Fe₃O₄ Bonded Pyridinium-3-carboxylic acid-N-sulfonic Acid Chloride as an Efficient Catalyst for the Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

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ABSTRACT
Fe₃O₄ bonded pyridinium-3-carboxylic acid-N-sulfonic acid chloride, as a magnetic and reusable catalyst, was reported for the one-pot multi-component synthesis of some 3,4-dihydropyrimidin-2(1H)-ones by the reaction of urea, ethyl acetoacetate and various aldehyde under solvent-free conditions. The products were identified by FT-IR, ¹H NMR and ¹³C NMR spectra and the catalyst was reused successfully for three times.

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Chemical Methodologies: http://www.chemmethod.com/
Graphical Abstract

Introduction

The synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) is very important in organic synthesis due to their significant biological activities. Some applications such as calcium-channel blocking activities, anti-bacterial, anti-mitotic, and cytotoxic properties were reported for these compounds [1, 2]. Moreover, DHPMs have some other properties including antihypertensive, anti-HIV, antitumor, and antiviral activities [3-9].

Biginelli reaction is a multi-component reaction between the ethyl acetoacetate as a β-dicarbonyl compound, aryl aldehyde and urea which is catalyzed by an acidic catalyst [10, 11]. Some methods were reported using different catalysts for the synthesis of DHPMs [12-29]. Compared to the previous methods, the presented catalyst has some advantages such as high yields and short reaction times.

Here we have used nano-Fe$_3$O$_4$ bonded pyridinium-3-carboxylic acid-N-sulfonic acid chloride as a highly efficient and reusable catalyst for one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones (Scheme 1). Compared to the previous methods, the presented catalyst showed some advantages such as high yields and short reaction times.

Scheme 1. The synthesis of 3,4-dihydropyrimidin-2(1H)-ones
Experimental

All the chemicals were purchased from the Fluka, Merck and Aldrich chemical companies. We recorded melting points of the compounds by electrothermal IA9100 melting point apparatus. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in DMSO-$d_6$ solutions using a bruker FX spectrometers. The chemical shift ($\delta$) was in ppm.

Procedure for the synthesis of nano Fe$_3$O$_4$@nicotinic acid

In a three-necked round-bottom flask, FeCl$_3$.6H$_2$O (0.0216 mol, 5.89 g), FeCl$_2$.4H$_2$O (0.011 mol, 2.17 g) and nicotinic acid (0.043 mol, 5.29 g) were dissolved in 100 mL of distilled water at room temperature. The homogeneous solution was stirred using a magnetic stirrer under the nitrogen atmosphere at 60 °C for 30 min. Then, the ammonia solution (25%, 15 mL) was added to this mixture and a black color suspension was obtained. Then the mixture was refluxed under the N$_2$ atmosphere at 90 °C for 6 h. After that, the black precipitate was separated using an external magnet and washed with distilled water for 5 times. The obtained nanoparticles were dried at 60 °C for 12 h [31].

Procedure for the synthesis of Fe$_3$O$_4$ bonded pyridinium-3-carboxylic acid-N-sulfonic acid chloride

Nano Fe$_3$O$_4$@nicotinic acid (0.5 g) was added to dry dichloromethane (6 mL) under sonication for 30 min and then added slowly to a 50 mL round-bottomed flask containing of a solution of chlorosulfonic acid (15 mmol, 1 mL) in dichloromethane (10 mL) and stirred for 3 h. The brown powder which obtained was separated using a permanent magnet, washed thoroughly with dichloromethane for several times and dried at 60 °C for 12 h [31-36].

Procedure for the synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Ethyl acetoacetate (1 mmol, 0.13 mL), benzaldehyde (1 mmol, 0.1 mL), urea (1 mmol, 0.06 g) and the catalyst (0.005 g) were poured in round-bottomed flask connected to a reflux condenser and the mixture was heated at 90 °C for 30 min. Then, the completion of the reaction was monitored by TLC and the reaction mixture was solved in warm ethanol (15 mL) and separated from catalyst. The catalyst was collected with an external magnet and reused for the next run. Then the pure product was obtained by recrystallization from the ethanol (96%).
Ethyl 4-(3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8a)

FT-IR (KBr) (cm⁻¹): 3349, 3227, 3113, 2977, 1693, 1642; ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 1.10 (t, 3H, CH₃, J = 6.80 Hz), 2.26 (s, 3H, CH₃), 4.00 (d, 2H, CH₂, J = 4.80 Hz), 5.17 (s, 1H, CH), 7.00 (d, 1H, ArH, J = 10 Hz), 7.09 (d, 2H, ArH, J = 6.8 Hz), 7.38 (q, 1H, ArH, J = 6.80 Hz), 7.81 (s, 1H, NH), 9.27 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 14.0, 17.7, 53.4, 59.2, 98.5, 112.8, 113.0, 113.9, 114.1, 122.1, 130.4, 130.5, 147.5, 147.6, 148.9, 151.9, 160.8, 163.2, 165.1.

