

RESEARCH PAPER

Green Synthesis of Poly(ethylene oxide)-coated Sulfonated Copper Ferrite Nanoparticles and its Highly Efficient Application in the Synthesis of Dihydropyrimidine Derivatives

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ABSTRACT

In this work, an immobilization of SO_3H groups on the surface of poly(ethylene oxide)-coated copper ferrite nanoparticles was reported. The prepared $\text{CuFe}_2\text{O}_4@ \text{PEO-SO}_3\text{H}$ is an effective, green, magnetically recoverable, bimetallic, eco-friendly, and heterogeneous solid acid catalyst. Using a green solvent in mild reaction conditions and short reaction times can provide several advantages for this work. The prepared nanocatalyst was characterized using conventional instrumental techniques such as Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM) images, energy-dispersive X-ray spectroscopy (EDX), elemental mapping, vibrating sample magnetometer (VSM) data, transmission electron microscopy (TEM), and X-ray diffraction (XRD) studies. The application of the present green nanocatalyst as a heterogeneous magnetic nanocomposite catalyst was investigated and developed for the green synthesis of chemically and biologically important dihydropyrimidines derivatives at room temperature in high-to-excellent yields via a simple and convenient method in a one-pot three component Biginelli condensation reaction. Due to the magnetic property of the catalyst, it can be easily recycled from the reaction mixture by an external magnet and reused without any considerable loss of activity.

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INTRODUCTION

Copper-iron oxide based catalysts have been widely used due to their biocompatibility, insensitivity to air and humidity, and easy removal from the reaction mixture with an external magnetic field [1-7]. In addition, they are a new type of functionalized products which can be largely used in biotechnology and nanotechnology [8,9]. Poly(ethylene oxide) (PEO) is a significant biocompatible polymeric material widely used for multipurpose applications and coating agents. Due

to their excellent properties such as hydrophilicity nontoxicity, nonimmunogenicity, flexibility, introducing many new protocols is of prime importance for preparing PEO-coated MNPs [10,11].

Dihydropyrimidines are important bioactive heterocyclic compounds which have analgesic, antiviral, antimicrobial, and anti-inflammatory effects, which are produced by condensing urea, thiourea, β -ketoesters or aryl aldehydes [12-15]. In recent years, design and synthesis of economical, universal, and recyclable catalysts for preparing

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DHPMs has been of central importance. In this regard, a variety of different catalysts and reaction modifications have been successfully employed to develop the existing array of DHPMs [16-18].

However, most of these reported procedures, unavoidably suffer from some characteristics such as strong acidic conditions, long and expensive procedures in tedious work-up, needing excessive amounts of hazardous chemical reagents, toxic solvents, complex handling, poor yields of the products, and failures in the synthetic method. In continuation of our efforts in the progress and optimization of green synthetic procedures [5-9,19], this research reports a novel strategy for the synthesis of magnetic poly(ethylene oxide)-coated copper ferrite nanoparticles-supported sulfonic acid ($\text{CuFe}_2\text{O}_4@\text{PEO-SO}_3\text{H}$) which is used as a catalyst for the synthesis of dihydropyrimidines (**4a-l**) (Scheme 1). This study offers a green protocol due to the use of a recyclable nanocatalyst and ethanol as a solvent at room temperature under mild and safe conditions.

As far as we know, it is the first time for the synthesis, characterization, and application of $\text{CuFe}_2\text{O}_4@\text{PEO-SO}_3\text{H}$ nanocomposite as an effective, green and eco-friendly nanocatalyst in the synthesis of dihydropyrimidine derivatives.

EXPERIMENTAL

General

All chemicals and solvents were obtained from Merck, and used directly without any further purification. Melting points (mp) were determined on an Electrothermal 9100 apparatus. FT-IR spectra were recorded using Shimadzu IR-470 spectrometer (KBr pellets). ^1H and ^{13}C NMR spectra were obtained at 250 and 62.5 MHz, respectively, on a Bruker DRX-250. The morphology and structure of the nanocatalyst were examined by field emission scanning electron microscope (FE-SEM, Hitachi S-4800). The energy-dispersive X-ray (EDX)

