Sonochemical synthesis of chromenes catalyzed by L-phenyl alanine-attached nano-Fe$_3$O$_4$@SiO$_2$

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ABSTRACT
An efficient multi-component synthesis of 10,10-dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-diones is described by a one-pot condensation reaction of aldehydes, dinedone and 4-hydroxycoumarin using L-phenyl alanine tethered to nano-Fe$_3$O$_4$@SiO$_2$ under ultrasonic irradiation. The catalyst has been characterized by Fourier-transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XRD), scanning electron microscope (SEM), Energy-dispersive X-ray spectroscopy (EDX), thermal gravimetric analysis (TGA) and vibrating-sample magnetometer (VSM). Atom economy, wide range of products, high catalytic activity, excellent yields in short reaction times, reusability of the catalyst and low catalyst loading are some of the important features of this protocol.

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Introduction
Ultrasound irradiation has been employed to accelerate a number of practicable reactions through the formation, growth, and implosive collapse of bubbles (1–3). Compounds with chromene structure are important substructures for both medicinal and synthetic organic chemists (4). Chromenes have received much attention due to their potency and wide spectrum of biological activities such as antimicrobial (5), antioxidant (6), antimalarial (7), antibacterial (8), and anticancer (9). Therefore, the development of facile, efficient, flexible and useful methods for the synthesis of chromenes is still favorable (10). Indeed, the synthesis of chromenes through multi-component reactions (MCRs) has attracted much attention due to excellent synthetic efficiency, experimental simplicity, inherent atom economy and their ability to create molecular complexity starting from simple substrates (11, 12). The core/shell Fe$_3$O$_4$ nanoparticles are easily prepared and have been widely studied due to their unique physical properties. The core/shell Fe$_3$O$_4$ nanoparticles can be recycled from the medium of reaction by external magnetic field (13, 14). The surface of MNPs can be functionalized simply through suitable surface modifications to provide the attachment of a variety of favorable functionalities (15–24). Therefor the modified magnetic nanoparticles with all these features are used for varied organic reactions under ultrasonic irradiations (25, 26). The ultrasound approach offers several advantages such as higher yields, enhanced organic reaction rates, milder reaction conditions, and waste minimization compared with traditional methods and saving money and energy. Compared to conventional
heating which provides thermal energy in the macro system, ultrasound irradiation is able to activate many organic reactions by providing the activation energy in micro environment (27–32). Herein we report an efficient method for the synthesis of L-phenyl alanine-supported Fe₃O₄@SiO₂ core/shell MNPs as an efficient catalyst for the preparation of 10,10-dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-diones by one-pot condensation of aldehydes, dimedone and 4-hydroxy coumarin under ultrasonic irradiation (Scheme 1).

Experimental

Materials

All commercially available reagents were used without further purification and purchased from the Merck Chemical Company in high purity. The used solvents were purified by standard procedure.

Apparatus

Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (Cu Kα radiation, λ = 0.154056 nm), at a scanning speed of 2°/min from 10° to 100° (2θ). Scanning electron microscope (SEM) of nanoparticles was performed on a Model FESEM. The magnetic properties of nanoparticles have been measured by a vibrating sample magnetometer (VSMF, PPMS-9 T) at 300 K Danesh Pajoh magnetic co. in Science and Technology Park, University of Kashan, Kashan Iran.

General procedure for the preparation of Fe₃O₄@SiO₂–L-phenyl alanine nanocatalyst

Nano-Fe₃O₄@SiO₂-L-phenyl alanine were prepared as following: at first, nano-Fe₃O₄@SiO₂ microspheres (1 g) was dispersed in ethanol (30 mL) and a solution of 24 mL of sodium oleate in a 200 mL three-necked flask was vigorously stirred under an inlet of nitrogen, then mixture was kept under ultrasonic irradiation 90 W for 30 min. The L-phenyl alanine (0.6 gr) was then added to the suspension under ultrasonic irradiation for 30 min and nitrogen protection for 1 h. MNPs were separated by an external magnet and washed with water and ethanol and dried in an oven at 50°C for 9 h.

