Tetrahedron Letters 49 (2008) 5531–5533

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iodine-mediated electrophilic cyclization of 2-alkynylbenzaldoximes leading to the formation of iodoisoquinoline *N*-oxides

Zhibao Huo, Hisamitsu Tomeba, Yoshinori Yamamoto *

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

ARTICLE INFO

Article history:
Received 9 June 2008
Revised 30 June 2008
Accepted 9 July 2008
Available online 12 July 2008

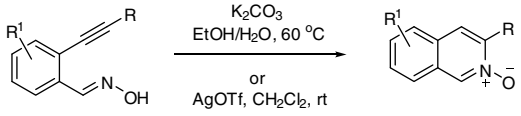
Keywords:
Electrophilic cyclization
Iodonium ion
Iodine
Isoquinoline *N*-oxide
2-Alkynylbenzaldoxime
Isoquinoline

ABSTRACT

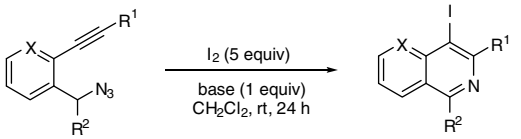
Reaction of 2-alkynylbenzaldoximes **1** with 5 equiv of iodine in EtOH at room temperature gives the corresponding iodoisoquinoline *N*-oxides **2** in good to excellent yields. The cyclization proceeds very smoothly and quickly without any additives such as bases under very mild reaction conditions.

Isoquinoline *N*-oxides are an important class of compounds because of their wide utility.[1] They have been considered as very useful intermediates for isoquinolines and their derivatives and are often seen as building blocks in biologically active compounds and functional materials.[2] Recently, isoquinoline *N*-oxides have been utilized as backbones of chiral ligands for asymmetric transformations, and several new compounds have been synthesized.[3] Due to their potential importance, several synthetic methods from 2-alkynylbenzaldoximes have been developed (Eq. 1). For example, Sakamoto et al.[4] reported the reaction of 2-alkynylbenzaldoximes in the presence of potassium carbonate in ethanol/water at 60 °C (Eq. 1). Shin et al.[5] reported that silver trifluoromethanesulfonate catalyzed the cyclization of 2-alkynylbenzaldoxime derivatives into the corresponding isoquinoline *N*-oxides in CH_2Cl_2 (Eq. 1). However, an analogous transformation via iodine-mediated electrophilic cyclization of 2-alkynylbenzaldoximes has not been developed.

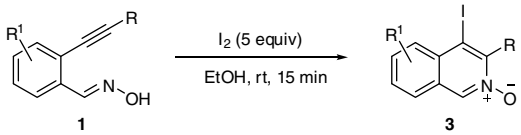
Previously, we reported the synthesis of 1,2-dihydroisoquinoline skeletons via AgOTf-catalyzed direct addition of pronucleophiles to *o*-alkynylarylaldimines[6] and via three-component coupling reaction with *ortho*-alkynylbenzaldehydes, primary amines and pronucleophiles in the presence of molecular sieves.[7] More recently, we reported[8] an entirely new method for the synthesis of 1,3,4-trisubstituted isoquinolines through iodine-mediated electrophilic cyclization of 2-alkynyl benzyl azides (Eq. 2). It occurred to us that iodine-mediated cyclization of 2-alkynylbenzaldoximes **1** might produce iodoisoquinoline *N*-oxides **2** (Eq. 3). With this in mind, we examined the iodine-mediated cyclization reaction of various 2-alkynylbenzaldoximes, and found that the reaction proceeded very smoothly to give the desired iodoisoquinoline *N*-oxides **2** in good to high yields (Eq. 3).



(1)



(2)



(3)

Initially, we tested the reaction of substrate **1a** in order to optimize the reaction conditions, and the results are summarized in Table 1. Cyclization of **1a** using 5 equiv of iodine and 1 equiv of $NaHCO_3$ as a base in CH_3NO_2 at room temperature for 15 min

* Corresponding author. Tel.: +81 22 795 6581; fax: +81 22 795 6784.
E-mail address: yoshi@mail.tains.tohoku.ac.jp (Y. Yamamoto).

