

β -Enaminones over recyclable nano-CoFe₂O₄: a highly efficient solvent-free green protocol

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Received: 6 February 2018 / Accepted: 24 April 2018 / Published online: 3 May 2018
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Abstract β -Enaminone and its derivatives have emerged among the finest bioactive intermediates. High yields of several β -enaminones (86–97%) are achieved through treatment of substituted aromatic and aliphatic amines with cyclic/acyclic 1,3-diketones, over the magnetically separable cobalt ferrite nanoparticles (CoFe₂O₄ NPs). The latter was prepared upon co-precipitation. Its purity, fine crystallinity, elemental distributions, morphology, magnetic features, and thermal stability were confirmed by Fourier transform infrared, X-ray diffraction, energy dispersive X-ray spectrometry, scanning electron microscopy, vibrating sample magnetometry, and thermal gravimetric analysis analyses. Thus, CoFe₂O₄ NPs acted as an excellent green heterogeneous nanocatalyst for synthesis of β -enaminones and gave good recyclability, while showing insignificant loss of their activity.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11164-018-3454-5>) contains supplementary material, which is available to authorized users.

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Graphical Abstract



Keywords Magnetic nanocatalyst · Cobalt ferrite · Bimetallic oxide · Synthons · β -Enaminones

Introduction

Bimetallic oxide nanoparticles (NPs) often show synergistic effects in catalyzing modern organic reactions [1–3]. They are involved in heterogeneous catalysis, improving the yield, simplification of reaction conditions, economic efficiency, providing high catalytic surface area, easy separation and workup, etc. In addition, the nanosize and magnetic properties of spinel ferrites have made them crucial in science and technology [4]. Nano-cobalt ferrite has attracted much attention because of its large surface-to-volume ratio, high magnetization, and magnetic behavior dependence on its size and shape [5–7]. Applications of $CoFe_2O_4$ nanocrystals involve environmental remediation, biomedical diagnosis, therapy, high-density magnetic storage, and catalytic innovative synthesis [8–10]. β -Enaminones are one of the finest bioactive intermediates. They are used for the synthesis of many important compounds including α,β -amino acids [11, 12], γ -amino alcohol [13], heterocycles [14], alkaloids [15, 16], quinolines [17], azocompounds [18], etc. β -Enaminones are employed as basic synthons for various drugs used as antitumor [19], antiepileptic [20], antibacterial [21, 22], anticonvulsant [23], antitussive [24], anti-inflammatory [25], etc. (Scheme 1).

Numerous procedures have been developed for synthesis of enaminones using different catalysts such as $ZrOCl_2 \cdot 8H_2O$ [26], $NaAuClO_4$ [27], Ag NPs [28], Cu NPs [29], $Zn(ClO_4)_2 \cdot 6H_2O$ [30], $Zn(OAc)_2 \cdot 2H_2O$ [31], $CeCl_3 \cdot 7H_2O$ [32], $ZrCl_4$ [33], SiO_2 -sulphuric acid [34], silica-supported $Fe(HSO_4)_3$ [35], bimetallic Ag–Cu alloy NPs [36], industrial-quality graphene oxide (IQGO) [37]. Here in continuation of our investigation [38, 39], we describe an economically sound, simple, and efficient protocol for the synthesis of pure β -enaminones, with minimal side-products, through the reaction of 1,3-dicarbonyl compounds and amines, using cobalt ferrite NPs as a reusable heterogeneous catalyst under solvent-free conditions (Scheme 2).

Experimental

Materials and physical techniques

All chemical reagents used in our experiments were purchased from Merck or Aldrich Chemical Company with high purity. All solvents were distilled, dried, and purified using standard procedures. Melting points were measured on an Electrothermal 9100 apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance instrument (DPX 300 MHz and DPX 75 MHz) in pure deuterated dimethylsulfoxide ($\text{DMSO-}d_6$) using tetramethylsilane (TMS) as an internal reference. Fourier transform infrared (FT-IR) spectra were recorded using KBr pellets on a Nicolet IR-100 infrared spectrometer. The powder X-ray diffraction (XRD) spectrum was recorded at room temperature using a Philips X-Pert 1710 diffractometer. The latter appeared with $\text{Co K}\alpha$ ($\alpha = 1.79285 \text{ \AA}$) with a voltage of 40 kV, a current of 40 mA, and was in the range of $20\text{--}80^\circ$ (2θ) with a scan speed of $0.02^\circ/\text{s}$. The particle morphology was examined by scanning electron microscopy (SEM) using a HITACHI S-4160 scanning electron microscope on gold-coated samples. Magnetic properties were obtained by a vibrating sample magnetometer/alternating gradient force magnetometer (VSM/AGFM, MDK Co., Iran).