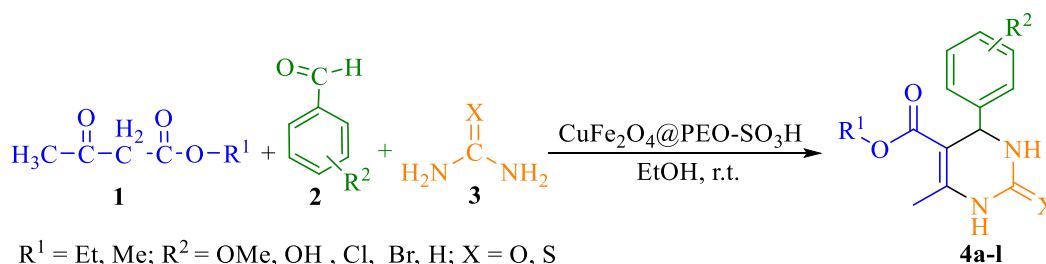
spectroscopy was applied to show the elemental composition of the nanocatalyst. The magnetic properties of the samples were investigated by a vibrating sample magnetometer (Meghnatis Kavir Kashan Co., Iran). X-ray diffraction patterns were performed by X' Pert Pro X-ray diffractometer (40 mA, 40 kV).

Preparation of CuFe_2O_4

Copper ferrite nanoparticles were prepared using the conventional co-precipitation technique by $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ under argon atmosphere. Using a typical procedure, 1.5 g (6.15 mmol) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ and 5.01 g (12.3 mmol) $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ were dissolved in 100 mL deionized water and stirred under argon atmosphere at room temperature. Then an alkaline solution contains 4.0 g NaOH in 20 mL deionized water was added dropwise during 10 minutes via syringe pump to the above solution under magnetic stirring. Upon the addition of alkaline solution, copper ferrite nanoparticles were formed as a black precipitate. The reaction mixture was heated to 90 °C under stirring for additional 5 h. Having magnetic properties, CuFe_2O_4 nanoparticles were separated using an external magnetic field and washed by 15 mL deionized water and then 15 mL EtOH, four times by each of these solvents. Then, the residue was dried for 24 h at 80 °C in air oven. Finally, the dried nanoparticles were calcinated for 5 h at 700 °C.

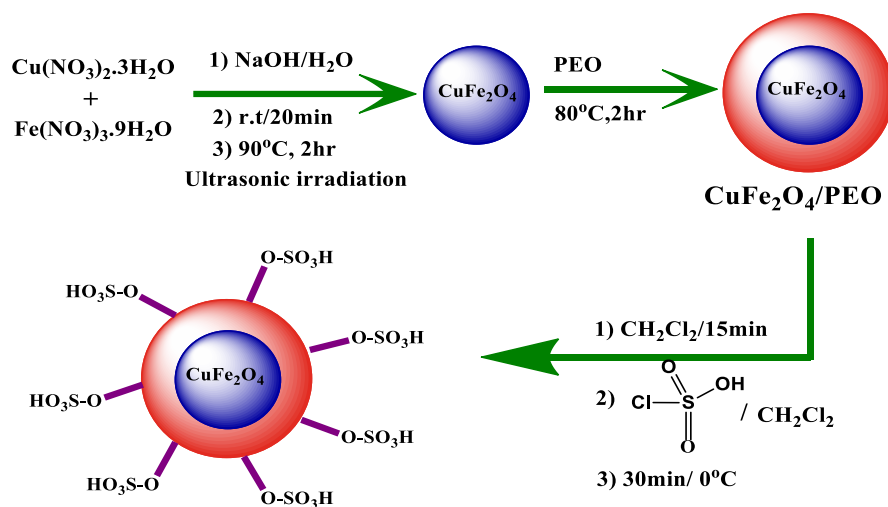
Preparation of $\text{CuFe}_2\text{O}_4@\text{PEO}$ nanocomposite

The CuFe_2O_4 nanoparticles (3 g) were added to the 250-mL flask and dispersed in 30 mL of water for 10 minutes. Then, 1.5 g of dissolved PEO in 60 mL water was gradually added and again stirred under ultrasonic bath for 2 h. After the addition of PEO over a period of 2 h, the mixture was magnetically stirred for 2 h at 80 °C. After the evaporation of water and the formation of brown



Scheme 1





gel, $\text{CuFe}_2\text{O}_4\text{@PEO}$ was separated by a magnetic bar and dried in a vacuum oven at 60°C .

