Ultrasonic Accelerated Efficient Synthesis of (1H-tetrazole-5-yl) Pyrazines Catalyzed by MgFe$_2$O$_4$ Nanoparticles as a Reusable Heterogeneous Catalyst

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ABSTRACT

An efficient synthesis of (1H-tetrazole-5-yl) pyrazines is achieved by one pot multi-component coupling reaction of α-dicarbonyl compounds, 2,3-diaminomaleonitrile and sodium azide using MgFe$_2$O$_4$ nanoparticles as a robust catalyst under ultrasonic irradiation. This novel synthetic method using MgFe$_2$O$_4$ nanoparticles is easier, faster than that of using other nanoparticles. MgFe$_2$O$_4$ nanoparticles have been characterized by X-ray diffraction (XRD) and scanning electron microscopy (SEM). The attractive advantages of the present process are atom economy, wide range of products, high catalytic activity, excellent yields, short reaction times and simple operational procedures. Use of simple and readily available starting materials, experimental simplicity, applying the sono-chemical methodology as an efficient method and innocuous means of activation in synthetic chemistry are some properties of this protocol. The reusability of the MgFe$_2$O$_4$ nanoparticles catalyst was examined and it was found that product yields decreased to a small extent on each reuse. The possibility of performing multicomponent reactions with a green catalyst under ultrasonic irradiation plays a prominent role in green chemistry.

INTRODUCTION

The pyrazine ring system is a structural sector of a great number of biologically active compounds. The pyrazine derivatives exhibit various pharmacological activities such as antibacterial [1,2], analgesic and anti-inflammatory [3], anticancer [4], and antibronchospastic [5]. The (1H-tetrazole-5-yl) pyrazine derivatives display variable biological properties including antiallergic [6,7], and anti-microbial [8]. Compounds containing the tetrazole moiety are utilized as TNF-α inhibitors [9], antiproliferative, antitumor [10], and antifungal activities [11]. Therefore, the development of easy procedures for the synthesis of (1H-tetrazole-5-yl) pyrazines is an attractive challenge. Recently, the performing multicomponent reactions with a heterogeneous catalyst under ultrasonic irradiation have attracted much attention. The ultrasound approach decreases reaction times, increases yields and minimizes side reactions by providing the activation energy in micro environment [12-14]. The ultrasonic irradiations accelerate an organic transformation at ambient conditions which otherwise require harsh conditions of temperature and pressure [15-17]. The synthesis of tetrozoles has been described in the presence of different catalysts such as CuFe$_2$O$_4$ nanoparticles [18], γ-Fe$_2$O$_3$ [19], Fe$_3$O$_4$@SiO$_2$ nanoparticles [20], silver nanoparticles [21], NiO nanoparticles [22], and

How to cite this article
nano-ZnS [23]. Many methods for the synthesis of tetrazoles and pyrazines are known, but due to their importance, the improvement of new synthetic approaches by mild reaction conditions remains enough scope for an efficient and reusable catalyst with high catalytic activity for the preparation of (1H-tetrazole-5-yl) pyrazines. Herein, we report the use of MgFe$_2$O$_4$ nanoparticles as catalyst for the preparation of (1H-tetrazole-5-yl) pyrazines by one pot multi-component coupling reaction of α-dicarbonyl compounds, 2,3-diaminomaleonitrile and sodium azide under ultrasonic irradiation (Fig. 1).

**MATERIALS AND METHODS**

**Materials and Apparatus**

All organic materials were prepared commercially from Sigma–Aldrich and Merck and were used without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 200 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope. FT-IR spectra were recorded with KBr pellets using a Magna-IR, spectrometer 550 Nicolet. NMR spectra were recorded on a Bruker 400 MHz spectrometer with DMSO-$d_6$ as solvent and TMS as internal standard. CHN compositions were measured by Carlo Erba Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X’pert Company with monochromatized Cu Kα radiation ($\lambda=1.5406$ Å). In order to investigate the particle size and morphology of the synthesis structures nano-MgFe$_2$O$_4$, SEM images of the products visualized by a SEM LEO 1455VP.

