$CoCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$ Catalyzed Biginelli Reaction. One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

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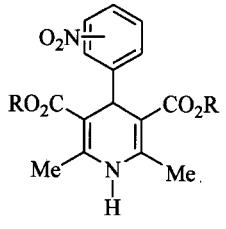
An efficient synthesis of 3,4-dihydropyrimidinones from aldehyde, β-keto ester and urea in ethanol using cobalt chloride hexahydrate or lanthanum chloride heptahydrate as a catalyst was described. Compared to the classical Biginelli reaction, this new method consistently has the advantage of good yields (56%—99%) as well as short reaction time (4—5 h).

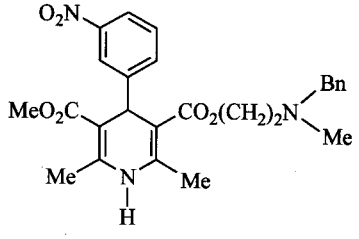
Keywords Biginelli reaction, dihydropyrimidine-2(1*H*)-ones, cobalt chloride hexahydrate, lanthanum chloride heptahydrate, one-pot process

Introduction

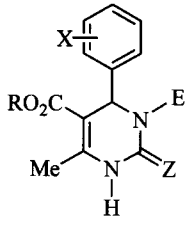
1,4-Dihydropyridines of the nifedipine type (*e.g.* **I**—**III**) are the most studied class of organic calcium channel medicine, which have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina.[1] In the past decade, interest has also been focused on aza-analogs! such as dihydropyrimidines of type **IV** (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[2] Several lead-compounds have been developed (*e.g.* SQ 32926 **V**) that are superior in potency and duration of antihypertensive activity to classical DHP drugs (Fig. 1).[2c-e] Dihydropyrimidine derivatives have exhibited important pharmacological properties, *e.g.* as the integral backbones of several calcium channel blockers, antihypertensive agents, α-1a-antagonists, and neuropeptide Y (NPY) antagonists.[2] Recently, several isolated marine alkaloids[3] with interesting biological activities also contain the dihydropyrimidinone-5-carboxylate core. Most notably among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[4] Thus, syntheses of these heterocyclic nucleus are of much current interest.



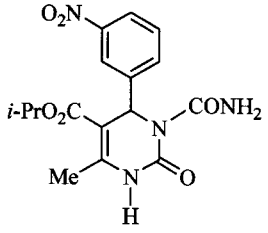
I nifedipine; R=Me, 2-NO_2
II nitrendipine; R=Et, 3-NO_2



III nicardipine



IV R = alkyl, Z = O, S
X = 2/3-NO_2, 2-CF_3
E = ester, acyl, amide



V SQ 32926

Fig. 1 Structures of nifedipine and aza-analogs.

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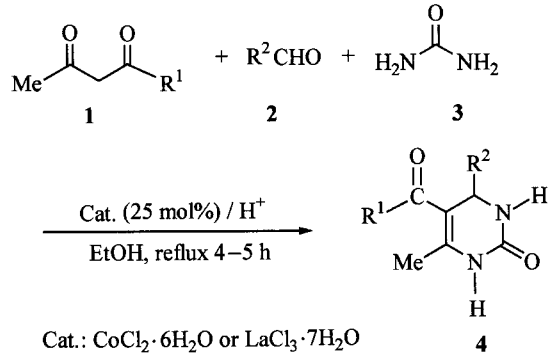
Whereas dihydropyridines of the nifedipine type (DHPs, *i.e.* **I**—**III**) are generally prepared by the well-known Hantzsch synthesis, aza-analogs of type **IV** (DHPMs) are readily available through the so-called Biginelli dihydropyrimidine synthesis (Scheme 1). In 1893, Italian chemist Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**) and urea (**3**).[5a] This reaction has been recently reviewed by Kappe.[5b] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this one-pot, three-component synthesis that precipitated on cooling of the reaction mixture, was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one (**4**). However, the one step protocol often provides only low to moderate yields of the desired target molecules **4** (20%—50%), in particular when substituted aromatic or aliphatic aldehydes are employed. Therefore, the search of milder and practical routes for the synthesis of dihydropyrimidin-2(1*H*)-ones by the Biginelli reaction continues to attract the attention of researchers. In recent years, several improved procedures for the preparation of DHPMs (Biginelli compounds) have been reported, either by modification of the classical one-pot Biginelli approach itself,[6-10] or by the development of novel, but more complex multistep strategies that give somewhat higher overall yields but lack the simplicity of the one-pot.[11] In addition, significant rate and yield enhancements were reported for Biginelli reactions carried out under microwave irradition,[12] and several combinatorial approaches towards DHPMs **IV** had been also advanced using solid phase or fluorous phase reaction conditions.[13] More recently, $LiClO_4$,[14] $Mn(OAc)_3 \cdot 2H_2O$,[15] Yb(III)-resin,[16] ultrasound-accelerated in the presence of ceric ammonium nitrateionic,[17] ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate or hexafluorophosphorate[18] as catalysts for the one-pot syntheses of dihydropyrimidinones were also reported.

