

## Ni<sup>2+</sup> supported on hydroxyapatite-core@shell $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles as new and green catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free condition

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### Abstract

The aim of this research is to study Ni<sup>2+</sup> supported on hydroxyapatite-core-shell magnetic  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup>) as a green and recyclable catalyst for the Biginelli reaction under solvent-free conditions. One-pot multi-component condensation of 1,3-dicarbonyl compounds, urea and aldehydes at 80 °C affords the corresponding compounds in high yields and in short reaction times using  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup>. The catalyst can be readily isolated using an external magnet and no obvious loss of activity was observed when the catalyst was reused in seven consecutive runs. The mean size and the surface morphology of the nanoparticles were characterized by transmission electron microscopy, scanning electron microscope, vibrating sample magnetometry, X-ray powder diffraction and Fourier transform infrared techniques.

**Keywords:**  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, Ni<sup>2+</sup> supported, nanoparticles, dihydropyrimidinone, solvent-free condition.

### Introduction

In the past decade, magnetic nanoparticles (MNPs) have been considered as attractive and interesting materials because of their high surface area and unique magnetic properties, moreover, they have a wide range of novel applications in various fields; such as magnetic fluids [1], catalysis [2], biology and medical applications [3] magnetic resonance imaging

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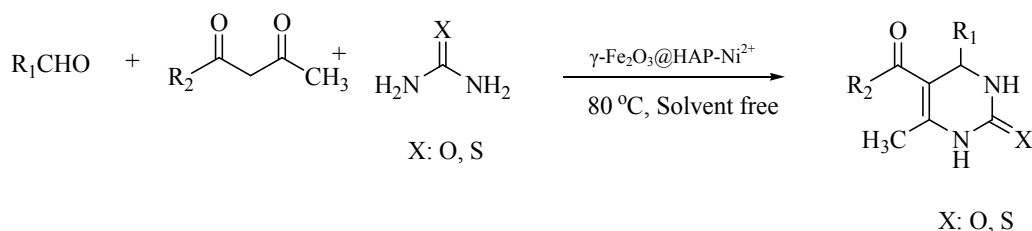
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(MRI) [4] data storage [5], and environmental remediation [6]. MNPs have recently been viewed as attractive materials either as catalysts or as supporters for immobilization of homogeneous and heterogeneous catalysts [7]. Moreover, they can be used in various organic reactions such as Knoevenagel reaction [8], nucleophilic substitution reactions of benzyl halides [9], epoxidation of alkenes [10], synthesis of  $\alpha$ -amino nitriles [11], hydrogenation of alkynes [12], esterifications [13], CO<sub>2</sub> cycloaddition reactions [14], Suzuki coupling reactions [15] and three-component condensations [16].

Dihydropyrimidine (DHPM) derivatives exhibit significant pharmacological activities such as calcium channel blockers, antihypertensive, anti-bacterial and anti-inflammatory agents, while they also possess cytotoxic activity and anticancer drugs [17]. The simple and direct procedure for the synthesis of DHPMs which was first reported by Pietro Biginelli in 1893 involves a three-

component one-pot condensation of benzaldehyde,  $\beta$ -keto ester, and urea under strongly acidic conditions [18]. In recent years, various synthetic procedures for the synthesis of DHPMs have been developed to improve and modify this reaction using different acids under classical reflux [19], solvent-free conditions [20,21] and microwave [22] or ultrasound irradiation [23] conditions. However, in spite of their potential utility, many of these reported one-pot syntheses suffer from drawbacks such as the requiring expensive reagents, strong acidic conditions, long reaction times, stoichiometric amount of catalysts, environmental pollution and low yields of the products and tedious workup.

In this research,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAP-Ni<sup>2+</sup> will be tested and analyzed as a new heterogeneous catalyst for one-pot synthesis of dihydropyrimidinones via three-component couplings of aromatic aldehyde,  $\beta$ -dicarbonyl, urea/thiourea under solvent free condition at 80 °C (Scheme 1).



