Reac Kinet Mech Cat (2018) 124:757–766
https://doi.org/10.1007/s11144-018-1361-9

Fe_3O_4 magnetic nanoparticles coated with a copolymer: a novel reusable catalyst for one-pot three-component synthesis of 2-amino-4*H*-chromene

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Received: 7 November 2017 / Accepted: 28 January 2018 / Published online: 15 February 2018

Abstract In this paper, an efficient method for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives is described. The method uses Fe_3O_4 magnetic nanoparticles coated with poly (ε-caprolactone)/poly (ethylene glycol)/poly (ε-caprolactone) (MNPs-Fe_3O_4/PCL–PEG–PCL) as a biodegradable and green catalyst under solvent-free conditions. The catalyst was prepared from PCL–PEG–PCL copolymer and MNPs-Fe_3O_4 and characterized by FT-IR, X-ray diffraction and SEM spectroscopy. Most aromatic aldehydes bearing electron-withdrawing or electron donating groups reacted successfully with malononitrile and dimedone under solvent-free conditions at 80 °C. The corresponding chromenes were isolated in good to excellent yields and the structures of them were confirmed by ^{1}H NMR and IR spectroscopy. The catalyst could be recovered using an external magnet without a considerable loss in its catalytic activity. Moreover, some advantages of this method are simplicity of procedure, easy separation of the catalyst, high yields, efficiency, stability and non-toxicity of the catalyst, short reaction times, and environmentally benign conditions.

Keywords 2-Amino-4*H*-chromene · Magnetic nanoparticles · Solvent-free condition · One-pot synthesis · PCL–PEG–PCL

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11144-018-1361-9) contains supplementary material, which is available to authorized users.

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Introduction

Chromene and its derivatives are an important class of heterocyclic compounds that have been shown various biological properties. Many of these compounds act as anti-viral [1], anti-inflammatory [2], antiproliferative [3], anti-tumor [4], anti-cancer [5], anti-estrogenic [6], antibacterial [7], anti-helminthic [8], anticonvulsant [9], sex pheromone [3], and antimalarial agents [10]. The synthesis of chromene derivatives has been attracted much attention of many researchers due to their biological properties. In recent years, different homogeneous or heterogeneous catalysts have been developed for the preparation of these compounds such as Fe_3O_4/SiO_2 [11], K_2CO_3 [12], $Ca(OH)_2$ [13], MgO [14], nano Ag/kaolin [15], Fe_3O_4-chitosan nanoparticles [16], hetero-polyacid [17], etc. Most of these methods have several drawbacks such as low yields of products, long reaction times, harsh reaction conditions, expensive reagents, the use of toxic catalysts, and cumbersome work-up. Therefore, it is necessary to introduce an efficient, safe, and green method for the synthesis of these compounds.

Recently, because of their interesting properties, magnetic nanoparticles have been used in many reactions as catalysts. However, these magnetic nanomaterials usually do not have thermal and chemical stability, and they would be aggregated and deformed during the chemical reactions. Therefore, the development of effective strategies for improving the chemical stability of magnetic nanoparticles is necessary. One way to overcome these challenges is the surface modification of magnetic nanoparticles using surface stabilizers and polymers [16, 18–21].

Magnetic nanoparticles (MNPs-Fe_3O_4)/poly (ε-caprolactone) [PCL]-co-poly ethylene glycol (PEG) [22] is magnetic nanocomposite including a biodegradable copolymer [PCL–PEG–PCL] which is covered by Fe_3O_4 nanoparticles. It has been found that these nanocomposites can play a significant role in antitumor drug delivery to fight lung tumors [23]. In the present study, we wish to investigate the catalytic activity of this new magnetic nanocomposite [MNPs-Fe_3O_4/PCL–PEG–PCL] in the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives from aldehydes, malononitrile, and dimedone under solvent-free conditions. It must be noted that it is the first application of this nanocomposite as a catalyst in organic transformations.

