*Tetrahedron* Vol 47, No 9, pp 1697-1706, 1991
Printed in Great Britain

0040-4020/91 $3 00+00


# APPLICATION OF ORGANOLITHIUM AND RELATED REAGENTS IN SYNTHESIS. PART 9[1]. SYNTHESIS AND METALLATION OF 4-CHLOROPICOLIN- AND 2-CHLOROISONICOTIN-ANILIDES. A USEFUL METHOD FOR PREPARATION OF 2,3,4-TRISUBSTITUTED PYRIDINES

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(*Received in UK 27 July* 1990)

The synthesis and metallation (nBuLi) of 4-chloropicolin- and 2-chloroisonicotinanilides (1) and (2) as a way of regiospecific transformation of picolinic and isonicotinic acids into 2,3,4-trisubstituted pyridines (9) and (10), is described. The anilide moiety (masking group) of the formed $C^3$-substituted chloro-anilides (9) and (10) appeared to be effectively removable on acid hydrolysis.

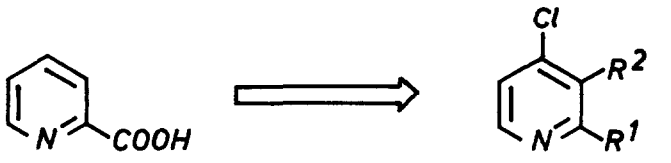
The current interest in ortho-substituted pyridine carboxylic acids as key starting materials for the preparation of numerous poly-heterocyclic compounds[2-16] including important natural products[3,8-10,13-15] has led us to examine methods for the synthesis of these systems.

Available methods of their preparation generally require total construction of the pyridine nucleus via divers multi-step reactions[19a]. More atractive route so far reported to ortho-substituted pyridine carboxylic acids is the directed lithiation of the amides[3-5,7-9,11,13,14,16] and (4,4-dimethyloxazolin-2-yl)-pyridine derivatives[2,6,10,12,15] (masked carboxylic acids) followed by reaction with electrophiles. However, most cases related only to specific instances.

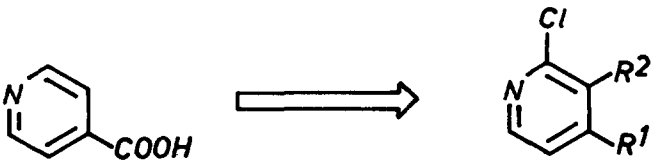
In a series of recent studies we have successfuly developed[1,7,11b,16] the transformation of the secondary picolin- and isonicotin-amides into $C^3$-substituted derivatives utilizing lithiation (nBuLi/THF) and subsequent electrophilic substitution with various electrophiles. This has promoted us to investigate

the lithiation of the chloro-pyridine carboxamides as an extension of the scope of our functionalization methodology centered around the regiospecific alkylation of the pyridine ring.

We now describe a novel efficient synthetic sequence for the transformation of the picolinic and isonicotinic acids into 2,3,4-trisubstituted pyridines (A) and (B).

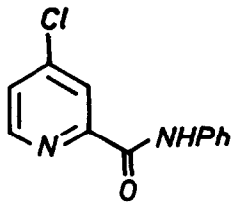



A




B

It has been demonstrated[11b,16a] that from amongst the secondary pyridine-carboxamides the N-phenyl-amides (anilides) are the most powerful directing group and that the anilide function should be considered the best choice for direct metallation of the masked picolin- and isonicotin-carboxylic acids.

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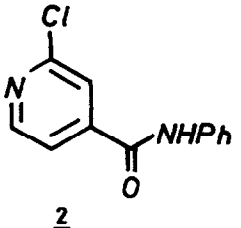