Preparation of $\text{CuFe}_2\text{O}_4\text{@PEO-SO}_3\text{H}$ nanocatalyst

A suction flask (500 mL filter flask), equipped with a constant pressure dropping-funnel and gas outlet tube connected to a vacuum system, contained an adsorbing alkaline solution. $\text{CuFe}_2\text{O}_4\text{@PEO}$ (3 g) in CH_2Cl_2 (60 mL) was added into the flask and then was sonicated for 15 minutes until all the mixture was dispersed. Then, a solution of chlorosulfonic acid (HSO_3Cl) (1.5 mL) in 30 mL 1,2-dichloroethane was added dropwise for 30 minutes at 0°C under stirring. After the addition of HSO_3Cl solution, the mixture was stirred for additional 90 minutes for removing any residual of HCl. By using an external magnet, $\text{CuFe}_2\text{O}_4\text{@PEO-SO}_3\text{H}$ was easily separated from the reaction medium and washed several times with CH_2Cl_2 . Finally, $\text{CuFe}_2\text{O}_4\text{@PEO-SO}_3\text{H}$ was dried in a vacuum at 60°C (Scheme 2).

General procedure for the synthesis of DHPM derivatives (4a-l)

In general, a mixture of an aryl aldehyde (3 mmol), a β -ketoester (3 mmol), urea or thiourea (3.15 mmol) and $\text{CuFe}_2\text{O}_4\text{@PEO-SO}_3\text{H}$ (0.012 g) were added to 6 mL absolute ethanol and stirred at 25°C . At the end of the reaction, which was monitored by thin-layer chromatography, the used catalyst was separated using an external magnetic field. Then, the purification of the crude product was carried out by recrystallization from hot ethanol, without any more purification.

RESULTS AND DISCUSSION

After the preparation of the nanocomposite catalyst, it was characterized by conventional analyses. Initially, FT-IR spectroscopy confirmed its preparation. Fig. 1 presents the FT-IR spectrum of the $\text{CuFe}_2\text{O}_4\text{@PEO-SO}_3\text{H}$ magnetic catalyst which confirms the preparation of the expected product. In Fig. 1a, the peak about 2852 and 2923 cm^{-1} is attributable to C-H in PEO. In Fig. 1b, the peak at 584 cm^{-1} is assignable to the Fe-O-Fe vibration of magnetite phase which can be obviously seen. In Fig. 1c, the wide and strong peak at near 3440 cm^{-1} can be attributed to O-H in PEO. In Fig. 1d, the stretching vibrations of C-H observed at 2852 and 2923 cm^{-1} confirm the successful composition of the PEO onto the surfaces of CuFe_2O_4 nanoparticles.

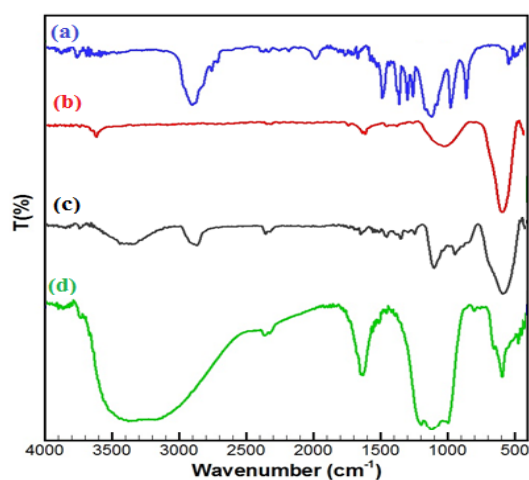


Fig. 1. The FT-IR spectra of (a) PEO, (b) CuFe_2O_4 , (c) $\text{CuFe}_2\text{O}_4/\text{PEO}$ and (d) $\text{CuFe}_2\text{O}_4/\text{PEO/SO}_3\text{H}$.

