A Rapid and Efficient Biginelli Reaction Catalyzed by Zinc Triflate

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An efficient and practical procedure for the synthesis of dihydropyrimidinones from aldehydes, 1,3-dicarbonyl compounds and urea under solvent-free reaction condition using zinc triflate as a catalyst is described. In comparison with the classical Biginelli reaction, the yields for this new procedure increased from 20%—50% to 75%—98% while the reaction time was significantly shortened from 18 h to 20 min.

Keywords Biginelli reaction, zinc triflate, solvent-free, dihydropyrimidinone

Introduction

In the past decade, dihydropyrimidinone derivatives have attracted considerable interest because of their promising activities as calcium channel blockers, antihypertensive agents and α-1a-antagonists.[1] Furthermore, several isolated marine alkaloids with interesting biological activities were also found to contain the 2-amino-1, 4-dihydropyrimidine-5-carboxylate core.[2] The most notable among them are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[3] Thus, synthesis of the heterocyclic nucleus contained in such compounds is of much current importance.

The classical Biginelli synthesis is a one-pot condensation using β-dicarbonyl compounds with aldehydes (aromatic and aliphatic aldehydes) and urea or thiourea in ethanol solution containing catalytic amounts of acid.[4] This method, however, takes long reaction time (18 h) under harsh reaction condition and only gives unsatisfactory yield. Therefore, to discover more practical routes for the synthesis of dihydropyrimidinones under milder reaction condition through the Biginelli reaction remains attractive. Recently, $BF_3 \cdot OEt_2$,[5] polyphosphate (PPE),[6] KSF clay,[7] indium chloride,[8] ferric chloride hexahydrate,[9] lanthanum chloride[10] and lanthanide triflate[11] were found to be effective for better transformation. More recently, several other improvements for the one-pot synthesis of dihydropyrimidinones were also reported.[12-19] However, many of these one-pot procedures generally require either strong acids or prolonged reaction time or high temperature. Meanwhile multistep synthesis of dihydropyrimidinones is also developed to produce higher yields, but lacks simplicity of one-pot system.[20] Furthermore, environmental concerns regarding chemical research and industry are increasing as well. An efficient chemical transformation involving coupling of three or more components in a single operation by a catalytic process avoiding stoichiometric toxic regents, large amount of solvents and expensive purification technique, represents a fundamental target of the modern organic synthesis.[21] Therefore, it is very important to develop new methods for synthesis under mild reaction conditions and with high yields.

Zinc triflate is a unique Lewis acid that is currently of great research interest.[22] In this paper, we describe a practical route for the Biginelli cyclocondensation reaction using zinc triflate as the catalyst under solvent-free condition (Scheme 1). This is a novel one-pot combination. The procedure is very simple giving high yields (75%—98%), and meanwhile greatly decreases environmental pollution.

Results and discussion

Initially, the Biginelli reactions were carried out under various conditions using zinc triflate as catalyst and benzaldehyde, ethyl acetoacetate and urea as the substrates. The results are summarized in Table 1. Acetonitrile was shown to be the best solvent (yield 90%) as compared with all other solvents. However, the best result was achieved by carrying out the reaction at 100 ℃ for 20 min in the presence of catalytic amount (20 mol%) of zinc triflate without any solvent. Under this condition, the yields increased from 20%—50% to 75%—98%, and the reaction time was significantly shortened from 18 h to 20 min, when compared to the classical Biginelli reaction.

