Preparation and characterization of silica-supported magnetic nanocatalyst and application in the synthesis of 2-amino-4*H*-chromene-3-carbonitrile derivatives

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Silica-supported magnetic nanoparticles were simply prepared in high yields and characterized by Fourier transforms infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), X-ray diffraction (XRD), transmission electron microscopy (TEM) and energy-dispersive X-ray spectroscopy (EDX) analyses. Then, $Fe_3O_4@SiO_2$ core-shell was used as a reusable and efficient heterogeneous nanocatalyst in a one-pot three-component condensation of various aromatic aldehydes, malononitrile and 1,3-dicarbonyl compounds to yield 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives as worthy structures under mild reaction conditions and easy work-up procedure.

Keywords

Nanocatalyst, Fe₃O₄@SiO₂, core-shell, multicomponent reaction, chromene.

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Introduction

Multicomponent reactions (MCRs) are an important tool in organic synthesis as they often allow the circumvention of multistep procedures by combining three or more molecules into one structure in a single step. An additional asset of the MCR approaches are the significant increase of the combinatorial possibilities, since a modification of final product is easily accomplished by implementing minor changes in the reaction setup; this obviously allows considerable savings in time and resources.¹ Moreover, MCR is a powerful tool in the synthesis of biologically active compounds² such as drug delivery,^{3,4} magnetic resonance imaging,⁵ biomolecular sensors,⁶ bioseparation,⁷ and magneto-thermal therapy.⁸

2-Amino-4*H*-chromenes and their derivatives are of significant importance as they possess a wide range of biological activities such as antimicrobial,⁹ sex pheromone,¹⁰ antitumor,¹¹ cancer therapy and central nervous system activity.¹² Moreover, some of these compounds could be used as inhibitors^{13,14} (Figure 1). Many compounds containing 2-amino-4*H*-chromene-3-carbonitriles as the structural units also find applications as cognitive enhancers in treatment of neurodegenerative diseases like Alzheimer's as well as for Parkinson's disease.¹⁵ In addition, these compounds have applications in fluorescence markers ¹⁶ cosmetics and pigments.¹⁷

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There are various literature reports on the synthesis of 2-amino-4*H*-chromene-3carbonitrile derivatives.¹⁸⁻²¹ Most of the methods reported for the synthesis of these valuable compounds suffer from one or more drawbacks such as harsh reaction conditions, low yields, long reaction times or expensive catalysts.²²⁻²⁶ Along with other reaction parameters such as solvent type, the nature of the catalyst plays a significant role in determining yield, selectivity, and general applicability. Thus, development of an inexpensive, general, and reusable catalyst by using MCRs strategy for the synthesis of 2amino-4*H*-chromene-3-carbonitriles is an issue of interest.

In continuation of our research on the introduction of new recoverable nanocatalysts in organic synthesis,²⁷⁻³² in this work, we report convenient and facile multicomponent, one-pot synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives **4a-p** via condensation of various aromatic aldehydes **1**, malononitrile **2** and 1,3-dicarbonyl compounds **3** in the presence of Fe₃O₄@SiO₂ coreshell nanostructure as an efficient, eco-friendly, superparamagnetic and heterogeneous catalyst (Scheme 1). According to our literature survey, this is the first report on the application of the present heterogonous composite nanocatalyst in the synthesis of 2-amino-4*H*-chromene-3-carbonitrile derivatives.

Results and discussion

 Fe_3O_4 nanoparticles and $Fe_3O_4@SiO_2$ nanocomposite were prepared by co-precipitation³² and modified Strober³³ methods, respectively. As can be seen in Figure 2, the comparative FT-IR spectra of the Fe₃O₄, SiO₂ and Fe₃O₄@SiO₂ magnetic nanocatalyst can

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verify the preparation of the expected product. The vibration band at 575 cm⁻¹ is induced by structure Fe--O vibration. The Si--OH vibration peak at 952 cm⁻¹ and the Si--O--Si vibration peak at around 1095 cm⁻¹ were also observed, indicating that the SiO₂ shell was successfully composed onto the surfaces of Fe₃O₄ nanoparticles.

To clarify the morphology of the nanocatalyst, SEM images of $Fe_3O_4@SiO_2$ are presented in Figure 3. As it obvious, obtained catalyst has a uniform and spherical morphology. In addition, as it proved in our previous work²⁷ and also in the literature report,³³ this nanocatalyst has core-shell structure.

