Scientific paper

Synthesis and Antibacterial Evaluation of Some New 1,4-Dihydropyridines in the Presence of Fe_3O_4@Silica Sulfonic Acid Nanocomposite as Catalyst

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Abstract

The synthesis of heterocyclic compounds has been a topic of significant interest because of their broad applications. In this research an effective and eco-friendly approach for the synthesis 1,4-dihydropyridines has been developed via the four-component reactions of arylamines, acetylenedicarboxylates, aromatic aldehydes and ethyl acetoacetate in the presence of Fe_3O_4@SiO_2@OSO_3H nanocomposite under solvent-free conditions. The advantages of this method involve the green reaction conditions, simple workup, broad substrates, excellent yields and the reuse of the nanocatalyst. One of the indicators to measure antimicrobial activity is Minimum Inhibitory Concentrations (MIC) that this measure and heterocyclic compounds synthesis inhibition zone diameter was measured on examined bacteria using well diffusion, disc diffusion and determination of antibiotic susceptibility. The results of all three methods suggested the susceptibility of *Staphylococcus aureus* to synthesized heterocyclic compounds. It can be concluded from the results that these compounds have high antibiotic properties and can be useful in other research and biomedical applications.

Keywords: 1,4-dihydropyridine, antibacterial activity, Fe_3O_4@silica sulfonic acid, nanocomposite, multi-component reaction, solvent-free

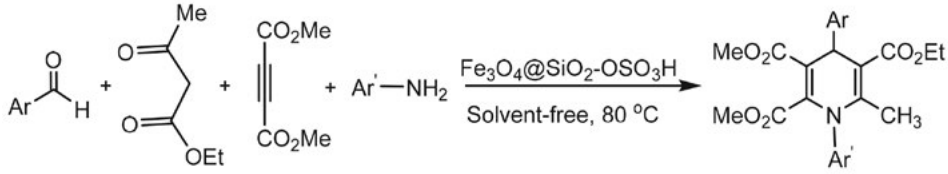
1. Introduction

Multi-component reactions (MCR) have appeared as an efficient and powerful approach in modern synthetic organic chemistry due to their valuable features such as: atomic economy, straightforward reaction design, atomic economy, and the opportunity to construct target compounds by introducing diverse elements in a single chemical event. Since all of the employed organic reagents are consumed and incorporated into the target compound, purification of products which results from MCR, is also simple.[1]

Many reactions proceed efficiently in the solid state.[2] Indeed, in many cases, solid-state organic reaction occurs more efficiently and selectively than its solution counterpart does, since molecules in a crystal are arranged tightly and regularly. Furthermore, the solid state reaction (or solvent-free reaction) has many advantages including reduced pollution, low costs and simplicity in process and handling, these factors are especially important in industry.[3–7]

1,4-dihydropyridines (1,4-DHPs) represent an important class of compounds which are found in many active biological products, such as vasodilator, bronchodilator and also they have been used as anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents.[8] Numerous synthetic methods have been reported for the preparation of 1,4-dihydropyridine derivatives under classical or modified conditions.[9–15]

1,4-dihydropyridines are generally synthesized by Hantzsch reaction which involve the condensation of aldehydes, β-ketoester and ammonia or ammonium acetate. In addition various catalysts like as TMSI,[16] $Yb(OTf)_3$,[17] CAN,[18] silica gel/$NaHSO_4$[19] and Sc(OTf)[11] have been utilized for the preparation of 1,4-dihydropyridines. On the other hand, different reagents and conditions have been employed for the oxidation of 1,4-DHPs.[20–23] In spite of po-



Scheme 1. One-pot synthesis of 1,4-DHPs catalyzed by Fe_3O_4@SiO_2-OSO_3H nanocomposite

tential utility of these reagents, most of the existing methods for the synthesis of 1,4-DHPs suffer from drawbacks such as low yields, long reaction times, occurrence of several side products, use of stoichimetric amount of reagents and strong oxidants, use of expensive and toxic transition metallic reagents. Therefore, exploring new catalytic system preferably in an environmentally benign method to overcome such drawbacks is a challenging task to the organic chemists.

In recent years, the magnetically sulfonic acids were applied as an effective nanocatalyst in many organic reactions such as: preparation of 3,6-di(pyridin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles,[24] pyrano coumarins,[25] amides,[26] quinazoline derivatives,[27] and formylation of alcohols and amines.[28]

In continue of our attempts towards the improvement of the synthetic methods using heterogeneous catalysts,[29–33]Here we report a new and efficient pathway for the preparation of 1,4-DHPs via multi-component synthesis of arylamine, dimethyl acetylenedicarboxylate, aromatic aldehyde and ethyl acetoacetate by using Fe_3O_4@silica sulfuric acid core–shell nanocomposite (Scheme 1).

2. Experimental

2. 1. Chemicals and Apparatus

Chemicals were purchased from the Sigma-Aldrich and Merck in high purity. All of the materials were of commercial reagent grade and were used without further purification. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope.NMR spectra were obtained on a Bruker DRX-400 MHz spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) with $CDCl_3$ assolvent using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. FT-IR spectrum was recorded on Magna-IR, spectrometer 550. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized Cu Kα radiation (λ = 1.5406 Å). Microscopic morphology of products was visualized by SEM (LEO 1455VP). The mass spectra were recorded on a Joel D-30 instrument at an ionization potential of 70 eV. The compositional analysis was done by energy dispersive analysis of X-ray (EDX, Kevex, Delta Class I).

