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Gallium(III) halides catalyzed, microwave enhanced, synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent free condition

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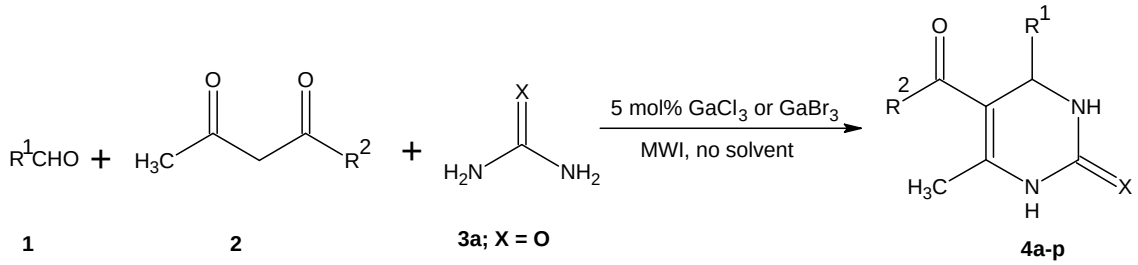
Gallium(III) halides catalyzed and microwave enhanced three component Biginelli reaction of aldehyde, 1,3-dicarbonyl compounds and urea or thiourea under solvent free conditions to afford 3,4-dihydropyrimidin-2-(1*H*)-ones in excellent yields is described. The present procedure for the production of dihydropyrimidinones describes the first ever catalytic activity of gallium(III) halides. This improved procedure is fairly simple, facile and environment friendly.

Keywords: Gallium(III) halides, 3,4-dihydropyrimidin-2-(1*H*)-ones, solvent less, microwave

Gallium, present in group IIIA of the periodic table along with indium, has ionization potential comparable with indium (Ga: FIP, 5.99 eV, E^o, Ga^{+3}/Ga = - 0.56 V; In: FIP, 5.79 eV, E^o, In^{+3}/In =0.345 V) which indicate that they should have similar chemical reactivities. Indium and its salts have been extensively explored in organic synthesis[1]. In contrast gallium and its salts have remained ignored and are now being investigated at a rapid pace. Applications of gallium(III) halides in organic synthesis[2] are developing quite fast to ensure that its utility matches that of indium. Gallium has been used to promote some major reactions like Reformatsky[3], Pechmann[4], Grignard[5] and simple allylation of indoles[6]. Herein is reported the novel utility of gallium(III) halides 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) are of current interest as these can be synthesized in a single step[7-9], even though originally these compounds were produced about a century ago[10]. These DHPMs and their derivatives are well known for their wide ranging pharmacological properties[11]. They find application as antihypertensive agents[12], anticarcinogenic agents[13], calcium channel blockers[14], α-1a-antagonists[15], neuropeptide Y (NPY) antagonists[16], anti-inflammatory[17] and analgesic agents[18]. 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[19], that may have potential application in the treatment of AIDS.

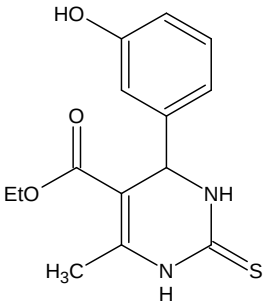
In continuation to the work[20,21] on microwave enhanced solvent free reactions, and use of gallium and its salt, it is desired to report gallium(III) halides catalyzed, one pot microwave enhanced three component coupling of aldehyde **1**, 1,3-dicarbonyl compounds **2** and urea **3a** or thiourea **3b** under solvent free conditions to produce 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) in excellent yields in few minutes time (**Scheme I**).

Of particular interest is the production of Monastrol (**Figure 1**) in a single step with high yield which is being developed as a lead compound for anti-cancer activity[22]. Under these conditions, reaction time was reduced dramatically and reaction completed within 1–1.5 min.



1 **2** **3a; X = O** **3b; X = S** **4a-p**

Scheme I



Monastrol

Figure 1

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 0.05 equivalent of $GaCl_3$ or $GaBr_3$ was found to be sufficient for these reactions and the use of less than 0.05 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. To be conclusive and for direct comparison, parallel reactions have also been investigated under conventional heating in solvent free conditions (**Table I**). The reaction proceeds smoothly and is completed in about 1.0 hr.

In conclusion, the present method employing gallium(III) halides is an efficient, one pot procedure for preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones in excellent yields. The reaction time is dramatically reduced to 1–1.5 min. It is non-hazardous as the use of low boiling solvents like acetonitrile is avoided. Also, this solvent free approach is nonpolluting 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 gallium(III) halides in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-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-(1*H*)-ones under microwave irradiation in solvent free condition

A mixture of aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea (3 mmol) and $GaCl_3$ or $GaBr_3$ (5 mol%) 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(1*H*)-one.

