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Condensed Heteroaromatic Ring Systems. IV.[1] Synthesis of Naphthyridine Derivatives by Cyclization of Aminopyridineacrylic Esters

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The reaction of aminohalopyridines with ethyl acrylate in the presence of palladium(II) acetate and triarylphosphine gave ethyl aminopyridineacrylates. The cyclization of the resulting acrylates under basic conditions gave naphthyridinones having a carbostyril-type moiety.

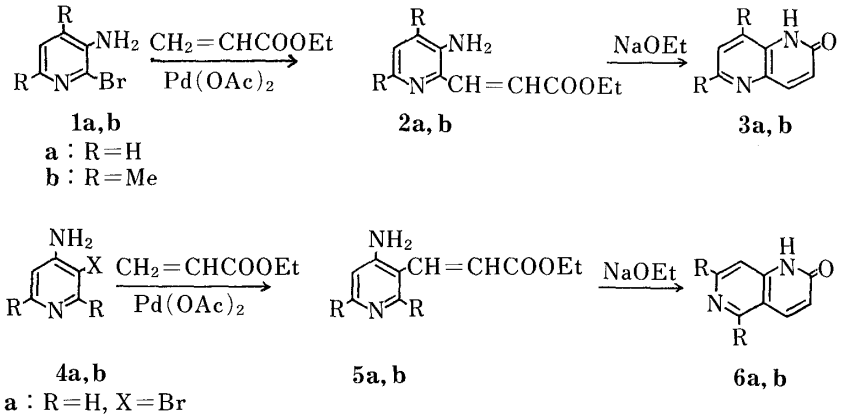
Keywords——intramolecular cyclization; palladium catalyst; ethyl acrylate; naphthyridinone; pyridineacrylic ester

As reported previously,[2] the palladium catalyzed cross-coupling reaction of halopyrimidines with ethyl acrylate yields the corresponding pyrimidineacrylates. When an amino group is present adjacent to the acrylate moiety thus introduced, cyclization between the amino group and the ethoxycarbonyl group under basic conditions gives pyridopyrimidine derivatives in satisfactory yields.[3]

As well as halopyrimidines, various halopyridine derivatives are known to react with ethyl acrylate under certain conditions.[2a,c] Thus, our next investigation was focussed on the syntheses of pyridopyridines (naphthyridines) by means of the above mentioned cross-coupling reactions; the results are described in the present paper.

When 3-amino-2-bromopyridine (**1a**) was allowed to react with ethyl acrylate under the reported conditions,[2] ethyl 3-amino-2-pyridineacrylate (**2a**) was obtained in good yield. On treatment with sodium ethoxide in boiling ethanol, **2a** was smoothly converted into 1,5-naphthyridin-2(1*H*)-one (**3a**). Similarly, 6,8-dimethyl-1,5-naphthyridin-2(1*H*)-one (**3b**) was synthesized from 3-amino-2-bromo-4,6-dimethylpyridine (**1b**) by this method.

In the case of 4-amino-3-halopyridine derivatives, 1,6-naphthyridin-2(1*H*)-ones were



1a,b
a : R=H
b : R=Me

2a,b

3a,b

4a,b
a : R=H, X=Br
b : R=Me, X=I

5a,b

6a,b

Chart 1

conveniently obtained. Namely, 4-amino-3-bromopyridine (**4a**) and 4-amino-3-iodo-2,6-dimethylpyridine (**4b**) reacted with ethyl acrylate to give the corresponding pyridineacrylates (**5a,b**). The products (**5a,b**) readily underwent cyclization under similar conditions, and the 1,6-naphthyridin-2(1*H*)-ones (**6a,b**) were obtained as expected.

