JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

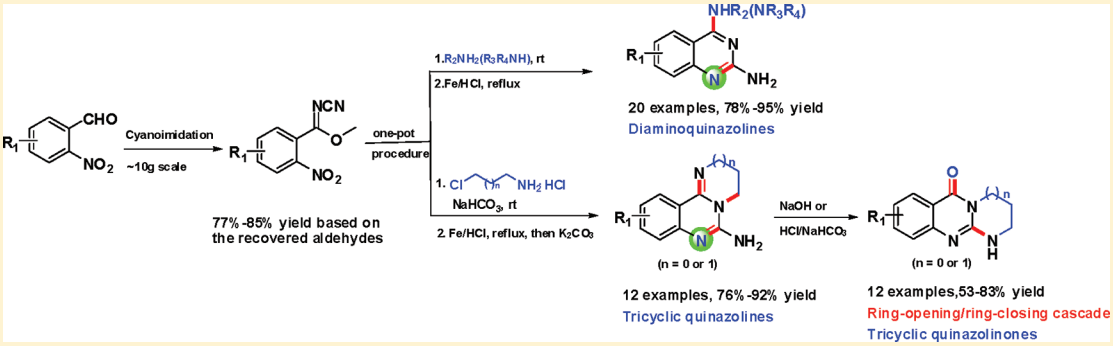
Synthesis of 2,4-Diaminoquinazolines and Tricyclic Quinazolines by Cascade Reductive Cyclization of Methyl *N*-Cyano-2-nitrobenzimidates

Ping Yin,[†] Nan Liu,[†] Yu-Xing Deng,[†] Yue Chen,[‡] Yong Deng,*[,†] and Ling He*[,†]

[†]Key Laboratory of Drug-Targeting and Drug-Delivery Systems of the Ministry of Education, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan, 610041, P. R. China

[‡]Department of Nuclear Medicine Affiliated Hospital, Luzhou Medical College, No. 25 Taiping Street, Luzhou, Sichuan, 646000, P. R. China

Supporting Information



ABSTRACT: An efficient route to N^4-substituted 2,4-diaminoquinazolines has been developed by employing tandem condensation of cyanoimidate−amine and reductive cyclization in iron−HCl system. This method is tolerant of a following intramolecular *N*-alkylation and produces two fused heterocycles in a one-pot procedure. This protocol is a facile two-step synthesis of tricyclic quinazolines, which is effected by potent cyanoimidation and tandem reductive cyclization from 2-nitrobenzaldehydes. Moreover, the forming process of tricyclic quinazolines has been investigated from the ring-opening/ring-closing cascade point of view. It is found that the preparation of tricyclic quinazolinones in good yields relies on the selective hydrolysis of tricyclic quinazolines in base or acid system.

INTRODUCTION

The development of efficient *N*-heterocycle formation by cascade reaction is significant for both natural product synthesis and medical chemistry studies. Quinazolines and quinazolones occur in various natural products[1] and listed drugs as the core structure, and many of them are identified for their noticeable biological activities.[2] Among the quinazolines libraries, the class of 2,4-diaminoquinazolines are very important pharmacophores presented in numerous marketed drugs. For example, prazosin, a selective α_1 adrenoceptor antagonist drug,[3] has a wide application in clinical therapy due to its prominent antihypertensive effect. As the new analogues of dihydrofolate reductase inhibitor methotrexate, trimetrexate and piritrexim[4] provide alternative antineoplastic protocols. Moreover, their prominent anticancer effects are extremely vital for the widespread drug resistance of methotrexate.[5] In addition, these lipophilic drugs play a new role in the treatment of *Pneumocystis carinii* pneumonia (PCP).[6] Other studies have shown that the quinazolinediamine derivatives have not only been applied as the well-known anticancer agent, but also exhibited some other remarkable functions, including SMN2 promoter activators[7] and selective inhibitors of trypanosomal and leishmanial dihydrofolate reductase.[8] Apart from the research above, some N^4-monosubstituted quinazolineamines serve as a key intermediate in the synthesis of opioid receptor like-1 (ORL1) antagonists.[9] Likewise, 2,3-dihydroimidazo[1,2-c]quinazolin-5-amine, containing a quinazolinediamine structure, is an important scaffold in a series of kinase inhibitors. They are effective for treatment of angiogenesis-mediated and hyper-proliferative diseases, including cancer, inflammation, and other kinase-associated disorders.[10]

Such versatility of 2,4-diaminoquinazolines is very attractive for organic synthesis, and distinct methods to achieve them have been developed. Traditional synthetic strategies mainly include the use of 2-aminobenzonitriles or 2-fluorobenzonitriles as the starting materials. Although the cyclization of substituted 2-aminobenzonitriles can react with various agents, such as guanidine, dicyandiamide, or chloroformamidine hydrochloride, the yields of these preparations are modest in most cases.[11] In comparison with previous results, the reaction of 2-fluorobenzonitrile

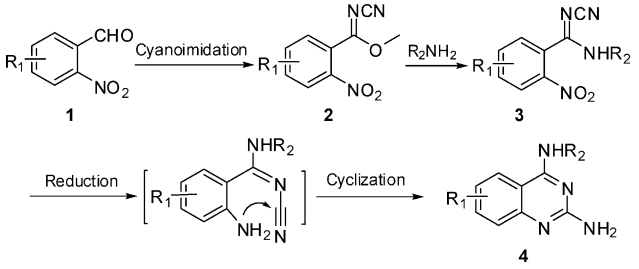
Received: November 24, 2011
Published: January 27, 2012

with guanidine carbonate gives an excellent yield, but it still needs a high temperature to promote cyclization.[12] *N*-Substituted 2,4-diaminoquinazolines are commonly obtained by 2,4-dichloroquinazolines that can be efficiently prepared from quinazoline-2,4-diones by refluxing in phosphorus oxychloride.[13] Despite its general universality, several disadvantages exist in this method; respectively, vigorous reagent $POCl_3$ has to be used in chlorination, and elevated temperature cannot be avoided in the coupling with amine at the 2-position. Furthermore, in the synthesis of N^4-monosubstituted 2,4-diaminoquinazoline, low yield is produced because of the poor coupling with ammonia.[9] Accordingly, there might be considerable benefits to developing various paths for the synthesis of diaminoquinazoline. Recently, solid-phase method has been employed to effect combinatorial libraries of 2,4-diaminoquinazolines in good yield and purity.[14] Another novel approach to 2,4-diaminoquinazolines is also facilitated by Cu-catalyzed Ullmann-type *N*-arylation from 2-bromobenzonitriles with guanidine.[15] To develop a more practical and economic methodology for the synthesis of 2,4-diaminoquinazolines, we have attempted to utilize the cyanoimidation of aldehydes as the initial architectonic strategy. Oxidative imidation of aldehydes has emerged as an attractive route to nitrogen-containing heterocycles.[16] Our previous work[17] has reported that cyanoimidation serves as a facile formation of cyanoimidate, which is an important intermediate for the synthesis of *N*-heterocyclic compounds.[18] To the best of our knowledge, the synthesis of diaminoquinazoline starting from *N*-cyano-2-nitrobenzimidate and amine has remained undeveloped. Herein, we demonstrate a one-pot procedure to prepare N^4-substituted 2,4-diaminoquinazolines and their polycyclic derivatives via reduction and intramolecular cyclization.

RESULTS AND DISCUSSION

Our proposed route to diaminoquinazolines used 2-nitrobenzaldehydes as the starting materials (Scheme 1). Initial investigation

Scheme 1. Proposed Route to Diaminoquinazolines



indicated the oxidative cyanoimidation of 2-nitrobenzaldehydes and the condensation with amine both performed in excellent yields. Hence, our following studies focused on the reductive conversion from 2-nitrobenzimidamides (**3**) to diaminoquinazolines (**4**).

We began the optimization with *N*′-cyano-*N*-(2-(dimethylamino)ethyl)-2-nitrobenzimidamide as the model substrate (Table 1). In preliminary hydrogen reduction catalyzed by 10 mmol % Pd/C, there was only trace product obtained (Table 1, entry 1). In contrast, Raney Ni (10 mmol %) catalytic hydrogenation gave a moderate yield (Table 1, entry 2). Reaction executed with sodium dithionite was observed with a similar result, but using $SnCl_2$ in EtOH did not obtain any of the desired products (Table 1, entries 3, 4). We also had attempted to choose Fe/NH_4Cl as the reductive agent and only yielded trace product (Table 1, entry 5). However, a dramatic increase was observed while the reductive iron was activated by a small amount of concentrate hydrochloride (Table 1, entry 6). Moreover, Fe/AcOH led to little decrease of yield (Table 1, entry 7). In the comparison of different acids, we concluded that strong acid was beneficial for effecting higher product yield (Table 1, entries 5, 6, and 7). Additionally, further optimization demonstrated that 4 equiv of iron elevated the yield (Table 1, entry 8), but prolongation of reaction time with more reductive agent did not give the better results (Table 1, entry 9).

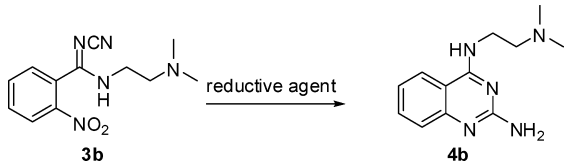
In our previous report, the optimization of cyanoimidation was processed. We thus decided to follow the same procedure, and several substrates with different substituted groups were used to test the universality in cyanoimidation of nitrobenzaldehydes. Parallel tests indicated that the addition of 4 Å MS promoted the conversion of aldehyde and reduced the generation of carboxylic ester. Presumably in this process, the molecular sieve acted as a dehydrating agent that promoted the condensation of aldehydes with cyanamide. We found that substrates with electron-withdrawing or electron-donating groups gave good results uniformly on a 0.06 mol scale. As shown in Table 2 (entries 1, 2, 5 and 6), 2-nitrobenzaldehyde and electron-poor aldehydes are converted to cyanoimidates in good yield. Meanwhile, cyanoimidation of nitrobenzaldehydes with electron-donating groups on the aryl rings also provided desired products in good yields (Table 2, entry 3 and 4).