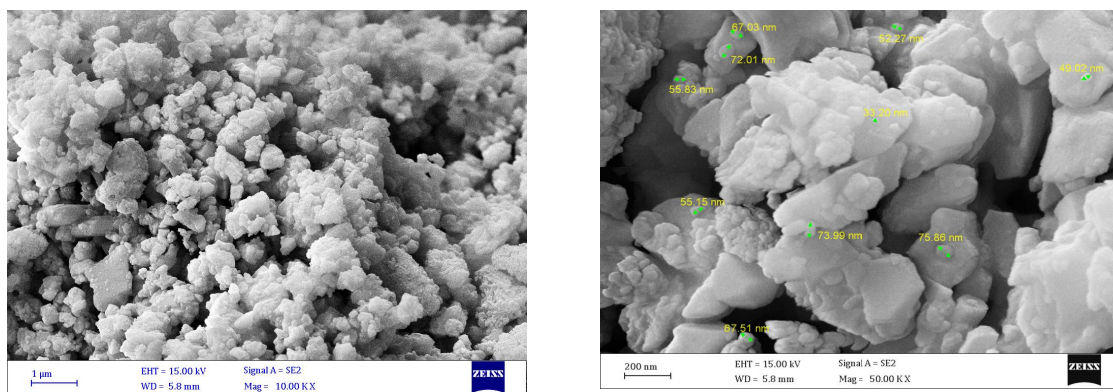


Fig. 2. FE-SEM images of $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ nanocatalyst at various magnifications.

The S=O absorption band at 1124 cm^{-1} proves the functionalization of SO_3H groups on the $\text{CuFe}_2\text{O}_4@PEO$ surface.

As shown in Fig. 2, the FE-SEM images of synthesized $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ confirm that the average size of $\text{CuFe}_2\text{O}_4@PEO\text{-OSO}_3\text{H}$ nanoparticles is about 35 nm.

Energy dispersive X-ray analysis (EDX) of the sample was conducted for the determination and characterization of the elements constituting the catalyst. As shown in the Fig. 3, there are mainly Fe, Cu, S and O atoms in the nanocomposite. Therefore, EDX analysis data indicated the presence of PEO and SO_3H in the prepared sample.

The EDX analysis for the $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ nanoparticles was shown in Fig. 4. In addition to the conventional SEM images, EDX mapping presented a significant picture of the distribution of the elements on the surface. This set of maps clearly illustrates the presence of all elements in the selected area of the nanostructure texture, e.g. iron,

copper, sulfur, and carbon.

In TEM image shown in Fig. 5, each CuFe_2O_4 core was made from small primary nanocrystals with a diameter of about 10 nm surrounded by $PEO\text{-SO}_3\text{H}$ shells with a thickness of nearly 20 nm. The prepared nanocatalyst shows a semispherical morphology and agglomerated structure.

The magnetization curve for the magnetic nanoparticles was recorded with vibrating sample magnetometer (VSM) at room temperature. It is remarkable to know that the magnetic nanoparticles (MNPs) have sufficient magnetic properties to be used in various applications. The results of magnetization measurements of nanoparticles was described in Fig. 6. Furthermore, the magnetic properties of CuFe_2O_4 MNPs were studied at 298 K using a vibrating sample magnetometer (VSM) that the magnetic hysteresis S-shape loops appeared and the saturation magnetization (M_s) was 20 emu/g. The saturation magnetization gradually reduced due to the covering of magnetite core

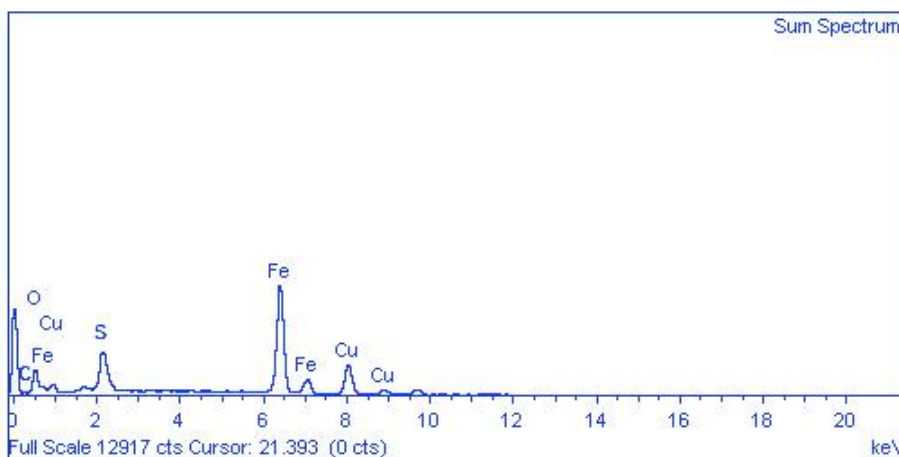


Fig. 3. EDX analysis of $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ nanocatalyst.

