镍催化的 8-氨基喹啉 C—H 键卤化反应合成 C(5)和 C(7)双卤代喹啉

郝文燕* 王昱赟 杨国敏 刘云云*

(江西师范大学化学化工学院 南昌 330022)

摘要 以廉价、低毒、易得的溴化镍做催化剂,实现了 8-氨基喹啉环上的氧化 C—H 键卤化反应.该方法利用氧气作为氧化剂,避免使用化学当量的高价碘盐等作为氧化剂,使得本反应更具经济性和环境友好性.在该催化体系下反应底物显示出良好的官能团兼容性和反应性,并以高的区域选择性高产率地制备了 C(5)和 C(7)双卤代喹啉.

关键词 镍催化; C—H 键卤化; *N*-溴代丁二酰亚胺; 8-氨基喹啉; 双卤代喹啉

Nickel-Catalyzed C—H Halogenation of 8-Aminoquinolines for the Synthesis of C(5) and C(7) Di-halogenated Quinolines

Hao, Wenyan* Wang, Yuyun Yang, Guomin Liu, Yunyun*

(College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang 330022)

Abstract A simple and efficient nickel-catalyzed oxidative halogenation (Cl, Br) of C(5) and C(7) C—H bond of 8-aminoquinoline amides has been developed. This method employed low-cost and easy availability nickel as catalyst and oxygen as oxidant. The reactions have good functional groups compatibility, giving highly selective C(5) and C(7) di-halogenated products in good to excellent yields.

Keywords Nickel-catalyze; C—H halogenation; *N*-bromo-succinimide; 8-aminoquinolines; dihalogenated quinoline

It is well documented that quinolines are very important *N*-heterocyclic compounds which are frequently found in biologically active natural products and pharmaceuticals.^[1] Among the numerous quinoline derivatives, the halogenated quinolines are a class of important one which often act as intermediates in the synthesis of substituted quinolines.^[2] Moreover, many halogenated quinolines such as clioquinol and chloroquine are frequently used as antibiotic and antimalaria agents in clinical application (Figure 1).^[3] Therefore, further development of more simple method for the synthesis of halogenated quinolines remains highly appealing.

Although many methods have been reported for the synthesis of halogenated quinolines, they are often confined to the functionalization of quinoline scaffolds mainly at the C(2), C(3), C(4), and C(8) positions.^[4,5] Reports involving halogenation of quinolines at the C(5) and C(7) position are quite rare.^[6] Recently, following the developments of transition metal catalyzed C—H activation strategies, some examples on C(5) functionalized quinolines have been achieved.^[7] However, to the best of our

Figure 1 Representative drugs containing the halogenated quinolines

knowledge, only two published examples on the simultaneous C(5) and C(7)-dihalogenation of quinoline are known. In 2015, Xie and coworkers^[6a] have developed an efficient method of Pd-catalyzed synthesis of 5,7-dichlorinated quinolines utilizing quinoline C—H haogenation. More recently, Zhang *et al.*^[6b] have developed an alternative version of such type to access 5,7-dibrominated quinolines by means of copper catalysis (Scheme 1). While drawbacks such as narrow substrate scope, noble metal catalyst, employment of stoichiometric oxidant *etc.* remain with the known synthetic methods, developing complementary catalytic method to run this di-halogenation pro-

* Corresponding author. E-mail: wenyanhao@jxnu.edu.cn; chemliuyunyun@jxnu.edu.cn

Received April 28, 2017; revised June 23, 2017; published online July 4, 2017.

Project supported by the National Natural Science Foundation of China (Nos. 21562024, 21762023) and the Scientific Research Fund of Jiangxi Provincial Education Department (No. GJJ160285).

国家自然科学基金(Nos. 21562024, 21762023)及江西省教育厅(No. GJJ160285)资助项目.

cess is still highly desirable.

Scheme 1 Recent methods for the synthesis of C(5) and C(7) di-halogenated quinolones

As a class of important first-row transition metal catalyst, nickel salts were frequently and widely employed in organic synthesis to construct various bioactive compounds due to its particular electronic properties, low cost and low toxicity. Indeed, nickel catalysts have been applied in many types of catalytic transformations such as coupling reactions,^[8] carbonylation reactions^[9] and heterocycle synthesis.^[10] However, there have been few reports of C—H bond halogenation utilizing a nickel catalyst.^[11] As our continuous interests in the development of nickel catalyzed synthesis and 8-aminoquinoline assisted C—H functionalization for the synthesis biologically relevant small molecules,^[12] we report herein a C—H halogenation reaction of 8-aminoquinolines that gave the 5,7-dihalo-generated products with cheap and easily available NiBr₂ catalyst.

1 Results and discussion

We began our studies by using amide (**1a**) and *N*-bromo-succinimide as the model substrates to optimize the reaction conditions, and the results are summarized in Table 1. When the reaction was carried out in the presence of NiCl₂ (20 mol%) in MeCN at 120 °C under O₂ overnight, the di-brominated amide (**3a**) was successfully isolated in 55%

yield (Table 1, Entry 1). The structure of **3a** was further confirmed by X-ray diffraction analysis (see the Supporting Information).

