Furopyridines. XXII [1]. Elaboration of the *C*-Substituents *alpha* to the Heteronitrogen Atom of Furo[2,3-*b*] -, -[3,2-*b*] -, -[2,3-*c*]- and -[3,2-*c*]pyridine

Shunsaku Shiotani* and Katsunori Tanigochi

Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3190, Toyama 930 Japan

Received December 2, 1997

The Grignard reaction of fused ring cyanopyridine derivatives **1a-d** with methyl- and phenylmagnesium bromide yielded the corresponding acylpyridine compounds **2a-d** and **3a-d**. Furopyridine *N*-oxides **4a-d** were converted into the compounds having a phenyl group at the α-position to the ring nitrogen **5a-d**. Reduction of **1a-d** and the carboxylic esters **6a-d** with diisobutylaluminium hydride yielded the corresponding amines **7a-d** and aldehydes **9a-d**. The aldehydes were converted to nitroethanol derivatives **10a-d** by condensation with nitromethane and acrylic ester compounds **11a-d** by the Wittig-Horner reaction with methyl diethyl phosphonoacetate.

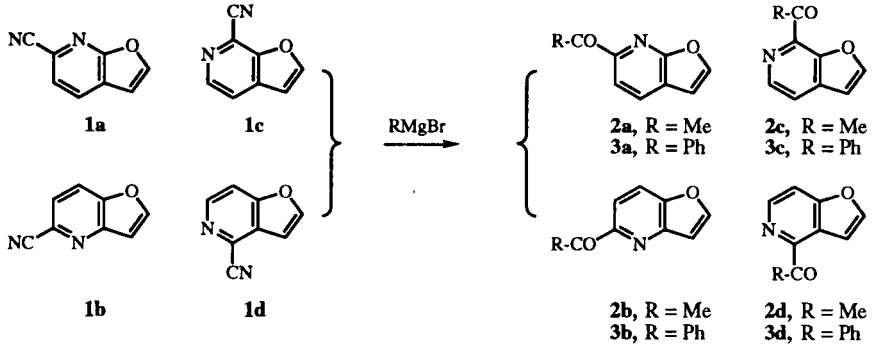
J. Heterocyclic Chem., **34**, 901 (1997).

In continuation of our interest in the chemistry of furopyridines, recently we reported the synthesis of cyanopyridine derivatives of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine by cyanation of the *N*-oxides of furopyridines and their conversion to the carboxamides and esters [1,2]. To the extend of our chemical studies of furopyridines and with the aim to find new compounds with possible biological activity, we describe in this paper conversion of the cyano group to the aminomethyl and acyl groups, and the ester to the aldehyde.

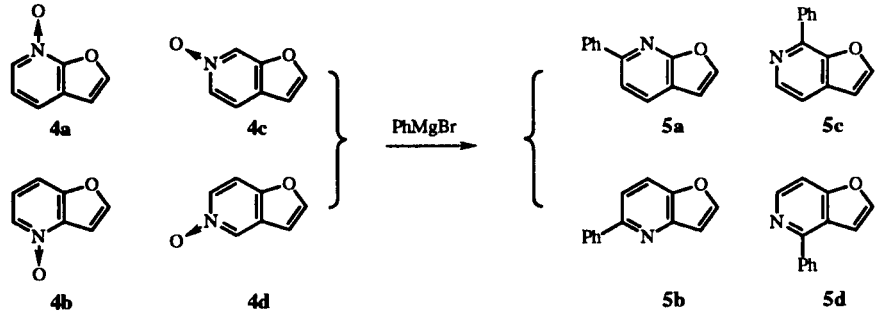
Reaction of 6-cyanofuro[2,3-*b*]- (**1a**), 5-cyanofuro-[3,2-*b*]- (**1b**), 7-cyanofuro[2,3-*c*]- (**1c**) and 4-cyanofuro-[3,2-*c*]pyridine (**1d**) with methylmagnesium bromide and phenylmagnesium bromide yielded the corresponding acetylfuropyridines **2a-d** and benzoylfuropyridines **3a-d** in yield of 65% for **2a** and 78% for **3a** from **1a**, 89% for **2b** and 86% for **3b** from **1b**, 89% for **2c** and 98% for **3c** from **1c** and 99% for **2d** and 97% for **3d** from **1d**. While, the Grignard reaction of furopyridine *N*-oxides **4a-d** with phenylmagnesium bromide yielded 6-phenylfuro[2,3-*b*]- (**5a**, 51%), 5-phenylfuro-[3,2-*b*]- (**5b**, 63%), 7-phenylfuro[2,3-*c*] (**5c**, 30%) and 4-phenylfuro[3,2-*c*]pyridine (**5d**, 31%) [3] respectively. These compounds showed signals of the pyridine ring as a pair of doublets (J = 7.9 Hz for **5a**, J = 7.9 Hz for **5b**, J = 5.3 Hz for **5c** and J = 5.8 Hz for **5d**). These facts indicated the position of the phenyl group of **5a** at C-6, **5b** at C-5, **5c** at C-7 and **5d** at C-4.

Though reduction of the cyano derivatives **1a-d** and carboxylic esters **6a-d** with lithium aluminium hydride did not give any single product yielding only resinous products, reduction with diisobutylaluminium hydride (DIBAL-H) gave the satisfactory results. Treatment of **1a-d** with 2 equivalent moles of DIBAL-H afforded the corresponding aminomethyl derivatives, which are unstable and readily resinified in the air at room temperature and therefore were characterized as the *N*-mesyl derivatives **8a-d**. Reduction of the nitriles with 1 equivalent mole of DIBAL-H gave a mixture of the aminomethyl compound and the starting nitrile in each case. The esters **6a-d** were converted to the corresponding aldehydes **9a-d** by reduction with 2 equivalent moles of DIBAL-H in fairly good yields. These results are somewhat different from those reported in the literatures [4] that reduction of a nitrile with 1 equivalent of DIBAL-H gives aldehyde and an ester with 2 equivalent moles yields alcohol.

