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ARTICLE TYPE

Biginelli reaction on Fe_3O_4-MWCNT nanocomposite: excellent reactivity and facile recyclability of the catalyst combined with ultrasound irradiation

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A highly efficient and improved synthetic methodology for the preparation of Dihydropyrimidinone derivatives using β-dicarbonyl compound, urea/thiourea and aromatic aldehydes using Fe_3O_4-MWCNT as a nanocatalyst under ultrasound irradiation is reported. The present method has promising features for the reaction response such as the shortest reaction time, excellent product yields, simple work-up procedure and operational simplicity. The advantages of this novel protocol as compared to other synthetic methods, are clean conversion, the amount of catalyst, high catalytic activity and ease of recovery from the reaction mixture using an external magnet, and several reuse times without significant losses in performance.

1. Introduction

Dihydropyrimidinones (DHPMs) and their derivatives, outcomes of the Biginelli reaction, are very important pharmacologically active molecules and have found applications as calcium channel blockers, α_{1a}-adrenrgic antagonists, antihypertensive agents, inhibitors of the fatty acid transporter, and mitotic kinesin inhibition.[1] Also, batzelladine alkaloids containing dihydropyrimidines core have been found to show potent anti-HIV activity.[2] The most simple and straight forward procedure for the synthesis of dihydropyrimidinones originally reported by Biginelli in 1893, involves the acid-catalyzed one-pot condensation of α,β-keto ester with an aldehyde and urea derivatives.[3] However, the yields of products were very low (just 20–50%).

This great biological importance of these heterocyclic compounds has prompted the development of new improved methodologies for Biginelli reaction, including transition metal Lewis acid catalysis,[4] solid phase synthesis,[5] ionic liquids,[6] activation with certain additives,[7] microwave-assisted synthesis technique,[8] ultrasound irradiation,[9] solvent-free techniques,[10] grinding techniques,[11] and many new catalysts.[12]

Recently, have witnessed an exponential growth in the applications of heterogeneous catalysis in organic reactions to carry out synthetic transformations as a consequence of its significance in terms of enviro-economical and practical aspects.[13] Among the heterogeneous catalysts, magnetic nanoparticles (MNPs) have emerged as a new class of heterogeneous nanocatalyst for organic process. An important feature of these nanocatalysts is simple separation of them using an external magnet without filtration.[14-16]

However, these nanoparticles have a great tendency to deform and aggregate during the course of chemical reactions and as a result the thermal and chemical stability of these nanostructures changes. The thermal and chemical stability of these nanoparticles play pivotal roles in tuning their properties in advanced applications especially catalytic activity.[16,17] Therefore, a large number of research on stabilizing magnetic nanoparticles have been carried out.[18–20] Most importantly in the field of molecular catalysis, the MNPs-supported catalysts show high catalytic activity and reusability and high degree of chemical stability in organic solvents.[21–24]

Recently, carbon nanotubes (CNTs) have been considered as catalyst supports for catalytic procedures due to their intriguing nanoscale dimensions, electrical properties, high specific surface area, uniform nanostructure, thermal and chemical stability.[25,26] Immobilization of magnetic nanoparticles using CNTs has drawn favorable attention because it prevents agglomeration and therefore enhances their performances.[27] Also, CNTs can serve not only as supports but also as components with synergistic and hybrid properties.[28,29]

Environmental concerns in chemical research are ever increasing. On the other hand, greener process involves mainly clean solvents or solvene-free, ultrasound irradiation and microwave irradiation. Ultrasound-assisted organic synthesis (UAOS) has increasingly been used in modern synthetic chemistry owing to its green credentials, because of its advantages including shorter reaction times, milder reaction conditions, higher yields, improved selectivity and clean reaction in comparison to classical

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methods.[30-32] During the ultrasound procedure in organic synthesis, intense local heating, high pressures, and extremely rapid cooling rates were produced by bubble collapse, based on acoustic cavitation resulting from the continuous formation, growth and implosive collapse of the bubbles in a solution. Chemical reactions could be droved by the transient and localized hot spots.[30-35]

In the context of our ongoing research project on the development of green methodologies for the synthesis of heterocyclic compounds of biological importance and the use of magnetic nanocatalysts in organic reactions.[36,37] here we would like to report for the first time, an effective improved synthetic method for the preparation 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones via the one-pot condensation an aromatic aldehyde, β-dicarbonyl compound, urea or thiourea, and Fe_3O_4-MWCNT as magnetic nanocatalysts under ultrasound irradiation (Scheme 1).

