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Calcium chloride catalyzed three component, one-pot condensation reaction: An efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

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$CaCl_2$ is an efficient, inexpensive and readily available catalyst for the three component, one-pot condensation reaction of an aldehyde, β-ketoester and urea in refluxing ethanol to afford the corresponding dihydropyrimidinones in high yield. This method provides an envirofriendly, easy workup and isolation process.

Keywords: Biginelli reaction, dihydropyrimidinones, calcium chloride, economical and ecofriendly

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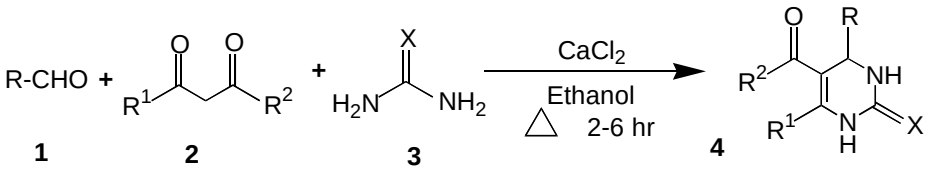
4-Aryldihydropyrimidinones and their derivatives are known to exhibit pharmacological activities as calcium channel blockers[1], antihypertensive agents[2], α-1a-antagonists[3] and neuropeptide Y (NPY) antagonists[4]. They are also known to exhibit a wide range of biological activities[5] such as antiviral, antitumor, antibacterial, and anti-inflammatory. Several marine alkaloids containing the dihydropyrimidine unit have shown interesting biological properties[6]. Most notably among them are batzelladine alkaloids, which were found to be potent HIV gp –120-CD4 inhibitors[7]. Therefore, the synthesis of dihydropyrimidinones gained much importance in organic synthesis. The simple and direct method reported by Biginelli in 1893, involves three component, one-pot condensation of a β-ketoester with an aldehyde and urea under strongly acidic conditions[8], suffers from low yields of products particularly in the case of substituted aromatic or aliphatic aldehydes[9]. Subsequently, multistep synthesis afforded high yields but lack of simplicity of original Biginelli one-pot protocol. Therefore, Biginelli reaction for the synthesis of dihydropyrimidinones has received renewed interest and several improved procedures have been reported such as conc. HCl[10], H_2SO_4[11], AcOH[12], $ZrCl_4$[13], $BiCl_3$[14], $InCl_3$[15], $InBr_3$[16], VCl_3[17], LiBr[18], $BF_3.OEt_2$[19], $ZnCl_2$[20], $FeCl_3.6H_2O$[21], $SnCl_2.2H_2O$-LiCl[22], $CuCl_2.2H_2O$/microwaves[23], $LaCl_3.7H_2O$[24], $CeCl_3.7H_2O$[25], NH_4Cl[26], $KHSO_4$[27], TFA[28], Amberlyst-15 or Nafron-H[29], KSF[30], CAN[31], *p*-TSA[32], $Bi(OTf)_3$[33], $Cu(OTf)_2$[34], $Ln(OTf)_3$[35], $LiClO_4$[36], Ionic liquids[37], $Mn(OAc)_3$[38], $Ag_3PW_{12}O_{40}$[39], Polyaniline-Bismoclite[40], Silica sulfuric acid[41], Boric acid[42], $Zn(OTf)_2$[43], $MgBr_2$[44], $CdCl_2$[45], soluble polymer supported liquid phase synthesis[46], $CdSO_4$[47], TMSCl/NaI[48], Polyphosphate ester (PPE)[49].

However, most of these methods required expensive reagents, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields and incompatibility with other functional groups. Thus, there is scope for further improvement towards the milder reaction conditions, high yields, and variation of the substitutents in all three components with commercially available reagents.

In recent years, the development of more economical and environmental friendly conversion processes is gaining interest in the chemical community. In continuation of our interest in developing novel methodologies[50] and synthesis[51], herein we report an efficient, practical, environmentally benign and high yielding method for the Biginelli three component, one-pot synthesis of dihydropyrimidinones using $CaCl_2$ as catalyst (**Scheme I**).

$CaCl_2$[52a] is inexpensive, commercially available reagent and recently shown as a very good catalyst to promote the aldol reaction of dimethyl silyl (DMS) enolates[52b]. In a typical experimental procedure a



Scheme I

solution of β-ketoester, aldehyde and urea in ethanol was heated under reflux in the presence of catalytic amount of $CaCl_2$ to give dihydropyrimidinones. The reaction mixture was then poured into crushed ice and the solid product separated was filtered. The crude product obtained was of high purity (90% by ^{1}H NMR).