Then, a wide range of structurally varied 1,3-dicarbonyl compounds (including β-keto ester and β-diketone) and aldehydes were tested and it was found that they gave the corresponding dihydropyrimidinones in good to excellent yields (Scheme 1). As shown in Table 2, all aryl aldehydes, with electron-withdrawing (**4c** 96%, **4l** 94%, **4u** 91%, **4y** 91%, **4z** 90%) or electron-donating (**4b** 96%, **4d** 97%, **4o** 96%, **4q** 89%, **4a′** 89%, **4b′** 97%) groups, gave goodyields. The terephthalaldehyde and isophthalaldehyde reacted with 1,3-dicarbonyl compounds and urea affording the corresponding bis-substituted products **4m** (94%) and **4n**

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Scheme 1

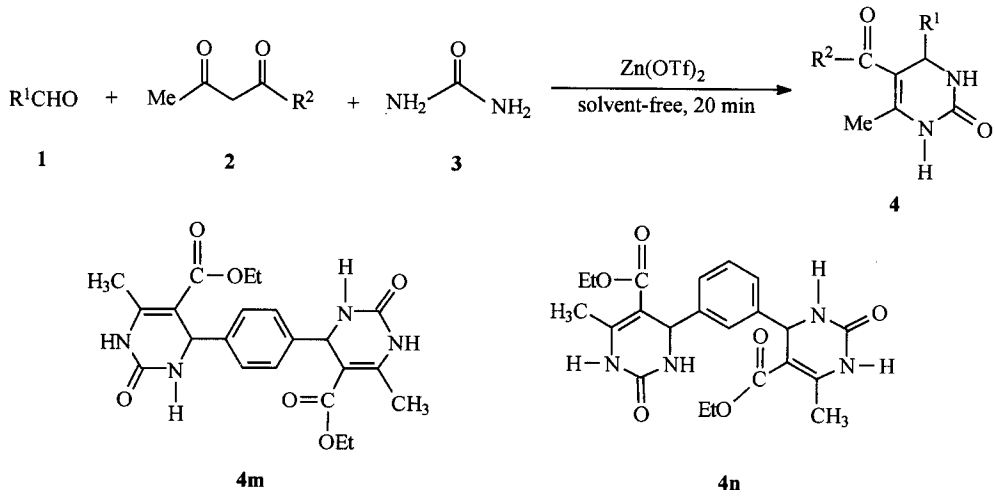


Table 1 Reaction of benzaldehyde, ethyl acetoacetate, and urea under different reaction conditions

Entry	Solvent	Amount of catalyst (mol%)	Time	Yield[a] (%)
1	H_2O	20	6 h[b]	4
2	THF	20	10.5 h[b]	86
3	Ethanol	20	6 h[b]	80
4	CH_2Cl_2	20	10.5 h[b]	71
5	Toluene	20	9 h[b]	77
6	CH_3CN	20	4.5 h[b]	90
7	1,4-Dioxane	20	6 h[b]	51
8	$ClCH_2CH_2Cl$	20	6 h[b]	34
9	$CHCl_3$	20	6 h[b]	40
10	None	0	20 min[c]	7.8
11	None	2.5	20 min[c]	58
12	None	5	20 min[c]	86
13	None	10	20 min[c]	90
14	None	20	20 min[c]	94
15	None	30	20 min[c]	95

[a] Isolated yield. [b] Reflux. [c] 100 ℃.

(89%) in good yields. In addition to the aryl aldehydes, aliphatic aldehydes were also very effective (**4i** 93%, **4j** 96%, **4k** 95%, **4v** 91%, **4w** 96%, **4x** 91%).

Recently, the mechanism of Biginelli reaction was investigated in detail by Kappe.[23] The zinc triflate-catalyzed Biginelli reaction may proceed through the acylimine intermediate (formed *in situ* by reaction of the aldehyde with urea), which is stabilized by the zinc ion, and the subsequent addition of the β-ketoester enolate to the acylimine, followed by cyclization and dehydration, affording the corresponding dihydropyrimidinones (Scheme 2).