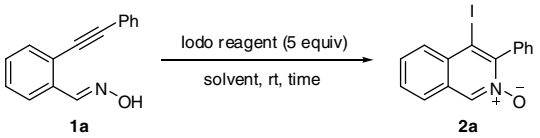
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.07.061

Table 1
Effect of iodo reagent and solvent on the formation of iodoisoquinoline *N*-oxide **2a** from **1a**[a]

Entry	Iodo reagent	Solvent	Time (min)	Yield of **2a**[b] (%)
1	I_2	CH_3NO_2	15	81[c]
2	I_2	CH_3NO_2	15	82
3	NIS	CH_3NO_2	30	(11)[c]
4	NIS	CH_3NO_2	60	(15)
5	ICl	CH_3NO_2	60	Mixture[d]
6	I_2	EtOH	15	(94)
7	I_2	H_2O	15	26[e]
8	I_2[f]	EtOH	150	(69)

[a] The reaction of **1a** was carried out in the presence of 5 equiv of iodo reagent at room temperature except as otherwise indicated.
[b] ^1H NMR yield was determined using 1,4-dioxane as an internal standard. Isolated yield is shown in parentheses.
[c] One equiv of $NaHCO_3$ was used.
[d] A mixture of iodo- and chloro-substituted isoquinoline *N*-oxides was obtained.
[e] Reaction temperature was 100 °C.
[f] Two equivalents of iodine were used.

provided the desired iodoisoquinoline *N*-oxide **2a** in 81% NMR yield (entry 1). To our surprise, the cyclization also proceeded smoothly without a base, giving the product in 82% NMR yield (entry 2). *N*-iodosuccinimide (NIS) was inefficient and gave the product in lower yields (entries 3 and 4). Use of ICl led to a mixture of iodo- and chloro-substituted isoquinoline *N*-oxides (entry 5). The use of ethanol, instead of nitromethane, gave the product **2a** in a higher yield (entry 6). The use of water as a solvent gave a very low yield even after increasing the reaction temperature up to 100 °C (entry 7). Decreasing the amount of iodine from 5 to 2 equiv also resulted in a lower yield (entry 8).



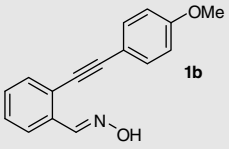
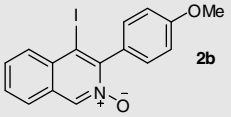
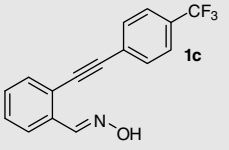
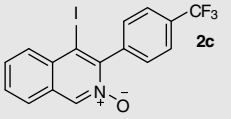
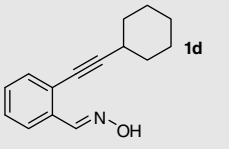
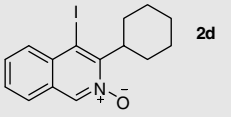
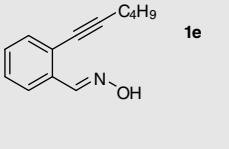
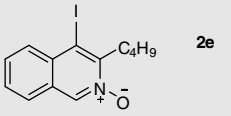
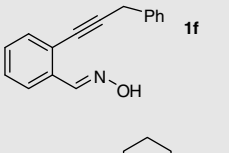
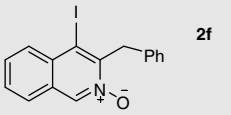
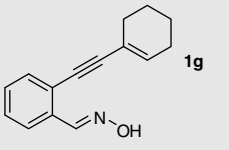
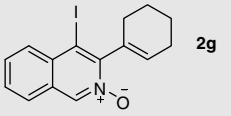
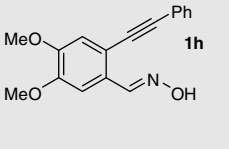
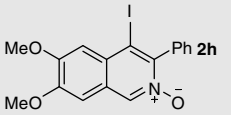
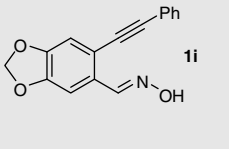
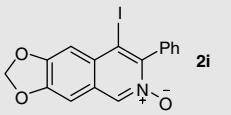
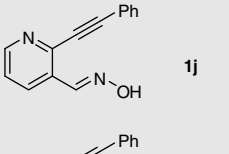
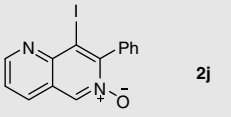
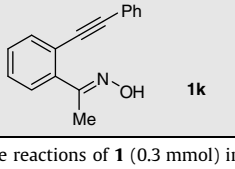
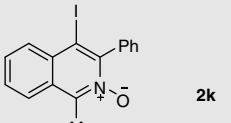
1a **2a** (4)

