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Highly selective introduction of heteroatom groups to isocyanides and its application to electrocyclic reactions*

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Abstract: Photoinduced cyclization of *o*-alkenylaryl isocyanides with (PhS)₂ in the presence of (PhTe)₂ affords the corresponding bisthiolated indene derivatives in good yields via radical cyclization process by thio radical. The procedure can be applied to the construction of tetracyclic systems by using bis(*o*-aminophenyl) disulfides in place of (PhS)₂. In sharp contrast, when *o*-alkynylaryl isocyanides are employed as the substrates, novel electrocyclic reactions take place upon photoirradiation or heating at 40~80 °C to generate quinoline 2,4-biradical species, which are trapped with organic diselenides, ditellurides, and molecular iodine to give the corresponding 2,4-diseleno-, ditelluro-, and diiodo-quinoline derivatives, respectively, in good yields. The obtained quinoline derivatives are useful synthetic intermediates; for example, cross-coupling reactions using 2,4-diiodoquinolines lead to the preparation of functionalized quinoline derivatives.

Keywords: electrocyclic reactions; isocyanides; organic dichalcogenide; radical additions; radical cyclization.

INTRODUCTION

Isocyanides (RNC) are useful C1 units in organic synthesis as well as building blocks for nitrogencontaining heterocycles [1]. Since isocyanides have an isoelectronic structure with carbon monoxide, they may react with carbon- and heteroatom-centered radical species (Z^{\bullet}) to generate the corresponding imidoyl radicals [\bullet C(=NR)-Z] [2]. Recently, we have developed a series of photoinduced radical addition reactions of organic dichalcogenides to carbon–carbon unsaturated compounds such as alkynes, alkenes, allenes, conjugated dienes, etc. [3]. These reactions involve the photoinduced homolysis of chalcogen–chalcogen single bonds as an initial step to generate the corresponding chalcogen-centered radicals. In this paper, we wish to report photoinduced radical addition reactions of organic dichalcogenides to isocyanides and their applications to cyclization reactions, which provide a useful tool to synthesize nitrogen-containing heterocyclic compounds (eq. 1).

$$ArY-YAr \xrightarrow{h\nu} 2 ArY \cdot \xrightarrow{RNC} NR \\ (Y = S, Se, Te) \qquad ArY \xrightarrow{} o$$
 addition or cyclization (1)

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RESULTS AND DISCUSSION

Photoinduced radical addition of organic dichalcogenides to isocyanides

Organic dichalcogenides such as $(PhS)_2$, $(PhSe)_2$, and $(PhTe)_2$ have their absorption maxima based on the $n \rightarrow \sigma^*$ transition in ultraviolet (UV), near-UV, and visible regions, respectively (Fig. 1), and therefore irradiation with these light sources causes homolytic cleavage of the chalcogen–chalcogen single bonds to generate the corresponding chalcogen-centered radicals (eq. 1). Thus, we examined the photoinduced reactions of diphenyl dichalcogenides with isocyanides.

When the reaction of 2,6-xylyl isocyanide with 5 equiv of diphenyl disulfide in the absence of solvent was conducted for 13 h upon irradiation with a tungsten lamp through Pyrex (hv >300 nm), 1,1-bisthiolation product was obtained in 74 % yield (eq. 2) [4]. The reaction may proceed via the formation of imidoyl radical intermediates by the reaction of the isocyanide with PhS•, and the subsequent S_H2 reaction of the imidoyl radical intermediates with (PhS)₂ leads to the 1,1-bisthiolation product. In the cases of aliphatic isocyanides, however, the desired bisthiolation did not take place at all, probably owing to the instability of the imidoyl radical intermediates.

As to the radical addition of $(PhSe)_2$ to isocyanides, both aromatic and aliphatic isocyanides did not undergo the photoinduced bisselenation, except isocyanide bearing a nitro group at the para position of the phenyl group (eq. 3). Owing to the weakness of the C–Se bond and the relative stability of PhSe• (compared with PhS•), the imidoyl radicals bearing phenylseleno group easily cause reverse reaction to reform isocyanides and PhSe•. In the case of *p*-nitrophenyl isocyanide, the inductive effect of the nitro group stabilizes the imidoyl radical intermediate and makes it possible to attain the desired 1,1-bisselenation reaction. As to the radical addition of $(PhTe)_2$ to isocyanides, no reaction occurred, because of the instability of the bistelluration products under photoirradiation conditions.