6,8-Dimethyl-1,7-naphthyridin-2(1*H*)-one (**11**) was synthesized by a similar method as follows. As compared with 4-chloropyridines, 4-iodopyridines are generally preferable for the palladium catalyzed cross-coupling reaction. Thus, 4-chloro-2,6-dimethyl-3-nitropyridine (**7**) was firstly transformed with sodium iodide in the presence of hydroiodic acid. The cross-coupling reaction of the product **8** with ethyl acrylate gave ethyl 2,6-dimethyl-3-nitropyridineacrylate (**9**) in good yield as expected. The reduction of **9** with sodium borohydride and stannous chloride in ethanol yielded the corresponding aminopyridine (**10**), which was cyclized to give **11**.

The synthesis of 1,8-naphthyridin-2(1*H*)-one (**14**) was accomplished by the following two routes. The reaction of 2-amino-3-iodopyridine (**12**) with ethyl acrylate gave ethyl 2-aminopyridineacrylate (**13**), which was cyclized to **14** under similar conditions. Alternatively, the reaction of 2-chloro-3-iodopyridine with ethyl acrylate occurred exclusively at the 3-position, and ethyl 2-chloro-3-pyridineacrylate (**16**) was obtained as a sole product. On treatment of **16** with ethanolic ammonia in a sealed tube, **14** was obtained without any complication.

In contrast to the above, the reaction of 2-bromo-4,6-dimethyl-3-pyridineacrylate (**17c**) with ammonia failed to give the cyclized product, and the corresponding amide (**17d**) was obtained.

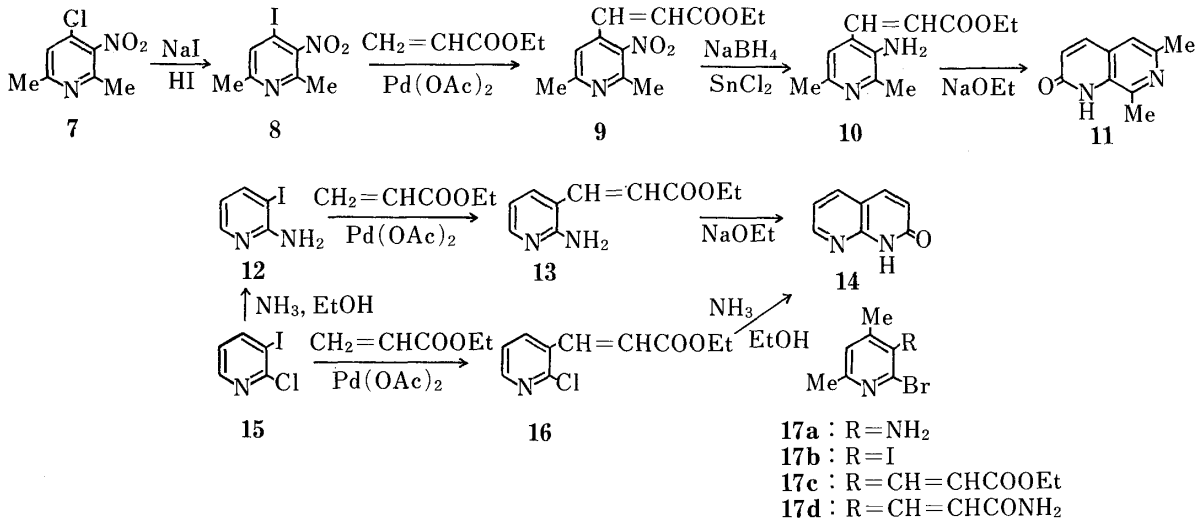


Chart 2

As described above, the present method is not applicable to the construction of 2,6- and 2,7-naphthyridine nuclei. However, we have already reported the synthesis of these naphthyridines, together with 1,6- and 1,7-naphthyridines, by means of palladium-catallized condensation of an appropriate halopyridinecarbonitrile with trimethylsilylacetylene, followed by cyclization of the resulting ethynylpyridinecarbonitrile. Thus, our investigations overall have provided one of preparative methods for the construction of all kinds of naphthyridine nuclei.