Figure 4 shows the results of the XRD patterns analysis of the magnetite silicasupported $Fe_3O_4@SiO_2$ nanoparticles. The results are suitably in accordance with standard patterns of an inverse cubic spinel Fe_3O_4 crystal structure, showing diffraction peaks at the predicted 20 angles. The intense and sharp peaks indicated that Fe_3O_4 crystals are highly crystalline. As can be seen, the resulted nanomaterials show only typical diffraction peaks of magnetite nanoparticles and there is no deviation raised from specific peaks attributable to the composite nanostructure.

The TEM images shown in Fig. 5 revealed that the silica--magnetite composites made as supports of the catalyst had good spherical morphologies and arranged core--shell structures; and the average particles size was 59.13 nm.

Furthermore, to confirm elemental composition of the $Fe_3O_4@SiO_2$ core-shell structures an energy-dispersive X-ray spectroscopy (EDX) spectra of the nanocatalyst was provided and indicated the presence of Si, O and Fe elements in the nanocomposite (Fig. 6).

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Initially, to optimize the reaction conditions for the synthesis of 2-amino-4*H*chromene-3-carbonitriles we have studied various parameters on the reaction of 3nitrobenzaldehyde (1 mmol), dimedone (1 mmol) and malononitrile (1 mmol) as a pilot test. First, the effect of catalyst amount on the reaction yield was studied. It was found that using 0.005 g of the $Fe_3O_4@SiO_2$ nanocatalyst is sufficient to complete the reaction and give **4a** after 35 min in 98% yield in 5 mL of EtOH as a green solvent at room temperature.

To compare the efficiency of ethanol, several solvents with different polarities were tested using the model reaction in the presence of $Fe_3O_4@SiO_2$. As it obvious from the results, it was found that ethanol is the superior solvent for this study than MeOH, H₂O, CH₃CN, CH₂Cl₂ and also solvent-free in the presence of 0.005 g of Fe₃O₄@SiO₂ catalyst at room temperature.

Finally, a comparison was made between the present work and others which were reported earlier for the synthesis of **4a**. The results summarized in Table 1 clearly demonstrate the superiority of the present work over all the earlier reported ones in energy consuming, high yield products along with green medium.

In order to investigate the scope and limitations of the present protocol and to show the application of $Fe_3O_4@SiO_2$ in synthesis of substituted 2-amino-4*H*-chromene-3-carbonitriles, a variety of their derivatives were synthesized under the optimized conditions from the three-component reaction of dimedone or 1,3-cyclohezanedione, diverse aldehyde and malononitrile at room temperature. The summarized results in Table

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2 show that all products were obtained in high-to-excellent yields after appropriate reaction times.

The suggested possible mechanism for the formation of 2-amino-4-aryl-5-oxo-5,6,7,8tetrahydro-4*H*-chromene-3-carbonitrile derivatives **4a-p** is shown in Scheme 2. In the proposed mechanism, $Fe_3O_4@SiO_2$, as a Lewis acid,^{40, 41} can increases the electrophilicity of the carbonyl groups on the aldehyde **1** and also dimedone **3** by means of a strong coordinate bond.⁴² Molecule **5** is the result of Lewis acid-catalyzed Knoevenagel condensation between the aldehyde and dimedone. This molecule acts as a Michael acceptor. Subsequent attack of malononitrile **2** makes the open-chain intermediate **6**. Finally, an intramolecular cyclization of intermediate **7** gave the desired products **4**.

To study the catalyst reusability, the model reaction was carried out by using 0.005 g of $Fe_3O_4@SiO_2$. After completion of the reaction, nanoparticles were separated by using an external magnet and washed with ethanol and water, dried and reused in another set of reaction. It was observed that the catalyst can be reused for five times without any significant reduction in product yield (Figure 7). In addition, no extra care should be taken in order to store or handle the catalyst in recovery process; because, it does not have any air or moisture sensitive nature.

Conclusions

In summary, we have developed a simple, green and extremely efficient protocol for the synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile scaffolds by condensation between aromatic aldehyde, malononitrile and 1,3-dicarbonyl compounds in

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presence of nano-Fe $_3O_4@SiO_2$ as an environmentally friendly and reusable superparamagnetic nanocatalyst with facile preparation process.

