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# PAPER



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Nano-ferrous ferric oxide (nano-Fe<sub>3</sub>O<sub>4</sub>): magnetite catalytic system for the one-pot four-component tandem imine/enamine formation-Knoevenagel– Michael-cyclocondensation reaction of dimedone, aldehydes, β-ketoesters and ammonium acetate under green media†

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In this work, magnetite nano-Fe<sub>3</sub>O<sub>4</sub> was applied as a green, efficient, heterogeneous and reusable catalytic system for the atomic economic preparation of hexahydroquinolines *via* the one-pot multi-component reaction of aryl aldehydes, dimedone (5,5-dimethylcyclohexane-1,3-dione),  $\beta$ -ketoesters and ammonium acetate at 50 °C under mild and solvent-free conditions. The catalyst was synthesized and characterized by several techniques including Fourier transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), vibrating sample magnetometry (VSM) and transmission electron microscopy (TEM). Also, optimization of the reaction conditions was investigated using the response surface method {Central Composite Design (CCD)}.

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Multi-component reactions (MCRs) are important in combinatorial chemistry due to their ability to prepare target compounds with more efficiency and atomic economy by the reaction of three or more compounds together in a single step. Moreover, MCRs increase simplicity and synthetic efficiency of the conventional organic transformations.<sup>1–5</sup>

Transition-metal catalyzed organic transformations are often carried out to follow the principles of "Green Chemistry" due to minimization of waste, cleaner auxiliaries, catalysts or reagents and minimum use of energy. Nanocatalysts are important as a bridge between heterogeneous and homogeneous catalysts.<sup>6</sup> One of the interesting properties of nanomaterials is that they have a high specific surface area of the active part, leading to an increase in contact with the reactants.<sup>7</sup> Moreover, a higher surface area gives the nanomaterials a more active surface; they are hard to be separated. Therefore, it is attractive to design a recoverable and well-dispersed catalyst. Magnetite nanoparticles (MNPs) as catalysts are very promising because of their magnetic properties and large specific surface area.<sup>8,9</sup> They can be collected very easily with a magnet for reuse to prevent loss of the catalyst. Recently, chemists have focused on catalytic aspects of nano-Fe $_3O_4$  to improve methods of catalytic activity.<sup>10-15</sup>

Improvement on the DHP ring, like the introduction of hetero atoms or variant substituents could not only result in decreased photosensitivity of these materials, but also enrich the diversity of DHPs chemistry and could modify structureactivity relationship bearing novel aspects into the molecular interactions.<sup>16,17</sup> It is also recognized that structural modification on the DHP periphery could result in important influence in their pharmacological activities.18,19 One of the categories of DHPs with an improved structural scaffold is hexahydroquinolines (HHQs) that could be obtained through Hantzsch synthesis utilizing aromatic aldehydes, dimedone, β-ketoesters and ammonium acetate via a one-pot multi-component reaction.<sup>20,21</sup> Quinoline derivatives with a 1,4-dihydropyridine scaffold are promising structures because of their pharmacological properties. This category of quinolines has diverse applications in medicinal chemistry, being used as antiasthmatic, antibacterial antihypertensive, anti-inflammatory, antimalarial, and tyrosine kinase inhibiting materials.<sup>22-27</sup> Additionally, some other protocols and catalysts have been developed for the synthesis of HHQs.28-39

Herein, we have introduced the nano-ferrous ferric oxide (nano-Fe<sub>3</sub>O<sub>4</sub>) as a highly efficient, stable, reusable and heterogeneous catalyst for the preparation of hexahydroquinolines, at 50 °C under solvent-free conditions (Scheme 1). Interestingly,

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Scheme 1 The one-pot four-component preparation of hexahydroquinolines catalyzed by nano-Fe $_3O_4$ .

the presented protocol has efficiently improved and solved some drawbacks in the preparation of the title compounds.

