The Cyclization Reaction of *Ortho*-Ethynylbenzaldehyde Derivatives into Isoquinoline Derivatives

Takao SAKAMOTO,* Atsushi NUMATA, and Yoshinori KONDO

Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki-aza-Aoba, Aoba-ku, Sendai 980–8578, Japan.
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In order to elucidate the reaction mechanism of the cyclization between an ethynyl group and an imino group at the *ortho*-position on an aromatic ring to afford isoquinolines, reaction of 2-ethynylbenzaldehydes under various conditions was examined. It is concluded that reaction proceeds *via* an ionic process and the isoquinoline 4-hydrogen atom derives from the solvent. In addition, it was found that 2-ethynylbenzaldehyde *O*-methyloximes underwent cyclization in the presence of primary and secondary alcohols to give 3-substituted isoquinolines.

Key words 2-ethynylbenzaldehyde; isoquinoline; *N*-oxide; cyclization; palladium-catalyzed reaction

The cyclization reaction which occurs between two *ortho*-positioned functional groups on aromatic or heteroaromatic rings is a useful construction method for aromatic- or heteroaromatic-condensed rings, because the method is considered to be independent of the electronic character of the aromatic ring component.[1] One example is the synthesis of condensed heterocycles containing an isoquinolinic nitrogen from *ortho*-ethynylarylaldehydes which can be easily prepared by palladium-catalyzed reaction of *ortho*-halo(or trifluoromethylsulfonyloxy)arylaldehydes with terminal alkynes.

Based on this concept, a facile method for the synthesis of isoquinoline 2-oxides from 2-ethynylbenzaldehyde oximes has already been reported by us.[2] As an extension of the method, we have also reported the synthesis of naphthyridines, carbolines, and their *N*-oxides from *ortho*-ethynylpyridinecarbaldehydes, *ortho*-ethynylindolecarbaldehydes, and their oximes.[3,4]

Our attention has been now turned to the cyclization reaction process which consists of the interaction between an ethynyl group and an imino group at the *ortho*-position of the aromatic or heteroaromatic rings. We now report a mechanistic investigation of the isoquinoline cyclization reaction from 2-ethynylbenzaldehydes, their oximes, and their *O*-methyloximes as substrates.

Initially, the cyclization reaction of 2-ethynylbenzaldehydes (**1a**—**d**), prepared by the palladium-catalyzed reaction of 2-bromobenzaldehyde with terminal alkynes under conventional conditions,[2] to the 3-substituted isoquinolines (**2a**—**d**) was examined. We have not previously reported this type of reaction, although the cyclization reaction of *ortho*-ethynylpyridinecarbaldehydes and *ortho*-ethynylindolecarbaldehydes to naphthyridines and carbolines has been reported.[3,4]

Using 2-(oct-1-yn-1-yl)benzaldehyde (**1a**) as a substrate, it was found that the cyclization reaction proceeded under several conditions shown in Table 1, and the conditions, using ammonia in ethanol gave relatively good results with respect to the yield of the isoquinolines (**2a**—**d**), *i.e.*, in 45—95% yields as shown in Table 1.

The isoquinoline cyclization reaction of 2-ethynylbenzaldehydes with ammonia or equivalent sources is presumed to proceed *via* the corresponding aldimine intermediates. However, since aldimines are generally unstable and the preparation of aldimines by another route is difficult, we chose the corresponding oximes as substrates to elucidate the course of the cyclization reaction. Although it is difficult to affirm in a strict sense that the reaction courses of 2-ethynylbenzaldehydes with ammonia or its equivalent to isoquinolines and of 2-ethynylbenzaldehyde oximes to isoquinoline 2-oxides are the same, we presume that the two cyclization reactions proceed principally *via* the same process.

Before considering the cyclization reaction courses of oximes, elucidation of the oxime stereochemistry is necessary, since the stereochemistry sometimes plays an important role. The ^{1}H-NMR spectra of the 2-(ethynyl)benzaldehyde oximes (**3a**—**d**) showed formyl protons at 8.57—8.65 ppm. Since it is known[5] that arylaldehyde oximes generally exist as stable *E*-isomers and the ^{1}H-NMR spectrum of (*E*)-4-bromobenzaldehyde oxime shows the formyl proton at 8.19 ppm, compounds (**3a**—**d**) which contain an ethynyl substituent at the *ortho*-position probably also exist as the *E*-isomers.