2. 2. Antimicrobial Activity Determination

2. 2. 1. Well Diffusion

Determining the inhibition zone of diffusion was performed by Well Agar Diffusion according to Douglas &Barki method.[34] On MRS broth, half McFarland bacterial suspension was cultured using plate spread method and after 5–10 minutes, wells were prepared (6mm) so that wells distance from plate edge was 1.5 cm and from each other was 2–2.5 cm.

Then a different concentration of oil (6 concentrations) was poured in the well (50 µl). Plates were placed in the refrigerator for 1–2 hours to let antimicrobial agents to distribute in the environment. Then plates were incubated for 24 hours at 37 °C. Then inhibition zone was measured using a caliper.

2. 2. 2. Determination of Antibiotic Susceptibility

In antimicrobial susceptibility test, Bauer-Kirby disk diffusion method was used on Muller-Hinton Agar and inhibition zone was studied on the basis of recommendations of the National Committee for Clinical Laboratory Standards (NCCLS).[35] Antibiotics used in this study include Vancomycin and Oxacillin.

2. 2. 3. Disk Diffusion Method

To examine antimicrobial activity of samples disk diffusion method was used in Mueller-Hinton agar. In this way, after the preparation of heterocyclic compounds in question, and examining their features, sterile paper discs with a diameter of 6 mm were prepared and stained with 20 ml of heterocyclic compounds then they were incubated for 24 hours at 37 °C. The bacteria were cultured on Mueller Hinton agar and were placed at appropriate intervals and a disk impregnated with solvent used as was witness. After 24 h of incubation the inhibition zone diameter was measured and evaluated.

2. 3. Preparation of Fe_3O_4 Nanoparticles

Fe_3O_4 MNPs were prepared according to a previously reported procedure by Zhang et. al using the chemical co-precipitation method.[36] Typically, $FeCl_3 \cdot 6H_2O$ (2.7 g) and $FeCl_2 \cdot 4H_2O$ (1 g) were dissolved in100 ml of 1.2 mmol l-1 aqueous HCl followed by ultrasonic bath for 30 min. Then, 1.25 mol l-1 aqueous NaOH (150 ml) was added un-

der vigorous stirring and a black precipitate was immediately formed. The resulting transparent solution was heated at 80 °C with rapid mechanical stirring under N_2 atmosphere. After vigorous stirring for 2 h, The black products were centrifuged, filtered out and washed with deionized water and alcohol for several times, and finally dried at 60 °C for12 h.

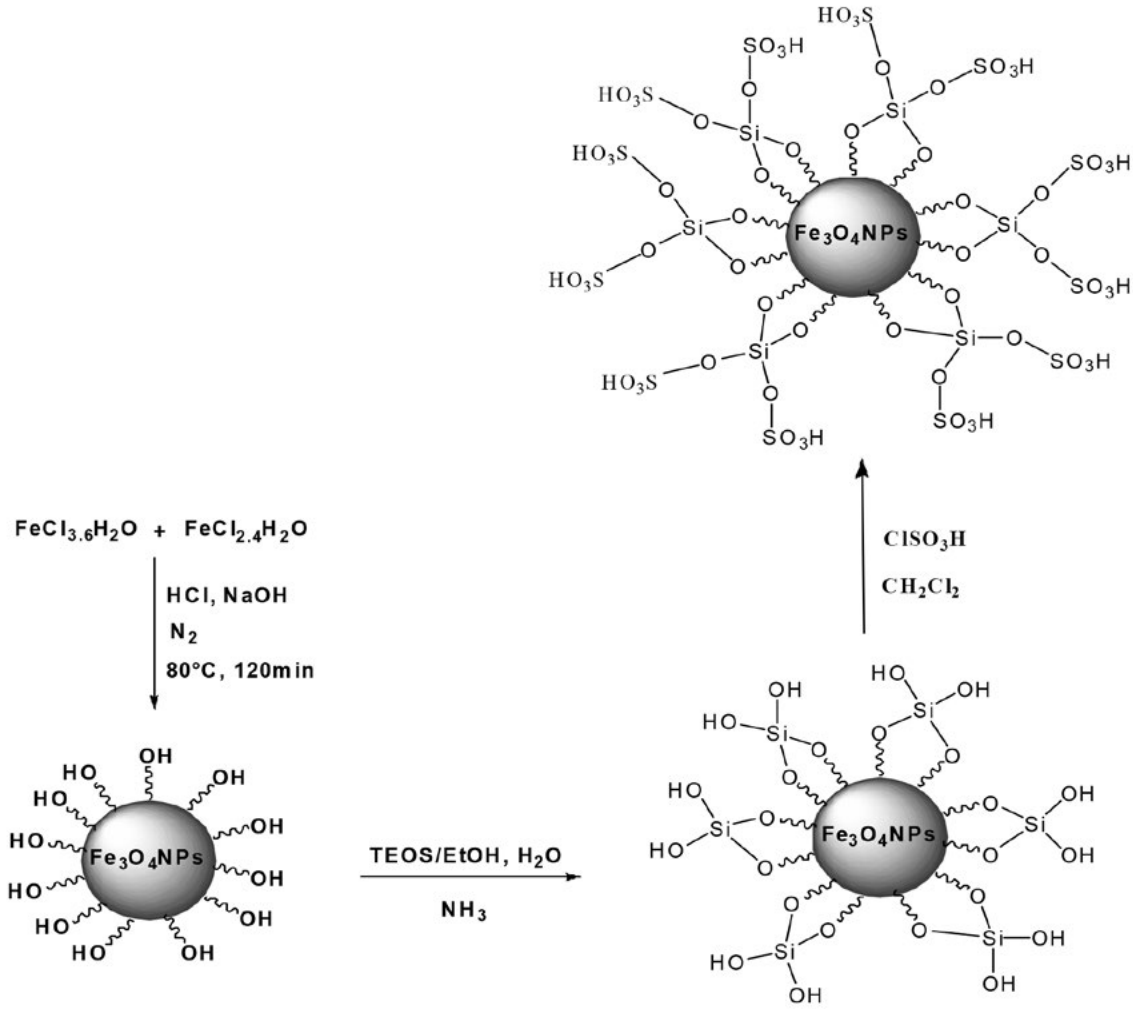
2. 4. Preparation of Fe_3O_4@SiO_2 Nanoparticles

