[Chem. Pharm. Bull. 33(2) 626—633 (1985)]

Condensed Heteroaromatic Ring Systems. III.[1,2] Synthesis of Naphthyridine Derivatives by Cyclization of Ethynylpyridinecarboxamides

TAKAO SAKAMOTO, YOSHINORI KONDO, and HIROSHI YAMANAKA*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received June 27, 1984)

Four kinds of naphthyridinones, *i.e.* 1,6-naphthyridin-5-one, 1,7-naphthyridin-8-one, 2,6-naphthyridin-2-one, and 2,7-naphthyridin-1-one derivatives, were commonly synthesized by the intramolecular cyclization of pyridinecarboxamides having an ethynyl group or β,β-dimethoxyethyl group adjacent to the carbamoyl group. The syntheses of the starting pyridine derivatives were easily accomplished by cross-coupling of the corresponding halopyridines with acetylenes.

Keywords——intramolecular cyclization; palladium catalyst; trimethylsilylacetylene; naphthyridinone; pyridineacetaldehyde; 1(2*H*)-isoquinolone

It is well known[3] that various *N*-heteroaromatic halides react smoothly with terminal acetylenes in the presence of an appropriate palladium–phosphine complex to give alkynyl-*N*-heteroaromatics. As an application of this method, we have recently reported[1] the synthesis of pyridopyrimidines by the palladium-catalyzed cross-coupling reaction of halopyrimidinecarboxylic ester with phenylacetylene and subsequent cyclization of the resulting phenylethynylpyrimidinecarboxylates by treatment with ethanolic ammonia. In the present paper, we report convenient syntheses of 1,6-, 1,7-, 2,6-, and 2,7-naphthyridinones by the cyclization of appropriate pyridinecarboxamides having an ethynyl group or β,β-dimethoxyethyl group adjacent to the carbamoyl group.

Firstly, we investigated the synthesis of phenylethynylpyridinecarboxylic acid derivatives by palladium catalyzed cross-coupling reaction and cyclization of the resulting compounds to the desired phenylnaphthyridinones (**4**, **8**, **12**, and **16**). When 2-chloro-4,6-dimethyl-3-pyridinecarbonitrile (**1**) was heated with phenylacetylene in triethylamine in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide, 4,6-dimethyl-2-phenylethynyl-3-pyridinecarbonitrile (**2**) was obtained in satisfactory yield. The partial hydrolysis of **2** with hydrogen peroxide under alkaline conditions gave 4,6-dimethyl-2-phenylethynyl-3-pyridinecarboxamide (**3**). On heating of **3** with sodium ethoxide in ethanol, cyclization between the carbamoyl group and the phenylethynyl group proceeded to give 2,4-dimethyl-7-phenyl-1,6-naphthyridin-5(6*H*)-one (**4**) in an overall yield of 52% from **1**.

The synthesis of 2,4-dimethyl-6-phenyl-1,7-naphthyridin-8(7*H*)-one (**8**) was accomplished in a similar manner. Namely, the reaction of 3-bromo-4,6-dimethyl-2-pyridinecarbonitrile (**5**) with phenylacetylene gave 4,6-dimethyl-3-phenylethynyl-2-pyridinecarbonitrile (**6**), which was hydrolyzed to give 4,6-dimethyl-3-phenylethynyl-2-pyridinecarboxamide (**7**). The cyclization of **7** under basic conditions afforded the desired compound (**8**) in 30% overall yield from **5**.

In the synthesis of 5,7-dimethyl-3-phenyl-2,6-naphthyridin-1(2*H*)-one (**12**), a carbamoyl group was introduced at the 4-position of 3-bromo-2,6-dimethylpyridine (**9**), before the cross-coupling reaction with phenylacetylene. That is, **9** was allowed to react with an amide radical

