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A CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite as a novel biopolymer-based catalyst in the synthesis of 1,4-dihydropyridines†

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A CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was successfully designed and prepared *via* graft copolymerization of AA and AMPS on CMC followed by the cross-linking addition of $FeCl_3$/$FeCl_2$. The synthesized hydrogel nanocomposite was characterized by Fourier-transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM), energy-dispersive X-ray (EDX) spectroscopy, elemental mapping, thermogravimetric analysis/differential thermal analysis (TGA/DTA), and vibrating sample magnetometry (VSM). The CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was employed as a biocompatible catalyst for the green synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives under thermal and ultrasound-assisted reaction conditions. High efficiency, low catalyst loadings, short reaction time, frequent catalyst recovery, environmental compatibility and mild conditions were found in both methods.

Introduction

Green chemistry is considered to increase the use of green and non-toxic materials. Applying catalytic methods in organic synthesis has become a very deep research field. The increasing need for reaction systems with catalytic green aspects and benign echo progress and advancement of eco-benign, cost-effective, high-atom-economy, and high-yield processes is highly desirable.[1–3]

The study, synthesis, and application of hybrid materials have been one of the active research areas in recent years due to their superior properties and high application potential.[4] Hydrogel-based hybrid materials are generally easy to design and manufacture.[5,6] Supramolecular hydrogels could be used as matrices for placing nanoparticles in nanocomposite gel hybrid materials.[7–9] Metal, non-metal or polymer nanoparticles (NPs) are widely used in the hydrogel matrix to formulate nanocomposites. The nanoparticles can yield nanocomposites with special properties such as magnetic, antibacterial, and catalytic activities.[10–15] However, rigid hydrogel matrices can reduce nanomaterial size and chemical and physical stability, facilitating handling, recovery, and reuse. Nanoparticle-gel hybrid materials have widespread applications including biosensors, chiral catalysts, and nonlinear optics. Hydrogel matrices could also perfectly reduce aggregation and improve biocompatibility, especially for magnetic nanoparticles. Various polysaccharides including polyvinyl alcohol (PVA), chitosan, and carboxymethyl cellulose (CMC) have been investigated.[16,17]

Multi-component reactions (MCRs) are known as an influential and potent tool for the design and synthesis of a wide range of organic compounds, especially biologically active heterocycles.[3,18–21] These are evaluated as valuable and efficient methods due to the time-saving, atom-economy, and environmentally friendly nature.[22–26] The Hantzsch reaction has been identified as one of the most widely used and effective multi-component reactions for the synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives. 1,4-DHP derivatives, as important nitrogen-containing heterocyclic compounds, displayed valuable pharmaceutical and biological activities. These are applied as anti-tumor, anti-hypertensive, anti-platelet aggregation, bronchodilator, neuroprotective drugs and so on. Moreover, calcium channel blockers such as felodipine, nifedipine, nimodipine, nicardipine, and amlodipine owe their medicinal properties to the 4-aryl-1,4-dihydropyridine moiety.[27,28] Therefore, the influential role of 1,4-DHP derivatives in the design of new drugs is intelligible. Consequently, their synthesis is one of the recent research challenges in chemistry and pharmaceuticals.

As an alternative energy source, ultrasound waves accelerate chemical reactions *via* the formation and collapse of transient cavitation bubbles.[29,30] Ultrasonic waves create high-energy hot spots, which reactant molecules absorb. Accordingly, sufficient energy is provided to overcome the reaction activation barrier, which accelerates the reaction. Thus, ultrasound-promoted reactions are expected to indicate advantages such as high chemical reactivity, high selectivity, a clean reaction process, excellent product yields, and short reaction time.[31–34]

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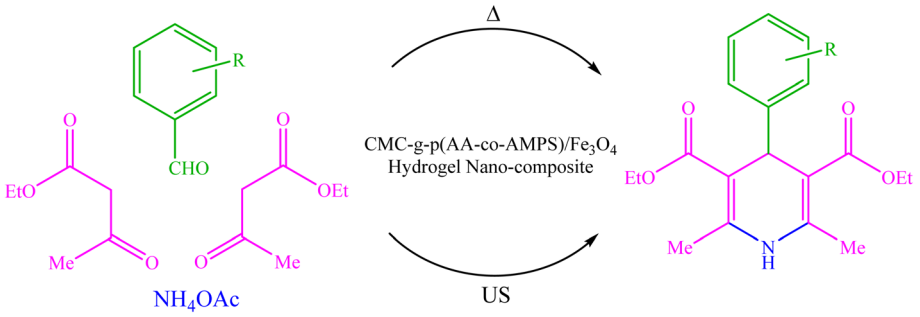
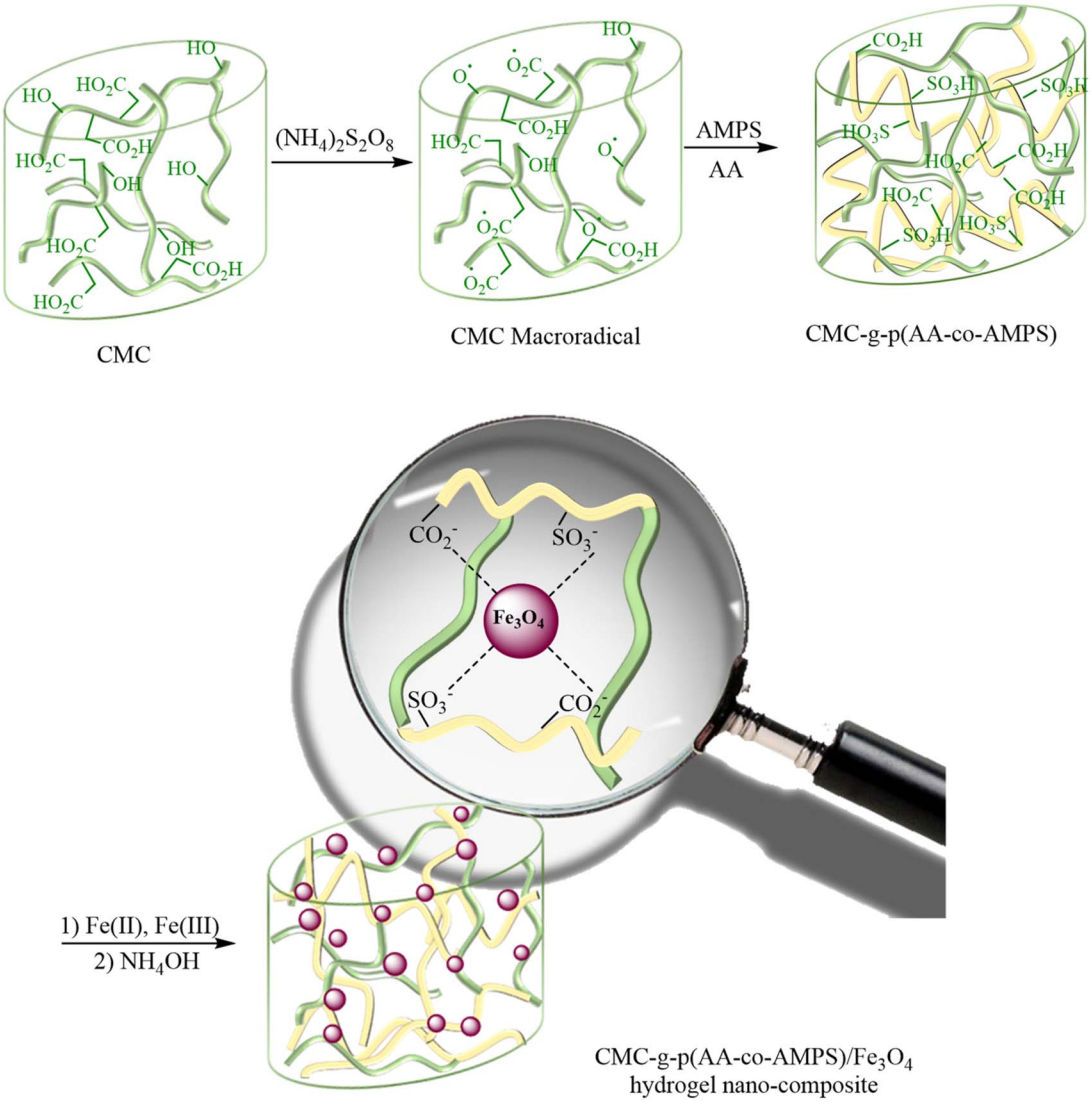


