Research Article

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Sono and nano: A perfect synergy for eco-compatible Biginelli reaction

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Abstract: In this study, we evaluated the performance of nano- γ -Fe₂O₃-SO₃H catalyst in the Biginelli reaction and synthesized 3,4-dihydropyrimidine-2-(1*H*)-ones. This reaction was carried out under solvent-free and ultrasonic irradiation conditions and belonged to one-pot multicomponent reactions (MCRs) with an adopted aromatic aldehyde, ethyl acetoacetate, and urea as starting materials for the beginning of the reaction. The synthesized materials were efficient in synthesizing 3,4-dihydropyrimidine-2-(1*H*)-ones via the Biginelli reaction under reaction conditions. Thus, the advantages of using nano- γ -Fe₂O₃-SO₃H in the Biginelli reaction are short reaction time, high efficiency, green method, solvent free, and cost-effective. Furthermore, nano- γ -Fe₂O₃-SO₃H as a heterogeneous catalyst can be recycled five times without significantly reducing catalytic activity.

Keywords: Biginelli reaction, nano- γ -Fe₂O₃-SO₃H, 3,4-dihydropyrimidine-2-(1*H*)-ones, ultrasonic irradiation

1 Introduction

In the last decade, many studies on nanocatalysts had been performed by researchers. Nanocatalyst research always has been one of the most exciting topics in green chemistry and nanochemistry. Catalysts generally have been classified into two categories: homogeneous and heterogeneous catalysts [1,2]. Nanocatalysts are a bridge between heterogeneous and homogeneous catalysts, while enjoying the benefits of both [3]. According to green chemistry demands, chemists have tried to produce high-activity

and high-efficiency catalysts to separate and recover from the reaction mixture, excellent selectivity, low-energy consumption, and long life [4,5]. Hence, various types of nanocatalysts have been fabricated and reported in the previous articles, such as carbon nanocatalysts [6], silica nanocatalysts [7], mineral nanotubes [8], nanometals [9], and metal oxide nanocatalysts [10]. Among the mentioned nanoparticles, metal nanocatalysts and metal oxide nanocatalysts have had significant applications due to their unique chemical and physical properties [11]. These substances have been considered as the basic and extensively used nanostructures. As mentioned earlier, nanocatalysts can be recovered by two centrifugation methods and filtration [2]. The disadvantage of these two methods is a significant reduction in the remaining value of nanocatalysts. Nevertheless, one practical way to tackle this problem is the fabrication of magnetic nanocatalysts [12,13].

Magnetic nanoparticles have a wide range of applications, including biotechnology, biomedicine, catalysis, and environmental remediation [14]. Also, they have several advantages like easy separation using an external magnet, reusability, high catalytic activity, and high chemical stability in different organic solvents [15,16]. The magnetic properties of these nanocatalysts have led to their facility recovery and separation from the reaction system [13,17]. Also, in recent years, magnetic nanoparticles have attracted the attention of many researchers, and among magnetic nanoparticles, iron nanoparticles are of particular importance [6,18]. Iron nanoparticles (ions) have been considered nontoxic Lewis acids and, in many cases, have been used as catalysts [19,20]. The magnetic iron nanoparticle applications are not limited to a specific field and include various fields such as magnetic hyperthermia [21,22], food science [23], magnetic resonance imaging (MRI) [24], fluid transfer, microbiology, and drug delivery [25–29].

Functionalized magnetic metal nanoparticles are an important aspect of interdisciplinary materials between chemistry and many other academic and industrial fields like biomedicine, pharmacology, optic, electronic, catalyst sciences, and technologies [30]. For instance, many studies were carried out on sulfonation of magnetic

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nanoparticles and their use in the synthesis of heterocyclic compounds; for example, Maleki fabricated $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-OSO}_3\text{H}$ heterogeneous catalyst and used it as a solid acid catalyst in the synthesis of pyrazinoporphyrazine derivatives and pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines with good efficiency [31,32]. In another work, Maleki *et al.* reported a $\text{Fe}_3\text{O}_4@\text{PEG-OSO}_3\text{H}$ catalyst and evaluated the performance in synthesizing dihydropyrimidine derivatives in the ethanol as solvent at ambient temperature [33]. This article evaluated the performance of sulfonic acid-functionalized metal oxide nanocatalyst (nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$) in the Biginelli reaction, which showed good activity and reusability [34].

