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SYNTHESIS OF 10-SUBSTITUTED PYRIDO[2,3-*b*][1,8]NAPHTHYRIDIN-5(10*H*)-ONES (ANTHYRIDIN-5(10*H*)-ONES) BASED ON THE REACTION OF BIS(2-CHLOROPYRIDIN-3-YL)METHANONES WITH PRIMARY AMINES

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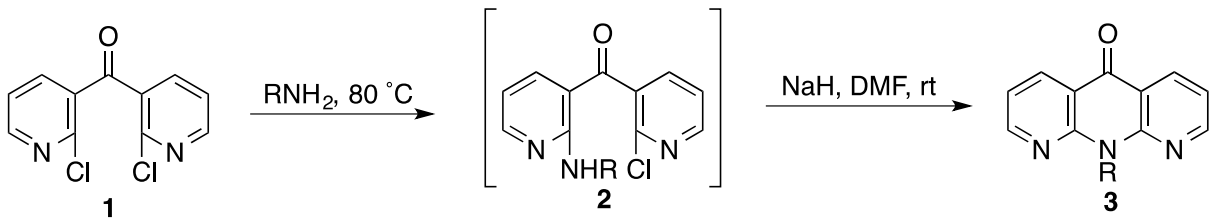
Abstract – An efficient method for the preparation of 10-substituted pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-ones, utilizing the reaction of bis(2-chloropyridin-3-yl)methanone, derived from 2-chloropyridine and 2-chloropyridine-3-carbaldehyde, with primary amines under heating at 80 ˚C, followed by sodium hydride promoted intramolecular ring closure of the resulting (2-aminopyridin-3-yl)(2-halopyridin-3-yl)methanone derivatives, has been developed. A similar sequence starting with (2-chloropyridin-3-yl)(3-chloropyridin-4-yl)methanone, derived from 3-chloropyridine and 2-chloropyridine-3-carbaldehyde, leads to the formation of 10-substituted pyrido[2,3-*b*][1,7]naphthyridin-5(10*H*)-ones.

The pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one ring system is an interesting heterocyclic skeleton, because some compounds with this system have been reported to exhibit biological activity.[1] In addition, a pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one derivative has been used in a hydrogen bond study.[2] The synthesis of these pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one derivatives is relied upon cyclization of 2-(2-pyridinylamino)-3-pyridinecarboxylic acid derivatives with concentrated sulfuric acid under very harsh conditions.[3] Therefore, we became interested in developing a convenient method for the general preparation of this type of heterocycles. In conjunction with our previously achieved syntheses of 10-substituted acridin-9(10*H*)-ones[4] and benzo[*b*][1,8]naphthyridin-5(10*H*)-ones,[5] we envisioned the synthesis of 10-substituted pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-ones (**3**) based on the reaction of

bis(2-chloropyridin-3-yl)methanone (**1**) with primary amines. In this paper, we wish to report the results of our study, which provide a facile method for the preparation of this type of pyridonaphthyridinones. This method was also successfully applied to the synthesis of 10-substituted pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-ones (**6**) starting with (2-chloropyridin-3-yl)(3-chloropyridin-4-yl)methanone (**4**). This is the first report on the construction of this ring system.

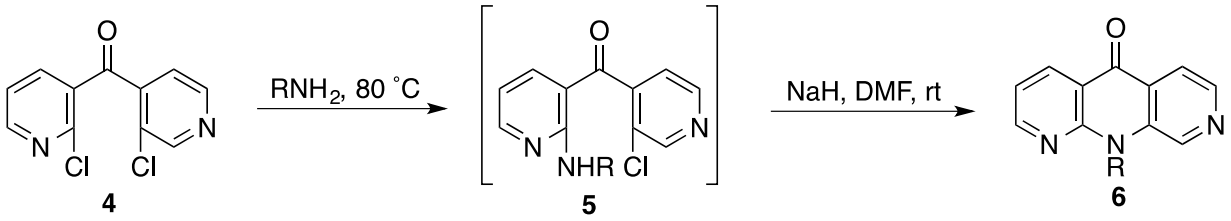
The preparation of **3** from **1**,[6] which was readily synthesized by the reaction of 2-chloro-3-lithiopyridine[7] with commercially available 2-chloropyridine-3-carbaldehyde followed by the PCC oxidation of the resulting bis(2-chloropyridin-3-yl)methanol under reported conditions,[8] was conducted according to the sequence illustrated in Scheme 1. When compound (**1**) and two equivalents of one of the primary amines were heated at 80 ˚C without using any solvents, substitution of an arylamino or an alkylamino group with one of the two chloro groups of **1** proceeded cleanly to afford the corresponding (2-aminopyridin-3-yl)(2-chloropyridin-3-yl)methanone derivatives (**2**). The progress of the substitution reaction could be monitored by TLC analyses on silica gel. Aromatic amines required longer heating (about 5 h) than aliphatic amines (about 2 h). This is probably ascribed to the lower nucleophilicity of aromatic amines than that of aliphatic amines. After removing primary amine hydrochlorides (see Experimental), the precursors (**2**) were then subjected to a treatment with sodium hydride in DMF at room temperature. Ring closure proceeded smoothly (within 10 min) to afford the desired products (**2**). The progress of the reaction could be also monitored by TLC analyses on silica gel. The yields obtained were generally good as can be seen from Table 1, Entries 1-7.



