Synthesis of 2,4,5-Trisubstituted Phenanthroimidazole Derivatives using SBA-Pr-SO$_3$H as a Nanocatalyst

Ghodsi Mohammadi Ziarani, Elham Tavaf, Vaezeh Fathi Vavsari and Alireza Badiei

Abstract

An efficient one-pot approach for the preparation of 2,4,5-trisubstituted phenanthroimidazole derivatives is described. The three-component reaction between 9,10-phenanthraquinone, benzaldehyde derivatives, and ammonium acetate proceeds in the presence of SBA-Pr-SO$_3$H as a nanoporous solid acid catalyst in short reaction times and good to excellent yields.

Keywords: Trisubstituted phenanthroimidazole; 9,10-Phenanthraquinone; SBA-Pr-SO$_3$H; Nanocatalyst; Heterogeneous catalysis

1. Introduction

Application of imidazole and their derivatives is unavoidable in the field of medicinal chemistry due to their biologically active properties as biocides, platelet aggregation inhibitors, analgetics, antibacterial, antitumor, and anti-inflammatory activity. Additionally, derivatives of imidazole conjugated with aromatic rings have been widely used as fluorescent dyes.

In recent years, several methods have been reported for the preparation of three-substituted imidazole derivatives from 9,10-phenanthraquinones, benzaldehyde derivatives and ammonium acetate using different catalysts such as I$_2$, mercaptopropylsilica, zirconium Schiff base, iron(III) triflate, sulfamic acid, and ionic liquid modified surface. Recently, mesoporous ordered silica materials such as SBA-15 have received more attention in the field of catalysis. As a well ordered hexagonal mesoporous silica, SBA-15 has relevant characteristics such as large uniform pore size, high surface area, thick walls, and high thermal stability which makes it a good candidate for preparing organic-inorganic hybrid materials and using as catalyst in different reactions. Furthermore, the propyl sulfonic acid modified SBA-15 can behave as an efficient Bronsted acid in organic synthesis. Due to our interest in the field of nano-heterogeneous acidic catalysts and based on different studies on applying SBA-Pr-SO$_3$H in organic synthesis, we have discovered a green and efficient method for the synthesis of 2,4,5-trisubstituted phenanthroimidazoles 4a-i using SBA-Pr-SO$_3$H. In our previous studies, we have already reported the efficient synthesis of benzimidazoquinazolinones and 1,2,4,5-tetrasubstituted imidazoles in the presence of SBA-Pr-SO$_3$H.

2. Experimental

2.1. Materials and Instrumentations

All chemicals were obtained commercially and used without further purification. The IR spectra were recorded on KBr disks using a FT-IR Bruker Tensor 27 instrument. Melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. $^1$H NMR and $^{13}$C NMR spectra were obtained by a Bruker 400 MHz and 100 MHz spectrometer, respectively, in either DMSO-$d_6$ or CDCl$_3$ solution. Mass spectra data were obtained by using a Network mass selective detector 5973 (Agilent). Scanning electron microscope (SEM) analysis

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was performed on a Philips XL-30 field-emission SEM operated at 16 kV, while TEM was carried out on a Tecnai G² F30 apparatus at 300 kV. Weight change curve in nitrogen was measured on a BAHR Thermo analyser STA 503 with the maximum heating rate of 20 °C/min.

2. 2. General Procedure for the Synthesis of 2,4,5-trisubstituted phenanthroimidazoles (4a–i)

The mixture of 9,10-phenanthraquinone (0.20 g, 1 mmol), benzaldehyde derivatives (1 mmol), and ammonium acetate (0.31 g, 4 mmol) was stirred in refluxing acetic acid (3 mL) for about 30 min using SBA-Pr-SO₃H (0.02 g) as the catalyst. The completion of the reaction was monitored by TLC technique (ethyl acetate/petroleum ether, 2:1). The precipitated product was filtered and dissolved in hot ethanol and DMF to remove the catalyst, and the solvent evaporated to obtain the pure product. The catalyst was subsequently washed with a diluted hydrochloric acid solution, distilled water, acetone and dried under reduced pressure, and reused for several times without significant loss of catalytic activity.33 Physical and spectroscopic data of two new compounds are given below.

