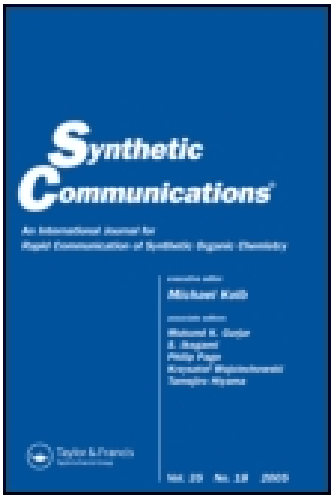


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Biginelli-Like Cyclocondensation Reaction: Efficient Synthesis of 4,6-Diarylpyrimidin-2(1H)-one Under Solvent-Free Conditions

Yisi Dai [a], Minxiang Cao [a], Mengjie Zhuang [a], Sheng Xia [a], Shujiang Tu [a b] & Liangce Rong [a b]

[a] College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, Jiangsu, China

[b] Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Xuzhou, Jiangsu, China

Published online: 11 Jul 2011.

To cite this article: Yisi Dai, Minxiang Cao, Mengjie Zhuang, Sheng Xia, Shujiang Tu & Liangce Rong (2011) Biginelli-Like Cyclocondensation Reaction: Efficient Synthesis of 4,6-Diarylpyrimidin-2(1H)-one Under Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:20, 3039-3044, DOI: 10.1080/00397911.2010.516619

To link to this article: http://dx.doi.org/10.1080/00397911.2010.516619

Synthetic Communications®, 41: 3039–3044, 2011

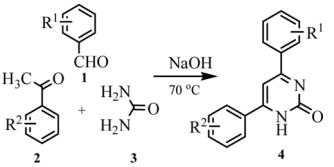
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.516619

BIGINELLI-LIKE CYCLOCONDENSATION REACTION: EFFICIENT SYNTHESIS OF 4,6-DIARYLPYRIMIDIN-2(1*H*)-ONE UNDER SOLVENT-FREE CONDITIONS

Yisi Dai,[1] Minxiang Cao,[1] Mengjie Zhuang,[1] Sheng Xia,[1] Shujiang Tu,[1,2] and Liangce Rong[1,2]

[1]*College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, Jiangsu, China*
[2]*Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Xuzhou, Jiangsu, China*

GRAPHICAL ABSTRACT



Abstract *An efficient and facile synthesis of 4,6-diarylpyrimidin-2(1*H*)-one via a Biginelli-like reaction of aromatic aldehydes, aromatic ketones, and urea in the presence of NaOH under solvent-free conditions using a heating method has been developed. Compared with the classical reaction conditions, this new synthetic method has the advantages of excellent yields, shorter reaction time, and mild reaction conditions.*

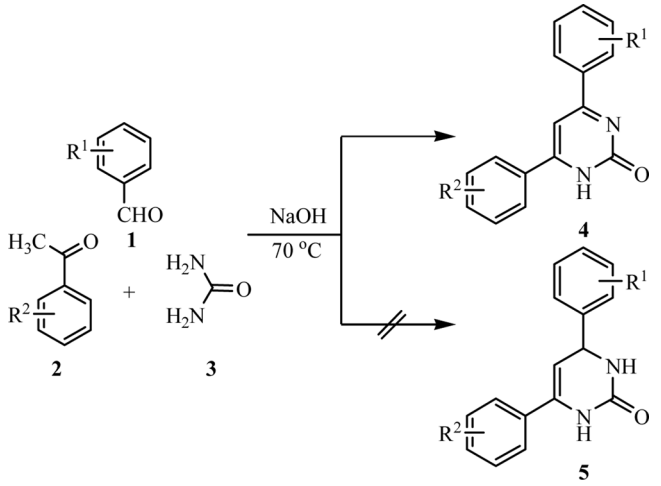
Keywords Biginelli-like reaction; 4,6-diarylpyrimidin-2(1*H*)-one; green chemistry; solvent-free synthesis

INTRODUCTION

The *N*-heterocyclic compounds, such as hydropyrimidinones, are very useful intermediates for the development of molecules of pharmaceutical or biological interest. These compounds show variable biological activities, such as antimalarial, anticonvulsant, anesthetic, antioxidant, antibacterial, and antiparasitic properties.[1–3] In addition, hydropyrimidinones have also attracted much attention in previous years because of their large is range of biological activities, including as calcium channel blockers.[4,5] So, synthesis of these compounds is an important topic in organic chemistry.