Scheme 1

Having achieved the effective substitution/ring closure sequence for the preparation of **3**, we subsequently turned our attention to apply the present sequence to the preparation of 10-substituted pyrido[2,3-*b*][1,7]naphthyridin-5(10*H*)-ones **6** from (2-pyridin-3-yl)(3-chloropyridin-4-yl)methanone (**4**), which was readily prepared *via* the reaction between 3-chloro-4-lithiopyridine[2] (derived from 3-chloropyridine) and 2-chloropyridine-3-carbaldehyde followed by the PCC oxidation of the resulting alcohol, with primary amines. As shown in Scheme 2, this starting ketone (**4**) was successfully used under the same conditions as described for the preparation of **3** and the desired products (**6**) were obtained, albeit in somewhat lower yields than those of **3** (Table 1, Entries 8 and 9). These results are most likely due to the low reactivity of

the 3-chloro group of (2-aminopyridin-3-yl)(3-chloropyridin-4-yl)methanone derivatives (**5**); ring closure of **5** under the same conditions as described for the preparation of **3** proceeded somewhat slowly (about 30 min) and uncleanly.



Scheme 2

Table 1. Preparation of pyridonaphthyridinones (**3**) and (**6**)

Entry	**1** or **4**	R	**3** or **6**	Yield/%[a]
1	**1**	Ph	**3a**	90
2	**1**	4-ClC_6H_4	**3b**	80
3	**1**	4-$MeOC_6H_4$	**3c**	82
4	**1**	Bn	**3d**	87
5	**1**	4-$MeOC_6H_4CH_2$	**3e**	88
6	**1**	$Ph(CH_2)_2$	**3f**	92
7	**1**	*n*-Decyl	**3g**	79
8	**4**	Ph	**6a**	71
9	**4**	Bn	**6b**	74

[a] Yields of isolated products.

In conclusion, we have demonstrated that 10-substituted pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-ones can be conveniently prepared and that the procedure can be applied to the synthesis of 10-substituted pyrido[2,3-*b*][1,7]naphthyridin-5(10*H*)-ones. The present synthesis may be of value because of the ready availability of the starting materials and the easiness of operations and may provide interesting pharmacophores.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr disks with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate

drying agents and distilled prior to use.

Starting Materials. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Bis(2-chloropyridin-3-yl)methanone (1).[6] This compound was prepared from 2-chloro-3-lithiopyridine[7] and 2-chloropyridine-3-carbaldehyde according to the reported procedure,[5] followed by the PCC oxidation of the resulting bis(2-chloropyridin-3-yl)methanol[1] under the reported conditions (yield: 70%).[8]

(2-Chloropyridin-3-yl)(3-chloropyridin-4-yl)methanone (4). This compound was prepared by the reaction of 3-chloro-4-lithiopyridine[7] with 2-chloropyridine-3-carbaldehyde according to the reported procedure,[1] followed by the PCC oxidation of the resulting (2-chloropyridin-3-yl)(3-chloropyridin-4-yl)methanol under the reported conditions.[8]

(2-Chloropyridin-3-yl)(3-chloropyridin-4-yl)methanol: yield: 71%; a white solid; mp 103–105 ˚C (hexane/CH_2Cl_2); IR 3224 cm^{-1}; ^1H NMR δ 3.10 (d, J = 4.0 Hz, 1H), 6.43 (d, J = 4.0 Hz, 1H), 7.27 (dd, J = 7.4, 5.2 Hz, 1H), 7.43 (d, J = 5.2 Hz, 1H), 7.60 (dd, J = 7.4, 2.3 Hz, 1H), 8.38 (dd, J = 5.2, 2.3 Hz, 1H), 8.54 (d, J = 5.2 Hz, 1H), 8.58 (s, 1H). Anal. Calcd for $C_{11}H_8Cl_2N_2O$: C, 51.79; H, 3.16; N, 10.98. Found: C, 51.70; H, 3.21; N, 10.83.

