Magnetic Fe\textsubscript{3}O\textsubscript{4} nanoparticles as a highly efficient catalyst for the synthesis of imidazoles under ultrasound irradiation

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ABSTRACT

To be fairly general and catalyst is easily separated by magnetic devices and can be reused without any apparent loss of activity for the reaction. Fe\textsubscript{3}O\textsubscript{4} nanoparticles were prepared by chemical coprecipitation method and was found to be a mild and effective catalyst for the efficient, one-pot, three-component synthesis of 2,4,5-trisubstituted imidazoles at room temperature under ultrasound irradiation. The high yields of products and short reaction time were attributed to the nanosize of about 20 nm in which the catalyst could act as a nanoreactor. This methodology is found.

Keywords: Fe\textsubscript{3}O\textsubscript{4} nanoparticles, Imidazole, Heterogeneous catalyst, Ultrasound irradiation.

1. Introduction

Nanotechnology is now expanding very rapidly, as result of the unique physical and chemical properties that nanoparticles (NPs) exhibit compared to bulk materials. Magnetic iron oxide nanoparticles (MNPs) have attracted much research interest over the recent years because of their inherent properties such as large surface area and fast response under applied external magnetic field, their superparamagnetism, high coercivity and low Curie temperature [1-3].

On the other hand, recent studies show that magnetic nanoparticles are excellent catalysts for organic reactions [4-6]. Additionally, the magnetic properties make the recovery of the catalyst compete by mean of an external magnetic field. These advantages even more attractive if such reactions can be conducted in aqueous media.

Imidazole derivatives are a very interesting class of heterocyclic compounds because they have many pharmacological properties and play important roles in biochemical processes [7, 8]. In recent years the synthesis of 2,4,5-trisubstituted imidazoles has been performed by catalysts such as Yb(OPf)\textsubscript{3} [9], ZrCl\textsubscript{4} [10], NiCl\textsubscript{2}.6H\textsubscript{2}O/Al\textsubscript{2}O\textsubscript{3} [11], silica sulfuric acid (SSA) [12], polymer-supported ZnCl\textsubscript{2} [13], and phosphomolybdic acid [14]. Also some catalysts used for 1,2,4,5-tetrasubstituted imidazoles include silica gel or zeolite InCl\textsubscript{3}.3H\textsubscript{2}O [15], silica gel/NaHSO\textsubscript{4} [16], HClO\textsubscript{4}-SiO\textsubscript{2} [17], heteropolyacids [18], BF\textsubscript{3}.SiO\textsubscript{2} [19], FeCl\textsubscript{2}.6H\textsubscript{2}O [20], and alumina [21] are applied as some common catalysts for 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles. Despite their potential utility, some of these methods are not environmentally friendly and suffer from one or more disadvantages, for example hazardous reaction conditions, complex work-up and purification, strongly acidic conditions, high temperature, use of toxic metal catalysts, poor yields, occurrence of side reactions, and long reaction time. Therefore, the development of clean, high-yielding and environmentally friendly approach is still a challenge for organic chemists in the synthesis of highly substituted imidazoles [21].

Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions [22-24]. UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of purer products in high yields, easier manipulation and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods, this technique is more convenient taking green chemistry concepts into account [25, 26]. However, the use of ultrasound in heterocyclic system is not fully explored [27-29].

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Fe$_3$O$_4$-MNPs were prepared using simple chemical coprecipitation described in the literature [39] with little modification. Typically, 20 mmol of FeCl$_3$·6H$_2$O and 10 mmol of FeCl$_2$·4H$_2$O were dissolved in 75 ml of distilled water in a three-necked bottom (250 ml) under Ar atmosphere for 1 h. Thereafter, under rapid mechanical stirring, 10 ml of NaOH (10 M) was added into the solution within 30 min with vigorous mechanical stirring and ultrasound treatment under continuous Ar atmosphere bubbling. After being rapidly stirred for 1 h, the resultant black dispersion was heated to 85°C for 1 h. The black precipitate formed was isolated by magnetic decantation, exhaustively washed with double-distilled water until neutrality, and further washed twice with ethanol and dried at 60°C in vacuum.

