Article

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Efficient Synthesis of a Series of Novel Octahydroquinazoline-5-Ones via a Simple on-Water Urea-Catalyzed Chemoselective Five-Component Reaction

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KEYWORDS: multi-component reaction, octahydroquinazoline-5-ones, water solvent, enaminones, synthetic method

ABSTRACT: Multi-component reactions (MCRs) have become a powerful tool for drug discovery and development owing to their advantages of fast and efficient construction of a large library of products with complexity and diversity. However, conventional MCRs usually proceed in environment-unfriendly organic solvents rather than in water, a green solvent used by nature for biological chemistry. Herein, a simple and efficient on-water urea-catalyzed chemoselective five-component reaction (5CR) has been developed for the synthesis of a series of novel octahydroquinazoline-5-ones (**6**), the derivatives of quinazolinones possessing diverse biological

activities. The molecular structure of **6** was confirmed by single-crystal X-ray diffraction. The 5CR can proceed at room temperature under normal atmospheric pressure in good yields and afford a large library of octahydroquinazoline-5-ones with various aromatic and aliphatic substituents at N-1, C-2 and N-3. In addition, a green method has been developed for the synthesis of enaminones, important intermediates in the 5CR and in synthetic chemistry.

INTRODUCTION

Quinazolinones are a class of important azaheterocycles possessing diverse biological activities[1], such as, anti-cancer,[2, 3] anti-bacterial,[4] anticonvulsant,[5, 6] antidepressant,[6] anti-inflammatory,[7] and antihypertension.[8] Different substituents or the same substituent at different positions usually show different influences on their biological activities. As shown in Figure 1, quinazolinones with different substituents and carbonyl at different positions **I** to **III** show antitumor,[2] antibiotic[9] and antihypertensive[8] activities, respectively. Therefore, the development of the efficient synthetic methods for various quinazolinones has attracted great interest from synthetic chemistry. Most of the reported methods are about the synthesis of quinazoline-4-ones[10-15] and quinazoline-2,4-(1*H*,3*H*)-diones.[16-19] Only a two-step reaction has been reported for the synthesis of quinazoline-5-ones[8] although octahydroquinazoline-5-ones, for example **III** in Figure 1, have been found to possess a high antihypertensive effect.[8]

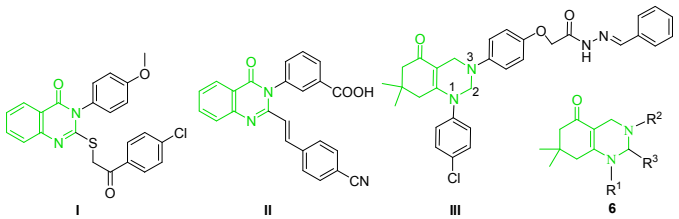


Figure 1. Examples of quinazolinones with different biological activities and the quinazoline-5-ones with substituents at N-1, C-2 and N-3 synthesized in the work.

The use of environment-benign substances is one of the main concerns of green chemistry. Water is a green solvent used by nature for biological chemistry. However, organic chemists give little consideration to water as a useful reaction solvent until the early work of Breslow showing how water enhances the Diels-Alder reactions.[20] Many organic reactions in water show that water exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[21, 22] Butler suggested that water should be high or at the top of the list when organic and industrial chemists seek to chose a solvent for synthesis, and divided the organic reactions using water as solvent into two typical types: pure in-water reactions of soluble reactants and pure on-water reactions of highly insoluble reactants.[22] Interestingly, on-water reactions normally exhibit substantial rate acceleration when insoluble reactants are stirred in aqueous suspension.[23] However, on-water reactions have received relatively little attention from organic synthetic chemistry. In term of catalysts, organocatalysts have become a thriving area in synthetic chemistry for the advantages such as being stable in air and water, available from biological materials, inexpensive and easy to prepare, simple to use and non-toxic.[24-26]

