Tetrahedron 67 (2011) 1665–1672

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient HCCP-mediated direct amination of quinazolin-4(3*H*)-ones

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ARTICLE INFO

Article history:
Received 25 September 2010
Received in revised form 17 December 2010
Accepted 28 December 2010
Available online 8 January 2011

Keywords:
Amination
Quinazolin-4(3*H*)-ones
4-Aminoquinazolines
Hexachlorocyclotriphosphazene

ABSTRACT

An efficient direct amination of quinazolin-4(3*H*)-ones has been developed. Treatment of quinazolin-4(3*H*)-ones with HCCP, DIPEA, and *N*-contained nucleophiles in acetonitrile could be able to form the corresponding 4-aminoquinazoline derivatives. Under the optimal reaction conditions, the amination products were achieved in good yields.

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1. Introduction

Nitrogen-containing heterocycles are present in a variety of biologically active compounds that can be used in a wide range of therapeutic areas.[1] Quinazoline derivatives are an important class of nitrogen-containing heterocycles, which display a wide variety of biological activities, such as anticonvulsant, antihypertensive, vasodilator, antiinflammatory, antibiosis, fibrinogen receptor antagonistic, and nanomolar Hedgehog antagonistic.[2] Among the family of quinazolines, 4-aminoquinazolines have been received particular interests because of their potential pharmacological activity.[3] For example, three drugs Gefitnib (Iressa), Erlotinib (Tarceva), and Lapatinib (Tykerb), derived from 4-aminoquinazolines, have been approved and marketed for non-small-cell lung cancer treatment (Fig. 1).[4]

4-Aminoquinazolines are usually synthesized from acid- or base-mediated amination of electron-deficient 4-chloroquinazolines via S_NAr substitution.[5] Alternatively, Tasler's group have reported a Pd-catalyzed Buchwald–Hartwig amination reaction to prepare the corresponding 4-aminoquinazolines from 4-chloroquinazolines.[6a] Very recently, we have also described a Pd-catalyzed selective amination of 4-chloroquinazolines with bifunctional amines.[6b] Both methods employ the same starting material 4-chloroquinazolines.[3–6] The common method for preparation of 4-chloroquinazolines is the chlorination of quinazolin-4(3*H*)-ones, which often require harsh and acidic conditions with $SOCl_2$, $POCl_3$, PCl_5 or their combinations as the chlorination reagents. However, these reagents are not environmentally benign, and the reaction conditions may cause destruction of some functional groups. In addition, many 4-chloroquinazoline derivatives are moisture sensitive and their purification and storage require special treatment.

In order to avoid the use of chlorination reagents and an individual activation step of the quinazolin-4(3*H*)-ones, a direct amination of quinazolin-4(3*H*)-ones via in situ activation is highly desirable for the synthesis of 4-aminoquinazoline derivatives. Phosphonium compounds, such as benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP) and its analogues (i.e., BroP, PyBOP, PyBroP), are efficient coupling reagents for amide bond formation between a carboxylic acid and an amine under mild conditions.[7] In recent years, they have also been successfully employed in the one-step aminations of cyclic amides and ureas.[8–13] Successful results have also been obtained in BOP-mediated direct amination of quinazolin-4(3*H*)-ones.[11b,c] In fact, when quinazolin-4(3*H*)-ones are treated with BOP in the presence of a base, a phosphonium intermediate **1** possessing an active C–O–P fragment is readily formed (Fig. 2), which subsequently undergoes S_NAr substitution with a reactive amine nucleophile to give the desired product.[11a–c,14] Unfortunately, BOP and its analogues are expensive, moreover, utilization of BOP generates end product HMPA, a highly carcinogenic chemical. We hoped that a less expensive and readily available activating reagent can be used as the BOP surrogate. The mechanism of the BOP-involved activation indicates that a compound, which can react with quinazolin-4(3*H*)-ones to form the active C–O–P fragment, could be considered to serve as this role. Hexachlorocyclotriphosphazene ($Cl_6N_3P_3$, HCCP), a bulky flame-retardant polyphosphazenes,[15] could be a good candidate. We assumed that quinazolin-4(3*H*)-ones can convert to

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doi:10.1016/j.tet.2010.12.067

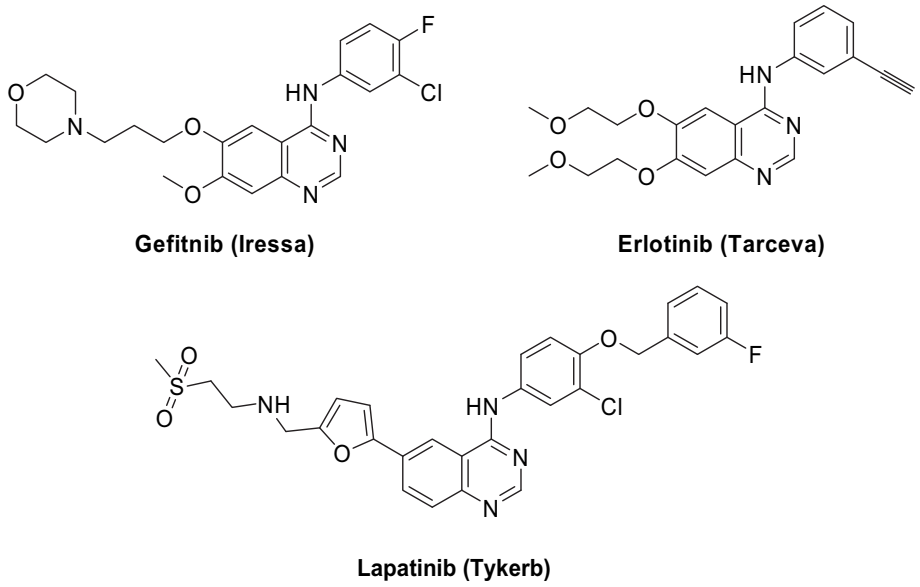


Fig. 1. The structures of commercialized 4-aminoquinazoline derivatives.