In recent years, the use of lanthanide(III) and cobalt(II) compounds as catalysts or promoters in organic synthesis has attracted great interest from many chemists.[19] In a previous communication,[20] it was reported that the $LaCl_3 \cdot 7H_2O$ can catalyze Biginelli reaction availably. However, the use of $CoCl_2 \cdot 6H_2O$ as a catalyst in the synthesis of pyrimidinones has not been reported yet. Herein, a general and practical route for the Biginelli cyclocondensation reaction using cobalt chloride hexahydrate or lanthanum chloride heptahydrate as a mild catalyst was reported. 3,4-Dihydropyrimidin-2(1*H*)-one (**4a**) can be obtained from the reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of $CoCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$ in 96% and 95% yield, respectively. This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidin-2(1*H*)-ones. In the presence of the $CoCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$ (2.5 mmol), the reaction of β-keto ester **1** (10 mmol), aldehyde **2** (10 mmol), and urea **3** (15 mmol) was carried out in a one-pot condensation in refluxing EtOH, which has previously been employed successfully in the Biginelli condensation as solvent. After the reaction was completed, the dihydropyrimidinones (**4a**—**4t**) precipitated from the reaction mixture. Meanwhile, even for aliphatic aldehydes (*i.e.* butyraldehyde and *iso*-butyraldehyde) which normally show extremely poor yields in the Biginelli reaction,[21] the corresponding dihydropyrimidin-2(1*H*)-ones (**4l**) and (**4m**) could be obtained in moderate yields (Table 1). In addition, the reactivity of aldehydes, 2,4-diketone and urea in the presence of $CoCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$ was examined. Thus, the Biginelli reactions of aromatic aldehydes, 2,4-pentanedione and urea at reflux for 4—5 h afford 5-acetyl-6-methyl-4-aromatic-3,4-dihydropyrimidin-2(1*H*)-one in 86%—98% yields. Under these conditions, the yields were significantly raised (56%—99%), and the reaction time was shortened from 18 h to 4—5 h.

Scheme 1



Recently, the mechanism of the Biginelli reaction was reinvestigated in detail by Kappe.[23] He proposed and established that the first step in this reaction, the acid-catalyzed formation of acyl imine intermediate by reaction of the aldehyde with urea, is the rate-limiting step. Interception of the iminium ion by ethyl acetoacetate produces

an open-chain ureide **7**, which subsequently cyclizes to the intermediate **8**, then elimination of water leads to the formation of dihydropyrimidinones **4**. The intermediate **8** was also isolated and characterized with ^{1}H NMR and X-ray diffraction analysis by Qian *et al*.[10b] In the current new reaction conditions, the cobalt or lanthanum ion may complex to the nitrogen of the imine to give intermediate **6**, thus activating the C = N bond toward nucleophile. So a mechanism for the Co(II) and La(III) promoted Biginelli reaction was proposed in Scheme 2.

