Direct Sulfanylation of 4-Quinazolinone via C–OH Bond Activation: An Efficient Route to 2-Aryl-4-sulfanylquinazolines

Yiyuan Peng,*[a] Guanyinsheng Qiu,[b] Qin Yang,[a] Jianjun Yuan,[a] Zhihong Deng[b]

[a] Key Laboratory of Small Fuctional Organic Molecule, Ministry of Education and College of Life Science, Jiangxi Normal University, Nanchang, Jiangxi 330022, P. R. of China
Fax +86(791)88120396; E-mail: yypeng@jxnu.edu.cn; E-mail: Yiyuanpeng@yahoo.com

[b] Key Laboratory of Green Chemistry, Jiangxi Province and College of Chemistry, Jiangxi Normal University, Nanchang, Jiangxi 330022, P. R. of China

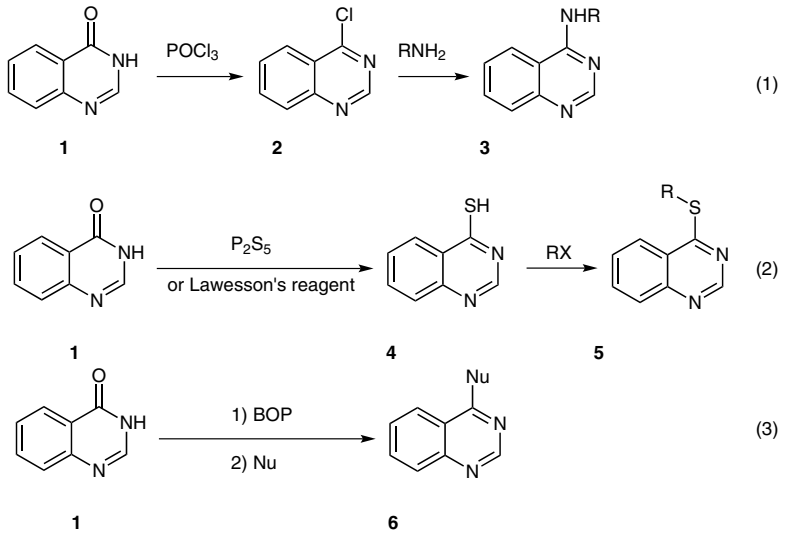
Received 3 January 2012; revised 5 February 2012

Abstract: The direct sulfanylation of 2-aryl-4-quinazolinones with thiols via C–OH bond activation under mild conditions is described. The method affords the corresponding 2-aryl-4-sulfanylquinazolines in good to excellent yield.

Key words: nitrogen heterocycles, multicomponent reactions, sulfinylations, thiols, bond activation

The quinazoline ring is a frequently encountered moiety in organic syntheses as well as in medicinal chemistry.[1] In addition, many alkaloids containing a quinazoline skeleton in the molecule exhibit remarkable biological activities such as anticonvulsant, antibacterial, antidiabetic, and anticancer activities.[2] Among this class of molecules, 4-functionalized quinazolines,[3] especially 4-alkyl(aryl)thioquinazolines,[4] have been demonstrated to be effective fungicides, anti-inflammatory, anticancer, antimicrobial and antihypertensive agents. Besides the applications in pharmaceuticals and agrochemicals, 4-alkyl(aryl)thioquinazolines are often used as intermediates in the preparation of fused heterocyclic compounds.[5] Consequently, many methods have been developed for the synthesis of 4-functionalized quinazoline derivatives.[6]

A literature survey reveals that 4-functionalized quinazolines mainly stem from 3*H*-quinazolin-4-one (4-quinazolinone) **1**. Three protocols have been developed for the synthesis of 4-functionalized quinazolines: (1) Activation the C–OH bond (carbonyl group) by halogenation with reagents such as $SOCl_2$, $POCl_3$, and PCl_5, and then animation of the 4-haloquinazoline **2**, affording the corresponding 4-functionalized quinazolines **3** (Scheme 1, equation 1).[3a–j,4a,6b] (2) Thionation of quinazolinones **1** with Lawesson's reagent or P_2S_5 in pyridine to give quinazolinethiones **4**, and then alkylation of **4** with haloalkylanes in the presence of sodium hydroxide to generate the corresponding 4-alkylthioquinazolines **5** (Scheme 1, equation 2).[4b,c,5b] (3) Activation of the C–OH group with phosphonium reagents such as benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate (BOP), and then nucleophilic substitution with nucleophiles or coupling with boronic acids to form 4-functionalized quinazolines **6** (Scheme 1, equation 3).[7]



Scheme 1

SYNTHESIS 2012, 44, 1237–1246
Advanced online publication: 01.03.2012
DOI: 10.1055/s-0031-1289731; Art ID: H00312SS

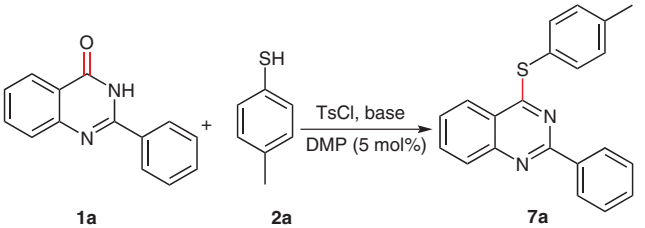
Nevertheless, some drawbacks associated with these methodologies, namely, harsh reaction conditions (such as relatively high reaction temperature, use of toxic reagents, or expensive phosphonium reagents, and low yield), multiple synthetic steps and complex workup procedures have not been overcome until now. Furthermore, most reported 4-substituted quinazolines are alkyl(aryl)amino, alkyl(aryl)oxy and alkylthio substituted quinazolines, and only relatively unusual methods have been reported for the preparation of 4-arylsulfanyl quinazolines.[4a,8] Therefore, the development of novel and efficient routes for rapid access to functionalized 4-aryl(alkyl)sulfanyl quinazolines under mild conditions is of high demand, due to their wide range of biological properties and importance in pharmaceutical science.