Multi-component reaction (MCR) is an ideal reaction mode which is consistent with the concept of green chemistry owing to its high efficiency. In addition, MCRs could be used to build structural diversity and complexity of compound libraries.[27-29] They have been recognized by the synthetic community in industry and academia as a preferred method to design and discover biologically active compounds.[30] Considering the MCR advantages, we are interested in the development of MCRs for the synthesis of novel heterocycles[31-35] and their biological properties.[36] We recently synthesized a series of novel C6-unsubstituted tetrahydropyrimidines (THPs) via a convenient urea-catalyzed chemoselective five-component reaction (5CR) of but-2-

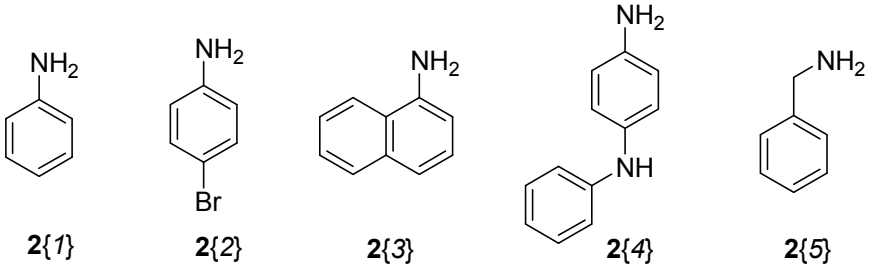
ynedioates, primary amines, formaldehyde and aromatic aldehydes.[37] According to the proposed 5CR mechanism,[37] we deduced that the 5CR might be developed as a 5CR for the synthesis of octahydroquinazoline-5-ones (**6**) in Figure 1. However, only trace of **6** was observed under the reaction conditions for the synthesis of THPs. Encouraged by Butler's suggestion about the use of water[22] and a few of efficient MCRs in water,[38-41] the influence of water on the 5CR synthesis of **6** was investigated. To our surprise, the 5CR for the synthesis of **6** proceeded smoothly in water at room temperature in higher yields using urea as catalyst and acetic acid (AcOH) as promoter which afford a simple and efficient method for the synthesis of a library of quinazoline-5-ones for investigation into their biological activities. Since some reactants or intermediates are highly insoluble, the 5CR is belong to on-water reaction.

RESULTS AND DISCUSSION

Screen of reaction conditions for the 5CR synthesis of 6{*1,1,1*}

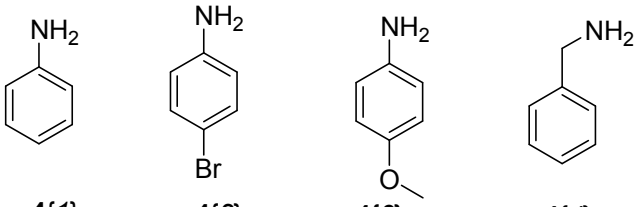
The structures of the diversity reagents used are shown in Figure 2. As shown in Scheme 1, our research began with the synthesis of 7,7-dimethyl-1,2,3-triphenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**6**{*1,1,1*}) via the 5CR of dimedone (**1**), aniline (**2**{*1*}), benzaldehyde (**3**{*1*}), aniline (**4**{*1*}) and formaldehyde (**5**). The 5CR was firstly conducted under the reaction conditions A for the synthesis of THPs[37] and only trace of **6**{*1,1,1*} was obtained. However, 54% of **6**{*1,1,1*} was obtained upon replacing **1** and **2**{*1*} by enaminone **7**{*1*}. These results means the conditions A is favourable for the four-component reaction (4CR) of **7**{*1*}, **3**{*1*}, **4**{*1*} and **5** but unfavorable for the condensation of **1** and **2**{*1*}. The 5CR could not proceed under the conditions (B)[42] for the condensation of **1** and **2**{*1*}. Since a 5CR has advantages of less operating, manpower- and material-saving over a 4CR, the study of the 5CR is needed for practical application.

