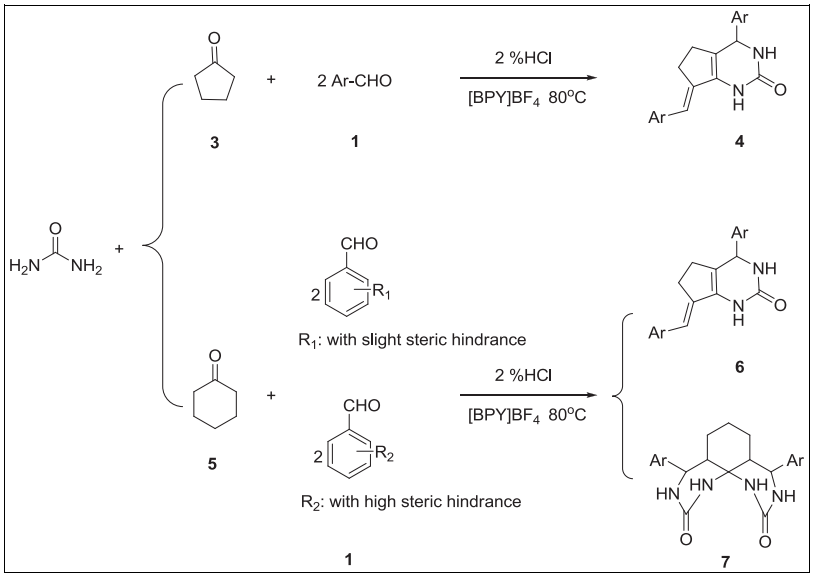
A Regioselective Biginelli-like Reaction Controlled by the Size of Alicyclic Mono-ketones

Yu Wan,[a,b] Rui Yuan,[a,b] Hua-hong Xu,[a,b] Chao Wang,[a,b] Jin-long Qi,[a,b] and Hui Wu[a,b]*

[a]School of Chemistry and Chemical Engineering, Jiangsu Normal University, Xuzhou, 221116, People's Republic of China
[b]Key Laboratory of Biotechnology on Medical Plant of Jiangsu Province, Xuzhou, 221116, People's Republic of China
*E-mail: wuhui72@126.com

Received September 26, 2012
DOI 10.1002/jhet.1893
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



A regioselective Biginelli-like reaction of alicyclic mono-ketones, aromatic aldehydes, and urea in ionic liquid [BPY]BF_4 has been investigated. The process is controlled by the size of alicyclic mono-ketones and the steric hindrance of aromatic aldehydes. The reaction of cyclopentanone with urea and aromatic aldehydes afforded 7-arylidene-3,4,6,7-tetrahydro-4-aryl-1*H*-cyclopenta[d]pyrimidin-2(5*H*)-ones (**4**). When cyclohexanone was used as the source of active methylene to react with urea and aldehydes with slight steric hindrance groups under the same condition, 8-arylidene-3,4,5,6,7, 8-hexahydro-4-arylquinazolin-2(1*H*)-ones (**6**), a homologue of **4**, were yielded, whereas 4,8-bisaryloc-tahydro-1*H*-pyrimido[5,4-*i*]-quinazoline-2,10(3*H*,11*H*)-diones (**7**) were obtained via the simple one-pot reaction of cyclohexanone, urea, and aromatic aldehydes with high steric hindrance groups. The possible transitional states and mechanism of the regioselective process were discussed.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

Selective synthesis of different products from the same materials by just choosing different reaction conditions, such as catalysis, substrates, and so on, is an interesting research topic for chemists [1–3].

Biginelli and Biginelli-like reactions, the most useful multicomponent reactions that assemble aldehydes, urea/thiourea, and enolizable carbonyls into dihydropyrimidinethiones provide robust tools for the creation of these important structural motifs [4–7]. Because the first description of the Biginelli reaction over a century ago [4], the research interest has long been focused on aromatic ketones and alicyclic1,3-diketones for efficiently providing access to dihydropyrimidinethiones [8–12].

In contrast, the Biginelli and Biginelli-like reactions of alicyclic mono-ketones with lower α-H activity have been a long-standing challenge. Only a few of Biginelli reaction using alicyclic mono-ketones as the source of active methylene have been reported [13–17]. However, some shortcomings such as using violent toxic organic solvents and expensive low-selective catalysts, rigorous condition, high reaction temperature, and long reaction times limited the scope of appropriate substrates. Especially, different reaction conditions always gave the same or analogous framework, which means poor structural diversity [18–20].