Experimental

General

All reagents used for this study were the products of Merck and Aldrich, which were used with no further purification. All yields are the isolated product yields which had been purified. Melting points were determined with Barnstead Electrothermal. To record IR spectra, a Shimadzu IR-470 spectrometer was utilized, and ^1H NMR data were obtained using a Bruker 300 MHz spectrometer in $CDCl_3$. The structures of the products were confirmed by their melting points, ^1HNMR, IR spectroscopy and compared with the literature. Besides, X-ray powder diffraction analysis was conducted on a Bruker AXS D8 ADVANCE X-ray diffractometer using a Cu tube in the range of $2\theta = 10–80°$. The size and shape of the particles were determined using scanning electron microscopy (TESCAN, VEGA SEM).

Preparation of copolymer PCL–PEG–PCL

The PCL–PEG–PCL was synthesized by the ring opening polymerization of 3-caprolactone with Sn(Oct) as the catalyst [34]. The polyethylene glycol was dried under a nitrogen atmosphere at 80 °C for 2 h. A mixture of 3-caprolactone (4 g), PEG (2 g), and Sn(Oct) (0.01 mmol) was stirred under a nitrogen atmosphere at 120 °C for 12 h. The product was cooled to room temperature and dissolved in dichloromethane. Then cold diethyl ether was added, and the precipitate was filtered, and the purification process was repeated twice more. The obtained product was dried under vacuum at room temperature for 24 h. The structure of PCL–PEG–PCL copolymer was confirmed by IR and ^{1}H NMR spectroscopy and compared with the literature [24].

Synthesis of Fe_3O_4 nanoparticles (MNPs)

Magnetic nanoparticles were synthesized by a chemical precipitation method. According to this method, the $FeCl_3 \cdot 6H_2O$ (34.6 mmol), $FeCl_2 \cdot 4H_2O$ (17.30 mmol) and 160 ml double distilled water were stirred under N_2 gas. Then, 20 ml NH_4OH (25%) was added dropwise to the mixture and stirred at 80 °C for 30 min. The reaction mixture was centrifuged at 5000 rpm for 20 min. The precipitated particles were washed twice with deionized water and collected by a strong permanent magnet [25].

Preparation of MNPs-Fe_3O_4/PCL–PEG–PCL

Two hundred mg of PCL–PEG–PCL copolymer was dissolved in methylene chloride (3 ml) and added to an aqueous solution of MNPs-Fe_3O_4 (10 mg in 1 ml distilled water). The mixture was homogenized under ultrasound irradiation for 3 min. Then, 20 ml solution of polyvinyl alcohol (1%) was added and homogenized again for 2 min. The solvent was concentrated, and the mixture was centrifuged at 6000 rpm for 15 min. The resulting solid was filtered and then dried to give the pure MNPs-Fe_3O_4/PCL–PEG–PCL.

General procedure for the preparation of 2-amino-4*H*-chromene derivatives

A mixture of the aldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), and catalyst (20 mg) was stirred at 80 °C under solvent-free conditions. The progress of the reaction was followed by TLC (*n*-hexane/ethyl acetate, 2/1). After the completion of the reaction, the catalyst was separated magnetically from the reaction mixture. The crude product was recrystallized from ethanol to give the pure compound.

Results and discussion

In continuation of our previous works on the development of new, green, and efficient reagents for the synthesis of biologically active heterocycles [26–30] herein, we wish to report the simple synthesis of 2-amino-4*H*-chromene derivatives using MNPs-Fe_3O_4/PCL–PEG–PCL as a reusable heterogeneous catalyst under solvent-free conditions (Scheme 1).

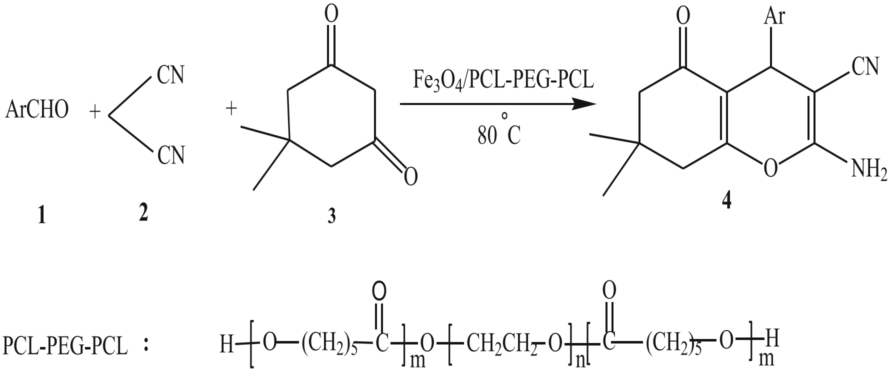
First, the catalyst was prepared from PCL–PEG–PCL copolymer and MNPs-Fe_3O_4 as explained in the experimental section and characterized by FT-IR, X-ray diffraction and SEM spectroscopy.

