Lanthanide Triflate Catalyzed Biginelli Reaction. One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Conditions

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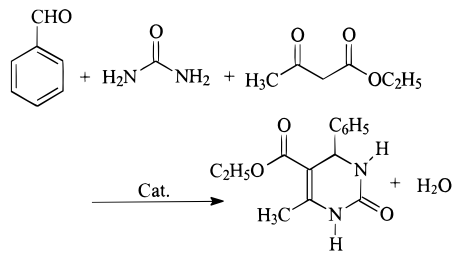
Introduction

Many dihydropyrimidinones and their derivatives are pharmacologically important as calcium channel blockers, antihypertensive agents, and α_1-1-a-antagonists.[1] Several recently[2] isolated marine alkaloids 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 HIVgp-120-CD4 inhibitors.[3] Therefore, many synthetic methods for preparing such compounds have been developed.[4] The Biginelli reaction, first described more than a century ago,[5] is a one-pot but low yielding (often 20−50%) condensation of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of catalytic amount of acid. Lewis acids (such as $BF_3{\cdot}OEt_2$) in combination with transition metal salts and a proper proton source were also found to be effective.[6] A polyphosphate ester was claimed to greatly improve the yield of the process.[7] Recently, it was reported that the acidic clay montmorillonite KSF could catalyze this reaction,[8]and that microwave also could promote the Biginelli three-component cyclocondensation reaction.[9] Subsequent multistep synthesis produced somewhat higher yields but lacked efficiency,[10] and the reported one-pot protocols normally require prolonged reaction time and high temperatures.

Scheme 1



7a

Environmental concerns in chemical research and industry are ever increasing.[11] The challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents, or even better, do not need solvents at all. Lanthanide triflates are unique Lewis acids that are currently of great research interest. They are unlike common Lewis acids, which are trapped nitrogen atoms of imines or tertiary amines that decompose readily in the presence of water so that more than stoichiometric amounts are required to complete the reaction. Conversely, lanthanide triflates are quite stable to water and reusable, as well as highly effective for the activation of imines. Therefore lanthanide triflates are unique catalysts compared to traditional Lewis acids in several important carbon−carbon bond forming reactions,[12] such as aldol condensations,[13] Fridel−Crafts acylations,[14] and aza Diels−Alder reactions,[15] and have found broad application. We have reported that glyoxylates react smoothly with alkenes[16] and in a one-pot synthesis of amino phosphonates from aldehydes[17] in the presence of a catalytic amount of ytterbium triflate. Herein we disclose a novel lanthanide triflate catalyzed Biginelli reaction applied to one-pot syntheses of dihydropyrimidinones under solvent-free conditions, which not only is very simple and high-yielding (81−99%) but also greatly decreases environmental pollution.

We have tested a variety of reaction conditions with the model reaction using lanthanide trifluoromethanesulfonates as a catalyst (Scheme 1). The results are summarized in Table 1. It seems that toluene is a much better solvent (yield 95%) than all others tested (such as dichloromethane (22%), tetrahydrofuran (56%), water−THF (28%), and water (24%)). The best results were achieved by carrying out the reaction at 100 °C for 20 min in the presence of catalytic amount $Yb(OTf)_3$ without any solvent. Reactions in "dry media"or under solvent-free conditions are especially appealing, as they provide an opportunity to work with an open vessel, thus avoiding the risk of high internal pressure development and with the possibility of upscaling the reactions to larger scale.[9] Under these conditions, the yields were significantly

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Table 1. Reaction of Benzaldehyde, Ethyl Acetoacetate, and Urea under Different Reaction Conditions

entry	solvent[a]	catalyst	amount of catalyst (mol %)	yield (%)[d]
1	H_2O	$Yb(OTf)_3$	5	24
2	H_2O−THF	$Yb(OTf)_3$	5	28
3	toluene	$Yb(OTf)_3$	5	95
4	CH_3CN	$Yb(OTf)_3$	5	83
5	CH_2Cl_2	$Yb(OTf)_3$	5	22
6	THF	$Yb(OTf)_3$	5	56
7	none[b]	$Yb(OTf)_3$	5	99
8	none	$Yb(OTf)_3$	20	98
9	none	$Yb(OTf)_3$	10	98
10	none	$Yb(OTf)_3$	2.5	96
11	none	$Yb(OTf)_3$	1.5	79
12	none	$Sc(OTf)_3$	5	96
13	none	$La(OTf)_3$	5	89
14	none	$YbCl_3$	5	66
15	none	Cp_2YbCl	5	45
16	none	$Yb(OTf)_3$[c]	5	96, 95, 97

[a] Refluxed for 6 h. [b] 100 °C for 20 min. [c] Catalyst was reused in three time. [d] Isolated yield.

