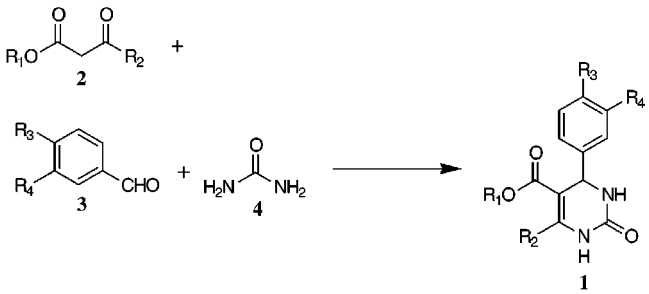
Unprecedented Catalytic Three Component One-Pot Condensation Reaction: An Efficient Synthesis of 5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones

Essa H. Hu,* Daniel R. Sidler,* and Ulf-H. Dolling

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

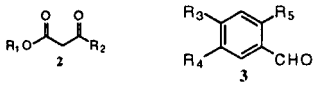
Received May 12, 1997

In the past decade, 4-aryl-dihydropyrimidinones **1** have emerged as the integral backbones of several calcium channel blockers, antihypertensive agents, and alpha-1 a-antagonists.[1] Strategies for the synthesis of the dihydropyrimidinone nucleus have varied from one-pot to multistep approaches. Biginelli's initial one-pot reflux of β-keto ester **2**, aryl aldehyde **3**, and urea, **4**, with catalytic acid in a protic solvent frequently afforded low (20−50%) yields.[2,3] Subsequent multistep syntheses produced somewhat higher yields but lacked the simplicity of the one-pot, one-step synthesis.[3]



Recently, we discovered a novel, one-pot combination of $BF_3{\cdot}OEt_2$, transition metal salt, and proton source that not only preserved the simplicity of Biginelli's one-pot reaction but also consistently produced 80−90% yields of the dihydropyrimidin-2(1H)-ones. For comparison, several 5-alkoxycarbonyl-4-aryl-dihydropyrimidinones **1** were synthesized using both our new conditions and traditional Biginelli reaction conditions (Table 1). Among the various conditions published for Biginelli's reaction,[4] we found Folkers' variation (catalytic H_2SO_4/EtOH, reflux 18 h)[4a,b] to be the most effective for the one-pot synthesis of our desired pyrimidinones. Both reaction conditions utilized a 1:1:1.5 ratio of β-keto ester **2**, aryl aldehyde **3**, and urea, **4**, in a one-pot condensation. Compared to Folkers' conditions, our method consistently produced higher yields.

Table 1. Dihydropyrimidinones Synthesized Using the New Condition versus Folkers' conditions



						yield (%)	
entry	R_1	R_2	R_3	R_4	R_5	*a*	*b*
1	Me	Et	F	F	H	82	55
2	Me	Et	H	H	H	81	42
3	Me	Et	OMe	H	H	85	25
4	Me	Et	Cl	H	H	89	66
5	Me	Et	NO_2	H	H	90	64
6	Me	Me	F	F	H	88	62
7	Me	Me	H	H	H	88	42
8	Me	Me	OMe	H	H	87	28
9	Me	Me	Cl	H	H	95	56
10	Me	Me	NO_2	H	H	92	41
11	Et	Et	F	F	H	82	61
12	Et	Et	H	H	H	83	41
13	Et	Et	OMe	H	H	79	40
14	Et	Et	Cl	H	H	84	46
15	Et	Et	NO_2	H	H	90	44
16	Et	Me	F	F	H	81	66
17	Et	Me	H	H	H	94	71
18	Et	Me	OMe	H	H	85	37
19	Et	Me	Cl	H	H	92	56
20	Et	Me	NO_2	H	H	91	54
21	Me	*t*-Bu	H	H	H	85	32
22	Et	Ph	H	H	H	70	10
23	Me	Me	H	Me	Me	96	62

[a] New reaction conditions: 1.3 equiv of $BF_3{\cdot}OEt_2$, 10 mol % CuCl, 10 mol % AcOH, in THF, reflux 18 h. [b] Folkers' conditions: [4a] catalytic H_2SO_4, in EtOH, reflux 18 h.