RESULTS AND DISCUSSION

In this paper, we reported the HCl (catalytic amount) catalyzed regioselective Biginelli-like reactions of alicyclic mono-ketones (cyclopentanone or cyclohexanone), aromatic aldehydes, and urea in ionic liquid [BPY]BF_4, which provided an efficient method to access **4**, **6**, and **7** via controllable reaction condition with structural diversity.

After the optimization of reaction conditions, we found that aromatic aldehydes **1**, urea **2**, and cyclopentanone **3** were stirred in a presence of a catalytic amount (0.04 mol%) of HCl at 80°C in [BPY]BF_{44} for 3–15 h to give the corresponding 7-arylidene-3,4,6,7-tetrahydro-4-aryl-1*H*-cyclopenta[*d*] pyrimidin-2(5*H*)-ones (**4**) (Scheme 1, Table 1) in moderate to high yields. The results in Table 1 indicated that the yields were badly influenced by steric hindrance and electronic effect of aromatic aldehyde. Aromatic aldehydes bearing group at ortho-position (entries **12–15**, Table 1) gave lower yields and needed obvious longer reaction time. Meanwhile, aromatic aldehydes with electron-withdrawing group (entries **2**, **4**, and **6–9**, Table 1) gave a higher yield than the ones with electron-donating group (entries **3**, **5**, **10**, and **11**, Table 1).

The results prompted us to use another alicyclic mono-ketone cyclohexanone (Scheme 2, Table 2). The results in Table 2 indicated that cyclohexanone can also display good function, but the reaction time was distinctly longer than that of cyclopentanone, because of the lower reactivity and more crowded conformation of cyclohexanone.

Interestingly, we found that the size of alicyclic mono-ketones is able to control the process of the Biginelli-like reaction. The reaction of cyclopentanone with urea and aromatic aldehydes mainly afforded 7-arylidene-3,4,6,7-tetrahydro-4-aryl-1*H*-cyclopenta[*d*]pyrimidin-2(5*H*)-ones (**4**). When cyclohexanone was used, under the same condition, two kinds of product were obtained via two proposed routes as outlined in Scheme 2. Aromatic aldehydes with slight steric hindrance groups (entries **1–5**, Table 2) mainly gave 8-aryl-benzylidene-3,4,5,6,7,8-hexahydro-4-aryl-quinaznolin-2 (1*H*)-ones (**6**), whereas 4,8-bisaryloctahy1*H*-pyrimido[5, 4-*i*]-quinazoline-2,10(3*H*,11*H*)-diones (**7**) were obtained as the main product.

From Scheme 3, we thought that **D** is the key intermediate in controlling the type of product. When cyclopentanone was used, the most stable conformation of **D** should be the uncrowded *trans*-transition state **I**; hence, the steric hindrance of aryl has little influence on the process of the reaction, so **4** is the main-product. Furthermore, –OH and –H are at trans-position, the elimination reaction seems to be favored.

When cyclohexanone was used, there are two possible transition states **II** and **III**. **II** is more suitable for the aromatic aldehydes with slight steric hindrance groups because the two fused six-membered rings of **II** are at *trans*-position, and the distance between –H on the bridge bond and benzene ring is far enough, as well as the distance between $–NH_2$ and carbonyl on pyrimidinone ring. Its –OH and –H are also at *trans*-position like **I**, so the elimination reaction is favored and **6** was afforded.

By contraries, **III** is less crowded than **II** and favored for aromatic aldehydes with high steric hindrance (for example, *ortho*-substituted ones). So, substitution reaction mainly took place and compound **7** was obtained.

Scheme 1

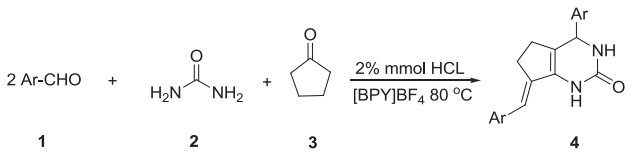


Table 1

The synthesis of 4 in [BPY]BF_4.