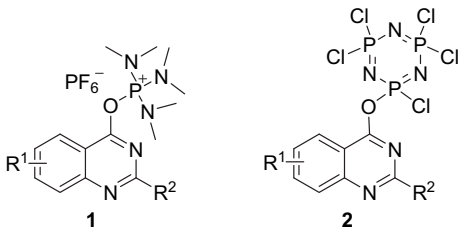


Fig. 2. Active phosphonium intermediates.

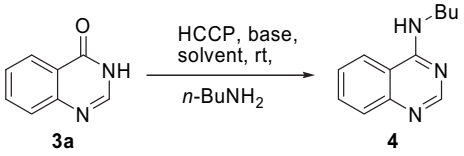
the above-mentioned active C–O–P fragment with HCCP (**2**, Fig. 2) or its analogues, since the Cl–P bond of HCCP can react with hydroxyl group, and thus promote direct amination.

2. Results and discussion

Our initial experiments proved that HCCP can promote the direct amination of quinazolin-4(3*H*)-one (**3a**) with *n*-butylamine. Thus, **3a** and *n*-butylamine were used as the model system for investigating the effects and amounts of solvent, base, and HCCP (Table 1). Although DBU was an efficient base in the BOP-mediated amination,[11b,c] it proved not to be the best in our case (entry 1). Diisopropylethylamine (DIPEA) was found to be most effective in comparison with others (entry 4). Inorganic bases K_2CO_3 and Cs_2CO_3 could also be employed (entries 5 and 6).

Previously, we hypothesized that the phosphonium intermediate **2** or its analogues was the crucial intermediate for the current direct amination. If this intermediate **2** or its analogues could be confirmed or separated, it would be beneficial to understand the reaction mechanism and further optimize reaction conditions. In a designed experiment, a mixture of **3a** (1 equiv), HCCP (1 equiv) and DIPEA (6.0 equiv) in acetonitrile was stirred for 1 h at room temperature. TLC showed that **3a** was completely converted to a new compound, which was relatively stable and readily isolable by flash chromatographic separation. Structural analyses confirmed that this compound was the desired phosphonium intermediate **2a** (R^1=R^2=H).[16] Decrease of the amount of HCCP from 1.0 to 0.8 equiv resulted in a loss of the yield (entry 7). By TLC monitoring, the experiment with 0.8 equiv of HCCP showed that **3a** could not be completely converted into the active intermediate **2a** even after prolonging the activation time to 12 h. These

Table 1
HCCP-mediated direct amination of **3a** with *n*-butylamine[a]



Entry	Base	Solvent	Yield[b] (%)
1	DBU	MeCN	70
2	DABCO	MeCN	74
3	TEA	MeCN	75
4	DIPEA	MeCN	90
5	K_2CO_3	MeCN	82
6	Cs_2CO_3	MeCN	81
7	DIPEA	MeCN	76[c]
8	DIPEA	THF	32
9	DIPEA	DMF	41
10	DIPEA	DCM	39
11	DIPEA	NMP	53
12	DIPEA	1,4-Dioxane	10
13	DIPEA	MeCN	65[d]
14	DIPEA	MeCN	89[e]

[a] Conditions: **3a** (0.5 mmol), HCCP (1.0 equiv), base (6.0 equiv), solvent (2 mL), rt, activation time (1 h), then *n*-$BuNH_2$ (6.0 equiv), 16 h.
[b] Isolated yield after chromatographic purification.
[c] HCCP (0.8 equiv).
[d] *n*-$BuNH_2$ (4.0 equiv).
[e] DIPEA (5.0 equiv).

results indicated that only one Cl–P bond in all six Cl–P bonds of an HCCP molecule could react with one **3a** molecule to form **2a** at room temperature. Thus, we proposed the mechanism of HCCP-mediated direct amination of **3a** as follows:(1) tautomerization of **3a** to 4-hydroxyquinazoline in the presence of DIPEA; (2) activation of 4-hydroxyquinazoline with HCCP generating the high reactive intermediate **2a**; (3) nucleophilic attack of *n*-butylamine to **2a** forming the product **4**.

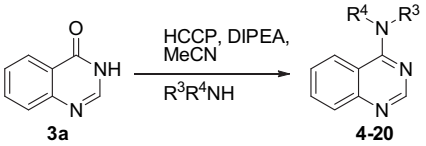
Results in Table 1 showed the solvent can greatly affect the HCCP-mediated amination, and acetonitrile was found to be the most suitable solvent (entries 4, 8–12). When nucleophile *n*-butylamine attacked **2a**, two competitive S_NAr substitutions are both present either on C–O bond or P–Cl bond. This could explain that only 65% yield of **4** was obtained when decreasing the amount of *n*-$BuNH_2$ from 6.0 equiv (entry 4) to 4.0 equiv (entry 13). On the other hand,

variation of the large excess amount of DIPEA from 6.0 equiv to 5.0 equiv did not significantly change the results (entry 4 versus entry 14). On the basis of these experimental data, a combination of 1.0 equiv of HCCP, 5.0 equiv of DIPEA, 6.0 equiv of amine, and acetonitrile as the reaction solvent were chosen as the optimal reaction conditions and were employed for the following studies.