This novel application of $BF_3{\cdot}OEt_2$, transition metal salt, and proton source for heterocyclic synthesis stemmed from the observation of a substantial yield increase when a one-pot reaction in acetic acid was run with $Cu(OAc)_2$ and $BF_3{\cdot}OEt_2$. Copper and $BF_3{\cdot}OEt_2$ were chosen as additives for their known carbonyl-activating abilities. While the amounts of acetic acid and copper have been optimized to catalytic (10 mol %) levels, $BF_3{\cdot}OEt_2$ must be used in slight excess (1.3 equiv). Boron trifluoride etherate has been found to be the most effective Lewis acid for this transformation, compared to BPh_3, $B(OCH_3)_3$, $B[N(CH_3)_2]_3$, BCl_3, or $TiCl_4$. Besides $Cu(OAc)_2$, several other transition metal salts, such as CuCl, $CuCl_2$, Cu_2O, $NiBr_2$, and $Pd(OAc)_2$, were similarly efficacious for the reaction. Catalytic acetic acid could be replaced by other proton sources, such as TFA or MeOH; however, replacement by mineral acids decreased reaction yields appreciably. Although there is a range of options available for the transition metal salts and acid catalysts, each component plays a critical role in the success of the reac-

(1) (a) Baldwin, J. J.; Claremon, D. A.; McClure, D. E. (Merck and Co., Inc.). U.S. Patent 4,609,494, 1986. (b) Baldwin, J. J.; Ptizenberger, S. M.; McClure, D. E. (Merck and Co., Inc.). U.S. Patent 4,675,321, 1987. (c) Atwal, K. S. (E. R. Squibb and Sons). U.S. Patent 4,684,655, 1987. (d) Atwal, K. S. (E. R. Squibb and Sons). U.S. Patent 4,684,656, 1987. (e) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Sato, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399. (f) 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. (g) 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. (h) Nagarathnam, D.; Chiu, G.; Dhar, T.; Wong, W.; Marzabadi, M.; Gluchowski, C.; Lagu, B.; Miao, S. PCT Int. Appl. WO 96/14846.

(2) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) Brown, D. J. *The Pyrimidines*; Wiley: New York, 1962; Chapter 12, p 440. For a review of the Biginelli reaction, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

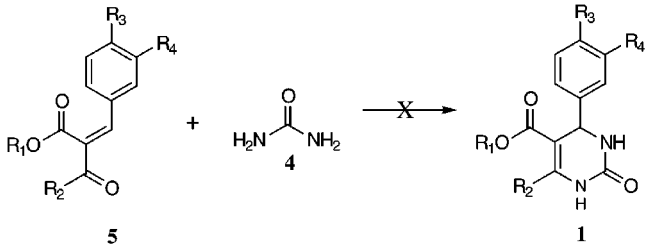
(3) (a) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189. (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898. (c) Barluenga, J.; Tomas, M.; Rubio, V.; Gotor, V. *J. Chem. Commun.* **1979**, 675. (d) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Tetrahedron Lett.* **1989**, *30*, 4573. (e) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819.

(4) (a) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 2886. (b) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3784. (c) Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 55. (d) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473. (e) Fissekis, J. D.; Sweet, F. *J. Am. Chem. Soc.* **1973**, *95*, 8741. (f) Chiba, T.; Hirotoshi, S.; Kato, T. *Heterocycles* **1984**, *22*, 493. (g) Gupta, R.; Gupta, A.; Paul, S.; Kachroo, P. *Indian J. Chem.* **1995**, *34B*, 151. (h) Gupta, R.; Gupta, A.; Paul, S.; Kachroo, P. *Indian J. Chem.* **1995**, *34B*, 61.

