A convenient green protocol for one-pot three-component synthesis of 2-amino-4H-chromene derivatives catalyzed by ilmenite (FeTiO$_3$) as an efficient and reusable catalyst in water

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A highly efficient and simple procedure for the synthesis of 2-amino-4H-chromene derivatives via one-pot, three-component reaction from various aldehydes, malononitrile, and α- or β-naphthol in the presence of a catalytic amount of ilmenite (FeTiO$_3$) is described. The advantages of this novel protocol include good yield, short reaction time, simple work-up, low toxicity and environmentally friendly catalyst. According to our results, FeTiO$_3$ (10 mol %) can be used as a catalyst for the synthesis of 2-amino-4H-chromene derivatives in water solvent under reflux conditions.

Key words: FeTiO$_3$, ilmenite, three-component reaction, 2-amino-4H-chromene derivatives, malononitrile, aldehydes.

INTRODUCTION

Multicomponent coupling reactions (MCRs) are emerging as useful tools for the carbon–carbon and carbon–heteroatom bond-forming reactions and for the synthesis of small drug-like molecules with several degrees of structural diversity [1]. One-pot multicomponent reactions provide the possibility of directly synthesizing a complex molecule without needing to isolate the intermediates, which has aroused researchers to design such reactions using different catalysts [2,3].

Ilmenite (FeTiO$_3$) is one of the most common minerals in the earth crust. FeTiO$_3$ is an interesting wide bandgap (2.58–2.9 eV) antiferromagnetic semiconductor with potential applications in spintronics, optoelectronics, high temperature integrated circuits, chemical catalysts, photo catalysts, etc. [4].

Aminochromenes and their derivatives are of considerable interest as they possess a wide range of biological properties [5], such as spasmyctotic, diuretic, anticoagulant, anticancer and antianaphylactic activities [6]. In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS associated dementia and Down’s syndrome, as well as for the treatment of schizophrenia and myoclonus [7].

Aminochromenes have been prepared by heating a mixture of malononitrile, aldehydes and activated phenols or naphthols in refluxing DMF or acetonitrile in the presence of hazardous organic bases such as piperidine and triethylamine [8, 9]. In the literature, a lot of synthetic methods for the synthesis of 2-amino-4H-chromene derivatives have been reported so far [10-26]. Most of these methods are associated with shortcomings like the use of costly, harmful and non-reusable catalysts, tedious separation procedures, long reaction time, tedious work up and use of toxic organic solvents.

To the best of our knowledge, the use of water as a clean solvent in the presence of ilmenite as a reusable catalyst for the synthesis of 2-amino-4H-chromene derivatives has not been reported.

In light of the above reports, and in continuation of our ongoing efforts to develop new methods in organic synthesis [27-38], herein we report our results for the synthesis of 2-amino-4H-chromene derivatives via a one-pot three-component reaction of various aldehydes (2), malononitrile (3) and α-, or β-naphthol (1) in the presence of FeTiO$_3$ as an efficient and reusable catalyst in water under reflux conditions (Scheme 1).

RESULTS AND DISCUSSION

As a part of a continuing effort in our laboratory towards the development of new methods in organic synthesis [27-38], in the present paper, a convenient and green protocol for the one-pot three-component synthesis of 2-amino-4H-
chromene derivatives catalyzed by ilmenite as a reusable catalyst in water is described.

To optimize the reaction conditions, the condensation reaction of α- or β-naphtol (1), benzaldehyde (2), and malononitrile (3) was tested as the model reaction using different amounts of FeTiO₃ at 40 or 100 °C under reflux conditions in the presence of various solvents. As shown in Table 1, FeTiO₃ (10 mol %) as a catalyst under reflux conditions afforded 2-amino-4H-chromene derivatives in 30 min with (4a = 87 %, and 5a = 86 %) of yield in water (Table 1, Scheme 2).

In the next section, in order to assess the efficiency and the scope of the catalyst for the preparation of 2-amino-4H-chromene derivatives, the reaction of α- or β-naphtol with various aldehydes and malononitrile was examined in the presence of 10 mol% of FeTiO₃ as a catalyst. The corresponding results are displayed in Table 2.

