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APPLICATION OF ORGANOLITHIUM AND RELATED REAGENTS IN SYNTHESIS. PART 7[1]. SYNTHESIS AND METALLATION OF 4-METHOXYPICOLIN- AND 2-METHOXYISONICOTIN-ANILIDES. A USEFUL METHOD FOR PREPARATION OF 2,3,4-TRISUBSTITUTED PYRIDINES

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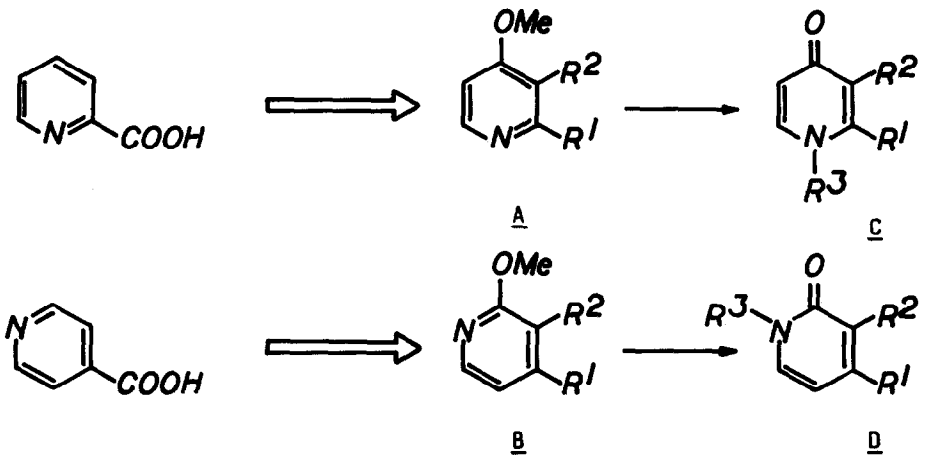
The synthesis and metallation of 4-methoxypicolin- and 2-methoxyisonicotin-anilides as a way of regiospecific transformation of picolinic and isonicotinic acids into 2,3,4-trisubstituted pyridines, is described. The resulted C^3-alkylated derivatives underwent smooth acid - catalysed conversion into the corresponding pyridones.

ortho-Substituted pyridine carboxylic acids are important key starting materials for the preparation of numerous heterocyclic compounds[2,3,4,5,6,7] including important natural products[5,8,9,10].

Available methods of their preparation generally requires total construction of the pyridine nucleus via divers multi-step reactions[11]. More atractive route so far reported to ortho-substituted pyridine carboxylic acids is the direct lithiation of the amides[2,4,5,7,8,9,10] and (4,4-dimethyloxazolin-2-yl)-pyridine derivatives[3,6] (masked carboxylic acids) followed by reaction with electrophiles. However, in the most cases related only to specific instances.

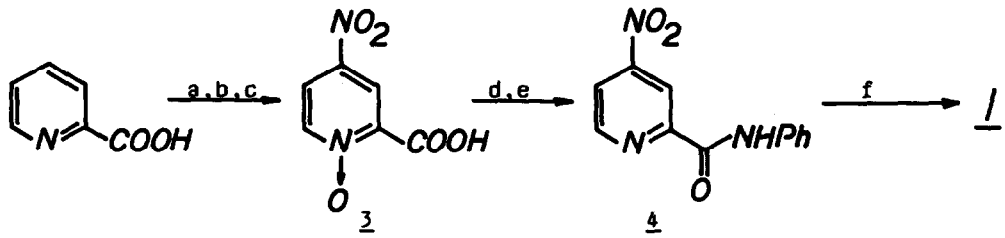
In a series of recent studies we have reported[4,7b] that the secondary carboxamide moiety provides excellent possibility for the regiospecific ortho-lithiation and subsequent electrophilic substitution of the pyridine ring. We have now studied the lithiation of the methoxy-pyridine carboxamides as an extention of the scope of our functionalization methodology.

We now describe a novel efficient synthetic sequences for the transformation of the picolin- and isonicotin acids into 2,3,4-trisubstituted pyridines (A) and (B), which are convenient starting materials for the preparation of the unsymmetricaly substituted pyridones (C) and (D).

