparticles are distributed in the range of 148–240 nm. In continuation, the existence of Ni, Fe and O in NiFe₂O₄ as well Ni, Fe, O, Si and S elements in NiFe₂O₄@SiO₂@SO₃H MNPs was clearly demonstrated by EDX analyses (Figures 5e and 6d). These analyses exhibited that the nucleus of NiFe₂O₄ were successfully encapsulated by sulfonated silica-layer moiety.











Figure 5. SEM images of NiFe₂O₄ [calcinated at 700 °C (a, b) and 900 °C (c, d)] and its EDX spectrum (e)











Figure 6. SEM images (a-c) and EDX spectrum (d) of NiFe₂O₄@SiO₂@SO₃H MNPs

3.2.3. XRD analysis

X-ray diffraction analysis is a useful technique to elucidate the phase purity and crystallinity structure of materials. In this context, the issue was investigated through the depicted X-ray diffractograms of NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H MNPs in Figure 7. According to XRD pattern of Figure 7a, the diffraction peaks at $2\Theta = 30.51^{\circ}, 35.9^{\circ}, 37.49^{\circ}, 43.58^{\circ}, 54.02^{\circ}, 57.58^{\circ}$ and 63.20° are corresponded to reflection planes of (220), (311), (222), (400), (422), (511) and (440) in NiFe₂O₄. This pattern represent that the prepared NiFe₂O₄ has a good phase purity and crystallinity in cubic spinel structure. The pattern is in an exact agreement with the standard one of NiFe₂O₄ (JCPDS 54-0964). Subsequently, Figure 7b represents XRD diffractogram of NiFe₂O₄@SiO₂@SO₃H MNPs. Comparing the XRD patterns of NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H MNPs shows that the sulfonated nanocatalyst has the phase purity and characteristic peaks of NiFe₂O₄. Because of high [noise/signal] ratio in the pattern, it is also demonstrated that SiO₂@SO₃H moiety was successfully immobilized on the surface of nano nucleus of NiFe₂O₄ [81].



Figure 7. XRD patterns of NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H MNPs

3.2.4. VSM analysis

In continuation, the magnetic behavior of NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H MNPs was studied by vibrating sample magnetometer (VSM) analysis. In this context, the magnetization curve for both of samples (Figure 8) reveals a nonlinear and reversible behavior with small hysteresis loop describing NiFe₂O₄ and NiFe₂O₄@ SiO₂@SO₃H have the property of soft ferromagnetic materials. As well, the magnetization (Ms) values of NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H are 28.15 and 20.24 emu·g⁻¹, respectively. Decreasing in magnetization value of NiFe₂O₄@SiO₂@SO₃H is attributed to the presence of sulfonated silica-layer moiety on the surface of NiFe₂O₄ nucleus. This level of magnetization (20.24 emu·g⁻¹) is enough for any magnetic separation.



Figure 8. Magnetization curves of NiFe₂O₄ and NiFe₂O₄@SiO₂@SO₃H MNPs

3.3. Hantzsch synthesis of 1,4-dihydropyridines catalyzed by NiFe₂O₄@SiO₂@SO₃H MNPs

At the next, catalytic activity of NiFe₂O₄@SiO₂@SO₃H MNPs was studied towards Hantzsch synthesis of 1,4dihydropyridines. In this context, the one-pot and three-component condensation reaction of 4-chlorobenzaldehyd (1 mmol), ethyl acetoacetate (2 mmol) and ammonia (2 mmol) was selected as a model reaction and progress of the condensation reaction was studied through the change of reaction-solvent and temperature as well the amount of nanocatalyst. The results of this investigation are summarized in Table 1. Entry 11 shows that using H₂O (at 70 °C), aqueous ammonia as the source of amine and 20 mg of NiFe₂O₄ @SiO₂@SO₃H was the requirement to afford high yield of the product.