Fe_3O_4@SiO_2 core-shell particles were prepared via modified Stöber sol-gel process.[37] 30 mg as-prepared Fe_3O_4submicrospheres were ultrasonically dispersed in a solution containing 160 mL ethanol, 40 mL water and 10 mL concentrated ammonia (28 wt%). Then, 0.4 mL TEOS was added dropwise to the solution under sonication, followed mechanically stirring for 3 h at room temperature. Subsequently, the resulting particles were separated using a magnet and washed with deionized water and ethanol. The step was repeated several times before drying at 60 °C for 12 h.

2. 5. Preparation of Fe_3O_4@SiO_2-SO_3H Nanocomposite

Fe_3O_4@SiO_2-SO_3H nanocompositewere prepared according to a previously reported procedure.[38]A 500-mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. Fe_3O_4@Silica (2.5 g) was added to the flask and dispersed by ultrasonics for 10 min in CH_2Cl_2 (75 mL). Chlorosulfonic acid (1.75 g, 1 mL, 15 mmol) in CH_2Cl_2 (20 mL) was added dropwise over a period of 30 min at room temperature. After completion of the addition, the mixture was shaken for 90 min, while the residual HCl was eliminated by suction. Then, the Fe_3O_4@Silica sulfonic acid was separated from the reaction mixture by a magnetic field and washed several times with dried CH_2Cl_2. Finally, Fe_3O_4@Silica sulfonic acid was dried under vacuum at 60 °C (Scheme 2).

The content of sulfonic acid was determined using back titration method. Firstly, the Fe_3O_4@SiO_2-OSO_3H nanocomposite (0.01 g) was added to aqueous solution of



Scheme 2. The reaction pathway for the preparation of Fe_3O_4@SiO_2-OSO_3H nanocomposite

KOH (2 mL, 0.1 mol/L) and the reaction mixture was stirred for 30 min. Then, the nanocatalyst was filtered and the clear solution was kept for further analysis. To obtain the amount of sulfonic acid loading on the Fe_3O_4@SiO_2-OSO_3H, the solution was titrated with HCl (0.1 mol/L) until neutralization. The H+ contain of the magnetic nanocatalyst was 0.28 mmol/g.

2. 6. General Procedure for the Preparation of 1,4-dihydropyridines

A mixture of arylamine (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) were stirred at room temperature for 10 min. Then aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol) and Fe_3O_4@SiO_2-SO_3H nanocomposite (0.2 g) were added to it. The mixture was heated to 80 °C under solvent-free condition for an appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was allowed to cool to room temperature and solid obtained was dissolved in dichloromethane, the catalyst was insoluble in CH_2Cl_2 and separated by using an external magnet. The solvent was evaporated and the residue was recrystallized from ethanol to afford the pure product.

All of the products were characterized and identified with ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopy techniques. Spectral data of the new products are given below.

5-ethyl-2,3-dimethyl-1-(4-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (5c):

Yellow solid; m.p. = 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (t, 3H, *J*=6.8 Hz, CH_3), 1.42 (s, 3H, CH_3), 3.35 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.15 (q, 2H, *J*=6.8 Hz, CH_2), 5.11 (s, 1H, CH), 6.85–7.40 (m, 8H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 17.3, 37.2, 52.0, 52.4, 54.1, 60.6, 106.4, 121.4, 128.1, 128.8, 130.1, 130.4, 132.1, 133.0, 142.4, 148.3, 149.3, 151.6, 163.5, 165.3, 168.1. FT-IR (KBr) *v*: 2989, 2841, 1750, 1697, 1640, 1584, 1530, 1509, 1435, 1355, 1311, 1290, 1251, 1232, 1207, 1135, 1111, 1081, 1033, 967, 934, 895, 856, 827, 802, 764cm^{-1}; MS (EI) (m/z): 510.16 (M^+); Anal. Calcd. For $C_{26}H_{26}N_2O_9$: C 61.17, H 5.13, N 5.49. Found C 61.01, H 5.18. N 5.53.