Scheme 1 Hantzsch synthesis of 1,4-DHP derivatives using CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite under both thermal and ultrasonic conditions.

Due to the recent challenges, new protocols for efficiently synthesizing 1,4-DHP derivatives under environmentally safe conditions are still demanded. In continuation of our previous works on the synthesis and application of nanocatalysts in heterocyclic synthesis,[35–43] herein we wish to report the design, synthesis, and use of biopolymer-based CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposites in the Hantzsch



Scheme 2 Synthesis of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite.

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synthesis of 1,4-DHP derivatives under both thermal and ultrasound-assisted conditions (Scheme 1).

Result and discussion

The CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was synthesized in the following two steps: (1) graft copolymerization of acrylic acid (AA) and 2-acrylamido-2-methylpropane sulfonic acid (AMPS) onto carboxymethyl cellulose (CMC) in the presence of ammonium persulfate (APS); (2) $FeCl_3$/$FeCl_2$ augmenting as cross-linking agents (Scheme 2). The graft copolymerization reaction was initiated *via* the generated sulfate anion radicals due to the thermal decomposition of APS. Sulfate anion radicals developed alkoxy radicals of CMC, copolymerized with AA and AMPS monomers. A three-dimensional network structure of CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposites was produced *via* the interaction of $-CO_2^-$ and $-SO_3^-$ chelating moieties from the copolymer and added $Fe^{(2+)}$ and $Fe^{(3+)}$ ions under the basic condition.[16,17,44–47]

The FT-IR spectra of bare CMC and CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposites were studied in 4000–400 cm^{-1} (Fig. 1). The FT-IR spectrum of bare CMC indicated that the peaks observed at 1427 and 1622 cm^{-1} were assigned to the symmetric and asymmetric stretching vibrations of CO_2^- groups (Fig. 1a). The explicit broad peak at 3434 cm^{-1} was attributed to the O–H stretching vibrations.[16] Additional signals were detected for the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite (Fig. 1b). The identified peaks at 1733, 1179, and 1035 cm^{-1} were assigned to C═O in AA, and the asymmetric and symmetric stretching vibrations of S═O in AMPS, respectively. The observed shifts of C═O and S═O groups could be attributed to the interaction of O atoms of carboxylic and sulfonic acid due to charge transfer interactions with Fe_3O_4 nanoparticles.[48] The Fe_3O_4 nanoparticles were stabilized inside the CMC hydrogel network *via* the interactions.

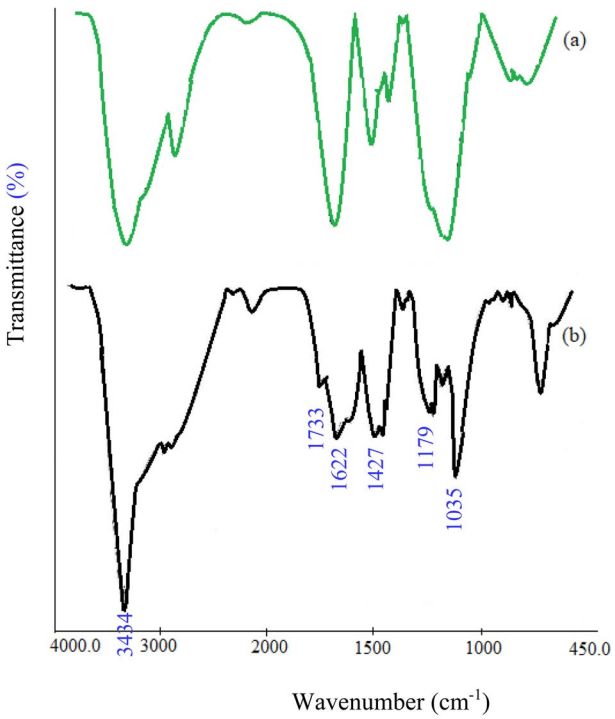

Fig. 1 Comparative FT-IR spectra of (a) bare CMC and (b) CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were considered as visual evidence of the shape, size and distribution of Fe_3O_4 nanoparticles on the surface and embedded in the CMC-*g*-poly(AA-*co*-AMPS) hydrogel matrix, respectively (Fig. 2). The images displayed no aggregation for Fe_3O_4 nanoparticles, indicating that the nanoparticles were uniformly embedded on the surface and within the CMC-*g*-poly(AA-*co*-AMPS) hydrogel matrix. The nanoparticles appeared nearly spherical, with an average diameter of about 18 nm. The identical dispersion of nanoparticles with homogeneous shapes and sizes among the hydrogel network is due to the network's uniform mesh size and distribution of functional groups. The small size favorably affects the number, surface area, and specific surface area of nanoparticles, while the aggregated/agglomerated nanoparticles significantly weaken the positive attributes of nanoparticles in nanocomposites. This occurrence affects the characteristics of nanoparticles and interface, which finally change the behavior of nanocomposites.[49] Accordingly, a strong chemical interaction was found between the carboxylate and sulfonate ions of the CMC-*g*-poly(AA-*co*-AMPS) hydrogel matrix and Fe_3O_4 nanoparticles due to the small particle size.[50]

Fe_3O_4 nanoparticles embedded in the CMC-*g*-poly(AA-*co*-AMPS) polymer were confirmed by energy-dispersive X-ray (EDX) analysis (Fig. 3a). The EDX spectrum of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite identified the presence of carbon (50.2%), sulfur (29.5%), and oxygen atoms in the hydrogel matrix, as well as iron (6.8%) and oxygen atoms of nanoparticles. Additionally, the dispensation pattern of structural elements in the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was well detected using elemental mapping, which confirmed the uniform Fe_3O_4 distribution on the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite surface (Fig. 3b).

Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite were performed at 0–800 °C in an N_2 atmosphere (Fig. 4). The first weight loss was observed at 150 °C, related to the removal of hydrogel moisture. The maximum degradation rate occurred between 250 and 350 °C, related to polymer degradation by intramolecular reactions such as esterification, anhydration, and the like between functional groups that exist in the polymer backbone. The remaining polymer components were completely broken down at 350–800 °C. Finally, 14.75% of the hydrogel remained at 800 °C, which can be attributed to the nanoparticles in the hydrogel.

