Pivalic acid assisted Biginelli reaction for synthesis of dihydropyrimidinones and dihydrothiopyrimidinones

Hari K Kadam\*\textsuperscript{a}, Anushri Laxman Gawas\textsuperscript{a}, Shruti Sagun Vernekar\textsuperscript{a}, Anika Arjun Chodankar\textsuperscript{a}, Saurabh Sudan Gaonkar\textsuperscript{a}, Lalitprabha N Salgaonkar\textsuperscript{a}, Tushar S Anvekar\textsuperscript{a}, Teotone Vaz\textsuperscript{a} & Shashank N Mhaldar\textsuperscript{b}

\textsuperscript{a}Department, of Chemistry, St. Xavier’s College, Mapusa, Goa 403 507, India
\textsuperscript{b}Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India
E-mail: harikadam05@gmail.com

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Herein is provided an alternate, simple, multigram scale, efficient route for Biginelli reaction for synthesis of dihydropyrimidinones using urea, ethylacetoacetate, and benzaldehyde with pivalic acid.

Keywords: One-pot synthesis, green chemistry, heterocycles, bioactive compounds, pivalic acid, dihydropyrimidinones

Dihydropyrimidinones are well known for their wide range of biological responses. They exhibit antitumor, antibacterial, antiviral, anti-inflammatory activities, etc. (Figure 1). Several alkaloids containing dihydropyrimidinone as core structural unit are isolated from marine sources and exhibit interesting pharmacological properties\textsuperscript{1-5}.

First prepared by Biginelli reaction, a multicomponent one-pot reaction involving urea, ethylacetoacetate and benzaldehyde, Dihydropyrimidinone and its derivatives are extensively studied with diverse catalyst, solvents, unconventional methods like microwave, ultrasound, solid supported reagents, transition metal salts, metal oxides, etc.\textsuperscript{6-10}

Multicomponent reactions are preferred strategy for organic synthesis due to their convergent character, economic nature and energy and time saving factor. Dihydropyrimidinones prepared by exploring several acid catalysts such as mineral acids, acetic acid, lewis acids, metal halides, etc. Acid catalysed activation of electrophiles is a most probable mode of catalytic action\textsuperscript{11-13}. However, a simple, fast, mild, low cost method is still encouraging\textsuperscript{14-19}.

Results and Discussion

We herein provide an alternate, simple and efficient route for synthesis of dihydropyrimidinones using urea, ethylacetoacetate and benzaldehyde with pivalic acid as catalyst as well as solvent. Pivalic acid is a water soluble, very low melting, mild and sterically hindered carboxylic proton donor\textsuperscript{20-24}.

The reaction when tried without any catalyst entails long reaction time and low yield. The amount of pivalic acid was then varied and optimised to give highest yield (Scheme I, Table I). Water miscibility of pivalic acid practically hindered its reusability.

The methodology was further explored with various other substituted benzaldehydes and thiourea to get corresponding dihydropyrimidinones and dihydrothiopyrimidinones\textsuperscript{26-34}. (Scheme II, Table II)

Figure 1 — Medicinally important compounds with dihydropyrimidinone framework

Scheme I — Optimisation study for dihydropyrimidinones and dihydrothiopyrimidinones with urea and thiourea respectively along with benzaldehyde and ethylacetoacetate
On successfully exploiting this methodology for several derivatives of Biginelli product, we herein propose a probable mechanism for the multicomponent reaction (Figure 2).

**Experimental Section**

**Representative procedure for dihydropyrimidinone 1a**

In a 100 mL round bottom flask, benzaldehyde (1 mL, 1.06 g, 0.01 mol), urea (0.91 g, 0.015 mol), ethylacetoacetate (1.3 mL, 1.301 g, 0.01 mol) and pivalic acid (1 mL), were stirred at 125°C for 2 h. After completion of the reaction, EtOH (5 mL) was added to this content and immediately poured into 500 mL beaker containing ice. The solid product was filtered, washed with EtOH:H₂O (1:1) mixture and dried in air. Analytically pure product (92 %, 2.41 g) was obtained as white solid on recrystallisation with EtOAc.

**Representative procedure for dihydrothiopyrimidinone, 1l**

In a 100 mL round bottom flask, benzaldehyde (1 mL, 1.06 g, 0.01 mol), thiourea (1.151 g, 0.015 mol), ethylacetoacetate (1.3 mL, 1.301 g, 0.01 mol) and pivalic acid (1 mL), were stirred at 135°C for 3 h. After completion of the reaction, EtOH (5 mL) was added to this content and immediately poured into 500 mL beaker containing ice. The solid product was filtered, washed with EtOH:H₂O (3:1) mixture and dried in air. Analytically pure product (73 %, 2.015 g) was obtained as yellow solid on recrystallisation with EtOAc.

**Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1a:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.09 (t, J = 7.2 \text{ Hz}, 3\text{H}), 2.24 (s, 3\text{H}), 3.98 (q, J = 7.2 \text{ Hz}, 2\text{H}), 5.14 (s, 1\text{H}), 7.24 (m, 3\text{H}), 7.33 (m, 2\text{H}), 7.75 (s, 1\text{H}), 9.20 (s, 1\text{H}). \end{align*} \]

**Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1b:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.11 (t, J = 7.2 \text{ Hz}, 3\text{H}), 2.23 (s, 3\text{H}), 3.71 (s, 3\text{H}), 3.98 (q, J = 7.2 \text{ Hz}, 2\text{H}), 5.09 (s, 1\text{H}), 6.86 (d, J = 8.8 \text{ Hz}, 2\text{H}), 7.15 (d, J = 8.8 \text{ Hz}, 2\text{H}), 7.68 (s, 1\text{H}), 9.16 (s, 1\text{H}). \end{align*} \]

**Ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1c:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.10 (t, J = 7.2 \text{ Hz}, 3\text{H}), 2.24 (s, 3\text{H}), 3.97 (q, J = 7.2 \text{ Hz}, 2\text{H}), 5.14 (s, 1\text{H}), 7.24 (m, 2\text{H}), 7.39 (m, 2\text{H}), 7.78 (s, 1\text{H}), 9.25 (s, 1\text{H}). \end{align*} \]

**Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1d:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.08 (t, J = 7.2 \text{ Hz}, 3\text{H}), 2.24 (s, 3\text{H}), 3.97 (q, J = 7.2 \text{ Hz}, 2\text{H}), 5.11 (s, 1\text{H}), 7.15 (m, 2\text{H}), 7.25 (m, 2\text{H}), 7.75 (s, 1\text{H}), 9.23 (s, 1\text{H}). \end{align*} \]

**Ethyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1e:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.16 (t, J = 7.2 \text{ Hz}, 3\text{H}), 2.21 (s, 3\text{H}), 4.05 (q, J = 7.2 \text{ Hz}, 2\text{H}), 5.40 (s, 1\text{H}), 6.88 (m, 1\text{H}), 6.93 (m, 1\text{H}), 7.35 (m, 1\text{H}), 7.91 (s, 1\text{H}), 9.32 (s, 1\text{H}). \end{align*} \]

**Ethyl 4-(3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1f:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.11 (t, J = 7.2 \text{ Hz}, 3\text{H}), 2.24 (s, 3\text{H}), 3.75 (s, 3\text{H}), 3.98 (q, J = 7.2 \text{ Hz}, 2\text{H}), 5.11 (s, 1\text{H}), 6.76 (s, 1\text{H}), 6.80 (m, 2\text{H}), 7.24 (t, J = 8.0 \text{ Hz}, 1\text{H}), 7.73 (s, 1\text{H}), 9.19 (s, 1\text{H}). \end{align*} \]

**Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1g:**

\[ \begin{align*} \text{H NMR} & (400 \text{ MHz}, \text{DMSO-}d_6): \delta 1.11 (t, J = 6.8 \text{ Hz}, 3\text{H}), 2.24 (s, 3\text{H}), 3.75 (s, 3\text{H}), 3.98 (q, J = 6.8 \text{ Hz}, 2\text{H}), 5.11 (s, 1\text{H}), 6.76 (s, 1\text{H}), 6.80 (m, 2\text{H}), 7.24 (t, J = 8.0 \text{ Hz}, 1\text{H}), 7.73 (s, 1\text{H}), 9.19 (s, 1\text{H}). \end{align*} \]
Table II — Synthesis of dihydropyrimidinones and dihydrothiopyrimidinones

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<sup>a</sup> Reaction condition for dihydropyrimidinone: Benzaldehyde (0.01 mol) Ethylacetoacetate (0.01 mol), Urea (0.015 mol), Pivalic acid (1 mL), 125 °C, 2 h.

<sup>b</sup> Reaction condition for dihydrothiopyrimidinone: Benzaldehyde (0.01 mol) Ethylacetoacetate (0.01 mol), Thiourea (0.015 mol), Pivalic acid (1 mL), 135 °C, 3 h. Isolated yield.
Ethyl 6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1h: 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.13 (t, $J$ = 6.8 Hz, 3H), 2.25 (s, 3H), 3.62 (s, 3H), 3.71 (s, 6H), 4.01 (q, $J$ = 6.4 Hz, 2H), 5.11 (s, 1H), 6.52 (s, 2H), 7.73 (s, 1H), 9.20 (s, 1H).

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1i: 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.10 (t, $J$ = 7.2 Hz, 3H), 2.24 (s, 3H), 3.97 (q, $J$ = 7.2 Hz, 2H), 5.14 (s, 1H), 7.25 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.4 Hz, 2H), 7.78 (s, 1H), 9.20 (s, 1H).

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1j: 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.08 (t, $J$ = 7.2 Hz, 3H), 2.29 (s, 3H), 4.00 (q, $J$ = 7.2 Hz, 2H), 5.17 (s, 1H), 7.22 (m, 2H), 7.28 (m, 2H), 7.36 (m, 2H), 9.66 (s, 1H), 10.35 (s, 1H).

Ethyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1m: 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.08 (t, $J$ = 7.2 Hz, 3H), 2.28 (s, 3H), 3.72 (s, 3H), 3.99 (q, $J$ = 7.2 Hz, 2H), 5.10 (s, 1H), 6.88 (d, $J$ = 8.8 Hz, 2H), 7.11 (d, $J$ = 8.8 Hz, 2H), 9.61 (s, 1H), 10.30 (s, 1H).

Ethyl 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1n: 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.16 (t, $J$ = 7.2 Hz, 3H), 2.28 (s, 3H), 3.72 (s, 3H), 3.99 (q, $J$ = 7.2 Hz, 2H), 5.10 (s, 1H), 6.88 (d, $J$ = 8.8 Hz, 2H), 7.11 (d, $J$ = 8.8 Hz, 2H), 9.61 (s, 1H), 10.30 (s, 1H).

Figure 2 — Probable mechanism for pivalic acid assisted formation of dihydropyrimidinones
Acknowledgements

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References