**Scheme 1.** Synthesis of chromene derivatives from various aromatic aldehydes, malononitrile and naphthols in water.

**Scheme 2.** Preparation of chromene derivatives from benzaldehyde, malononitrile and naphthols in the presence of FeTiO₃ as a catalyst.

\[ \text{FeTiO}_3 \text{(10 mol %)} \rightarrow \text{Water (5 mL), Reflux} \]

\[ \text{CN} \]

\[ \text{NH}_2 \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{CN} \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{NH}_2 \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{CN} \]

\[ \text{NH}_2 \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{CN} \]

\[ \text{NH}_2 \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{CN} \]

\[ \text{NH}_2 \]

\[ \text{O} \]

\[ \text{Ar} \]
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Table 1. Optimization of conditions for the synthesis of 2-amino-4H-chromene derivatives from 4-chlorobenzaldehyde, malononitrile, and α- or β-naphthol in the presence of different amounts of FeTiO₃ as a catalyst at different temperatures.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst (mol %)</th>
<th>T (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>4a</th>
<th>5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol</td>
<td>10</td>
<td>60</td>
<td>35</td>
<td>75</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Methanol</td>
<td>10</td>
<td>60</td>
<td>30</td>
<td>82</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Dichloromethane</td>
<td>10</td>
<td>40</td>
<td>60</td>
<td>52</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Acetonitrile</td>
<td>10</td>
<td>60</td>
<td>40</td>
<td>82</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>10</td>
<td>90</td>
<td>30</td>
<td>79</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Water</td>
<td>10</td>
<td>90</td>
<td>30</td>
<td>81</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Water</td>
<td>5</td>
<td>90</td>
<td>30</td>
<td>64</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Water</td>
<td>Catalyst-free</td>
<td>Reflux</td>
<td>6 h</td>
<td>40</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Solvent-free</td>
<td>10</td>
<td>100</td>
<td>60</td>
<td>72</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: α-naphthol (1 mmol), or β-naphthol (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol) and solvent (5 mL) in the presence of FeTiO₃ as a catalyst. b Isolated yield

Scheme 3 A proposed mechanism for the preparation of 2-amino-4H-chromene derivatives from various aldehydes, malononitrile and α-naphthol.
As shown in Table 2, the presence of electron-donating groups on the aromatic aldehydes resulted in low yields of the corresponding products and the reaction was sluggish. The presence of electron-withdrawing groups, however, resulted in shorter reaction times and higher yields. Using α-naphthol or β-naphthol had no effect on the reaction time or yield of the corresponding products.

The proposed mechanism for the preparation of 2-amino-3-cyano-4-phenyl-4H-benzo[h]chromene from benzaldehyde, malononitrile, and α-naphthol in the presence of FeTiO₃ as a catalyst is depicted in Scheme 3. According to the literature [10-19], benzylidene malononitrile, containing an electron-poor C=C double bond, is formed quantitatively by Knoevenagel addition of malononitrile to the aromatic aldehyde in the presence of FeTiO₃ as a catalyst. Ortho C-alkylation of the electrophilic C=C double bond by α-naphthol gives the intermediate (I). The latter converts via tautomerization to intermediate (II) which is then cyclized by nucleophilic attack of an OH group on the cyano (CN) moiety to give intermediate (III). Subsequent tautomerization produced the 2-amino-3-cyano-4-phenyl-4H-benzo[h]chromene (4a).

