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ORIGINAL ARTICLE

Ultrasound-assisted synthesis of β -amino ketones via a Mannich reaction catalyzed by Fe_3O_4 magnetite nanoparticles as an efficient, recyclable and heterogeneous catalyst



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Abstract In this study, magnetite nanoparticles (Fe_3O_4 MNPs) were introduced as a heterogeneous novel catalyst for ultrasound-assisted stereoselective synthesis of β -amino carbonyl during Mannich reaction. For this propose, MNPs with particle size lower than 40 nm were synthesized via a chemical precipitation method. The prepared MNPs were characterized by IR, XRD and SEM and the applicability of the synthesized MNPs for catalysis of Mannich reaction was investigated. An orthogonal array design (OAD) was employed to study the effects of various parameters on the reaction conditions. In order to have the highest reaction yield, the effects of various experimental parameters (four parameters at four levels) including the type of solvent, temperature, amount of catalyst (MNPs) and reaction time were studied with the orthogonal array design method and optimized.

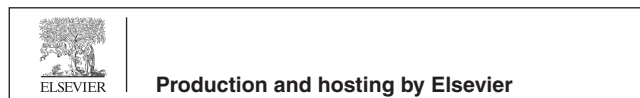
The present methodology offers several advantages, such as good yields, short reaction times and a recyclable catalyst with a very easy work up. In addition, the obtained results indicated that MNPs can be used as an effective and inexpensive catalyst for stereoselective synthesis of β -amino carbonyl by a one-pot three component condensation of aldehydes, ketones and amines.

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1. Introduction

The development of catalyst for synthetic methods has become an important research area, aiming to make the synthesis simpler, to save energy and to prevent toxicity in chemical processes. Many organic catalysts (especially the homogeneous catalysts) are ecologically harmful and their use should be minimized. Therefore, the applications of heterogeneous catalysts are better selection than homogeneous ones.

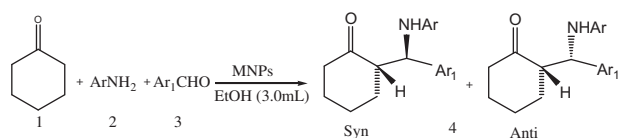


Figure 1 One-pot three-component direct Mannich reaction.

Magnetic nanoparticles (MNPs) are useful in several fields such as analytical biochemistry, (Taylor et al., 2000) medical science (Jiang et al., 2005), biotechnology (Kim et al., 2006) and particularly in the organic reactions, where they can be used as a catalyst in stereoselective reactions.

In this work, Fe_3O_4 of MNPs was used as a heterogeneous and efficient catalyst for the ultrasound-assisted synthesis of β -amino carbonyl compounds (Mannich reaction) through a one-pot, three-component reaction of aldehydes, amines and ketones. The Mannich reaction is an important method for the synthesis of β -amino carbonyl compounds, which are significant synthetic intermediates for various pharmaceuticals and natural products (Notz et al., 2003). In addition, recent development in using a three-component protocol made the Mannich reaction even more valuable in asymmetric synthesis (Chen et al., 2008; Liu et al., 2007; Das et al., 2009; Samet et al., 2009; Wang et al., 2009; Sharghi and Jokar, 2010).

MNPs are stable, inexpensive, experimentally convenient and safe reagents, which can be easily synthesized and employed for many organic reactions. From an environmental point of view, MNPs offer advantages due to the easy recovery of the reaction without filtration or centrifugation. To the best of our knowledge, the direct Mannich type reaction catalyzed by MNPs has not previously been reported.

In this study, the MNPs are introduced as an effective and highly stereoselective catalyst for the one-pot synthesis of β -amino carbonyl compounds via a multicomponent reaction of aryl aldehydes, anilines, and cyclohexanone or acetophenone (Fig. 1).