In a continuation of our interest in sulfanylation of heterocyclic ring molecules,[9,10] we envisioned that 4-quinazolinones might also be suitable starting materials for the synthesis of 4-sulfanylquinazolines in the presence of *p*-toluenesulfonyl chloride as C–OH bond activator, despite the fact that some literature reports have revealed that the activation of the C–OH of amides is difficult.[7] To verify the practicality of this projected route, we started to investigate the feasibility of this transformation.

Initially, a set of experiments was carried out using 2-phenyl-4-quinazolinone (**1a**) and 4-methylbenzenethiol (**2a**) as model substrates. At the outset, *p*-toluenesulfonyl chloride (*p*-TsCl, 1.5 equiv) was utilized as an activator and a catalytic amount (5 mol%) of 4-*N*,*N*-dimethylpyridine (DMP) was employed as an additive (Table 1). The reaction was performed in different solvents with potassium carbonate (3 equiv) as the base at ambient temperature. When the reaction was performed in water and PEG400, no product was detected (Table 1, entries 1 and 2). Fortunately, in a mixture of tetrahydrofuran and water (1:1), the desired product 2-phenyl-4-*p*-tolylsulfanyl-quinazolinone (**7a**) was isolated in 20% yield (Table 1, entry 3). When the reaction was conducted in acetonitrile, the yield was increased to 65% (Table 1, entry 4). Further screening demonstrated that dichloromethane was the best choice of solvent (Table 1, entry 5; 72% yield). Subsequently, the effect of bases was tested. Moderate to good yields were observed when K_3PO_4 or NaOH was used as the base (Table 1, entries 6 and 7). No product was detected when pyridine or imidazole was employed (Table 1, entries 8 and 9). Finally, we found that the reaction worked efficiently in the presence of triethylamine, with 81% isolated yield (Table 1, entry 10). Control experiments showed that no reaction occurred without the addition of DMP (Table 1, entry 11), *p*-toluenesulfonyl chloride (Table 1, entry 12), or base (Table 1, entry 13). It is also noteworthy that this reaction could be carried out under an air atmosphere without loss of yield.

The generality and scope of this reaction were then investigated under the optimized conditions [*p*-TsCl (1.5 equiv), Et_3N (3.0 equiv), DMP (5 mol%), CH_2Cl_2, r.t.]; the results are summarized in Table 2. For most cases, the corresponding products were obtained in good to excellent yields when 2-aryl-4-quinazolinones were used as substrates. For the reactions of 2-phenyl-4-quinazolinone, benzenethiols with electron-withdrawing groups or electron-donating groups on the aromatic backbone were all good partners under the optimum conditions, which afforded the desired product **7a**–**e** in excellent yields (Table 2, entries 1–5). Similarly, aliphatic thiols such as benzyl thiol and *n*-propyl thiol, also worked well, with good yields being obtained in the reactions (Table 2, entries 6 and 7). Other aryl groups on the 2-position of 4-quinazolinone were also examined, and it was found that all reactions proceeded smoothly to generate the corresponding products **7h**–**s** in good to excellent yields (Table 2, entries 8–19). Subsequent investigations indicated that the group on the 2-position of 4-quinazolinone was crucial in the reactions. Neither the corresponding intermediate (4-*p*-toluenesulfonyl-2-alkylquinazoline) nor the desired product was detected when 4-quinazolinone **1f** was treated with *p*-TsCl under the optimized conditions (Table 2, entry 20). Reaction of 2-alkyl-4-quinazolinones **1g** or **1h** also failed (Table 2, entry 21), probably because the corresponding 4-tosylate intermediates failed to form (indicated by TLC). More reactive sulfonating agents

Table 1 Optimization of the Direct Sulfanylation of 4-Quinazolinone **1a**



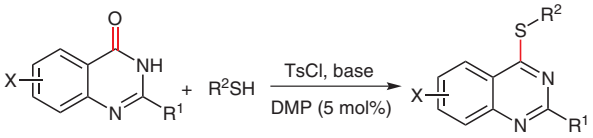
1a **2a** **7a**

Entry	Solvent	Base	Yield (%)[a]
1	H_2O	K_2CO_3	–
2	PEG400	K_2CO_3	–
3	H_2O–THF (1:1)	K_2CO_3	20
4	MeCN	K_2CO_3	65
5	CH_2Cl_2	K_2CO_3	72
6	CH_2Cl_2	K_3PO_4	69
7	CH_2Cl_2	NaOH	59
8	CH_2Cl_2	pyridine	–
9	CH_2Cl_2	imidazole	–
10	CH_2Cl_2	Et_3N	81
11[b]	CH_2Cl_2	Et_3N	–
12[c]	CH_2Cl_2	Et_3N	–
13	CH_2CH_2	–	–

[a] Isolated yield based on 4-quinazolinone (**1a**).
[b] Without the addition of DMP.
[c] Without the addition of *p*-toluenesulfonyl chloride.

such as MsCl and Tf_2O were tested in the reaction of **1f**, however, the corresponding product was not detected by TLC. Reaction of fluoro-substituted 2-phenyl-4-quinazolinone **1i** with 4-methylbenzenethiol was explored subsequently, which gave rise to the desired product **7t** in 82% yield (Table 2, entry 22).