In comparison with multistep procedures in organic synthesis, one-pot multicomponent reactions (MCRs), as procedures in which three or more substances combine to produce a product, have many advantages such as synthesizing of the various compounds in a short reaction time, no need for solvents, less money consumption, crude materials, etc. [35–38]. Also, the synthesis of dihydropyrimidines (DHPMs) in the Biginelli reaction is done through a one-pot three-component reaction [19,39,40]. In this reaction, ethyl acetoacetate, aldehyde, and urea (or thiourea), in the presence of Lewis acids or mineral acids as the catalyst, participate as starting materials to yield dihydropyrimidines. DHPMs are of excellent importance in recent decades and have attracted much attention due to their many therapeutic properties, medicinal properties, and biological activities, including antiviral, antihypertensive, antibacterial, and antitumor properties [41,42]. Indeed, 3,4-dihydropyrimidine-2-(1*H*)-ones is an attractive structure in organic chemistry synthesis because it has been used in many synthetic drugs and biologically active natural products and plays a fundamental role as a precursor in the synthesis of many heterocyclic compounds [43]. This compound had synthesized with many homogeneous and heterogeneous catalysts; For instance, $\text{Bi}(\text{NO}_3)_3$ [44], $\text{Cu}(\text{OTf})_2$ [45], $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ [46], RuCl_3 [47], TiCl_4 [48], examples of homogeneous catalysts, especially Lewis acids, have been developed to increase product performance. These catalysts have disadvantages such as expensiveness, difficult separation, reusability, and difficult recovery. Heterogeneous catalysts compared to homogeneous catalysts are free from these problems and include cost-effectiveness, easy separation, reusability, better performance, and high yield [49].

Herein, we investigated the effect of immobilization of $\text{-SO}_3\text{H}$ groups on $\gamma\text{-Fe}_2\text{O}_3$ nanomagnetic particles as substrate and made a highly efficient functional magnetic acid catalyst. This article has tried to provide a practical and valuable procedure for synthesizing 3,4-dihydropyrimidine-2-(1*H*)-

ones in the Biginelli reaction using a nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ catalyst under ultrasonic irradiation and solvent-free conditions.

As a green manner, ultrasonic irradiation has attracted much attention to researchers for several applications, such as organic synthesis in chemical reactions. Compared to traditional approaches, this method is more favorable, faster, simpler, and easily controlled. The formation, growth, and collapse of acoustic bubbles are among the sonic effects during organic reactions. Acceleration of reactions under sonic conditions can be due to cage effects and acoustic cavitation, which provides high temperature and pressure in a few seconds and accelerates the reactions [50]. We found that anchoring $\text{-SO}_3\text{H}$ group on the magnetic support and utilizing it as a catalyst in the Biginelli reaction under solvent-free and ultrasonic conditions were very effective for synthesizing DHPM. Also, ultrasonic irradiation, especially in the presence of a solid acid catalyst, was very influential in accelerating the reaction, and it had a significant effect on the reaction process [51,52].

2 Results and discussion

2.1 Characterization of the catalyst

2.1.1 Effect of catalyst amount on the production performance of DHPMs

Various experiments had performed to achieve the optimal reaction conditions, including the type of solvent and catalyst, temperature, and the value of raw materials used in the Biginelli reaction. In summary, we chose benzaldehyde, urea, and ethyl acetoacetate as a model to achieve optimal reaction conditions. In the first stage of optimization, various iron catalysts such as Fe, $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, bulk- Fe_2O_3 , nano- $\gamma\text{-Fe}_2\text{O}_3$, nano- $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$, bulk- $\text{Fe}_2\text{O}_3\text{-SO}_3\text{H}$, nano- $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2\text{-SO}_3\text{H}$, and nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ in solvent-free conditions were evaluated to obtain the optimal catalyst to achieve the reaction product. A summary of the results presented in Table 1 shows that no products had formed when Fe and bulk- Fe_2O_3 had been used as catalysts in the reaction (Table 1, entries 1 and 4). Subsequently, $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalysts with minor functions did not show significant efficiency in the reaction (entries 2 and 3). Nano- $\gamma\text{-Fe}_2\text{O}_3$ and nano- $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$ showed higher yields than the previous catalysts used, respectively, 25–20%, but generally did not have an impressive efficiency for reaction improvement.