After the preparation of cyanoimidates, we focused on the synthesis of different substituted diaminoquinazolines. Having established the optimal conditions, we then wished to combine the condensation and reductive cyclization into a one-pot reaction. Gratifyingly, the cascade process of different cyanoimidates with amines output good yield in most instances (Table 3). Treated with methyl *N*-cyano-2-nitrobenzimidate (**2a**), simple primary amines substituted with aliphatic chains or rings were easily converted to diaminoquinazolines by Fe/HCl (Table 3, entries 1, 3, 9, and 10), and substitution containing aryl groups also yielded good results (Table 3, entries 4, 11). From several examples, we excitedly found that the reaction bore hydroxyl radical by using aminoalcohols (Table 3, entries 6, 12, 13, 15, and 19). The investigation of secondary amines also gave good yields in presence of more amines and reductive agents. Notably, unsubstituted diaminoquinazoline was accessed in nearly quantitative yield by using ammonia−water (Table 3, entry 18). The cascade reactions were also performed with various substitutes to study the electronic effect of the cyanoimidates, and satisfactory results were observed (Table 3, entries 14−17, 19, and 20). However, the optimal condition was not fit for arylamine, and no desired product was obtained.

Inspired by the synthetic potential of the efficient reduction and cyclization, we wished to expand the research to the construction of tricyclic quinazolines derivatives. A continuous 3-*N*-alkylation of quinazoline core was adopted to achieve another heterocyclic ring by using chloroalkylamines. The one-pot reaction employed by additional K_2CO_3 provided excellent results in tandem transformations involving neutralization and *N*-alkylation. Moreover, the tricyclic quinazolines (**5**) could undergo a ring-opening/ring-closing cascade with NaOH or HCl/$NaHCO_3$ to achieve the formation of quinazolinone. Simultaneously, the tandem intramolecular reaction afforded the framework of tricyclic guanidine, whose functional groups embedded into polycyclic architecture are very significant for total synthesis[19] and

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649−2658

Table 1. Reduction of 2-Nitrobenzimidamide (3b)[a]

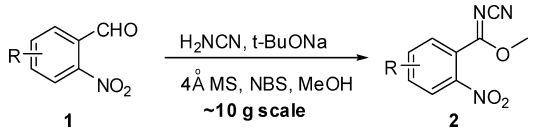


3b 4b

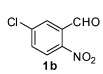
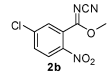
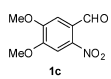
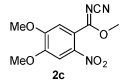
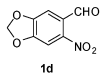
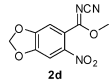
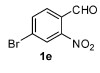
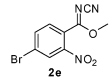
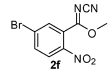
entry	reductive agent	temp/time	solvent	yield (%)[b]
1	Pd/C (10 mmol %), H_2	rt/6 h	MeOH	trace
2	Ni (10 mmol %), H_2	rt/24 h	MeOH	52
3	$Na_2S_2O_4$	35 °C/2 h	EtOH/H_2O	41
4	$SnCl_2$	80 °C/3 h	EtOH	0
5	Fe/NH_4Cl	95 °C/3 h	H_2O	trace
6	Fe/HCl	64 °C/3 h	MeOH	83
7	Fe/AcOH	64 °C/3 h	MeOH	79
8[c]	**Fe/HCl**	**64 °C/3 h**	**MeOH**	**88**
9[d]	Fe/HCl	64 °C/10 h	MeOH	86

[a]Conditions: reactions were conducted on a 0.2 mmol scale using 1 equiv of substrate (**3b**), 2 equiv of reductive agents (except catalytic hydrogenation), and 3 mL of solvents. [b]Isolated yield. [c]The reaction was carried out with 4 equiv of iron (1.8 mmol). [d]The reaction was carried out with 6 equiv of iron (2.7 mmol).

Table 2. Cyanoimidation of 2-Nitrobenzaldehydes[a]



1 2

entry	substrate	product	% yield (conversion)[b]
1	 1a	 2a	80(98)/78(94)[c]
2	 1b	 2b	85(94)/77(90)[c]
3	 1c	 2c	78(88)
4	 1d	 2d	84(90)
5	 1e	 2e	77(96)
6	 1f	 2f	83(97)

[a]Conditions: substrate (0.06 mol), NH_2CN (0.24 mol), *t*-BuONa (0.24 mol), and 4 Å molecular sieve (10 g), MeOH (500 mL), rt for 0.5 h; then NBS (0.24 mol), 50 °C, 12 h. [b]The isolated yields were obtained by the average of two parallel tests and based on the recovered aldehydes. [c]Control test without 4 Å MS.

organocatalysis.[20] Accordingly, these characteristics have attracted considerable attention in their synthetic method research.[21]

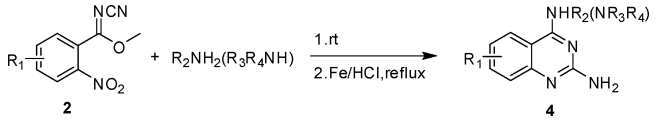
To explore the utility of these cascade reactions, the scope of various cyanoimidates was studied. As illustrated in Table 4, 2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (**5a**) was obtained in excellent yield from methyl *N*-cyano-2-nitrobenzimidate (**2a**) and 2-chloroethanamine (Table 4, entry 1). The tandem reaction could also tolerate different substitutes at benzene ring of cyanoimidates (Table 4, entries 2−6). Performed with 3-chloropropan-1-amine, various derivatives of 3,4-dihydro-2*H*-pyrimido[1,2-c]quinazolin-6-amines were provided in good yields as well (Table 4, entries 7−12).

Further studies of tricyclic quinazolines had shown that cleavage of 2*H*-pyrimidine ring proceeded readily in the presence of sodium hydrate[22] and gave quinazolinones in good yield (Table 4, entries 7−12). Nevertheless, this method was not suitable for 2*H*-imidazole series and only produced trace product. Because of the disappointing ring-opening results of base, we adopted the use of diluted hydrochloric acid to advance the hydrolysis,[23] which was proven to be effective after neutralization using sodium bicarbonate in further cyclization. The intramolecular cascade of methyl *N*-cyano-2-nitrobenzimidate (**5a**) afforded 2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (**6a**) in good yield (Table 4, entry 1). Therefore, efforts to transform the tricyclic substrates are focused on other substituents, and moderate yields are obtained (Table 4, entries 2−6). The effect of acid hydrolysis was carried out into 2*H*-pyrimidine derivatives, which only generated inferior results (Table 4, entries 7−9). In addition, two selected compounds **5h** and **6g** were further verified by X-ray crystallography.[24]

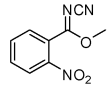
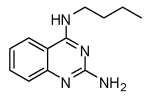
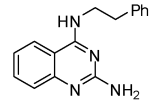
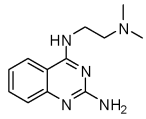
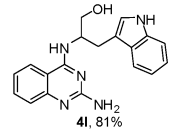
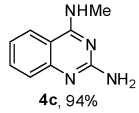
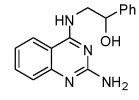
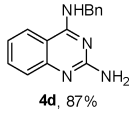
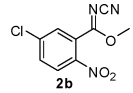
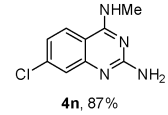
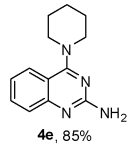
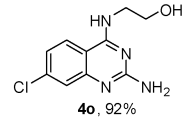
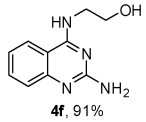
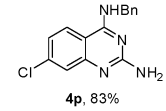
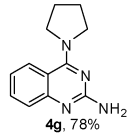
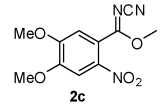
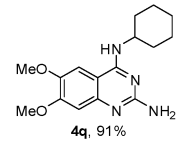
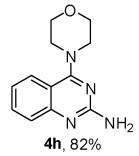
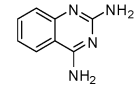
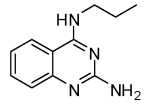
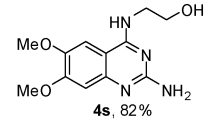
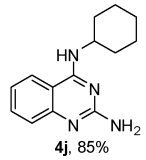
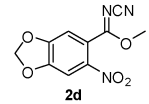
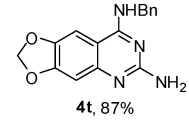
Finally, we attempted to study the tentative mechanism and the formation of side products in the ring-opening/ring-closing cascade reaction. Hydrolysis of 2*H*-pyrimidine derivatives had been chosen as the model reaction (Scheme 2), which led to the formation of ring-opening products 2-aminoquinazolinones (**7**), along with unexpected coproduct (**8**). Actually, ring-opening intermediates were generated as a hydrochloride form that hindered the coming cyclization. Once the aminoquinazolinone hydrochlorides were neutralized with base, they afforded tricyclic guanidine product (**6**) via smooth intramolecular cyclization in refluxing ethanol and water. Besides, monoacetylation of the unstable intermediates were readily achieved in acetic anhydride−triethylamine system, which provided another available framework of 2-aminoquinazolin-4(3*H*)-ones. Several aspects of the findings uncovered that there may be a selective hydrolysis in the ring-opening process of tricyclic quinazolines. Hydrolysis of 2*H*-pyrimidine series deduced by base selectively gave desired products uniquely, which was superior to the acidolysis. However, acid allowed a more powerful hydrolysis