Synthesis of 10, 10-dimethyl-7-(phenyl)-10, 11-dihydrochromeno[4,3-b]chromene-6, 8(7H, 9H)-diones (4a-h)

A mixture of benzaldehydes (0.11 g, 1 mmol), dimedone (0.14 g, 1 mmol) and 0.05 gr of nano-Fe₃O₄@SiO₂-L-phenyl alanine in 10 mL ethanol was sonicated at 60 W for 6–10 min. Then 4-hydroxy coumarin (0.17 g, 1 mmol) was added to mixture. After completion of the reaction, 10 mL ethanol was added to the reaction mixture and nano-Fe₃O₄@SiO₂-L-phenyl alanine was separated by external magnetic field. The precipitate was washed with ethanol to afford the pure product and then dried well under vacuum pump.

Characterization of compounds

10,10-Dimethyl-7-(4-methylphenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione (4a)

white powder; yield: 86%, mp 174–176°C, IR (KBr): νmax 3124.3, 2964.6, 2867.0, 1728.0, 1662.9, 1611.7, 1369.3, 1197.9, 1053.7, 758.5 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆): 7.87 (d, 1H, J = 8.2, 1.8 Hz), 7.59–7.56 (m, 1H), 7.40–7.27 (m, 4H), 7.07 (d, 2H, J = 8.2 Hz), 6.55 (s, 1H), 2.77 (d, 1H, J = 17.2 Hz), 2.67 (d, 1H, J = 17.2 Hz), 2.36 (d, 1H, J = 16.6 Hz), 2.27 (d, 1H, J = 16.6 Hz), 2.27 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H) ppm 13CNMR (100 MHz, DMSO-d₆): 195.8, 161.7, 160.5, 152.4, 139.6, 136.5, 132.2, 129.1, 128.4, 128.3, 124.5, 122.7, 116.9, 115.2, 113.8, 106.8, 50.8, 40.9, 33.2, 32.3, 29.3, 27.6, 21.2 ppm; Anal. Calcd. for C₂₅H₂₂O₄: C, 77.70; H, 5.74. Found: C, 77.52; H, 5.64. MS (EI) (m/z): 386.

Scheme 1. Nano- Fe₃O₄@SiO₂–L-phenyl catalyzed synthesis of 10,10-Dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-diones.
10,10-Dimethyl-7-(2-chlorophenyl)-10,11-dihydrochroomeno[4,3-b] chromene-6,8(7H,9H)-dione (4d)

white powder; yield: 87%, mp 228–230°C, IR (KBr): \( \nu_{\text{max}} \) 3069, 2958, 2871, 1731, 1665, 1612, 1546, 1494, 1368, 1298, 1276, 1242, 1226, 1169, 1132, 1046, 507, 40.8, 33.2, 29.1, 27.4. Anal. Calcd. for C\(_{24}\)H\(_{19}\)ClO\(_4\): C, 70.85; H, 4.71. Found: C, 70.57; H, 4.84. MS (EI) (m/z): 450 [M]+, 408 [M+2]+.

10,10-Dimethyl-7-(4-nitrophenyl)-10,11-dihydrochroomeno[4,3-b] chromene-6,8(7H,9H)-dione (4e)

white powder; yield: 86%, mp 175–177°C, IR (KBr): \( \nu_{\text{max}} \) 3085.6, 2978.6, 2604.8, 1719.0, 1652.4, 1607.5, 1525.8, 1356.8, 1180.7, 814.6, 763.5 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): 8.15–8.07 (m, 2H), 7.69–7.54 (m, 5H), 7.34 (m, 5H), 6.24 (s, 1H), 2.70–2.65 (m, 1H), 2.38–2.33 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H). \(^13\)C NMR (100 MHz, DMSO-d\(_6\)): 195.7, 162.3, 161.2, 154.6, 141.1, 133.4, 132.3, 130.0, 128.7, 127.9, 124.3, 122.4, 116.9, 114.9, 113.6, 106.4, 50.7, 40.8, 33.2, 32.3, 29.2, 27.4. Anal. Calcd. for C\(_{24}\)H\(_{19}\)NO\(_4\): C, 69.06; H, 4.59; N, 3.36. Found: C, 69.16; H, 4.67; N, 3.34. MS (EI) (m/z): 417.