Table 2. Ytterbium Triflate Catalyzed Synthesis of Different Dihydropyrimidinones under Solventless Conditions[a]

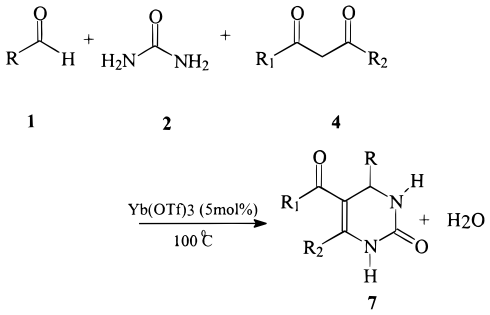
entry	R	R_1	R_2	product	yield (%)[b]
1	C_6H_5	C_2H_5O	CH_3	**7a**	98
2	4-(CH_3O)-C_6H_4	C_2H_5O	CH_3	**7b**	96
3	4-(NO_2)-C_6H_4	C_2H_5O	CH_3	**7c**	94
4	4-(Cl)-C_6H_4	C_2H_5O	CH_3	**7d**	97
5	4-(F)-C_6H_4	C_2H_5O	CH_3	**7e**	94
6	2,4-$(Cl)_2$-C_6H_3	C_2H_5O	CH_3	**7f**	89
7	4-(CF_3)-C_6H_4	C_2H_5O	CH_3	**7g**	87[c]
8	2-(Br)-C_6H_4	C_2H_5O	CH_3	**7h**	97[c]
9	C_6H_5CH═CH	C_2H_5O	CH_3	**7i**	81
10	n-Bu	C_2H_5O	CH_3	**7j**	87[c]
11	i-Pr	C_2H_5O	CH_3	**7k**	83
12	C_6H_5	CH_3	CH_3	**7l**	94
13	4-(CH_3O)-C_6H_4	CH_3	CH_3	**7m**	91
14	4-(NO_2)-C_6H_4	CH_3	CH_3	**7n**	90
15	C_6H_5	C_6H_5	CF_3	**7o**	96
16	C_6H_5	2-thienyl	CF_3	**7p**	94
17	C_6H_5	CH_3O	CH_3	**7q**	98
18	4-(CH_3O)-C_6H_4	CH_3O	CH_3	**7r**	99
19	4-(NO_2)-C_6H_4	CH_3O	CH_3	**7s**	91
20	2,4-$(Cl)_2$−C_6H_3	CH_3O	CH_3	**7t**	83
21	4-(F)-C_6H_4	CH_3O	CH_3	**7u**	81

[a] 100 °C for 20 min. [b] Isolated yield. [c] 100 °C for 40 min.

raised (81−99% vs for the classical Biginelli method), and the reaction time was shortened from 18 h to 20 min. All the lanthanide trifluoromethanesulfonates examined showed good catalytic effects, but $Yb(OTf)_3$ was particularly effective for this transformation and could be reused three times without showing any loss of activity (with the yields of the product **7a** being 96%, 95%, and 97% yield, respectively). In contrast, other lanthanide compounds such as $YbCl_3$ and Cp_2YbCl gave lower yields (66% and 45%) at the first use.

Several aromatic and aliphatic aldehydes were examined under the optimized conditions: with 5 mol % $Yb(OTf)_3$ at 100 °C for 20 min in the absence of any solvent. The results are listed in Table 2. In all cases, the three-component reaction proceeded smoothly and very fast to give the corresponding dihydropyrimidinones (Scheme 2) in high yield. Compared to the classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate the variation in all the three components. Besides the β-ketone ester, the aromatic β-diketone and heterocyclic β-diketone (**7o** and **7p**) can also be employed. Pentanedione (**7l**−**n**) can be

Scheme 2



used as substrate without causing any decrease in yield. Most importantly, aromatic aldehydes carrying either electron-donating (**7b** 96%, **7m** 91%, and **7r** 99% yield) or electron-withdrawing (**7c**−**g**, **7n**, and **7s**−**u**) substituents all reacted very well, giving excellent yields; many of the pharmacological relevant substitution patterns on the 4-aryl ring can thus be introduced with high efficiency.[18]