Table 1 Screening of reaction conditions for dibromination of quinolines^a

Entry	Catalyst	Oxidant	Base	Solvent	Yield/% of 3a/2a
1	NiCl ₂	O ₂	—	MeCN	55/30
2	NiBr ₂	O ₂	—	MeCN	87/—
3	Ni(acac) ₂	O ₂	—	MeCN	60/20
4	Ni(NO ₃) ₂	O ₂	—	MeCN	57/33
5	—	O ₂	—	MeCN	—/85
6	NiBr ₂	BQ	—	MeCN	55/27
7	NiBr ₂	TBHP	—	MeCN	65/25
8	NiBr ₂	Ag ₂ O	—	MeCN	60/30
9	NiBr ₂	O ₂	Cs ₂ CO ₃	MeCN	30/54
10	NiBr ₂	O ₂	Na ₂ CO ₃	MeCN	28/60
11	NiBr ₂	O ₂	NaHCO ₃	MeCN	33/59
12	NiBr ₂	O ₂	—	Toluene	55/35
13	NiBr ₂	O ₂	—	PET	—/25
14	NiBr ₂	O ₂	—	DCM	—/82
15	NiBr ₂	O ₂	—	DCE	15/45
16 ^b	NiBr ₂	O ₂	—	MeCN	84/15
17 ^c	NiBr ₂	O ₂	—	MeCN	87/12
18 ^d	NiBr ₂	O ₂	—	MeCN	85/14

^a Reaction conditions: **1a** (0.25 mmol), NiBr₂ (20 mol%), NBS (2.0 equiv.), MeCN (2.0 mL), stirred at 120 °C, under O₂ overnight, isolated yields. ^b The reaction temperature is 100 °C. ^c The reaction temperature is 110 °C. ^d The reaction temperature is 130 °C.

Next, different nickel catalysts in the reaction were then screened and NiBr₂ was found to be the best choice which provides the di-brominated product in 87% yield (Table 1, Entries 2~4). Meanwhile, a blank experiment indicated that the nickel catalyst was the key factor, because the desired product **3a** was not obtained in the absence of nickel catalyst (Table 1, Entry 5). Furthermore, screening of different oxidants proved the O₂ was the best choice, providing the desired product in 87% yield, and the other oxidants such as 1,4-benzoquinone (BQ), *tert*-butyl hydroperoxide (TBHP), Ag₂O gave lower yields (Table 1, Entries 6~8). Different bases such as Cs₂CO₃, K₂CO₃, K₃PO₄ were screened subsequently. The results indicated that they were substantially less effective (Table 1, Entries 9~11). In order to insight into the effect of solvent on the reaction, a variety of solvents such as *N,N*-dimethylformamide

(DMF), dimethyl sulfoxide (DMSO), and tetrahydrofuran (THF) were also examined. The experiment results revealed that attempts to exchange the solvent failed to improve product yield (Table 1, Entries 12~15). Finally, different temperatures on the reaction were investigated. Either higher or lower temperature from 100 °C to 130 °C can improve the yield (Table 1, Entries 2 and 16~18). Therefore, the optimized condition was to use a combination of NiBr₂ (20 mol%) as catalyst and O₂ as oxidant in MeCN at 120 °C (Table 1, Entry 2).

With this optimum condition in hand, we proceeded to investigate the reaction of NBS with different 8-amidoquinoline derivatives. Generally, the dibromination showed excellent functional group tolerance toward diversely substituted 8-amidoquinolines (Table 2). Both electron-withdrawing and electron-donating aromatic substitutions of carboxamides were turned into the corresponding halogenation products in good yields (**3b**~**3k**). From the results, it can be concluded that the reactants with electron-donating substituents afforded the desired products in higher yields compare to those with electron-withdrawing groups (**3d** 90% yield and **3k** 91% yield). In addition, naphthalene substituent was also a suitable substrate for this reaction, affording the product **3l** in 82% yield. Moreover, the reaction of NBS with thiophene-fused carbox-

amides also took place efficiently, providing *N*-(5,7-dibromoquinolin-8-yl)-thiophene-2-carboxamide (**3m**) in 77% yield. The carboxamides with alkyl substitutions were also went smoothly in high yields. For instance, *N*-(quinolin-8-yl)acetamide and *N*-(quinolin-8-yl)cyclohexanecarboxamide could act as good reaction substrates under the optimized conditions. The desired products **3n** and **3o** were obtained in yields of 80% and 81%, respectively. In the further study, it is found that chlorination could be occurred as well as bromination at the C(5) and C(7) position of quinolines, and deliver the desire dichlorination products **3p** and **3q** in good yield. On the other hand, substitution at the quinoline moiety was also explored. The electron-donating methyl-substituents (**1r**) and electron-withdrawing fluorine-substituents (**1s**) delivered the desired products **3r** and **3s** in moderate yields.

