Highly Efficient and Magnetically Recoverable Niobium Nanocatalyst for the Multicomponent Biginelli Reaction

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A new magnetically recoverable nanocatalyst was prepared by coating magnetite with niobium oxide ($Fe_3O_4@Nb_2O_5$) by using a simple wet impregnation method. The $Fe_3O_4@Nb_2O_5$ nanocatalyst was fully characterized, and its catalytic activity was evaluated by using the one-pot, three-component Biginelli reaction, with the aim to synthesize 1,4-dihydropyrimidinones, a class of compounds with diverse pharmacological properties. The developed protocol was applied to a wide range of aliphatic and aromatic substrates, and structurally diverse products were obtained in excellent yields. Compared with copper and nickel nanocatalysts, the $Fe_3O_4@Nb_2O_5$ nanocatalyst demonstrated superior catalytic activity at a remarkably low catalyst loading (0.1 mol%). This niobium nanocatalyst could be easily separated from the reaction mixture with an external magnet and was reused several times without any loss of its catalytic activity. Moreover, although the Biginelli reaction is a century-old reaction, its mechanism is still a controversial subject, and our investigation provided an insight into the reaction mechanism.

Introduction

Catalysis is one of the most important fields in organic synthesis and has been receiving considerable attention from both academia and industry.[1] In this field, transition-metal compounds are a significant class of catalysts because they are widely used in some of the most important transformations in organic synthesis,[2] such as C—C bond formation, oxidation reactions, and reduction reactions.[3] Thus, various homogeneous catalysts were developed in the last decade and used as tools in the most diverse types of organic transformations.[4] However, despite their numerous advantages, homogeneous catalysts suffer the drawback of difficult separation from the reaction medium on completion of the reaction.[5]

The difficulty in catalyst separation has led to the development of new heterogeneous catalysts for organic transformations, and supported-heterogeneous catalysts, also called "semi-heterogeneous" or "quasi-homogeneous" catalysts, have been used as excellent tools for improving and developing environmentally benign protocols.[6] Several advantages of supporting catalysts on nanosized materials have been observed, such as a substantial increase in the surface area of the catalyst promotes its contact with the reactants, which is consistent with homogeneous catalysis,[7] along with the additional feature of the catalyst recovery, which makes the process eco-friendly and less expensive.[8]

For designing and synthesizing different nanocatalysts for specific applications, many solid supports have been used, for example, silica,[9] carbon,[10] alumina,[11] and polymers.[12] Among these supports, magnetic nanoparticles such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are considered as ideal supports for the immobilization of catalytic materials because they are inexpensive, chemically stable, and easy to prepare and can be recovered by applying an external magnetic field.[13] Several transition metals, such as palladium,[14] nickel,[15] cobalt,[16] copper,[17] cerium,[18] molybdenum,[19] ruthenium,[20] and rhodium,[21] have been immobilized on a magnetic matrix. Notwithstanding the advances in this field, there are still a range of opportunities for the design, synthesis, and application of improved magnetically recoverable nanocatalysts.

Until recently, niobium compounds have been known for their advantageous features as a support for catalysts in a wide range of reactions, mostly in catalytic oxidation reactions.[22] Even though there are a few differences in physicochemical properties of niobium and those of its neighbors in the periodic table (vanadium, molybdenum, and zirconium), the catalytic behavior and high acidity of niobium compounds are different from those demonstrated by compounds of the neighboring elements. Niobium catalysts demonstrate high acidity on their surface, demonstrating high activity and selectivity, even in the presence of water in the reaction medium.[23]

Because of its exceptional chemical properties, niobium is an inexpensive metal that is abundant in Earth's crust.

Considering all these facts and the low application of niobium compounds in organic synthesis,[24] a wide window is now open for the exploitation of niobium species as catalysts in acid-demanding chemical processes, such as multicomponent reactions.

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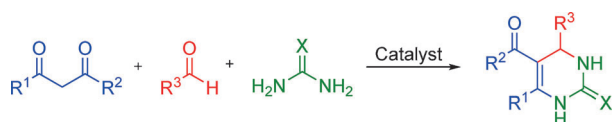
Scheme 1. Biginelli reaction. $R^1 = H$, alkyl; $R^2 = O$–alkyl; $R^3 = H$, alkyl, aryl, heteroaryl; $X = O$, S, NR.

Scheme 2. Synthesis of the niobium nanocatalyst.

In this context, the Biginelli reaction[25] (Scheme 1), a century-old reaction, is one of the most well-designed methodologies used for the synthesis of dihydropyrimidinone (DHPM) or thione derivatives, an important family of compounds known for their diverse pharmacological properties, which act as antibacterial, antiviral, and calcium channel modulators as well as anticancer and antihypertensive agents.[26–32] The reported biological activities of DHPMs encourage research groups to build structurally diverse libraries of bioactive compounds that are active even as racemates.[33, 34]

Because DHPM derivatives are widely used, many approaches for their synthesis can be found in the literature.[35] Nevertheless, most protocols have severe limitations, for example, low yields, high cost and catalyst loadings, and low catalyst recovery and recyclability.