The recycled hydrogel nanocomposite implied amplified magnetic properties compared to the fresh sample by increasing the magnetic saturation value (M_s) to 1.55 emu g^{-1}, with nonzero remanent magnetization (M_r) and coercivity (C_e), indicating ferromagnetism behavior (Fig. 5b).[51,52] The enhanced magnetic property, nonzero remanent magnetization, and

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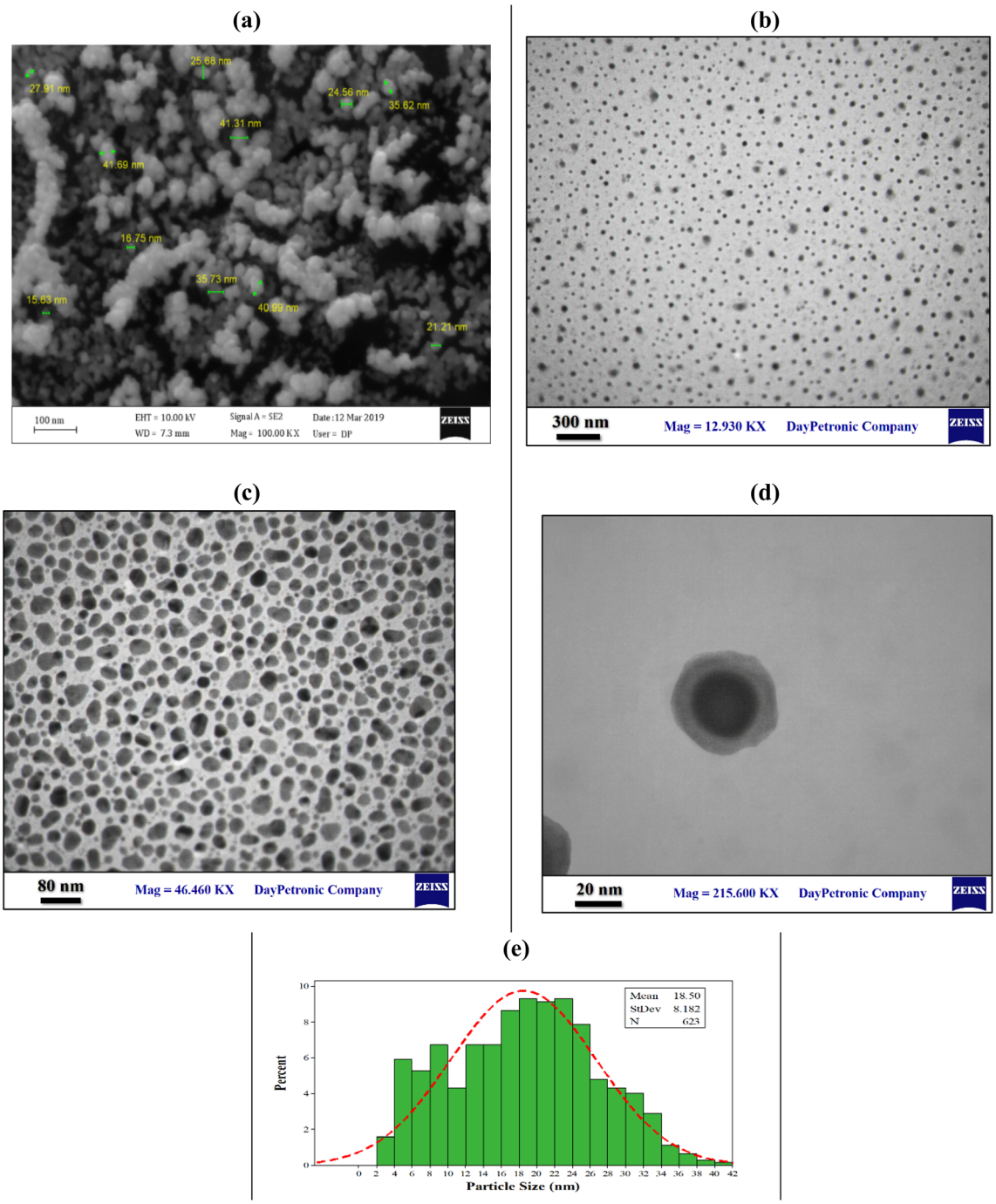

Fig. 2 SEM image (a), TEM images (b–d), and size distribution (e) of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite.

coercivity for the recycled hydrogel nanocomposite were probably due to the partial degradation of the hydrogel and the release of Fe_3O_4 nanoparticles.[52,53]

The produced CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was evaluated as a catalyst for the Hantzsch synthesis of 1,4-dihydropyridine (1,4-DHP) under thermal and ultrasound-assisted conditions (Scheme 1). The effects of catalyst loading, solvent, and temperature were investigated to optimize the model reaction parameters of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate synthesis (Table 1). While low yields of products were detected in H_2O, EtOH, $PhCH_3$, CH_2Cl_2, and CH_3CN solvents, solvent-free conditions resulted in good efficiency in 20 min (Table 1, entries 1–6). Then, a series of equivalent reactions with different catalyst loadings were used to investigate the role of CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposites in the reaction rate and efficiency (Table 1, entries 6–10). A gradual increase in catalyst loading (0–30 wt%) was scrutinized. Only a small amount of product was acquired without the hydrogel nanocomposite, while the maximum efficiency was found due

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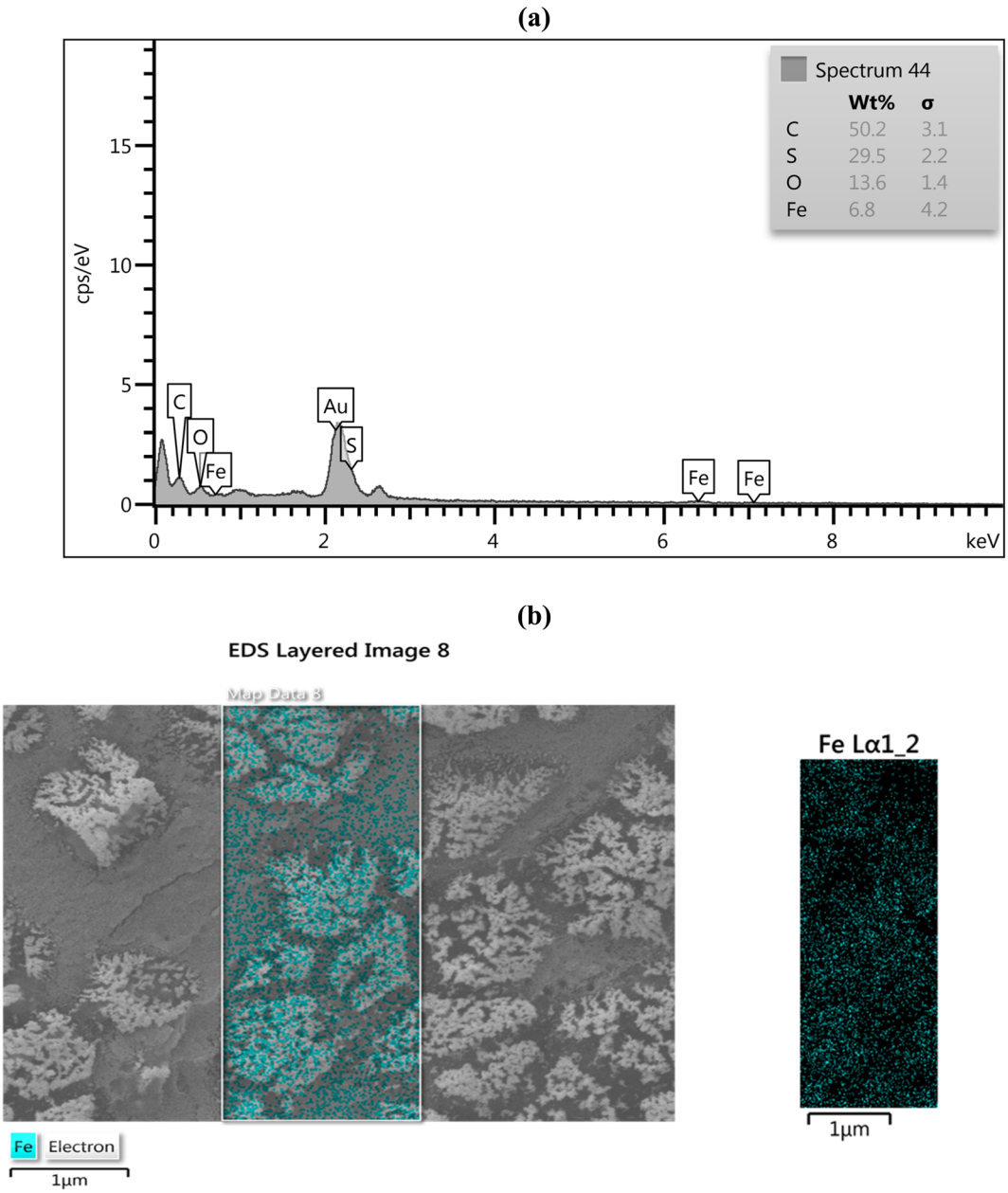