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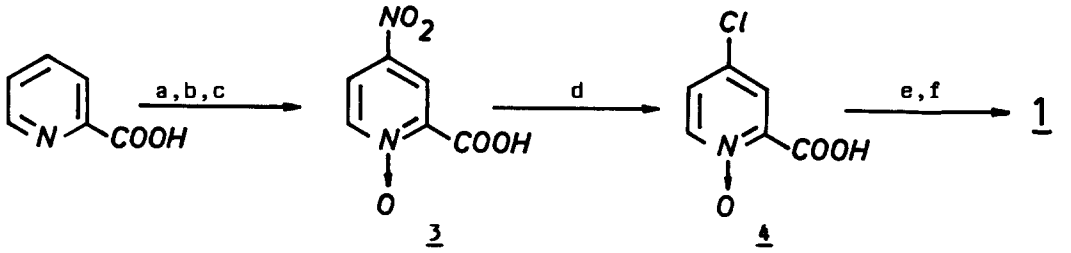
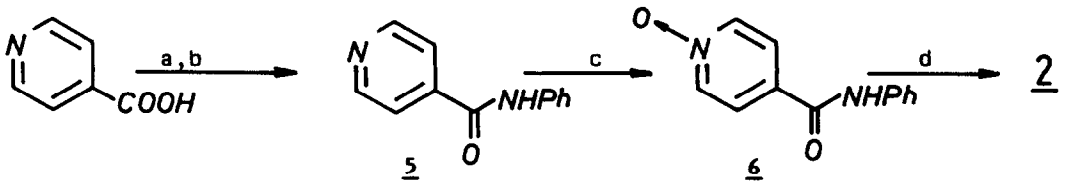
Therefore, in our first experiments, the preparation of the chloro-anilides (1) and (2) applying the corresponding acids as starting materials, was developed. The picolinic acid in the sequence of oxidation and nitration was converted into 4-nitropicolinic acid 1-oxide (3)[17], that on reaction with hydrogen chloride in methanol gave 4-chloropicolinic acid 1-oxide (4)[18]. The N-oxide (4) on reaction with phosphorus trichloride was reduced[19b], and chlorinated to give 4-chloropicolinoylchloride, which on reaction with aniline yielded 4-chloropicolinanilide (1). The 2-chloroisonicotinanilide (2) was prepared from isonicotinic acid as has been recently described[16b] via the sequence of the reactions depicted in the scheme.




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



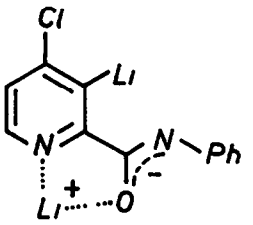

a) $SOCl_2$; b) $PhNH_2/Et_3N/CHCl_3$; c) $H_2O_2$/AcOH; d) $PCl_5/POCl_3$

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

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 chloro-anilides (1) and (2) reacted in THF with 2.1 mol equivalents of nBuLi (amide/-78°C/nBuLi/0.5h/or 0°C) were efficiently converted into the corresponding bis(N- and $C^3$-)lithiated chloro-anilides (7) and (8), as it has been demonstrated by the subsequent MeOD quenching (yield quantitative, independent of time 0.5 - 5h. and temperature -78°C - 20°C of lithiation) or reactions with electrophiles. The generated lithiated chloro-anilides appeared to be stable at room temperature, and no possible formation of pyridynes (at least by noticeable quantities), was observed. That differentiate them substantially from the lithiated meta-chloro masked carboxylic acids of the benzene series. It has been recently[20] demonstrated that the 2-lithio-3-(4,4-dimethyloxazolin-2-yl)chlorobenzene (generated at -78°C) on heating up to 0°C was converted into a benzyne.

A wide range of electrophiles was employed to react with the lithiated species. In each case, with one exception, this gave a single product in good yield. The lithiated chloro-anilides (7) and (8) reacted with an exces of MeI (3 mol equivalents mono produced mono- and/or di-methylated derivatives. Thus, the



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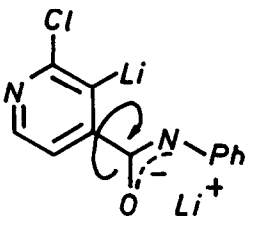

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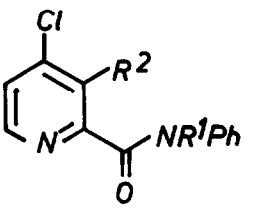

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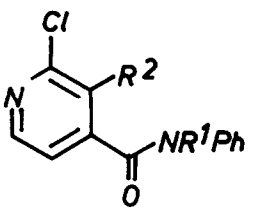
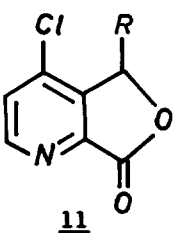


10

a: $R^1$= H, $R^2$= D; b: $R^1$= H, $R^2$= Me; c: $R^1$= $R^2$= Me; d: $R^1$= H, $R^2$= $SiMe_3$; e: $R^1$= H, $R^2$= CH(OH)Me; f: $R^1$= H, $R^2$= $CH(OH)C_6H_4OMe$-p; g: $R^1$= H, $R^2$= CHO



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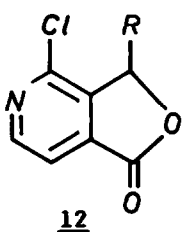

