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An improved synthesis of Biginelli-type compounds via phase-transfer catalysis

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Tetra-butyl ammonium bromide (TBAB)

ABSTRACT

3,4-Dihydropyrimidin-2(1*H*)-one, 3,4-dihydropyrimidin-2(1*H*)-thione, and 3,4-dihydropyrimidin-2(1*H*)-imine derivatives were synthesized by modified Biginelli cyclocondensation reaction in a time-efficient manner with near quantitative yields starting from appropriately substituted aromatic aldehyde, β-ketoester and either urea, thiourea or guanidine as constituent synthons using tetra-butyl ammonium bromide (TBAB) as catalyst for the first time.

Dihydropyrimidines are an important class of compounds exhibiting broad spectra of pharmacological activities such as anti-inflammatory, anti-microbial, α-1a-adrenergic receptor antagonist, and antihypertensives.[1,2] The development of dihydropyrimidine templates as pharmacologically active compounds contributed toward Biginelli cyclocondensation applications in drug industry. The contemporary advances in marine natural products chemistry with structure diversification in dihydropyrimidine nucleus also found synthetic attention[3–7] from Biginelli reaction. More recently, advances in the involvement of newer catalytic systems involvement in solid phase, parallel and other combinatorial synthetic approaches contributed toward expansion of Biginelli cyclocondensation applications. The three-component cyclocondensation reaction constituting aldehyde, β-ketoester, and urea in an acidic medium[3] was refluxed using ethanolic/methanolic HCl in the classical synthesis while other solvent-cum-acidic catalytic systems such as THF–HCl and dioxane–HCl were also employed with H_2SO_4 as a replaceable acidic source in later developments. The major drawbacks associated with acid-catalyzed reactions were lower yields[1] (from 26% to 60%), particularly for tri and tetra-substituted aldehydes of aromatic and aliphatic origins as well as extended reaction times from 24 to 36 h. The increasing interest in this class of compounds led to the development of other synthetic strategies with alternate catalysts. The recent interests in Biginelli cyclocondensation for its tailor-made suitability in high throughput synthesis[8] have found Lewis acid catalysts, for example, $Mn(OAc)_3.2H_2O$[9], $Cu(OTf)_2$[10], VCl_3[11], $Yb(OTf)_3$,[12] and $LaCl_3{\cdot}7H_2O$[13], which significantly improved the reaction output with reduced reaction times. The polymer-supported, resin-bound isothiourea[14], poly(4-vinylpyridine-co-divinyl benzene–Cu-II) complex[15], ceria/vinyl-pyrimidine polymer nanocomposite[16], *N*-butyl-*N*,*N*-dimethyl-α-phenyl-ethyl ammonium bromide,[17] and various other catalysts have been successfully used for syntheses of Biginelli products.

In search of an inexpensive and environmentally benign catalyst, tetra-butyl ammonium bromide (TBAB) was tested as an alternative catalyst with various substrates. The cost, availability, and compatibility across phases in biphasic organic-aqueous layer heterogeneous reaction systems, with water as solvent, TBAB was found to be a better catalyst. The current work describes this approach toward Biginelli reaction with higher versatility for the introduction of new substitution patterns. We report, herein, the use of tetra-butyl ammonium bromide as an environment friendly, bio-compatible, inexpensive, neutral, and high yielding (90–96%) as well as short time-path (40–120 min) catalyst in producing new heterocyclic products in comparison to other known methodology. This observation is also of significant importance for laboratory and bulk scales preparation of Biginelli-type products in wet and solid phase chemistry.