Fig. 3 EDX analysis (a) and (b) elemental mapping of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite.

to 10 wt% catalyst loading. The reaction yield was estimated to be almost constant with a further increase in the amount of catalyst (Table 1, entries 6–10). Next, the model reaction was evaluated with similar conditions and catalyst loadings at different temperatures (Table 1, entries 11–13). Notably, the most appropriate outcome was obtained at 80 °C. Finally, the best time to perform the reaction was estimated to be about 20 min (Table 1, entries 14 and 15).

Additionally, the model reaction was explored under ultrasound conditions (Table 1, entries 16–24). Ultrasonic waves improved the reaction, so that the reaction was carried out at 40 °C with a higher efficiency than that under thermal conditions (Table 1, entry 21).

Several aryl/heteroaryl aldehydes were carried out in the Hantzsch synthesis of 1,4-DHP using CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposites (10 wt%) under thermal and ultrasonic conditions to assay the scope of the current protocol (Table 2). The synthesis of 1,4-DHP derivatives was performed under optimal conditions with various aryl aldehydes containing electron-withdrawing and electron-donating groups as well as halogens with high efficiency and at the right time. Aryl aldehydes containing electron-donor groups decreased the reaction rate, while electron-acceptor groups and halogens indicated a greater tendency to carry out the Hantzsch reaction. Moreover, high yields of products were found for heteroaryl aldehydes (Table 2, entries 17–20).[28,54–60]

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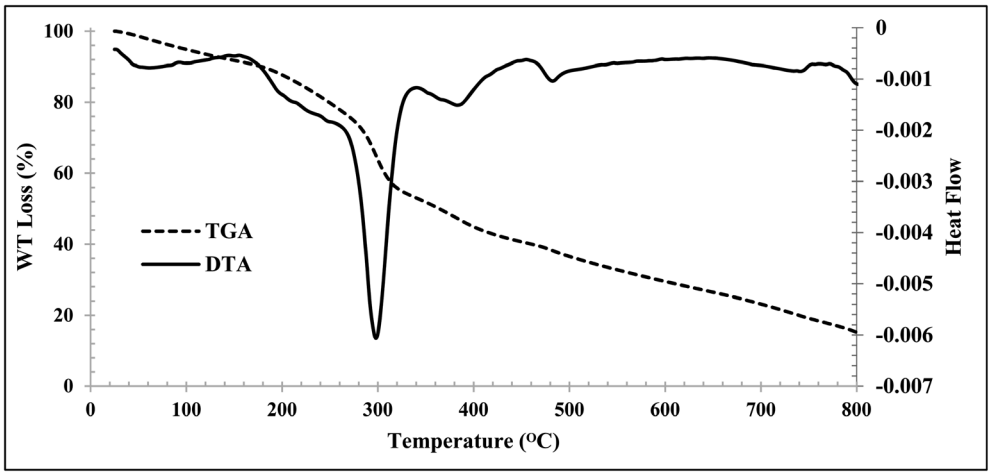

Fig. 4 TGA (dash line) and DTG (solid line) analysis of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite.

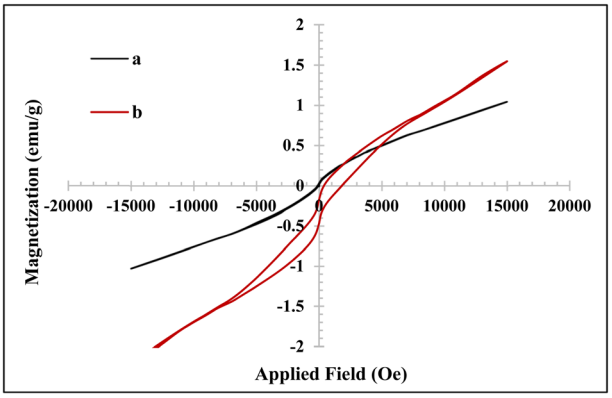

Fig. 5 VSM diagram of (a) a fresh CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite and (b) recycled CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite after six times.

Recently, the application of nanocatalysts in organic synthesis has been considered. Table 3 presents the comparative performance of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite and other nanocatalysts previously used in the Hantzsch synthesis of 1,4-dihydropyridine. The results introduced the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite as one of the most efficient nanocatalysts in the Hantzsch synthesis of 1,4-dihydropyridine under conventional and ultrasound-assisted conditions (Table 3, entries 10 and 11).[28,55,58,61–66]

Catalyst recycling is one of the most important advantages that make catalysts important for commercial applications. Therefore, the recyclability of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite in the Hantzsch reaction under optimized conditions was investigated (Fig. 6). The hydrogel nanocomposite can be applied at least six times without significantly decreasing the catalytic activity in this reaction.

There was a plausible mechanism proposed for the synthesis of 1,4-dihydropyridine (1,4-DHP) using the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite (Scheme 3).[27] Ethyl acetoacetate (EAA) reacted with the activated aldehyde *via* Knoevenagel condensation to form intermediate **A**. Intermediate **B** was obtained from ammonium acetate and the second equivalent of EAA in an acidic medium. The CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite catalyzed Michael's addition and reactions of intermediates **A** and **B**. Finally, cyclocondensation of intermediate **C** was performed to obtain the product.

Experimental

Materials and equipment

All materials and reagents were purchased from reputable commercial companies including Merck, Sigma-Aldrich, and Alfa-Aesar and then used without further purification. TLC was performed to monitor the purity of the synthesized compounds. IA 9200 Electrothermal apparatus was used to evaluate the melting points without any correction. FT-IR spectra were recorded using a PerkinElmer spectrometer with KBr disks at 400–4000 cm^{-1}. A Model LBKFB from Desert Precision Magnet Company was used for vibrating sample magnetometry (VSM) at room temperature to study the magnetic properties. The elements were determined using a Numerix DXP-X10P energy-dispersive X-ray spectrometer (EDX). Scanning electron microscopic (SEM) images were obtained using a SIGMA VP-500-Zeiss. Transmission electron microscopy (TEM) was carried out using a Zeiss-EM10C microscope operating at an accelerating voltage of 100 kV. Thermogravimetric analysis (TGA) was performed at 15–800 °C in a nitrogen atmosphere using a PerkinElmer instrument of Pyris 1PT-1600. A WUC-A03H from Daihan Scientific Company was employed for ultrasonic waves. Bruker Avance DRX-300 and DRX-75 were applied for recording ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra, respectively.

