GREEN ONE-POT SYNTHESSES of 1H- AND 4H-CHROMENES DERIVATIVES USING SiO$_2$-Pr-SO$_3$H AS CATALYST

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Synthesis of 2-benzylidenemalononitrile and 1H- and 4H-chromenes derivatives was improved using sulfonic acid functionalized silica (SiO$_2$-Pr-SO$_3$H) as an efficient heterogeneous solid acid catalyst. 1H- and 4H-Chromenes prepared via a simple green one-pot procedure from the reaction of aromatic aldehydes, α-naphtol (or β-naphtol) and malononitrile using SiO$_2$-Pr-SO$_3$H in water media in high yields.

INTRODUCTION

The chromene or benzopyran substructure is frequently found in naturally occurring heterocycles that exhibit biological activity$^{1,2}$ such as spasmolytic, diuretic, anticoagulant, anticancer and anti-anaphylactic activity.$^{3-5}$ They can be used for the treatment of neurodegenerative diseases, including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS connected dementia and Down’s syndrome, and then treatment of schizophrenia and myoclonus.$^6$

A few methods for the synthesis of chromene derivatives have been reported in literature such as employing aluminum oxide,$^7$ H$_4$[NaP$_5$W$_{11}$O$_{41}$]$^8$ methan sulfonic acid$^9$ and ammonium cerium (IV) nitrate as catalyst.$^{10}$

In recent years, much attention was afforded to the heterogeneous catalysts due to economic and environmental considerations.$^{11}$ These acid catalysts are generally more reactive, eco-friendly, and convenient to handle, with shorter reaction times, simpler work up, high yield of products and better recoverability than most of other catalysts.$^{12-16}$ Application of these catalysts is a grateful approach in green organic synthesis. Thus, in continuation of our studies in this field,$^{17-20}$ we explored the catalytical activity of sulfonic acid functionalized silica (SiO$_2$-Pr-SO$_3$H) as a highly efficient heterogeneous acid catalyst toward the synthesis of 1H- and 4H-chromenes and 2-benzylidenemalononitrile derivatives.

RESULTS AND DISCUSSION

We originally considered the solvent effects in condensation of aromatic aldehydes 1 with α-naphtol 3 (or β-naphtol 5) and malononitrile 2 in the presence of SiO$_2$-Pr-SO$_3$H to produce 1H- and
4H-chromene derivatives (Scheme 1). As a model of reaction, the condensation of α-naphthol, 4-NO₂-benzaldehyde and malononitrile was applied in different solvents such as in H₂O and EtOH, and in solvent-free condition (Table 1). Among the tested solvents, the best result was obtained in aqueous media in excellent yield and in other conditions, the main product was just benzylidenemalononitrile. So, this reaction was developed with different aldehydes in aqueous media and the results were demonstrated in the Table 2. This reaction was completed within 1.5-5.5 hour in high yields. After completion of the reaction (monitored by thin layer chromatography (TLC)), the crude product was dissolved in methanol, the heterogeneous solid catalyst was removed simply by filtration, and after cooling of the filtrate, the pure crystals of products were obtained. The acid catalyst can be reactivated by simple washing subsequently using diluted acid solution, acetone and water, and then reused without considerable loss of reactivity. The new products were characterized by IR and NMR spectroscopy data for new compounds. Melting points are compared with reported values in literature as shown in Table 2.

The reaction of aromatic aldehydes 1 and malononitrile 2 in the presence of SiO₂-Pr-SO₃H at 120 °C under solvent-free conditions was performed to afford various alkenes in excellent yields (Scheme 2). The results were summarized in Table 3.

![Scheme 1](image)

**Scheme 1**

**Table 1**

<table>
<thead>
<tr>
<th>No</th>
<th>Product</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td>EtOH</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image" /></td>
<td>H₂O</td>
<td>90</td>
</tr>
</tbody>
</table>
**Table 2**

Synthesis of 4*H*-chromenes 4 /1*H*-chromenes 6 catalyzed by SiO$_2$-Pr-SO$_3$H in water