Table 1. Optimization experiments for the reaction of 4-chlorobenzaldehyde (1 mmol), ethyl acetoacetate(2 mmol) and an amine source (2 mmol) catalyzed by NiFe2O4@SiO2@SO3H MNPs								
Entry	Ni-Catalyst (mg)	Solvent (2 mL)	Temp. (°C)	Amine source (2 mmol)	Time (min)	Yield (%)		
1	-	EtOH	50	aq. NH₃	300	5		
2	-	H ₂ O	50	aq. NH₃	300	5		
3	20	EtOH	50	aq. NH₃	45	60		
4	20	H ₂ O	50	aq. NH₃	30	85		
5	20	EtOH-H ₂ O (1:1)	50	aq. NH₃	30	70		
6	20	EtOAc	50	aq. NH₃	200	45		
7	20	CH₃CN	50	aq. NH₃	200	50		
8	20	DMF	50	aq. NH₃	120	50		
9	20	Solvent-free	50	aq. NH₃	60	50		
10	20	H ₂ O	25	aq. NH₃	120	60		
11	20	H ₂ O	70	aq. NH₃	20	95		
12	10	H ₂ O	70	aq. NH₃	20	60		
13	20	H ₂ O	70	NH ₄ OAc	120	70		
14	20	H ₂ O	70	NH ₄ Cl	120	60		

The capability of NiFe₂O₄@SiO₂@SO₃H MNPs for Hantzsch synthesis of 1,4-dihydropyridines was further studied by one-pot condensation reaction of structurally diverse aromatic aldehydes, ethyl acetoacetate and ammonia at the optimized reaction conditions. The results of this investigation are illustrated in Table 2. The Table shows that various aryl aldehydes including electron releasing or withdrawing functionalities were efficiently participated in the condensation reaction within 20–100 min to give the corresponding diester 1,4-DHPs in high o excellent yields.

Table 2.	Preparation of diester 1,4	4-dihydropyr	idines catalyzed	l by NiFe2O4@	SiO2-SO3H M	INPs ^a		
Ar-CHO + 2 CH ₃ COCH ₂ CO ₂ Et + NH ₃ $\xrightarrow{\text{NiFe}_2O_4@SO_2@SO_3H}_{\text{H}_2O, 70 °C}$ $\xrightarrow{\text{EtO}_2C}_{\text{NH}}$ $\xrightarrow{\text{CO}_2\text{Et}}_{\text{H}_2O, 70 °C}$ $\xrightarrow{\text{NiFe}_2O_4@SO_2@SO_3H}_{\text{H}_2O, 70 °C}$ $\xrightarrow{\text{Store}}_{\text{H}_2O, 70 °$								
Entry	Ar-	Product	Time (min)	Yield (%) ^b	M.p. (°	C) [65–68]		
					Found	Reported		
1	C ₆ H ₄	5a	40	85	156–157	156–158		
2	2-CIC ₆ H ₄	5b	30	95	144–145	146–147		
3	4-CIC ₆ H ₄	5c	20	95	150–152	150–152		
4	2,4-Cl ₂ C ₆ H ₃	5d	40	97	151–153	152–155		
5	3-OH,4-MeOC ₆ H₃	5e	45	75	242–245	240-242		

6	4-MeOC ₆ H ₄	5f	40	75	153–155	154–156		
7	3-MeOC ₆ H ₄	5g	35	70	151–153	153–155		
8	4-MeC ₆ H ₃	5h	80	75	135–137	135–137		
9	4-OHC ₆ H ₄	5i	70	70	234–236	233–235		
10	$4-O_2NC_6H_4$	5j	80	100	131–132	130–132		
11	3-02NC6H4	5k	100	95	164–165	163–164		
12	3-NO ₂ ,4-CIC ₆ H ₃	51	90	90	230–232	231–233		
^a All reaction the present	^a All reactions were carried out with the molar ratio of aryl aldehyde/ethyl acetoacetate/aq. Ammonia (1:2:2) in the presence of 20 mg papocatalyst in $H_{2}O(2 \text{ m} + 70 \text{ °C})$ ^b Yield refers to isolated pure product							

The possibility of this synthetic protocol was also examined by the one-pot condensation reaction of 4hydroxycoumarin as another source of 1,3-dicarbonyl compounds with aromatic aldehydes and aqueous ammonia. The experiments resulted that the mentioned conditions for Hantzsch synthesis of 1,4-DHPs with ethyl acetoacetate was also efficient for Hantzsch synthesis with 4-hydroxycoumarin. Therefore structurally diverse aromatic aldehydes (1 mmol), 4-hydroxycoumarin (2 mmol) and aqueous ammonia (2 mmol) were reacted in the one-pot manner with 20 mg of NiFe₂O₄@SiO₂@SO₃H MNPs. The results of this investigation are illustrated in Table 3. The Table shows that all reactions were carried out successfully within 10–45 min to afford dichromeno-1,4-DHPs in high to excellent yields. As well, electron-withdrawing functionalities on aromatic rings prolonged the reaction times. In contrast, electron-releasing groups accelerated the rate of condensation reaction.

