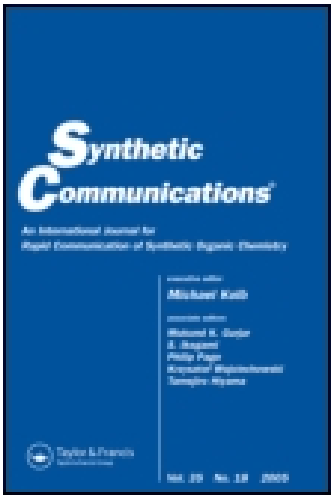

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

One-Pot Synthesis of 4-Aminoquinazolines by Hexamethyldisilazane-Mediated Reaction of Quinazolin-4(3H)-ones with Amines

Zhen-Lu Shen [a], Xiao-Fei He [a], Yi-Ming Hong [a], Xin-Quan Hu [a], Wei-Min Mo [a], Bao-Xiang Hu [a] & Nan Sun [a]
[a] College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou, China
Accepted author version posted online: 30 Jun 2011.Published online: 09 Jun 2011.

To cite this article: Zhen-Lu Shen, Xiao-Fei He, Yi-Ming Hong, Xin-Quan Hu, Wei-Min Mo, Bao-Xiang Hu & Nan Sun (2011) One-Pot Synthesis of 4-Aminoquinazolines by Hexamethyldisilazane-Mediated Reaction of Quinazolin-4(3H)-ones with Amines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:24, 3644-3653, DOI: 10.1080/00397911.2010.519843

To link to this article: http://dx.doi.org/10.1080/00397911.2010.519843

Synthetic Communications®, 41: 3644–3653, 2011

ISSN: 0039-7911 print/1532-2432 online
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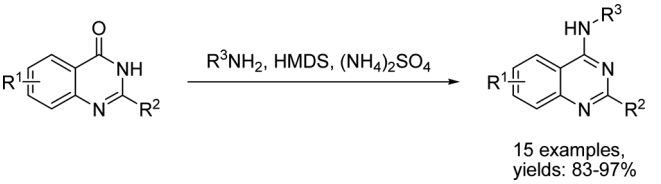
ONE-POT SYNTHESIS OF 4-AMINOQUINAZOLINES BY HEXAMETHYLDISILAZANE-MEDIATED REACTION OF QUINAZOLIN-4(3*H*)-ONES WITH AMINES

Zhen-Lu Shen, Xiao-Fei He, Yi-Ming Hong, Xin-Quan Hu, Wei-Min Mo, Bao-Xiang Hu, and Nan Sun

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou, China

GRAPHICAL ABSTRACT



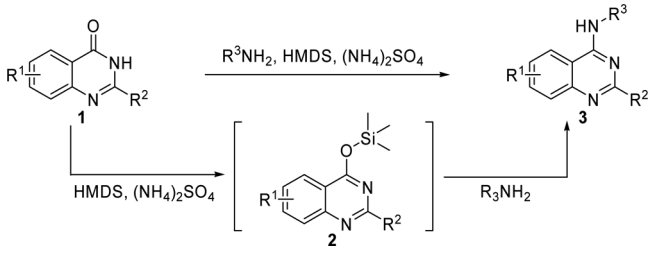
Abstract *Hexamethyldisilazane-mediated reaction of quinazolin-4(3*H*)-ones with primary amines led to facile formation of 4-aminoquinazolines through tandem silylation and substitution in a single pot. Excellent yields of the products (83–97%) and environmental friendliness (avoiding the use of chlorination reagents) are the advantages of this method.*

Keywords Amination; aminoquinazolines; hexamethyldisilazane; quinazolin-4(3*H*)-ones

INTRODUCTION

Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. Quinazoline derivatives are an important class of nitrogen-containing heterocycles, which display a wide variety of biological activities such as anticonvulsant,[1] antihypertensive, vasodilator,[2] anti-inflammatory,[3] and antibiosis[4] activities and has been used as fibrinogen receptor antagonists,[5] nanomolar Hedgehog antagonists,[6] and specific matrix metalloproteinase-13 inhibitors.[7] Among the family of quinazolines, 4-aminoquinazolines have received particular interest because of their pharmacological properties.[8–12] Gefitinib [ZD1839, Iressa, 4-(3′-chloro-4′-fluroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline], derived from 4-aminoquinazolines, has

Received September 20, 2009.
Address correspondence to Zhen-Lu Shen or Wei-Min Mo, College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, China. E-mail: zhenlushen@zjut.edu.cn or mowm@zjut.edu.cn



Scheme 1. One-pot synthesis of 4-aminoquinazolines mediated by HMDS.