Next, we also explored the iodination under the standard condition. To our surprise, we only got the mono-iodination product at the C(5) position of quinoline (Scheme 3).

In order to insight into the reaction mechanism more clearly, a series of control experiments were carried out. The reaction was suppressed completely by using the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) probably suggesting that the reaction may follow a

Table 2 Substrate scope of the dibromination and dichlorination reaction^a

^a Reaction conditions: **1a** (0.25 mmol), NiBr₂ (20 mol%), NXS (2.0 equiv.), MeCN (2.0 mL), stirred at 120 °C, under O₂, overnight, isolated yields.

Scheme 3 Iodination reaction under the standard condition

radical pathway. Further experiments about reaction atmosphere replaced with nitrogen gas were also carried out, the yields of products is 40%. This phenomenon indicates that NBS has a dual role in the bromination, not only producing the bromine radical also oxidizing the intermediate instead of O_2 in the process of bromination. Only mono-bromination product at the C(5) position of quinoline was obtained in the absence of nickel catalyst and mono-bromination product at the C(5) position of quinoline could not further turn into the C(5) and C(7) di-bromination quinoline without nickel as the catalyst. These two phenomena show that the nickel is the key in formation the bromination product at the C(7) position of quinoline. Treating **2a** with NBS under the standard condition gave **3a** in a yield of 85%, indicating that **2a** is most likely an intermediate for the formation of **3a** from **1a**. The reaction was also completely suppressed by treating **2a** with NBS and $NiBr_2$ in the presence of 2 equiv. of TEMPO, indicating that the C(7) halogenation of **2a** may mainly proceed via a radical pathway.

On the basis of the above results and previous reports,^[13] a plausible mechanism for the formation of **3a** is proposed in Scheme 4. First, a radical $Br\cdot$ was generated from NBS under the high temperature, which then reacted with 8-aminoquinoline amides (**1a**) to generate the intermediate **A**. Subsequently, intermediate **A** transferred to a radical intermediate **B** through electron delocalization. Then, Intermediate **B** was trapped by $Br\cdot$ in the system to form the intermediate **C**, which underwent isomerization to give the C(5) halogenation product **2a**. Second, **2a** coordinates with $NiBr_2$ to give intermediate **D**. Then intermediate **D** was attacked by $Br\cdot$ and the intermediate turned into complex **E** through a single electron transfer process (SET). Soon afterwards, the intermediate **E** transformed into **F** through oxidation. After a proton transfer process, reductive elimination occurs with **F** to afford terminal product **3a**.

Scheme 3 Investigation of the mechanism of reaction

2 Conclusion

In conclusion, we have described an efficient route for the synthesis of C(5) and C(7) di-halogenated quinoline derivatives via a nickel-catalyzed C—H halogenation reaction of 8-aminoquinolines. The reaction proceeds smoothly under mild conditions, leading to the diverse products in good to excellent yields. More transformations incorporating C—H halogenation reaction for the synthesis of biologically interesting molecules are ongoing in our laboratory.

3 Experimental section

3.1 General procedure for the synthesis of product 3

A 50 mL of schlenk tube was equipped with a magnetic stir bar and charged with the mixture of **1** (0.25 mmol),

Scheme 4 Proposed mechanism for the formation of **3a**

NXS (2.0 equiv.), NiBr_2 (10.9 mg, 20 mol%), in MeCN (2.0 mL) under O_2 . The mixture was stirred at 120 °C for overnight. After completion, the mixture was cooled to room temperature and diluted with water (10 mL), extracted with EtOAc (10 mL $\times$ 3). The combined organic phase was dried over Na_2SO_4 . After filtering, the acquired solution was collected and the solvent was removed at reduced pressure. The residue was subjected to silica gel column chromatography to give pure products **3** by using mixed petroleum ether and ethyl acetate [$V(\text{petroleum ether}) : V(\text{ethyl acetate}) = 5 : 1$].

N-(5,7-Dibromoquinolin-8-yl)benzamide (**3a**): Yield 87%, white solid. m.p. 156.0~157.0 °C [lit.^[6b] 156~157 °C]; ^1H NMR (400 MHz, CDCl_3) δ : 9.15 (s, 1H), 8.84 (dd, $J=4.2, 1.6$ Hz, 1H), 8.50 (dd, $J=8.5, 1.4$ Hz, 1H), 8.11 (s, 1H), 8.08 (d, $J=4.0$ Hz, 2H), 7.64~7.47 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.4, 150.6, 143.8, 136.2, 134.5, 134.1, 134.0, 132.3, 128.7, 128.1, 126.9, 122.8, 120.2, 118.9.