4: yield: 52%; a white solid; mp 63–65 ˚C (hexane/CH_2Cl_2); IR 1691 cm^{-1}; ^1H NMR δ 7.43–7.45 (m, 2H), 7.98 (dd, J =7.4, 1.7 Hz, 1H), 8.68 (d, J = 5.2 Hz, 1H), 8.60 (ddd, J = 5.2, 1.7, 1.1 Hz, 1H), 8.72 (s, 1H). Anal. Calcd for $C_{11}H_6Cl_2N_2O$: C, 52.20; H, 2.39; N, 11.07. Found: C, 52.02; H, 2.57; N, 11.02.

General Procedure for the Preparation of 10-Substituted Pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-ones (Anthyridin-5(10*H*)-ones) (3) and pyrido[2,3-*b*][1,7]naphthyridin-5(10*H*)-ones (6). A mixture of **1** or **4** (1.0 mmol) and a primary amine (2.0 mmol) was heated at 80 ˚C until complete consumption of the starting material had been confirmed by TLC analyses (SiO_2, AcOEt/hexane 1:2) (for aromatic amines about 5 h and for aliphatic amines about 2 h). After cooling to rt, CH_2Cl_2 (20 mL) was added and the precipitate was filtered off. The filtrate was concentrated by evaporation and dissolved in DMF (3 mL), and NaH (60% in mineral oil; 1.0 mmol) was added in portions at rt. After 10 min for **3** and 30 min for **6**, water (20 mL) was added, and the mixture was extracted with AcOEt (3 × 15 □mL). The combined extracts were washed with water (3 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized to afford **3** or **6**.

10-Phenylpyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3a): a beige solid; mp 314–316 ˚C (decomp) (hexane/$CHCl_3$); IR 1649 cm^{-1}; ^1H NMR δ 7.28 (dd, J = 7.8, 4.5 Hz, 2H), 7.34 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.63 (t, J = 7.3 Hz, 2H), 8.66 (d, J = 4.5 Hz, 2H), 8.81 (d, J = 7.8Hz, 2H); ^{13}C NMR δ 117.31, 118.51, 128.56, 129.55, 129.90, 136.45, 138.31, 152.80, 154.26, 178.72. HR-MS. Calcd for $C_{17}H_{12}N_3O$ (M+H): 274.0980. Found: m/z 274.0979. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N,

15.38. Found: C, 74.62; H, 4.11; N, 15.32.

10-(4-Chlorophenyl)pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3b): a pale-yellow solid; mp 214–217 ˚C (decomp) (hexane/$CHCl_3$); IR 1663 cm^{-1}; ^1H NMR δ 7.29–7.33 (m, 4H), 7.60 (d, *J* = 8.6 Hz, 2H), 8.68 (dd, *J* = 4.6, 1.7 Hz, 2H), 8.81 (dd, *J* = 7.4, 1.7 Hz, 2H); ^{13}C NMR δ 117.26, 118.77, 129.97 (2 overlapped Cs), 131.19, 134.53, 136.60, 152.47, 154.24, 178.66. HR-MS. Calcd for $C_{17}H_{11}ClN_3O$ (M+H): 308.0590. Found: *m*/*z* 308.0579. Anal. Calcd for $C_{17}H_{10}ClN_3O$: C, 66.35; H, 3.28; N, 13.65. Found: C, 66.10; H, 3.17; N, 13.68.

10-(4-Methoxyphenyl)pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3c): a beige solid; mp 321–323 ˚C (decomp) (hexane/$CHCl_3$); IR 1653 cm^{-1}; ^1H NMR δ 3.92 (s, 3H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.30 (dd, *J* = 7.7, 4.6 Hz, 2H), 8.72 (dd, *J* = 4.6, 2.3 Hz, 2H), 8.82 (dd, *J* = 7.7, 2.3 Hz, 2H); ^{13}C NMR δ 55.34, 114.94, 117.25, 118.50, 130.51, 130.57, 136.47, 152.88, 154.38, 159.30, 178.81. HR-MS. Calcd for $C_{18}H_{14}N_3O_2$ (M+H): 304.1086. Found: *m*/*z* 304.1076. Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.22; H, 4.30; N, 13.70.

10-(Phenylmethyl)pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3d): a yellow solid; mp 181–183 ˚C (hexane/CH_2Cl_2); IR 1654 cm^{-1}; ^1H NMR δ 6.30 (s, 2H), 7.21–7.25 (m, 3H), 7.31 (dd, *J* = 8.0, 4.6 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H), 8.79 (dd, *J* = 8.0, 2.3 Hz, 2H), 8.83 (dd, *J* = 4.6, 2.3 Hz, 2H); ^{13}C NMR δ 44.92, 117.40, 118.33, 127.00, 127.73, 128.23, 136.58, 138.10, 151.34, 154.19, 178.75. HR-MS. Calcd for $C_{18}H_{14}N_3O$ (M+H): 288.1137. Found: *m*/*z* 288.1136. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.28; H, 4.64; N, 14.57.