S0022-3263(97)00846-3 CCC: $15.00
Published on Web 04/28/1998

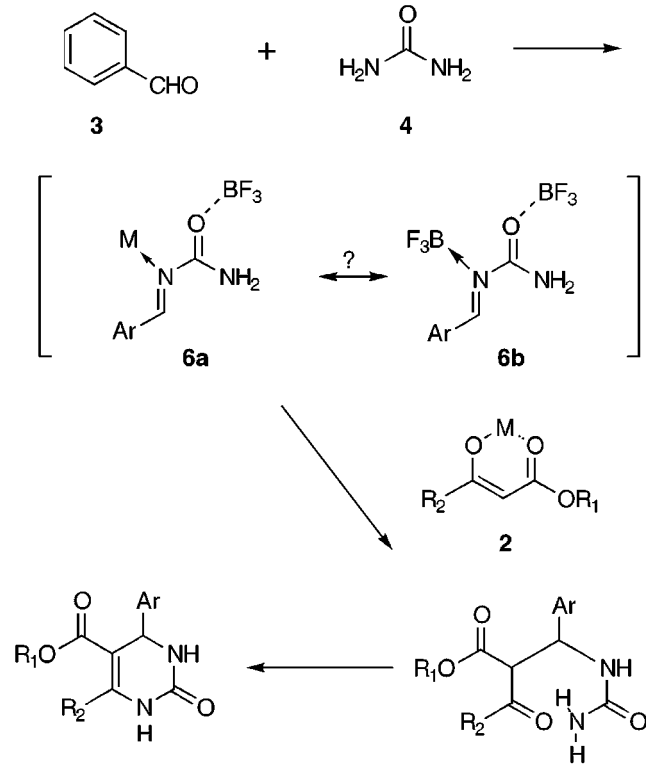
tion. In fact, omission of any one of the three reagents, $BF_3{\cdot}OEt_2$, transition metal salt, or proton source, from the reaction conditions lowers the yield by 20−50%.

Our one-pot heterocycle synthesis seems to involve an unusual cooperation of boron and its two cocatalysts. $BF_3{\cdot}OEt_2$ and copper have been known to catalyze Michael addition to α,β-unsaturated ketones via a boron−copper complex.[5] In these reports, premixed boron−copper complexes enhanced the reaction performance. However, when we premixed $BF_3{\cdot}OEt_2$ and the transition metal salt in our reaction, no increase in the reaction rate or yield was observed. Similarly, benzylidene **5** has been postulated as a key intermediate in the mechanism of the Biginelli reaction.[4e] Yet, when **5**, prepared independently by condensation of **2** and **3** under Lehnert's conditions,[6] was combined with urea and subjected to the one-pot BF_3/Cu/acid conditions, only low (<5%) yields of pyrimidinones **1** were obtained. In fact, when the reaction of **2**, **3**, and **4** with $BF_3{\cdot}OEt_2$/Cu/acid was monitored by HPLC, slow formation of **5** was seen as a reaction



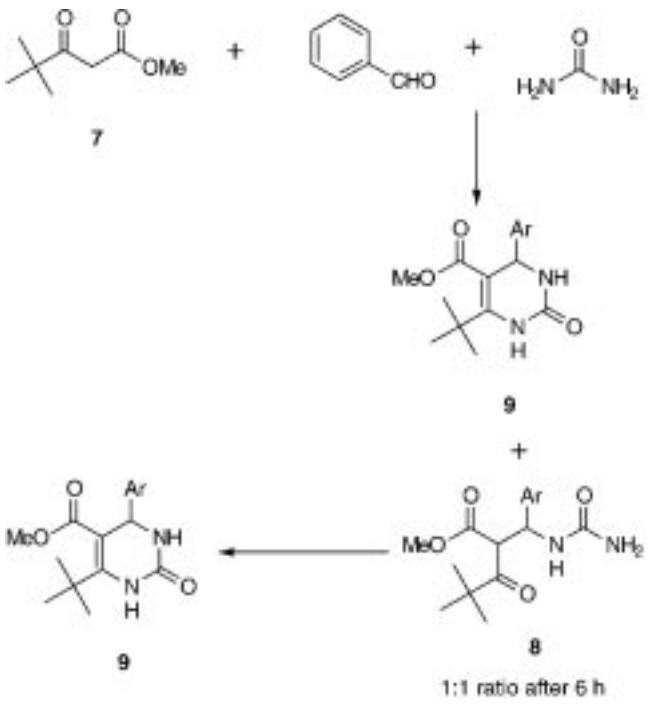
byproduct in 1−2% yield. Thus, mechanistic pathways proceeding through benzylidene intermediate **5** or mimicking the $BF_3{\cdot}OEt_2$-mediated organocuprate addition to α,β-unsaturated ketones and esters seem unlikely.

We propose a mechanism similar to that of Folkers and Johnson[4b] and to that of Kappe[7] for the Biginelli reaction wherein formation of acyl imine intermediate **6**, formed by reaction of the aldehyde with urea and stabilized by



either BF_3 or the transition metal, is the key, rate-limiting step. Subsequent addition of the β-keto ester enolate, followed by cyclization and dehydration, would afford the dihydropyrimidinone.