Furthermore, questions about the efficacy of solvent-free and/or catalyst-free reactions and the effect of heating versus microwave irradiation still lead to discussions in the scientific community. To overcome these drawbacks, which have thrown us toward the search of new, better, and benign conditions for the Biginelli reaction, we present herein the synthesis, characterization, and application of an efficient, eco-friendly, and highly recoverable nanocatalyst comprising niobium oxide supported on magnetite ($Fe_3O_4@Nb_2O_5$).

The catalytic activity of this new magnetically recoverable niobium nanocatalyst was evaluated for the synthesis of a wide range of DHPM derivatives with high structural diversity through the Biginelli reaction. A comparison of the efficiency of this new nanocatalyst with that of other known transition-metal nanocatalysts has revealed interesting and promising results.

Results and Discussion

Nanocatalyst characterization

The Fe_3O_4 nanoparticles used as a solid support for the catalyst were prepared through coprecipitation by using urea as the pH-controlling agent. The $Fe_3O_4@Nb_2O_5$ nanocatalyst was synthesized by using a simple wet impregnation method with ammonium niobate oxalate hydrate ($C_4H_4NNbO_9\cdot 3H_2O$) as the niobium source (Scheme 2). The hydrolysis of the niobium precursor in alkaline medium leads to the aggregation of niobium hydroxides over the surface of Fe_3O_4 nanoparticles, which undergo condensation to eliminate water and form the Nb_2O_5 layer.

Both the support and the final nanocatalyst were fully characterized by using XRD, inductively coupled plasma optical emission spectroscopy, high-resolution TEM (HRTEM), scanning
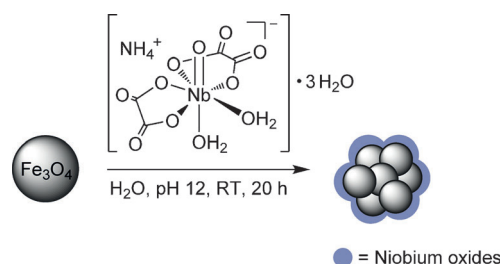
TEM (STEM), and temperature-programmed desorption of ammonia.

The HRTEM images of the nanocatalyst (Figure 1) show that the particles exhibited an equiaxed morphology and are within the nanosize range (15–40 nm), with some tendency to clustering. Moreover, a layer around a small cluster of nanoparticles can be seen in Figure 1 b.
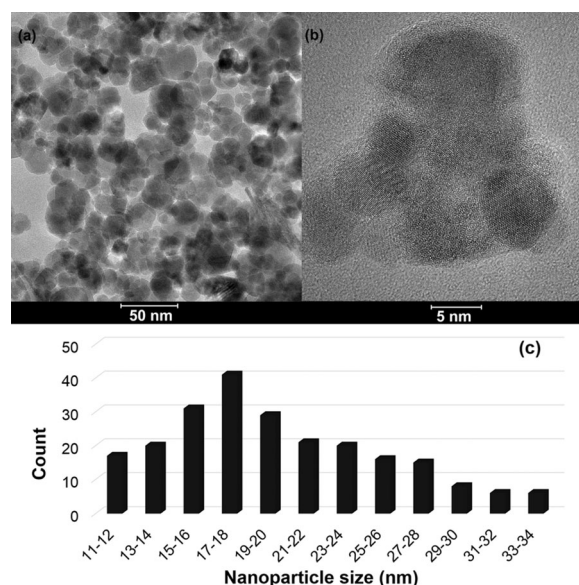
Figure 1. a) TEM image, b) HRTEM image, and c) particle size distribution analysis of the niobium nanocatalyst.

To comprehend the formation of this layer around the nanoparticles and to evaluate the incorporation of Nb_2O_5 into the Fe_3O_4 nanoparticle surface, STEM analysis was performed. The results are depicted in Figure 2, part a of which shows the details of the bright-field STEM image and the line along which the energy-dispersive X-ray spectroscopy (EDS) line profiles of the niobium nanocatalyst (part b) were recorded.

The EDS line profile (Figure 2b) shows the niobium and iron compositions along the line shown in Figure 2a. Notably, the niobium composition is constant along the entire line. The iron composition is higher in the center of the nanoparticle cluster and lower at the edges: at the left edge of the sample (from 0 to 15 nm), the iron composition is constant and almost zero, whereas in the center (from 16 to 125 nm), the iron composi-
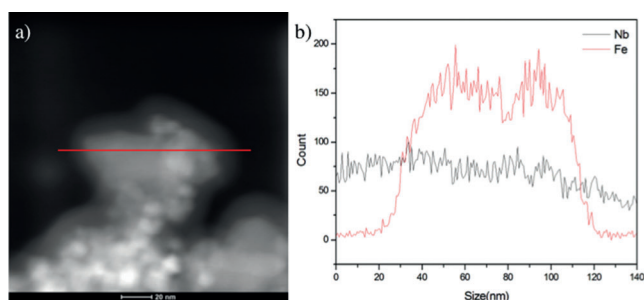
Figure 2. a) Bright-field STEM image showing the amorphous Nb_2O_5 on the Fe_3O_4 surface, and b) EDS line profile. Scale bar = 20 nm.