Further, we examined the reactivity of aliphatic aldehydes, β-dicarbonyl compounds, and urea in the presence of ytterbium triflate. Thus, with a catalytic amount of $Yb(OTf)_3$ the Biginelli reaction of aliphatic aldehydes such as n-valeric and isobutyric aldehyde, β-dicarbonyl compounds, and urea without any solvent at 100 °C for 20−40 min affords 4-butyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**7j)** and 5-(ethoxycarbonyl)-4-isopropyl-6-methyl-3,4-dihydropyrimidinon-2(1*H*)-one (**7k**) in 87% and 83% yield, respectively. Similarly, an α,β-unsaturated aldehyde also gives the product **7i** (81% yield). Therefore, aliphatic aldehydes exhibited analogous behavior to that of aromatic aldehydes.

Moreover, the reaction of *p*-nitrobenzaldehyde and urea with 2,2,6,6-tetramethyl-3,5-heptanedione catalyzed by lanthanide triflate, contrary to our expectation, gives an intermediate **3**, and the end product was not observed, presumably because of steric hindrance of the β-diketone (Scheme 3). To prove whether the imine was produced, we added ethyl acetoacetate to the reaction mixture of *p*-nitrobenzaldehyde and urea with 2,2,6,6-tetramethyl-3,5-heptanedione (catalyzed by lanthanide triflate), and after 60 min 5-(ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one was obtained. Under the same reaction conditions, treatment of *p*-nitrobenzaldehyde and urea with 2,2,6,6-tetramethyl-3,5-heptanedione and acetoacetone yields 5-acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one too. Therefore the Biginelli reaction must first form an acyl imine intermediate **3**, by the reaction of the aldehyde with urea and activated by lanthanide coordination which is the key and rate-limiting step. Subsequent addition of the β-carbonyl compound, followed by cyclization and dehydration, would afford the dihydropyrimidinone.

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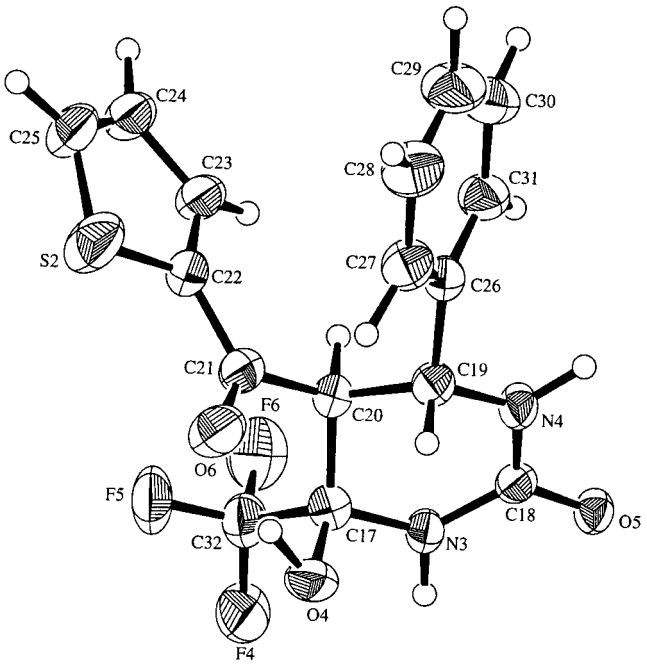
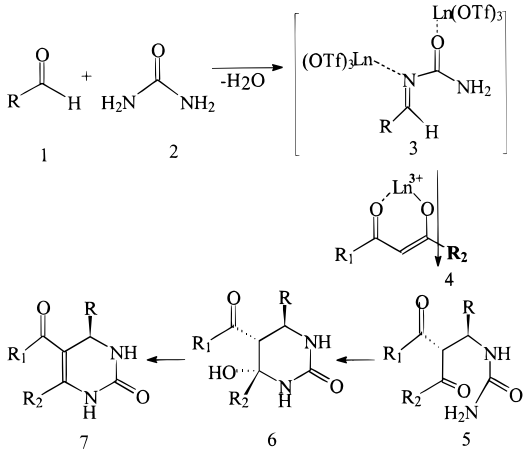
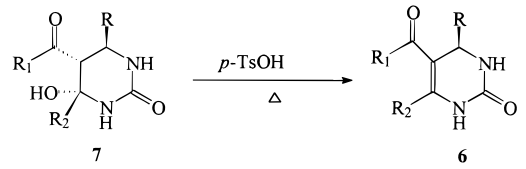


Figure 1. X-ray molecular structure of **6p** with the atom numbering scheme.