2. Experimental

2.1. Materials and apparatus

All chemicals were purchased from Fluka and Merck (Darmstadt, Germany). For mixing chemicals, a universal Ultrasonic DSA100-SK₂ was used. SEM images were obtained with a XI-300 scanning electron microscope (Philips, Japan). IR spectra were determined on a Shimadzo FTIR-470 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on 300 MHz Bruker DRX-500 spectrometers with solutions in CDCl_3 in the presence of tetramethylsilane as internal standard. X-ray diffractometer pattern of synthesized MNPs was obtained with an X-ray diffractometer (JCPDS No. 19-629). Melting points were obtained by a thermo scientific 9100 apparatus. For separation of magnetic catalyst from the solution a Nd-Fe-B strong magnet ($10 \times 5 \times 4$ cm, 1.4 Tesla) was used and magnetic properties were analyzed using a vibrating sample magnetometer (VSM, LDJ 9600).

For the synthesis of β -aminocarbonyl compounds, a mixture of benzaldehyde (2.5 mmol), aniline (2.5 mmol), cyclohexanone or acetophenone (3.0 mmol) and MNPs (1.0 – 1.5 mg mL^{-1}) was sonicated in ethanol (3.0 mL) at room tem-

perature for 30–75 min and the reaction products were monitored with TLC. After completion of the reaction, the products which connected to MNPs were separated from the solution with a permanent magnet. Finally, the reaction product was eluted from the MNPs with hot ethanol and the catalyst was removed by a permanent magnet. Then, in order to crystallize the product, the ethanolic solution containing product was kept at room temperature. Finally, the collected product was filtrated and washed via ethanol (95%).

2.2. Synthesis of Fe_3O_4 MNPs

Fe_3O_4 MNPs were chemically synthesized with a little modification in the methodology already described in the literature (Faraji et al., 2010). Briefly, 6.3 g $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, 4.0 g $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and 1.7 mL HCl (12 mol L^{-1}) were dissolved in 50 mL of deionized water in a beaker in order to prepare the stock solution of ferrous and ferric chloride. After that, the solution was degassed with argon gas and heated to 80°C in a reactor. Simultaneously, 250 mL of a 1.5 mol L^{-1} ammonia solution was slowly added to the solution under argon gas protection and vigorous stirring (1000 rpm). During the process, the solution temperature was kept constant at 80°C and argon gas was purged to prevent the intrusion of oxygen. After completion of the reaction, the obtained precipitate of Fe_3O_4 MNPs was separated from the reaction medium by the magnetic field, and then was washed four times with 500 mL doubly distilled water. Finally, the obtained Fe_3O_4 MNPs were resuspended in 500 mL of degassed deionized water. The concentration of obtained Fe_3O_4 MNPs was 6.2 mg mL^{-1} .

2.3. General procedure for the synthesis of β -aminocarbonyl compounds using cyclohexanone

Under the optimum conditions, a mixture of benzaldehyde (2.5 mmol), aniline (2.5 mmol), cyclohexanone (3 mmol) and MNPs (4.0 mg) was sonicated in ethanol (3.0 ml) at room temperature for 45 min. The reaction products were monitored by TLC. After completion of the reaction, products were separated from solution and characterized by FTIR, ^1H NMR and ^{13}C NMR and were identified by comparison of the spectral data and melting points with those reported in the literature. To show the generality and scope of this new protocol, different aromatic aldehydes and aromatic amines were used as bearing electron-withdrawing and electron-donating groups in addition to cyclohexanone. The reaction gave the corresponding products in good to excellent yields. The effects of electron-withdrawing and electron-donating substituent are summarized in Table 1.

The *anti*- and *syn*-isomers were identified by the coupling constants (J) of the vicinal protons adjacent to $\text{C}=\text{O}$ and NH in ^1H NMR spectra (Loh et al., 2000). The coupling constants for *anti*-isomers are reported to be bigger than those of *syn*-isomers (Ranu et al., 2002).