As shown in Chart 2, ionic processes, represented by paths A and B, are considered as possible reaction courses from the oximes to isoquinoline 2-oxides. Although path A is the most probable one between the two possible ionic mechanisms, path B, which involves benzoxazepine intermediates, can not be excluded. If the reaction proceeds according to paths A and B, the hydrogen at the 4-position of the isoquinoline is expected to arise from the starting oximes (H^A) or solvent (H^B). We then tried the cyclization reaction in various solvents as shown in Table 2.

The reaction in the presence of a strong proton donor such as *p*-toluenesulfonic acid (TsOH) or acetic acid gave **4** in high yields and the reaction in the presence of a weak proton donor such as methanol or ethanol also gave **4**. Moreover, the cyclization reaction in monodeuteriomethanol (CH_3OD) gave only 4-deuterio-3-hexylisoquinoline 2-oxide.

It is considered that the benzoxazepine intermediates in

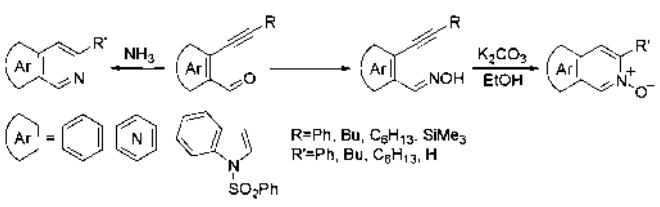
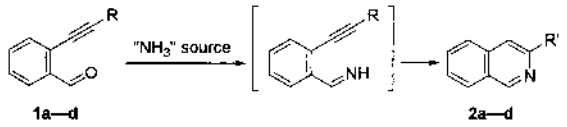


Chart 1

* To whom correspondence should be addressed. e-mail: Sakamoto@mail.pharm.tohoku.ac.jp

Table 1. Cyclization Reaction of 2-Ethynylbenzaldehydes (**1a**—**d**) to 3-Substituted Isoquinolines (**2a**—**d**)



Compd. No.	R	Conditions				Compd. No.	R′	Yield (%) [Recovery]
		"NH_3" source	Solvent	Temp. (°C)	Time (h)			
1a	C_6H_{13}	NH_3	EtOH	80 (sealed)	2	**2a**	C_6H_{13}	60 [7]
1a	C_6H_{13}	$HCOONH_4$	EtOH	Reflux	12	**2a**	C_6H_{13}	13 [74]
1a	C_6H_{13}	$HCOONH_4$	EtOH	80 (sealed)	2	**2a**	C_6H_{13}	40 [49]
1a	C_6H_{13}	$(NH_4)_2CO_3$	EtOH	Reflux	2	**2a**	C_6H_{13}	—[69]
1a	C_6H_{13}	$(NH_4)_2CO_3$	EtOH	80 (sealed)	2	**2a**	C_6H_{13}	40 [29]
1a	C_6H_{13}	H_2NCHO	—	100	12	**2a**	C_6H_{13}	21 [36]
1b	Bu	NH_3	EtOH	80 (sealed)	2	**2b**	Bu	95 [—]
1c	Ph	NH_3	EtOH	80 (sealed)	2	**2c**	Ph	45 [—]
1d	$SiMe_3$	NH_3	EtOH	80 (sealed)	2	**2d**	H	50 [—]