Synthesis of CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite

Sodium-carboxymethyl-cellulose (CMC) (1.0 g) was dissolved in water, and the solution was transferred to a three-necked

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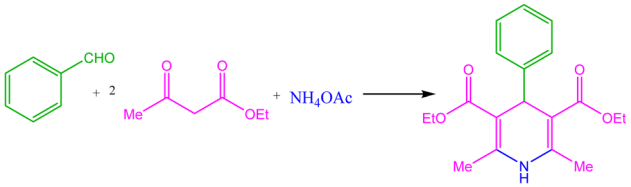
Table 1 The effect of catalyst loading, solvent, and temperature in the Hantzsch synthesis of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate using the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite[a,b]



Entry	Catalyst	Catalyst loading (wt%)	Solvent	Temperature (°C)	Time (min)	Yield[c] (%)
1	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	H_2O	Reflux	20	24
2	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	EtOH	Reflux	20	82
3	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	$PhCH_3$	Reflux	20	70
4	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	CH_2Cl_2	Reflux	20	60
5	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	CH_3CN	Reflux	20	75
6	**CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]**	**10**	**—**	**80**	**20**	**87**
7	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	—	—	80	40	12
8	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	5	—	80	30	69
9	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	20	—	80	20	81
10	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	30	—	80	20	80
11	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	—	60	40	71
12	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	—	90	20	87
13	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	—	100	20	87
14	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	—	80	10	79
15	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[a]	10	—	80	40	87
16	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	10	H_2O	Reflux	15	31
17	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	10	EtOH	Reflux	15	86
18	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	10	$PhCH_3$	Reflux	15	72
19	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	10	CH_2Cl_2	Reflux	15	63
20	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	10	CH_3CN	Reflux	15	79
21	**CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]**	**10**	**—**	**40**	**10**	**90**
22	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	—	—	40	20	18
23	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	5	—	40	20	74
24	CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4[b]	20	—	40	15	89

[a] Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.5 mmol) under thermal conditions. [b] Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.5 mmol) under ultrasound-assisted conditions. [c] Isolated yields.

reactor equipped with a mechanical stirrer and set in a warm water bath at 80–85 °C. Then, 2-acrylamido-2-methylpropane sulfonic acid (AMPS) (2.0 g), ammonium persulfate (APS) (0.08 g), and acrylic acid (AA) (2.0 g) were added to the reaction mixture and allowed to polymerize for 60 min. Followed by cooling, a solution of $FeCl_3 \cdot 6H_2O/FeCl_2 \cdot 4H_2O$ (1/4) was poured dropwise into the reaction mixture. After one hour of stirring, an ammonia solution (20 mL) was added to form Fe_3O_4 nanoparticles within the polymer matrix under continuous stirring for half an hour at room temperature.

Finally, the produced CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was dehydrated with ethanol and then dried at 50 °C overnight.

General experimental procedure for Hantzsch synthesis using CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposites

A mixture of aryl aldehyde (1 mmol), ammonium acetate (1.5 mmol), ethyl acetoacetate (2 mmol), and CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite (10 wt%) was added in a round-bottomed flask at 80 °C. Moreover, the reaction mixture was once again subjected to ultrasonic irradiation at 40 °C for a suitable time. The reaction progression was monitored by thin-layer chromatography (TLC). After the reaction, ethanol was applied to obtain the product. The hydrogel nanocomposite was filtered, washed, dried, and prepared for the next use. The products were purified by recrystallization with ethanol/water.

Spectral data of 1,4-dihydropyridine (1,4-DHP)

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a). Mp: 158–160 °C (155–160 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.11 (t, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.96 (m, 4H, $2CH_2$), 4.85 (s, 1H, CH), 7.07–7.21 (m, 4H, Ph), 8.79 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.14, 18.20, 58.95, 101.83, 125.83, 127.33, 127.81, 145.31, 148.15, 166.92.

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4b). Mp: 164–166 °C (162 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.10 (t, 6H, $2CH_3$), 2.27 (s, 6H,

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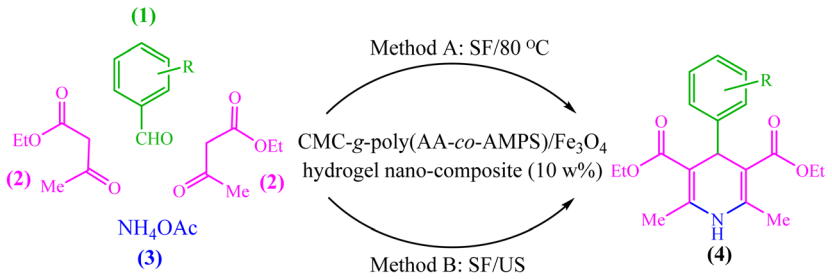
Table 2 The Hantzsch synthesis of 1,4-DHPs using the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite



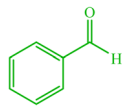
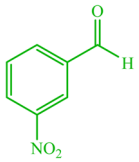
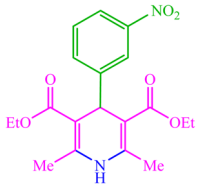
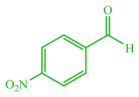
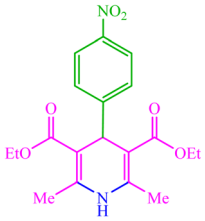
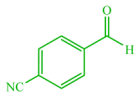
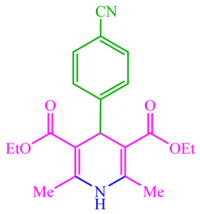
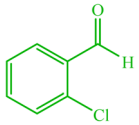
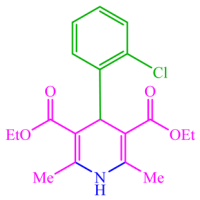
Entry	Aldehyde	Product	Method A[a] Time (min)	Method A[a] Yield[c] (%)	Method B[b] Time (min)	Method B[b] Yield[c] (%)	Mp (°C) (lit.)
1		**4a**	20	87	10	90	158–160 (155–160) (28)
2		 **4b**	10	90	10	93	164–166 (162) (28)
3		 **4c**	10	90	10	95	129–133 (127–132) (28)
4		 **4d**	—	—	10	80	162–166 (166–167) (54)
5		 **4e**	10	80	—	—	214 (216–217) (55)

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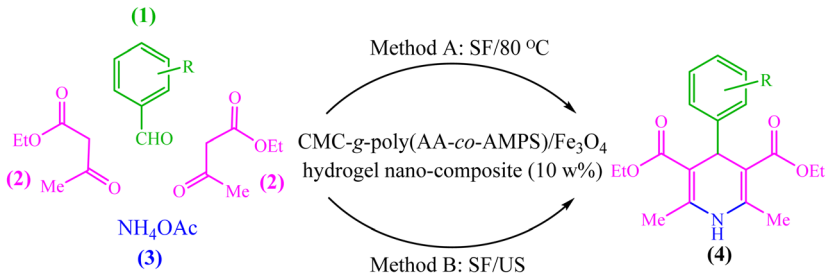
Table 2 (*Contd.*)