**Preparation of MgFe$_2$O$_4$ nanoparticles**

In a typical preparation, MgSO$_4$, Fe(NO$_3$)$_3$·9H$_2$O, NaCl and NaOH were mixed (molar ratio 1:2:10:8) and ground together in an agate mortar for 30 min. The reaction started easily during the mixing procedure, accompanied by release of heat. As the reaction continued, the mixture became mushy and underwent gradual changes in color from colorless to light red (~1 min) and finally brown (~10 min). The mixture was then placed in a quartz crucible, inserted into a quartz tube, annealed at 700 °C for 1 h, and subsequently cooled to room temperature. Samples were collected, washed several times with distilled water, and dried at 120 °C overnight in a drying oven [24].

**General procedure for the synthesis of (1H-tetrazole-5-yl) pyrazines**

A mixture of α-dicarbonyl (1 mmol), 2,3-diaminomaleonitrile (1 mmol), and sodium azide (1.5 mmol or 3 mmol) and nano-MgFe$_2$O$_4$ (0.4 mol%) in DMSO (3 mL) was sonicated at 50 W power. After completion of the reaction confirmed by TLC (eluent: EtOAc/n-hexane, 1:1),

![Fig. 1. Synthesis of (1H-tetrazole-5-yl) pyrazines using nano-MgFe$_2$O$_4$](image-url)
the catalyst was separated magnetically and the heterogeneous catalyst was recovered. Then the solvent was removed. To the residue was added 10 mL of 2 N HCl with vigorous stirring causing the 3-(1H-tetrazole-5-yl) pyrazines.

**Representative spectral data**

3-(1H-tetrazole-5-yl) pyrazine-2-carbonitrile (4a):

Cream powder, m.p. 174-176 ºC; IR (KBr) cm⁻¹: 3401, 2125, 1670, 1544; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.73 (1H, CH), 8.94 (1H, s, CH); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 117.2, 126.4, 143.9, 147.9, 148.1, 158.0; Anal. calcd for C₁₉H₁₂N₂O: C, 64.64; H, 2.37; N, 32.98; Found: C, 64.53; H, 2.32; N, 32.98.

5,6-diphenyl-3-(1H-tetrazole-5-yl) pyrazine-2-carbonitrile (4b):

Yellow powder, m.p. 160-161 ºC; IR (KBr) cm⁻¹: 3435, 2230, 1690, 1545, 1448, 708; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.36-7.51 (10H, m, H-Ar); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 128.8, 130.2, 130.3, 136.7, 137.9, 152.3, 154.3; Anal. calcd for C₁₈H₁₄N₂O: C, 62.33; H, 3.92; N, 25.44; Found: C, 62.15; H, 3.85; N, 25.44.

5,6-bis(4-methoxyphenyl)-3-(1H-tetrazole-5-yl) pyrazine-2-carbonitrile (4c):

Yellow powder, m.p. 250-252 ºC; IR (KBr) cm⁻¹: 3538, 1543, 1454; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 3.79 (6H, s, OMe), 6.973-6.994 (4H, d, J = 8.4 Hz, H-Ar); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 55.7, 55.8, 114.4, 114.8, 116.2, 123.3, 128.7, 129, 131.5, 131.7, 132.1, 137.8, 152.7, 153.4, 161.2, 161.4; Anal. calcd for C₁₉H₁₈N₂O₂: C, 66.45; H, 3.41; N, 30.14; Found: C, 66.37; H, 3.35; N, 30.09.

9-(1H-tetrazole-5-yl)acenaphtho[1,2-b]pyrazine-8-carbonitrile (4d):

Brown powder, m.p. 238-240 ºC; IR (KBr) cm⁻¹: 3434, 3100, 2236, 1613, 1450; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.99-8.03 (2H, m, H-Ar), 8.42-8.54 (4H, m, H-Ar); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 116.5, 124.3, 127.4, 127.6, 127.9, 128.1, 128.4, 134.5, 143.4, 148.1, 148.8, 158.4; Anal. calcd for C₁₉H₁₄N₂O: C, 64.64; H, 2.37; N, 32.98; Found: C, 64.53; H, 2.32; N, 32.82.