We have been unable to observe **6a** or **6b** by ^1H or ^{13}C NMR or by in situ IR experiments. However, when the reaction was run with a bulky β-keto ester substituent (i.e., *tert*-butyl ketone **7**) the intermediate ureide **8** was



observed in a 1:1 ratio with the corresponding dihydropyrimidinone **9** after 6 h. Continued reaction converted **8** into **9**. In addition, isolated **8** could be resubjected to the reaction conditions to afford **9**. The inability of **5** to undergo cyclization under these reaction conditions and the observation of ureide **8** as a reaction intermediate support this proposed mechanistic pathway.

In addition to its simplicity, this reaction has one salient feature in its ability to tolerate a variety of substituted β-keto esters and aryl aldehydes (Table 1). Most literature examples of the Biginelli variants use simple β-keto esters, such as methyl acetoacetate, in the condensation reaction. The efficacy of Biginelli's reaction is substrate dependent with the use of more highly functionalized or sterically encumbered keto esters leading to severely reduced yields. Likewise, existing synthetic strategies have shown a great deal of variability in yield depending on the aryl aldehyde used. As evidenced in Table 1, our three-component reaction afforded uniformly high yields, regardless of the keto ester or aldehyde substituents.

The discovery and development of these catalytic reaction conditions have led to a general method for the direct preparation of substituted dihydropyrimidinones in high yields from readily available starting materials. Further investigations of the scope and mechanism of this reaction are under way.

(5) Kocovsky, P.; Dvorak, D. *Tetrahedron Lett.* **1986**, *27*, 5015.
(6) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723.
(7) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.

Experimental Section

Melting points were determined by using the Thomas-Hoover capillary melting point apparatus and were uncorrected. IR spectra were obtained as thin films on disposable, poly(tetrafluoroethylene) cards on a Nicolet Magna-IR spectrometer 550. ^{1}H and ^{13}C spectra were recorded on a Bruker AM-250 NMR spectrometer (operating at 250 and 62.9 MHz, respectively), and the chemical shifts were reported in ppm (δ unit) downfield from TMS. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Water content was determined by Karl Fisher titration on the EM Science AquaStar C2000 titrator.

General Procedure for the Synthesis of Dihydropyrimidinones. A 50 mL three-neck round-bottom flask under N_2 and fitted with a thermocouple and reflux condenser was charged with sieve dried THF (30 mL), β-keto ester (15.4 mmol), aryl aldehyde (15.4 mmol), urea (23.1 mmol), $BF_3{\cdot}OEt_2$ (20.0 mmol), CuCl (1.54 mmol), and glacial acetic acid (1.54 mmol). The mixture was heated to reflux (at 65 °C) for 8−18 h. The solution was cooled to room temperature and quenched with 10% Na_2CO_3 (30 mL). EtOAc (30 mL) was added, the layers were separated, and the green aqueous solution was removed. The organic layer was distilled and replaced with toluene (ca. 40 mL), cooled to room temperature, and aged overnight. The resulting suspension was filtered in vacuo, and the collected solid was rinsed with toluene (1 × 10 mL) and dried in vacuo at 40 °C to afford the desired product as crystalline solid.

4-(3,4-Difluorophenyl)-6-ethyl-5-methoxycarbonyl-3,4-dihydropyrimidin-2(1H)-one: entry **1** (82% yield) mp 182−5 °C; IR (THF) 3237, 3112, 2960, 2879, 1701, 1634, 1517 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.31 (s, 1H), 7.80 (s, 1H), 7.40 (m, 1H), 7.20 (m, 1H), 7.06 (m, 1H), 5.14 (d, J = 3.4 Hz, 1H), 3.54 (s, 3H), 2.65 (m, 2H), 1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.1, 154.8, 152.0, 142.2, 117.6, 117.4, 115.2, 114.9, 97.4, 52.8, 50.8, 24.0, 12.8; MS *m/e* 297 (M + H, 100), 279 (M + H, 37), 183 (M + H, 15), 148 (M + H, 30), 130 (M + H, 20). Anal. Calcd for $C_{14}H_{14}N_2O_3F_2$: C, 56.76; H, 4.76; N, 9.46. Found: C, 56.85; H, 4.70; N, 9.35.