**Scheme 1.**

## **Experimental**

### *General*

Aromatic aldehyde and other chemical materials were purchased from Fluka and Merck and were used without further purification. All Products were characterized by comparison of their physical data, IR and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra and physical properties with those reported in the literature. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. IR spectra of the compounds were obtained on a PerkinElmer spectrometer version 10.03.06 using a KBr disk. The particle morphology was examined by SEM and TEM.

### **Preparation of $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup>**

$\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> were prepared as reported in the literature [24]. The Iron oxide magnetic particles (IOMP) were synthesized by co-precipitation method in the basic condition. IOMP/HAP was prepared by the impregnation method according to known procedures with some modifications. Then, hydroxyapatite-encapsulated  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (0.6 g) was introduced into 100 ml of distilled water containing 6.4 mmol of NiCl<sub>2</sub>.6H<sub>2</sub>O. The mixture was stirred (500 rpm) for 48 h, then filtered, and washed several times with ethanol.

The recovered solid was dried at 50 °C overnight. The mean size and the surface morphology of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> were characterized by TEM, SEM, VSM, XRD and FTIR techniques.

### **General procedure for the preparation of DHPMs**

A mixture of aldehyde (1 mmol),  $\beta$ -dicarbonyl compound (1 mmol), urea or thiourea (1.5 mmol), and  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> (20 mg) was heated while stirring at 80 °C for 10-20 min. During the reaction process, a solid product was spontaneously formed. After the completion of the reaction, it was monitored by TLC (*n*-hexane:ethyl acetate; 3:2), then, 7 mL of ethanol was added to the reaction mixture and was stirred and heated for 10 min. Then, The reaction mixture was poured onto crushed ice and the solid product collected by filtration and washed with cold ethanol and a mixture of ethanol-water. The solid product was recrystallized from ethanol. The residual catalyst in the reaction vessel was washed and dried and then subjected to the next run directly.

## Results and discussion

As it was already mentioned, the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> is a new, highly efficient and reusable lewis acid catalyst which can be used for the Biginelli reaction under solvent-free conditions. Moreover, we have carried out the reaction of benzaldehyde, acetylacetone, and urea. Different reaction conditions have been studied for optimization. The best results were obtained with the ratio of 1:1:1.5 for

benzaldehyde, ethyl acetoacetate, urea and 20 mg of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> as catalyst at 80 °C.

After optimizing the conditions, we examined the generality of these conditions to other reactions of  $\beta$ -dicarbonyl, urea (or thiourea), and various aldehydes in the presence of optimized  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> (Table 1). The conversion was completed during 10–20 min.

**Table 1.** Synthesis of 3,4-dihydropyrimidinones using  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> as catalyst

Entry	R <sub>1</sub>	R <sub>2</sub>	X	Time[min]	Yield <sup>a,b</sup> [%]	m.p. (°C)	
						Found	Reported
1	H	Me	O	10	92	230-232	233-235 [20]
2	4-NO <sub>2</sub>	Me	O	15	75	208-209	207-209 [20]
3	4-Cl	Me	O	10	81	225-226	223-224 [20]
4	4-OMe	Me	O	10	89	163-165	166-168 [20]
5	4-Me	Me	O	10	88	192-194	193-194 [25]
6	H	Me	S	15	84	227-230	229-231 [20]
7	4-Cl	Me	S	15	76	228-230	227-229 [20]
8	2-OH	Me	S	12	82	241-243	240-243 [20]
9	4-NO <sub>2</sub>	Me	S	15	72	106-109	105-107 [20]
10	H	OEt	O	15	90	198-200	202-205 [25]
11	4-Me	OEt	O	15	89	212-215	214-216 [25]
12	2-NO <sub>2</sub>	OEt	O	12	76	203-205	220-221 [25]
13	4-NO <sub>2</sub>	OEt	O	20	79	204-206	207-209 [25]
14	4-OMe	OEt	O	12	82	205-207	202-204 [25]
15	4-Cl	OEt	O	12	80	253-255	210-212 [25]
16	H	OEt	S	15	85	210-212	210-212 [25]
17	4-Me	OEt	S	15	83	151-153	189-192 [25]

<sup>a</sup>All products were characterized by spectroscopic data.