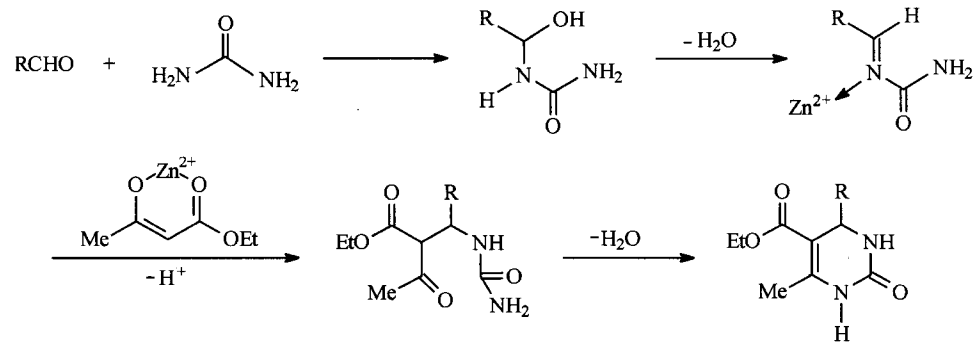
In conclusion, we have developed a rapid and efficient method for the synthesis of the Biginelli compounds. By using zinc triflate (20 mol%) as the catalyst under solvent-free reaction conditions, the yields can be increased from 20%—

Table 2 Zinc triflate-catalysed efficient synthesis of dihydropyrimidinones under solvent-free conditions[a]

Entry	R^1	R^2	Product	Yield[b] (%)
1	C_6H_5	OEt	**4a**	94
2	3-$NO_2C_6H_4$	OEt	**4b**	96
3	4-$OMeC_6H_4$	OEt	**4c**	96
4	4-$NO_2C_6H_4$	OEt	**4d**	97
5	2-ClC_6H_4	OEt	**4e**	97
6	Furyl	OEt	**4f**	77[c]
7	2-F-6-ClC_6H_3	OEt	**4g**	82
8	4-$N(CH_3)_2C_6H_4$	OEt	**4h**	75
9	CH_3CH_2	OEt	**4i**	93
10	$CH_3CH_2CH_2$	OEt	**4j**	96
11	$(CH_3)_2CHCH_2$	OEt	**4k**	95
12	3,4-$OCH_2OC_6H_3$	OEt	**4l**	94
13	Terephthalyl	OEt	**4m**	94
14	Isophthalyl	OEt	**4n**	89
15	3-$NO_2C_6H_4$	OMe	**4o**	96
16	C_6H_5	OMe	**4p**	98
17	4-$NO_2C_6H_4$	OMe	**4q**	89
18	2-ClC_6H_4	OMe	**4r**	89
19	Furyl	OMe	**4s**	81[d]
20	2-F-6-ClC_6H_3	OMe	**4t**	83
21	4-$N(CH_3)_2C_6H_4$	OMe	**4u**	91
22	CH_3CH_2	OMe	**4v**	91
23	$CH_3CH_2CH_2$	OMe	**4w**	96
24	$(CH_3)_2CHCH_2$	OMe	**4x**	91
25	3,4-$OCH_2OC_6H_3$	OMe	**4y**	91
26	4-$OMeC_6H_4$	OMe	**4z**	90
27	4-$NO_2C_6H_4$	Me	**4a′**	89
28	3-$NO_2C_6H_4$	Me	**4b′**	97
29	2-ClC_6H_4	Me	**4c′**	95
30	C_6H_5	Me	**4d′**	86

[a] 100 ℃ for 20 min. [b] Isolated yield. [c] 100 ℃ for 30 min. [d] 100 ℃ for 40 min.

Scheme 2



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50% to 75%—98%, while the reaction time was significantly shortened from 18 h to 20 min compared with the classical Biginelli reaction. Therefore, this $Zn(OTf)_2$-catalysed Biginelli reaction is a simple, high-yielding and timesaving procedure.

Experimental

General

Melting points were determined by using a Yanaco micro melting point apparatus and were not corrected. IR spectra were recorded on a Bruker Vector 22 spectrometer using KBr pellets for solids. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AM 400 (400 MHz) or AM 500 (500 MHz) spectrometer using DMSO-d_6 as the solvent and using TMS as internal standard. Mass spectra were obtained on an HP 5989B MS spectrometer at an ionization potential of 70 eV.