Scheme 2

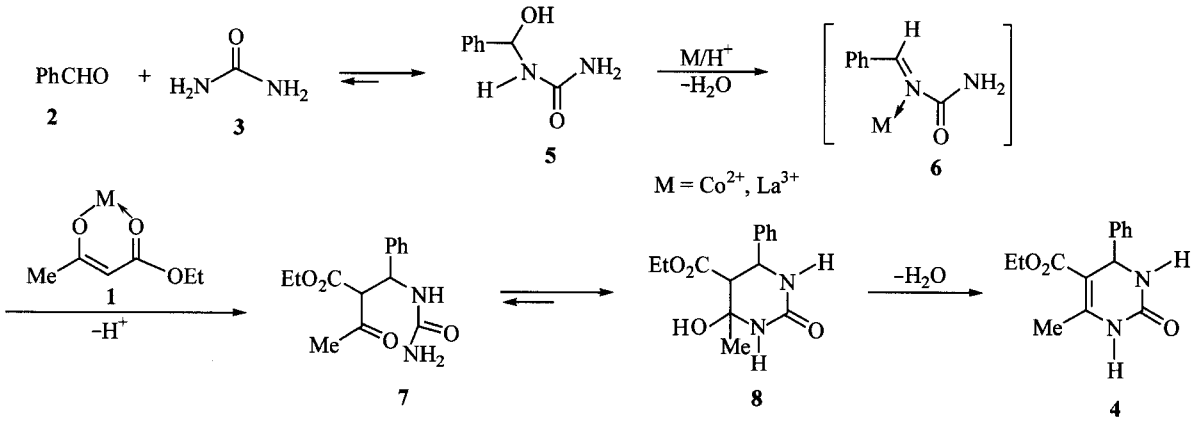


Table 1 Cobalt(II) and lanthanum(III) catalyzed synthesis of dihydropyrimidinones

DHPM	R^1	R^2	Yield (%)[a]		
			A[b]	B[c]	C[d]
4a	OEt	C_6H_5	96	95	78
4b	OEt	4-$CH_3OC_6H_4$	99	93	61
4c	OEt	3,4-$(OCH_2O)C_6H_3$	86	91	49
4d	OEt	4-OHC_6H_4	98	89	67
4e	OEt	4-$NO_2C_6H_4$	96	80	58
4f	OEt	4-ClC_6H_4	98	92	56
4g	OEt	3-ClC_6H_4	86	87	56
4h	OEt	3-BrC_6H_4	92	97	58
4i	OEt	2-HOC_6H_4	66	76	19
4j	OEt	Furyl-	67	67	36
4k	OEt	2,4-$(Cl)_2C_6H_3$	91	93	69
4l	OEt	$CH_3CH_2CH_2$	69	60	15
4m	OEt	$(CH_3)_2CH$	59	56	10
4n	OEt	4-OH-3-$CH_3OC_6H_3$	86	92	43
4o	OEt	4-$NMe_2C_6H_4$	81	78	
4p	Me	C_6H_5	98	95	
4q	Me	4-$CH_3OC_6H_4$	96	91	
4r	Me	4-ClC_6H_4	93	96	
4s	Me	3-ClC_6H_4	90	86	
4t	Me	3-BrC_6H_4	98	92	
4u	Me	2,4-$(Cl)_2C_6H_3$	89	93	

[a] Isolated yield. [b] Method A: new reaction conditions (cat. $CoCl_2 \cdot 6H_2O$/HCl in EtOH, reflux 4 h). [c] Method B: new reaction conditions (cat. $LaCl_3 \cdot 7H_2O$/HCl in EtOH, reflux 5 h). [d] Method C: classical Biginelli conditions[6,20,22] (cat. HCl in EtOH, reflux 18 h).

In summary, it has been developed a simple and efficient modification for the direct preparation of substituted dihydropyrimidinones from readily available starting materials. By using $CoCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$ as a catalyst, the yields of the one-pot Biginelli reaction can be increased from 20%—50% to 56%—99%, while the reaction time was shortened from 18 h to 4—5 h. This improved modification of Biginelli reaction is a sim-

ple, high-yielding, time-saving, and environmentally friendly process. Therefore, this is an important alternative to the synthesis of 3,4-dihydropyrimidinones.