5-ethyl-2,3-dimethyl-4-(4-bromophenyl)-1-(4-methoxyphenyl)-6-methyl-1,4 dihydropyridine-2,3,5-tricarboxylate (5e):

Yellow solid; m.p. = 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (t, 3H, *J*=6.5 Hz, CH_3), 1.42 (s, 3H, CH_3), 4.14 (s, 3H, OCH_3), 4.20 (s, 3H, OCH_3), 4.25 (s, 3H, OCH_3), 4.50 (q, 2H, *J*=6.5 Hz, CH_2), 5.45 (s, 1H, CH), 6.83–6.87 (d, 2H, *J*=7.8 Hz, ArH), 7.23–7.31 (m, 4H, ArH), 7.48–7.51 (d, 2H, *J*=7.8 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 17.8, 37.7, 51.5, 52.4, 55.1, 60.9, 106.4, 121.4, 128.1, 128.8, 130.1, 130.4, 132.1, 132.9, 142.4, 148.0, 148.3, 150.6, 158.2, 164.9, 167.3. FT-IR (KBr) *v*: 2954, 2840, 1745, 1704, 1641, 1586, 1511, 1437, 1367, 1326, 1283, 1250, 1205, 1085, 1032, 966, 924, 855, 826, 792, 761cm^{-1}; MS (EI) (m/z): 543.09 (M^+); Anal. Calcd. For $C_{26}H_{26}BrNO_7$: C 57.36, H 4.81, N 2.57. Found C 57.25, H 4.89. N 2.61.

5-ethyl-2,3-dimethyl-4-(4-bromophenyl)-1-(4-chlorophenyl)-6-methyl-1,4-dihydropyridine-2,3,5-tricarboxylate (5f):

Yellow solid; m.p. = 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, 3H, *J*=7.1 Hz, CH_3), 1.45 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 4.24 (q, 2H, *J*=7.1 Hz, CH_2), 5.16 (s, 1H, CH), 6.83–7.41 (m, 8H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 17.9, 37.5, 51.59, 52.4, 60.8, 105.1, 106.3, 129.1, 130.0, 130.3, 130.9, 131.5, 133.0, 136.6, 142.8, 144.3, 145.9, 158.2, 164.9, 167.0. FT-IR (KBr) *v*: 2983, 2948, 1744, 1703, 1640, 1588, 1488, 1432, 1366, 1326, 1279, 1247, 1210, 1122, 1084, 1035, 1007, 965, 923, 826cm^{-1}; MS (EI) (m/z): 547.04 (M^+); Anal. Calcd. For $C_{25}H_{23}BrClNO_6$: C 54.71, H 4.22, N 2.55. Found C 54.62, H 4.28. N 2.70.

5-ethyl-2,3-dimethyl-6-methyl-4-(thiophen-2-yl)-1-(*p*-tolyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (5m):

Yellow solid; m.p. = 112–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, 3H, *J*=7.5 Hz, CH_3), 1.56 (s, 3H, CH_3), 2.11(s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.10 (q, 2H, *J*=7.5 Hz, CH_2), 5.21 (s, 1H, CH), 6.93–7.54 (m, 7H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 17.1, 21.2, 35.6, 51.8, 52.4, 61.5, 111.3, 122.1, 129.8, 131.3, 132.1, 133.7, 134.5, 138.0, 147.1, 148.9, 150.3, 152.8, 164.1, 167.1, 168.6. FT-IR (KBr) *v*: 2971, 2854, 1743, 1691, 1655, 1573, 1522, 1509, 1421, 1311, 1293, 1255, 1144, 1112, 1021, 998, 926, 833, 812, 764 cm^{-1}; MS (EI) (m/z): 455.53 (M^+); Anal. Calcd. For $C_{24}H_{25}NO_6S$: C 63.28, H 5.53, N 3.07. Found C 63.12, H 5.62. N 2.12.

5-ethyl-2,3-dimethyl-4-(furan-2-yl)-6-methyl-1-(p-tolyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (5n):

Yellow solid; m.p. = 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, 3H, *J*=7.3 Hz, CH_3), 1.52 (s, 3H, CH_3), 2.15(s, 3H, CH_3), 3.81(s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.06 (q, 2H, *J*=7.3 Hz, CH_2), 5.17 (s, 1H, CH), 6.97–7.68 (m, 7H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 16.9, 22.3, 35.3, 50.9, 52.1, 61.5, 111.1, 121.8, 130.6, 132.7, 134.31, 135.1, 135.9, 140.4, 145.3, 149.7, 151.6, 155.84, 163.2, 166.9, 167.4. FT-IR (KBr) *v*: 2953, 2871, 1747, 1688, 1643, 1592, 1526, 1522, 1423, 1308, 1273, 1253, 1226, 1118, 1026, 998, 923, 841, 771 cm^{-1}; MS (EI) (m/z): 439.46 (M^+); Anal. Calcd. For $C_{24}H_{25}NO_7$: C 65.59, H 5.73, N 3.19. Found C 65.68, H 5.77. N 3.11.

3. Results and Discussion

In the preliminary experiments Fe_3O_4@SiO_2-OSO_3H nanocomposite was prepared and characterized by EDX, FE-SEM and FT-IR analysis.

The morphology and structure of the prepared sample was characterized by scanning electron microscopy (FE-SEM). As shown in Figure 1 the average particle size of the prepared Fe_3O_4@SiO_2-OSO_3H nanocomposite has been found to be 8–10 nm.