General procedure for $Zn(OTf)_2$-catalyzed preparation of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free reaction conditions

The mixture of aldehyde (**1**, 1 mmol), 1,3-dicarbonyl compound (**2**, 1.5 mmol), urea (**3**, 1.5 mmol) and $Zn(OTf)_2$(72.6 mg, 0.2 mmol) [for entries 13 and 14 in Table 2, aldehyde (**1**, 1 mmol), 1,3-dicarbonyl compound (**2**, 2.5 mmol), urea (**3**, 3 mmol) and $Zn(OTf)_2$(145.2 mg, 0.4 mmol)] were heated at 100 ℃ under stirring for 20 min. Then water was added, and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was washed three times by ether, and then recrystallized from ethanol to afford the pure product **4**. All products were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectra analyses.

5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4a**) m.p. 205—206 ℃ (Lit.[13] 203—205 ℃).

5-Ethoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimi-din-2(1H)-one (**4b**) M.p. 228—230 ℃ (Lit.[13] 227—228 ℃).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4c**) M.p. 202—204 ℃ (Lit.[18] 201—202 ℃).

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4d**) M.p. 209—211 ℃ (Lit.[11] 207—210 ℃).

5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4e**) M.p. 214—216 ℃ (Lit.[13] 214—215 ℃).

5-Ethoxycarbonyl-4-(2-furyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4f**) M.p. 207—208 ℃ (Lit.[12] 205 ℃).

5-Ethoxycarbonyl-4-(2-fluoro-6-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4g**) M.p. 262—264 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H, NH), 7.61 (s, 1H, NH), 7.14—7.34 (m, 3H, ArH), 5.86 (s, 1H, H-4), 3.83—3.91 (*m*, 2H, OCH_2CH_3), 2.20 (s, 3H, $PhCH_3$), 0.95 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR δ: 164.9, 162.8, 160.3, 150.7, 149.4, 133.6, 129.5, 125.6, 114.6, 94.3, 58.7, 48.8, 17.7, 13.7; IR (KBr) ν: 3350, 3239, 3125, 2984, 1700, 1636 cm^{-1}; MS *m/z* (%): 312 (M^+, 5.47).

5-Ethoxycarbonyl-4-(4-(N,N-dimethylamino)phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4h**) M.p. 255—258 ℃ (Lit.[18] 256—258 ℃).

5-Ethoxycarbonyl-4-ethyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4i**) M.p. 179—181 ℃; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.82 (s, 1H, NH), 7.18 (s, 1H, NH), 4.03—4.09 (m, 3H, H-4 and OCH_2CH_3), 2.16 (s, 3H, $PhCH_3$), 1.41—1.44 (m, 2H, CH_2CH_3), 1.17 (t, J = 6.0 Hz, 3H, OCH_2CH_3), 0.78 (t, J = 7.5 Hz, 3H, CH_2CH_3,); ^{13}C NMR δ: 165.3, 152.6, 148.1, 98.7, 58.8, 51.2, 29.4, 17.5, 14.0, 8.31; IR (KBr) ν: 3250, 3123, 2962, 1723, 1703, 1675 cm^{-1}; MS *m/z* (%): 212 (M^+, 0.43).

5-Ethoxycarbonyl-4-propyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4j**) M.p. 176—178 ℃ (Lit.[19] 178—180 ℃).

5-Ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4k**) M.p. 185—186 ℃; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.86 (s, 1H, NH), 7.32 (s, 1H, NH), 4.01—4.10 (m, 3H, H-4 and OCH_2CH_3),

2.16 (s, 3H, $PhCH_3$), 1.69—1.71 (m, 1H, $CH_2CH(CH_3)_2$), 1.35—1.40 (m, 1H, $CH_2CH(CH_3)_2$), 1.17 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.10—1.14 (m, 1H, $CH_2CH(CH_3)_2$), 0.85 (d, J = 6.5 Hz, 6H, $CH_2CH(CH_3)_2$); ^{13}C NMR δ: 165.1, 152.6, 147.9, 100.2, 58.8, 48.1, 45.8, 23.5, 22.7, 21.3, 17.4, 14.0; IR (KBr) ν: 3447, 3244, 3112, 2951, 1701, 1652 cm^{-1}; MS m/z (%): 241 (M^+ + 1, 1.08).