Experimental

Melting points were unicorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on an varian INOVA-400 NMR spectrometer using TMS as internal standard. Elemental analyses and IR spectra were measured on a Perkin-Elmer 2400 microanalyser and a Bruck E-QUINOX55 spectrophotometer as KBr pellets, respectively. Mass spectra were determined on an HP-5800A mass spectrometer.

General procedure for the preparation of 3,4-*dihydropyrimidinones using* $CoCl_2 \cdot 6H_2O$ *or* $LaCl_3 \cdot 7H_2O$ *as a catalyst*

A solution of β-keto ester (**1**) (10 mmol), the appropriate aldehyde (**2**) (10 mmol), urea (**3**) (15 mmol), catalyst ($CoCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$, 2.5 mmol) and conc. HCl (1—2 drops) in EtOH (20 mL) was heated under reflux for 4—5 h. After cooling, the reaction mixture was poured onto 100 g of crushed ice. Stirring was continued for several miniutes. The solid products were filtered, washed with cold water (2 × 50 mL) and a mixture (1:1) of ethanol-water (3 × 20 mL), dried and recrystallised from hot ethanol.

5-*Ethoxycarbonyl*-6-*methyl*-4-*phenyl*-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4a**) M.p. 202—203 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.17 (s, 1H), 7.72 (s, 1 H), 7.21—7.32 (m, 5H), 5.14 (s, 1H), 3.98 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 152.2, 148.4, 144.9, 128.4, 127.3, 126.3, 99.3, 59.2, 54.0, 17.8, 14.1; IR (KBr) ν: 3414, 3230, 3109, 2936, 1702, 1649, 1599 cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_3$: C 64.62, H 6.15, N 10.77; found C 64.65, H 6.20, N 10.86.

5-*Ethoxycarbonyl*-6-*methyl*-4-(4-*methoxyphenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4b**) M.p. 201—202 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.14 (s, 1H), 7.66 (s, 1 H), 7.14 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.08 (d, J = 2.8 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.71 (s, 3H), 2.23 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 158.4, 152.2, 148.0, 137.1, 127.4, 113.7, 99.6, 59.1, 55.0, 53.3, 17.7, 14.1; IR (KBr) ν: 3415, 3241, 3114, 2954, 1708, 1646, 1512 cm^{-1}. Anal. calcd for $C_{15}H_{18}N_2O_4$: C 62.07, H 6.21, N 9.66; found C 62.18, H 6.26, N 9.86.

5-*Ethoxycarbonyl*-6-*methyl*-4-(3,4-*methylenedioxyphenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4c**) M.p. 188—189 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.16 (s, 1H), 7.66 (s, 1 H), 6.83 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.96 (s, 2H), 5.05 (d, J = 3.2 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.3, 152.0, 148.2, 147.2, 146.3, 138.8, 119.3, 107.9, 106.6, 100.9, 99.3, 59.1, 53.6, 17.7, 14.1; IR (KBr) ν: 3414, 3233, 3107, 2965, 1696, 1638, 1495 cm^{-1}. Anal. calcd for $C_{15}H_{16}N_2O_5$: C 59.21, H 5.26, N 9.21; found C 59.37, H 5.42, N 9.36.

5-*Ethoxycarbonyl*-6-*methyl*-4-(4-*hydroxyphenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4d**) M.p. 226—228 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.32 (s, 1H), 9.11 (s, 1H), 7.61 (s, 1 H), 7.02 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.04 (d, J = 3.2 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 156.6, 152.2, 147.8, 135.5, 127.4, 115.0, 99.8, 59.1, 53.5, 17.8, 14.1; IR (KBr) ν: 3417, 3241, 3120, 2984, 1687, 1649, 1512 cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_4$: C 60.87, H 5.80, N 10.14; found C 61.12, H 5.74, N 10.32.