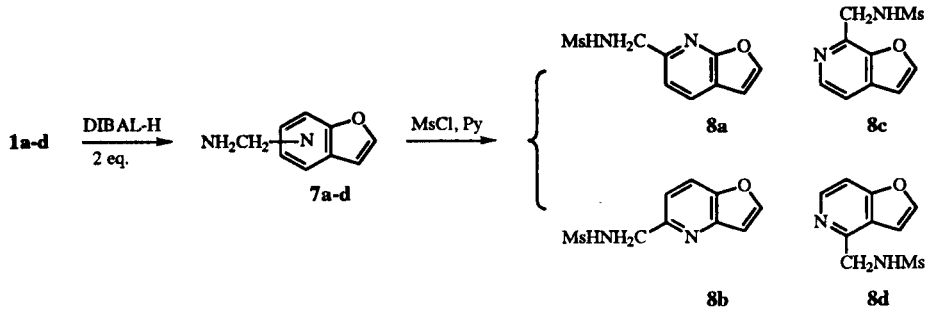
Scheme 1



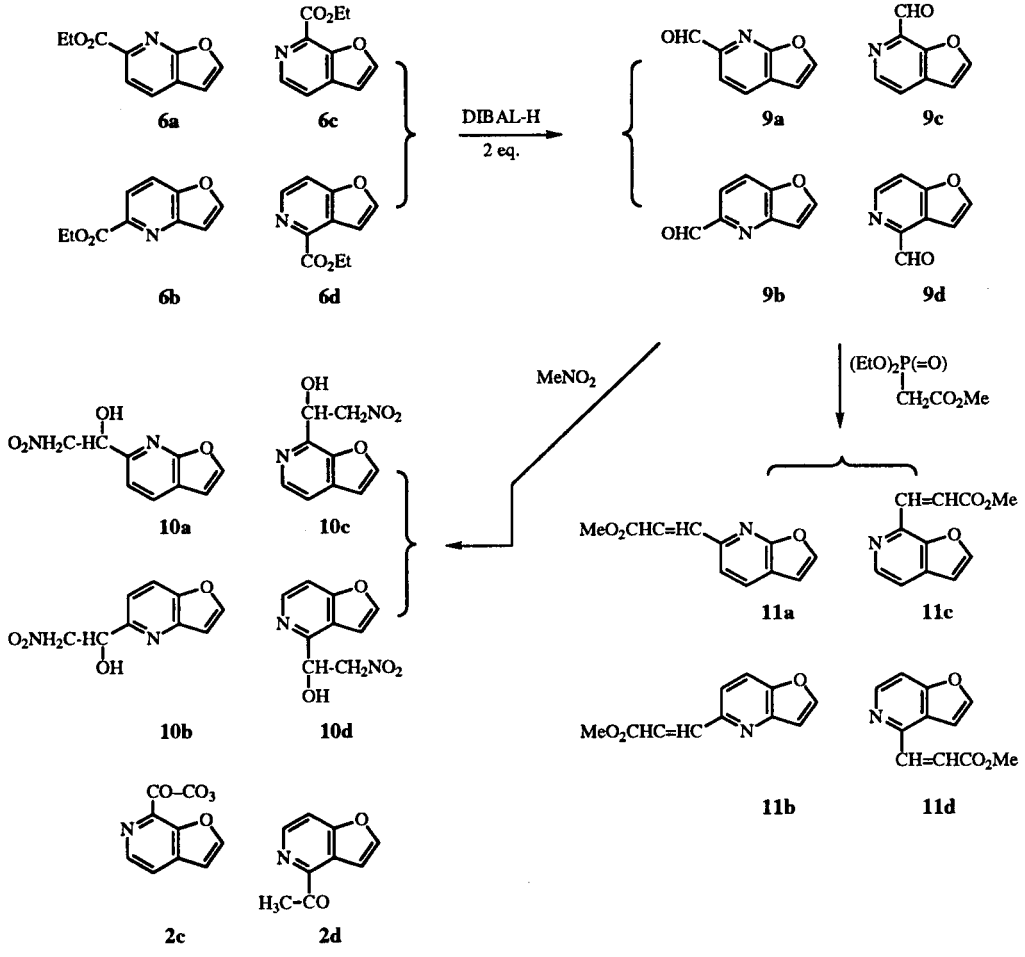
Scheme 2



Scheme 3

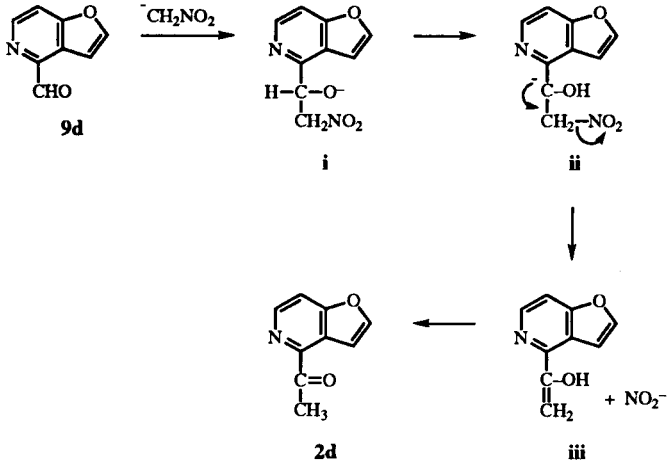


Scheme 4



Condensation of the aldehydes **9a-d** with nitromethane afforded the corresponding nitroethanol compounds **10a-d** as the major product. Unexpectedly, in the cases of **9c** and **9d**, isoquinoline isosteres, 7-acetylfuro[2,3-*c*]- (**2c**) and 4-acetylfuro[3,2-*c*]pyridine (**2d**) were isolated from the reaction mixture in yield of 22% and 15% respectively. Barrows reported that condensation of 1-formylisoquinoline with nitromethane afforded the nitroethanol compound [5]. Krohn *et al* [6] reported the condensation of the oxoalkyl anthraquinones with nitromethane to give tertiary alcohols accompanying elimination of the nitro group. The reaction path for the formation of **2c** and **2d** can not be explained by the mechanism proposed for the condensation of the oxoalkyl anthraquinones. Thus, formation of **2c** and **2d** would be interpreted as follows (Chart 1): Attack of the nitromethyl anion to the aldehyde forms nitromethylated alkoxide anion **i**, in which the hydrogen atom at the aldehyde carbon would transfer to form the carbanion **ii**. Nitrite anion would be eliminated from the intermediate **ii** accompanying electron transfer to give an enol **iii**, which would isomerize to give the ketone **2c** or **2d**. At this stage, however, the driving force for the transformation of the alkoxide anion **i** to the carbanion **ii** can not be explained.