6-Ethyl-5-methoxycarbonyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one: entry **2** (81% yield) mp 133−5 °C; IR ($CHCl_3$) 3224, 3108, 3026, 2954, 1700, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.43 (s, 1H), 7.28 (m, 5H), 6.07 (s, 1H), 5.36 (d, J = 2.8 Hz, 1H), 3.61 (s, 3H), 2.71 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8, 156.8, 152.3, 143.7, 128.8, 127.9, 126.4, 100.2, 55.5, 51.1, 25.3, 12.5, 11.6; MS *m/e* 260.1 (50), 245.1 (59), 201.1 (72), 183.0 (100), 151.0 (95); HRMS calcd for $C_{14}H_{16}N_2O_3$ (M^+) 260.1161, found 260.1180.

6-Ethyl-5-methoxycarbonyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one: entry **3** (85% yield) mp 105−7 °C; IR ($CHCl_3$) 3230, 3112, 2954, 1710, 1644, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H), 7.21 (m, 2H), 6.81 (d, J = 8.6 Hz, 2H), 6.09 (s, 1H), 5.32 (s, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 2.71 (m, 2H), 1.21 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8, 159.3, 159.3, 151.8, 136.2, 127.6, 114.1, 100.5, 55.2, 54.9, 54.9, 50.9, 25.2, 12.4; MS *m/e* 290.1 (30), 275.1 (65), 231.1 (85), 183.1 (100), 151.0 (58); HRMS calcd for $C_{15}H_{18}N_2O_4$ (M^+) 290.1267, found 290.1266.

4-(4-Chlorophenyl)-6-ethyl-5-methoxycarbonyl-3,4-dihydropyrimidin-2(1H)-one: entry **4** (89% yield) mp 149−152 °C; IR (CH_2Cl_2) 3236, 3107, 2973, 2947, 1702, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1H), 7.21 (m, 4H), 6.70 (s, 1H), 5.31 (d, J = 2.9 Hz, 1H), 3.61 (s, 3H), 2.67 (m, 2H), 1.17 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 154.3, 152.6, 142.2, 133.6, 128.9, 127.8, 99.9, 54.6, 51.2, 25.2, 12.5l; MS *m/e* 295 (M + H, 100), 277 (M + H, 25), 183 (M + H, 26), 148 (M + H, 37), 130 (M + H, 31). Anal. Calcd for $C_{14}H_{15}N_2O_3Cl$: C, 57.05; H, 5.13; N, 9.50. Found: C, 56.84; H, 5.20; N, 9.43.

5-Methoxycarbonyl-6-ethyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: entry **5** (90% yield) mp 184−7 °C; IR (THF) 3239, 3112, 2973, 2877, 1705, 1643, 1608, 1523 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.37 (s, 1H), 8.21 (d, J = 8.7 Hz, 2H), 7.89 (s, 1H), 7.50 (d, J = 8.7 Hz, 2H), 5.27 (d, J = 3.4 Hz, 1H), 3.54 (s, 3H), 2.70 (m, 2H), 1.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.0, 155.0, 151.9, 151.7, 146.6, 127.4, 123.8, 53.3, 50.8, 24.0, 12.8; MS *m/e* 306 (M + H, 75), 188 (M + H, 42), 183 (M + H, 15), 148 (M + H, 45), 130 (M + H, 100). Anal. Calcd for $C_{14}H_{15}N_3O_5{\cdot}0.2(H_2O)$: C, 54.44; H, 5.03; H, 13.60. Found: C, 54.25; H, 5.09; N, 13.26.

4-(3,4-Difluorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry **6** (88% yield) mp 224−6 °C; IR (THF) 3368, 3227, 3102, 2952, 1698, 1644, 1611, 1516 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.33 (s, 1H), 7.83 (s, 1H), 7.38 (m, 1H), 7.21 (m, 1H), 7.07 (m, 1H), 5.15 (d, 1H), 3.53 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.5, 151.8, 149.3, 142.2, 122.7, 117.6, 115.2, 115.0, 98.2, 52.9, 50.7, 17.7; MS *m/e* 283 (M + H, 100), 265 (M + H, 20), 169 (M + H, 10), 148 (M + H, 15). Anal. Calcd for $C_{13}H_{12}N_2O_3F_2{\cdot}0.(H_2O)$: C, 54.78; H, 4.67; N, 9.83. Found: C, 54.55; H, 4.36; N, 9.46.