Fig. 1 UV-vis spectra of (PhS)₂, (PhSe)₂, and (PhTe)₂.

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Photoinduced bischalcogenation of isocyanides by using dichalcogenide mixed systems

Some kinetic data are of great importance for predicting the radical addition reactions of organic dichalcogenides to unsaturated compounds. The reactivity of the addition of phenylseleno radical to carbon–carbon unsaturated bonds is relatively lower by the factor of about 10–50, compared with the corresponding thio radical [5]. As to the addition of PhTe• to unsaturated bond, there is no kinetic data reported, but it is predicted that PhTe• may be less reactive compared with PhSe•. On the other hand, the rate constants for the S_H2 reaction are estimated to be $7.6 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ for (PhS)₂, $1.2 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for (PhSe)₂, and $4.8 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for (PhTe)₂ by using the free radical clock system of the 5-hexenyl radical [6]. These kinetic data indicate that (PhSe)₂ and (PhTe)₂ exhibit excellent carbon radical capturing abilities, compared with (PhS)₂, by the factor of approximately 160 and 640, respectively.

With these kinetic considerations in mind, we next examined the photoirradiated reactions of aromatic isocyanides with $(PhS)_2$ and $(PhSe)_2$ [or $(PhTe)_2$].

When a reaction of 2,6-xylyl isocyanide with equimolar amounts of $(PhS)_2$ and $(PhSe)_2$ was conducted upon irradiation with the light of wavelength over 300 nm, the corresponding thioselenation product was obtained successfully in excellent yield. Compared with single systems of $(PhS)_2$ or $(PhSe)_2$, the $(PhS)_2$ - $(PhSe)_2$ mixed system is effective for the radical addition to isocyanides. This is because of the efficient radical addition of PhS• to isocyanides and the efficient trapping of the imidoyl radical intermediates by $(PhSe)_2$. Table 1 summarizes the results of thioselenation of various aromatic isocyanides. Similar conditions can be employed with a variety of aromatic isocyanides, and the desired thioselenated products were obtained in excellent yields (entries 1–5) [4].

Table 1 Selective thioselenation of isocyanides using (PhS)₂-(PhSe)₂^a.

Ar-	−NC + (PhS) ₂ +	· (PhSe	$\Rightarrow)_2 \xrightarrow{h \nu (>300 \text{ nm})} \text{Ar}$	−N≕ SePh
entry	isocyanide	time, h	product	yield, % ^b
1	✓NC	5	⟨>−N=< SPh SePh	98
2	MeO-	5	MeO-	63
3 4 ^d	O ₂ N-	1.5 3	$O_2N \rightarrow N \rightarrow SePh$	90 ^c 92 ^e
5	F ₃ C-	2	$F_3C \longrightarrow N \stackrel{\text{SPh}}{\underset{\text{SePh}}{\longrightarrow}} N$	86

^a Reaction conditions: isocyanide (0.25 mmol), (PhS)₂ (0.25 mmol), (PhSe)₂ (0.25 mmol), CDCl₃ (0.5 mL), *hv*. tungsten lamp (500 W, Pyrex), 40 °C.
 ^b Isolated yield. ^c Diselenide adduct was formed in 10 % yield. ^d (PhSe)₂ (0.15 mmol). ^e Diselenide adduct was formed in 2 % yield.

Ph
$$\frown$$
 NC + (PhS)₂ + (PhSe)₂ $\xrightarrow{h_{\mathcal{V}}(>300 \text{ nm})}$ Ph \frown N= \overleftarrow{SPh}
1.0 equiv.
0.23 equiv.
81%
47%
(4)

Next, we examined the photoirradiated reactions of aliphatic isocyanides with $(PhS)_2$ and $(PhSe)_2$. When a mixture of benzyl isocyanide, $(PhS)_2$, and $(PhSe)_2$ was irradiated with a tungsten lamp through Pyrex, surprisingly, 1,1-bisthiolation product, which could not be obtained by the reaction of aliphatic isocyanides with $(PhS)_2$ alone, was obtained in a moderate yield without formation of any selenated products (eq. 4). The desired bisthiolation could take place even in the presence of catalytic amounts of $(PhSe)_2$.