Table 3. Hantzsch synthesis of dichromeno-1,4-DHPs catalyzed by NiFe ₂ O ₄ @SiO ₂ @SO ₃ H MNPs ^a									
A	$Ar-CHO + 2 \qquad \qquad$								
Entry	Δr-	Product	Time (min)	Vield (%) ^b	M.p. (°C)	[69–72]			
Litery	74	Troduct			Found	Reported			
1	C ₆ H ₄	6a	20	95	186–188	185–187			
2	2-CIC ₆ H ₄	6b	25	90	216–218	217–220			
3	4-CIC ₆ H ₄	6c	20	98	222–224	222–225			
4	3-OH,4-MeOC ₆ H₃	6d	10	85	212-216	210–215			
5	4-OH,3-MeOC ₆ H ₃	6e	10	90	208–213	209–214			
6	3-MeOC ₆ H ₄	6f	15	90	179–183	178–182			
7	2-MeOC ₆ H ₃	6g	10	85	194–197	195–198			
8	4-MeC ₆ H ₄	6h	15	90	190–193	191–194			
9	4-OHC ₆ H ₄	6i	20	85	174–177	173–178			
10	4-O ₂ NC ₆ H ₄	6j	45	80	211–213	210-212			
11	3-O2NC6H4	6k	30	75	208–210	209–213			
12	3-O ₂ N,4-CIC ₆ H ₃	61	40	80	200–203	201–205			
^a All reacti the preser	ons were carried out wi nce of 20 mg nanocataly	th the molar st in H₂O (2 n	ratio of aryl alde nL, 70 °C). ^b Yield	hyde/4-hydrox refers to isolat	ycoumarin/aq. am ed pure product.	monia (1:2:2) in			

Although the exact mechanism of this synthetic protocol is not clear, however, a depicted mechanism (Figure 9) could be outlined for the role of nanocatalyst catalyzing the synthesis of 1,4-DHPs. Sulfonated silica-layered nickel ferrite primarily activates the carbonyl moiety of aromatic aldehyde. Then, enol-form of β -dicarbonyls reacts with activated aldehyde to form Knoevenagel intermediate **II**. At the next, through the

acid activation of intermediate II and its Michael addition with enol-form of β -ketoester, intermediate IV is produced. Finally, by the reaction of intermediate IV with ammonia and ring closing of intermediate VI, formation of 1,4-DHP is taken place.



Figure 9. A proposed mechanism for Hantzsch synthesis of 1,4-DHPs catalyzed by NiFe₂O₄@SiO₂@SO₃H MNPs

The usefulness and capability of NiFe₂O₄@SiO₂@SO₃H MNPs in Hantzsch synthesis of 1,4-DHPs **5c** [diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate] and **6c** [7-(4-chlorophenyl)-7,14-dihydro-6H,8H-dichromeno[4,3-b:3',4'-e]pyridine-6,8-dione] was also highlighted by a comparison with the previously reported promoters (Tables 4 and 5). A case study shows that in terms of reaction times, reusability of the nanocatalyst and yield of the products, the present work exhibited the perfect efficiency than the other promoters.

