Design, Preparation and Characterization of MoO₃H-functionalized Fe₃O₄@SiO₂ Magnetic Nanocatalyst and Application for the One-pot Multicomponent Reactions

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Abstract
Molybdic acid-functionalized silica-based Fe₃O₄ nanoparticles (Fe₃O₄@SiO₂-MoO₃H) are found to be a powerful and magnetically recyclable nanocatalyst. The morphology and structure of this nanocatalyst were investigated by Fourier transform infrared spectroscopy (FT-IR), energy dispersive X-ray spectroscopy (EDX), transmission electron microscopy (TEM), field emission scanning electron microscopy (FE-SEM), thermo gravimetric analyses (TGA), X-ray diffraction (XRD) and vibrating sample magnetometer (VSM) techniques. The high catalytic activity of this catalyst was investigated in the synthesis of pyrano[2,3-c]chromenes, representing potent biologically active compounds. The catalyst can be readily separated by applying an external magnet device and recycled up to 8 times without significant decrease in its catalytic activity, which makes it highly beneficial to address the industrial needs and environmental concerns. Fe₃O₄@SiO₂-MoO₃H has many advantages, such as low cost, low toxicity, ease of preparation, good stability, high reusability and operational simplicity.

Keywords: Fe₃O₄@SiO₂-MoO₃H, Magnetically recyclable nanocatalyst, Pyrano[2,3-c]chromenes, Biological activity

1. Introduction
Nowadays, the design and synthesis of efficient, reusable, easily separable, low toxicity, low cost, and insoluble acidic nanocatalysts have become an important area of research in chemistry.¹ The use of nanoparticles as heterogeneous catalysts has attracted considerable attention because of the interesting structural features and high levels of catalytic activity associated with these materials.²

Magnetic nanoparticles (MNP) are widely applied in various fields, such as magnetic resonance imaging (MRI) contrast agents, biomedical science, bioseparation and hyperthermia.³-⁶ Transition metal nanoparticles are used as efficient catalysts for various synthetic organic transformations due to their high surface area-to-volume ratio and coordination sites which are mainly responsible for their catalytic activity.⁷ Because the Fe₃O₄ nanoparticles will aggregate quickly into large bunches and therefore lose their unique properties, various surface modification methods have been developed to modify the surface of naked Fe₃O₄ nanoparticles to improve the dispersibility, stability, biocompatibility and biodegradability for specific purposes. The resulting modified Fe₃O₄ nanoparticles have been extensively used for various applications.⁸ Among them, the silica coating is a very good surface modifier,
because of its excellent stability, biocompatibility, nontoxicity and ease of furthered conjugation with various functional groups, thus enabling the coupling and labeling of biotargets with high selectivity and specificity.9–11 Development of MCRs can lead to new efficient synthetic methodologies to afford many small organic compounds in the field of modern organic, bioorganic, and medicinal chemistry.10 Hence, MCRs are considered as a pivotal theme in the synthesis of many important heterocyclic compounds, such as pyranocoumarin derivatives nowadays.12 In continuation of our research on the introduction of recoverable catalysts in organic synthesis,13–16 recently, we disclosed that Fe₃O₄ can be used as a novel magnetic nanocatalyst for the synthesis of 1,8-dioxododecahydroacridine derivatives.17 In this work, we demonstrate high catalytic activity of this new catalyst in the synthesis of pyranocoumarin derivatives as potent biologically active compounds.

It is also interesting to note that the catalyst can be recovered and reused several times.