tion is considerably higher; at the right edge of the sample (from 126 to 140 nm), the iron composition is again zero. These results suggest that Nb_2O_5 completely coats the nanoparticle cluster and forms a 15 nm thick layer around it. The EDS results are fairly interesting because the formation of a layer around the Fe_3O_4 support eliminates any possibility of iron oxides participating in catalytic reactions. The EDS elemental maps were also acquired at low magnification to confirm the homogeneity of Nb_2O_5 on the Fe_3O_4 surface (Figure 3).
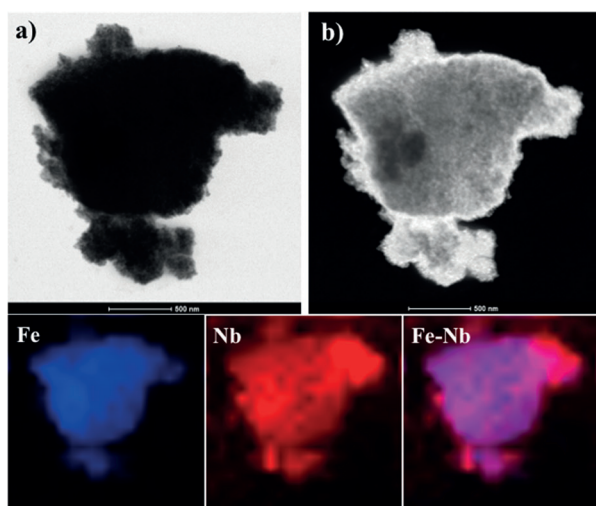

Figure 3. EDS elemental maps of $Fe_3O_4@Nb_2O_5$: a) bright-field STEM image, b) dark-field STEM image, c) Fe map, d) Nb map, and e) Fe + Nb map. Scale bars = 500 nm.

These maps also revealed that the surface of the nanocatalyst is rich in niobium, and the combined results of electron microscopy suggested that the nanocatalyst forms a well-defined layer around Fe_3O_4, which forms a core–shell structure.

The powder XRD measurements confirmed the Fe_3O_4 crystallographic phase and the average size of the crystallites, estimated by the Debye–Scherrer equation, was 17 nm (Figure S1). The powder XRD patterns of $Fe_3O_4@Nb_2O_5$ showed only the characteristic diffraction peaks of Fe_3O_4 (as expected) because of the amorphous character of $Nb_2O_5 \cdot n H_2O$.[36] The exact amount of niobium in the nanocatalyst was determined from inductively coupled plasma optical emission spectroscopy analysis, and it was found to be 6.5 wt%.

The temperature-programmed desorption of ammonia was performed to study the effect of the $Nb_2O_5 \cdot n H_2O$ shell, also known as niobic acid, on the acidity of the nanocatalyst. The results reveal that the acidity of the nanocatalyst is at least 13 times higher than that observed with Fe_3O_4 nanoparticles (see details in the Supporting Information).

To evaluate the effect of the Nb_2O_5 shell on the magnetic properties of this material, measurements were performed on a superconducting quantum interference device. The magnetization curves of both the Fe_3O_4 sample and the niobium nanocatalyst is shown in Figure 4. The saturation magnetization of the Fe_3O_4 sample was 82 emu g^{-1} and of the niobium nanocatalyst 70 emu g^{-1}, which indicates that the functionalization of Fe_3O_4 with niobium species did not affect its magnetic behavior considerably.
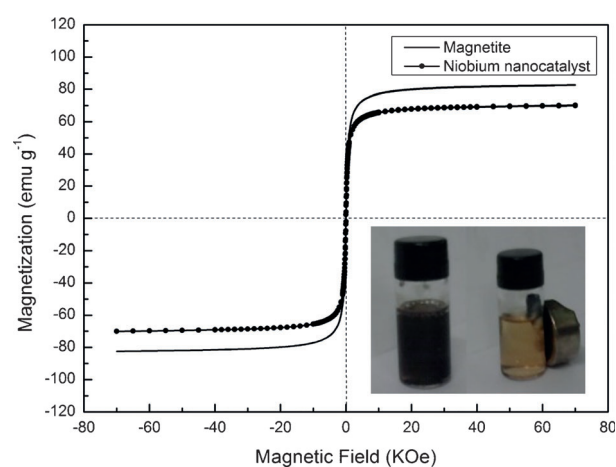

Figure 4. Magnetization curves of Fe_3O_4 and the niobium nanocatalyst. Inset: Catalyst separated from reaction medium by a magnet.

Evaluation of the catalytic activity of the niobium nanocatalyst in the DHPM synthesis

The catalytic activity of the niobium nanocatalyst was evaluated in the synthesis of DHPMs through the Biginelli reaction. Thus, the multicomponent reaction between benzaldehyde, ethyl acetoacetate, and urea was chosen as the model reaction to search for optimal conditions. Bearing this in mind, different benign solvents and catalysts as well as catalyst loadings were studied (Table 1).