We have undertaken the synthesis of different derivatives of 3,4-dihydropyrimidin-2(1*H*)-one, 3,4-dihydropyrimidin-2(1*H*)-thione, and 3,4-dihydropyrimidin-2(1*H*)-imines from a variety of substrates from aromatic aldehydes, ethylacetoacetate **18** and either urea/ thiourea or guanidine. The benzaldehyde derivatives with substitutions in the aromatic ring with 4-methyl, *n*-halogens (*n* = varying ring substitution positions), 2-hydroxy, *n*-methoxy,

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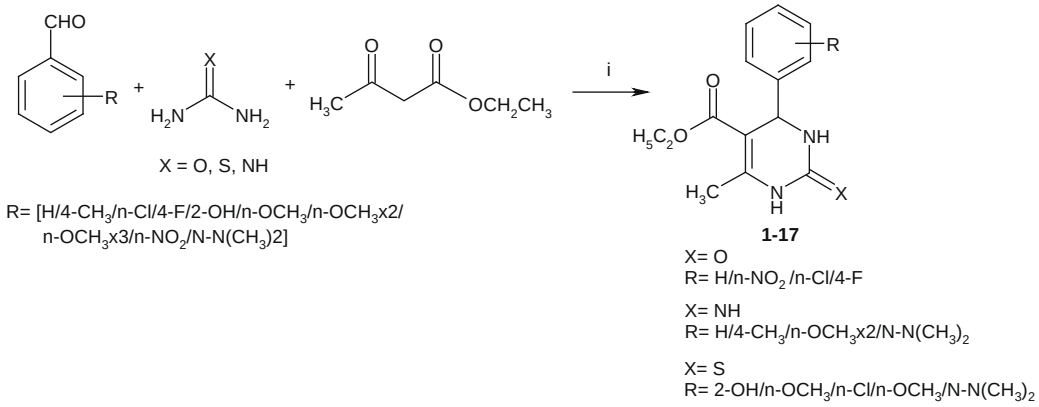


Scheme 1. General synthetic scheme of compounds **1**–**17**. Reagents and conditions: (i) TBAB (1.5 M), aq KOH (10% w/v), 100 °C, 40–120 min.

Table 1
Molecular formulae, melting point, time-cycle, and yield comparison profiles of compounds **1**–**17**