already been approved by the U.S. Food and Drug Administration for the treatment of advanced non-small-cell lung cancer (NSCLC).[13]

Generally, 4-aminoquinazolines are obtained through S_NAr substitution of 4-chloroquinazolines with the appropriate amines, while 4-chloroquinazolines are prepared from the corresponding quinazolin-4(3*H*)-ones via a chlorination reaction. The chlorination reagents include $SOCl_2$, $POCl_3$, and PCl_5, and the chlorination reactions are often performed under harsh conditions.[8–14] However, several disadvantages exist in this method for the synthesis of 4-aminoquinazolines. These chlorination reagents are not environmentally benign, and the chlorination conditions may destroy sensitive functional groups in the molecules. In addition, many of 4-chloroquinazolines are moisture sensitive and will hydrolyze to quinazolin-4(3*H*)-ones. To overcome these inherent problems, recently some efficient phosphonium reagents, such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), have been developed to active quinazolin-4(3*H*)-ones and successfully avoid the chlorination step during the synthesis of 4-aminoquinazolin-4(*3H*)-ones.[15,16] However, these reagents are usually very expensive, and most of them are toxic. Herein, we report a hexamethyldisilazane (HMDS)–mediated, single-pot, facile synthesis of 4-aminoquinazolines from quinazolin-4(3*H*)-ones and amines in excellent yield (Scheme 1).

RESULTS AND DISCUSSION

It was reported that HMDS could in situ activate the hydroxyl group in N-heterocycles via silylation to enable the substitution by primary amines.[17–20] Quinazolin-4(3*H*)-ones **1**, as the conventional tautomerizable heterocycle, possessed the common interconvertible structural unit [−C(=O)−NH−] (lactam form) and [−C(−OH)=N-] (phenol form). We speculated that the silylation of the phenol form could occurr in situ and the resulting reactive intermediate **2** could readily undergo the substitution by primary amines to generate 4-aminoquinazolines **3** (Scheme 1).

After carefully optimizing the reaction conditions, we were pleased to find that the amination of quinazolin-4(3*H*)-one **1a** with benzylamine mediated by HMDS could be completed in 2 h. The crude product was purified by column chromatography to afford product **3a** with excellent yield (97%). Subsequently, to examine the efficiency and applicability of this protocol, the reaction was extended to other substituted quinazolin-4(3*H*)-ones and substituted primary amines. To our delight,

these reactions proceeded smoothly to afford a series of 4-aminoquinazoline derivatives **3** in excellent yields (Table 1, entries 2–15). Only reaction times showed the effects of substituents to the activity. The strong electron-withdrawing nitro group would efficiently active quinazoline structure, and the reaction time of amination of **1i** with benzylamine could be shortened to 1.5 h (Table 1, entry 9). When 5-methyl-1*H*-pyrazol-3-amine was used as the amination reagent, complete conversion of **1a** could not be achieved though the reaction time was prolonged to 14 h (Table 1, entry 15). The experimental results listed in Table 1 showed that the scope of the reaction is quite broad in regard to the quinazolin-4(3*H*)-ones and primary amines.