< Scheme 1>

2. Results and discussion

The first step entails the synthesis of highly stable Fe_3O_4-MWCNT. The preparation procedure of Fe_3O_4-MWCNTs is illustrated in scheme 2.[38] As it shows, acid-treated MWCNTs are functionalized with negative carboxylic groups which have affinity with positive ferrous and ferric ions. After the addition of NH_3 aqueous solution, Fe_3O_4 nanoparticles will be formed on the surface of MWCNTs.

<Scheme 2>

The XRD patterns of oxidized MWCNTs and Fe_3O_4-MWCNT nanocomposites are shown in Fig.1. The diffraction of the Fe_3O_4 nanoparticles observed in nanocomposite including the peaks at 2θ=26.30°, 30.54°, 35.92°, 43.62°, 54.02°, 57.54° and 63.16°in Fig. 1 (a). These data are in good agreement with that of Fe_3O_4 particles (JCPDS card No. 88-0315) reported before. The broad peak located at approximately 2θ = 26.2° is characteristic of a MWCNTs in Fig. 2 (b) (JCPDS card No. 75-1621).[38]

<Fig. 1>

Typical TEM micrographs for the oxidized MWCNTs and SEM of Fe_3O_4-MWCNT are shown in Fig. 2. The MWCNTs with tubular structure have the diameters of 20–40 nm and lengths of several microns (Fig. 3 (a)). The Fe_3O_4 nanoparticles are deposited onto the surface of MWCNTs under ultrasonication process (Fig. 3 (b) and (c)).

<Fig. 2>

Typical magnetization curve as a function of applied field at room temperature (300 K) are shown in Fig. 3. The Fe_3O_4-MWCNT nanocomposites have a saturated magnetization of *Ms* 31.2 emu/g. Also, there is no pronounced hysteresis loop, which indicates that both the retentivity and the coercivity of the composites are zero.[38]

<Fig. 3>

To investigate the catalytic activity of Fe_3O_4-MWCNTs composites, we carried out the Biginelli reaction between benzaldehyde, ethyl acetoacetate, and urea as the model under various conditions and ultrasound irradiation. When the molar ratio is 1:1:1.5, the reaction gave the best results. A wide variety of iron catalysts including $FeCl_3.6H_2O$ $FeCl_2{\cdot}4H_2O$, bulk Fe_3O_4, nano-Fe_3O_4, MWCNT and Fe_3O_4-MWCNTs were employed for sonochemically synthesis of **4a** at 40 ˚C. The results are presented in Table 1. When $FeCl_3.6H_2O$ and $FeCl_2{\cdot}4H_2O$ was used as a catalyst, the Biginelli condensation products were obtained in low yields. Also in some cases the products could not be isolated and the catalyst could not be reused for further cycles. When we used bulk Fe_3O_4 the yield becomes still lower with no reusability of the catalyst. However, when the reaction was conducted in the presence of nano-Fe_3O_4 catalyst the yield of the condensation product was increased from 30% to 55%. But due to the colloidal nature of the Fe_3O_4 nanocatalyst it was reused for only three cycles. It was noted that when Fe_3O_4 nanoparticles were immobilized into MWCNTs (having high surface area) the catalytic activity of the nanocatalyst becomes much higher than that of the corresponding nano-Fe_3O_4 catalyst. Moreover, in this case the magnetic nanocatalyst can be recycled 15 times and magnetic separation was easily achieved by using a simple bar magnet. The difference in the catalytic activity between the simple and supported catalytic systems might be explained on the basis of the highly dispersed Fe_3O_4 on MWCNT. Interestingly, when the reaction was carried out in the presence of (0.03 g) Fe_3O_4-MWCNTs, it led to the desired product in 75% yield (Table 1, Entry 5).