Entry	Ar	Compound	Time/h	Isolated yield/%
1	C_6H_5	**4a**	5	87
2	4-FC_6H_4	**4b**	4	84
3	4-$CH_3C_6H_4$	**4c**	5	68
4	4-$NO_2C_6H_4$	**4d**	4	89
5	4-IC_6H_4	**4e**	5	75
6	4-CNC_6H_4	**4f**	3	85
7	3-$NO_2C_6H_4$	**4g**	5	86
8	3-BrC_6H_4	**4h**	5	81
9	3-FC_6H_4	**4i**	5	87
10	3,4-$OCH_2OC_6H_5$	**4j**	6	79
11	4-$CH_3OC_6H_4$	**4k**	6	74
12	2-$CH_3OC_6H_4$	**4l**	6	58
13	2,3-$(CH_3O)_2C_6H_3$	**4m**	6	54
14	2-BrC_6H_4	**4n**	15	55
15	2-ClC_6H_4	**4o**	12	59

Scheme 2

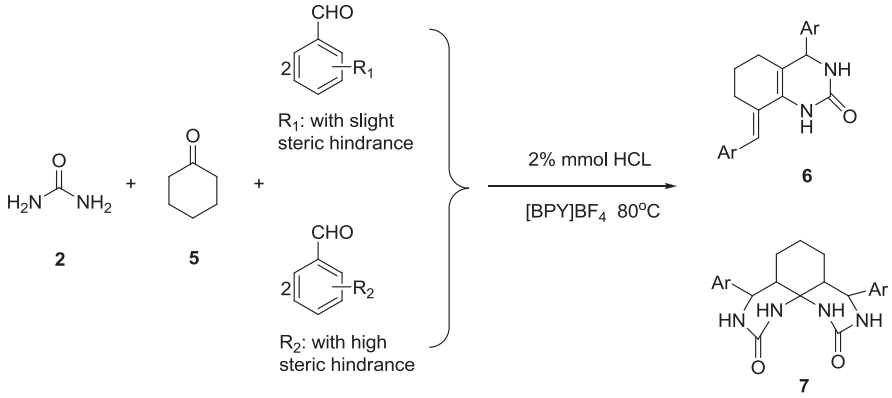


Table 2

Synthesis of **6** and **7** in $[BPY]BF_4$.

Entry	Product	Ar	Time/ h	Isolated yield/ %	
				6	7
1	**6a**	C_6H_4	10	82	—
2	**6b**	4-$NO_2C_6H_4$	12	81	—
3	**6c**	4-ClC_6H_4	8	79	—
4	**6d**	4-BrC_6H_4	6	85	—
5	**6e**	4-$CH_3C_6H_4$	10	82	—
6	**6a**	4-FC_6H_4	10	86	—
7	**6b**	4-IC_6H_4	14	78	—
8	**7c**	3,4-$OCH_2OC_6H_3$	9	—	82
9	**7d**	3,4,5-$(CH_3O)_3C_6H_2$	15	—	84
10	**7e**	3-$NO_2C_6H_4$	8	—	87
11	**7f**	3-BrC_6H_4	8	—	82
12	**7g**	3-FC_6H_4	8	—	79
13	**7h**	2-$CH_3OC_6H_4$	12	—	67
14	**7i**	2-FC_6H_4	15	—	68
15	**7j**	2-ClC_6H_4	12	—	62

Therefore, we supposed that the high regioselective reaction is mainly determined by the size and special preponderant conformation of alicyclic mono-ketones, whereas aromatic ketones did not have these characteristics.

In summary, we have discovered that the size of two alicyclic mono-ketones (cyclopentanone or cyclohexanone) is able to control the process of the Biginelli-like reaction. The reaction of cyclopentanone with urea and aromatic aldehydes mainly afforded 7-arylidene-3,4,6,7-tetrahydro-4-aryl-1*H*-cyclopenta[*d*] pyrimidin-2(5*H*)-ones (**4**). When cyclohexanone was used, by changing the steric hindrance of substituent on aromatic aldehydes, under the same condition, two kinds of product were obtained via different ways. 8-arylbenzylidene-3,4,5,6,7,8-hexahydro-4-aryl-quinazolin-2 (1*H*)-ones (**6**) could be derived from aromatic aldehydes with slight steric hindrance groups, whereas 4,8-bisaryloctahydro-1*H*-pyrimido[5,4-*i*]-quinazoline-2,10(3*H*,11*H*)-diones (**7**) were obtained as the main product in a simple one-pot process. These reactions have an advantage of obtaining complex products with a various of structural diversity via simple method.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. NMR spectra were measured in DMSO-d_6 with Me_4Si as the internal standards on a Bruker Avance DPX-400 (Bruker Corporation, Germany) at room temperature. IR spectra were recorded on Bruker FTIR spectrometer, absorbance were reported in reciprocal centimeter. Mass spectra were determined by using a Bruker TOF-MS high-resolution mass spectrometer.