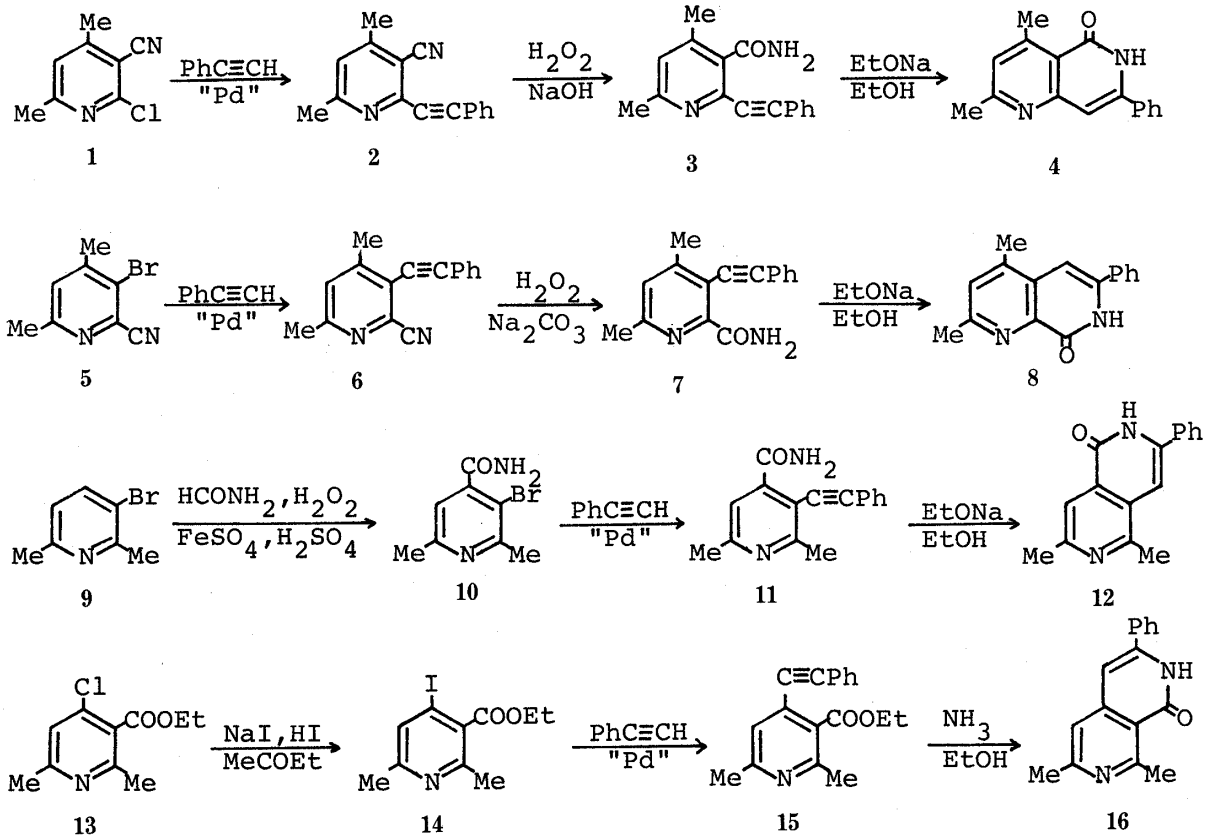


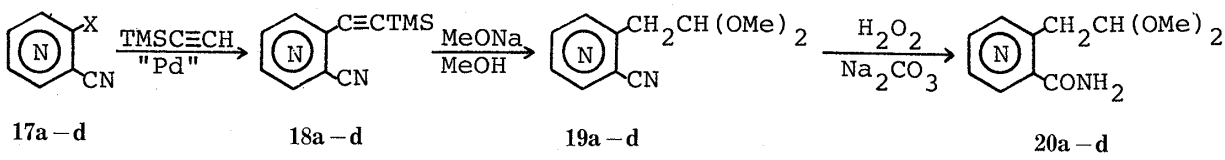
Chart 1

generated from formamide with 30% hydrogen peroxide in the presence of ferrous sulfate according to the method reported by Minisci *et al.*[4] 3-Bromo-2,6-dimethyl-4-pyridinecarboxamide (**10**) thus obtained reacted with phenylacetylene under the same conditions as above to give 2,6-dimethyl-3-phenylethynyl-4-pyridinecarboxamide (**11**). The cyclization of **11** under basic conditions gave **12** in 45% overall yield from **10**.

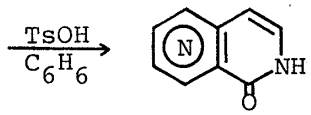
6,8-Dimethyl-3-phenyl-2,7-naphthyridin-1(2*H*)-one (**16**) was synthesized in a manner similar to that employed in our previous pyridopyrimidine synthesis.[1] Ethyl 4-iodo-2,6-dimethyl-3-pyridinecarboxylate (**14**) prepared from the corresponding chloro derivative (**13**) cross-coupled smoothly with phenylacetylene to give ethyl 2,6-dimethyl-4-phenylethynyl-3-pyridinecarboxylate (**15**). When **15** was heated with ethanolic ammonia in a sealed tube, **16** was obtained in 65% overall yield from **14**.