<Table 1>

The results indicated that the solvents had a significant effect on the Biginelli product yield. The use of dichloromethane as solvent gave poor yields (Table 2, Entry 1). Solvents like CH_3CN DMF, and toluene gave moderate yields (Table 2, Entries 2, 3 and 4). The best conversion was observed when the reaction was performed in EtOH (Table 2, Entry 9). Based on these results, EtOH was then selected as the solvent for the Biginelli condensation. The effect of reaction temperature on the model reaction in the presence of Fe_3O_4-MWCNTs under ultrasound irradiation was also observed. As shown in Table 2, when the temperature was 50 ˚C, the yield of **4a** was 98%. Consequently, the reaction temperature played an efficient role in this reaction.

<Table 2>

To test the generality of this Biginelli reaction, various aldehydes were used. As shown in Tables 3, a series of aromatic aldehydes were successfully employed to prepare the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones in excellent yields. Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving excellent yields.

<Table 3>

The possible reaction pathway for the Biginelli condensation mediated by Fe_3O_4-MWCNTs is outlined in scheme 3. The electrophilicity of the carbonyl carbon atom of both aldehyde and active methylene compound (here ethyl acetoacetate) increases through coordinate bonds owing to Fe_3O_4 empty orbital. Then the aromatic aldehyde and ethyl acetoacetate undergo aldol type condensation to offer the corresponding aldol-type product. Moreover, electron deficient sites present at the surface of the Fe_3O_4 nanoparticle grafted MWCNTs could coordinate with the N-donor sites of urea and activate it for the 1,4-addition reaction of urea. This leads to the aldol type intermediate (A) to generate ureides (B) that ultimately cyclize to Biginelli products (C) with the elimination of a water molecule.[42] Here the role of the magnetic nanoparticles is firstly easy magnetic recovery and

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separation. Further, the surface Fe-sites in the Fe_3O_4 grafted nanocatalyst could stabilize the urea molecules by adsorbing at its surface, which facilitates the reaction, and the high surface area of the supporting mesoporous host is necessary for the high turn-over frequency of the reaction.[42]

<Scheme 3>

Magnetic separation is a more attractive and simple technique than the filtration or centrifugation techniques as it prevents the loss of the nanocatalyst and increases the reusability of the nanocatalyst. The recycling performance of the Fe_3O_4-MWCNTs in the model reaction was also inverstigated. Surprisingly, this catalyst demonstrated excellent recoverability and reusability. After completion of the reaction, the isolated Fe_3O_4-MWCNTs was washed with ethyl acetate, oven dried and then directly used for the next cycle reaction without further purification. The recycled catalyst could be reused 15 times without any significant loss of its activity under ultrasonication (Fig. 4).