General procedure for the synthesis of 4 in ionic liquid. A mixture of aromatic aldehyde **1** (4.0 mmol), urea **2** (5.0 mmol), and cyclopentanone **3** (2.0 mmol), 2% HCl (0.04 mol%) was simply stirred in $[BPY]BF_4$ (2 mL) at 80°C for 3–15 h (monitored by TLC). Upon and on completion, the reaction mixture was poured into water and $[BPY]BF_4$ was removed by filtration. The product was purified by recrystallization with EtOH (95%)-DMF (10:1).

General procedure for the synthesis of 6 and 7 in ionic liquid. A mixture of aromatic aldehyde **1** (4.0 mmol), urea **2** (5.0 mmol), cyclohexanone **5** (2.0 mmol), and 2% HCl (0.04 mol %) was simply stirred in $[BPY]BF_4$ (2 mL) at 80°C for 6–15 h (monitored by TLC). The following procedures were same as the synthesis of **4**.

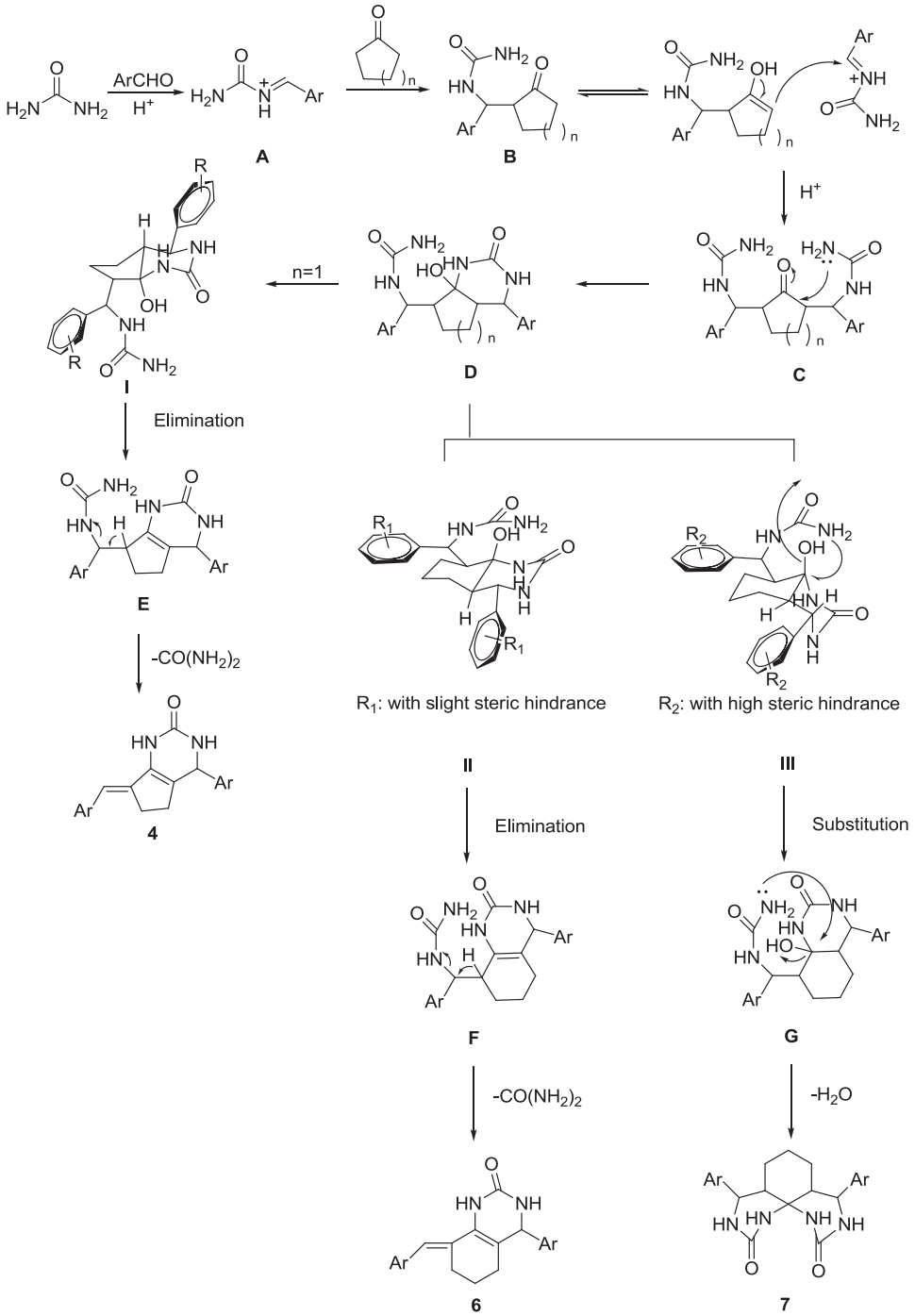
The known compounds (**4a**, **4b**, **4c**, **4d**, **4f**, **4g**, **4i**, **4k**, **4l**, **4o**, **4n** in Table 1 and **6a**, **7a**, **7b, 7c**, **7e**, **7h**, **7i**, **7j** in Table 2) have been identified by comparison of spectral data with literature [18,20].