Preparation of magnetic CoFe_2O_4 NPs

Initially, magnetic CoFe_2O_4 NPs were prepared by chemical co-precipitation of chloride salt of Fe^{3+} and Co^{2+} ions with a molar ratio of 2:1. Typically, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5.8 g, 0.02 mol) and CoCl_2 (1.3 g, 0.01 mol) were dissolved in 100 mL of deionized water at 80°C under N_2 atmosphere and vigorous stirring. Then, 10 mL of 25% NH_4OH was quickly injected into the reaction mixture in one portion. The addition of the base to the $\text{Co}^{2+}/\text{Fe}^{3+}$ salt solution results in immediate formation of a black precipitate of magnetic NPs (MNPs). The reaction was continued for another 60 min and the mixture was cooled to room temperature. The black precipitate was washed with doubly warm distilled water and dried in vacuum overnight.

General procedure for synthesis of β -enaminones

CoFe_2O_4 MNPs (0.01 g) were added to a mixture of 1,3-diketone (1 mmol) and amine (1 mmol) at 80°C and stirred in an oil bath for an appropriate time under solvent-free conditions. After the completion of the reaction (monitored by thin-layer chromatography), the product was extracted with hot ethanol (3 mL), catalyst was separated by an external magnet, washed several times with water and ethanol, and dried under vacuum at room temperature, to prepare for a later run.

Results and discussion

Characterization of the catalyst

In continuation of our previous work [38, 39], we report the use of CoFe₂O₄ as a heterogeneous nanocatalyst, with high efficiency for the synthesis of β -enaminones. Cobalt ferrite is prepared and characterized via FT-IR, VSM, energy-dispersive X-ray spectrometry (EDX), SEM, thermal gravimetric analysis (TGA), and XRD analyses.

FT-IR spectroscopy

Among FT-IR peaks of CoFe₂O₄, the strong absorption at 597.54 cm⁻¹ corresponds to the M–O tetrahedral site of the spinel structure and shows the basic nature of the NPs (Fig. 1). The broad bands at 3405.11 and 1628.29 cm⁻¹ are attributed to the hydroxyl groups stretching and bending vibrations of water, respectively.

X-ray diffraction

According to International Center for Diffraction Data PDF cards 3-864 and 22-1086, CoFe₂O₄ NPs have a cubic structure (Fig. 2) [40, 41]. The powder XRD pattern in the high-angle region of $5 \leq 2\theta \leq 80$ for the sample of CoFe₂O₄ shows six different peaks at 2θ about 35.1°, 41.4°, 50.9°, 63.5°, 67.5°, and 74.4° marked by their indices (220), (311), (400), (422), (511), and (440), respectively. The sharp peaks and the lack of additional peaks confirm the purity and the good crystallinity of the prepared nanocatalyst.

EDX analyses

The chemical composition of the product is further examined using EDX, which reveals Co and Fe elemental distributions in CoFe₂O₄ (Fig. 3).