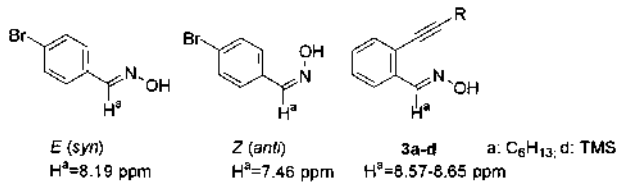


Fig. 1

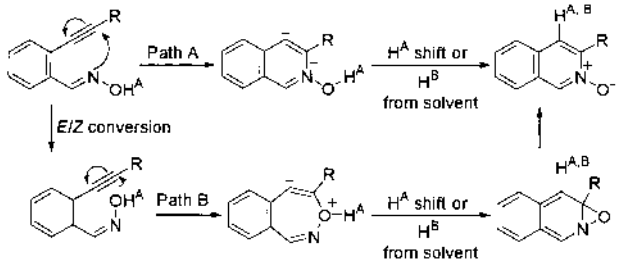


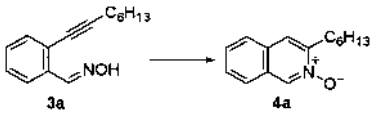
Chart 2

path B rearrange to give oxazirine intermediates which finally afford isoquinoline 2-oxides (**4**). Furthermore, it is presumed that the oxazirine intermediates could be deoxygenated by reaction with triphenylphosphine to give isoquinolines. Since the reaction of 2-(trimethylsilylethynyl)benzaldehyde oximes (**3d**) in the presence of triphenylphosphine gave isoquinoline 2-oxide (**4d**) and no isoquinolines (**2**), we concluded that path B does not operate during the cyclization reaction process.

We next examined the cyclization reaction of 2-(oct-1-yn-1-yl)benzaldehyde *O*-methyloxime (**5**), which has no acidic hydrogen, under the various conditions shown in Table 3 in order to determine whether the hydrogen at the 4-position of the isoquinoline 2-oxides comes from the hydrogen of the oximes or from the solvent used in path A. The cyclization of **5a** in acetic acid gave 3-hexylisoquinoline 2-oxide (**4a**) in 39% yield together with the starting material (**5a**) (run 1).

These results showed that compound **5a**, which has no acidic hydrogen, can be cyclized to give **4a** in acidic media, and the probable *N*-methoxyisoquinolinium intermediate is demethylated under the given reaction conditions. Concerning the dealkylation reaction of *N*-alkoxyazinium derivatives giving the corresponding *N*-oxides, Katritzky reported[6] that the reaction of 1-methoxypyridinum *p*-toluenesulfonate with sodium acetate in acetic acid gave pyridine 1-oxide. The demethylation may occur by attack of the acetoxyl anion on the methyl group, but a detailed mechanism is still not presently available.

Table 2. Cyclization Reaction of 2-(Oct-1-yn-1-yl)benzaldehyde Oxime (**3a**) to 3-Hexylisoquinoline 2-Oxide (**4a**)

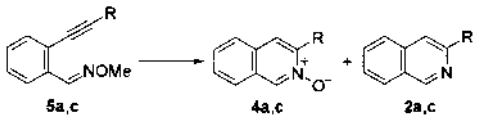


Run	Reaction conditions				Yield (%)
	Solvent	Additive	Temp. (°C)	Time (h)	
1	PhMe	—	Reflux	48	67
2	PhMe	TsOH	80	48	88
3	AcOH	AcONa	80	48	98
4	AcOH	—	80	48	95
5	EtOH	—	Reflux	24	64
6	EtOH	—	Reflux	48	65
7	MeOH	—	Reflux	48	96

In addition to the above results, we were also interested in the formation of isoquinoline (**2a**) from **5** although the yields were low (runs 2—4). The reaction of **5** in ethanol in a sealed tube at 180 °C for 48 h gave **2a** in 90% yield (run 5). The reaction in toluene proceeded in 40—78% yields in the presence of primary or secondary alcohols (runs 7—9), but gave **2a** in low yield in the absence of alcohols (run 6). Moreover, the cyclization reaction of **5a** in monodeuteriomethanol (CH_3OD) gave the 4-deuterio-3-hexylisoquinoline.

Although dealkoxylation of *N*-alkoxyazinium derivatives in the presence of nucleophiles has been reported,[6] we assumed that the reaction proceeded *via* the course shown in Chart 3. Namely, the betaine intermediate produced by thermal reaction of 2-ethynylbenzaldehyde *O*-methyloximes abstracts a proton from the alcohols, as shown in Table 3 to give the *N*-methoxyisoquinolinium intermediates which react with the resulting alkoxides. The alkoxide adducts eliminate

Table 3. Cyclization Reaction of 2-Ethynylbenzaldehyde *O*-Methyloxime (**5**)



