Shahrzad Abdolmohammadi* and Maryam Afsharpour

An operationally simple green procedure for the synthesis of dihydropyrimido[4,5-\textit{d}]pyrimidinetriones using CuI nanoparticles as a highly efficient catalyst

Abstract: A green, efficient and simple protocol was developed for the synthesis of dihydropyrimido[4,5-\textit{d}]pyrimidinetrione derivatives via a coupling reaction of 6-aminouracils, aromatic aldehydes and urea in aqueous media in the presence of nano-crystalline CuI at room temperature. The products were obtained in high yields. CuI nanoparticles can be recycled three times without significant loss of catalytic activity.

Keywords: aqueous media; CuI nanoparticles (CuI NPs); dihydropyrimido[4,5-\textit{d}]pyrimidinetriones; reusability of catalyst.

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1 Introduction

Recently, nanostructured metal salts as efficient heterogeneous catalysts have gained a tremendous amount of interest in many different organic reactions on the ground of their ability to enhance the reaction rate, simplicity of operation, reusability of the catalyst and higher yields of products, which is due to their small size and large surface area [1, 2]. CuI nanoparticles (CuI NPs) are a Lewis acid heterogeneous catalyst which has been studied for the synthesis of organic compounds and others, owing to its unique properties [3–10].

Pyrimidopyrimidines are important building blocks for several biologically and pharmacologically active compounds which are known to possess antibacterial [11], antiviral [12], antioxidant [13], antitumor [14] and hepatoprotective properties [15].

During the course of the studies on the synthesis of substituted pyrimido[d]pyrimidines, several modified procedures have been developed [16–19]. To the best of our knowledge, however, a synthesis of dihydropyrimido[4,5-\textit{d}]pyrimidinetrione derivatives catalyzed by CuI NPs has not been reported up to now. Therefore, we wish to report herein a very simple and efficient route for the synthesis of dihydropyrimido[4,5-\textit{d}]pyrimidinetrione derivatives in the presence of a catalytic amount of CuI NPs in aqueous media at room temperature.

2 Results and discussion

Herein we describe how CuI NPs promote the cyclocondensation reaction of 6-aminouracils 1, aromatic aldehydes 2 and urea (3) in water affording 5-aryl-5,8-dihydropyrimido[4,5-\textit{d}]pyrimidine-2,4,7(1\textit{H},3\textit{H},6\textit{H})-triones 4\textit{a}–\textit{e} and 1,3-dimethyl-5-aryl-5,8-dihydropyrimido[4,5-\textit{d}]pyrimidine-2,4,7(1\textit{H},3\textit{H},6\textit{H})-triones 4\textit{f}–\textit{j} in high yields (Scheme 1).

In this study, first the CuI NPs catalyst was prepared readily according to a procedure reported by Salavati-Niasari and co-workers [20]. The scanning electron microscope (SEM) image of the product shows that the average size of the particles was in the range of 30–40 nm and that they show a triangular shape (Fig. 1).

In order to confirm the structure and purity of the catalyst, X-ray diffraction (XRD) analyses were carried out. The XRD pattern of CuI nanoparticles is in accordance with the standard data. Most of the reflection peaks in Fig. 2 can be attributed to the cubic phase CuI with space group \textit{F}\text{\textbar}3\text{\textbar}m and a cell constant of 6.0545 Å (JCPDS 82:2111). The sharp peaks in Fig. 2 indicated a high crystallinity of CuI NPs.

The reaction of 6-aminouracil, 4-bromobenzaldehyde and urea was selected as a model and performed under various reaction conditions. The results are summarized in Table 1.
Table 1: Synthesis of 5-(4-bromophenyl)-5,8-dihydropyrimido[4,5-d]pyrimidinetrione derivatives using CuI NPs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No catalyst</td>
<td>H2O</td>
<td>r. t.</td>
<td>8</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>CuI NPs (10 %)</td>
<td>H2O</td>
<td>r. t.</td>
<td>2.5</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>CuI NPs (15 %)</td>
<td>H2O</td>
<td>r. t.</td>
<td>2</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>CuI NPs (20 %)</td>
<td>H2O</td>
<td>r. t.</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>CuI NPs (15 %)</td>
<td>H2O</td>
<td>reflux</td>
<td>1</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>CuI NPs (15 %)</td>
<td>EtOH</td>
<td>r. t.</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>CuI NPs (15 %)</td>
<td>CH3CN</td>
<td>r. t.</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>CuI NPs (15 %)</td>
<td>CH2Cl2</td>
<td>r. t.</td>
<td>4</td>
<td>74</td>
</tr>
</tbody>
</table>

*aIsolated yield.

that the yield is not affected by increase of the temperature (Table 1, entries 3 and 5). As for the reaction media, it was found that the reaction performed in aqueous media gave the best results.