Received July 16, 2009.

Address correspondence to Liangce Rong, College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, Jiangsu, China. E-mail: lcrong2005@yahoo.com



Scheme 1. Reaction of aromatic aldehydes, aromatic ketones, and urea.

The Biginelli reaction is one of the most important reactions to synthesize 3,4-dihydropyrimidin-2-(1*H*)-one in a one-pot reaction of aldehyde, α-ketoester, and urea. In past years, many methods have been reported to improve this reaction because of its harsh reaction conditions, such as long reaction times, high temperatures, low yields, expensive catalysts, and harmful and difficult-to-handle reagents, especially on a large scale.[6] At the same time, many Biginelli-like reactions also have been reported and many pyridine-like derivatives have been synthetized.[7]

Because it avoids using an organic solvent in the reactions, solvent-free synthesis is regarded as one of the important methods in current green chemistry. Herein, we report a Biginelli-like cyclocondensation reaction to prepare 4,6-diarylpyrimidin-2(1*H*)-one derivatives from aromatic aldehydes, aromatic ketones, and urea using NaOH as catalyst under solvent-free conditions (Scheme 1).

The reaction process could be depicted as follows: the aromatic aldehydes **1**, aromatic ketones **2**, and urea **3** were put in a mortar to blend together in the presence

Table 1. Synthesis of 4,6-diarylpyrimidin-2(1*H*)-one

Entry	R^1	R^2	Product	Yields (%)
1	H	4-CH_3O	**4a**	90
2	H	3-Cl	**4b**	85
3	H	4-Cl	**4c**	91
4	3,4-$(CH_3)_2$	4-CH_3	**4d**	80
5	4-CH_3	H	**4e**	85
6	4-F	H	**4f**	88
7	4-Br	H	**4g**	92
8	2-Cl	H	**4h**	82
9	3-Cl	H	**4i**	86
10	4-Cl	H	**4j**	92
11	2,4-Cl_2	H	**4k**	90
12	3,4-Cl_2	H	**4l**	88

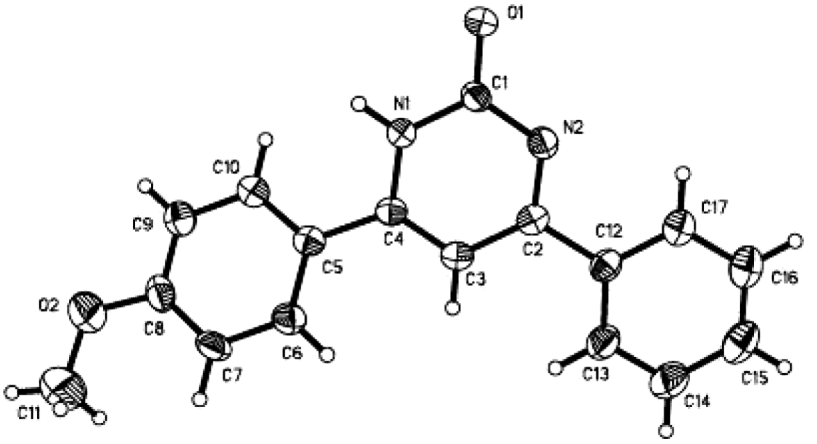


Figure 1. Structure of compound **4a**.