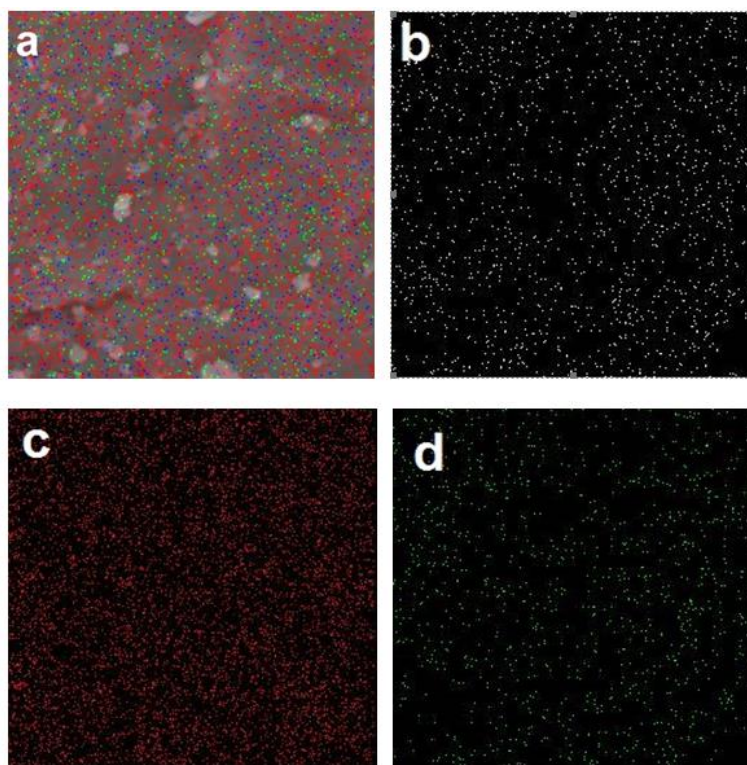


Fig. 4. EDX elemental mappings of selected area of: a) Fe, b) C, c) Cu and d) S.

with nonmagnetic PEO layers and the surface functionalized with sulfonic acid groups.

Fig. 7 shows the XRD measurements performed with PEO coated CuFe_2O_4 for identifying the crystal phases present in the samples. The XRD pattern of the $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H indicates all the major peaks corresponding to CuFe_2O_4 . The diffraction angles (2θ) of 31.21, 36.07, 44.15, 54.39 and 63.85 can be assigned to 2 2 0, 3 1 1, 0 0 4, 2 2 4, 3 3 3, and 4 4 0 planes, respectively, which are in accordance with the CuFe_2O_4 reference pattern (JCPDS# 77-0010) [20]. Moreover, XRD patterns

of $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H showed a peak around $2\theta = 25$ which is related to PEO- SO_3H polymer (The symbol *) confirming the formation of PEO- SO_3H on the surface of CuFe_2O_4 .

To study the catalytic ability of $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H , a pilot reaction was performed via the reaction of 3 mmol of β -diketone, 3 mmol of aromatic aldehyde, and 3.15 mmol of urea or thiourea. First, the effect of different amounts of the catalyst on the reaction yield was determined. As the results show in Table 1, the synthesis of **4a** in 98% yield was completed after 20 minutes at

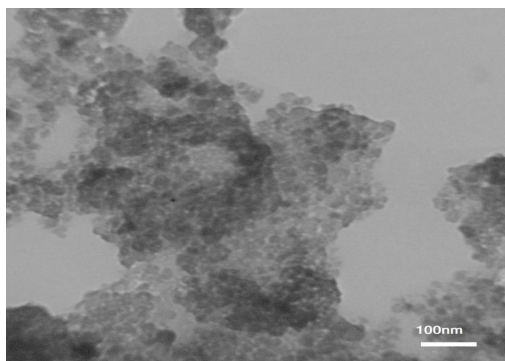


Fig. 5. The TEM image of $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H nanocatalyst with scale of 100 nm.