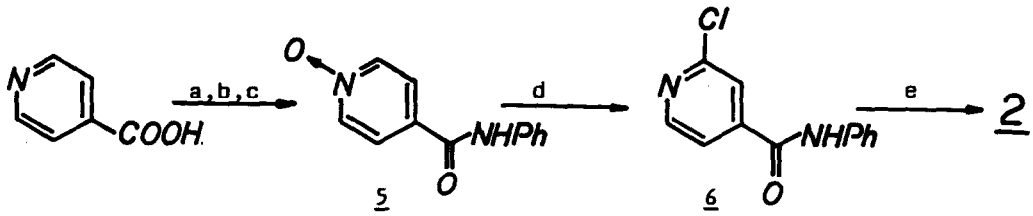


It has been demonstrated[1,7b] that from amongst of the secondary pyridine-carboxamides the N-phenyl-amides (anilides) are the most powerfull directing group and that the anilide function should be considered the best choice for direct metallation of the masked picolin- and isonicotin-carboxylic acids.

Therefore, in our first experiments, the preparation of the methoxy-anilides (1) and (2) applying the corresponding acids as starting materials, was developed. The picolinic acid in the sequence of oxidation and nitration was converted into 4-nitropicolinic acid-1-oxide (3)[12]. The N-oxide (3) on reaction with phosphorus trichloride was reduced[13a] and chlorinated to give 4-nitropicolinoyl chloride, which reacted with aniline yielded 4-nitro-picolinanilide (4). The 4-nitroanilide (4) subjected to react with sodium methoxide in methanol at room temperature produced the 4-methoxypicolin-anilide (1). The 2-methoxyisonicotinanilide (2) was prepared from isonicotinic acid via the following sequence of reactions; Isonicotinic acid at first was converted into N-phenylisonicotinamide[7b], which on oxidation by peracetic acid furnished isonicotinanilide-1-oxide (5). The deoxychlorination[13b] (boiling phosphorous oxychloride) of the N-oxide (5) gave 2-chloroanilide (6) that on treatment with sodium methoxide in boiling methanol yielded the 2-methoxy-isonicotinanilide (2).



a) KOH; b) H_2O_2/AcOH; c) HNO_3/H_2SO_4; d) $PCl_3/CHCl_3$; e) $PhNH_2/Et_3N/CH_2Cl_2$; f) MeONa/MeOH

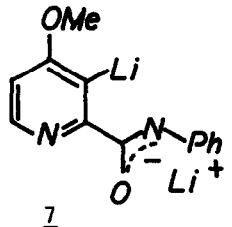


a) $SOCl_2$; b) $PhNH_2/Et_3N/CHCl_3$; c) H_2O_2/AcOH; d) $PCl_5/POCl_3$; e) MeONa/MeOH

Metallation - Electrophilic Substitution of the Anilides (1) and (2); Synthesis of an Unsymmetricaly Substituted 2- and 4-Pyridones

From amongst the bases used for the lithiation, n-butyllithium (nBuLi) in tetrahydrofuran (THF) as solvent was selected as this is the system most frequently used.

The methoxy-anilides (1) and (2) in the presence of N,N,N′,N′-tetramethylethylenediamine (TMEDA) reacted in THF with 2.1 mol equivalents of nBuLi (amide - TMEDA/-78°C/nBuLi/0.5h/ → -23°C/2h) were efficiently converted into the corresponding bis(N- and C^3-)lithiated anilides (7) and (8), as it has been demonstrated by the subsequent reaction with electrophiles. Treatment of the solution of the lithiated species with electrophiles (MeI and p-MeO-C_6H_4-CHO) afforded the desired products (9) and (10). The lithiated methoxyanilides (7) and (8) reacted with an excess of MeI (3 mol equivalents) produced mono- and/or dimethylated derivatives. Thus, the 4-methoxypicolinanilide (1) gave monomethylated product (9a) which was accompanied by traces of dimethylated compound (9b), that has been observed by ^1H NMR of the row material and not isolated as a pure compound. In the case of the 2-methoxyisonicotinanilide (2), entirely the dimethylated anilide (10b) was formed. The hydroxy products (9c) and (10c) without isolation on acid-driven cyclization (5% - H_2SO_4 at room temperature) yielded the corresponding lactones (11) and (12).