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, t=triplet, q=quartet, m=multiplet, and br s=broad singlet.

Ethyl 3-Amino-2-pyridineacrylate (2a)——A mixture of 3-amino-2-bromopyridine (**1a**)[4] (1.73 g, 10 mmol), ethyl acrylate (1.5 g, 15 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), PPh_3 (60 mg, 0.23 mmol), and Et_3N (2.25 g, 22.5 mmol) was heated in a sealed tube at 120 °C for 24 h. After dilution with H_2O, the mixture was 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. The $CHCl_3$ eluate gave yellow needles, mp 132—135 °C, which were recrystallized from hexane. Yield 1.28 g (67%). IR ($CHCl_3$) cm^{-1}: 3480, 3390, 1710. ^{1}H-NMR ($CDCl_3$): 1.36 (3H, t, J=7.0 Hz), 4.2 (2H, br s), 4.30 (2H, q, J=7.0 Hz), 6.70 (1H, d, J=17.0 Hz), 6.9—7.2 (1H, m), 7.53 (1H, d, J=17.0 Hz), 7.6—7.9 (1H, m), 8.0—8.2 (1H, m). *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.31; H, 6.34; N, 14.39.

3-Amino-2-bromo-4,6-dimethylpyridine (1b)——Aqueous (30%) H_2O_2 (10 ml) was added dropwise to a mixture of 3-amino-4,6-dimethylpyridine[5] (6.05 g, 50 mmol) and 47% HBr (30 ml) at 0 °C. After reaction at 10 °C for 2 h, the mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract gave colorless needles, mp 57—58 °C, which were recrystallized from hexane. Yield 7.0 g (70%). IR ($CHCl_3$) cm^{-1}: 3510, 3390. ^{1}H-NMR ($CDCl_3$): 2.16 (3H, s), 2.36 (3H, s), 3.90 (2H, br s), 6.75 (1H, s). *Anal.* Calcd for $C_7H_9BrN_2$: C, 41.82; H, 4.51; N, 13.93. Found: C, 41.67; H, 4.30; N, 13.72.

Ethyl 3-Amino-4,6-dimethyl-2-pyridineacrylate (2b)——A mixture of **1b** (1.0 g, 5 mmol), ethyl acrylate (0.75 g, 7.5 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), tris(*o*-tolyl)phosphine (POT) (72 mg, 0.24 mmol), Et_3N (0.75 g, 7.5 mmol), and dimethylformamide (DMF) (1 ml) was heated in a sealed tube at 140 °C for 24 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The C_6H_6 eluate gave yellow needles, mp 104—105 °C, which were recrystallized from hexane. Yield 0.77 g (70%). IR ($CHCl_3$) cm^{-1}: 3500, 3390, 1710. ^{1}H-NMR ($CDCl_3$): 1.30 (3H, t, J=7.0 Hz), 2.16 (3H, s), 2.40 (3H, s), 3.83 (2H, br s), 4.25 (2H, q, J=7.0 Hz), 6.87 (1H, s), 6.93 (1H, d, J=16.0 Hz), 7.88 (1H, d, J=16.0 Hz). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.71. Found: C, 65.53: H, 7.22; N, 12.50.

1,5-Naphthyridin-2(1*H*)-one (3a)——A mixture of **2a** (1.0 g, 5.2 mmol) and an EtONa–EtOH solution [prepared from Na (0.45 g, 20 mmol) and dry EtOH (20 ml)] was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from acetone to give colorless needles, mp 253—256 °C. Lit.[6] mp 256 °C. Yield 0.55 g (72%). IR ($CHCl_3$) cm^{-1}: 3380, 1675. ^{1}H-NMR (CF_3COOH): 7.34 (1H, d, J=12.0 Hz), 7.4—7.6 (1H, m), 7.9—8.2 (1H, m), 8.65 (1H, d, J=12.0 Hz), 8.7—8.9 (1H, m).