<sup>b</sup>Yield after Purification.

Reaction rate and yield depend on the groups on the benzaldehydes. Accordingly, electron donating/withdrawing feature of the using aryl aldehydes with strong electron with

drawing substituents, including nitro group, requires a relatively longer reaction time with lower yields, whereas aryl aldehydes carrying electron donating groups gave excellent yields in a shorter reaction time.

As it can be seen in Table 3,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>@HAp-Ni<sup>2+</sup> NPs as a catalyst afforded good results in comparison to the other catalysts. In order to evaluate the efficiency of our introduced method, more recently developed methods were compared with our present method on the basis of the yields and reaction times parameters, the results are given in Table 2.

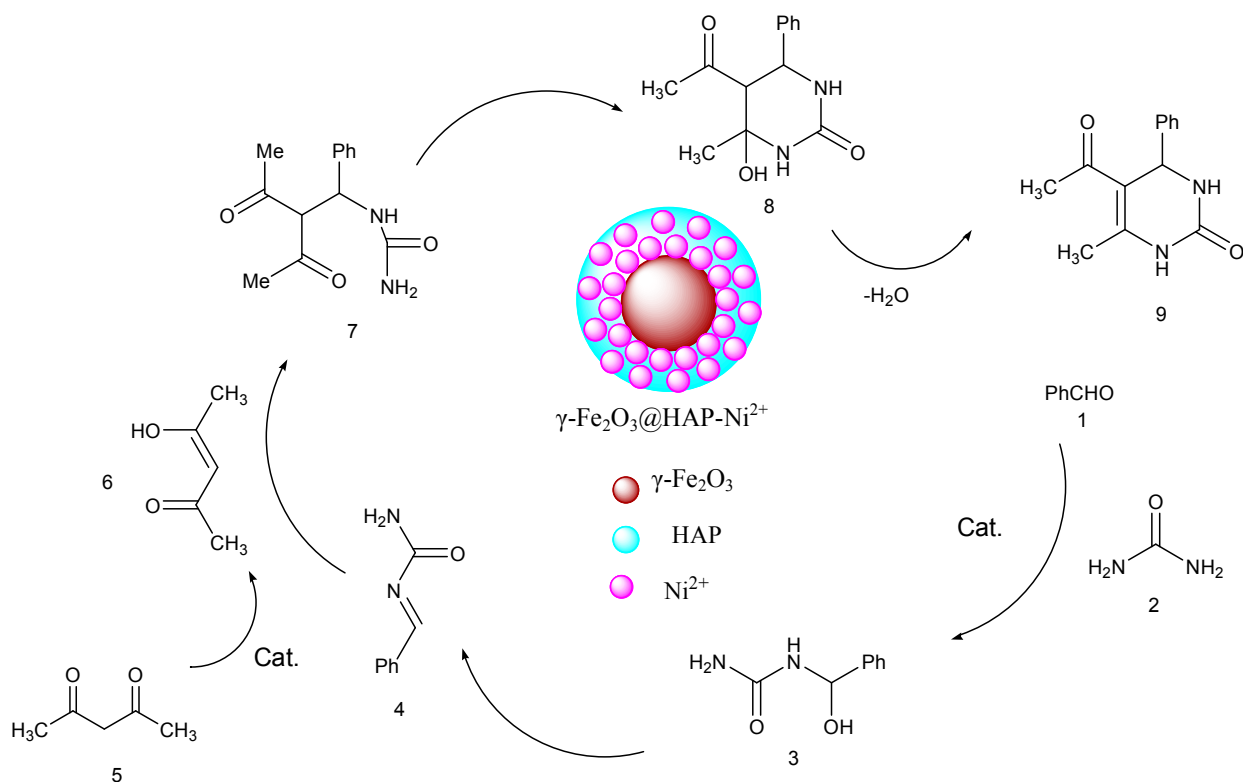
Catalyst reusability is of major importance for the large scale operations and it is economical. The recovery or reusability of the catalyst was studied using benzaldehyde, acetylacetone, and urea as model reaction. Since the catalyst can be separated from the reaction mixture using an external magnetic field, it was recovered with a simple magnet after the dilution of the reaction mixture with ethanol. The catalyst was consecutively reused seven times without any noticeable loss of its catalytic activity.

