# Furopyridines. XXV [1]. Synthesis of 5-Substituted Furo [2,3-*b*]pyridines

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Derivatives (**2-8**) of furo[2,3-*b*]pyridine having a substituent at the β-position to the ring nitrogen were prepared from the 5-nitro compound **1** *via* the Sandmeyer reaction.

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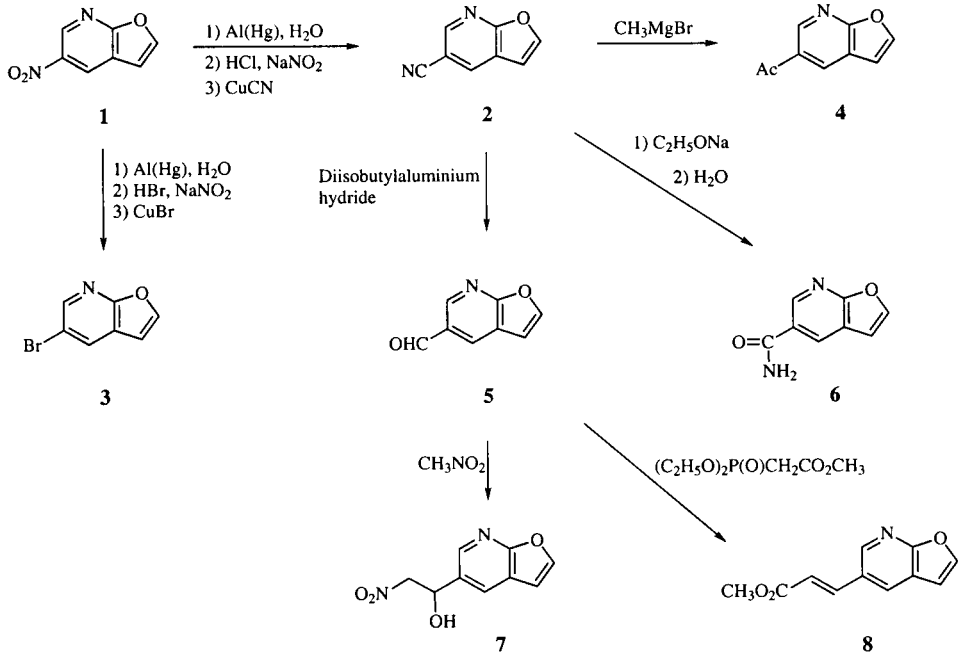
In the course of our research work on the chemistry of furopyridines, we have reported the syntheses of many types of derivatives of furopyridines having substituents at the furan moiety and/or at the α- or γ-position to the ring nitrogen of the pyridine ring. Though it is very difficult to introduce a substituent at the β-position to the ring nitrogen by direct substitution upon the pyridine ring, fortunately, syntheses of 5-nitro, 5-amino and 5-carboxyl derivatives of furo[2,3-*b*]pyridne were reported by Snyder *et al.* [2], McFarland *et al.* [3] and Bhupathy *et al.* [4]. We report herein, as an extension of the chemistry of furopyridines, the conversion of the 5-amino group in furo[2,3-*b*]pyridine to several carbon-substituents *via* a Sandmeyer reaction.

Reduction of 5-nitrofuro[2,3-*b*]pyridine (**1**) with aluminium amalgam yielded the 5-amino compound [3] in good yield. The diazotization of the amino group and the subsequent reaction with cuprous cyanide and with cuprous bromide afforded 5-cyano- **2** and 5-bromofuro[2,3-*b*]pyridine (**3**) in 68% and 47% yield respectively.

The Grignard reaction of **2** with methylmagnesium bromide gave 5-acetylfuro[2,3-*b*]pyridine (**4**) in 66% yield. We reported in a recent paper that α-formylpyridine derivatives of furopyridines were efficiently obtained by the reduction of the corresponding carboxylic esters with diisobutylaluminium hydride but not by the reduction of the cyano compounds with diisobutylaluminium hydride [5]. In contrast, reduction of the cyano group in compound **2** with diisobutylaluminium hydride in dichloromethane afforded the 5-formyl derivative **5** in 33% yield accompanying recovery of **2** (41%) [6]. Reaction of the nitrile **2** with sodium ethoxide in absolute ethanol for 48 hours at room temperature and treatment of the reaction mixture with water yielded the corresponding amide **6** (35%) and the starting nitrile (35%). This result was in contrast to those of α-cyanopyridine derivatives of furopyridines, in which these compounds afforded the corresponding ethyl imidate as a sole product [5]. Condensation of **5** with nitromethane afforded 5-(1-

Scheme



hydroxy-2-nitroethyl)furo[2,3-*b*]pyridine (**7**) in 54% yield. The Wittig-Horner reaction of **5** with methyl diethyl phosphonoacetate gave methyl β-(5-furo[2,3-*b*]pyridyl)-acrylate (**8**) in 99% yield.