To study the feasibility of this reaction, several examples were studied under similar conditions to synthesize the dihydropyrimidinones and the results are summarized in **Table I**. The important feature of this procedure is survival of a variety of functional groups such as nitro (**4g** and **4v**), halides (**4c** and **4t**), hydroxy (**4d**), methoxy (**4b, 4i** and **4j**) and conjugated C=C double bond (**4m**). Another aspect of this method, aliphatic aldehyde hexanal (**4p**) also reacted well with β-ketoester to give the dihydropyrimidinone in good yield. Such aldehydes normally show extremely poor yields in Biginelli reaction[9]. 4-Heteroaryl-3,4-dihydropyrimidin-2-(1*H*)-ones reported an excellent activity against the viruses of the trachoma and exhibits modest antibacterial activity[53]. Since 4-heteroaryl-3,4-dihydropyrimidin-2-(1*H*)-ones have significant activity, we have further extended the present method successfully with substituted pyridine derivative such as 2-chloro-5-methylpyridine-3-carboxaldehyde[51] (**4o**), which is key intermediate in the synthesis of several biologically active molecules. The obtained product **4o** was new and well characterized. Finally, usefulness of this methodology has also been extended with the thiourea in similar manner to provide the corresponding dihydropyrimidine-2(1*H*)-thiones **4q** and **4r** in high yields, which are important biologically active molecules. The mechanism of the Biginelli reaction may proceed through the imine intermediate formed from the aldehyde and urea, stabilized by the calcium ion, followed by the addition of the β-keto ester enolate and cyclodehydration to afford the dihydropyrimidine (**Scheme II)**. So, we proposed a mechanism similar to that of Kappe[54] for the calcium promoted Biginelli reaction (**Scheme II**).

In conclusion, we have developed a simple, efficient and general method for the synthesis of dihydropyrimidinones using the inexpensive, less toxic and commercially available catalyst. Moreover, the present method offered several advantages including high yields, shorter reaction times, simple work-up procedures and also has the ability to tolerate a wide variety of substituents in all three components which makes it a useful process for the synthesis of dihydropyrimidinones.

Experimental Section

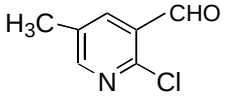
General. Melting points were obtained on a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 740 FT–IR spectrometer; ^{1}H NMR on a Gemini 200 MHz spectrometer in $CDCl_3$ with TMS as internal standard; and mass spectra on a VG Micro Mass 7070H.

Typical procedure. A solution of ethyl acetoacetate (1 g, 7.6 mmoles), anisaldehyde (1.05 g, 7.6 mmoles) and urea (0.55 g, 9.2 mmoles) in ethanol (20 mL) was refluxed in the presence of $CaCl_2$ (0.168 g, 20 mol%) for 2 hr (TLC). The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystalised from ethanol to afford 5-(ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one **4b**.

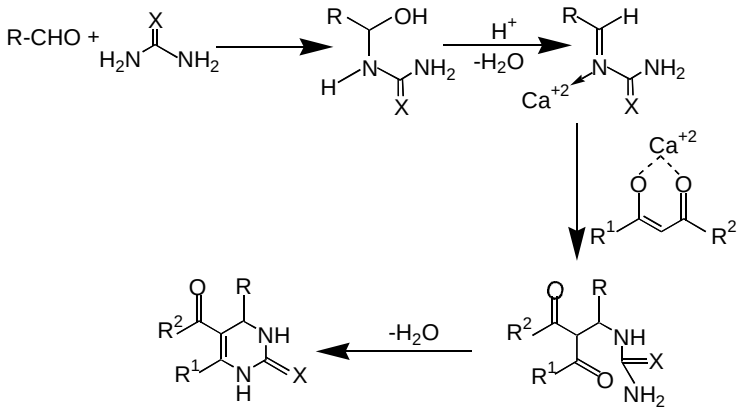
5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 4b: m.p. 199-202°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 9.17 (s, 1H), 7.68 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.88 (d, 2H, J = 8.5 Hz), 5.09 (s, 1H), 3.98 (q, 2H, J = 7.0 Hz), 3.71 (s, 3H), 2.24 (s, 3H), 1.10 (t, 3H); IR (KBr): 3241, 1700, 1637 cm^{-1}; Mass: m/z 290; Anal.Calcd for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.20; N, 9.66. Found: C, 61.77; H, 6.22; N, 9.56%.

5-(Ethoxycarbonyl)-4-(4-N,N-dimethylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 4f: m.p. 232-34°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 9.12 (s, 1H), 7.60 (s, 1H), 7.02 (d, 2H, J = 7.6 Hz), 6.80 (d, 2H, J = 7.6 Hz), 5.12 (d, 1H, J = 3.3 Hz), 4.05 (q, 2H, J = 7.4 Hz), 2.64 (s, 6H), 2.22 (s, 3H), 1.20 (t, 3H); IR (KBr): 3425, 3238, 3256, 2985, 1695, 1565, 1240, 790 cm^{-1}; Mass: m/z 303; Anal.Calcd for $C_{16}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.32; H, 6.96; N, 13.89%.