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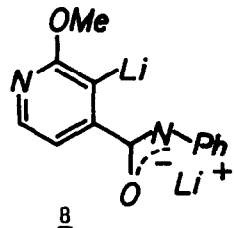

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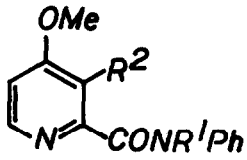

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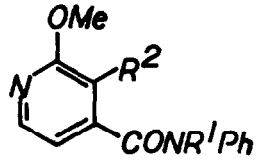

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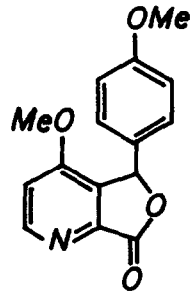

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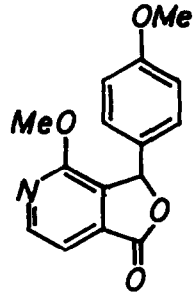

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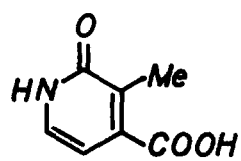
a, R^1= H; R^2= Me
b, R^1= R^2= Me
c, R^1= H; R^2= $CH(OH)C_6H_4OMe$-p

The described methodology relating to the introducing of the alkyl substituent at the 3-position of the 4-methoxypicolin- and 2-methoxyisonicotin-anilides shows considerable versatility for the regiospecific synthesis of the 2,3,4-trisubstituted pyridines. This, coupled with the quantitative removal of the anilide and/or methoxy moiety on acid hydrolysis to the carboxylic acids and other functional groups should allow access to a wide variety of pyridines.



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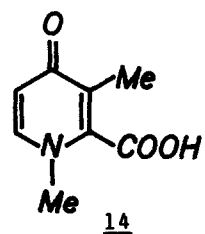

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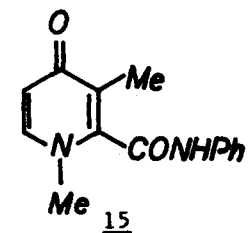

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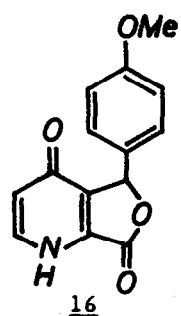

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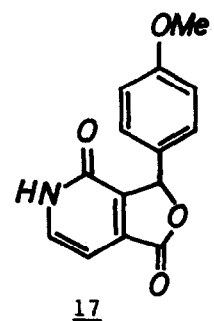

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Thus, the methylated anilide (10b) reacted with boiling hydrochloric acid (15% - HCl) afforded acid (13). On the other hand, the methylated anilide (9a) (under using conditions) gave N-methylated pyridone (14). Treatment of (9a) at room temperature with concentrated hydrochloric acid, produced the anilide (15). This last, indicates that the observed O → N rearrangement in the case of 3-methyl-4-methoxypicolinanilide (9a) is the process undergoing under very mild conditions. That has been already precedented, that the thermal conversion[14] e.g. 4-methoxypyridine into N-methyl-4-pyridone is brought about to relatively mild conditions by acid - catalysis[15].

The lactones (11) and (12) on the reaction with boiling hydrochloric acid resulted in the corresponding pyridone-lactones (16) and (17).

Experimental

Melting points of the products were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra are of solution in $CHCl_3$ or KBr discs using a Zeiss-Jena Specord 71-IR. ^1H - NMR spectra were obtained with a Varian EM-360, or a Tesla BS-467 using Me_4Si as an internal standard. n-Butyllithium (nBuLi) (Aldrich) was used without further purification. Tetrahydrofuran (THF) was dried with calcium hydride and used directly after distillation under argon from sodium. N,N,N′,N′-Tetramethylethylenediamine (TMEDA) was purified by the known method[16]. Electrophiles were purified by standard methods before use.

4-Methoxypicolinanilide (1)

(a) 4-Nitropicolin acid-1-oxide (3) was prepared by the procedure of Profft and Steinke[12], m.p. 145-147°C (lit.[12], m.p. 148°C).