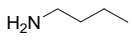
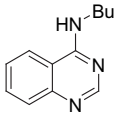
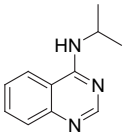
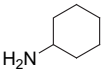
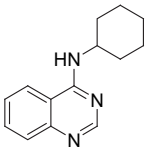
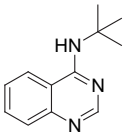
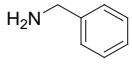
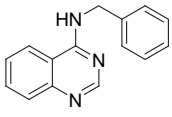
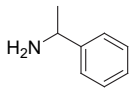
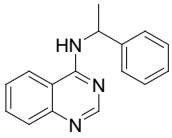
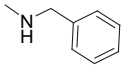
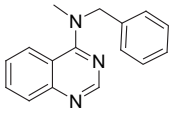
The results of HCCP-mediated direct amination between **3a** and various *N*-containing nucleophiles are summarized in Table 2. Less hindered primary and secondary amines smoothly reacted with **3a** at room temperature to afford the desired products in good yields (entries 1–3 and 5–7), while sterically hindered amines, for example, *tert*-butylamine, are much difficult substrates for this transformation even at a higher reaction temperature (entry 4). Nitrogen heterocycles, such as pyrrolidine, piperidine, morpholine, and imidazole were also tested as nucleophiles in the HCCP-mediated amination of **3a** to afford the desired products in high yields (entries 8–11). It is noteworthy that imidazole, which was regarded as a weak and less reactive nucleophile in the previous reported direct amination,[11b] can conveniently complete the transformation in this HCCP-mediated direct amination (entry 11). When a bifunctional heteroaromatic amine, 5-methyl-1*H*-pyrazol-3-amine, was used as the nucleophile, **3a** was selectively aminated with the primary amino group of 5-methyl-1*H*-pyrazol-3-amine to form product **15** in moderate yield (entry 12). Anilines were much weaker nucleophiles compared to the alkylamines. Not surprisingly, no desired amination products were formed at room temperature. However, moderate yields were observed under reflux conditions (entries 13–17). An electron-deficient aniline proved to be less efficient (entry 15).

Table 3 listed the results of HCCP-mediated direct aminations between *n*-butylamine and a variety of substituted quinazolin-4(3*H*)-ones. An array of substituted quinazolin-4(3*H*)-ones were suitable for this HCCP-mediated amination reaction and gave the desired product in good yields at room temperature (entries 1–6).

Table 2
HCCP-mediated amination of **3a** with various *N*-containing Nucleophiles[a]

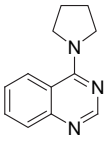
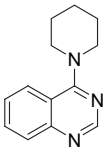
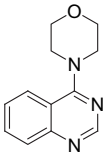
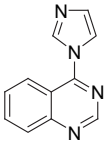
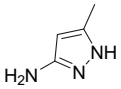
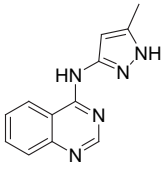
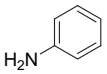
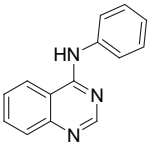
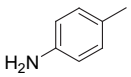
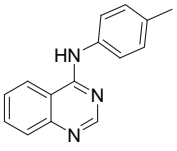
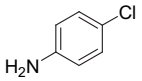
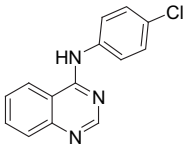
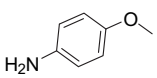
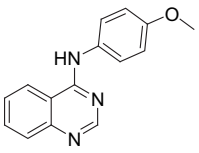
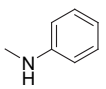
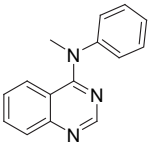


3a **4-20**

Entry	R^3R^4NH	Product		Time (h)	Yield[b] (%)
1			**4**	16	89
2			**5**	16	88
3			**6**	16	82
4			**7**	24	53[c]
5			**8**	16	90
6			**9**	16	87
7			**10**	16	83

(*continued on next page*)

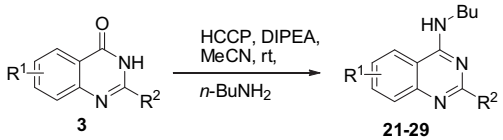
Table 2 (*continued*)

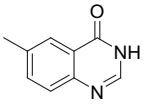
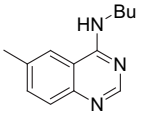
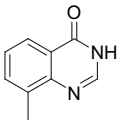
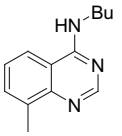
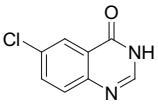
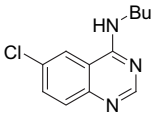
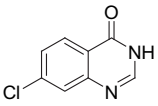
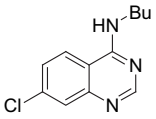
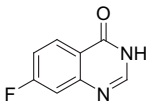
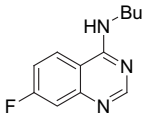
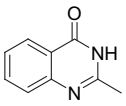
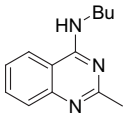
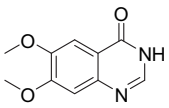
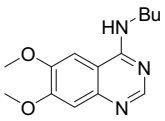
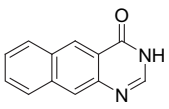
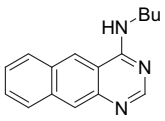
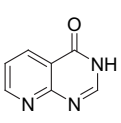
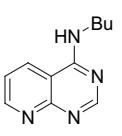
Entry	R^3R^4NH	Product		Time (h)	Yield[b] (%)
8			**11**	1	80
9			**12**	16	79
10			**13**	3	92
11			**14**	1.5	89
12			**15**	16	64
13			**16**	5	72[d]
14			**17**	6	68[d]
15			**18**	9	41[d]
16			**19**	6	63[d]
17			**20**	7	61[d]