Compounds **2-8** showed, in each pmr spectrum, signals of two furan protons and two pyridine protons as doublets respectively. In the ir spectrum compound **2** exhibited a cyano absorption at 2233 $cm^{-1}$, **4** a carbonyl at 1677 $cm^{-1}$, **5** a carbonyl at 1688 $cm^{-1}$, **6** absorption of amide at 1659 ($\nu_{C=O}$), 3403 and 3193 $cm^{-1}$ ($\nu_{N-H}$), **7** absorption of hydroxyl at 3500-3100 (broad) ($\nu_{O-H}$) and 1088 $cm^{-1}$ ($\nu_{C-O}$) and nitro group at 1556 and 1359 $cm^{-1}$, and **8** absorption of ester at 1712 ($\nu_{C=O}$) and 1173 $cm^{-1}$ ($\nu_{C-O}$). Thus, the structures of these compounds were characterized.

## EXPERIMENTAL

All melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were recorded on a JASCO FT/IR 7300 spectrometer. The pmr spectra were recorded on a JEOL, MAC-FX (90 MHz) and/or JEOL FX-A400 (400 MHz) instrument in deuteriochloroform with tetramethylsilane as an internal reference. The mass spectra were taken by using JEOL, JMS-OISG-2 instrument. Column Chromatography was performed with silica gel (Chromatography Silica Gel BW-820MH, Fuji Silysia Chemical Ltd) or alumina (Merck, Aluminium Oxide 90 Active, Neutral).

5-Cyanofuro[2,3-*b*]pyridine **2**.

To a mixture of **1** (715 mg, 4.36 mmoles), mercuric chloride (30 mg) and water (1 ml) in ether (150 ml) was added aluminium foil cut in small peices (330 mg, 12.2 mmoles) at 0°. The mixture was stirred for 3 hours at room temperature, filtered through a sintered glass filter with a Celite pad. The filtrate was dried over magnesium sulfate and evaporated to give 510 mg of crude 5-amino derivative, which was used for the next step without any further purification.

To a solution of the crude 5-amino compound (510 mg) in hydrochloric acid (35%, 10 ml) a solution of sodium nitrite (295 mg, 4.3 mmoles) in water (2 ml) with stirring at 0-5° during 10 minutes, and the reaction mixture was stirred at this temperature for 15 minutes and neutralized with sodium bicarbonate. To this mixture was added benzene (10 ml) and a solution of cuprous cyanide (426 mg, 4.8 mmoles) and sodium cyanide (370 mg, 7.5 mmoles) in water (5 ml) at 0° during 30 minutes. After being stirred for 3 hours at room temperature, the reaction mixture was filtered through a sintered glass filter with a Celite pad. The filtrate was separated and the aqueous layer was extracted with benzene. The organic layer and the extract were combined, dried (magnesium sulfate) and evaporated to give a solid mass. Recrystallization of the residue from hexane-acetone yielded 5-cyano compound **2** (470 mg, 68%) as colorless crystals, mp 131-135°; ir (potassium bromide): 3152, 3118, 3077, 2233, 1604, 1582, 1533, 1467, 1385, 1282, 1259, 1125, 1029, 915, 753 $cm^{-1}$; pmr: δ 8.64 (d, J = 2.1 Hz, 1H, H-6), 8.26 (d, J = 2.1 Hz, 1H, H-4), 7.87 (d, J = 2.7 Hz, 1H, H-2), 6.90 (d, J = 2.7 Hz, 1H, H-3).

*Anal.* Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.45. Found: C, 66.75; H, 3.01; N, 19.43.

5-Bromofuro[2,3-*b*]pyridine **3**.