In contrast, when bulk- $\text{Fe}_2\text{O}_3\text{-SO}_3\text{H}$ had used, due to the presence of SO_3H groups, a significant increase in the

Table 1: Iron-based catalyzed Biginelli 3,4-dihydropyrimidin-2-(1*H*)-ones^a

Entry	Catalyst (0.1 g)	Time (h:min)	Yield (%) ^b
1	Fe	03:00	—
2	FeCl ₂ ·4H ₂ O	03:00	Trace
3	FeCl ₃ ·6H ₂ O	03:00	Trace
4	Bulk-Fe ₂ O ₃	03:00	—
5	Nano-γ-Fe ₂ O ₃	03:00	25
6	Nano-γ-Fe ₂ O ₃ @SiO ₂	03:00	20
7	Bulk-Fe ₂ O ₃ -SO ₃ H	03:00	65
8	Nano-γ-Fe ₂ O ₃ @SiO ₂ -SO ₃ H	03:00	95
9	Nano-γ-Fe ₂ O ₃ -SO ₃ H	03:00	95

^aBenzaldehyde:ethyl acetoacetate:urea = 1.2:1:1.5, solvent-free, 60°C; ^bYields refer to isolated products.

reaction yield (65%) had observed compared to previous catalysts. Therefore, the study of magnetic iron particles coated by nonmagnetic acid sulfonic (SO₃H) groups had considered because of their supporting effect. As you know, to eliminate the lack of active surface in heterogeneous catalysts, a substrate is usually used as catalyst support [2]. According to the previous information, the higher the activity level, especially for a heterogeneous catalyst, the higher the reactive active sites and the higher the catalyst efficiency, resulting in an increased reaction rate [2]. From the values obtained in Table 1, it can be seen that a significant difference had been observed between the catalyst in the bulk state (bulk-Fe₂O₃-SO₃H) and nano-state due to the particle size (nano-γ-Fe₂O₃-SO₃H). Finally, nano-γ-Fe₂O₃@SiO₂-SO₃H and nano-γ-Fe₂O₃-SO₃H catalysts were made with the highest efficiency (95%) at 3 h and free-solvent conditions (entries 8 and 9). Therefore, we use nano-γ-Fe₂O₃-SO₃H as the optimal catalyst in our study. In the second stage of optimization, different amounts of catalysts (nano-γ-Fe₂O₃-SO₃H) were evaluated. Table 2 demonstrates that all the catalyst consumption values have created the desired product. So when we used the catalyst from 0.05 to 0.15 g, we

Table 2: Influence of the amount of nano-γ-Fe₂O₃-SO₃H on the Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones^a

Entry	γ-Fe ₂ O ₃ -SO ₃ H (g)	Time (h:min)	Yield (%) ^b
1	0.05	3:00	53
2	0.07	3:00	69
3	0.09	3:00	92
4	0.1	3:00	95
5	0.15	3:00	95

^aBenzaldehyde:ethyl acetoacetate:urea = 1.2:1:1.5, solvent free, 60°C; ^bYields refer to isolated products.

The bold entry (entry 4) shows the optimal amount of fabricated catalyst in the Biginelli reaction.

obtained about 53–95% efficiency. The results show that the lesser the amount of nano-γ-Fe₂O₃-SO₃H used, the lower the yield obtained, and when less than the table's values are used (0.05<), the reaction takes longer to produce the product. In contrast, the higher the amount of the catalyst used at a fixed time, the higher the efficiency. Therefore, we obtained 0.1 g of nano-γ-Fe₂O₃-SO₃H as the optimal amount to continue the reaction (entry 4).

In the third stage of optimization, we evaluated the effect of temperature and solvent. As presented in Table 3, this reaction showed better results in solvent-free conditions than when a particular solvent had been used. In the next step, with solvent-free conditions, we examined different temperatures to perform the reaction. According to Table 3 (entry 6), the highest yield at 60°C (3:00 h, 95% yield) had been obtained [53]. Therefore, the results show that temperature changes significantly affect the final performance and increase the reactants. Then, solvent-free conditions and at a temperature of 60°C, we performed the reaction in the presence of ultrasonic radiation and found that this radiation's effect increased the reaction's performance in a shorter time and provided more favorable conditions (00:50 h, 97% yield). Therefore, the optimal conditions for the model reaction are shown in entry 7.

