CuFe$_2$O$_4$ nanoparticles: an efficient heterogeneous magnetically separable catalyst for synthesis of some novel propynyl-1H-imidazoles derivatives


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**A R T I C L E   I N F O**

Article history:
Received 5 December 2014
Received in revised form 28 January 2015
Accepted 16 February 2015
Available online 20 February 2015

Keywords:
Magnetic CuFe$_2$O$_4$ nanoparticles
Efficient catalyst
Recovered catalyst
1,2,4,5-Tetrasubstituted imidazoles and non-chromatographic methods

**A B S T R A C T**

The non-toxic magnetic CuFe$_2$O$_4$ nanoparticles have been synthesized, characterized, and used as an efficient catalyst for synthesis of new derivatives for 1,2,4,5-tetrasubstituted imidazoles in excellent yields. The synthesized compounds work-up easy and purification of products are performed without chromatographic methods. The catalyst can be recovered for the subsequent reactions and reused without any appreciable loss.

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1. Introduction

During the past decades, advances in nanoscience and nanotechnology have pushed forward the synthesis of functional magnetic nanoparticles (MNPs), which is one of the most active research areas in advanced materials. MNPs that have unique magnetic properties and other functionalities have enabled a wide spectrum of applications.\(^1\) CuFe$_2$O$_4$ magnetic nanoparticles are approximately 20–30 nm in size containing a single magnetic domain with a single magnetic moment and exhibit superparamagnetism.\(^2\) Copper/iron oxide based catalysts are environmentally compatible, air and moisture insensitive, and separation from reaction mixture is very simple by means of an external magnetic field.\(^3\)–\(^5\) Surface functionalized copper/iron oxide magnetic nanoparticles (MNPs) are a kind of novel functional materials, which have been widely used in biotechnology and analysis. Magnetic nanocatalysts can easily be separated and recycled from the products by an external magnet. Moreover, their catalytic performance is enhanced, for the available surface area of the nonporous MNPs is external and the internal diffusion is practically avoided.\(^6\)

In recent years, being focused on green chemistry using environmentally benign reagents and conditions is one of the most fascinating developments in synthesis of widely used organic compounds.\(^7\)–\(^9\) Imidazoles are a class of heterocyclic compounds that contain nitrogen and are currently under intensive focus due to their wide range of applications, because they have many pharmacological properties and play important roles in biochemical processes.\(^10\),\(^11\) The potential and wide range of application of the imidazole pharmacophore may be attributed to its hydrogen bond donor–acceptor ability as well as its high affinity for metals. Many of the substituted imidazoles are known as inhibitors of p38 MAP kinase, fungicides, herbicides, plant growth regulators, antibacterial, antitumor, pesticides, and therapeutic agents.\(^12\)–\(^17\) In 1882, Radziszewski and Japp reported the first synthesis of the highly substituted imidazole from a 1,2-dicarbonyl compound, different aldehydes, and ammonia.\(^18\),\(^19\)

The propargyl moiety is known to play an important role in providing neuro- and mitochondria-protecting properties of propargyl group-containing anti-depressants, selegiline and rasagiline.\(^20\)–\(^22\) There are many methods for the synthesis of poly-substituted imidazoles such as condensation of diones, aldehydes, primary amines, and ammonia in the presence of various acid catalysts.\(^23\)–\(^25\) N-alkylation of trisubstituted imidazoles\(^26\) and condensation of benzil or benzoin acetate with aldehydes, primary amines, and ammonia in the presence of copper acetate.\(^27\),\(^28\) The first mentioned method is the most well-known and classical
method. However, some of these methods involve long reaction times and unsatisfactory yields. Therefore, improvements in these syntheses have been sought continuously.