5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one: entry **7** (88% yield) mp 209−212 °C; IR (THF) 3361, 3231, 3089, 3030, 2945, 1750, 1705, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.30 (m, 5H), 5.70 (s, 1H), 5.39 (d, J = 2.7 Hz, 1H), 3.62 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.7, 152.0, 148.5, 144.6, 128.3, 127.2, 126.0, 98.9, 53.7, 50.7, 17.7; MS *m/e* 246.1 (20), 231.1 (28), 187.1 (27), 169.0 (100), 137.0 (41); HRMS calcd for $C_{13}H_{14}N_2O_3$ (M^+) 246.1004, found 246.0999.

5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry **8** (87% yield) mp 192−4 °C; IR ($CHCl_3$) 3232, 3104, 3003, 2950, 2837, 1698, 1645, 1609, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 7.23 (m, 2H), 6.82 (m, 2H), 5.97 (s, 1H), 5.31 (d, J = 2.0 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.6, 151.0, 143.8, 133.5, 125.1, 111.5, 52.7, 52.5, 48.5, 16.1; MS *m/e* 276.1 (35), 261.1 (75), 217.1 (85), 169.0 (100), 137.0 (58); HRMS calcd for $C_{14}H_{16}N_2O_4$ (M^+) 276.1110, found 276.1079.

4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry **9** (95% yield) mp 204−7 °C; IR (THF) 3238, 3114, 2950, 2875, 1702, 1645 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.27 (s, 1H), 7.78 (s, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 5.14 (d, J = 3.3 Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.6, 151.9, 148.9, 143.5, 131.7, 128.3, 128.0, 98.5, 53.2, 50.7, 17.7; MS *m/e* 281 (M + H, 100), 263 (M + H, 20), 188 (M + H, 30), 169 (M + H, 20), 148 (M + H, 37), 130 (M + H, 41). Anal. Calcd for $C_{13}H_{13}N_2O_3Cl{\cdot}0.1(H_2O)$: C, 54.92; H, 4.75; N, 9.85. Found C, 54.96; H, 4.49; N, 9.85.

5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: entry **10** (92% yield) mp 235−7 °C; IR (DMF) 3366, 3233, 3113, 2951, 1703, 1643, 1598, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.39 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 5.28 (s, 1H), 3.53 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.5, 151.7, 149.5, 146.6, 127.5, 123.7, 97.9, 53.4, 50.8, 17.8; MS *m/e* 276.1 (25), 232.1 (15), 186.1 (15), 169.1 (100), 137.0 (48); HRMS calcd for $C_{13}H_{13}N_3O_5$ (M^+) 291.0855, found 291.0883.

4-(3,4-Difluorophenyl)-5-ethoxycarbonyl-6-ethyl-3,4-dihydropyrimidin-2(1H)-one: entry **11** (82% yield) mp 146−8 °C; IR ($CHCl_3$) 3236, 3110, 2980, 2940, 1705, 1643, 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H), 7.06 (m, 3H), 6.39 (s, 1H), 5.33 (d, J = 3.0 Hz, 1H), 4.08 (m, 2H), 2.70 (m, 2H), 1.19 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.0, 153.8, 152.3, 140.8, 122.5, 117.6, 117.3, 115.7, 115.5, 100.0, 60.2, 54.6, 25.3, 14.1, 12.5; MS *m/e* 311 (M + H, 100), 293 (M + H, 18), 197 (M + H, 10), 148 (M + H, 15), 114 (M + H, 10). Anal. Calcd for $C_{15}H_{16}N_2O_3F_2$: C, 58.06; H, 5.20; N, 9.03. Found: C, 57.66; H, 5.38; N, 8.98.

5-Ethoxycarbonyl-6-ethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one: entry **12** (83% yield) mp 128−131 °C; IR ($CHCl_3$) 3230, 3106, 3030, 2979, 2938, 1701, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 7.26 (m, 5H), 6.42 (s, 1H), 5.35 (d, J = 2.5 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 2.69 (m, 2H), 1.16 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.4, 154.2, 152.2, 143.9, 128.7, 127.8, 126.5, 100.3, 59.9, 55.4, 25.2, 14.1, 12.6; MS *m/e* 275 (M + H, 100), 257 (M + H, 21), 197 (M + H, 15), 148 (M + H, 15). Anal. Calcd for $C_{15}H_{18}N_2O_3{\cdot}0.1(H_2O)$: C, 65.25; H, 6.65; N, 10.15. Found: C, 65.04; H, 6.44; N, 10.15.