5-Ethoxycarbonyl-4-(3,4-methylenedioxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4l**) M.p. 193—194℃ (Lit.[18] 188—189 ℃).

1,4-Bis(6-methyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1H)-on-4-yl) benzene (**4m**) M.p. 269—270 ℃ (dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.10 (s, 2H, 2 × NH), 7.64 (s, 2H, 2 × NH), 7.18 (s, 4H, ArH), 5.12 (d, J = 2.5 Hz, 2H, 2 × H-4), 3.97—4.00 (m, 4H, 2 × OCH_2CH_3), 2.24 (s, 6H, 2 × $PhCH_3$), 1.08 (t, J = 7.0 Hz, 6H, 2 × OCH_2CH_3); ^{13}C NMR δ: 165.7, 152.1, 148.6, 143.6, 126.2, 98.8, 53.3, 50.7, 17.7; IR (KBr) ν: 3310, 3249, 3124, 2978, 1703, 1644 cm^{-1}; MS m/z (%): 442 (M^+, 1.39).

1,3-Bis(6-methyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1H)-on-4-yl) benzene (**4n**) M.p. 244—246 ℃ (dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.04 (d, 2H, 2 × NH), 7.63 (s, 2H, 2 × NH), 7.12—7.26(m, 4H, ArH), 5.11 (s, 2H, 2 × H-4), 3.95—3.99 (m, 4H, 2 × OCH_2CH_3), 2.23 (s, 6H, 2 × $PhCH_3$), 1.07—1.10 (m, 6H, 2 × OCH_2CH_3); ^{13}C NMR δ: 165.7, 152.5, 148.8, 148.7, 145.5, 129.9, 128.9, 128.8, 125.8, 125.7, 124.5, 99.7, 99.6, 59.6, 54.4, 54.3, 18.1, 14.5; IR (KBr) ν: 3350, 3238, 3112, 2977, 1699, 1639 cm^{-1}; MS m/z (%): 442 (M^+, 5.82).

5-Methoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4o**) M.p. 240—241 ℃ (dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.31 (s, 1H, NH), 8.09—8.13 (m, 2H, ArH), 7.85 (s, 1H, NH), 7.63—7.70 (m, 2H, ArH), 5.31 (d, J = 3.0 Hz, 1H, H-4), 3.35 (s, 3H, $COOCH_3$), 2.28 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 165.5, 151.7, 149.6, 147.8, 146.6, 132.8, 130.1, 122.3, 120.8, 98.0, 53.3, 50.8, 17.8; IR (KBr) ν: 3358, 3244, 3102, 2957, 1701, 1641 cm^{-1}; MS m/z (%): 291 (M^+, 5.86).

5-Methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4p**) M.p. 210—212 ℃ (Lit.[5] 209—216 ℃).

5-Methoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4q**) M.p. 237—239 ℃ (Lit.[11] 235—237 ℃).

5-Methoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4r**) M.p. 226—229 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.21 (s, 1H, NH), 7.59 (s, 1H, NH), 7.25—7.40 (m, 4H, ArH), 5.62 (d, J = 2.5 Hz, 1H, H-4), 3.45 (s, 3H, $COOCH_3$), 2.30 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 165.4, 151.3, 149.3, 141.4, 131.6, 129.4, 129.0, 128.6, 127.6, 97.6, 51.3, 50.6, 17.6 ; IR (KBr) ν: 3367, 3221, 3103, 2948, 1714, 1698 cm^{-1}; MS m/z (%): 280 (M^+, 5.13).