To a solution of crude 5-amino compound obtained from 5-nitro compound **1** (214 mg, 1.3 mmoles) in hydrobromic acid (47%, 3.0 ml) was added a solution of sodium nitrite (92 mg, 1.3 mmoles) in water (1.0 ml) during 10 minutes at 0°. After being stirred for 15 minutes at this temperature, the mixture was neutralized with sodium bicarbonate. To this mixture was added a mixture prepared by dissolving cuprous bromide (235 mg, 1.6 mmoles) in diluted hydrobromic acid (37%, 1.0 ml and water 3.0 ml), and neutralizing with sodium bicarbonate with stirring at 0° during 30 minutes. The reaction mixture was stirred at room temperature for 3 hours and extracted with benzene. The residue of the dried (magnesium sulfate) extract was purified by chromatography on a silica gel (20 g) column eluting with hexane-ethyl acetate (95:5) to give **3** (120 mg, 47%) as colorless crystals of mp 49-54° (from hexane-acetone); ir (potassium bromide): 3156, 3115, 3077, 1527, 1439, 1381, 1243, 1156, 1132, 1026, 919, 888, 743 $cm^{-1}$; pmr: δ 8.36 (d, J = 2.1 Hz, 1H, H-6), 8.04 (d, J = 2.1 Hz, 1H, H-4), 7.72 (d, J = 2.6 Hz, 1H, H-2), 6.74 (d, J = 2.6 Hz, 1H, H-3); ms: m/z (relative intensity) 199 ($M^+$+2, 48), 198 ($M^+$+1, 13), 197 (M+, 50), 169 (20), 149 (10), 137 (11), 118 (16), 100 (20), 90 (63); hrms: 196.9483. ($M^+$, Calcd. for $C_7H_4NOBr$: 196.9476).

*Anal.* Calcd. for $C_7H_4NOBr$: C, 42.46; H, 2.04; N, 7.07. Found: C, 42.33; H, 2.16; N, 7.03.

5-Acetylfuro[2,3-*b*]pyridine **4**.

To a solution of **2** (123 mg, 0.85 mmole) in dry tetrahydrofuran (5.0 ml) was added a solution of methymagnesium bromide (0.771 ml, 3.0 *M*, 2.1 mmoles) in tetrahydrofuran by syringe over a period of 5 minutes at 0° under nitrogen atmosphere and stirring. After being stirred for 2 hours at room temperature, the mixture was treated with 0.5 *M* sulfuric acid and stirred for 5 minutes. After evaporation of most of the tetrahydrofuran under reduced pressure, the mixture was basified with aqueous ammonia solution and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated. The residual solid mass was chromatographed on a silica gel column eluting with hexane-ethyl acetate (3:1) to give compound **4** (90 mg, 66%), mp 164-167° (from acetone-ether, colorless crystals); ir (potassium bromide): 3143, 3115, 3091, 2924, 2856, 1677, 1605, 1591, 1537, 1380, 1359, 1290, 1255, 1160, 1132, 1015, 921, 761 $cm^{-1}$; pmr: δ 8.96 (d, J = 2.1 Hz, 1H, H-6), 8.54 (d, J = 2.1 Hz, 1H, H-4), 7.80 (d, J = 2.6 Hz, 1H, H-2), 6.89 (d, J = 2.6 Hz, 1H, H-3), 2.70 (s, 3H, -CO-Me).

*Anal.* Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.22; H, 4.46; N, 8.77.

5-Formylfuro[2,3-*b*]pyridine **5**.

To a solution of **2** (147 mg, 1.0 mmole) in dichloromethane (9.0 ml) was added a solution of diisobutylaluminium hydride (1.1 ml, 1.0 *M*, 1.1 mmoles) in dichloromethane with stirring at -50° under nitrogen atmosphere. After being stirred for 15 minutes [6] at this temperature, the mixture was treated with saturated aqueous sodium potassium tartrated solution, and separated the layers. The aqueous layer was extracted with chloroform. The organic layer and extract were combined, dried (magnesium sulfate) and evaporated to give a crystalline mass, which was chromatographed on a silica gel column elut-

ing with hexane-ethyl acetate (17:3) to yield compound **5** (49 mg, 33%) and the starting nitrile **2** (60 mg, 41%). Compound **5** had mp 105-110° (from acetone-ether, colorless crystals); ir (potassium bromide): 3147, 3111, 3054, 3004, 2802, 2773, 1688, 1605, 1586, 1539, 1375, 1256, 1136, 1114, 1019, 980, 910, 890, 752 $cm^{-1}$, pmr: δ 10.18 (s, 1H, -CHO), 8.86 (d, J = 2.0 Hz, 1H, H-6), 8.47 (d, J = 2.0 Hz, 1H, H-4), 7.84 (d, J = 2.3 Hz, 1H, H-2), 6.93 (d, J = 2.3 Hz, 1H, H-3).

*Anal.* Calcd. for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.33; H, 3.51; N, 9.60.

Reaction of **2** with Sodium Ethoxide.

A mixture of compound **2** (153 mg, 1.1 mmoles) and sodium ethoxide (360 mg, 4.2 mmoles) in absolute ethanol (8 ml) was stirred at room temperature for 48 hours. After evaporation of the solvent, the residue was treated with chloroform and water. The chloroform layer was dried (magnesium sulfate) and evaporated to give a crystalline mass, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (7:3) to give 60 mg (35%) of the amide **6** and 53 mg (35%) of the starting nitrile **2**.

Furo[2,3-*b*]pyridine-2-carboxamide **6**.