The FT-IR spectra of MNPs-Fe_3O_4, PCL–PEG–PCL copolymer, and synthesized MNPs-Fe_3O_4/PCL–PEG–PCL nanocomposite are given in Fig. 1. The absorption bands at 570 cm^{-1} presented in Fig. 1a was attributed to Fe–O bond. In Fig. 1c, the main bands were observed at 3439 (O–H) 2945 and 2867 cm^{-1} (C–H), 1725 (C=O), 1245 (C–O, ester group) and 1193 (C–O ether group). The FT-IR spectra of MNPs-Fe_3O_4/PCL–PEG–PCL is presented in Fig. 1b. The observed band at 1725 was attributed to ester carbonyl group of copolymer.

The XRD patterns of Fe_3O_4, PCL–PEG–PCL, and Fe_3O_4/PCL–PEG–PCL illustrate the crystalline structures of them (Fig. 2). The comparison of Fig. 2a–c demonstrates that the characteristic peaks of Fe_3O_4 did not change after coating with PCL–PEG–PCL.

The average diameter of MNPs-Fe_3O_4 was estimated approximately 55.8 nm by SEM micrograph (Fig. 3a). Fig. 3b clearly shows that MNPs-Fe_3O_4/PCL–PEG–PCL were successfully synthesized in nanoscale dimensions.

In order to consider the catalytic activity of MNPs-Fe_3O_4/PCL–PEG–PCL, the reaction of 4-nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), and dimedone



Scheme 1 One-pot synthesis of 4*H*-chromene derivatives from aldehyde (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol) catalyzed by MNPs-Fe_3O_4/PCL–PEG–PCL (20 mg) at 80 °C under solvent-free conditions

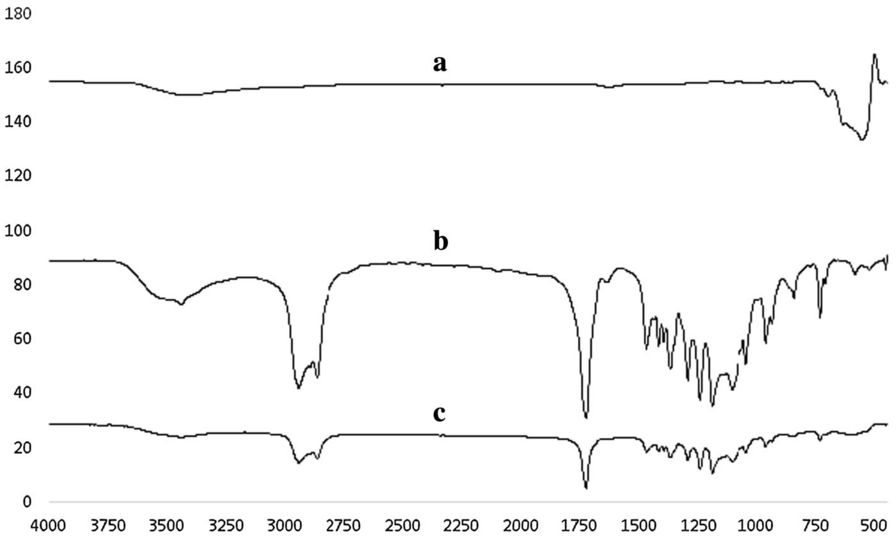


Fig. 1 The FT-IR spectra of (*a*) MNPs Fe_3O_4, prepared of $FeCl_3{\cdot}6H_2O$, $FeCl_2{\cdot}4H_2O$, and NH_4OH (*b*) MNPs-Fe_3O_4/PCL–PEG–PCL prepared from Fe_3O_4 nanoparticles, and PCL–PEG–PCL copolymer, (*c*) PCL–PEG–PCL prepared of 3-caprolactone, PEG, and Sn(Oct) at room temperature