The search for optimal conditions for the Biginelli reaction using the newly developed niobium nanocatalyst started by studying the catalyst loading. To understand how this parameter affected the reaction, three reactions were performed with ethanol as the solvent at 80 °C (Table 1, entries 1–3). The yields of these three reactions indicated that the catalyst loading has a significant effect on the reaction result, and with use of a high catalyst loading (10 mol%; entry 1), no product formation was observed, whereas small loadings (1 and 0.1 mol%; entries 2 and 3) afforded products in excellent yields. No product was formed with the high catalyst loading perhaps because of the high acidity of niobium, which may have interacted with urea, preventing it from reacting as required. This hy-

Table 1. Optimization of the reaction conditions for the synthesis of DHPMs through the Biginelli reaction.
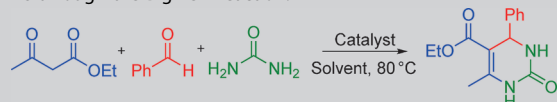
| Entry[a]	Catalyst	Catalyst loading [mol%]	Solvent	Yield[b] [%]
1	$Fe_3O_4@Nb_2O_5$	10	ethanol	0
2	$Fe_3O_4@Nb_2O_5$	1	ethanol	99
3	$Fe_3O_4@Nb_2O_5$	0.1	ethanol	99
4	$Fe_3O_4@Nb_2O_5$	0.1	water	20
5	$Fe_3O_4@Nb_2O_5$	0.1	glycerol	52
6	$Fe_3O_4@Nb_2O_5$	0.1	PEG 400	39
7	$Fe_3O_4@Nb_2O_5$	0.1	–	98[c]
8	Nb_2O_5	0.1	ethanol	24
9	Fe_3O_4	0.6[d]	ethanol	60
10	–	–	ethanol	54

[a] Unless otherwise specified, all the reactions were performed with benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol), and catalyst (0.1 mol%) in the presence of ethanol (500 μL) in a closed vial at 80 °C for 12 h; [b] Isolated yields; [c] Solvent-free reaction performed with a benzaldehyde/ethyl acetoacetate/urea molar ratio of 1:2:2 at 80 °C for 2 h; [d] 1.6 mg Fe_3O_4 (equal to the amount used as support for 0.1 mol% loadings of niobium nanocatalyst).

pothesis was not thoroughly studied; however, the isolation of the Knoevenagel intermediate as the single product of the reactions performed with high catalyst loadings strongly suggests that niobium withdraws the urea component from the reaction. Moving forward to the investigation of the effect of the solvent on this catalytic system, five reactions were performed with 0.1 mol% of the niobium nanocatalyst loading in the presence of eco-friendly solvents, such as water, glycerol, polyethylene glycol 400 (PEG 400), and ethanol (entries 3–6), or in the absence of a solvent (entry 7). The best solvent for this reaction protocol proved to be ethanol (entry 3), in which the desired product was isolated in 99% yield. The reaction performed in water afforded a low yield (entry 4), which could be due to the low solubility of chemicals in this polar solvent, whereas similar complications were observed for glycerol (entry 5). With PEG 400 as the solvent, the separation of the desired DHPMs from the reaction medium was compromised, which caused the yield to decrease to 39% (entry 6).

In the absence of a solvent (entry 7), the reaction afforded the Biginelli product in 98% yield after 2 h. However, if the solvent-free approach was applied to the multicomponent reaction using other substituted benzaldehydes, the reaction did not proceed well, probably owing to the physical state and low solubility of the aldehydes in other components of the reaction. The limitations of the solvent-free Biginelli reaction have already been revealed by other research groups.[37]

To examine the significance of supporting the catalyst on Fe_3O_4 nanoparticles, we performed the reaction with bulk Nb_2O_5 as a catalyst (entry 8), with bare Fe_3O_4 nanoparticles (entry 9), and without any nanocatalyst (entry 10). Under optimal reaction conditions, the reactions performed without any catalyst (entry 10) and with bare Fe_3O_4 nanoparticles (entry 5) gave similar moderate yields whereas the reaction performed