Next, the synthesis of unsubstituted naphthyridinones (**21a—d**) containing an isocarbostyrile-type structure was investigated. As reported previously, chloro- and bromo-*N*-heteroaromatics generally react with trimethylsilylacetylene in the presence of the palladium–phosphine complex,[3c] and the trimethylsilylethynyl-*N*-heteroaromatics thus obtained are readily convertible to the corresponding β,β-dimethoxyethyl-*N*-heteroaromatics by treatment with sodium methoxide in methanol.[5]

Accordingly, four kinds of unsubstituted naphthyridinones were expected to be synthesized by means of the intramolecular condensation of appropriate β,β-dimeoxyethylpyridinecarboxamides as a key reaction. When 2-trimethylsilylethynyl-3-pyridinecarbonitrile (**18a**), obtained by the reaction of 2-chloro-3-pyridinecarbonitrile (**17a**) with trimethylsilylacetylene, was heated with sodium methoxide in methanol, 2-(β,β-dimethoxyethyl)-3-pyridinecarbonitrile (**19a**) was formed in satisfactory yield. The hydrolysis of **19a** with hydrogen peroxide under alkaline conditions afforded the corresponding carboxamide (**20a**). On treat-



17a–d 18a–d 19a–d 20a–d



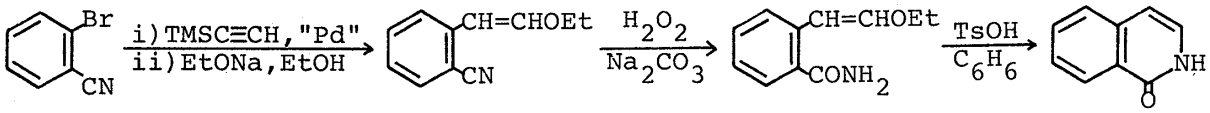
21a–d

17a : 2-chloro-3-pyridinecarbonitrile
17b : 3-bromo-2-pyridinecarbonitrile
17c : 3-chloro-4-pyridinecarbonitrile
17d : 4-chloro-3-pyridinecarbonitrile

Chart 2

ment with *p*-toluenesulfonic acid (TsOH) in boiling benzene, cyclization between the carbamoyl group and the formylmethyl group derived from the dimethoxyethyl group by hydrolysis converted **20a** to the desired 1,6-naphthyridin-5(6*H*)-one (**21a**). This method was successfully applied to the synthesis of the other unsubstituted naphthyridinones (**21b—d**) from the corresponding halopyridinecarbonitriles (**17b—d**) with experimental simplicity.

Finally, the synthesis of 1(2*H*)-isoquinolone (**25**) through this route was examined. 2-Bromobenzonitrile (**22**) was smoothly converted into 2-(*β*-ethoxyethenyl)benzonitrile (**23**) by cross-coupling with trimethylsilylacetylene and subsequent ethanolysis of the resulting crude product. The cyclization of the benzamide (**24**) derived from **23** gave 1(2*H*)-isoquinolone (**25**), which was identical with an authentic specimen.



22 23 24 25

Chart 3

The cyclization of ethynylpyridinecarboxamides may have wide applicability to the synthesis of isocarbostyrile-type naphthyridinones, provided that the starting halopyridinecarbonitriles (or carboxamides) are readily available, because the steps in Charts 1 and 2 are experimentally simple and provide high yields of the products.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s = singlet, d = doublet, q = quartet, m = multiplet, and br s = broad singlet.

4,6-Dimethyl-2-phenylethynyl-3-pyridinecarbonitrile (2)——A mixture of 2-chloro-4,6-dimethyl-3-pyridinecarbonitrile[6] (**1**) (1.67 g, 10 mmol), phenylacetylene (1.5 g, 15 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (3 ml) was heated in a sealed tube at 100 °C for 12 h. The mixture was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using benzene as an eluent. Recrystallization from hexane gave colorless scales, mp 118—120 °C. Yield 2.0 g (85%). IR ($CHCl_3$) cm^{-1}: 2200. ^{1}H-NMR ($CDCl_3$): 2.56 (3H, s), 2.67 (3H, s), 7.16 (1H, s), 7.3—8.0 (5H, m). *Anal.* Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.90; H, 5.43; N, 11.85.

4,6-Dimethyl-2-phenylethynyl-3-pyridinecarboxamide (3)——A mixture of **2** (1.1 g, 4.7 mmol), 30% H_2O_2 (2 ml),

3 N NaOH (1 ml), and MeOH (15 ml) was stirred at 50 °C for 12 h. After removal of the MeOH, the residue was diluted with H_2O. The precipitate was collected and recrystallized from MeOH to give colorless prisms, mp 250—252 °C. Yield 0.82 g (70%). IR (KBr) cm^{-1}: 3310, 3100, 2200, 1680. ^{1}H-NMR (CF_3COOH): 2.80 (3H, s), 2.87 (3H, s), 7.3—8.2 (6H, m). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.53; H, 5.82; N, 10.95.