Run	R	Reaction Conditions				Yield (%)		
		Solvent	Additive	Temp. (°C)	Time (h)	**4**	**2a**	**5**
1	C_6H_{13}	AcOH	—	80	48	39	—	52
2	C_6H_{13}	AcOH	AcONa	80	48	64	4	—
3	C_6H_{13}	EtOH	—	80	48	—	3	68
4	C_6H_{13}	EtOH	K_2CO_3	80	12	—	7	89
5	C_6H_{13}	EtOH	—	180 (sealed)	48	—	90	—
6	C_6H_{13}	PhMe	—	180 (sealed)	48	—	27	33
7	C_6H_{13}	PhMe	$PhCH_2OH$ (excess)	180 (sealed)	24	—	78	—
8	C_6H_{13}	PhMe	$PhCH_2CH_2OH$ (1 eq)	180 (sealed)	48	—	40	30
9	C_6H_{13}	PhMe	cyclohexanol (2 eq)	180 (sealed)	48	—	54	23
10	Ph	PhMe	Ph_2CHOH (1 eq)	180 (sealed)	48	—	87	—
11	Ph	EtOH	—	180 (sealed)	48	—	98	—
12	Ph	PhMe	MeOH (0.3 eq)	180 (sealed)	48	—	86	14

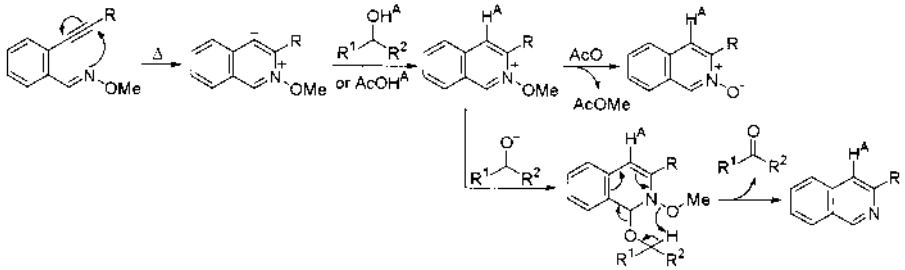


Chart 3

the corresponding carbonyl compound and isoquinolines as shown in Chart 3. Indeed, benzophenone was isolated from the reaction of **5a** with diphenylmethanol.

In conclusion, the cyclization reaction between an ethynyl group and an imino group both existing at the *ortho*-position of aromatic or heteroaromatic rings proceeds through an ionic process, path A shown in Chart 2, and the hydrogen at the 4-position of the isoquinolines come from the protic solvent. Moreover, it was found that 2-ethynylbenzaldehyde oximes underwent cyclization to give 3-substituted isoquinoline 2-oxides in protic media and 2-ethynylbenzaldehyde *O*-methyloximes cyclized in the presence of primary or secondary alcohols to give 3-substituted isoquinolines.

Experimental

General All melting points and boiling points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H-NMR spectra were recorded on Varian Gemini 2000 (300 MHz) and Hitachi R-300 (300 MHz) spectrometers. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as the internal reference, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets, br=broad, and br s=broad singlet. Mass spectra (MS) and high resolution mass spectra (HR-MS) were recorded on JMS-DX303 and JMS-AX500 instruments.

General Procedure for Synthesis of 2-Ethynylbenzaldehydes (1) A mixture of 2-bromobenzaldehyde (2 mmol), an alkyne (2.5—4 mmol), $Pd(PPh_3)_2Cl_2$ (60 mg), CuI (30 mg), Et_3N (300 mg), and *N*,*N*-dimethylformamide (DMF) (10 ml) was stirred at room temperature −50 °C for 1—15 h. The mixture was diluted with H_2O, and extracted with Et_2O. The residue obtained from the ethereal extract was purified by silica gel column chromatography using AcOEt–hexane (1 : 10) as eluent. The product was purified by distillation.

2-(Oct-1-yn-1-yl)benzaldehyde (**1a**): Yellow oil, bp 97 °C (3 mmHg). Yield 80%. IR (liquid) cm^{-1}: 2220, 1700. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.0 Hz), 1.30—1.44 (4H, m), 1.46—1.49 (2H, m), 1.59—1.67 (2H, m), 2.48 (2H, t, J=7.0 Hz), 7.38—7.41 (1H, m), 7.50—7.53 (2H, m), 7.87—7.91 (1H, m), 10.55 (1H, s). MS *m/z*: 214 (M^+). HR-MS *m/z*: 214.1321 (Calcd for $C_{15}H_{18}O$: 214.1358).

