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New Access to 2,3-Disubstituted Quinolines through Cyclization of *o*-Alkynylisocyanobenzenes

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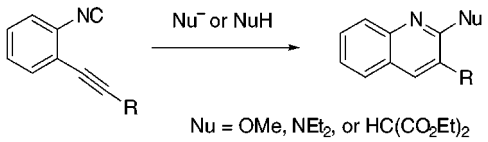
ABSTRACT



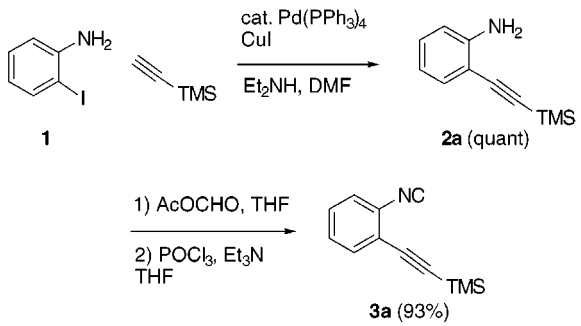
***o*-Alkynylisocyanobenzenes underwent nucleophile-induced intramolecular cyclization to give 2,3-disubstituted quinoline derivatives in high yields. In addition to the oxygen and nitrogen nucleophiles such as methanol and diethylamine, the nucleophilic carbon of the enolate of malonate induced the cyclization effectively. Reaction of 1,4-di(trimethylsilylethynyl)-2,3-diisocyanobenzene with methanol afforded 2,9-dimethoxy-1,10-phenanthroline in good yield.**

Cyclization of ortho-functionalized aryl isocyanides has been an attractive strategy for the synthesis of nitrogen-containing heterocyclic aromatic compounds. This protocol has provided an effective synthetic method for five-membered heterocyclic aromatics including indole derivatives.[1−3] On the other hand, six-membered ring formation with ortho-functionalized aryl isocyanides has only been reported quite recently.[4,5]

In a very recent paper, Rainier and co-workers reported the synthesis of indole derivatives by radical cyclization of *o*-alkynylisocyanobenzenes.[6] They briefly described the formation of quinolines as undesired byproducts of the radical cyclization. The appearance of this paper prompted us to publish our quinoline synthesis by the cyclization of *o*-alkynylisocyanobenzenes.[7] Herein, we report a new and versatile synthesis of substituted quinolines through nucleophile-triggered 6-endo cyclization of *o*-alkynylisocyanobenzenes, which are readily available from *o*-iodoaniline and alkynes.

o-(Trimethylsilylethynyl)isocyanobenzene (**3a**) was prepared in high yield from *o*-iodoaniline (**1**) and trimethylsilylacetylene via Sonogashira−Hagihara coupling and *N*-formylation, followed by dehydration (Scheme 1).[8] The compound **3a** could be isolated by silica gel column chromatography.

Scheme 1. Synthesis of *o*-(Trimethylsilylethynyl)isocyanobenzene **3a**



(1) For anionic cyclizations, see: Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 3532. Ito, Y.; Kobayashi, K.; Saegusa, T. *Tetrahedron Lett.* **1979**, *20*, 1039. Haefliger, W.; Knecht, H. *Tetrahedron Lett.* **1984**, *25*, 289. Orita, A.; Fukudome, M.; Ohe, K.; Murai, S. *J. Org. Chem.* **1994**, *59*, 477.

(2) For Lewis acid mediated cyclization, see: Ito, Y.; Kobayashi, K.; Saegusa, T. *Chem. Lett.* **1980**, 1563.

(3) For radical cyclizations, see: Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. Shinada, T.; Miyachi, M.; Itagaki, Y.; Naoki, H.; Yoshihara, K.; Nakajima, T. *Tetrahedron Lett.* **1996**, *37*, 7099.

(4) Kobayashi, K.; Matoba, T.; Irisawa, S.; Matsumoto, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1998**, 551.

(5) Synthesis of quinolines by radical reaction of aryl isocyanide with *o*-alkynyliodobenzenes was reported. See: Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67 and references therein.