of a small amount of NaOH (0.2 g) as catalyst, and then the mixture was placed into a round flask and left at 70 °C to react. The reactions could be finished in about 10–15 min and the product, 4,6-diarylpyrimidin-2(1*H*)-one 4, could be gained with excellent yields. The results of reactions are listed in Table 1. Previously,[7a] 3,4-dihydropyrimidin-2(1*H*)-ones **5** has been prepared from the reaction of aromatic aldehydes, aromatic ketones, and urea using a Lewis acid ($FeCl_3 \cdot 6H_2O$-TMSCl) as catalyst; however, in our research, we did not find 3,4-dihydropyrimidin-2(1*H*)-ones **5**. Instead, 4,6-diarylpyrimidin-2(1*H*)-one **4** was obtained with good yields. We think the different catalysts resulted in the different results of the reaction.

From Table 1, we saw that the all reactions were carried out smoothly, and we also found that the nature of substitute groups in the aldehydes or ketones has no significant effect on this reaction. The structures of **4** were characterized by ^{1}H NMR, infrared (IR) and high-resolution mass spectrometry (HRMS). In particular, the measured data of HRMS was in accord with the corresponding calculated data, so the deduced structures of products were right. The structure of **4a** was additionally confirmed by x-ray diffraction analysis. The crystal structure of **4a** is shown in Fig. 1.

In conclusion, we have successfully developed an efficient and facile method to prepare a variety of 4,6-diarylpyrimidin-2(1*H*)-one derivatives via the multicomponent reactions of different aromatic aldehydes, aromatic ketones, and urea under solvent-free conditions. Because no toxic organic solvent was used and the basic catalyst (NaOH) was employed, this method presents an efficient and facile route for the synthesis of these compounds.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were obtained in dimethylsulfoxide (DMSO-d_6) solution with Me4Si as internal standard using a Bruker-400 spectrometer. HRMS spectra were obtained with a Bruker micrOTOF-Q 134 instrument. X-ray diffractions were recorded on a Siemens P4 or Simart-1000 diffractometer.

General Procedure for the Syntheses of 4,6-Diarylpyrimidin-2 (1*H*)-one Derivatives

Aromatic aldehyde **1** (2 mmol), aromatic ketone **2** (2 mmol), urea **3** (3 mmol), and NaOH (0.2 g) were added to a mortar. The mixture was blended together and then shifted into a round flask. The reagent was heated about 70 °C under atmospheric conditions, and the reaction could be finished within 10–15 min. The reaction mixture was poured into water, and the product was filtered, dried, and recrystallized from 95% ethanol.

Data

6-(4-Methoxyphenyl)-4-phenylpyrimidin-2(1*H*)-one (4a). Mp 252–253 °C; IR (KBr, ν, cm^{-1}): 3279, 3095, 2998, 2834, 1618, 1514, 1459, 1420, 1394, 1339, 1262, 1174, 1038, 991, 821, 776 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.86 (3H, s, OCH_3), 7.10 (2H, d, $J = 8.8$ Hz, ArH), 7.50 (1H, s, C^5-H), 7.54–7.59 (3H, m, ArH,), 8.14–8.19 (4H, m, ArH), 11.96 (1H, s, NH); HRMS m/z calculated for $C_{17}H_{14}N_2O_2$ [M + H]: 279.1134; found: 279.1144.

6-(3-Chlorophenyl)-4-phenylpyrimidin-2(1*H*)-one (4b). Mp 219–220 °C; IR (KBr, ν, cm^{-1}): 3305, 3069, 2886, 1625, 1496, 1456, 1398, 1329, 1197, 995, 858, 764, 682 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.50–7.57 (5H, m, ArH), 7.62–7.65 (1H, m, ArH), 8.18–8.19 (3H, m, ArH), 8.30 (1H, s, C^5-H), 12.16 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}ClN_2O$ [M + H]: 283.0638; found: 283.0643.