5-Ethoxycarbonyl-6-ethyl-4-(4-methoxyphenyl)-3,4-dihydroyprimidin-2(1H)-one: entry **13** (79% yield) mp 145−8 °C; IR (CH_2Cl_2) 3232, 3105, 2978, 2937, 1693, 1643, 1610, 1586, 1519 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.39 (s, 1H), 5.31 (s, 1H), 4.05 (q, J = 7.0 Hz, 2H), 3.75 (s, 3H), 2.69 (m, 2H), 1.18 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.3, 159.3, 153.3, 151.4, 136.3, 127.7, 114.1, 100.8, 59.8, 55.2, 25.2, 14.0, 12.4; MS *m/e* 305 (M + H, 100),

287 (M + H, 25), 275 (M + H, 20), 197 (M + H, 25), 136 (M + H, 26). Anal. Calcd for $C_{16}H_{20}N_2O_4 \cdot 0.1(H_2O)$: C, 62.77; H, 6.65; N, 9.15. Found: C, 62.52; H, 6.50; N, 9.10.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-ethyl-3,4-dihydropyrimidin-2(1H)-one: entry **14** (84% yield) mp 140−2 °C; IR (THF) 3235, 3112, 2978, 2938, 2876, 1697, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.54 (s, 1H), 7.24 (m, 4H), 6.41 (s, 1H), 5.34 (d, J = 2.9 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 2.67 (m, 2H), 1.17 (q, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 165.1, 153.9, 152.1, 142.3, 133.6, 128.8, 127.9, 100.2, 60.1, 54.9, 25.3, 14.1, 12.5; MS *m/e* 309 (M + H, 100), 311 (M + H, 30), 291 (M + H, 25), 148 (M + H, 30), 130 (M + H, 40). Anal. Calcd for $C_{15}H_{17}N_2O_3Cl \cdot 0.1(H_2O)$: C, 58.01; H, 5.58; N, 9.02. Found: C, 57.64; H, 5.59; N, 9.03.

5-Ethoxycarbonyl-6-ethyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: entry **15** (90% yield) mp 221−4 °C; IR (THF) 3224, 3107, 2976, 2936, 2875, 1700, 1638, 1596, 1519 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.34 (s, 1H), 8.20 (m, 2H), 7.86 (s, 1H), 7.49 (m, 2H), 5.27 (d, J = 3.4 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 2.65 (m, 2H), 1.12 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 164.6, 154.7, 151.9, 146.6, 132.0, 127.5, 123.7, 97.3, 59.3, 53.5, 24.0, 13.8, 12.8; MS *m/e* 321 (M + H, 21), 320 (M + H, 70), 188 (M + H, 25), 148 (M + H, 30), 130 (M + H, 100). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.02; H, 5.45; N, 12.96.