2,4-Dimethyl-7-phenyl-1,6-naphthyridin-5(6*H*)-one (4)——An EtOH–EtONa solution [prepared from dry EtOH (20 ml) and Na (0.46 g, 20 mmol)] of **3** (0.5 g, 2 mmol) was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O. The precipitate was collected and recrystallized from MeOH to give colorless prisms, mp 244—245 °C. Yield 0.44 g (88%). IR (KBr) cm^{-1}: 3200, 1700. ^{1}H-NMR (CF_3COOH): 3.00 (3H, s), 3.62 (3H, s), 7.4—7.9 (7H, m). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.64; H, 5.77; N, 10.88.

3-Bromo-4,6-dimethylpyridine——3-Amino-4,6-dimethylpyridine[7] (6.4 g, 53 mmol) was diazotized by Talik's method[8] using a mixture of CuBr [prepared from $CuSO_4 \cdot 5H_2O$ (20 g), $NaHSO_3$ (5 g), and KBr (20 g)] and 47% HBr (30 ml) with addition of $NaNO_2$ (6 g) in H_2O at 10 °C. The reaction mixture was stirred at room temperature for 30 min, then heated on a steam bath at 80 °C for 20 min. The reaction mixture was cooled and made alkaline with aq. KOH. Insoluble material was filtered off, and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under atmospheric pressure to give a pale yellow liquid, bp 205—210 °C. Yield 5.5 g (56%). Picrate: yellow needles (MeOH), mp 166—168 °C. ^{1}H-NMR (CCl_4): 2.30 (3H, s), 2.40 (3H, s), 6.92 (1H, s), 8.40 (1H, s). *Anal.* Calcd for $C_{13}H_{11}BrN_4O_7$ (picrate): C, 37.61; H, 2.67; N, 13.50. Found: C, 37.46; H, 2.45; N, 13.51.

3-Bromo-4,6-dimethylpyridine 1-Oxide——A mixture of 3-bromo-4,6-dimethylpyridine (5.5 g, 30 mmol), 35% H_2O_2 (15 ml), and AcOH (30 ml) was heated at 110 °C for 20 h. After dilution with H_2O, the reaction mixture was concentrated, and the residue was made alkaline with K_2CO_3. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. Recrystallization from hexane gave colorless needles, mp 117—119 °C. Yield 3.5 g (59%). ^{1}H-NMR ($CDCl_3$): 2.33 (3H, s), 2.42 (3H, s), 7.08 (1H, s), 8.40 (1H, s). IR (KBr) cm^{-1}: 1250. *Anal.* Calcd for C_7H_8BrNO: C, 41.61; H, 3.99; N, 6.93. Found: C, 41.54; H, 4.08; N, 6.65.

3-Bromo-4,6-dimethyl-2-pyridinecarbonitrile (5)——A mixture of 3-bromo-4,6-dimethylpyridine 1-oxide (2.53 g, 12.5 mmol), trimethylsilyl cyanide (3.75 g, 38 mmol), Et_3N (5 g), and MeCN (20 ml) was refluxed for 20 h. After removal of the MeCN, the residue was diluted with H_2O. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. Recrystallization from cyclohexane gave colorless needles, mp 78—79 °C. Yield 1.7 g (64%). IR ($CHCl_3$) cm^{-1}: 2220. ^{1}H-NMR ($CDCl_3$): 2.45 (3H, s), 2.52 (3H, s), 7.23 (1H, s). *Anal.* Calcd for $C_8H_7BrN_2$: C, 45.53; H, 3.34; N, 13.27. Found: C, 45.68; H, 3.41; N, 13.03.

4,6-Dimethyl-3-phenylethynyl-2-pyridinecarbonitrile (6)——A mixture of **5** (1.06 g, 5 mmol), phenylacetylene (0.75 g, 7.5 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (2 ml) was heated at 100 °C for 24 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using benzene as an eluent. Recrystallization from hexane gave colorless leaflets, mp 119—120 °C. Yield 0.7 g (60%). IR ($CHCl_3$) cm^{-1}: 2200. ^{1}H-NMR ($CDCl_3$): 2.50 (3H, s), 2.55 (3H, s), 7.1—7.8 (6H, m). *Anal.* Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.45; H, 5.39; N, 11.71.