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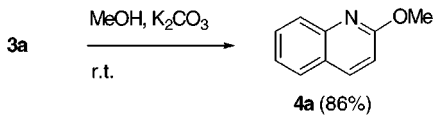
The compound **3a** was stirred in methanol in the presence of potassium carbonate at room temperature. Six-membered ring formation accompanied by the cleavage of the silicon−carbon bond was completed within 6 h, giving 2-methoxyquinoline (**4a**) in 86% yield (eq 1). The reaction was

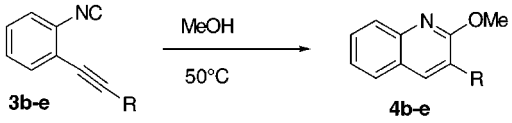


(1)

significantly retarded in the absence of the base (36% conversion after 48 h). No trace of the indole derivative was observed in the reaction mixture.

Reactions of internal alkynes **3b**−**e** other than TMS derivative **3a** proceeded in the absence of base at 50 °C to afford the corresponding 3-substituted 2-methoxyquinolines in good yields (Table 1).

Table 1. Synthesis of 2-Methoxyquinolines by Cyclization of *o*-Alkynylisocyanobenzenes with Methanol[a]

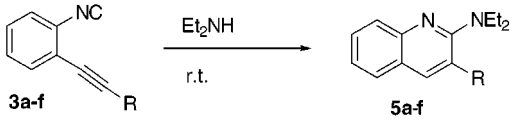


entry	**3** (R)	product (yield, %)
1	**3b** (*t*-Bu)	**4b** (76)
2	**3c** (*c*-Hex)	**4c** (71)
3	**3d** (CH_2OCH_3)	**4d** (66)
4	**3e** (Ph)	**4e** (86)

[a] A mixture of **3** (0.5 mmol) and methanol (0.5 mL) was stirred for 20 h at 50 °C.

Use of diethylamine as the nucleophile rather than methanol resulted in the formation of 3-substituted 2-(diethylamino)quinolines **5** in better yields (Table 2). Note that **5a** was produced in high yield even in the presence of K_2CO_3

Table 2. Synthesis of 2-(Diethylamino)quinolines by Cyclization of *o*-Alkynylisocyanobenzenes with Et_2NH[a]

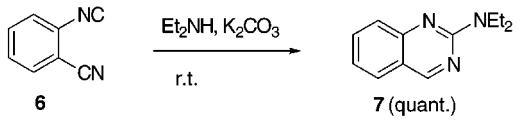


entry	**3** (R)	product (yield, %)
1[b]	**3a** (TMS)	**5a** (92)
2	**3b** (*t*-Bu)	**5b** (86)
3	**3c** (*c*-Hex)	**5c** (80)
4	**3d** (CH_2OCH_3)	**5d** (65)
5	**3e** (Ph)	**5e** (94)
6	**3f** (1-*c*-hexenyl)	**5f** (86)

[a] A mixture of **3** (1 mmol) and diethylamine (5 mL) was stirred for 24 h at room temperature unless otherwise noted. [b] In the presence of potassium carbonate (0.5 mmol).

(entry 1). The cyclization reactions of other isonitriles **3b**−**f** with Et_2NH proceeded at room temperature in the absence of potassium carbonate. An isocyanide bearing an enynyl group at the ortho position (**3f**) also provided the corresponding alkenylquinoline **5f** in high yield (entry 6).

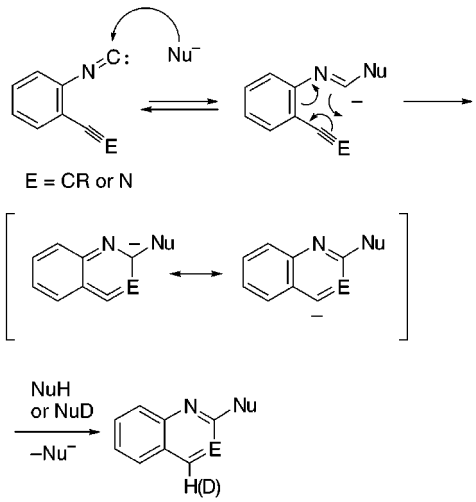
To gain insight into the reaction mechanism, the reaction of *o*-isocyanobenzonitrile (**6**) was examined under similar conditions used for **3**. Interestingly, 2-diethylaminoquinazoline (**7**) was formed in high yield through the diethylamine-induced cyclization in the same manner as the reaction of **3** (eq 2).