2.4. General procedure for the synthesis of 2,4,5-trisubstituted imidazoles

To a solution of 1,2-diketones derivatives (1 mmol), aldehyde (1 mmol), ammonium acetate (0.4 g, 5 mmol) in 10 ml ethanol, MNPs (5 mol%) was added and the reaction mixture was exposed to ultrasonic irradiation at room temperature. The progress of reaction was followed by TLC. After the reaction was completed, the catalyst was separated by an external magnet and reused as such for the next experiment. The reaction mixture was dissolved in acetone and filtered. The filtrate was concentrated on a rotary evaporator under reduced pressure and the solid product obtained was washed with water and recrystallized from acetone–water 9:1 (v/v). Pure products were obtained in excellent yields, as summarized in Table 3. Most of the products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

The selected spectral data

2-(3-nitrophenyl)-4,5-bis(4-methoxyphenyl)-1H-imidazole (5o). Yellow solid. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3428 (NH), 1615 (C=O), 1523 (C=N), 1460 (N=O), 1348 (N-H). H NMR (400 MHz, DMSO-d$_6$/ppm) $\delta$: 12.92 (s, 1H, NH), 7.64 (d, 1H, J=8.4 Hz, Ar-H), 5.20 (d, 1H, J=8.2 Hz, Ar-H), 8.20 (d, 1H, J=8.2 Hz, Ar-H), 7.75 (t, 1H, J=8.2 Hz, Ar-H), 7.47 (d, 2H, J=8.4 Hz, Ar-H), 7.43 (d, 2H, J=8.4 Hz, Ar-H), 7.00 (d, 2H, J=8.4 Hz, Ar-H), 6.90 (d, 2H, J=8.4 Hz, Ar-H), 3.80 (s, 3H, OMe), 3.75 (s, 3H, OMe); 13C NMR (100 MHz, DMSO-d$_6$/ppm) $\delta$: 159.4, 158.6, 148.8, 143.1, 137.5, 132.5, 131.4, 130.8, 130.2, 128.8, 128.7, 127.9, 123.5, 122.7, 119.7, 114.6, 114.1, 55.7, 55.5; Anal. Calcd. for C$_{32}$H$_{28}$N$_4$O$_8$: C=68.82; H=4.77; N=10.47%. Found: C=68.79; H=4.75; N=10.44%.

2-(3-methoxyphenyl)-4,5-bis(4-methoxyphenyl)-1H-imidazole (5p). White solid. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3430 (N-H), 1608 (C=C), 1519 (C=N), 1246 (C=O); H NMR (400 MHz, DMSO-d$_6$/ppm) $\delta$: 12.50 (s, 1H, NH), 7.64 (d, 1H, J=8.0 Hz, Ar-H), 7.62 (s, 1H, Ar-H), 7.36-7.46 (m, 5H, Ar-H), 7.00 (d, 2H, J=8.4 Hz, Ar-H), 6.91 (dd, 1H, J=8.4, 2.2 Hz, Ar-H)
123

Fig. 1. FT-IR spectra of Fe₃O₄-MNPs.

Hz, Ar-H), 6.87 (d, 2H, J=8.4 Hz, Ar-H), 3.82 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.74 (s, 3H, OMe); ¹³C NMR (100 MHz, DMSO-d₆ ppm) δC: 160.0, 158.9, 158.2, 145.1, 136.2, 132.3, 130.2, 128.6, 128.2, 127.2, 124.1, 117.0, 115.5, 114.4, 114.3, 110.5, 55.6, 55.5, 55.5 ppm; Anal. Calcd. for C₂₄H₂₂N₂O₃: C=74.59; H=5.74; N=7.25%. Found: C=74.58; H=5.75; N=7.24%.

