Nano-Fe₃O₄ as a heterogeneous recyclable magnetically separable catalyst for synthesis of nitrogen fused imidazoheterocycles via double C-N bond formation

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ABSTRACT

An efficient and convenient approach towards the synthesis of nitrogen fused imidazoheterocycles through double C-N bond formation in a single step has been achieved with a good range of substituted phenacyl bromides in the presence of magnetically recoverable Fe₃O₄ as a green heterogeneous nanocatalyst. The present approach was found to be environmentally benign and economically feasible in view of its ease of application, low cost and easy separation. Developed methodology has several advantages such as wide scope of substrates, easily available catalyst, operationally simple and high yield. Moreover, the magnetically separable catalyst was easily separated from the reaction mixture using an external magnet and recycled up to four times without much lost in its catalytic activity.

Keywords: Magnetically separable nanocatalyst, Imidazoheterocycles, Heterogeneous catalyst, C-N bond formation, Cyclocondensation, Azaheterocycles, Ferrite.

1. Introduction

Fused bicyclic heterocycles containing more than one nitrogen are important structural motifs found in numerous natural products and bioactive molecules [1-3]. Amongst these bicyclic nitrogen fused heterocycles, imidazoheterocycles are privileged scaffolds with wide range of biological activities, especially as antiulcer [4], anticancer [5], anti-inflammatory [6], antiviral [7], immunomodulatory [8], immunosuppressive [9] agents and in the treatment of cystic fibrosis [10].

Several commercially nitrogen fused imidazole drugs, such as imidazopyridine core containing alpidem [11], zolimidine[12], zolpidem[13], necopidem [14], saripidem [14], olprinone [15], imidazo[2,1-b]thiazole core containing levamisole [16] and benzo[d]imidazo [2,1-b]thiazole derivatives (YM-201627 [17]) as well as 11C-labelled imidazo[2,1-b]benzothiazole [18] have been developed by the modification of imidazole fused with either pyridine, thiazole or benzothiazole heterocyclic nuclei (Fig. 1). Due to an interesting biological importance displayed on a broad range of therapeutic classes, in the recent years the synthesis of nitrogen bridge bicyclic imidazo[2,1-b] pyridine/thiazole or benzothiazole derivatives have received significant attention from the pharmaceutical industries [19,20].

In the past, few synthetic strategies had been developed for the preparation of imidazoheterocycles, which can be achieved by the condensation reaction of 2-aminopyridine or 2-aminothiazole with two carbon synthones such as phenacyl halide [21-29], diazo aryl ketone [30] or α-tosyl ketones[31,32] derivatives in presence of the basic or neutral conditions [19,20]. Also, copper catalysed one pot three-component coupling of 2-aminopyridine with aldehyde and acetylene has been reported [33]. Condensation of the bromocarbonyl compound [21-29] with 2-amino pyridine/thiazole compounds in refluxing acetone or ethanol or using different catalysts and reaction conditions requires a long reaction time [19,20]. The proposed reaction process involves the crucial steps for the formation of two C-N bonds, the first step is nucleophilic substitution

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of bromide by nitrogen of 2-aminoheterocycle and the
second is dehydrative condensation and preparing the
N-fused heterocyclic scaffold.

In recent years, several methods and developments
have been reported for the synthesis of imidazo
[1,2-a]pyridine, imidazo[1,2-a]thiazole and imidazo
[1,2-a]benzothiazole derivatives. In spite of that, these
methods have their own merits and drawbacks of green
chemistry [21-29]. Many of the developed procedures
require harsh reaction conditions, expensive and toxic
reagents, tedious work-up, prolonged reaction time, low
yields and use of the non-recyclable catalysts; there is
no any efficient greener approach. The recovery and
reusability of the catalysts are also a major problem.
Therefore, the demand for green and eco-friendly
procedures using recycled catalysts necessitated
developing an alternative method for the synthesis of
imidazoheterocycles.

Magnetically separable nano-ferrite (Fe₃O₄)
has attracted much attention in the previous decade,
owing to its unique features, low preparation cost, high
thermal stability [34-36]. In addition, magnetic
nanoparticles (Fe₃O₄) show their paramagnetic
nature; due to this property, nano-Fe₃O₄ is very
popular as a heterogeneous catalyst and it can be easily
separated from the reaction mixture using an
external magnet. Magnetic nano-Fe₃O₄ particles have
developed as viable alternatives to conventional
materials, because of robust, thermally stable, readily
available and high catalytic activities in various organic
transformations. The nano-sized particles enhance the
exposed surface area of the active component of the
catalyst which increases the interaction between
reactants and catalysts dramatically [37,38]. The nano-
sized catalysts bridge the gap between heterogeneous
and homogeneous catalysts and these results in
conserving the required characteristics of both systems
[36].