Scheme 3



Scheme 4



6o: R= C_6H_5; R_1= C_6H_5; R_2= CF_3
6p: R= C_6H_5; R_1= Thienyl; R_2= CF_3

It is noteworthy that the intermediate **6p** was isolated in the Biginelli reaction and was characterized by X-ray diffraction analysis. Treatment of benzoyltrifluoroacetone or 2-thienoyltrifluoroacetone with benzaldehyde and urea gives hexahydropyrimidine **6o** or **6p** (Scheme 4) as the only isolable product in diastereomerically pure form (98% or 99% yield). The X-ray analysis of compound **6p** was then performed to confirm that the molecular structure is indeed as shown in Figure 1. The trans relationships between the 2-thienoyl group and both phenyl group and trifluoromethyl group in the hexahydropyrimidine ring of **6p** are in agreement with the ^{1}H NMR analysis; the $J_{H-H} \approx 11$ Hz is observed for the protons H-5 and H-4. Moreover, there exists hydrogen-bonding between the oxygen atom of carbonyl group and hydrogen of hydroxyl group in the compound. A related hexahydropyrimidine intermediate from the Biginelli reaction was also isolated[19] and its structure established by X-ray crystallography when we finished this work.

When intermediates **6o** or **6p** were heated to reflux in toluene in the presence of a strong acid (*p*-TsOH), elimination of water from **6o** or **6p** occurs yielding dihydropyrimidinone **7o** or **7p**. Undoubtedly, the unique electronic properties of the CF_3 group in this case prevent the elimination step from **6o** or **6p** to **7o** or **7p**[18]

In summary, this report discloses a new and simple modification of the Biginelli dihydropyrimidinones synthesis. By using $Yb(OTf)_3$ as a catalyst and under solvent-free reaction conditions, the yields of the one-pot Biginelli reaction can be increased from 20 to 50%[6] to 81−99% while the reaction time was shortened from 18 to 48 h to 20 min. In addition the catalyst can be easily recovered and reused. It not only led to economical automation but also reduces hazardous pollution to achieve environmentally friendly processes. Moreover the formation of acyl imine intermediate was proved indirectly and structure of hexahydropyrimidinone as the only isolated product in the Biginelli reaction was characterized by X-ray diffraction analysis. This $Yb(OTf)_3$ catalytic one-pot synthesis of dihydropyrimidinones therefore is a simple, high-yielding, timesaving, and environmentally friendly process.

Experimental Section

Melting points were determined on a Kofler hot stage. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 M Hz/or 400M Hz in DMSO-d_6 using TMS as internal standard. ^{13}C NMR spectral measurements were performed at 75 M Hz using DMSO-d_6 as an internal standard. IR spectra were obtained on FTS-185. Mass spectra were determined on a Finigan 8230 mass spectrometer.

Lanthanide Triflate Catalyzed Synthesis of Different Dihydropyrimidinones under Solventless Conditions. Aldehyde (2.5 mmol), *β*-dicarbonyl compound (2.5 mmol), urea (3.7 mmol), and $Yb(OTf)_3$ (0.125 mmol, 5 mol %) were heated at 100 °C under stirring for 20 min. Then water was added, and the product was extracted with ethyl acetate. After the organic layer was dried (Na_2SO_4) and evaporated, the residue was recrystallized by ethyl acetate and hexane to products **7**.

The catalyst remaining in the aqueous phase can be recovered by removing the water through heating and then drying under vacuum at 100 °C for 2 h.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (7a): mp 201−203 °C; ^{1}H NMR: $\delta = 9.20$ (s, 1H, NH), 7.75 (s, 1H, NH), 7.28 (m, 5H, arom CH), 5.14 (s, 1H, CH), 3.97 (q, $J = 7.1$ Hz, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, $J = 7.1$ Hz, 3H, OCH_2); IR (KBr): 3242, 1721, 1637 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.25; N, 10.92.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7b): mp 199−201 °C; ^{1}H

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(20) To a stirred mixture of 5-benzoyl-4-phenyl-hexahydropyrimidine (**6o**) or 5-thienoyl-4-phenyl- hexahydropyrimidine (**6p**) (2.0 mmol) and *p*-TsOH (1.0 mmol) in in toluene (5 mL) were heated to reflux for 2 h. Then water was added, and the product was extracted with ethyl acetate. After the organic layer was dried (Na_2SO_4) and evaporated, the residue was recrystallized by ethyl acetate and hexane to products **7o** or **7p** in 98% or 95% yield.