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649−2658

Table 3. Synthesis of Diaminoquinazolines[a,b]



2 4

entry	substrate	product	entry	substrate	product
1	 2a	 4a, 92%	11	2a	 4k, 83%
2	2a	 4b, 86%	12	2a	 4l, 81%
3[c]	2a	 4c, 94%	13	2a	 4m, 88%
4	2a	 4d, 87%	14[b]	 2b	 4n, 87%
5[d]	2a	 4e, 85%	15	2b	 4o, 92%
6	2a	 4f, 91%	16	2b	 4p, 83%
7[d]	2a	 4g, 78%	17	 2c	 4q, 91%
8[d]	2a	 4h, 82%	18[e]	2a	 4r, 95%
9	2a	 4i, 94%	19	2c	 4s, 82%
10	2a	 4j, 85%	20	 2d	 4t, 87%

[a]Conditions: (1) cyanoimidates (1 mmol) and amines (1.5 mmol, 1.5 equiv), MeOH (2 mL), rt for 3 h. (2) iron (9 mmol, 4 equiv), concentrated hydrochloric acid (0.6 mL), reflux for 3 h. [b]Isolated yield after silica gel chromatography. [c]25% aqueous methylamine was used with the corresponding molar ratio. [d]3 mmol amines (3 equiv), 13.5 mmol iron (6 equiv) and 1 mL of concentrated hydrochloric acid were used. [e]25% ammonia−water was used with the corresponding molar ratio.

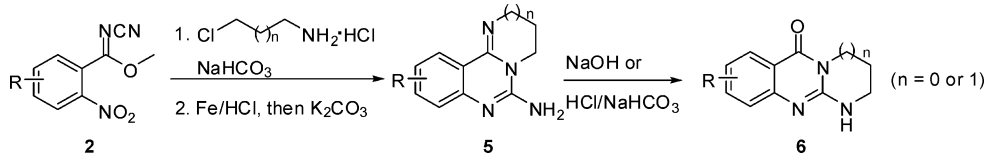
for the 2*H*-imidazole series than base because of the stability of five-membered rings. These two complementary routes exhibited an efficacious hydrolysis in executing the ring-opening/ring-closing cascade and furnished a practical preparation of tricyclic quinazolinones.

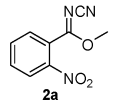
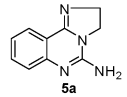
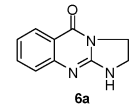
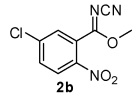
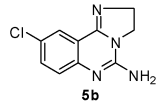
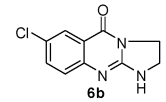
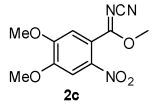
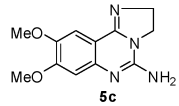
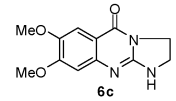
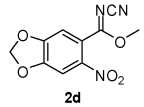
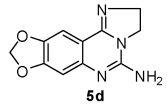
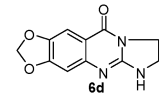
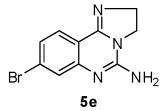
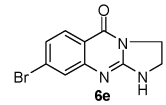
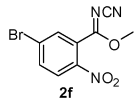
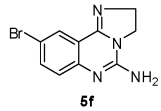
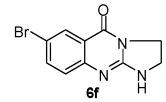
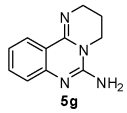
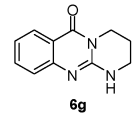
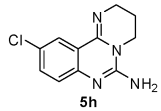
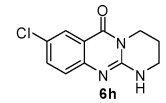
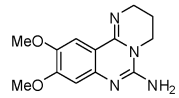
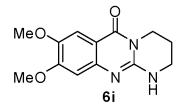
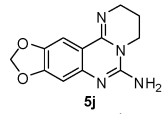
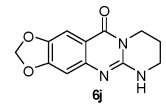
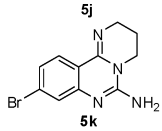
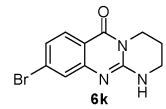
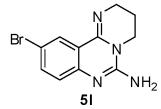
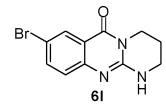
CONCLUSIONS

Potent cyanoimdiation and reductive cyclization serve as a uniquely effective synthesis to N^4-monosubstituted diamino-quinazoline from *ortho*-nitroaldehydes, and they can also

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649−2658

Table 4. Scope of Cascade Reactions



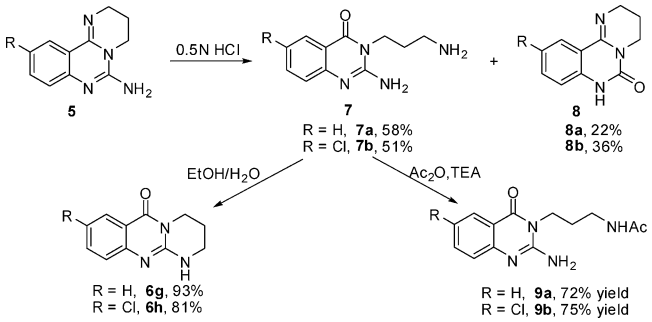
entry	substrate	product 5[a]	yield of 5 (%)[b]	product 6[c]	yield of 6 (%)[b]
1	 2a	 5a	89	 6a	72
2	 2b	 5b	92	 6b	68
3	 2c	 5c	84	 6c	53[d]
4	 2d	 5d	82	 6d	64[d]
5	 2e	 5e	76	 6e	61
6	 2f	 5f	82	 6f	63
7	**2a**	 5g	81	 6g	81(52[e])
8	**2b**	 5h	83	 6h	78(46[e])
9	**2c**	 5i	85	 6i	83(42[e])
10	**2d**	 5j	77	 6j	75
11	**2e**	 5k	85	 6k	80
12	**2f**	 5l	79	 6l	73

[a]Conditions: (1) chloroalkylamines hydrochloride (1 mmol, 2 equiv) and $NaHCO_3$ (1 mmol, 2 equiv), rt for 0.5 h; then cyanoimidates (0.5 mmol), 50 °C, 6 h. (2) iron (4.5 mmol, 4 equiv), concentrated hydrochloric acid (0.4 mL), reflux for 3 h; then potassium carbonate (5 mmol), reflux for additional 6 h. [b]Isolated yield after silica gel chromatography. [c]Conditions: For 2*H*-imidazole series, **5** (0.2 mmol), HCl (0.5 mol/L)/EtOH (5:1) 30 mL, reflux for 6 h; then $NaHCO_3$ (20 mmol), reflux for additional 72 h. For 2*H*-pyrimidine series, **5** (0.2 mmol), 0.01 N NaOH/EtOH (5:1) 30 mL, reflux for 72 h. [d]The reaction time of acidolysis was 12 h. [e]Conditions of 2*H*-imidazole series (acidolysis) were used for contrast tests.

provide tricyclic quinazolines via the similar facile route. What deserved to be mentioned was the formation of two heterocycles accomplished in a one-pot procedure. Subsequently, the significant ring-opening/ring-closing cascade of tricyclic quinazolines was demonstrated to afford quinazolinones including cyclic guanidine. Continued efforts to explore the

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649–2658

Scheme 2. Study of Ring-Opening Process



bioactivities of these heterocycles will be made in the further studies.

EXPERIMENTAL SECTION

^{1}H NMR experiments were recorded on a 400 MHz spectrometer, and ^{13}C NMR experiments were recorded on a 100 MHz spectrometer. The mass spectra (ESI/HRMS) were recorded on mass spectrometer. 4 Å molecular sieves were dried at 200 °C under vacuum for 12 h and grinded before use. Methanol was predried over 4 Å molecular sieves. Flash chromatography on silica gel (300−400 mesh) was performed.

General Procedure for Cyanoimidation. To a 1 L oven-dried flask with a solution of aldehydes (**1**, 0.06 mol), NH_2CN (0.24 mol, 10.09 g), and 4 Å molecular sieve (10.0 g) in MeOH (500 mL) was added *t*-BuONa (0.24 mol, 23.06 g) in portions (the temperature was controlled by an ice bath and not allowed to exceed 35 °C), and the mixture was stirred at 25 °C for 0.5 h. Then, NBS (0.24 mol, 42.72 g) was added to the reaction mixture, which cooled in an ice bath. Then, the reaction mixture was allowed to warm up and stirred at 50 °C for 12 h. The solvent was removed by vacuum distillation, and then $CHCl_3$ (400 mL)/saturated aqueous $Na_2S_2O_3$ (300 mL) were added to the residue and stirred for 10 min. The mixture was filtered, and the filtrate was extracted with another $CHCl_3$ (2 × 200 mL). The organic layer was combined, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by flash column chromatography to afford the product.

*Methyl N-Cyano-2-nitrobenzimidate (**2a**; Table 2; Entry 1).* Eluent petroleum ether/chloroform/ethyl acetate (100:20:10 to 100:40:10). Yield, 9.65 g, 80% (based on the recovered aldehyde). White solid: mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 150.4, 134.6, 132.7, 129.2, 126.3, 125.2, 112.6, 58.0; HRMS (M + H$^+$) calcd for $C_9H_8N_3O_3$ 206.0566, found 206.0565.