5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl]-2-methoxyphenol (5q). Ash-gray solid. IR (KBr, v_max/cm⁻¹): 3424 (N–H), 3320 (O–H), 1615 (C=C), 1504 (C=N), 1249 (C–O); ¹H NMR (400 MHz, DMSO-d₆, ppm) δH: 12.26 (s, 1H, NH), 9.11 (s, 1H, OH), 7.52 (s, 1H, Ar-H), 7.37-7.46 (m, 6H, Ar-H), 6.98 (d, 2H, J= 8.4 Hz, Ar-H), 6.86 (d, 2H, J= 8.4 Hz, Ar-H), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.73 (s, 3H, OMe); ¹³C NMR (100 MHz, DMSO-d₆ ppm) δC: 159.1, 158.7, 148.4, 146.9, 145.6, 129.8, 129.2, 128.4, 126.3, 126.0, 123.5, 124.1, 116.8, 114.3, 114.0, 113.2, 112.5, 56.1, 55.5, 55.1; Anal. Calcd. for C₂₄H₂₂N₂O₄: C=71.63; H=5.51; N=6.96%. Found: C=71.61; H=5.49; N=6.95%.

3. Result and Discussion

In this paper, we describe a simple and high yielding protocol for the synthesis of 2,4,5-trisubstituted imidazoles involving the three-component, one-pot condensation of aldehyde, 1,2-diketone, and NH₄OAc using Fe₃O₄ nanoparticles as a novel and eco-friendly heterogeneous catalyst.

3.1. Characterization of the prepared Fe₃O₄-MNPs

Fig. 2 shows the Fourier transform infrared (FTIR) spectra of magnetic nanoparticles. The Fe–O stretching vibration near 580 cm⁻¹, O–H stretching vibration near 3432 cm⁻¹ and O–H deformed vibration near 1629 cm⁻¹ were observed [31]. Fig. 2 presents the XRD-diffraction patterns of the prepared MNPs. The position and relative intensities of all peaks conform well with standard XRD pattern of Fe₃O₄ (JCPDS card No. 85-1436) indicating retention of the crystalline cubic spinel structure of MNPs. The XRD patterns of the particles show six characteristic peaks reveal a cubic iron oxide phase (2Θ = 18.35, 30.27, 35.53, 42.95, 53.60, 57.18, 62.69, 71.31, 74.14). These are related to their corresponding indices (1 1 0), (2 2 0), (3 1 1), (4 0 0), (3 3 1), (4 2 2), (5 1 1), (4 4 0) and (5 3 1) respectively. It is implied that the resultant nanoparticles are pure Fe₃O₄ with a spinel structure and that the grafting process did not induced any phase change of Fe₃O₄ [32]. The crystal size of MNPs can be determined from the XRD pattern by using Debye–Scherrer’s equation:

\[ D(h k l) = \frac{0.94 \lambda}{\beta \cos \theta} \]
$D(hk l)$ is the average crystalline diameter, 0.94 is the Scherrer’s constant, $\lambda$ is the X-ray wavelength, $\beta$ is the half width of XRD diffraction lines and $\theta$ is the Bragg’s angle in degree. Here, the (3 1 1) peak of the highest intensity was picked out to evaluate the particle diameter of the nanoparticles. Size of MNPs were calculated to be 18 nm.

XRD. SEM image shows the nanoparticles are well dispersed and uniform in shape and size.

3.2. Evaluation of the catalytic activity of MNPs through the synthesis of 2,4,5-trisubstituted imidazoles

To achieve suitable conditions for the synthesis of 2,4,5-trisubstituted imidazoles, various reaction conditions have been investigated in the reaction of 4-methoxybenzaldehyde 3b, benzil 1a, and ammonium acetate as a model reaction (Scheme 2). We examined the effect of different solvents such as EtOH, MeOH, THF, DMF, CH$_3$CN, and DCM on model reaction under ultrasound irradiation (frequencies of 40 kHz) at room temperature. The results were summarized in Table 1. The use of 4 mol% of MNPs in ethanol afforded

$^a$Reaction of benzil, 4-methoxybenzaldehyde and ammonium acetate (1:1:5) in presence of SA-MNPs (4 mol%) as a catalyst under ultrasonic waves (frequencies of 40 kHz).

$^b$Isolated yield based on aldehyde.
The best results were obtained using 5 mol% of the catalyst under both conditions (Table 2, entry 4). As shown, in the absence of catalyst the yield of the product was found to be low (Table 2, entry 1).