NMR: δ = 9.17 (s, 1H, NH), 7.68 (s, 1H, NH), 7.15 (d, `J = 8.6 Hz, 2H; arom CH), 6.88 (d, J = 8.5 Hz, 2H; arom CH), 5.09 (s, 1H, CH), 3.98 (q, J = 7.0 Hz, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3), 1.10 (t, J = 7.0 Hz, 3H, CH_3); IR (KBr): 3241, 1700, 1637 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.20; N, 9.66. Found: C, 61.65; H, 6.21; N 9.58.

5-(Ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (7c): mp 207−210 °C; ^{1}H NMR: δ = 9.37 (s, 1H, NH), 8.23 (d, J = 8.76 Hz, 2H, arom CH), 7.91 (s, 1H, NH), 7.52 (d, J = 8.69 Hz, 2H, arom CH), 5.28 (d, J = 3.2 Hz, 1H, CH), 3.99 (q, J = 7.1 HZ, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.10 (t, J = 7.1 Hz, 3H, CH_3); IR (KBr): 3235, 2981, 1724,1702, 1645, 1594 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.92; N, 13.77. Found: C, 54.80; H, 4.95; N, 13.77.

4-(4-Chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7d): mp 210−212 °C; ^{1}H NMR: δ = 9.26 (s, 1H, NH), 7.79 (d, J = 3.1 Hz, 1H, NH), 7.40 (d, J = 0.5 Hz, 2H arom CH), 7.25 (d, J = 8.5 Hz, 2H; arom CH), 5.14 (s, 1H, CH), 3.99 (q, J = 7.0 Hz, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, J = 7.0 Hz, 3H, CH_3); IR (KBr): 3241, 1700, 1645 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_2O_3Cl$: C, 57.14; H, 5.10; N 9.52. Found: C, 56.99; H, 5.09; N, 9.60.

4-(4-Fluorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7e): mp 175−177 °C; ^{1}H NMR: δ = 9.25 (s, 1H, NH), 7.77 (s, 1H, NH), 7.21 (m, 4H; arom CH), 5.15 (s, 1H, CH), 3.99 (q, J = 7.1 Hz, 2H, OCH_2), 2.26 (s, 3H CH_3), 1.09 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.3, 162.9, 159.8, 152.0, 148.6, 141.1, 128.3, 115.1, 99.2, 59.3, 53.3, 17.8, 14.1; IR (KBr): 3243, 1698, 1638 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 278 (M, 12), 249 (100). Anal. Calcd for $C_{14}H_{15}N_2O_3F$: C, 60.43; H, 5.40; N, 10.07. Found: C, 60.07; H, 5.50; N, 10.18.

4-(2,4-Dichlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7f): mp 238−240 °; ^{1}H NMR: δ = 9.33 (s, 1H, NH), 7.77 (s, 1H, NH), 7.57 (s, 1H; arom CH), 7.42 (d, J = 8.4 Hz, 1H, arom CH), 7.32 (d, J = 8.4 Hz, 1H, arom CH), 5.60 (s, 1H, CH), 3.90 (q, J = 7.1 Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.00 (t, J = 7.1 HZ, 3H, CH_3); ^{13}C NMR: δ = 165.0, 151.3, 149.7, 141.0, 132.8, 130.4, 128.8, 128.1, 97.6, 59.3, 51.3, 17.8, 14.0; IR (KBr): 3357, 1697, 1635 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 329 (M, 4), 183 (100). Anal. Calcd for $C_{14}H_{14}N_2O_3Cl_2$: C, 51.08; H, 4.29; N, 8.51. Found: C, 51.14; H, 4.27; N, 8.53.

5-(Ethoxycarbonyl)-6-methyl-4-(4-(trifluoromethyl)-phenyl)-3,4-dihydropyrimidin-2(1*H*)-one (7g): mp 173−175 °C; ^{1}H NMR: δ = 9.33 (s, 1H, NH), 7.86 (d, J = 2.9 Hz, 1H, NH), 7.72 (d, J = 8.2 Hz, 2H; arom CH), 7.47 (d, J = 8.2 Hz, 2H; arom CH), 5.25 (d, J = 2.8 Hz, 1H, CH), 4.00 (q, J = 7.1 Hz, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.12 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.2, 152.0, 149.3, 149.1, 149.0, 128.3,127.8, 126.9, 126.1, 125.5, 98.6, 59.4, 53.7, 17.8, 14.0; IR (KBr):3237, 1703, 1647 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 328 (M, 12), 183 (100). Anal. Calcd for $C_{15}H_{15}N_2O_3F_3$: C, 54.88; H, 4.57; N, 8.54. Found: C, 54.52; H, 4.58; N 8.56.