Herein, we report a simple and high yielding protocol for the synthesis of new derivatives of 1,2,4,5-tetrasubstituted imidazoles synthesized by four-component 1,2-diketone with an aldehyde, propargylamine, and ammonium acetate using magnetic CuFe₂O₄ nanoparticles as a novel and eco-friendly heterogeneous catalyst.29–31

2. Results and discussion

In this contribution, the preparation, high activation, and regeneration of CuFe₂O₄ nanoparticles as a high efficient catalyst in organic synthesis are shown.

The morphology and structure of the prepared CuFe₂O₄ nanoparticles were characterized by SEM, EDS (see Supplementary data), TEM, and XRD, which confirmed the successful preparation of nanoparticles.

Fig. 1(a) shows the TEM images of CuFe₂O₄ nanoparticles. The mean diameter is about 24 nm from the calculated histogram (see Fig. 1(b)).

The crystal structure of the CuFe₂O₄ nanoparticles was studied by XRD analyses after calcination at 800°C. The sizes of magnetic CuFe₂O₄ nanoparticles were determined from the XRD pattern by using Scherrer’s equation and found to be 23.5 nm, which is matched with the value obtained from the calculated histogram.

Using magnetic CuFe₂O₄ nanoparticles not only gives high yield, purity, and short reaction time but also is a cheap, speedy, facile, and eco-friendly method throughout the course of the reaction.

When reacted benzil 1 with aldehyde 2, propargylamine 3, and ammonium acetate 4 using magnetic CuFe₂O₄ nanoparticles as a novel and eco-friendly heterogeneous catalyst gave new derivatives for 1,2,4,5-tetrasubstitutedimidazoles 5a–p (Scheme 1).

![Fig. 1. (a) TEM image for the prepared CuFe₂O₄ nanoparticles. (b) Calculated histogram.](image)

![Scheme 1. Synthesis of 1,2,4,5-tetrasubstitutedimidazoles 5a–p.](image)

Designing organic reactions in aqueous media is another attractive area in green chemistry. Water is an abundant and environmentally benign solvent. This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion almost instantaneously, and pure product was obtained, without using any chromatographic techniques, simply by recrystallization from ethanol. Moreover the structure of compound 5b was confirmed via X-ray crystallographic analysis, the data of X-ray were given in Supplementary data (see Fig. 2, Table 1).

The investigated reaction in a magnetically recoverable CuFe₂O₄ nanoparticles produced a high yield. The results are presented in Table 2 show that the optimum condition was obtained with 10 mol % CuFe₂O₄ MNPs. The reaction yield with increasing amount of CuFe₂O₄ MNPs was not substantially increased.

The reaction mixture worked up by using three types of catalysts were examined, i.e., CuFe₂O₄ powder, CuFe₂O₄ nanoparticles fresh, and recovered CuFe₂O₄ nanoparticles.32 The highest yield of product in the shortest time was obtained using CuFe₂O₄ nanoparticles, which may be due to greater diffusion of CuFe₂O₄ nanoparticles in the reaction mixture. The recovered catalyst was found to be similar to the fresh CuFe₂O₄ nanoparticles. See Table 3.

To understand the role of iron in the present catalytic system, two independent reactions with 10 mol % of nano Fe₃O₄ and CuFe₂O₄ catalysts were carried out under the optimized reaction conditions. As can be seen in Table 4, low yield was observed with nano Fe₃O₄, clearly indicating that Cu is the active catalytic center in this reaction. An increase in yield (Table 4) with CuFe₂O₄ nanoparticles shows that iron plays a constructive role, possibly in the reoxidation of copper during the catalytic cycle.33

The stability of magnetically recoverable CuFe₂O₄ nanoparticles and its activity were investigated in recycling experiments for the reaction between benzil, benzaldehyde propargylamine, and ammonium acetate under the optimized conditions. After each cycle, the catalyst was separated magnetically, washed with ethanol, and dried at 60°C under vacuum to remove residual solvents then used for the next cycle. CuFe₂O₄ MNPs could be reused up to six times without any significant loss of the initial catalytic activity (cf. Fig. 3).