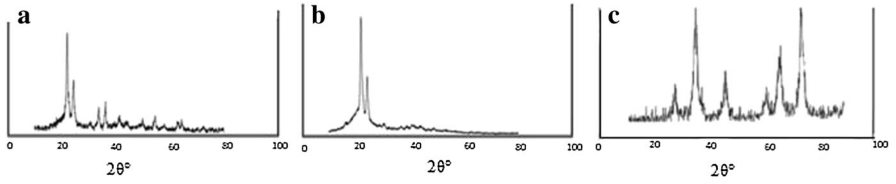


Fig. 2 The powder XRD pattern of **a** MNPs-Fe_3O_4/PCL–PEG–PCL prepared from Fe_3O_4 nanoparticles and PCL–PEG–PCL copolymer, **b** PCL–PEG–PCL prepared of 3-caprolactone, PEG, and Sn(Oct), **c** MNPs-Fe_3O_4 prepared of $FeCl_3{\cdot}6H_2O$, $FeCl_2{\cdot}4H_2O$, and NH_4OH using a Cu tube in the range of $2\theta = 10–80°$ at room temperature

(1 mmol) was selected as the model reaction and an optimization was done to identify the optimum amount of catalyst, the best solvent, and the suitable temperature (Table 1). The best result was obtained in the presence of 20 mg of the catalyst at 80 °C under solvent-free conditions (Table 1, entry 3). No product was observed in the absence of the catalyst within 20 min (Table 1, entry 7). Furthermore, the model reaction was performed in the presence of PCL–PEG–PCL and MNPs-Fe_3O_4 as the catalyst under optimized reaction conditions which led to no product formation in the case of copolymer and the reaction was performed very slowly in the presence of MNPs-Fe_3O_4 (Table 1, entries 8, 9). Therefore, it can be concluded that modified Fe_3O_4 NPs with PCL–PEG–PCL is more effective than pure Fe_3O_4 NPs for the synthesis of 4*H*-chromene derivatives.

The results in Table 1 indicate that using 20 mg MNPs-Fe_3O_4/PCL–PEG–PCL as the catalyst at 80 °C under solvent-free conditions is the most suitable condition for the synthesis of 2-amino-4*H*-chromene derivatives. After obtaining the optimum

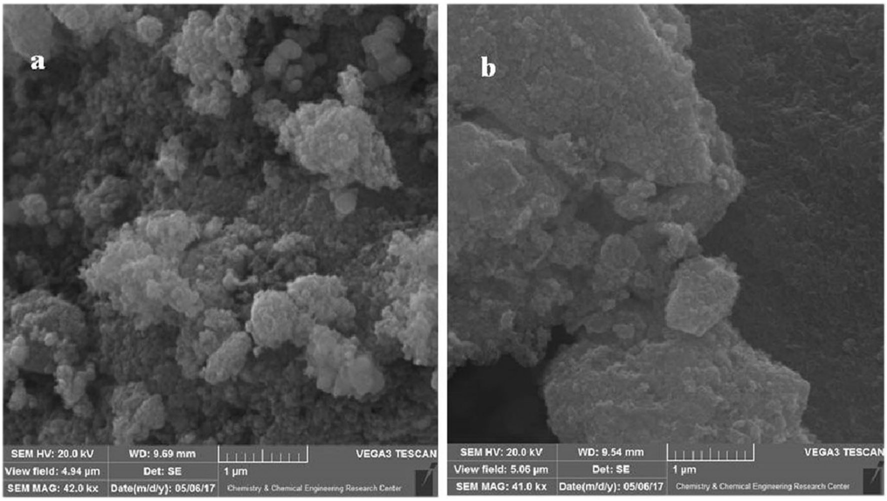


Fig. 3 SEM images of **a** MNPs-Fe_3O_4 prepared of $FeCl_3 \cdot 6H_2O$, $FeCl_2 \cdot 4H_2O$, and NH_4OH, **b** Fe_3O_4/PCL–PEG–PCL prepared from Fe_3O_4 nanoparticles and PCL–PEG–PCL copolymer at room temperature