Experimental section

General

All the solvents, chemicals and reagents were purchased from Merck, Sigma and Aldrich. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Fourier transforms infrared spectroscopy (FT-IR) spectra were recorded on a Shimadzu IR-470 spectrometer by the method of KBr pellet. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500 and 125 MHz, respectively. Scanning electron micrograph (SEM) images were taken with Zeiss-DSM 960A microscope with attached camera. The crystalline phase of the nanoparticles were recognized by means of X-ray diffraction (XRD) measurements using Cu K α radiation ($\lambda = 1.54$ Ű, 40 kV, 40 mA) on a STOE powder diffraction system in the 20 range of 10--80°. Transmission electron microscopy (TEM) images were obtained through Zeiss EM 900 electron microscope operating at 80 kV. Energy-dispersive X-ray spectroscopy (EDX) spectra were recorded on Numerix DXP--X10P.

Preparation of Fe₃O₄ nanoparticles

 Fe_3O_4 nanoparticles were prepared by co-precipitation of Fe_3O_4 from a mixture of $FeCl_2$ and $FeCl_3$ (1:2, molar ratio) upon addition of $NH_3 \cdot H_2O$. In a typical reaction, 1.72 g $FeCl_2$ and 4.7 g $FeCl_3$ were mixed in 80 mL de-ionized water and heated to 80°C in a three

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necked flask. While vigorously stirring the reaction mixture, 10 mL of $NH_3 \cdot H_2O$ was introduced by syringe and the heating continued for 40 min. Black precipitate was produced immediately by adding $NH_3 \cdot H_2O$. The precipitation reaction is as follows:

$$\mathbf{Fe}^{2+} + 2\mathbf{Fe}^{3+} + \mathbf{8OH}^{-} \Longrightarrow \mathbf{Fe}_{3}\mathbf{O}_{4} + \mathbf{4H}_{2}\mathbf{O}$$

The obtained Fe_3O_4 precipitate was washed repeatedly with de-ionized water until pH value decreased to 7 and then dried at 80°C in an oven.

Preparation of core-shell Fe₃O₄@SiO₂ nanoparticles

The synthesis of core-shell $Fe_3O_4@SiO_2$ nanoparticles was performed by modifying the Strober method via the hydrolysis of tetraethylorthosilicate (TEOS) in the presence of Fe_3O_4 nanoparticles. In a typical synthesis of 60 nm core-shell $Fe_3O_4@SiO_2$ nanoparticles (with a silica shell thickness of 20 nm), 45 mg as-prepared 20 nm hydrophilic Fe_3O_4 nanoparticles were dispersed in 16 mL of water by using an ultrasonic water bath, then mixing with 2 mL of aqueous ammonia solution (25 wt%) and 80 mL of ethanol. Next, 0.8 mL of TEOS was added drop wise into the Fe_3O_4 nanoparticle solution under violent stirring at room temperature. The stirring continued at room temperature for 24 h. The products were separated by an external magnet and washed with water several times. The final product was collected and dried at 50°C.

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General procedure for the synthesis of 2-amino-4H-chromene-3-carbonitrile derivatives 4a-p

A reaction mixture of an aldehyde **1** (1 mmol), malononitrile **2** (1 mmol), and dimedone **3a** or 1,3-cyclohezanedione **3b** (1 mmol) were added to EtOH (5 mL) including nano- $Fe_3O_4@SiO_2$ (0.005 g); and stirred at room temperature for the appropriate time. After completion of the reaction (TLC monitoring), the catalyst was separated easily by an external magnet and reused as such for the next experiments. Most of the products were isolated pure just by recrystallization from hot EtOH and no more purification was needed.

Spectral data of 2-amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 4d

Colourless crystals: mp 200-202°C. FT-IR (KBr) (v_{max} , cm⁻¹): 3392, 3323, 3190, 2962, 2192, 1654. ¹H NMR (500 MHz, DMSO-- d_6): δ (ppm) = 0.94 (3H, s, CH₃), 1.03 (3H, s, CH₃), 1.03-1.07 (2H, m, CH₂), 2.10 (1H, d, J = 16.0 Hz, CH₂), 2.25 (1H, d, J = 16.0 Hz, CH₂), 4.18 (1H, s, CH), 7.06 (2H, br s, NH₂), 7.12 (2H, d, J = 8.1 Hz, H-Ar), 7.48 (2H, d, J = 8.1 Hz, H-Ar). ¹³C NMR (125 MHz, DMSO- d_6): δ (ppm) = 27.7, 29.1, 32.6, 36.0, 40.5, 50.8, 58.6, 113.1, 120.3, 120.5, 130.3, 132.0, 145.0, 159.3, 163.5, 196.6.