To gain insight into the role of $(PhSe)_2$, the reaction of benzyl isocyanide with $(PhS)_2$ and $(PhSe)_2$ was monitored by taking the ¹H NMR spectra over a period of 50 h, and it was found that the thioselenation product was formed in the initial stage to convert gradually to the bisthiolation product under photoirradiation condition. The results clearly indicate that thioselenation occurs under kinetic control. Therefore, the reverse reaction from the thioselenation product generates the imidoyl radical intermediate, which may be trapped with PhSeSPh, yielding the bisthiolation product with regeneration of PhSe•.

Table 2 summarizes the results of a variety of aliphatic isocyanides with $(PhS)_2$ in the presence of $(PhSe)_2$. When the reaction of primary alkyl isocyanide with $(PhS)_2$ and $(PhSe)_2$ was conducted in the absence of solvent, the desired bisthiolated product was obtained in a good yield (entry 3). On the other hand, in the case of isocyanides bearing a more bulky substituent, the reaction did not proceed effectively (entry 7), probably because the imidoyl radical intermediate was unstable to decompose to *tert*-butyl radical and PhSCN [7].

RNC	+ (PhS) ₂	+ (PhS	e) ₂ -	hv CDCl ₃ , 40 °C	► ^R `N=<	SPh SPh
	1 equiv.	1 equ	liv.			
entry	R		time,	h p	roduct	yield, % ^a
1	ⁿ Bu	1.0 M	46	\sim	SPh	51
2 ^b		1.0 M	46		SPh	46
3		neat	56			78
4	^c Hex	0.5 M	50	\square	SPh	39 (55)
5		0.5 M	80	\searrow	SPh	46
6 🤇	Сн₂сн	l ₂ neat	23	\bigcirc	N=(SPh SPh	58 ^c
7	^t Bu	neat	20	\rightarrow	−N= SeP	trace h

Table 2 Bisthiolation of aliphatic isocyanides with $(PhS)_2$ in the presence of $(PhSe)_2$.

^a Isolated (NMR) yield. ^b hv>400 nm. ^c (PhSe)₂ (0.5 equiv.).

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Photoinduced cyclization

The obtained thioselenation products can convert to the β -lactam framework by formal [2 + 2] cyclization with ketene equivalents. When the [2 + 2] cyclization of the thioselenated product with 2 equiv of phenoxyacetyl chloride in the presence of triethylamine was performed, the desired β -lactam derivative was obtained successfully.

Moreover, this thioselenation and [2 + 2] cyclization sequence is applied to the synthesis of carbacephem derivatives (Scheme 1). When the reaction of (diethoxyphosphoryl)methyl isocyanide with (PhS)₂ and (PhSe)₂ was performed under the photoirradiation conditions, the corresponding thioselenated compound was formed in 96 % yield. The thioselenation product reacted with methoxyacetyl chloride in the presence of triethylamine to give a β -lactam derivative in 79 % yield. When the reaction of the β -lactam derivative with 3-buten-2-one was conducted in the presence of ^{*n*}Bu₃SnH and AIBN, the seleno group of the β -lactam was selectively converted into the 3-butanonyl group. Then, the desired carbacephem derivative was obtained in excellent yield by the intramolecular Horner–Emmons reaction.



Scheme 1 Synthesis of carbacephem framework.

We next examined the photoinduced thiotelluration of isocyanides with $(PhS)_2$ and $(PhTe)_2$ (eq. 5) [8]. Although usual isocyanides such as 2,6-xylyl isocyanide, *p*-methoxyphenyl isocyanide, and benzylisocyanide did not afford the corresponding thiotellurated products at all, aryl isocyanides bearing an electron-withdrawing group such as *p*-nitro, *p*-trifluoromethyl, and *p*-cyano, provided the desired thiotelluration products successfully in good yields. Aryl isocyanides bearing weak electron-withdrawing groups such as *p*-chloro and *m*-methoxy groups provided the corresponding thiotelluration products in moderate yields.

