Knoevenagel condensation of isatins with malononitrile/ethyl cyanoacetate in the presence of sulfonic acid functionalized silica (SBA-Pr-SO₃H) as a new nano-reactor

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1. Introduction

The Knoevenagel condensation is one of the most effective and general reactions for the formation of carbon-carbon bonds [1]. Furthermore, isatin has been extensively used in organic synthesis [2,3]. There are various reports about the application of isatin in Knoevenagel condensation [4-7]. Many of these products present significant biological activities [8] or they are used in the synthesis of natural products [9,10]. Malononitrile as a versatile reagent has been widely used in condensation reactions to give a variety of addition products and heterocyclic compounds [11]. Condensation of malononitrile or ethyl cyanoacetate with isatin and its derivatives to prepare 2-oxindolin-3-ylidene malononitrile/cyanoacetate using different solvents such as ethanol [12,13], methanol [14], and DMSO [15] has been studied. Microwave irradiation [16-18] and grinding in the presence of 1-5 equiv. of water [19] are the other methods for the synthesis of these compounds.

Recently, different mesoporous ordered silicas such as SBA-15 have received great attention in organic synthesis. These materials characterized by large surface area, hexagonal arrangement of uniform pores, thick walls, and high hydrothermal stability. Organic functional groups have been incorporated onto the mesoporous silica materials by either grafting or co-condensation methods [20,21]. These organic-inorganic hybrids are a new class of materials that have been extensively investigated in the field of catalysis. Many sulfonic acid functionalized SBA-15 mesoporous silicas have been reported as catalysts in different organic transformations [22-25].

Here, in continuation of our studies, on the application of heterogeneous solid catalysts to organic synthesis [26-30] we report our results on the condensation of isatin with malononitrile or ethyl cyanoacetate in the presence of sulfonic acid functionalized nanoporous silica (SBA-Pr-SO₃H) as a new nano-reactor.

2. Experimental

2.1. Instrumentation

All chemicals were obtained commercially and used without further purification. The IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ¹H NMR spectra was run on a Bruker DPX, at 250 MHz in CDCl₃ using TMS as an internal standard. GC-Mass analysis was performed on a GC-Mass model 5973 network mass selective detector, GC 6890 Agilent. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV while TEM was carried out on a Tecnai G²F30 at 300 kV.

2.2. Synthesis

2.2.1. Synthesis and functionalization of SBA-15

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report [28] and the modified SBA-15-Pr-SO₃H was used as nanoporous solid acid catalyst in the following reaction.
2.2.2. General procedure for the synthesis of 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives

To a mixture containing isatin derivative 1 (1 mmol) and malononitrile or ethyl cyanoacetate 2 (1 mmol) in water (5 mL), was added SBA-Pr-SO$_3$H (0.02 g) and stirred under reflux condition as reported in Table 1. After completion of reaction (TLC monitoring), the generated solid was dissolved in hot ethanol, filtered for removing the insoluble catalyst and then the filtrate was cooled to afford the pure product 3a (Scheme 1).

2-(2-Oxoindolin-3-ylidene) malononitrile (3a): Color: Red. Yield: 95%. M.p.: 239-240 °C. FT-IR (KBr, v cm$^{-1}$): 3358, 3299, 3134, 2928, 2880, 2195, 1718, 1663, 1609, 1365, 1294, 792.

2-(5-Chloro-2-oxoindolin-3-ylidene) malononitrile (3b): Color: Red. Yield: 90%. M.p.: 228-230 °C. FT-IR (KBr, v cm$^{-1}$): 3571, 3508, 3131, 3064, 2967, 2235, 1729, 1595, 1460, 825. ^1H^ NMR (250 MHz, CDCl$_3$, δ, ppm): 11.36 (s, 1H, NH), 7.76 (s, 1H, ArH), 7.61 (d, J = 5.25 Hz, 1H, ArH), 6.96 (d, J = 5 Hz, 1H, ArH). MS (EI, m/z (%)): 229 (M$^+$, 100), 203 (51), 175 (19), 139 (55), 112 (17), 87 (12).

2-(5-Bromo-2-oxoindolin-3-ylidene) malononitrile (3c): Color: Red. Yield: 93%. M.p.: 236-238 °C. FT-IR (KBr, v cm$^{-1}$): 3580, 3513, 3102, 2851, 2237, 1727, 1619, 1594, 1466, 849. ^1H^ NMR (250 MHz, CDCl$_3$, δ, ppm): 11.36 (s, 1H, NH), 7.89 (s, 1H, ArH), 7.63 (d, J = 5.25 Hz, 1H, ArH), 6.92 (d, J = 4.25 Hz, 1H, ArH). MS (EI, m/z (%)): 273 (M$^+$, 20), 245 (8), 167 (24), 149 (100), 139 (32), 112 (16), 71 (32), 57 (61), 43 (58).


3. Results and discussion

In this manuscript, 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives 3a-h were synthesized via a simple, mild and effective reaction of isatins 1 and malononitrile or ethyl cyanoacetate 2 in the presence of nanoporous solid acid catalyst (SBA-Pr-SO$_3$H) in aqueous medium (Scheme 1). Considering solvent effects in this reaction, it was found that water is the solvent of choice which results in high product yields in shorter reaction times (Table 2). Four substituted isatins were subjected to this reaction to investigate the generality of this method and corresponding products were successfully synthesized (Table 1). It was found that when ethyl cyanoacetate was used, the reaction time was longer than those with malononitrile. After completion of the reaction (monitored by TLC), the crude product was dissolved in hot ethanol, the heterogeneous solid catalyst was removed by simple filtration, and after cooling of the filtrate, the pure crystals of products were obtained as red crystals.