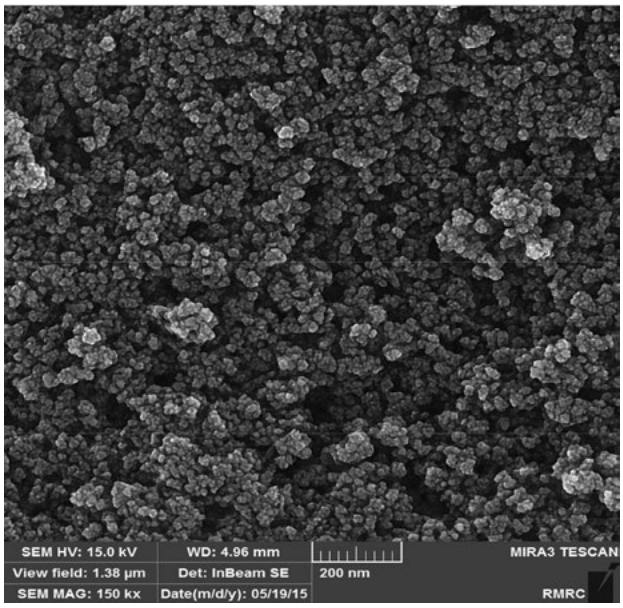


Figure 1. FE-SEM image of Fe_3O_4@SiO_2-OSO_3H nanocomposite

Further information about the chemical structure of Fe_3O_4@SiO_2-OSO_3Hnanocomposite was obtained from FT-IR spectroscopy (Figure 2). The analysis indicated three strong absorption bond at 586 cm^{-1} corresponding to the vibration of Fe-O in Fe_3O_4. The next strong peak at 1080 cm^{-1} is attributed to the Si–O–Si bond stretching of Fe_3O_4@SiO_2-SO_3H. The weak intensity band at 968 cm^{-1} can be ascribed to the stretching of non-bridging oxygen atoms in Si–OH bond. Therefore, silica coating on the surface of Fe_3O_4 was confirmed by these absorption bonds. The presence of sulfonyl groups is proved by 1217$cm^{-1}$and 1128cm^{-1} bonds that were covered by a stronger absorption of Si-O bond at 1080 cm^{-1}. The last strong peak appeared at about 2600–3700 cm^{-1} due to the stretching of OH groups in the SO_3H.

The chemical purity of the samples as well as their stoichiometry was tested by EDX study. The EDX spec-