Ethyl 4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9a)

FT-IR (KBr) (cm⁻¹): 3243, 3116, 2979, 1723, 1703; ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 1.11 (s, 3H, CH₃), 2.26 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 5.15 (s, 1H, CH), 7.25–7.45 (m, 4H, ArH), 7.80 (s, 1H, NH), 9.28 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 14.0, 17.8, 53.5, 59.2, 98.5, 121.5, 125.2, 129.1, 130.1, 130.7, 147.4, 148.9, 151.9, 165.1.

Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (10a)

FT-IR (KBr) (cm⁻¹): 3444, 3348, 3248, 3118, 2929, 1720, 1701; ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 1.11 (t, 3H, CH₃, J = 6.40 Hz), 2.22 (s, 3H, CH₃), 2.84 (s, 6H, 2CH₃), 3.97 (d, 2H, CH₂, J = 6.40 Hz), 5.02 (s, 1H, CH), 6.65 (d, 2H, ArH, J = 7.60 Hz), 7.03 (d, 2H, ArH, J = 7.60 Hz), 7.58 (s, 1H, NH), 9.08 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 14.1, 17.7, 53.2, 59.0, 99.8, 112.1, 126.8, 132.6, 147.5, 149.7, 152.2, 165.4.

Ethyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (11a)

FT-IR (KBr) (cm⁻¹): 3244, 3115, 2980, 1726, 1704; ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 1.09 (t, 3H, CH₃, J = 6.4 Hz), 2.25 (s, 3H, CH₃), 3.98 (d, 2H, CH₂, J = 6.4 Hz), 5.13 (s, 1H, CH), 7.19 (d, 2H, J = 7.20 Hz, ArH), 7.53 (d, 2H, J = 8.40 Hz, ArH), 7.79 (s, 1H, NH), 9.27 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 14.0, 17.7, 53.4, 59.2, 98.7, 120.2, 128.5, 131.2, 144.1, 148.7, 151.8, 165.1.

Results and discussion

In this work, we have used Fe₃O₄ bonded pyridinium-3-carboxylic acid-N-sulfonic acid chloride nanoparticles as a catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones. Firstly, Fe₃O₄@nicotinic acid was prepared by refluxing method of iron (II), iron (III) ions and nicotinic acid and then adding aqueous solution of ammonia. Secondly, Fe₃O₄@nicotinic acid was functionalized by ClSO₃H to produce Fe₃O₄ bonded pyridinium-3-carboxylic acid sulfonic acid chloride as reusable magnetic catalyst (Scheme 2).
In the next step, the reaction of ethyl acetoacetate, urea and benzaldehyde was selected as a model reaction and different amounts of catalyst, various temperatures and the use of different solvents were studied on this reaction (Table 1). As seen in Table 1, the expected product was prepared in high yield and low reaction time using 0.005 g of catalyst at 90 °C under solvent free condition. By increasing the temperature, no improvement was observed in the results. Also, the model reaction was tested at the absence of catalyst at 90 °C, and the yield of the product was found to be very low (Table 1, entry 14).
Table 1. Effect of different amounts of the catalyst, temperature and various solvents on the reaction of ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), urea (1 mmol)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (g)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.001</td>
<td>90</td>
<td>-</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>0.003</td>
<td>90</td>
<td>-</td>
<td>30</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>0.005</td>
<td>90</td>
<td>-</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>0.007</td>
<td>90</td>
<td>-</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>0.009</td>
<td>90</td>
<td>-</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>0.01</td>
<td>90</td>
<td>-</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>0.005</td>
<td>60</td>
<td>-</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>0.005</td>
<td>80</td>
<td>-</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>0.005</td>
<td>100</td>
<td>-</td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>0.005</td>
<td>Reflux</td>
<td>H₂O</td>
<td>30</td>
<td>Trace</td>
</tr>
<tr>
<td>11</td>
<td>0.005</td>
<td>Reflux</td>
<td>Ethyl acetate</td>
<td>30</td>
<td>Trace</td>
</tr>
<tr>
<td>12</td>
<td>0.005</td>
<td>Reflux</td>
<td>n-Hexane</td>
<td>30</td>
<td>Trace</td>
</tr>
<tr>
<td>13</td>
<td>0.005</td>
<td>Reflux</td>
<td>CHCl₃</td>
<td>30</td>
<td>Trace</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>90</td>
<td>-</td>
<td>90</td>
<td>Trace</td>
</tr>
</tbody>
</table>

*a*Isolated yield

After the optimization of the reaction condition, to study of the scope and generality of the reaction, the condensations of ethyl acetoacetate, urea and different aldehydes using Fe₃O₄ bonded pyridinium-3-carboxylic acid-N-sulfonic acid chloride as a catalyst were examined in the approved condition to prepare various 3,4-dihydropyrimidin-2(1H)-ones. The results are depicted in Table 2.