Probably, interaction between MNP catalyst and the transition state in this reaction conduces to the formation of *anti*- or *syn*-isomer (Bigdeli et al., 2007; Wu et al., 2007). A plausible mechanism is shown in Fig. 2. If hydrogen bonding occurs among MNPs, imine and enol form of cyclohexanone, the aryl and phenyl group would be *anti*- to each other, so there is min-

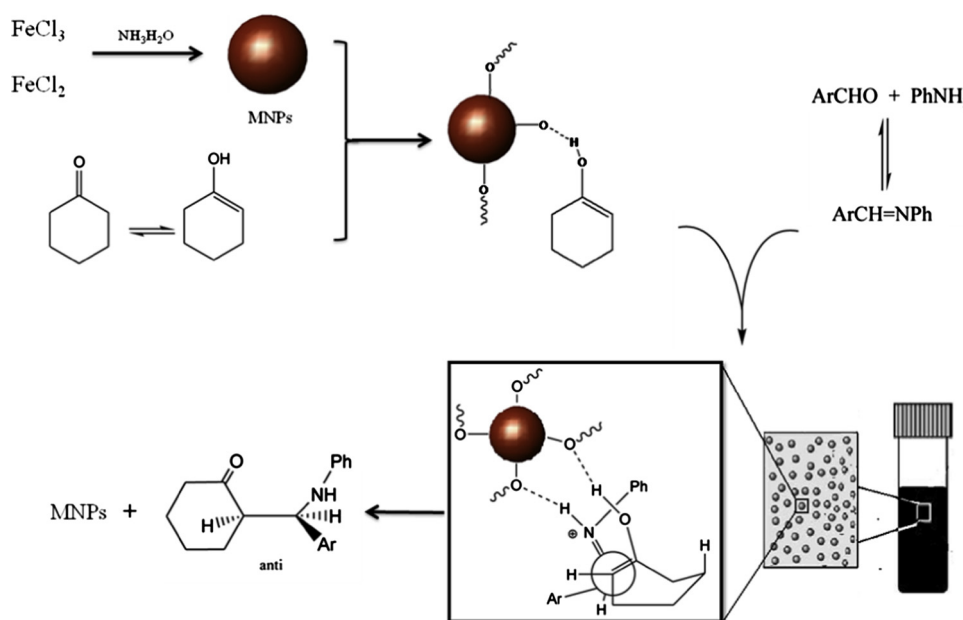
Table 1 Mannich-type reaction of aromatic aldehydes, anilines, and cyclohexanones in EtOH for 45 min.

Entry	Ar ₁	Ar	Yield (%) ^a	Anti/syn ^b	MP (°C) ^c
1	C ₆ H ₅	Ph	90	99/1	138–140 (Bigdeli et al., 2007)
2	2-NO ₂ C ₆ H ₄	Ph	90	40/60	159–160 (Lu and Cai, 2010)
3	2-Naphthyl	Ph	80	99/1	129–131 (Bigdeli et al., 2007)
4	4-BrC ₆ H ₄	Ph	75	90/10	110–112 (Bigdeli et al., 2007)
5	4-ClC ₆ H ₄	Ph	75	98/2	69–70 (Bigdeli et al., 2007)
6	4-NO ₂ C ₆ H ₄	Ph	80	99/1	123–125 (Nemati et al., 2011)
7	2-ClC ₆ H ₄	Ph	80	98/2	150–151 (Bigdeli et al., 2008)
8	C ₆ H ₅	4-BrC ₆ H ₄	90	99/1	98–99 (Yang et al., 2006)
9	C ₆ H ₅	4-MeC ₆ H ₄	75	98/2	118–119 (Kidwai et al., 2009)

^a Isolated yields, products were confirmed by ¹H NMR.

^b Anti/syn ratio was determined by ¹H NMR.

^c Melting point.

**Figure 2** Possible mechanism.

imum steric repulsion between methylene groups in cyclohexanones and the aryl group, as well as MNPs and H. Therefore, this transition state conduces to *anti*-isomer. Because complete *anti*-selectivity is observed, it can be concluded that powerful hydrogen bonding exists between MNPs, imine and enol form of cyclohexanon.