2,3-diphenyl-5,6-di(1H-tetrazole-5-yl) pyrazine (5a):

White powder, m.p. 255-256 ºC; IR (KBr) cm⁻¹: 3428, 3123, 1683, 1549; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.15 (2H, s, H-Ar); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 140.2, 146.5, 153.7; Anal. calcd for C₁₉H₁₄N₂O: C, 33.34; H, 1.87; N, 64.80; Found: C, 33.26; H, 1.81; N, 64.89.

2,3-diphenyl-5,6-di(1H-tetrazole-5-yl) pyrazine (5b):

Cream powder, m.p. 207-209 ºC; IR (KBr) cm⁻¹: 3538, 1543, 1454; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 3.79 (6H, s, OMe), 6.973-6.994 (4H, d, J = 8.4 Hz, H-Ar); 7.853-7.874 (4H, d, J = 8.4 Hz, H-Ar); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 55.7, 114.4, 129.4, 131.5, 131.7, 132.0, 151.8, 160.9; Anal. calcd for C₁₉H₁₄N₂O₂: C, 56.07; H, 3.76; N, 32.69; Found: C, 56.14; H, 3.85; N, 32.57.

### RESULTS AND DISCUSSION

The XRD patterns for MgFe₂O₄ nanoparticle is shown in Fig. 2. The pattern agrees well with the reported pattern for MgFe₂O₄ nanoparticles (JCPDS No. 71-1232). The crystalline size was calculated from FWHM using Scherrer's formula and was observed to be 25-30 nm. The morphology and particle size of MgFe₂O₄ NPs was investigated by scanning electron microscopy (SEM) as shown in Fig. 3. The SEM images prove particles with diameters in the range of nanometers. Initially, we focused on systematic evaluation of diverse catalysts for the model reaction of oxalaldehyde (1 mmol), 2,3-diaminomaleonitrile (1 mmol), and sodium azide (1.5 mmol) in different solvents. We employed various conditions and found that the reaction gave satisfying result in the presence of nano-MgFe₂O₄ as catalyst. As show in Table 1, 0.40 mol % of nano-MgFe₂O₄ was not improved. The model reaction was carried out in the presence of various catalysts such as nano-MgO, nano-NiO, nano-Fe₃O₄, nano-NiFe₂O₄.
J. Safaei-Ghomi et al. / MgFe$_2$O$_4$ nanoparticles catalyzed the synthesis of pyrazines under Ultrasonic irradiation

and nano-MgFe$_2$O$_4$. When the reaction was carried out using MgFe$_2$O$_4$ nanoparticles as the catalyst under ultrasonic irradiation, the product could be obtained in good yield.

In continuation of this method, the model reaction was performed with 0.40 mol % of nano-MgFe$_2$O$_4$ in DMSO in various powers of ultrasonic irradiation to explore the appropriate power of ultrasonic irradiation. It is clear from Table 2 that, reactions under the effect of ultrasound give excellent yields of products in short reaction times due to inrush of liquid from one side of the surface of the catalyst because of the collapse of the cavitation bubbles. This high pressure jet of the liquid is supposed to activate the surface of the solid catalyst and consequently increase the rate of the reaction [25-27]. Therefore, it was observed that the reaction in the presence of 0.40 mol % of nano-MgFe$_2$O$_4$ and under ultrasonic irradiation with the power of 50W gave the best result as the obtained product with 95% isolated yield during 10 minutes. With these promising results...
in hand, we turned to explore the possibility of the reaction using diverse α-dicarbonyl compounds as substrates under the optimized reaction conditions (Table 3).