Table 2 Direct Sulfanylation of 4-Quinazolinone via C–OH Bond Activation



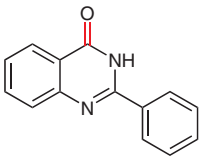
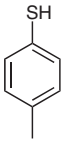
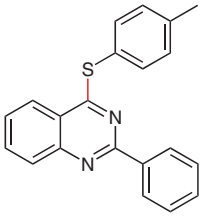
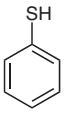
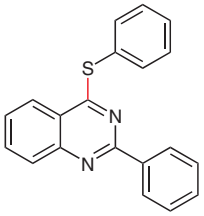
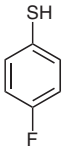
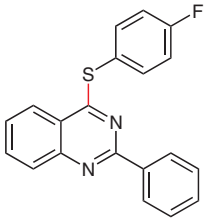
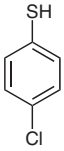
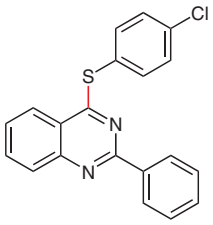
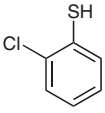
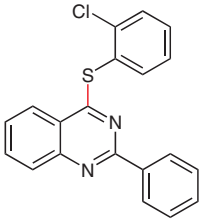
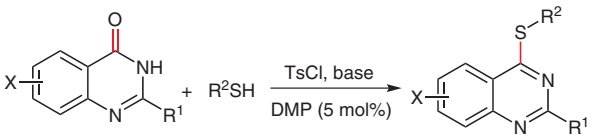
Entry	Substrate	Thiol	Base	Yield (%)[a]
1	 **1a**		 **7a**	81
2	**1a**		 **7b**	83
3	**1a**		 **7c**	87
4	**1a**		 **7d**	85
5	**1a**		 **7e**	81

Table 2 Direct Sulfanylation of 4-Quinazolinone via C–OH Bond Activation (continued)



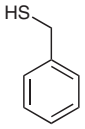
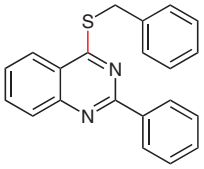
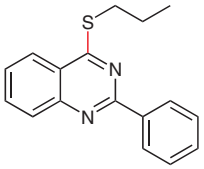
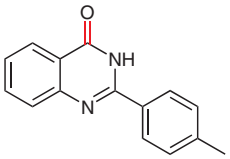
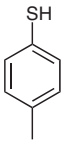
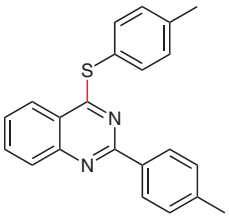
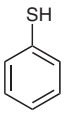
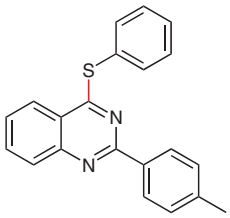
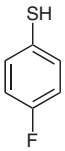
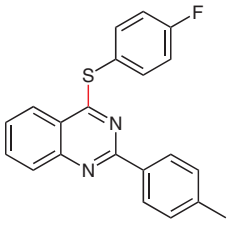
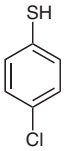
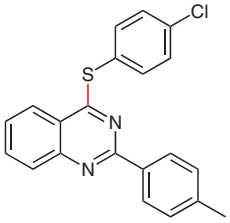
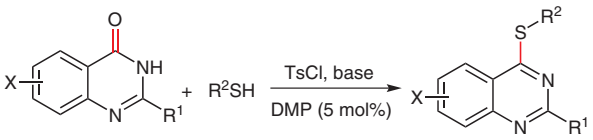
Entry	Substrate	Thiol	Base	Yield (%)[a]
6	**1a**		 **7f**	80
7	**1a**		 **7g**	71
8	 **1b**		 **7h**	79
9	**1b**		 **7i**	81
10	**1b**		 **7j**	85
11	**1b**		 **7k**	80

Table 2 Direct Sulfanylation of 4-Quinazolinone via C–OH Bond Activation (continued)