2.3.1. 4.2.2-((4-chlorophenyl)(phenylamino)methyl)cyclohexanone (Table 1, entry 5)

MP = 69–70 °C, 753; ¹H NMR (300 MHz; CDCl₃; Me₄Si): δ 7.4–7.38 (dd, 2H, $J = 7.4$ Hz and $J = 2.4$ Hz), 7.16 (t, 2H, $J = 5.4$ Hz), 7.28–7.06 (m, 3H), 6.68 (t, 1H, $J = 6.9$ Hz), 6.58 (d, 2H, $J = 8.1$ Hz), 4.72 (d, 0.02H, syn, $J = 4.41$ Hz), 4.57(d, 0.98H, anti, $J = 6.72$ Hz), 2.83 (s, 1H), 2.27–2.17 (m, 2H), 1.85–1.63 (m, 6H); ¹³C NMR (300 MHz, CDCl₃, mixture of diastereoisomers): δ 212.46, 146.84, 140.79, 131.83, 131.75, 131.64, 131.55, 131.45, 129.46, 129.28, 129.14, 129.11, 120.90, 117.95, 117.87, 114.08, 113.70, 57.62, 57.17, 56.96, 56.36, 42.39, 42.09, 31.52, 28.85, 27.75, 27.09, 24.88, 24.2; FTIR

(KBr): ν_{\max}/cm : 1 3393, 1713, 1600, 1493, 1275, 1011; Anal. Calcd for C₁₉H₂₀BrON: C, 63.70; H, 5.58; N, 3.91. Found: C, 63.68; H, 5.61, N, 3.98.

2.4. General procedure for the synthesis of β -aminocarbonyl compounds using acetophenone

Under the optimum conditions, the one-pot, three-component Mannich reaction using acetophenone was also studied. Hence, a mixture of benzaldehyde (2.5 mmol), aniline (2.5 mmol), acetophenone (3 mmol) and MNPs (6.0 mg) was sonicated in ethanol (3 ml) at room temperature for 75 min. The reaction was monitored by TLC. It was found that the corresponding β -amino carbonyl compounds were formed in good to moderate yields. The results are summarized in Table 2.

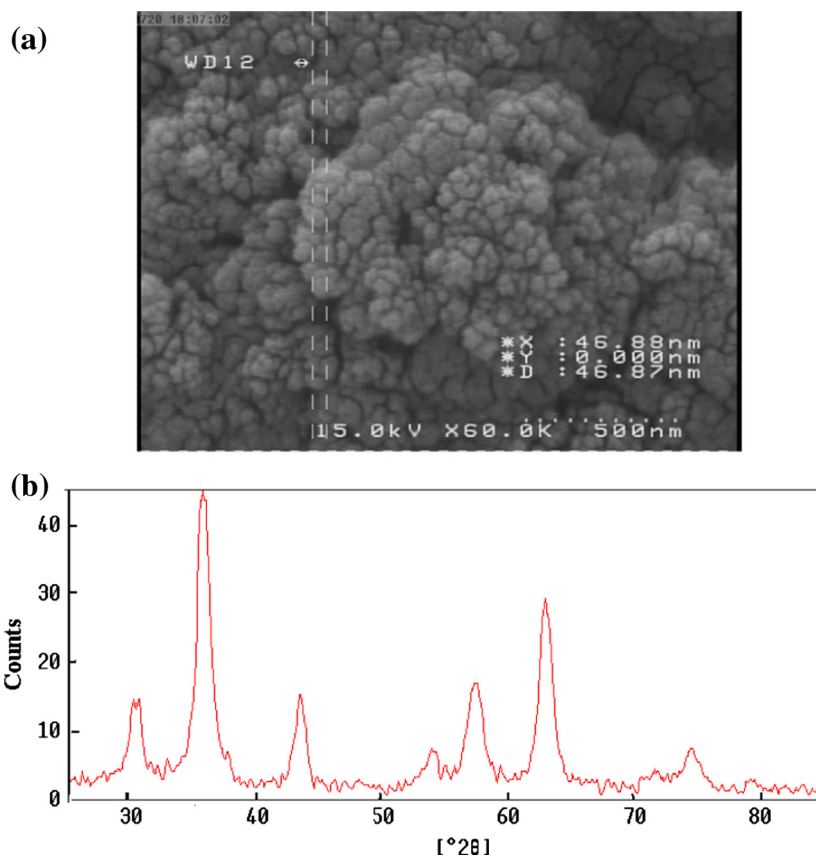
According to the results, acetophenone was less reactive than cyclohexanone and required a greater quantity of catalyst and longer reaction times to achieve the desired products.