(b) 4-Nitropicolinanilide (4). To the solution of N-oxide (3) (9.2 g, 0.05 mol) in $CHCl_3$ (50 ml) phosphorus trichloride (30 ml) was added, and the mixture was heated till boiling for 1.5 h. On when the mixture cooled, the solvent and excess of phosphorus trichloride were evaporated till dryness. To the residue dissolved in $CHCl_3$ (50 ml) the mixture of aniline (18.6 g, 0.2 mol) and triethylamine (30 ml) in $CHCl_3$ (20 ml) was added dropwise and left overnight. Then additional amount of $CHCl_3$ (50 ml) was added, and washed with water, 10% hydrochloric acid and water. The organic layer was dried ($MgSO_4$) and evaporated till dryness. The residue was purified on column chromatography (silica gel - $CHCl_3$). The solid product crystallized from MeOH as yellowish crystals of 4-nitropicolinanilide (4) (10.45 g, 86%), m.p. 145-147°C. (Found: C, 59.5; H, 3.9; N, 17.0. Calc. for $C_{12}H_9N_3O_3$: C, 59.3; H, 3.7; N, 17.3%); IR ($CHCl_3$) 3350 cm^{-1} (NH), 1700 cm^{-1} (CO), 1390 cm^{-1} and 1260 cm^{-1} (NO_2); ^1H - NMR ($CDCl_3$) 9.9 - 9.6 (1H, m, NH-H), 8.9 (1H, s, 3-H), 8.6 (1H, d, J 5Hz, 6-H), 8.2 - 8.0 (1H, m, 5-H), 7.9 - 7.0 (5H, m, Ph-H).

(c) 4-Methoxypicolinanilide (1). To the solution of sodium methoxide (0.46 g, 0.02 mol) in MeOH (40 ml) 4-nitropicolinanilide (4) (2.44 g, 0.01 mol) was added and the mixture was stirred for 4 h and left overnight. Then the solvent was evaporated and the formed colourless residue after washing with water and crystallization from cyclohexane gave 4-methoxypicolinanilide (1) (2.1 g, 93%) m.p. 94-96°C. (Found: C, 68.9; H, 5.4; N, 12.0. Calc. for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.4; N, 12.3%); IR ($CHCl_3$) 1700 cm^{-1} (CO); ^1H - NMR ($CDCl_3$) 10.1 - 9.8 (1H, m, NH-H), 8.2 (1H, d, J 5Hz, 6-H), 7.9 - 6.9 (6H, m, 3- and Ph-H), 6.8 (1H, dd, J 2 and 5Hz, 5-H), 3.7 (3H, s, OMe-H).

2-Methoxyisonicotinanilide (2)

(a) Isonicotinanilide-1-oxide (5). Isonicotinanilide (prepared as described[7b] in 78% yield, m.p. 174-175°C) (79.3 g, 0.4 mol) and hydrogen peroxide (100 ml) in AcOH (240 ml) were heated for 5 h at 85°C; then hydrogen peroxide (100 ml) was added and heating continued for 5 h. After the reaction, the mixture was evaporated, and to the residue water (250 ml) was added. The precipitated solid as colourless crystals of isonicotinanilide-1-oxide (5) (69.5 g, 81%) m.p. 220-224°C (decomp.). (Found: C, 67.3; H, 4.9; N, 12.9. Calc. for $C_{12}H_{11}N_2O_2$: C, 67.3; H, 4.7; N, 13.1%).

(b) 2-Chloroisonicotinanilide (6). To the solution of phosphorus pentachloride (30 g) in phosphorus oxychloride (40 ml) N-oxide (5) (21.4 g, 0.1 mol) was added and the whole lot heated up to 130°C for 1.5 h. On when the mixture cooled, the excess of phosphorus oxychloride was evaporated and to the residue water with ice was added and made alkaline with K_2CO_3. The precipitated yellow solid crystallized from EtOH (80%) as yellowish crystals of 2-chloro-isonicotinanilide (6) (15.1 g, 65%) m.p. 174.5-176.5°C. (Found: C, 61.8; H, 4.0; N, 11.8; Cl, 15.0. Calc. for $C_{12}H_9ClN_2O$: C, 61.9; H, 3.9; N, 12.0; Cl, 15.2%); IR (KBr) 3250 cm^{-1} (NH), 1660 cm^{-1} (CO); ^1H - NMR (DMSO-d_6) 10.6 - 10.2 (1H, m, NH-H), 8.4 (1H, d, J 5Hz, 6-H), 8.0 - 6.6 (7H, m, 3-, 5- and Ph-H).