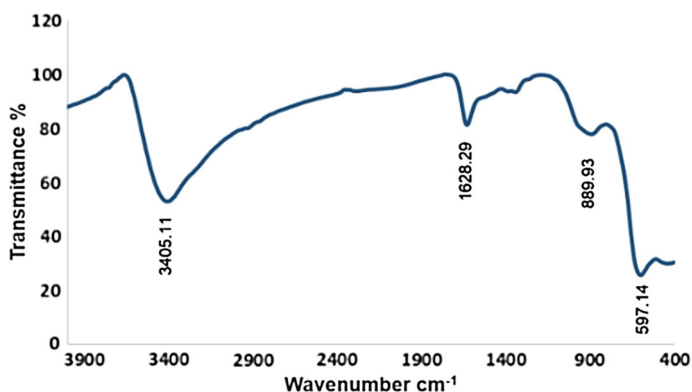


Fig. 1 FT-IR spectrum of CoFe₂O₄ NPs

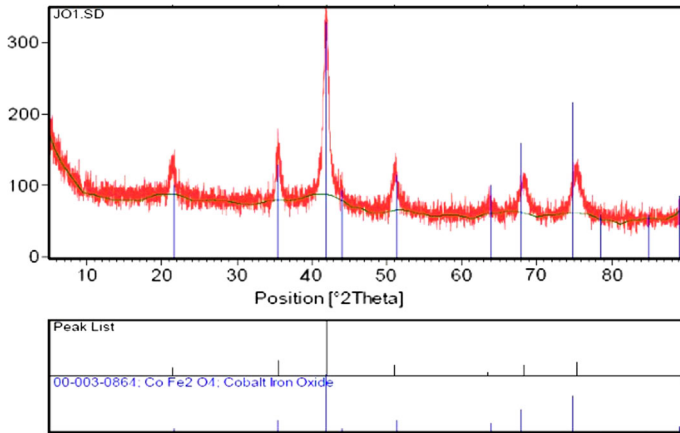


Fig. 2 XRD pattern of the catalyst CoFe_2O_4 NPs

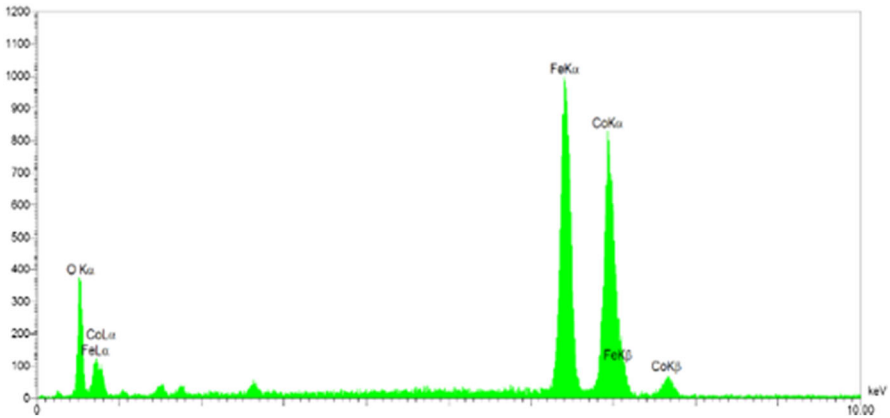


Fig. 3 Energy-dispersive spectrometry (EDX) results of CoFe_2O_4 NPs

SEM

The size and morphology of CoFe_2O_4 NPs are estimated via SEM (Fig. 4). Uniformly dispersed spherical particles are observed, along with weak agglomerations. The obtained histogram of the SEM image shows a narrow maximum particle size distribution in the range of 10–30 nm.

VSM

The magnetic features of the catalyst, which accounts for its easy recovery, is confirmed using a VSM in the range from +1 to −1 T. Room temperature-specific magnetization (M) versus applied magnetic field (H) curve measurements of the sample indicate a saturation magnetization value (M_s) of 17 emu g^{-1} (Fig. 5).