10,10-Dimethyl-7-(4-bromophenyl)-10,11-dihydrochroomeno[4,3-b] chromene-6,8(7H,9H)-dione (4f)

orange powder; yield: 96%, mp 233–235°C, IR (KBr): \( \nu_{\text{max}} \) 3076.4, 2969.2, 2608.4, 1723.6, 1657.5, 1608.5, 1519.7, 1344.9, 1189.6, 764.3 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): 8.17 (d, 1H, \( J = 8.8 \) Hz), 8.14 (d, 2H, \( J = 8.0 \) Hz), 7.68–7.54 (m, 5H), 6.34 (s, 1H), 2.75 (m, 2H), 2.70 (d, 1H, \( J = 16.0 \) Hz), 1.18 (s, 3H). 13C NMR (100 MHz, DMSO-d\(_6\)): 195.7, 162.4, 160.2, 154.9, 152.6, 149.4, 146.8, 132.3, 129.5, 124.4, 123.7, 122.5, 116.7, 114.1, 113.3, 105.3, 50.6, 40.8, 32.1, 29.3, 27.5. Anal. Calcd. for C\(_{24}\)H\(_{18}\)Cl\(_2\)O\(_4\): C, 65.32; H, 4.11. Found: C, 65.25; H, 4.22. MS (EI) (m/z): 440.

Results and discussion

We commenced our investigation by testing the reaction of 4-nitrobenzaldehyde (0.11 g, 1 mmol), dimedone (0.140 g, 1 mmol), and 4-hydroxycoumarin (0.17 g, 1 mmol)
1 mmol) as a model reaction for the synthesis of chromenes. We studied the effects of the catalyst and solvent on the synthesis of 10, 10-dimethyl-7-(4-nitrophenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8-(7H,9H)-dione derivatives under ultrasonic irradiation in ethanol. Catalytic effects of three types of catalysts including NEt₃, MgO, nano-Fe₃O₄, nano-Fe₃O₄@SiO₂ and nano-Fe₃O₄@SiO₂-L-phenylalanine were investigated in the reaction of 4-nitroaldehyde, dimedone and 4-hydroxy coumarin as listed in Table 1. The results show that the reaction was carried out efficiently in the presence of nano-Fe₃O₄@SiO₂-L-phenylalanine. The highest yield was obtained by 0.05 g of nano-Fe₃O₄@SiO₂-L-phenylalanine nanoparticle under ultrasonic irradiation with the power of 40 W in ethanol. When the reaction was carried out under reflux conditions, it gave low yields of products and took longer reaction times, while the same reaction was carried out under ultrasonic irradiation to give good yields of products in short reaction times. The probable explanation for the positive association of irradiation is that the ultrasonic irradiation could increase the number of active cavitation bubbles and the size of the individual bubbles, both of which are expected to result in higher maximum collapse temperature and accelerated respective reaction.

We also applied Fe₃O₄@SiO₂-L-phenyl alaninenan catalyst in synthesis tetrahydrochromeno [4,3-b]chromene-6,8-dione derivatives from various aromatic aldehydes under similar condition as represented in Table 2. The results of this table indicate that the excellent yields were achieved in the presence of nano-Fe₃O₄@SiO₂-L-phenyl alanine (0.05 g). Electron-withdrawing substituents for aromatic aldehydes were given good to excellent yields of tetrahydrochromeno[4,3-b]chromene-6,8-diones (Table 2).

To compare the efficiency of Nano- Fe₃O₄@SiO₂-L-phenyl alanine with the reported catalysts for the sono-synthesis of 10,10-dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione derivatives, we have tabulated the results in Table 3. As Table 3 indicates, Nano-Fe₃O₄@SiO₂-L-phenyl alanine is superior with respect to the reported catalysts in terms of reaction time, yield and conditions. In addition, our catalyst was recyclable for five times. High catalytic activity and ease of recovery from the reaction mixture through magnetic field, and several reuse times without significant losses in performance are additional eco-friendly attributes of this catalytic system. TON and TOF of the nano-catalyst were provided. TON and TOF of the reactions clearly indicates that the method will be very useful for the synthesis of chromenes. (TON/TOF (min⁻¹)) = 9300/1550).