(c) 2-Methoxyisonicotinanilide (2). To the solution of sodium methoxide (3.45 g, 0.15 mol) in MeOH (50 ml) 2-chloroisonicotinanilide (6) (6.98 g, 0.03 mol) was added and the mixture was heated till boiling for 16 h. Then the solvent was evaporated and the formed colourless residue after washing with water and crystallization from benzene gave 2-methoxyisonicotinanilide (2) (3.56 g, 52%) m.p. 165-166°C. (Found: C, 68.0; H, 5.4; N, 11.9. Calc. for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.3; N, 12.2%); IR (KBr) 3450 cm^{-1} (NH) and 1680 cm^{-1} (CO); ^1H - NMR (CD_3COCD_3) 10.0 - 9.5 (1H, m, NH-H), 8.3 (1H, d, J 5Hz, 6-H), 8.0 - 7.6 (2H, m, 3- and 5-H), 7.5 - 7.0 (5H, m, Ph-H), 3.9 (3H, s, OMe-H).

General Procedure for the Metallation - Electrophilic Substitution of the Anilides (1) and (2

To the anilide (1) or (2) (0.01 mol) with TMEDA (0.022 mol) stirred in THF (40 ml) at -78°C nBuLi (0.022 mol) was added dropwise. The solution was held at -78°C for 0.5 h, then allowed to rise to -23°C and kept at -23°C for 2 h. The whole lot was cooled to -78°C and electrophile (MeI - 0.03 mol; p-$MeOC_6H_4CHO$ - 0.011 mol) in THF (10 ml) was added. The reaction after 15 min at -78°C was allowed to regain room temperature and stirred at this conditions for 2 h, and then aqueous NH_4Cl (10 ml) was added. The mixture was taken up to $CHCl_3$, the organic layer was separated and dried ($MgSO_4$). The solvent was removed to give a semisolid residue. The product was isolated by column chromatography (silica gel, benzene - ethyl acetate) then purified by crystallization. In the case of hydroxy - product (9c) or (10c) the appropriate one was treated with 5% H_2SO_4 (30 ml) and left for 3 d. The crude lactone (11) or (12) was then filtered, washed with diisopropyl ether and purified by column chromatography (silica gel, $CHCl_3$) and recrystallization.

3-Methyl-4-methoxypicolinanilide (9a), (76%) m.p. 128-130°C (heptane); (Found: C, 69.1; H, 5.8; N, 11.6. Calc. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.8; N, 11.5%); IR (KBr) 1780 cm^{-1} (CO); ^1H - NMR ($CDCl_3$) 10.3 - 9.8 (1H, m, NH-H), 8.2 (1H, d, J 5Hz, 6-H), 7.6 - 6.9 (5H, m, Ph-H), 6.7 (1H, d, J 5Hz, 5-H), 3.7 (3H, s, OMe-H), 2.5 (3H, s, Me-H).

3,N-Dimethyl-2-methoxyisonicotinanilide (10b), (67%) m.p. 109-112°C (hexane); (Found: C, 70.0; H, 6.3; N, 10.9. Calc. for $C_{15}H_{16}N_2O_2$: C, 70.3; H, 6.3; N, 10.9%); IR (KBr) 1650 cm^{-1} (CO); ^1H - NMR ($CDCl_3$) 7.7 (1H, d, J 5Hz, 6-H), 7.5 - 6.6 (5H, m, Ph-H), 6.5 (1H, d, J 5Hz, 5-H), 3.7 (3H, s, OMe-H), 3.6 (3H, s, NMe-H), 2.0 (3H, s, Me-H).

7-Methoxy-1-(p-methoxyphenyl)-furo[3,4-b]pyridine-3(1H)-one (11), (71%) m.p. 162-163°C (benzene); (Found: C, 66.2; H, 5.0; N, 5.4. Calc. for $C_{15}H_{13}NO_4$: C, 66.5; H, 4.7; N, 5.2%); IR (KBr) 1760 cm^{-1} (CO); ^1H - NMR ($CDCl_3$) 8.7 (1H, d, J 5Hz, 5-H), 7.3 - 6.7 (5H, m, 6- and Ph-H), 6.3 (1H, s, 1-H), 3.8 (3H, s, OMe-H), 3.7 (3H, s, OMe-H).

4-Methoxy-3-(p-methoxyphenyl)-furo[3,4-c]pyridine-1(3H)-one (12), (62%) m.p. 127-129°C (benzene - heptane); (Found: C, 66.2; H, 4.9; N, 5.1. Calc. for $C_{15}H_{13}NO_4$: C, 66.5; H, 4.7; N, 5.2%); IR (KBr) 1780 cm^{-1} (CO); ^1H - NMR ($CDCl_3$) 8.3 (1H, d, J 5Hz, 6-H), 7.4 (1H, d, J 5Hz, 7-H), 7.2 - 6.7 (4H, m, Ph-H), 6.3 (1H, s, 3-H), 3.8 (3H, s, OMe-H), 3.7 (3H, s, OMe-H).