N-(5,7-Dibromoquinolin-8-yl)-4-fluorobenzamide (**3b**): Yield 83%, white solid. m.p. 178.6~179.8 °C; ^1H NMR

(400 MHz, CDCl_3) δ : 9.16 (s, 1H), 8.84 (d, $J=4.0$ Hz, 1H), 8.51 (d, $J=8.3$ Hz, 1H), 8.13~8.05 (m, 3H), 7.57 (dd, $J=8.7, 3.7$ Hz, 1H), 7.19 (t, $J=8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.3 (d, $^1J_{\text{CF}}=252$ Hz), 164.4, 150.6, 143.7, 136.3, 134.5, 133.9, 130.5 (d, $^3J_{\text{CF}}=9$ Hz), 130.1, 127.0, 122.9, 120.5, 119.1, 115.8 (d, $^2J_{\text{CF}}=22$ Hz); HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{10}\text{Br}_2\text{FN}_2\text{O}$ [$\text{M}+\text{H}$] $^+$ 422.9138, found 422.9139.

N-(5,7-Dibromoquinolin-8-yl)-4-(trifluoromethyl)benzamide (**3c**): Yield 85%, white solid. m.p. 205.4~206.6 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.23 (s, 1H), 8.85 (dd, $J=4.3, 1.6$ Hz, 1H), 8.54 (dd, $J=8.5, 1.6$ Hz, 1H), 8.18 (d, $J=8.1$ Hz, 2H), 8.13 (s, 1H), 7.77 (d, $J=8.1$ Hz, 2H), 7.59 (q, $J=8.5, 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.2, 150.7, 143.8, 137.1, 136.3, 134.4, 134.0, 133.7, 133.6, 128.5, 127.0, 125.8 (q, $J=4$ Hz), 125.0, 123.0, 122.3, 120.8, 119.5; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{10}\text{Br}_2\text{F}_3\text{N}_2\text{O}$ [$\text{M}+\text{H}$] $^+$ 472.9106, found 472.9107.

N-(5,7-Dibromoquinolin-8-yl)-4-methylbenzamide (**3d**): Yield 90%, white solid. m.p. 166.0~167.0 °C [lit.^[6b] 166~167 °C]; ^1H NMR (400 MHz, CDCl_3) δ : 9.12 (s, 1H), 8.85 (dd, $J=4.3, 1.6$ Hz, 1H), 8.52 (dd, $J=8.5, 1.5$ Hz, 1H), 8.12 (s, 1H), 7.97 (d, $J=8.0$ Hz, 2H), 7.56 (q, $J=4.2$ Hz, 1H), 7.32 (d, $J=8.0$ Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.3, 150.5, 143.8, 142.9, 136.0, 134.4, 134.3, 131.1, 129.4, 128.1, 126.9, 122.8, 120.1, 118.7, 21.6.

4-(*tert*-Butyl)-*N*-(5,7-dibromoquinolin-8-yl)benzamide (**3e**): Yield 94%, white solid. m.p. 219.2~221.6 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.51 (s, 1H), 8.79 (dd, $J=4.3, 1.6$ Hz, 1H), 8.44 (dd, $J=8.6, 1.5$ Hz, 1H), 8.07 (s, 1H), 8.00 (d, $J=8.4$ Hz, 2H), 7.50~7.44 (m, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.3, 155.8, 150.4, 143.9, 136.1, 134.4, 134.3, 131.0, 127.9, 127.9, 126.9, 125.6, 122.8, 120.6, 118.8, 35.0, 31.2; HRMS (ESI^+) calcd for $\text{C}_{20}\text{H}_{19}\text{Br}_2\text{N}_2\text{O}$ [$\text{M}+\text{H}$] $^+$ 460.9859, found 460.9857.

N-(5,7-Dibromoquinolin-8-yl)-2-fluorobenzamide (**3f**): Yield 79%, white solid. m.p. 148.1~149.8 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.27 (d, $J=13.1$ Hz, 1H), 8.91 (dd, $J=4.2, 1.6$ Hz, 1H), 8.51 (dd, $J=8.5, 1.6$ Hz, 1H), 8.23 (td, $J=7.8, 1.9$ Hz, 1H), 8.12 (s, 1H), 7.59~7.54 (m, 2H), 7.32 (td, $J=7.6, 1.1$ Hz, 1H), 7.26~7.21 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.3, 161.1 (d, $^1J_{\text{CF}}=248$ Hz), 159.9, 151.1, 144.3, 136.0, 134.2, 134.0 (d, $^3J_{\text{CF}}=9$ Hz), 133.8, 132.6, 127.1, 124.9, 122.8, 121.3, 119.8, 116.4 (d, $^2J_{\text{CF}}=24$ Hz); HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{10}\text{Br}_2\text{FN}_2\text{O}$ [$\text{M}+\text{H}$] $^+$ 422.9138429, found 422.9139.

2-Chloro-*N*-(5,7-dibromoquinolin-8-yl)benzamide (**3g**): Yield 75%, white solid. m.p. 178.4~179.7 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.88 (s, 2H), 8.48 (d, $J=8.3$ Hz, 1H), 8.09 (s, 1H), 7.91 (d, $J=7.2$ Hz, 1H), 7.55 (q, $J=4.0$ Hz, 1H), 7.48 (d, $J=7.6$ Hz, 1H), 7.44~7.36 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.2, 150.9, 144.1, 136.0, 134.6, 134.4, 134.3, 133.5, 131.8, 131.7, 130.7, 127.0, 127.0, 122.9, 120.8, 119.6; HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{10}\text{Br}_2\text{ClN}_2\text{O}$ [$\text{M}+\text{H}$] $^+$ 438.8843, found 438.8845.