### Table 1. Optimization of reaction conditions using different catalysts.

| Entry | Solvent (condition) | Catalyst | Time (min) | Yield (%) |
|-------|---------------------|----------|------------|-----------|
| 1     | H₂O (reflux)        | NEt₃ (0.05 g) | 240 | 25 |
| 2     | EtOH (reflux)       | NEt₃ (0.05 g) | 240 | 58 |
| 3     | CH₃CN (reflux)      | NEt₃ (0.05 g) | 200 | 49 |
| 4     | H₂O₂ (reflux)       | MgO (0.05 g) | 250 | 32 |
| 5     | EtOH (reflux)       | MgO (0.05 g) | 150 | 45 |
| 6     | CH₃CN (reflux)      | MgO (0.05 g) | 250 | 42 |
| 7     | EtOH (reflux)       | Nano-Fe₃O₄ (0.05 g) | 120 | 28 |
| 8     | H₂O (reflux)        | Nano-Fe₃O₄ (0.05 g) | 120 | 22 |
| 9     | EtOH (reflux)       | Nano-Fe₃O₄@SiO₂ (0.05 g) | 120 | 35 |
| 10    | H₂O (reflux)        | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.05 g) | 30 | 62 |
| 11    | EtOH (reflux)       | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.05 g) | 20 | 80 |
| 12    | CH₃CN (reflux)      | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.05 g) | 25 | 69 |
| 13    | EtOH (US)           | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.05 g) | 6 | 96 |
| 14    | EtOH (US)           | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.07 g) | 10 | 95 |
| 15    | EtOH (US)           | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.03 g) | 15 | 86 |

*aAldehydes(1 mmol), dimedone (1 mmol) and 4-hydroxyCoumarin (1 mmol).  
*bUltrasonic irradiation (40 W).  
*cIsolated yield.

### Table 2. Synthesis of 10,10-dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione derivatives.

| Entry | Product | Aldehydes | Time (min) | Yield (%) | m.p. °C | m.p. °C |
|-------|---------|-----------|------------|-----------|---------|---------|
| 1     | 4a      | 4-Me-C₆H₄ | 10 | 86 | 174–176 | 174–176 |
| 2     | 4b      | 4-OME–C₆H₄ | 10 | 74 | 191–188 | 191–190 |
| 3     | 4c      | 2-Cl-C₆H₄ | 8 | 87 | 228–230 | 230 |
| 4     | 4d      | 4-Cl-C₆H₄ | 6 | 92 | 270–258 | 271 |
| 5     | 4e      | 2,4-Cl-C₆H₄ | 10 | 81 | 207–208 | 208 |
| 6     | 4f      | 4-NO₂-C₆H₄ | 6 | 96 | 233–235 | 235 |
| 7     | 4g      | 3-NO₂-C₆H₄ | 7 | 88 | 225–228 | 227 |
| 8     | 4h      | 4-Br-C₆H₄ | 8 | 86 | 175–169 | 177 |

*aAldehydes(1 mmol), dimedone (1 mmol) and 4- hydroxyCoumarin (1 mmol).  
*bIsolated yield.

### Table 3. Comparison of catalytic activity of Nano-Fe₃O₄@SiO₂-L-phenyl alanine with other reported catalysts.

| Entry | Catalyst (condition) | Time (min) | Yield (%) | (Ref) |
|-------|----------------------|------------|-----------|-------|
| 1     | nano-silica sulfuric acid (nano-SSA) (0.015 g) | 180 | 78 | (33) |
| 2     | Ionic liquid [DMDBS][HSO₄] (10 mol%) | 240 | 93 | (35) |
| 3     | Mg(ClO₄)₂ (0.04 g) | 30 | 90 | (36) |
| 4     | FeCl₃/sodium dodecyl sulfate | 240 | 56 | (37) |
| 5     | p-toluene sulfonic acid | 300 | 70 | (38) |
| 6     | H₃P·W₁₁O₃₃ | 30 | 85 | (39) |
| 7     | Nano-Fe₃O₄@SiO₂-L-phenylalanine (0.05 g) | 6 | 96 | This work |