6-(4-Chlorophenyl)-4-phenylpyrimidin-2(1*H*)-one (4c). Mp 192–194 °C; IR (KBr, ν, cm^{-1}): 3324, 3060, 1653, 1556, 1489, 1358, 1175, 1091, 1013, 998, 820, 700, 694, 648 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.20 (1H, s, C^5-H), 7.46–7.48 (3H, m, ArH), 7.52 (2H, dd, $J = 1.6$ Hz, $J = 1.6$ Hz, ArH), 8.10–8.12 (2H, m, ArH), 8.17 (2H, d, $J = 8.0$ Hz, ArH), 12.12 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}ClN_2O$ [M + H]: 283.0638; found: 283.0636.

4-(3,4-Dimethylphenyl)-6-p-tolylpyrimidin-2(1*H*)-one (4d). Mp > 300 °C; IR (KBr, ν, cm^{-1}): 3330, 3100, 2918, 1623, 1538, 1506, 1455, 1418, 1392, 1338, 1250, 1185, 990, 915, 808, 715, 596 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.31 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.40 (3H, s, CH_3), 7.32 (1H, d, $J = 8.0$ Hz, ArH), 7.37 (2H, d, $J = 8.0$ Hz, ArH), 7.47 (1H, m, ArH), 7.88–7.90 (1H, m, ArH), 7.97 (1H, s, C^5-H), 8.06 ~ 8.08 (2H, m, ArH), 11.98 (1H, s, NH); HRMS m/z calculated for $C_{19}H_{18}N_2O$ [M + H]: 291.1497; found: 291.1496.

6-Phenyl-4-*p*-tolylpyrimidin-2(1*H*)-one (4e). Mp 271–273 °C (lit.[6e] 287–290 °C); IR (KBr, ν, cm^{-1}): 3298, 3097, 3007, 2901, 1616, 1460, 1393, 1339, 1183, 994, 919, 809, 774, 689, 596 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.41 (3H, s, CH_3), 7.37 (2H, d, $J = 8.4$ Hz, ArH), 7.54–7.60 (4H, m, ArH, C^5-H), 8.09 (2H, s, ArH), 8.16 (2H, br, ArH), 12.08 (1H, s, NH); HRMS m/z calculated for $C_{17}H_{14}N_2O$ [M + H]: 263.1184; found: 263.1192.

4-(4-Fluorophenyl)-6-phenylpyrimidin-2(1*H*)-one (4f). Mp 159–161 °C; IR (KBr, ν, cm^{-1}): 3301, 3059, 2906, 1614, 1557, 1509, 1356, 1231, 1155, 993, 821, 766, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.27 (2H, t, $J = 8.4$ Hz,

$J = 8.4$ Hz, ArH), 7.35 (1H, s, C^5-H), 7.46–7.47 (3H, m, ArH), 8.15 (2H, d, $J = 4.0$ Hz, ArH), 8.23 (2H, dd, $J = 6.0$ Hz, $J = 6.0$ Hz, ArH), 11.99 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}FN_2O$ [M + H]: 267.0934; found: 267.0945.

4-(4-Bromophenyl)-6-phenylpyrimidin-2(1*H*)-one (4g). Mp 255–256 °C (lit.>[6e] 251–254 °C); IR (KBr, ν, cm^{-1}): 3401, 3058, 1647, 1610, 1488, 1447, 1072, 1010, 821, 768, 697 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.60 (4H, t, $J = 8.0$ Hz, $J = 8.0$ Hz, ArH), 7.66 (1H, d, $J = 8.0$ Hz, ArH), 7.71 (1H, m, ArH), 8.18 (3H, d, $J = 6.8$ Hz, ArH), 8.27 (1H, s, C^5-H), 12.17 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}BrN_2O$ [M + H]: 327.0133; found: 327.0137.

4-(2-Chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (4h). Mp 220–223 °C; IR (KBr, ν, cm^{-1}): 3342, 3030, 2926, 1659, 1577, 1538, 1455, 1396, 1337, 1053, 994, 758, 689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.24 (1H, s, C^5-H), 7.54–7.57 (5H, m, ArH), 7.64 (2H, d, $J = 7.2$ Hz, ArH), 8.14 (2H, d, $J = 7.2$ Hz, ArH), 12.24 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}ClN_2O$ [M + H]: 283.0638; found: 283.0643.

