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# Synthesis of 2,4-Diiodoquinolines via the Photochemical Cyclization of *o*-Alkynylaryl Isocyanides with Iodine

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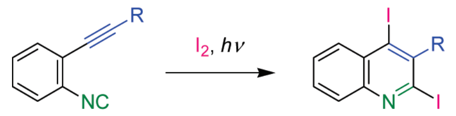

Upon photoirradiation of *o*-alkynylaryl isocyanides in the presence of iodine, the intramolecular cyclization of *o*-alkynylaryl isocyanides proceeds to afford the corresponding 2,4-diiodoquinolines in good yields. 2,4-Diiodoquinolines can be employed in transition metal-catalyzed cross-coupling reactions.

Quinolines are contained in numerous natural products such as alkaloids and bioactive compounds, and therefore, they are often used for designing many pharmacological molecules.[1] In particular, quinoline derivatives containing halogen atoms are one of the significant raw materials for preparing functionalized quinolines because of their bioactivities[2] and synthetic utilities, which result from the fact that selective conversion of C−X bonds (X = halogen atoms) into C−C or C−E bonds (E = O, N, S) is possible through the use of organic lithium reagents, Grignard reagents, or transition metal catalysts.[3] Although many methods have been developed for the synthesis of quinoline frameworks, highly selective methods for the preparation of quinoline derivatives under mild reaction conditions would be useful in advanced research areas.[4,5]

Isocyanides are one of the promising precursors for the preparation of *N*-heterocycles such as pyrroles, indoles, and quinolines in the presence of nucleophiles, transition metal catalysts, and radical mediators.[6−8] In contrast to the many reports on the synthesis of pyrrole and indole derivatives, selective preparation methods for quinoline derivatives are limited.[9] Recently, we have developed a method for the photochemical cyclization of *o*-alkynylaryl isocyanides with diphenyl ditelluride; the method affords the corresponding 2,4-bistellurated quinolines.[10] In this paper, we report the

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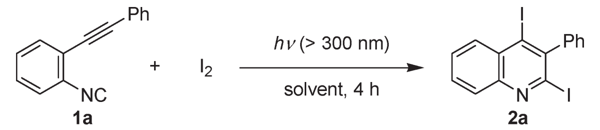
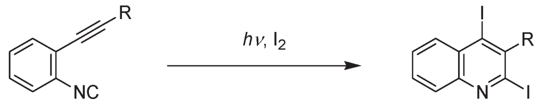
**TABLE 1. Photochemical Cyclization of Isocyanide 1a with Iodine**[a]



| entry | iodine | solvent | yield of **2a** (%)[b] |
|---|---|---|---|
| 1 | 0.5 equiv | $CHCl_3$ | 45 |
| 2 | 1.0 equiv | $CHCl_3$ | 66 |
| 3 | 1.5 equiv | $CHCl_3$ | 65 |
| 4[c] | 1.0 equiv | $CHCl_3$ | ND |
| 5 | 1.0 equiv | MeOH | (56) |
| 6 | 1.0 equiv | acetone | (54) |
| 7 | 1.0 equiv | MeCN | (62) |
| 8 | 1.0 equiv | AcOEt | (34) |
| 9 | 1.0 equiv | THF | (32) |
| 10 | 1.0 equiv | toluene | (32) |
| 11 | 1.0 equiv | hexane | (22) |
| 12[c,d] | 1.0 equiv | $Et_3N$ | 48 |

[a] Reaction conditions: isocyanide (**1a**, 0.10 mmol); iodine; $CDCl_3$ (0.50 mL); room temperature; 4 h; *hν*: irradiation with a high-pressure Hg lamp through a Pyrex filter (> 300 nm). [b] Yields in parentheses were determined by $^1H$ NMR. The yields were based on **1a**. [c] In the dark. [d] Reaction conditions: isocyanide (**1a**, 0.10 mmol); iodine; triethylamine (0.50 mL); room temperature; 4 h.

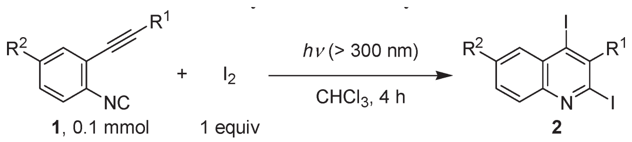
synthesis of 2,4-diiodoquinolines through the photochemical cyclization of *o*-alkynylaryl isocyanides (eq 1).