Chart 1



The aldehydes **9a-d** were also converted to the methyl acrylate compounds **11a-d** by Wittig-Horner reaction with methyl diethylphosphonoacetate in yield of 68% for **11a**, 98% for **11b**, 53% for **11c** and 96% for **11d**.

The ^1H nmr spectra of derivatives **2b, 3b, 5b, 8b, 9b, 10b** and **11b** of furo[3,2-*b*]- and those of **2d, 3d, 5d, 8d, 9d, 10d** and **11d** of -[3,2-*c*]pyridine showed long-range coupling occurred between H-3 and H-7. It is worth noting that the formyl compound **9a** and **9b** exhibited another zig-zag coupling between the aldehyde proton and H-4 of **9a** (J = 0.6 Hz) and H-7 of **9b** (J = 0.6 Hz). These facts suggested the all *trans* configuration between the aldehyde proton and H-4 of **9a** and H-7 of **9b**, which resemble to the configuration between H-3 and H-7 of derivatives of furo[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine [7].

EXPERIMENTAL

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 ^1H and ^{13}C nmr were taken on a JEOL A-400 (400MHz) or a JEOL MAC-FX (90 MHz) instrument with tetramethylsilane as an internal reference in deuteriochloroform. The mass spectra were obtained by using JEOL JMS-OISG-2 spectrometer. Column chromatography was conducted on silica gel (Chromatography Silica Gel, BW-820MH, Fuji Silysia Chemical Ltd).

General Procedure for the Grignard Reaction of 6-Cyanofuro-[2,3-*b*]- **1a**, 5-Cyanofuro[3,2-*b*]- **1b**, 7-Cyanofuro[2,3-*c*]- **1c** and 4-Cyanofuro[3,2-*c*]pyridine **1d** with Methylmagnesium Bromide

A solution of cyano compound **1a, 1b, 1c** or **1d** (160 mg, 1.11 mmoles) in dry tetrahydrofuran (10 ml) was added to a stirred solution of methylmagnesium bromide (1.0 ml, 3.0*M*, 3.0 mmoles) in tetrahydrofuran by syringe over a period of 5 minutes at -10° under nitrogen atmosphere. After stirring at room temperature for 2 hours, the reaction mixture was treated with 0.5*M* sulfuric acid and stirred at room temperature for 5 minutes. After evaporation of the solvent under reduced pressure, the residual mixture was basified with ammonium hydroxide solution and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated. The residue was chromatographed on a silica gel (35 g) column using chloroform as an eluent to give 116 mg (65%) of 6-acetylfuro[2,3-*b*]pyridine **2a**, 159 mg (89%) of 5-acetylfuro-[3,2-*b*]pyridine **2b**, 159 mg (89%) of 7-acetylfuro[2,3-*c*]pyridine **2c** and 177 mg (99%) of 4-acetylfuro[3,2-*c*]pyridine **2d**.

Compound **2a**.

This compound had mp 89-91° (colorless crystals, from ether-hexane); ir (potassium bromide): 3132, 3105, 3011, 2927, 1685, 1580, 1524, 1365, 1352, 1275, 1258, 1172, 1140, 1023, 857 cm^{-1}; ^1H nmr δ 8.07 (almost s, 2H, H-4 and H-5), 7.89 (d, J = 2.4 Hz, 1H, H-2), 6.88 (d, J = 2.4 Hz, 1H, H-3), 2.78 (s, 3H, MeCO-); ms: m/z (relative intensity) 161 (M^+, 60), 146 (33), 133 (20), 119 (43), 118 (100), 91 (19), 64 (24), 63 (34); hrms: 161.0477. (M^+, Calcd. for $C_9H_7NO_2$: 161.0476.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.48; H, 4.71; N, 8.84.

Compound **2b**.

This compound had mp 113-117° (colorless crystals, from ether-hexane); ir (potassium bromide): 3091, 3068, 3042, 3005, 2925, 1684, 1603, 1565, 1534, 1417, 1361, 1280, 1170, 1017, 852, 803 cm^{-1}; ^1H nmr δ 8.09 (d, J = 8.8 Hz, 1H, H-6), 7.95 (d, J = 2.1 Hz, 1H, H-2), 7.83 (dd, J = 8.8, 0.9 Hz, 1H, H-7), 7.07 (dd, J = 2.1, 0.9 Hz, 1H, H-3), 2.79 (s, 3H, MeCO-); ms: m/z (relative intensity) 161 (M^+, 24), 131 (22), 119 (27), 118 (28), 69 (89); hrms: 161.0478. M^+, Calcd. for $C_9H_7NO_2$: 161.0476.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.83; H, 4.47; N, 8.69.

Compound **2c**.

This compound had mp 118-121° (colorless crystals, from acetone-ether); ir (potassium bromide): 3132, 3091, 3068, 3042, 3005, 2925, 1688, 1596, 1414, 1362, 1345, 1278, 1258, 1149, 1032, 996, 842 cm^{-1}; ^1H nmr δ 8.50 (d, J = 5.0 Hz, 1H, H-5), 7.91 (d, J = 2.1 Hz, 1H, H-2), 7.77 (d, J = 5.0 Hz, 1H, H-4), 6.88 (d, J = 2.1 Hz, 1H, H-3), 2.84 (s, 3H, MeCO-); ms: m/z (relative intensity) 161 (M^+, 56), 133 (43), 119 (51), 118 (55), 64 (25), 63 (31); hrms: 161.0481. M^+, Calcd. for $C_9H_7NO_2$: 161.0476.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.08; H, 4.44; N, 8.75.