Table 1 Optimization of reaction conditions

Entry	Solvent	Temperature (°C)	Cat. (mg)	Time (min)	Yield (%)
1	–	25	20	110	90
2	–	60	20	90	90
3	–	80	20	10	96
4	–	100	20	10	95
5	–	80	25	10	96
6	–	80	15	30	91
7	–	80	–	20	–
8	–	80	20[a]	100	–
9	–	80	20[b]	45	87
10	EtOH	Reflux	20	20	90
11	EtOH/H_2O (1:1)	Reflux	20	90	93
12	CH_3CN	Reflux	20	40	89
13	EtOAc	Reflux	20	45	100

[a] *Cat.* PCL–PEG–PCL

[b] *Cat.* Fe_3O_4

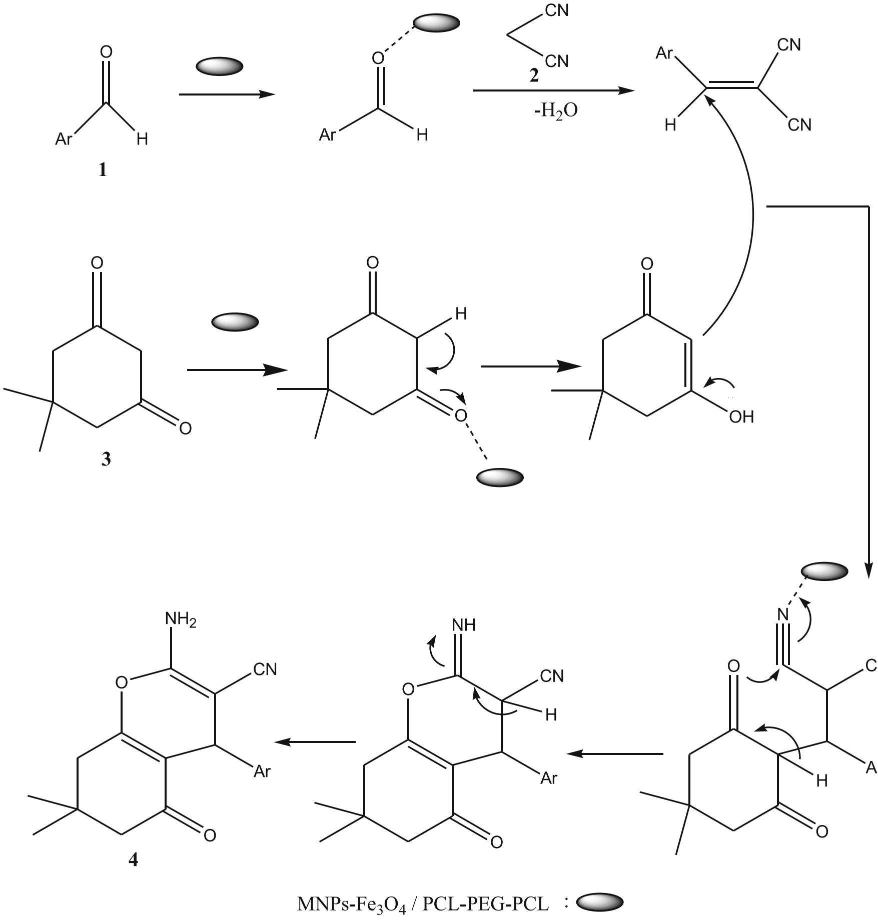
conditions, the generality of this method was studied by the reaction of various aromatic aldehydes with malononitrile and dimedone at 80 °C under solvent-free conditions (Table 2).

Most aromatic aldehydes bearing electron-withdrawing or electron donating groups reacted successfully under these conditions and the corresponding

Table 2 One-pot synthesis of 2-amino-4*H*-chromene derivatives using MNPs-Fe_3O_4/PCL–PEG–PCL

Entry	Ar	Product	Time (min)	Yield (%)[a]	mp (Lit. mp) [ref.] (°C)
1	C_6H_5CHO	**4a**	12	83	229–230 (229–231) [31]
2	4-ClC_6H_4CHO	**4b**	18	90	209–211 (212–214) [31]
3	4-$OCH_3C_6H_4CHO$	**4c**	20	87	195–197 (195) [11]
4	2-$OCH_3C_6H_4CHO$	**4d**	15	95	204–206 (205–207) [32]
5	4-$NO_2C_6H_4CHO$	**4e**	10	95	178–179 (179–180) [31]
6	3-$NO_2C_6H_4CHO$	**4f**	12	88	206–208 (206) [31]
7	4-BrC_6H_4CHO	**4g**	12	89	198–200 (197–199) [33]
8	Furan-2-carbaldehyde	**4h**	22	75	202–204 (203–205) [31]
9	Isatin	**4i**	25	89	302–304 (> 300) [31]