[a] Conditions: **3a** (0.5 mmol), HCCP (1.0 equiv), DIPEA (5.0 equiv), MeCN (2 mL), rt, activation time (1 h), then *N*-containing nucleophile (6.0 equiv).
[b] Isolated yield after chromatographic purification.
[c] After addition of *t*-$BuNH_2$, the mixture was stirred at 45 °C.
[d] MeCN (5 mL), after addition of nucleophile, the mixture was stirred under reflux.

When 8-methylquinazolin-4(3*H*)-one (**3c**) or 8-methylquinazolin-4(3*H*)-one (**3g**) was used as the substrate, a longer activation time was essential for a full conversion to phosphonium intermediate **2** (entries 2 and 6). When 6,7-dimethoxyquinazolin-4(3*H*)-one (**3h**) containing two methoxy groups was used as the substrate, activation should be performed under reflux condition (entry 7). In addition, a more complex substrate benzo[*g*]quinazolin-4(3*H*)-one (**3i**) was also converted to **28** in 73% yield (entry 8). Pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**3j**), with a nitrogen incorporated in the distal aromatic ring, was transformed to **29** in 85% yield (entry 9).

Table 3
HCCP-mediated amination of Quinazolin-4(3*H*)-ones with *n*-$BuNH_2$[a]



Entry	Quinazolin-4(3*H*)-one		Product		Time (h)	Yield[b] (%)
1		**3b**		**21**	16	63
2		**3c**		**22**	16	80[c]
3		**3d**		**23**	3	80
4		**3e**		**24**	3	69
5		**3f**		**25**	2	86
6		**3g**		**26**	6	74[c]
7		**3h**		**27**	2	65[d]
8		**3i**		**28**	16	73[e]
9		**3j**		**29**	2	85

[a] Conditions: **3** (0.5 mmol), HCCP (1.0 equiv), DIPEA (5.0 equiv), MeCN (2 mL), rt, activation time (1 h), then *n*-$BuNH_2$ (6.0 equiv).
[b] Isolated yield after chromatographic purification.
[c] Activation time (20 h).
[d] Activation and amination were performed under reflux conditions.
[e] Activation time (3 h).

In summary, we have successfully developed an HCCP-mediated amination of quinazolin-4(3*H*)-ones with various amines. This direct amination is mild, economical, and suitable for a wide range of less expensive amine nucleophiles including primary and secondary amines, heteroarylamines, and substituted anilines. This methodology would facilitate the syntheses of 4-aminoquinazolines derivatives in medicinal chemistry.

3. Experimental section

3.1. General

^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), and ^{31}P NMR (202 MHz) spectra were obtained on a Bruker Avance III spectrometer. $CDCl_3$ and DMSO-d_6 were used as the solvent with tetramethylsilane (TMS) as the internal standard or 85% H_3PO_4 as external standard. Low and high resolution mass spectra were recorded in the ESI mode on an Agilent 6210 LC/TOF mass spectrometer. Melting points were measured using XRL-1 melting point instrument and are uncorrected. Quinazolin-4(3*H*)-ones were synthesized from anthranilic acids and amidines–acetate, and their structures were confirmed by MS, ^{1}H NMR, and ^{13}C NMR. Other reagents were purchased from supplier and used without any further treatment.

3.2. General procedure for HCCP-mediated amination of quinazolin-4(3*H*)-ones

Quinazolin-4(3*H*)-ones (**3**, 0.5 mmol), HCCP (173.9 mg, 0.5 mmol, 1 equiv), DIPEA (323.8 mg, 2.5 mmol, 5 equiv), and MeCN (2 mL) were added to a nitrogen purged vial. The reaction mixture was stirred at room temperature for 1 h as activation time. The reactions were monitored by TLC. Then *N*-containing nucleophile (3.0 mmol, 6 equiv) was added, and the reaction mixture was stirred at room temperature for an appropriate time. After the mixture was concentrated under reduced pressure, the residue was purified by chromatography on silica gel to afford the corresponding products 4-aminoquinazolines (**4**–**29**).

*3.2.1. 4-(n-Butylamino)quinazoline (**4**).* The reaction time was 16 h. The product was obtained as a yellow solid in 89% yield, mp: 107–110 °C. ^{1}H NMR ($CDCl_3$) 8.67 (s, 1H), 7.84 (d, *J*=8.5 Hz, 1H), 7.68–7.76 (m, 2H), 7.46–7.49 (m, 1H), 5.67 (br s, 1H), 3.65–3.69 (m, 2H), 1.72–1.75 (m, 2H), 1.47–1.51 (m, 2H), 1.00 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 159.5, 155.5, 149.4, 132.5, 128.6, 125.9, 120.5, 115.0, 41.2, 31.5, 20.3, 13.9. MS (ESI), *m*/*z*, 202.1 (MH^+).