N-(5,7-Dibromoquinolin-8-yl)-3-fluorobenzamide (**3h**):

Yield 79%, white solid. m.p. 152.1~152.4 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.43 (s, 1H), 8.81 (dd, $J=4.3$, 1.6 Hz, 1H), 8.46 (dd, $J=8.5$, 1.6 Hz, 1H), 8.07 (s, 1H), 7.84 (d, $J=8.4$ Hz, 1H), 7.72 (dt, $J=9.3$, 2.0 Hz, 1H), 7.53 (q, $J=8.5$, 4.2 Hz, 1H), 7.44 (td, $J=8.0$, 5.4 Hz, 1H), 7.27~7.22 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.2, 162.8 (d, $^1J_{\text{CF}}=246$ Hz), 150.6, 143.9, 136.2, 134.4, 133.8, 130.4 (d, $^3J_{\text{CF}}=8$ Hz), 127.0, 123.5 (d, $^2J_{\text{CF}}=29$ Hz), 122.9, 120.7, 119.4, 119.1, 115.3, 115.2; HRMS (ESI $^+$) calcd for $\text{C}_{16}\text{H}_{10}\text{Br}_2\text{FN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 422.9138, found 422.9138.

3-Bromo-*N*-(5,7-dibromoquinolin-8-yl)benzamide (**3i**): Yield 81%, white solid. m.p. 175.2~177.5 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.48 (s, 1H), 8.81 (dd, $J=4.2$, 1.6 Hz, 1H), 8.45 (dd, $J=8.6$, 1.6 Hz, 1H), 8.16 (s, 1H), 8.05 (s, 1H), 7.97 (d, $J=8.0$ Hz, 1H), 7.65 (d, $J=8.0$ Hz, 1H), 7.53 (q, $J=4.2$ Hz, 1H), 7.31 (t, $J=7.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.1, 150.7, 143.9, 136.2, 135.8, 135.2, 134.4, 133.7, 131.2, 130.2, 127.0, 126.5, 122.9, 122.9, 120.8, 119.5; HRMS (ESI $^+$) calcd for $\text{C}_{16}\text{H}_{10}\text{Br}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 482.8338, found 482.8338.

N-(5,7-Dibromoquinolin-8-yl)-3-methylbenzamide (**3j**): Yield 79%, white solid. m.p. 146.7~148.2 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.15 (s, 1H), 8.85 (d, $J=3.2$ Hz, 1H), 8.50 (d, $J=8.4$ Hz, 1H), 8.11 (s, 1H), 7.88~7.86 (m, 2H), 7.56 (q, $J=4.0$ Hz, 1H), 7.40 (d, $J=4.5$ Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.6, 150.5, 143.7, 138.6, 136.2, 134.5, 134.1, 133.9, 133.1, 128.7, 128.6, 126.9, 125.1, 122.8, 120.2, 118.8, 21.4; HRMS (ESI $^+$) calcd for $\text{C}_{17}\text{H}_{13}\text{Br}_2\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 418.9389, found 418.9388.

N-(5,7-Dibromoquinolin-8-yl)-3,5-dimethylbenzamide (**3k**): Yield 91%, white solid. m.p. 158.5~160.2 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 8.84 (d, $J=4.0$ Hz, 1H), 8.48 (d, $J=8.4$ Hz, 1H), 8.09 (s, 1H), 7.68 (s, 2H), 7.54 (q, $J=4.0$ Hz, 1H), 7.21 (s, 1H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.7, 150.6, 143.8, 138.5, 136.1, 134.5, 134.2, 133.9, 133.8, 126.9, 125.8, 122.8, 120.3, 118.8, 21.3; HRMS (ESI $^+$) calcd for $\text{C}_{18}\text{H}_{15}\text{Br}_2\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 432.9547, found 432.9547.

N-(5,7-Dibromoquinolin-8-yl)-2-naphthamide (**3l**): Yield 82%, white solid. m.p. 174.7~176.9 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.39 (s, 1H), 8.83 (d, $J=4.2$ Hz, 1H), 8.58 (s, 1H), 8.48 (d, $J=8.5$ Hz, 1H), 8.11~8.06 (m, 2H), 7.93~7.85 (m, 3H), 7.59~7.51 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.6, 150.6, 143.9, 136.1, 135.2, 134.4, 134.2, 132.6, 131.2, 129.2, 128.9, 128.6, 128.0, 127.8, 126.9, 126.8, 124.3, 122.8, 120.3, 119.0; HRMS (ESI $^+$) calcd for $\text{C}_{20}\text{H}_{13}\text{Br}_2\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 454.9389, found 454.9389.