4,6-Dimethyl-3-phenylethynyl-2-pyridinecarboxamide (7)——A mixture of **6** (0.58 g, 2.5 mmol), 3 N Na_2CO_3 (15 ml), 15% H_2O_2 (10 ml), and acetone (15 ml) was stirred at room temperature for 20 h. After removal of the acetone, the residue was diluted with H_2O. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallized from benzene to give colorless prisms, mp 193—195 °C. Yield 0.43 g (69%). IR (KBr) cm^{-1}: 3400, 3170, 1680. ^{1}H-NMR (CF_3COOH): 2.93 (3H, s), 3.00 (3H, s), 7.3—7.9 (5H, m), 8.03 (1H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.57; H, 5.78; N, 10.90.

2,4-Dimethyl-6-phenyl-1,7-naphthyridin-8(7*H*)-one (8)——An EtOH–EtONa solution [prepared from dry EtOH (10 ml) and Na (0.92 g, 40 mmol)] of **7** (0.25 g, 1 mmol) was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O. The precipitate was collected and recrystallized from acetone to give pale yellow scales, mp 241—243 °C. Yield 0.18 g (72%). IR (KBr) cm^{-1}: 3160, 1690. ^{1}H-NMR (CF_3COOH): 3.06 (3H, s), 3.13 (3H, s), 7.4—7.9 (6H, m), 8.03 (1H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.63; H, 5.95; N, 10.91.

3-Bromo-2,6-dimethyl-4-pyridinecarboxamide (10)——Aq. H_2O_2 (30%) (4 ml) was added to a mixture of 3-bromo-2,6-dimethylpyridine[8] (**9**) (1.86 g, 10 mmol), conc. H_2SO_4 (0.6 ml) and formamide (60 ml) under stirring and cooling (0—10 °C), and then $FeSO_4 \cdot 7H_2O$ (8.34 g, 30 mmol) was added to the mixture under stirring at 10—20 °C. After being stirring for an additional 20 min, the mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallized from acetone to give colorless prisms, mp 182—185 °C. Yield 1.50 g (65%). IR (KBr) cm^{-1}: 3310, 3100, 1680. ^{1}H-NMR (CF_3COOH): 2.90 (3H, s), 3.02 (3H, s), 7.83 (1H, s). *Anal.* Calcd for $C_8H_9BrN_2O$: C, 41.95; H, 3.96; N, 12.23. Found: C, 42.07; H, 4.21; N, 12.11.

2,6-Dimethyl-3-phenylethynyl-4-pyridinecarboxamide (11)——A mixture of **10** (1.15 g, 5 mmol), phenylacetylene (0.75 g, 7.5 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), Et_3N (1.2 ml), and dimethylformamide (2 ml) was heated in a sealed tube at 120 °C for 20 h. The mixture was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using AcOEt as an eluent. Recrystallization from MeOH gave colorless needles, mp 253—255 °C. Yield 0.77 g (62%). IR (KBr) cm^{-1}: 3320, 3110, 2200, 1680. ^{1}H-NMR (CF_3COOH): 3.00 (3H, s), 3.15 (3H, s), 7.2—7.9 (5H, m), 8.10 (1H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78;

H, 5.64; N, 11.19. Found: C, 76.53; H, 5.37; N, 11.06.

5,7-Dimethyl-3-phenyl-2,6-naphthyridin-1(2*H*)-one (12)——An EtOH–EtONa solution [prepared from dry EtOH (10 ml) and Na (0.23 g, 10 mmol)] of **11** (0.3 g, 1.2 mmol) was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O. The precipitate was collected and recrystallized from MeOH to give colorless prisms, mp 253—255 °C. Yield 0.22 g (73%). IR (KBr) cm^{-1}: 3400, 1680. ^{1}H-NMR (CF_3COOH): 3.05 (3H, s), 3.26 (3H, s), 7.1—8.0 (7H, m). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.46; N, 11.19. Found: C, 76.52; H, 5.41; N, 10.96.

Ethyl 4-Iodo-2,6-dimethyl-3-pyridinecarboxylate (14)——A mixture of ethyl 4-chloro-2,6-dimethyl-3-pyridinecarboxylate[9] (**13**) (2.26 g, 20 mmol), NaI (14.9 g, 100 mmol), 57% HI (0.5 ml), and 2-butanone (50 ml) was refluxed for 20 h. After removal of the 2-butanone, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallized from hexane to give colorless scales, mp 62—63 °C. Yield 3.80 g (62%). IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, J=7 Hz), 2.46 (3H, s), 2.53 (3H, s), 4.40 (2H, q, J=7 Hz), 7.47 (1H, s). *Anal.* Calcd for $C_{10}H_{12}INO_2$: C, 39.36; H, 3.97; N, 4.59. Found: C, 39.29; H, 3.68; N, 4.31.

