Thermal Aza-Bergman Cyclization of *o*-Alkynylaryl Isocyanides with Organic Diselenide, Ditelluride, and Iodine Leading to 2,4-Difunctionalized Quinolines

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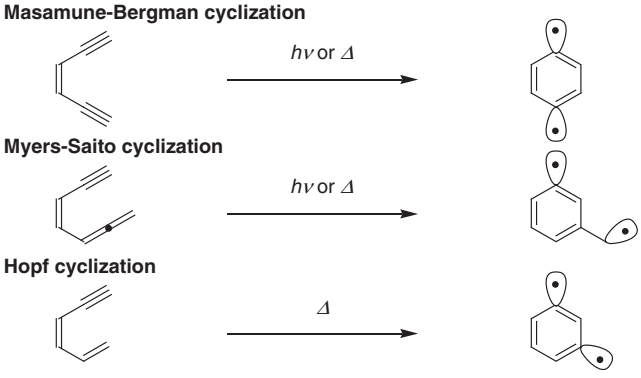
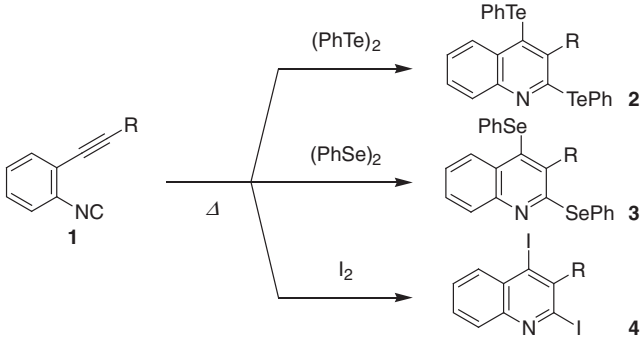
Thermal aza-Bergman cyclization of *o*-alkynylaryl isocyanides has been achieved in the presence of organic dichalcogenides. The reactions can be induced upon heating at 40 °C to afford the corresponding 2,4-dichalcogenated quinolines. In addition, similar conditions can be also employed with iodine to form 2,4-diiodoquinolines.

Bergman cyclization is one of the most efficient methods for the preparation of 6-membered ring structures (Scheme 1).[1] The Masamune–Bergman cyclization of (*Z*)-3-hexen-1,5-diyne forms 1,4-benzenediyl biradical species.[2] Similarly, the Myers–Saito cyclization of (*Z*)-1,2,4-heptatrien-6-yne forms the corresponding biradical species,[3] as shown in Scheme 1. The Hopf cyclization of (*Z*)-1,3-hexadien-5-yne forms 1,3-benzenediyl biradical species.[4] Recently, Bergman-type cyclization reactions were applied to several substrates having ketene,[5] ketenimine,[6] and carbodiimide units;[7] these cyclization reactions afford the corresponding heterocycles.

Isocyanides have been shown to be effective candidates for the preparation of *N*-heterocycles,[8] especially methods for the synthesis of *N*-heterocycles from isocyanides with an unsaturated bond, which can be induced by radical species,[9] nucleophiles,[10] and transition-metal catalysts.[11]

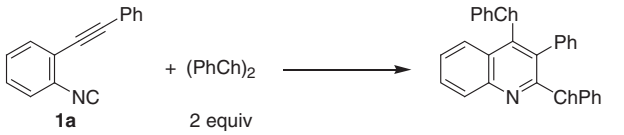


Scheme 1. A series of Bergman cyclizations.



Scheme 2. Thermal aza-Bergman cyclization of isocyanide **1**.

Table 1. Thermal Reaction of Isocyanide **1a**[a)]



Entry	Ch	Temperature/°C	Product	Yield/%[b)]
1	Te	80	**2a**	78
2	Te	60	**2a**	74
3	Te	40	**2a**	73 (73)
4	Se	40	**3a**	85 (84)
5	Se	60	**3a**	62
6	Se	80	**3a**	57
7	S	40	**5a**	0
8	S	60	**5a**	0
9	S	80	**5a**	0

a) Reaction conditions: isocyanide (**1a**, 0.05 mmol), organic dichalcogenide (0.10 mmol), $CDCl_3$ (0.5 mL), 4 h. b) Yields were determined by ^{1}H NMR using 1,3,5-trioxane as an internal standard. Values in parentheses are isolated yields.