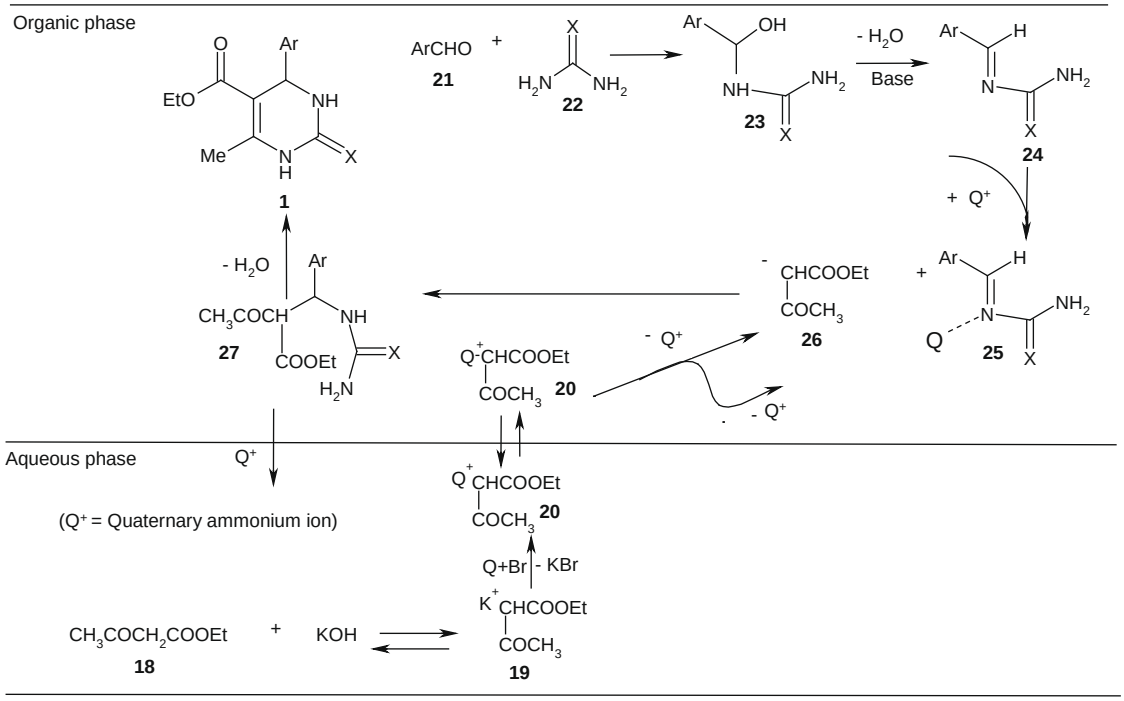
Compd	Substitution		Molecular formulae	Melting point (°C)		Time (min)	Yield[a] (%)
	R	X		Found	Reported		
1	H	O	$C_{14}H_{16}N_2O_3$	204–206	200–202	40	96[b]
2	2-Nitro	O	$C_{14}H_{15}N_3O_5$	216–218	—	45	94[c]
3	3-Nitro	O	$C_{14}H_{15}N_3O_5$	225–227	225–227	45	90[b]
4	4-Nitro	O	$C_{14}H_{15}N_3O_5$	210–212	205–207	55	90[b]
5	4-Chloro	O	$C_{14}H_{15}ClN_2O_3$	207–209	209–211	50	88[b]
6	4-Fluro	O	$C_{14}H_{15}FN_2O_3$	186–188	—	50	88[d]
7	2-Hydroxy	S	$C_{14}H_{16}N_2O_3S$	206–208	—	70	80
8	4-Methoxy	S	$C_{15}H_{18}N_2O_3S$	141–143	138–140	60	96[b]
9	2-Chloro	S	$C_{14}H_{15}ClN_2O_2S$	219–221	—	50	90
10	3-Chloro	S	$C_{14}H_{15}ClN_2O_2S$	240–242	—	65	96
11	3,4-Dimethoxy	S	$C_{16}H_{20}N_2O_4S$	212–214	—	65	90
12	4-*N*,*N*-Dimethyl amino	S	$C_{16}H_{21}N_3O_2S$	209–210	209–210	100	94[e]
13	H	NH	$C_{14}H_{17}N_3O_2$	176–178	—	45	92
14	4-Methyl	NH	$C_{15}H_{19}N_3O_2$	Oil	—	75	89
15	2,3,4-Trimethoxy	NH	$C_{17}H_{23}N_3O_5$	125–127	—	55	87
16	3,4-Dimethoxy	NH	$C_{16}H_{21}N_3O_4$	101–103	—	60	89
17	4-*N*,*N*-Dimethyl amino	NH	$C_{16}H_{22}N_4O_2$	163–165	—	120	94

[a] Isolated yield.
[b] Ref. 20.
[c] Ref. 9.
[d] Ref. 21.
[e] Ref. 19.

varying nitro positions and *N*,*N*-dimethylamino groups were reacted with urea, thiourea, and guanidine to furnish a series of products **1–17** (Scheme 1, Table 1). The higher yields and shorter reaction times validated the mechanistic approach suggested by Kappe[18], whereby the aldol adduct **24** formed from aromatic aldehyde derivative and urea variant is approached by the β-keto ester in enolate form as the attacking species (Scheme 2).

The TBAB plays an important role as a catalyst in the synthesis of dihydropyrimidine and other related derivatives and product variants with O, S, and NH as the C-2 substitution in dihydropyrimidine nucleus. The TBAB participation in catalyzing the Biginelli reaction can be understood by proposed mechanism (Scheme 2). The reaction of β-keto ester, that is, ethylacetoacetate **18** with KOH affords the adduct **19** (K^+-enolate), which is further transformed to entity **20** (Q^+-enolate) by ion-exchange between Q^+ (quaternary ammonium ion) from Q^+ Br^- and K^+-enolate ion **19** in the aqueous media. The quaternary ammonium ion-based entity **20** (Q^+-enolate) loses the quaternary ammonium ions (Q^+) to produce **26** (β-keto ester enolate), an equivalent of base-supported-proton-abstraction-anionic entity. **26** reacts with **25**, a (Q^+···C=N) electrophilic system generated by addition of Q^+ to imine adduct **24** (C=N) that itself is obtained from an aldol adduct amine **23** by the reaction between starting aldehyde **8** and corresponding urea **22** in organic phase to produce the open-chain uride product **27**. The proposed mechanism between aldehyde and urea/ thiourea/ guanidine generates an acyl imine intermediate **24**, which reacts with quaternary ammonium ion generated from TBAB is supported by a similar mechanism of formation of an intermediate **25** stabilized by participation of lone pair of acyl imine *N* electrons (Nandurkar et al.[22]). The intermediate product **27** undergoes cyclization with removal of one mole of water molecule leading to desired 3,4-dihydropyrimidin-2(1*H*)-one as the final product **1**.