N-(5,7-Dibromoquinolin-8-yl)thiophene-2-carboxamide (**3m**): Yield 77%, yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 9.59 (s, 1H), 8.84 (d, $J=4.0$ Hz, 1H), 8.48 (d, $J=8.4$ Hz, 1H), 8.08 (s, 1H), 7.87 (d, $J=3.7$ Hz, 1H), 7.56~7.54 (m, 2H), 7.12 (t, $J=4.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.9, 150.5, 143.9, 138.5, 136.3, 134.5, 133.6, 131.4, 130.1, 127.9, 127.0, 122.9, 120.8, 119.2; HRMS (ESI $^+$) calcd for $\text{C}_{14}\text{H}_9\text{Br}_2\text{N}_2\text{OS}$ $[\text{M}+\text{H}]^+$

410.8797, found 410.8797.

N-(5,7-dibromoquinolin-8-yl)acetamide (**3n**): Yield 80%, white solid. m.p. 87~88 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.86 (dd, $J=4.4$, 1.6 Hz, 1H), 8.46 (dd, $J=8.8$, 1.6 Hz, 2H), 8.05 (s, 1H), 7.53 (q, $J=4.4$ Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 168.7, 150.8, 144.2, 136.1, 134.2, 133.9, 130.9, 128.8, 127.0, 122.7, 23.7; HRMS (ESI $^+$) calcd for $\text{C}_{11}\text{H}_9\text{Br}_2\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 342.9076, found 342.9078.

N-(5,7-Dibromoquinolin-8-yl)cyclohexanecarboxamide (**3o**): Yield 81%, white solid. m.p. 97~98 °C (lit.^[6b] 202~203 °C); ^1H NMR (400 MHz, CDCl_3) δ : 8.86 (dd, $J=4.2$, 1.6 Hz, 1H), 8.46 (dd, $J=8.5$, 1.6 Hz, 1H), 8.28 (s, 1H), 8.03 (s, 1H), 7.54 (dd, $J=8.5$, 4.2 Hz, 1H), 2.52 (tt, $J=11.6$, 3.5 Hz, 1H), 2.16~2.10 (m, 2H), 1.91~1.85 (m, 2H), 1.75~1.62 (m, 3H), 1.41~1.28 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 174.1, 150.6, 144.0, 135.9, 134.3, 133.9, 126.9, 122.7, 120.5, 118.8, 45.9, 29.7, 25.8, 25.7.

N-(5,7-Dichloroquinolin-8-yl)benzamide (**3p**): Yield 64%, yellow solid. m.p. 111.3~113.3 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.23 (s, 1H), 8.86 (dd, $J=4.3$, 1.6 Hz, 1H), 8.52 (dd, $J=8.5$, 1.6 Hz, 1H), 8.11~8.04 (m, 2H), 7.74 (s, 1H), 7.59~7.46 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.4, 150.6, 143.5, 133.9, 133.5, 132.3, 131.5, 129.9, 128.7, 128.6, 128.6, 128.1, 125.2, 122.4; HRMS (ESI $^+$) calcd for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 317.0243, found 317.0242.

N-(5,7-Dichloroquinolin-8-yl)acetamide (**3q**): Yield 62%, yellow solid. m.p. 180.3~180.5 °C (lit.^[6a] 179~180 °C); ^1H NMR (400 MHz, CDCl_3) δ : 8.87 (dd, $J=4.0$, 1.6 Hz, 1H), 8.67 (brs, 1H), 8.49 (dd, $J=4.0$, 1.6 Hz, 1H), 7.68 (s, 1H), 7.51~7.55 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 168.8, 150.7, 143.8, 136.1, 133.5, 131.8, 128.4, 125.3, 122.6, 122.3, 23.6.

N-(5,7-Dibromo-6-methylquinolin-8-yl)benzamide (**3r**): Yield 65%, white solid. m.p. 188.2~188.7 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.19 (s, 1H), 8.76 (dd, $J=4.4$, 1.6 Hz, 1H), 8.58 (dd, $J=8.8$, 1.2 Hz, 1H), 8.07 (d, $J=7.2$ Hz, 2H), 7.57 (t, $J=7.6$ Hz, 1H), 7.47~7.52 (m, 3H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.7, 149.8, 142.4, 137.4, 136.6, 134.1, 134.0, 132.2, 128.7, 128.1, 127.2, 125.1, 122.9, 120.8, 25.8; HRMS (ESI $^+$) calcd for $\text{C}_{17}\text{H}_{12}\text{Br}_2\text{N}_2\text{NaO}$ $[\text{M}+\text{Na}]^+$ 440.9209, found 440.9214.