[a] Isolated yields



Scheme 2 A plausible mechanism for the synthesis of 2-amino-4*H*-chromene derivatives from aldehyde, malononitrile, and dimedone using MNPs-Fe3O4/PCL–PEG–PCL

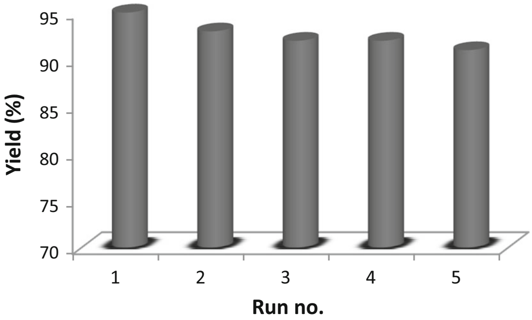


Fig. 4 Comparison of efficiency of separated MNPs-Fe_3O_4/PCL–PEG–PCL by an external magnet as catalyst in the synthesis of **4e** from 4-nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol) catalyzed by MNPs-Fe_3O_4/PCL–PEG–PCL (20 mg) at 80 °C under solvent-free conditions for five times

Table 3 Comparison of the efficiency of some catalysts used in the synthesis of 4*H*-chromene derivatives with MNPs-Fe_3O_4/PCL–PEG–PCL

Catalyst	Condition	Yield (%)	Time [ref.] (min)
MNPs-Fe_3O_4/PCL–PEG–PCL (20 mg)	Solvent-free/85 °C	75–95	10–25 [This work]
MNPs-Fe_3O_4/NH_2 (0.04 g)	Ethanol : H_2O/sonication	80–96	15–40 [33]
SBNPTT (0.1 g)[a]	Solvent-free/80 °C	75–93	10–50 [34]
Fe_3O_4/SiO_2-Met (30 mg)[b]	Ethanol, H_2O/reflux	85–94	60 [11]
ZnO (0.003 g)	Ethanol/reflux	75–95	10 [32]
Aminopropylated sillica gel (10 mol%)	H_2O/70 °C	87–96	45–120 [35]
MSNs (10 mg)[c]	EtOH/60 °C	86–98	10–45 [31]

[a] silicabonded n-propyl piperazine

[b] Metformin

[c] Mesoporous silica nanoparticles

chromenes were isolated in good to excellent yields. Furthermore, isatin produced 2-amino-7,7-dimethyl-2’,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3’-indoline]-3-carbonitrile in good yield (Table 2, entry 9).

A plausible mechanism for the synthesis of 2-amino-4*H*-chromene derivatives using MNPs-Fe_3O_4/PCL–PEG–PCL as a heterogeneous catalyst is shown in Scheme 2. First, a Knoevenagel condensation reaction between aldehyde and malononitrile is performed. In this mechanism, the role of Fe_3O_4/PCL–PEG–PCL is to activate carbonyl and nitrile groups for nucleophilic attacks.

In addition, the reusability of the catalyst was examined in the model reaction. After the completion of the reaction, the catalyst was separated by an external magnet from the reaction mixture, washed three times with 5 ml of ethanol, dried, and reused in the synthesis of **4e** for five times without a considerable loss in its catalytic activity (Fig. 4).

In order to show the importance of this study, the catalyst's efficiency was compared with some other catalysts in the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives (Table 3). The results obviously demonstrate that the preference of MNPs-Fe_3O_4/PCL–PEG–PCL over the previously used catalysts with respect to the yields and times of reactions.

Conclusion

In this study, a new, green, and efficient procedure is reported for the synthesis of 4*H*-chromene derivatives using MNPs-Fe_3O_4/PCL–PEG–PCL. The simplicity of procedure, easy separation of the catalyst, short reaction times, reusability, stability, and non-toxicity of the catalyst in addition to the high yields of products and the absence of solvent are the advantages of this methodology.

Acknowledgements We are thankful to the Islamic Azad University Arak-Branch for its financial support.

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