*3.2.2. 4-(Isopropylamino)quinazoline (**5**).* The reaction time was 16 h. The product was obtained as a white solid in 88% yield, mp: 167–170 °C. ^{1}H NMR ($CDCl_3$) 8.67 (s, 1H), 7.84 (d, *J*=8 Hz, 1H), 7.70–7.74 (m, 2H), 7.44–7.47 (m, 1H), 5.60 (br s, 1H), 4.54–4.61 (m, 1H), 1.36 (d, *J*=6.5 Hz, 6H). ^{13}C NMR 158.7, 155.4, 149.3, 132.4, 128.5, 125.8 , 120.4, 114.9, 42.9, 22.7. MS (ESI), *m*/*z*, 188.1 (MH^+).

*3.2.3. 4-(Cyclohexylamino)quinazoline (**6**).* The reaction time was 16 h. The product was obtained as a white solid in 82% yield, mp: 138–140 °C. ^{1}H NMR ($CDCl_3$) 8.65 (s, 1H), 7.83 (d, *J*=8.5 Hz, 1H), 7.68–7.74 (m, 2H), 7.44–7.47 (m, 1H), 5.61 (br s, 1H), 4.24–4.30 (m, 1H), 2.14–2.17 (m, 2H), 1.79–1.83 (m, 2H), 1.69–1.73 (m, 1H), 1.46–1.55 (m, 2H), 1.25–1.35 (m, 3H). ^{13}C NMR 158.7, 155.5, 149.4, 132.4, 128.5, 125.8, 120.4, 114.9, 49.7, 33.1, 25.7, 24.9. MS (ESI), *m*/*z*, 227.6 (MH^+).

*3.2.4. 4-(tert-Butylamino)quinazoline (**7**).* After addition of *t*-$BuNH_2$, the mixture was stirred at 45 °C for 24 h. The product was obtained as a white solid in 53% yield, mp: 129–131 °C. ^{1}H NMR ($CDCl_3$) 8.65 (s, 1H), 7.82 (d, *J*=8 Hz, 1H), 7.68–7.72 (m, 1H), 7.63 (d, *J*=8 Hz, 1H), 7.42–7.45 (m, 1H), 5.59 (br s, 1H), 1.61 (s, 9H). ^{13}C NMR 159.0, 155.0, 149.3, 132.2, 128.7, 125.8, 120.3, 115.4, 52.8, 28.9. MS (ESI), *m*/*z*, 202.1 (MH^+).

*3.2.5. 4-(Benzylamino)quinazoline (**8**).* The reaction time was 16 h. The product was obtained as a white solid in 90% yield, mp: 168–170 °C. ^{1}H NMR ($CDCl_3$) 8.71 (s, 1H), 7.86 (d, *J*=8 Hz, 1H), 7.71–7.76 (m, 2H), 7.31–7.47 (m, 6H), 6.07 (br s, 1H), 4.88 (d, *J*=5.5 Hz, 2H). ^{13}C NMR 159.4, 155.5, 149.5, 138.1, 132.8, 129.0, 128.7, 128.1, 127.9, 126.2, 120.6, 114.9, 45.4. MS (ESI), *m*/*z*, 235.6 (MH^+).

*3.2.6. 4-((α-Methyl)benzylamino)quinazoline (**9**).* The reaction time was 16 h. The product was obtained as a white solid in 87% yield, mp: 106–108 °C. ^{1}H NMR ($CDCl_3$) 8.66 (s, 1H), 7.84 (d, *J*=8 Hz, 1H), 7.71–7.75 (m, 2H), 7.44–7.46 (m, 3H), 7.30–7.38 (m, 2H), 7.27–7.29 (m, 1H), 6.01 (br s, 1H), 5.62–5.68 (m, 1H), 1.69 (d, *J*=6.5 Hz, 3H). ^{13}C NMR 158.6, 155.4, 149.4, 143.2, 132.6, 128.8, 128.6, 127.6, 126.4, 126.0, 120.5, 114.9, 50.2, 21.8. MS (ESI), *m*/*z*, 250.1 (MH^+).

*3.2.7. 4-(N-Benzyl-N-methylamino)quinazoline (**10**).* The reaction time was 16 h. The product was obtained as a yellow liquid in 83% yield. ^{1}H NMR ($CDCl_3$) 8.71(s, 1H), 7.88–7.93 (m, 2H), 7.68–7.72 (m, 1H), 7.32–7.43 (m, 6H), 4.98 (s, 2H), 3.29 (s, 3H). ^{13}C NMR 163.9, 154.0, 151.8, 137.1, 132.3, 128.9, 128.4, 127.6, 127.2, 125.03, 124.98, 116.1, 57.1, 39.5. MS (ESI), *m*/*z*, 250.1 (MH^+).

*3.2.8. 4-(Pyrrolidin-1-yl)quinazoline (**11**).* The reaction time was 1 h. The product was obtained as a white solid in 80% yield, mp: 39–42 °C. ^{1}H NMR ($CDCl_3$) 8.59 (s, 1H), 8.14 (t, *J*=0.5 Hz, 1H), 7.80–7.82 (m, 1H), 7.66–7.69 (m, 1H), 7.35–7.38 (m, 1H), 3.92 (t, *J*=6.5 Hz, 4H), 2.03–2.06 (m, 4H). ^{13}C NMR 159.7, 154.5, 151.5, 131.9, 128.1, 125.3, 124.3, 116.5, 51.0, 25.7. MS (ESI), *m*/*z*, 200.1 (MH^+).