To examine the scope of the presented method, we studied the reaction of some substituted aromatic...
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Aldehydes with 6-aminouracil or 1,3-dimethyl-6-aminouracil and obtained the corresponding products in high to excellent yields. The results are summarized in Table 2. The structures of the products 4a–j were confirmed by IR, 1H NMR spectral data and elemental analyses.

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>M. p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C6H5</td>
<td>H</td>
<td>5.5</td>
<td>96</td>
<td>245–247</td>
</tr>
<tr>
<td>4b</td>
<td>4-Br-C6H4</td>
<td>H</td>
<td>4</td>
<td>97</td>
<td>211–212</td>
</tr>
<tr>
<td>4c</td>
<td>4-Cl-C6H4</td>
<td>H</td>
<td>6</td>
<td>96</td>
<td>294–296</td>
</tr>
<tr>
<td>4d</td>
<td>4-OCH3-C6H5</td>
<td>H</td>
<td>5</td>
<td>98</td>
<td>285–287</td>
</tr>
<tr>
<td>4e</td>
<td>4-CH2-C6H5</td>
<td>H</td>
<td>6</td>
<td>97</td>
<td>249–251</td>
</tr>
<tr>
<td>4f</td>
<td>C6H5</td>
<td>CH3</td>
<td>4.5</td>
<td>95</td>
<td>&gt;300 (dec.)</td>
</tr>
<tr>
<td>4g</td>
<td>4-Br-C6H4</td>
<td>CH3</td>
<td>4</td>
<td>95</td>
<td>&gt;300 (dec.)</td>
</tr>
<tr>
<td>4h</td>
<td>4-Cl-C6H4</td>
<td>CH3</td>
<td>5.5</td>
<td>94</td>
<td>&gt;300 (dec.)</td>
</tr>
<tr>
<td>4i</td>
<td>4-OCH3-C6H5</td>
<td>CH3</td>
<td>4.5</td>
<td>93</td>
<td>&gt;300 (dec.)</td>
</tr>
<tr>
<td>4j</td>
<td>4-CH2-C6H5</td>
<td>CH3</td>
<td>6</td>
<td>91</td>
<td>&gt;300 (dec.)</td>
</tr>
</tbody>
</table>

*Yields refer to those of pure isolated products characterized by IR, 1H NMR spectral data and by elemental analyses; in all cases, the reaction mixture was stirred in water at room temperature for the appropriate time.

In view of environmentally friendly methodologies, the recyclability of the catalyst is an important factor. For this reason, the reusability of the CuI nanoparticles was evaluated in a model reaction under the optimized reaction conditions. The catalyst was recovered by a method described in the general procedure (Experimental section). The recovered catalyst was used in the three next runs. The results show that the yield of the product in every cycle was only slightly reduced (Fig. 3).

A plausible mechanism for the formation of the product would be as follows: CuI facilitates the Knoevenagel condensation of 6-aminouracil 1 and aromatic aldehyde 2 for the formation of alkene 7, through Lewis acid sites (Cu+) which are coordinated to the oxygen of the aldehyde, and activates it for the nucleophilic attack by 6-aminouracil. The subsequent Michael-type addition of urea (3) to alkene 7, followed by cyclization and elimination of ammonia, gives product 4 (Scheme 2).

3 Conclusion

Copper(I) iodide nanoparticles were found to catalyze the three-component reaction of 6-aminouracils, aromatic...
aldehydes and urea in water as a green solvent efficiently, affording dihydropyrimido[4,5-d]pyrimidinetriones derivatives in high to excellent yields after an easy work-up. This catalyst is readily recovered after completion of the reaction and can be reused at least three times without deactivation. Finally, this general and simple procedure provides opportunities for practical application of CuI nanoparticles as an efficient heterogeneous catalyst.

4 Experimental section

4.1 Materials and methods

All chemicals used in this work were purchased from Merck and Fluka in high purity (Kimiaexir Chemical Company, Tehran, Iran). Melting points were determined with Electrothermal 9100 apparatus and were uncorrected (East Tehran Branch, Islamic Azad University, Tehran, Iran). FT-IR spectra were obtained using a Bruker, Equinox 55, Golden Gate Gate Micro-ATR spectrometer (Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran). 1H NMR spectra were run on a Bruker DRX-500 AVANCE at 500 MHz using TMS as internal standard and [D6]DMSO as a solvent (Sharif University of Technology, Tehran, Iran). Elemental analyses were carried out using a Foss-Heraeus CHN-O-Rapid analyzer (polymer and Petrochemical Institute, Tehran, Iran). The microscopic morphology of the catalyst was visualized by a scanning electron microscope LEO 1455VP (Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran). Powder X-ray diffraction data were obtained on a Philips, X’Pert diffractometer using Cu Kα radiation (λ = 1.54 Å) (Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran).