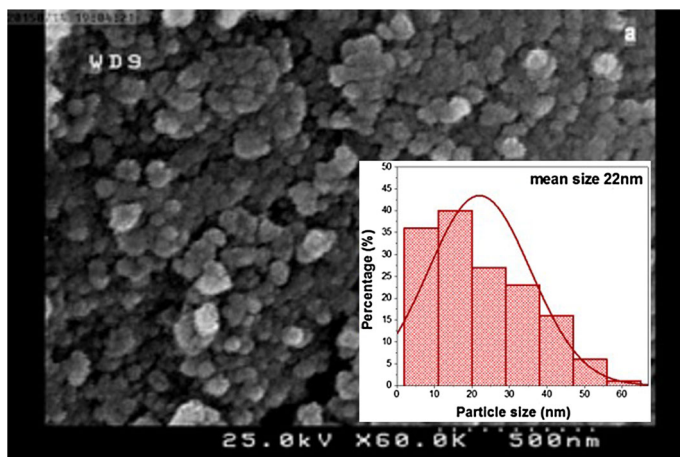


Fig. 4 SEM analysis of the CoFe₂O₄ NP catalyst

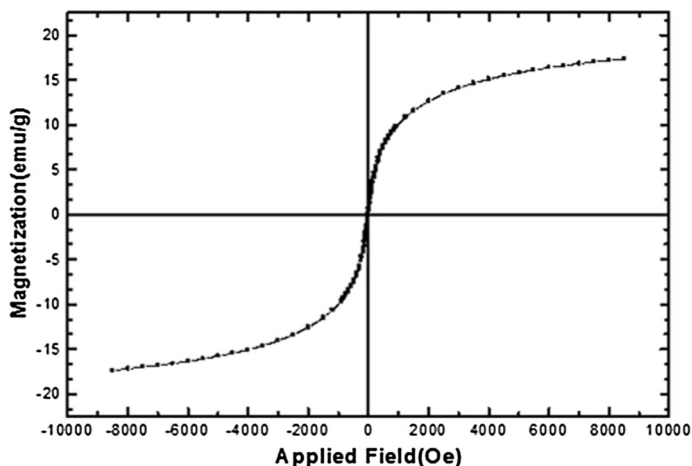


Fig. 5 Vibrating sample magnetometer curve for CoFe₂O₄ NPs

Thermal analyses

TGA/differential thermal analyses (TGA/DTA) of CoFe₂O₄ NPs are recorded over a temperature range of room temperature to 900 °C at rate of 10 °C min⁻¹ (Fig. 6). The thermogram shows an initial weight loss at 100 °C due to water desorption. The slight weight loss below 350 °C may be due to dehydration of water or loss of hydroxyl groups present on the surface of the spinel structure; no further mass loss is detected up to 800 °C, which indicates the thermal stability of the catalyst [42, 43].

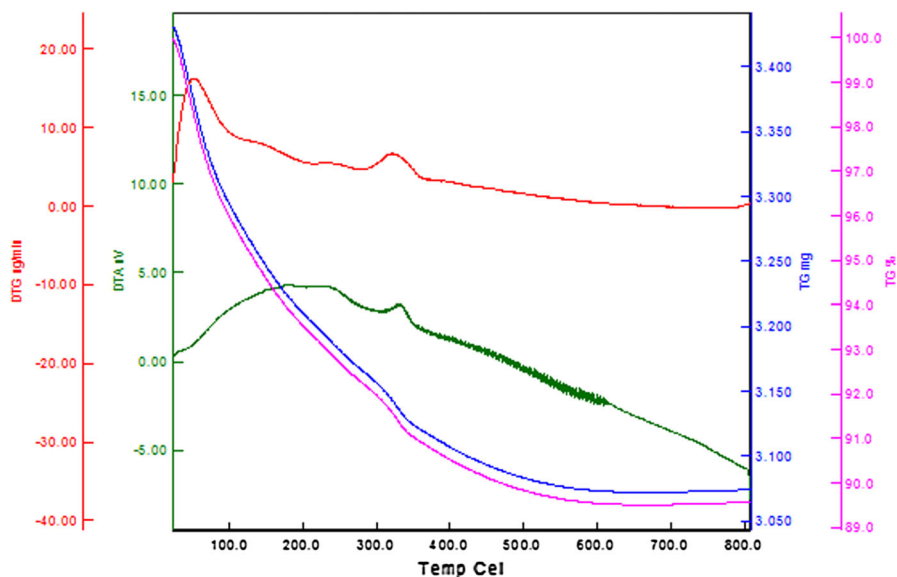


Fig. 6 TGA/DTA/differential thermogravimetry analysis of CoFe_2O_4 NPs

Catalytic activity

After characterization of CoFe_2O_4 , its activity was probed as a heterogeneous catalyst in the preparation of β -enaminones. To access the optimum conditions, we employed model reaction of acetyl acetone (1 mmol), and benzylamine (1 mmol) over various amounts of the nanocatalyst under solvent-free conditions at various temperatures (Table 1). Firstly, the effect of temperature was examined with

Table 1 Optimization of the reaction conditions

Entry	Catalyst (mg)	Temperature ($^{\circ}\text{C}$)	Time (h)	Yield (%) ^a
1	10	25	3	15
2	10	40	3	37
3	10	60	3	60
4	10	70	3	88
5	10	80	3	96
6	10	80	2	84
7	15	80	3	96
8	10	90	3	97
9	5	80	3	82
10	10	80	4	96
11	–	100	6	43
12	–	80	3	27
13 ^b	10	80	3	77
14 ^c	10	80	3	86

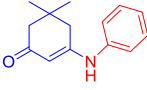
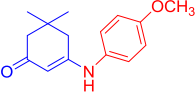
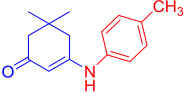
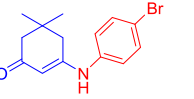
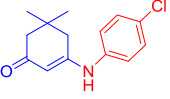
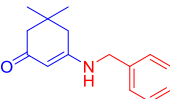
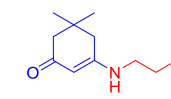
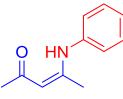
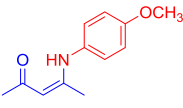
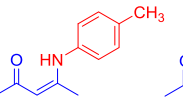
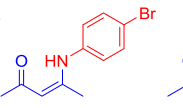
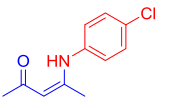