The spectral data of new products are given in the succeeding text

7-(4-iodobenzylidene)-3,4,6,7-tetrahydro-4-(4-iodophenyl)-1H-cyclopenta[d]pyrimidin-2(5H)-one (4e). mp: 267–268°C; IR (KBr, ν, cm^{-1}): 3317, 2925, 1658, 1582, 1028, 976, 774; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.80 (1H, s, NH), 7.74–7.76 (2H, d, $J = 8.2$ Hz, ArH), 7.68–7.70 (2H, d, $J = 8.2$ Hz, ArH), 7.24 (1H, s, C^2–H), 7.08–7.16 (4H, m, ArH), 6.58 (1H, s, NH), 5.14 (1H, s, C^{14}–H), 2.71–2.90 (2H, m, CH_2), 2.36–2.42 (1H, m, CH_2), 1.96–2.02(1H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 53.03, 142.99, 141.86, 140.13, 137.83, 137.50, 137.33, 137.23, 137.19, 136.08, 129.92, 128.86, 118.72, 115.84, 93.34, 91.47, 90.85, 56.91, 28.34, 28.20; HRMS: *m/z* calcd for $C_{20}H_{16}I_2N_2O$ [M + 1], 554.9352; found, 554.9345.

7-(3-bromobenzylidene)-4-(3-bromophenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4h). mp: 286–288°C; IR (KBr, ν, cm^{-1}): 3352, 2906, 1634, 1579, 1546, 768; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.84 (1H, s, NH), 7.49–7.52 (1H, m, ArH), 7.46 (2H, s, ArH), 7.29–7.38 (6H, m, ArH), 6.62 (1H, s, NH), 5.22 (1H, s, C^{14}–H), 2.77–2.89 (2H, m, CH_2),

Scheme 3



2.40–2.44 (1H, m, CH_2), 1.99–2.05 (1H, m, CH_2) ^{13}C NMR (100 MHz, DMSO-d6) δ: 162.26, 153.00, 145.90, 140.81, 140.10, 136.11, 130.87, 130.60, 130.36, 130.02, 129.17, 128.67, 126.77, 125.61, 121.88, 118.98, 115.48, 56.78, 35.76, 30.77, 28.28, 28.22; HRMS: *m/z* calcd for $C_{20}H_{16}Br_2N_2O$ [M + 1], 457.9629; found, 457.9605.

7-((benzo[d][1,3]dioxol-5-yl)methylene)-4-(benzo[d][1,3]dioxol-6-yl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4j). mp: 280–282°C; IR (KBr, ν, cm^{-1}): 3351, 2906, 1628, 1529, 749; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.67 (1H, d, *J* = 0.4 Hz, NH), 7.14 (1H, s, ArH), 7.17–7.20 (3H, m, ArH), 6.73–6.81 (3H, m, ArH), 6.55 (1H, s, NH), 6.01 (2H, d, *J* = 2.0 Hz, ArH) 5.07 (1H, s, C^{15}–H), 2.77–2.80 (2H, m, CH_2), 2.33–2.39 (1H, m, CH_2), 2.00–2.06 (1H, m, CH_2) ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.10, 147.46, 147.42, 146.52, 145.49, 137.53, 137.26, 135.89, 132.07, 122.18, 119.69, 117.71, 116.49, 108.44, 108.12, 107.37, 106.81, 100.98, 100.91, 57.04, 28.24, 28.16; HRMS: *m/z* calcd for $C_{22}H_{18}N_2O_5$ [M + 1], 391.1216; found, 391.1208.