The plausible mechanism for the synthesis of highly substituted propynyl-1H-imidazoles in the 10 mol % of CuFe₂O₄ magnetic nanoparticles is outlined in Scheme 2. The reaction proceeds via the diamine intermediate A, which is formed by the activation of aldehyde carbonyl group by CuFe₂O₄ magnetic nanoparticles. Condensation of diamine with 1,2-diketone followed by dehydration, and then rearrangement through the imino intermediate B yielded the desired product.

Finally after sixth cycle of using the prepared CuFe₂O₄ catalyst for the investigated reaction, we make TEM analysis and the size found to be 26 nm (see Fig. 4).
CuFe₂O₄ magnetic nanoparticles are excellent catalysts for organic reactions. Additionally, the magnetic properties make possible the complete recovery of the catalyst by means of an external magnetic field, could be reused up to sixth times without any significant loss of the initial catalytic activity. These advantages

### Table 1
CuFe₂O₄ nanoparticles catalyzed benzyl for the synthesis of 1,2,4,5-tetrasubstituted imidazoles 5a–p

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Ar</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeO-Ph</td>
<td>40</td>
<td>95</td>
<td>9</td>
<td>4-Br-Ph</td>
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<td>90</td>
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<tr>
<td>2</td>
<td>4-Cl-Ph</td>
<td>35</td>
<td>93</td>
<td>10</td>
<td>2,4-Br-Ph</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>4-NO₂-Ph</td>
<td>40</td>
<td>92</td>
<td>12</td>
<td>4-NO₂-Ph</td>
<td>40</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>2-MeO-Ph</td>
<td>50</td>
<td>90</td>
<td>13</td>
<td>2-NO₂-Ph</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>3,5-MeO-Ph</td>
<td>50</td>
<td>92</td>
<td>16</td>
<td>2-Thiophenyl</td>
<td>45</td>
<td>89</td>
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**Table 2**
Amount of catalyst and the corresponding yield of the product

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
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<td>2</td>
<td>62</td>
<td>9</td>
<td>4</td>
<td>90</td>
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<tr>
<td>2</td>
<td>4</td>
<td>75</td>
<td>6</td>
<td>10</td>
<td>95</td>
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<tr>
<td>3</td>
<td>6</td>
<td>80</td>
<td>7</td>
<td>11</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>88</td>
<td>8</td>
<td>12</td>
<td>95</td>
</tr>
</tbody>
</table>

**Table 3**
The effect of different morphological structures of CuFe₂O₄ on the reaction yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuFe₂O₄ powder</td>
<td>180</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>CuFe₂O₄ MNPs fresh</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>CuFe₂O₄ MNPs recovered</td>
<td>30</td>
<td>95</td>
</tr>
</tbody>
</table>

**Table 4**
The reaction yield in presence of Fe₃O₄ and CuFe₂O₄ catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe₃O₄ MNPs</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>CuFe₂O₄ MNPs</td>
<td>30</td>
<td>95</td>
</tr>
</tbody>
</table>

**3. Conclusion**

CuFe₂O₄ magnetic nanoparticles are excellent catalysts for organic reactions. Additionally, the magnetic properties make possible the complete recovery of the catalyst by means of an external magnetic field, could be reused up to sixth times without any significant loss of the initial catalytic activity. These advantages...
become even more attractive if such reactions can be conducted in aqueous media.

4. Experimental

4.1. General

All chemicals used in the investigation were commercial products and distilled or recrystallized before use. All melting points were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ¹H NMR spectra were recorded on a Bruker DRX 400 MHz using TMS as an internal reference and DMSO-d₆ as a solvent. Mass spectra were performed on a Shimadzu GC-MS-QP 1000 mass spectrometer at 70 eV. All compounds were checked for their purity on TLC plates.