with bulk Nb2O5 (entry 8) gave a lower yield. These results confirm that the catalytic activity derives from the highly acidic niobium species present on the nanocatalyst surface as well as that it is increased significantly by the increase in the surface area of the catalyst, which is a result of supporting the active phase in a nanosized material. After obtaining the optimal reaction conditions, we focused on comprehending how other analogous magnetically recoverable transition-metal catalysts affect the reaction. To accomplish this, the efficiency of the niobium nanocatalyst was compared with that of the already known copper and nickel nanocatalysts under optimal reaction conditions. Our results (Figure 5) indicate that both the nature
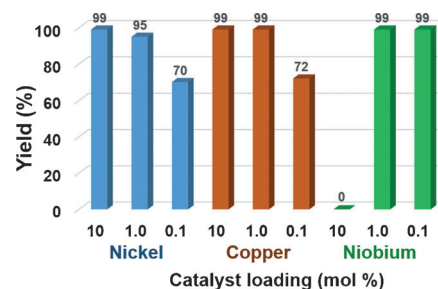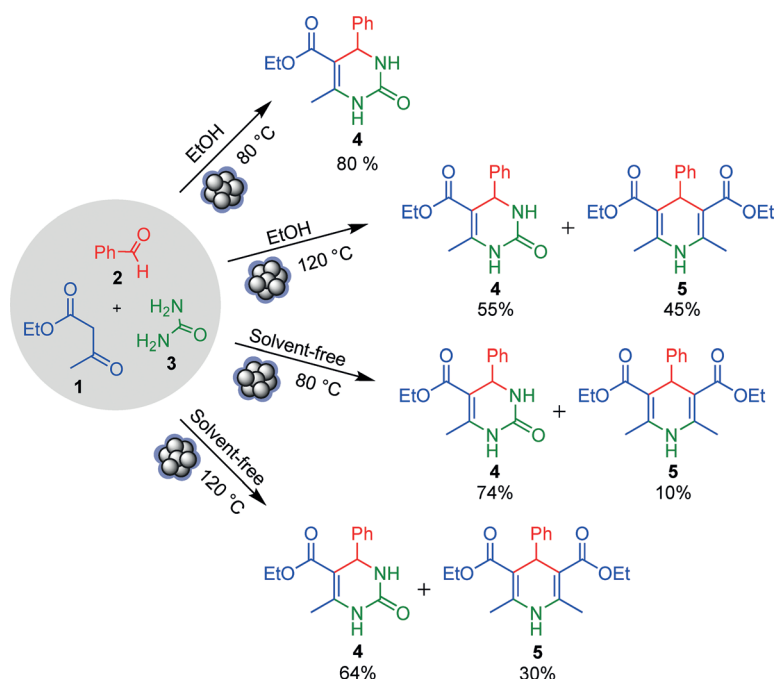

Figure 5. Evaluation of the catalyst effect on the Biginelli reaction.

and the loading of the nanocatalyst have a significant effect on the yields of the Biginelli product. As shown in Figure 5, if the three nanocatalysts were evaluated at a 10 mol% loading, the niobium nanocatalyst afforded no product because the Knoevenagel intermediate was the only isolated product (93% yield) whereas copper and nickel nanocatalysts produced DHPMs in high yields (99% for both).

With the decrease in the catalyst loading to 1 mol%, all three nanocatalysts afforded good yields: 99% for both copper and niobium nanocatalysts and 95% for nickel. At a nanocatalyst loading of 0.1 mol%, full conversion was achieved only with the niobium nanocatalyst, whereas the nickel and copper nanocatalysts demonstrated a diminished performance and afforded the product in only 70 and 72% yields, respectively. To study the effect of microwave irradiation on this catalytic system, four experiments were performed at 80 and 120 °C either with ethanol as a solvent or without any solvent. The results of these experiments (Scheme 3) indicated that microwave irradiation does not have a pronounced effect on the reaction performance in the presence of a solvent, which is in accordance with previous studies by Kappe and co-workers.[38]

As depicted in Scheme 3, the reaction performed in the presence of ethanol at 80 °C afforded an 80% yield after 2 h and the Knoevenagel adduct was isolated as a byproduct. Even after longer reaction times (4 h) under the same conditions, the reaction could not be completed, and the isolated yield of DHPM **4** was slightly higher (86%). If the temperature was increased to 120 °C, the Knoevenagel adduct **5** was completely consumed after 30 min; however, a byproduct, 1,4-dihydropyridine (DHP; **5**, also known as the Hantzsch ester), was observed; the DHP product is formed through the condensation of benzaldehyde, 2 equiv. of the β-ketoester, and ammo-

Scheme 3. Evaluation of the Biginelli reaction under microwave irradiation.

ed in Figure 6, in the first run the components were converted to the desired product (>99% isolated yield). In the subsequent runs, the conversion to the DHPM products was complete, and the isolated yields began decreasing only after the seventh run.

In addition to pointing out the advantage of the use of low-loading catalysts, the recyclability studies of $Fe_3O_4@Nb_2O_5$ showed that this catalyst could be reused several times without any loss of its catalytic activity.

The mechanism of the Biginelli reaction is still a controversial subject; however, it is already known that the reaction that leads to the formation of the DHPM product can occur

nia, which is produced in situ by the decomposition of the urea component, a common side reaction that occurs in the presence of water at temperatures above 90 °C. Under these reaction conditions, the DHP product was formed in 35% yield whereas the DHPM product was formed in 55% yield. If the reaction was performed in the absence of any solvent, the yield at 80 °C was 10% more than the yield at 120 °C, and in both cases the Hantzsch ester was isolated as a byproduct.