Table 2 Mannich-type reaction of aromatic aldehydes, anilines, and acetophenone for 75 min.

Entry	Ar ₁	Ar	Yield (%) ^a	MP (°C) ^b
1	C ₆ H ₅	Ph	80	168–169 (Bigdeli et al., 2007)
2	4-MeC ₆ H ₄	Ph	80	135–137 (Bigdeli et al., 2007)
3	4-ClC ₆ H ₄	Ph	80	131–133 (Bigdeli et al., 2007)
4	4-NO ₂ C ₆ H ₄	Ph	70	104–105 (Ranu et al., 2002)
5	C ₆ H ₅	4-ClC ₆ H ₅	75	164–166 (Lu and Cai, 2010)
6	C ₆ H ₅	4-MeC ₆ H ₅	80	165–167 (Bigdeli et al., 2007)

^a Isolated yields, products were confirmed by ¹H NMR.

^b Melting point.

**Figure 3** Characterization of the Fe₃O₄ MNPs. (a) SEM image of the Fe₃O₄ MNPs, (b) XRD pattern of the synthesized Fe₃O₄ MNPs.

2.4.1. 3-(4-chlorophenylamino)-1,3-diphenylpropan-1-one (Table 2, entry 5)

MP = 164–166 °C; ¹H NMR (300 MHz; CDCl₃; Me₄Si): δ 7.89 (d, *J* = 7.76 Hz, 2H), 7.46–7.42 (m, 1H), 7.38–7.24 (m, 4H), 7.16–7.12 (m, 3H), 7.09 (dd, *J* = 7.9, *J* = 1.95 Hz, 2H), 6.42 (d, *J* = 8.3 Hz, 2H), 4.97–4.93 (m, 1H), 3.52 (d,d, *J* = 5, *J* = 16.3 Hz, 1H), 3.26 (d,d, *J* = 7.3, *J* = 17.3 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 199.3, 143.57, 140.11, 128.96, 128.52, 128.17, 126.81, 124.36, 114.77, 59.4, 49.0; FTIR (KBr): ν_{max}/cm: 3372, 1667, 1285, 703. Anal. Calc. for C₂₁H₁₈BrNO: C 66.31, H 4.73, N 3.68; Found: C 66.01, H 5.05, N 3.58.

2.5. Characterization of the MNPs

Characterization of synthesized Fe₃O₄ MNPs was done using FTIR, XRD and SEM methods (Fig. 3). It is most important

Table 3 Factors and parameters for Taguchi orthogonal array design.

Levels	Factors			
	A	B	C	E
	Solvent	Temperature	Amount of MNPs (mg)	Time (min)
1	EtOH	5	2.0	30
2	H ₂ O	15	4.0	45
3	Di-ethylether	25	6.0	60
4	THF	35	8.0	75

that Fe₃O₄ MNPs should possess a sufficient magnetic and super paramagnetism property for magnetic carrier technology (MCT) practical application. Fe₃O₄ MNPs exhibited typical super paramagnetic behavior due to not exhibiting hysteresis,

Table 4 OA₁₆ (4⁴) experimental design for the Mannich reaction.