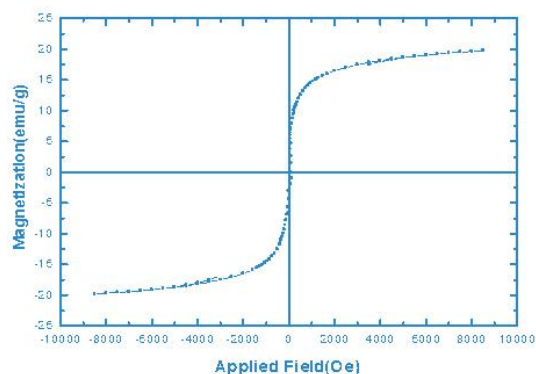
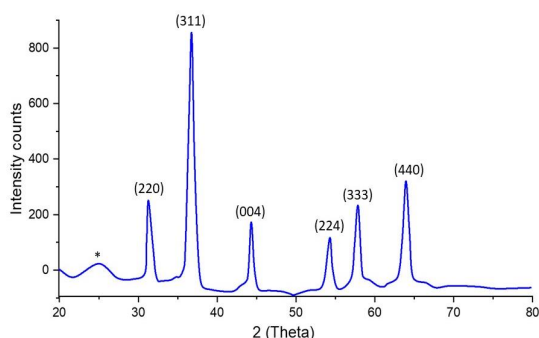


Fig. 6. VSM magnetization curves of $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H .



Fig. 7. XRD patterns of $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$.

room temperature in 4 mL of ethanol using 0.012 g of the $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ as the catalyst. In order to prove the capability of ethanol, a number of solvents with various polarity values including MeOH, H_2O , MeCN, and DMF were investigated by the model reaction in the presence of $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$. The results revealed that EtOH is the best solvent for this work in the presence of 0.012 g of the $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ catalyst at room

temperature.

The generality of the $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ nanocatalyst for the synthesis of DHPMs was evaluated by synthesizing several products under optimized conditions. A ratio of 2:2:2.1 mmol of an aromatic aldehyde, β -ketoester, urea or thiourea and 0.015 g of nanocatalyst in EtOH (6 mL) as a choice green solvent were stirred at room temperature and resulted in high yields of products. As shown in Table (2), the results of this study demonstrate that electron-rich and electron-deficient aldehydes operated successfully and underwent the Biginelli condensation reaction. Substituents with electron-withdrawing groups generated the products with larger amounts and fast reaction time than electron-donating groups. For example, 4-chlorobenzaldehyde gave a higher yield compared to 4-methoxybenzaldehyde. Additionally, the para-substituted group had less steric hindrance than ortho- or meta-position (Table 2, entries 1, 6, 7, 9 and 11).

As presented in Table 3, various types of

Table 1. Optimizing of the reaction conditions.

Entry	Catalyst (g)	Solvent	Temperature	Time (min)	Yield ^a (%)
1	-	EtOH	reflux	120	25
2	0.005	EtOH	r.t.	60	75
3	0.007	EtOH	r.t.	60	88
4	0.008	EtOH	r.t.	20	98
5	0.009	EtOH	r.t.	20	98
6	0.008	EtOH	r.t.	30	98
7	0.008	H_2O	r.t.	100	50
8	0.008	EtOH/ H_2O	r.t.	100	75
9	0.008	MeOH	r.t.	100	80
10	0.008	MeCN	r.t.	100	65
11	0.008	DMF	r.t.	100	65
12	0.008	-	r.t.	100	45
13	0.015	-	r.t.	100	55
14	0.02	-	80 °C	100	70

^a Isolated yields



Table 2. Synthesis of DHPMs (4a-l) by using CuFe₂O₄@PEO-SO₃H nanocatalyst.