2. 3. Spectral Data of New Products

2-(2,4-Dimethoxyphenyl)-1H-phenanthro[9,10-d]imidazole (4h)

IR (KBr, ν_max): 3523, 3430, 3048, 2987, 2942, 2833, 1935, 1603, 1462, 1371, 1311, 1266, 1204, 1161, 1083, 1022, 935, 747, 714, 564, 434 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ: 3.87 (s, 3H, CH₃), 4.03 (s, 3H, CH₃), 6.76 (dd, 1H, J=11.5 Hz, J=3 Hz, ArH), 6.80 (d, 1H, J=11.4 Hz, ArH), 8.20 (d, 1H, J=10.3 Hz, ArH), 8.81–8.88 (m, 2H, ArH), 13.82 (s, 1H, NH) ppm. ¹³C NMR (100 MHz, DMSO-d₆) δ: 55.5, 55.9, 98.5, 105.9, 111.8, 111.9, 121.9, 122.4, 122.5, 123.7, 123.9, 125, 126.6, 126.8, 126.9, 127, 127.3, 127.4, 131.1, 136.2, 147.3, 157.8, 161.6 ppm. MS (m/z, %): 362 (M⁺, 100), 336(9), 190(86), 171(18), 163(53), 136(18).

3. Results and Discussion

The reaction of 9,10-phenanthraquinone (1), 4-chlorobenzaldehyde (2a), and ammonium acetate (3) was selected for optimizing conditions and investigating the role of nanocatalyst, SBA-Pr-SO₃H (Scheme 1). In order to study the solvent effect, different solvents were tested including solvent-free system at ambient temperature and at 120 °C, refluxing in water, ethanol and/or acetic acid as green solvents. As shown in Table 1, the best yield was obtained under refluxing in acetic acid in the presence of SBA-Pr-SO₃H (0.02 g). On the other hand, to indicate the catalyst effect, the results of different catalysts were compared with SBA-Pr-SO₃H under modified conditions (Figure 1). Clearly, SBA-Pr-SO₃H led to both, shorter reaction times and higher yields. After optimizing the reaction conditions, several aromatic aldehydes were used for the synthesis of 2,4,5-trisubstituted phenanthroimidazoles (Figure 2), which are listed in Table 2.

The proposed mechanism is shown in Scheme 2. In the first step, aldehyde carbonyl group is protonated on the SBA-Pr-SO₃H surface acidic sites. The activated carbonyl group is susceptible to the nucleophilic attack of ammonia, produced from the ammonium acetate (3), and gives the intermediate (4'). Condensation of 9,10-phenanthraquinone (1) with intermediate 4' through an imination process and proton replacement in intermediate 4'', produces the desired products 4a–i.

![Scheme 1. Model reaction of 9,10-phenanthraquinone 1, 4-chlorobenzaldehyde 2a, and ammonium acetate 3 for the synthesis of 4a.](image-url)
SBA-15 was synthesized according to the reported method. Then, its internal surface was modified by using (3-mercaptopropyl)trimethoxysilane, and further oxidation with H2O2 in methanol, producing SBA-Pr-SO3H, which was characterized via different techniques, including TGA, SEM and TEM analysis. The weight reduction in TGA analysis (Figure 3) in the temperature range of 200–600 °C, indicates that propyl sulfonic acid groups were grafted onto the pores of silica material and that the average amount is 1.2 mmol/g. The mass loss before 200 °C is due the adsorbed water onto the pores of SBA-Pr-SO3H. SEM image of SBA-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Condition</th>
<th>Time (min)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>SBA-Pr-SO3H</td>
<td>–</td>
<td>r.t.</td>
<td>24 h</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>SBA-Pr-SO3H</td>
<td>–</td>
<td>120 °C</td>
<td>N. R.</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>SBA-Pr-SO3H</td>
<td>H2O</td>
<td>Reflux</td>
<td>&gt;5 h</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>SBA-Pr-SO3H</td>
<td>EtOH</td>
<td>Reflux</td>
<td>&gt;5 h</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>SBA-Pr-SO3H</td>
<td>CH3COOH</td>
<td>Reflux</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>CH3COOH</td>
<td>Reflux</td>
<td>10</td>
<td>90</td>
</tr>
</tbody>
</table>

Figure 1. Comparison of reaction times and product yields for the synthesis of 4 using different catalysts including I2, mercaptopropylsilica (MPS), p-toluenesulfonic acid (p-TSA), NH2SO3H, supported ionic liquid-like phase (SILLP), and SBA-Pr-SO3H.