2. Experimental

2.1. General

The chemicals were purchased from Merck and Aldrich chemical companies. The reactions were monitored by TLC (silica gel 60 F 254, hexane : EtOAc). Fourier transform infrared (FT-IR) spectroscopy spectra were recorded on a Shimadzu-470 spectrometer, using KBr pellets, and the melting points were determined on a KRUSS model instrument. ¹H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer at 400 MHz, with DMSO-d₆ used as the solvent and TMS as the internal standard. X-Ray diffra tion (XRD) pattern was obtained by Philips X Pert Pro X diffractometer operated at 100 kV. Field emission scanning electron microscopy (SEM) and X-ray energy dispersive spectroscopy (EDS) analyses were carried out on a Philips XL30, operated at a 20 kV accelerating voltage. Thermogravimetric analyses (TGA) were conducted on a Rheometric Scientific Inc. 1998 thermal analysis apparatus under a N₂ atmosphere at a heating rate of 10 °C/min. The magnetic measurement was carried out in a vibrating sample magnetometer (Model 7407 VSM system, Lake Shore Cryotronic, Inc., Westerville, OH, USA) at room temperature.

2.2. General Procedure for the Preparation of nano-Fe₃O₄ (1)

FeCl₃ · 6H₂O (20 mmol) and FeCl₂ · 4H₂O (10 mmol) were dissolved in distilled water (100 mL) in a three-necked round-bottom flask (250 mL). The resulting transparent solution was heated at 90 °C with rapid mechanical stirring under N₂ atmosphere for 1 h. A solution of concentrated aqueous ammonia (10 mL, 25 wt%) was then added to the solution in a drop-wise manner over a 30 min period using a dropping funnel. The reaction mixture was then cooled to room temperature and the resulting magnetic particles collected with a magnet and rinsed thoroughly with distilled water.

2.3. General Procedure for the Preparation of nano-Fe₃O₄@SiO₂ (2)

Nano-Fe₃O₄@SiO₂ (2) was synthesized according to a previously published literature method. Magnetic nano particles (1.0 g) were initially diluted via the sequential addition of water (20 mL), ethanol (60 mL) and concentrated aqueous ammonia (1.5 mL, 28 wt%). The resulting dispersion was then homogenized by ultrasonic vibration in a water bath. A solution of TEOS (0.45 mL) in ethanol (10 mL) was then added to the dispersion in a drop-wise manner under continuous mechanical stirring. Following a 12 h period of stirring, the resulting product was collected by magnetic separation and washed three times with ethanol.

2.4. General Procedure for the Preparation of nano-Fe₃O₄@SiO₂·OMoO₃·H (3)

To an oven-dried (125 °C, vacuum) sample of nano-Fe₃O₄@SiO₂ 60 (2 g) in a round bottomed flask (50 mL) equipped with a condenser and a drying tube, thiouyl chloride (8 mL) was added and the mixture in the presence of CaCl₂ as a drying agent was refluxed for 48 h. The resulting dark powder was filtered and stored in a tightly capped bottle. To a mixture of Fe₃O₄@SiO₂·Cl (1 g) and sodium molybdate (0.84 g) in hexane (5 mL) was added. The reaction mixture was stirred under refluxing conditions (70 °C) for 4 h. After completion of the reaction, the mixture was filtered and washed with distilled water, and dried and then stirred in the presence of 0.1 N HCl (20 mL) for an hour. Finally, the mixture was filtered, washed with distilled water, and dried to afford nano-Fe₃O₄@SiO₂·OMoO₃·H.

2.5. General Procedure for the Preparation of Pyrano[2,3-c]coumarin Derivatives 7

Malononitrile 4 (1.1 mmol), aromatic aldehyde 5 (1 mmol), 4-hydroxycoumarin 6 (1 mmol), and nano-Fe₃O₄@SiO₂·OMoO₃·H (0.02 g) were added to a 10 mL mixture EtOH/H₂O (50/50) in a 25-mL pyrex flask and refluxed for an appropriate time (Table 3). The reaction progress was controlled by thin layer chromatography (TLC) using hexane/EtOAc (1:1). After completion of the reaction, the solvent was removed under vacuum, the cru-
de products 7 were obtained after recrystalization from EtOH.