(2)

On the basis of this finding, the mechanism shown in Scheme 2 is presumed. Initial attack of the nucleophile to

Scheme 2. Possible Mechanism of the Cyclization of *o*-Alkynylisocyanobenzenes and *o*-Isocyanobenzonitrile Induced by Nucleophiles



the isocyano carbon of **3** (E = CR) or **6** (E = N) produces the corresponding imidoyl anion. The intermediate undergoes a 6π electrocyclization to give a bicyclic allene or a ketenimine intermediate,[9] which is rapidly protonated to afford the corresponding product **4**, **5**, or **7**.[10] Although the addition[11] of alcohols and amines to ordinary isonitriles is known to be very sluggish in the absence of catalysts, the facile electrocyclization following the reversible attack of the nucleophile may have favorably driven **3** to the formation

(6) Rainier, J. D.; Kennedy, A. R.; Chase, E. *Tetrahedron Lett.* **1999**, *40*, 6325.

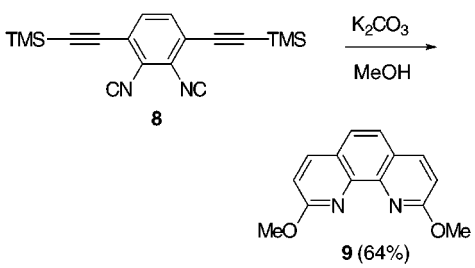
(7) A part of this paper was presented at the 76th Chemical Society of Japan National Meeting, March, 1999, Yokohama, 4C303.

(8) For the use of **3a** in a palladium-mediated cyclization, see: Onitsuka, K.; Segawa, M.; Takahashi, S. *Organometallics* **1998**, *17*, 4335.

(9) Intermediacy of reactive cyclic allenes was discussed. See: Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378.

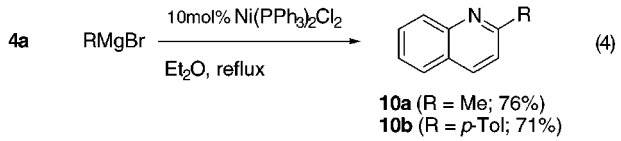
of the quinolines. It is worth noting that deuterium was quantitatively incorporated at the 3- and 4-positions of the quinoline **4a** produced, when the cyclization of **3a** was carried out in CH_3OD in the presence of potassium carbonate. The incorporation of the deuterium to the 3-position indicates that deuteriodesilylation with CH_3OD/K_2CO_3 may be involved prior to the cyclization reaction.

The new cyclization was successfully applied to the synthesis of phenanthroline derivatives **9**. The treatment of dialkynyldiisocyanobenzene **8** with methanol in the presence of potassium carbonate afforded the double cyclization product **9** in good yield (eq 3).



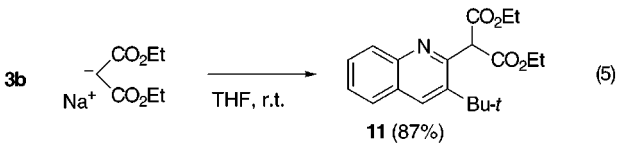
(3)

The 2-methoxyquinoline derivative **4a** prepared by this method was synthetically elaborated using Ni-catalyzed cross-coupling reaction with Grignard reagents as exemplified in eq 4.[12]



(4)

A further synthetic application of the present reaction is demonstrated by the cyclization of *o*-alkynylisocyanobenzenes (**3**) induced by carbon nucleophiles. Thus, the sodium enolate of diethylmalonate reacted with **3b** at room temperature to give **11** in 87% yield via C−C bond formation at the isocyano carbon (eq 5).



(5)

This example demonstrates the potential utility of this cyclization reaction for the efficient synthesis of a variety of quinoline derivatives. Investigations to explore cyclizations induced by other carbon nucleophiles are now underway.

Supporting Information Available: Experimental procedures and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) One of the reviewers suggested a mechanism involving a initial 6π cyclization of **3**, which affords a cyclic allenyl intermediate with a carbene site at the 2-position, followed by trapping with methanol or diethylamine. Although we also considered this alternative mechanism, the mechanism proposed by us may be more likely at this moment, if it is taken into account that each alkynylisocyanobenzene **3** exhibited different reaction rates toward the two different reactants, i.e., methanol and dimethylamine. Indeed, we would expect very similar reaction rate for the two reactions, if the generation of the highly reactive allenyl carbene intermediate is involved in the reaction.

(11) Saegusa, T.; Ito, Y. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; p 65.

(12) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246.