Trial No.	Solvent	Temperature	Amount of MNPs (mg)	Time
1	THF	25	6.0	45
2	Di-ethylether	25	4.0	30
3	H ₂ O	25	2.0	75
4	THF	35	6.0	75
5	THF	15	4.0	45
6	Di-ethylether	5	6.0	60
7	THF	25	8.0	60
8	Di-ethylether	35	2.0	45
9	H ₂ O	5	8.0	45
10	Di-ethylether	15	8.0	75
11	EtOH	5	4.0	75
12	EtOH	5	2.0	30
13	H ₂ O	15	6.0	30
14	EtOH	15	2.0	60
15	EtOH	35	8.0	30
16	H ₂ O	35	4.0	60

remanence and coercivity. The large saturation magnetization of Fe₃O₄ MNPs was 76 emu/g, which is sufficient for magnetic separation with a conventional magnet. The SEM image of the prepared MNPs is shown in Fig. 3a. Based on the SEM image, the Fe₃O₄ surface morphology analysis demonstrated the agglomeration of many ultrafine particles with a diameter of about 40 nm. As shown in Fig. 3b, the XRD analysis of Fe₃O₄ MNPs indicated peaks with 2θ at 29.72, 35.57, 43.17,

57.15 and 62.77 which are characteristic peaks of Fe₃O₄, indicating the purity of the synthesized Fe₃O₄.

3. Results and discussion

3.1. Method development

In the proposed procedure, to establish the optimum conditions and achieve maximum yield, various parameters affecting the synthesis of β -amino carbonyl were studied using the Taguchi orthogonal array design (OAD). The Taguchi method is a type of fractional factorial design in which orthogonal array is used to assign the selected factors to a serial of experimental combinations (Shariati and Golshekan, 2011). The results of the OAD experiments can be treated by the analysis of variance (ANOVA). In ANOVA, the effects of different factors on the response function can be evaluated by computing *F*-ratio (variances ratio) and percent contribution (PC) values for each factor (Roy, 1990; Zhu and Ju, 2004). In all optimizing experiments 2.5 mmol benzaldehyde, 2.5 mmol aniline, 3.0 mmol cyclohexanone or acetophenone were mixed and glass tubes with 5.0 mL volumes were used for optimization.

3.2. Experimental design and data analysis

The effects of four experimental parameters including type of solvent, temperature, amount of MNPs and reaction time on