*Methyl 5-Chloro-N-cyano-2-nitrobenzimidate (**2b**; Table 2; Entry 2).* Eluent petroleum ether/chloroform/ethyl acetate (100:10:10 to 100:20:10). Yield, 11.51 g, 85% (based on the recovered aldehyde). White solid: mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 8.8, 2.4 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 151.8, 141.6, 132.6, 129.1, 127.8, 126.7, 112.1, 58.3; HRMS (M + Na$^+$) calcd for $C_9H_6ClN_3NaO_3$ 261.9995, found 261.9993.

*Methyl N-Cyano-4,5-dimethoxy-2-nitrobenzimidate (**2c**; Table 2; Entry 3).* Eluent petroleum ether/chloroform/ethyl acetate (100:15:10 to 100:40:10). Yield, 10.88 g, 78% (based on the recovered aldehyde). Yellow solid: mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.92 (s, 1H), 4.07 (s, 3H), 4.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 153.6, 150.9, 139.0, 120.1, 112.8, 109.9, 107.7, 57.9, 56.9, 56.7; HRMS (M + Na$^+$) calcd for $C_{11}H_{11}N_3NaO_5$ 288.0596, found 288.0612.

*Methyl N-Cyano-6-nitrobenzo[d][1,3]dioxole-5-carbimidate (**2d**; Table 2; Entry 4).* Eluent petroleum ether/chloroform/ethyl acetate (100:10:10 to 100:20:10). Yield, 11.16 g, 84% (based on the recovered aldehyde). Yellow solid: mp 142−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 6.92 (s, 1H), 6.24 (s, 2H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 152.6, 150.4, 122.3, 112.6, 107.7, 105.8, 104.2, 58.1; HRMS (M + Na$^+$) calcd for $C_{10}H_7N_3NaO_5$ 272.0283, found 272.0283.

*Methyl 4-Bromo-N-cyano-2-nitrobenzimidate (**2e**; Table 2; Entry 5).* Eluent petroleum ether/chloroform/ethyl acetate (100:10:10 to 100:20:10). Yield, 12.64 g, 78% (based on the recovered aldehyde). White solid: mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 1.6 Hz, 1H), 7.97 (dd, J = 8.0, 2.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 149.0, 137.5, 130.2, 128.5, 126.7, 124.8, 112.3, 58.2; HRMS (M + Na$^+$) calcd for $C_9H_6BrN_3NaO_3$ 305.9490, found 305.9492.

*Methyl 5-Bromo-N-cyano-2-nitrobenzimidate (**2f**; Table 2; Entry 6).* Eluent petroleum ether/chloroform/ethyl acetate (100:10:10 to 100:20:10). Yield, 13.72 g, 83% (based on the recovered aldehyde). White solid: mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 1H), 7.90 (dd, J = 8.8, 2.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 149.4, 135.6, 131.8, 129.7, 127.7, 126.5, 112.0, 58.2; HRMS (M + Na$^+$) calcd for $C_9H_6BrN_3NaO_3$ 305.9490, found 305.9496.

General Procedure for Synthesis of N^4-Substitued 2,4-Diaminoquinazolines. Cyanoimidates (**2**, 1 mmol) and amines (1.5 mmol, 1.5 equiv) were dissolved in MeOH (4 mL), and the mixture was stirred at room temperature for 3 h and diluted with additional MeOH (25 mL), followed by the addition of iron (9 mmol, 502 mg, 4 equiv) and concentrated hydrochloric acid (0.6 mL). The final temperature was elevated to reflux for 3 h. Excess sodium bicarbonate (15 mmol, 1.26 g) was added to neutralize the diaminoquinazoline and percitipate remnant ferri iron. The reaction was kept refluxing for an additional 2 h and operated by kieselguhr filteration. The filtrate solution was evaporated by vacuum distillation, and the residue was purfied by flash column chromatography to afford product **4**.

*N^4-Butylquinazoline-2,4-diamine (**4a**; Table 3; Entry 1).* Eluent dichloromethane/methanol (100:15). Yield, 199 mg, 92%. White solid: mp 165−166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08−8.06 (m, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.39 (s, 2H), 3.51−3.47 (m, 2H), 1.66−1.58 (m, 2H), 1.41−1.31 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 159.8, 150.0, 132.7, 123.2, 123.1, 120.7, 111.0, 40.3, 30.9, 20.0, 14.0; HRMS (M + H$^+$) calcd for $C_{12}H_{17}N_4$ 217.1453, found 217.1458.

*N^4-(2-(Dimethylamino)ethyl)quinazoline-2,4-diamine (**4b**; Table 3; Entry 2).* Eluent dichloromethane/methanol/triethylamine (100:15:0.5). Yield, 198 mg, 86%. Light yellow solid: mp 139−140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.6 Hz), 6.26 (s, 2H), 3.60 (m, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.24 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 160.5, 151.4, 133.1, 124.3, 123.2, 121.1, 111.3, 58.1, 45.5, 38.5; HRMS (M + H$^+$) calcd for $C_{12}H1_8N_5$ 232.1562, found 232.1566.

*N^4-Methylquinazoline-2,4-diamine (**4c**; Table 3; Entry 3).* Eluent dichloromethane/methanol (100:20). Yield, 163 mg, 94%. White solid: mp 209−211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.29 (s, 2H), 2.96 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 160.2, 150.6, 132.6, 123.7, 123.0, 120.6, 111.1, 27.9; HRMS (M + H$^+$) calcd for $C_9H_{11}N_4$ 175.0984, found 175.0983.

*N^4-Benzylquinazoline-2,4-diamine (**4d**; Table 3; Entry 4).* Eluent dichloromethane/methanol (100:8). Yield, 218 mg, 87%. White solid: mp 115−118 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.38−7.23 (m, 6H), 7.06 (t, J = 7.6 Hz, 1H), 6.24 (s, 2H), 4.75 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 160.3, 151.4, 134.0, 132.8, 128.5, 127.6, 127.0, 124.0, 123.1, 120.6, 110.9, 43.5; HRMS (M + H$^+$) calcd for $C_{15}H_{15}N_4$ 251.1297, found 251.1294.

*4-(Piperidin-1-yl)quinazolin-2-amine (**4e**; Table 3; Entry 5).* Eluent dichloromethane/methanol (100:8). Yield, 194 mg, 85%. Yellow solid: mp 201−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.4 Hz, 1H), 7.62−7.59 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.99 (s, 2H), 3.68 (m, 4H), 1.68

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649−2658

(m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 157.5, 149.2, 133.4, 126.3, 122.1, 121.5, 111.2, 50.5, 25.8, 24.3; HRMS (M + H$^+$) calcd for $C_{13}H_{17}N_4$ 229.1453, found 229.1458.

*2-(2-Aminoquinazolin-4-ylamino)ethanol (**4f**; Table 3; Entry 6).* Eluent dichloromethane/methanol (100:15). Yield, 185 mg, 91%. White solid: Decomp 268 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.02 (s, 2H), 4.90 (s, 1H), 3.61−3.53 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 160.7, 152.3, 132.4, 124.5, 123.1, 120.0, 111.1, 59.8, 43.3; HRMS (M + H$^+$) calcd for $C_{10}H_{13}N_4O$ 205.1089, found 205.1081.

*4-(Pyrrolidin-1-yl)quinazolin-2-amine (**4g**; Table 3; Entry 7).* Eluent dichloromethane/methanol (100:10). Yield, 167 mg, 78%. Light yellow solid: Decomp 272 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.27 (s, 2H), 3.82 (t, J = 6.0 Hz, 4H), 1.94 (t, J = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 157.2, 145.5, 132.9, 126.6, 121.5, 121.1, 111.7, 51.1, 25.3; HRMS (M + H$^+$) calcd for $C_{12}H_{15}N_4$ 215.1297, found 215.1290.

*4-Morpholinoquinazolin-2-amine (**4h**; Table 3; Entry 8).* Eluent dichloromethane/methanol (100:8). Yield, 189 mg, 82%. Yellow solid: mp 162−164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.45 (s, 2H), 3.79 (t, J = 4.4 Hz, 4H), 3.55 (t, J = 4.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 159.8, 154.3, 132.7, 125.6, 125.3, 120.5, 111.8, 66.3, 50.3; HRMS (M + H$^+$) calcd for $C_{12}H_{15}N_4O$ 231.1246, found 231.1245.

*N^4-Propylquinazoline-2,4-diamine (**4i**; Table 3; Entry 9).* Eluent dichloromethane/methanol (100:8). Yield, 190 mg, 94%. White solid: mp 163−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.0 Hz, 1H), 7.87 (t, J = 8.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.12 (s, 2H), 3.42 (q, J = 6.0 Hz, 2H), 1.68−1.61 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 160.4, 151.4, 132.5, 124.0, 123.1, 120.3, 111.0, 42.3, 22.1, 11.8; HRMS (M + H$^+$) calcd for $C_{11}H_{15}N_4$ 203.1297, found 203.1301.

*N^4-Cyclohexylquinazoline-2,4-diamine (**4j**; Table 3; Entry 10).* Eluent dichloromethane/methanol (100:10). Yield, 207 mg, 85%. White solid: Decomp 261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.20 (s, 2H), 4.17−4.12 (m, 1H), 1.92−1.90 (m, 2H), 1.79−1.76 (m, 2H), 1.67−1.63 (m, 1H), 1.43−1.27 (m, 4H), 1.20−1.11 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 159.7, 150.8, 132.6, 123.5, 123.4, 120.3, 111.0, 49.1, 32.4, 25.6, 25.4; HRMS (M + H$^+$) calcd for $C_{14}H_{19}N_4$ 243.1610, found 243.1606.