4.2 General procedure for the preparation of CuI NPs catalyst

The catalyst was prepared by the precipitation approach. Cu(NO3)2·3H2O was used as the Cu source. First, a D-(+)-glucose solution was added drop-wise to the stirred solution of copper nitrate in order to reduce Cu(II) to Cu(I), followed by adding LiI solution. The mixture was stirred for 30 min at room temperature. When the reaction was completed, a gray precipitate was obtained. The resulted solid was filtered and washed with de-ionized water and absolute EtOH, respectively, and then dried in vacuo for several hours to give the pure catalyst [20].

4.3 General procedure for the synthesis of compounds 4a–j

A mixture of 6-aminouracil 1 (2 mmol), aromatic aldehyde 2 (2 mmol), urea 3 (2.5 mmol) and CuI NPs (2.9 mg, 15 mol%) in water (4 mL) was stirred at room temperature for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was filtered. The solid residue was diluted with DMF (10 mL) and centrifuged at 2000–3000 rpm for 5 min to remove the CuI catalyst which was washed with DMF and dried at 100 °C for several hours in a vacuum for reuse. The organic solution was then poured into ice-cold water (10 mL) to give a solid precipitate, which was filtered off and recrystallized from DMF and H2O to afford the pure product.

4.3.1 5-Phenyl-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4a)

Colorless powder, yield 248 mg (96 %). M. p. 245–247 °C (lit. 247–250 °C [17]). – IR (KBr, cm–1): νmax = 3403, 3313, 3175, 1707, 1643, 1596. – 1H NMR: δ = 5.49 (s, 1 H, CH), 7.16 (m, 5 H, HAr), 7.55 (s, 1 H, NH), 10.15 (s, 1 H, NH), 11.43 (s, 2 H, NH) ppm. – Anal. for C12H10N4O3 (258.24): calcd. C 55.81, H 3.90, N 21.69; found C 55.69, H 3.67, N 21.55 %.

4.3.2 5-(4-Bromophenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4b)

Pale-yellow powder, yield 327 mg (97 %). M. p. 211–212 °C (lit. 210–212 °C [17]). – IR (KBr, cm–1): νmax = 3376, 3262, 3039, 1699, 1620, 1515. – 1H NMR: δ = 5.60 (s, 1 H, CH), 7.32 (m, 4 H, HAr), 8.59 (s, 1 H, NH), 10.02 (s, 1 H, NH), 11.30 (s, 2 H, NH) ppm. – Anal. for C12H9BrN4O3 (337.13): calcd. C 42.75, H 2.69, N 16.62; found C 42.59, H 2.75, N 16.44 %.

4.3.3 5-(4-Chlorophenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4c)

Colorless powder, yield 281 mg (96 %). M. p. 294–295 °C (lit. 294–295 °C [17]). – IR (KBr, cm–1): νmax = 3392, 3250, 3074, 1716, 1637, 1554. – 1H NMR: δ = 5.21 (s, 1 H, CH), 7.33 (m, 4 H, HAr), 7.72 (s, 1 H, NH), 8.55 (s, 1 H, NH), 11.13 (s, 2 H, NH) ppm. – Anal. for C12H9ClN4O3 (292.68): calcd. C 49.25, H 3.10, N 19.14; found C 49.12, H 3.26, N 19.05 %.
4.3.4 5-(4-Methoxyphenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4d)

Colorless powder, yield 282 mg (98 %). M. p. 258–287 °C (lit. 285–287 °C [17]). – IR (KBr, cm⁻¹): νmax = 3405, 3338, 3212, 1683, 1536. – ¹H NMR: δ = 3.77 (s, 3 H, OCH3), 5.18 (s, 1 H, CH), 6.95 (m, 4 H, H Ar), 8.30 (s, 1 H, NH), 8.75 (s, 1 H, NH), 11.12 (s, 1 H, NH), 11.37 (s, 1 H, NH) ppm. – Anal. for C13H10ClN4O3 (321.7): calcd. C 52.43, H 3.14, N 15.34; found C 52.57, H 3.23, N 15.37 %.

