Synthesis of 2-Halogenated Quinolines by Halide-Mediated Intramolecular Cyclization of *o*-Alkynylaryl Isocyanides

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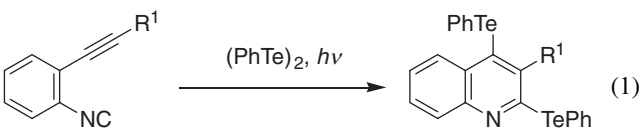
When *o*-alkynylaryl isocyanides **1** are treated with triethylamine in chloroform, intramolecular chlorinating cyclization of the isocyanides takes place, affording the corresponding 2-chlorinated quinoline derivatives **2** in good to excellent yields, selectively. Bromoform can be also used for the brominating cyclization of **1**. Furthermore, fluorinating and iodinating cyclization of *o*-alkynylaryl isocyanides has been attained by the selection of fluoride and iodide (ion) sources.

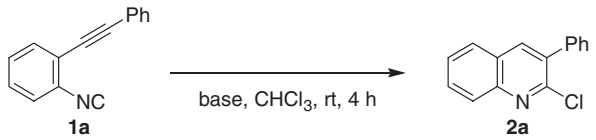
Quinoline and their derivatives are contained in numerous natural products such as alkaloids, and many of them display a wide variety of biological activities.[1] Therefore, quinoline motifs are often used for the design of many synthetic compounds with pharmacological properties. Although a number of synthetic methods of quinoline derivatives have been elucidated hitherto, new synthetic approaches under mild reaction conditions with high selectivity for construction of quinoline rings are still expected in advanced research areas.[2,3] Isocyanides are promising candidates for the synthesis of *N*-heterocycles such as pyrroles, indoles, and quinolines.[4,5] In our recent report, we have developed the photoinduced intramolecular cyclization of *o*-alkynylaryl isocyanides in the presence of diphenyl ditelluride, affording the corresponding 2,4-bistellurated quinoline derivatives (eq 1).[6]



(1)

During the course of our research for extending the synthesis of quinolines including several heteroatom units based on the cyclization of *o*-alkynylaryl isocyanides, we found that the reaction of *o*-alkynylaryl isocyanides **1** in the presence of triethylamine in chloroform produced 2-chloroquinoline derivatives **2** under mild conditions (eq 2).

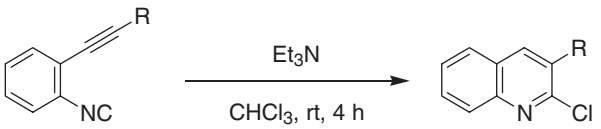
Table 1. Bases-Mediated Chlorinating Cyclization of Isocyanide **1a**[a)]



1a **2a**

Entry	Base	Amounts	Yield/%[b)]
1	^{t}BuNH$_2$	0.5 mL	trace
2	Et$_2$NH	0.5 mL	trace
3	Et$_3$N	0.5 mL	93 (89)
4	^{t}BuONa	0.02 mmol	6
5	K$_2$CO$_3$	0.02 mmol	9

a) Reaction conditions: 2-(phenylethynyl)phenyl isocyanide (**1a**, 0.01 mmol), base, $CHCl_3$ (0.5 mL), room temperature, 4 h. b) Determined by ^{1}H NMR. Value in parenthesis is isolated yield.



1 **2** (2)

We first examined the screening of bases for the intramolecular cyclization of *o*-alkynylaryl isocyanide in chloroform (Table 1). When 2-(phenylethynyl)phenyl isocyanide (**1a**) was treated with diethylamine or *t*-butylamine in $CHCl_3$, 2-chloro-3-phenylquinoline (**2a**) was not produced, and instead, the corresponding 2-aminated quinolines were obtained mainly (Entries 1 and 2).[7] In contrast, the reaction of **1a** in $CHCl_3$ by using triethylamine afforded the desired quinoline **2a** in 89% yield, selectively (Entry 3). Sodium *t*-butoxide and potassium carbonate were less effective for the desired chlorinating cyclization (Entries 4 and 5). These results suggested the formation of ammonium salts (Et_3N^+H X^-) from chloroform and triethylamine as a key intermediate.[8]