*N^4-Phenethylquinazoline-2,4-diamine (**4k**; Table 3; Entry 11).* Eluent dichloromethane/methanol (100:8). Yield, 220 mg, 83%. White solid: mp 187−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.31−7.15 (m, 7H), 6.89 (s, 2H), 3.75−3.70 (m, 2H), 2.97 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 158.3, 146.8, 139.7, 133.5, 129.0, 128.6, 126.4, 123.5, 121.9, 121.5, 110.7, 42.6, 34.6; HRMS (M + H$^+$) calcd for $C_{16}H_{17}N_4$ 265.1453, found 265.1452.

*2-(2-Aminoquinazolin-4-ylamino)-3-(1H-indol-3-yl)propan-1-ol (**4l**; Table 3; Entry 12).* Eluent dichloromethane/methanol (100:10). Yield, 269 mg, 81%. Yellow solid: mp 153−155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 6.4 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 6.4 Hz, 1H), 7.32−6.97 (m, 6H), 6.58 (s, 2H), 4.90 (br, 1H), 4.62 (m, 1H), 3.62 (m, 2H), 3.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 158.9, 148.3, 136.3, 133.2, 127.8, 123.7, 123.5, 122.2, 121.3, 121.0, 118.7, 118.5, 111.7, 111.6, 110.9, 62.6, 53.8, 26.3; HRMS (M + H$^+$) calcd for $C_{19}H_{20}N_5O$ 334.1668, found 334.1660.

*2-(2-Aminoquinazolin-4-ylamino)-1-phenylethanol (**4m**; Table 3; Entry 13).* Eluent dichloromethane/methanol (100:8). Yield, 247 mg, 88%. White solid: mp 127−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.51−7.46 (m, 3H), 7.35 (t, J = 7.6 Hz, 2H), 7.27−7.21 (m, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.28 (s, 2H), 5.63 (s, 1H), 4.99 (dd, J = 8.0, 3.2 Hz, 1H), 3.79−3.73 (m, 1H), 3.44−3.38 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 160.2, 151.3, 144.4, 132.7, 128.3, 127.3, 126.3, 124.0, 123.3, 120.6, 111.1, 70.9, 49.5; HRMS (M + H$^+$) calcd for $C_{16}H_{17}N_4O$ 281.1402, found 281.1395.

*6-Chloro-N^4-methylquinazoline-2,4-diamine (**4n**; Table 3; Entry 14).* Eluent dichloromethane/methanol (100:8). Yield, 181 mg, 87%. White solid: mp 205−208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13−8.07 (m, 2H), 7.48 (dd, J = 8.8, 2.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.46 (s, 2H), 2.94 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 160.2, 149.6, 132.6, 125.7, 124.1, 122.3, 111.8, 27.9; HRMS (M + H$^+$) calcd for $C_9H_{10}ClN_4$ 209.0594, found 209.0587.

*2-(2-Amino-6-chloroquinazolin-4-ylamino)ethanol (**4o**; Table 3; Entry 15).* Eluent dichloromethane/methanol (100:10). Yield, 220 mg, 92%. White solid: mp 202−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 2.0 Hz, 1H), 8.01 (s, 1H), 7.49 (dd, J = 8.8, 2.0 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.32 (s, 2H), 4.78 (t, J = 4.8 Hz, 1H), 3.61−3.60 (m, 2H), 3.53 (q, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 160.0, 150.4, 132.7, 126.1, 124.0, 122.5, 111.9, 59.6, 43.5; HRMS (M + H$^+$) calcd for $C_{10}H_{12}ClN_4O$ 239.0700, found 239.0704.

*N^4-Benzyl-6-chloroquinazoline-2,4-diamine (**4p**; Table 3; Entry 16).* Eluent dichloromethane/methanol (100:5). Yield, 236 mg, 83%. White solid: mp 189−191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83(s, 1H), 8.26 (s, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.39−7.24 (m, 6H), 6.63 (s, 2H), 4.73 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 157.0, 142.7, 138.6, 134.3, 128.6, 128.2, 127.4, 126.9, 123.7, 121.8, 111.5, 45.7; HRMS (M + H$^+$) calcd for $C_{15}H_{14}ClN_4$ 285.0907, found 285.0903.

*N^4-Cyclohexyl-6,7-dimethoxyquinazoline-2,4-diamine (**4q**; Table 3; Entry 17).* Eluent dichloromethane/methanol (100:10). Yield, 274 mg, 91%. Light yellow solid: mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.59 (s, 1H), 6.76 (s, 1H), 6.56 (s, 2H), 4.23−4.15 (m, 1H), 3.84 (s, 6H), 1.94−1.92 (m, 2H), 1.82−1.79 (m, 2H), 1.69−1.66 (m, 1H), 1.46−1.12 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 158.0, 158.0, 154.3, 145.4, 104.2, 103.2, 102.6, 56.5, 55.7, 49.3, 32.6, 25.6, 25.5; HRMS (M + H$^+$) calcd for $C_{16}H_{23}N_4O_2$ 303.1821, found 303.1831.

*Quinazoline-2,4-diamine (**4r**; Table 3; Entry 18).* Eluent dichloromethane/methanol (100:20). Yield, 152 mg, 95%. White solid: mp 246−248 °C; (lit.[12] mp 254−258 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.29 (s, 2H), 7.19 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 165.9, 157.4, 137.6, 129.2, 128.8, 125.1, 115.5; HRMS (M + H$^+$) calcd for $C_8H_9N_4$ 161.0827, found 161.0825.

*2-(2-Amino-6,7-dimethoxyquinazolin-4-ylamino)ethanol (**4s**; Table 3; Entry 19).* Eluent dichloromethane/methanol (100:20). Yield, 217 mg, 82%. Light yellow solid: mp 264−265 °C; ^{1}H NMR (400 MHz, D_2O) δ 6.72 (s, 1H), 6.14 (s, 1H), 3.82 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.58 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 156.8, 156.8, 151.5, 151.0, 143.2, 99.4, 98.9, 95.0, 57.0, 53.5, 53.3, 40.7; HRMS (M + H$^+$) calcd for $C_{12}H_{17}N_4O_3$ 265.1301, found 265.1303.

*N^8-Benzyl-[1,3]dioxolo[4,5-g]quinazoline-6,8-diamine (**4t**; Table 3; Entry 20).* Eluent dichloromethane/methanol (100:15). Yield, 255 mg, 87%. Light yellow solid: mp 258−260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.66 (s, 1H), 7.37−7.30 (m, 4H), 7.23 (t, J = 7.2 Hz, 1H), 6.76 (s, 1H), 6.48 (s, 2H), 6.10 (s, 2H), 4.72 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 158.2, 152.4, 146.3, 143.7, 139.7, 128.5, 127.6, 127.0, 104.1, 102.0, 100.5, 43.6; HRMS (M + H$^+$) calcd for $C_{16}H_{15}N_4O_2$ 295.1195, found 295.1196.

General Procedure for Synthesis of Tricyclic Quinazolines (5). Chloroalkylamines hydrochloride (1 mmol, 2 equiv) and $NaHCO_3$ (1 mmol, 84 mg, 2 equiv) were stirred in 2 mL of MeOH at rt for 30 min, and then cyanoimidates (**2**, 0.5 mmol) were added and stirred at 50 °C for 6 h. Then, iron (4.5 mmol, 251 mg, and 4 equiv), concentrated hydrochloric acid (0.4 mL), and additional MeOH (25 mL) were added, and the reaction was performed to reflux. After 3 h, potassium carbonate (5 mmol, 691 mg) was added, and the reaction was stirred for additional 6 h in refluxing methanol. The final mixture

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649−2658

was filtered through Celite. The filtrate was evaporated by vacuum distillation, and the residue was purified by flash column chromatography to afford product **5**.

*2,3-Dihydroimidazo[1,2-c]quinazolin-5-amine (**5a**; Table 4; Entry 1).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 83 mg, 89%. White solid: mp 261−264 °C; ^{1}H NMR (400 MHz, D_2O/5% TFA) δ 8.06−7.97 (m, 2H), 7.55−7.51(m, 2H), 4.58−4.56 (m, 2H), 4.39 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O/5% TFA) δ 155.3, 145.2, 137.4, 135.8, 124.6, 124.3, 115.1, 102.7, 44.0, 42.9; HRMS (M + H$^+$) calcd for $C_{10}H_{11}N_4$ 187.0984, found 187.0987.

*9-Chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (**5b**; Table 4; Entry 2).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 101 mg, 92%. White solid: Decomp 283 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 8.4, 2.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.74 (s, 2H), 3.98−3.86 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.0, 151.0, 149.1, 133.0, 125.6, 124.6, 124.1, 115.1, 52.6, 45.8; HRMS (M + H$^+$) calcd for $C_{10}H_{10}ClN_4$ 221.0594, found 221.0589.

*8,9-Dimethoxy-2,3-dihydroimidazo[1, 2-c]quinazolin-5-amine (**5c**; Table 4; Entry 3).* Eluent dichloromethane/methanol/triethylamine (100:20:0.5). Yield, 103 mg, 84%. White solid: Decomp 291 °C; ^{1}H NMR (400 MHz, D_2O/5% TFA) δ 7.41 (s, 1H), 6.90 (s, 1H), 4.51 (t, J = 9.2 Hz, 2H), 4.31 (t, J = 9.2 Hz, 2H), 3.90 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, D_2O/5% TFA) δ 156.3, 153.6, 145.5, 144.6, 133.3, 103.0, 103.0, 96.7,96.6, 95.0, 54.3, 53.6, 43.9, 42.3; HRMS (M + H$^+$) calcd for $C_{12}H_{15}N_4O_2$ 247.1195, found 247.1193.

