A Facile Synthesis of 1,6-Naphthyridin-5(6*H*)-ones

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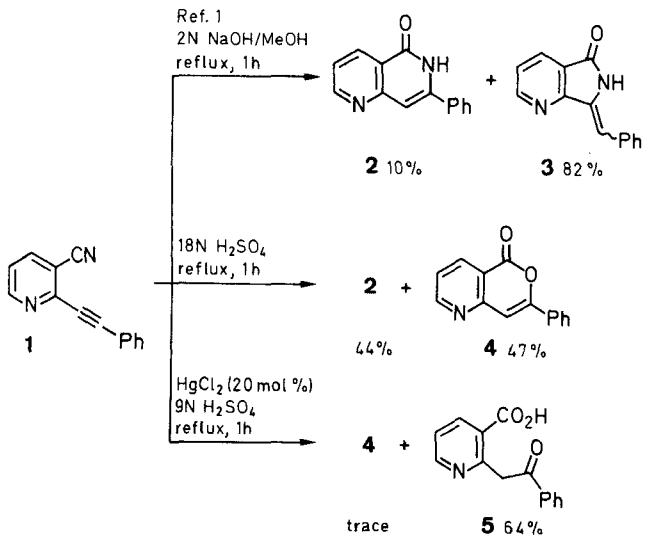
3-Cyano-2-(phenylethynyl)pyridine (**1**) was cyclized intramolecularly under acidic conditions to give 1,6-naphthyridin-5(6*H*)-one (**2**) and 5*H*-pyrano[4,3-*b*]pyridin-5-one (**4**). Pyranopyridine **4** was readily transformed to **2** or naphthyridinone **9** having an alkyl substituent at 6-position.

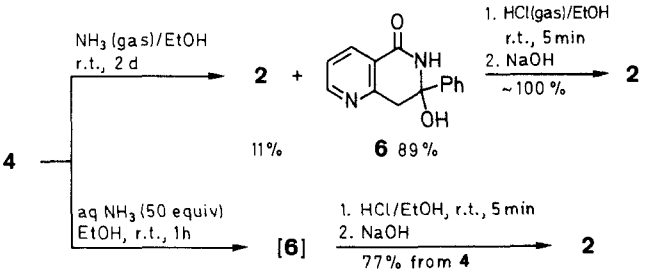
We recently reported the intramolecular cyclization of vicinally functionalized ethynylpyridines leading to various bicyclic pyridines.[1] Among them 1,6-naphthyridin-5(6*H*)-ones are important compounds because of their biological activities such as muscle relaxing,[2] antiinflammatory,[2] antibacterial,[3] and antimalarial activities.[4] However, the known synthetic methods[2-8] for them suffer from some restrictions. Our attempt to synthesize 7-phenyl-1,6-naphthyridin-5(6*H*)-one (**2**) by cyclization of 3-cyano-2-(phenylethynyl)pyridine (**1**), which was prepared by the direct ethynylation of 3-cyanopyridine *N*-oxide,[9] under basic conditions gave only a small amount of naphthyridinone **2**, but pyrrolopyridine **3** as a major product.[1] Here we report facile cyclization of ethynylpyridine givng the title compounds under acidic conditions.

Ethynylpyridine **1** was refluxed in 18 N sulfuric acid to afford 1,6-naphthyridinone **2** and 7-phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (**4**)[10,11] in 44% and 47% yields, respectively. When 2 N or 9 N sulfuric acid was used, the starting compound **1** was almost recovered. On the other hand, both hydration of the triple bond and hydrolysis of cyano group were observed in 9 N sulfuric acid in the presence of mercury dichloride as catalyst[10] to give 2-phenacylpyridine-3-carboxylic acid (**5**) along with a trace amount of pyranopyridine **4** (Scheme **A**).