5-*Ethoxycarbonyl*-6-*methyl*-4-(4-*nitrophenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4e**) M.p. 208—209 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.32 (s, 1H), 8.28 (d, J = 8.4 Hz, 2H), 7.89 (s, 1 H), 7.63 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 3.2 Hz, 1H), 3.94 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.3, 152.2, 152.1, 149.6, 146.9, 127.9, 124.0, 98.5, 59.7, 53.9, 18.0, 14.2; IR (KBr) ν: 3416, 3237, 3085, 2941, 1728, 1694, 1588, 1509 cm^{-1}. Anal. calcd for $C_{14}H_{15}N_3O_5$: C 55.08, H 4.92, N 13.77; found C 55.34, H 4.80, N 13.92.

5-*Ethoxycarbonyl*-6-*methyl*-4-(4-*chlorophenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4f**) M.p. 215—216 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.23 (s, 1H), 7.75 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 5.14 (d, J = 2.8 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.2, 151.9, 148.7,

143.8, 131.8, 128.4, 128.2, 98.8, 59.3, 53.4, 17.8, 14.1; IR (KBr) ν: 3419, 3246, 3112, 2980, 1708, 1646, 1487 cm^{-1}. Anal. calcd for $C_{14}H_{15}ClN_2O_3$: C 57.05, H 5.13, N 9.50; found C 57.12, H 5.20, N 9.46.

5-Ethoxycarbonyl-6-methyl-4-(3-chlorophenyl)-3, 4-dihydropyrimidin-2(1H)-one (**4g**) M.p. 192—193 ℃; ^1H NMR (CD_3COCD_3) δ: 8.31 (s, 1H), 7.26—7.37 (m, 4H), 6.93 (s, 1H), 5.37 (d, J = 3.2 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3COCD_3) δ: 166.1, 152.6, 149.1, 148.3, 134.5, 131.1, 128.2, 127.5, 125.9, 100.8, 60.2, 55.6, 18.4, 14.5; IR (KBr) ν: 3416, 3224, 3098, 2980, 2926, 1704, 1651, 1593 cm^{-1}; MS (70 eV) m/z (%): 294 (M^+, 5.63), 265 (37.47), 221 (24.01), 183 (100.00), 155 (39.33), 137 (33.51). Anal. calcd for $C_{14}H_{15}ClN_2O_3$: C 57.05, H 5.13, N 9.50; found C 57.27, H 4.90, N 9.44.

5-Ethoxycarbonyl-6-methyl-4-(3-bromophenyl)-3, 4-dihydropyrimidin-2(1H)-one (**4h**) M.p. 185—186 ℃; ^1H NMR (DMSO-d_6) δ: 9.26 (s, 1H), 7.78 (s, 1H), 7.22—7.45 (m, 4H), 5.14 (d, J = 3.2 Hz, 1H), 3.95 (q, J = 7.2 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.2, 151.9, 148.9, 147.5, 130.8, 130.2, 129.2, 125.3, 121.5, 98.6, 59.3, 53.6, 17.8, 14.1; IR (KBr) ν: 3416, 3228, 3113, 2976, 2932, 1705, 1654, 1613, 1589 cm^{-1}; MS (70 eV) m/z (%): 339 (M^+ + H, 22.23), 341 (M^+ + 2 + H, 20.48), 309 (20.70), 311 (19.88), 265 (13.96), 267 (11.73), 183 (100.00), 155 (30.64), 137 (21.34). Anal. calcd for $C_{14}H_{15}BrN_2O_3$: C 49.55, H 4.42, N 8.26; found C 49.60, H 4.40, N 8.15.

5-Ethoxycarbonyl-6-methyl-4-(2-hydroxyphenyl)-3, 4-dihydropyrimidin-2(1H)-one (**4i**) M.p. 201—203 ℃; ^1H NMR (DMSO-d_6) δ: 9.33 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.87 (s, 1 H), 7.49 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 3.2 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.1, 152.0, 151.8, 149.4, 146.7, 127.7, 123.8, 98.2, 59.4, 53.7, 17.9, 14.1; IR (KBr) ν: 3414, 3236, 3119, 2984, 1720, 1702, 1644, 1521 cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_4$: C 60.87, H 5.80, N 10.14; found C 60.72, H 6.01, N 10.25.