Photoinduced radical cyclization of *o*-alkenylaryl isocyanides by using a $(PhS)_{2}$ - $(PhTe)_{2}$ mixed system

Isocyanides, having an unsaturated bond at a suitable position, are expected to undergo radical cyclization reactions initiated by chalcogen-centered radicals. At first, we attempted radical cyclization reaction of o-alkenylaryl isocyanides by using the (PhS)₂-(PhSe)₂ mixed system, but the reaction provided a complex mixture including 1,1-thioselenation product of isocyanide unit, cyclic thioselenation product, and cyclic bisthiolation product (Scheme 2). In contrast, the photoinduced reaction of o-alkenylaryl isocyanides by using the (PhS)₂-(PhTe)₂ mixed system led to the formation of cyclic bisthiolation product selectively [9]. Compared with carbon–selenium bonds, carbon–tellurium bonds are unstable under photoirradiation conditions, and are replaced with stable carbon–sulfur bonds.



Scheme 2 Radical cyclization of *o*-alkenylaryl isocyanide.

We next examined the scope and limitation of this indole synthesis, and the results are summarized in Table 3. Ester, ketone, and phenyl groups at the terminal position of the vinyl group are tolerant of the photoinduced cyclization. This reaction afforded the corresponding bisthiolated indoles in moderate to good yields (entries 2–4). Isocyanides having substituents on the phenyl group also underwent the photoinduced cyclization to give indole derivatives (entries 5–7). In the case of the isocyanide bearing acrylonitrile group, a trace amount of the desired bisthiolated indole was formed, and 2-phenylthioindole-3-carbaldehyde was obtained as the major product in 71 % yield (entry 8). The indole carbaldehyde was formed via the formation of bisthiolated indole and the following hydrolysis.

When 2-allylphenyl isocyanide was used as the substrate, the 6-*exo* radical cyclization reaction takes place by using $(PhS)_2$ - $(PhTe)_2$ mixed systems to give the corresponding quinoline derivatives in moderate yields (eq. 6).



Nitrogen-containing heterocycles such as indoles and quinolines are present in a number of natural products such as alkaloids, and many of them indicate valuable bioactivities. Therefore, indole and quinoline derivatives have been often designed and synthesized as new pharmaceutical active agents. Therefore, development of new methods for the preparation of various indole and quinoline derivatives is of great importance in pharmaceutical sciences as well as organic synthesis. Heterocycles having organosulfur groups are also important in the fields of pharmacology, materials sciences, and organic synthesis.

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Table 3 Photoinduced cyclization of several isocyanides with (PhS)₂ in the presence of (PhTe)₂^a.

^a Reaction conditions: isocyanide (0.15 mmol), (PhS)₂ (0.23 mmol), (PhTe)₂ (0.23 mmol), CHCl₃ (0.4 mL), *hv*. irradiation with a high-pressure Hg lamp through a glass filter (>400 nm), r.t., 24 h. ^{*b*} Isolated yield. ^{*c*} 31 h. ^{*d*} 18 h. ^{*e*} 30 h.

When the photoinduced reaction of methyl 3-(2-isocyanophenyl)acrylate with bis(2-aminophenyl) disulfide was examined in the presence of $(PhTe)_2$, the desired bisthiolated indole was not observed. Surprisingly, however, the tetracyclic compound, methyl (12H-benzo[4,5]thiazolo[2,3-*b*] quinazolin-12-yl)acetate, which had both dihydroquinazoline and benzothiazole units, was obtained in 71 % yield (eq. 7). 3-(2-Isocyanophenyl)acrylonitrile also afforded the similar tetracyclic compound in 65 % yield. Conclusive determination of the structure of the tetracyclic product (12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-yl)acetonitrile was unambiguously ascertained through X-ray crystal analysis (Fig. 2).



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Fig. 2 ORTEP diagram of (12H-Benzo[4,5]thiazolo[2,3-b]quinazolin-12-yl)acetonitrile [9].

A plausible reaction pathway for the formation of tetracyclic compounds is shown in Scheme 3. The photoinduced thiotelluration of *o*-ethenylaryl isocyanides and the following nucleophilic substitution of the phenyltelluro group by the amino group at the *ortho*-position lead to the formation of benzo-thiazole derivatives. Then, intramolecular aza-Michael addition reaction affords tetracyclic compounds.



Scheme 3 A plausible pathway for the photoinduced cyclization of isocyanides with bis(2-aminophenyl) disulfide.