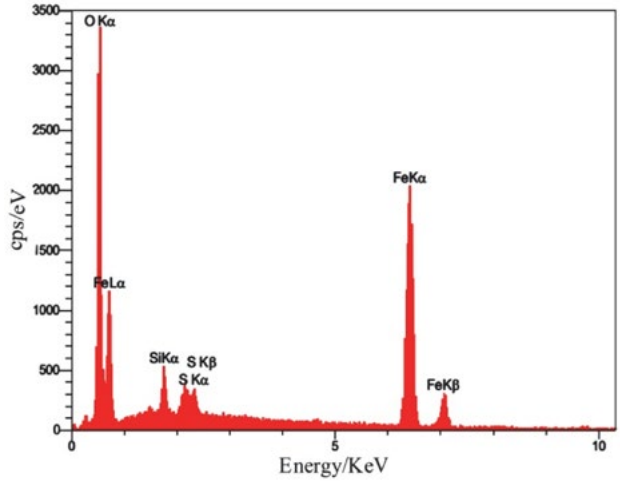


Figure 3. The EDX spectrum of Fe_3O_4@SiO_2-OSO_3H nanocomposite

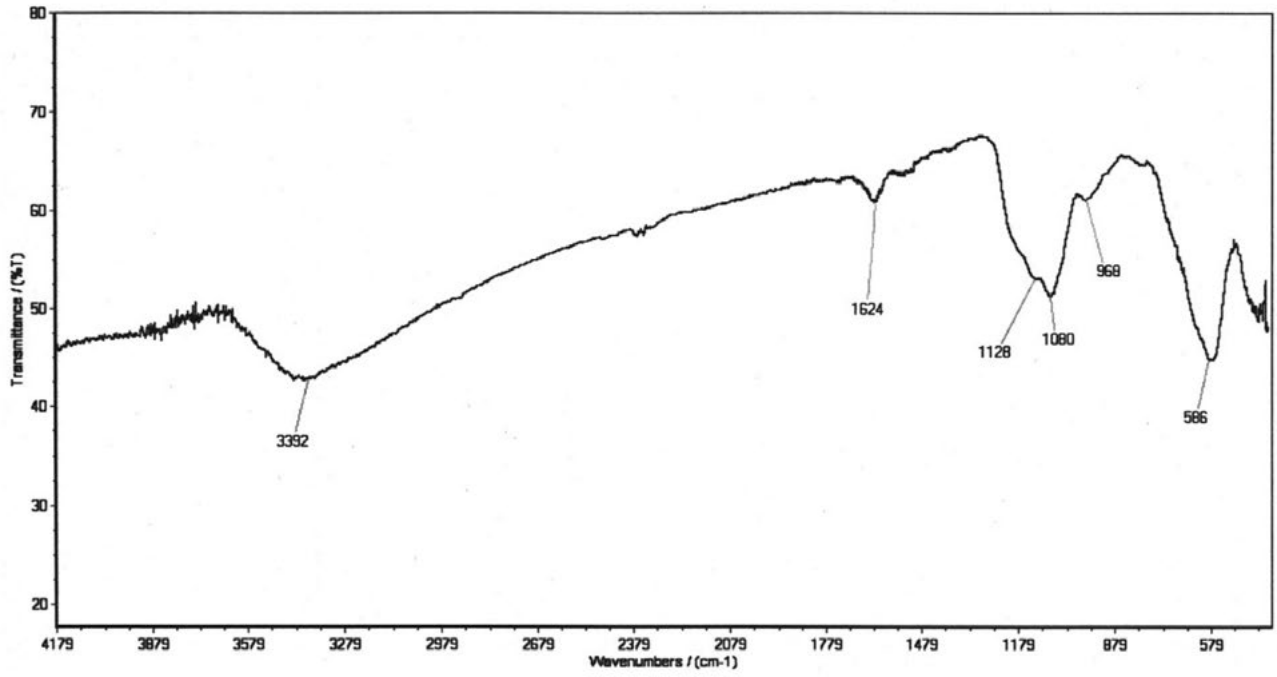


Figure 2. FT-IR spectrum of Fe_3O_4@SiO_2-OSO_3H nanocomposite

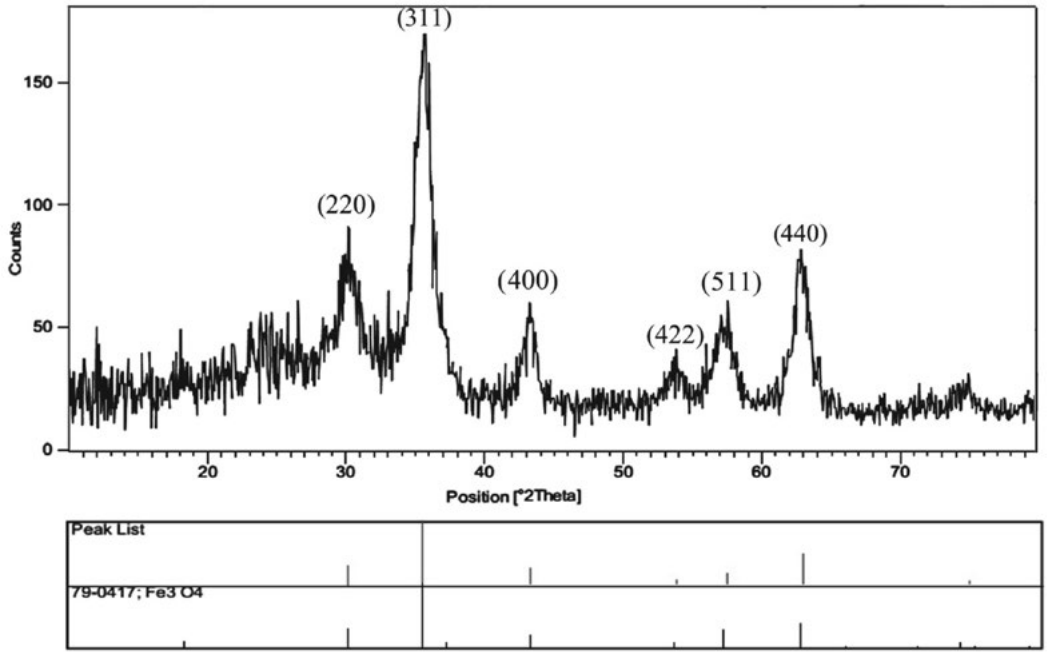


Figure 4. The XRD pattern of Fe_3O_4@SiO_2-OSO_3H nanocomposite

trum of Fe_3O_4@SiO_2-OSO_3Hnanocomposite shows that the elemental compositions are (Fe, O, S and Si) which have posse's nanostructure (Figure 3).

Figure 4 shows the XRD pattern of the prepared Fe_3O_4@SiO_2-OSO_3H. All the XRD patterns show raising background which is attributed to X-ray fluorescence since Cu-Kα has been used as the X-ray source during the measurements.

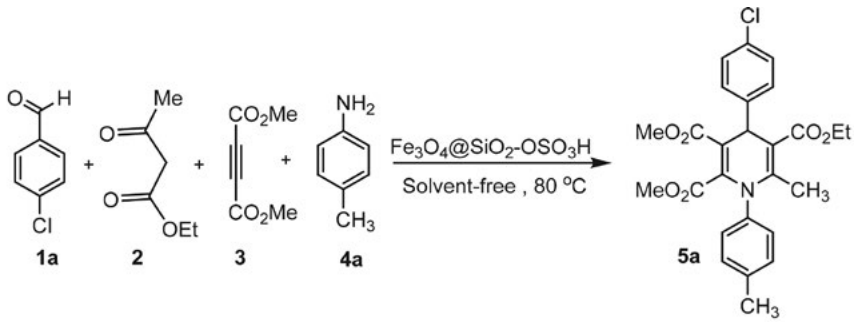
The reflections of XRD pattern of Fe_3O_4@Silica sulfonic acid (2θ = 30.2 °, 36.4 °, 43.7 °, 53.5 °, 56.3 °, 62.3 °, and 73.8 °) in Figure 4 confirm the synthesis of cubic normal spinel Fe_3O_4 (JCPDS file no. 79–0417).[39] These results represent the stability of the crystalline phase of Fe_3O_4 nanoparticles during silica coating and surface sulfonic acid functionalization.