5-Ethoxycarbonyl-6-methyl-4-(4-furyl)-3, 4-dihydropyrimidin-2(1H)-one (**4j**) M.p. 202—204 ℃; ^1H NMR (DMSO-d_6) δ: 9.22 (s, 1H), 7.74 (s, 1H), 7.53 (s, 1H), 6.33 (d, J = 2.8 Hz, 1H), 6.07 (d, J = 2.8 Hz, 1H), 5.20 (d, J = 3.6 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 2.22 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.0, 155.9, 152.4, 149.3, 142.1, 110.3, 105.3, 96.8, 59.2, 47.7, 17.7, 14.1; IR (KBr) ν: 3413, 3239, 3119, 2984, 1702, 1644, 1457 cm^{-1}. Anal. calcd for $C_{12}H_{14}N_2O_4$: C 62.61, H 6.09, N 12.17; found C 62.84, H 6.02, N 12.32.

5-Ethoxycarbonyl-6-methyl-4-(2, 4-dichlorophenyl)-3, 4-dihydropyrimidin-2(1H)-one (**4k**) M.p. 249—250 ℃; ^1H NMR (DMSO-d_6) δ: 9.33 (s, 1H), 7.77 (s, 1H), 7.31—7.57 (m, 3H), 5.59 (d, J = 2.8 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 164.7, 151.0, 149.5, 140.9, 132.6, 132.5, 130.2, 128.6, 127.9, 97.4, 59.0, 51.1, 17.6, 13.8; IR (KBr) ν: 3415, 3219, 3104, 2969, 1699, 1641 cm^{-1}; MS (70 eV) m/z (%): 328 (M^+, 6.69), 330 (M^+ + 2, 4.10), 299 (47.18), 293 (68.72), 255 (40.00), 183 (100.00), 155 (32.82), 137 (25.64); Anal. calcd for $C_{14}H_{14}Cl_2N_2O_3$: C 51.06, H 4.26, N 8.51; found C 51.32, H 4.43, N 8.24.

5-Ethoxycarbonyl-6-methyl-4-(n-propyl)-3, 4-dihydropyrimidin-2(1H)-one (**4l**) M.p. 178—180 ℃; ^1H NMR ($CDCl_3$) δ: 8.55 (s, 1H), 6.30 (s, 1H), 4.31 (s, 1 H), 4.15 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.40—1.59 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 165.9, 154.9, 146.8, 101.5, 59.8, 51.2, 39.1, 18.4, 17.5, 14.3, 13.7; IR (KBr) ν: 3414, 3247, 3119, 1709, 1676, 1646 cm^{-1}. Anal. calcd for $C_{11}H_{18}N_2O_3$: C 58.41; H 7.96, N 12.39; found C 58.70, H 8.02, N 12.20.

5-Ethoxycarbonyl-6-methyl-4-(iso-propyl)-3, 4-dihydropyrimidin-2(1H)-one (**4m**) M.p. 197—198 ℃; ^1H NMR ($CDCl_3$) δ: 8.61 (s, 1H), 6.31 (s, 1H), 4.23 (s, 1 H), 4.16 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.85 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 166.2, 155.3, 147.1, 100.2, 59.8, 56.8, 34.5, 18.4, 15.6, 14.3; IR (KBr) ν: 3413, 3237, 3106, 1700, 1646 cm^{-1}. Anal. calcd for $C_{11}H_{18}N_2O_3$: C 58.41, H 7.96, N 12.39;

found C 58.48, H 7.72, N 12.18.

5-*Ethoxycarbonyl*-6-*methyl*-4-(4-*hydroxy*-3-*methoxyphenyl*)-3, 4-*dihydropyrimidin*-2(1*H*)-*one* (**4n**) M.p. 231—232 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.15 (s, 1H), 8.95 (s, 1H), 7.66 (s, 1H), 6.80 (s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 8.4 Hz, 1H), 5.05 (d, J = 2.8 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 2.22 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.3, 152.1, 147.8, 145.6, 135.8, 118.1, 115.1, 110.7, 99.4, 59.0, 55.4, 53.4, 17.6, 14.0; IR (KBr) ν: 3536, 3243, 3116, 2971, 2934, 1700, 1644, 1515 cm^{-1}. Anal. calcd for $C_{15}H_{18}N_2O_5$: C 58.82, H 5.88, N 9.15; found C 58.47, H 6.01, N 9.36.