4-(3-Chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (4i). Mp 210–212 °C; IR (KBr, ν, cm^{-1}): 3214, 3078, 2888, 1625, 1576, 1497, 1339, 1330, 1198, 995, 765, 683, 593 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.56–7.62 (4H, m, ArH), 7.66 (2H, d, $J = 8.0$ Hz, ArH), 8.20 (3H, s, ArH), 8.30 (1H, s, C^5-H), 12.17 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}ClN_2O$ [M + H]: 283.0638; found: 283.0645.

4-(4-Chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (4j). Mp 242–244 °C (lit.[6e] 258–260 °C); IR (KBr, ν, cm^{-1}): 3311, 3105, 3059, 2900, 1614, 1538, 1438, 1337, 1178, 1090, 994, 821, 764, 685 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.37 (1H, s, C^5-H), 7.47–7.48 (3H, m, ArH), 7.51 (2H, d, $J = 8.0$ Hz, ArH), 8.14 (2H, d, $J = 8.4$ Hz, ArH), 8.20 (2H, d, $J = 8.4$ Hz, ArH), 12.18 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{11}ClN_2O$ [M + H]: 283.0638; found: 283.0644.

4-(2,4-Dichlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (4k). Mp 223–225 °C; IR (KBr, ν, cm^{-1}): 3315, 3027, 2932, 1664, 1587, 1448, 1393, 1142, 1098, 995, 777, 689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.55–7.69 (6H, m, ArH), 7.85 (1H, s, C^5-H), 8.12–8.13 (2H, br, ArH), 12.26 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{10}Cl_2N_2O$ [M + H]: 317.0248; found: 317.0248.

4-(3,4-Dichlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (4l). Mp > 290 °C; IR (KBr, ν, cm^{-1}): 3280, 3094, 2893, 1616, 1578, 1536, 1497, 1475, 1442, 1398, 1331, 1269, 1229, 1202, 1163, 1133, 1097, 1026, 997, 909, 855, 832, 767, 684, 645, 595 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.56–7.59 (3H, m, ArH), 7.80 (1H, s, C^5-H), 7.84 (1H, d, $J = 8.8$ Hz, ArH), 8.19–8.24 (3H, m, ArH), 8.51 (1H, d, $J = 2.0$ Hz, ArH), 12.16 (1H, s, NH); HRMS m/z calculated for $C_{16}H_{10}Cl_2N_2O$ [M + H]: 317.0248; found: 317.0243.

X-ray crystallography for 4a. Empirical formula $C_{17}H_{14}N_2O_2$, $Fw = 278.30$, $T = 298(2)$ K, orthorhombic, $a = 7.3081$ (17) Å, $b = 13.462$ (3) Å, $c = 27.986$ (7) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2753.2$ (11) $Å^3$, $Z = 8$, $Dc = 1.343$ Mg/m^3, λ (MoKα) = 0.71073 Å, $\mu = 0.090$ mm^{-1}, $F(000) = 1168$. $1.46° < \theta < 25.01°$, $R = 0.0671$, $wR = 0.2225$, $S = 1.034$, largest diff. peak and hole: 0.633 and −0.345 e $Å^{-3}$.

ACKNOWLEDGMENTS

We thank the Natural Science Foundation of Jiangsu Education Department (No. 08KJB150017) and the Foundation of Xuzhou Normal University (No. 10XLS02) for financial support.