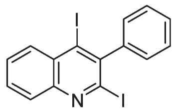
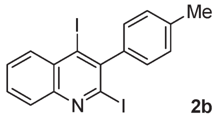
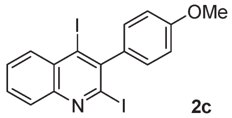
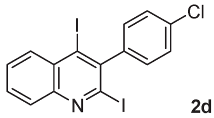
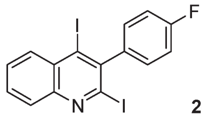
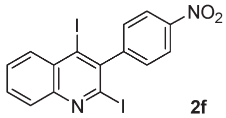
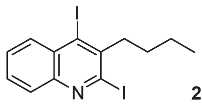
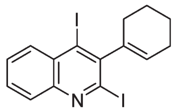
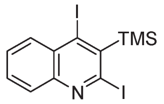
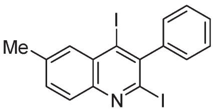
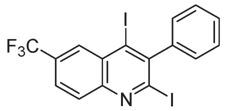


(1)

We examined the optimization of the photoinduced cyclization of 2-(phenylethynyl)phenyl isocyanide (**1a**) in the presence of iodine (Table 1). Upon photoirradiation, isocyanide **1a** underwent iodocyclization to selectively afford 2,4-diiodo-3-phenylquinoline (**2a**) (entries 1−3). The yield of **2a** increased with the amount of $I_2$. In contrast, no reaction took place in the dark (entry 4). Thus, the reaction required photoirradiation. We also examined the photochemical reaction of **1a** with $I_2$ in several solvents. Upon treatment in methanol, acetone, and acetonitrile, diiodoquinoline **2a** was formed in moderate to good yields (entries 5−7). In the cases of ethyl acetate, tetrahydrofuran, toluene, and hexane, low yields of **2a** were obtained (entries 8−11). When isocyanide **1a** was treated with $I_2$ in triethylamine in the dark, 2,4-diiodoquinoline **2a** was obtained in 48% yield (entry 12). We have previously reported the nucleophilic cyclization of *o*-alkynylaryl isocyanides by using haloform and triethylamine. The cyclization yields 2-halogenated quinolines.[6f] Accordingly, the cyclization reaction in the case of triethylamine proceeded via the addition of an iodide anion to the isocyano group, as well as intramolecular cyclization and iodine abstraction from molecular iodine. Photochemical reactions of isocyanide **1a** with $Br_2$, *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccinimide (NIS) were also carried out. Unfortunately, the reaction with $Br_2$ gave a complex mixture, and NCS and NBS were not effective in inducing cyclization. In the case of NIS, 2,4-diiodoquinoline **2a** was obtained in 27% yield.

**TABLE 2. Photochemical Cyclization of Isocyanides 1 with Iodine**[a]

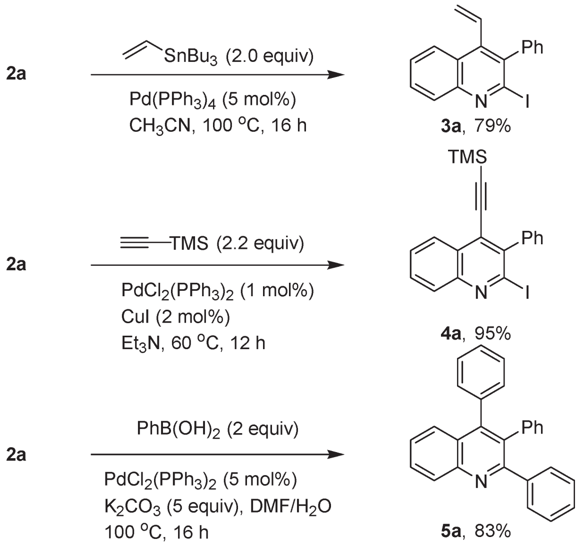


| entry | $R^1$ | $R^2$ | 1 | product | 2 | yield (%) |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$- | H- | **1a** |  | **2a** | 66 |
| 2 | 4-Me-$C_6H_4$- | H- | **1b** |  | **2b** | 61 |
| 3 | 4-MeO-$C_6H_4$- | H- | **1c** |  | **2c** | 64 |
| 4 | 4-Cl-$C_6H_4$- | H- | **1d** |  | **2d** | 71 |
| 5 | 4-F-$C_6H_4$- | H- | **1e** |  | **2e** | 42 |
| 6 | 4-$O_2N$-$C_6H_4$- | H- | **1f** |  | **2f** | 0 |
| 7 | $CH_3(CH_2)_3$- | H- | **1g** |  | **2g** | 56 |
| 8 | 1-cyclohexenyl- | H- | **1h** |  | **2h** | 65 |
| 9 | TMS- | H- | **1i** |  | **2i** | 10 |
| 10 | $C_6H_5$- | Me- | **1j** |  | **2j** | 46 |
| 11 | $C_6H_5$- | $CF_3$- | **1k** |  | **2k** | 86 |

