Tandem Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and barbituric acid derivatives using isonicotinic acid as an efficient catalyst

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1. Introduction

Tandem reaction, as a significant strategy in organic synthesis, is a reaction in which several bonds are generated in some steps without isolating of any intermediates, changing reaction conditions and adding reagents. This reaction is often fast due to its intramolecular nature, clean reaction condition, and high atomic economy [1-5].

Preparation of pyrano[2,3-d]pyrimidine dione derivatives is significant due to their antitumor, antibacterial, antihypertensive, hepatoprotective, cardiotoxic, vasodilator, bronchodilators, and antiallergic properties [6]. Moreover, some of them can be widely applied as antimalarial [7], antifungal [8], analgesics [9], and herbicidal materials [10]. Several protocols have been introduced for the preparation of pyrano[2,3-d]pyrimidine dione derivatives by the multi-component reaction of barbituric acid derivatives, various aldehydes and malononitrile [11-16]. However, due to the importance of these compounds, new and efficient preparation methods are still needed.

Having this issue in mind, we have prepared pyrano[2,3-d]pyrimidine dione derivatives by the tandem Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and barbituric acid derivatives in the presence of isonicotinic acid as an efficient organocatalyst (Scheme 1).
2. Materials and Methods

All chemicals were purchased from Merck and Fluka Chemical Companies. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. The 1H NMR (250 MHz) and 13C NMR (62.5 MHz) were recorded on a Bruker Avance DPX, FT-NMR spectrometers, δ in ppm.

Procedure for the synthesis of pyrano[2,3-d]pyrimidine diones

A mixture of barbituric acid derivatives (2 mmol), aldehyde (2 mmol), malononitrile (2.2 mmol), isonicotinic acid (10 mol%) and 10 mL EtOH/H₂O (19:1) was added to a 25 mL round-bottomed flask connected to a reflux condenser and stirred in an oil-bath at 60 °C. Then, the crude product was purified by recrystalization in a mixture of ethanol and water (9:1) to give the desired product.

7-amino-5-(4-bromophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (2)

m.p.: 228-230 °C; Yield: 91%; 1H-NMR (DMSO-d₆ 250 MHz): δ 4.20 (s, 1H), 7.14-7.17 (m, 4H), 7.43-7.46 (m, 2H), 11.04 (s, 1H), 12.06 (s, 1H). 13C-NMR (DMSO-d₆ 62.5 MHz): δ 35.6, 58.7, 88.3, 119.4, 120.1, 130.1, 131.5, 144.0, 149.9, 152.7, 158.0, 162.8.

3. Results and Discussion

In order to optimize the reaction conditions we have considered the reaction of barbituric acid derivatives (2 mmol), 4-chlorobenzaldehyde (2 mmol), malononitrile (2.2 mmol) as a model reaction. This reaction was tested at the presence of different amounts of isonicotinic acid at 40-80 °C. The reaction was efficient with 10 mol% of isonicotinic acid at 60 °C, and it gave the expected product in high yield within a short reaction time.

Table 1. The effect of different amounts of the catalyst, and various temperatures on the reaction of barbituric acid, 4-chlorobenzaldehyde and malononitrile in ethanol as solvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>60</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>60</td>
<td>22</td>
<td>90</td>
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<td>3</td>
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<td>60</td>
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</tr>
<tr>
<td>4</td>
<td>10</td>
<td>40</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Reflux</td>
<td>20</td>
<td>70</td>
</tr>
</tbody>
</table>

*a The ratio of ethanol to water is 19 to 1; *b Isolated yield

In the next step, the model reaction was tested at the presence of several solvents using 10 mol% of isonicotinic acid. The model reaction was tested in various solvents such as H₂O, ethanol, ethyl acetate, and acetone in comparison with ethanol/H₂O (19:1). As shown in Table 2, the best result was obtained in ethanol/H₂O (19:1).

Table 2. The effect of various solvents on the reaction of barbituric acid, 4-chlorobenzaldehyde and malononitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>H₂O</td>
<td>60</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Ethanol</td>
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<td>25</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Ethyl acetate</td>
<td>60</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Acetone</td>
<td>Reflux</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>-</td>
<td>60</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

*a Isolated yield; *b The ratio of ethanol to water is 19 to 1.

To investigate the generality and scope of the catalysts, we have studied various aromatic aldehydes using isonicotinic acid in EtOH/H₂O (19:1) at 60 °C to furnish a series of pyrano[2,3-d]pyrimidine dione derivatives. Various aromatic aldehydes containing electron-withdrawing substituents, electron-releasing substituents and halogens on their aromatic rings were used successfully in this reaction, and obtained the corresponding products in high yields and in short reaction times (Table 3).

Table 3. The synthesis of pyrano[2,3-d]pyrimidine diones using isonicotinic acid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>M.p. °C (Lit.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Pyrano[2,3-d]pyrimidine Dione" /></td>
<td>35</td>
<td>76</td>
<td>210-213 (210-212)[16]</td>
</tr>
</tbody>
</table>
In a plausible mechanism (as shown in Scheme 2), at first, malononitrile is reacted with carbonyl group of aldehyde which is activated by isonicotinic acid and gives intermediate I after removing one molecule of H₂O. Barbituric acid converts to enole form after tautomerisation and attacks to cyanoolefin compound (I) as Michael acceptor to prepare II. Finally, **Scheme 2.** The purposed mechanism for the synthesis of pyrano[2,3-d]pyrimidine diones
cyclocondensation of II prepares III which is converted to expected product.

4. Conclusion

We have synthesized pyrano[2,3-d]pyrimidine dione derivatives by the tandem Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and barbituric acid derivatives at the presence of isonicotinic acid.

Acknowledgements

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Conflict of interest

The authors declare that they have no competing interests.

References