### Table 2. Synthesis of 2-amino-4H-chromene derivatives using ilmenite as a catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Phenol</th>
<th>Product</th>
<th>Time/min</th>
<th>Yield /%</th>
<th>Mp/°C</th>
<th>Lit ± Mp/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>α- Naphthol</td>
<td>4a</td>
<td>30</td>
<td>87</td>
<td>209-211</td>
<td>210-211 [39]</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC₆H₄</td>
<td>α- Naphthol</td>
<td>4b</td>
<td>35</td>
<td>91</td>
<td>231-232</td>
<td>231-232 [42]</td>
</tr>
<tr>
<td>3</td>
<td>2-ClC₆H₄</td>
<td>α- Naphthol</td>
<td>4c</td>
<td>35</td>
<td>90</td>
<td>209-238</td>
<td>236-237 [11]</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Cl₂C₆H₃</td>
<td>α- Naphthol</td>
<td>4d</td>
<td>35</td>
<td>91</td>
<td>220-222</td>
<td>222-224 [46]</td>
</tr>
<tr>
<td>5</td>
<td>4-NO₂C₆H₄</td>
<td>α- Naphthol</td>
<td>4e</td>
<td>37</td>
<td>91</td>
<td>230-232</td>
<td>231-234 [18]</td>
</tr>
<tr>
<td>6</td>
<td>3-NO₂C₆H₄</td>
<td>α- Naphthol</td>
<td>4f</td>
<td>40</td>
<td>89</td>
<td>208-210</td>
<td>208-211 [24]</td>
</tr>
<tr>
<td>7</td>
<td>4-FC₆H₄</td>
<td>α- Naphthol</td>
<td>4g</td>
<td>40</td>
<td>90</td>
<td>228-230</td>
<td>229-231 [42]</td>
</tr>
<tr>
<td>8</td>
<td>4-MeOC₆H₄</td>
<td>α- Naphthol</td>
<td>4h</td>
<td>30</td>
<td>85</td>
<td>194-195</td>
<td>195-196 [10]</td>
</tr>
<tr>
<td>9</td>
<td>3-OHC₆H₄</td>
<td>α- Naphthol</td>
<td>4i</td>
<td>35</td>
<td>80</td>
<td>230-232</td>
<td>228-232 [46]</td>
</tr>
<tr>
<td>10</td>
<td>4-BrC₆H₄</td>
<td>α- Naphthol</td>
<td>4j</td>
<td>30</td>
<td>90</td>
<td>243-244</td>
<td>241-243 [41]</td>
</tr>
<tr>
<td>11</td>
<td>4-MeC₆H₄</td>
<td>α- Naphthol</td>
<td>4k</td>
<td>30</td>
<td>84</td>
<td>205-206</td>
<td>205-206 [39]</td>
</tr>
<tr>
<td>12</td>
<td>4-HOC₆H₄</td>
<td>α- Naphthol</td>
<td>4l</td>
<td>35</td>
<td>85</td>
<td>244-246</td>
<td>245-247 [43]</td>
</tr>
<tr>
<td>13</td>
<td>C₆H₅</td>
<td>β- Naphthol</td>
<td>5a</td>
<td>30</td>
<td>86</td>
<td>279-280</td>
<td>278-280 [42]</td>
</tr>
<tr>
<td>14</td>
<td>4-ClC₆H₄</td>
<td>β- Naphthol</td>
<td>5b</td>
<td>35</td>
<td>90</td>
<td>209-210</td>
<td>208-210 [42]</td>
</tr>
<tr>
<td>16</td>
<td>2,4-Cl₂C₆H₃</td>
<td>β- Naphthol</td>
<td>5d</td>
<td>35</td>
<td>90</td>
<td>220-222</td>
<td>219-222 [47]</td>
</tr>
<tr>
<td>17</td>
<td>4-NO₂C₆H₄</td>
<td>β- Naphthol</td>
<td>5e</td>
<td>40</td>
<td>91</td>
<td>230-232</td>
<td>188-189 [42]</td>
</tr>
<tr>
<td>18</td>
<td>3-NO₂C₆H₄</td>
<td>β- Naphthol</td>
<td>5f</td>
<td>50</td>
<td>94</td>
<td>211-213</td>
<td>210-212 [41]</td>
</tr>
<tr>
<td>19</td>
<td>4-FC₆H₄</td>
<td>β- Naphthol</td>
<td>5g</td>
<td>55</td>
<td>94</td>
<td>231-232</td>
<td>232-233 [45]</td>
</tr>
<tr>
<td>20</td>
<td>4-MeOC₆H₄</td>
<td>β- Naphthol</td>
<td>5h</td>
<td>30</td>
<td>83</td>
<td>190-192</td>
<td>191-193 [42]</td>
</tr>
<tr>
<td>21</td>
<td>4-MeC₆H₄</td>
<td>β- Naphthol</td>
<td>5i</td>
<td>35</td>
<td>82</td>
<td>205-206</td>
<td>270-272 [40]</td>
</tr>
</tbody>
</table>