Compound **2d**.

This compound had mp 72-74° (colorless crystals, from ether-hexane); ir (potassium bromide): 3163, 3128, 3069, 3021, 2925, 2855, 1692, 1528, 1434, 1359, 1263, 1158, 1117, 1026, 907, 844 cm^{-1}; ^1H nmr δ 8.56 (d, J = 5.3 Hz, 1H, H-6), 7.77 (d, J = 2.1 Hz, 1H, H-2), 7.60 (dd, J = 5.3, 0.9 Hz, 1H, H-7), 7.56 (dd, J = 2.1, 0.9 Hz, 1H, H-3), 2.81 (s, 3H, MeCO-); ms: m/z (relative intensity) 161 (M^+, 81), 133 (55), 119 (100), 118 (72), 91 (72), 90 (23), 64 (27), 63 (44); hrms: 161.0477. M^+, Calcd. for $C_9H_7NO_2$: 161.0476.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.47; N, 8.71.

General Procedure for the Grignard Reaction of **1a**, **1b**, **1c** and **1d** with Phenylmagnesium Bromide.

To a stirred solution of phenylmagnesium bromide (2.5 ml, 1.0*M*, 2.5 mmoles) in tetrahydrofuran was added a solution of cyano compound **1a**, **1b**, **1c** or **1d** (160 mg, 1.11 mmoles) in dry tetrahydrofuran (10 ml) by syringe over a period of 5 minutes at -10° under nitrogen atmosphere. After stirring at room temperature for 2 hours, the reaction mixture was treated with 0.5*M* sulfuric acid and stirred at room temperature for 5 minutes. After evaporation of the solvent under reduced pressure, the residual mixture was basified with ammonium hydroxide solution and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated. The residue was chromatographed on a silica gel (35 g) column using chloroform as an eluent to give 193 mg (78%) of 6-benzoylfuro[2,3-*b*]pyridine **3a**, 213 mg (86%) of 5-benzoylfuro[3,2-*b*]pyridine **3b**, 243 mg (98%) of 7-benzoylfuro[2,3-*c*]pyridine **3c** and 240 mg (97%) of 4-benzoylfuro[3,2-*c*]pyridine **3d**.

Compound **3a**.

Recrystallization of **3a** from ether-hexane gave a pure sample of mp 94-95°; ir (potassium bromide): 3141, 3124, 3074, 3035, 2920, 1651, 1597, 1577, 1519, 1402, 1355, 1324, 1275, 1126, 1028, 971, 855 cm^{-1}; ^1H nmr δ 8.13 (d, J = 7.6 Hz, 1H, H-5), 8.12 (d, J = 7.6 Hz, 1H, H-4), 7.89 (d, J = 2.4 Hz, 1H, H-2), 6.90 (d, J = 2.4 Hz, 1H, H-3), 8.16-8.01 and 7.62-7.48 (m, 5H, PhCO-).

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.51; H, 4.18; N, 6.25.

Compound **3b**.

This compound was purified by recrystallization from acetone to give a pure sample of mp 127-129° (colorless crystals); ir (potassium bromide): 3233, 3113, 3046, 1654, 1598, 1535, 1413, 1343, 1279, 1192, 1179, 1105, 1012, 965, 899 cm^{-1}; ^1H nmr δ 8.07 (d, J = 8.5 Hz, 1H, H-6), 8.04 (d, J = 2.4 Hz, 1H, H-2), 7.91 (dd, J = 8.5, 0.9 Hz, 1H, H-7), 7.08 (dd, J = 2.4, 0.9 Hz, 1H, H-3), 8.16-7.96 and 7.62-7.41 (m, 5H, PhCO-).

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.54; H, 4.14; N, 6.21.

Compound **3c**.

Recrystallization of the crude **3c** from ether gave an analytically pure sample of **3c** as colorless cubes, mp 71-73°; ir (potassium bromide): 3141, 3118, 3065, 3042, 1658, 1596, 1578, 1528, 1417, 1291, 1267, 1122, 1020, 900, 759 cm^{-1}; ^1H nmr 8.54 (d, J = 5.0 Hz, 1H, H-5), 7.87 (d, J = 2.3 Hz, 1H, H-2), 7.76 (d, J = 5.0 Hz, 1H, H-4), 6.91 (d, J = 2.3 Hz, 1H, H-3), 8.16-8.05 and 7.61-7.41 (m, 5H, PhCO-).

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.71; H, 4.20; N, 6.29.

Compound **3d**.

This compound had mp 111-113° (colorless crystals, from ether); ir (potassium bromide): 3148, 3092, 3031, 1652, 1596, 1527, 1423, 1260, 1214, 1127, 1003, 875 cm^{-1}; ^1H nmr 8.62 (d, J = 5.6 Hz, 1H, H-6), 7.79 (d, J = 2.1 Hz, 1H, H-2), 7.62 (dd, J = 5.6, 0.9 Hz, 1H, H-7), 7.42 (dd, J = 2.1, 0.9 Hz, 1H, H-3), 8.21-8.10 and 7.63-7.48 (m, 5H, PhCO-).

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.70; H, 4.24; N, 6.27.

General Procedure for the Grignard Reaction of *N*-Oxides **4a**, **4b**, **4c** and **4d** of Furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]-and -[3,2-*c*]-pyridine with Phenylmagnesium Bromide.

To a stirred solution of phenylmagnesium bromide (3.5 ml, 1.0*M*, 3.5 mmoles) in tetrahydrofuran was added a solution of furopyridine *N*-oxide **4a**, **4b**, **4c** or **4d** (270 mg, 2.0 mmoles) in dry tetrahydrofuran (15 ml) by syringe over a period of 5 minutes at -10° under a nitrogen atmosphere. After stirring at room temperature for 2 hours, the reaction mixture was treated with 0.5*M* sulfuric acid and stirred at room temperature for 5 minutes. After evaporation of the solvent under reduced pressure, the residual mixture was basified with ammonium hydroxide solution and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated. The residue was chromatographed on a silica gel (35 g) column using chloroform as an eluent to give 199 mg (51%) of 6-phenylfuro[2,3-*b*]pyridine **5a**, 246 mg (63%) of 5-phenylfuro[3,2-*b*]pyridine **5b**, 117 mg (30%) of 7-phenylfuro[2,3-*c*]pyridine **5c** and 121 mg (31%) of 4-phenylfuro[3,2-*c*]pyridine **5d**.

