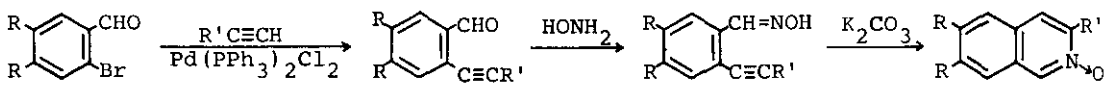
CONDENSED HETEROAROMATIC RING SYSTEMS. XI.[1]
A FACILE SYNTHESIS OF ISOQUINOLINE N-OXIDES

Takao Sakamoto, Yoshinori Kondo, Norio Miura, Kazuhiko Hayashi,
and Hiroshi Yamanaka*
Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

Abstract——— Isoquinoline 2-oxides (5a-f) were obtained by the cyclization of 2-ethynylbenzaldehyde oxime (4a-f) under basic conditions. The starting compounds (4a-f) were easily synthesized by the palladium-catalyzed reaction of 2-bromobenzaldehydes (1 and 2) with terminal acetylenes, and subsequent oximation of the resulting 2-ethynylbenzaldehydes (3a-f).

As an application of palladium-catalyzed reactions of aryl halides with terminal acetylenes,[2] we have previously reported the isocarbostyril cyclization of 2-ethynylbenzamides, which was prepared by the reaction of 2-halobenzonitriles and terminal acetylenes.[3] Meanwhile, treatment of acylhydrazones of 2-ethynylbenzaldehydes with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) or potassium carbonate has been known to give isoquinolilne N-acylimines.[4] From these points of view, our next interest focussed on the direct synthesis of isoquinoline N-oxides according to the similar manner mentioned above. The present paper deals with a facile synthesis of isoquinoline N-oxides from o-bromobenzaldehydes.



1,2
1:R=H
2:R=OMe

3a-f
a:R=H,R'=Ph
b:R=H,R'=Bu
c:R=H,R'=SiMe3
(5c:R'=H)

4a-f
d:R=OMe,R'=Ph
e:R=OMe,R'=Bu
f:R=OMe,R'=SiMe3
(5f:R'=H)

5a-f

Chart 1

The reaction of 2-bromobenzaldehyde (1) with phenylacetylene in dimethylformamide (DMF) at 50°C for 1.5 h in the presence of a catalytic amount of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine gave 2-(phenylethynyl)benzaldehyde (3a) in satisfactory yield. When the aldoxime (4a), prepared by the conventional manner from 3a, was heated with potassium carbonate in ethanol at 60°C, 3-phenylisoquinoline 2-oxide (5b) was obtained. Similarly, 3-butylisoquinoline 2-oxide (5b) was synthesized by the reaction of 1 with 1-hexyne and subsequent cyclization of the corresponding aldoxime (4b) under a weakly basic condition. In the case of 2-(trimethylsilylethynyl)benzaldehyde oxime (4c), the trimethylsilyl group was removed during the cyclization, and unsubstituted isoquinoline 2-oxide (5c) was obtained as a sole product.

In addition to the above, the reactions employing 4,5-dimethoxy-2-bromobenzaldehyde (2) as a starting material suggested that the method was applicable to the preparation of isoquinoline 2-oxides containing some electron-donating substituents at the benzene ring. Namely, the reaction of 2 with trimethylsilylacetylene proceeded to give the ethynyl compound (3f) without difficulties. The oximation of 3f, followed by cyclization under the same conditions as the above, gave 6,7-dimethoxyisoquinoline 2-oxide (5f), as expected. The yields and physical constants of all products are listed in Table I, II, and III.

Although something remains to be done for the versatility of this reaction, experimental simplicity in every step is considered to be advantage for the preparation of isoquinoline 2-oxides.

EXPERIMENTAL

Ethynylbenzaldehydes (3a-f) (General Procedure)

A mixture of a 2-bromobenzaldehyde (10 mmol), an acetylene derivative (20 mmol), $Pd(PPh_3)_2Cl_2$ (300 mg), CuI (150 mg), Et_3N (15 mmol), and DMF (10 ml) was stirred at 40-50°C for 1-2 h. The mixture was diluted with H_2O, and extracted with ether. The residue, obtained from the ethereal extract, was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The product, obtained from the C_6H_6 eluate, was purified by distillation or recrystallization.