The use of TBAB preserved the classical simplicity of Biginelli one-pot synthesis and remarkably improved the yield profile and time to complete the reaction (Table 1) in shorter span (40–120 min) than the reported longer times (6–7 h to previous 24–36 h). In order to further improve the reaction time and product yield profile, the effects of ratios of three synthon components namely, β-keto ester, aromatic aldehyde and urea, thiourea or guanidine with varying concentrations of TBAB as catalyst were test run. The optimized best yields and time profiles were obtained with a molar ratio of 1:1:1:0.15 of β-keto ester, aromatic aldehyde, urea/ thiourea or guanidine and TBAB as catalyst, respectively.



Scheme 2. Proposed mechanism of Biginelli reaction using TBAB.

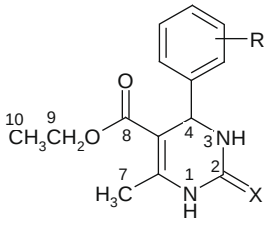


Figure 1. General structures of compounds **1**–**17**.

The general synthetic scheme for 3,4-dihydropyrimidin-2(1*H*)-one, 3,4-dihydropyrimidin-2(1*H*)-thione, 3,4-dihydropyrimidin-2(1*H*)-imine, and their derivatives[23] (**1**–**17**) has been depicted in Scheme 1. The structures of all the new synthesized compounds (Fig. 1) were established on the basis of their spectral (IR, ^{1}H NMR, mass spectra) and elemental analysis data.[24] The melting point, time required for preparation, and yield percentage of all the products have been summarized in Table 1.