The scope of the intramolecular cyclization of 2-alkynylbenzaldoximes is summarized in Table 2.[9] Arylacetylenes bearing methoxy and trifluoromethyl groups **1b** and **1c** on the aromatic ring afforded the corresponding cyclized products **2b** and **2c**, respectively, in good yields, indicating that the substituents on the aromatic ring did not exert a significant influence upon the cyclization (entries 1 and 2). The reactions of **1d**, **1e**, and **1f**, having cyclohexyl, *n*-butyl, and benzyl groups at the alkyne terminus, under the standard conditions, proceeded smoothly to give the desired products **2d**, **2e**, and **2f**, respectively, in good to high yields (entries 3–5). The cyclization of **1g** afforded the desired product **2g** in a high yield (entry 6). The 2-alkynylbenzaldoximes **1h** and **1i**, in which the aromatic ring was substituted with RO groups, gave the corresponding iodoisoquinoline *N*-oxides **2h** and **2i** in good to high yields (entries 7 and 8). Replacing a carbon atom of the aromatic ring with a nitrogen atom did not affect the cyclization; the reaction proceeded very smoothly to afford the product **2j** in 72% yield, although a prolonged reaction time was required (entry 9). Iodoisoquinoline *N*-oxide **2k** was not obtained from ketoxime **1k** under the present conditions (entry 10).

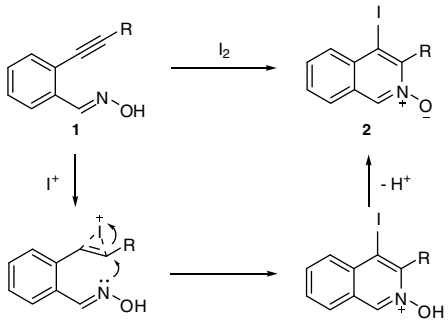
A plausible mechanism for the formation of iodoisoquinoline *N*-oxides **2** via iodine-mediated electrophilic cyclization of 2-alkynylbenzaldoximes **1** is illustrated in Scheme 1. Coordination of the iodonium cation to the alkyne activates the triple bond toward nucleophilic attack of the oxime nitrogen, leading to the iodoisoquinoline intermediate. Subsequent elimination of a proton results in the formation of iodoisoquinoline *N*-oxide **2**.

We were also interested in further manipulation of compounds **2**. For example, α-cyanation using TMSCN is known (Eq. 5),[10] and

Table 2
Iodine-mediated cyclization of 2-alkynylbenzaldoximes **1** to iodoisoquinoline *N*-oxides **2**[a]

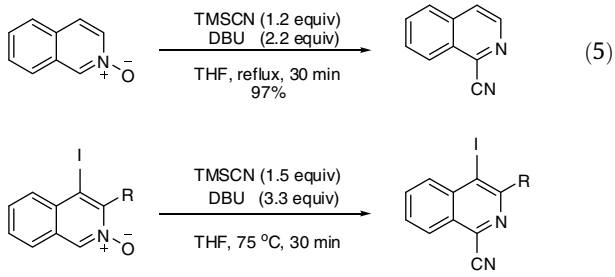
Entry	Substrate	Product (**2**)	Yield of **2**,[b] (%)	Mp (°C)
1	 **1b**	 **2b**	86	206–207
2	 **1c**	 **2c**	80	198–199
3	 **1d**	 **2d**	71	199–200
4	 **1e**	 **2e**	65	192–193
5	 **1f**	 **2f**	92	205–206
6	 **1g**	 **2g**	90	200–201
7	 **1h**	 **2h**	75	249–250
8	 **1i**	 **2i**	85	274–275
9	 **1j**	 **2j**	72[c]	236–237
10	 **1k**	 **2k**	—[d]	—

[a] The reactions of **1** (0.3 mmol) in the presence of iodine (5 equiv) were carried out at room temperature in EtOH for 15 min.
[b] Isolated yields.
[c] Reaction time was 30 min.
[d] Starting material decomposed at 60 °C.



Scheme 1. A plausible mechanism for the formation of **2**.

we thought that application of this α-cyanation to our iodoisoquinoline *N*-oxides would lead to formation of 1,3,4-trisubstituted isoquinolines. The reactions of iodoisoquinoline *N*-oxides **2a**, **2f**, and **2g** were carried out in THF at 75 °C for 30 min in the presence of TMSCN and DBU to give the desired cyanoisoquinolines **3a**, **3f**, and **3g** in high yields (Eq. 6).[11]



In conclusion, we have developed a new and efficient procedure for the synthesis of 3,4-disubstituted iodoisoquinoline *N*-oxides from 2-alkynylbenzaldoximes. We also demonstrated that 1,3,4-trisubstituted isoquinolines may be derived from these iodoisoquinoline *N*-oxides. Further studies to extend the scope of this procedure are in progress in our laboratory.