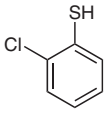
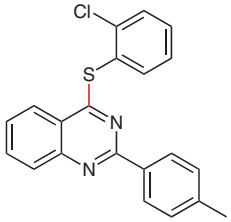
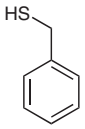
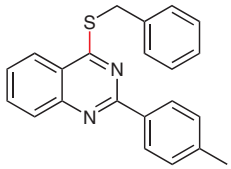
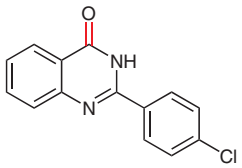
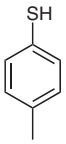
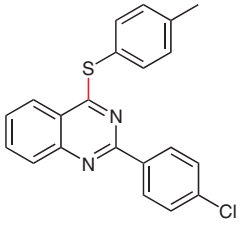
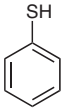
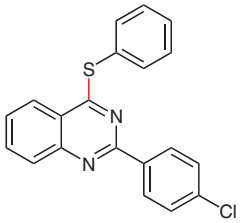
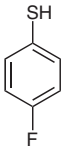
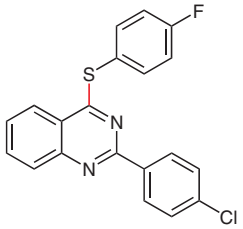
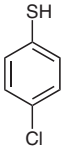
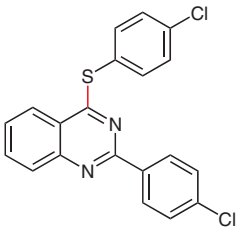
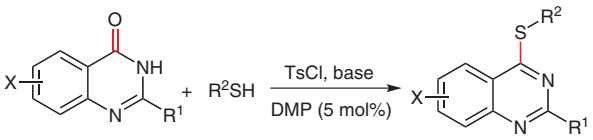
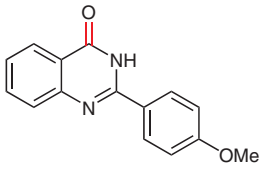
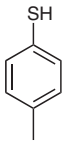
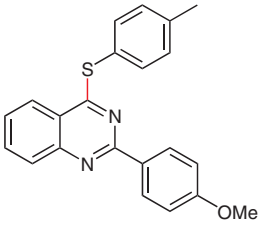
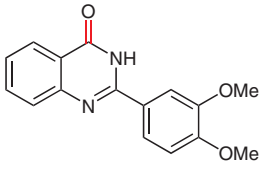
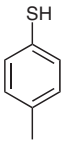
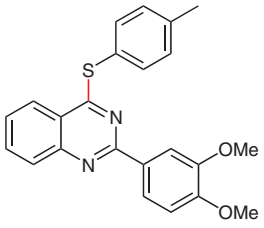
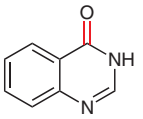
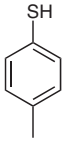
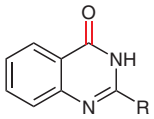
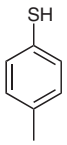
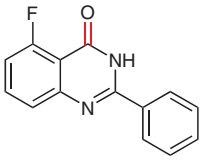
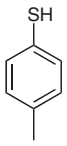
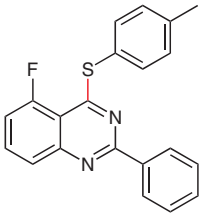
Entry	Substrate	Thiol	Base	Yield (%)[a]
12	**1b**		 **7l**	77
13	**1b**		 **7m**	77
14	 **1c**		 **7n**	79
15	**1c**		 **7o**	72
16	**1c**		 **7p**	85
17	**1c**		 **7q**	88

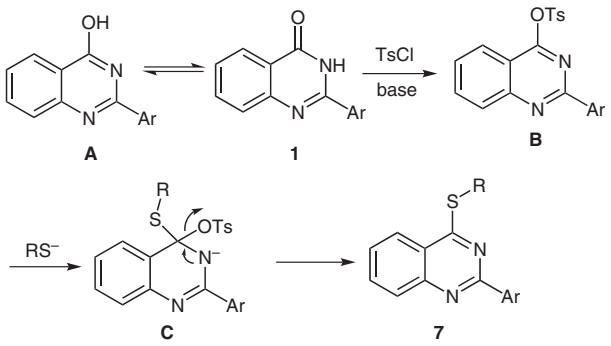
Table 2 Direct Sulfanylation of 4-Quinazolinone via C–OH Bond Activation (continued)



Entry	Substrate	Thiol	Base	Yield (%)[a]
18	 **1d**		 **7r**	78
19	 **1e**		 **7s**	71
20	 **1f**		–	0
21	 **1g**: R = *n*-Pr **1h**: R = *n*-Bu		–	0
22	 **1i**		 **7t**	82

[a] Isolated yield based on 4-quinazolinone.

A possible mechanism is proposed in Scheme 2. 4-Quinazolin-4-ol **A** would isomerize to quinazolinone **1**. Treatment of quinazolinone with *p*-TsCl in the presence of base would lead to the formation of tosylate **B**. Nucleophilic addition of thiols and subsequent elimination would generate the desired 4-arylsulfanylquinazoline **7**. The aromatic ring in the 2-position allows better π-electron delocalization, which may stabilized the tautomeric lactim form, and also enhance the nucleophilicity of the OH group. Thus, the tosylate, a key intermediate, can be readily formed when the 2-position is substituted with an aromatic group.



Scheme 2

In conclusion, we have described a facile and efficient route for the synthesis of 4-sulfanylquinazoline via direct sulfanylation of 4-quinazolinone with thiols under mild conditions. The highly effective transformation is performed at room temperature under an air atmosphere. The efficiency of this method combined with its operational simplicity makes it attractive for further library construction.

All reactions were performed in round-bottom flasks at r.t. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical TLC was performed using glass plates pre-coated with 0.25 mm, 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Solvents were re-distilled prior to use in the reactions. Other commercial reagents were used as received. NMR samples were run in $CDCl_3$ and ^1H NMR was referenced to TMS; ^{13}C NMR was referenced to $CDCl_3$. All chemical shift values are quoted in ppm and coupling constants are quoted in Hz.

Quinazolines 7; General Procedure

Quinazolinone (0.1 mmol), Et_3N (0.3 mmol), and DMP (0.005 mmol) in CH_2Cl_2 (2.0 mL) were added to a round-bottom flask. After 2 min stirring, TsCl (0.15 mmol) was added, then, after 30 min, the thiol (0.12 mmol) was added. The mixture was allowed to stir at r.t. for 5 h. After completion of the reaction, the mixture was removed under reduced pressure. The residue was purified by passing through a column of silica gel (petroleum ether–EtOAc, 100:1) to give the desired compound **7**.

2-Phenyl-4-*p*-tolylsulfanylquinazoline (7a)

Yield: 26.6 mg (81%); white solid; mp 116–117 °C.