Different species of aromatic aldehyde, including both electron-donating and withdrawing groups, were selected for reaction with ethyl acetate and urea in the presence of 0.1 g of catalyst to produce DHPMs. The results in Table 4 show that all aldehyde derivatives formed the desired product with acceptable yields. According to the recorded data, it can be concluded that due to the decrease in electrophilic properties of the carbonyl functional group, the reaction with electron donor aldehydes takes longer than with the acceptor group aldehydes. The products were characterized by FT-IR, ¹³C NMR, and ¹H NMR spectroscopy and compared

Table 3: Effect of solvent and temperature on the nano-γ-Fe₂O₃-SO₃H catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones^a

Entry	Solvent	Temperature (°C)	Time (h:min)	Yield (%) ^b
1	H ₂ O	Reflux	05:00	15
2	EtOH	Reflux	05:00	91
3	CH ₃ CN	Reflux	05:00	91
4	—	RT	05:00	30
5	—	RT ^c	03:00	42
6	—	60	03:00	95
7	—	60^c	00:50	97
8	—	70	03:00	89
9	—	90	03:00	86
10	—	120	03:00	63

^aBenzaldehyde:ethyl acetoacetate:urea = 1.2:1:1.5, nano-γ-Fe₂O₃-SO₃H (0.1 g); ^bYields refer to isolated products; ^cUltrasonic condition.

The bold entry (entry 7) indicates optimal conditions (solvent and temperature) in the Biginelli reaction.

Table 4: Nano- γ -Fe₂O₃-SO₃H catalyzed Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones^a

Entry	R	R ¹	Product	Time (h:min)	Yield (%) ^b	TON ^c	TOF (h ⁻¹) ^d
1		OEt	4a	00:50	97	267	320.4
2		OEt	4b	00:55	95	272	296.7
3		OEt	4c	01:10	88	278.8	238.3
4		OEt	4d	00:45	92	285.2	380.3
5		OEt	4e	01:00	85	297.9	297.9
6		OEt	4f	01:00	90	283	283
7		OEt	4g	00:45	91	273.4	364
8		OEt	4h	00:55	97	310	338.2
9		OEt	4i	00:55	92	257.5	280.9
10		OEt	4j	00:45	89	312.5	416.7
11		OEt	4k	00:30	95	278	556
12		OMe	5a	01:00	81	270	270
13		OMe	5b	00:50	96	313	375.6

(Continued)

Table 4: Continued

Entry	R	R ¹	Product	Time (h:min)	Yield (%) ^b	TON ^c	TOF (h ⁻¹) ^d
14		OMe	5c	01:10	87	299	256.3
15		OMe	5d	00:55	93	275	300
16		OMe	5e	01:00	85	281	281
17		OMe	5f	00:50	90	288	345.6
18		OMe	5g	01:00	92	284	284
19		OMe	5h	00:50	90	275	330
20		OMe	5i	00:55	91	261	284.7
21		OMe	5j	00:50	90	320	384

^aAll products were characterized by FT-IR, ¹H NMR, and ¹³C NMR spectroscopic data; ^bYield refers to isolated products; ^cTON: moles of produced product from one mol of catalyst; ^dTOF: TON per unit of time (h).

with credible samples (see Supplementary Material). In summary, it can be concluded that replacing different groups in different situations with the Aryl group has not had a significant impact on product production and has shown good product returns.

attacked by the urea compound's nitrogen atom, which causes the compound to dehydrate and form an imine as an intermediate. The next step, β -keto ester enolate, has been added to the reaction medium and attacked the formed imine. Then, due to intramolecular linkages, cycloaddition was performed. Finally, the desired product (DHPM) has been synthesized with cyclodehydration.

3 Reaction mechanism

Scheme 1 presents a satisfactory mechanism for synthesizing 3,4-dihydropyrimidine-2-(1H)-ones in the Biginelli reaction. The acid catalyst (nano- γ -Fe₂O₃-SO₃H) first activates the carbonyl functional group aldehydes. The carbonyl has then

4 Comparison of catalyst

To appraise the activity of the catalyst constructed in this study, the performance of this catalyst (nano- γ -Fe₂O₃-SO₃H)

Scheme 1: A possible mechanism for synthesizing 3,4-dihydropyrimidine-2-(1H)-ones utilizing nano- γ - Fe_2O_3 - SO_3H .

was compared with other catalysts in the synthesis of 3,4-dihydropyrimidine-2-(1H). The results are presented in Table 5. The nano- γ - Fe_2O_3 - SO_3H catalyst shows a very high conversion rate and high efficiency in a short

reaction time. The catalyst was quickly recovered from the reaction mixture and reused at least five times without significant loss of catalytic performance.

5 Reusability of catalyst

One of the essential aspects of the present methodology is the recyclability of the catalyst. It was distinguished that this catalyst could be reused several times. The magnetic properties, easy separation, and reusability of the catalyst attracted particular attention. At the end of the first cycle, the catalyst was removed from the reaction medium by an external magnet, washed with acetone, and dried at ambient temperature. It has then transferred to the reaction medium for reuse in the next cycle. As a consequence (Figure 1), this catalyst's reusability had investigated in five consecutive cycles. According to the diagrams shown in Figure 1, it can be concluded that the performance of the catalyst did not decrease significantly during five consecutive cycles.