After exploring all major aspects of the Biginelli reaction by using the newly developed niobium nanocatalyst, we investigated the scope of the reaction for the synthesis of DHPMs (Scheme 4). Under optimal reaction conditions, the reaction was performed at 80 °C with ethanol as an eco-friendly solvent and a low nanocatalyst loading (0.1 mol%). The formation of DHPM products was not affected by steric and electronic effects in the aryl moiety of the aldehydes, because both substrates having one or more electron-donating or -withdrawing groups led to the formation of products **4** and **6–17**, with yields in the range of 84–95%. With aliphatic aldehydes, products **18** and **19** were obtained, with yields decreasing from excellent to good (78 and 76%, respectively). Similarly, the choice of urea or thiourea did not have a significant effect on the yields, which were achieved in the range of 83–92% (products **20–25**).
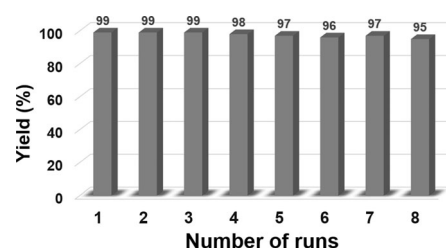
After evaluating the scope of the Biginelli reaction by using the new niobium catalytic system, we focused on the recyclability of the nanocatalyst and scaling up of the reaction (Figure 6).

To accomplish that, the reactions were performed on a 10 mmol scale under optimal reaction conditions. After the completion of the reaction, the nanocatalyst was separated from the reaction medium with a magnet, washed with ethanol, dried under vacuum, and reused several times. As depict-

Figure 6. Evaluation of the recyclability of the niobium nanocatalyst.

through three different pathways[39] in which the process starts by the formation of three possible intermediates: Knoevenagel, iminium, or enamine (Scheme 5). To gain insight into the reaction mechanism in the presence of the niobium nanocatalyst, we performed an experiment under optimal reaction conditions, in which the composition of the reaction medium was monitored over time by injecting aliquots withdrawn from the reaction medium at regular time intervals in GC–MS analysis (Figure 7). As shown in Figure 7, the concentration of the initial GC–MS injection (at $t = 30$ min) was approximately 70% for the Knoevenagel adduct and 30% for the Biginelli product. As the reaction proceeded, the intermediate concentration decreased quickly whereas the Biginelli product concentration increased. This finding suggests that the reaction evaluated under optimal reaction conditions occurs via the Knoevenagel intermediate mechanism.

On the basis of the experimental observations and the assumption that the reaction occurs via the Knoevenagel intermediate mechanism, we proposed a catalytic cycle (Scheme 6). In the proposed reaction mechanism, the reaction starts with the Knoevenagel condensation between the β-ketoester **A** and the aldehyde **B**, forming the adduct **C**, which, after water elimi-
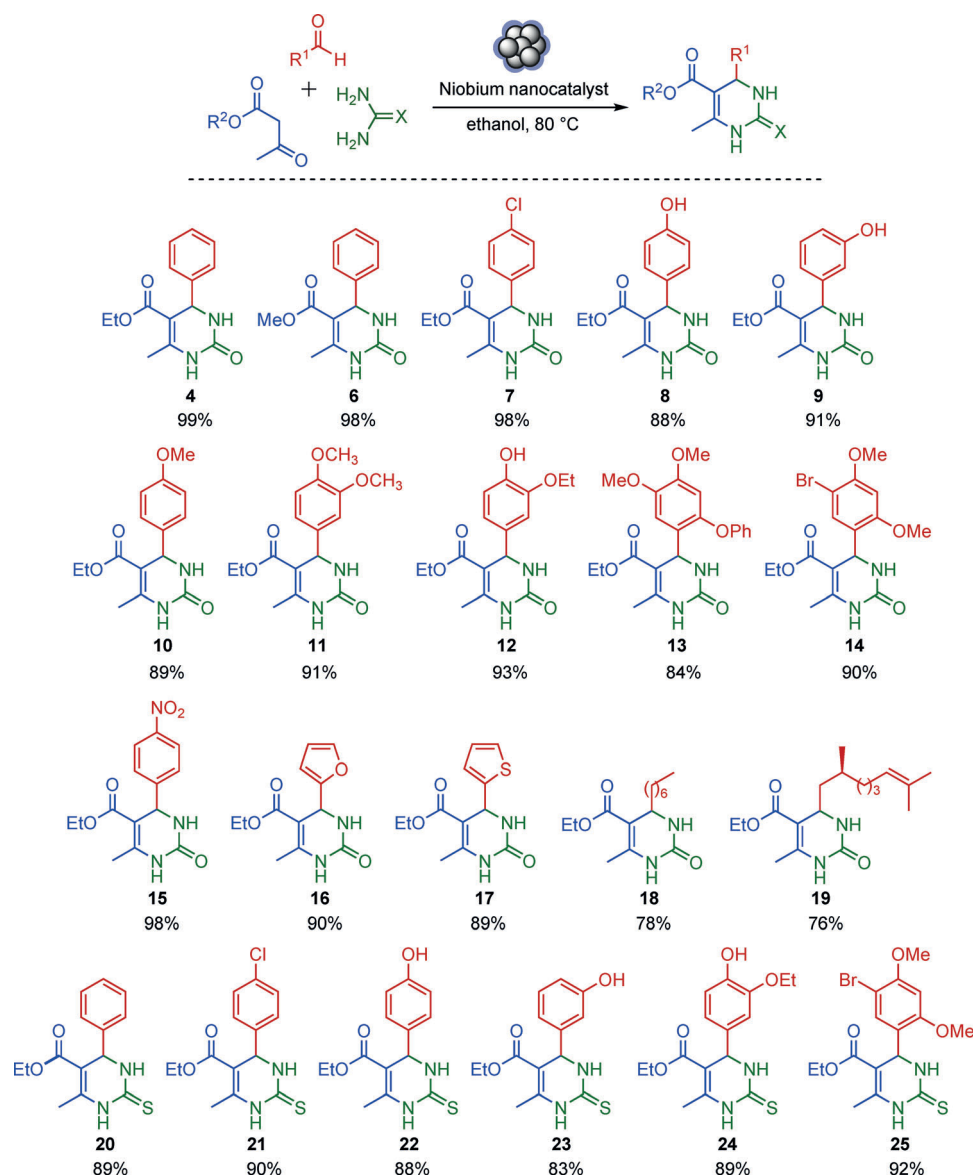
Scheme 4. Scope of the reaction for the synthesis of DHPMs by Biginelli condensation.
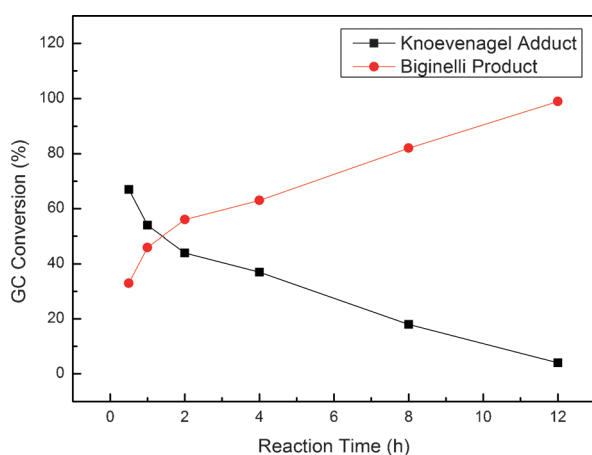
nation, gives α,β-conjugated enone **D**. This intermediate is attacked by an amino group of a urea or thiourea molecule **E**, which gives **F**.