Ethyl 2,6-Dimethyl-4-phenylethynyl-3-pyridinecarboxylate (15)——A mixture of **14** (3.05 g, 10 mmol), phenylacetylene (1.50 g, 15 mmol), $Pd(PPh_3)_2Cl_2$ (320 mg), CuI (160 mg), and Et_3N (20 ml) was stirred at room temperature for 24 h. After removal of the Et_3N, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. Distillation of the $CHCl_3$ eluate gave a colorless liquid, bp 145—149 °C (5 mmHg). Yield 2.12 g (76%). IR ($CHCl_3$) cm^{-1}: 2200, 1720. ^{1}H-NMR ($CDCl_3$): 1.38 (3H, t, J=7 Hz), 2.55 (3H, s), 2.60 (3H, s), 2.47 (2H, q, J=7 Hz), 7.15 (1H, s), 7.2—7.7 (5H, m). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.01. Found: C, 77.25; H, 6.30; N, 5.29.

6,8-Dimethyl-3-phenyl-2,7-naphthyridin-1(2*H*)-one (16)——An EtOH solution (20 ml) of **15** (0.70 g, 2.5 mmol) was saturated with NH_3 gas, and the mixture was heated in a sealed tube at 120 °C for 12 h. After removal of the EtOH, the residue was recrystallized from MeOH to give colorless prisms, mp 252—255 °C. Yield 0.53 g (85%). IR (KBr) cm^{-1}: 3370, 1670. ^{1}H-NMR (CF_3COOH): 3.42 (3H, s), 3.76 (3H, s), 7.5—7.8 (7H, m). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.03; H, 5.82; N, 11.06.

General Procedure for the Preparation of *β,β*-Dimethoxyethylpyridinecarbonitriles (19a—d)——A mixture of halopyridinecarbonitrile (**17a**, 2-chloro-3-;[10] **17b**, 3-bromo-2-;[11] **17c**, 3-chloro-4-;[12] **17d**, 4-chloro-3-pyridinecarbonitrile[13]) (10 mmol), trimethylsilylacetylene (1.2 g, 12 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (3 ml) was heated in a sealed tube at 100 °C for 20 h. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using benzene as an eluent. The liquid (**18a**, 62%; **18b**, 72%; **18c**, 55%; **18d**, 76%) obtained from the benzene eluate was added to an MeOH–MeONa solution, prepared from dry MeOH (20 ml) and Na (0.46 g, 20 mmol), and the mixture was refluxed for 5 h. After removal of the MeOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. Distillation of the $CHCl_3$ eluate gave a colorless liquid.

General Procedure for the Preparation of *β,β*-Dimethoxyethylpyridinecarboxamides (20a—d)——A mixture of **19a—d** (2.5 mmol), 3 N Na_2CO_3 (10 ml), 15% H_2O_2 (10 ml), and acetone (5 ml) was stirred at room temperature for 6 h. After removal of the acetone, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallized from the solvent shown in Table III to give colorless crystals.

General Procedure for the Preparation of Naphthyridinones (21a—d)——A mixture of **20a—d** (0.3 g), TsOH (30 mg), and benzene (10 ml) was refluxed for 20 h. After removal of the benzene, the residue was purified by SiO_2 column chromatography using AcOEt as an eluent. Recrystallization from the solvent shown in Table V gave colorless crystals.

TABLE I. Yields, Boiling Points, and Analytical Data for **19a—d**

No.	Yield (%) (from **17**)	bp (°C) (mmHg)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
19a	52 (32)	103—105 (2)	$C_{10}H_{12}N_2O_2$	62.48 (62.74	6.29 6.50	14.58 14.15)
19b	63 (45)	95—98 (3)	$C_{10}H_{12}N_2O_2$	62.48 (62.79	6.29 6.49	14.58 14.20)
19c	47 (26)	101—104 (3)	$C_{10}H_{12}N_2O_2$	62.48 (62.73	6.29 6.35	14.58 14.31)
19d	78 (59)	105—110 (3)	$C_{10}H_{12}N_2O_2$	62.48 (62.52	6.29 6.27	14.58 14.45)