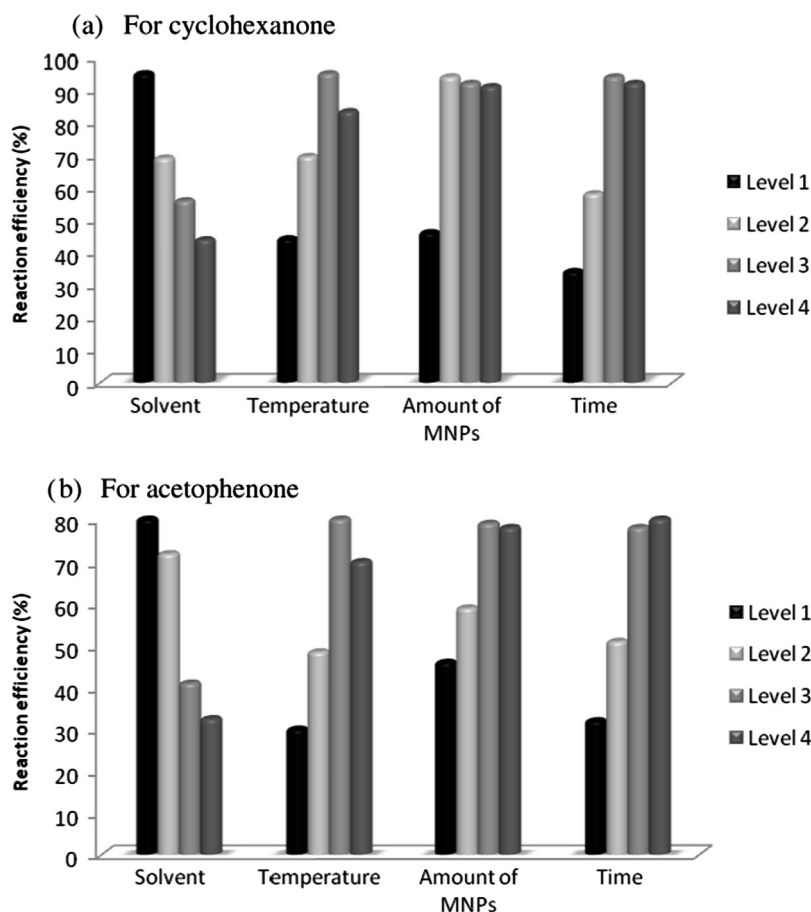


Figure 4 The response graph illustrating the variation of the mean yield values plotted against various reaction parameters.

Table 5a ANOVA results for experimental responses in the OA₁₆ (4⁴) matrix (for cyclohexanone).

Factor	DOF ^a	Sum of squares	Variance	F-Ratio ^b	Pure sum of squares	PC ^c (%)
Solvent	3	0.305	0.105	3.52	0.232	13.1
Temperature	3	0.290	0.158	4.19	0.212	12.2
Amount of MNPs (C)	3	1.335	0.461	21.3	1.235	50.56
Time (E)	3	0.644	0.252	12.16	0.68	22.92
Error	32	0.032	0.002			1.22
Total	31	2.606				100.00

^a Degrees of freedom.

^b *F*, critical value is 3.24 (*p* < 0.05).

^c Percent of contribution.

Table 5b ANOVA results for experimental responses in the OA₁₆ (4⁴) matrix (for acetophenone).

Factor	DOF ^a	Sum of squares	Variance	F-Ratio ^b	Pure sum of squares	PC ^c (%)
Solvent	3	0.305	0.116	3.82	0.214	12.2
Temperature	3	0.290	0.169	3.79	0.221	14.1
Amount of MNPs (C)	3	1.105	0.402	19.2	1.076	39.06
Time (E)	3	0.794	0.311	14.26	0.87	30.42
Error	32	0.052	0.004			1.52
Total	31	2.546				100.00

^a Degrees of freedom.

^b *F*, critical value is 3.24 (*p* < 0.05).

^c Percent of contribution.

the synthesis of β -amino carbonyl compounds were studied at four levels using Taguchi OA₁₆ design. The used levels and the OA₁₆ (4⁴) matrix that were employed to assign the considered factors are shown in Tables 3 and 4, respectively.

The designing of table was done via experimental design 7.0 software. For increasing the precision of the optimization process, each trial was repeated twice (*n* = 32) using cyclohexanone or acetophenone. The sequence of each experiment was randomized to avoid any personal or subjective bias. Analysis of variance (ANOVA) was used to assess the OA design results. For ANOVA calculations, yield of product was used and the results of the sum of squares (SS) for different variables were calculated.

The mean values of the four levels of each parameter revealed how the yield changes with variation of the level of each factor. Fig. 4 shows the mean yield as a function of the levels of the studied parameter. For cyclohexanone, maximum yield of reaction was obtained at ethanol solvent, 25 °C temperature, 4.0 mg of the Fe₃O₄ MNPs and 45 min reaction time and for acetophenone the maximum yield of reaction was obtained at ethanol, 25 °C, 6.0 mg of the Fe₃O₄ MNPs and 75 min. The ANOVA results (Tables 5a and 5b) showed that the most important parameter contributing to the reaction efficiency was the amount of MNPs.

4. Conclusion

In this study, the applications of MNPs as a catalyst and ultrasonic-assisted method in Mannich reactions using aldehydes, amines, and ketones were investigated. The use of MNPs and ultrasonic-assisted method as an alternative to other synthesis methods offers several advantages, such as high yield

and reaction rate, short reaction times, low running costs and a recyclable catalyst with a very easy procedure. The magnetite cores of catalyst permitted the magnetic separation of product from solution. This greatly improved the separation rate of product while avoiding the time-consuming column passing or filtration operation. The adsorbed products were easily desorbed with hot ethanol solution and no carryover was observed in the next reaction.

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