Table I. o-Ethynylbenzaldehydes (3a-f)

No.	Yield (%)	bp/mmHg [mp] (°C)	IR cm^{-1} ($CHCl_3$)	^{1}H-NMR δ (ppm) (CCl_4)
3a	82	173/3	2210 1700	7.1-7.6(8H,m),7.6-8.0(1H,m),10.51(1H,s)
3b	66	140/3	2210 1690	0.95(3H,t,J=7Hz),1.2-2.0(4H,m),2.50(2H,t,J=7Hz) 7.1-7.6(3H,m),7.6-8.0(1H,m),10.47(1H,s)
3c	88	105/3	2150 1690	0.27(9H,s),7.3-7.7(3H,m),7.7-8.1(1H,m) 10.47(1H,s)
3d	67	[138-140]	1680	3.92(3H,s),3.98(3H,s),7.05(1H,s),7.2-7.8(6H,m) 10.53(1H,s)[a]
3e	67	viscous oil	2220 1680	1.00(3H,t,J=7Hz),1.3-1.9(4H,m),2.45(2H,t,J=7Hz) 3.88(6H,s),6.76(1H,s),7.24(1H,s),10.28(1H,s)
3f	77	[115-116]	2120 1680	0.29(9H,s),3.94(3H,s),7.01(1H,s),7.40(1H,s) 10.45(1H,s)[a]

a) In $CDCl_3$.

Ethynylbenzaldehyde Oximes (4a-f) (General Procedure)

A solution of a 2-ethynylbenzaldehyde (7 mmol) in EtOH (10 ml) was added to a solution of $NH_2OH \cdot HCl$ (11 mmol) and AcONa (11 mmol) in H_2O (2 ml). The mixture was heated at 60°C for 30 min, then was concentrated in vacuo. The residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 1 N $NaHCO_3$. The product, obtained from the $CHCl_3$ extract, was purified by recrystallization.

Table II. o-Ethynylbenzaldehyde Oximes (4a-f)

No.	Yield (%)	mp (°C)	IR cm^{-1} ($CHCl_3$)	^{1}H-NMR δ (ppm) (CCl_4)
4a	80	91-93	2200	7.1-7.7(8H,m),7.7-8.2(1H,m),8.67(1H,s),9.06(1H,s)
4b	99	viscous oil	2220	0.95(3H,t,J=7Hz),1.2-2.0(4H,m),2.45(2H,t,J=7Hz) 7.0-7.6(3H,m),7.6-8.0(1H,m),8.54(1H,s) 9.34(1H,br s)
4c	83	87-88	2280	0.28(9H,s),7.1-7.6(3H,m),7.6-8.0(1H,m),8.57(1H,s) 9.13(1H,s)
4d	95	148-149	2180	3.93(6H,s),7.00(1H,s),7.2-7.8(6H,m),8.4-9.0 (1H,br s),8.70(1H,s)[a]
4e	88	102-103	2190	0.95(3H,t,J=7Hz),1.2-1.9(4H,m),2.45(2H,t,J=7Hz) 3.88(6H,s),6.85(1H,s),7.27(1H,s),8.3-9.4 (1H,br),8.55(1H,s)[a]
4f	93	145-146.5	2130	0.28(9H,s),3.93(6H,s),6.97(1H,s),7.37(1H,s) 8.63(1H,s),8.5-8.9(1H,br)[a]

a) In $CDCl_3$.

Isoquinoline 2-Oxides (5a-f) (General Procedure)

A mixture of a 2-ethynylbenzaldehyde oxime (5 mmol) in EtOH (10 ml) was added to a solution of K_2CO_3 (5 mmol) in H_2O (2 ml). The mixture was heated at 60°C for 1-5 h (monitoring by TLC), and then was concentrated in vacuo. The residue was extracted with $CHCl_3$. The product, obtained from the $CHCl_3$ extract, was purified by recrystallization or distillation.

Table III. Isoquinoline 2-Oxides (5a-f)

No.	Yield (%)	mp(°C)	^{1}H-NMR δ (ppm) ($CDCl_3$)
5a	39	142-144	7.3-8.0(10H,m),8.92(1H,s)
5b	78	81-82	1.00(3H,t,J=7Hz),1.2-2.2(4H,m),3.07(2H,t,J=7Hz),7.1-7.9 (5H,m),8.85(1H,s)
5c	44	99-101[a)]	7.3-8.0(5H,m),8.10(1H,dd,J=7 and 2Hz),8.88(1H,d,J=2Hz)
5d	35	204-206	4.03(6H,s),6.95(1H,s),7.05(1H,s),7.3-8.0(6H,m),9.78(1H,s)
5e	78	127-128	1.00(3H,t,J=7Hz),1.2-2.1(4H,m),3.03(2H,t,J=7Hz) 4.00(6H,s),6.91(1H,s),7.00(1H,s),7.43(1H,s),8.69(1H,s)
5f	43	105-106	4.03(6H,s),7.00(1H,s),7.08(1H,s),7.50(1H,d,J=7Hz) 8.10(1H,dd,J=7 and 2Hz),8.68(1H,d,J=2Hz)

a) Lit.[5] mp 105-106°C.

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Received, 9th May, 1986