6,8-Dimethyl-1,5-naphthyridin-2(1*H*)-one (3b)——A mixture of **2b** (0.55 g, 2.5 mmol) and an EtONa–EtOH solution [prepared from Na (0.23 g, 10 mmol) and dry EtOH (10 ml)] was refluxed for 2 h. After removal of the EtOH, the residue was diluted with H_2O, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from MeOH to give colorless needles, mp 272—275 °C. Yield 0.31 g (71%). IR (KBr) cm^{-1}: 3370, 1680. ^{1}H-NMR (CF_3COOH): 2.50 (6H, s), 7.03 (1H, d, J=10.0 Hz), 7.45 (1H, s), 8.00 (1H, s). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.72; H, 5.56; N, 16.20.

Ethyl 4-Amino-3-pyridineacrylate (5a)——A mixture of 4-amino-3-bromopyridine (**4a**)[7] (1.59 g, 10 mmol), ethyl acrylate (1.5 g, 15 mmol), $Pd(OAc)_2$ (50 mg, 0.22 mmol), POT (120 mg, 0.39 mmol), Et_3N (1.5 g, 15 mmol), and MeCN was heated in a sealed tube at 120 °C for 48 h. After dilution with H_2O, the mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The C_6H_6 eluate gave pale yellow needles, mp 74—76 °C, which were recrystallized from hexane. Yield 1.25 g (65%). IR ($CHCl_3$) cm^{-1}: 3490, 3400, 1715. ^{1}H-NMR ($CDCl_3$): 1.34 (3H, t, J=7.0 Hz), 4.25 (2H, q, J=7.0 Hz), 5.10 (2H, br s), 6.65 (1H, d, J=17.0 Hz), 7.10 (1H, d, J=8.0 Hz), 7.45 (1H, d, J=17.0 Hz), 7.65 (1H, d, J=8.0 Hz), 7.86 (1H, s). *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.23; H, 6.15: N, 14.33.

Ethyl 4-Amino-2,6-dimethyl-3-pyridineacrylate (5b)——A mixture of 4-amino-3-iodo-2,6-dimethylpyridine (**4b**)[8] (1.15 g, 5 mmol), ethyl acrylate (0.6 g, 6 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), Et_3N (0.6 g, 6 mmol), and DMF (2 ml) was heated in a sealed tube at 140 °C for 24 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave colorless needles, mp 176—177 °C, which were recrystallized from C_6H_6. Yield 0.82 g (74%). IR ($CHCl_3$) cm^{-1}: 3530, 3400, 1720. ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, J=7.0 Hz), 2.36 (3H, s), 2.46 (3H, s), 4.23 (2H, q, J=7.0 Hz), 4.30 (2H, s), 6.23 (1H, d, J=17.0 Hz), 6.32 (1H, s), 7.76 (1H, d, J=17.0 Hz). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.64; H, 7.51; N, 12.69.

1,6-Naphthyridin-2(1*H*)-one (6a)——A mixture of **5a** (1.0 g, 5.2 mmol) and an EtONa–EtOH solution [prepared from Na (0.45 g, 20 mmol) and dry EtOH (20 ml)] was refluxed for 2 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from MeOH to give colorless needles, mp 285—287 °C. Lit.[9] mp 290 °C. Yield 0.51 g (67%). IR ($CHCl_3$) cm^{-1}: 3390, 1670. ^{1}H-NMR (CF_3COOH): 6.82 (1H, d, J=10.0 Hz), 7.35 (1H, d, J=9.0 Hz), 7.65 (1H, d, J=10.0 Hz), 7.95 (1H, d, J=9.0 Hz), 8.43 (1H, s).

