

Note

Microwave enhanced, solvent free green protocol for the production of 3,4-dihydropyrimidine-2-(1*H*)-ones using $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ as a catalyst

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3,4-Dihydropyrimidine-2-(1*H*)-ones are synthesized *via* a multicomponent reaction of aldehyde, urea or thiourea and 1,3-dicarbonyl compounds using microwave irradiation catalyzed by 10 mol% $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 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-(1*H*)-ones, aldehyde, urea or thiourea, 1,3-dicarbonyl compounds, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, microwave, multicomponent reaction.

Use of multicomponent reactions (MCRs) is the need of present century and is primarily driven by pharmaceutical industries¹. Also present day concern is development of green processes because of pollution avoiding awareness and fast developments are there to develop solvent free processes². 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. $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ has been used to promote some major reactions of organic chemistry like Beckmann³, hydrogenation⁴, dehydration⁵ and synthesis of 1,4-dihydropyridines and their aromatization⁶. Herein we report the novel utility of this catalyst $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ in the production of 3,4-dihydropyrimidin-2-(1*H*)-ones and 3,4-dihydropyrimidin-2-(1*H*)-thiones. The synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) is of current interest as these molecules have shown promising biological properties and can be synthesized in a single step⁷⁻⁹, even though originally these compounds were produced about a century ago¹⁰. The pharmacological properties¹¹ namely are antihypertensive agents¹², anticarcinogenic agents¹³, calcium channel blockers¹⁴, α -1a-antagonists¹⁵, neuropeptide Y (NPY) anta-

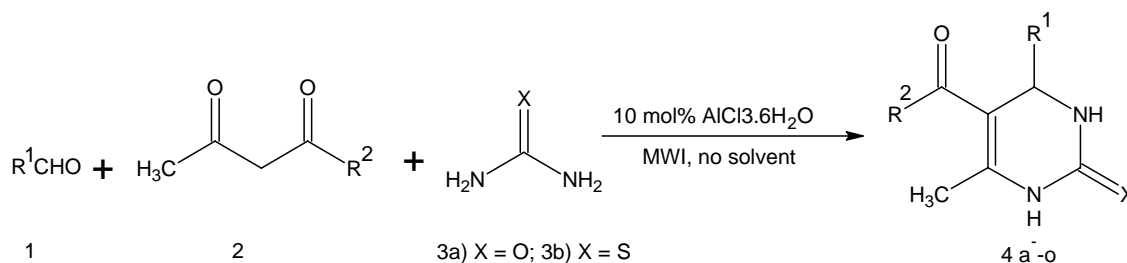
gonists¹⁶, anti-inflammatory¹⁷ and analgesic agents¹⁸. Additionally, DHPM unit is also present in the natural marine alkaloids batzelladine A and B which are the first low molecular weight natural products to inhibit the binding of HIV gp 120 to CD4 cells¹⁹, that may have potential application in the 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 activity²⁰.

As mentioned earlier, the use of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ being safe catalytic system is of current interest and in continuation to our interest in aluminum reagent^{3,4} 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-(1*H*)-ones (**Table I**, entries 13,14, 15). When urea was replaced with thiourea the corresponding 3,4-dihydropyrimidin-2-(1*H*)-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 $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 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 $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ is an efficient, one pot procedure for preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones in excellent yields. The reaction time is dramatically



Scheme I

Table I — AlCl₃.6H₂O mediated synthesis of 3,4-dihydropyrimidin-2-(1H)-ones under solvent free conditions

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

^aAll products were characterized by m.p. and spectral (IR, ¹H NMR) data.

^bReaction carried out under microwave irradiation in solvent free condition. ^cYields refers to pure isolated products.

^dValue in parenthesis indicates lit. m.p.

reduced to 1.5-3.0 min. It is non-hazardous as the use of low boiling solvents like acetonitrile is avoided. Also this solvent free approach is non-polluting and does not employ any toxic materials quantifying it as a green approach to Biginelli reaction. 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 AlCl₃.6H₂O 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 240C analyzer. ¹H 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 mmol), 1,3-dicarbonyl compound (2 mmol), urea (3 mmol) and AlCl₃.6H₂O (10 mole%) were placed in an Erlenmeyer flask and then irradiated in a microwave oven at 220 W for the required duration (Table I).

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, 1555 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 10.39 (s, 1H), 9.67 (s, 1H), 7.41 (d, J = 4.2 Hz, 1H), 7.00-6.85 (m, 2H), 5.39 (s, 1H), 4.06 (q, J = 6.8 Hz, 2H), 2.29 (s, 1H), 1.16 (t, J = 6.8 Hz, 3H). Anal. Found: C, 51.14; H, 4.89; N, 9.83. $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$ requires C, 51.02; H, 5.00; N, 9.93%.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, 4e: m.p. 201-02°C; IR (KBr): 3412, 3229, 1710, 1639 cm^{-1} ; ^1H NMR (DMSO- d_6): 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), 2.24 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). Anal. Found: C, 64.67; H, 6.13; N, 10.83. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ requires C, 64.62; H, 6.15; N, 10.77%.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 4f: m.p. 212-13°C; IR (KBr): 3420, 3242, 1708, 1645 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 9.20 (s, 1H), 7.76 (s, 1H), 7.40 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H) 5.16 (s, 1H), 3.95 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H). Anal. Found: C, 57.13; H, 5.09; N, 9.44. $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$ requires C, 57.05; H, 5.13; N, 9.50%.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one, 4g: m.p. 208-10°C; IR (KBr): 3415, 3236, 1715, 1675 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 9.28 (s, 1H), 8.26 (d, J = 8.7 Hz, 2H), 7.80 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H) 5.26 (s, 1H), 3.93 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7.0 Hz, 3H). Anal. Found: C, 55.14; H, 4.95; N, 13.69. $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_5$ requires C, 55.08; H, 4.92; N, 13.77%.

4-(3-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 4h: m.p. 192-93°C; IR (KBr): 3416, 3230, 1706, 1642 cm^{-1} ; ^1H NMR (DMSO- d_6): 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. $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$ 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- d_6): 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. $\text{C}_{14}\text{H}_{16}\text{N}_3\text{O}_4$ requires C, 60.87; H, 5.80; N, 10.14%.

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one, 4n: m.p. 190-91°C; IR (KBr): 3415, 3232, 1700, 1598 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 9.15 (s, 1H), 7.67 (s, 1H), 7.21 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H) 5.16 (s, 1H), 3.67 (s, 3H), 2.22 (s, 3H), 2.10 (s, 3H). Anal. Found: C, 64.77; H, 6.06; N, 10.65. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ requires C, 64.62; H, 6.15; N, 10.77%.

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