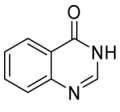
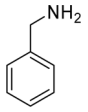
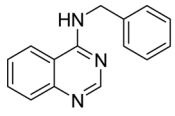
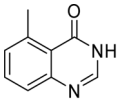
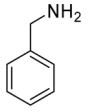
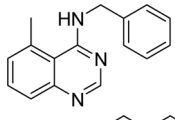
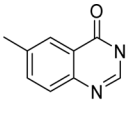
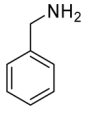
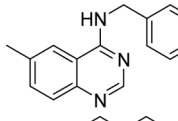
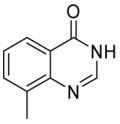
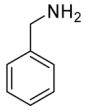
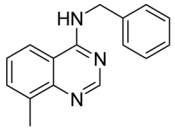
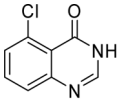
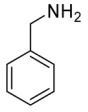
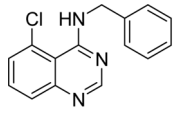
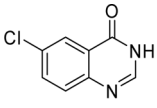
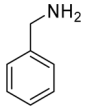
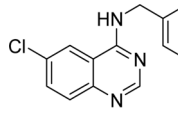
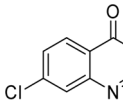
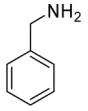
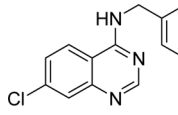
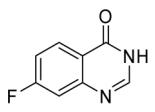
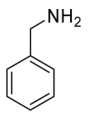
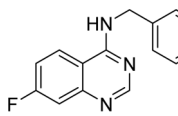
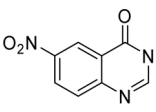
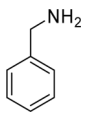
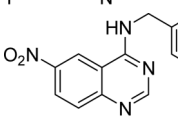
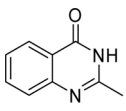
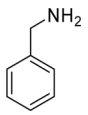
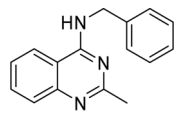
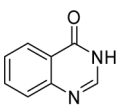
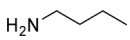
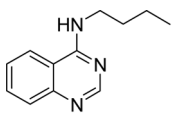
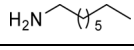
As a contrast, quinazolin-4(3*H*)-ones **1** were chlorinated with $POCl_3$ to generate 4-chloroquinazolines. In most cases, the yields of the chlorination products were in a range of 38% to 87% (**1a** 72%, **1c** 87%, **1d** 82%, **1f** 80%, **1g** 70%, **1h** 41%, **1i** 38%, and **1j** 85%). Though chlorination of 5-methylquinazolin-4(3*H*)-one **1b** or 5-chloroquinazolin-4(3*H*)-one **1e** has been reported,[21] the major products were not the desired compounds when they were chlorinated under our reaction conditions. The infrared (IR) spectra of chlorination product of **1e** showed a peak at 1694 cm^{-1}, which might be attributed to a carbonyl group. Its spectral data are listed as follows: ^{1}H NMR ($CDCl_3$), δ 7.69–7.71 (m, 1H), 7.79–7.80 (m, 1H), 7.87–7.91 (m, 1H), 7.98–8.00 (m, 1H), 8.12–8.15 (t, 1H, $J = 8$ Hz), 8.25–8.27 (m, 1H), 8.71 (s, 1H), 9.52 (s, 1H). ^{13}C NMR ($CDCl_3$), δ 118.32, 119.41, 127.31, 127.89, 128.63, 130.48, 131.86, 132.95, 135.30, 135.39, 145.88, 150.08, 153.21, 154.61, 155.73, 158.46. HRMS (ESI), m/z, 343.0152 [$M + H^+$]. Based on this information, we can conclude that its molecular formula should be $C_{16}H_8Cl_2N_4O$ and its structure was assigned in Fig. 1. The chlorination product of **1b** was also presented in Fig. 1. It is obvious that the one-pot HMDS-mediated synthesis of 4-aminoquinazolines was more powerful than the traditional synthetic method with a separate chlorination step of quinazolin-4(3-*H*)-ones.

In conclusion, we have developed an efficient method for the synthesis of 4-aminoquinazolines by HMDS-mediated reaction of quinazolin-4(3*H*)-ones with primary amines. Excellent yields of the products and environmental friendliness are the advantages of this method.

EXPERIMENTAL

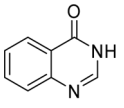
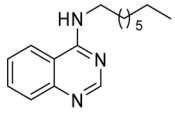
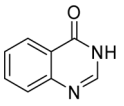
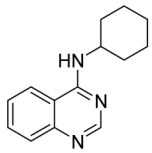
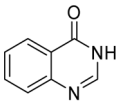
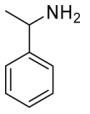
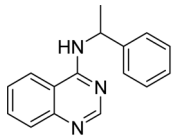
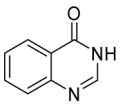
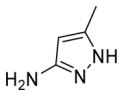
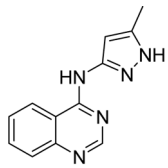
Melting points were measured using an XRL-1 melting-point instrument and were uncorrected. Fourier transform (FT)–IR spectra were recorded on a Nicolet instrument, Avetar 370. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance III (500 MHz) spectrometer. Dimethylsulfoxide (DMSO-d_6) and $CDCl_3$ were used as solvents with tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HRMS) were recorded on an Agilent 6210 LC/TOF mass spectrometer. The reactions were monitored by thin-layer chromatography (TLC) associating with gas chromatography (GC) or high-performance liquid chromatography (HPLC). Quinazolin-4(3*H*)-ones were synthesized from anthranilic acids and amidines-acetate, and their structures were confirmed by mass spectrometry (MS), ^{1}H NMR, and ^{13}C NMR. Other reagents were purchased from suppliers and used without any further treatment.