primary amines 2{*1-5*}



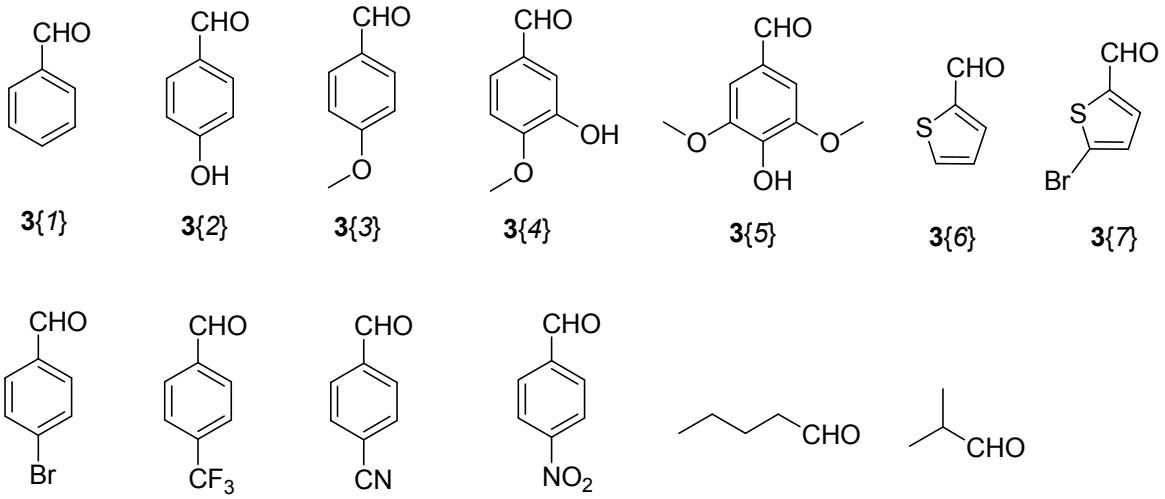
2{*1*} **2**{*2*} **2**{*3*} **2**{*4*} **2**{*5*}

primary amines 4{*1-4*}



4{*1*} **4**{*2*} **4**{*3*} **4**{*4*}

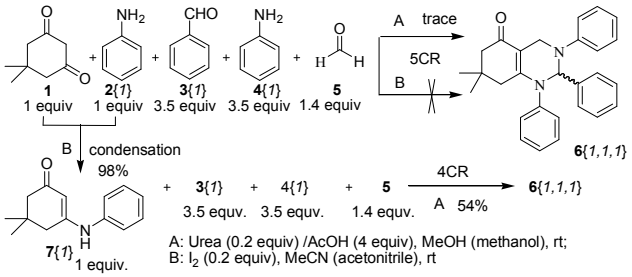
aldehyde 3{*1-13*}



3{*1*} **3**{*2*} **3**{*3*} **3**{*4*} **3**{*5*} **3**{*6*} **3**{*7*}

3{*8*} **3**{*9*} **3**{*10*} **3**{*11*} **3**{*12*} **3**{*13*}

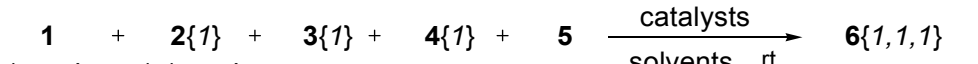
Figure 2. Molecular structures of the diversity reagents used in the work.



Scheme 1. 4CR and 5CR synthesis of **6**{*1,1,1*}.