The most probable mechanism for this reaction is shown in Scheme 2. Initially, the solid acid catalyst protonates the carbonyl group of isatin 1, which then condenses with CH-acidic group of malononitrile or ethyl cyanoacetate 2 through a fast Knoevenagel condensation to afford the desired products 3a-h (Scheme 2).

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### Table 1. SBA-Pr-SO$_3$H catalyzed the synthesis of 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives 3a-h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield (%)</th>
<th>M.p. (°C)</th>
<th>M.p. (Lit.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>95</td>
<td>239-240</td>
<td>239 [31]</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>90</td>
<td>226-230</td>
<td>225-227 [32]</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>93</td>
<td>236-238</td>
<td>220-221 [19]</td>
</tr>
<tr>
<td>4</td>
<td>NO$_2$</td>
<td>90</td>
<td>262-264</td>
<td>260-261 [4]</td>
</tr>
<tr>
<td>5</td>
<td>CO$_2$Et</td>
<td>10</td>
<td>208-209</td>
<td>196-198 [12]</td>
</tr>
<tr>
<td>6</td>
<td>CO$_2$Et</td>
<td>15</td>
<td>225-227</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>CO$_2$Et</td>
<td>15</td>
<td>85</td>
<td>238-239</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>15</td>
<td>85</td>
<td>230-231</td>
</tr>
</tbody>
</table>

### Table 2. Solvent effects on the synthesis of 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives 3a-h.

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>Yield of 3a (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>EtOH/H$_2$O (1:1)</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$O</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Neat (120 °C)</td>
<td>80</td>
</tr>
</tbody>
</table>

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Scheme 1
Literature surveys reveal that various conditions have been employed for the synthesis of 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives. Table 3 illustrates a comparison of the effectiveness of various catalysts used in the synthesis of these compounds.

The high yields of reactions are attributed to the high efficiency of nanopore size about 6 nm of solid acid catalyst, which could act as a nano-reactor (Figure 1). A schematic illustration for the preparation of SBA-Pr-SO₃H was shown in Figure 2.

Table 3. Comparison of different conditions in the synthesis of 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives 3a-h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Condition*</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Year</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperidine</td>
<td>EtOH</td>
<td>Reflux</td>
<td>240</td>
<td>73</td>
<td>1958</td>
<td>[12]</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>MeOH</td>
<td>Stir. (r.t.)</td>
<td>15</td>
<td>77</td>
<td>1972</td>
<td>[14]</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>EtOH</td>
<td>Stir. (r.t.)</td>
<td>90</td>
<td>93</td>
<td>1989</td>
<td>[13]</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>Heating</td>
<td></td>
<td>120</td>
<td>92</td>
<td>1989</td>
<td>[15]</td>
</tr>
<tr>
<td>5</td>
<td>Neutral alumina</td>
<td>-</td>
<td>MW</td>
<td>5</td>
<td>78</td>
<td>1999</td>
<td>[16]</td>
</tr>
<tr>
<td>6</td>
<td>Triethanolamine</td>
<td>EtOH</td>
<td>Stir. (r.t.)</td>
<td>120</td>
<td>70</td>
<td>2007</td>
<td>[33]</td>
</tr>
<tr>
<td>7</td>
<td>Tris(2-hydroxy-ethyl)amine</td>
<td>EtOH</td>
<td>Heating</td>
<td>60</td>
<td>90</td>
<td>2008</td>
<td>[34]</td>
</tr>
<tr>
<td>8</td>
<td>Neutral alumina</td>
<td>MeOH</td>
<td>Stir. (r.t.)</td>
<td>20</td>
<td>96</td>
<td>2009</td>
<td>[4]</td>
</tr>
<tr>
<td>9</td>
<td>DBU</td>
<td>EtOH</td>
<td>Heating</td>
<td>15</td>
<td>88</td>
<td>2009</td>
<td>[35]</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>H₂O (1-5 equiv.)</td>
<td>Grinding</td>
<td>15</td>
<td>99</td>
<td>2011</td>
<td>[19]</td>
</tr>
<tr>
<td>11</td>
<td>SBA-Pr-SO₃H</td>
<td>H₂O</td>
<td>Reflux</td>
<td>5</td>
<td>95</td>
<td>This work</td>
<td></td>
</tr>
</tbody>
</table>

* r.t.: Room temperature.
First, the calcined SBA-15 silica was functionalized with [3-mercaptopropyl] trimethoxysilane (MPTS) and then, the thiol groups could be completely oxidized into sulfonic acid groups by hydrogen peroxide. The texture properties of SBA-15 and SBA-Pr-SO$_3$H such as the surface area, average pore diameter, and pore volume have been measured. The surface of the catalyst was analyzed by different methods such as TGA, BET and other methods which were confirmed that the organic groups (propyl sulfonic acid) were immobilized into the pores [28].

Figure 3 illustrates the SEM and TEM images of SBA-Pr-SO$_3$H. SEM image (Figure 3a) shows uniform particles about 1 μm. The same morphology was observed for SBA-15. It can be concluded that morphology of solid was saved without change during the surface modifications. On the other hand, the TEM image (Figure 3b) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-SO$_3$H was not collapsed during two steps reactions.

4. Conclusion

In summary an efficient method for Knoevenagel condensation of isatins with malonitrile or ethyl cyanoacetate in the presence of a catalytic amount of SBA-Pr-SO$_3$H in aqueous medium was described. We have demonstrated that sulfonic acid functionalized SBA-15 is a remarkably efficient catalyst for the synthesis of 2-oxoindolin-3-ylidene malononitrile/cyanoacetate derivatives 3a-h. Short reaction times, excellent product yields, being environmentally benign, and simple workup procedure are the advantages of this methodology.

Acknowledgements

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References