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Pivalic acid assisted Biginelli reaction for synthesis of dihydropyrimidinones and dihydrothiopyrimidinones

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Herein is provided an alternate, simple, multigram scale, efficient route for Biginelli reaction for synthesis of dihydropyrimidinones using urea, ethylacetatoacetate, 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 dihydropyri midinone as core structural unit are isolated from marine sources and exhibit interesting pharmacological properties[1-5].

First prepared by Biginelli reaction, a multicomponent one-pot reaction involving urea, ethylacetoacetate and benzaldehyde, Dihydropyri midinone and its derivatives are extensively studied with diverse catalyst, solvents, unconventional methods like microwave, ultrasound, solid supported reagents, transition metal salts, metal oxides, *etc*[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[11-15]. However, a simple, fast, mild, low cost method is still encouraging[16-20].

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[21-25].

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 dihydrothio pyrimidinones[26-34]. (Scheme II, Table II)

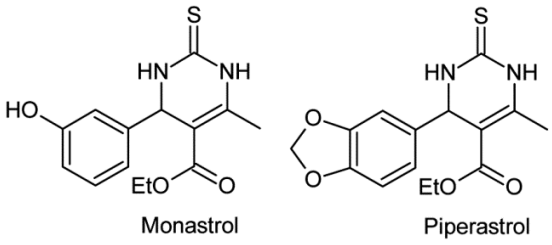
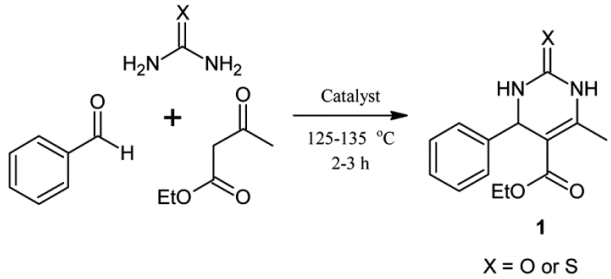


Figure 1 — Medicinally important compounds with dihydropyrimidinone framework

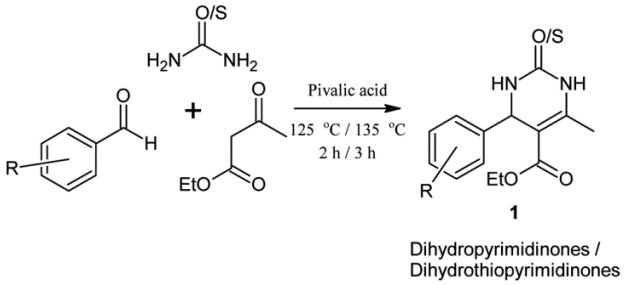


Scheme I — Optimisation study for dihydropyrimidinones and dihydrothiopyrimidinones with urea and thiourea respectively along with benzaldehyde and ethylacetoacetate

Table I — Optimisation study for dihydropyrimidinones and dihydrothiopyrimidinones

Entry	Pivalic acid	For Dihydropyrimidinones [a]		For Dihydrothiopyrimidinones [b]	
		Reaction conditions & Time	Yield (%)	Reaction conditions & Time	Yield (%)
1	1 mL	RT, 4 h	20	RT, 4 h	<2
2	1 mL	80 ºC, 2 h	55	125 ºC, 2 h	25
3	1 mL	125 ºC, 2 h	92	135 ºC, 3 h	73
4	2 mL	125 ºC, 2 h	91	135 ºC, 3 h	74
5	-	125 ºC, 4 h	48	135 ºC, 4 h	5

[a] Reaction condition for dihydropyrimidinone: Benzaldehyde (0.01 mol) Ethylacetoacetate (0.01 mol), Urea (0.015 mol).
[b] Reaction condition for dihydrothiopyrimidinone: Benzaldehyde (0.01 mol) Ethylacetoacetate (0.01 mol), Thiourea (0.015 mol).



Scheme II — Derivatives of dihydropyrimidinones and dihydrothiopyrimidinones

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 125ºC 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:H_2O (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 135ºC 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:H_2O (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-tetrahydro pyrimidine-5-carboxylate, 1a: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, J = 7.2 Hz, 3H), 2.24 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 5.14 (s, 1H), 7.24 (m, 3H), 7.33 (m, 2H), 7.75 (s, 1H), 9.20 (s, 1H).

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2, 3,4-tetrahydropyrimidine-5-carboxylate, 1b: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 3.71 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 5.09 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.68 (s, 1H), 9.16 (s, 1H).

Ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1c: ^{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), 7.24 (m, 2H), 7.39 (m, 2H), 7.78, (s, 1H), 9.25 (s, 1H).

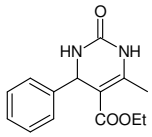
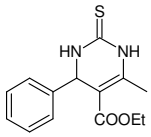
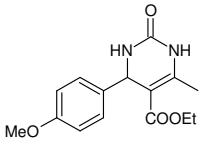
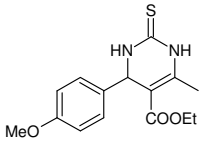
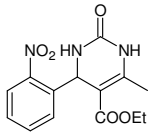
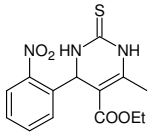
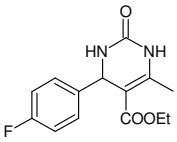
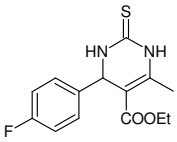
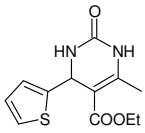
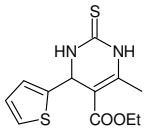
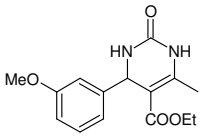
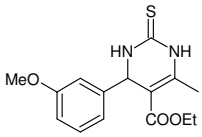
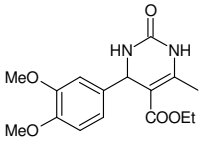
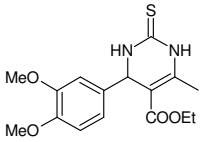
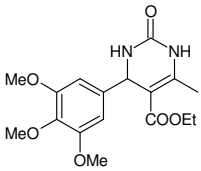
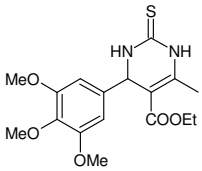
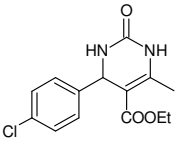
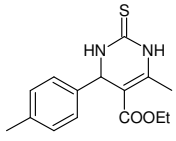
Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1d: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, J = 7.2 Hz, 3H), 2.24 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 5.14 (s, 1H), 7.15 (m, 2H), 7.25 (m, 2H), 7.75 (s, 1H), 9.23 (s, 1H).

Ethyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1e: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, J = 7.2 Hz, 3H), 2.21 (s, 3H), 4.05 (q, J = 7.2 Hz, 2H), 5.40 (s, 1H), 6.88 (m, 1H), 6.93 (m, 1H), 7.35 (m, 1H), 7.91 (s, 1H), 9.32 (s, 1H).

Ethyl 4-(3-methoxyphenyl)-6-methyl-2-oxo-1,2, 3,4-tetrahydropyrimidine-5-carboxylate, 1f: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, J = 7.2 Hz, 3H), 2.24 (s, 3H), 3.75 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 5.11 (s, 1H), 6.76 (s, 1H), 6.80 (m, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.73 (s, 1H), 9.19 (s, 1H).

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1g: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, J = 6.8

Table II — Synthesis of dihydropyrimidinones and dihydrothiopyrimidinones[a]

Entry	Product **1**	Yield (%)[b]	Entry	Product **1**	Yield (%)[b]
a		92	j		73
b		92	k		73
c		79	l		78
d		87	m		94
e		97	n		85
f		94	o		65
g		82	p		72
h		76	q		94
i		91	r		78

[a] Reaction condition for dihydropyrimidinone: Benzaldehyde (0.01 mol) Ethylacetoacetate (0.01 mol), Urea (0.015 mol), Pivalic acid (1 mL), 125 ºC, 2 h.
Reaction condition for dihydrothiopyrimidinone: Benzaldehyde (0.01 mol) Ethylacetoacetate (0.01 mol), Thiourea (0.015 mol), Pivalic acid (1 mL), 135 ºC, 3 h. [b] Isolated yield.