Figure 2. Schematic synthesis of 2,4,5-trisubstituted phenanthroimidazoles (4).

Scheme 2. The proposed mechanism for the synthesis of 2,4,5-trisubstituted phenanthroimidazoles (4).
Table 2: Synthesis of 2,4,5-trisubstituted phenanthroimidazoles (4) in the presence of SBA-Pr-SO₃H under reflux conditions in acetic acid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp (Lit.)</th>
</tr>
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<td>95</td>
<td>263–265</td>
<td>275–276¹⁴</td>
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<td>2</td>
<td>4-F</td>
<td><img src="image2.png" alt="Image" /></td>
<td>20</td>
<td>96</td>
<td>205–208</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>4-OMe</td>
<td><img src="image3.png" alt="Image" /></td>
<td>10</td>
<td>95</td>
<td>265–267</td>
<td>265–257¹⁴</td>
</tr>
<tr>
<td>4</td>
<td>4-Me</td>
<td><img src="image4.png" alt="Image" /></td>
<td>10</td>
<td>97</td>
<td>292–295</td>
<td>290–292¹⁵</td>
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<tr>
<td>5</td>
<td>4-OH</td>
<td><img src="image5.png" alt="Image" /></td>
<td>20</td>
<td>97</td>
<td>&gt;300</td>
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<tr>
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<td>3-NO₂</td>
<td><img src="image6.png" alt="Image" /></td>
<td>20</td>
<td>90</td>
<td>278–280</td>
<td>271–272¹⁶</td>
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<tr>
<td>7</td>
<td>2,4-(Cl)₂</td>
<td><img src="image7.png" alt="Image" /></td>
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<td>8</td>
<td>2,4-(OMe)₂</td>
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<td>20</td>
<td>93</td>
<td>203–205</td>
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<tr>
<td>9</td>
<td>2,6-(Cl)₂</td>
<td><img src="image9.png" alt="Image" /></td>
<td>20</td>
<td>90</td>
<td>230–232</td>
<td>New</td>
</tr>
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</table>

¹ Typical reaction conditions: 9,10-phenanthraquinone (1 mmol), benzaldehyde (1 mmol), and ammonium acetate (4 mmol) in the presence of SBA-Pr-SO₃H (0.02 g) were stirred in refluxing acetic acid (3 mL).
Pr-SO$_3$H showed same morphology as obtained for SBA-15, proving this process didn’t change the structure of SBA-15 itself (Figure 4). TEM image also demonstrated the presence of channels onto the SBA-Pr-SO$_3$H structure which were not collapsed after modification.

4. Conclusion

In conclusion, we have developed a novel three-component reaction to prepare 2,4,5-trisubstituted phenanthroimidazoles (4) from 9,10-phenanthraquinones, benzaldehyde derivatives and ammonium acetate. High yields, mild reaction conditions, simple purification, and the ability to recycle the heterogenous nanocatalyst, SBA-Pr-SO$_3$H, make this method an ecologically friendly for the synthesis of 4. This protocol expands the new pathways for employing green catalysts to design other similar multicomponent reactions.

5. Acknowledgements

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6. References


Ziarani et al.: Synthesis of 2,4,5-Trisubstituted Phenanthroimidazole ...
V prispevku je predstavljena učinkovita enostopnijska reakcija priprave 2,4,5-trisubstituiranih fenantroimidazolnih derivatov. Trikomponentna reakcija med 9,10-fenantrokinonom, različnimi derivati benzaldehda in amoničnim acetatom, v prisotnosti SBA-Pr-SO₃H kot trnega, nanoporoznega kislega katalizatorja, poteka hitro, s kratkimi reakcijskimi časi in odličnimi izkoristi.