CLEAN SYNTHESIS OF PYRANO[2,3-D]PYRIMIDINES USING ZNO NANO-POWDERS

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Abstract: ZnO nano-powders were used for the one-pot synthesis of pyrano[2,3-d]pyrimidines via the solvent-free multi-component reaction of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile, in good to excellent yields of products.

Keywords: multi-component reaction; 1,3-dimethylbarbituric acid; pyrano[2,3-d]pyrimidines; ZnO nano-powders

Introduction

Nitrogen- and oxygen-containing heterocyclic compounds are of considerable interest, as they are a class of natural and synthetic compounds that possess a great variety of biological and pharmaceutical activities.\textsuperscript{1-12} For example, pyrano[2,3-d]pyrimidines are important structural components of both natural and synthetic biologically active compounds. Pyrano[2,3-d]pyrimidines show antitumor,\textsuperscript{13} hepatoprotective,\textsuperscript{14} antibronchitic\textsuperscript{15} and anti-AIDS activity.\textsuperscript{16}

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Among all the reported methods for the entitled compounds, the multi-component condensation reaction of aromatic aldehydes, barbituric acid derivatives and malononitrile has gained significant attention in the scientific community. Many different bases were proved to be viable catalysts for this reaction. However, the established reaction systems based on the use of homogeneous catalysts are often plagued by many intrinsic problems including corrosion, difficulty of catalyst recycling and the generation of waste.\textsuperscript{17-23}

Thus, the discovery of new synthetic methodologies that facilitate the preparation of organic compounds is of great interest. One approach to address the abovementioned challenges involves the development of new environmentally friendly catalysts for the condensation reaction. Therefore, the scope of the present work was to achieve the multi-component condensation reaction of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile to afford pyrano[2,3-\textit{d}]pyrimidines by using ZnO nano-powders as a green, environmentally friendly catalyst (Scheme 1).

\begin{equation}
\begin{array}{c}
\text{H}_3\text{C} - \text{N} - \text{O} - \text{Ar}(\text{R}) - \text{CHO} + \text{CH}_2(\text{CN})_2 \\
\text{ZnO nano-powders} \\
\text{Solvent-Free; 90 oC H}_3\text{C} \\
\end{array}
\end{equation}

1: \text{Ar} = \text{Ph} \quad 5: \text{Ar} = 2,4-\text{diClPh} \\
2: \text{Ar} = 4-\text{MePh} \quad 6: \text{Ar} = 4-\text{BrPh} \\
3: \text{Ar} = 4-\text{Cl-Ph} \quad 7: \text{Ar} = 4-\text{FPh} \\
4: \text{Ar} = 3-\text{NO}_2\text{Ph} \quad 8: \text{Ar} = 3-\text{ClPh} \\

Yields: 78-98

\textbf{Scheme 1.} Preparation of pyrano[2,3-\textit{d}]pyrimidines using ZnO nano-powders.

\textbf{Results and Discussion}

The morphological evolution of the catalyst was investigated using SEM images of the sample and the results are revealed in Figure 1. As shown in Figure 1, the particles of ZnO nano-powders are relatively
homogeneous in size and shape, and are uniform spheres having less than 100nm in size.

Figure 1. FE-SEM micrograph of ZnO nano-powders.

The catalytic activity of the prepared nano-powders was examined in the condensation reactions of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile, in order to afford pyrano[2,3-d]pyrimidines in better yields (Table 1). The progress of the reaction was monitored by TLC. After completion, reaction work-ups afforded the pure products in good yields (Table 1, Compound numbers 1-8).

The reactions worked well with almost all the aldehydes. However, aromatic aldehydes bearing electron withdrawing groups showed better reactivity, therefore the reactions were completed in a shorter time.
Table 1. Preparation of pyrano[2,3-d]pyrimidines using ZnO nano-powders as catalysts (0.25 mmol).