As shown in Table 1, the reaction conditions for the 5CR synthesis of **6**{*1,1,1*} were optimized. Based on the conditions for the synthesis of THPs[37] (entry 1), the influence of solvents was firstly investigated (entries 2-6). Surprisingly, water is the most suitable solvent for the 5CR (entry 6). By screening the amount of AcOH (entries 7-9) and urea (entries 10 and 11), the yield of **6**{*1,1,1*} increased to 72% (entry 10). Then, the influence of catalysts was studied (entries 12-15). It can be seen that the yield of **6**{*1,1,1*} decreased sharply when only AcOH or urea was used (comparing entry 10 and 12/13) or when proline or $Cu(AcO)_2$ was used as catalyst (comparing entry 10 and 14/15). These results indicate that urea is an efficient catalyst for the 5CR when AcOH was used as a promoter. The screen (entries 16-22) of the amount of reactants **3**{*1*}, **4**{*1*} and **5** leads to the enhancement of the 5CR product yield (76%) (entry 21). The suitable reaction time is 24 h (entry 24). Therefore, the optimal reaction conditions for the 5CR synthesis of **6**{*1,1,1*} are **1**:**2**{*1*}:**3**{*1*}:**4**{*1*}:**5**:urea:AcOH=1:1.1:4:3:1.4:0.3:2. Under the optimal conditions, the yield (84%) of **6**{*1,1,1*} synthesized by the 5CR is similar to that (85%) synthesized by the 4CR (Scheme 1). It is worth mentioning that the yield (96%) of the condensation reaction of **1** and **2**{*1*} promoted by AcOH in water is similar to that (98%) catalyzed by I_2 in MeCN[42] and higher than that (60%) catalyst-free in water.[43] In addition, the reaction time (3 h) of the on-water AcOH-promoted condensation is shorter than that (24 h) of the on-water catalyst-free one.[43]

Table 1. Optimization of conditions for the 5CR synthesis of **6**{*1,1,1*}[a]



entry	solvent	**3**{*1*}	**4**{*1*}	**5**	catalyst /equiv	AcOH	*t* /h	yield[b] /%
1	MeOH	3.5	3.5	1.4	urea/0.2	4	5	trace
2	EtOH	3.5	3.5	1.4	urea/0.2	4	5	trace
3	MeCN	3.5	3.5	1.4	urea/0.2	4	5	trace
4	DMF	3.5	3.5	1.4	urea/0.2	4	5	trace
5	DCM	3.5	3.5	1.4	urea/0.2	4	5	40
6	H_2O	3.5	3.5	1.4	urea/0.2	4	5	60
7	H_2O	3.5	3.5	1.4	urea/0.2	3	5	62
8	H_2O	3.5	3.5	1.4	urea/0.2	2	5	68
9	H_2O	3.5	3.5	1.4	urea/0.2	1	5	54
10	H_2O	3.5	3.5	1.4	urea/0.3	2	5	72
11	H_2O	3.5	3.5	1.4	urea/0.4	2	5	70
12	H_2O	3.5	3.5	1.4		2	5	45
13	H_2O	3.5	3.5	1.4	urea/0.3		5	39
14	H_2O	3.5	3.5	1.4	proline/0.4	4	5	38
15	H_2O	3.5	3.5	1.4	$Cu(AcO)_2$/0.1	4	5	50
16	H_2O	3.5	3	1.4	urea/0.3	2	5	72
17	H_2O	3.5	2	1.4	urea/0.3	2	5	60
18	H_2O	3.5	3	1.2	urea/0.3	2	5	68
19	H_2O	3.5	3	1.6	urea/0.3	2	5	71
20	H_2O	3	3	1.4	urea/0.3	2	5	68
21	H_2O	4	3	1.4	urea/0.3	2	5	76

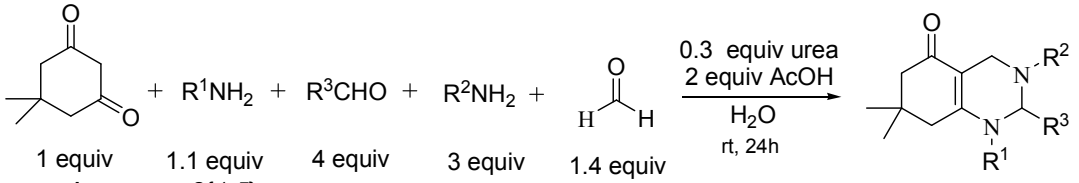
22	H_2O	4.5	3	1.4	urea/0.3	2	5	75
23	H_2O	4	3	1.4	urea/0.3	2	12	79
24	H_2O	4	3	1.4	urea/0.3	2	24	84/85[c]
25	H_2O	4	3	1.4	urea/0.3	2	48	82