Herein, we describe a mild and efficient approach to the
synthesis of imidazoheterocycle derivatives through
double C-N bond formation using nano-Fe₃O₄ as
catalyst (Scheme 1). To the best of our knowledge, there
has been no report on nano-ferrite catalysed synthesis of
fused azaheterocycles.
Scheme 1. Nano-Fe₃O₄ catalysed imidazopyridine synthesis reaction.

2. Experimental

2.1. Chemicals and Instruments

All chemicals were purchased from Sigma-Aldrich and S.D. Finechem companies and used without further purification. Reactions have been monitored by Thin Layer Chromatography on 0.2 mm precoated plates of silica gel G60 F254 (Merck). Visualisation was made with UV light or with an iodine vapour. Melting point ranges were determined in open capillaries and are uncorrected. All yields were referred to isolated products after purification. ¹H NMR spectra were recorded on BRUKER AVANCE II 400MHz and ¹³C NMR spectra were recorded on BRUKER AVANCE II 100MHz Spectrophotometer in DMSO-d₆ using TMS as the internal standard. The chemical shift values are recorded on δ-scale and the coupling constants (J) are in hertz. The X-ray diffraction (XRD) patterns were recorded on Bruker AXS D8 Advance X-ray diffractometer using monochromatic Cu-Kα radiation having wavelength λ = 1.5406 Å. Scanning Electron Microscope (SEM) images were obtained on S-4800 Type-II, HITACHI Japan.

2.2. Preparation of Fe₃O₄ nanoparticles

Fe₃O₄ nanoparticles were prepared by the quantitative modification of the reported process [39]. FeSO₄·7H₂O (6.95 g) and Fe₂(SO₄)₃ (10g) were dissolved in 300 mL water in a 500 mL beaker. NH₄OH (25%) was added slowly to adjust the pH of the solution to 10. Then, the reaction mixture was continuously stirred for 1 h at 60 °C. The precipitated brown coloured nanoparticles were separated by external magnate, washed with water until the pH reached up to 7, then dried at 120 °C for 1 h. Ferrite was characterised by FTIR, XRD and SEM.

2.3. General procedure for the synthesis of imidazoheterocycles:

2-Aminoazaheterocycle (1 mmol), substituted phenacyl bromide (1 mmol) and nano-Fe₃O₄ (10 mol%) were added into ethanol (5 mL) in a round bottom flask and stirred at refluxed temperature. The progress of the reaction was monitored on TLC (Toluene: Methanol 9:1 v/v). After completion of the reaction, the reaction mixture was diluted with ethyl acetate (10 mL) and the nano catalyst was separated by the external magnet. After separation of catalyst the product was extracted using water, the organic solvent is evaporated and the obtained product was recrystallized with aqueous ethanol.

3. Results and Discussion

3.1. Catalyst characterization

The FT-IR spectrum analysis suggests two ranges of the absorption bands (Fig. 2). In the range of 400–1000 cm⁻¹, two characteristic absorption bands of Fe-O bond were observed at v = 570 and 630 cm⁻¹ for the Fe₃O₄ MNPs. The second broad absorption band at about 3410 cm⁻¹ represents a stretching mode of H₂O molecules and indicates that a large number of OH groups are presented on the surface of the MNPs.

Fig. 2. FT-IR spectra of catalyst a) Fresh, b) after 3rd run.
The XRD pattern of the Fe₃O₄ MNPs (Fig. 3) showed a series of diffraction peaks at 2θ° of 30.29°, 35.66°, 43.32°, 53.66°, 57.36°, 63.01° and 74.49° which can be assigned to (220), (311), (400), (422), (511), (440) and (620) planes respectively. The diffraction patterns are well matched with the literature [39] and no diffraction peaks of other impurities was observed.

The SEM analysis suggests that the Fe₃O₄ MNPs are nanocrystalline morphology of the catalyst (Fig. 4). The image of Fe₃O₄ MNPs clearly indicates that NPs are uniform in the average particle size range of 60±15 nm. These results are in good harmony with the XRD analysis.

![Fig. 3. XRD spectra of catalyst a) Fresh, b) after 3rd run.](image)