First of all, the catalyst (nano-Fe<sub>3</sub>O<sub>4</sub>) was prepared according to the previous literature.15,40 The synthesized catalyst was identified by X-ray diffractometer (XRD), vibrating sample magnetometer (VSM), Fourier transform infrared spectroscopy (FT-IR) and transmission electron microscopy (TEM). To confirm that the magnetite was correctly produced, in the first step, the XRD pattern of it was studied. XRD pattern of Fe<sub>3</sub>O<sub>4</sub> nanoparticles reveal at  $2\theta \approx 30.24^\circ$ ,  $35.62^\circ$ ,  $43.33^\circ$ ,  $53.63^\circ$ , 57.29° and 62.80° respectively, that was confirmed by the reported value (JCPDS 01-1111) (Fig. S1a<sup>+</sup>). The average crystallite size D was calculated using the Debye-Sherrer equation  $(D = K\lambda/(\beta \cos \theta), \lambda$  the X-ray wavelength, where K is Scherrer constant,  $\beta$  the peak width of half-maximum, and  $\theta$  is the Bragg diffraction angle). The obtained average size of the catalyst by this equation, was about 9 nm, which is basically in a good accordance with the transmission electron micrographs of the nano-Fe<sub>3</sub>O<sub>4</sub> (Fig. S1b<sup>†</sup>).

In the second step, magnetic property of the catalyst was also recorded by a vibrating sample magnetometer (VSM) at 298 K. The magnetization graph reveal which the magnetization saturated up to 60 emu  $g^{-1}$  at an applied field of 7000 Oe and confirmed the super paramagnetic properties at room temperature (Fig. S2†).

Finally, to further prove the preparation of the catalyst, an FT-IR spectrum of  $Fe_3O_4$  was investigated. As it is shown in Fig. S3,<sup>†</sup> the peak at 582 cm<sup>-1</sup> is related to the interactions of Fe–O bonds in structure of nano-Fe<sub>3</sub>O<sub>4</sub>.

After the full characterization of nano-Fe<sub>3</sub>O<sub>4</sub>, we tested the catalytic activity of it to promote the preparation of hexahydroquinolines. For this purpose, a mixture of dimedone, 4-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate in the present of nano-Fe<sub>3</sub>O<sub>4</sub> under solvent-free condition was chosen as model reaction, optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)} with five replicate at central point for developing a second order model with 19 runs (Table S1<sup>†</sup>). Three variables that can effect on yield and time of the reaction are temperature (A with levels of the variables 35 to 65 °C), amount of catalyst (B with levels of the variables 2.8 to 8.2 mol%) and amount of ammonium acetate (C with levels of the variables 2.2 to 2.8 mmol). The levels of the variables and the corresponding response values of the CCD are shown in Table S2.† Yield and time of the reaction were used as the dependent variables and were fitted to a quadratic polynomial model. After programming optimization (Table S3 and S4†), two polynomial response surface models based on significant levels and actual values for time and yield were obtained (Fig. 1 and 2).

$$\text{Time} = +7.33 - 1.02A - 4.73B + 2.74B^2 \tag{1}$$

$$\text{Yield} = +88.89 + 1.86A + 6.17B - 1.18A^2 - 3.02B^2 \qquad (2)$$

For finding of accurate optimum area, with using of obtained equations and calculation of desirability functions, the results showed that accurate optimal operational conditions was (A = 50 °C, B = 5 mol%, C = 2.5 mmol) (Fig. 3). It should be mentioned that corresponding maximum prediction conversion was 95.96% in introduced optimal point.

In the next step, the accuracy of the theoretical results, were examined by empirical research. For this purpose, as model reaction, a mixture of dimedone (1 mmol), 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.2 mmol), was stirred in the presence of different amounts of nano-Fe<sub>3</sub>O<sub>4</sub> at range of 25 to 80 °C under solvent-free condition. The respective results are displayed in Table 1. As it can be seen in Table 1, indicates that 0.0116 g (5 mol%) of Fe<sub>3</sub>O<sub>4</sub>



Fig. 1 Three dimensional response surfaces for the effect of factors on the reaction time.



Fig. 2 Three dimensional response surfaces for the effect of factors on the reaction yield.



Fig. 3 Effect of temperature and catalyst on the desirability function.

nanoparticles was suitable to catalyze the reaction at 50  $^{\circ}$ C. In this reaction condition, the desired hexahydroquinoline was efficiently prepared in 92% yield within 5 min (Table 1, entry 2) which is in a good accordance with the response surface method.