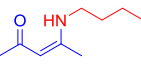
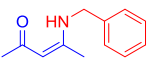
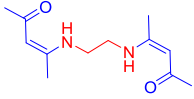
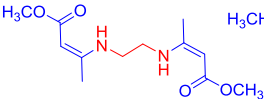
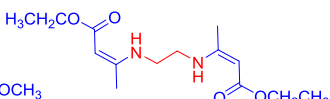
Reaction conditions: acetyl acetone (1 mmol), benzylamine (1 mmol), solvent-free

^aIsolated yield

^bReaction conditions: CoCl_2 , acetyl acetone (1 mmol), benzylamine (1 mmol), solvent-free

^cReaction conditions: $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, acetyl acetone (1 mmol), benzylamine (1 mmol), solvent-free

Table 2 Synthesis of β -enaminones in the presence of CoFe₂O₄ NPs under solvent-free condition

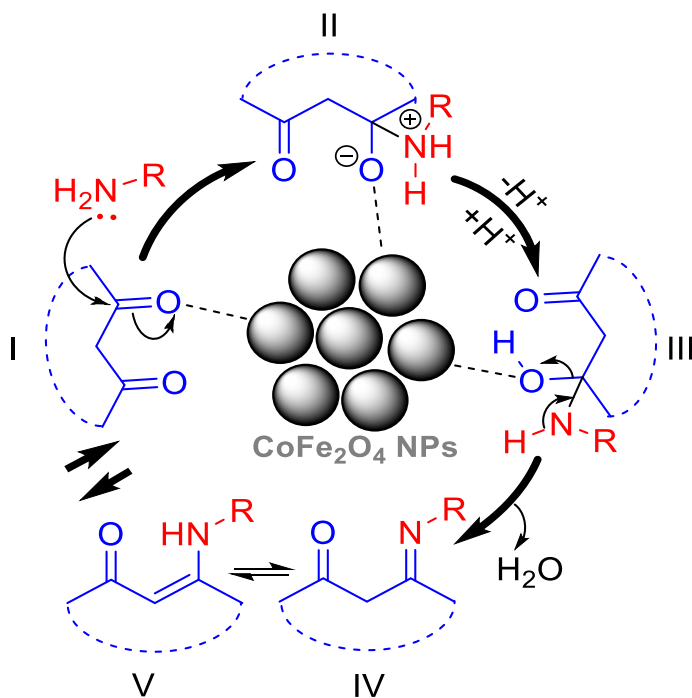
 a, 93%	 b, 90%	 c, 92%	 d, 90%	
 e, 88%	 f, 95%	 g, 94%		
 h, 92%	 i, 90%	 j, 91%	 k, 88%	 l, 86%
 m, 93%	 n, 97%	 o, 96%		
 q ^a , 91%	 y ^a , 88%	 z ^a , 87%		

Reaction conditions: 1,3-diketone (1 mmol), amine (1 mmol), solvent-free, 80 °C, 3 h

Isolated yield

^aReaction conditions: 1,3-diketone (2 mmol), amine (1 mmol), solvent-free, 80 °C, 3 h

constant amounts of the catalyst. The yield of the desired enaminones rose at higher temperatures, requiring shorter reaction times. It is noticed that the temperature plays a crucial role in the present system. A decrease in temperature results in reduced yield with traces of the product at room temperature. In order to find the effectiveness of the catalyst, the model reaction is studied with different amounts of the catalyst (5, 10, 15 mg) at various times in solvent-free conditions. The best result is obtained when the reaction reaches 96% conversion in 3 h with 10 mg of the catalyst. Increasing the amount of the catalyst from 10 to 15 mg does not significantly affect the yield of the product formed. In the absence of the catalyst, no improvement of the product yield is observed at temperatures > 80 °C. Also, to distinguish between the roles of homogeneous versus that of heterogeneous catalysts, the reactions were run under similar conditions with comparable amounts of Co²⁺, Fe³⁺, and CoFe₂O₄ NPs, giving product yields of 77, 86, and 96%, respectively (Table 1).