< Fig. 4>

3. Experimental

3.1. Chemicals and apparatus

Chemical reagents in high purity were purchased from Merck and Aldrich and were used without further purification. MWNTs were purchased from Nanotech Port Co. (Taiwan). These MWNTs were produced via the chemical vapor deposition (CVD, or sometimes called catalytic pyrolysis) method. The outer diameter of CNT was between 20–40 nm. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. FT-IR spectra were obtained with potassium bromide pellets in the range 400-4000 cm^{-1} with a Perkin–Elmer 550 spectrometer. The element analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin–Elmer 240c analyzer. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (CuK, radiation, λ= 0.154056 nm), at a scanning speed of 2°/min from 10° to 100° (2θ). Transmission electron microscopy (TEM) images were obtained on a Philips EM208 transmission electron microscope with an accelerating voltage of 100 kV. Scanning electron microscope (SEM) was performed on a FEI Quanta 200 SEM operated at a 20 kV accelerating voltage. The samples for SEM were prepared by spreading a small drop containing nanoparticles onto a silicon wafer and being dried almost completely in air at room temperature for 2 h, and then were transferred onto SEM conductive tapes. The transferred sample was coated with a thin layer of gold before measurement. Purity of the compounds synthesized was monitored by TLC, visualizing with ultraviolet light. Sonication was performed in Shanghai Branson-BUG40-06 ultrasonic cleaner (with a frequency of 35 kHz and a nominal power 200 W). A circulating water bath (DC2006, Shanghai Hengping Apparatus Factory) with an accuracy of 0.1 K was adopted to keep the reaction temperature at a constant. The known products were characterized by ^1H and ^{13}C NMR, IR data and melting point respectively and compared with the reported values. All yields refer to isolated products after purification.

3.2. Catalyst preparation

Fe_3O_4-MWCNT were prepared using chemical coprecipitation described in the literature.[38] The MWCNTs were treated by adding 30 mL of sulfuric and nitric acid mixture (3:1 in volume) in an ultrasonic bath at 60 °C for 5 h. The mixture was diluted by distillated water and it was filtrated. The acid-treated MWCNTs was washed by distillated water and dried by vacuum oven. Next, 48 mg acid-treated MWCNTs were dispersed in 30 mL of distilled water by sonication for 30 min. Then 40.5 mg of $FeCl_3$-$6H_2O$ and 60 mg of $FeCl_2$-$4H_2O$ were added g for 30 min under Ar atmosphere. 4 ml of concentrated NH_3-H_2O diluted with 20 mL of distilled water was added into the mixture and then the solution was heated to 60 °C for 2 h. The reaction mixture was then centrifuged, washed with distilled water and dried at 50 °C.

3.3. General procedure for Fe_3O_4-MWCNTs mediated synthesis of dihydropyrimidinones /thiones via Biginelli condensation under ultrasound irradiation

In a two-necked flask, a solution of benzaldehyde (1 mmol, 106 mg), ethyl acetoacetate (1 mmol, 132 mg) and urea (1.5 mmol, 90 mg) in 5 ml of absolute ethanol, the Fe_3O_4-MWCNTs nanocatalyst (30 mg) was sonicated at 50 °C, for appropriate times (monitored by TLC). After completed reaction magnetic catalyst was separated by an external magnet. The reaction mixture was evaporated to remove solvent The residue was stirred in water (3×15 mL) and then filtered. The solid was washed with hexane (3×15 mL) and re-crystallized from ethanol to give the pure product.

4. Conclusions

We have developed Fe_3O_4-MWCNT nanocomposits as a robust, and magnetically recoverable heterogeneous catalyst for the one-pot Biginelli condensation for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones under ultrasound irradiation. The magnetic nature of this heterogeneous nanocatalyst allows for its easy separation from the reaction mixture by using a simple bar magnet. This method offers several advantages including green procedure, short reaction time, excellent yields, and simple work-up, ease of separation, as well as the ability to tolerate a wide variety of substitutions in the reagents.

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Table 1. Screening of iron catalysts for the formation of **4a.**[a]

Entry	Catalyst (g)	Time (min)	Yield (%)
1	$FeCl_3.6H_2O$ (0.03)	45	35
2	$FeCl_2{\cdot}4H_2O$ (0.03)	45	25
3	bulk Fe_3O_4 (0.03)	40	40
4	nano-Fe_3O_4 (0.03)	35	50
5	MWCNTs	40	35
6	Fe_3O_4-MWCNTs (0.03)	35	75
7	Fe_3O_4-MWCNTs (0.02)	35	50
8	Fe_3O_4-MWCNTs (0.025)	35	62
9	Fe_3O_4-MWCNTs (0.035)	35	75
10	None	120	-

[a] Under ultrasonic waves at 40 °C in EtOH.