5,7-Dimethyl-1,6-naphthyridin-2(1*H*)-one (6b)——A mixture of **5b** (0.55 g, 2.5 mmol) and an EtONa–EtOH solution [prepared from Na (0.23 g, 10 mmol) and dry EtOH (10 ml)] was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O and extractd with $CHCl_3$. The $CHCl_3$ extract was recrystallized from AcOEt to give

colorless needles, mp 263—264 °C. IR ($CHCl_3$) cm^{-1}: 3380, 1680. ^1H-NMR (CF_3COOH): 2.89 (3H, s), 3.12 (3H, s), 7.23 (1H, d, $J=12.0$ Hz), 7.63 (1H, s), 8.42 (1H, d, $J=12.0$ Hz). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.05; H, 5.93; N, 16.00.

4-Iodo-2,6-dimethyl-3-nitropyridine (8)——A mixture of 4-chloro-2,6-dimethyl-3-nitropyridine (**7**)[10] (1.86 g, 10 mmol), NaI (4.5 g, 30 mmol), 57% HI (1.0 ml), and 2-butanone (30 ml) was refluxed for 12 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract gave colorless scales, mp 149—150 °C, which were recrystallized from hexane. Yield 2.31 g (83%). IR (KBr) cm^{-1}: 1550, 1360. ^1H-NMR ($CDCl_3$): 2.53 (6H, s), 7.55 (1H, s). *Anal.* Calcd for $C_7H_7IN_2O_2$: C, 30.24; H, 2.54; N, 10.07. Found: C, 29.94; H, 2.60; N, 9.88.

Ethyl 2,6-Dimethyl-3-nitro-4-pyridineacrylate (9)——A mixture of **8** (1.39 g, 5 mmol), ethyl acrylate (0.75 g, 7.5 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), Et_3N (0.75 g, 7.5 mmol), and MeCN (1.0 g) was heated in a sealed tube at 120 °C for 24 h. After dilution 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. The $CHCl_3$ eluate gave pale yellow needles, mp 124—125 °C, which were recrystallized from hexane. Yield 0.71 g (57%). IR ($CHCl_3$) cm^{-1}: 1710. ^1H-NMR ($CDCl_3$): 1.35 (3H, t, $J=7.0$ Hz), 2.51 (6H, s), 4.30 (2H, q, $J=7.0$ Hz), 6.53 (1H, d, $J=16.0$ Hz), 7.26 (1H, s), 7.56 (1H, d, $J=16.0$ Hz). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; N, 5.64; N, 11.20. Found: C, 57.14; H, 5.59; N, 11.08.

Ethyl 3-Amino-2,6-dimethyl-4-pyridineacrylate (10)——Sodium borohydride (0.39 g, 10 mmol) was added to a mixture of **9** (1.25 g, 5 mmol), $SnCl_2 \cdot 2H_2O$ (1.13 g, 5 mmol), and EtOH (50 ml) at 70 °C, and the mixture was heated at 70 °C for 1 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extractd with $CHCl_3$. The $CHCl_3$ extract was recrystallized from hexane to give yellow needles, mp 93—94 °C. Yield 0.70 g (64%). IR ($CHCl_3$) cm^{-1}:3480, 3390, 1715. ^1H-NMR ($CDCl_3$): 1.36 (3H, t, $J=7.0$ Hz), 2.43 (6H, s), 3.80 (2H, br s), 4.25 (2H, q, $J=7.0$ Hz), 6.45 (1H, d, $J=17.0$ Hz), 6.95 (1H, s), 7.83 (1H, d, $J=17.0$ Hz). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.29; H, 7.31; N, 12.67.

6,8-Dimethyl-1,7-naphthyridin-2(1*H*)-one (11)——A mixture of **10** (0.55 g, 2.5 mmol) and an EtONa–EtOH solution [prepared from Na (0.23 g, 10 mmol) and EtOH (10 ml)] was refluxed for 1 h. After removal of the EtOH, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from acetone to give colorless needles, mp 245—251 °C. Yield 0.34 g (78%). IR ($CHCl_3$) cm^{-1}: 3380, 1670. ^1H-NMR (CF_3COOH): 2.92 (3H, s), 3.23 (3H, s), 7.35 (1H, d, $J=12.0$ Hz), 7.59 (1H, s), 8.70 (1H, d, $J=12.0$ Hz). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.72; H, 5.61; N, 15.90.