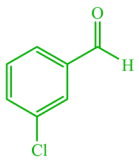
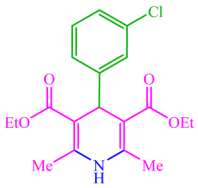
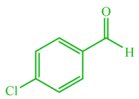
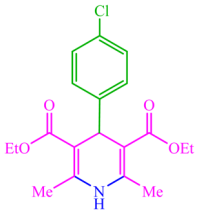
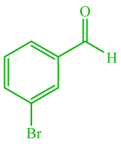
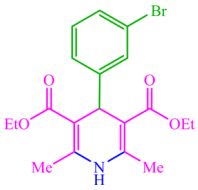
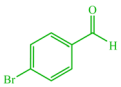
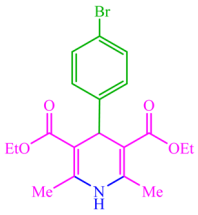
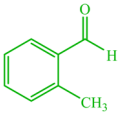
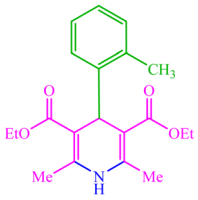
Entry	Aldehyde	Product	Method A[a] Time (min)	Method A[a] Yield[c] (%)	Method B[b] Time (min)	Method B[b] Yield[c] (%)	Mp (°C) (lit.)
6		 **4f**	10	85	10	90	138–140 (140) (28)
7		 **4g**	10	87	10	98	150–154 (150–152) (56)
8		 **4h**	10	77	10	85	231–235 (230) (28)
9		 **4i**	10	77	10	78	162–165 (164–165) (28)
10		 **4j**	20	90	—	—	178 (179) (28)

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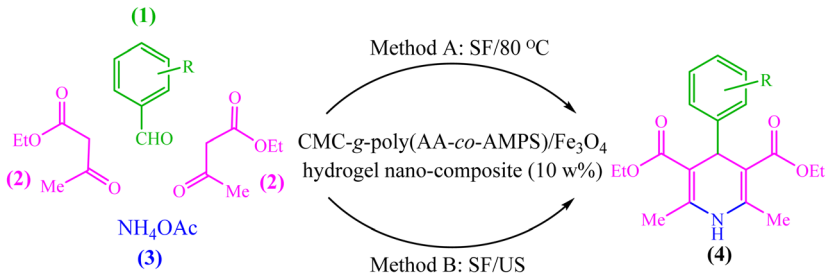
Table 2 (*Contd.*)



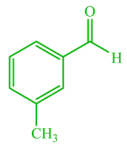
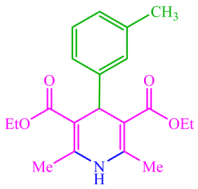
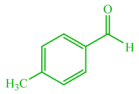
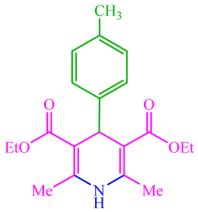
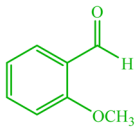
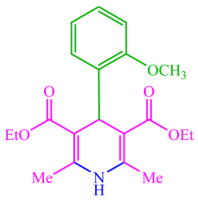
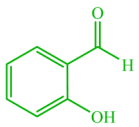
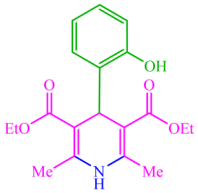
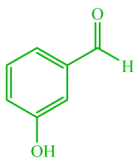
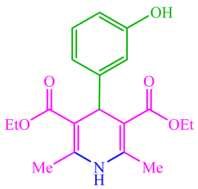
Entry	Aldehyde	Product	Method A[a] Time (min)	Method A[a] Yield[c] (%)	Method B[b] Time (min)	Method B[b] Yield[c] (%)	Mp (°C) (lit.)
11		 **4k**	15	85	—	—	126 (123–125) (55)
12		 **4l**	15	80	10	82	135 (135) (28)
13		 **4m**	30	80	10	95	156–158 (156) (28)
14		 **4n**	30	83	10	96	118–120 (117–118) (57)
15		 **4o**	15	98	10	98	186 (187–189) (58)

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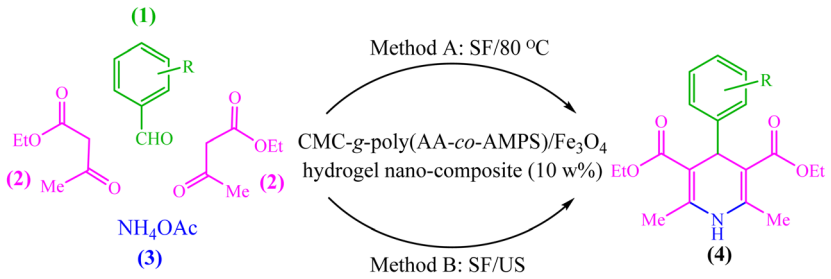
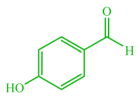
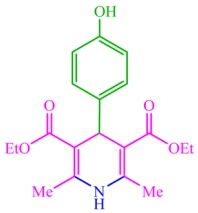
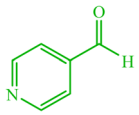
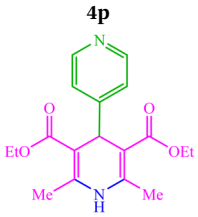
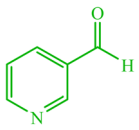
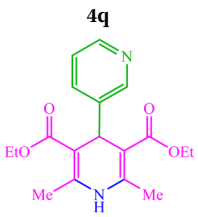
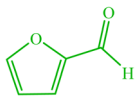
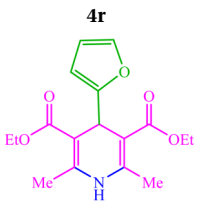
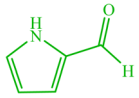
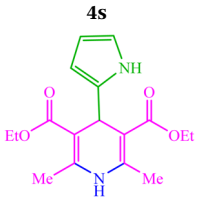
Table 2 (*Contd.*)



Entry	Aldehyde	Product	Method A[a] Time (min)	Method A[a] Yield[c] (%)	Method B[b] Time (min)	Method B[b] Yield[c] (%)	Mp (°C) (lit.)
16		 **4p**	10	98	10	98	223–226 (222) (28)
17		 **4q**	15	92	10	93	177–180 (176–178) (59)
18		 **4r**	15	90	10	90	190–192 (191–192) (60)
19		 **4s**	10	90	10	92	160–163 (159–161) (59)
20		 **4t**	10	87	10	90	210–212 (214–216) (60)

[a] Reaction conditions: benzaldehyde derivatives (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.5 mmol) at 80 °C. [b] Reaction conditions: benzaldehyde derivatives (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.5 mmol) at 40 °C under ultrasound-assisted conditions. [c] Isolated yields.