Compound **5a**.

This compound had mp 61-64° (colorless crystals, from ether-hexane); ir (potassium bromide): 3142, 3120, 3066, 2923, 2852, 1614, 1588, 1521, 1460, 1440, 1400, 1343, 1251, 1124, 1022, 831 cm^{-1}; ^1H nmr δ 7.95 (d, J = 7.9 Hz, 1H, H-4), 7.68 (d, J = 7.9 Hz, 1H, H-5), 7.68 (d, J = 2.4 Hz, 1H, H-2), 6.75 (d, J = 2.4 Hz, 1H, H-3), 8.13-8.03 and 7.61-7.24 (m, 5H, Ph-).

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.36; H, 4.76; N, 7.24.

Compound **5b**.

This compound had mp 77-78° (colorless crystals, from ether); ir (potassium bromide): 3139, 3091, 3044, 2926, 1854, 1610, 1574, 1533, 1416, 1263, 1112, 1022, 881 cm^{-1}; ^1H nmr δ 7.87 (d, J = 2.3 Hz, 1H, H-2), 7.75 (dd, J = 7.9, 0.9 Hz, 1H, H-7), 7.66 (d, J = 7.9 Hz, 1H, H-6), 7.06 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 8.06-7.95 and 7.58-7.37 (m, 5H, Ph-).

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.35; H, 4.75; N, 7.13.

Compound **5c**.

This compound had mp 56-61° (colorless crystals, from ether); ir (potassium bromide): 3146, 3084, 3045, 3028, 2924, 2852, 1596, 1581, 1574, 1461, 1445, 1404, 1271, 1187, 1175, 1037, 871, 833 cm^{-1}; ^1H nmr δ 8.51 (d, J = 5.3 Hz, 1H, H-5), 7.80 (d, J = 2.1 Hz, 1H, H-2), 7.50 (d, J = 5.3 Hz, 1H, H-4), 6.85 (d, J = 2.1 Hz, 1H, H-3), 8.43-8.32 and 7.66-7.42 (m, 5H, Ph-).

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.20; H, 4.74; N, 7.21.

Compound **5d**.

This compound had mp 86-90° (lit mp 91-92° [3]) (colorless crystals, from ether); ir (potassium bromide): 3140, 3088, 3038, 2925, 1602, 1569, 1537, 1441, 1260, 1146, 1032, 1021, 923, 798 cm^{-1}; ^1H nmr δ 8.58 (d, J = 5.8 Hz, 1H, H-6), 7.68 (d, J = 2.3 Hz, 1H, H-2), 7.42 (dd, J = 5.8, 0.9 Hz, 1H, H-7), 7.06 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 8.01-7.90 and 7.59-7.38 (m, 5H, Ph-).

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.15; H, 4.77; N, 7.22.

General Procedure for the Preparation of 6-Mesylaminomethylfuro[2,3-*b*]- **8a**, 5-Mesylaminomethylfuro[3,2-*b*]- **8b**, 7-Mesylaminomethylfuro[2,3-*c*]- **8c** and 4-Mesylaminomethylfuro[3,2-*c*]pyridine **8d**.

To a solution (suspension) of cyano compound **1a, 1b, 1c** or **1d** (100 mg, 0.69 mmole) in 5 ml of dry dichloromethane was added diisobutylaluminium hydride (1.4 ml, 1.0*M* solution in dichloromethane, 1.4 mmoles) at -5° under nitrogen atmosphere with stirring. After stirring for 15 minutes at -5°, the mixture was treated with saturated aqueous sodium potassium tartrate solution (5 ml), and the layers were separated. The aqueous layer was extracted with chloroform. The organic layers were combined, dried over magnesium sulfate and evaporated under reduced pressure to afford 108 mg of crude amine **7a, 7b, 7c** or **7d** as a slightly brown syrup, which was used in the next step without any purification.

A mixture of the crude amine (108 mg), pyridine (0.3 ml) and methanesulfonyl chloride (150 mg, 1.3 mmoles) in dichloromethane (5 ml) was stirred for 20 hours at room temperature under a nitrogen atmosphere. To the reaction mixture was added 5 ml of water. The organic layer was separated and the aqueous layer was extracted with chloroform. The organic layers were combined, dried over magnesium sulfate and evaporated. The residual solid was chromatographed on a silica gel (12 g) column using chloroform as an eluent to give 105 mg (67%) of 6-mesylaminomethylfuro[2,3-*b*]- **8a**, 72 mg (46%) of 5-mesylaminomethylfuro[3,2-*b*]- **8b**, 67 mg (43%) of 7-mesylaminomethylfuro[2,3-*c*]- **8c** and 129 mg (82%) of 4-mesylaminomethylfuro[3,2-*c*]pyridine **8d**.

Compound **8a**.

This compound had mp 112-114° (colorless crystals, from acetone-ether); ir (potassium bromide): 3277, 3217, 3150, 3130, 3026, 3004, 2928, 1595, 1531, 1405, 1314, 1151, 1128, 1022, 973, 861 cm^{-1}; ^1H nmr δ 7.95 (d, J = 8.0 Hz, 1H, H-4), 7.70 (d, J = 2.3 Hz, 1H, H-2), 7.27 (d, J = 8.0 Hz, 1H, H-5), 6.79 (d, J = 2.3 Hz, 1H, H-3), 5.57 (broad, 1H, -NH-), 4.55 (d, J = 5.8 Hz, 2H, $-CH_2-$), 2.94 (s, 3H, $MeSO_2-$).