2-Amino-3-iodopyridine (12)——A mixture of 2-chloro-3-iodopyridine (**15**)[11] (4.78 g, 20 mmol) and EtOH (30 ml) saturated with NH_3 was heated in a sealed tube at 180 °C for 48 h. After removal of the solvent, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract gave colorless needles, mp 90—91.5 °C, which were recrystallized from hexane. Yield 3.5 g (67%). IR ($CHCl_3$) cm^{-1}: 3510, 3400. ^1H-NMR ($CDCl_3$): 4.6—5.6 (2H, br), 6.3—6.5 (1H, m), 7.7—8.1 (2H, m). *Anal.* Calcd for $C_5H_5IN_2$: C, 27.30; H, 2.29; N, 12.73. Found: C, 27.15; H, 2.33; N, 12.57.

Ethyl 2-Amino-3-pyridineacrylate (13)——A mixture of **12** (2.20 g, 10 mmol), ethyl acrylate (1.2 g, 12 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), Et_3N (2.25 g, 22.5 mmol), and MeCN (2 ml) was heated in a sealed tube at 120 °C for 24 h. After dilution 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. The $CHCl_3$ eluate gave yellow needles, mp 77—79 °C, which were recrystallized from hexane. Yield 1.5 g (78%). IR ($CHCl_3$) cm^{-1}: 3500, 3390, 1710. ^1H-NMR ($CDCl_3$): 1.33 (3H, t, $J=7.0$ Hz), 4.28 (2H, q, $J=7.0$ Hz), 4.80 (2H, br s), 6.33 (1H, d, $J=16.0$ Hz), 6.6—6.9 (1H, m), 7.5—7.9 (2H, m), 8.0—8.2 (1H, m). *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.32; H, 6.12; N, 14.30.

2-Chloro-3-iodopyridine (15)——Sodium nitrite (7.0 g, 0.1 mol) in H_2O (30 ml) was added to a mixture of 3-amino-2-chloropyridine[11] (8.0 g, 62 mmol) and 6 N HCl (60 ml) at 0 °C. Then KI (25 g, 0.15 mol) in H_2O (30 ml) was added below 20 °C. The mixture was stirred at room temperature for 30 min and heated at 60 °C for 30 min, then made alkaline with 3 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aq. Na_2SO_3 and dried over K_2CO_3. The $CHCl_3$ was removed, and the residue was recrystallized from hexane to give colorless needles, mp 92—94 °C. Yield 8.9 g (60%). ^1H-NMR ($CDCl_3$): 6.8—7.1 (1H, m), 8.1—8.3 (2H, m). *Anal.* Calcd for C_5H_3ClIN: C, 25.08; H, 1.26; N, 5.85. Found: C, 25.31; H, 1.32; N, 5.76.

Ethyl 2-Chloro-3-pyridineacrylate (16)——A mixture of **15** (2.39 g, 10 mmol), ethyl acrylate (1.2 g, 12 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), and Et_3N (2.2 g, 22 mmol) was heated in a sealed tube at 120 °C for 24 h. After dilution 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. The $CHCl_3$ eluate gave a colorless liquid on distillation, bp 132—136 °C (3 mmHg). IR ($CHCl_3$) cm^{-1}: 1715. ^1H-NMR ($CDCl_3$): 1.35 (3H, t, $J=7.0$ Hz), 4.23 (2H, q, $J=7.0$ Hz), 6.35 (1H, d, $J=16.0$ Hz), 7.1—7.4 (1H, m), 7.7—8.1 (2H, m), 8.2—8.5 (1H, m). *Anal.* Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.61; H, 4.68; N, 6.71.