*3.2.9. 4-(Piperidin-1-yl)quinazoline (**12**).* The reaction time was 16 h. The product was obtained as a yellow liquid in 79% yield. ^{1}H NMR ($CDCl_3$) 8.71 (s, 1H), 7.87 (d, *J*=8.5 Hz, 2H), 7.70–7.73 (m, 1H), 7.42–7.45 (m, 1H), 3.71–3.73 (m, 4H), 1.77–1.81 (m, 6H). ^{13}C NMR 164.9, 154.1, 151.7, 132.3, 128.5, 125.2, 125.1, 116.8, 51.0, 26.0, 24.8. MS (ESI), *m*/*z*, 214.1 (MH^+).

*3.2.10. 4-(Morpholino)quinazoline (**13**).* The reaction time was 3 h. The product was obtained as a yellow solid in 92% yield, mp: 87–90 °C. ^{1}H NMR ($CDCl_3$) 8.77 (s, 1H), 7.88–7.94 (m, 2H), 7.74–7.77 (m, 1H), 7.46–7.49 (m, 1H), 3.90–3.92 (m, 4H), 3.79 (t, *J*=4.5 Hz, 4H). ^{13}C NMR 164.7, 154.0, 151.7, 132.6, 128.8, 125.6, 124.7, 116.6, 66.8, 50.3. MS (ESI), *m*/*z*, 216.2 (MH^+).

*3.2.11. 4-(1H-Imidazol-1-yl)quinazoline (**14**).* The reaction time was 1.5 h. The product was obtained as a yellow solid in 89% yield, mp: 112–114 °C. ^{1}H NMR (DMSO-d_6) 9.26 (s, 1H), 8.46 (s, 1H), 8.13–8.46 (m, 3H), 7.97 (t, *J*=1.0 Hz, 1H), 7.86–7.89 (m, 1H), 7.29 (t, *J*=1.0 Hz, 1H). ^{13}C NMR 155.1, 154.1, 152.1, 138.1, 135.2, 130.1, 129.4, 128.4, 124.7, 120.4, 117.5. MS (ESI), *m*/*z*, 197.1 (MH^+).

*3.2.12. 4-((5-Methyl-1H-pyrazol-3-yl)amino)quinazoline (**15**)*[6b]. The reaction time was 16 h. The product was obtained as a white solid in 64% yield, mp: 279–280 °C. ^{1}H NMR (DMSO-d_6) 12.18 (br s, 1H), 10.31 (br s, 1H), 8.58–8.61 (m, 2H), 7.74–7.83 (m, 2H), 7.54–7.57 (m, 1H), 6.58 (br s, 1H), 2.27 (m, 3H).

*3.2.13. 4-(Phenylamino)quinazoline (**16**).* MeCN (5 mL) was used as the solvent. After addition of aniline, the mixture was stirred under reflux for 5 h. The product was obtained as a white solid in 72% yield, mp: 222–224 °C. ^{1}H NMR (DMSO-d_6) 9.81 (s, 1H), 8.57–8.62 (m, 2H), 7.86–7.90 (m, 3H), 7.80–7.81(m, 1H), 7.64–7.67 (m, 1H), 7.39–7.43 (m, 2H), 7.13–7.17 (m, 1H). ^{13}C NMR 157.8, 154.5, 149.7,

139.2, 133.0, 128.5, 127.8, 126.2, 123.8, 123.0, 122.5, 115.2. MS (ESI), *m*/*z*, 222.2 (MH^+).

*3.2.14. 4-(p-Tolylamino)quinazoline (**17**).* MeCN (5 mL) was used as the solvent. After addition of *p*-toluidine, the mixture was stirred under reflux for 6 h. The product was obtained as a white solid in 68% yield, mp: 190–192 °C. ^{1}H NMR ($CDCl_3$) 8.75 (s, 1H), 7.91–7.92 (m, 2H), 7.78–7.81 (m, 1H), 7.53–7.59 (m, 4H), 7.21–7.23 (m, 2H), 2.36 (s, 3H). ^{13}C NMR 157.8, 155.0, 149.8, 135.4, 134.7, 132.9, 129.7, 128.8, 126.6, 122.4, 120.4, 115.1, 20.9. MS (ESI), *m*/*z*, 236.3 (MH^+).

*3.2.15. 4-(4-Chlorophenylamino)quinazoline (**18**).* MeCN (5 mL) was used as the solvent. After addition of 4-chlorobenzenamine, the mixture was stirred under reflux for 9 h. The product was obtained as a white solid in 41% yield, mp: 194–196 °C. ^{1}H NMR ($CDCl_3$) 8.77 (s, 1H), 7.93–7.96 (m, 2H), 7.82 (t, *J*=7.5 Hz, 1H), 7.72 (d, *J*=9 Hz, 2H), 7.67 (br s, 1H), 7.58 (t, *J*=7.5 Hz, 1H), 7.38 (d, *J*=9 Hz, 2H). ^{13}C NMR 157.5, 154.7, 149.8, 136.8, 133.2, 129.7, 129.1, 128.9, 126.9, 123.2, 120.4, 115.1. MS (ESI), *m*/*z*, 256.3 (MH^+).