4-(3,4-Difluorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry **16** (81% yield) mp 185−6 °C; IR (THF) 3240, 3115, 2980, 2941, 1704, 1647, 1517 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.30 (s, 1H), 7.81 (s, 1H), 7.39 (m, 1H), 7.21 (m, 1H), 7.07 (m, 1H), 5.15 (d, J = 3.3 Hz, 1H), 3.98 (m, 2H), 2.26 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.0, 151.7, 149.0, 142.4, 122.8, 117.5, 117.3, 115.3, 115.0, 59.2, 53.0, 17.7, 13.9; MS *m/e* 298 (M + H, 15), 297 (M + H, 100), 279 (M + H, 15), 183 (M + H, 10), 148 (M + H, 15). Anal. Calcd for $C_{14}H_{14}N_2O_3F_2 \cdot 0.1(H_2O)$: C, 56.41; H, 4.80; N, 9.40. Found: C, 56.34; H, 4.75; N, 9.34.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one: entry **17** (94% yield) mp 202−4 °C; IR (THF) 3235, 3109, 2976, 2936, 1725, 1702, 1648, 1599 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.21 (s, 1H), 7.76 (d, J = 2.5 Hz, 1H), 7.27 (m, 5H), 5.15 (d, J = 3.2 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.2, 152.0, 148.2, 144.7, 128.3, 127.1, 126.1, 99.2, 59.1, 53.9, 17.7, 13.9; MS *m/e* 261 (M + H, 100), 243 (M + H, 52), 213 (M + H, 15), 217 (M + H, 15), 148 (M + H, 32). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.38; H, 6.28; N, 10.65.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry **18** (85% yield) mp 201−3 °C; IR (THF) 3225, 3098, 2928, 2835, 1710, 1651, 1613, 1583, 1513 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.13 (s, 1H), 7.65 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.09 (d, J = 3.2 Hz, 1H), 3.97 (q, J =7.1 Hz, 2H), 3.72 (s, 3H), 2.24 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.3, 158.0, 152.0, 147.5, 136.9, 127.3, 113.6, 99.9, 59.0, 54.9, 53.2, 17.6, 14.0; MS *m/e* 261.1 (100), 217.1 (70), 183.1 (52), 155.0 (50), 137.0 (25); HRMS calcd for $C_{15}H_{18}N_2O_4$ (M^+) 290.1267, found 290.1286.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry **19** (92% yield) mp 213−5 °C; IR (THF) 3233, 3093, 2976, 2933, 1701, 1643 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.39 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.13 (s, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 151.8, 143.7, 131.7, 128.3, 128.1, 98.7, 59.1, 53.3, 17.7, 13.9; MS *m/e* 265.0 (65), 221.0 (35), 183.1 (100), 155.0 (42), 137.0 (35); HRMS calcd for $C_{14}H_{15}N_2O_3Cl$ (M^+) 294.0771, found 294.0787.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: entry **20** (91% yield) mp 208−211 °C; IR (THF) 3230, 3109, 2977, 1701, 1641, 1591, 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.37 (s, 1H), 8.20 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 2.46 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 5.27 (d, J = 1.6 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.27 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 164.9, 151.9, 151.7, 149.3, 146.6, 127.5, 123.7, 59.3, 53.6, 17.8, 13.9; MS *m/e* 276.1 (75), 183.1 (100), 169.1 (30), 155.0 (40), 137.0 (48); HRMS calcd for $C_{14}H_{15}N_3O_5$ (M^+) 305.1012, found 305.0980.

Compound 8: inseparable 1:1 mixture of diastereomers; IR (CH_2Cl_2) 3478, 3377, 2970, 1739, 1708, 1688 cm^{-1}; ^1H NMR (CD_3CN) δ 7.26 (m, 12H), 6.77 (d, J = 9.7, 1H), 6.56 (d, J = 9.8, 1H), 5.55 (m, 1H), 5.50 (m, 1H), 5.10 (br s, 2H), 4.59 (d, J = 6.5, 1H), 4.57 (d, J = 9.2, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 0.93 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (CD_3CN) δ 210.9, 208.0, 169.3, 169.0, 159.4, 142.2, 141.9, 129.4, 128.5, 128.4, 128.4, 127.9, 59.7, 57.9, 55.4, 55.1, 53.2, 53.2, 46.3, 46.2, 26.4, 26.1, 26.0.

Compound 9: entry 21 (88% yield); IR (CH_2Cl_2) 3246, 3185, 2952, 1693, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (s, 6H), 7.18 (s, 1H), 5.14 (d, J = 2.8 Hz, 1H), 3.49 (s, 3H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.6, 153.9, 149.1, 142.3, 128.4, 127.6, 126.4, 102.1, 56.6, 51.1, 35.5, 28.1.

5-Ethoxycarbonyl-4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one: entry **22** (70% yield) mp 157−9 °C; IR (CH_2Cl_2) 3214, 3086, 2980, 1699, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (s, 1H), 7.37 (m, 10H), 6.55 (s, 1H), 5.43 (s, 1H), 3.84 (q, J = 7.0 Hz, 2H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.3, 153.2, 147.1, 143.5, 135.1, 129.5, 128.8, 128.2, 128.1, 128.0, 126.6, 102.4, 60.0, 55.8, 13.6. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 71.01; H, 5.70; N, 8.59.

4-(2,5-Dimethylphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one: entry 23 (96% yield) mp 275−7 °C; IR (CH_2Cl_2): 3356, 3201, 3083, 2943, 1697, 1641 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.15 (s, 1H), 7.60 (s, 1H), 6.96 (m, 3H), 5.36 (d, J = 2.5, 1H), 3.45 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.7, 151.5, 148.3, 143.0, 135.1, 131.5, 130.1, 127.8, 126.9, 99.0, 50.6, 50.4, 20.8, 18.1, 17.7. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.82; H, 6.60; N, 10.15.

JO970846U