We next examined the triethylamine-mediated intramolecular cyclization of several isocyanides and these results are summarized in Table 2. Similar conditions could be also employed with isocyanide **1b** bearing a 4-methylphenyl group, forming the corresponding quinoline derivative **2b** in good yield (Entry 2). Chloro and fluoro substituents were tolerant of this reaction to produce **2c** and **2d** in good yields, respectively (Entries 3 and 4). In particular, isocyanides **1e** and **1f** with electron-withdrawing groups such as 4-nitro or 4-cyano afforded the corresponding **2e** or **2f** in high yields (Entries 5 and 6). Furthermore, isocyanide **1g** containing an aliphatic group at the 2-position of an ethynyl unit could be also used, providing **2g** in good yield (Entry 7). Under further examination, we investigated the reaction of isocyanide **1a** with bromoform. When isocyanide **1a** was treated with bromoform in the presence of triethylamine, 2-bromo-3-phenylquinoline (**3a**) was obtained in 81% yield (Entry 8).[9] To apply the synthesis of 2-fluoroquinoline derivatives, which are important in the pharmaceutical industry, we examined the reaction of isocyanide **1a** with several fluorine sources, because gaseous fluoroform (CHF_3) could not be employed as a fluoride source conveniently. The reaction using CsF as a fluoride source

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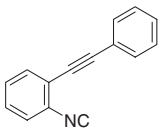
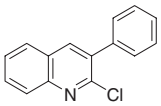
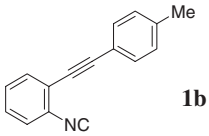
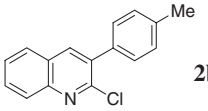
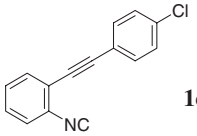
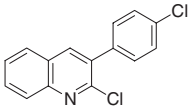
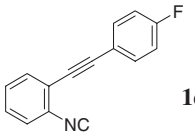
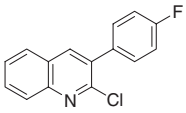
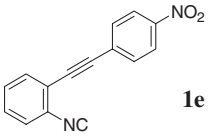
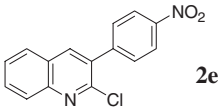
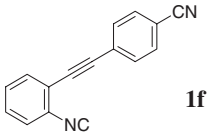
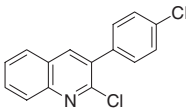
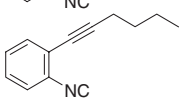
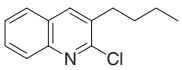
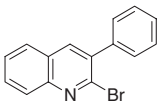
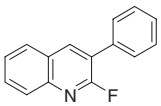
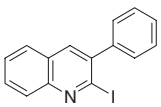
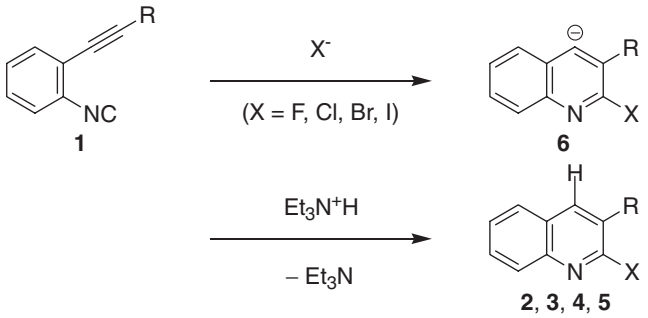
Table 2. Synthesis of 2-Halogenated Quinolines **2**[a)]