*3.2.16. 4-(4-Methoxyphenylamino)quinazoline (**19**).* MeCN (5 mL) was used as the solvent. After addition of 4-methoxybenzenamine, the mixture was stirred under reflux for 6 h. The product was obtained as a yellow solid in 63% yield, mp: 169–171 °C. ^{1}H NMR (DMSO-d_6) 8.72 (s, 1H), 7.90 (t, *J*=8 Hz, 2H), 7.78–7.81 (m, 1H), 7.54–7.58 (m, 3H), 7.47 (br s, 1H), 6.96 (d, *J*=7.5 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR 158.0, 157.1, 155.0, 149.5, 133.0, 130.8, 128.6, 126.6, 124.5, 120.5, 114.9, 114.4, 55.5. MS (ESI), *m*/*z*, 252.3 (MH^+).

*3.2.17. 4-(N-Methyl-N-phenylamino)quinazoline (**20**).* MeCN (5 mL) was used as the solvent. After addition of *N*-methylbenzenamine, the mixture was stirred under reflux for 7 h. The product was obtained as a yellow solid in 61% yield, mp: 68–70 °C. ^{1}H NMR ($CDCl_3$) 8.85 (s, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 7.57–7.60 (m, 1H), 7.39 (t, *J*=8.0 Hz, 1H), 7.27–7.30 (m, 2H), 7.18–7.19 (m, 2H), 7.03–7.05 (m, 2H), 3.65 (s, 3H). ^{13}C NMR 161.8, 154.3, 151.4, 148.5, 131.9, 130.0, 128.4, 126.5, 126.3, 125.8, 125.0, 116.8, 42.5. MS (ESI), *m*/*z*, 256.3 (MH^+).

*3.2.18. 4-(n-Butylamino)-6-methyl-quinazoline (**21**).* The reaction time was 16 h. The product was obtained as a yellow solid in 63% yield, mp: 104–107 °C. ^{1}H NMR ($CDCl_3$) 8.63 (s, 1H), 7.73 (d, *J*=8.5 Hz, 1H), 7.54–7.56 (m, 1H), 7.49 (s, 1H), 5.80 (br s, 1H), 3.64–3.68 (m, 2H), 2.50 (s, 3H), 1.69–1.75 (m, 2H), 1.44–1.52 (m, 2H), 0.99 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 159.1, 154.6, 147.5, 135.9, 134.3, 128.2, 119.6, 114.7, 41.1, 31.43, 21.7, 20.2, 13.8. HRMS (ESI), *m*/*z*, 216.1508 [MH^+], calcd for $C_{13}H_{18}N_3$, 216.1501.

*3.2.19. 4-(n-Butylamino)-8-methyl-quinazoline (**22**).* The activation time was 20 h, and the reaction time was 16 h. The product was obtained as a white solid in 80% yield, mp: 94–96 °C. ^{1}H NMR ($CDCl_3$) 8.73 (s, 1H), 7.54–7.59 (m, 2H), 7.33–7.36 (m, 1H), 5.76 (br s, 1H), 3.63–3.67 (m, 2H), 2.69 (s, 3H), 1.68–1.74 (m, 2H), 1.45–1.50 (m, 2H), 0.99 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 159.7, 154.4, 148.2, 136.6, 132.7, 125.3, 118.0, 114.6, 41.2, 31.4, 20.2, 17.9, 13.8. HRMS (ESI), *m*/*z*, 216.1498 [MH^+], calcd for $C_{13}H_{18}N_3$, 216.1501.

*3.2.20. 4-(n-Butylamino)-6-chloroquinazoline (**23**).* The reaction time was 3 h. The product was obtained as a white solid in 80% yield, mp: 148–150 °C. ^{1}H NMR (DMSO-d_6) 8.47 (s, 1H), 8.43 (d, *J*=2.0 Hz, 1H), 8.33 (t, *J*=5.0 Hz, 1H), 7.77 (dd, *J*=9.0 Hz; *J*=2.0 Hz, 1H), 7.69 (d, *J*=9.0 Hz, 1H), 3.51–3.55 (m, 2H), 1.60–1.66 (m, 2H), 1.34–1.42 (m, 2H), 0.93 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 158.6, 155.5, 147.8, 132.7, 129.6, 129.5, 122.0, 115.8, 40.3, 30.5, 19.7, 13.7. MS (ESI), *m*/*z*, 236.2 (MH^+).

*3.2.21. 4-(n-Butylamino)-7-chloroquinazoline (**24**).* The reaction time was 3 h. The product was obtained as a white solid in 69% yield, mp: 164–167 °C. ^{1}H NMR (DMSO-d_6) 8.47 (s, 1H), 8.40 (d, *J*=5.5 Hz, 1H), 8.29 (d, *J*=9.0 Hz, 1H), 7.70 (d, *J*=2.0 Hz, 1H), 7.56 (dd, *J*=9.0, 2.0 Hz, 1H), 3.51–3.55 (m, 2H), 1.60–1.65 (m, 2H), 1.34–1.41 (m, 2H), 0.93 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 159.2, 156.3, 150.1, 137.0, 126.2, 125.8, 125.0, 113.6, 40.2, 30.5, 20.0, 13.7. HRMS (ESI), *m*/*z*, 236.0961 [MH^+], calcd for $C_{12}H_{15}ClN_3$, 236.0955.