4-(2-Bromophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7h): mp 206−208 °C; ^{1}H NMR: δ = 9.29 (s, 1H, NH), 7.71 (s, 1H, NH), 7.57 (d, J = 7.9 Hz, 1H, arom CH), 7.34 (m, 2H, arom CH), 7.19 (m, 1H, arom CH), 5.61 (d, J = 2.2 Hz, 1H, CH), 3.89 (q, J = 7.1 Hz, 2H, OCH_2), 2.30 (s, 3H, CH_3), 0.99 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.0, 151.3, 149.3, 143.4, 132.6, 129.4,128.8 128.4, 122.3, 98.3, 59.1, 54.0, 17.6, and 14.0; IR (KBr): 3344, 1686, 1635 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 339 (M, 21), 42 (100). Anal. Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.57; H, 4.47; N, 8.26. Found: C, 49.71; H, 4.50; N 8.24.

5-(Ethoxycarbonyl)-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1*H*)-one (7i): mp 232−235 °C; ^{1}H NMR: δ = 9.13 (s, 1H, NH), 7.53 (d, J = 1.9 Hz, 1H, NH), 7.21−7.46 (m, 5H, arom CH), 6.37 (d, J = 15.9 Hz, 1H, H−C═CH), 6,20 (dd, J = 15.8, 6.0 Hz, 1H, CH═C−H), 4.74 (d, J = 5.80 Hz, 1H, CH), 4.09 (m, 2H, OCH_2), 2.21 (s, 3H, CH_3), 1.20 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.1, 152.6, 148.5, 136.2, 130.0, 128.6, 128.1, 127.5, 126.2, 97.8, 59.2, 51.8, 17.7, 14.2; IR (KBr): 3241, 1704, 1650 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 286 (M, 17), 259 (100); HRMS calcd for $C_{16}H_{18}N_2O_3$ 286.1346; found 286.1317.

4-Butyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7j): mp 157−158 °C; ^{1}H NMR: δ = 8.92 (s, 1H, NH), 7.31 (s, 1H, NH), 4.05 (m, 2H, OCH_2), 2.16 (s, 3H, CH_3), 1.38−1.15 (m, 9H, $(CH_2)_3CH_3$), 0.85 (t, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.4, 152.7, 148.2, 99.4, 59.7, 59.0, 49.90, 36.4, 25.9, 21.9, 20.7, 17.6, 14.2, 14.0; IR (KBr): 3248, 1722, 1647 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 241 (M + 1, 12), 183 (100). Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 59.96; H, 8.39; N, 11.66. Found: C, 58.58; H, 8.13; N 11.57.

5-(Ethoxycarbonyl)-4-isopropyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7k): mp 194−195 °C; ^{1}H NMR: δ = 8.86 (s, 1H, NH), 7.26 (s, 1H, NH), 4.04 (m, 2H, OCH_2), 3.96 (t, J = 3.6 Hz, 1H, CH), 2.18 (s, 3H, CH_3), 1.68 (m, 1H, CH), 1.19 (t, J = 7.1 Hz, 3H, CH_3), 0.82 (d, J = 6.9 Hz, 3H, CH_3), 0.74 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.8, 153.2, 148.4, 98.2, 59.1, 55.5, 34.6, 18.5, 17.7, 16.0, 14.2; IR (KBr): 3234, 3106, 1692, 1645 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 227 (M + 1, 54), 183 (100). Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.40; H, 8.01; N, 12.44.

5-Aceto-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (7l): mp 233−236 °C; ^{1}H NMR: δ = 9.16 (s, 1H, NH), 7.78 (s, 1H, NH), 7.22−7.36 (m,5H, arom CH), 5.25 (d, J = 2.4 Hz, 1H, CH), 2.24 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3); ^{13}C NMR: δ = 194.4, 158.5, 152.1, 147.8, 136.9, 127.7, 113.9, 109.6, 55.1, 53.3, 30.18, 18.8; IR (KBr): 3257 1699, 1673 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 230 (M, 57), 229 (M − 1, 100); HRMS for $C_{13}H_{14}N_2O_2$: 230.1102; found 230.1055.