5-*Ethoxycarbonyl*-6-*methyl*-4-(4-*dimethylaminophenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4o**) M.p. 256—257 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.07 (s, 1H), 7.57 (s, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 5.02 (d, J = 3.2 Hz, 1H), 3.96 (q, J = 7.2 Hz, 2H), 2.83 (s, 6H), 2.22 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.5, 152.3, 149.7, 147.5, 132.6, 126.9, 112.2, 99.9, 59.1, 53.3, 17.7, 14.1; IR (KBr) ν: 3420, 3245, 3117, 2976, 1704, 1647, 1527 cm^{-1}. Anal. calcd for $C_{16}H_{21}N_3O_3$: C 63.37, H 6.93, N 13.86; found C 63.55, H 6.80, N 13.72.

5-*Acetyl*-6-*methyl*-4-*phenyl*-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4p**) M.p. 237—238 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.17 (s, 1H), 7.82 (s, 1H), 7.23—7.34 (m, 5H), 5.26 (d, J = 3.2 Hz, 1H), 2.29 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 194.2, 152.0, 147.9, 144.2, 128.4, 127.2, 126.3, 109.5, 53.7, 30.2, 18.8; IR (KBr) ν: 3416, 3260, 3126, 2925, 1706, 1675, 1605 cm^{-1}. Anal. calcd for $C_{13}H_{14}N_2O_2$: C 67.83, H 6.09, N 12.17; found C 67.98, H 6.29, N 12.01.

5-*Acetyl*-6-*methyl*-4-(4-*methoxyphenyl*)-3, 4-*dihydropyrimidin*-2(1*H*)-*one* (**4q**) M.p. 183—184 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.14 (s, 1H), 7.75 (s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.19 (d, J = 3.2 Hz, 1H), 3.71 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 194.4, 158.5, 152.1, 147.8, 136.4, 127.6, 113.9, 109.6, 55.1, 53.3, 30.2, 18.8; IR (KBr) ν: 3414, 3232, 3122, 2951, 1702, 1593, 1509 cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_3$: C 64.62, H 6.15, N 10.77; found C 64.80, H 6.14, N 10.98.

5-*Acetyl*-6-*methyl*-4-(4-*chlorophenyl*)-3, 4-*dihydropyrimidin*-2(1*H*)-*one* (**4r**) M.p. 226—227 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.22 (s, 1H), 7.85 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.25 (d, J = 3.2 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 194.2, 152.1, 148.5, 143.2, 131.9, 128.5, 128.4, 109.6, 53.1, 30.4, 19.0; IR (KBr) ν: 3414, 3288, 3116, 2928, 1701, 1618, 1466 cm^{-1}. Anal. calcd for $C_{13}H_{13}ClN_2O_2$: C 58.98, H 4.91, N 10.59; found C 59.12, H 5.22, N 10.76.

5-*Acetyl*-6-*methyl*-4-(3-*chlorophenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4s**) M.p. 283 ℃ (dec); ^{1}H NMR (DMSO-d_6) δ: 9.24 (s, 1H), 7.87 (s, 1H), 7.17—7.37 (m, 4H), 5.25 (d, J = 3.2 Hz, 1H), 2.29 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 194.1, 152.1, 148.7, 146.6, 133.0, 130.5, 127.3, 126.3, 124.9, 109.4, 53.2, 30.5, 19.0; IR (KBr) ν: 3415, 3272, 3118, 2917, 1705, 1614, 1470 cm^{-1}. Anal. calcd for $C_{13}H_{13}ClN_2O_2$: C 58.98, H 4.91, N 10.59; found C 59.23, H 5.08, N 10.82.