Photoinduced electrocyclic reactions of *o*-alkynylaryl isocyanides with $(PhSe)_2$, $(PhTe)_2$, or hydrogen sources

During the course of our studies on the photoinduced cyclization of isocyanides with heteroatom compounds, we next examined the cyclization of *o*-alkynylaryl isocyanides using several heteroatom compounds. We first examined the photochemical reaction of 2-(phenylethynyl)phenyl isocyanide with diphenyl dichalcogenides, such as diphenyl disulfide, diphenyl diselenide, and diphenyl ditelluride (eq. 8) [10]. When the isocyanide was treated with diphenyl disulfide upon photoirradiation, no reaction took place at all. In contrast, the photochemical reaction of the isocyanide with 1 equiv of diphenyl diselenide afforded the 2,4-bisselenated quinoline in 46 % yield. The yield of the quinoline derivatives successfully increased when 3 equiv of (PhSe)₂ were used. Furthermore, diphenyl ditelluride could also be employed for the photochemical cyclization, leading to the corresponding 2,4-bistellurated quinoline. When the same reactions of the isocyanide with (PhSe)₂ or (PhTe)₂ were performed in the dark, no cyclization took place. These results indicate that the intramolecular cyclization reactions of *o*-alkynylaryl isocyanides require the photoirradiation.



We next examined the scope and limitations of this photochemical cyclization with organic dichalcogenides using several isocyanides, and the results are summarized in Table 4.

 R^2Y

	NC	+	(R ² Y);	hv(>)	300 nm, Y 400 nm, Y DCl ₃ , r.t., 4	= Se) = Te) h	R ¹ N YR ²			
entry	R ¹	R ²	Y	yield (%) ^b	entry	R ¹	R ²		Y	yield (%) ^b
1	C_6H_5	C_6H_5	{ Se Te	67 50	7	1-cyclohexenyl	C_6H_5	{	Se Te	82 71
2	4–Me–C ₆ H₄		∫ Se	72	8	TMS			Se	9
	0 4		l Te	42	9	C_6H_5	4–Me–C ₆ H ₄		Se	74
3	4-MeO-C ₆ H ₄		Se	73				ſ	Se	79
			(le	51	10		$4-MeO-C_6H_4$	ł	Те	42
4	4-CI-C ₆ H ₄		Se To	72	11		4–CI–C∈H₄	t	Se	66
5	4–F–C∈H₄		Se	54 63				٢	Se	70
	0.4		∫ Se	73	12		4-F-C ₆ H ₄	1	Те	67
6	ⁿ Bu		Te	82	13		Bn	,	Se	<10

Table 4 Photochemical reaction of isocyanides with organic dichalcogenides^a.

R¹

^a Reaction conditions: isocyanide (0.10 mmol), organic dichalcognide (0.20 mmol), CDCl₃ (0.5 mL), r.t., 4 h. ^b Isolated yield.

Isocyanides bearing methyl, methoxy, chloro, and fluoro substituents on the arylethynyl groups underwent the photochemical intramolecular cyclization successfully, affording the corresponding 2,4-bisselenated quinolines in good yields (entries 2–5). Isocyanide having 1-hexynyl or (1-cyclo-hexenyl)ethynyl group at the *ortho*-position could also undergo the photochemical cyclization (entries 6 and 7). However, isocyanide containing a TMS group gave a low yield of the cyclization product, probably because of the bulkiness of the TMS group (entry 8). Similar conditions could be employed with several diaryl diselenides, leading to the corresponding quinolines in good yields (entries 9–12). When dibenzyl diselenide was used for this photochemical reaction, the corresponding quinoline was obtained in lower yield (entry 13). This is most probably due to the lower carbon radical capturing ability of aliphatic diselenides compared with that of aromatic diselenides.

The photochemical reaction of isocyanides with organic ditelluride was also examined. A variety of isocyanides underwent selective cyclization with organic ditellurides to give the corresponding 2,4-bistellurated quinoline derivatives successfully, as shown in Table 4.

To get insight into the reaction pathway for the present cyclization reactions, we examined the photochemical reaction of an isocyanide in the presence of efficient hydrogen-transfer reagents (eq. 9).