*2,3-Dihydro-[1,3]dioxolo[4,5-g]imidazo[1,2-c]quinazolin-5-amine (**5d**; Table 4; Entry 4).* Eluent dichloromethane/methanol/triethylamine (100:20:0.5). Yield, 94 mg, 82%. Light yellow solid: Decomp 310 °C; ^{1}H NMR (400 MHz, D_2O/5% TFA) δ 7.22 (s, 1H), 6.88 (s, 1H), 6.12 (s, 2H), 4.45 (t, J = 9.6 Hz, 2H), 4.24 (t, J = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O/5% TFA) δ 155.8, 153.8, 145.2, 144.6, 135.2, 101.9, 100.0, 99.8, 96.3, 94.9, 94.8, 43.9, 42.3; HRMS (M + H$^+$) calcd for $C_{11}H_{11}N_4O_2$ 231.0882, found 231.0879.

*8-Bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (**5e**; Table 4; Entry 5).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 101 mg, 76%. White solid: Decomp 271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 7.08 (dd, J = 8.4, 1.6 Hz, 1H), 6.88 (s, 2H), 3.98−3.88 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 151.8, 151.4, 127.1, 126.5, 125.5, 123.7, 113.0, 52.6, 45.7; HRMS (M + H$^+$) calcd for $C_{10}H_{10}BrN_4$ 265.0089, found 265.0071.

*9-Bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (**5f**; Table 4; Entry 6).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 109 mg, 82%. White solid: Decomp 279 °C; (lit.[25] mp > 260 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 8.8, 2.4 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.77 (s, 2H), 3.99−3.85 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 151.2, 149.3, 135.3, 127.1, 125.8, 116.1, 112.0, 53.3, 45.7; HRMS (M + H$^+$) calcd for $C_{10}H_{10}BrN_4$ 265.0089, found 265.0081.

*3,4-Dihydro-2H-pyrimido[1,2-c]quinazolin-6-amine (**5g**; Table 4; Entry 7).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 81 mg, 81%. White solid: mp 266−267 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 7.2 Hz, 1H), 7.36−7.32 (m, 1H), 6.99−6.92 (m, 2H), 6.67 (s, 2H), 3.73 (t, J = 6.0 Hz, 2H), 3.45 (t, J = 5.6 Hz, 2H), 1.87 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.7, 146.9, 146.9, 132.1, 124.6, 123.1, 121.4, 117.8, 43.3, 42.5, 20.0; HRMS (M + H$^+$) calcd for $C_{11}H_{13}N_4$ 201.1140, found 201.1142.

*10-Chloro-3,4-dihydro-2H-pyrimido[1,2-c]quinazolin-6-amine (**5h**; Table 4; Entry 8).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 97 mg, 83%. White solid: mp 271−273 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 2.4 Hz, 1H), 7.30 (dd, J = 8.8, 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.68 (s, 2H), 3.69 (t, J = 5.6 Hz, 2H), 3.44 (t, J = 5.2 Hz, 2H), 1.83 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 145.9, 144.9, 131.3, 125.0, 124.7, 123.7, 120.4, 43.2, 43.1, 20.1; HRMS (M + H$^+$) calcd for $C_{11}H_{12}ClN_4$ 235.0750, found 235.0746.

*9,10-Dimethoxy-3,4-dihydro-2H-pyrimido[1,2-c]quinazolin-6-amine (**5i**; Table 4; Entry 9).* Eluent dichloromethane/methanol/triethylamine (100:20:0.5). Yield, 110 mg, 85%. Light yellow solid: Decomp 263 °C; ^{1}H NMR (400 MHz, D_2O/5% TFA) δ 7.44 (s, 1H), 6.83 (s, 1H), 4.03 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.63 (t, J = 5.6 Hz, 2H), 2.22 (t, J = 5.6 Hz, 2H); HRMS (M + H$^+$) calcd for $C_{13}H_{17}N_4O_2$ 261.1352, found 261.1357.

*3,4-Dihydro-2H-[1,3]dioxolo[4,5-g]pyrimido[1,2-c]quinazolin-6-amine (**5j**; Table 4; Entry 10).* Eluent dichloromethane/methanol/triethylamine (100:20:0.5). Yield, 94 mg, 77%. Light yellow solid: Decomp 253 °C; ^{1}H NMR (400 MHz, D_2O/5% TFA) δ 7.32 (s, 1H), 6.84 (s, 1H), 6.10 (s, 2H), 4.02 (t, J = 6.0 Hz, 2H), 3.61 (t, J = 5.2 Hz, 2H), 2.22 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O/5% TFA) δ 159.3, 154.8, 151.0, 150.3, 136.6, 106.6, 104.8, 103.2,103.1, 99.4, 99.3, 47.6, 41.4, 19.7; HRMS (M + H$^+$) calcd for $C_{12}H_{13}N_4O_2$ 245.1039, found 245.1045.

*9-Bromo-3,4-dihydro-2H-pyrimido[1,2-c]quinazolin-6-amine (**5k**; Table 4; Entry 11).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 118 mg, 85%. White solid: Decomp 274 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (t, J = 8.4 Hz, 1H), 7.09−7.03 (m, 2H), 6.82 (s, 2H), 3.69 (t, J = 5.6 Hz, 2H), 3.43 (t, J = 5.2 Hz, 2H), 1.86 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.7, 148.8, 145.8, 126.6, 125.1, 125.0, 123.7, 117.6, 43.2, 42.8, 20.0; HRMS (M + H$^+$) calcd for $C_{11}H_{12}BrN_4$ 279.0245, found 279.0248.

*10-Bromo-3,4-dihydro-2H-pyrimido[1,2-c]quinazolin-6-amine (**5l**; Table 4; Entry 12).* Eluent dichloromethane/methanol/triethylamine (100:10:0.5). Yield, 110 mg, 79%. White solid: Decomp 261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.4, 2.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.70 (s, 2H), 3.69 (t, J = 6.0 Hz, 2H), 3.44 (t, J = 5.6 Hz, 2H), 1.87−1.81(m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 146.3, 144.9, 134.1, 126.7, 125.4, 120.6, 112.5, 43.1, 43.1, 20.1; HRMS (M + H$^+$) calcd for $C_{11}H_{12}BrN_4$ 279.0245, found 279.0252.

General Procedure A for Synthesis of Tricyclic Quinazolinones (6a−6f). Tricyclic quinazolines (**5**, 0.2 mmol) were dissolved in 25 mL of HCl (0.5 mol/L) and 5 mL of EtOH, and then the reaction was heated to refluxing vigorously. After 6 h, excess $NaHCO_3$ (20 mmol, 1.68 g) was added and kept refluxing for additional 72 h. Then, the solvent was removed under reduced pressure, and the residue was purfied by flash column chromatography.

*2,3-Dihydroimidazo[2,1-b]quinazolin-5(1H)-one (**6a**; Table 4; Entry 1).* Eluent dichloromethane/methanol (100:2). Yield, 27.1 mg, 72%. White solid: mp 264−268 °C; (lit.[26] 263−265 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 4.11 (t, J = 8.4 Hz, 2H), 3.62 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 154.9, 151.4, 134.1, 126.0, 124.5, 121.8, 117.4, 42.4, 39.5; HRMS (M + H$^+$) calcd for $C_{10}H_{10}N_3O$ 188.0824, found 188.0825.

*7-Chloro-2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-one (**6b**; Table 4; Entry 2).* Eluent dichloromethane/methanol (100:3). Yield, 30.2 mg, 68%. White solid: mp 277−279 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 4.11 (t, J = 8.4 Hz, 2H), 3.63 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 155.1, 150.3, 134.1, 126.6, 125.6, 124.9, 118.5, 42.5, 39.5; HRMS (M + H$^+$) calcd for $C_{10}H_9ClN_3O$ 222.0434, found 222.0434.

*7,8-Dimethoxy-2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-one (**6c**; Table 4; Entry 3).* Eluent dichloromethane/methanol (100:3). Yield, 26.2 mg, 53%. Yellow solid: Decomp 269 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.26 (s, 1H), 6.71 (s, 1H), 4.08 (t, J = 8.4 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.60 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 154.7, 154.4, 147.4, 145.3, 109.6, 105.9, 105.8, 55.8, 55.8, 42.5, 39.6; HRMS (M + H$^+$) calcd for $C_{12}H_{14}N_3O_3$ 248.1035, found 248.1031.

*7,8-Dihydro-[1,3]dioxolo[4,5-g]imidazo[2,1-b]quinazolin-10(6H)-one (**6d**; Table 4; Entry 4).* Eluent dichloromethane/methanol (100:3). Yield, 29.6 mg, 64%. Yellow solid: Decomp 303 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 1H), 7.22 (s, 1H), 6.69 (s, 1H), 6.07 (s, 2H), 4.07 (t, J = 8.4 Hz, 2H), 3.59 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 154.5, 153.1, 149.2, 143.7, 110.9, 103.4,

dx.doi.org/10.1021/jo2023697 | J. Org. Chem. 2012, 77, 2649−2658

102.8, 102.0, 42.5, 39.7; HRMS (M + H^+) calcd for $C_{11}H_{10}N_3O_3$ 232.0722, found 232.0721.

*8-Bromo-2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-one (**6e**; Table 4; Entry 5).* Eluent dichloromethane/methanol (100:3). Yield, 32.3 mg, 61%. White solid: Decomp 284 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 1.2 Hz, 1H), 7.24 (dd, J = 8.4, 1.2 Hz, 1H), 4.10 (t, J = 8.4 Hz, 2H), 3.64 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 155.6, 152.8, 127.9, 127.7, 126.5, 124.5, 124.6, 116.5, 42.4, 39.6; HRMS (M + H^+) calcd for $C_{10}H_9BrN_3O$ 265.9929, found 265.9938.