2-(Hex-1-yn-1-yl)benzaldehyde (**1b**)[2]: Yellow oil, bp 105 °C (3 mmHg). Yield 66%. IR ($CHCl_3$) cm^{-1}: 2210, 1690. ^{1}H-NMR ($CHCl_3$) δ: 0.95 (3H, t, J=7.0 Hz), 1.20—2.00 (4H, m), 2.50 (2H, t, J=7.0 Hz), 7.10—7.60 (3H, m), 7.60—8.00 (1H, m), 10.47 (1H, s).

2-(Phenylethynyl)benzaldehyde (**1c**)[2]: Yellow oil, bp 173 °C (3 mmHg). Yield 82%. IR (liquid) cm^{-1}: 2210, 1700. ^{1}H-NMR ($CDCl_3$) δ: 7.10—7.60 (8H, m), 7.60—8.00 (1H, m), 10.51 (1H, s).

2-(Trimethylsilylethynyl)benzaldehyde (**1d**)[2]: Colorless oil, bp 105 °C (3 mmHg). Yield 88%. IR (liquid) cm^{-1}: 2150, 1690. ^{1}H-NMR ($CDCl_3$) δ: 0.27 (9H, s), 7.30—7.70 (3H, m), 7.70—8.10 (1H, m), 10.47 (1H, s).

General Procedure for Synthesis of Isoquinolines (2) A solution of 2-ethynylbenzaldehydes (**1**) (1 mmol) was allowed to react under the conditions shown in Table 1 ["NH_3"source: $HCOONH_4$ (630 mg, 10 mmol), $(NH_4)_2CO_3$ (1.141 g, 10 mmol) in EtOH (10 ml); H_2NCHO (5 ml)]. After concentration of the reaction mixture *in vacuo*, saturated aqueous K_2CO_3 solution was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$–EtOH (100 : 1) as eluent. The product was purified by recrystallization or distillation.

3-Hexylisoquinoline (**2a**): Colorless liquid, bp 105 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.6 Hz), 1.31—1.40 (6H, m), 1.81 (2H, t, J=7.5 Hz), 2.93 (2H, t, J=7.5 Hz), 7.47 (1H, s), 7.52 (1H, t, J=7.5 Hz), 7.65 (1H, t, J=8.5 Hz), 7.75 (1H, d, J=7.5 Hz), 7.93 (1H, d, J=8.5 Hz), 9.21 (1H, s). MS *m/z*: 213 (M^+). HR-MS *m/z*: 213.1472 (Calcd for $C_{15}H_{19}N$: 213.1517).

3-Butylisoquinoline (**2b**)[7]: Colorless liquid, bp 150 °C (20 mmHg). ^{1}H-

NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.0 Hz), 1.10—2.20 (4H, m), 2.94 (2H, t, J=7.0 Hz), 7.30—8.10 (5H, m), 9.20 (1H, s).

3-Phenylisoquinoline (**2c**): Colorless granules from hexane, mp 101—102 °C, (lit.[8] mp 102.5—103.5 °C). ^{1}H-NMR ($CDCl_3$) δ: 7.30—8.30 (10H, m), 9.34 (1H, s).

Isoquinoline (**2d**)[9]: Colorless liquid, bp 70 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 7.40—8.20 (5H, m), 8.56 (1H, d, J=6.0 Hz), 9.28 (1H, s).

General Procedure for Preparation of 2-Ethynylbenzaldehyde Oximes (3) A solution of 2-ethynylbenzaldehyde (**1**) (1 mmol) in EtOH (5 ml) was added to hydroxylamine hydrochloride (104 mg, 1.5 mmol) and AcONa (123 mg, 1.5 mmol). The mixture was stirred at room temperature for 1—15 h, and concentrated *in vacuo*. Saturated aqueous K_2CO_3 solution was added and the mixture extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$–EtOH (100 : 1) as eluent. The product was purified by recrystallization from hexane.