To optimize the reaction conditions the condensation of *p*-toluidine (1 mmol), dimethyl acetylenedicarboxylate (1 mmol), 4-chlorobenzaldehyde (1 mmol) and ethyl acetoacetate (1 mmol), as a model reaction, were studied in the presence of different amounts of Fe_3O_4@SiO_2-OSO_3H nanocomposite under solvent-free conditions (Scheme 3). The respective results in Table 1 indicate that the best results were attained when the reaction was performed by using 0.02g of the catalyst at 80 °C. To demonstrate that heat cannot thermodynamically promote the reaction in the absence of catalyst; the model reaction was examined at 80 °C under catalyst-free conditions. In these

Table 1. The Effect of the catalyst amount and temperature on the model study

Entry	Catalyst (g)	Temp. (°C)	Time (min)	Yields(%) [a]
1	–	80	120	trace
2	0.03	80	60	91
3	**0.02**	**80**	**60**	**91**
4	0.01	80	90	82
5	0.02	50	90	71
6	0.02	100	70	91

[a] Isolated yield.



Scheme 3. The model reaction for the synthesis of 1,4-dihydropyridine 5a

conditions, desired product was obtained in trace after 120 min. This observation indicated clearly that heat cannot promote the reaction without catalyst. Thus presence of catalyst is essential for this reaction.

After optimization of the reaction conditions, the efficiency and scope of the catalyst were evaluated by the reaction of arylamines, dimethyl acetylenedicarboxylate, aryl aldehydes and ethyl acetoacetate by using 0.02 g of Fe_3O_4@SiO_2-OSO_3H nanocomposite at 80 °C. The corresponding results are summarized in Table 2. As it can be seen from Table 2, all reactions proceeded efficiently to afford the desired 1,4-dihydro-pyridines in high yields and short reaction times. Therefore, Fe_3O_4@SiO_2-OSO_3H nanocomposite was efficient to catalysis the one-pot four-component reactions.

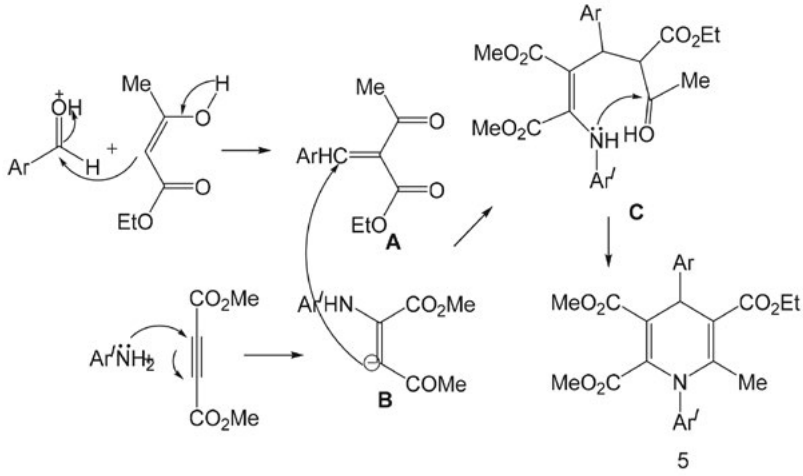
The influence of electron-withdrawing and electron-donating substituents on the aromatic ring of aldehydes upon the reaction yields and times was investigated. The results in Table 2 show that the aromatic aldehydes bearing both electron-donating and electron-withdrawing groups presented excellent yield of desired products.

A plausible mechanism for the preparation of highly functionalized dihydropyridines using Fe_3O_4@SiO_2-OSO_3H nanocomposite has on the basis of our experimental results together with some literature[40] been shown in Scheme 3. It is likely that Fe_3O_4@SiO_2-OSO_3H MNPs acts as a Bronsted acid and increases the electrophilicity of the carbonyl groups of the aldehydes and intermediates. Firstly, the Knoevenagel condensation of aromatic aldehyde with ethyl acetoacetate is suggested to give the intermediate A, Then nucleophilic attack of arlymine to dimethyl acetylenedicaroboxylate leads to formation of intermediate B. Secondly, the Michael addition of β-enamino ester intermediate (B) to arylidenecyanoacetate (A) afforded the addition of intermediate (C). At last in intermediate(C), the intramolecularnucleophilic addition of amino group to carbonyl group formed the final 1,4- dihydropyridine(Scheme 4).

Table 2. The synthesis of 1,4-dihydropyridines using Fe_3O_4@SiO_2-SO_3H under solvent-free conditions at 80 °C.

Entry	Ar	Ar/	Product	Time (min)	Yield (%)	Lit. m.p (°C)	M.p (°C)
1	4-Cl-Ph	4-CH_3-Ph	5a	60	91	132–133	(133–135)[40]
2	3-NO_2-Ph	4-CH_3-Ph	5b	60	89	137–138	(135–137)[40]
3	4-NO_2-Ph	4-OCH_3-Ph	5c	45	93	170–172	–
4	3-NO_2-Ph	4-OCH_3-Ph	5d	70	90	154–156	(155–157)[40]
5	4-Br-Ph	4-OCH_3-Ph	5e	60	92	145–147	–
6	4-Br-Ph	4-Cl-Ph	5f	70	85	127–129	–
7	4-Cl-Ph	4-Cl-Ph	5g	60	85	131–133	(132–134)[40]
8	3-NO_2-Ph	4-Cl-Ph	5h	70	88	143–145	(143–145)[40]
9	4-Cl-Ph	4-OCH_3-Ph	5i	50	87	128-130	(129–131)[40]
10	4-OCH_3-Ph	4-CH_3-Ph	5j	80	83	109–112	(110–112)[40]
11	4-F-Ph	4-CH_3-Ph	5k	60	90	105–107	(104–106)[40]
12	3-NO_2-Ph	Ph	5l	70	88	153–155	(151–153)[40]
13	Thiophen-2-yl	4-CH_3-Ph	5m	80	85	112–115	–
14	Furan-2-yl	4-CH_3-Ph	5n	75	90	105–106	–

[a]Isolated yield.