IR (KBr): 1952, 1899, 1822, 1639, 1612, 1558, 1539, 1482, 1454, 1442, 1375, 1336, 984, 762, 701, 687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 7.34–7.40 (m, 5 H), 7.55–7.60 (m, 3 H), 7.83–7.87 (m, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 8.18–8.20 (m, 1 H), 8.20–8.26 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 121.9, 123.7, 124.0, 126.8, 128.3, 128.4, 129.0, 129.9, 130.4, 133.7, 136.0, 137.8, 139.7, 149.3, 158.9, 171.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{17}N_2S$: 329.1112; found: 329.1115.

2-Phenyl-4-phenylsulfanylquinazoline (7b)

Yield: 26.1 mg (83%); white solid; mp 120–121 °C.

IR (KBr): 1639, 1616, 1558, 1537, 1483, 1341, 1309, 1080, 986, 699, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.39 (m, 3 H), 7.53–7.56 (m, 3 H), 7.60 (s, 1 H), 7.70–7.72 (m, 2 H), 7.83–7.87 (m, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.18–8.23 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.9, 123.7, 126.8, 127.6, 128.3, 128.4, 129.1, 129.2, 129.5, 130.4, 133.7, 136.2, 137.7, 149.4, 158.9, 171.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{15}N_2S$: 315.0956; found: 315.0952.

4-(4-Fluorophenylsulfanyl)-2-phenylquinazoline (7c)

Yield: 28.9 mg (87%); white solid; mp 148–149 °C.

IR (KBr): 3056, 1886, 181, 1614, 1590, 1577, 1538, 1493, 1484, 1340, 1309, 1160, 823, 697, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.26 (m, 2 H), 7.38–7.40 (m, 3 H), 7.6 (d, *J* = 8.4 Hz, 1 H), 7.66–7.69 (m, 2 H), 7.85–7.87 (m, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 8.21–8.23 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.3 (d, *J* = 22 Hz), 121.8, 122.8, 123.6, 126.9, 128.3, 129.1, 130.5, 133.8, 137.6, 138.3, 149.4, 158.9, 162.5 (d, *J* = 249 Hz), 170.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{14}N_2SF$: 333.0862; found: 333.0855.

4-(4-Chlorophenylsulfanyl)-2-phenylquinazoline (7d)

Yield: 29.7 mg (85%); white solid; mp 161–162 °C.

IR (Br): 3090, 1891, 1815, 1640, 1613, 1556, 1540, 1482, 1445, 1338, 1310, 1141, 1088, 987, 756, 705, 658 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.42 (m, 3 H), 7.50–7.52 (m, 2 H), 7.55 (m, 3 H), 7.84–7.88 (m, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 8.14 (d, *J* = 8.4 Hz, 1 H), 8.22–8.24 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.8, 123.6, 126.2, 128.4, 129.1, 129.3, 133.9, 135.9, 137.4, 137.5, 149.4, 158.9, 170.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{14}ClN_2S$: 349.0566; found: 349.0574.

4-(2-Chlorophenylsulfanyl)-2-phenylquinazoline (7e)

Yield: 28.3 mg (81%); white solid; mp 124–125 °C.

IR (KBr): 3057, 1641, 1559, 1538, 1484, 1339, 1309, 1143, 755, 700, 659 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.41 (m, 4 H), 7.51 (d, *J* = 1.6 Hz, 1 H), 7.59 (s, 1 H), 7.65 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.77 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.86 (s, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 8.16–8.21 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.9, 123.7, 127.4, 128.3, 128.4, 129.1, 129.6, 130.2, 131.2, 133.8, 137.6, 138.4, 140.3, 149.5, 158.9, 169.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{14}ClN_2S$: 349.0566; found: 349.0574.

4-Benzylsulfanyl-2-phenylquinazoline (7f)

Yield: 26.3 mg (80%); light-yellow solid; mp 148–149 °C.

IR (film): 3054, 2987, 2305, 1537, 1483, 1421, 1265, 1028, 738, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.78 (s, 2 H), 7.26–7.33 (m, 3 H), 7.46–7.52 (m, 6 H), 7.77–7.82 (m, 1 H), 7.99–8.62 (m, 2 H), 8.62–8.64 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8, 122.3, 123.8, 126.7, 127.5, 128.5, 128.7, 129.0, 130.6, 133.7, 137.2, 138.0, 149.0, 158.8, 170.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{17}N_2S$: 329.112; found: 329.1111.

4-Butylsulfanyl-2-phenylquinazoline (7g)

Yield: 19.9 mg (71%); light-yellow liquid.

IR (film): 3054, 2987, 2305, 1614, 1560, 1536, 1484, 1265, 740, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.6 Hz, 3 H), 1.85–1.90 (m, 2 H), 3.42 (t, *J* = 7.2 Hz, 2 H), 7.40–7.51 (m, 4 H), 7.71–7.75 (m, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.60 (dd, *J* = 1.6, 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.6, 31.6, 122.7, 123.8, 126.5, 128.5, 129.0, 130.5, 133.5, 138.2, 148.9, 158.8, 171.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2S$: 281.1112; found: 281.1115.

2-*p*-Tolyl-4-*p*-tolylsulfanylquinazoline (7h)
Yield: 27.1 mg (79%); white solid; mp 173–174 °C.

IR (film): 3057, 2921, 1906, 1642, 1608, 1559, 1537, 1484, 1450, 1376, 1334, 1308, 988, 759, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.48 (s, 3 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.51–7.55 (m, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.80–7.84 (m, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.12 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 121.9, 123.7, 124.2, 126.5, 128.4, 128.9, 129.1, 129.9, 133.6, 135.1, 136.0, 139.6, 140.6, 149.4, 159.0, 171.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2S$: 343.1269; found: 343.1271.