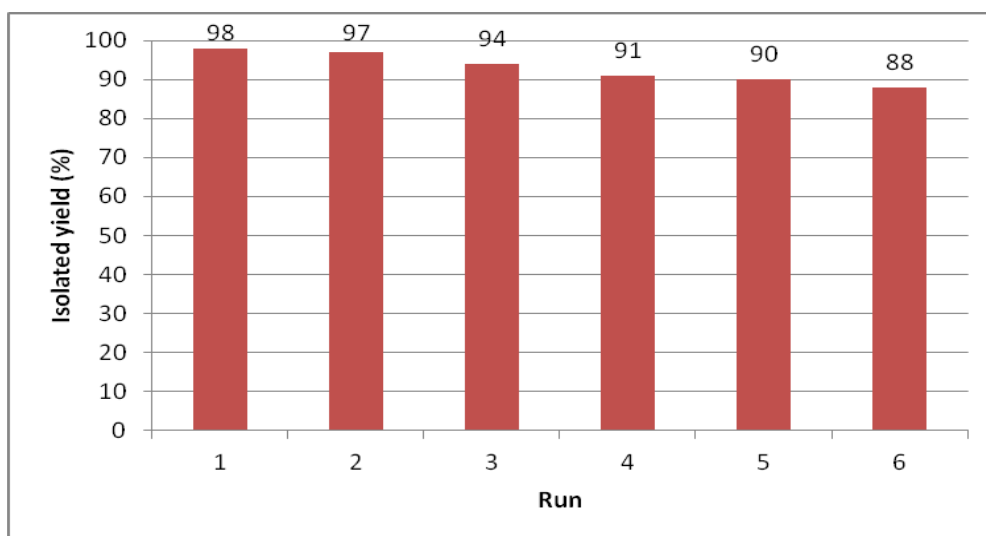
Entry	R ¹	R ²	X	Product	Time (min)	Yield ^a (%)	Mp (°C)	
							Found	Reported
1	Et	4-Cl	O	4a	20	98	211-213	212-214 [21]
2	Me	4-OMe	S	4b	55	91	154-156	153-155 [22]
3	Me	3-OH	O	4c	40	92	219-220	220-222 [23]
4	Me	4-OMe	O	4d	50	91	195-196	194-195 [24]
5	Et	3-OH	O	4e	45	93	219-220	221-222 [25]
6	Et	4-Br	O	4f	30	96	214.5	213-214 [26]
7	Et	4-Cl	S	4g	25	96	181.5	179-180 [27]
8	Et	H	O	4h	35	95	201-203	201-203 [28]
9	Me	4-Cl	S	4i	25	96	242-244	241-243 [29]
10	Et	3-OH	S	4j	45	90	182-184	181-185 [30]
11	Et	4-Br	S	4k	30	95	179.5	178-180 [31]
12	Et	H	O	4l	35	94	204-205	204-206 [32]
13	Et	3-O ₂ N	O	4m	15	96	225-226	224-226 [33]
14	Et	4-OH	O	4n	40	92	230-231	231-233 [33]
15	Et	4-F	O	4o	20	97	181-182	181-183 [34]
16	Me	H	O	4p	30	94	215-218	215-218 [31]
17	Me	4-Cl	O	4q	25	97	204-206	205-207 [31]

^a Isolated yields

Table 3. A comparison of the effects of some catalysts with that of the present nanocatalyst on the model reaction.

Entry	Catalyst	Temperature (°C)	Time	Yield ^a (%)	Ref.
1	Nano-CuFe ₂ O ₄ @PEO-SO ₃ H	r.t.	20 min	98	This work
2	Nano-CuFe ₂ O ₄ @PEO	r.t.	45 min	90	This work
3	Nano-CuFe ₂ O ₄	r.t.	50 min	85	This work
4	PEO-SO ₃ H	r.t.	60 min	80	This work
5	PEO	r.t.	48 h	75	This work
6	-	reflux	2 h	25	This work
7	Montmorillonite KSF	130	48 h	77	[35]
8	Silica-sulfuric acid	reflux	6 h	91	[36]
9	H ₃ PMo ₁₂ O ₄₀	reflux	5 h	80	[37]
10	ZrOCl ₂ .8H ₂ O	100	2 h	56	[38]