Scheme 4. Proposed reaction pathway for the synthesis of 1,4-dihydropyridines

3. 1. Results of Antimicrobial Activities:

3. 1. 2. Well Diffusion Method

Among the bacterial strains studied inhibition diameters of Staphylococcus aureus in the presence of 5-ethyl 2,3-dimethyl 1-(4-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (5c), 5-ethyl 2,3-dimethyl 4-(4-bromophenyl)-1-(4-methoxyphenyl)-6-methyl-1,4-dihydropyridine-2,3,5-tricarboxylate (5e), 5-ethyl 2,3-dimethyl 4-(4-bromophenyl)-1-(4-chlorophenyl)-6-methyl-1,4-dihydropyridine-2,3,5-tricarboxylate (5f)were 16, 15 and 17 mm respectively. But other bacterial strains showed no inhibition zone.

3. 1. 3. Determination of Antibiotic Susceptibility

The results of the antibiogram for Staphylococcus aureus strain showed that this bacterium is sensitive to Vancomycin antibiotic

3. 1. 4. Disc Diffusion Method

In this test, as well as well diffusion method inhibition diameters of Staphylococcus aureus in the presence of 5-ethyl 2,3-dimethyl 1-(4-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (5c), 5-ethyl 2,3-dimethyl 4-(4-bromophenyl)-1-(4-methoxyphenyl)-6-methyl-1,4-dihydropyridine-2,3,5-tricarboxylate (5e), 5-ethyl 2,3-dimethyl 4-(4-bromophenyl) -1-(4-chlorophenyl)-6-methyl-1,4-dihydropyridine-2, 3,5-tricarboxylate (5f) was 15, 14, 16 mm respectively.

3. 2. Recycling and the Reusability of the Catalyst

Reusability is one of the most significant properties of the prepared catalysts. Upon completion of the reaction, dichloromethane was added to the reaction mixture, the catalyst was insoluble in CH_2Cl_2 and it could therefore be recycled by a simple filtration. The nanocatalyst was then washed three to four times with methanol and dried at 80 °C for 7 h for the next runs. To investigate the reusability of the catalyst, the model study was repeated using recovered Fe_3O_4@silica sulfonic acid nanocomposite under optimized reaction conditions. The summarized results of Table 3 show that the nanocatalyst could be reused for five times with a minimal loss of its activity. In addition, sulfonic acid contain of the Fe_3O_4@SiO_2@OSO_3H was evaluated by back titrationafter five runs (0.24 mmol/g) that shows no significant loss in activity.

Table 3. Reusability of the Fe_3O_4@SiO_2-OSO_3H nanocatalyst

Number of cycle	Yield (%) [a]
1	91
2	90
3	90
4	88
5	85

[a] Yields refer to the isolated pure product

4. Conclusion

In conclusion, we have developed a simple and efficient approach for the synthesis of 1,4-dihydropyridines by one-pot four-component reaction of arylamine, dimethyl acetylenedicarboxylate, aromatic aldehyde and ethyl acetoacetate in the presence of Fe_3O_4@SiO_2-OSO_3H nanocatalyst under solvent-free conditions. The present methodology offers several advantages, such as good yields, short reaction times, ease of separation, recyclability of the magnetic nanocatalyst, simple purification and environmentally benign. These compounds showed high antibiotic properties and can be useful in other research and biomedical applications.

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Povzetek

Sinteza heterocikličnih spojin je zaradi njihove široke uporabe velikega pomena. V tej raziskavi smo s pomočjo reakcij štirih rektantov arilaminov, acetilendikarboksilatov, aromatskih aldehidov in etil acetoacetata v prisotnosti nanocompozita Fe_3O_4@SiO_2@OSO_3H razvili sintezno metodo za pripravo 1,4-dihidropiridinov. Prednosti opisane metode so: okolju prijazni reakcijski pogoji, enostaven način izvedbe, širok nabor substratov, odlični izkoristki in ponovna uporaba nanokatalizatorja. Eden od indikatorjev za merjenje protimikrobne aktivnosti je minimalna inhibitorna koncentracija (MIC), ki je bila na preiskovanih bakterijah izmerjena s premerom območja inhibicije rasti od prisotnosti sinteziranih heterocikličnih spojin z uporabo delucijske difuzije, difuzije diska in določanja občutljivosti na antibiotike. Rezultati vseh treh metod so pokazali občutljivost *Staphylococcus aureus* na sintetizirane heterociklične spojine. Iz rezultatov lahko sklepamo, da imajo te spojine dobre antibiotične lastnosti in so lahko uporabne tudi pri drugih raziskovalnih in biomedicinskih aplikacijah.