2-(Oct-1-yn-1-yl)benzaldehyde Oxime (**3a**): Brown oil, bp 115 °C (3 mmHg). Yield 83%. IR (liquid) cm^{-1}: 3300, 2220. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.0 Hz), 1.31—1.44 (4H, m), 1.46—1.49 (2H, m), 1.58—1.66 (2H, m), 2.46 (2H, t, J=7.0 Hz), 7.27—7.30 (2H, m), 7.32—7.44 (1H, m), 7.80 (1H, br), 7.82—7.83 (1H, m), 8.65 (1H, s). MS m/z: 229 (M^+). HR-MS m/z: 229.1449 (Calcd for $C_{15}H_{19}NO$: 229.1467).

2-(Trimethylsilylethynyl)benzaldehyde Oxime (**3d**): Colorless needles from hexane, mp 87—88 °C (lit.[2] mp 87—89 °C). Yield 83%. IR ($CHCl_3$) cm^{-1}: 2280. ^{1}H-NMR ($CHCl_3$) δ: 0.28 (9H, s), 7.10—7.60 (3H, m), 7.60—8.00 (1H, m), 8.57 (1H, s), 9.13 (1H, s).

General Procedure for Cyclization of 2-(Oct-1-yn-1-yl)benzaldehyde Oxime (3a) 2-(Oct-1-yn-1-yl)benzaldehyde oxime (**3a**) (100 mg, 0.44 mmol) in solvent (10 ml) was heated for 12—48 h, as shown in Table 2 [additive: TsOH (172 mg, 1 mmol), AcONa (82 mg, 1 mmol)]. After concentration of the reaction mixture, the residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$–EtOH (100 : 1) as eluent to give 3-hexylisoquinoline 2-oxide (**4a**) as colorless needles, mp 63—66 °C (recrystallized from hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.24—1.50 (6H, m), 1.79—1.84 (2H, m), 3.04 (2H, t, J=7.3 Hz), 7.52—7.58 (3H, m), 7.67—7.75 (2H, m), 8.85 (1H, s). Ms m/z: 229 (M^+). *Anal*. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.44; H, 8.38; N, 6.06.

Reaction of 2-(Trimethylsilylethynyl)benzaldehyde Oxime (3d) with K_2CO_3 in the Presence of PPh_3 A mixture of 2-(trimethylsilylethynyl)-benzaldehyde oxime (**3d**) (0.65 g, 3 mmol), K_2CO_3 (0.41 g, 3 mmol), and PPh_3 (0.78 g, 3 mmol) in EtOH (6 ml) was heated at 60 °C for 5 h. After removal of EtOH *in vacuo*, saturated aqueous K_2CO_3 solution was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$–EtOH (100 : 1) as eluent to give isoquinoline 2-oxide (**4d**) (0.26 g, 60%), mp 99—101 °C (lit.[10] mp 105—106 °C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.30—8.00 (5H, m), 8.10 (1H, dd, J=7.0, 2.0 Hz), 8.88 (1H, d, J=2.0 Hz).

Cyclization Reaction of 2-(Oct-1-yn-1-yl)benzaldehyde Oxime (3a) in CH_3OD A solution of 2-(oct-1-yn-1-yl)benzaldehyde oxime (**3a**) (50 mg, 0.22 mmol) in CH_3OD (5 ml) was refluxed for 48 h. After removal of the solvent *in vacuo*, saturated aqueous K_2CO_3 solution was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using $CHCl_3$–EtOH (100 : 1) as eluent to give 4-deuterio-3-hexylisoquinoline as colorless needles (29 mg, 58%). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J=7.0 Hz), 1.26—1.50 (6H, m), 1.81 (2H, t, J=7.7 Hz), 3.04 (2H, t, J=7.3 Hz), 7.53—7.59 (2H, m), 7.68—7.76 (2H, m), 8.86 (1H, s). The deuteration ratio was estimated by integration of ^{1}H-NMR signals (D content, 100%).

General Procedure for Preparation of 2-Ethynylbenzaldehyde *O*-Methyloximes (5) A solution of 2-ethynylbenzaldehyde (**3**) (1 mmol) in EtOH (5 ml) was added to *O*-methylhydroxylamine hydrochloride (125 mg, 1.5 mmol) and AcONa (123 mg, 1.5 mmol). The mixture was stirred at room temperature for 12 h, then concentrated *in vacuo*. H_2O was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using hexane–AcOEt (100 : 1) as eluent. The product was purified by distillation.