7-(2,3-dimethoxybenzylidene)-3,4,6,7-tetrahydro-4-(2,3-dimethoxyphenyl)-1H-cyclopenta[d]pyrimidin-2(5H)-one (4m). mp: 247–248°C; IR (KBr, ν, cm^{-1}): 3328, 2925, 1667, 1524, 767; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.94 (1H, NH), 7.07–7.11 (1H, t, J = 6.0 Hz, ArH), 6.95–7.02 (4H, m, ArH), 6.88–6.91 (1H, t, J = 4.8 Hz, C^2–H), 6.83 (1H, dd, J = 6.4 Hz, ArH), 6.73 (1H, s, NH), 3.79–3.81 (6H, d, J = 6.8 Hz, 2*OCH_3), 3.74 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 2.70–2.76 (2H, m, CH_2), 2.30–2.36 (1H, m, CH_2), 1.93–1.99 (1H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.49, 152.53, 152.14, 146.37, 145.67, 139.86, 136.65, 136.13, 131.73, 124.23, 123.54, 119.89, 119.54, 118.38, 111.86, 111.03, 110.97, 60.43, 60.35, 55.69, 55.61, 51.57, 28.29, 28.16; HRMS: *m/z* calcd. for $C_{24}H_{26}N_2O_5$ [M + 1], 422.1842; found, 422.1833.

4-(benzo[d][1,3]dioxol-5-yl)-8-((benzo[d][1,3]dioxol-5-yl) methylene)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one (6a). mp: 280–281°C; IR (KBr, ν, cm^{-1}): 3326, 2897, 1664, 1548, 787, 763; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.01 (1H, s, NH), 7.15 (1H, s, NH), 6.86–6.92 (3H, m, ArH), 6.78–6.80 (3H, m, ArH), 6.75–6.77 (1H, dd, J = 8.0 Hz, C^2–H), 6.01 (4H, d, J = 2.8 Hz, 2*OCH_2O), 4.69 (1H, s, C^{16}–H), 2.56–2.61 (1H, m, CH2), 2.38–2.45 (1H, m, CH_2), 1.98–2.04 (1H, m, CH_2), 1.75–1.83 (1H, m, CH_2), 1.52–1.58 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.11, 147.45, 147.07, 146.57, 145.81, 138.14, 131.25, 128.87, 128.51, 123.04, 121.69, 119.97, 111.54, 109.18, 108.08, 106.98, 100.96, 100.90, 59.09, 26.46, 25.88, 22.23; HRMS: *m/z* calcd for $C_{23}H_{20}N_2O_5$ [M + 1], 405.1372; found, 405.1360.

8-(3,4,5-trimethoxybenzylidene)-3,4,5,6,7,8-hexahydro-4-(3,4,5-trimethoxyphenyl)quinazolin-2(1H)-one (6b). mp: 273–275°C; IR (KBr, ν, cm^{-1}): 3246, 2893, 1645, 1612, 1558, 743; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.03 (1H, s, NH), 7.15 (1H, s, NH), 6.83 (1H, s, C^2–H), 6.60 (4H, s, ArH), 4.77 (1H, s, C^{18}–H), 3.77 (12H, d, J = 3.2 Hz, 4*OCH_3), 3.66 (6H, d, J = 4.4 Hz, 2*OCH_3), 2.65–2.70 (1H, m, CH_2), 2.48–2.49 (1H, m, CH_2), 2.03–2.09 (1H, m, CH_2), 1.84–1.89 (1H, m, CH_2), 1.55–1.62 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.18, 152.94, 152.49, 139.45, 137.03, 136.46, 132.80, 129.50, 128.71, 122.07, 112.71, 111.48, 109.07, 106.80, 105.90, 104.22, 60.10, 60.05, 60.00, 59.55, 56.12, 56.09, 55.96, 55.87, 26.53, 25.99, 22.34; HRMS: *m/z* calcd for $C_{27}H_{32}N_2O_7$ [M + 1], 497.2210; found, 497.2198.