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Table 2. The effect of solvent and temperature on the synthesis of **4a**.

Entry	Solvent	T/°C	Time (min)	Yield (%)
1	CH_2Cl_2	40	50	25
2	CH_3CN	40	35	65
3	DMF	40	35	67
4	PhMe	40	35	70
5	THF	40	40	45
6	EtOH	40	35	75
7	EtOH	30	40	58
8	EtOH	45	20	85
9	**EtOH**	**50**	**20**	**98**
10	EtOH	55	20	98
11	EtOH	60	20	97

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Table 3. Synthesis of dihydropyrimidinones (thiones) catalyzed with Fe$_3$O$_4$-MWCNTs in EtOH under ultrasound irradiation at 50 ˚C.

Entry	Ar	X	R^1	Product	Time (min)	Yield (%)	M.p (˚C)		Ref.
							Foun	**Reporte**	
1	Ph	O	OEt	**4a**	20	98	205-206	204-206	39
2	3-Cl-C$_6$H$_4$	O	OEt	**4b**	25	98	195-196	194-196	40
3	3-NO$_2$-C$_6$H$_4$	O	OEt	**4c**	20	97	222-224	222-224	40
4	2-Tiophen	O	OEt	**4d**	20	96	215-217	216-218	41
5	Ph	S	OEt	**4e**	20	93	205-206	206-207	39
6	4-OMe-C$_6$H$_4$	S	OEt	**4f**	30	90	151-152	150-152	39
7	Ph	O	Me	**4g**	20	96	213-214	212-215	39
8	Ph	S	Me	**4h**	25	94	220-221	220-222	39
9	4-OMe-C$_6$H$_4$	S	Me	**4i**	25	90	169-170	168-170	39
10	3-NO$_2$-C$_6$H$_4$	S	Me	**4j**	25	88	210-212	210-212	39

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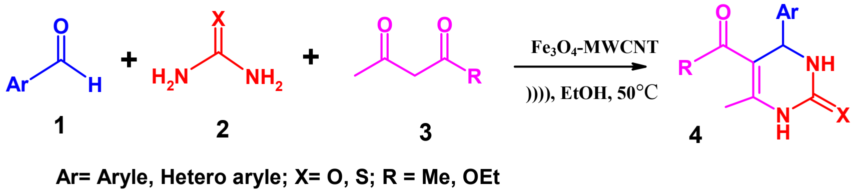

Scheme 1. Synthesis of dihydropyrimidinones under ultrasound irradiatin.

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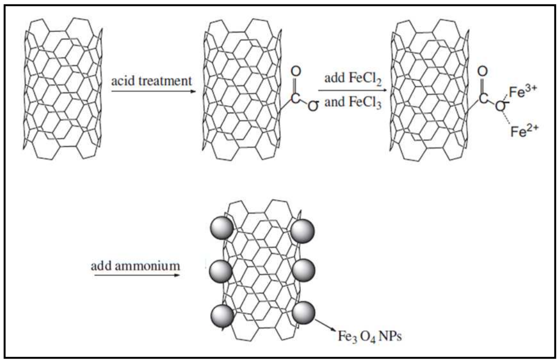

Scheme 2. Simplified schematic representation of the preparation of Fe_3O_4-MWCNTs.[38]