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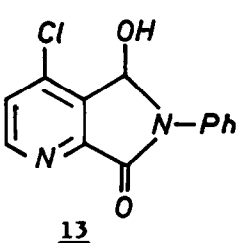
a: R = Me; b: R = $C_6H_4OMe$-p



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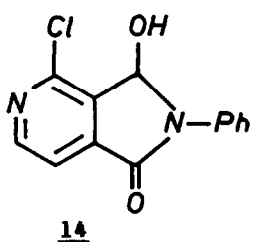
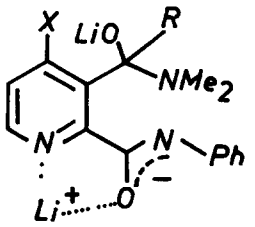


14

4-chloro-picolinanilide (1) gave mono-methylated product (9b) (64.8%), which was accompanied by di-methylated compound (9c) (19.2%). In the case of the 2-chloro-isonicotinanilide (2), entirely the di-methylated anilide (10c) (82.6%) was formed. In both cases (under the conditions used) MeI appeared to be inert towards N-alkylation of the pyridine nucleus. The lithiated species reacted with $Me_3SiCl$, MeCHO, p-$MeOC_6H_4CHO$ and DMF to give single product in each case;

silylated compounds (9d) (48%) and (10d) (61%), hydroxy products (9e), (10e), (9f) and (10f) and formyl-derivatives (9g) and (10g), respectively. The hydroxy products without isolation on acid - driven cyclization (25% - $H_2SO_4$ at room temperature) yielded the corresponding lactones (11a) (74.9%), (12a) (92.6%), (11b) (63.0%) and (12b) (59.4%). The formylated derivatives upon hydrolytic workup spontaneously cyclized into aza-isoindolinones (13) (46.0%) and (14) (80.6%).

The reaction of the bis-lithiated chloro-anilides (7) and (8) with N,N-dimethylbenzamide failed. That is in contrast with the recantly described effective benzoylation of the bis-lithiated anilides[16a]. It has been, as well, described[16a] that the formed adducts of the lithiated species across the carbonyl group of N,N-dimethylbenzamide (15c) and (16c) (formed via SET process[21]) are not stable at room temperature, and the slow retro cross - addition reaction has been observed. Therefore, the deficiency of the corresponding products which would be derived via hydrolytic workup of the adducts (15d) and (16d) could be accounted for by their extreme instability and/or impeding of their formation arising from steric hindrance caused by meta chlorine substituent of the bis-lithiated chloro-anilides (7) and (8)

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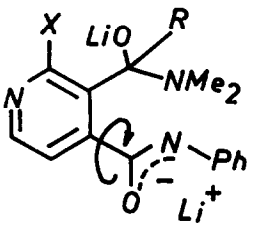
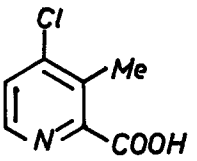



16

a. X= H, R= H; b X= Cl, R= H, c: X= H, R= Ph; d: X= Cl, R= Ph

The observed decreased yield in the transformation of the 4-chloropicolin-anilide (1) into the aza-isoindolinone (13) comparatively to very effective conversion of the 2-chloroisonicotinanilide (2) into (14), and independence of this process, in the cases of the picolin- and isonicotin-anilides, which formed the corresponding products[22] via the adducts (15a) and (16a), that is most probably due to the 2-pyridyl nitrogen atom; this provides a strong bidentate ligand for the lithium counter ion, that brings about the formation of the stable chelates (7) or (15). This especially increases steric hindrance around the C-Li bond of (7) and overcrowding for the adducts (15).

The described methodology relating to the introduction of the alkyl substituent at the 3-position of the 4-chloropicolin- and 2-chloroisonicotin-anilides shows considerable versatility for the regiospecific synthesis of the 2,3,4-trisubstituted pyridines. This coupled with the effective removal of the anilide

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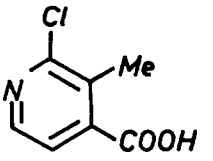


18

moiety on acid hydrolysis to the carboxylic acids and other functional groups should allow access to a wide variety of pyridines.

Thus, the methylated chloro-anilides (9b), (9c) and (10c) upon reaction with boiling sulphuric acid (50% - $H_2SO_4$) afforded the corresponding methylated acids (17) and (18). It has been found, that the silylated chloro-anilides (9d) and (10d) in the presence of potassium fluoride in boiling methanol were quantitatively proto - desilylated. This indicates that the introduction of the trimethyl silyl group at the 3-position of the chloro-anilides (1) and (2) could be recognized as a good blocking[23] readily removable group.