Table 1. Synthesis of 4-aminoquinazolines by HMDS-mediated reaction of quinazolin-4(3*H*)-ones with amines[a]

Entry	Quinazolin-4(3*H*)-ones	Amines	Time (h)	Products	Yield[b] (%)
1	 **1a**		2	 **3a**	97
2[c]	 **1b**		14	 **3b**	88
3	 **1c**		2	 **3c**	95
4	 **1d**		4.5	 **3d**	92
5	 **1e**		2	 **3e**	93
6	 **1f**		3	 **3f**	93
7	 **1g**		2	 **3g**	95
8	 **1h**		2	 **3h**	92
9	 **1i**		1.5	 **3i**	95
10	 **1j**		2.5	 **3j**	93
11[d]	 **1a**		1.5	 **3k**	95
12			2		96

(*Continued*)

Table 1. Continued

Entry	Quinazolin-4(3*H*)-ones	Amines	Time (h)	Products	Yield[b] (%)
	 **1a**			 **3l**	
13[c]	 **1a**		14	 **3m**	92
14	 **1a**		13	 **3n**	95
15[c]	 **1a**		14	 **3o**	83

[a]*N*(Quinazolin-4(3*H*)-one)/*N*(amine)/*N*(HMDS)/*N*[$(NH_4)_2SO_4$] = 1:1.4:1.4:0.1.
[b]Yields refer to isolated pure products.
[c]*N*(Quinazolin-4(3*H*)-one)/*N*(amine)/*N*(HMDS)/*N*[$(NH_4)_2SO_4$] = 1:2:2:0.1.
[d]The reaction was performed in a sealed vessel.

General Procedure for Synthesis of 4-Aminoquinazolines Mediated by HMDS

Quinazolin-4(3*H*)-ones **1** (0.40 mmol), amines (0.56 mmol), HMDS (0.56 mmol), and $(NH_4)_2SO_4$ (0.04 mmol) were added to a 5-mL glass tube with magnetic stirring bar. Then the tube was placed in an oil bath, which was preheated to 125 °C. The mixture was stirred for 1.5–16 h. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. Then it was diluted with CH_2Cl_2 and purified through a column of silica gel to obtain the pure product **3**. All of the new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

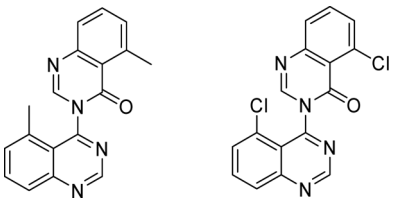


Figure 1. Chlorination products of **1b** and **1e**.

General Procedure for the Chlorination of Quinazolin-4(3*H*)-ones with $POCl_3$

Quinazolin-4(3*H*)-ones **1** (8 mmol), 20 mL of $POCl_3$, and 1 mL of diisopropylethylamine were added to a 100-mL flask. After refluxing for 2.5 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in cold dichloromethane and washed with cold 1 M HCl (100 mL × 2). After drying over $MgSO_4$ and filtering, K_2CO_3 was added to the organic layer to neutralize the residual acid. Then the organic phase was concentrated, and the resulting residue was chromatographed on silica gel to afford the desired product 4-chloroquinazolines.

Data

***N*-Benzylquinazolin-4-amine (3a).**[22] White solid, mp 168–170 °C. IR ν_{max} (KBr)/cm^{-1} 3228, 3060, 2966, 2935, 1619, 1575, 1541, 1495, 1415, 1340. ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.86 (d, $J = 8.0$ 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 ($CDCl_3$) δ 159.35, 155.46, 149.50, 138.09, 132.77, 128.95, 128.69, 128.12, 127.89, 126.18, 120.57, 114.88, 45.43. MS (ESI) m/z 250.1 ($M + H^+$).

***N*-Benzyl-5-methylquinazolin-4-amine (3b).** Pale yellow oil. IR ν_{max} (KBr)/cm^{-1} 3498, 3060, 3029, 2924, 2872, 1578, 1524, 1349. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.55–7.58 (m, 1H), 7.31–7.43 (m, 5H), 7.20 (d, $J = 7.0$ Hz, 1H), 6.35 (br, s, 1H), 4.85 (d, $J = 5.0$ Hz, 2H), 2.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 160.72, 154.60, 151.45, 138.18, 132.75, 131.87, 129.18, 128.93, 127.80, 127.72, 127.04, 115.45, 46.02, 24.32. HRMS (ESI) m/z 250.1332 ($M + H^+$), calcd. for $C_{16}H_{15}N_3 + H^+ = 250.1339$.