*3.2.22. 4-(n-Butylamino)-7-fluoroquinazoline (**25**).* The reaction time was 2 h. The product was obtained as a white solid in 86% yield, mp: 120–124 °C. ^{1}H NMR ($CDCl_3$) 8.64 (s, 1H), 7.73–7.76 (m, 1H), 7.45–7.47 (m, 1H), 7.18–7.22 (m, 1H), 5.83 (br s, 1H), 3.65–3.69 (m, 2H), 1.69–1.75 (m, 2H), 1.44–1.51 (m, 2H), 0.99 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 165.0 (d, *J*=251.3 Hz), 159.4, 156.5, 151.4 (d, *J*=12.5 Hz), 123.1 (d, *J*=10.0 Hz), 115.6 (d, *J*=25.0 Hz), 112.7 (d, *J*=21.3 Hz), 111.9, 41.3, 31.5, 20.3, 13.9. HRMS (ESI), *m*/*z*, 220.1261 [MH^+], calcd for $C_{12}H_{15}FN_3$, 220.1250.

*3.2.23. 4-(n-Butylamino)-2-methyl-quinazoline (**26**).* The activation time was 20 h, and the reaction time was 6 h. The product was obtained as a white solid in 74% yield, mp: 114–116 °C. ^{1}H NMR ($CDCl_3$) 7.75–7.77 (m, 1H), 7.66–7.69 (m, 2H), 7.36–7.39 (m, 1H), 5.72 (br s, 1H), 3.65–3.69 (m, 2H), 2.64 (s, 3H), 1.67–1.73 (m, 2H), 1.43–1.51 (m, 2H), 0.99 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 164.4, 159.4, 149.9, 132.3, 127.7, 124.9, 120.3, 112.9, 40.8, 31.5, 26.7, 20.2, 13.8. MS (ESI), *m*/*z*, 216.2 (MH^+).

*3.2.24. 4-(n-Butylamino)-6,7-dimethoxy-quinazoline (**27**).* The activation time was 1 h, and the reaction time was 2 h. Activation and amination were performed under reflux conditions. The product was obtained as a white solid in 65% yield, mp: 130–132 °C. ^{1}H NMR ($CDCl_3$) 8.56 (s, 1H), 7.15 (s, 1H), 7.05 (s, 1H), 6.13 (t, *J*=5 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.61–3.65 (m, 2H), 1.64–1.71 (m, 2H), 1.40–1.45 (m, 2H), 0.93 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 158.5, 154.2, 154.0, 148.9, 146.2, 108.7, 107.5, 99.9, 56.09, 56.06, 41.2, 31.6, 20.2, 13.8. HRMS (ESI), *m*/*z*, 262.1551 [MH^+], calcd for $C_{14}H_{20}N_3O_2$, 262.1556.

*3.2.25. 4-(n-Butylamino)benzo[g]quinazoline (**28**).* The activation time was 3 h, and the reaction time was 16 h. The product was obtained as a yellow solid in 73% yield, mp: 220–223 °C. ^{1}H NMR ($CDCl_3$) 8.67 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 7.96–8.00 (m, 2H), 7.54–7.56 (m, 1H), 7.49–7.51 (m, 1H), 6.21 (br s, 1H), 3.73–3.77 (m, 2H), 1.76–1.82 (m, 2H), 1.50–1.55 (m, 2H), 1.02 (t, *J*=7.5 Hz, 3H). ^{13}C NMR 159.9, 154.9, 144.5, 135.7, 131.1, 128.5, 128.0, 127.6, 126.0, 125.7, 120.5, 114.9, 41.4, 31.4, 20.3, 13.8. HRMS (ESI), *m*/*z*, 252.1503 [MH^+], calcd for $C_{16}H_{19}N_3$, 252.1501.

*3.2.26. 4-(n-Butylamino)pyrido[2,3-d]pyrimidine (**29**).* The reaction time was 2 h. The product was obtained as a white solid in 85% yield, mp: 164–167 °C. ^{1}H NMR ($CDCl_3$) 9.04–9.05 (m, 1H), 8.85 (s, 1H), 8.26–8.28 (m, 1H), 7.39–7.41 (m, 1H), 6.36 (br s, 1H), 3.68–3.72 (m, 2H), 1.70–1.76 (m, 2H), 1.43–1.51 (m, 2H), 0.99 (d, *J*=7.5 Hz, 3H). ^{13}C NMR 160.8, 158.8, 158.3, 155.7, 131.0, 121.2, 109.8, 41.5, 31.2, 20.2, 13.8. HRMS (ESI), *m*/*z*, 203.1303 [MH^+], calcd for $C_{11}H_{15}N_4$, 203.1297.

*3.2.27. Phosphonium intermediate **2a**.* White solid. ^{1}H NMR ($CDCl_3$), δ 8.91 (s, 1H), 8.17 (d, *J*=8.0 Hz, 1H), 8.08 (d, *J*=8.5 Hz, 1H), 7.97–8.00 (m, 1H), 7.71–7.75 (m, 1H). ^{13}C NMR 162.0 (d, *J*=8.8 Hz), 152.7, 152.6, 135.2, 128.8, 128.3, 123.1, 115.6 (d, *J*=8.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$), δ 24.01 (d, *J*=60.6 Hz), 15.01 (t, *J*=60.6 Hz). MS (ESI), *m*/*z*, 455.8233 [MH^+], calcd for $C_8H_5ClN_5OP_3$, 455.8228.

Acknowledgements

The authors gratefully acknowledge the financial support of the Natural Science Foundation of China (NSFC, 20876149, 20772111), the Zhejiang Provincial Natural Science Foundation of China

(Y4090517), and the Key Science and Technology Innovation Team of Zhejiang Province (2009R50002).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.12.067.

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16. NMR spectra: see Supplementary data.