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References and notes

1. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
2. Grover, G. I.; Dzwonczyk, S.; McMullen, D. M.; Normadin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289.
3. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
4. Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *38*, 3828.
5. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosses, C. D.; Mai, S.; Truneh, A.; Faulkner, D. J.; Cart, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Wesley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182.
6. Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K. B.; Faulkner, D. J.; Batzelladines, F. I. *J. Org. Chem.* **1997**, *62*, 1814.
7. Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977.
8. Sucholeiki, I. *High-Throughput Synthesis: Principles and Practices*; Marcel Decker: New York, 2001.
9. Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873.
10. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305.
11. Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 6497.
12. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
13. Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075.
14. Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2001**, *10*, 49.
15. Yarapathi, R. V.; Kurva, S.; Tammishetti, S. *Catal. Commun.* **2004**, *5*, 511.
16. Sabitha, G.; Reddy, K. B.; Yadav, J. S.; Shailaja, D.; Sivudu, K. *Tetrahedron Lett.* **2005**, *46*, 8221.
17. Reddy, K. R.; Reddy, C. V.; Mahesh, M.; Raju, P. V. K. *Tetrahedron Lett.* **2003**, *44*, 8173.
18. Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.
19. Su, W.; Li, J.; Zheng, Z.; Shen, Y. *Tetrahedron Lett.* **2005**, *46*, 6037.
20. Shabaani, A.; Bazgir, A.; Teimouri, F. *Tetrahedron Lett.* **2003**, *44*, 857.
21. Dondoni, A.; Massi, A. *Tetrahedron Lett.* **2001**, *42*, 7975.
22. Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *J. Mol. Catal. A: Chem.* **2007**, *271*, 14.
23. *General method for synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, 3,4-dihydropyrimidin-2(1H)-thione, and 3,4-dihydropyrimidin-2(1H)-imine derivatives* (**1**–**17**): Benzaldehyde or appropriately substituted corresponding benzaldehyde derivatives (10 mmol), ethyl acetoacetate (10 mmol) and either urea/thiourea or guanidines (10 mmol) were mixed together followed by addition of 10% aqueous KOH (0.5 g in 5 mL water) and catalytic amount of solid tetra-butyl ammonium bromide (0.483 g, 1.5 M) in a 100 mL round-bottomed flask. The reaction mixture was heated with stirring at 100 °C for appropriate time (Table 1). The progress of reaction was monitored by TLC and after completion, the resultant mass was poured into crushed ice and solid obtained was filtered through Buckner funnel, washed with ice-cold water, twice with petroleum-ether, and air-dried over Buckner. The obtained oily material was separated, neutralized with 5% aq HCl, water washed, dried over anhydrous sodium sulphate, and concentrated under vacuo. The solid crude products were recrystallized from ethanol.
24. *Spectroanalytical data for new compounds*: 5-Ethoxycarbonyl-6-methyl-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**7**): IR (KBr): 3425, 3367, 1701, 1653, 1359, 1292 cm^{-1}: ^{1}H NMR (300 MHz, MeOH-d_4): δ 1.04 (t, J = 7.2 Hz, 3H, CH_3-10), 2.15 (s, 3H,CH_3-7), 4.10 (d, 1H, Ar-OH), 4.22 (q, J = 7.2, 4.3 Hz , 2H, CH_2O-9), 4.22 (s, 1H, CH-4), 7.21–6.81 (m, 4H, Ar-H), 8.46 (s, 1H, NH-1), 9.57 (s, 1H, NH-3): Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97%. Found: C, 57.56; H, 5.48; N, 9.56; S, 10.98.
5-Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)thione (**9**): IR (KBr): 3319, 3270, 2969, 1695, 1645, 1358, 1311 cm^{-1}: ^{1}H NMR (300 MHz, MeOH-d_4): δ 1.18 (t, J = 7.2 Hz, 3H, CH_3-10), 2.0 (s, 3 H, CH_3-7), 4.12 (q, J = 7.2, 4.3 Hz, 2H, CH_2O-9), 5.11 (s, 1H, CH-4), 7.4–6.8 (m, 4H, Ar-H): 7.43

(s, 1H, NH-3), 9.26 (s, 1H, NH-1). Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$. C, 54.10; H, 4.86; N, 9.01; S, 10.32. Found: C, 54.16; H, 4.82; N, 9.06; S, 10.28.

5-Ethoxycarbonyl-6-methyl-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-thione (**10**): IR (KBr): 3420, 3284, 2975, 1710, 1641, 1353, 1285 cm^{-1}: ^1H NMR (300 MHz, MeOH-d_4): δ 1.18 (t, J = 7.5 Hz, 3H, CH_3-10), 2.23 (s, 3 H,CH_3-7), 4.12 (q, J = 7.4, 4.4 Hz, 2H, CH_2O-9), 4.12 (s, 1H, CH-4), 7.29–6.23 (m, 4H, Ar-H), 7.40 (s, 1H, NH-1), 9.32 (s, 1H, NH-3): Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01; S, 10.32. Found: C, 54.08; H, 4.83; N, 9.05; S, 10.31.

5-Ethoxycarbonyl-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (**11**): IR (KBr): 3426, 3134, 2982, 1698, 1633, 1368, 1325, 1287 cm^{-1}: ^1H NMR (300 MHz,MeOH-d_4): δ 1.20 (t, J = 7.9 Hz, 3H, CH_3-10), 2.34 (s, 3 H, CH_3-7), 3.4 (s, 3H, Ar-OCH_3-3′), 3.88 (s, 3H, Ar-OCH_3-4′), 4.12 (q, J = 7.9, 4.6 Hz, 2H, CH_2O-9), 5.26 (s, 1H, CH-4), 6.9 (s, 1H, NH-3), 7.81–6.84 (m, 3H, Ar-H), 9.56 (s, 1H, NH-3); MS: m/z 336 (M^+, $C_{16}H_{20}N_2O_4S^+$, 62%), 291 (23), 277 (100), 263 (18), 232 (14), 204 (16). Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53. Found: C, 57.15; H, 5.97; N, 8.36; S, 9.52.