***N*-Benzyl-6-methylquinazolin-4-amine (3c).**[23] White solid, mp 182–184 °C. IR ν_{max} (KBr)/cm^{-1} 3275, 1584, 1538, 1420, 1352, 1314. ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.56–7.58 (m, 1H), 7.46 (s, 1H), 7.33–7.43 (m, 5H), 5.93 (br, s, 1H), 4.87 (d, $J = 5.5$ Hz, 2H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.00, 154.70, 147.79, 138.29, 136.15, 134.58, 128.89, 128.38, 128.10, 127.79, 119.75, 114.73, 45.39, 21.69. MS (ESI) m/z 250.1 ($M + H^+$).

***N*-Benzyl-8-methylquinazolin-4-amine (3d).** White solid, mp 156–158 °C. IR ν_{max} (KBr)/cm^{-1} 3250, 3126, 2935, 1585, 1531, 1492, 1417, 1357, 1329. ^{1}H NMR ($CDCl_3$) δ 8.78 (s, 1H), 7.60 (d, $J = 7.0$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.32–7.42 (m, 6H), 5.96 (br, s, 1H), 4.87 (d, $J = 5.5$ Hz, 2H), 2.71 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.67, 154.43, 148.47, 138.22, 136.85, 132.93, 128.90, 128.04, 127.80, 125.59, 118.14, 114.59, 45.47, 17.98. HRMS (ESI) m/z 250.1353 ($M + H^+$), calcd. for $C_{16}H_{15}N_3 + H^+ = 250.1339$.

***N*-Benzyl-5-chloroquinazolin-4-amine (3e).** White solid, mp 60–62 °C. IR ν_{max} (KBr)/cm^{-1} 3430, 3059, 3026, 2925, 1606, 1577, 1533, 1484, 1401, 1341. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.04 (br, s, 1H), 7.75–7.76 (m, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 7.30–7.43 (m, 6H), 4.86 (d, $J = 5.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 158.87, 155.39, 152.22, 137.81, 131.89, 128.84, 128.45, 128.17, 128.07, 127.72, 127.64,

113.14, 45.82. HRMS (ESI) m/z 270.0793 ($M+H^+$), calcd. for $C_{15}H_{12}ClN_3+H^+=270.0793$.

***N*-Benzyl-6-chloroquinazolin-4-amine (3f).** White solid, mp 170–172 °C. IR ν_{max} (KBr)/cm^{-1} 3232, 3101, 3072, 2964, 1572, 1542, 1493, 1418, 1340, 1324. ^1H NMR ($CDCl_3$) δ 8.69 (s, 1H), 7.81(d, $J=9.5$ Hz, 1H), 7.66–7.68 (m, 2H), 7.32–7.42 (m, 5H), 5.91 (br, s, 1H), 4.86 (d, $J=5.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 158.53, 155.61, 148.09, 137.77, 133.40, 131.52, 130.34, 128.94, 128.11, 127.94, 120.11, 115.56, 45.50. HRMS (ESI) m/z 270.0793 ($M+H^+$), calcd. for $C_{15}H_{12}ClN_3+H^+=270.0792$.

***N*-Benzyl-7-chloroquinazolin-4-amine (3g).** White solid, mp 180–181 °C. IR ν_{max} (KBr)/cm^{-1} 3444, 3217, 3101, 3028, 2964, 1609, 1570, 1540, 1446, 1338. ^1H NMR ($CDCl_3$) δ 8.68 (s, 1H), 7.84 (d, $J=2.0$ Hz, 1H), 7.65 (d, $J=9.0$ Hz, 1H), 7.31–7.40 (m, 6H), 6.07 (br, s, 1H), 4.86 (d, $J=5.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 159.19, 156.41, 150.40, 138.78, 137.80, 128.92, 128.09, 127.92, 127.72, 126.87, 122.17, 113.23, 45.45. MS (ESI) m/z 270.1 ($M+H^+$).

***N*-Benzyl-7-fluoroquinazolin-4-amine (3h).** White solid, mp 202–203 °C. IR ν_{max} (KBr)/cm^{-1} 3240, 3074, 3030, 2935, 1627, 1579, 1544, 1458, 1340. ^1H NMR ($CDCl_3$) δ 8.68 (s, 1H), 7.72–7.75 (m, 1H), 7.48–7.50 (m, 1H), 7.31–7.42 (m, 5H), 7.18–7.22 (m, 1H), 6.02 (br, s, 1H), 4.87 (d, $J=5.0$ Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 164.38 (d, $J=401.98$ Hz), 159.21, 156.20, 151.21 (d, $J=20.2$ Hz), 139.24, 128.31, 127.23, 126.81, 125.94 (d, $J=16.16$ Hz), 115.04 (d, $J=38.38$ Hz), 112.04, 111.41 (d, $J=32.32$ Hz), 43.56. HRMS (ESI) m/z 254.1096 ($M+H^+$), calcd. for $C_{15}H_{12}FN_3+H^+=254.1088$.