10-[(4-Methoxyphenyl)methyl]pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3e): a yellow solid; mp 193–196 ˚C (hexane/$CHCl_3$); IR 1651 cm^{-1}; ^1H NMR δ 3.76 (s, 3H), 6.23 (s, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.31 (dd, *J* = 8.0, 4.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 8.78 (dd, *J* = 8.0, 2.3 Hz, 2H), 8.85 (dd, *J* = dd, *J* = 4.6, 2.3 Hz, 2H); ^{13}C NMR δ 44.27, 55.16, 113.58, 117.45, 118.28, 129.50, 130.21, 136.59, 151.34, 154.15, 158.62, 178.69. HR-MS. Calcd for $C_{19}H_{16}N_3O_2$ (M+H): 318.1242. Found: *m*/*z* 318.1249. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.75; H, 5.03; N, 13.37.

10-(2-Phenylethyl)pyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3f): a pale-yellow solid; mp 210–213 ˚C (hexane/$CHCl_3$); IR 1649 cm^{-1}; ^1H NMR δ 3.12–3.15 (m, 2H), 5.25–5.28 (m, 2H), 7.18–7.36 (m, 5H), 7.39 (d, *J* = 7.4 Hz, 2H), 8.77 (dd, *J* = 8.0, 1.7 Hz, 2H), 8.85 (dd, *J* = 4.6, 1.7 Hz, 2H); ^{13}C NMR δ 34.36, 43.47, 117.38, 118.04, 126.29, 128.34, 129.03, 136.50, 139.24, 151.17, 154.17, 178.58. HR-MS. Calcd for $C_{19}H_{16}N_3O$ (M+H): 302.1293. Found: *m*/*z* 302.1284. Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.52; H, 5.09; N, 13.87.

10-Decylpyrido[2,3-*b*][1,8]naphthyridin-5(10*H*)-one (3g): a pale-yellow solid; mp 97–99 ˚C (hexane/$CHCl_3$); IR 1660 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.27–1.64 (m, 14H), 1.82–1.86 (m,

2H), 5.01 (t, *J* = 7.4 Hz, 2H), 7.28 (dd, *J* = 4.6, 1.7 Hz, 2H), 8.78 (dd, *J* = 4.6, 1.7 Hz, 2H), 8.82 (dd, *J* = 7.4, 1.7 Hz, 2H); ^{13}C NMR δ 14.09, 22.67, 27.07, 28.22, 29.33, 29.43, 29.59, 29.66, 31.89, 42.39, 117.34, 117.92, 136.49, 151.29, 154.10, 178.61. HR-MS. Calcd for $C_{21}H_{28}N_3O$ (M+H): 338.2232. Found: *m*/*z* 338.2227. Anal. Calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.06; N, 12.45. Found: C, 74.53; H, 8.17; N, 12.38.

10-Phenylpyrido[2,3-*b*][1,7]naphthyridin-5(10*H*)-one (6a): a pale-yellow solid; mp 265–267 ˚C (hexane/$CHCl_3$); IR 1651 cm^{-1}; ^{1}H NMR δ 7.32 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.4 Hz, 2H), 8.27 (d, *J* = 5.2 Hz, 1H), 8.44 (s, 1H), 8.56 (d, *J* = 5.2 Hz, 1H), 8.70 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.83 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR δ 117.19, 118.20, 118.73, 125.84, 129.60, 129.65, 130.62, 136.61, 137.23, 137.79, 141.63, 141.99, 151.87, 154.82, 178.32. HR-MS. Calcd for $C_{17}H_{12}N_3O$ (M+H): 274.0980. Found: *m*/*z* 274.0968. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.67; H, 4.12; N, 15.30.

10-(Phenylmethyl)pyrido[2,3-*b*][1,7]naphthyridin-5(10*H*)-one (6b): a yellow solid; mp 194–196 ˚C (hexane/CH_2Cl_2); IR (KBr) 1648 cm^{-1}; ^{1}H NMR δ 6.16 (br s, 2H), 7.20 (d, *J* = 7.4 Hz, 2H), 7.25–7.32 (m, 3H), 7.36 (dd, *J* = 7.4, 5.2 Hz, 1H), 8.26 (d, *J* = 5.2 Hz, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.82–8.84 (m, 2H), 9.09 (s, 1H); ^{13}C NMR δ 46.71, 117.39, 118.63, 118.75, 126.15, 126.58, 127.69, 129.02, 136.02, 136.23, 136.94, 140.50, 141.91, 150.88, 154.75, 178.09. HR-MS. Calcd for $C_{18}H_{14}N_3O$ (M+H): 288.1137. Found: *m*/*z* 288.1118. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.21; H, 4.58; N, 14.40.

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