[a] Reaction was carried out with **1** (0.5 mmol), **2**{*1*} (0.55 mmol), AcOH in 2 mL solvents at room temperature for 3 h, followed by adding **4**{*1*}, 38% **5, 3**{*1*} and different catalysts sequentially and then kept stirring for desired time. [b] Isolated yield. [c]4CR yield. MeOH: methanol; EtOH: ethanol; MeCN: acetonitrile; DMF: dimethylformide; DCM: dichloromethane.

Scope of the urea-catalyzed 5CR for the synthesis of 6

With the optimized conditions (entry 24 in Table 1), the scope of the 5CR synthesis of **6** was investigated. As shown in Table 2, the scope of the urea-catalyzed 5CR is wide, that is, both aliphatic and aromatic amines could be used as reactants **2** and **4**, and both aliphatic and aromatic aldehydes could be used as reactant **3**, which lead to easy construction of a large library of **6** with different aliphatic and aromatic substituents R^1, R^2 and R^3. Using aromatic aldehydes with different substituents, including strong electron-donating (entry 2-5) and -withdrawing (entries 10 and 11) substituents, as reactant **3**, the 5CR proceeded smoothly in medium to good yields (entries 1-11). When aliphatic aldehydes, such as *n*-valeraldehyde and *iso*-butyraldehyde, were used as reactant **3**, similar product yields were obtained (comparing entries 12/13 and 1). These results indicate that aldehydes show no significant influence on the 5CR. The case is similar for aniline (entry 1), aromatic amines with electron-donating, weak electron-withdrawing and larger-size substituents (entries 14-18) and aliphatic benzylamine (entries 19 and 20) as reactants **2** and **4**. However, when aromatic amine with strong electron-withdrawing substituent, such as nitro, was used as reactant **2** or **4**, no target product could be produced. The molecular structure of **6**{*1,1,12*} was confirmed by single-crystal X-ray diffraction (Figure 3).

Table 2. Scope of the 5CR synthesis of quinazolinones **6**[a]



Entry	R^1	R^2	R^3	**6**	yield (%)[b]
1	**2**{*1*}	**4**{*1*}	**3**{*1*}	**6**{*1,1,1*}	84
2	**2**{*1*}	**4**{*1*}	**3**{Balamurugan, #201}	**6**{*1,1,2*}	68
3	**2**{*1*}	**4**{*1*}	**3**{*3*}	**6**{*1,1,3*}	71
4	**2**{*1*}	**4**{*1*}	**3**{*4*}	**6**{*1,1,4*}	83
5	**2**{*1*}	**4**{*1*}	**3**{*5*}	**6**{*1,1,5*}	61
6	**2**{*1*}	**4**{*1*}	**3**{*6*}	**6**{*1,1,6*}	80
7	**2**{*1*}	**4**{*1*}	**3**{*7*}	**6**{*1,1,7*}	83
8	**2**{*1*}	**4**{*1*}	**3**{*8*}	**6**{*1,1,8*}	73
9	**2**{*1*}	**4**{*1*}	**3**{*9*}	**6**{*1,1,9*}	84
10	**2**{*1*}	**4**{*1*}	**3**{*10*}	**6**{*1,1,10*}	74
11	**2**{*1*}	**4**{*1*}	**3**{*11*}	**6**{*1,1,11*}	65
12	**2**{*1*}	**4**{*1*}	**3**{*12*}	**6**{*1,1,12*}	85
13	**2**{*1*}	**4**{*1*}	**3**{*13*}	**6**{*1,1,13*}	83
14	**2**{*1*}	**4**{Balamurugan, #201}	**3**{*1*}	**6**{*1,2,1*}	82
15	**2**{Balamurugan, #201}	**4**{Balamurugan, #201}	**3**{*8*}	**6**{*2,2,8*}	66
16	**2**{*1*}	**4**{*3*}	**3**{*1*}	**6**{*1,3,1*}	80
17	**2**{*3*}	**4**{*1*}	**3**{*1*}	**6**{*3,1,1*}	74
18	**2**{*4*}	**4**{*1*}	**3**{*1*}	**6**{*4,1,1*}	70
19	**2**{*1*}	**4**{*4*}	**3**{*1*}	**6**{*1,4,1*}	72
20	**2**{*5*}	**4**{*4*}	**3**{*1*}	**6**{*5,4,1*}	67