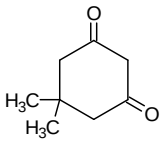
General experimental procedure for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in conventional heating in solvent free condition.

A mixture of aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea (3 mmol) and $GaCl_3$ or $GaBr_3$ (5 mol%) were stirred under heating at 90°C for the required duration (**Table I**). After completion of reaction (TLC), the mixture was cooled, water (10 mL) added and the mass stirred for 5 min. The solid thus obtained was filtered and purified by recrystallization from ethanol to afford 3,4-dihydropyrimidin-2-(1*H*)-ones.

Spectroscopic characterization data of selected compounds

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-pyrimidin-2(1*H*)-one, 4a: m.p. 201-02°C; IR (KBr): 3412, 3229, 1710, 1639 cm^{-1}; ^{1}H 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

Table I — Gallium(III) chloride mediated synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent free conditions

Entry	Product[a]	R^1	R^2	X	Reaction time (min)[b]		Yield (%)[b,c]		m.p. (°C)[d]
					A	B	A	B	
1	**4a**	C_6H_5	OEt	O	1	55	96	94	201-02 (202-03)(Ref.17)
2	**4b**	*p*-Cl-C_6H_4	OEt	O	1	55	95	95	212-13 (210-12)(Ref.17)
3	**4c**	*p*-NO_2-C_6H_4	OEt	O	1	55	96	92	208-10 (207-10)(Ref.17)
4	**4d**	*m*-Cl-C_6H_4	OEt	O	1	55	94	90	192-93
5	**4e**	*p*-MeO-C_6H_4	OEt	O	1.5	60	93	94	200-01 (199-01)(Ref.17)
6	**4f**	*m*-OH-C_6H_4	OEt	S	1.5	60	92	89	179-80
7	**4g**	$(CH_3)_2CH$	OEt	O	1.5	75	90	91	194-95 (194-95)(Ref.16)
8	**4h**	*n*-Bu	OEt	O	1.5	70	89	90	156-58 (156-58)(Ref.16)
9	**4i**	2-Furyl	OEt	O	1.5	65	88	87	204-05 (204-05)(Ref.17)
10	**4j**	C_6H_5	OEt	S	1.5	60	86	85	208-209 (208-10)(Ref.17)
11	**4k**	*p*-Cl-C_6H_4	OEt	S	1.5	70	85	86	192-194 (192-95)(Ref.17)
12	**4l**	2-Thienyl	OEt	S	1.5	75	83	81	214-216 (215-17)(Ref.17)
13	**4m**	C_6H_5	Me	O	1.5	70	92	90	210-11 (209-12)(Ref.17)
14	**4n**	*p*-CH_3O-C_6H_4	Me	O	1.5	75	93	91	190-91 (191-93)(Ref.16)
15	**4o**	*p*-NO_2-C_6H_4	Me	O	1.5	75	95	93	235-38 (235-38)(Ref.16)
16	**4p**	*p*-Cl-C_6H_5		O	2.5	65	93	91	>250

[a] All product were characterized by m.p. and spectral (IR, ^{1}H NMR) data.
[b] A: reaction carried out under microwave irradiation in solvent free condition. B: reaction carried out under thermal condition in solvent free condition
[c] Yields refers to pure isolated products.
[d] Value in parenthesis indicates lit. m.p.

(t, *J* = 7.2 Hz, 3H). Anal. Found: C, 64.67; H, 6.13; N, 10.83. $C_{14}H_{16}N_2O_3$ requires C, 64.62; H, 6.15; N, 10.77%.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4b: m.p. 212-13°C; IR (KBr): 3420, 3242, 1708, 1645 cm^{-1}; ^{1}H 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. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; N, 9.50%.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one, 4c: m.p. 208-10°C; IR (KBr): 3415, 3236, 1715, 1675 cm^{-1}; ^{1}H 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. $C_{14}H_{15}N_3O_5$ requires C, 55.08; H, 4.92; N, 13.77%.

4-(3-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4d: 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. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; N, 9.50%.

5-Ethoxycarbonyl-6-methyl-4-(isopropyl)-3, 4-dihydropyrimidin-2(1*H*)-one, 4g: 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. $C_{14}H_{16}N_3O_4$ requires C, 60.87; H, 5.80; N, 10.14%.

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3, 4-dihydropyrimidin-2(1*H*)-thione, 4l: 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. $C_{12}H_{14}N_2O_2S_2$ requires C, 51.02; H, 5.00; N, 9.93%.

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3, 4-dihydropyrimidin-2(1*H*)-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. $C_{14}H_{16}N_2O_3$ requires C, 64.62; H, 6.15; N, 10.77%.

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