8-(4-bromobenzylidene)-4-(4-bromophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one (6c). mp: 274–275°C; IR (KBr, ν, cm^{-1}): 3324, 2895, 1659, 1528, 798, 763; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.16 (1H, s, NH), 7.53–7.59 (4H, m, ArH), 7.24–7.29 (5H, m, ArH), 6.86 (1H, s, NH), 4.79 (1H, d, J = 1.2 Hz, C^{15}–H), 2.53–2.58 (1H, m, CH_2), 2.36–2.42 (1H, m, CH_2), 2.02–2.07 (1H, m, CH_2), 1.71–1.77 (1H, m, CH_2), 1.52–1.55 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.07, 143.27, 136.42, 132.29, 131.47, 131.18, 131.05, 130.98, 130.85, 130.68, 129.00, 128.67, 120.98, 120.57, 119.60, 111.90, 58.77, 26.35, 25.84, 22.13; HRMS: *m/z* calcd for $C_{21}H_{18}Br_2N_2O$ [M + 1], 472.9786; found, 472.9778.

8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one (6e). mp: 269–270°C; IR (KBr, ν, cm^{-1}): 3321, 2886, 1637, 1526, 793, 753; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.16 (1H, s, NH), 7.40–7.46 (4H, m, ArH), 7.32 (4H, d, J = 8.4 Hz, ArH), 7.29 (1H, s, C^2–H), 6.89 (1H, s, NH), 4.81 (1H, d, J = 1.2 Hz, C^{15}–H), 2.54–2.61 (1H, m, CH_2), 2.36–2.43 (1H, m, CH_2), 2.02–2.09 (1H, m, CH_2), 1.72–1.79 (1H, m, CH_2), 1.52–1.56 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.10, 142.87, 136.07, 132.22, 132.05, 131.53, 131.14, 131.05, 130.85, 130.77, 130.62, 130.53, 130.48, 130.25, 129.34, 128.64, 128.54, 128.41, 128.37, 128.32, 128.29, 128.12, 123.78, 120.92, 111.92, 58.71, 26.35, 25.85, 22.14; HRMS: *m/z* calcd for $C_{21}H_{18}N_2O$ [M + 1], 385.0796; found, 385.0779.

4,8-bis(4-iodophenyl)octahydro-1H-pyrimido[5,4-i]-quinazoline-2,10(3H,11H)-dione (7d). mp: >300°C; IR (KBr, ν, cm^{-1}): 3357, 3274, 2932, 1589, 1667, 1551, 764; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.70–7.74 (4H, m, ArH), 7.27 (1H, d, J = 0.8 Hz, NH), 7.09–7.11 (4H, d, J = 8.4 Hz, ArH), 6.87 (1H, s, NH), 6.63 (1H, s, NH), 6.56 (1H, d, J = 0.4 Hz, NH), 4.92 (1H, d, J = 2.8 Hz, R_3CH), 4.51–4.54 (1H, d, J = 15.2 Hz, R_3CH), 1.91–1.99 (2H, m, CH_2), 1.36–1.46 (2H, m, CH_2), 1.20–1.24 (1H, m, R_3CH), 1.11–1.15 (1H, m, R_3CH), 0.82–0.89 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) δ: 180.20, 159.20, 153.02, 149.44, 142.99, 140.13, 137.32, 137.23, 137.18, 136.08, 129.91, 128.85, 119.07, 118.72, 115.84, 112.72, 111.92, 93.33, 91.47, 56.90, 28.21; HRMS: *m/z* calcd for $C_{22}H_{22}I_2N_4O_2$[M + 1], 628.9832; found, 628.9825.

4,8-bis(3-bromophenyl)octahydro-1H-pyrimido[5,4-i]-quinazoline-2,10(3H,11H)-dione (7f).. mp: >300°C; IR (KBr, ν, cm^{-1}): 3327, 2895, 1661, 1543, 797, 753; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.46–7.52 (4H, m, ArH), 7.30–7.36 (4H, m, ArH), 7.29 (1H, s, NH), 6.85 (1H, d, J = 6.0 Hz, NH), 6.70 (1H, s, NH), 6.63 (1H, d, J = 1.2 Hz, NH), 4.96 (1H, d, J = 3.2 Hz, R_3CH), 4.60 (1H, d, J = 11.2 Hz, R_3CH), 1.98–2.04 (2H, m, CH_2), 1.40–1.49 (2H, m, CH2), 1.24–1.28 (1H, m, R_3CH), 1.10–1.17 (1H, m, R_3CH), 0.82–0.91 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.94, 160.85, 159.08, 155.33, 153.98, 144.60, 143.20, 130.42, 130.33, 130.01, 129.92, 123.57, 123.54, 122.73, 114.61, 114.40, 114.14, 113.93, 113.72, 113.50, 67.33, 52.65, 52.37, 42.68, 42.18, 35.77, 21.86, 21.46, 18.14; HRMS: *m/z* calcd for $C_{22}H_{22}Br_2N_4O_2$ [M + 1], 533.0110; found, 533.0100.