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38. Found: C, 47.80; H, 4.41; N, 12.32.

Compound **8b**.

This compound had mp 144-146° (colorless crystals, from acetone-ether); ir (potassium bromide): 3143, 3118, 3080, 3046, 2926, 2841, 2722, 1608, 1581, 1472, 1419, 1324, 1309, 1277, 1137, 1115, 1088, 1027, 970, 856, 798 cm^{-1}; ^1H nmr δ 7.89 (d, J = 2.1 Hz, 1H, H-2), 7.79 (dd, J = 8.5, 0.9 Hz, 1H, H-7), 7.23 (d, J = 8.5 Hz, 1H, H-6), 6.96 (dd, J = 2.1, 0.9 Hz, 1H, H-3), 5.69 (broad, 1H, -NH-), 4.55 (d, J = 5.2 Hz, 2H, $-CH_2-$), 2.92 (s, 3H, $MeSO_2-$).

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38. Found: C, 47.82; H, 4.34; N, 12.36.

Compound **8c**.

This compound had mp 144-147° (colorless crystals, from acetone-ether); ir (potassium bromide): 3351, 3131, 3031, 2941, 2839, 2722, 1618, 1578, 1476, 1420, 1314, 1177, 1138, 1071, 1029, 967, 842, 769 cm^{-1}; ^1H nmr δ 8.35 (d, J = 5.3 Hz, 1H, H-5), 7.79 (d, J = 2.3 Hz, 1H, H-2), 7.53 (d , J = 5.3 Hz, 1H, H-4), 6.86 (d, J = 2.3 Hz, 1H, H-3), 5.88 (broad, 1H, -NH-), 4.80 (d, J = 4.9 Hz, 2H, $-CH_2-$), 2.94 (s, 3H, $MeSO_2-$).

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38. Found: C, 47.89; H, 4.41; N, 12.31.

Compound **8d**.

This compound had mp 113-116° (colorless crystals, from acetone); ir (potassium bromide): 3437, 3142, 3112, 3025, 2938, 2824, 2709, 1596, 1440, 1330, 1309, 1240, 1134, 1099, 1073, 1031, 970, 839 cm^{-1}; ^1H nmr δ 8.44 (d, J = 5.6 Hz, 1H, H-6), 7.71 (d, J = 2.3 Hz, 1H, H-2), 7.43 (dd , J = 5.6, 0.9 Hz, 1H, H-7), 6.94 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 6.10 (broad, 1H, -NH-), 4.70 (d, J = 3.5 Hz, 2H, $-CH_2-$), 2.93 (s, 3H, $MeSO_2-$).

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38. Found: C, 47.78; H, 4.45 N, 12.22.

General Procedure for the Preparation of 6-Formylfuro[2,3-*b*]- **9a**, 5-Formylfuro[3,2-*b*]- **9b**, 7-Formylfuro[2,3-*c*]- **9c** and 4-Formylfuro[3,2-*c*]pyridine **9d**.

To a suspension of carboxylic ester **6a, 6b, 6c** or **6d** (120 mg, 0.63 mmole) in 5 ml of dry dichloromethane was added diisobutylaluminium hydride (1.4 ml of 1.0*M* solution in dichloromethane, 1.4 mmoles; for compound **6c**, used 0.82 ml (0.82 mmole)) at -5° (in the case of **6a**, the reaction was carried out at -50°) under nitrogen atmosphere with stirring. After being stirred for 15 minutes at -5°, the mixture was treated with saturated aqueous sodium potassium tartrate solution (5 ml), and separated the layers. The aqueous layer was extracted with chloroform. The organic layers were combined, dried over magnesium sulfate and evaporated to afford solid residue, which was recrystallized from ether-hexane to give a pure sample of 6-formylfuro[2,3-*b*]- **9a** (78 mg, 84%), 5-formylfuro[3,2-*b*]- **9b** (68 mg, 74%), 7-formylfuro[2,3-*c*]- **9c** (91 mg, 98%) and 4-formylfuro[3,2-*c*]pyridine **9d** (81 mg, 88%).

Compound **9a**.

This compound had mp 93-97° (colorless crystals); ir (potassium bromide): 3142, 3031, 2927, 2852, 1697, 1586, 1523, 1373,1357, 1310, 1272, 1235, 1139, 1108, 1022, 885, 840 cm^{-1}; ^1H nmr δ 10.10 (d, J = 0.6 Hz, 1H, -CHO), 8.10 (dd, J = 8.5, 0.6 Hz, 1H, H-4), 8.00 (d, J = 8.5 Hz, 1H, H-5), 7.95 (d, J = 2.6 Hz, 1H, H-2), 6.92 (d, J = 2.6 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.50; H, 3.62; N, 9.57.

Compound **9b**.

This compound had mp 94-95° (colorless crystals); ir (potassium bromide): 3136, 3114, 2924, 2873, 1694, 1605, 1538, 1417, 1277, 1154, 1126, 1098, 1016, 832, 792 cm^{-1}; ^1H nmr δ 10.16 (d, J = 0.6 Hz, 1H, -CHO), 8.04 (d, J = 8.5 Hz, 1H, H-6), 8.03 (d, J = 2.3 Hz, 1H, H-2), 7.90 (ddd, J = 8.5, 0.9, 0.6 Hz, 1H, H-7), 7.13 (dd, J = 2.3, 0.9 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.39; H, 3.49; N, 9.51.

Compound **9c**.

This compound had mp 88-89° (colorless crystals); ir (potassium bromide): 3394, 3150, 3125, 2925, 2826, 1706, 1603, 1533, 1422, 1234, 1195, 1013, 863, 850, 756 cm^{-1}; ^1H nmr δ 10.32 (S, 1H, -CHO), 8.63 (d, J = 5.3 Hz, 1H, H-5), 7.94 (d, J = 2.3 Hz, 1H, H-2), 7.82 (d, J = 5.3 Hz, 1H, H-4), 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, 64.92; H, 3.64; N, 9.37.

Compound **9d**.