4-Phenylsulfanyl-2-*p*-tolylquinazoline (7i)
Yield: 26.6 mg (81%); white solid; mp 147–148 °C.

IR (Br): 3060, 2918, 1609, 1559, 1539, 1485, 1450, 1337, 1308, 1177, 756, 687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.51–7.57 (m, 4 H), 7.69–7.71 (m, 2 H), 7.81–7.85 (m, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 8.16–8.18 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 121.8, 123.7, 126.5, 127.7, 128.4, 129.0, 129.1, 129.4, 133.7, 135.0, 136.2, 140.6, 149.5, 159.0, 170.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{17}N_2S$: 329.1112; found: 329.1115.

4-(4-Fluorophenylsulfanyl)-2-*p*-tolylquinazoline (7j)
Yield: 29.5 mg (85%); white solid; mp 196–197 °C.

IR (KBr): 3053, 2917, 2855, 1887, 1818, 1631, 1591, 1451, 1380, 732, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 7.17–7.24 (m, 4 H), 7.54 (d, *J* = 7.2 Hz, 1 H), 7.65 (dd, *J* = 6.4, 7.2 Hz, 2 H), 7.82 (d, *J* = 7.2 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.09–8.13 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 116.2 (d, *J* = 22 Hz), 121.7, 122.9, 123.6, 126.7, 128.4, 129.0, 129.1, 133.8, 134.4, 138.3, 140.8, 149.4, 159.0, 162.5 (d, *J* = 248 Hz), 170.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}FN_2S$: 347.1018; found: 347.1012.

4-(4-Chlorophenylsulfanyl)-2-*p*-tolylquinazoline (7k)
Yield: 29.0 mg (80%); white solid; mp 206–208 °C.

IR (KBr): 3050, 2917, 1898, 1818, 1607, 1576, 1557, 1542, 1478, 1451, 1377, 1324, 1094, 818, 732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.48–7.56 (m, 3 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.83 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.10–8.12 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 121.7, 123.5, 126.3, 126.9, 128.4, 129.0, 129.2, 129.9, 133.8, 134.8, 135.9, 137.4, 140.8, 149.5, 159.0, 170.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}ClN_2S$: 363.0723; found: 363.0732.

4-(2-Chlorophenylsulfanyl)-2-*p*-tolylquinazoline (7l)
Yield: 27.9 mg (77%); white solid; mp 159–161 °C.

IR (KBr): 3057, 2917, 1925, 1810, 1608, 1558, 1541, 1482, 1456, 1379, 1335, 987, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.39–7.41 (m, 1 H), 7.50 (d, *J* = 1.6 Hz, 1 H), 7.56–7.58 (m, 1 H), 7.65 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.77 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.84 (d, *J* = 1.2 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 121.9, 123.7, 126.5, 127.5, 128.4, 129.0, 129.9, 130.9, 133.7, 134.9, 138.5, 140.3, 140.7, 149.6, 159.0, 169.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}ClN_2S$: 363.0723; found: 363.0724.

4-Benzylsulfanyl-2-*p*-tolylquinazoline (7m)
Yield: 26.4 mg (77%); white solid; mp 136–137 °C.

IR (KBr): 1815, 1608, 1539, 1450, 1376, 1316, 1249, 1000, 868, 760, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 4.78 (s, 2 H), 7.26–7.34 (m, 5 H), 7.47–7.51 (m, 3 H), 7.79 (s 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 8.51 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 33.8, 122.2, 123.7, 126.4, 127.4, 128.5, 128.7, 128.9, 129.2, 129.3, 133.6, 135.7, 137.3, 140.8, 149.1, 158.9, 170.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2S$: 343.1269; found: 343.1274.

2-(4-Chlorophenyl)-4-*p*-tolylsulfanylquinazoline (7n)
Yield: 28.7 mg (79%); white solid; mp 136–137 °C.

IR (KBr): 3032, 2921, 1957, 1919, 1893, 1816, 1784, 1614, 1593, 1577, 1493, 1451, 1376, 1335, 1252, 1088, 998, 756, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 7.31–7.35 (m, 4 H), 7.54–7.58 (m, 3 H), 7.85 (t, *J* = 8.4 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 8.15–8.19 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 121.9, 123.7, 123.9, 127.2, 128.5, 128.6, 129.0, 129.7, 129.9, 133.8, 136.1, 136.3, 136.6, 139.8, 149.2, 158.0, 171.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}ClN_2S$: 363.0723; found: 363.0725.

2-(4-Chlorophenyl)-4-phenylsulfanylquinazoline (7o)
Yield: 25.1 mg (72%); white solid; mp 214–215 °C.

IR (KBr): 3048, 1921, 1816, 1614, 1592, 1560, 1482, 1450, 1382, 1335, 1089, 843, 756, 693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.8 Hz, 2 H), 7.53–7.59 (m, 4 H), 7.68–7.70 (m, 2 H), 7.86 (d, *J* = 1.2 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.15–8.19 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.9, 123.7, 127.0, 127.5, 128.5, 129.0, 129.2, 129.6, 129.7, 133.9, 136.2, 136.3, 136.6, 140.3, 157.9, 171.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{14}ClN_2S$: 349.0566; found: 349.0574.

2-(4-Chlorophenyl)-4-(4-fluorophenylsulfanyl)quinazoline (7p)
Yield: 31.2 mg (85%); white solid; mp 247–248 °C.