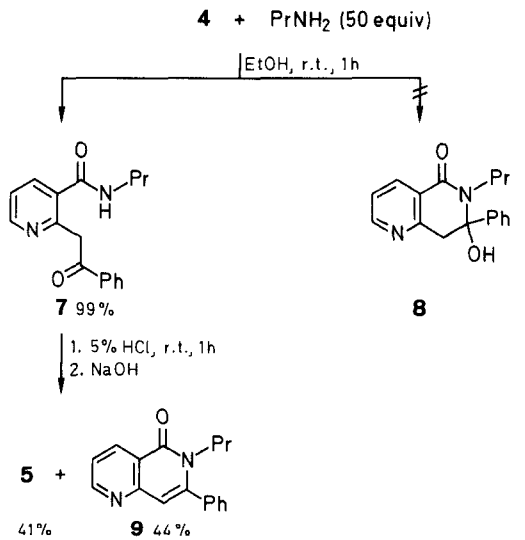
Scheme **A**

While Wibberley reported a conversion method of pyranopyridine **4** into naphthyridinone **2**,[8] similar treatment of **4** with gaseous ammonia in ethanol mainly produced dihydronaphthyridinone **6**[12] and the expected naphthyridinone **2** was obtained only in a very low yield. By bubbling hydrogen chloride gas into an ethanol solution of the dihydro derivative **6**,[2] dehydration proceeded to give naphthyridinone **2** quantitatively. It was found that this reaction does not need such a long time as that of Wibberley, nor bubbling of ammonia or hydrogen chloride gases. Thus the reaction of **4** with 50 equivalents of aqueous ammonia in ethanol readily underwent even in one hour to form **6**, which was successively converted to naphthyridinone **2** in one-pot. These results show that pyrano[4,3-*b*]pyridine **4** is equivalent to 1,6-naphthyridin-5(6*H*)-one **2** and that the latter can be efficiently prepared not only from ethynylpyridine **1** but also from 2-(phenylethynyl)nicotinic acid via the pyranopyridine **4** reported in our previous paper[1] (Scheme **B**).



Scheme **B**

Furthermore, synthesis of naphthyridinone, bearing an alkyl substituent at 6-position, from pyranopyridine **4** was examined by treatment with propylamine instead of ammonia. Contrary to our expectation, the product was phenacylpyridine **7** instead of the anticipated dihydronaphthyridinone **8**. Successive treatment of **7** with hydrochloric acid caused ready cyclization to form 7-phenyl-6-propyl-1,6-naphthyridin-5(6*H*)-one (**9**). In this reaction, no change was observed when sodium hydroxide was used as a cyclizing reagent.[2] Since it is also possible to convert pyridinecarboxylic acid **5** into the



Scheme **C**

1,6-naphthyridin-5(6*H*)-ones,[7] ethynylpyridine **1** would be the useful synthetic intermediate of naphthyridinones (Scheme **C**).

In summary, 1,6-naphthyridin-5(6*H*)-one **2** was easily synthesized from the functionalized ethynylpyridine **1**, and the reaction leading to 6-alkylated naphthyridinone[2,5,7,13] is expected to be applicable to the syntheses of a variety of 6-substituted derivatives.

Melting points are uncorrected. Mass spectra were obtained using a Shimadzu GCMS-QP2000 mass spectrometer and HRMS was recorded with a JEOL JMS-DX303 mass spectrometer. IR spectra were recorded on a Hitachi 270-30 IR spectrometer and ^{1}H-NMR spectra were measured on JEOL FT-NMR JMN FX90Q at 90 MHz or JEOL FT-NMR GSX at 270 MHz with TMS as an internal standard.

7-Phenyl-1,6-naphthyridin-5(6*H*)-one (2) and 7-Phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (4):
Ethynylpyridine **1** (102 mg, 0.5 mmol) is refluxed in 18 N H_2SO_4 (10 mL) for 1 h. Aq NaOH is added to the mixture and the product is extracted with CH_2Cl_2 (4 × 30 mL) under weakly acidic or neutral conditions. If the mixture is basified, pyranopyridine **4** would decompose.[8] The organic layer is dried ($MgSO_4$) and concentrated. The crude product is separated by column chromatography on silica gel using hexane/EtOAc (3:1) to give **4** as colorless plates; yield: 52 mg (47%); mp 135–136°C (Lit.[10] mp 134–135°C) and hexane/EtOAc (1:3) to give **2** as colorless needles; yield: 49 mg (44%); mp 239–240°C (Lit.[7] mp 229–230°C).

2-Phenacylpyridine-3-carboxylic Acid (5):
Ethynylpyridine **1** (102 mg, 0.5 mmol) is refluxed in 9 *N* H_2SO_4 (10 mL) for 1 h in the presence of $HgCl_2$ (27 mg, 0.1 mmol). The mixture is worked up as described above. The crude product is chromatographed on a silica gel column using $CHCl_3$/EtOAc (1:1) as an eluent to give **5**. The product recrystallized from $CHCl_3$/MeOH to give colorless needles; yield: 77 mg (64%); mp 180°C (dec) (Lit.[7] mp 175–177°C).

7,8-Dihydro-7-hydroxy-7-phenyl-1,6-naphthyridin-5(6*H*)-one (6):
A solution of 25% aq NH_3 (1.7 g, 25 mmol) in EtOH (5 mL) is added to a solution of pyranopyridine **4** (112 mg, 0.5 mmol) in EtOH (6 mL) and stirred for 1 h at r.t. The reaction mixture is concentrated *in vacuo* and the residue is recrystallized from CH_2Cl_2 to give **6** as colorless plates; yield: 102 mg (85%); mp 181–184°C (dec). The compound is too susceptible to dehydration to obtain satisfactory microanalyses.