This compound had mp 68-73° (colorless crystals); ir (potassium bromide): 3150, 3093, 3034, 2923, 2851, 1713, 1529, 1429, 1372, 1273, 1237, 1133, 995, 852, 825, 802 cm^{-1}; ^1H nmr δ 10.26 (s, 1H, -CHO), 8.69 (d, J = 5.6 Hz, 1H, H-6), 7.84 (d, J = 2.3 Hz, 1H, H-2), 7.66 (dd, J = 5.6, 0.9 Hz, 1H, H-7), 7.55 (dd, J = 2.3, 0.9 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.04; H, 3.69; N, 9.30.

General Procedure for the Condensation of **9a, 9b, 9c** and **9d** with Nitromethane.

To a solution of aldehyde **9a, 9b, 9c** or **9d** (80 mg, 0.54 mmole) and nitromethane (57 mg, 0.93 mmole) in absolute methanol (5 ml) was added a solution of sodium methoxide (30 mg, 0.55 mmole) in methanol (1.0 ml) by syringe under a nitrogen atmosphere and stirring at -15°. The mixture was stirred at -15° for 2.5 hours and at room temperature for 0.5 hour, treated with water, acidified with acetic acid, basified with sodium bicarbonate and evaporated under reduced pressure to remove the methanol. The residue was diluted with water, extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated to give a solid residue. Further processing of the residue is indicated in a subsequent paragraph.

6-(1-Hydroxy-2-nitroethyl)furo[2,3-*b*]pyridine **10a**.

The crude residue (85 mg) from **9a** was purified by chromatography on a silica gel (5 g) column eluting with chloroform to give 71 mg (63%) of **10a**. This compound had mp 84-86° (colorless crystals, from ether-hexane); ir (potassium bromide): 3373, 3155, 3150, 2923, 2852, 1550, 1529, 1409, 1382, 1124, 1110, 1082, 1020, 900, 890, 849, 839 cm^{-1}; ^1H nmr δ 8.02 (d, J = 8.0 Hz, 1H, H-4), 7.74 (d, J = 2.7 Hz, 1H, H-2), 7.44 (dd, J = J = 8.0, 0.6 Hz, 1H, H-5), 6.82 (d, J = 2.7 Hz, 1H, H-3), 5.69-5.49 (complex m, 1H, H-α), 4.90 (dd, J = 12.9, 4.4 Hz, 1H, H-β_1), 4.71 (dd, J = 12.9, 7.9 Hz, 1H, H-β_2), 3.93 (broad d, J = 6.7, 1H, OH).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.02; H, 3.93; N, 13.53.

5-(1-Hydroxy-2-nitroethyl)furo[3,2-*b*]pyridine **10b**.

The crude residue (93 mg) from **9b** was purified by chromatography on a silica gel (5 g) column eluting with chloroform to give 80 mg (71%) of **10b**. This compound had mp 74-77° (colorless crystals, from ether); ir (potassium bromide): 3131, 3127, 3120, 2922, 2849, 2739, 1581, 1552, 1417, 1382, 1282, 1156, 1103, 1023, 839, 795 cm^{-1}; ^1H nmr δ 7.91 (d, J = 2.3 Hz, 1H, H-2), 7.84 (dd, J = 8.5, 0.6 Hz, 1H, H-7), 7.38 (d, J = 8.5 Hz, 1H, H-6), 6.96 (dd, J = 2.3, 0.6 Hz, 1H, H-3), 5.69 (complex m, 1H, H-α), 4.86 (dd, J = 12.9, 4.1 Hz, 1H, H-β_1), 4.66 (dd, J = 12.9, 7.9 Hz, 1H, H-β_2), 4.42 (m, 1H, OH).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.19; H, 3.97; N, 13.42.

7-(1-Hydroxy-2-nitroethyl)furo[2,3-*c*]pyridine **10c** and 7-Acetylfuro[2,3-*c*]pyridine **2c**.

The crude residue (75 mg) from **9c** was chromatographed on a silica gel (5 g) column eluting with chloroform to give 27 mg (24%) of **10c** and 19 mg (22%) of **2c**. Compound **2c** was identified by comparison of the ir and ^1H nmr spectra with those of the sample obtained by the reaction of **1c** with methylmagnesium bromide. Compound **10c** had mp 85-89° (colorless crystals, from etherhexane); ir (potassium bromide): 3144, 3091, 2923, 2852, 2730, 1620, 1550, 1530, 1469, 1426, 1381, 1333, 1292, 1250, 1178, 1034, 880, 833, 771 cm^{-1}; ^1H nmr δ 8.40 (d, J = 5.3 Hz, 1H, H-5), 7.82 (d, J = 2.3 Hz, 1H, H-2), 7.60 (d, J = 5.3 Hz, 1H, H-4), 6.91 (d, J = 2.3 Hz, 1H, H-3), 5.90 (dd, J = 8.2, 3.6 1H, H-α), 5.03 (dd, J = 12.6, 3.6 Hz, 1H, H-β_1), 4.66 (dd, J = 12.6, 8.2 Hz, 1H, H-β_2), 5.10 (broad s, 1H, OH).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.11; H, 3.88; N, 13.45.

4-(1-Hydroxy-2-nitroethyl)furo[2,3-*c*]pyridine **10d** and 4-Acetylfuro[2,3-*c*]pyridine **2d**.

The crude residue (110 mg) from **9d** was chromatographed on a silica gel (5 g) column eluting with chloroform to give 93 mg (82%) of **10d** and 13 mg (15%) of **2d**. Compound **2d** was identified by comparison of the ir and ^1H nmr spectra with those of the sample obtained by the reaction of **1d** with methylmagnesium bromide. Compound **10d** was very unstable (yellow solid, mp 68-85°) and rapidly resinified by heating above 50°, therefore this compound could not be purified by recrystallization and resulted in poor elemental analyses. The ^1H nmr spectrum of **10d** indicated that the proposed structure was the correct one; ^1H nmr δ 8.42 (d, J = 5.9 Hz, 1H, H-6), 7.74 (d, J = 2.3 Hz, 1H, H-2), 7.46 (dd, J = 5.9, 0.9 Hz, 1H, H-7), 7.06 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 5.87 (dd, J = 5.5, 4.7Hz, 1H, H-α), 4.87 (dd, J = 14.4, 5.5 Hz, 1H, H-β_1), 4.80 (dd, J = 14.4, 5.5 Hz, 1H, H-β_2).