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Aldehyde</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M.p.[°C][lit. M.p.]&lt;sup&gt;Ref.&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>CHO</td>
<td>3</td>
<td>89</td>
<td>219-222 [219-222]&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>4</td>
<td>78</td>
<td>203-205 [202-203]&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>2.5</td>
<td>86</td>
<td>210-212 [239-241]&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td>1.5</td>
<td>98</td>
<td>201-203 [204]&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>CHO</td>
<td>4</td>
<td>78</td>
<td>251-253 [211-212]&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>2</td>
<td>89</td>
<td>209-211 [235]&lt;sup&gt;23&lt;/sup&gt;</td>
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<tr>
<td>7</td>
<td>CHO</td>
<td>2.5</td>
<td>96</td>
<td>234-236 [229-232]&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>CHO</td>
<td>2.3</td>
<td>83</td>
<td>223-225 [247-248]&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>Isolated yield; All product were characterized on the basis of their NMR analysis.

**Experimental**

All reagents were purchased from Merck or Sigma-Aldrich and used without further purification. Field Emission Scanning Electron Microscope
Preparation of ZnO nano-powders

To a solution of ZnCl\textsubscript{2} (30 mmol in 100 mL water), 50 mL of hexane and subsequently 50 mL of ethanol was added. The mixture was stirred for 10 min. Then, an aqueous solution of ammonia (10\% V/V) was added to the solution drop-wise under vigorous magnetic stirring. The mixture was stirred continuously for 10 min. The resulting precipitate was washed with water several times and dried in an oven at 100 °C for 1 h, followed by calcination at 500 °C for 2 h.

General procedure

A mixture of aldehyde (1 mmol), 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1 mmol), and ZnO nano-powders (0.25 mmol) was heated at 90°C and maintained until completion (for reaction times, see Table 1). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was dissolved in hot EtOH. The catalyst was removed by simple filtration. The solvent was then concentrated and the crude products were purified by crystallization from EtOH. The spectral data of selected compounds is given below:

7-amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 1, Entry 1): \textsuperscript{1}H-NMR (400 MHz, DMSO-d\textsubscript{6}): \(\delta = 3.04\) (s, 3H, CH\textsubscript{3}), \(3.34\) (s, 3H, CH\textsubscript{3}), \(4.31\) (s, 1H, CH), \(7.16\) (t, \(J = 7.8\) Hz, 1H), \(7.22\) (d, \(J = 7.8\) Hz, 2H), \(7.34-7.38\) (m, 4H).

7-amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-p-tolyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 1, Entry 2): \textsuperscript{1}H-NMR (400 MHz, DMSO-d\textsubscript{6}): \(\delta = 2.49\) (s, 3H, CH\textsubscript{3}), \(3.34\) (s, 3H, CH\textsubscript{3}), \(4.31\) (s, 1H, CH), \(7.16\) (t, \(J = 7.8\) Hz, 1H), \(7.22\) (d, \(J = 7.8\) Hz, 2H), \(7.34-7.38\) (m, 4H).
MHz, DMSO-d$_6$): $\delta =$ 2.23 (s, 3H, CH$_3$), 3.05 (s, 3H, CH$_3$), 3.36 (s, 3H, CH$_3$), 4.27 (s, 1H, CH), 7.07 (d, $J =$ 7.8 Hz, 2H), 7.16 (d, $J =$ 7.8 Hz, 2H), 7.32 (s, 2H, NH$_2$).

7-amino-5-(2,4-dichlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 1, Entry 5): $^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta =$ 3.06 (s, 3H, CH$_3$), 3.38 (s, 3H, CH$_3$), 4.87 (s, 1H, CH), 7.48 (s, 2H, NH$_2$), 7.54-7.75 (m, 3H, ArH).

Conclusions

In summary, a high-yielding one-pot condensation reaction of 1,3-dimethylbarbituric acid, aromatic aldehydes and malononitrile for the synthesis of pyrano[2,3-d]pyrimidines using ZnO nano-powders as catalysts was developed. Various aromatic aldehydes afforded the corresponding products is high yields.

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References