An intramolecular attack of the remaining amino group of the urea moiety on the neighboring carbonyl group forms the six-membered structure **G**, which regenerates the nanocatalyst. Finally, the elimination of water gives the Biginelli product.

Conclusions

Herein, we have developed and characterized a highly efficient magnetically recoverable niobium nanocatalyst from inexpensive precursors magnetite and ammonium niobate(V) oxalate hydrate. This new niobium nanocatalyst has great advantages compared with nickel and copper nanocatalysts, especially in terms of the amount of the catalyst required in the reaction. If the niobium nanocatalyst is used in the acid-demanding multicomponent Biginelli reaction, it proves to be quite effective and affords dihydropyrimidinone/thione products in good to excellent yields with a low catalyst loading (0.1 mol%) under optimal reaction conditions. Moreover, owing to its magnetic behavior, the nanocatalyst can be recovered easily and reused several times without any loss of its catalytic activity. Robustness, magnetically recoverable nature, and high efficiency are the notable features of this nanocatalyst. Further investigation of this nanocatalytic system in other acid-demanding organic transformations is ongoing in our laboratory.

Experimental Section

General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 spectrometer (400 and 100 MHz, respectively). All NMR spectra were obtained with DMSO-d_6. Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under UV light or stained with KMnO$_4$ solution.