5-Methoxycarbonyl-4-(2-furyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4s**) M.p. 231—232 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.26 (s, 1H, NH), 7.77 (s, 1H, NH), 7.55 (s, 1H, furyl-H), 6.34 (d, J = 3.0 Hz, 1H, furyl-H), 6.08 (d, J = 3.0 Hz, 1H, furyl-H), 5.18 (d, J = 3.2 Hz, 1H, H-4), 3.56 (s, 3H, $COOCH_3$), 2.23 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 165.4, 155.7, 152.3, 149.5, 142.1, 110.2, 105.2, 96.4, 50.7, 47.5, 17.6; IR (KBr) ν: 3316, 3118, 2955, 1707, 1673 cm^{-1}; MS m/z (%): 236 (M^+, 38.91).

5-Methoxycarbonyl-4-(2-fluoro-6-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4t**) M.p. 279—280 ℃ (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.31 (s, 1H, NH), 7.62 (s, 1H, NH), 7.14—7.32 (m, 3H, ArH), 5.86 (s, 1H, H-4), 3.42 (s, 3H, $COOCH_3$), 2.19 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 165.4, 162.9, 160.4, 150.7, 149.3, 133.5, 129.2, 125.6, 114.9, 94.2, 50.3, 48.9, 17.7; IR (KBr) ν: 3357, 3237, 3122, 2982, 1701, 1638 cm^{-1}; MS m/z (%): 298 (M^+, 5.32).

5-Methoxycarbonyl-4-(4-(N, N-dimethylamino) phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4u**) M.p. 251—253 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.14 (s, 1H, NH), 7.63 (s, 1H, NH), 7.02 (d, J = 8.5 Hz, 2H, ArH), 6.64 (d, J = 8.5 Hz, 2H, ArH), 5.02 (d, J = 3.0 Hz, 1H, H-4), 3.51 (s, 3H, $COOCH_3$), 2.84 (s, 6H, $N(CH_3)_2$), 2.23 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 165.8, 152.2, 149. 6, 147.8, 132.3, 126.7, 112.2, 99.5, 53.0, 50.6, 17.6; IR (KBr) ν: 3248, 3113, 2951, 1717, 1684 cm^{-1}; MS m/z (%): 289 (M^+, 60.85).

5-Methoxycarbonyl-4-ethyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4v**) M.p. 184—185 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.96 (s, 1H, NH), 7.30 (s, 1H, NH), 4.01—4.03 (m, 1H, H-4), 3.59 (s, 3H, $COOCH_3$), 2.16 (s, 3H, $PhCH_3$) 1.39 (q, J = 7.5 Hz, 2H, CH_2CH_3), 0.77 (t, J = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR δ: 165.9, 152.7, 148.6, 98.5, 51.3, 50.7, 29.5, 17.7, 8.4; IR (KBr) ν: 3249, 3118, 2961, 1728, 1708, 1680 cm^{-1}; MS m/z (%): 198 (M^+, 0.59).

5-Methoxycarbonyl-4-propyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4w**) M.p. 174—175 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.94 (s, 1H, NH), 7.31 (s, 1H, NH), 4.03 (t, J = 3.2 Hz, 1H, H-4), 3.59 (s, 3H, $COOCH_3$), 2.15 (s, 3H, $PhCH_3$) 1.19—1.40 (m, 4H, $CH_2CH_2CH_3$), 0.82 (t, J = 6.7 Hz, 3H, $CH_2CH_2CH_3$,); ^{13}C NMR δ: 165.8, 152.6, 148.3, 99.1, 50.6, 49.8, 17.6, 16.9, 13.6; IR (KBr) ν: 3442, 3252, 3123, 2957, 1726, 1708, 1653 cm^{-1}; MS m/z (%): 212 (M^+, 0.43).