5-Ethoxycarbonyl- 6-methyl-4-phenyl- 3,4- dihydropyrimidin-2(1H)-imine (**13**): IR (KBr): 3340, 3287, 2875, 1641 cm^{-1}: ^1H NMR (300 MHz, MeOH-d_4): δ 1.16 (t, J = 7.1 Hz , 3H, CH_3-10), 2.33 (s, 3 H, CH_3-7), 3.34 (s, 1H, NH-2), 4.08 (q, J = 7.1, 4.8 Hz, 2H, CH_2O-9), 5.30 (s, 1H, CH-4), 7.30–7.23 (m, 5H, Ar-H), 8.48 (s,1H, NH-3), 9.48 (s, 1H, NH-1)., MS: m/z 259 (M^+ $C_{14}H_{17}N_3O_2$, 46%), 217 (25), 214 (100), 186 (13), 172 (16), 144 (18). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.82; H, 6.63; N, 16.24.

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-imine (**14**): IR (KBr): 3219, 3115, 2965, 1641 cm^{-1}: ^1H NMR (300 MHz, MeOH-d_4): δ 1.64 (s, 3H, Ar-CH_3-4′), 1.69 (t, J = 7.9 Hz, 3H, CH_3-10), 2.40 (s, 3 H, CH_3-7), 5.47 (s, 1H, CH-4), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH_2O-9), 7.30–7.23 (m, 5H, Ar-H), 7.41 (s, 1H, NH-3), 9.34 (s, 1H, NH-1); Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found C, 65.95; H, 7.02; N, 15.34.

5-Ethoxycarbonyl-6-methyl-4-(2,3,4-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-imine (**15**): IR (KBr): 3257, 3104, 2976, 1641 cm^{-1}: ^1H NMR (300 MHz, MeOH-d_4): δ 1.64 (s, 3H, Ar-CH_3-4′), 1.69 (t, J = 7.9 Hz, 3H, CH_3-10), 2.40 (s, 3 H, CH_3-7), 5.47 (s, 1H, CH-4), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH_2O-9), 7.28 (s, 1H, NH-3), 7.30–7.23 (m, 5H, Ar-H), 8.92 (s, 1H, NH-1), Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.64; N, 12.03. Found C, 58.47; H, 6.62; N, 12.05.

5-Ethoxycarbonyl-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-imine (**16**): IR (KBr): 3371, 3134, 2975, 1641 cm^{-1}: ^1H NMR (300 MHz, MeOH-d_4): δ 1.64 (s, 3H, Ar-CH_3-4′), 1.69 (t, J = 7.9 Hz , 3H, CH_3-10), 2.40 (s, 3 H, CH_3-7), 5.47(s, 1H, CH-4), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH_2O-9), 7.30–7.23 (m, 5H, Ar-H), 7.31 (s, 1H, NH-3),9.97 (s, 1H, NH-1), Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found C, 60.21; H, 6.65; N, 13.14.

5-Ethoxycarbonyl-6-methyl-4-(4-N,N-dimethylamino)-3,4-dihydropyrimidin-2(1H)-imine (**17**): IR (KBr): 3319, 3114, 2965, 1650 cm^{-1}: ^1H NMR (300 MHz, MeOH-d_4): δ 1.64 (s, 3H, Ar-CH_3-4′), 1.69 (t, J = 7.9 Hz , 3H, CH_3-10), 2.40 (s, 3 H, CH_3-7), 5.47 (s, 1H, CH-4), 3.27 (s, 1H, =NH-2), 3.35 (q, J = 7.9, 4.4 Hz, 2H, CH_2O-9), 8.21 (s, 1H, NH-1), 9.48 (s, 1H, NH-3), 7.30–7.23 (m, 5H, Ar-H); Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found C, 63.53; H, 7.29; N, 18.49.