Using the optimized reaction conditions, this process was demonstrated by the wide range of substituted and structurally diverse aldehydes to synthesize the corresponding products in high to excellent yields (Table 3, method A). Aldehydes bearing either electron-withdrawing or electron-donating groups perform equally well in the reaction and all imidazoles were obtained in high yields. For more examination of the influence of ultrasound irradiation in this transformation, comparison of the reaction under two

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### Table 3. One-pot synthesis of 2,4,5-trisubstituted imidazoles catalyzed by MNPs in EtOH under ultrasound irradiation at room temperature (method A) and reflux conditions (method B).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzil</th>
<th>$R_1,R_2$</th>
<th>Aldehyde</th>
<th>$R_3$</th>
<th>Product $^b$</th>
<th>Method A</th>
<th>Method B</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (min) / Yield (%)</td>
<td>Time (min) / Yield (%)</td>
<td>Found</td>
</tr>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>3a</td>
<td>H</td>
<td>5a</td>
<td>25/96</td>
<td>120/90</td>
<td>271-273</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>H</td>
<td>3b</td>
<td>$p$-OMe</td>
<td>5b</td>
<td>30/94</td>
<td>180/87</td>
<td>230-231</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>H</td>
<td>3c</td>
<td>$p$-Me</td>
<td>5c</td>
<td>35/88</td>
<td>150/83</td>
<td>229-232</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>H</td>
<td>3d</td>
<td>$m$-Br</td>
<td>5d</td>
<td>30/94</td>
<td>150/90</td>
<td>302-304</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>H</td>
<td>3e</td>
<td>$m$-OH</td>
<td>5e</td>
<td>30/90</td>
<td>150/85</td>
<td>260-261</td>
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<tr>
<td>6</td>
<td>1a</td>
<td>H</td>
<td>3f</td>
<td>$m$-NO$_2$</td>
<td>5f</td>
<td>30/89</td>
<td>150/84</td>
<td>268-270</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>H</td>
<td>3g</td>
<td>$m$-OMe</td>
<td>5g</td>
<td>30/90</td>
<td>120/90</td>
<td>258-260</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>H</td>
<td>3h</td>
<td>$m$-OH, $p$-OMe, $m$-OMe</td>
<td>5h</td>
<td>30/96</td>
<td>120/93</td>
<td>215-216</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>H</td>
<td>3i</td>
<td>$m$-OMe</td>
<td>5i</td>
<td>30/92</td>
<td>120/90</td>
<td>255-257</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>OMe</td>
<td>3a</td>
<td>H</td>
<td>5j</td>
<td>35/95</td>
<td>130/90</td>
<td>202-204</td>
</tr>
<tr>
<td>11</td>
<td>1b</td>
<td>OMe</td>
<td>3b</td>
<td>$p$-OMe</td>
<td>5k</td>
<td>45/93</td>
<td>180/83</td>
<td>184-186</td>
</tr>
<tr>
<td>12</td>
<td>1b</td>
<td>OMe</td>
<td>3c</td>
<td>$p$-Me</td>
<td>5l</td>
<td>43/95</td>
<td>180/85</td>
<td>187-189</td>
</tr>
<tr>
<td>13</td>
<td>1b</td>
<td>OMe</td>
<td>3d</td>
<td>$m$-Br</td>
<td>5m</td>
<td>35/94</td>
<td>160/85</td>
<td>250-252</td>
</tr>
<tr>
<td>14</td>
<td>1b</td>
<td>OMe</td>
<td>3e</td>
<td>$m$-OH</td>
<td>5n</td>
<td>35/95</td>
<td>160/83</td>
<td>229-231</td>
</tr>
<tr>
<td>15</td>
<td>1b</td>
<td>OMe</td>
<td>3f</td>
<td>$m$-NO$_2$</td>
<td>5o</td>
<td>35/94</td>
<td>160/84</td>
<td>242-244</td>
</tr>
<tr>
<td>16</td>
<td>1b</td>
<td>OMe</td>
<td>3g</td>
<td>$m$-OMe</td>
<td>5p</td>
<td>35/95</td>
<td>160/87</td>
<td>235-236</td>
</tr>
<tr>
<td>17</td>
<td>1b</td>
<td>OMe</td>
<td>3h</td>
<td>$m$-OH, $p$-OMe, $m$-OMe</td>
<td>5q</td>
<td>35/97</td>
<td>140/90</td>
<td>131-133</td>
</tr>
<tr>
<td>18</td>
<td>1b</td>
<td>OMe</td>
<td>3i</td>
<td>$m$-OMe</td>
<td>5r</td>
<td>35/93</td>
<td>140/89</td>
<td>194-196</td>
</tr>
</tbody>
</table>

$^a$ Benzil (1 mmol), Aldehyde (1 mmol), NH$_2$OAc (5 mmol), MNPs (5 mol%).