Table 2. The synthesis of 3,4-dihydropyrimidin-2(1H)-ones using Fe₃O₄ bonded pyridinium-3-carboxylic acid sulfonic acid chloride

<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>1a</td>
<td><img src="image1.png" alt="Image" /></td>
<td>30</td>
<td>95</td>
<td>202-204 (204-206) [28]</td>
</tr>
<tr>
<td>2a</td>
<td><img src="image2.png" alt="Image" /></td>
<td>25</td>
<td>90</td>
<td>240-242 (236-237) [37]</td>
</tr>
<tr>
<td>3a</td>
<td><img src="image3.png" alt="Image" /></td>
<td>25</td>
<td>91</td>
<td>258-260 (260-261) [23]</td>
</tr>
<tr>
<td>4a</td>
<td><img src="image4.png" alt="Image" /></td>
<td>35</td>
<td>89</td>
<td>240-242 (237-239) [26]</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Isolated Yield</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5a</td>
<td><img src="image1" alt="Structure" /></td>
<td>30</td>
<td>90</td>
<td>226-228 (228-232) [19(c)]</td>
</tr>
<tr>
<td>6a</td>
<td><img src="image2" alt="Structure" /></td>
<td>25</td>
<td>93</td>
<td>211-213 (210-212) [27]</td>
</tr>
<tr>
<td>7a</td>
<td><img src="image3" alt="Structure" /></td>
<td>25</td>
<td>95</td>
<td>177-180 (173-177) [38]</td>
</tr>
<tr>
<td>8a</td>
<td><img src="image4" alt="Structure" /></td>
<td>30</td>
<td>94</td>
<td>210-212 (209-211) [37]</td>
</tr>
<tr>
<td>9a</td>
<td><img src="image5" alt="Structure" /></td>
<td>35</td>
<td>98</td>
<td>190-192 (188-190) [27]</td>
</tr>
<tr>
<td>10a</td>
<td><img src="image6" alt="Structure" /></td>
<td>30</td>
<td>92</td>
<td>227-229 (228-230) [29]</td>
</tr>
<tr>
<td>11a</td>
<td><img src="image7" alt="Structure" /></td>
<td>30</td>
<td>94</td>
<td>200-202 (195-198) [26]</td>
</tr>
</tbody>
</table>

*a* Isolated yield

In a mechanism which was suggested by Kappe [30], aldehyde, which was activated by acidic catalyst, reacted with urea to give I and then, after removing of one molecule of water II was prepared. In the next step, the ethyl acetoacetate was added to II bond which was activated by the
catalyst and finally the product was obtained by the nucleophilic attack using the amine group onto the carbonyl group in intermediate III (Scheme 3).

Scheme 3. The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones in the presence of nano-Fe₃O₄ bonded pyridinium-3-carboxylic acid-N-sulfonic acid chloride

Reusability of Fe₃O₄ bonded pyridinium-3-carboxylic acid sulfonic acid chloride was also tested upon the reaction of ethyl acetoacetate, urea and benzaldehyde. After completion of the reaction, warm EtOH (15 mL) was added to the reaction mixture and stirred for 3 min. The reaction mixture was dissolved in warm ethanol and the catalyst is not dissolved. Then the catalyst was separated with an external magnet and then reused for another reaction. We observed that the catalytic activity of the catalyst was restored for three successive runs within the limits of the experimental errors (Figure 1).
Figure 1. The reusability of Fe$_3$O$_4$ bonded pyridinium-3-carboxylic acid-$N$-sulfonic acid chloride

Conclusions

In summary, Fe$_3$O$_4$ bonded pyridinium-3-carboxylic acid-$N$-sulfonic acid chloride as a novel heterogeneous was introduced as an efficient and reusable catalyst for the synthesis of some 3,4-dihydropyrimidin-2(1$H$)-ones by the one-pot multi-component reaction of urea, ethyl acetoacetate and various aldehyde containing electron withdrawing substituents, electron-releasing substituents and halogens. High yields, short reaction times, reusability of the catalyst, simple work up and solvent-free condition are some advantages of the presented work.

Acknowledgements

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Conflict of Interest

We have no conflicts of interest to disclose.

References

[35] Zolfigol M.A., Moosavi-Zare A.R., Zarei M. *C. R. Chimie*, 2014, **17**:1264

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