5-Methoxycarbonyl-4-isobutyl-6-methyl-3, 4-dihydropyrimidin-2(1H)-one (**4x**) M.p. 178—179 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.88 (s, 1H, NH), 7.32 (s, 1H, NH), 4.05—4.08 (m, 1H, H-4), 3.60 (s, 3H, $COOCH_3$), 2.16 (s, 3H, $PhCH_3$), 1.67—1.69 (m, 1H, $CH_2CH(CH_3)_2$), 1.35—1.39 (m, 1H, $CH_2CH(CH_3)_2$), 1.09—1.14 (m, 1H, $CH_2CH(CH_3)_2$), 0.85 (d, J = 6.5 Hz, 6H, $CH_2CH(CH_3)_2$); ^{13}C NMR δ: 165.7, 152.6, 148.0, 100.2, 50.5, 48.2, 45.8, 23.4, 22.7, 21.4, 17.5; IR (KBr) ν: 3442, 3252, 2957, 1726, 1708, 1653 cm^{-1}; MS m/z (%): 227 (M^+ + 1, 0.63).

5-Methoxycarbonyl-4-(3,4-(methylenedioxy)phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4y**) M.p. 238—239 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.20 (s, 1H, NH), 7.69 (s, 1H, NH), 6.67—6.85 (m, 3H, ArH), 5.98 (s, 2H, OCH_2O), 5.05 (d, J = 3 Hz, 1H, H-4), 3.53 (s, 3H, $COOCH_3$), 2.24 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 165.7, 152.0, 148.5, 147.2, 146.3, 138.6, 119.1, 107.9, 106.5, 100.8, 98.9, 53.4 50.7, 17.7; IR (KBr) ν: 3367, 3221, 3102, 2952, 1711, 1693 cm^{-1}; MS m/z (%): 290 (M^+, 55.34).

5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4z**) M.p. 194—196 ℃ (Lit.[11] 191—193 ℃).

5-Aceto-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4a′**) M.p. 231—232 ℃ (dec.) (Lit.[11] 230 ℃ (dec.))

5-Aceto-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4b′**) M.p. 268—270 ℃ (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.33 (s, 1H, NH), 7.98 (s, 1H, NH), 7.61—8.12 (m, 4H, ArH), 5.40 (d, J = 3.2 Hz, 1H, H-4), 2.32 (s, 3H, $COCH_3$), 2.19 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 193.9, 151.9, 149.0, 147.8, 146.3, 132.9, 130.1, 122.2, 121.0, 109.4, 52.9, 30.5, 19.0; IR (KBr) ν: 3349, 3273, 3062, 1715, 1680 cm^{-1}; MS m/z (%): 275 (M^+, 4.34).

5-Aceto-4-(2-chlorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one (**4c′**) M.p. 252—254 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.18 (s, 1H, NH), 7.61 (s, 1H, NH), 7.28—7.43 (m, 4H, ArH), 5.67 (s, 1H, H-4), 2.33 (s, 3H, $COCH_3$), 2.04 (s, 3H, $PhCH_3$); ^{13}C NMR δ: 193.8, 151.4, 148.7, 140.7, 131.7, 129.5, 129.2, 128.4, 127.7, 108.3, 51.4, 30.0, 18.7; IR (KBr) ν: 3243, 3093, 2940, 1704, 1623 cm^{-1}; MS m/z (%): 265 (M^+, 2.04).

5-Aceto-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4d′**) M.p. 235—236 ℃ (Lit.[11] 233—236 ℃).

References

1 (a) 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.
(b) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806.
(c) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutoy, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254 and references cited therein.
2 Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828.
3 (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.
4 Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
5 Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
6 Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.
7 Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465.
8 Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
9 Lu, J.; Ma, H. *Synlett* **2000**, 63.
10 Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075.
11 Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
12 Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341.
13 Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873.
14 Dondoni, A.; Massi, A. *Tetrahedron Lett.* **2001**, *42*, 7975.
15 Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1939.
16 Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 5917.
17 Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, 863.
18 Lu, J.; Bai, Y. *Synthesis* **2002**, 466.
19 Lu, J.; Bai, Y.; Guo, Y.; Wang, Z.; Ma, H. *Chin. J. Chem.* **2002**, *20*, 385.
20 O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185.
21 Mizuno, N.; Misono, M. *Chem. Rev.* **1998**, *98*, 199.
22 Ishimaru, K.; Kojima, T. *J. Org. Chem.* **2000**, *65*, 8395.
23 Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.

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