Figure 7. Evaluation of reaction medium composition monitored over time by GC-MS.
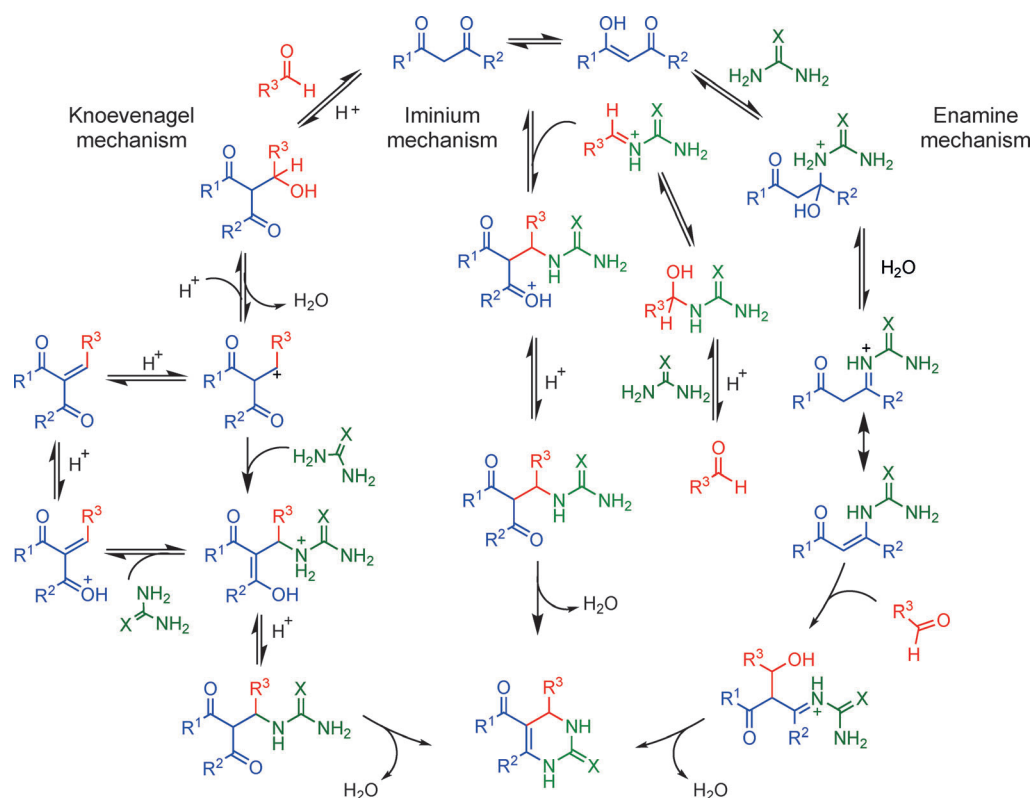
Scheme 5. Possible mechanisms for the Biginelli reaction.
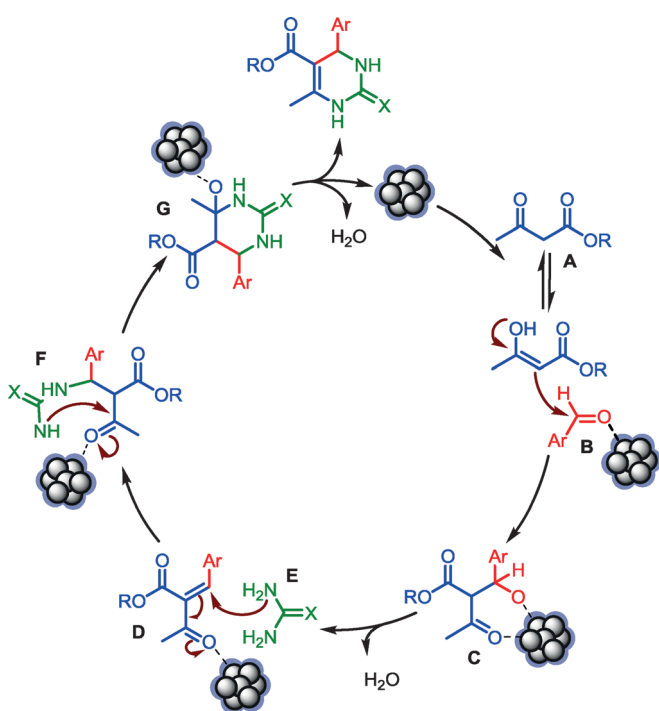
Scheme 6. Catalytic cycle proposed for the Biginelli reaction via the Knoevenagel intermediate mechanism.

Preparation of Fe₃O₄ nanoparticles

FeCl₃·6 H₂O (5.4 g, 33 mmol) and urea (3.6 g, 60 mmol) were dissolved in water. The mixture was stirred at 90 °C for 2 h. After cooling to RT, FeCl₂·4 H₂O (2.0 g, 15 mmol) was added to the solution and the pH was adjusted to 10 with NaOH solution (0.1 mol L⁻¹). The obtained hydroxides were treated in an ultrasonic bath for 30 min. After aging for 12 h, the fine black powder (Fe₃O₄) was washed several times with distilled water and separated with a magnet. The washing process was repeated until the pH of the suspension became neutral. The obtained solid was washed once with ethanol and dried under vacuum.

Preparation of the nanocatalysts

General procedure: The nanocatalysts were prepared by using the wet impregnation method, in which Fe₃O₄ (2 g) was dispersed in water followed by the addition of the metal oxide precursor salt (C₄H₄NNbO₉·n H₂O, CuCl₂·2 H₂O, and Ni(NO₃)₂·2 H₂O for niobium, copper, and nickel nanocatalyst, respectively, to obtain 10 wt %). After stirring the mixture for 1 h at RT, the pH was adjusted to 12 with NaOH solution (1 mol L⁻¹). After stirring the mixture for 20 h at RT, the nanocatalysts obtained were washed with distilled water and separated with a magnet. The washing process was repeated until the pH of the suspension became neutral. The obtained solid was washed once with ethanol and dried under vacuum.

Niobium nanocatalyst-mediated synthesis of DHPMs by Biginelli condensation

General procedure: A mixture of aldehyde (1 mmol), acetoacetate (1 mmol), urea or thiourea (1.5 mmol), ethanol (500 µL), and niobi-

um nanocatalyst (1.5 mg, 0.1 mol%) was stirred in a 10 mL closed test tube at 80 °C for 12 h. After cooling to RT, the catalyst was separated from the reaction medium with a magnet and washed several times with ethanol. The combined organic layers were concentrated and purified by using flash column chromatography on silica gel with hexane/acetate as an eluent.

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