IR (KBr): ν = 3416 (NH), 1688 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 3.35 (br s, 1 H, OH), 3.50 (s, 2 H, CH_2), 6.57 (br s, 1 H, NH), 7.2–7.8 (m, 6 H, Ph, 3-H), 8.36 (dd, 1 H, J = 7.6, 1.4 Hz, H-4), 8.63 (dd, 1 H, J = 5.2, 1.4 Hz, H-2).

MS (DEI): m/z (%) = 222 ($M^+ - H_2O$, 100), 77 (Ph, 20).

***N*-Propyl-2-phenacylpyridine-3-carboxamide (7):**
Propylamine (2.1 mL, 25 mmol) is added to a solution of pyranopyridine **4** (112 mg, 0.5 mmol) in EtOH (11 mL) and stirred for 1 h at r.t. The mixture is concentrated and chromatographed on a silica gel column using hexane/EtOAc (1:1) as an eluent to give **7** as yellow plates; yield: 140 mg (99%); mp 94–95°C.

$C_{17}H_{18}N_2O_2$	calc.	C 72.32	H 6.43	N 9.92
(282.3)	found	71.96	6.53	9.86

IR (neat): ν = 3292 (NH), 1692 (PhC=O), 1640 cm^{-1} (br, NC=O, C=C).

^{1}H-NMR ($CDCl_3$): δ = 0.77 (t, 3 H^e, J = 7.3 Hz, CH_3), 0.93 (t, 3 H^k, J = 7.3 Hz, CH_3), 1.4–1.8 (m, 2 H^e + 2 H^k, CCH_2C), 3.33 (dt, 2 H^k, J = 7.0, 6.2 Hz, NCH_2), 3.46 (dt, 2 H^e, J = 7.0, 6.2 Hz, NCH_2), 4.77 (s, 2 H^k, CH_2C=O), 6.3–6.5 (br, 1 H^e, NH), 6.51 (s, 1 H^e, CH=), 7.0–7.2 (br, 1 H^k, NH), 7.2–7.9 (m, 6 H^e + 4 H^k, $C_6H_5{}^e$ + *m,p*-$C_6H_5{}^k$ + H-5), 7.85 (dd, 1 H^k, J = 7.8, 1.6 Hz, H-4), 8.11 (dd, 2 H^k, J = 8.6, 1.4 Hz, *o*-$C_6H_5{}^k$), 8.32 (dd, 1 H^e, J = 7.8, 1.6 Hz, H-4), 8.43 (dd, 1 H^e, J = 4.9, 1.6 Hz, H-6), 8.55 (dd, 1 H^k, J = 4.9, 1.6 Hz, H-6), 15.5–15.8 (br, 1 H^e, OH) (H^e: enol form, H^k: keto form; In general enol forms of phenacylpyridines are relatively as stable as keto forms[14]).

MS (DEI): m/z (%) = 282 (M^+, 2), 196 (M^+ – CONHPr, 17), 105 (PhCO, 100), 77 (Ph, 64).

7-Phenyl-6-propyl-1,6-naphthyridin-5(6*H*)-one (9):
Phenacylpyridinecarboxamide **7** (140 mg, 0.5 mmol) is dissolved in 5% HCl (25 mL) and stirred for 1 h at r.t. The mixture is basified with NaOH and extracted with CH_2Cl_2 (4 × 30 mL). The organic layer is dried ($MgSO_4$) and concentrated. The residue is purified by column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent to give naphthyridinone **9** as pale yellow oil; yield 58 mg (44%).

HRMS: calc. for $C_{17}H_{16}N_2O$ (M^+): 264.1263, found: 264.1289.

IR (neat): ν = 1654 (C=O), 1622 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$): δ = 0.74 (t, 3 H, J = 7.4 Hz, CH_3), 1.4–1.8 (m, 2 H, CCH_2C), 3.8–4.0 (m, 2 H, NCH_2), 6.68 (d, 1 H, J = 0.6 Hz, H-8), 7.38 (dd, 1 H, J = 8.1, 4.6 Hz, H-3), 7.3–7.6 (m, 5 H, C_6H_5), 8.71 (ddd, 1 H, J = 8.1, 1.9, 0.6 Hz, H-4), 8.90 (dd, 1 H, J = 4.6, 1.9 Hz, H-2).

MS (DEI): m/z (%) = 264 (M^+, 11), 263 (M^+ – H, 18), 222 ($M^+ - C_3H_6$, 100).

The aqueous layer is acidified with 2 N HCl and extracted with CH_2Cl_2 (4 × 30 mL). The extract is dried ($MgSO_4$) and concentrated to give 2-phenacylpyridine-3-carboxylic acid (**5**); yield: 50 mg (41%).

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