![Fig. 4. FEG SEM images of catalyst a-c) Fresh, d) after 3rd run.](image)
At the onset of the research, we made a conscious effort to develop a catalytic system that would address the limitations of the previously reported reactions. During the preliminary studies, 2-amino pyridine and phenacyl bromide were used as a model system. A series of experiments were performed to optimize various reaction parameters, such as the catalyst, catalyst loading, solvent, temperature and time (Table 1). Initially we developed the best magnetically separable catalysts; Fe₃O₄ and MFe₂O₄ (M= Cu²⁺, Zn²⁺, Mn²⁺ and Ni²⁺), have been synthesized by thermal decomposition and were subsequently screened for the model system of reaction. Among the catalysts examined, nano-Fe₃O₄ was found to be the best, providing excellent yields of the desired product 3a (Table 1, entries 1-8). We further studied catalysts concentration ranging from 5 to 12 mol%; increasing the catalyst loadings from 5 to 10 mol% raises the yield of product 3a up to 91%. Further increase of catalyst concentration to 12 mol% did not improve the yield of 3a (Table 1 entries 8-10). As the solvent has an impact on the overall process, the effect of various solvents (Table 2, entries 1-6) were examined; the best results was obtained with ethanol which afforded 3a in 91% yield (Table 2 entry 1). We also studied the effect of the temperature and the study showed that the yield 3a increases with increasing reaction temperature from 60°C to reflux (Table 2 entry 1, 8). The reaction time was optimized at four hours, a further increase of time to 5 hours did not increases the yield of 3a (Table 1 entry 8, 10).

**Table 1. Effect of reaction parameters on the imidazopyridine synthesis reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading (mol %)</th>
<th>Time (h)</th>
<th>Yield (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>--</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>Bulk Fe₃O₄</td>
<td>10</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>Bulk MnFe₂O₄</td>
<td>10</td>
<td>5</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>Bulk NiFe₂O₄</td>
<td>10</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>Bulk CuFe₂O₄</td>
<td>10</td>
<td>5</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>Bulk ZnFe₂O₄</td>
<td>10</td>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Nano Fe₃O₄</td>
<td>10</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>Nano Fe₃O₄</td>
<td>10</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>Nano Fe₃O₄</td>
<td>5</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>Nano Fe₃O₄</td>
<td>12</td>
<td>5</td>
<td>91</td>
</tr>
</tbody>
</table>

^aReaction conditions: 2-Aminopyridine (1mmol), Phenacyl bromide (1mmol), ethanol (5mL) at reflux temperature.  
^bIsolated yields.

**Table 2. Effect of solvent, temperature and time on model reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol</td>
<td>reflux</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>reflux</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>reflux</td>
<td>4</td>
<td>54</td>
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<tr>
<td>4</td>
<td>Chloroform</td>
<td>reflux</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>reflux</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>100</td>
<td>4</td>
<td>54</td>
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<tr>
<td>7</td>
<td>Ethanol</td>
<td>reflux</td>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>Ethanol</td>
<td>60</td>
<td>4</td>
<td>68</td>
</tr>
</tbody>
</table>

^aReaction conditions: 2-Aminopyridine (1mmol), Phenacyl bromide (1mmol), nano-Fe₃O₄ (10 mol %), solvent (5mL).  
^bIsolated yields.
Having optimized reaction conditions in hand, we explore the substrate scope of the ferrite catalysed N-fused heterocycles synthesis by using 2-aminopyridine, 2-aminothiazole or 2-aminobenzothiazole with various substituted phenacyl bromides containing different functional groups. We observed that electron donating and also electron withdrawing substituents provide remarkable yield of products. Gratifyingly this protocol tolerated a variety of common functional groups such as alkyl, ether, halogen and nitro groups regardless of the positions. The results of these reactions are summarized in Table 3.

In order to make our catalytic system more economical, we focused on the reusability of the nano-Fe₃O₄ catalysts in this cyclisation reaction. The catalysts exhibited remarkable activity observed in all four recycles. After completion of the reaction according to TLC, the reaction mixture was diluted with ethyl acetate. The external magnet was touched to wall of the sealed tube and the reaction mixture was decanted into the small beaker. The catalyst was washed with ethanol (3×5 ml) and dried for 1 h at 120 °C in an oven. Then the catalyst was used directly in the reusability studies. The catalyst was recycled four times (The yields were 91, 86, 81 and 73 %, respectively) and gave constant yields. The third run of recycling catalyst (before fourth run), we have analysed the catalyst by FTIR, XRD and FESEM analysis. All of these analyses clearly match with fresh catalyst.

To determine the ability of nano-Fe₃O₄ in preparation of imidazopyridine, the efficiency of nano-Fe₃O₄ for the reaction of 2-Aminopyridine with Phenacyl bromide was compared with previously reported catalysts in the literature, and results are presented in Table 4. Thus, this procedure with nano-Fe₃O₄ as the catalyst seems superior to other recently reported synthetic methods.

### 4. Conclusions

We have reported the synthesis of N-bridge fused heterocyclic compounds. In this method, ferrite catalysed two C-N bond formations are the crucial steps for heterocyclisation to deliver the N-fussed heterocyclic scaffold. Notably, the current process provides a simple, efficient, environmentally benign and practical route for facial access to valuable azaheterocycles in good yields.