*aIsolated yield.
A probable mechanism for the reaction using nano-Fe$_3$O$_4$@SiO$_2$-L-phenyl alanine nanoparticle has been illustrated in Scheme 2. The synthesis of 10,10-dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione derivatives involves aldol condensation, Michael addition, cyclization and isomerization, respectively. These processes performed on the nano-Fe$_3$O$_4$@SiO$_2$-L-phenyl alanine which has highly effective catalytic behavior in terms of its high surface area. The formation of product can be rationalized by initial aldol condensation reaction between an aldehyde and dimedone; then, Michael addition reaction between $\alpha$, $\beta$-unsaturated carbonyl (intermediate (I)) and 4-hydroxy coumarin gives intermediate (II) followed by cyclodehydration would give the desired 10,10-Dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione derivatives in the presence of nano-Fe$_3$O$_4$@SiO$_2$-L-phenyl alanine (Scheme 2). The amino groups distributed on the surface of Fe$_3$O$_4$@SiO$_2$ activate the C=O groups for better reaction with nucleophiles through hydrogen bonding (40, 41). Nanoparticles exhibit good catalytic activity due to their large surface area and active sites which are mainly responsible for their catalytic activity. As it obvious, obtained catalyst has a uniform and spherical morphology (see supporting information figure S3). These surface atoms behave as the centers where the chemical reactions could be catalytically activated. Nanoscale heterogeneous catalysts present higher surface areas, which are mainly responsible for their catalytic activity.

The reusability is one of the significant properties of this catalyst. The reusability of Fe$_3$O$_4$@SiO$_2$-L-phenyl alanine was studied for the reaction of 4-nitrobenzaldehyde, dimedone and 4- hydroxycoumarin and it was found that product yields decreased to a small extent on each reuse (run 1, 96%; run 2, 95%; run 3, 95%; run 4, 93%; run 5, 93%). After completion of the reaction, the nanocatalyst was easily separated using an external magnet. The recovered magnetite nanoparticles were washed several times with acetone and then dried at room temperature (Figure 1). Ideally, introducing neat processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions has received significant attention in recent years.

To determine the extent of Fe leaching after the reactions, we have used the hot filtration test (42). For this aim, we have studied the model reaction between 4-nitrobenzaldehyde, dimedone and 4- hydroxycoumarin under optimized condition. The reaction mixture was filtered after 50% conversion to remove the catalyst. Continuation of the reaction under the same conditions showed 52% conversion after 6 min. This result shows that the amount of leaching of the catalyst into the reaction mixture should be low and confirms that the catalyst acts heterogeneously in the reaction.

To determine the degree of leaching of the metal from the heterogeneous catalyst, the catalyst was removed by filtration and the Fe amount in reaction
medium after each reaction cycle was measured through inductively coupled plasma-atomic emission spectroscopy (ICP-AES). The analysis of the reaction mixture by the ICP technique showed that the leaching of Fe was negligible (The leaching of Fe in five continuous runs was found to be \( \leq 0.08 \) ppm). We believe that, this is also the possible reason for the extreme stability of the nanocatalyst presented herein.

**Conclusions**

In this research a simple and efficient procedure is developed for the synthesis of 10,10-dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione heterocyclic systems using nano-Fe\(_3\)O\(_4@\)SiO\(_2\)-L-phenyl alanine as a magnetic catalyst under ultrasonic irradiation. The catalyst is recyclable and provides excellent yields of 10,10-Dimethyl-7-(phenyl)-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione. The advantages of this method are the use of an efficient catalyst, reusability of the catalyst, little catalyst loading, low reaction times and easy separation of products.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

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**References**

[1] Mousavi, S.A.; Montazerozohori, M.; Masoudiasl, A.; Mahmoudi, G.; White, J.M. *Ultrason. Sonochem.* 2018, 46, 26-35.
[2] Nuchter, M.; Ondruschka, B.; Jungnickel, A.; Muller, U. *J. Phys Org. Chem.* 2000, 13, 579–586.
[3] Li, J.T.; Wang, S.X.; Chen, G.F.; Li, T.S. *Curr Org. Synth.* 2005, 2, 415–436.
[4] Wanga, F.; Liu, Y.; Chen, F.; Qu, M.; Shi, M. *Tetrahedron Lett.* 2015, 56, 2393–2396.
[5] Patil, S.A.; Patil, S.A.; Patil, R. *Future Med. Chem.* 2015, 7, 893–909.