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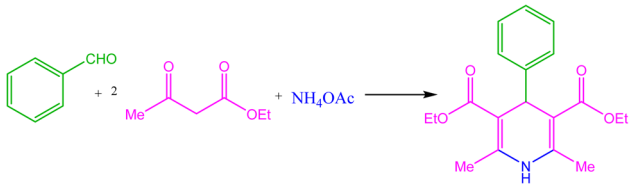
Table 3 A comparative performance of diverse nanocatalysts in the Hantzsch synthesis of 1,4-DHPs



Entry	Catalyst	Reaction condition	Time (min)	Yield (%)	References
1	Chitosan nanoparticle (100 wt%)	Solvent free/80 °C	20	90	61
2	MWCNTs–$CONHCH_3$ (1 wt%)	EtOH/80 °C	240	85	62
3	Fe_3O_4/SiO_2–PDA nanocatalyst (50 wt%)	EtOH/US	10	89	58
4	γ-Fe_2O_3/Cu@cellulose nanobiocomposite (3 wt%)	Solvent free/RT	25	87	63
5	MCGC nanocatalyst (15 wt%)	EtOH/US	15	95	64
6	MCGC nanocatalyst (15 wt%)	EtOH/reflux	17	92	64
7	$CoFe_2O_4$@SiO_2–NH_2–Co^{II} nanoparticles (150 wt%)	H_2O, EtOH/reflux	150	85	65
8	BNPs@$SiO_2(CH_2)_3NHSO_3H$ nanocatalyst (60 wt%)	Solvent free/80 °C	30	97	66
9	COF–SO_3H nanoporous (20 wt%)	Solvent free/90 °C	10	93	55
10	Ch-rhomboclase nanocomposite (1.8 mol%)	Solvent free/80 °C	60	95	28
11	**CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite (10 wt%)**	**Solvent free/80 °C**	**20**	**87**	**This work**
12	**CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite (10 wt%)**	**Solvent free/US**	**10**	**90**	**This work**

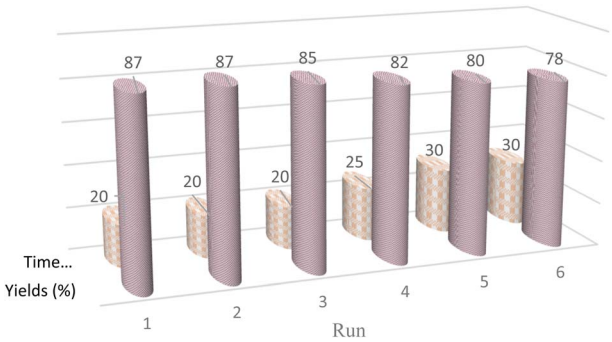


Fig. 6 Recyclability diagram of the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite in the Hantzsch synthesis.

$2CH_3$), 3.96 (m, 4H, $2CH_2$), 4.96 (s, 1H, CH), 7.51–7.95 (m, 4H, Ph), 8.97 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.00, 18.19, 59.16, 101.06, 121.00, 121.90, 129.50, 134.21, 145.32, 147.39, 150.27, 166.47.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c). Mp: 129–133 °C (127–132 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.11 (t, 6H, $2CH_3$), 2.26 (s, 6H, $2CH_3$), 3.97 (m, 4H, $2CH_2$), 4.96 (s, 1H, CH), 7.38–8.11 (d of d, 4H, Ph), 8.97 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.08, 18.19, 59.16, 100.79, 123.24, 123.55, 145.78, 146.26, 155.44, 166.47.

Diethyl 4-(4-cyanophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4d). Mp: 162–166 °C (166–167 °C[54]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.10 (t, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.97 (m, 4H, $2CH_2$), 4.89 (s, 1H, CH), 7.30–7.68 (d of d, 4H, Ph), 8.93 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.34, 18.49, 59.76, 101.87, 118.24, 125.55, 134.35, 145.78, 146.84, 155.41, 167.00.

Diethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e). Mp: 214 °C (216–217 °C[55]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.10 (t, 6H, $2CH_3$), 2.26 (s, 6H, $2CH_3$), 3.96 (m, 4H, $2CH_2$), 4.83 (s, 1H, CH), 7.28–7.68 (m, 4H, Ph), 8.69 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.05, 18.61, 59.18, 101.88, 124.68, 124.76, 128.43, 132.01, 144.57, 148.71, 155.44, 166.54.

Diethyl 4-(3-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f). Mp: 137–140 °C (140 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.09 (t, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.97 (m, 4H, $2CH_2$), 4.82 (s, 1H, CH), 7.08–7.26 (m, 4H, Ph), 8.87 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.05, 18.61, 59.16, 101.79, 124.80, 125.15, 132.13, 144.78, 148.67, 155.42, 166.47.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4g). Mp: 150–154 °C (150–152 °C[56]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.09 (t, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.97 (m, 4H, $2CH_2$), 4.81 (s, 1H, CH), 7.10–7.23 (d of d, 4H, Ph), 8.85 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.05, 18.61, 59.17, 101.78, 125.27, 132.34, 146.76, 155.28, 166.49.

Diethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h). Mp: 231–235 °C (230 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.08 (t, 6H, $2CH_3$), 2.20 (s, 6H, $2CH_3$), 3.95 (m, 4H, $2CH_2$), 5.18 (s, 1H, CH), 6.97–7.41 (m, 4H, Ph), 8.80 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.18, 19.16, 59.70, 102.32, 123.17, 126.73, 128.59, 129.38, 134.05, 145.08, 151.35, 167.18.

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i). Mp: 162–165 °C (164–165 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.11 (t, 6H, $2CH_3$), 2.24 (s, 6H, $2CH_3$), 3.97 (m, 4H, $2CH_2$), 4.82 (s, 1H, CH), 7.07–7.39 (d of d, 4H, Ph), 8.80 (s, 1H, NH); ^{13}C NMR (75 MHz,

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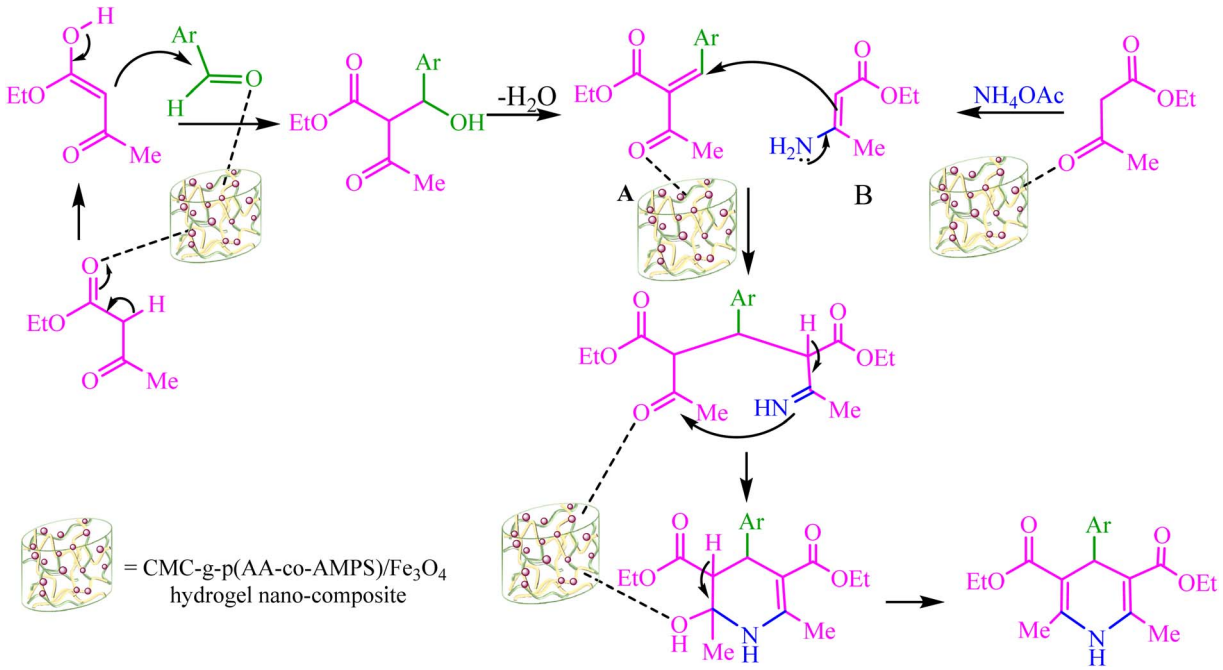

Scheme 3 Plausible mechanism for the Hantzsch synthesis of 1,4-DHP derivatives using the CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite.