[a] Reaction conditions: *o*-alkynylaryl isocyanide (**1**, 0.10 mmol); iodine (0.10 mmol); $CHCl_3$ (0.50 mL); room temperature; 4 h; *hν*: irradiation with a high-pressure Hg lamp through a Pyrex filter (> 300 nm).

We next examined the scope and limitation of the photochemical reactions of several isocyanides **1** with iodine (Table 2). The reaction of isocyanides **1b**, **1c**, and **1d** bearing 4-methyl-, 4-methoxy-, and 4-chlorophenylethynyl groups at the *ortho* position afforded the corresponding 2,4-diiodoquinolines **2b**, **2c**, and **2d** in good yields (entries 2−4). The reaction of 2-(4-fluorophenylethynyl)phenyl isocyanide (**1e**)

**SCHEME 1. Palladium-Catalyzed Cross-Coupling Reactions of 2,4-Diiodoquinoline 2a**



also provided quinoline **2e** in 42% yield (entry 5). However, 2,4-diiodoquinoline **2f** was not obtained from the reaction mixture of **1f**, which bears a nitro group. Instead, oligomerization of **1f** took place preferentially (entry 6). Similar conditions can be employed with isocyanides **1g** and **1h** that have 1-hexynyl and 2-(1-cyclohexenyl)ethynyl groups, giving quinolines **2g** and **2h** in 56% and 65% yields, respectively (entries 7 and 8). In contrast, the reaction of isocyanide **1i** led to low yield of **2i**, probably due to the bulkiness of the TMS group (entry 9). Similar conditions could be employed for isocyanides having 4-methyl or 4-trifluoromethyl groups at the isocyanobenzene moieties, and the corresponding quinolines **2j** and **2k** were obtained in 46% and 86% yields, respectively (entries 10 and 11).[11,12]

2,4-Diiodoquinolines are promising for use as synthetic intermediates to prepare functionalized quinoline derivatives. We have demonstrated palladium-catalyzed cross-coupling reactions using 2,4-diiodoquinoline derivatives **2** (Scheme 1).[13] The Migita−Kosugi−Stille cross-coupling reaction of **2a** selectively affords 4-ethenyl-2-iodo-3-phenylquinoline (**3a**) in 79% yield. The Sonogashira cross-coupling reaction also can be applied to **2a**; this leads to the formation of 4-alkynyl-2-iodoquinoline **4a** in quantitative yield. It is noteworthy that the cross-coupling reactions take place selectively at the 4-position of **2a** even in the presence of approximately 2 equivalent of vinyl stannane or acetylene. In the case of the Suzuki−Miyaura cross-coupling reaction, the palladium-catalyzed reaction of diiodoquinoline **2a** proceeds at both the 2- and 4-positions of **2a**, providing 2,3,4-triphenylquinoline (**5a**) in 83% yield. Unfortunately, the Mizoroki−Heck reaction of quinoline **2a** does not proceed, and instead, the formation of 3-phenylquinoline is observed.

In summary, we have developed a method for the photochemical cyclization of *o*-alkynylaryl isocyanides with iodine. The photochemical cyclization yields 2,4-diiodoquinolines, which are difficult to synthesize by using existing methods. The reaction proceeds under mild conditions and readily affords the appropriate products. We have also demonstrated the synthetic application of 2,4-diiodoquinolines to palladium-catalyzed cross-coupling reactions, which can be expected to afford a wide variety of multifunctionalized quinoline derivatives.

## Experimental Section

**General Procedure for the Photochemical Iodocyclization of *o*-Alkynylaryl Isocyanide.** In an NMR tube (Φ = 5 mm, length = 180 mm), 2-(phenylethynyl)phenyl isocyanide (**1a**, 20 mg, 0.10 mmol), iodine (25.4 mg, 0.20 mmol, 1.0 equiv), and $CHCl_3$ (0.50 mL) were taken under ambient atmosphere, and the reaction was carried out for 4 h; the reaction was irradiated with a high-pressure Hg lamp through a Pyrex filter ($h\nu > 300$ nm). After the photoirradiation, the resulting mixture was concentrated in vacuo and purified by PTLC (Hex:AcOEt = 9:1) to give 2,4-diiodo-3-phenylquinoline (**2a**, 30.6 mg, 0.067 mmol, 67%) as a white solid.

