Microwave enhanced, solvent free green protocol for the production of 3,4-dihydropyrimidine-2-(1H)-ones using AlCl₃·6H₂O as a catalyst

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3,4-Dihydropyrimidine-2-(1H)-ones are synthesized via a multicomponent reaction of aldehyde, urea or thiourea and 1,3-dicarbonyl compounds using microwave irradiation catalyzed by 10 mol% AlCl₃·6H₂O under solvent-free conditions. The catalyst being reported here is cheap, safe to handle and the whole procedure is eco-friendly.

Keywords: 3,4-Dihydropyrimidine-2-(1H)-ones, aldehyde, urea or thiourea, 1,3-dicarbonyl compounds, AlCl₃·6H₂O, microwave, multicomponent reaction.

Use of multicomponent reactions (MCRs) is the need of present century and is primarily driven by pharmaceutical industries. Also present day concern is development of green processes because of pollution avoiding awareness and fast developments are there to develop solvent free processes. These methodologies are being adopted for reducing time, money, energy and are eco-friendly. The multicomponent reactions are being explored vigorously during last two decades or so. AlCl₃·6H₂O has been used to promote some major reactions of organic chemistry like Beckmann, hydrogenation, dehydration and synthesis of 1,4-dihydropyridines and their aromatization. Herein we report the novel utility of this catalyst AlCl₃·6H₂O in the production of 3,4-dihydropyrimidin-2-(1H)-ones and 3,4-dihydropyrimidin-2-(1H)-thiones. The synthesis of 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs) is of current interest as these molecules have shown promising biological properties and can be synthesized in a single step even though originally these compounds were produced about a century ago. The pharmacological properties namely are antihypertensive agents, anticarcinogenic agents, calcium channel blockers, α-1a-agonists, neuropeptide Y (NPY) antagonists, anti-inflammatory and analgesic agents. Additionally, DHPM unit is also present in the natural marine alkaloids batzelladine A and B which are the first low molecular weight natural products to inhibit the binding of HIV gp 120 to CD4 cells, that may have potential application in the treatment of AIDS. Of particular interest is the production of Monastrol in a single step with high yield which is being developed as a lead compound for anti-cancer activity.

As mentioned earlier, the use of AlCl₃·6H₂O being safe catalytic system is of current interest and in continuation to our interest in aluminum reagent, herein we report its use in Biginelli reaction under solvent free conditions and enhanced by microwave irradiation (Scheme I).

Under these conditions, the reaction time was reduced dramatically and reaction completed within 1.5-3.0 min. Various aromatic, aliphatic and heterocyclic aldehydes have been employed in this reaction successfully which is testimony to the large scope of this catalyst system. Acetylacetone was also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2-(1H)-ones (Table I, entries 13, 14, 15). When urea was replaced with thiourea the corresponding 3,4-dihydropyrimidin-2-(1H)-thiones were obtained with comparable results. Thus, variations in all three components have been accommodated very comfortably.

This condensation process is fairly general and several functionalities like nitro, chloro, hydroxyl and methoxy survived during the course of reaction and of special interest is the production of monastrol in a single step with high yield. Acid sensitive aldehyde such as furfural also worked well without the formation of any side product. Roughly 0.1 equivalent of AlCl₃·6H₂O was found to be sufficient for these reactions and the use of less than 0.1 equivalents was not optimal. The use of large amount of catalyst was also found to be unfruitful. The reaction proved to be very reproducible and could be carried out in a domestic microwave oven as well as in designed Prolabo Microwave Module Synthwave S-402.

In conclusion, the present method employing AlCl₃·6H₂O is an efficient, one pot procedure for preparation of 3,4-dihydropyrimidin-2-(1H)-ones in excellent yields. The reaction time is dramatically
The present study describes the first ever use and catalytic activity of AlCl$_3$.6H$_2$O in the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones. In addition to this, it involved mild reaction conditions and simple work-up. The present study describes the first ever use and catalytic activity of AlCl$_3$.6H$_2$O in the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones.

**Experimental Section**

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased from commercial source and used as received. IR spectra were recorded in KBr discs on a Perkin-Elmer 24OC analyzer. $^1$H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer using TMS as internal standard. The progress of reaction was monitored by TLC run on silica gel G (Merck).

**General experimental procedure for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones**

A mixture of aldehyde (2 mmole), 1,3-dicarbonyl compound (2 mmole), urea (3 mmole) and AlCl$_3$.6H$_2$O (10 mole%) were placed in an Erlenmeyer flask and then irradiated in a microwave oven at 220 W for the required duration (Table I).