^a Isolated yields

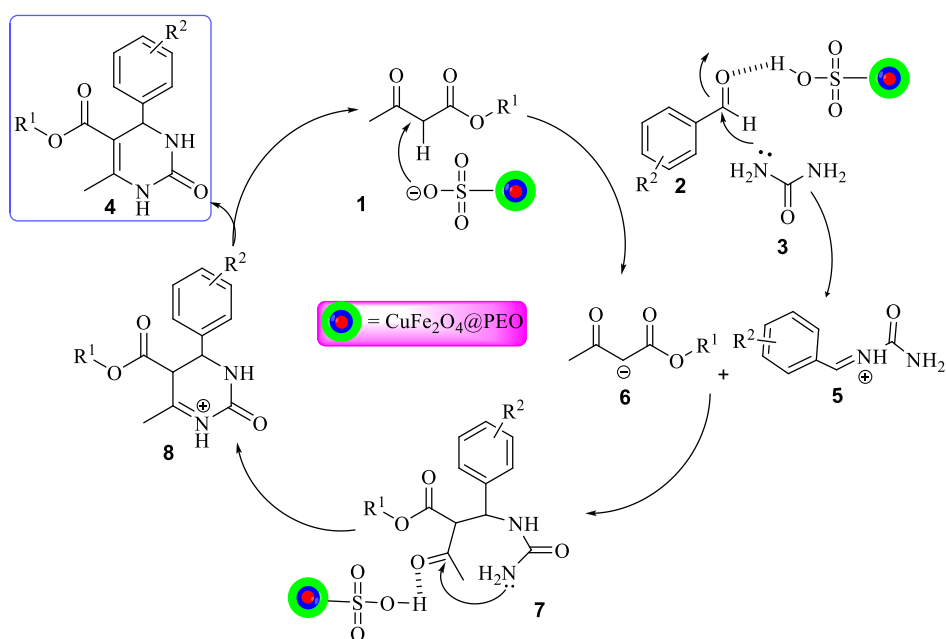
Fig. 8. Recycling of $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ nanocatalyst in the synthesis of 4a.

catalysts in several solvents were examined to confirm the efficiency of $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ for the synthesis of dihydropyrimidine derivatives (**4a**). The obtained results proved that the synthesis of (**4a**) using $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$ was performed at lower temperature. Another significant advantage of this nanocatalyst is that it can be recovered and reused efficiently for several times.

After the completion of the reaction, in order for further evaluating the recoverability of this

nanocatalyst, it was separated and collected by an external magnet, washed with EtOH, and H_2O , and dried. Then, it was reused in the next reactions in the same ratio of catalyst and other reaction conditions. As shown in Fig. 8, the experiments clearly indicate that the prepared catalyst, $\text{CuFe}_2\text{O}_4@PEO\text{-SO}_3\text{H}$, is highly stable at least within six repeated runs.

The Biginelli reaction mechanism is still under debate, without any agreement on the actual pathway. At least, three mechanisms have



been offered for the Biginelli reaction, which include iminium, enamine, and Knoevenagel mechanisms. The plausible mechanism for the synthesis of DHPMs (**4a-1**) is shown in Scheme 3. The first step, like Mannich condensation reaction, is the condensation of an aldehyde with a urea or thiourea, utilizing the nanocatalyst at room temperature. The obtained iminium (**6**) reacts as an electrophile in the nucleophilic addition of the β -ketoester carbanion (**5**) (generated from **1** attached via anion form of the catalyst) for the synthesis of intermediate (**7**). Then, the product (**8**) was achieved by condensation reaction between ketone carbonyl group of the resulting adduct with the NH_2 group of urea. At the end, the products **4** were achieved by an imine-enamine tautomerization of (**8**) [18].

CONCLUSION

In this work, for the first time, $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H was synthesized and its application as a magnetic nanocatalyst in the multicomponent synthesis of dihydropyrimidine derivatives was reported. The catalyst was synthesized through an easy process under mild conditions and then characterized by FT-IR spectra, EDX, VSM, XRD analyses, TEM and SEM images. Then, the effective synthesis of dihydropyrimidine derivatives were prepared with a number of aromatic aldehydes, β -ketoester, urea or thiourea with catalytic amount of the magnetically recoverable $\text{CuFe}_2\text{O}_4@$ PEO- SO_3H nanocatalyst in ethanol as a green solvent. It is notable that in most reported studies, this reaction was conducted under reflux condition during long reaction times; however, in this work, all the reactions were carried out at room temperature and with high yields of products.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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