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Upon photoirradiation of o-(phenylethynyl)phenyl isocyanide in the presence of tributyltin hydride [or tributylgermyl hydride, tris(trimethylsilyl)silane, etc.], intramolecular cyclization took place to afford 3-phenylquinoline in 82 % yield without formation of 2- or 4-tributylstannyl-3-phenylquinoline [or the corresponding tributylgermyl-, tris(trimethylsilyl)silyl-derivatives etc.]. If the photochemical cyclization using hydrogen-transfer reagents involves the radical cyclization process via the addition of heteroatom-centered radicals to an unsaturated bond, 2- or 4-heteroatom-substituted quinolines should be formed. In addition, the UV–vis spectrum of the isocyanide indicates that its absorption reaches 500 nm. Therefore, these results strongly suggest that a photochemical electrocyclic reaction of o-alkynylaryl isocyanides takes place to form the corresponding biradical species, which abstract hydrogens from hydrogen-transfer reagents (Scheme 4). Therefore, the photoirradiated cyclization reactions of o-alkynylaryl isocyanides with organic diselenides and ditellurides may proceed via the same photochemical electrocyclic reaction, followed by homolytic substitution (S_H2) reaction of the formed biradical species with organic dichalcogenides.



Scheme 4

Similarly, photochemical reaction of *o*-alkynylaryl isocyanides in the presence of alkanethiols such as phenylmethanethiol and ethanethiol and benzeneselenol gave 2,4-dihydrogenated quinoline derivatives with excellent selectivity (eq. 9).

Ph	+	<i>E−H</i> 2 equiv.	<i>hν</i> (> 300 nm) CDCl ₃ , r.t., 4 h	Ph N H	
		ⁿ Bu₃SnH		76 %	
		^c HexSH		84 %	
		PhCH ₂ SH		89 %	(9)
		EtSH		88 %	
		PhSH		46 % ^a	
		PhSeH		70 %	
		ⁿ Bu₃GeH		61 %	
		(TMS) ₃ SiH		53 %	
				(Isolated yields)	

^a2-Phenylthio-3-phenylquinoline was also obtained in 41% yield.

Nucleophilic cyclization reactions of *o*-alkynylaryl isocyanides with arenethiols and ammonium halides

Photochemical reaction of *o*-(phenylethynyl)phenyl isocyanide with benzenethiol gave 3-phenylquinoline and 2-phenylthio-3-phenylquinoline in 46 and 41 % yields, respectively. The selective syntheses of 2-substituted quinolines by the reaction of *o*-alkynylaryl isocyanides with nucleophiles were already

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reported [11]. Thus, the formation of 2-thiolated quinoline derivatives may include similar nucleophilic addition of the thiolate anion to the isocyano groups due to the higher acidity of arenethiols compared with alkanethiols. Then, the reaction of the isocyanide with benzenethiol in the presence of triethyl-amine in the dark provided the corresponding 2-phenylthiolated quinoline derivative in 78 % yield. By using this method, a variety of 2-arenethiolated quinoline derivatives could be synthesized successfully.

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 in the presence of triethylamine in chloroform produced 2-chloroquinoline derivatives under mild conditions (eq. 10) [12]. Furthermore, we investigated the reaction of *o*-(phenylethynyl)phenyl isocyanide with bromoform in the presence of triethylamine, which afforded 2-bromo-3-phenylquinoline in 81 % yield. To apply the synthesis of 2-fluoroquinoline derivatives, which are important in the pharmaceutical industry, we examined the reaction of *o*-(phenyl-ethynyl)phenyl isocyanide with several fluorine sources, because gaseous fluoroform (CHF₃) could not be employed as a fluoride source conveniently.



Thus, we examined the reaction of the isocyanide with tetrabutylammonium fluoride as a fluorine source, which afforded 2-fluoroquinoline in almost quantitative yield. Similarly, treatment of the isocyanide with tetrabutylammonium iodide provided 2-iodoquinoline in 88 % yield. A plausible reaction pathway for the triethylamine-mediated intramolecular halogenating cyclization of *o*-alkynylaryl isocyanides may involve the following: the formation of quaternary ammonium halides ($[Et_3NH]^+X^-$), followed by nucleophilic attack of halide anions to isocyanides cause ionic cyclization to give the corresponding 2-halogenated quinoline derivatives after protonation.