Table I — Synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones using $CaCl_2$

Product[a]	R	R^1	R^2	X	Time (hr)	Yield[b] (%)	m.p. (°C) Found	m.p. (°C) Reported
4a	C_6H_5	Me	OEt	O	2	94	200-201	202-04
4b	4-(OMe)-C_6H_4	Me	OEt	O	2	98	199-202	200-01
4c	4-Cl-C_6H_4	Me	OEt	O	5	88	201-211	213-15
4d	4-OH-C_6H_4	Me	OEt	O	5	92	198-201	199-200
4e	4-(Me)-C_6H_4	Me	OEt	O	4	96	169-71	172
4f	4-(NMe_2)-C_6H_4	Me	OEt	O	6	93	232-34	230-32
4g	4-(NO_2)-C_6H_4	Me	OEt	O	6	93	209-12	208-11
4h	3-(OPh)-C_6H_4	Me	OEt	O	4	96	192-94	194
4i	3,4-$(OCH_3)_2$-C_6H_3	Me	OEt	O	3	94	176-77	175-78
4j	3,4,5-$(OCH_3)_3$-C_6H_2	Me	OEt	O	4	92	179-81	180-82
4k	3,4-(OCH_2O)-C_6H_3	Me	OEt	O	3	90	187-88	188-89
4l	$C_{10}H_7$	Me	OEt	O	5	88	247-48	246-48
4m	C_6H_5-CH=CH	Me	OEt	O	4	98	229-32	232-35
4n	2-Furfuryl	Me	OEt	O	4	85	203-05	205
4o		Me	OEt	O	3	92	198	—
4p	C_5H_{11}	Me	OEt	O	4	86	161-62	163
4q	4-(OMe)-C_6H_4	Me	OEt	S	5	85	152-54	150-51
4r	4-(OH)-C_6H_4	Me	OEt	S	6	82	192-93	193-94
4s	C_6H_5	Me	OMe	O	2	94	210-12	209-12
4t	4-Cl-C_6H_4	Me	OMe	O	5	88	202-04	204-06
4u	4-(OMe)-C_6H_4	Me	OMe	O	2	98	190-92	192-94
4v	4-(NO_2)-C_6H_4	Me	OMe	O	6	93	233-35	235-37

[a]All the products were well characterized by its ^{1}H NMR, IR, Mass and compared with authentic compounds.
[b]Isolated and unoptimised yields and melting points are uncorrected.



Scheme II

5-(Ethoxycarbonyl)-4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 4j: m.p. 179-81°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 9.23 (s, 1H), 7.75 (s, 1H), 6.53 (s, 2H), 5.13 (s, 1H), 4.02 (q, 2H, *J* = 6.68 Hz), 3.72 (s, 9H), 2.25 (s, 3H), 1.13 (t, 3H, *J* = 7.0 Hz); IR (KBr): 3228, 3116, 2925, 2845, 1710, 1646, 1515 cm^{-1}; Mass: m/z 350, Anal.Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.28; N, 8.00. Found: C, 58.30; H, 6.23; N, 8.04%.

5-(Ethoxycarbonyl)-4-(3,4-methylenedioxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 4k: m.p. 187-88°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 9.16

(s, 1H), 7.52 (s, 1H), 6.81 (d, 1H, *J* = 7.6 Hz), 6.75 (s, 1H), 6.66 (d, 1H, *J* = 7.4 Hz), 5.95 (s, 2H), 5.50 (d, 1H, *J* = 3.6 Hz), 4.02 (q, 2H, *J* = 7.00 Hz), 2.26 (s, 3H), 1.12 (t, 3H); IR (KBr): 3358, 3236, 2954, 1710, 1645, 1495 cm^{-1}, Mass: m/z 304; Anal.Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.26; N, 9.21. Found: C, 59.18; H, 5.30; N, 9.16%.

5-(Ethoxycarbonyl)-4-(2-chloro-5-methylpyridine)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 4o: m.p. 198°C; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 9.2 (s, 1H), 8.05 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 5.6 (s, 1H), 3.98 (q, 2H), 2.4 (s, 3H), 2.25 (s, 3H), 1.10 (t, 3H); IR (KBr): 3365, 3238, 3126, 2985, 1711, 1665, 1239, 1090 cm^{-1}; Mass: m/z 309; Anal.Calcd for $C_{14}H_{16}ClN_3O_3$: C, 54.28; H, 5.17; N, 13.57. Found: C, 54.26; H, 5.14; N, 13.46%.

5-(Ethoxycarbonyl)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2 (1*H*)-thione 4r: m.p. 192-93°C; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 9.8 (brs, 1H), 9.15 (brs, 1H), 9.10 (brs, 1H), 7.00 (d, 2H, *J* = 9.12 Hz), 6.65 (d, 2H, *J* = 9.14 Hz), 5.10 (s, 1H), 4.00 (q, 2H, *J* = 7.5 Hz), 2.24 (s, 3H), 1.18 (t, 3H, *J* = 7.5 Hz); IR (KBr): 3448, 3190, 3044, 1706, 1650 cm^{-1}; Mass: m/z 292, Anal.Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.53; H, 5.47; N, 9.58. Found: C, 57.56; H, 5.52; N, 9.54%.

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