$^b$ All products were characterized by $^1$H NMR, $^{13}$C NMR, IR and MS spectra.

$^c$ Isolated yield.
A plausible mechanism for the formation of trisubstituted imidazoles is envisaged in Scheme 3. Aldehyde and 1,2-diketone are first activated by MNPs (Fe$^{3+}$) to afford A and B respectively. Then, imine intermediate (A), condenses further with the carbonyl carbon of 1,2 diketone imine (B) and formation of carbocation (C) followed by attack of imine nitrogen to positive center and dehydration to afford the iso-imidazole (E), which rearranges via [1,5] sigmatropic shift to the required imidazole (Scheme 3). It was suggested that ultrasound irradiation activates the reaction mixture by inducing high local temperatures and pressure generated inside the cavitation bubble and its interfaces when it collapses and accelerates the reaction rate and shortens the reaction time [36].

The possibility of recycling the catalyst was examined using the reaction of benzil, benzaldehyde, and ammonium acetate under optimized conditions. Upon completion, the catalyst was separated by an external magnet and was washed with acetone, and the recycled catalyst was saved for the next reaction. The recycled catalyst could be reused five times without any further treatment. No observation of any appreciable loss in the catalytic activity of nanocatalyst was observed (Fig. 5).

In order to show the merit of the present work in comparison with the other reported catalysts, we compared the reactions of MNPs with Ionic liquid [EMIM]OAc,

![Scheme 3](image)

**Table 4.** Comparison of Fe$_3$O$_4$ with other catalysts reported in the literature for the synthesis imidazoles $^a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount; condition</th>
<th>Time</th>
<th>Yield$^b$ (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ionic liquid [EMIM]OAc</td>
<td>10 mol%; EtOH, u.s, r.t</td>
<td>1.5 h</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Zr(acac)$_4$</td>
<td>20 mol%; EtOH, u.s, r.t</td>
<td>45 min</td>
<td>88</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>Zinc (II) [tetra(4-methylphenyl)] Porphyrin</td>
<td>3 μmol; EtOH, u.s, r.t</td>
<td>70 min</td>
<td>94</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>BO$_3$H$_3$</td>
<td>5 mol; EtOH 50%, u.s, r.t</td>
<td>30 min</td>
<td>98</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>MNPs</td>
<td>5 mol; EtOH, u.s, r.t</td>
<td>25 min</td>
<td>96</td>
<td>This work</td>
</tr>
</tbody>
</table>

$^a$ Benzil (1 mmol), Aldehyde (1 mmol), NH$_4$OAc (5 mmol).

$^b$ Isolated yields.
Fig. 5. Recyclability of MNPs in the reaction of benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (5 mmol) under ultrasonic waves (40 KHz) at room temperature.

$\text{Zr}(\text{acac})_4$, Zinc (II) [tetra(4-methylphenyl)] Porphyrin, and $\text{BO}_3\text{H}_2$ for the preparation of imidazole (4a) in Table 4. The results showed that MNPs is a better catalyst with respect to reaction times and yields of the products. Also magnetic Fe$_3$O$_4$ 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. The superiority of Fe$_3$O$_4$ nanocatalyst is in many different fields due to their intrinsic properties such as high surface area, low toxicity, super paramagnetic behavior, and easy separation and recovery from the reaction medium by magnetic decantation.

4. Conclusion

An efficient and environmentally friendly method has been developed for the preparation of 2-aryl-4,5-diphenyl imidazoles catalyzed by MNPs under ultrasonic irradiation. This method offers several advantages including high yield, short reaction time, simple work-up procedure, ease of separation, and recyclability of the magnetic catalyst, as well as the ability to tolerate a wide variety of substitutions in the reagents.

Acknowledgements

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References