General Procedure for the Wittig-Horner Reaction of **9a, 9b, 9c** and **9d** with Methyl Diethyl Phosphonoacetate.

To a stirred suspension of sodium hydride (15 mg of 60% dispersion in mineral oil, 0.37 mmole, washed with hexane) in dry tetrahydrofuran (6 ml) was added a solution of methyl diethylphosphonoacetate (80 mg, 0.37 mmole) in tetrahydrofuran (2 ml) by syringe under a nitrogen atmosphere with stirring at room temperature. After stirring an additional 20 minutes, the mixture was cooled at 0° and a solution of aldehyde **9a, 9b, 9c** or **9d** (50 mg, 0.34 mmole) in tetrahydrofuran (3 ml) was added to the mixture by syringe. The cooling bath was removed and stirring was continued at room temperature for 18 hours. After evaporation of the solvent, the residual mixture was treated with chloroform

and water. The chloroform layer was dried (magnesium sulfate) and evaporated to give a crystalline mass which was purified by recrystallization to give methyl β-(6-furo[2,3-*b*]pyridyl)acrylate **11a** (47 mg, 68%), methyl β-(5-furo[3,2-*b*]pyridyl)acrylate **11b** (67.5 mg, 98%), methyl β-(7-furo[2,3-*c*]pyridyl)acrylate **11c** (36.5 mg, 53%) and methyl β-(4-furo[3,2-*c*]pyridyl)acrylate **11d** (66 mg, 96%), respectively.

Compound **11a**.

This compound had mp 122-124°(colorless crystals, from acetone-hexane); ir (potassium bromide): 3142, 3117, 3060, 2998, 2951, 1709, 1645, 1581, 1526, 1440, 1358, 1272, 1204, 1161, 973, 890, 833 cm^{-1}; ^1H nmr δ 7.94 (d, J = 7.6 Hz, 1H, H-4), 7.36 (d, J = 15.8 Hz, 1H, H-β), 7.77 (d, J = 2.3 Hz, 1H, H-2), 7.37 (d, J = 7.6 Hz, 1H, H-5), 6.99 (d, J = 15.8 Hz, 1H, H-α), 6.80 (d, J = 2.3 Hz, 1H, H-3), 3.83 (s, 3H, Me).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.17; H, 4.53; N, 6.91.

Compound **11b**.

This compound had mp 154-156° (colorless crystals, from acetone-ether); ir (potassium bromide): 3143, 3121, 3050, 2954, 1714, 1648, 1602, 1537, 1416, 1344, 1271, 1207, 1161, 1132, 982, 822, 791 cm^{-1}; ^1H nmr δ 7.89 (d, J = 2.3 Hz, 1H, H-2), 7.82 (d, J = 15.8 Hz, 1H, H-β), 7.77 (dd, J = 8.5, 0.9 Hz, 1H, H-7), 7.40 (d, J = 8.5 Hz, 1H, H-6), 6.99 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 6.93 (d, J = 15.8 Hz, 1H, H-α), 3.83 (s, 3H, Me).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.26; H, 4.53; N, 6.92.

Compound **11c**.

This compound had mp 83-87° (colorless crystals, from ether); ir (potassium bromide): 3144, 3115, 3013, 2954, 2924, 2851, 1709, 1649, 1599, 1417, 1310, 1260, 1167, 1128, 1023, 979, 880, 836 cm^{-1}; ^1H nmr δ 8,48 (d, J = 5.0 Hz, 1H, H-5), 8.10 (d, J = 16.1 Hz, 1H, H-β), 7.81 (d, J = 2.1 Hz, 1H, H-2), 7.56 (d, J = 5.0 Hz, 1H, H-4), 7.24 (d, J = 16.1 Hz, 1H, H-α), 6.86 (d, J = 2.1 Hz, 1H, H-3), 3.86 (s, 3H, Me).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.28; H, 4.58; N, 6.90.

Compound **11d**.

This compound had mp 119-120° (colorless crystals, from ether-hexane); ir (potassium bromide): 3153, 3124, 2947, 1702, 1646, 1575, 1534, 1446, 1360, 1304, 1290, 1254, 1160, 1012, 984, 825 cm^{-1}; ^1H nmr δ 8.54 (d, J = 5.6 Hz, 1H, H-6), 8.01 (d, J = 15.8 Hz, 1H, H-β), 7.74 (d, J = 2.3 Hz, 1H, H-2), 7.44 (dd, J = 5.6, 0.9 Hz, 1H, H-7), 7.11 (d, J = 15.8 Hz, 1H, H-α), 7.06 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 3.89 (s, 3H, Me).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.16; H, 4.50; N, 6.87.

REFERENCES AND NOTES

[1] Part **XXI**: S. Shiotani and K. Taniguchi, *J. Heterocyclic Chem.*, **34**, 493 (1997).

[2] S. Shiotani and K. Taniguchi, *J. Heterocyclic Chem.*, **33**, 1051 (1996).

[3] W. Herz and S. Tocker, *J. Am. Chem. Soc.*, **77**, 3554 (1955).

[4] E. Winterfeldt, *Synthesis*, 617 (1975).

[5] R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).

[6] K. Krohn and W. Priyono, *Angew. Chem., Int. Ed. Engl.*, **25**, 339 (1986).

[7a] J. H. McFarland, W. A. Essary, L. Cilenti, W. Cozart and P. E. McFarland, *J. Heterocyclic Chem.*, **12**, 705 (1975); [b] S. Gronowitz, C. Westerlund and A. -B. Hörnfeldt, *Acta Chem. Scand. B*, **29**, 233 (1975); [c] S. Shiotani and H. Morita, *J. Heterocyclic Chem.*, **19**, 1207 (1982).