TABLE II. Spectral Data for **19a—d**

No.	IR ($CHCl_3$) cm^{-1} –CN	^{1}H-NMR ($CDCl_3$) δ (ppm) –OCH_3	–$CH<^{O-}_{O-}$	–CH_2–	Ring protons
19a	—	3.36 (6H, s)	4.65 (1H, t, J=6 Hz)	3.30 (2H, d, J=6 Hz)	7.0—7.4 (1H, m), 7.7—8.0 (1H, m) 8.5—8.8 (1H, m)
19b	2200	3.40 (6H, s)	4.56 (1H, t, J=5 Hz)	3.33 (2H, d, J=5 Hz)	7.3—7.6 (1H, m), 7.7—8.0 (1H, m) 8.5—8.7 (1H, m)
19c	—	3.40 (6H, s)	4.60 (1H, t, J=5 Hz)	3.35 (2H, d, J=5 Hz)	8.2—8.8 (3H, m)
19d	2200	3.35 (6H, s)	4.56 (1H, t, J=5 Hz)	3.10 (2H, d, J=5 Hz)	7.37 (1H, d, J=6 Hz) 8.65 (1H, d, J=6 Hz), 8.80 (1H, s)

TABLE III. Yields, Melting Points, and Analytical Data for **20a—d**

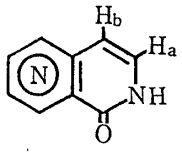
No.	Yield (%)	mp (°C)	Appearance (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
20a	73	124—126	Prisms (Cyclohexane)	$C_{10}H_{14}N_2O_3$	57.13 (56.98	6.71 6.53	13.33 13.12)
20b	61	107—109	Needles (Hexane)	$C_{10}H_{14}N_2O_3$	57.13 (56.84	6.71 6.51	13.33 13.30)
20c	61	153—155	Needles (Benzene)	$C_{10}H_{14}N_2O_3$	57.13 (57.26	6.71 6.85	13.33 13.27)
20d	69	73—75	Needles (Hexane–acetone)	$C_{10}H_{14}N_2O_3$	57.13 (56.92	6.71 6.66	13.33 13.27)

TABLE IV. Spectral Data for **20a—d**

No.	IR ($CHCl_3$) cm^{-1} –NH_2	$>C=O$	^{1}H-NMR ($CDCl_3$) δ (ppm) –NH_2	–OCH_3	–$CH<^{O-}_{O-}$	–CH_2–	Ring protons
20a	3300 3100	1680	5.9—6.4 (2H, br s)	3.40 (6H, s)	4.70 (1H, t, J=6 Hz)	3.33 (2H, d, J=6 Hz)	7.1—7.5 (1H, m) 7.9—8.3 (1H, m) 8.5—8.9 (1H, m)
20b	3320 3100	1670	5.6—6.2 (2H, br s)	3.42 (6H, s)	4.62 (1H, t, J=6 Hz)	3.35 (2H, d, J=6 Hz)	7.3—7.7 (1H, m) 7.8—8.1 (1H, m) 8.5—8.8 (1H, m)
20c	3320 3100	1680	5.8—6.5 (2H, br s)	3.40 (6H, s)	4.65 (1H, t, J=6 Hz)	3.37 (2H, d, J=6 Hz)	8.3—8.8 (3H, m)
20d	3310 3120	1670	5.6—6.3 (2H, br s)	3.41 (6H, s)	4.60 (1H, t, J=6 Hz)	3.25 (2H, d, J=6 Hz)	7.40 (1H, d, J=6 Hz) 8.72 (1H, d, J=6 Hz) 8.83 (1H, s)

2-(β-Ethoxyethenyl)benzonitrile (23)——A mixture of 2-bromobenzonitrile (**22**) (1.82 g, 10 mmol), trimethylsilylacetylene (1.2 g, 12 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (3 ml) was heated in a sealed tube at 120 °C for 20 h. The mixture was diluted with H_2O, and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using benzene as an eluent. The crude product obtained from the benzene eluate was added to an EtOH–EtONa solution prepared from dry EtOH (60 ml) and Na (0.92 g, 40 mmol), and the mixture was

TABLE V. Naphthyridinones (**21a—d**)



No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR (KBr) cm^{-1}		^{1}H-NMR (CF_3COOH) δ (ppm)		
			>NH	>C=O	H_a	H_b	Pyridine ring protons
21a	55	241—243[a] (MeOH)	3380	1690	7.56 (1H, d, J=8 Hz)	6.73 (1H, d, J=8 Hz)	7.4—7.9 (1H, m) 8.70 (1H, d, J=6 Hz) 9.10 (1H, d, J=8 Hz)
21b	72	234—235[b] (MeOH)	3400	1680	7.35 (1H, d, J=6 Hz)	6.60 (1H, d, J=6 Hz)	7.6—7.9 (1H, m) 8.1—8.3 (1H, m) 8.5—8.7 (1H, m)
21c	42	235—237[c] (MeOH)	3380	1700	7.42 (1H, d, J=7 Hz)	6.80 (1H, d, J=7 Hz)	7.83 (1H, d, J=7 Hz) 8.23 (1H, d, J=7 Hz) 9.20 (1H, s)
21d	82	263—265[d] (AcOEt–MeOH)	3380	1670	7.56 (1H, d, J=7 Hz)	6.63 (1H, d, J=7 Hz)	7.73 (1H, d, J=6 Hz) 8.30 (1H, d, J=6 Hz) 9.33 (1H, s)