IR (KBr): 3056, 2924, 1960, 1922, 1885, 1615, 1592, 1558, 1489, 1451, 1334, 1232, 1089, 1012, 842, 756, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.26 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.60–7.68 (m, 3 H), 7.87 (t, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 8.14–8.18 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.5 (d, *J* = 24 Hz), 121.8, 123.6, 127.1, 128.5, 128.7, 129.0, 129.7, 134.1, 136.0, 136.8, 138.3, 138.4, 149.2, 157.9, 162.9 (d, *J* = 248 Hz), 171.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{13}ClFN_2S$: 367.0472; found: 367.0474.

2-(4-Chlorophenyl)-4-(4-chlorophenylsulfanyl)quinazoline (7q)
Yield: 33.8 mg (88%); white solid; mp 230–231 °C.

IR (film): 3053, 2924, 2854, 1921, 1854, 1614, 1576, 1451, 1378, 756, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.60–7.63 (m, 3 H), 7.87 (t, *J* = 8.4 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.14 (d, *J* = 8.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.8, 123.6, 126.0, 128.5, 128.7, 129.1, 129.3, 129.7, 134.1, 136.1, 136.8, 137.3, 137.4, 149.3, 158.0, 170.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{13}Cl_2N_2S$: 383.0177; found: 383.0182.

5-Fluoro-2-phenyl-4-*p*-tolylsulfanylquinazoline (7r)
Yield: 27.9 mg (78%); light-yellow solid; mp 161–162 °C.

IR (KBr): 3067, 2921, 1899, 1768, 1625, 1557, 1475, 1450, 1363, 1350, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 7.22–7.25 (m, 1 H), 7.31–7.39 (m, 5 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 5.6 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 8.10–8.13 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 111.8, 112.6 (d, *J* = 15 Hz), 124.7 (d, *J* = 10 Hz), 125.0, 128.2 (d, *J* = 21 Hz), 128.6, 129.3 (d, *J* = 14 Hz), 130.6, 133.1, 136.1 (d, *J* = 13 Hz), 137.2, 139.8, 151.6, 157.3 (d, *J* = 257 Hz), 159.0, 170.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}FN_2S$: 347.1018; found: 347.1024.

2-(4-Methoxyphenyl)-4-phenylsulfanylquinazoline (7s)
Yield: 27.6 mg (71%); white solid; mp 122–123 °C.

IR (KBr): 2960, 2035, 1903, 1607, 1556, 1452, 1376, 1251, 1176, 746, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 3.84 (s, 3 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.50–7.59 (m, 3 H), 7.78–7.82 (m, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 8.14–8.19 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 55.3, 113.6, 121.6, 123.7, 124.1, 126.3, 128.7, 129.9, 130.1, 130.4, 133.6, 136.0, 139.6, 149.4, 158.9, 161.6, 171.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2OS$: 359.1218; found: 359.1224.

2-(3,4-Dimethoxyphenyl)-4-*p*-tolylsulfanylquinazoline (7t)
Yield: 28.4 mg (82%); white solid; mp 142–143 °C.

IR (film): 2998, 2837, 2031, 1899, 1600, 1519, 1378, 1234, 1175, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.77 (s, 3 H), 3.92 (s, 3 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 2 H), 7.53–7.60 (m, 3 H), 7.69 (s, 1 H), 7.80–7.89 (m, 1 H), 7.97–8.00 (m, 2 H), 8.15 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 55.5, 55.9, 110.6, 110.9, 121.5, 121.6, 123.7, 124.2, 126.4, 128.7, 129.9, 130.5, 133.7, 136.4, 148.4, 139.5, 149.3, 158.5, 161.6, 171.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_2S$: 389.1324; found: 389.1326.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (grant nos. 20962010 and 21162012), Jiangxi Provincial Department of Science and Technology (for Jiangxi's Key Laboratory of Green Chemistry), and the Science Foundation of Education Department of Jiangxi province (grant no. GJJ10386) for their financial support.

References

(1) For examples, see: (a) Deng, Y. J.; Zhou, X. L.; Desmoulin, S. K.; Wu, J. M.; Cherian, C.; Hou, Z. J.; Matherly, L. H.; Gangjee, A. *J. Med. Chem.* **2009**, *52*, 2940. (b) Kabri, Y.; Gellis, A.; Vanelle, P. *Green Chem.* **2009**, *11*, 201. (c) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659. (d) Lau, H.; Ferlan, J. T.; Brophy, V. H.; Rosowsky, A.; Sibley, C. H. *Antimicrob. Agents Chemother.* **2001**, *45*, 187. (e) Desai, P.; Naik, B.; Desai, C. M.; Patel, D. *Asian J. Chem.* **1998**, *10*, 615. (f) Dempcy, R. O.; Skibo, E. B. *Biochemistry* **1991**, *30*, 8480. (g) Calvert, A. H.; Jones, T. R.; Dady, P. J.; Grzelakowskasztabert, B.; Paine, R. M.; Taylor, G. A.; Harrap, K. R. *Eur. J. Cancer* **1980**, *16*, 713.

(2) (a) Chen, K.; Al Aowad, A. F.; Adelstein, S. J.; Kassis, A. I. *J. Med. Chem.* **2007**, *50*, 663. (b) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476. (c) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742. (d) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 697. (e) Chan, J. H.; Baccanari, D. P.; Tansik, R. L.; Boytos, C. M.; Rudolph, S. K.; Brown, A. D.; Hong, J. S.; Kuyper, L. F.; Jones, M. L. *J. Heterocycl. Chem.* **1997**, *34*, 145.