5-Aceto-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (7m): mp 168−130 °C; ^{1}H NMR: δ = 9.16 (s, 1H, NH), 7.78 (s, 1H, NH), 7.16 (d, J = 8.7 HZ, 2H, arom CH), 6.88 (d, J = 8.7 Hz, 2H, arom CH), 5.20 (d, J = 3.0 Hz, 1H, CH), 3.72 (s, 3H, CH_3CO), 2.28 (s, 3H, CH_3), 2.07 (s, 3H, OCH_3); ^{13}C NMR: δ = 194.4, 158.5, 152.1, 147.8, 136.4, 127.7, 113.9, 109.6, 55.1, 53.3, 30.2, 18.8; IR (KBr): 3242, 1714, 1624,cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 260 (M, 44), 259 (M − 1, 100); HRMS for $C_{14}H_{16}N_2O_3$: 260.1133; found 260.1160

5-Acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (7n): mp 230 (dec); ^{1}H NMR: δ = 9.40 (s, 1H, NH), 8.21 (d, J = 8.4 Hz, 2H, arom,CH), 7.93 (s, 1H, NH), 7.51 (d, J = 8.7 Hz, 2H, arom CH), 5.39 (s, 1H, CH), 2.32 (s, 3H, CH_3CO), 2.19 (s, 3H, CH_3); ^{13}C NMR: δ = 194.0, 152.0, 151.6, 149.1, 146.7, 127.7, 123.8, 109.5, 53.1, 30.7, 19.1; IR (KBr): 3241, 1699, 1627 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 275 (M, 29), 274 (M − 1, 43), 153 (100); HRMS for $C_{13}H_{13}N_3O$: 275.0937; found 275.0906.

5-Benzoyl-4-phenyl-hexahydropyrimidine (6o): mp 198−200 °C; ^{1}H NMR: δ = 7.67 (m, 2H, NH), 7.51−7.10 (m, 10H, arom CH), 4.98 (d, J = 11.1 Hz, 1H, CH), 4.39 (d, J = 11.1 Hz, 1H, CH); ^{13}C NMR: δ = 195.8, 154.0, 138.4, 137.3, 133.4, 128.6, 128.4, 128.3, 127.8, 81.7, 54.7, 48.1; IR (KBr): 3220, 1718, 1684 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 365 (M+1, 1), 241 (100), 207 (25). Anal. Calcd for $C_{18}H_{13}N_2O_3F_3$: C, 59.34; H, 4.15; N, 7.96. Found: C, 59.32; H, 4.15; N, 7.64.

5-Benzoyl-4-phenyl-6-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (7o): mp 160−162 °C; ^{1}H NMR: δ = 9.86 (s, 1H, NH), 7.93 (s, 1H, NH), 7.66 (m, 3H, arom, CH), 7.48 (m, 2H, arom, CH), 7.25 (m, 5H, arom, CH), 5.22 (s, 1H, CH); ^{13}C NMR: δ = 192.4, 151.9, 141.1, 135.9, 134.1, 128.9, 128.8, 128.3 126.6, 114.6,57.1; IR (KBr): 3246, 1705, 1670 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 345 (M − 1, 4), 346 (M, 14), 77 (100); HRMS for $C_{18}H_{13}N_2O_2F_3$: 346.0929; found 346.0922.

5-Thienoyl-4-phenyl-hexahydropyrimidine (6p): mp 192−195 °C; ^{1}H NMR: δ = 7.84 (m, 2H, thiene CH), 7.76 (s, 1H, NH), 7.39 (s, 1H, thiene CH), 7.37 (s, 1H, NH), 7.27 (s, 1H, OH), 7.17−7.05 (m, 5H, arom, CH), 4.93 (d, J = 11.2 Hz, 1H, CH), 4.25 (d, J = 11.1 Hz, 1H, CH); IR (KBr): 3442, 3202, 1680, 1662 cm^{-1}; ^{13}C NMR: δ = 188.3, 153.9, 145.6, 144.9, 138.1, 136.1, 135.4, 133.9, 128.3, 128.1, 127.6, 127.1, 124.6, 121.8, 81.3, 54.4, 49.7. MS (70 eV, EI): *m*/*z* (%): 371 (M − 1, 14), 241 (100); IR (KBr): 3398, 1698, 1683 cm^{-1}. Anal. Calcd for $C_{16}H_{13}F_3N_2O_3S$: C, 51.89; H, 3.51; N, 7.56. Found: C, 51.62; H, 3.94; N, 6.88. HRMS for $C_{16}H_{13}F_3N_2O_3S$: 370.0659; found 370.0653.