4.2. Preparation of the magnetic nanoparticles (MNPs)

Nano-CuFe₂O₄ was prepared with a modified method according to the literature. Nano-CuFe₂O₄ was prepared with a modified method according to the literature.³³ 1.51 g Cu(NO₃)₂·3H₂O and 5.04 g Fe(NO₃)₃·9H₂O were dissolved in 100 ml distilled water, then added into 50 ml 4 mol/l NaOH solution followed by heating and aging at 90 °C for 2 h. The prepared nanoparticles were centrifuged, washed with water, and dried at 80 °C overnight. Finally the powder was calcined at 800 °C for 2 h. The Fourier-transform infrared spectroscopy (FTIR) data were obtained on a Perkin Elmer 577 Spectrophotometer, using the KBr pellet technique, in the wavelength range of 400–1800 cm⁻¹. The stoichiometry was examined using energy dispersive X-ray spectroscopy (EDS). Transmission electron microscopy (TEM, JEOL 2000 EX II) observations were obtained at an acceleration voltage of 200 kV. FTIR and X-ray diffraction confirmed the formation of the CuFe₂O₄³⁴ᵃ,b (see Supplementary data).

4.3. General procedure for 1,2,4,5-tetrasubstituted imidazoles (5a–p)

In a 50 ml round bottom flask benzil (1 mmol), aldehyde (1 mmol), propargylamine (1 mmol), and ammonium acetate (1 mmol) were taken in the presence of 10 mol% of CuFe₂O₄ nanoparticles in ethanol/water (15 ml) 1:3 (v/v). Then the reaction mixture was refluxed for a specified time. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated magnetically. The reaction mixture was allowed to stand overnight. The solid material was filtered off, washed with water, dried, and recrystallized from ethanol to furnish pure propynyl-1H-imidazoles derivatives.

4.4. 2,4,5-Triphenyl-1-(2-propynyl)-1H-imidazole 5a

FTIR (KBr, cm⁻¹): 2951, 2122, 1646, 1490; ¹H NMR (400 MHz, CDCl₃): δ 7.82–7.12 (m, 15H), 4.90 (s, 2H), 2.29 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 165.3, 135.1, 133.6, 132.5, 130.2, 128.7, 128.2, 127.7, 127.6, 126.8, 126.1, 125.9, 124.8, 124.6, 123.5, 80.9, 76.2, 40.2; ESI MS (m/z): 334.4 (M⁺).

4.5. 2-(4-Methoxyphenyl)-4,5-diphenyl-1-(2-propynyl)-1H-imidazole 5b

FTIR (KBr, cm⁻¹): 2944, 2123, 1646, 1491; ¹H NMR (400 MHz, CDCl₃): δ 7.98–6.86 (m, 14H), 4.91 (s, 2H), 3.75 (s, 3H), 2.28 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 165.3, 160.2, 135.1, 132.3, 132.4, 130.2, 128.7, 126.8, 126.1, 126.0, 125.0, 124.8, 124.4, 123.5, 117.2, 80.9, 76.2, 56.0, 40.2; ESI MS (m/z): 364.4 (M⁺).

4.6. 2-(4-Chlorophenyl)-4,5-diphenyl-1-(2-propynyl)-1H-imidazole 5c

FTIR (KBr, cm⁻¹): 2949, 2120, 1646, 1490; ¹H NMR (400 MHz, CDCl₃): δ 7.87–7.12 (m, 14H), 4.90 (s, 2H), 2.30 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 165.3, 153.5, 135.0, 132.6, 132.5, 130.8, 130.2,
4.8. 2-(3-Nitrophenyl)-4,5-diphenyl-1-(2-propynyl)-1H-imidazole 5d

FTIR (KBr, cm⁻¹): 2933, 2121, 1648, 1494; ¹H NMR (400 MHz, CDCl₃): δ 8.08–7.74 (m, 14H), 4.92 (s, 2H), 2.31 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 165.3, 147.9, 141.8, 135.0, 132.5, 130.3, 130.2, 128.7, 126.8, 126.0, 125.9, 125.7, 124.8, 124.6, 123.4, 80.9, 76.2, 40.2; ESI MS (m/z): 379.3 (M+).
References and notes