Table 4. Synthesis of diester 1,4-DHP 5c by NiFe ₂ O ₄ @SiO ₂ @SO ₃ H and other reported promoters									
Entry	Catalyst	Time (min)	Yield (%)	Condition	Temp (°C)	Reusability	Ref.		
1	NiFe ₂ O ₄ @SiO ₂ @SO ₃ H	20	95	H ₂ O	70	7	*		
2	Alginic acid	60	92	EtOH	reflux	6	55		
3	AICl ₃ ·6H ₂ O	130	76	Solvent-free	60	-	56		
4	MgAl ₂ -hydrotalcite	360	65	CH₃CN	r.t.	-	57		
5	MgO NPs	165	90	EtOH	reflux	3	58		
6	TiO ₂ NPs	160	90	EtOH	80	5	59		

7	Montmorillonite K10	30	91	EtOH	80	3	60
8	Chitosan-CuSO ₄	65	95	EtOH	reflux	5	61
9	Cellulose sulfuric acid	120	78	Solvent-free	80	-	62
10	CeO ₂	60	74	Solvent-free	80	5	63
11	[PS-IM(CH ₂) ₄ SO ₃ H][HSO ₄]	140	90	EtOH	reflux	4	64
10	PPh ₃	120	81	EtOH	reflux	_	65
* Prese	ent work						

Table 5. Synthesis of coumarin-based 1,4-DHP 6c by NiFe ₂ O ₄ @SiO ₂ @SO ₃ H and other reported promoters								
Entry	Catalyst	Time (min)	Yield (%)	Condition	Reusability	Ref.		
1	NiFe ₂ O ₄ @SiO ₂ @SO ₃ H	20	95	H₂O (70 °C)	7	*		
2	Fe ₃ O ₄ @SiO ₂	20	88	H ₂ O (reflux)	4	69		
3	Guanidinium-sulfonic acid	120	86	H₂O (reflux)	4	70		
4	Silica gel	25	65	Microwave	-	71		
5	Acidic alumina	14	75	Microwave	-	71		
6	Lactic acid	150	79	ethyl-L-lactate (100 °C)	-	72		
*Prese	*Present work							

3.4. Recycling of NiFe₂O₄@SiO₂@SO₃H MNPs

The green and economic aspect of this synthetic protocol was further studied by examining the possibility of sulfonated Ni-nanocatalyst for reusing at the next runs of the condensation reaction. To do this, progress of the model reaction (4-chlorobenzaldehyde, ethyl acetoacetate and ammonia) in the presence of NiFe₂O₄ $@SiO_2@SO_3H$ MNPs was investigated. When the reaction was completed, the nanocatalyst was magnetically separated from the reaction mixture and then washed with EtOAc followed by drying at 80 °C. The model reaction was again charged with the freshly components of the condensation reaction and the recovered Ni-nanocatalyst. The summarized results in Figure 10 show that the sulfonated Ni-nanocatalyst was reused for 7 consecutive cycles without the significant loss of catalytic activity.



Figure 10. Reusability of NiFe₂O₄@SiO₂@SO₃H MNPs in the synthesis of 1,4-DHP 5c

4. Conclusions

In this study, the synthesis of sulfonic acid anchored on silica-layered nickel ferrite, NiFe₂O₄@SiO₂@SO₃H, was investigated. The prepared nanocatalyst was then characterized using FT-IR, SEM, EDX, XRD and VSM analyses. The sulfonated Ni-nanocatalyst showed the perfect catalytic activity towards Hantzsch synthesis of 1,4-DHPs using ethyl acetoacetate/4-hydroxycoumarin, aromatic aldehydes and ammonia. All reactions

were carried out in H_2O (at 70 °C) within 10–100 min to afford the products in high to excellent yields. The current protocol represents remarkable advantages in terms of easy preparation and the magnetic property of the sulfonated Ni-nanocatalyst, high yield of the products, short reaction times, wide tolerance of starting materials, benefits of using water as a green and economic solvent as well as the perfect reusability of the magnetic nanocatalyst.

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Anchored sulfonic acid on silica-layered NiFe₂O₄: a magnetic solid acid nanocatalyst for Hantzsch synthesis of 1,4-dihydropyridines

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In this study, the immobilization of sulfonic acid on silica-layered nickel ferrite, NiFe₂O₄@SiO₂@SO₃H, was investigated. The prepared sulfonated Ni-nanocatalyst exhibited the perfect catalytic activity towards Hantzsch synthesis of 1,4-dihydropyridines via the one-pot condensation reaction of ethyl acetoacetate/4-hydroxycoumarin, aromatic aldehydes and ammonia in H₂O within 10–100 min.