Photoinduced electrocyclic reactions of o-alkynylaryl isocyanides with diiodine

Molecular iodine (I_2) is also a candidate as a trapping reagent toward biradical intermediates generated from *o*-alkynylaryl isocyanides upon photoirradiation. Thus, we examined the synthesis of 2,4-diiodoquinolines by the photochemical cyclization of *o*-alkynylaryl isocyanides with I_2 [13]. Upon irradiation with a high-pressure mercury lamp through Pyrex (hv > 300 nm), *o*-alkynylaryl isocyanides underwent iodocyclization to selectively afford 2,4-diiodo-3-phenylquinoline in good yields (Table 5). By using this method, a wide range of substituted 2,4-diiodinated quinoline derivatives could be prepared successfully.



Table 5 Photochemical cyclization of isocyanides with iodine^a.

^a Reaction conditions: *o*-alkynylaryl isocyanide (0.10 mmol), iodine (0.10 mmol), CHCl₃ (0.50 mL), r.t., 4 h, *hv* irradiation with a high-pressure Hg lamp through a Pyrex filter (> 300 nm).

2,4-Diiodinated quinolines are promising for use as synthetic intermediates to prepare functionalized quinoline derivatives. We demonstrated palladium-catalyzed cross-coupling reactions using 2,4-diiodoquinoline derivatives (Scheme 5). The Migita–Kosugi–Stille cross-coupling reaction of 2,4-diiodo-3-phenylquinoline selectively afforded 4-ethenyl-2-iodo-3-phenylquinoline in 79 % yield. The Sonogashira cross-coupling reaction also could be applied to 2,4-diiodo-3-phenylquinoline; this leads to the formation of 4-alkynyl-2-iodoquinoline in quantitative yield. It is noteworthy that the crosscoupling reactions take place selectively at the 4-position of 2,4-diiodo-3-phenylquinoline even in the presence of approximately 2 equiv of vinylstannane or silylacetylene. In the case of the Suzuki–Miyaura cross-coupling reaction, the palladium-catalyzed reaction of 2,4-diiodo-3-phenylquinoline proceeded at both the 2- and 4-positions, providing 2,3,4-triphenylquinoline in 83 % yield.



Scheme 5 Palladium-catalyzed cross-coupling reactions of 2,4-diiodoquinoline.

Thermal electrocyclic reactions of *o*-alkynylaryl isocyanides with $(PhSe)_2$, $(PhTe)_2$, or I_2

It is known that some of electrocyclic reactions can be induced not only by photoirradiation but also by heating. Thus, we examined a series of electrocyclic reactions of *o*-alkynylaryl isocyanides upon heating [14]. Upon heating at 80 °C, the reaction of *o*-(phenylethynyl)phenyl isocyanide with (PhTe)₂ afforded the corresponding 2,4-bistellurated quinoline in 78 % yield (Table 6). The thermal reaction with (PhSe)₂ at 40 °C afforded 2,4-bisselenated quinoline in 85 % yield, successfully. In contrast, the thermal reaction of *o*-alkynylaryl isocyanides with (PhS)₂ did not proceed at all.

The reactions of *o*-alkynylaryl isocyanides with molecular iodine at 80 °C gave the corresponding 2,4-diiodoquinolines in moderate yields. In general, the thermal electrocyclic reaction of (*Z*)-hex-3-ene-1,5-diyne derivatives requires heating at approximately 200 °C [15]. In noteworthy contrast, the functional array in *o*-(phenylethynyl)phenyl isocyanides allows thermal electrocyclic reactions to proceed in the much lower temperature range of 40–80 °C.



Table 6 Thermal reaction of several isosyanides^a.

^a Reaction conditions: isocyanide (0.05 mmol), dichalcogenide (0.10 mmol), CDCl₃ (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.

CONCLUSION

A highly selective method for introducing thio, seleno, and telluro groups into isocyanides has been developed based on the elucidation of the relative reactivities of organic dichalcogenides and chalcogen-centered free radicals. The application of these photoinduced radical addition reactions to cyclization reactions of *o*-vinyl and *o*-allyl substituted phenyl isocyanides provides useful tools to indole and quinoline derivatives, respectively. In particular, the photoinduced reaction of *o*-ethenylaryl isocyanides with bis(2-aminophenyl) disulfide affords tetracyclic compounds in one portion. Furthermore, novel photoinduced or thermal electrocyclic reactions of *o*-alkynylaryl isocyanides with (PhSe)₂, (PhTe)₂, and I₂ have been developed. By using these methods, a wide range of substituted quinoline derivatives can be synthesized successfully.

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