4,8-bis(3-fluorophenyl)octahydro-1H-pyrimido[5,4-i]-quinazoline-2,10(3H,11H)-dione (7g).. mp: >300°C; IR (KBr, ν, cm^{-1}): 3312, 2901, 1659, 1530, 787, 756; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.38–7.45 (2H, m, ArH), 7.30 (1H, s, NH), 7.09–7.16 (6H, m, ArH), 6.88 (1H, s, NH), 6.70 (1H, s, NH), 6.63 (1H, s, NH), 5.00 (1H, d, J = 3.2 Hz, R_3CH), 4.61–4.63 (1H, d, J = 11.2 Hz, R_3CH), 2.01–2.04 (2H, m, CH_2), 1.40–1.47 (2H, m, CH_2), 1.23–1.26 (1H, m, R_3CH), 1.13–1.18 (1H, m, R_3CH), 0.84–0.91 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.94, 160.85, 159.08, 155.33, 153.98, 144.60, 143.20, 130.42, 130.33, 130.01, 129.92, 123.57, 123.54, 122.73, 114.61, 114.40, 114.14, 113.93, 113.72, 113.50, 67.33, 52.65, 52.37, 42.68, 42.18, 35.77, 21.86, 21.46, 18.14; HRMS: *m/z* calcd for $C_{22}H_{22}F_2N_4O_2$[M + 1], 413.1711; found, 413.1700.

Acknowledgments. We are grateful to the foundation of the "Priority Academic Program Development of Jiangsu Higher Education Institutions," "Key Basic Research Project in Jiangsu University" (No. 10KJA430050, 11KJB150017), the "Graduate Innovation Project in Jiangsu Province" (No. CXZZ11_0904, CXZZ12_0979), and "College Students' Practice Innovation Training Program in Jiangsu Province" for financial support.

REFERENCES AND NOTES

[1] Kappe, C. O. In Multicomponent Reactions; Zhu, J. P., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005, p 95.

[2] Ramön, D. J.; Yus, M. Angew Chem Int Ed 2005, 44, 1602.

[3] Burke, M. D.; Schreiber, S. L. Angew Chem Int Ed 2004, 43, 46.

[4] Luna, A. P.; Bonin, M.; Micouin, L.; Husson, H. J Am Chem Soc 2002, 124, 12098.
[5] Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. J Am Chem Soc 2003, 125, 4692.
[6] Ma, S. M.; Zhang, J. J Am Chem Soc 2003, 125, 12386.
[7] Biginelli, P. Gazz Chim Ital 1893, 23, 360.
[8] Dondoni, A.; Massi, A. Acc Chem Res 2006, 39, 451.
[9] Kappe, C. O. Acc Chem Res 2000, 33, 879.
[10] Saini, A.; Kumar, S.; Sandhu, J. S. J Indian Chem Soc 2007, 10, 959.
[11] Hu, E. H.; Sidler, D. R.; Dolling, U. H. J Org Chem 1998, 63, 3454.
[12] Peng, J. J.; Deng, Y. Q. Tetrahedron Lett 2001, 42, 5917.
[13] Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. Tetrahedron Lett 2003, 44, 6497.
[14] Bose, D. S.; Fatima, L.; Mereyala, H. B. J Org Chem 2003, 68, 587.
[15] Bose, A. K.; Manhas, M. S.; Pednekar, S.; Ganguly, S. N.; Dang, H.; He, W.; Mandadi, A. Tetrahedron Lett 2005, 46, 1901.
[16] Abelman, M.; Smith, S.; James, D. Tetrahedron Lett 2003, 44, 4559.
[17] Wang, Z. T.; Xu, L. W.; Xia, C. G.; Wang, H. Q. Tetrahedron Lett 2004, 45, 7951.
[18] Zhu, Y. L.; Huang, S. L.; Pan, Y. J. Eur J Org Chem 2005, 11, 2354.
[19] Liang, B.; Wang, X. T.; Wang, J. X.; Duan, Z. Y. Tetrahedron 2007, 63(9), 1981.
[20] Zhang, H. H.; Zhou, Z. Q.; Yao, Z. G.; Xu, F.; Shen, Q. Tetrahedron Lett 2009, 50, 1622.