[a] Reaction was carried out with **1** (1 mmol), **2** (1.1 mmol), AcOH (2 mmol) in 4 mL water at room temperature for 3 h, followed by adding **4** (3 mmol), 38% **5** (1.4 mmol)，**3** (4 mmol) and urea (0.3 mmol) sequentially and then kept stirring for 24 h. [b]Isolated yield.

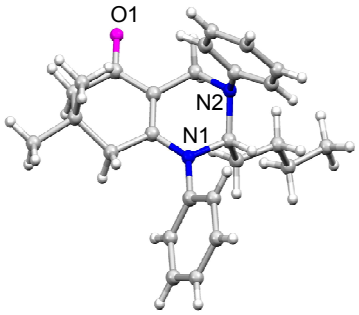
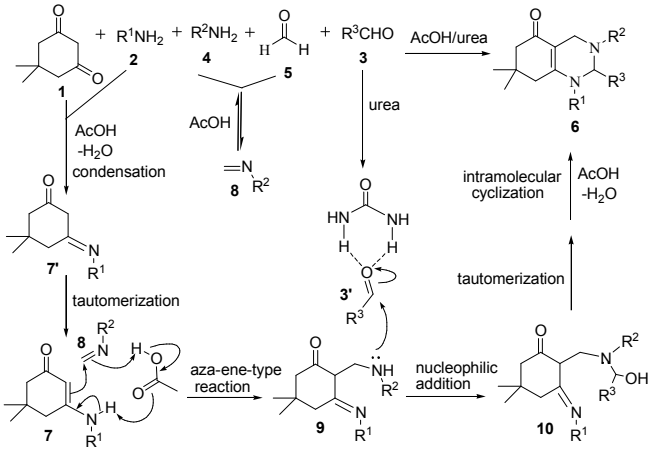


Figure 3. Molecular structure of **6**{*1,1,12*} in a single crystal (CCDC 995978).

Possible mechanism of the 5CR synthesis of 6

According to the obtained experimental results, the possible mechanism of the 5CR synthesis of **6** was proposed. As depicted in Scheme 2, under AcOH catalysis the condensation reaction of dimedone **1** with primary amine **2** leads to the formation of intermediate **7'** that transforms to enaminone **7** via keto-enol tautomerization. Intermediate **9** is expected to be produced via an aza-ene-type reaction[33, 44] rather than via a Mannich-type reaction[45] because Mannich-type reaction product could not be observed if the primary amine **2** was replaced by secondary amine *N*-methyl aniline. Reactant **3** is activated by urea[24, 37, 46, 47] and converts to an active form **3'** that reacts with **9** and hence forms intermediate **10**. Finally, target product **6** is generated via the intramolecular cyclization of **10**. The proposed 5CR mechanism includes four elementary steps: condensation, aza-ene-type reaction, nucleophilic addition and intramolecular cyclization. According to the proposed mechanism, aromatic amines with electron-donating substituents are favorable for the 5CR but those with electron-withdrawing substituent are not favorable. As for the influence of the substituents of reactant aldehydes on the 5CR, the opposite is the case. The 5CR reactivity mainly depends on the nucleophilicity of reactants amines because the reactants

aldehydes are activated by urea and AcOH. These well explain the substituent influence of aromatic amines and aldehydes on the 5CR for the synthesis of **6**.



Scheme 2. Possible mechanism of the urea-catalyzed chemoselective 5CR for the synthesis of **6**.