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### Table 3. Nano-Ferrite catalyzed synthesis of 3a-r.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azole (1)</th>
<th>Phenacyl Bromide (2)</th>
<th>Product (3)</th>
<th>Yield (mol%)</th>
<th>m.p. (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a</td>
<td>91</td>
<td>128-130</td>
<td>129-131</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>3b</td>
<td>86</td>
<td>132-134</td>
<td>132-134</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>3c</td>
<td>89</td>
<td>134-136</td>
<td>135-136</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2d</td>
<td>3d</td>
<td>90</td>
<td>204-206</td>
<td>206-208</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>OBr2</td>
<td>eBr2e</td>
<td>Br3e</td>
<td>84</td>
<td>212-214</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>OBr2f</td>
<td>NO22f</td>
<td>NO23f</td>
<td>87</td>
<td>204-206</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>S-NH21b</td>
<td>2a</td>
<td>84</td>
<td>148-150</td>
<td>148-150 [40]</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2b</td>
<td>OCH3S3h</td>
<td>82</td>
<td>156-158</td>
<td>154-156 [40]</td>
</tr>
<tr>
<td>9</td>
<td>1b</td>
<td>2c</td>
<td>86</td>
<td>142-144</td>
<td>147-149 [40]</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>2d</td>
<td>Cl3j</td>
<td>88</td>
<td>162-164</td>
<td>163-165 [40]</td>
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<tr>
<td>11</td>
<td>1b</td>
<td>2e</td>
<td>Br3k</td>
<td>84</td>
<td>178-180</td>
<td>181-183 [40]</td>
</tr>
<tr>
<td>12</td>
<td>1b</td>
<td>2f</td>
<td>NO23l</td>
<td>88</td>
<td>234-236</td>
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<tr>
<td>13</td>
<td>1c</td>
<td>S-NH21c</td>
<td>2a</td>
<td>74</td>
<td>104-106</td>
<td>106 [17]</td>
</tr>
<tr>
<td>14</td>
<td>1c</td>
<td>2b</td>
<td>OCH3S3n</td>
<td>76</td>
<td>180-182</td>
<td>181 [17]</td>
</tr>
<tr>
<td>15</td>
<td>1c</td>
<td>2c</td>
<td>CH3S3o</td>
<td>70</td>
<td>120-122</td>
<td>124 [17]</td>
</tr>
<tr>
<td>16</td>
<td>1c</td>
<td>2d</td>
<td>Cl3p</td>
<td>80</td>
<td>158-160</td>
<td>160 [17]</td>
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<tr>
<td>17</td>
<td>1c</td>
<td>2e</td>
<td>Br3q</td>
<td>76</td>
<td>166-168</td>
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<tr>
<td>18</td>
<td>1c</td>
<td>2f</td>
<td>NO23r</td>
<td>76</td>
<td>286-288</td>
<td>284 [17]</td>
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Note: Reaction conditions: 2-Aminoazaheterocycle (1 mmol), substituted phenacyl bromide (1 mmol), nano-Fe3O4 (10 mol %), ethanol (5mL) reflux, time 4h.
Isolated yields.
Table 4. Comparison of catalytic activity of Nano Fe$_3$O$_4$ with other reported catalysts used for preparation of imidazopyridine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (Conc.)</th>
<th>Solvent</th>
<th>Temp. ($^\circ$C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>1</td>
<td>Catalyst free</td>
<td>Ethanol</td>
<td>50</td>
<td>48</td>
<td>71-80</td>
<td>[23]</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$ (1 equiv.)</td>
<td>Water</td>
<td>RT</td>
<td>4.3</td>
<td>56</td>
<td>[21]</td>
</tr>
<tr>
<td>3</td>
<td>Triethyl amine (1 equiv.)</td>
<td>Water</td>
<td>RT</td>
<td>5.1</td>
<td>55</td>
<td>[21]</td>
</tr>
<tr>
<td>4</td>
<td>MgO (1 equiv.)</td>
<td>Water</td>
<td>RT</td>
<td>2.1</td>
<td>92</td>
<td>[21]</td>
</tr>
<tr>
<td>5</td>
<td>Na$_2$CO$_3$ (1.5 equiv.)</td>
<td>1,4-Dioxane-Water (2:1)</td>
<td>Refluxed</td>
<td>22</td>
<td>94</td>
<td>[27]</td>
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<tr>
<td>6</td>
<td>Neutral Al$_2$O$_3$ (10 equiv.)</td>
<td>Solvent free</td>
<td>RT</td>
<td>3</td>
<td>85</td>
<td>[25]</td>
</tr>
<tr>
<td>7</td>
<td>Nano Fe$_3$O$_4$ (10 mol%)</td>
<td>Ethanol</td>
<td>Refluxed</td>
<td>4</td>
<td>91</td>
<td>This work</td>
</tr>
</tbody>
</table>

*Compare with 1 equivalent 2-Aminopyridine.

*Isolated yields.

References