Table 5: Comparison of nano- γ - Fe_2O_3 - SO_3H with other works for the 3,4-dihydropyrimidin-2-(1H)-ones^a

Entry	Catalyst	Condition	Time (h:min)	Yield (%)	Ref.
1	Fe(III)/bentonite	Acetonitrile, 80°C	07:00	95	[39]
2	Cu(OTf) ₂	CH ₃ CN, 25°C	12:00	85	[45]
3	PFAMPS	EtOH, reflux	05:00	87	[20]
4	NH ₄ H ₂ PO ₄ /MCM-41	Solvent-free, 100°C	05:00	72	[43]
5	<i>p</i> -Sulfonic acid calixarenes	EtOH, Reflux	08:00	69	[54]
6	Nano- γ - Fe_2O_3 - SO_3H	Solvent-free, 80°C	00:50	97	This work

Figure 1: Recycling of catalysts in the Biginelli reaction.

Figure 2: The TEM image of nano- γ -Fe₂O₃-SO₃H and particle size dispersion diagram of nano- γ -Fe₂O₃-SO₃H fresh (c and d) and reuse (a and b) catalysts.

6 TEM analysis

In this article, TEM analysis is used to examine the surface changes of the catalyst. We here evaluated fresh (Figure 2a) and reuse (Figure 2c) the catalyst. As shown in Figure 2, the obtained images show that the particles are spherical, and the use of catalyst in five successive cycles did not significantly affect the catalyst's surface morphology and particle size. To obtain the average particle size, we measured the dimensions of approximately 100 particles using a histogram diagram. Figure 2b and d show that the average particle size is 17.5 and 20.46 nm, respectively.

7 Conclusion

We have successfully synthesized 3,4-dihydropyrimidine-2-(1H)-ones by a solid acid nanocatalyst (nano- γ -Fe₂O₃-SO₃H). The catalytic activity of nano- γ -Fe₂O₃-SO₃H was checked out through a one-pot synthesis of 3,4-dihydropyrimidine-2-(1H)-ones via the Biginelli reaction. We applied catalyst in

Scheme 2: Procedure for preparation of nano- γ -Fe₂O₃-SO₃H.

Scheme 3: Synthesis of Biginelli 3,4-dihydropyrimidin-2-(1*H*)-ones catalyzed by $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$.

a solvent-free condition at 60°C and ultrasonic irradiation to promote the reaction to this aim. The result was successful, and the catalyst yielded a high efficiency in the reaction. Besides, nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ includes advantages such as magnetic separator and reusability, so that after five runs, no reduction trend was observed. As a result, this article presented an economical, green, and appropriate investigation to synthesize 3,4-dihydropyrimidine-2-(1*H*)-ones. Therefore, the newly synthesized nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ could be used as a promising heterogeneous catalyst for a wide range of multifunctional applications.

8 Experimental

8.1 The general method for preparing catalyst (nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$)

According to the previously reported work [7], the nano- $\gamma\text{-Fe}_2\text{O}_3$ had prepared using the coprecipitation method [55]. Nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ was being fabricated using a suction flask equipped with a constant pressure drop funnel and a gas inlet tube to conduct HCl gas on an adsorbent solution charged with nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ nanoparticles as catalysis (Scheme 2). This catalyst (nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$) was made at room temperature by reaction of magnetic nanoparticles with chlorosulfonic acid. Therefore, 1.1636 g (0.0099 mmol) of chlorosulfonic acid was added dropwise for 30 min. After the end of the reaction, HCl gas had extracted from the reaction medium as the only by-product. The final mixture had stirred for 30 min to obtain a solid brown color from sulfonic acid (3.8 g).

8.2 Method of synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones

In this section, as shown in Scheme 3, urea (1.5 mmol), benzaldehyde (1.2 mmol), ethyl acetoacetate (1 mmol),

and catalyst (0.1 g) made utilized at 60°C under ultrasonic irradiation and free solvent for the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones in the Biginelli reaction [53]. After completing the reaction, due to the magnetic properties of the nano- $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$, the reaction mixture was continuously stirred. After 10 s, a clear mixture is obtained, and the catalyst has been separated from the solution by simple decantation. Finally, the catalyst was washed with acetone and air dried for later use.

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Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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