5-*Acetyl*-6-*methyl*-4-(3-*bromophenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4t**) M.p. 289—290 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.26 (s, 1H), 7.88 (s, 1H), 7.22—7.46 (m, 4H), 5.26 (d, J = 3.2 Hz, 1H), 2.30 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 194.0, 151.9, 148.6, 146.8, 130.7, 130.1, 129.1, 125.2, 121.6, 109.3, 53.1, 30.4, 18.9; IR (KBr) ν: 3415, 3281, 3115, 2915, 1703, 1614, 1469 cm^{-1}. Anal. calcd for $C_{13}H_{13}BrN_2O_2$: C 50.49, H 4.21, N 9.06; found C 50.72, H 4.43, N 9.29.

5-*Acetyl*-6-*methyl*-4-(2,4-*dichlorophenyl*)-3,4-*dihydropyrimidin*-2(1*H*)-*one* (**4u**) M.p. 226—228 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.32 (s, 1H), 7.80 (s, 1H), 7.27—7.60 (m, 4H), 5.62 (s, 1H), 2.34 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 193.7, 151.3, 148.9, 140.0, 132.7, 132.6, 129.8, 128.9, 127.9, 108.3, 51.1, 30.2, 18.8; IR (KBr) ν: 3414, 3280, 3124, 2963, 1705, 1664, 1616 cm^{-1}. Anal. calcd for $C_{13}H_{12}Cl_2N_2O_2$: C 52.17, H 4.01, N 9.36; found C 52.40, H 4.13, N 9.25.

References

1 Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv. Drug Res.* **1987**, *16*, 309.

2 (a) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Ham-

aguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satah, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399.
(b) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629.
(c) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'eilly, B. C. *J. Med. Chem.* **1991**, *34*, 806.
(d) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'eilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254.
(e) Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289.
(f) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.

3 Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828 and references therein.

4 (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182.
(b) Rama Rao, A. V.; Gujar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369.
(c) Snider, B.B.; Chen, J.; Patil, A. D.; Freyer, A. *Tetrahedron Lett.* **1996**, *37*, 6977.

5 (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(b) For a review of the Biginelli reaction, see Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

6 Hu, E. H.; Sidler, D. R.; Dolling, Ulf-H. *J. Org. Chem.* **1998**, *63*, 3454.

7 Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.

8 Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465.

9 Singh, K.; Singh, J.; Deb, P. K. Singh, H. *Tetrahedron* **1999**, *55*, 12873.

10 (a) Lu, J.; Ma, H. *Synlett* **2000**, 63.
(b) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
(c) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
(d) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, 863.
(e) Yadav, J. S.; SubbaReddy, B. V.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341.

11 (a) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185.
(b) Atwal, K. S.; O' Reilley, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189.
(c) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898.
(d) Shutalev, A. D.; Kuksa, V. A. *Khim. Geterotsikl. Soedin* **1997**, 105.
(e) Shutalev, A. D.; Kishko, E. A.; Sivova, N.; Kuznetsov, A. Y. *Molecules* **1998**, *3*, 100.

12 (a) Gupta, R.; Gupta, A. K.; Paul, S.; Kachroo, P. L. *Indian J. Chem., Sect. B.* **1995**, *34*, 151.
(b) Stefani, H. A.; Gatti, P. M. *Synth. Commun.* **2000**, *30*, 2165.
(c) Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799.

13 (a) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819.
(b) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823.
(c) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917.

14 Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341.

15 Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873.

16 Dondoni, A.; Massi, A. *Tetrahedron Lett.* **2001**, *42*, 7975.

17 Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1939.

18 Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 5917.

19 (a) Imamoto, T. *Lanthanides in Organic Synthesis*, Academic Press, New York, **1994**.
(b) Kobayashi, S. *Synlett* **1994**, 689.
(c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

20 Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075.

21 Eynde, J. J. V.; Audiart, N.; Canonne, V.; Michel, S.; Haverbeke, Y. V.; Kapple, C. O. *Heterocycles* **1997**, *45*, 1967.

22 (a) Folkers, K.; Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 3751.
(b) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3361.
(c) Eynde, J. J. V.; Audiart, N.; Canonne, V.; Michel, S.; Y. Haverbeke, V.; Kapple, C. O. *Heterocycles* **1997**, *45*, 1967.
(d) Singh, K.; Singh, J.; Deb, P. K.; Singh, H. *Tetrahedron* **1999**, *55*, 12873.

23 Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.

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