a) Lit.[14] mp 243—244.5 °C. *b*) Lit.[14] mp 236—239 °C.
c) *Anal.* Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.36; H, 4.18; N, 19.13.
d) Lit.[14] mp 260—262 °C.

refluxed for 6 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 96—100 °C (2 mmHg). Yield 1.05 g (61%). IR ($CHCl_3$) cm^{-1}: 2160. ^{1}H-NMR ($CDCl_3$): 1.37 (3H, t, J=7 Hz), 4.05 (2H, q, J=7 Hz), 5.63 (1H, d, J=7 Hz), 6.43 (1H, d, J=7 Hz), 7.1—7.9 (4H, m). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.45; H, 6.52; N, 8.01.

2-(β-Ethoxyethenyl)benzamide (24)——A mixture of **23** (1.0 g, 5.77 mmol), 3 N Na_2CO_3 (30 ml), 15% H_2O_2 (30 ml), and acetone (20 ml) was stirred at room temperature for 4 h. After removal of the acetone, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallized from hexane to give colorless needles, mp 145—147 °C. Yield 0.82 g (74%). IR ($CHCl_3$) cm^{-1}: 3300, 3120, 1680. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, t, J=7 Hz), 4.10 (2H, q, J=7 Hz), 5.65 (1H, d, J=7 Hz), 5.8—6.3 (2H, br s), 6.45 (1H, d, J=7 Hz), 7.2—7.9 (4H, m). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.32; H, 6.91; N, 7.24.

1(2*H*)-Isoquinolone (25)——A mixture of **24** (0.5 g, 2.61 mmol), TsOH (20 mg), and benzene (20 ml) was refluxed for 8 h. After removal of the benzene, the residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallized from benzene to give colorless prisms, mp 208—209 °C (lit.[15] mp 209—210 °C). Yield 0.31 g (82%). IR (KBr) cm^{-1}: 3390, 1670. ^{1}H-NMR (CF_3COOH): 6.65 (1H, d, J=7 Hz), 7.23 (1H, d, J=7 Hz) 7.3—7.7 (4H, m).

References and Notes

1) Part I: T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 2410 (1982).
2) Part II: T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 2417 (1982).
3) *a*) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **26**, 3843 (1978); *b*) H. Yamanaka, M. Shiraiwa, K. Edo, and T. Sakamoto, *ibid.*, **27**, 270 (1979); *c*) T. Sakamoto, M. Shiraiwa, Y. Kondo, and H. Yamanaka, *Synthesis*, **1983**, 3121; *d*) A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Pharm. Bull.*, **28**, 3488 (1980); *e*) Y. Akita and A. Ohta, *Heterocycles*, **19**, 329 (1982).
4) A. Arnone, M. Cecere, R. Galli, F. Minisci, M. Perchinunno, O. Porta, and G. Gardini, *Gazz. Chim. Ital.*, **103**, 13 (1973).
5) T. Sakamoto, Y. Kondo, M. Shiraiwa, and H. Yamanaka, *Synthesis*, **1984**, 245.
6) R. P. Mariella and J. L. Leech, *J. Am. Chem. Soc.*, **71**, 331 (1949).
7) M. Julia, J. Igolen, and H. Pinhas, *Bull. Soc. Chim. Fr.*, **1966**, 2381.
8) T. Talik, Z. Talik, and H. B. Oganowska, *Synthesis*, **1974**, 293.
9) G. B. Backman and R. S. Barker, *J. Org. Chem.*, **14**, 97 (1949).

10) E. C. Tayler, Jr. and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).
11) T. Sakamoto, S. Kaneda, S. Nishimura, and H. Yamanaka, *Chem. Pharm. Bull.*, **33**, 565 (1985).
12) J. Rokach and Y. Girard, *J. Heterocyclic Chem.*, **15**, 683 (1978).
13) T. Wieland and H. Biener, *Chem. Ber.*, **96**, 266 (1963).
14) J. J. Boldwin, K. Mensler, and G. S. Ponticello, *J. Org. Chem.*, **43**, 4878 (1978).
15) D. Bain, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **105**, 2397 (1914).