*7-Bromo-2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-one (**6f**; Table 4; Entry 6).* Eluent dichloromethane/methanol (100:3). Yield, 33.7 mg, 63%. White solid: Decomp 323 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.67−7.65 (m, 1H), 7.15 (d, J = 8.8 Hz, 2H), 4.11 (t, J = 8.4 Hz, 2H), 3.63 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 155.2, 150.6, 136.8, 128.0, 126.9, 119.1, 113.4, 42.6, 39.6; HRMS (M + H^+) calcd for $C_{10}H_9BrN_3O$ 265.9929, found 265.9943.

General Procedure B for Synthesis of Tricyclic Quinazolinones (6g−6l). Tricyclic quinazolines (**5**, 0.2 mmol) were added to 25 mL of NaOH (0.01 mol/L) and 5 mL of EtOH. Then, the mixture was heated to refluxing vigorously for 72 h. Then, the solvent was removed under reduced pressure, and the residue was purfied by flash column chromatography.

*3,4-Dihydro-1H-pyrimido[2,1-b]quinazolin-6(2H)-one (**6g**; Table 4; Entry 7).* Eluent dichloromethane/methanol (100:5). Yield, 32.5 mg, 81%. White solid: mp 237−238 °C; (lit.[27] 237 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (dd, J = 8.0, 1.2 Hz, 1H), 7.70 (s, 1H), 7.54−7.50 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 3.94 (t, J = 5.6 Hz, 2H), 3.29 (t, J = 5.6 Hz, 2H), 1.96 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 150.4, 150.2, 134.3, 126.5, 123.6, 120.9, 116.1, 39.9, 38.7, 20.2; HRMS (M + H^+) calcd for $C_{11}H_{12}N_3O$ 202.0980, found 202.0984.

*8-Chloro-3,4-dihydro-1H-pyrimido[2,1-b]quinazolin-6(2H)-one (**6h**; Table 4; Entry 8).* Eluent dichloromethane/methanol (100:5). Yield, 37.0 mg, 78%. White solid: mp 261−264 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 8.8, 2.4 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 3.93 (t, J = 6.0 Hz, 2H), 3.30−3.27 (m, 2H), 1.95 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 150.8, 149.4, 134.8, 126.2, 125.6, 125.0, 117.2, 40.5, 39.0, 20.2; HRMS (M + H^+) calcd for $C_{11}H_{11}ClN_3O$ 236.0591, found 236.0588.

*8,9-Dimethoxy-3,4-dihydro-1H-pyrimido[2,1-b]quinazolin-6(2H)-one (**6i**; Table 4; Entry 9).* Eluent dichloromethane/methanol (100:5). Yield, 43.2 mg, 81%. Yellow solid: Decomp 263 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (s, 1H), 7.22 (s, 1H), 6.59 (s, 1H), 3.91 (t, J = 5.6 Hz, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.27 (m, 2H), 1.94 (t, J = 5.6 Hz, 2H); HRMS (M + H^+) calcd for $C_{13}H_{16}N_3O_3$ 262.1192, found 262.1189.

*8,9-Dihydro-6H-[1,3]dioxolo[4, 5-g]pyrimido[2,1-b]quinazolin-11(7H)-one (**6j**; Table 4; Entry 10).* Eluent dichloromethane/methanol (100:5). Yield, 36.6 mg, 75%. Light yellow solid: Decomp 268 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.17 (s, 1H), 6.57 (s, 1H), 6.04 (s, 2H), 3.89 (t, J = 5.6 Hz, 2H), 3.26−3.24 (m, 2H), 1.92 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 153.6, 149.9, 148.6, 143.4, 109.8, 103.2, 102.5, 102.0, 40.1, 39.0, 20.6; HRMS (M + H^+) calcd for $C_{12}H_{12}N_3O_3$ 246.0879, found 246.0875.

*9-Bromo-3,4-dihydro-1H-pyrimido[2,1-b]quinazolin-6(2H)-one (**6k**; Table 4; Entry 11).* Eluent dichloromethane/methanol (100:5). Yield, 44.9 mg, 80%. White solid: Decomp 271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.26 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 3.90 (t, J = 5.2 Hz, 2H), 3.28 (t, J = 5.2 Hz, 2H), 1.95 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 151.6, 150.9, 128.6, 127.9, 125.5, 123.6 115.1, 39.8, 38.6, 19.8; HRMS (M + H^+) calcd for $C_{11}H_{11}BrN_3O$ 280.0085, found 280.0099.

*8-Bromo-3,4-dihydro-1H-pyrimido[2,1-b]quinazolin-6(2H)-one (**6l**; Table 4; Entry 12).* Eluent dichloromethane/methanol (100:5). Yield, 41.1 mg, 73%. White solid: Decomp 276 °C; (lit.[21b] mp > 206 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92−7.90 (m, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 3.92 (t, J = 5.6 Hz, 2H), 3.28 (t, J = 5.6 Hz, 2H), 1.98−1.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 150.9, 149.9, 137.2, 128.7, 126.5, 117.9, 112.4, 40.4, 20.3; HRMS (M + H^+) calcd for $C_{11}H_{11}BrN_3O$ 280.0085, found 280.0088.

General Procedure for Ring-Opening Acidolysis. Tricyclic quinazolines (0.5 mmol) was added to 25 mL of HCl (0.5 mol/L), and then the reaction was kept refluxing for 6 h. When the completion of acidolysis was verified by TLC monitoring, the reaction was allowed to cool to room temperature and neutralized by $NaHCO_3$ (20 mmol). The mixture was extracted with $CHCl_3$/MeOH (30:1), and then the organic phase was concentrated and purified by flash column chromatography to afford the major product (**7**) and the coproduct (**8**).

*2-Amino-3-(3-aminopropyl)quinazolin-4(3H)-one (**7a**; Scheme 2).* Eluent dichloromethane/methanol/triethylamine (100:5:0.5 to 100:20:0.5). Yield, 63.1 mg, 58%. White solid: Decomp 226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.05 (t, J = 6.4 Hz, 2H), 2.59 (t, J = 6.4 Hz, 2H), 1.76 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 152.9, 150.1, 134.3, 126.7, 124.0, 121.6, 116.4, 39.4, 37.9, 30.2; HRMS (M + H^+) calcd for $C_{11}H_{15}N_4O$ 219.1246, found 219.1250.

*3,4-Dihydro-2H-pyrimido[1,2-c]quinazolin-6(7H)-one (**8a**; Scheme 2).*[21] Yield, 22.7 mg, 22%. White solid: mp 242−244 °C; (lit.[28] mp 250−251 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (br, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 3.95 (t, J = 6.0 Hz, 2H), 3.67(t, J = 5.6 Hz, 2H), 1.98 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 145.8, 136.4, 132.2, 125.9, 123.2, 116.6, 114.5, 44.6, 40.9, 20.4.

*2-Amino-3-(3-aminopropyl)-6-chloroquinazolin-4(3H)-one (**7b**; Scheme 2).* Eluent dichloromethane/methanol/triethylamine (100:5:0.5 to 100:25:0.5). Yield, 63.8 mg, 51%. White solid: Decomp 261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 4.03 (t, J = 6.8 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 1.76 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 153.0, 148.8, 134.3, 126.1, 125.4, 125.2, 117.2, 39.5, 37.7, 29.6; HRMS (M + H^+) calcd for $C_{11}H_{14}ClN_4O$ 253.0856, found 253.0861.

*10-Chloro-3,4-dihydro-2H-pyrimido[1,2-c]quinazolin-6(7H)-one (**8b**; Scheme 2).* Yield, 42.3 mg, 36%. White solid: mp 257−261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.45 (dd, J = 8.4, 2.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 3.73 (t, J = 5.6 Hz, 2H), 3.49 (t, J = 5.6 Hz, 2H), 1.81 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.4, 144.1, 136.4, 131.8, 126.1, 124.5, 117.6, 116.7, 44.0, 40.2, 20.1; HRMS (M + H^+) calcd for $C_{11}H_{11}ClN_3O$ 236.0591, found 236.0588.

General Procedure for Acetylation of Intermediate Quinazolinones. To a solution of quinazolinones (**7**, 0.2 mmol) in dichloromethane (20 mL) were added acetic anhydride (0.6 mmol, 61.3 mg) and triethylamine (0.6 mmol, 60.7 mg), and the reaction was stirred at room temperature for 2 h. After completion of the reaction as indicated by TLC, The reaction mixture was washed by aqueous K_2CO_3 and dried over anhydrous $MgSO_4$. The organic phase was concentrated by vacuum distillation, and the residue was purfied by flash column chromatography to afford product **9**.

*N-(3-(2-Amino-4-oxoquinazolin-3(4H)-yl)propyl)acetamide (**9a**; Scheme 2).* Eluent dichloromethane/methanol (100:5). Yield, 37.5 mg, 72%. White solid: mp 218−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.03 (s, 2H), 3.99 (t, J = 7.6 Hz, 2H), 3.11−3.09 (m, 2H), 1.80 (s, 3H), 1.72 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 161.1, 152.4, 148.9, 134.4, 126.2, 125.5, 125.3, 117.3, 39.8, 36.6, 27.7, 23.0; HRMS (M + H^+) calcd for $C_{13}H_{17}N_4O_2$ 261.1352, found 261.1345.