To compare the efficiency of the solution *versus* solvent-free conditions, a mixture of dimedone (2 mmol), 4-nitrobenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (2.4 mmol), as model reaction, using nano- $Fe_3O_4$  in some various solvents was heated in an oil-bath (50 °C). Low yields of the product was isolated, even after elongated reaction times. Using solvents, such as  $CH_2Cl_2$ ,  $CHCl_3$ , EtOAc, EtOH,  $H_2O$ , acetone and THF, the product was obtained in low yields (Table 2).

To investigate the efficacy and the generality of the catalyst, dimedone was reacted with various aromatic aldehydes (benzaldehyde as well as aryl aldehyde containing electronwithdrawing groups, electron-donating groups and halogens),  $\beta$ -ketoesters (ethyl and methyl acetoacetate) and ammonium acetate under the optimized reaction conditions; the results are summarized in Table 3. As it is clear from Table 3, all reactions proceeded efficiently to give the desired hexahydroquinoline derivatives in high yields and in short reaction times. Therefore, nano-Fe<sub>3</sub>O<sub>4</sub>, was a highly efficient and general catalyst for the preparation of HHQs.

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Table 2Effect of various solvents on the reaction of dimedone (1mmol), 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol)and ammonium acetate (1.2 mmol), in the presence of nano-Fe $_3O_4$ (0.0116 g, 5 mol%)

Entry <sup>a</sup>	Solvent	Temp. (°C)	Time (min)	Yield <sup>b</sup> (%)	
	ouol		25		
1	CHCI <sub>3</sub>	50	25	80	
2	EtOAc	50	30	78	
3	EtOH	50	21	81	
4	$CH_2Cl_2$	Reflux	19	83	
5	$H_2O$	50	35	70	
6	Acetone	Reflux	15	85	
7	THF	50	20	81	
8 <sup>c</sup>	—	50	5	92	

<sup>&</sup>lt;sup>*a*</sup> All reactions were carried out at 50 °C except entries 4 and 6, which was proceeded at reflux condition. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> The reaction was proceeded in the absence of solvent.

In another investigation, recyclability of nano-Fe<sub>3</sub>O<sub>4</sub> was studied. For this purpose, the reaction of dimedone (1 mmol), 4nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.2 mmol) was performed in the presence of nano-Fe<sub>3</sub>O<sub>4</sub> (0.0116 g, 5 mol%) at 50 °C. After completion of the reaction, the reaction mixture was cooled to room temperature; ethanol (95%) (20 mL) was added, stirred and refluxed for 3 min. The catalyst was collected by a magnet and separated from the solution of product and remaining starting materials. The remained catalyst was washed with hot ethyl acetate (10 mL) and dried to use for the next run. Catalytic activity of nano-Fe<sub>3</sub>O<sub>4</sub> was restored within the limits of the experimental errors for 12 successive recycle runs (Fig. 4).

In a plausible mechanism (Scheme 2) which is supported by the literature,<sup>29,31,33,38,39</sup> at first dimedone is converted to its enol form using nano-Fe<sub>3</sub>O<sub>4</sub> as Lewis acid and reacted to activated aldehyde (by nano-Fe<sub>3</sub>O<sub>4</sub>) to give intermediate **I**. Also, the activated  $\beta$ -ketoester (by the catalyst) and ammonia (resulted from ammonium acetate) affords enamine **II**. Then, the intermediate **I** and enamine **II** react with each other to produce intermediate **III. III** is converted to **IV** by tautomerization, and intermediate **IV** gives **V** by intramolecular nucleophilic attack of the NH<sub>2</sub> group to the activated carbonyl group and then removing one molecule H<sub>2</sub>O. As a result, hexahydroquinonine forms by tautomerization of **V**.