DMSO-d_6) δ (ppm): 14.18, 19.16, 59.70, 102.32, 121.04, 131.41, 131.64, 142.97, 150.71, 167.18.

Diethyl 2,6-dimethyl-4-(*o*-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (4j). Mp: 178 °C (179 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, 2CH_3), 2.21 (s, 3H, CH_3), 2.24 (s, 6H, 2CH_3), 3.97 (m, 4H, 2CH_2), 4.91 (s, 1H, CH), 6.87–7.13 (m, 4H, Ph), 8.76 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.17, 18.16, 18.31, 21.32, 58.96, 102.01, 122.63, 125.60, 135.78, 136.53, 145.24, 148.11, 166.97.

Diethyl 2,6-dimethyl-4-(*m*-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (4k). Mp: 126 °C (123–125 °C[55]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, 2CH_3), 2.21 (s, 3H, CH_3), 2.24 (s, 6H, 2CH_3), 3.97 (m, 4H, 2CH_2), 4.91 (s, 1H, CH), 6.90–7.09 (m, 4H, Ph), 8.74 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.17, 18.16, 18.23, 21.20, 58.95, 101.85, 124.50, 126.53, 127.78, 128.04, 136.52, 145.24, 148.11, 166.97.

Diethyl 2,6-dimethyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (4l). Mp: 135 °C (135 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, 2CH_3), 2.22 (s, 3H, CH_3), 3.72 (s, 6H, 2CH_3), 3.95 (m, 4H, 2CH_2), 4.79 (s, 1H, CH), 6.96–7.02 (m, 4H, Ph), 8.71 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.21, 18.23, 21.32, 59.16, 101.01, 124.51, 134.67, 145.03, 150.27, 166.97.

Diethyl 4-(2-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4m). Mp: 156–158 °C (156 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, 2CH_3), 2.21 (s, 6H, 2CH_3), 3.81 (s, 3H, CH_3), 3.95 (m, 4H, CH_2), 4.78 (s, 1H, CH), 6.90–7.44 (m, 4H, Ph), 8.65 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.02, 18.05, 18.31, 56.10, 58.87, 102.01, 112.21, 120.07, 125.14, 133.78, 135.37, 145.12, 148.04, 166.92.

Diethyl 4-(2-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4n). Mp: 118–120 °C (117–118 °C[57]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, 2CH_3), 2.22 (s, 3H, CH_3), 3.95 (m, 4H, 2CH_2), 4.73 (s, 1H, CH), 6.53–7.15 (m, 4H, Ph), 8.65 (s, 1H, NH), 9.00 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.02, 18.05, 36.90, 58.87, 101.85, 112.04, 120.01, 124.56, 133.48, 134.94, 145.11, 147.96, 166.47.

Diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4o). Mp: 186 °C (187–189 °C[58]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.13 (t, 6H, 2CH_3), 2.20 (s, 3H, CH_3), 3.95 (m, 4H, 2CH_2), 4.70 (s, 1H, CH), 6.51–7.17 (m, 4H, Ph), 8.67 (s, 1H, NH), 9.01 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.00, 18.07, 36.93, 58.83, 101.92, 112.04, 120.13, 124.55, 133.69, 134.89, 145.19, 148.06, 166.32.

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4p). Mp: 222 °C (223–226 °C[28]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, 2CH_3), 2.22 (s, 6H, CH_3), 3.96 (m, 4H, 2CH_2), 4.73 (s, 1H, CH), 6.54–6.92 (d of d, 4H, Ph), 8.65 (s, 1H, NH), 9.01 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.01, 18.19, 59.15, 101.00, 124.11, 134.21, 145.03, 150.22, 166.47.

Diethyl 2,6-dimethyl-1,4-dihydro-[4,4′-bipyridine]-3,5-dicarboxylate (4q). Mp: 177–180 °C (176–178 °C[59]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.11 (t, 6H, 2CH_3), 2.19 (s, 3H, CH_3), 3.95 (m, 4H, 2CH_2), 4.97 (s, 1H, CH), 7.36–8.12 (d of d, 4H, Ph), 8.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.10, 18.19, 59.01, 101.17, 123.31, 123.56, 145.77, 155.35, 166.51.

Diethyl 2′,6′-dimethyl-1′,4′-dihydro-[3,4′-bipyridine]-3′,5′-dicarboxylate (4r). Mp: 190–192 °C (191–192 °C[60]); ^{1}H NMR (300

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MHz, DMSO-d_6) δ (ppm): 1.10 (t, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.96 (m, 4H, $2CH_2$), 4.80 (s, 1H, CH), 7.35–8.22 (m, 4H, Ph), 8.71 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.10, 18.19, 59.01, 101.06, 123.40, 134.82, 143.32, 146.07, 166.51.

Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4s). Mp: 160–163 °C (159–161 °C[59]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, $2CH_3$), 2.26 (s, 3H, CH_3), 4.01 (m, 4H, $2CH_2$), 4.86 (s, 1H, CH), 6.12–7.36 (m, 3H, Ar), 8.90 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.05, 18.19, 31.20, 59.17, 101.03, 105.16, 106.00, 140.10, 146.19, 148.17, 150.51, 166.04.

Diethyl 2,6-dimethyl-4-(1*H*-pyrrol-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4t). Mp: 210–212 °C (214–216 °C[60]); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.12 (t, 6H, $2CH_3$), 2.26 (s, 3H, CH_3), 4.01 (m, 4H, $2CH_2$), 4.85 (s, 1H, CH), 6.12–7.37 (m, 3H, Ar), 8.91 (s, 1H, NH), 10.53 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.05, 18.19, 31.20, 59.17, 101.12, 105.14, 106.00, 140.21, 146.18, 148.17, 150.50, 166.04.

Conclusion

A biopolymer-based nanocatalyst, a CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite, has been successfully synthesized by graft copolymerization of AA and AMPS onto CMC, followed by the cross-linking of $FeCl_3$/$FeCl_2$. The CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was analyzed by FT-IR spectroscopy, SEM, TEM, EDX analysis, TGA, and VSM, which emphasized the proposed structure, size, morphology, thermal stability, and magnetic properties. Biocompatibility, high reactivity, favorable recyclability, availability, and economy can be mentioned as the advantages of the green hydrogel nanocatalyst. The CMC-*g*-poly(AA-*co*-AMPS)/Fe_3O_4 hydrogel nanocomposite was applied as an effective catalyst for the synthesis of 1,4-dihydropyridine (1,4-DHP) under solvent-free conditions by both thermal and ultrasound methods. The noteworthy advantages of this method included green and mild reaction conditions, short reaction time, and high yields of products.

Conflicts of interest

There are no conflicts to declare.

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