This compound had mp 221-224° (from acetone, colorless crystals); ir (potassium bromide): 3403, 3193, 3126, 3100, 1659, 1620, 1537, 1412, 1382, 1260, 1177, 1123, 1021, 928, 884, 777 $cm^{-1}$; pmr (deuteriomethanol): δ 8.81 (d, J = 2.1 Hz, 1H, H-6), 8.57 (d, J = 2.1 Hz, 1H, H-4), 7.97 (d, J = 2.6 Hz, 1H, H-2), 7.01 (d, J = 2.6 Hz, 1H, H-3).

*Anal.* Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.51; H, 3.69; N, 17.35.

5-(1-Hydroxy-2-nitroethyl)furo[2,3-*b*]pyridine **7**.

To a mixture of **5** (45 mg, 0.31 mmole) and nitromethane (32 mg, 0.53 mmole) in absolute methanol (4.0 ml) was added a solution of sodium methoxide (17 mg, 0.32 mmole) in methanol (1.0 ml) by syringe at -15° under nitrogen atmosphere and stirring. After being stirred at -15° for 2.5 hours and at room temperature for 0.5 hours, the mixture was treated with water (1.0 ml), acidified with acetic acid, basified with sodium bicarbonate and evaporated under reduced pressure. The residue was diluted with water (5 ml), extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated to leave a pale yellow solid mass, which was chromatographed on a silica gel (5 g) column eluting with hexane-ethyl acetate (4:1) to afford compound **7** (35 mg, 54%) and the starting aldehyde (4 mg, 9%). Compound **7** had mp 130-134° (from acetone-hexane, colorless crystals); ir (potassium bromide): 3500-3100 (broad), 3190, 3133, 2922, 2896, 2854, 1601, 1556, 1538, 1400, 1377, 1359, 1330, 1240, 1129, 1088, 1021, 920, 911, 879, 761 $cm^{-1}$; pmr: δ 8.37 (d, J = 2.2 Hz, 1H, H-6), 8.06 (d, J = 2.2 Hz, 1H, H-4), 7.77 (d, J = 2.4 Hz, 1H, H-2), 6.82 (d, J = 2.4 Hz, 1H, H-3), 5.66 (ddd, J = 9.5, 3.9, 3.2 Hz, 1H, H-α), 4.69 (dd, J = 13.7, 9.5 Hz, 1H, H-β), 4.58 (dd, J = 13.7, 3.2 Hz, 1H, H-β'), 3.08 (d, J = 3.9 Hz, 1H, OH).

*Anal.* Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.76; H, 4.03; N, 14.31.

Methyl β-(5-Furo[2,3-*b*]pyridyl)acrylate **8**.

To a stirred suspension of sodium hydride (11 mg of 60% dispersion in mineral oil, 0.26 mmole, washed with hexane) in dry tetrahydrofuran (5.0 ml) was added a solution of methyl diethylphosphonoacetate (55 mg, 0.26 mmole) in tetrahydrofuran (1.0 ml) by syringe under nitrogen atmosphere and stirring at room temperature. After an additional stirring for 20 minutes, the mixture was cooled at 0°, and to this mixture was added a solution of **5** (35 mg, 0.24 mmole) in tetrahydrofuran (3.0 ml) by syringe with stirring. The cooling bath was removed and stirring was continued for 17 hours at room temperature. After evaporation of the solvent, the residue was treated with chloroform and water. The chloroform layer was dried over magnesium sulfate and evaporated to leave a crystalline mass, which was chromatographed on a silica gel (5 g) column eluting with hexane-ethyl acetate (17:3) to yield **8** (48 mg, 99%) as colorless crystals of mp 144-147° (from acetone); ir (potassium bromide): 3147, 3119, 2953, 2920, 2850, 1712, 1633, 1603, 1584, 1536, 1439, 1385, 1341, 1306, 1260, 1201, 1175, 1139, 1129, 1020, 864, 747 $cm^{-1}$; pmr: δ 8.49 (d, J = 2.1 Hz, 1H, H-6), 8.11 (d, J = 2.1 Hz, 1H, H-4), 7.81 (d, J = 16.2 Hz, 1H, H-β), 7.78 (d, J = 2.3 Hz, 1H, H-2), 6.82 (d, J = 2.3 Hz, 1H, H-3), 6.51 (d, J = 16.2 Hz, 1H, H-α), 3.84 (s, 3H, -OMe).

*Anal.* Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: 64.92; H, 4.55; N, 6.92.

## REFERENCES AND NOTES

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[6] When the diisobutylaluminium hydride reduction was carried out for a longer time (1.0 hour), both the yield of aldehyde **5** and the recovery of the nitrile were much reduced and gave only a resinous product from which no compound could be isolated.