3. Results and Discussion

3.1. Characterization of Fe₃O₄@SiO₂-OMoO₃H

As can be seen in Scheme 1, from the reaction Fe₃O₄@SiO₂ nanoparticles 2 with thionyl chloride, the Fe₃O₄@SiO₂-Cl has been prepared. The Fe₃O₄@SiO₂-OMoO₃H 3 was prepared from nucleophilic substitution of Fe₃O₄@SiO₂-Cl with anhydrous sodium molybdate in n-hexane (Scheme 1).

The resulting MNP acid catalyst was characterized by XRD, FT-IR, TEM, SEM, TGA and EDX. The transmission electron microscopy (TEM) image of Fe₃O₄@SiO₂-MoO₃H powder reveals the spherical Fe₃O₄@SiO₂-MoO₃H powder with an average particle sizes of about 10–30 nm (Fig. 1a).

Surface morphology, particle shape and size distribution features of Fe₃O₄@SiO₂-MoO₃H nanoparticles were examined by FE-SEM (Fig. 1b).

The successful incorporation of molybdate groups was also confirmed by EDAX analysis (Fig. 1c), which showed the presence of Fe, Si, Mo and O elements.

Fig. 2a shows the XRD patterns of Fe₃O₄ particles powder before modification. The following peak signals at 2θ = 30.1°, 35.4°, 43.1°, 53.6°, 57°, and 62.8° corres...
The thermogravimetric analysis (TGA) was used to study the thermal stability of the acid catalyst (Fig. 3). The first weight loss which occurred below 150 °C, displayed a mass loss that was attributable to the loss of adsorbed solvent or trapped water from the catalyst. A weight loss of approximately 5% weight occurred between 300 and 500 °C which can be attributed to the loss of molybdate groups covalently bound to silica surface. Thus, it can be concluded that the catalyst is stable up to 300 °C.

Figure 2. X-ray powder diffraction patterns of (a) Fe₃O₄ NPs, (b) Fe₃O₄@SiO₂-OMoO₃H.
Figure 3. TGA curve of Fe₃O₄@SiO₂-MoO₃H.
Figure 4. Magnetization curves for the prepared Fe₃O₄ MNPs (a) and Fe₃O₄@SiO₂-MoO₃H (b).
wer than that of bare MNPs (59.14 emu g⁻¹) due to the presence of coated shell.

3.2. Application of Fe₃O₄@SiO₂-MoO₃H for the Synthesis of Pyrano[2,3-c]chromenes

In continuation of our studies on developing novel, efficient, and green procedures for the synthesis of organic compounds using safe catalysts,¹⁹–²¹ we decided to prepare pyrano[2,3-c]chromenes 7 via the synthesis by condensation between malononitrile 4, aromatic aldehydes 5, and 4-hydroxycoumarin 6 in the presence of catalytic amounts of Fe₃O₄@SiO₂-MoO₃H (Scheme 2).

In order to explore the catalytic efficiency of Fe₃O₄@SiO₂-MoO₃H, the model reaction was carried out under the catalyst-free conditions and compared with the one carried out in the presence of Fe₃O₄@SiO₂-MoO₃H and nano-Fe₃O₄. The obtained results showed higher yields for the reaction with the addition of Fe₃O₄@SiO₂-MoO₃H (94% yield) compared to the catalyst-free reaction (13% yield) and with the reaction with the addition of nano-Fe₃O₄ (86% yield).

The influence of the solvent was studied when the model reaction was performed using Fe₃O₄@SiO₂-MoO₃H, a mixture of H₂O/EtOH (1:1) was opted as the reaction medium. It should be noted that the reaction progress in pure water and/or absolute ethanol was considerable, however it was not better than in the mixture of these two solvents. From different ratios of H₂O/EtOH mixtures, equal mixture H₂O/EtOH (1:1) was considered as the most effective ratio.