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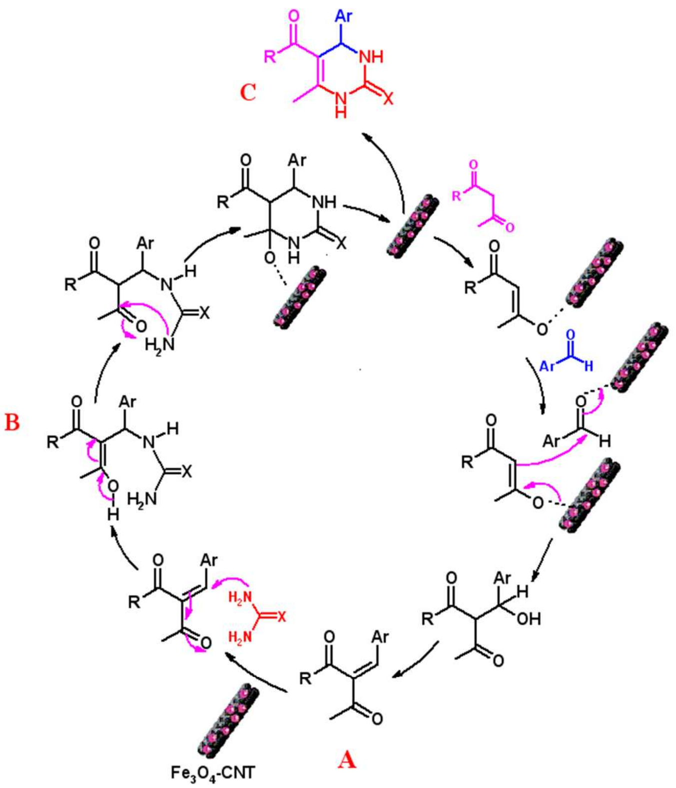

Scheme 3. Catalytic cycle for the Biginelli condensation reaction.

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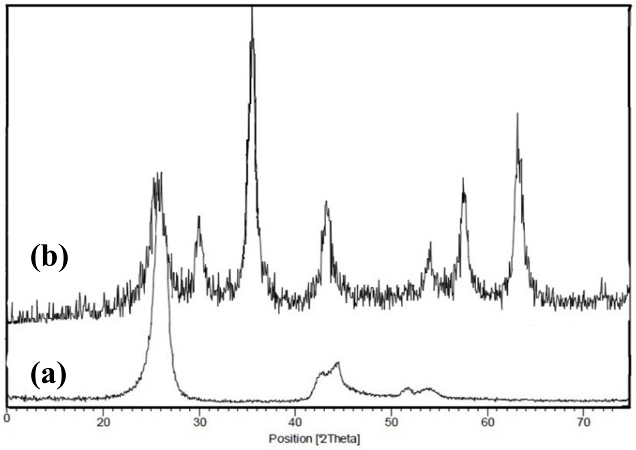

Fig. 1. XRD scattering patterns of: (a) functionalized CNTs; (b) Fe_3O_4-MWCNTs composites.

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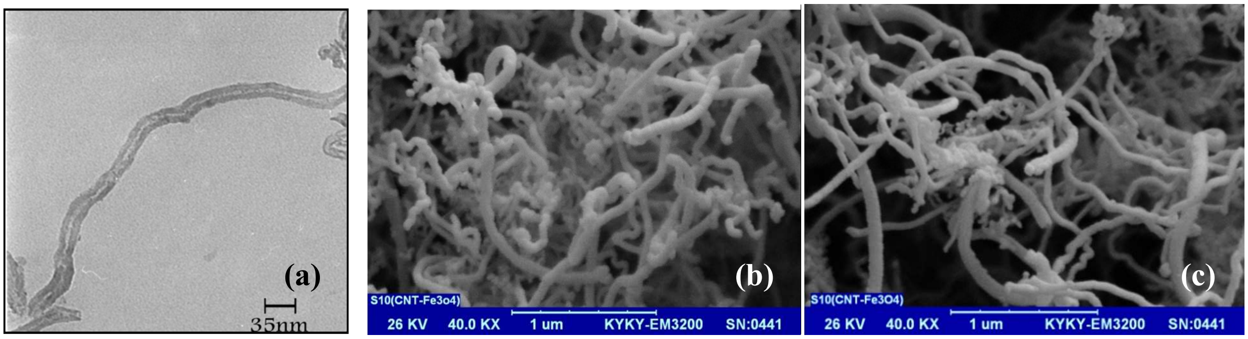

Fig. 2. Images of the samples (a) TEM of the pristine MWCNTs, (b) and (c) SEM of Fe_3O_4-MWCNTs.