*Reaction conditions: α- or β-naphthol (1 mmol), aldehyde (1 mmol), malononitrile (1 mmol) and water (5 mL) in the presence of FeTiO₃ as a catalyst under reflux conditions; † Isolated yield; ‡ All known compounds were characterized by comparing their spectral (FT-IR) and physical data with those reported.
Reusability is one of the important properties of this catalyst. In order to check the reusability of the catalyst, the reaction of benzaldehyde, malononitrile and α-naphtol was studied under similar conditions in the presence of 10 mol% of FeTiO₃ (Table 2, Entry 1). After the completion of the reaction, the catalyst was separated by an external magnet, and after several washings with acetone and distilled water the activated catalyst was reused to assess its efficiency in subsequent reaction cycles without any appreciable loss of its activity.

**Fig. 1.** Recycling of FeTiO₃ as a catalyst investigated for the synthesis of 2-amino-4H-chromene derivatives by the reaction of benzaldehyde, malononitrile and α-naphtol as a model reaction.

**CONCLUSIONS**

To summarize, herein, an efficient and eco-compatible method for the synthesis of 2-amino-4H-chromene derivatives via a one-pot three-component reaction of α- or β-naphthol with malononitrile and aromatic aldehydes in the presence of FeTiO₃ as a catalyst was developed. The operational simplicity, easy work-up, short reaction time, together with the use of non-toxic and commercially available catalyst are the remarkable features of the procedure.

**EXPERIMENTAL**

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco FT-IR 6300 spectrometer. All obtained products are known compounds and were identified by comparing their physical and spectral data (FT-IR) with those reported in the literature. The progress of reactions was monitored by thin layer chromatography (TLC).

**Synthesis of 2-amino-4H-chromene derivatives catalyzed by FeTiO₃.** General procedure: A mixture of aldehyde (1 mmol), malononitrile (1 mmol), α- or β-naphthol (1 mmol) and FeTiO₃ (10 mol %) was added to a test tube and was heated in an oil bath under reflux conditions in water (5 mL) for the appropriate time (Table 2). After the completion of the reaction (monitored by TLC), the mixture was allowed to cool and the catalyst was removed by an external magnet. Then, the solvent was evaporated and the solid residue was recrystallized from ethanol (95%) to afford the pure 2-amino-4H-chromene derivatives.

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УДОБЕН ЗЕЛЕН ПРОТОКОЛ ЗА ЕДНО-СТАДИЙНА ТРИ-КОМПОНЕНТНА СИНТЕЗА НА 2-АМИНО-4H-ХРОМЕНОВИ ПРОИЗВОДНИ, КАТАЛИЗИРАНИ ОТ ИЛМЕНИТ(FeTiO₃) КАТО ЕФЕКТИВЕН И МНОГОКРАТНО УПОТРЕБЯВАН КАТАЛИЗАТОР ВЪВ ВОДНА СРЕДА

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(Резюме)

Описана е високо-ефективна и проста процедура за синтезата на 2-амино-4H-хроменови производни чрез едностадийна трикомпонентна реакция от различни алдехиди, малононитрил и α- или β-нафтол в присъствие на катализатор от илменит (FeTiO₃). Предимствата на новия протокол включват добър добив, кратко време, просто изпълнение, ниска токсичност и екологично съобразен катализатор. Според нашите резултати FeTiO₃ (10 % мол.) може да се използва за тази синтеза във водна среда с рефлукс.