**2,4-Diiodo-3-phenylquinoline (2a):** white solid; mp 183−184 °C; $^1$H NMR (300 MHz, $CDCl_3$, ppm) $\delta$ 7.15−7.23 (m, 1H), 7.42−7.56 (m, 4H), 7.59−7.79 (m, 2H), 8.00−8.13 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) $\delta$ 121.6, 127.3, 127.5, 128.3, 128.5, 128.9, 129.0, 129.2, 129.4, 130.7, 133.2, 145.8, 147.1; IR (NaCl, cm$^{-1}$) 3043, 3022, 1545, 1470, 1442, 1375, 1329, 1281, 1136, 1088, 1072, 1028, 961, 874, 758, 696; HRMS (FAB) calcd for $C_{15}H_{10}I_2N$ $[M + H]^+$ 457.8903, found 457.8884.

**Procedure for Suzuki−Miyaura Cross-Coupling Reaction of 2,4-Diiodoquinoline 2a.** A mixture of 2,4-diiodo-3-phenylquinoline (**2a**, 46 mg, 0.10 mmol), phenylboronic acid (24 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (3.5 mg, 5 mol %), and $K_2CO_3$ (69 mg, 0.50 mmol) in DMF (4 mL) and $H_2O$ (1 mL) was heated at 100 °C for 16 h in a nitrogen atmosphere. To the resulting mixture was added $H_2O$, then the organic portion was extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$, filtrated, and removed in vacuo. The resulting crude oil was purified by PTLC (eluted with hexane:AcOEt = 9:1) to give 2,3,4-triphenylquinoline (**5a**, 30 mg, 0.083 mmol, 83%) as a white solid.

**2,3,4-Triphenylquinoline (5a):** white solid; mp 199−201 °C; $^1$H NMR (400 MHz, $CDCl_3$, ppm) $\delta$ 6.85−6.92 (m, 2H), 6.97−7.03 (m, 3H), 7.10−7.16 (m, 2H), 7.18−7.23 (m, 3H) 7.24−7.31 (m, 3H), 7.34−7.40 (m, 2H), 7.45 (ddd, $J$ = 1.2, 6.8, 8.2 Hz, 1H), 7.58 (dd, $J$ = 1.2, 8.2 Hz, 1H), 7.73 (ddd, $J$ = 1.2, 6.8, 8.2 Hz, 1H), 8.26 (d, $J$ = 8.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, ppm) $\delta$ 126.3, 126.5, 126.6, 126.6, 127.2, 127.3, 127.6, 127.6, 127.7, 129.3, 129.7, 129.9, 130.3, 131.3, 132.9, 136.9, 138.3, 141.1, 147.3, 147.6, 159.0; MS (EI) $m/z$ 357 ($M^+$, 100).

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(11) A plausible reaction pathway for the photochemical diiodocyclization of *o*-alkynylaryl isocyanides may involve the photochemical aza-Bergman cyclization that yields 2,4-biradical species. The sequential abstraction of iodine by the 2,4-biradical species affords the corresponding 2,4-diiodoquinolines. Indeed, a theoretical study on the (*Z*)-enyne isocyanide system suggests the possibility of aza-Bergman cyclization. See: Debbert, S. L.; Cramer, C. J. *Int. J. Mass Spectrom.* **2000**, *201*, 1.

(12) To clarify the reaction pathway, we also conducted the photochemical reaction of isocyanide **1a** with tributyltin hydride, which has excellent carbon-radical-capturing ability. The reaction afforded 3-phenylquinoline in 76% yield, and 2-tributylstannyl-3-phenyl quinoline was not obtained. These results strongly suggest that the photochemical reaction of *o*-alkynylaryl isocyanides follows the aza-Bergman cyclization via the formation of 2,4-biradical species.

(13) The structures of quinolines **3a** and **4a** were determined by treatment with organolithium reagents. Upon treatment of **3a** and **4a** with butyllithium, new singlet peaks were observed at 9.03 and 8.99 ppm in the $^1$H NMR spectra, respectively. Both peaks indicated the formation of the corresponding 2-hydroquinolines by the elimination of iodide.

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**Supporting Information Available:** General experimental procedures, characterization data, and $^1$H and $^{13}$C NMR spectra for products, and an ORTEP diagram of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.