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 Table 1. A comparison of some catalysts effects with the present nanocatalyst on the model reaction.

En		Temperatu	Tim	Yield
try	Catalyst	re (°C)	e	(%)
1	SiO ₂	80	75m	80
	$Cu(II)^2$		in	
2	SiO ₂	80	4h	60
	Nano-		35m	
3	Fe ₃ O ₄ @SiO	r.t.	in	98
3	Fe ₃ O ₄ @SiO 2	r.t.	in	98
3	Fe ₃ O ₄ @SiO 2	r.t. 80	in 4.5h	98 52
3 4 5	Fe ₃ O ₄ @SiO 2 - THAM ³⁴	r.t. 80 r.t.	in 4.5h 2h	98 52 91

Table 2. Synthesis of 2-amino-4H-chromene-3-carbonitriles**4a-p** by using nano- $Fe_3O_4@SiO_2$.

Entr y	Aldehyde	1,3- Dicarbonyl compound	Product	Time (min)	Yield ^a (%)	Mp Found	d (°C) Reporte d
1	3-NO ₂ - C ₆ H ₄ CHO	За	NO2 O NH2 4a	35	98	213- 214	213- 217 ³⁶
2	2-NO ₂ - C ₆ H ₄ CHO	За	NO2 NH2 4b	40	97	218- 220	220- 221 ³⁷
3	4-NO ₂ - C ₆ H ₄ CHO	3 a	NO2 0 0 NH2 4с	40	97	180- 182	178- 179 ²
4	4-Br- C ₆ H₄CHO	3 a	Br CN O NH2 4d	40	95	200- 202	196- 198 ³⁷

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5	4-Cl- C ₆ H₄CHO	3 a	CN CN NH2 4e	40	91	212- 214	213- 215 ³⁶
6	2-СІ- С ₆ Н ₄ СНО	За	of the second se	40	89	289- 291	290- 291 ²
7	C ₆ H₅CHO	3a	см мн ₂ 4g	45	83	229- 231	231- 235 ³⁶
8	4-Ме- С ₆ Н ₄ СНО	3a	or the second se	55	86	220- 222	217- 219 ³⁸
9	4-MeO- C ₆ H₄CHO	3 a	OMe CN CN NH ₂ 4j	11 5	87	200- 202	196- 198 ³⁸

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10	4-НО- С ₆ Н₄СНО	3 a	он СN 0 NH2 4j	13 5	83	205- 206	204- 205 ³⁶
11	3-NO ₂ - C ₆ H ₄ CHO	3b	NO2 O NH2 4k	35	91	204- 205	201- 203 ³⁹
12	4-NO ₂ - C ₆ H ₄ CHO	3b		40	89	222- 225	223- 225 ³⁷
13	4-Br- C ₆ H₄CHO	3b	Br CN CN NH2 4m	45	94	239- 242	238- 240 ³⁷
14	4-Cl- C₀H₄CHO	3b	CI CI CN CN NH2 4n	45	88	221- 223	220- 222 ³⁹

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15	4-МеО- С ₆ H ₄ CHO	3b		11 5	95	197- 199	199- 202 ³⁷
16	4-НО- С ₆ Н ₄ СНО	3b	OH OCN OCN NH2 4p	13 5	82	244- 247	244- 246 ³⁷

^a Isolated yield.

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Fig. 1. Examples of 2-amino-4*H*-chromene-3-carbonitrile-based biological and pharmaceutical compounds

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Fig. 2. FT-IR spectra of Fe₃O₄, SiO₂ and Fe₃O₄@SiO₂ nanocatalyst.



Fig. 3. SEM image of Fe₃O₄@SiO₂ nanocatalyst.

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Fig. 4. XRD pattern of Fe₃O₄@SiO₂ nanocatalyst.

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Fig. 5. TEM image of $Fe_3O_4@SiO_2$ core-shell structures.

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Fig. 6. EDX of the $Fe_3O_4@SiO_2$ nanocatalyst.

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Fig. 7. Recycling of the nanocatalyst for the synthesis of 4a.

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Scheme 1. Fe₃O₄@SiO₂ catalyzed MCRs leading to chromenes 4a-p.

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Scheme 2. The proposed mechanism for the formation of 2-amino-4*H*-chromene-3-carbonitriles4a-p.

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