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp (Lit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>α-Naphthol</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>5</td>
<td>95</td>
<td>211-212</td>
<td>212-214$^{21}$</td>
</tr>
<tr>
<td>2</td>
<td>α-Naphthol</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td><img src="image4" alt="Chemical structure" /></td>
<td>4.5</td>
<td>90</td>
<td>242-244</td>
<td>239-241$^{21}$</td>
</tr>
<tr>
<td>3</td>
<td>α-Naphthol</td>
<td><img src="image5" alt="Chemical structure" /></td>
<td><img src="image6" alt="Chemical structure" /></td>
<td>5.5</td>
<td>91</td>
<td>214-215</td>
<td>212-214$^{21}$</td>
</tr>
<tr>
<td>4</td>
<td>α-Naphthol</td>
<td><img src="image7" alt="Chemical structure" /></td>
<td><img src="image8" alt="Chemical structure" /></td>
<td>5</td>
<td>95</td>
<td>248-249</td>
<td>247-249$^{21}$</td>
</tr>
<tr>
<td>5</td>
<td>α-Naphthol</td>
<td><img src="image9" alt="Chemical structure" /></td>
<td><img src="image10" alt="Chemical structure" /></td>
<td>5</td>
<td>89</td>
<td>180-181</td>
<td>178-180$^{21}$</td>
</tr>
<tr>
<td>6</td>
<td>β-Naphthol</td>
<td><img src="image11" alt="Chemical structure" /></td>
<td><img src="image12" alt="Chemical structure" /></td>
<td>4</td>
<td>93</td>
<td>248</td>
<td>248$^{21}$</td>
</tr>
<tr>
<td>7</td>
<td>β-Naphthol</td>
<td><img src="image13" alt="Chemical structure" /></td>
<td><img src="image14" alt="Chemical structure" /></td>
<td>4.5</td>
<td>95</td>
<td>184-185</td>
<td>185-186$^{21}$</td>
</tr>
</tbody>
</table>
Table 2 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzaldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp (Lit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>β-Naphthol</td>
<td><img src="image1.png" alt="Image" /></td>
<td>5.5</td>
<td>97</td>
<td>278-280</td>
<td>278-279&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Resorcinol</td>
<td><img src="image2.png" alt="Image" /></td>
<td>5.5</td>
<td>93</td>
<td>161-162</td>
<td>162-163&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Resorcinol</td>
<td><img src="image3.png" alt="Image" /></td>
<td>1.5</td>
<td>98</td>
<td>111-112</td>
<td>114-115&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Scheme 2

Table 3

Synthesis of 2-benzylidenemalononitrile derivatives 7 using SiO$_2$-Pr-SO$_3$H under solvent free conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzaldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp (Lit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Chloro-</td>
<td><img src="image4.png" alt="Image" /></td>
<td>5</td>
<td>95</td>
<td>161-162</td>
<td>167-168&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>4-Hydroxy-</td>
<td><img src="image5.png" alt="Image" /></td>
<td>4.5</td>
<td>90</td>
<td>185-186</td>
<td>188&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>No.</td>
<td>Name</td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>R4</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3-Nitro-</td>
<td>H-CN-CN-</td>
<td>NO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-Methoxy-</td>
<td>H-CN-CN-</td>
<td>MeO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-Dimethylamino-</td>
<td>H-CN-CN-</td>
<td>Me2N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2-Methoxy-</td>
<td>MeO-CN-CN-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-Methyl-</td>
<td>H-CN-CN-</td>
<td>Me</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>H-CN-CN-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4-Nitro</td>
<td>H-CN-CN-</td>
<td>O2N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 (continued)
The suggested mechanism for the SiO$_2$-Pr-SO$_3$H catalyzed one-pot three component reaction was illustrated in Scheme 3. At first, solid acid catalyst protonates the carbonyl group to facilitate preparation of compound $\text{9}$ through the Knoevenagel condensation. The Michael addition of $\alpha$-naphtol $\text{3}$ to compound $\text{9}$ followed by cyclization and tautomerisation affords the desired final product $\text{4}$ in high yield.

The syntheses of $1H$- and $4H$-chromenes have been studied with several catalysts and solvents in literature as shown in Table 4. In contrast with other existing methods, the present methodology offers several advantages such as excellent yields, a simple procedure, short reaction times, easy synthesis, simple work-up and greener conditions using sulfonic acid functionalized silica (SiO$_2$-Pr-SO$_3$H) as an efficient catalyst.

### EXPERIMENTAL

**General information**

IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by the capillary tube method with an electro thermal 9200 apparatus. The $^1$H NMR (250 MHz) was run on a Bruker DPX, 250 MHz. Gas chromatography-mass spectrometry (GC-MS) analysis was performed on an Agilent 6890-5973 GC/MS detector.