*N-(3-(2-Amino-6-chloro-4-oxoquinazolin-3(4H)-yl)propyl)-acetamide (**9b**; Scheme 2).* Eluent dichloromethane/methanol (100:5). Yield, 44.0 mg, 75%. White solid: mp 225−226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.19−7.17 (m, 3H), 3.98 (t, J = 7.2 Hz, 2H), 3.12−3.07 (m, 2H), 1.80 (s, 3H), 1.71 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.4, 161.0, 152.3, 148.8, 134.3,

126.1, 125.5, 125.2, 117.2, 39.6, 36.5, 27.6, 22.9, 22.8; HRMS (M + H^+) calcd for $C_{13}H_{16}ClN_4O_2$ 295.0962, found 295.0963.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of products. X-ray data of compounds (**5h** and **6g**) are provided in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lhe2001@sina.com (L.H.); dengyongy@sohu.com (Y.D.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Science Foundation of China (No. 21072131).

■ REFERENCES

(1) For selected reviews, see: (a) D'yakonov, A. L.; Telezhenetskaya, M. V. *Chem. Nat. Comput.* **1997**, *33*, 221−267. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166−187. (c) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787−9826.

(2) For selected reviews, see: (a) He, N.-Q.; Yan, S.-J; Lin, J. *Huaxue Tongbao* **2010**, *73*, 314−325. (b) Salagierski, M.; Sosnowski, M. *Cent. Eur. J. Urol.* **2009**, *62*, 228−232. (c) Kaur, P.; Kaur, A.; Kaur, R.; Kaur, K. *J. Global Pharma Technol.* **2010**, *2*, 35−39.

(3) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49−57.

(4) (a) Graffner-Nordberg, M.; Fyfe, M.; Brattsand, R.; Mellgård, B.; Hallberg, A. *J. Med. Chem.* **2003**, *46*, 3455−3462. (b) Graffner-Nordberg, M.; Kolmodin, K.; Åqvist, J.; Queener, S. F.; Hallberg, A. *J. Med. Chem.* **2001**, *44*, 2391−2402. (c) Graffner-Nordberg, M.; Marelius, J.; Ohlsson, S.; Persson, A.; Swedberg, G.; Andersson, P.; Andersson, S. E.; Åqvist, J.; Hallberg, A. *J. Med. Chem.* **2000**, *43*, 3852−3861.

(5) Pineda, P.; Kanter, A.; McIvor, R. S.; Benkovic, S. J.; Rosowsky, A.; Wagner, C. R. *J. Med. Chem.* **2003**, *46*, 2816−2818.

(6) (a) *Am. J. Hosp. Pharm.* **1994**, *51*, 591−592. (b) Fulton, B.; Wagstaff, A. J.; McTavish, D. *Drugs* **1995**, *49*, 563−576. (c) Takimoto, C. H.; Allegra, C. J. *Oncology* **1995**, *9*, 645−656.

(7) (a) Singh, J. *Abstracts of Papers*, 239th ACS National Meeting, San Francisco, CA, March 21−25, 2010; American Chemical Society: Washington, D.C., 2010; MEDI. (b) Butchbach, M. E. R.; Singh, J.; Thorsteinsdottir, M.; Saieva, L.; Slominski, E.; Thurmond, J.; Andresson, T.; Zhang, J.; Edwards, J. D.; Simard, L. R.; Pellizzoni, L.; Jarecki, J.; Burghes, A. H. M.; Gurney, M. E. *Hum. Mol. Genet.* **2010**, *19*, 454−467. (c) Thurmond, J.; Butchbach, M. E. R.; Palomo, M.; Pease, B.; Rao, M.; Bedell, L.; Keyvan, M.; Pai, G.; Mishra, R.; Haraldsson, M.; Andresson, T.; Bragason, G.; Thosteinsdottir, M.; Bjornsson, J. M.; Coovert, D. D.; Burghes, A. H. M.; Gurney, M. E.; Singh, J. *J. Med. Chem.* **2008**, *51*, 449−469. (d) Singh, J.; Thurmond, J.; Pease, B.; Rao, M.; Palomo, M.; Pai, G.; Bedell, L.; Keyvan, M.; Mishra, R.; Zhang, J.; Onua, E.; Bjarnadottir, E.; Haraldsson, M.; Andresson, T.; Gunnseinsdottir, T.; Atlason, P.; Sigthorsson, G.; Bragason, G.; Thorsteinsdottir, M.; Gurney, M. *Abstracts of Papers*, 230th ACS National Meeting, Washington, D.C., Aug 28−Sept 1, 2005; American Chemical Society: Washington, D.C., 2005; MEDI.

(8) (a) Berman, J. D.; King, M.; Edwards, N. *Antimicrob. Agents Chemother.* **1989**, *33*, 1860−1863. (b) Khabnadideh, S.; Pez, D.; Musso, A.; Brun, R.; Perez, L. M. R.; Gonzalez−Pacanowska, D.; Gilbert, I. H. *Bioorg. Med. Chem.* **2005**, *13*, 2637−2649.

(9) Okano, M.; Mito, J.; Maruyama, Y.; Masuda, H.; Niwa, T.; Nakagawa, S.; Nakamura, Y.; Matsuura, A. *Bioorg. Med. Chem.* **2009**, *17*, 119−132.

(10) (a) Haddach, M.; Pierre, F. PCT Int. Appl., WO 2011035019, 2011. (b) Henteman, M. F.; Scott, W.; Wood, J.; Johnson, J.; Redman, A.; Bullion, A.; Guernon, L. PCT Int. Appl., WO 2009091550, 2009. (c) Hentemann, M.; Wood, J.; Scott, W.; Michels, M.; Campbell, A.; Bullion, A.; Rowley, R. B.; Redman, A. PCT Int. Appl., WO 2008070150, 2008.

(11) (a) Rosowsky, A.; Marini, J. L.; Nadel, M. E.; Modest, E. J. *J. Med. Chem.* **1970**, *13*, 882−886. (b) Rosowsky, A.; Chen, H. *J. Org. Chem.* **2001**, *66*, 7522−7526.

(12) Hynes, J. B.; Pathak, A.; Panos, C. H.; Okeke, C. C. *J. Heterocycl. Chem.* **1988**, *25*, 1173−1177.

(13) (a) Dehnhardt, C. M.; Venkatesan, A. M.; Chen, Z.; Ayral−Kaloustian, S.; Dos Santos, O.; Delos Santos, E.; Curran, K.; Follettie, M. T.; Diesl, V.; Lucas, J.; Geng, Y.; DeJoy, S. Q.; Petersen, R.; Chaudhary, I.; Brooijmans, N.; Mansour, T. S.; Arndt, K.; Chen, L. *J. Med. Chem.* **2010**, *53*, 897−910. (b) Millen, J.; Riley, T. N.; Waters, I. W.; Hamrick, M. E. *J. Med. Chem.* **1985**, *28*, 12−17.

(14) (a) Wilson, L. J. *Org. Lett.* **2001**, *3*, 585−588. (b) Dener, J. M.; Lease, T. G.; Novack, A. R.; Plunkett, M. J.; Hocker, M. D.; Fantauzzi, P. P. *J. Comb. Chem.* **2001**, *3*, 590−597.

(15) Yang, X.-B.; Liu, H.-X.; Fu, H.; Qiao, R.-Z.; Jiang, Y.-Y; Zhao, Y.-F. *Synlett* **2010**, 101−106.

(16) (a) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474−1480. (b) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638−643. (c) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197−2199.

(17) Yin, P.; Ma, W.-B.; Chen, Y.; Huang, W.-C.; Deng, Y.; He, L. *Org. Lett.* **2009**, *11*, 5482−5485.

(18) (a) M'Hamed, M. O.; M'Rabet, H.; Efrit, M. L. *C. R. Chim.* **2007**, *10*, 1147−1156. (b) Zarguil, A.; Boukhris, S.; El Efrit, M. L. *Tetrahedron Lett.* **2008**, *49*, 5883−5886. (c) He, R. J.; Ching, S. M.; Lam, Y. L. *J. Comb. Chem.* **2006**, *8*, 923−928. (d) Che, J.; Raghavendra, M. S.; Lam, Y. L. *J. Comb. Chem.* **2009**, *11*, 378−384. (e) Huffman, K. R.; Schaefer, F. C. *J. Org. Chem.* **1963**, *28*, 1816−1821.

(19) (a) Evans, P. A.; Qin, J.; Robinson, J. E.; Bazin, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 7417−7419. (b) Arnold, M. A.; Day, K. A.; Durón, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 13255−13260. (c) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782−10783.

(20) (a) Leow, D.; Lin, S.-S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem.* **2008**, *120*, 5723−5727. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160.

(21) (a) Larraufie, M.-H.; Ollivier, C.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 2178−2181. (b) Pereira, M.-F.; Thiéry, V.; Besson, T. *Tetrahedron* **2007**, *63*, 847−854. (c) Clews, J.; Curtis, A. D. M.; Malkin, H. *Tetrahedron* **2000**, *56*, 8735−8746.

(22) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2009**, *50*, 1105−1109.

(23) (a) Zielinski, W.; Kudelko, A. *J. Heterocycl. Chem.* **2002**, *39*, 1289−1292. (b) Hynes, J. B.; Singh, S. K.; Fetzer, O.; Shane, B. *J. Med. Chem.* **1992**, *35*, 4078−4085. (c) Gangjee, A.; Kothare, M.; Kisliuk, R. L. *J. Heterocycl. Chem.* **2000**, *37*, 1097−1102.

(24) For single crystal X-ray structure data of compounds **5h** and **6g**, see the Supporting Information.

(25) Pereira, M. -F.; Alexandre, F. R.; Thiery, V.; Besson, T. *Tetrahedron Lett.* **2004**, *45*, 3097−3099.

(26) Wagner, G.; Bunk, E. *Pharmazie* **1979**, *34*, 209−213.

(27) Dean, W. D.; Papadopoulos, E. P. *J. Heterocycl. Chem.* **1982**, *19*, 1117−1124.

(28) Mizuhara, T.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2009**, *45*, 3413−3415.