***N*-Benzyl-6-nitroquinazolin-4-amine (3i).[24]** Yellow solid, mp 226–228 °C. IR ν_{max} (KBr)/cm^{-1} 3234, 3084, 3028, 2929, 1625, 1585, 1495, 1446, 1328.^1H NMR ($CDCl_3$) δ 8.81 (s, 1H), 8.71 (d, $J=2.0$ Hz, 1H), 8.50–8.53 (m, 1H), 7.96 (d, $J=9.5$ Hz, 1H), 7.37–7.45 (m, 5H), 6.28 (br, s, 1H), 4.92(d, $J=5.5$ Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 160.23, 158.23, 152.82, 144.06, 138.62, 129.13, 128.35, 127.49, 126.99, 126.32, 120.61, 114.04, 43.90. MS (ESI) m/z 281.1 ($M+H^+$).

***N*-Benzyl-2-methylquinazolin-4-amine (3j).[25]** White solid, mp 180–184 °C. IR ν_{max} (KBr)/cm^{-1} 3427, 3219, 3115, 1575, 1539, 1386, 1353. ^1H NMR ($CDCl_3$) δ 7.79 (d, $J=8.5$ Hz, 1H), 7.65–7.70 (m, 2H), 7.30–7.42 (m, 6H), 5.94 (br, s, 1H), 4.88 (d, $J=5.5$ Hz, 2H), 2.67 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.45, 159.26, 150.02, 138.47, 132.56, 128.79, 128.17, 127.76, 127.69, 125.11, 120.44, 112.87, 45.24, 26.61. MS (ESI) m/z 250.1 ($M+H^+$).

***N*-Butylquinazolin-4-amine (3k).[15]** Yellow solid, mp 107–110 °C. IR ν_{max} (KBr)/cm^{-1} 3258, 3129, 2959, 2922, 2855, 1619, 1578, 1543, 1470, 1422, 1348, 1324. ^1H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 159.54, 155.52, 149.42, 132.53, 128.64, 125.94, 120.46, 115.00, 41.19, 31.48, 20.27, 13.89. MS (ESI) m/z 202.1 ($M+H^+$).

***N*-Octylquinazolin-4-amine (3l).** Yellow solid, mp 60–62 °C. IR ν_{max} (KBr)/cm^{-1} 3221, 2956, 2927, 2854, 1581, 1542, 1498, 1356, 1326. ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 7.84 (d, $J = 8.5$ Hz, 1H), 7.71–7.74 (m, 2H), 7.44–7.47 (m, 1H), 5.90 (br, s, 1H), 3.64–3.68 (m, 2H), 1.72–1.75 (m, 2H), 1.26–1.45 (m, 10H), 0.88 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 159.54, 155.36, 149.15, 132.54, 128.44, 125.95, 120.47, 114.93, 41.49, 31.80, 29.38, 29.33, 29.22, 27.07, 22.63, 14.06. MS (ESI) m/z 258.2 ($M + H^+$).

***N*-Cyclohexylquinazolin-4-amine (3m).[16]** White solid, mp 138–140 °C. IR ν_{max} (KBr)/cm^{-1} 3450, 3235, 3058, 2932, 2854, 1617, 1579, 1535, 1497, 1426, 1362, 1323. ^{1}H NMR ($CDCl_3$) δ 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 (d, $J = 7.0$ Hz, 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 ($CDCl_3$) δ 158.67, 155.47, 149.38, 132.43, 128.48, 125.79, 120.42, 114.92, 49.65, 33.06, 25.66, 24.94. MS (ESI) m/z 227.6 ($M + H^+$).

***N*-(1-Phenylethyl)quinazolin-4-amine (3n).[26]** White solid, mp 106–108 °C. IR ν_{max} (KBr)/cm^{-1} 3250, 3059, 2980, 1619, 1575, 1531, 1419, 1358, 1318. ^{1}H NMR ($CDCl_3$) δ 8.66 (s, 1H), 7.84 (d, $J = 8.0$ 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 (d, $J = 7.0$ Hz, 1H), 5.62–5.68 (m, 1H), 1.69 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 158.64, 155.43, 149.44, 143.24, 132.61, 128.83, 128.59, 127.57, 126.35, 126.02, 120.52, 114.87, 50.18, 21.78. MS (ESI) m/z 250.1 ($M + H^+$).