N-(5,7-Dibromo-6-fluoroquinolin-8-yl)benzamide (**3s**): Yield 59%, white solid. m.p. 203.3~204.3 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.34 (s, 1H), 8.79 (d, $J=3.6$ Hz, 1H), 8.51 (d, $J=8.0$ Hz, 1H), 8.08 (d, $J=7.2$ Hz, 2H), 7.56~7.62 (m, 3H), 7.52 (t, $J=7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.2, 154.3 (d, $^1J_{\text{CF}}=245$ Hz), 149.6 (d, $^4J_{\text{CF}}=3$ Hz), 140.3, 136.1 (d, $^4J_{\text{CF}}=3$ Hz), 135.4, (d, $^3J_{\text{CF}}=7$ Hz), 133.8, 132.5, 128.8, 128.1 (d, $^2J_{\text{CF}}=29$ Hz), 126.9 (d, $^4J_{\text{CF}}=3$ Hz), 110.8 (d, $^2J_{\text{CF}}=27$ Hz), 102.9, (d, $^2J_{\text{CF}}=24$ Hz), 100.0; HRMS (ESI $^+$) calcd for $\text{C}_{16}\text{H}_9\text{Br}_2\text{FN}_2\text{NaO}$ $[\text{M}+\text{Na}]^+$ 444.8958, found 44.8948.

N-(5-Iodoquinolin-8-yl)benzamide (**3t**): Yield 66%, white solid. m.p. 154~157 °C (lit.^[6c] 154~157 °C); ^1H NMR (400 MHz, CDCl_3) δ : 10.75 (s, 1H), 8.82 (dd, $J=$

4.2, 1.6 Hz, 1H), 8.71 (d, $J=8.3$ Hz, 1H), 8.39 (dd, $J=8.5$, 1.6 Hz, 1H), 8.13 (d, $J=8.3$ Hz, 1H), 8.07 (dd, $J=6.5$, 1.7 Hz, 2H), 7.59~7.54 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.4, 148.9, 140.8, 139.4, 138.3, 135.5, 134.9, 132.1, 129.7, 128.9, 127.3, 123.2, 117.9, 89.5.

4-(*tert*-Butyl)-*N*-(5-iodoquinolin-8-yl)benzamide (**3u**): Yield 75%. yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 10.52 (s, 1H), 8.59 (dd, $J=4.2$, 1.5 Hz, 1H), 8.52 (d, $J=8.3$ Hz, 1H), 8.14 (dd, $J=8.5$, 1.5 Hz, 1H), 7.92~7.86 (m, 3H), 7.43 (d, $J=8.4$ Hz, 2H), 7.32 (dd, $J=8.5$, 4.2 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ : 165.3, 155.6, 148.8, 140.7, 139.3, 138.3, 135.6, 132.0, 129.6, 127.2, 125.8, 123.2, 117.8, 89.4, 35.1, 31.2; HRMS (ESI^+) calcd for $\text{C}_{20}\text{H}_{20}\text{IN}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 431.0615, found 431.0614.

Supporting Information The ^1H NMR and ^{13}C NMR spectra for compound **3** and the single crystal data of compound **3a**. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn>.