1,8-Naphthyridin-2(1*H*)-one (14)——i) A mixture of **13** (0.96 g, 5 mmol) and an EtONa–EtOH solution [prepared from Na (0.45 g, 20 mmol) and dry EtOH (20 ml)] was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from AcOEt to give pale yellow needles, mp 192—194 °C. Lit.[12] mp 197—198 °C. Yield 0.61 g (83%).

ii) A mixture of **16** (0.53 g, 2.5 mmol) and EtOH (30 ml) saturated with NH_3 was heated in a sealed tube at 180 °C for 24 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The product from the $CHCl_3$ extract was recrystallized from AcOEt to give pale yellow needles, mp 191—192 °C. Yield 0.27 g (74%). IR ($CHCl_3$) cm^{-1}: 3380, 1670. ^{1}H-NMR ($CDCl_3$): 6.73 (1H, d, J=10.0 Hz), 7.1—7.4 (1H, m), 7.75 (1H, d, J=10.0 Hz), 7.8—8.1 (1H, m), 8.7—8.9 (1H, m).

2-Bromo-3-iodo-4,6-dimethylpyridine (17b)——Sodium nitrite (1.0 g, 14 mmol) in H_2O (10 ml) was added to a mixture of 3-amino-2-bromo-4,6-dimethylpyridine (**17a**) (2.4 g, 12 mmol) and 6 N HCl (10 ml) at 0 °C. Then KI (3.0 g, 18 mmol) in H_2O (5 ml) was added to the mixture below 20 °C. The mixture was stirred at room temperature for 30 min and heated at 60 °C for 1 h. The mixture was made alkaline with 3 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aq. Na_2SO_3 and dried over K_2CO_3. The $CHCl_3$ was removed, and the residue was recrystallized from hexane to give colorless scales, mp 62—63 °C. Yield 3.0 g (81%). ^{1}H-NMR ($CDCl_3$): 2.45 (6H, s), 6.93 (1H, s). *Anal.* Calcd for C_7H_7BrIN: C, 26.95; H, 2.26; N, 4.49. Found: C, 27.21; H, 2.32; N, 4.53.

Ethyl 2-Bromo-4,6-dimethyl-3-pyridineacrylate (17c)——A mixture of **17b** (0.93 g, 3 mmol), ethyl acrylate (0.40 g, 4 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), and Et_3N (1 g, 10 mmol) was heated in a sealed tube at 100 °C for 24 h. After dilution 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. The $CHCl_3$ eluate gave colorless liquid, bp 135—140 °C (4 mmHg). Yield 0.7 g (82%). IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, t, J=7.0 Hz), 2.36 (3H, s), 2.50 (3H, s), 4.30 (2H, q, J=7.0 Hz), 6.16 (1H, d, J=16.0 Hz), 7.00 (1H, s), 7.75 (1H, d, J=16.0 Hz). *Anal.* Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.55; H, 4.82; N, 4.70.

2-Bromo-4,6-dimethyl-3-pyridineacrylamide (17d)——A mixture of **17c** (0.4 g, 1.4 mmol) and EtOH (20 ml) saturated with NH_3 was heated in a sealed tube at 180 °C for 24 h. After removal of the solvent, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract gave colorless needles, mp 254—257 °C, which were recrystallized from MeOH. Yield 250 mg (70%). IR (KBr) cm^{-1}: 3320, 3150. ^{1}H-NMR (CF_3COOH): 2.73 (3H, s), 2.90 (3H, s), 6.76 (1H, d, J=16.0 Hz), 7.75 (1H, s), 7.85 (1H, d, J=16.0 Hz). *Anal.* Calcd for $C_{10}H_{11}BrN_2O$: C, 47.08; H, 4.35; N, 10.98. Found: C, 47.32; H, 4.15; N, 10.56.

References and Notes

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