**Table 2.** Comparison of catalytic ability of catalysts.

Entry	R <sub>1</sub> /R <sub>2</sub> /X	Catalyst/solvent/temperature	Time (min)	Yield (%)	Reference
1	H/OEt/O	CSC-Star-SO <sub>3</sub> -AlCl <sub>2</sub> /Acetonitrile/80 °C	690	95	26
2	H/OEt/O	Mg-Al-CO <sub>3</sub> (Ca-Al-CO <sub>3</sub> )/Solvent-free/80 °C	35	84(69)	27
3	H/OEt/O	Poly(1-vinyl-3-(3-sulfopropyl)imidazolium hydrogen sulfate/Ethanol/ 80 °C	420	90	28
4	H/OEt/O	bio-glycerol based carbon/Acetonitrile/75-80 °C	240	90	29
5	H/OEt/O	[Bmim]BF <sub>4</sub> /Solvent free/100 °C	30	90	30
6	4-Me/OEt/O	PVSA/Ethanol(Water)/90 °C	60	88(94)	31
7	4-Me/Me/O	Fe <sub>3</sub> O <sub>4</sub> NPs/Solvent free/ 80 °C	33	84	32
8	4-Me/Me/O	$\gamma$ -Fe <sub>2</sub> O <sub>3</sub> @HAp- Fe <sup>2+</sup> NPs/Solvent free/80 °C	10	88	This work
9	H/OEt/O	$\gamma$ -Fe <sub>2</sub> O <sub>3</sub> @HAp- Fe <sup>2+</sup> NPs/Solvent free/80 °C	15	90	This work
10	4-Me/OEt/O	$\gamma$ -Fe <sub>2</sub> O <sub>3</sub> @HAp- Fe <sup>2+</sup> NPs/Solvent free/80 °C	15	89	This work

According to the mechanism,  $\gamma$ - $\text{Fe}_2\text{O}_3@ \text{HAp-Ni}^{2+}$  NPs catalyzed the readily insitu formation of dihydropyrimidinones product. This makes the  $\gamma$ - $\text{Fe}_2\text{O}_3@ \text{HAp-Ni}^{2+}$  capable of bonding with the carbonyl oxygen, and increases the reactivities of the parent carbonyl compounds. The aldehyde reacts with urea to form an acyl imine intermediate 3, which immediately eliminates one molecule of  $\text{H}_2\text{O}$  to produce a conjugated imino-ketone as a

Michael system 4. In addition, in the presence of  $\gamma$ - $\text{Fe}_2\text{O}_3@ \text{HAp-Ni}^{2+}$  NPs, the formation of highly stable enol of the  $\beta$ -ketoester 5 is somehow facilitated in the reaction mixture. Addition of the enol 6 to the imino-ketone 4 via a Michael addition reaction results in the formation of 7, after intramolecular cycloaddition formation of 8, and subsequently with the elimination of a molecule of  $\text{H}_2\text{O}$  results in 9 (Scheme 2).



**Scheme 2.**

In sum, we have developed a mild, simple  $\text{Fe}_2\text{O}_3@ \text{HAp-Ni}^{2+}$  at 80 °C under solvent free and green procedure for the one-pot synthesis conditions. Moreover, the mild reaction of dihydropyrimidinones/thiones in the conditions, high yield of products, easy work- presence of a catalytic amount of  $\gamma$ - up, ready availability of the catalyst,

compatibility with various functional groups and the ecologically clean procedure, will make the present method a useful and important addition to the present methodologies for the Biginelli synthesis. In this way, the catalyst can be easily recovered by simple magnetic decantation and reused several times with no loss of activity.

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