Recently, we have developed the photochemical aza-Bergman cyclization of *o*-alkynylaryl isocyanides in the presence of diselenides, ditellurides, and iodine.[12] These cyclizations afford 2,4-diselenated quinolines, 2,4-ditellurated quinolines, and 2,4-diiodoquinolines, respectively. In addition, the photochemical reaction of *o*-alkynylaryl isocyanides with hydrogen-transfer reagents such as tributyltin hydride affords the corresponding 2,4-dihydrogenated quinolines, selectively. These results strongly suggest that the photochemical cyclization of *o*-alkynylaryl isocyanides proceeds through the formation of 2,4-biradical species as the intermediate (see the structure **A** in Scheme 4). Considering that various types of Bergman cyclization reactions can be induced not only by photoirradiation but also by heating, a thermal aza-Bergman cyclization of *o*-alkynylaryl isocyanides would be expected to take place.[13] In this paper, we report the thermal aza-Bergman cyclization of *o*-alkynylaryl isocyanides in the presence of organic diselenide, ditelluride, or iodine. The cyclization affords the corresponding 2,4-disubstituted quinolines (Scheme 2).

At first, we examined the thermal reaction of 2-(phenylethynyl)phenyl isocyanide (**1a**) in the presence of organic dichalcogenides under several conditions (Table 1). Upon heating at 80 °C, the reaction of isocyanide **1a** with $(PhTe)_2$

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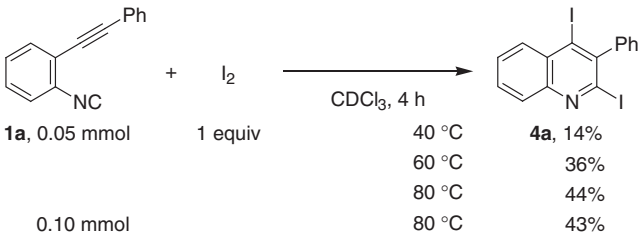


Scheme 3. The reaction of isocyanide **1a** with iodine.

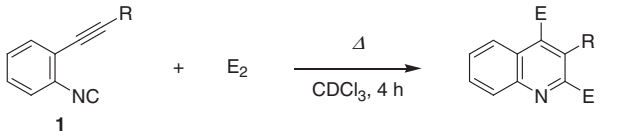
afforded 2,4-ditellurated quinoline **2a** in 78% yield (Entry 1). When the reaction was performed at 60 and 40 °C, quinoline **2a** was obtained in 74% and 73% yields, respectively (Entries 2 and 3). The thermal reaction with $(PhSe)_2$ at 40 °C afforded 2,4-diselenated quinoline **3a** in 85% yield, successfully (Entry 4). Increasing the temperature (60 and 80 °C) resulted in the decrease in the yields of quinoline **3a** (62% and 57%, respectively). In these cases, the starting isocyanide was not recovered (Entries 5 and 6). This is probably due to side-reactions, e.g., a thermal addition of $(PhSe)_2$ to aromatic acetylenes, which proceeds at 80 °C to produce the corresponding vicinally diselenated alkenes.[14] Next the synthesis of 2,4-dithiolated quinoline **5a** was attempted, but the thermal reaction of **1a** with $(PhS)_2$ did not proceed (Entries 7–9).

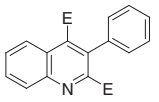
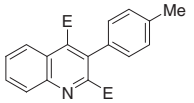
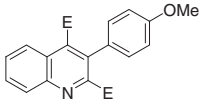
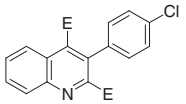
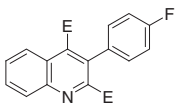
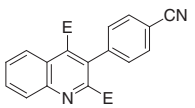
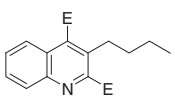
The thermal reaction of **1a** with iodine was also examined (Scheme 3). The reaction of isocyanide **1a** with iodine at 40 °C provided 2,4-diiodoquinoline **4a** in 14% yield.[12b,15] The yields of 2,4-diiodoquinoline **4a** increased to 44% by increasing the reaction temperature to 80 °C.

Scope and limitation of this thermal reaction was examined and the results are summarized in Table 2. Isocyanides **1b** and **1c**, which bear 4-methylphenyl and 4-methoxyphenyl groups, underwent the ditellurated and diselenated cyclization to afford the corresponding quinolines **2b**, **3b**, **2c**, and **3c** in 78%, 55%, 67%, and 62% yields, respectively (Entries 4, 5, 7, and 8). Halide substituents such as chloride and fluoride are tolerant of the reaction conditions, and the corresponding quinolines **2d**, **3d**, **2e**, and **3e** were obtained successfully (Entries 10, 11, 13, and 14). In the case of isocyanide **1f**, low yields of quinolines **2f** and **3f** were obtained (the oligomerization of **1f** proceeded preferentially) (Entries 16 and 17). 2-(1-Hexynyl)phenyl isocyanide (**1g**) could also afford quinolines **2g** and **3g** in 78% and 72% yields, respectively (Entries 19 and 20). The reactions of isocyanides **1a**, **1b**, **1c**, **1d**, **1e**, and **1g** with iodine at 80 °C gave the corresponding 2,4-diiodoquinolines **4a**, **4b**, **4c**, **4d**, **4e**, and **4g**, respectively (Entries 3, 6, 9, 12, 15, and 21). Unfortunately, the reaction of **1f** with iodine formed a trace amount of **4f**. Instead, the oligomer of **1f** was obtained as the major product (Entry 18). In general, the thermal Bergman cyclization of (*Z*)-3-hexen-1,5-diyne derivatives requires heating at approximately 200 °C.[16] It is noteworthy that the present thermal aza-Bergman cyclization proceeds upon heating at 40–80 °C.