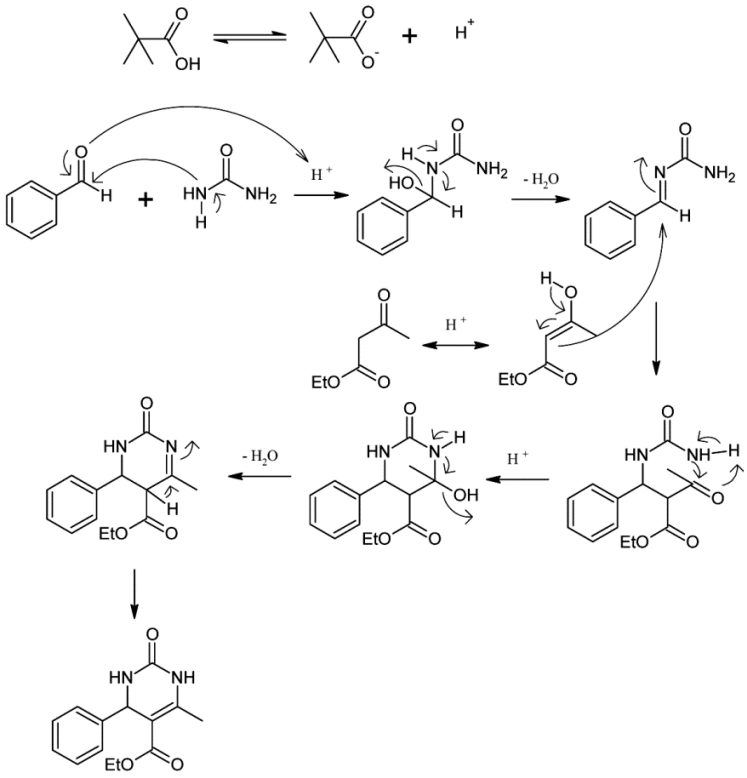


Figure 2 — Probable mechanism for pivalic acid assisted formation of dihydropyrimidinones

Hz, 3H), 2.24 (s, 3H), 3.71 (s, 6H), 4.00 (q, *J* = 6.8 Hz, 2H), 5.09 (s, 1H), 6.71 (s, 1H), 6.87 (m, 2H), 7.68 (s, 1H), 9.15 (s, 1H).

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 1.09 (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), 9.26 (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, 1H), 7.36 (m, 2H), 9.66 (s, 1H), 10.35 (s, 1H).

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1k: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (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-4-(2-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1l: ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 2H), 5.95 (s, 1H), 7.53 (m, 2H), 7.76 (m, 2H), 7.93 (m, 1H), 9.63 (s, 1H), 10.48 (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), 3.98 (q, *J* = 7.2 Hz, 2H), 5.16 (s, 1H), 7.18 (m, 4H), 9.66 (s, 1H), 10.38 (s, 1H).

Ethyl 6-methyl-4-(thiophen-2-yl)-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), 2.26 (s, 3H), 4.06 (q, *J* = 7.2 Hz, 2H), 5.42 (s, 1H), 6.89 (m, 1H), 6.97 (m, 1H), 7.40 (m, 1H), 9.79 (s, 1H), 10.49 (s, 1H).

Ethyl 4-(3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1o: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, *J* = 7.2 Hz, 3H), 2.28 (s, 3H), 3.72 (s, 3H), 4.01 (q, *J* = 7.2 Hz,

2H), 5.14 (s, 1H), 6.77 (m, 2H), 6.86 (m, 1H), 7.27 (m, 1H), 9.65 (s, 1H), 10.35 (s, 1H).

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1p: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, J = 7.2 Hz, 3H), 2.28 (s, 3H), 3.71 (s, 6H), 3.99 (q, J = 7.2 Hz, 2H), 5.11 (s, 1H), 6.69 (m, 1H), 6.82 (s, 1H), 6.90 (s, 1H), 9.61 (s, 1H), 10.31 (s, 1H).

Ethyl 6-methyl-2-thioxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1q: ^{1}H NMR (400 MHz, DMSO-d_6): δ. 1.14 (t, J = 6.8 Hz, 3H), 2.28 (s, 3H), 3.62 (s, 3H), 3.72 (s, 6H), 4.03 (q, J = 6.4 Hz, 2H), 5.14 (s, 1H), 6.50 (s, 2H), 9.63 (s, 1H), 10.35 (s, 1H).

Ethyl 6-methyl-4-(4-methylphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 1r: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 4.01 (q, J = 7.2 Hz, 2H), 5.12 (s, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 9.62 (s, 1H), 10.31 (s, 1H).

Conclusion

The pivalic acid has been used for the first time for an alternate, mild, one-pot, multicomponent, multigram scale, efficient method for Biginelli reaction for the synthesis of dihydropyrimidinones.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgements

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