REFERENCES

1. Morita, H.; Sato, Y.; Chang, K.-L.; Choo, C. Y.; Itokawa, H.; Takeya, K.; Kobayashi, J. Samoquasine A, a benzoquinazoline alkaloid from the seeds of *Annona squamosa*. *J. Nat. Prod.* **2000**, *63*, 1707–1708.
2. Rosowsky, A.; Huang, P. C.; Papathanasopoulos, N.; Modest, E. J. Quinazolines, 12: 1,3-Diaminobenzo[*f*]quinazolines containing long-chain alkyl or chloro substituents on the central ring: Synthesis and biological evaluation as candidate antifolate and antimalarial agents. *J. Med. Chem.* **1974**, *17*, 1217–222.
3. Godde, F.; Toulme, J. J.; Moreau, S. Benzoquinazoline derivatives as substitutes for thymine in nucleic acid complexes: Use of fluorescence emission of benzo[g]quinazoline-2,4-(1-*H*,3*H*)-dione in probing duplex and triplex formation. *Biochemistry* **1998**, *37*, 13765–13775.
4. Ballard, P.; Bradbury, R. H.; Hennequin, L. F. A.; Hickinson, M.; Johnson, P. D.; Kettle, J. G.; Klinowska, T.; Morgentin, R.; Ogilvie, D. J.; Olivier, A. 5-Substituted 4-anilinoquinazolines as potent, selective, and orally active inhibitors of erbB2 receptor tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4226–4229.
5. Pendergast, W.; Dickerson, S. H.; Johnson, J. V.; Dev, I. K.; Ferone, R.; Duch, D. S.; Smith, G. K. Benzoquinazoline inhibitors of thymidylate synthase: Enzyme inhibitory activity and cytotoxicity of some sulfonamidobenzoylglutamate and related derivatives. *J. Med. Chem.* **1993**, *36*, 3464–3471.
6. (a) Singh, K.; Singh, J.; Deb, P. K.; Singh, H. An expedient protocol of the Biginelli dihydropyrimidine synthesis using carbonyl equivalents. *Tetrahedron* **1999**, *55*, 12873–12880; (b) Shaabani, A.; Bazgir, A.; Teimouri, F. Ammonium chloride–catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent-free conditions. *Tetrahedron Lett.* **2003**, *44*, 857–859; (c) Mabry, J.; Ganem, B. Studies on the Biginelli reaction: A mild and selective route to 3,4-dihydropyrimidin-2(1*H*)-ones via enamine intermediates. *Tetrahedron* **2006**, *47*, 55–56; (d) Wang, X. C.; Quan, Z. G.; Wang, F.; Wang, M. G.; Zhang, Z.; Li, Z. PEG-SO_3H as catalyst for 3,4-dihydropyrimidones via Biginelli reaction under microwave and solvent-free condition. *Synth. Commun.* **2006**, *36*, 451–456; (e) Heravi, M. M.; Ranjbar, L.; Derikvand, F.; Alimadadi, B. Three-component one-pot synthesis of 4,6-diarylpyrimidin-2(1H)-ones under solvent-free conditions in the presence of sulfamic acid as a green and reusable catalyst. *Mol. Divers.* **2008**, *12*, 191–196.
7. (a) Wang, Z. T.; Xu, L. W.; Xia, C. G.; Wang, H. Q. Novel Biginelli-like three-component cyclocondensation reaction: Efficient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones. *Tetrahedron Lett.* **2004**, *45*, 7951–7953; (b) Wang, L. M.; Sheng, J.; Zhang, L.; Han, J. W.; Fan, Z. Y.; Tian, H.; Qian, C. T. Facile $Yb(OTf)_3$ promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction. *Tetrahedron* **2005**, *61*, 1539–1543; (c) Yarım, M.; Sarac, S.; Kılıc, F. S.; Erol, K. Synthesis and in vitro calcium antagonist activity of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives. *Farmaco* **2003**, *58*, 17–24; (d) Abelman, M. M.; Smith, St C.; Jamesa, D. R. Cyclic ketones and substituted-keto acids as alternative substrates for novel Biginelli-like scaffold syntheses. *Tetrahedron Lett.* **2003**, *44*, 4559–4562.