Hydrolysis of the Methylated Anilides (9a) and (10b)

(a) The methylated anilide (9a) or (10b) (0.005 mol) was heated to reflux with 4M hydrochloric acid (25 ml) for 7 h. On when the mixture cooled, the solvent was evaporated till dryness to give a solid residue. To the residue water (5 ml) was added and the solution was adjusted with potassium hydroxide to pH=8 and extracted with toluene. The aqueous layer was adjusted to pH=3.5 with hydrochloric acid, then water was removed under reduced pressure to give a yellowish solid compound, which was purified by crystallization.

3-Methyl-2-pyridone-4-carboxylic acid (13), (86%) m.p. 295-304°C (decomp.) (EtOH); (Found: C, 54.4; H, 5.1; N, 9.1. Calc. for $C_7H_7NO_3$: C, 54.5; H, 5.2; N, 9.1%); IR (KBr) 1680 cm^{-1} and 1620 cm^{-1} (CO); ^1H - NMR (CF_3COOH) 8.0 (1H, d, J 6Hz, 6-H), 7.4 (1H, d, J 6Hz, 5-H), 2.5 (3H, s, Me-H)

1,3-Dimethyl-4-pyridone-2-carboxylic acid (14), (94%) m.p. 190-192°C (decomp.) (EtOH); (Found: C, 57.7; H, 5.4; N, 8.3. Calc. for $C_8H_9NO_3$: C, 57.8; H, 5.4; N, 8.3%); IR (KBr) 1670 cm^{-1} and 1620 cm^{-1} (CO); ^1H - NMR (CF_3COOH) 8.5 (1H, d, J 6Hz, 6-H), 7.4 (1H, d, J 6Hz, 5-H), 4.3 (3H, s, NMe-H), 2.7 (3H, s, Me-H).

(b) The methylated anilide (9a) (0.004 mol) was treated with conc. hydrochloric acid (10 ml) and the formed suspension kept for 2 d at room temperature. The solid was filtered washed with water as colourless crystals of 1,3-dimethyl-4-pyridone-2-carboxanilide (15), (96%) m.p. 204-208°C; (Found: C, 69.3; H, 5.8; N, 11.4. Calc. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.8; N, 11.5%); IR (KBr) 1680 cm^{-1} and 1610 cm^{-1} (CO); ^1H - NMR (CF_3COOH) 9.5 (1H, s, NH-H), 8.45 (1H, d, J 6Hz, 6-H), 7.6 - 7.1 (6H, m, 5- and Ph-H), 4.1 (3H, s, NMe-H), 2.5 (3H, s, Me-H).

Hydrolysis of the Lactones (11) and (12)

The appropriate lactone (11) or (12) (0.0012 mol) was treated with 4M hydrochloric acid (5 ml) and heated to reflux for 3 h, and then evaporated till dryness to give the product after washing of the residue with acetone.

1-(p-Methoxyphenyl)-furo[3,4-b]pyridine-3,7(1H,4H)-dione (16), (84%) m.p. 265-270°C (decomp.); (Found: C, 65.4; H, 4.2; N, 5.3. Calc. for $C_{14}H_{11}NO_4$: C, 65.3; H, 4.3; N, 5.4%); IR (KBr) 1780 cm^{-1} and 1650 cm^{-1} (CO); ^1H - NMR (CF_3COOH) 8.8 (1H, d, J 6Hz, 6-H), 7.8 (1H, d, J 6Hz, 5-H), 7.4 - 6.8 4H, m, Ph-H), 6.7 (1H, s, 1-H), 3.8)3H, s, OMe-H).

3-(p-Methoxyphenyl)-furo[3,4-c]pyridine-1,4(3H,5H)-dione (17). (78%) m.p. 249-254°C (decomp.); (Found: C, 65.2; H, 4.4; N, 5.4. Calc. for $C_{14}H_{11}NO_4$: C, 65.3; H, 4.3; N, 5.4%);

IR (KBr) 1770 cm^{-1} and 1660 cm^{-1} (CO); ^1H - NMR (CF_3COOH) 7.9 (1H, d, J 6Hz, 6-H), 7.3 - 6.6 (5H, m, 7- and Ph-H), 6.5 (1H, s, 3-H), 3.8 (3H, s, OMe-H).

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