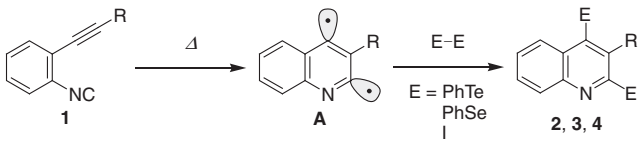
A possible reaction pathway for the thermal reaction of *o*-alkynylaryl isocyanides **1** is shown in Scheme 4.[17] Upon heating, *o*-alkynylaryl isocyanides **1** undergo aza-Bergman cyclization to generate the corresponding 2,4-biradical species **A**. Then, the 2,4-biradical species **A** is captured by diphenyl ditelluride,[18] diphenyl diselenide,[18] or iodine[19] to form the corresponding 2,4-disubstituted quinolines.

Table 2. Thermal Reaction of Several Isocyanides **1**[a]



Entry	1	E	Product		Yield/%[b]
1	1a	PhTe–		2a	73
2		PhSe–		3a	84
3[c]		I–		4a	44
4	1b	PhTe–		2b	78
5		PhSe–		3b	55
6[c]		I–		4b	49
7	1c	PhTe–		2c	67
8		PhSe–		3c	62
9[c]		I–		4c	46
10	1d	PhTe–		2d	51
11		PhSe–		3d	60
12[c]		I–		4d	44
13	1e	PhTe–		2e	74
14		PhSe–		3e	82
15[c]		I–		4e	25
16	1f	PhTe–		2f	18
17		PhSe–		3f	7
18[c]		I–		4f	trace
19	1g	PhTe–		2g	78
20		PhSe–		3g	72
21[c]		I–		4g	67

a) Reaction conditions: isocyanide (**1**, 0.05 mmol), dichalcogenide (0.10 mmol), $CDCl_3$ (0.5 mL), 40 °C, 4 h. b) Isolated yield. c) Iodine (0.05 mmol) was used in place of organic dichalcogenides, and the reaction was carried out at 80 °C.



Scheme 4. A possible reaction pathway.

In summary, a novel thermal aza-Bergman cyclization of *o*-alkynylaryl isocyanides with diphenyl diselenide, diphenyl ditelluride, and iodine has been developed. These reactions provide the corresponding 2,4-difunctionalized quinolines selectively. It is noteworthy that the present aza-Bergman cyclization proceeds at lower temperatures than the thermal Bergman cyclization of 1,2-diethynylbenzene derivatives.

Experimental

Typical Procedure for the Synthesis of 2,4-Difunctionalized Quinolines, e.g., 2,4-Ditellurated Quinolines. A mixture of 2-(phenylethynyl)phenyl isocyanide (**1a**, 0.05 mmol) and diphenyl ditelluride (0.10 mmol) in $CDCl_3$ (0.5 mL) was heated at 40 °C for 4 h. After the reaction was

complete, the resulting mixture was concentrated in vacuo. The crude mixture was purified by PTLC on silica gel (eluent: hexane/AcOEt = 9/1), giving 3-phenyl-2,4-bis(phenyltellanyl)quinoline (**2a**, 22.4 mg, 0.037 mmol, 73%).

3-Phenyl-2,4-bis(phenyltellanyl)quinoline (2a): Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (t, $J = 7.2$ Hz, 2H), 7.13–7.18 (m, 3H), 7.29–7.56 (m, 10H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 6.6$ Hz, 2H), 8.22 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.0, 118.0, 126.6, 127.5, 128.3, 128.5, 129.0, 129.2, 129.4, 129.5, 129.7, 133.4, 134.9, 135.1, 136.7, 139.8, 143.3, 147.2, 148.8, 149.0; IR (NaCl, cm^{-1}): 3053, 1651, 1574, 1537, 1472, 1435, 1367, 1333, 1312, 1279, 1132, 1080, 1063, 1016, 997, 756, 733, 689; HRMS (EI): calcd for $C_{27}H_{19}NTe_2$ $[M]^+$ 616.9642, found 616.9635.

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Supporting Information

Experimental procedures and characterization data for quinoline derivatives. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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