CONCLUSION

We have developed an efficient and simple urea-catalyzed chemoselective 5CR for the synthesis of a series of novel octahydroquinazoline-5-ones **6**. The 5CR can proceed in water at room temperature in good yields. The reported octahydroquinazoline-5-ones[8] only have aromatic substituents at N-1 and N-3 positions and were synthesized via a two-step reaction: the condensation of **1** and **2** in toluene under reflux and the three-component reaction (3CR) of **7**, **4** and **5** in EtOH under reflux in 65-85% (only 3CR yield). Compared with the reported method for the synthesis of the quinazoline-5-ones, the 5CR for the synthesis of **6** possesses advantages of green solvent (water), power-saving (rt), less operating procedures (one-pot reaction), higher overall yield and more diverse products (the substituents are not only at N-1 and N-3 but also at C-2 at which the substitution is very difficult via conventional synthetic methods owing to steric hindrance, moreover, these substituents are not only aryl but also alkyl). Therefore, the simple and efficient 5CR affords easy access to construction of a large library of octahydroquinazoline-

5-ones for investigation into their biological activities. In addition, we have developed a new greener synthetic method for the synthesis enaminones **7** that are important synthetic intermediates and have attracted great interest in synthetic chemistry.[48-50] The investigation into the biological activities and optical properties of **6** is underway in our group.

EXPERIMENTAL

General procedure for the synthesis of octahydroquinazoline-5-ones 6 in Table 2

All reactions were run with the following steps: (a) dimedone **1** (1 mmol, 140 mg), primary amine **2** (1.1 mmol) and AcOH (2 mmol, 120 μL) were added in a tube with 4 mL distilled water and kept stirring for 3 h; (b) amine **4** (3 mmol), 38% formaldehyde **5** (1.4 mmol, 112 μL), aldehyde **3** (4 mmol) and urea (0.3 mmol, 18 mg) were successively added into the above mixture and kept stirring at room temperature for 24 h**.** After the reactions were completed, the product mixtures were extracted with dichloromethane three times. The organic phase was dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, then purified by preparative TLC with petroleum ether-ethyl acetate (6:1−1:1) as eluent to afford the desired products **6** in 61−85% yields.

1,2,3,4,7,8-hexahydro-7,7-dimethyl-1,2,3-triphenylquinazolin-5(6*H*)-one 6{*1,1,1*}. White solid, 84% yield; Mp: 167–168℃; IR ν_{max} (KBr): 3059, 2955, 2926, 1625, 1587, 1572, 1492, 1450, 1388, 1293, 1258, 1193, 1174, 1154, 1122, 1077, 1031, 1010, 931, 758, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.33 – 7.22 (m, 5H), 7.05 (d, J = 8.3 Hz, 2H), 6.94 (m, 3H), 6.20 (s, 1H), 4.40 (d, J = 17.0 Hz, 1H), 3.63 (d, J = 17.0 Hz, 1H), 2.38 (d, J = 16.5 Hz, 1H), 2.28 (s, 2H), 2.17 (d, J = 16.5 Hz, 1H), 1.05 (d, J = 9.0 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 193.96, 155.83, 149.40, 143.75, 138.73, 129.43, 129.22, 128.73, 128.33, 126.92, 126.81, 126.57, 120.95, 118.54, 106.14,

81.44, 50.13, 41.65, 40.13, 33.02, 28.83, 28.01 ppm; MS (ESI): *m/z* 409 ($M + H^+$, 100); Anal. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91; N, 6.86. Found: C, 81.85; H, 6.84; N, 6.64.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization data, the ^1H NMR and ^{13}C NMR spectra of octahydroquinazoline-5-ones **6**. This information is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

MCR, Multi-component reaction; 5CR, five-component reaction; THPs, tetrahydropyrimidines; 4CR, four-component reaction; rt: room temperature; AcOH, acetic acid; MeOH: methanol; EtOH: ethanol; MeCN: acetonitrile; DMF: dimethylformide; DCM: dichloromethane; TLC, thin layer chromatography.

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