(3) For examples of 4-aminoquinazolines, see: (a) Sirisoma, N.; Pervin, A.; Zhang, H.; Jiang, S. C.; Willardsen, J. A.; Anderson, M. B.; Mather, G.; Pleiman, C. M.; Kasibhatla, S.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2009**, *52*, 2341. (b) Murai, M.; Sekiguchi, K.; Nishioka, T.; Miyoshi, H. *Biochemistry* **2009**, *48*, 688.. (c) Chappie, T. A.; Humphrey, J. M.; Allen, M. P.; Estep, K. G.; Fox, C. B.; Lebel, L. A.; Liras, S.; Marr, E. S.; Menniti, F. S.; Pandit, J.; Schmidt, C. J.; Tu, M. H.; Williams, R. D.; Yang, F. V. *J. Med. Chem.* **2007**, *50*, 182. (d) Yang, S.; Liu, G.; Song, B. A.; Jin, L. H.; Hu, D. Y.; Zhang, S. M. *Chin. J. Org. Chem.* **2006**, *26*, 1429; *Chem. Abstr.* **2007**, *147*, 301104. (e) Kanuma, K.; Omodera, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Semple, G.; Tran, T. A.; Kramer, B.; Hsu, D.; Casper, M.; Thomsen, B.; Beeley, N.; Sekiguchi, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2565. (f) Liu, G.; Song, B. A.; Sang, W. J.; Yang, S.; Jin, L. H.; Ding, X. *Chin. J. Org. Chem.* **2004**, *24*, 1296; *Chem. Abstr.* **2004**, *142*, 134667. (g) Shreder, K. R.; Wong, M. S.; Nomanbhoy, T.; Leventhal, P. S.; Fuller, S. R. *Org. Lett.* **2004**, *6*, 3715. (h) Tobe, M.; Isobe, Y.; Tomizawa, H.; Nagasaki, T.; Takahashi, H.; Fukazawa, T.; Hayashi, H. *Bioorg. Med. Chem.* **2003**, *11*, 383. (i) Rewcastle, G. W.; Denny, W. A.; Bridges, A. J.; Zhou, H. R.; Cody, D. R.; McMichael, A.; Fry, D. W. *J. Med. Chem.* **1995**, *38*, 3482. (j) Rachid, Z.; Brahimi, F.; Qiu, Q. Y.; Williams, C.; Hartaley, J. M.; Hartaley, J. A.; Jean-Claude, B. J. *J. Med. Chem.* **2007**, *50*, 2605. (k) Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koenig, J. R.; Turner, S.; Jinkerson, T.; Drizin, I.; Hannick, S. M.; Macri, B. S.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J.; Stewar, K. D.; Oie, T.; Jarvis, M. F.; Surowy, C. S.; Faltynek, C. R.; Lee, C. H. *J. Med. Chem.* **2005**, *48*, 744.

(4) For examples of 4-alkyl(aryl)thioquinazolines, see (a) Liu, G.; Liu, C. P.; Ji, C. N.; Sun, L.; Wen, Q. W. *Chin. J. Org. Chem.* **2008**, *28*, 525; *Chem. Abstr.* **2009**, *150*, 121577. (b) Ma, Y.; Liu, F.; Yan, K.; Song, B. A.; Yang, S.; Hu, D. Y.; Jin, L. H.; Xue, W. *Chin. J. Org. Chem.* **2008**, *28*, 1268; *Chem. Abstr.* **2009**, *150*, 352066. (c) Xu, G. F.; Song, B. A.; Bhadury, P. S.; Yang, S.; Zhang, P. Q.; Jin, L. H.; Xue, W.; Hu, D. Y.; Lu, P. *Bioorg. Med. Chem.* **2007**, *15*, 3768.

(5) (a) 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. *J. Med. Chem.* **1996**, *39*, 918. (b) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413.

(6) For examples, see: (a) Zhang, Y. D.; Xu, C. L.; Houghten, R. A.; Yu, Y. P. *J. Comb. Chem.* **2007**, *9*, 9. (b) Wéber, C.; Bielik, A.; Szendrei, G. I.; Greiner, I. *Tetrahedron Lett.* **2002**, *43*, 2971. (c) Nakamura, H.; Onagi, S. *Tetrahedron Lett.* **2006**, *47*, 2539. (d) Seijas, J. A.; Văsquez-Tato, M. P.; Martinez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215.

(7) (a) Wacharasindhu, S.; Bardhan, S.; Wan, Z.-K.; Tabei, K.; Mansour, T. S. *J. Am. Chem. Soc.* **2009**, *131*, 4174. (b) Kang, F.-A.; Sui, Z. H.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300. (c) Wan, Z. K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194. (d) Wan, Z. K.; Wacharasindhu, S.; Binnun, E.; Mansour, T. *Org. Lett.* **2006**, *8*, 2425.

(8) Homogeneous cross-coupling reactions based on either copper(I) or palladium have been developed for aromatic thiother syntheses, see: (a) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (b) Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 187. (c) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *12*, 2180. (d) Cai, L. S.; Cuevas, J.; Peng, Y. Y.; Pike, V. W. *Tetrahedron Lett.* **2006**, *47*, 4449.

(9) Peng, Y. Y.; Zeng, Y. Y.; Qiu, G. Y. S.; Cai, L.; Pike, V. W. *J. Heterocycl. Chem.* **2010**, *47*, 1240.

(10) Peng, Y. Y.; Wen, Y. F.; Mao, X. C.; Qiu, G. Y. S. *Tetrahedron Lett.* **2009**, *50*, 2405.