Scheme 3 A plausible mechanism for catalytic synthesis of β -enaminones over CoFe_2O_4 NPs

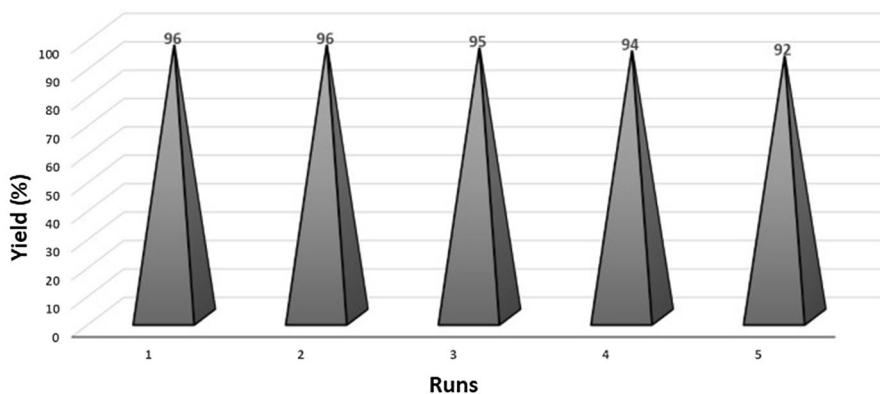


Fig. 7 Recyclability of CoFe_2O_4 NPs in catalytic synthesis of β -enaminones

Using these optimized reaction conditions, we extended the scope and efficiency of this protocol by reaction of substituted aromatic and aliphatic amines, with cyclic/acyclic 1,3-diketone (Table 2). Substituents present (electron withdrawing or electron donating) on the aromatic rings of the amines do not significantly affect the yield of the desired products. As the results indicate, this procedure is uniformly effective for both aliphatic and aromatic amines. For practical applications,

Table 3 Activity of CoFe₂O₄ NPs versus those of other catalysts in catalytic synthesis of β -enaminones

Entry	Catalyst	Condition	Yield (%) ^b	Ref.
1	Ag NPs	CH ₃ OH/60 °C/8 h	90	[28]
2	Zn(OAc) ₂ ·H ₂ O	CH ₃ OH/60 °C/48 h	86	[31]
3	Fe(NO ₃) ₃ ·9H ₂ O	CHCl ₃ /r.t./90 min	88	[44]
4	CuO NPs	60 °C/9 h	83	[45]
5	IQGO	60 °C/3 h	85	[37]
6	CoFe ₂ O ₄ NPs	80 °C/3 h	92	–

^bIsolated yield

diamines are used as nucleophiles to obtain bis-(β -enaminones) and bis-(β -enamino esters; Table 2q, y, z).

Following our plausible mechanism, CoFe₂O₄ NPs appears to act as a Lewis acid by increasing the electrophilicity of the carbonyl groups of diketones, giving I. The amine's nucleophilic attack on the activated carbonyl group of I leads to intermediate II. Subsequent loss of water from III affords imine IV, which may render V through tautomerisation (Scheme 3).

Upon completion of the reactions, potential catalyst recycling was probed using the model reaction under described reaction conditions. After completion of the reaction, the catalyst was readily separated by an external magnet and washed with ethanol. It was dried under vacuum and reused directly in the next cycle where no significant loss of its activity was observed (Fig. 7).

In order to investigate the efficiency of this procedure in comparison with known methods reported in the literature, the activity of CoFe₂O₄ NPs was probed against others in catalytic synthesis of (*Z*)-4-(phenylamino)pent-3-en-2-one (Table 3).

Conclusion

In continuation of our attempts to make important synthons for biological compounds, a heterogeneous nanocatalyst, CoFe₂O₄ NPs, was fabricated and fully characterized. Subsequently, it was employed in an efficient, one-pot, solvent-free preparation of a number β -enaminone derivatives with minimal side-products (86–97%). Specifically, this achievement was reached through treatment of substituted aromatic and aliphatic amines with cyclic/acyclic 1,3-diketones over the magnetically separable CoFe₂O₄ NPs. Other than high yields, the nanocatalyst offers several promising advantages, including short reaction time, easy handling, simple work up procedure, product purity, ease of separation, and recyclability of the catalyst. A control test involving comparable amounts of Co²⁺, Fe³⁺, and CoFe₂O₄ NPs under similar conditions clearly indicated higher efficiency of the latter heterogeneous nanocatalyst over the former homogeneous ions. The magnetic properties of CoFe₂O₄ NPs help easy separation from the reaction mixture. The introduced magnetically stable nanocatalyst could be reused in five successive runs with no significant structural change or loss of activity.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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