## 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. Electrophiles were purified by standard methods before use.

4-Chloropicolinanilide (1)

(a) 4-Nitropicolin acid-1-oxide (3) was prepared by the procedure of Profft and Steinke[17], m.p. 145-147°C (lit.[17], m.p. 148°C).

(b) 4-Chloropicolin acid-1-oxide (4). Through the boiling solution of N-oxide (3) (70.4 g, 0.4 mol) in methanol (900 ml) the stream of hydrogen chloride was passed for 5 h. On when the mixture cooled the whole lot was left overnight at room temperature. Then the solvent was evaporated till dryness. To the residue water (200 ml) and ice (100 g) were added and the mixture was made alkaline with $Na_2CO_3$, and extracted with $CHCl_3$. The layers were separated, then the water layer was acidified with hydrochloric acid. The precipitated solid crystallized from water as colourless crystals of 4-chloropicolin acid-1-oxide (4) (48.4 g, 69.4%), m.p. 141-143°C (lit.[18], m.p. 142°C). IR (KBr) 1680 $cm^{-1}$ (C=O); $^1H$ - NMR (DMSO) 8.6 (1H, d, J 5Hz, 6-H), 8.2 (1H, d, J 2Hz, 3-H), 7.8 (1H, dd, J 2 and 5Hz, 5-H).

(c) 4-Chloropicolinanilide (1). To the solution of N-oxide (4) (17.3 g, 0.1 mol) in $CHCl_3$ (100 ml) phosphorus trichloride (50 ml) was added, and the mixture was heated till boiling for 0.5 h.

Then from the cooled mixture, the solvent and excess of phosphorus trichloride were evaporated. To the residue $CHCl_3$ (100 ml) was added and stirred for 10 min. and the solvent evaporated till dryness. To the residue dissolved in $CHCl_3$ (100 ml) the mixture of aniline (30 ml) and triethylamine (60 ml) in $CHCl_3$ (30 ml) was added dropwise and left overnight. Then the whole lot was washed with 10% hydrochloric acid (100 ml) and water (200 ml). The organic layer was dried ($MgSO_4$) and evaporated till dryness. The residue was purified on column chromatograpgy (silica gel - $CHCl_3$). The solid product crystallized from heptane as colourless crystals of 4-chloropicolinanilide (1) (16.0 g, 68.8%), m.p. 92-94°C. (Found: C, 61.9; H, 3.9; N, 12.2; Cl, 15.2. Calc. for $C_{12}H_9N_2ClO$: C, 61.9; H, 3.9; N, 12.0; Cl, 15.2%); IR ($CHCl_3$) 1690 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 9.8 (1H, br.s, N-H), 8.4 (1H, d, J 5Hz, 6-H), 8.2 (1H, d, J 2Hz, 3-H), 7.8 - 8.1 (6H, m, 5- and Ph-H).

General Procedure for the Metallation - Electrophilic Substitution of the Anilides (1) and (2) To the anilide (1) or (2) (0.01 mol) in THF (50 ml) at -78°C nBuLi (0.022 mol) was added dropwise. The solution was held at -78°C for 0.5 h, and electrophile: MeOD (2 ml), MeI (0.033 mol), $Me_3SiCl$ (0.022 mol), MeCHO (0.033 mol), p-$MeOC_6H_4CHO$ (0.011 mol) of DMF (0.011 mol), was added. The mixture after 1 h at -78°C was allowed to rise to room temperature and stirred at this conditions for 1 h, and then water (5 ml) was added. To the mixture $CHCl_3$ (50 ml) was added, and the layers were separated and organic one dried ($MgSO_4$). The water layer after acidification (pH 1-2) with hydrochloric acid gave compounds (11a), (12a), (14) and part of (13), which then were purified by crystallization. From the organic layer the solvent was removed and the residue chromatographed by column chromatography (silica gel - benzene, chloroform and chloroform - ether 8:2) and gave products (9a), (10a), (9b), (9c), (10c), (9d), (10d) and additional part of (13), which were purified by crystallization. In the case of the hydroxy product (9f) or (10f), the formed residue after evaporation of the solvent was stirred with 25% sulphuric acid (30 ml) at room temperature for 3 days. Then the mixture was extracted with $CHCl_3$ (3 30 ml) and after separation of the layers, organic one evaporated till dryness, and formed lactones (11b) or (12b) was isolated by column chromatography (silica gel - benzene, chloroform, chloroform - ether 8:2) and then purified by crystallization.