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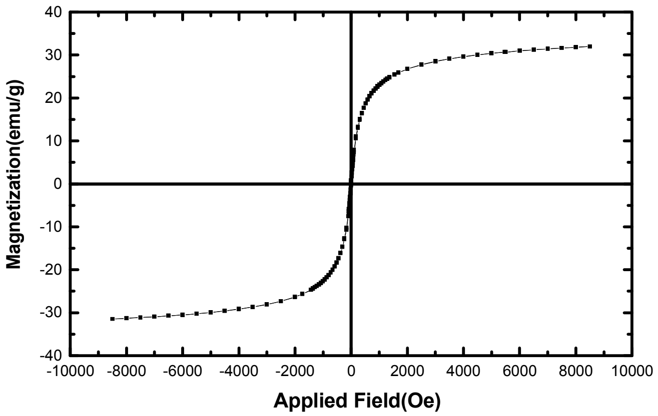

Fig. 3. Magnetization curve for the Fe_3O_4-MWCNTs at room temperature.

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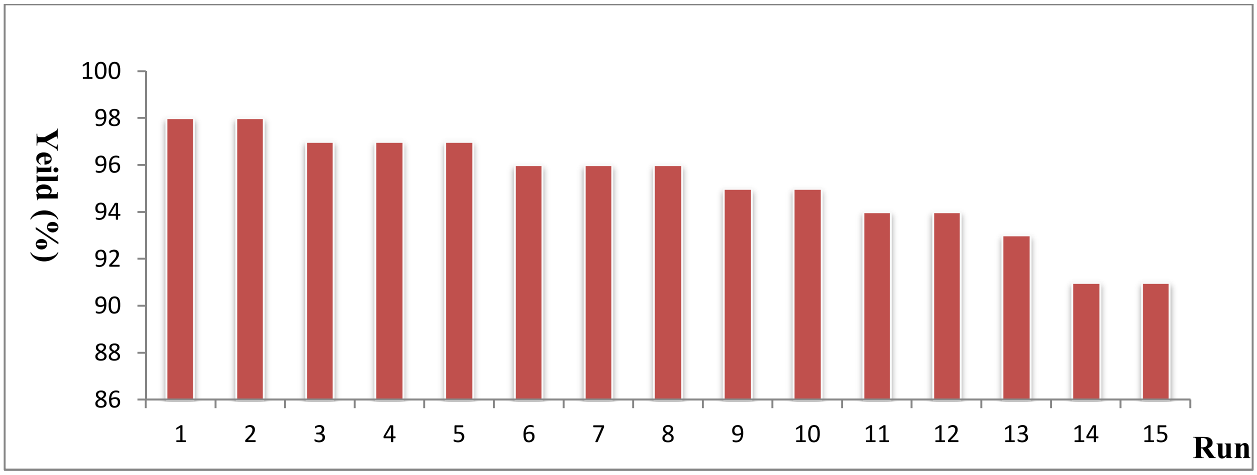

Fig. 4. Reusability and recycling of nanocatalyst for synthesis of **4a** under ultrasound irradiation.

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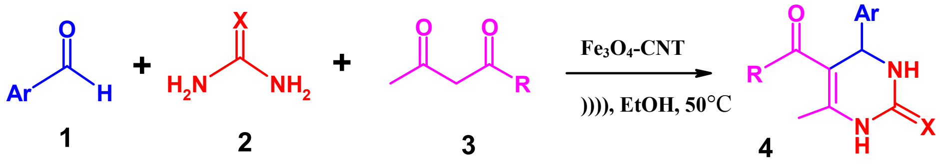
Graphical Abstract

Biginelli reaction on Fe_3O_4-MWCNT nanocomposite: excellent reactivity and facile recyclability of the catalyst combined with ultrasound irradiation

Javad Safari, Zohre Zarnegar



Ar= Aryle, Hetero aryle; X= O, S; R = Me, OEt