Entry	Substrate	Product	Yield/%[b)]
1	 **1a**	 **2a**	89
2	 **1b**	 **2b**	79
3	 **1c**	 **2c**	81
4	 **1d**	 **2d**	83
5	 **1e**	 **2e**	94
6	 **1f**	 **2f**	88
7	 **1g**	 **2g**	76
8[c)]	**1a**	 **3a**	81
9[d)]	**1a**	 **4a**	trace
10[e)]	**1a**	**4a**	trace
11[f)]	**1a**	**4a**	trace
12[g)]	**1a**	**4a**	98
13[h)]	**1a**	 **5a**	19
14[i)]	**1a**	**5a**	88

a) Reaction conditions: isocyanide (**1**, 0.10 mmol), $CHCl_3$ (1.0 mL), Et_3N (1.0 mL), room temperature, 4 h. b) Isolated yield. c) $CHBr_3$ (1.0 mL) was used in place of $CHCl_3$. d) CsF (0.20 mmol) was used as fluorine sources in place of Et_3N. e) KF (0.20 mmol) was used in place of Et_3N. f) $AgBF_4$ (0.20 mmol) was used in place of Et_3N. g) TBAF (0.20 mmol) was used in place of Et_3N. h) CHI_3 (0.20 mmol) was used in place of $CHCl_3$. i) TBAI (0.15 mmol) was used in place of Et_3N.

formed trace amounts of 2-fluoro-3-phenylquinoline (**4a**) (Entry 9). In the cases of potassium fluoride and silver tetrafluoroborate, trace amounts of 2-fluoroquinoline **4a** was also produced (Entries 10 and 11). These fluorine sources showed poor solubility toward organic solvents, and therefore, the desired fluorinating cyclization may require fluorine sources with good solubility in organic solvents. Thus, we



Scheme 1. A plausible reaction pathway.

examined the reaction of isocyanide **1a** with tetrabutylammonium fluoride as a fluorine source, which afforded 2-fluoroquinoline **4a** in almost quantitative yield (Entry 12). When iodoform was employed in this reaction, unfortunately low yield of 2-iodo-3-phenylquinoline (**5a**) was formed (Entry 13). However, treatment of isocyanide **1a** with tetrabutylammonium iodide[10] provided 2-iodoquinoline **5a** in 88% yield (Entry 14).

A plausible reaction pathway for the triethylamine-mediated intramolecular halogenating cyclization of *o*-alkynylaryl isocyanide is shown in Scheme 1. Initially, the formation of quaternary ammonium halide ($Et_3N^+H\ X^-$) takes place.[11] The addition of the generated halide ion to isocyano group, the intramolecular cyclization to give carbanion **6**, and the protonation of **6** produce the corresponding quinoline derivatives.

In summary, we have described a convenient intramolecular cyclization of *o*-alkynylaryl isocyanides with chloroform and bromoform in the presence of triethylamine, affording the corresponding 2-chlorinated and 2-brominated quinoline derivatives, respectively, in moderate to high yields. In addition, fluorinating and iodinating cyclization of *o*-alkynylaryl isocyanides has been attained by the selection of fluorine and iodine sources.

Experimental

General Procedure for the Triethylamine-Mediated Intramolecular Cyclization with Chlorination of *o*-Alkynylaryl Isocyanide. To a mixture of 2-(phenylethynyl)phenyl isocyanide (**1a**, 0.10 mmol) in chloroform (1.0 mL) was added triethylamine (1.0 mL), and the mixture was stirred for 4 h at room temperature. After the reaction, the resulting mixture was concentrated in vacuo and purified by PTLC (hexane:EtOAc = 9:1) to give 2-chloro-3-phenylquinoline (**2a**, 21.3 mg, 0.089 mmol, 89%) as colorless oil.

2-Chloro-3-phenylquinoline (2a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.64 (m, 6H), 7.76 (dt, $J = 1.5$, 7.7 Hz, 1H), 7.85 (d, $J = 7.1$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.2, 127.3, 127.5, 128.3, 129.6, 130.4, 134.8, 137.6, 138.8, 146.9, 149.6; IR (NaCl, cm^{-1}): 3056, 3030, 1560, 1487, 1396, 1364, 1339, 1134, 1092, 966, 912, 883, 779, 752, 698; MS (EI) *m/z* (relative intensity): 239 (M^+, 100), 241 (48), 240 (26), 242 (9).