**Preparation of catalyst**

**Synthesis of 3-Mercaptopropylsilica (MPS) and its oxidation:** To 20 g of SiO$_2$ in dry toluene, 25 mL of (3-mercaptopropyl)trimethoxysilane was added, and the reaction mixture was heated at reflux for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropylsilica (MPS), which was washed with acetone and dried under vacuum. 3-Mercaptopropylsilica (MPS) (20 g) was oxidized with H$_2$O$_2$ (50 mL) and one drop of H$_2$SO$_4$ in methanol (20 mL) for 24 h at room temperature and then the mixture was filtered and...
washed with H₂O, and acetone to obtain the SiO₂-Pr-SO₃H catalyst. The modified SiO₂-Pr-SO₃H was dried and used as a solid acid catalyst in the organic synthesis.

**General procedure for the preparation of 2-benzyldenemalononitrile derivatives**

The SiO₂-Pr-SO₃H (0.1 g) was activated under vacuum and then after cooling to room temperature, aromatic aldehyde 1 (1 mmol) and malononitrile 2 (1 mmol) were added to it. The mixture was heated in solvent free condition at 120 °C for an appropriate time. The completion of reaction was indicated by thin layer chromatography, the resulting solid product was distilled in ethyl acetate, filtered for removing the unsoluble catalyst and then the filtrate was cooled to give the pure product. The spectroscopic and analytical data for products are presented in the following part. Finally, the catalyst was washed with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without loss of considerable activity.

1- Dicyano-2-(4-chlorophenyl) ethylene (7a): mp: 161-162 °C. IR (KBr): υ max = 3280, 3018, 2280, 1580, 1220 cm⁻¹.

2- Dicyano-2-(4-hydroxyphenyl) ethylene (7b): υ max = 3021, 2210, 1580, 1160 cm⁻¹. Mass: m/z 184 [M+1]⁺.

3- Dicyano-2-(4-nitrophenyl) ethylene (7c): mp: 157-158 °C. IR (KBr): υ max = 3032, 2225, 1608, 1518 cm⁻¹.

4- Dicyano-2-(4-dichlorophenyl) ethylene (7d): mp: 176-177 °C. IR (KBr): υ max = 3021, 2206, 1608 cm⁻¹. Mass: m/z 184 [M+1]⁺.

5- Dicyano-2-(4-3-nitrophenyl) ethylene (7e): mp: 176-177 °C. IR (KBr): υ max = 3021, 2206, 1608 cm⁻¹. Mass: m/z 184 [M+1]⁺.

6- Dicyano-2-(4-methoxyphenyl) ethylene (7f): mp: 111-112 °C. IR (KBr): υ max = 3460, 3335, 2196 cm⁻¹. Mass: m/z 184 [M+1]⁺.

7- Dicyano-2-(4-phenyl) ethylene (7g): mp: 176-177 °C. IR (KBr): υ max = 3021, 2206, 1608 cm⁻¹. Mass: m/z 184 [M+1]⁺.

**General procedure for the preparation of 4H-chromenes and 1H-chromenes derivatives**

The SiO₂-Pr-SO₃H (0.1 g) was activated under vacuum and then after cooling to room temperature, aromatic aldehyde 1 (1 mmol), malononitrile 2 (1 mmol), α-naphthol 3 (or β-naphthol 5) and 10 ml water as solvent was added to it. The mixture was refluxed for an appropriate time. The completion of reaction was indicated by thin layer chromatography, the resulting solid product and catalyst was filtered and then the filtrate was dissolved in ethanol, filtered for removing the unsoluble catalyst and then the filtrate again was cooled to afford the pure product. Finally, the catalyst was washed with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without loss of considerable activity.


2-amino-4-(4-nitrophenyl)-4H-benzo[1]chromene-3-carbonitrile (4b): mp 242-244 °C. IR (KBr) υ max = 3473, 3351, 2189, 1572, 1101 cm⁻¹. Mass: m/z 221 [M+1]⁺.


CONCLUSIONS

In summary, environmentally benign sulfonic acid functionalized silica (SiO$_2$-Pr-SO$_3$H) as a solid acid catalyst assisted us to improve the synthesis of 1H- and 4H-chromenes in a three component reaction of aromatic aldehydes, α-naphtol (or β-naphtol) and malononitrile under solvent free conditions. Simple procedure, reusability of the catalyst and non-chromatographic purification of products, i.e. simple recrystallization got our attention to this process.

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REFERENCES