4.3.5 5-(4-Methylphenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4e)

Colorless powder, yield 264 mg (97 %). M. p. 249–251 °C (lit. 248–250 °C [17]). – IR (KBr, cm⁻¹): νmax = 3387, 3295, 3086, 1698, 1606, 1584. – ¹H NMR: δ = 2.87 (s, 3 H, CH3), 5.89 (s, 1 H, CH), 7.07 (m, 4 H, H Ar), 7.93 (s, 1 H, NH), 10.02 (s, 1 H, NH), 10.93 (s, 2 H, NH) ppm. – Anal. for C13H12N4O3 (282.26): calcd. C 54.17, H 4.20, N 19.44; found C 54.08, H 4.06, N 19.53 %.

4.3.6 1,3-Dimethyl-5-phenyl-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4f)

Colorless powder, yield 272 mg (95 %). M. p. >300 °C (dec.) (lit. 324 °C (dec.) [18]). – IR (KBr, cm⁻¹): νmax = 3328, 3115, 1698, 1643, 1585. – ¹H NMR: δ = 3.09 (s, 3 H, CH3), 3.34 (s, 3 H, CH3), 5.22 (s, 1 H, CH), 7.32 (m, 5 H, H Ar), 8.09 (s, 1 H, NH), 9.81 (s, 1 H, NH) ppm. – Anal. for C15H16N4O4 (316.31): calcd. C 56.86, H 5.17, N 17.84%; found C 56.86, H 5.17, N 17.84 %.

4.3.7 1,3-Dimethyl-5-(4-bromophenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4g)

Yellow powder, yield 347 mg (95 %). M. p. >300 °C (dec.) (lit. 307 °C (dec.) [18]). – IR (KBr, cm⁻¹): νmax = 3323, 3088, 1712, 1644, 1600. – ¹H NMR: δ = 3.07 (s, 3 H, CH3), 3.34 (s, 3 H, CH3), 5.20 (s, 1 H, CH), 7.41 (m, 4 H, H Ar), 8.10 (s, 1 H, NH), 9.88 (s, 1 H, NH) ppm. – Anal. for C15H14BrN4O4 (365.19): calcd. C 46.05, H 3.59, N 15.34; found C 45.94, H 3.45, N 15.27 %.

4.3.8 1,3-Dimethyl-5-(4-chlorophenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4h)

Colorless powder, yield 301 mg (94 %). M. p. >300 °C (dec.) (lit. 312 °C (dec.) [18]). – IR (KBr, cm⁻¹): νmax = 3332, 3126, 1691, 1654, 1604. – ¹H NMR: δ = 3.08 (s, 3 H, CH3), 3.35 (s, 3 H, CH3), 5.20 (s, 1 H, CH), 7.35 (m, 4 H, H Ar), 8.10 (s, 1 H, NH), 9.85 (s, 1 H, NH) ppm. – Anal. for C15H13ClN4O4 (320.73): calcd. C 52.43, H 4.09, N 17.47; found C 52.32, H 3.99, N 17.39 %.

4.3.9 1,3-Dimethyl-5-(4-methoxyphenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4i)

Pale-yellow powder, yield 294 mg (93 %). M. p. >300 °C (dec.) (lit. 307 °C (dec.) [18]). – IR (KBr, cm⁻¹): νmax = 3532, 3095, 1681, 1646, 1596. – ¹H NMR: δ = 3.08 (s, 3 H, CH3), 3.37 (s, 3 H, CH3), 3.70 (s, 3 H, OCH3), 5.18 (s, 1 H, CH), 7.10 (m, 4 H, H Ar), 8.03 (s, 1 H, NH), 9.80 (s, 1 H, NH) ppm. – Anal. for C15H14O4N4 (316.31): calcd. C 56.96, H 5.10, N 17.71; found C 56.86, H 5.17, N 17.84 %.

4.3.10 1,3-Dimethyl-5-(4-methylphenyl)-5,8-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,6H)-trione (4j)

Pale-yellow powder, yield 273 mg (91 %). M. p. >300 °C (dec.) (lit. 315 °C (dec.) [18]). – IR (KBr, cm⁻¹): νmax = 3310, 3115, 1687, 1656, 1601. – ¹H NMR: δ = 2.25 (s, 3 H, CH3), 3.10 (s, 3 H, CH3), 3.35 (s, 3 H, CH3), 5.19 (s, 1 H, CH), 7.16 (m, 4 H, H Ar), 8.04 (s, 1 H, NH), 9.81 (s, 1 H, NH) ppm. – Anal. for C15H16N4O4 (300.32): calcd. C 59.99, H 5.37, N 18.66; found C 59.61, H 5.49, N 18.44 %.

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References