2-(Oct-1-yn-1-yl)benzaldehyde *O*-Methyloxime (**5a**): Yellow oil, bp 140 °C (3 mmHg). Yield 98%. IR (liquid) cm^{-1}: 2210. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=6.9 Hz), 1.30—1.64 (8H, m), 2.44 (2H, t, J=6.9 Hz), 3.99 (3H, s), 7.25—7.28 (2H, m), 7.38-7.41 (1H, m), 7.84—7.88 (1H, m), 8.57 (1H, s). MS m/z: 243 (M^+). HR-MS m/z: 243.1635 (Calcd for $C_{16}H_{21}NO$: 243.1623).

2-Phenylethynylbenzaldehyde *O*-Methyloxime (**5c**): Yellow liquid, bp 140 °C (3 mmHg). Yield 85%. IR (liquid) cm^{-1}: 2210. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 7.32—7.38 (5H, m), 7.53—7.57 (3H, m), 7.91—7.94 (1H, m), 8.66 (1H, s). MS m/z: 235 (M^+). HR-MS m/z: 235.0973 (Calcd for $C_{16}H_{13}NO$: 235.0997).

General Procedure for Cyclization of 2-Ethynylbenzaldehyde *O*-Methyloxime (5) A solution of 2-ethynylbenzaldehyde *O*-methyloxime (**5**) (1 mmol) in a solvent (10 ml) under the conditions shown Table 3 was heated at 80—180 °C for 12—48 h [additive: AcONa (82 mg, 1 mmol), K_2CO_3 (138 mg, 1 mmol), benzyl alcohol (198 mg, 1 mmol), 2-phenethyl alcohol (122 mg, 1 mmol), cyclohexanol (100 mg, 1 mmol)]. After concentration of the reaction mixture *in vacuo*, saturated aqueous K_2CO_3 solution was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using hexane–AcOEt (100 : 1) as eluent. The product was purified by distillation.

Cyclization Reaction of 2-(Oct-1-yn-1-yl)benzaldehyde *O*-Methyloxime (5a) in CH_3OD A solution of 2-(oct-1-yn-1-yl)benzaldehyde *O*-methyloxime (**5a**) (100 mg, 0.41 mmol) in CH_3OD (10 ml) was heated at 180 °C for 48 h. After removal of the solvent *in vacuo*, saturated aqueous K_2CO_3 solution was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The residue was purified by silica gel column chromatography using hexane–AcOEt (10 : 1) as eluent to give 4-deuterio-3-hexylisoquinoline as a colorless liquid (75 mg, 85%). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J=6.6 Hz), 1.31—1.40 (6H, m), 1.81 (2H, t, J=7.5 Hz), 2.93 (2H, t, J=7.5 Hz), 7.52 (1H, t, J=7.5 Hz), 7.65 (1H, t, J=8.5 Hz), 7.75 (1H, d, J=7.5 Hz), 7.93 (1H, d, J=8.5 Hz), 9.21 (1H, s). The deuteration ratio was determined from by integration of ^{1}H-NMR signals (D content, 89%).

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References

1) Sakamoto T., Kondo Y., Yamanaka H., *Heterocycles*, **27**, 2225—2249 (1988).
2) Sakamoto T., Kondo Y., Miura N., Hayashi K., Yamanaka H., *Heterocycles*, **24**, 2311—2314 (1986).
3) Numata A., Kondo Y., Sakamoto T., *Synthesis*, **1999**, 306—311.
4) Sakamoto T., Numata A., Saito H., Kondo Y., *Chem. Pharm. Bull.*, **47**, 1740—1743 (1999).
5) Fenselau A. H, Hamamura E. H., Moffatt J. G., *J. Org. Chem*., **35**, 3546—3552 (1970).
6) Coats N. A., Katritzky A. R., *J. Org. Chem.*, **24**, 1836—1837 (1959).
7) Lehmkuly J. N., *Chem. Ber*., **30**, 897 (1897).
8) Bradsher C. K., Wallis T. G., *J. Org. Chem.*, **43**, 3817—3820 (1978).
9) Pouchert I. C., Behnke J. (ed.), "The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra," Vol. 3, Aldrich Chemical Co. Ltd., 1993, p. 456.
10) Robison M. M., Robison B. L., *J. Org. Chem.*, **21**, 1337—1314 (1956).