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**Table I — AlCl$_3$.6H$_2$O mediated synthesis of 3,4-dihydropyrimidin-2-(1H)-ones under solvent free conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product$^a$</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>X</th>
<th>Reaction time (min.)$^b$</th>
<th>Yield (%)$^{b,c}$</th>
<th>m.p. ($^\circ$C)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>C$_6$H$_5$</td>
<td>OEt</td>
<td>O</td>
<td>2.5</td>
<td>90</td>
<td>208-209 (208-10)$^{17}$</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>p-Cl-C$_6$H$_4$</td>
<td>OEt</td>
<td>S</td>
<td>3.0</td>
<td>93</td>
<td>192-194 (192-95)$^{17}$</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>2-Thienyl</td>
<td>OEt</td>
<td>S</td>
<td>2.0</td>
<td>83</td>
<td>214-216 (215-17)$^{17}$</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>m-OH-C$_6$H$_4$</td>
<td>OEt</td>
<td>S</td>
<td>1.5</td>
<td>90</td>
<td>179-80</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>C$_6$H$_5$</td>
<td>OEt</td>
<td>O</td>
<td>2.0</td>
<td>97</td>
<td>201-02 (202-03)$^{17}$</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>p-Cl-C$_6$H$_4$</td>
<td>OEt</td>
<td>O</td>
<td>2.5</td>
<td>95</td>
<td>212-13 (210-12)$^{17}$</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>p-NO$_2$-C$_6$H$_4$</td>
<td>OEt</td>
<td>O</td>
<td>3.0</td>
<td>96</td>
<td>208-10 (207-10)$^{17}$</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>m-Cl-C$_6$H$_4$</td>
<td>OEt</td>
<td>O</td>
<td>2.5</td>
<td>95</td>
<td>192-93</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>p-MeO-C$_6$H$_4$</td>
<td>OEt</td>
<td>O</td>
<td>1.5</td>
<td>91</td>
<td>200-201 (199-201)$^{17}$</td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>(CH$_3$)$_2$CH</td>
<td>OEt</td>
<td>O</td>
<td>1.5</td>
<td>93</td>
<td>194-95 (194-95)$^{16}$</td>
</tr>
<tr>
<td>11</td>
<td>4k</td>
<td>n-Bu</td>
<td>OEt</td>
<td>O</td>
<td>2.0</td>
<td>89</td>
<td>156-58 (156-58)$^{16}$</td>
</tr>
<tr>
<td>12</td>
<td>4l</td>
<td>2-Furyl</td>
<td>OEt</td>
<td>O</td>
<td>1.5</td>
<td>85</td>
<td>204-05 (204-05)$^{17}$</td>
</tr>
<tr>
<td>13</td>
<td>4n</td>
<td>C$_6$H$_5$</td>
<td>Me</td>
<td>O</td>
<td>2.5</td>
<td>91</td>
<td>210-11 (209-12)$^{16}$</td>
</tr>
<tr>
<td>14</td>
<td>4o</td>
<td>p-CH$_3$O-C$_6$H$_4$</td>
<td>Me</td>
<td>O</td>
<td>2.0</td>
<td>90</td>
<td>190-91 (191-93)$^{16}$</td>
</tr>
<tr>
<td>15</td>
<td>4p</td>
<td>p-NO$_2$-C$_6$H$_4$</td>
<td>Me</td>
<td>O</td>
<td>3.0</td>
<td>95</td>
<td>235-38 (235-38)$^{16}$</td>
</tr>
</tbody>
</table>

$^a$All product were characterized by m.p. and spectral (IR, $^1$H NMR) data.
$^b$Reaction carried out under microwave irradiation in solvent free condition. $^c$Yields refers to pure isolated products.
$^d$Value in parenthesis indicates lit. m.p.
After completion of reaction (TLC), the mixture was cooled to RT and poured into water (10 mL) and stirred for 5 min. The solid thus obtained was filtered and purified by recrystallization from ethanol to afford 3,4-dihydropyrimidin-2(1H)-one.

Spectroscopic characterization data

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-thione, 4c: m.p. 214-16°C; IR (KBr): 3423, 3243, 1651 cm⁻¹; ¹H NMR (DMSO-d₆): δ 10.39 (s, 1H), 9.67 (s, 1H), 7.41 (d, J = 4.2 Hz, 1H), 7.00-6.85 (m, 2H), 2.24 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). Anal. Found: C, 51.14; H, 4.95; N, 9.83. C₁₂H₁₄N₂O₂S₂ requires C, 51.02; H, 4.89; N, 9.93.

5-Ethoxycarbonyl-6-methyl-4-(isopropyl)-3,4-dihydropyrimidin-2(1H)-one, 4f: m.p. 201-02°C; IR (KBr): 3416, 3239, 1704, 1651 cm⁻¹; ¹H NMR (DMSO-d₆): δ 9.18 (s, 1H), 7.73 (s, 1H), 7.20-7.30 (m, 5H), 5.14 (s, 1H), 3.98 (q, J = 7.2 Hz, 2H), 2.22 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). Anal. Found: C, 64.67; H, 6.13; N, 10.77. C₁₄H₁₆N₃O₄ requires C, 64.62; H, 6.15; N, 10.77%

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 4h: m.p. 192-93°C; IR (KBr): 3416, 3239, 1706, 1642 cm⁻¹; ¹H NMR (DMSO-d₆): δ 9.02 (s, 1H), 7.50 (s, 1H) 7.16-7.35 (m, 4H), 5.20 (s, 1H), 4.02 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H). Anal. Found: C, 57.16; H, 5.15; N, 9.39. C₁₄H₁₅ClN₂O₃ requires C, 57.05; H, 5.13; N, 9.50%.

5-Ethoxycarbonyl-6-methyl-4-(isopropyl)-3,4-dihydropyrimidin-2(1H)-one, 4j: m.p. 194-95°C; IR (KBr): 3416, 3239, 1704, 1651 cm⁻¹; ¹H NMR (DMSO-d₆): δ 8.67 (s, 1H), 6.38 (s, 1H), 4.28 (s, 1H), 4.12 (q, J = 7.3 Hz, 2H), 2.27 (s, 3H), 1.80 (m, 1H) 1.26 (t, J = 7.1 Hz, 3H)), 0.94 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). Anal. Found: C, 60.98; H, 5.72; N, 10.08. C₁₄H₁₆N₃O₃ requires C, 60.87; H, 5.80; N, 10.14%.

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References

8 For the use of sonication in this reaction see (a) Zhang X, Li Y & Wang C L J, J Mol Catal A: Chemical, 253, 2006, 207; (b) Li J -T, Han L -F, Yang J -H & Li T -S, Ultrasonic Sonochem, 10, 2003, 119.