After optimization of the reaction conditions, in order to extend the scope of this reaction, a wide range of aromatic aldehydes was used with 3 and 5 (Table 2). All the products were characterized by comparison of their spectra and physical data with those reported in the literature.²²–²⁵ As shown in Table 2, the new catalyst fortunately also works very well for the preparation of a vast variety of pyrano[2,3-c]coumarin derivatives 7a–n. The present method not only affords the products 7 in excellent yields, but also avoids the problems associated with catalyst cost, handling, safety and pollution.

**Table 1. Optimization of the model reaction by using various solvents and amount of Fe₃O₄@SiO₂-MoO₃H**

| Entry | Catalyst (mol%) | Solvent         | Yield (%) |
|-------|-----------------|-----------------|-----------|
| 1     | 5               | CH₂Cl₂          | 60        |
| 2     | 5               | CH₃Cl           | 65        |
| 3     | 5               | EtOH            | 90        |
| 4     | 5               | MeOH            | 80        |
| 5     | 5               | H₂O             | 70        |
| 6     | –               | H₂O/EtOH        | Trace     |
| 7     | 1               | H₂O/EtOH        | 94        |
| 8     | 3               | H₂O/EtOH        | 88        |
| 9     | 5               | H₂O/EtOH        | 86        |
| 10    | 10              | H₂O/EtOH        | 85        |

*Isolated yields.*

**Table 2. Synthesis of pyrano[2,3-c]coumarin derivatives 7 using Fe₃O₄@SiO₂-MoO₃H**

| Product | Ar               | Time (min) | Yield (%) | Mp (°C)  |
|---------|------------------|------------|-----------|----------|
| 7a      | C₆H₅              | 30         | 96        | 262–264  |
| 7b      | 4-MeO-C₆H₄        | 18         | 92        | 240–242  |
| 7c      | 2-Cl-C₆H₄         | 25         | 78        | 260–262  |
| 7d      | 3-NO₂-C₆H₄        | 35         | 81        | 255–257  |
| 7e      | 4-NO₂-C₆H₄        | 75         | 73        | 248–250  |
| 7f      | 4-Me-C₆H₄         | 70         | 87        | 250–252  |
| 7g      | 4-Cl-C₆H₄         | 50         | 90        | 258–260  |
| 7h      | thiophene-2-yl    | 75         | 70        | 234–236  |
| 7i      | 3-Br-C₆H₄         | 20         | 91        | 272–274  |
| 7j      | 2-Cl-6-F-C₆H₃     | 30         | 95        | 278–290  |
| 7k      | 4-benzyloxy-C₆H₄ | 450        | 84        | 275–277  |
| 7l      | 1-naphthyl        | 90         | 90        | 260–262  |
| 7m      | 4-isopropyl-C₆H₄ | 40         | 92        | 239–241  |
| 7n      | cyclohexyl        | 25         | 86        | 265–267  |

**Scheme 2. Synthesis of 1,8-dioxo-octahydroxanthene derivatives 7 by Fe₃O₄@SiO₂-MoO₃H.**

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3. 3. Reusability of the Fe$_3$O$_4$@SiO$_2$-MoO$_3$H

The main disadvantage for many of the reported methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. In this process, as outlined in Fig. 5., the recycled catalyst can be used in up to eight cycles, during which there are negligible losses in the catalytic activity.

![Figure 5. Reusability of Fe$_3$O$_4$@SiO$_2$-MoO$_3$H for the synthesis of 7a.](image)

4. Conclusions

In summary, we found Fe$_3$O$_4$@SiO$_2$-OMoO$_3$H to be an effective acidic magnetic nanocatalyst which successfully catalyzed the reaction between 4-hydroxycoumarin, various aromatic aldehydes and malononitrile to produce new and known pyranochromens of potential synthetic and pharmaceutical interest. High catalytic activity under solvent free conditions, high yields, a clean process, reusable several times without loss of activity or selectivity simple catalyst preparation, easy separation after the reaction by a magnet and green conditions are the advantages of these protocols.

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