Table 1 Effect of the catalyst amount and temperature on the reaction between dimedone, 4-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate

Entry	Catalyst	Catalyst amount (g)	Temp. (°C)	Time (min)	Yield <sup>a</sup> (%)
1	Nano-Fe <sub>3</sub> O <sub>4</sub>	0.0116	25	17	85
2	Nano-Fe <sub>3</sub> O <sub>4</sub>	0.0116	50	5	92
3	Nano-Fe <sub>3</sub> O <sub>4</sub>	0.0116	60	5	92
4	Nano-Fe <sub>3</sub> O <sub>4</sub>	0.0116	80	5	92
6	Nano-Fe <sub>3</sub> O <sub>4</sub>	0.0068	50	13	79
7	Nano-Fe <sub>3</sub> O <sub>4</sub>	0.0162	50	7	91

<sup>a</sup> Isolated yield.

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Time (min) Yield<sup>a</sup> (%) M.p.  $^{\circ}$ C (lit.)

Table 3 The solvent-free synthesis of HHQs from dimedone, aryl aldehydes,  $\beta$ -ketoesters and ammonium acetate catalyzed by nano-Fe\_3O\_4 at 50 °C

Table 3 (Contd.)

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Entry	Product	Time (min)	Yield <sup>a</sup> (%)	M.p. °C (lit.)		NO <sub>2</sub>			
1		6	89	204–205 (203–205) [20]	13		14	92	227–229 (229–231) [39]
2		5	92	245-247 (242-244) [24]	14		11	91	205–207
3		7	91	256–258 (257–259) [23]	15		6	89	256–259 (257–259) [38]
4		7	89	262–263 (260–261) [23]	16	он	5	90	231–233 (235–236) [39]
	OH				17	OMe H	5	85	233–235 (228) [41]
5		6	91	238–240 (232–234) [23]	18		8	89	238–240 (246) [41]
6		8	86	250–252 (255–257) [20]	19		4	92	208–209 (207) [41]
7		8	90	229–230 (235–237) [20]	20		9	87	248–249 (245) [41]
8		6	91	248–250 (245–246) [22]	21		6	90	205-206
9		8	87	255-256 (256-257) [39]	22		7	85	266–268 (—) [42]
10		5	91	244-245 (243-245) [38]	23	OEt of the second secon	8	85	232-233
11	OH OCEL	6	90	220–221 (211–213) [38]	24		6	92	214–216 (220) [43]
12	OMe	10	91	256–258 (260–262) [39]	<sup>a</sup> Isola	ated yield.			



Fig. 4 The condensation of dimedone with 4-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate in the presence of recycled nano-Fe $_3O_4$ .



Scheme 2 Plausible mechanism for the synthesis of hexahydroquinolines using nano-Fe $_3O_4$  as catalyst.

## Conclusions

In summary, we have introduced nano-Fe<sub>3</sub>O<sub>4</sub> as a reusable, stable, general and heterogeneous catalyst for the one-pot multi-component reaction between dimedone, aryl aldehydes,  $\beta$ -ketoesters and ammonium acetate leading to hexahy-droquinolines. Also, optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)} which was in a good accordance with empirical research. The promising points for the presented method are efficiency, generality, high yields of the products, short reaction times, simplicity, cleaner reaction profile, low cost, ease preparation and reusability of the catalyst.<sup>44</sup>

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- 44 Materials: all chemicals were purchased from Merck or Fluka Chemical Companies. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The <sup>1</sup>H NMR (400 or 300 MHz) and <sup>13</sup>C NMR (100 or 75 MHz) were run on a BrukerAvance DPX-250 FT-NMR spectrometer ( $\delta$  in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. General procedure for the preparation of hexahydroquinolines: to a mixture of dimedone (0.28 g, 2 mmol), aryl aldehyde (2 mmol), β-ketoester (2 mmol) and ammonium acetate (0.185 g, 2.4 mmol) in a test tube, was added nano-Fe<sub>3</sub>O<sub>4</sub> (0.0232 g, 5 mol%), and the resulting mixture was firstly stirred magnetically, and after solidification of the reaction mixture with a small rod, at 50 °C. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature. Then, ethanol (95%) (20 mL) was added, stirred and refluxed for 3 min. The catalyst was collected by a magnet and separated from the solution of product and remaining starting materials. The crude product was purified by recrystallization from ethanol (95%). In this work, the catalyst was recovered and reused for 12 times without any significant changes in the yield and the reaction time.