References and notes

1. Bentley, K. W. In *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998; Vol. 1.
2. (a) Dzierszinski, F.; Coppin, A.; Mortuaire, M.; Dewally, E.; Slomianny, C.; Ameisen, J.-C.; Debels, F.; Tomavo, S. *Antimicrob. Agent. Chemother.* **2002**, *46*, 3197; (b) Kletsas, D.; Li, W.; Han, Z.; Papadopoulos, V. *Biochem. Pharmacol.* **2004**, *67*, 1927; (c) Mach, U. R.; Hackling, A. E.; Perachon, S.; Ferry, S.; Wermuth, C. G.; Schwartz, J.-C.; Sokoloff, P.; Stark, H. *ChemBioChem* **2004**, *5*, 508; (d) Muscarella, D. E.; O'Brian, K. A.; Lemley, A. T.; Bloom, S. E. *Toxicol. Sci.* **2003**, *74*, 66.
3. (a) Petrowitsch, T.; Eilbracht, P. *Synlett* **1997**, 287; (b) Derdau, V.; Laschat, S.; Jones, P. G. *Heterocycles* **1998**, *48*, 1445; (c) Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Synlett* **1995**, 1085; (d) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529; (e) O'Neil, I. A.; Turner, C. D.; Kalindjian, S. B. *Synlett* **1997**, 777; (f) Derdau, V.; Laschat, S.; Hupe, E.; König, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1001.
4. (a) Sakamoto, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311; (b) Sakamoto, T.; Numata, A.; Kondo, Y. *Chem. Pharm. Bull.* **2000**, *48*, 669.
5. The following paper was published during the preparation of the present manuscript: Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924.
6. Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 5526.
7. Asao, N.; Iso, K.; Yudha, S. *Org. Lett.* **2006**, *8*, 4149.
8. Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4764.
9. The procedure for the synthesis of isoquinoline *N*-oxide **2a**is as follows. To a 5 mL screw capped vial equipped with a magnetic stirring bar were added 2-phenylalkynylbenzaldoxime (66.4 mg, 0.3 mmol), iodine (380.7 mg, 1.5 mmol) and dry ethanol (3 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 15 min, and the progress of the reaction was monitored by TLC (hexane/ethyl acetate; 2:1). After complete consumption of the starting material, saturated aqueous $Na_2S_2O_3$ was added, and stirring was continued for 5–15 min. The mixture was extracted with CH_2Cl_2 (2×20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOH; 50/1–5/1) to afford product **2a** in 94% yield (97.9 mg). Mp: 230–231 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.37 (m, 2H), 7.58–7.48 (m, 3H), 7.70–7.61 (m, 3H), 8.08 (d, J = 8.0 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 101.79, 125.21, 128.37, 128.64, 129.42, 129.58, 129.76, 130.33, 131.72, 132.54, 136.78, 137.21, 151.04; IR (KBr) 1307, 1171, 1119, 773, 752 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{10}INO$ ([M+Na]$^+$) 369.9705. Found. 369.9699.
10. Miyashita, A.; Kawashima, T.; Iijima, C.; Higashino, T. *Heterocycles* **1992**, *33*, 211.
11. The procedure for the synthesis of cyanoisoquinoline **3a** from **2a** is as follows. To a 5 mL screw capped vial equipped with a magnetic stirring bar were added compound **2a** (104.1 mg, 0.3 mmol), TMSCN (0.06 mL, 0.45 mmol), DBU (0.15 mL, 0.99 mmol) and THF (3 mL). The reaction mixture was stirred at 75 °C for 30 min, and the progress of the reaction was monitored by TLC (hexane/ethyl acetate; 5:1). After complete consumption of the starting material, the reaction mixture was cooled to room temperature, saturated aqueous NH_4Cl was added, and stirring was continued for 5–15 min. The mixture was extracted with CH_2Cl_2 (2×20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate; 20/1–5/1) to afford product **3a** in 84% yield (89.3 mg). Mp: 161–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.46 (m, 3H), 7.64–7.59 (m, 2H), 7.86 (t, J = 8.0 Hz, 1H), 7.95 (t, J = 8.0 Hz, 1H), 8.35 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 103.84, 115.13, 125.75, 127.90, 128.07, 128.90, 129.67, 130.28, 133.29, 133.45, 134.25, 139.10, 142.08, 157.83. IR (KBr) 2228, 1537, 1264, 916, 766, 744 cm^{-1}; HRMS (EI) calcd for $C_{16}H_9IN_2$ ([M+Na]$^+$) 378.9708. Found. 378.9703.