3-*n*-Butyl-2-chloroquinoline (2g): White solid; mp 42–43 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, $J = 7.4$ Hz, 3H), 1.47 (qui, $J = 7.4$ Hz, 2H), 1.73 (qui, $J = 7.6$ Hz, 2H), 2.88 (t, $J = 7.7$ Hz, 2H), 7.53 (t like, $J = 8.1$ Hz, 1H), 7.67 (t like, $J = 7.6$ Hz, 1H), 7.77 (d, $J = 7.7$ Hz, 1H), 7.96 (s, 1H), 8.00 (d,

$J = 8.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 22.4, 31.4, 33.1, 126.9, 127.1, 128.2, 129.5, 131.1, 137.2, 141.5, 146.3; IR (NaCl, cm^{-1}): 3051, 3034, 2953, 2926, 2868, 1558, 1541, 1506, 1456, 1339, 1219, 1132, 1038, 901, 870, 772, 758, 669; MS (EI) m/z (relative intensity): 219 (M^+, 100), 221 (33), 220 (13), 222 (2).

Procedure for the Triethylamine-Mediated Intramolecular Brominating Cyclization of *o*-Alkynylaryl Isocyanide. To the mixture of 2-(phenylethynyl)phenyl isocyanide (**1a**, 0.10 mmol) in bromoform (1.0 mL) was added triethylamine (1.0 mL), and the mixture was stirred for 4 h at room temperature. After the reaction, the resulting mixture was concentrated in vacuo and purified by PTLC (hexane:EtOAc = 9:1) to give 2-bromo-3-phenylquinoline (**3a**, 23.1 mg, 0.081 mmol, 81%) as slight yellow oil.

2-Bromo-3-phenylquinoline (3a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.75 (m, 5H), 7.60 (t like, $J = 7.4$ Hz, 1H), 7.75 (t like, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 8.06 (s, 1H), 8.10 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.4, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 129.7, 130.4, 137.9, 138.4, 139.9, 144.4, 146.5; IR (NaCl, cm^{-1}): 3057, 3031, 1556, 1539, 1506, 1487, 1456, 1389, 1360, 1339, 1219, 1130, 1080, 959, 775, 698; MS (EI) m/z (relative intensity): 283 (M^+, 100), 285 (88), 284 (13), 286 (15); HRMS (FAB) calcd for $C_{15}H_{11}BrN$ $[M + H]^+$ 284.0075, found 284.0049.

Procedure for the Intramolecular Fluorinating Cyclization of Isocyanide 1a with Tetrabutylammonium Fluoride. In a 30 mL round bottom flask were placed 2-(phenylethynyl)-phenyl isocyanide (**1a**, 20 mg, 0.10 mmol) and tetrabutylammonium fluoride (1.0 M in hexane solution, 0.20 mmol, 0.20 mL) in chloroform (1.0 mL), and the mixture was stirred for 4 h at room temperature under ambient atmosphere. The resulting mixture was concentrated in vacuo and purified by PTLC (hexane:EtOAc = 9:1) to give 2-fluoro-3-phenylquinoline (**4a**, 21.8 mg, 0.098 mmol, 98%) as colorless oil.

2-Fluoro-3-phenylquinoline (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.60 (m, 3H), 7.57 (t like, $J = 7.3$ Hz, 1H), 7.67 (d, $J = 7.3$ Hz, 2H), 7.74 (t like, $J = 7.6$ Hz, 1H), 7.89 (d, $J = 9.2$ Hz, 1H), 7.99 (d, $J = 9.2$ Hz, 1H), 8.30 (d, $J = 9.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.1, 124.7, 126.4, 127.5, 127.8, 128.5, 128.7, 129.0, 130.4, 134.8, 140.5, 144.9, 158.4; MS (EI) m/z (relative intensity): 223 (M^+, 100), 224 (22), 225 (2).

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Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for 2-halogenated quinoline derivatives. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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9 When, in place of $CHBr_3/Et_3N$, TBABr was employed for the brominating cyclization, **3a** was obtained in 88% isolated yield.

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11 The use of TBACl as a chloride ion source produced **2a** in 99% yield. This result strongly suggested the formation of Cl ion from $CHCl_3$ with Et_3N.