References

- [1] (a) Kouznetsov, V. V.; Mendez, L. Y.; Gomez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141.
(b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.
(c) Tokoro, Y.; Nagai, A.; Kokado, K.; Chujo, Y. *Macromolecules* **2009**, *42*, 2988.
(d) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488.
(e) Liu, G.; Yi, M.; Liu, L.; Wang, J.; Wang, J. *Chem. Commun.* **2015**, *51*, 2911.
- [2] (a) Madrid, P. B.; Sherrill, J.; Liou, A. P.; Weisman, J. L.; Derisi, J. L.; Guy, R. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1015.
(b) Tardito, S.; Barilli, A.; Bassanetti, I.; Tegoni, M.; Bussolati, O.; Franchi-Gazzola, R.; Mucchino, C.; Marchio, L. *J. Med. Chem.* **2012**, *55*, 10448.
(c) Abouelhassan, Y.; Garrison, V. G.; Burch, M.; Wong, W.; Norwood, V. M.; Huigens, R. W. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5076.
(d) Vippagunta, S. R.; Dorn, A.; Matile, H.; Bhattacharjee, A. K.; Karle, J. M.; Ellis, W. Y.; Ridley, R. G.; Vennerstrom, J. L. *J. Med. Chem.* **1999**, *42*, 4630.
(e) Bhat, S.; Shim, J. S.; Zhang, F.; Chong, C. R.; Liu, J. O. *Org. Biomol. Chem.* **2012**, *10*, 2979.
(f) Borchardt, R. T. *J. Med. Chem.* **1973**, *16*, 382.
(g) Liu, Y.-C.; Wei, J.-H.; Chen, Z.-F.; Liu, M.; Gu, Y.-Q.; Huang, K.-B.; Li, Z.-Q.; Liang, H. *Eur. J. Med. Chem.* **2013**, *69*, 554.
- [3] (a) Jiang, H.; Taggart, H.; Zhang, X.; Benbrook, D. M.; Lind, S. E.; Ding, W.-Q. *Cancer Lett.* **2011**, *312*, 11.
(b) Heidary, D. K.; Howerton, B. S.; Glazer, E. C. *J. Med. Chem.* **2014**, *57*, 8936.
- [4] (a) Sun, K.; Lv, Y.; Wang, J.; Sun, J.; Liu, L.; Jia, M.; Liu, X.; Z. Li, Z.; Wang, X.; *Org. Lett.* **2015**, *17*, 4408.
(b) Wasa, M.; Worrell, B. T.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.
(c) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070.
(d) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.
- (e) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296.
- [5] (a) Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525.
(b) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780.
(c) Chen, Q.; du Jourdin, X. M.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958.
(d) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. *J. Am. Chem. Soc.* **2010**, *132*, 11887.
- [6] (a) Guo, H.; Chen, M.; Jiang, P.; Chen, J.; Pan, L.; Wang, M.; Xie, C.; Zhang, Y. *Tetrahedron* **2015**, *71*, 70.
(b) Xu, J.; Zhu, X.; Zhou, G.; Ying, B.; Ye, P.; Su, L.; Shen, C.; Zhang, P. *Org. Biomol. Chem.* **2016**, *14*, 3016.
(c) Liu, X. X.; Wu, Z. Y.; Luo, X. L.; He, Y. Q.; Zhou, X. Q.; Fan, Y. X.; Huang, G. S. *RSC Adv.* **2016**, *6*, 71485.
- [7] (a) Gu, L.; Lu, T.; Zhang, M.; Tou, L.; Zhang, Y. *Adv. Synth. Catal.* **2013**, *355*, 1077.
(b) Nishina, Y.; Takami, K. *Green Chem.* **2012**, *14*, 2380.
(c) Nishina, Y.; Hashimoto, H.; Kimura, N.; Miyata, N.; Fujii, T.; Ohtanid, B.; Takada, J. *RSC Adv.* **2012**, *2*, 6420.
(d) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924.
(e) Podgorsek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424.
(f) Zhang, J.; Hao, X.; Wang, Z.; Ren, C.; Niu, J.; Song, M. *Chin. J. Org. Chem.* **2017**, *37*, 1237 (in Chinese).
(张家恒, 郝新奇, 王正龙, 任常久, 牛俊龙, 宋毛平, 有机化学, **2017**, *37*, 1237.)
(g) Luo, F.; Long, Y.; Li, Z.; Zhou, X. *Acta Chim. Sinica* **2016**, *74*, 805 (in Chinese).
(罗飞华, 龙洋, 李正凯, 周向葛, 化学学报, **2016**, *74*, 805.)
- [8] For selected example, (a) Zhang, J.; Chen, T.; Yang, J.; Han, L. *Chem. Commun.* **2015**, *51*, 7540.
(b) Li, X.; Feng, Z.; Jiang, Z.; Zhang, X. *Org. Lett.* **2015**, *17*, 5570.
(c) Li, K.; Wu, Q.; Lan, J.; You, J. *Nat. Commun.* **2015**, *6*, 8404.
(d) Jin, L.; Wan, L.; Feng, J.; Cai, C. *Org. Lett.* **2015**, *17*, 4726.
- [9] (a) Cho, C. S.; Lee, J. W.; Lee, D. Y.; Shim, S. C.; Kim, T. J. *Chem. Commun.* **1996**, 2115.
(b) Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Org. Chem.* **2015**, *80*, 11618.
(c) Tjutrins, J.; Shao, J.; Yempally, V.; Bengali, A. A.; Arndtsen, B. A. *Organometallics* **2015**, *34*, 1802.
(d) Lo, W.; Hu, C.; Berenson, T.; Tracer, N.; Shlian, D.; Khaloo, M.; Benhaim, A.; Jiang, J. *Chem. Commun.* **2015**, *51*, 9432.
(e) Hoshimoto, Y.; Ohata, T.; Sasaoka, Y.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2014**, *136*, 15877.
- [10] (a) Ohashi, M.; Kishizaki, O.; Ikeda, H.; Ogoshi, S. *J. Am. Chem. Soc.* **2009**, *131*, 9160.
(b) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371.
(c) Yeh, C. H.; Korivi, R. P.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4892.
(d) Stolley, R. M.; Duong, H. A.; Thomas, D. R.; Louie, J. J. *Am. Chem. Soc.* **2012**, *134*, 15154.
(e) Thakur, A.; Facer, M. E.; Louie, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12161.
- [11] Zhan, B.-B.; Liu, Y.-H.; Hu, F.; Shi, B.-F. *Chem. Commun.* **2016**, *52*, 4934.
- [12] (a) Hao, W. Y.; Tian, J.; Li, W.; Shi, R.; Huang, Z.; Lei, A. W. *Chem. Asian J.* **2016**, *11*, 1664.
(b) Wan, J.-P.; Li, Y.; Liu, Y. *Org. Chem. Front.* **2016**, *3*, 768.
(c) Liu, Y.; Huang, M.; Wei, L. *Asian J. Org. Chem.* **2017**, *6*, 41.
- [13] He, Y.; Zhao, N.; Qiu, L.; Zhang, X.; Fan, X. *Org. Lett.* **2016**, *18*, 6054.

(Cheng, F.)