Table 2. Study of the effect of ultrasonic irradiation on the formation of (1H-tetrazole-5-yl) pyrazines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Power (W)</th>
<th>Time (min)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>20</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>15</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>10</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 1. Optimization of reaction conditions using different catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (condition)</th>
<th>Catalyst (mol)%</th>
<th>Time (min)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene (reflux)</td>
<td>—</td>
<td>600</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>EtOH (reflux)</td>
<td>—</td>
<td>400</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (reflux)</td>
<td>—</td>
<td>400</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>DMSO (90 ºC)</td>
<td>—</td>
<td>140</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>DMSO (90 ºC)</td>
<td>nano-MgO (0.9 mol%)</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>DMSO (90 ºC)</td>
<td>nano-Fe₂O₃ (0.8 mol%)</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>DMSO (90 ºC)</td>
<td>nano-MgFe₂O₄ (0.6 mol%)</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>DMSO (90 ºC)</td>
<td>nano-NiO (0.9 mol%)</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>DMSO (90 ºC)</td>
<td>nano-NiFe₂O₄ (0.6 mol%)</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>DMSO (US)</td>
<td>nano-MgFe₂O₄ (0.4 mol%)</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>DMSO (US)</td>
<td>nano-MgFe₂O₄ (0.6 mol%)</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>DMSO (US)</td>
<td>nano-NiFe₂O₄ (0.6 mol%)</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>13</td>
<td>DMSO (US)</td>
<td>—</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>14</td>
<td>DMSO (US)</td>
<td>nano-Fe₂O₃ (0.8 mol%)</td>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>15</td>
<td>DMSO (US)</td>
<td>nano-NiFe₂O₄ (0.6 mol%)</td>
<td>10</td>
<td>82</td>
</tr>
</tbody>
</table>

a oxalaldehyde (1 mmol), 2,3-diaminomaleonitrile (1 mmol), and sodium azide (1.5 mmol)
b Isolated yields

c Ultrasonic irradiation (50 W)

After completion of the reaction, the catalyst was separated magnetically from the reaction mixture and washed with Et₂O, air-dried and then reused directly in the model reaction of oxalaldehyde (1 mmol), 2,3-diaminomaleonitrile (1 mmol), and sodium azide (1.5 mmol) by 0.40 mol% of nano-MgFe₂O₄ under ultrasonic irradiation in DMSO. The results demonstrated that the catalyst exhibited high but slowly decreasing activity in six consecutive cycles, which might be attributed to the slight loss of catalyst during the reaction and recovery processes (Fig. 4).

A plausible mechanism for the preparation of (1H-tetrazole-5-yl) pyrazines using nano-

**Fig. 4. Reusability of MgFe₂O₄ nanoparticles catalyst for the preparation of 4a**
MgFe\(_2\)O\(_4\) is shown in Fig. 5. The formation of products can be rationalized by initial formation of pyrazine-2,3-dicarbonitriles by a condensation reaction of \(\alpha\)-dicarbonyl compounds and 2,3-diaminomaleonitrile. Subsequent [2+3] cycloaddition reaction of pyrazine-2,3-dicarbonitriles with the sodium azide to afford (1H-tetrazole-5-yl) pyrazines. In this mechanism the nano-MgFe\(_2\)O\(_4\) as a highly efficient and green catalyst activates the C=O and C≡N groups for better reaction with nucleophiles.

**CONCLUSION**

In conclusion, we have developed an atom-efficient, high-yielding protocol for the synthesis of (1H-tetrazole-5-yl) pyrazines by one pot multi-component coupling reaction of \(\alpha\)-dicarbonyl compounds, 2,3-diaminomaleonitrile and sodium azide using MgFe\(_2\)O\(_4\) nanoparticles as a robust catalyst under ultrasonic irradiation. The attractive advantages of the present process are atom economy, wide range of products, high catalytic activity, excellent yields, short reaction times and simple operational procedures.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(\alpha)-dicarbonyl compounds</th>
<th>Product</th>
<th>4a-5c</th>
<th>Time (min)</th>
<th>Yield(%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 4a | 10 | 95 |
| 2     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 4b | 10 | 97 |
| 3     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 4c | 15 | 92 |
| 4     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 4d | 10 | 95 |
| 5     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 5a | 10 | 94 |
| 6     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 5b | 10 | 95 |
| 7     | \[
\begin{array}{c}
\text{H} \\
\text{C}=\text{O} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{C}
\end{array}
\] | 5c | 15 | 91 |

* Isolated yields
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CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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