***N*-(5-Methyl-1*H*-pyrazol-3-yl)quinazolin-4-amine (3o).[27]** White solid, mp 279–280 °C. IR ν_{max} (KBr)/cm^{-1} 3271, 3177, 3072, 2928, 2868, 1625, 1599, 1550, 1483, 1403, 1320. ^{1}H NMR (DMSO-d_6) δ 12.18 (br, s, 1H), 10.31 (br, s, 1H), 8.58–8.61 (m, 2H), 7.74–7.83 (m, 2H), 7.56 (t, $J = 7.5$ Hz, 1H), 6.58 (br, s, 1H), 2.27 (m, 3H). ^{13}C NMR (DMSO-d_6) δ 157.47, 155.00, 149.84, 147.67, 139.16, 133.25, 128.00, 126.57, 123.69, 115.49, 98.47, 11.45. HRMS (ESI) m/z 226.1083 ($M + H^+$), calcd. for $C_{12}H_{12}N_5 + H^+ = 226.1087$.

ACKNOWLEGMENTS

The authors are grateful to the financial support of the National Natural Science Foundation of China (NSFC, 20876149) and the Zhejiang Provincial Natural Science Foundation of China (Y4090517).

REFERENCES

1. Hori, M.; Iemura, R.; Hara, H.; Ozaki, A.; Sukamoto, T.; Ohtaka, H. Novel 4-phenoxy-2-(1-piperazinyl)quinazolines as potent anticonvulsive and antihypoxic agents. *Chem. Pharm. Bull.* **1990**, *38*, 681.
2. Havera, H. J.; Vidrio, H. J. Derivatives of 1,3-disubstituted 2,4(1*H*,3*H*)-quinazolinediones as possible peripheral vasodilators or antihypertensive agents. *J. Med. Chem.* **1979**, *22*, 1548.
3. Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. Substituted isoquinolines and quinazolines as potential antiinflammatory

agents: Synthesis and biological evaluation of inhibitors of tumor necrosis factor α. *J. Med. Chem.* **1999**, *42*, 3860.
4. Kung, P. P.; Casper, M. D.; Cook, K. L.; Wilson-Lingardo, L.; Risen, L. M.; Vickers, T. A.; Ranken, R.; Blyn, L. B.; Wyatt, J. R.; Cook, P. D.; Ecker, D. J. Structure–activity relationships of novel 2-substituted quinazoline antibacterial agents. *J. Med. Chem.* **1999**, *42*, 4705.
5. Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Bardwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. J. Nonpeptide glycoprotein IIb/IIIa inhibitors: Substituted quinazolinediones and quinazolinones as potent fibrinogen receptor antagonists. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483.
6. Brunton, S. A.; Stibbard, J. H. A.; Rubin, L. L.; Kruse, L. I.; Guicherit, O. M.; Boyd, E. A.; Price, S. Potent inhibitors of the hedgehog signaling pathway. *J. Med. Chem.* **2008**, *51*, 1108.
7. Li, J. J.; Nahra, J.; Johnson, A. R.; Bunker, A.; O'Brien, P.; Yue, W. S.; Ortwine, D. F.; Man, C. F.; Baragi, V.; Kilgore, K.; Dyer, R. D.; Han, H. K. Quinazolinones and pyrido[3,4-d]pyrimidin-4-ones as orally active and specific matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. *J. Med. Chem.* **2008**, *51*, 835.
8. Liu, L. T.; Yuan, T. T.; Liu, H. H.; Chena, S. F.; Wub, Y. T. Synthesis and biological evaluation of substituted 6-alkynyl-4-anilinoquinazoline derivatives as potent EGFR inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6373.
9. Mortlock, A. A.; Foote, K. M.; Heron, N. M.; Jung, F. H.; Pasquet, G.; Lohmann, J. J. M.; Warin, N.; Renaud, F.; De Savi, C.; Roberts, N. J.; Johnson, T.; Dousson, C. B.; Hill, G. B.; Perkins, D.; Hatter, G.; Wilkinson, R. W.; Wedge, S. R.; Heaton, S. P.; Odedra, R.; Keen, N. J.; Crafter, C.; Brown, E.; Thompson, K.; Brightwell, S.; Khatri, L.; Brady, M. C.; Kearney, S.; McKillop, D.; Rhead, S.; Parry, T.; Green, S. Discovery, synthesis, and in vivo activity of a new class of pyrazoloquinazolines as selective inhibitors of Aurora B kinase. *J. Med. Chem.* **2007**, *50*, 2213.
10. Rewcastle, G. W.; Palmer, B. D.; Bridges, A. J.; Showalter, H. D. H.; Sun, L.; Nelson, J.; McMichael, A.; Kraker, A. J.; Fry, D. W.; Denny, W. A. Tyrosine kinase inhibitors, 9: Synthesis and evaluation of fused tricyclic quinazoline analogues as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor. *J. Med. Chem.* **1996**, *39*, 918.
11. Barlaam, B.; Ballard, P.; Bradbury, R. H.; Ducray, R.; Germain, H.; Hickinson, D. M.; Hudson, K.; Kettle, J. G.; Klinowska, T.; Magnien, F.; Ogilvie, D. J.; Olivier, A.; Pearson, S. E.; Scott, J. S.; Suleman, A.; Trigwell, C. B.; Vautier, M.; Whittaker, R. D.; Wood, R. A new series of neutral 5-substituted 4-anilinoquinazolines as potent, orally active inhibitors of erbB2 receptor tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 674.
12. Luth, A.; Lowe, W. Syntheses of 4-(indole-3-yl)quinazolinese—A new class of epidermal growth factor receptor tyrosine kinase inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 1478.
13. Barker, A. J.; Gibson, K. H.; Grundy, W.; Godfrey, A. A.; Barlow, J. J.; Healy, M. P.; Woodburn, J. R.; Ashton, S. E.; Curry, B. J.; Scarlett, L.; Henthorn, L.; Richards, L. Studies leading to the identification of ZD1839 (Iressa^{TM}): An orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1911.
14. Zhang, Y. D.; Xu, C. L.; Houghten, R. A.; Yu, Y. P. Scaffold approach for solid-phase synthesis of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines. *J. Comb. Chem.* **2007**, *9*, 9.
15. Wan, Z. K.; Wacharasindhu, S.; Binnun, E.; Mansour, T. An efficient direct amination of cyclic amides and cyclic ureas. *Org. Lett.* **2006**, *8*, 2425.
16. Wan, Z. K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. The scope and mechanism of phosphonium-mediated S_NAr reactions in heterocyclic amides and ureas. *J. Org. Chem.* **2007**, *72*, 10194.