4-Phenyl-5-thienoyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1*H*)-one (7p): mp 99−102 °C; ^{1}H NMR: δ = 9.79 (s, 1H, NH), 8.03 (d, J = 5.0 Hz, 1H, thiene CH), 7.90 (s, 1H, NH), 7.52 (d, J = 3.8 Hz, 1H, thiene CH), 7.34−7.11 (m, 5H, arom CH), 5.25 (s, 1H, CH); IR (KBr): 3200, 1670 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 353 (M+1, 13), 352 (M, 3), 111 (100); HRMS for $C_{16}H_{11}F_3N_2O_2S$: 352.0494; found 352.0456.

5-(Methoxycarbonyl)-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7q): mp 207−210 °C; ^{1}H NMR: δ = 9.23 (s, 1H, NH), 7.77 (d, J = 3.0 Hz 1H, NH), 7.35−7.22 (m, 5H, arom CH), 5.15 (d, J = 2.8 Hz, 1H, CH), 3.53 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); IR (KBr): 3331, 1695, 1651 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.70; N, 11.37. Found: C, 63.57; H, 5.77; N, 11.14.

5-(Methoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7r): mp 191−193 °C; ^{1}H NMR: δ = 9.19 (s, 1H, NH), 7.69 (s, 1H, NH), 7.14 (d, J = 8.7 Hz, 2H, arom CH), 6.88 (d, J = 8.7 Hz, 2H, arom CH), 5.09 (d, J = 2.7 Hz, 1H, CH), 3.72 (s, 3H, CH_3OCO), 3.53 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); IR (KBr): 3360, 1697, 1645 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.80; N, 10.14. Found: C, 60.23; H, 5.89; N, 10.04.

5-(Methoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7s): mp 235−237 °C; ^{1}H NMR: δ = 9.36 (s, 1H, NH), 8.21 (d, J = 8.8 Hz, 2H, arom CH), 7.90 (d, J = 2.7 Hz, 1H, NH), 7.51 (d, J = 8.8 Hz, 2H, arom CH), 5.29 (d, J = 2.7 Hz, 1H, CH), 3.54 (s, 3H, CH_3OCO), 2.27 (s, 3H, CH_3); IR (KBr): 3362, 3221, 1711, 1635, cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_3O_5$: C, 53.60; H, 4.47; N, 14.43. Found: C, 53.63; H, 4.53; N, 13.88.

4-(2,4-Dichlorophenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7t): mp 254−255 °C; ^{1}H NMR: δ = 9.33 (s, 1H, NH), 7.77 (s, 1H, NH), 7.55 (d, J = 1.6 Hz, 1H, arom CH), 7.41 (dd, J = 8.4, 1.6 Hz, 2H, arom CH), 7.32 (d, J = 8.4 Hz, 1H, arom CH), 5.56 (s, 1H, CH), 3.46 (s, 3H, CH_3OCO), 2.54 (s, 3H, CH_3) ^{13}C NMR: δ = 167.0, 152.8, 151.3, 142.5, 134.3, 131.9, 130.5, 129.7, 99.0, 52.8, 52.4, 19.4; IR (KBr): 3360, 1696, 1645 cm^{-1}; MS (70 eV, EI): m/z (%): 315 (M, 27), 169 (100). Anal. Calcd for $C_{13}H_{12}N_2O_3Cl_2$: C, 49.50; H, 3.83; N, 8.89. Found: C, 49.60; H, 3.85; N, 8.88.

4-(4-Fluorophenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (7u): mp 192−194 °C; ^{1}H NMR: δ = 9.27 (s, 1H, NH), 7.79 (s, 1H, NH), 7.29 (m, 4H, arom CH), 5.16 (d, J = 3.0 Hz, 1H, CH), 3.54 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR: δ = 166.6, 165.8, 163.0, 159.8, 152.1, 148.8, 141.0, 132.2, 128.3, 115.4, 99.0, 53.2, 50.9, 17.9; IR (KBr): 3326, 1682, 1603 cm^{-1}; MS (70 eV, EI): m/z (%): 264 (M, 13), 169 (100). Anal. Calcd for $C_{13}H_{13}N_2O_3F$: C, 59.08; H, 4.96; N, 10.6. Found: C, 59.48; H, 4.55; N, 10.07.

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Supporting Information Available: ^{1}H NMR spectra of the compounds synthesized**.** This material is available free of charge via the Internet at http://pubs.acs.org.

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