17. Singer, R. A.; Dore, M. Practical amination of nitropyridones by silylation. *Org. Process Res. Dev.* **2008**, *12*, 1261.
18. Vorbruggen, H. Simple amination of aromatic hydroxy-nitrogen heterocycles. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 305.
19. Vorbruggen, H.; Krolikiewicz, K. Amination, III: Trimethylsilanol as leaving group, V: Silylation–amination of hydroxy N-heterocycles. *Chem. Ber.* **1984**, *117*, 1523.
20. Nishikawa, S.; Kumazawa, Z.; Kashimura, N.; Maki, S. Nishikimi, Y. Sythesis and cytokinin activity of 4- and 2,4-substituted pyrido[3,4-*d*]pyrimidines. *Agric. Biol Chem.* **1986**, *50*, 495.
21. Mitidieri-Costanza, A.; Sleiter, G. The reaction of 5-methyl-4-phenoxyquinazoline with piperidine in isooctane: Further evidence for steric inhibition of bifunctional catalysis. *J. Prakt. Chem.* **1985**, *327*, 865.
22. Gulevskaya, A. V.; Maes, B. U. W.; Meyers, C.; Herrebout, W. A.; van der Veken, B. J. C–N bond formation by the oxidative alkylamination of azines: Comparison of $AgPy_2MnO_4$ versus $KMnO_4$ as oxidant. *Eur. J. Org. Chem.* **2006**, 5305.
23. Breza, N.; Pato, J.; Orfi, L.; Hegymegi-Barakonyi, B.; Banhegyi, P.; Varkondi, E.; Borbely, G.; Petak, I.; Keri, G. Synthesis and characterization of novel quinazoline type inhibitors for mutant and wild-type EGFR and RICK kinases. *J. Recept. Sig. Transd.* **2008**, *28*, 361.
24. Hou, T. J.; Zhu, L. L.; Chen, L. R.; Xu, X. J. Mapping the binding site of a large set of quinazoline type EGF-R inhibitors using molecular field analyses and molecular docking studies. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 273.
25. Kurteva, V. B.; Zlatanova, V. N.; Dimitrov, V. D. Solvent-free synthesis of a series of differently N-substituted 4-amino-2-methylquinazolines under microwave irradiation. *Arkivoc* **2006**, *1*, 46.
26. Lee, Y. B.; Ahn, C. H. Quinazoline derivatives and therapeutic use thereof. U.S. Patent Appl. 0187231, 2007.
27. Shen, Z. L.; Hong, Y. M.; He, X. F.; Mo, W. M.; Hu, B. X.; Sun, N.; Hu, X. Q. Switching the chemoselectivity in the amination of 4-chloroquinazolines with aminopyrazoles. *Org. Lett.* **2010**, *12*, 552.