4-Chloro-3-methylpicolinanilide (9b), (64.8%) m.p. 84-86°C (hexane); (Found: C, 63.3; H, 4.8; N, 11.0; Cl, 14.4. Calc. for $C_{13}H_{11}N_2OCl$: C, 63.3; H, 4.5; N, 11.3; Cl, 14.4%); IR ($CHCl_3$) 1685 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 10.0 (1H, br.s, N-H), 8.2 (1H, d, J 5Hz, 6-H), 7.8 - 7.0 (6H, m, 5- and Ph-H), 2.8 (3H, s, Me-H).

4-Chloro-3,N-dimethylpicolinanilide (9c), (19.2%) m.p. 72-74°C (hexane); (Found: C, 64.5; H, 5.3; N, 10.7; Cl, 13.5. Calc. for $C_{14}H_{13}N_2OCl$. C, 64.5; H, 5.0; N, 10.7; Cl, 13.6%); IR ($CHCl_3$) 1650 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 8.2 (1H, d, J 5Hz, 6-H), 7.0 - 6.7 (6H, m, 5- and Ph-H), 3.4 (3H, s, NMe-H), 2.3 (3H, s, Me-H).

2-Chloro-3,N-dimethylisonicotinanilide (10c), (82.6%) m.p. 75-77°C (hexane); (Found: C, 64.7; H, 5.1; N, 10.6; Cl, 13.3. Calc. for $C_{14}H_{13}N_2OCl$: C, 64.5; H, 5.0; N, 10.7; Cl, 13.6%); IR ($CHCl_3$)

1650 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 8.0 (1H, d, J 5Hz, 6-H), 7.5 - 6.7 (6H, m, 5- and Ph-H), 3.5 (3H, s, NMe-H), 2.5 (3H, s, Me-H).

4-Chloro-3-trimethylsilylpicolinanilide (9d), (48%) m.p. 85-87°C (hexane); (Found: C, 58.9; H, 5.4; N, 9.0; Cl, 11.5. Calc. for $C_{15}H_{17}N_2OClSi$: C, 59.1; H, 5.6; N, 9.2; Cl, 11.6%); IR (KBr) 1690 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 9.5 (1H, br.s, N-H), 8.3 (1H,d, J 5Hz, 6-H), 7.8 - 7.0 (6H, m, 5- and Ph-H), 0.5 (9H, s, $SiMe_3$-H).

2-Chloro-3-trimethylsilylisonicotinanilide (10d), (61%) m.p. 185-187°C (hexane - benzene 8:2), (Found: C, 51.9; H, 5.8; N, 9.4; Cl, 11.4. Calc. for $C_{15}H_{17}N_2OClSi$: C, 59.1; H, 5.6; N, 9.2; Cl, 11.6%); IR (KBr) 1660 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 8.6 (1H, d, J 5Hz, 6-H), 7.9 (1H, br.s, N-H), 7.7 - 7.0 (6H, m, 5- and Ph-H), 0.5 (9H, s, $SiMe_3$-H).

7-Chloro-1-methyl-furo[3,4-b]pyridine-3(1H)-one (11a), (74.9%) m.p. 143-145°C (acetone); (Found: C, 52.6; H, 3.4; N, 7.7; Cl, 19.2. Calc. for $C_8H_6NO_2Cl$: C, 52.3; H, 3.3; N, 7.7; Cl, 19.3%); IR ($CHCl_3$) 1785 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 8.7 (1H, d, J 5Hz, 5-H), 7.5 (1H, d, J 5Hz, 6-H), 5.6 (1H, q, J 7Hz, 1-H), 1.8 (3H, d, J 7Hz, Me-H).

4-Chloro-3-methyl-furo[3,4-c]pyridine-1(3H)-one (12a), (92.6%) m.p. 85-87°C (methanol - water); (Found: C, 52.6; H, 3.5; N, 7.6; Cl, 19.2. Calc. for C H NO Cl: C, 52.3; H, 3.3; N, 7.6; Cl, 19.3%); IR ($CHCl_3$) 1780 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 8.8 (1H, d, J 5Hz, 6-H), 7.6 (1H, d, J 5Hz, 7-H), 5.6 (1H, q, J 7Hz, 3-H), 1.9 (3H, d, J 7Hz, Me-H).

7-Chloro-1-(p-methoxyphenyl)-furo[3,4-b]pyridine-3(1H)-one (11b), (63.0%) m.p. 141-143°C (ethanol); (Found: C, 60.7; H, 5.7; N, 5.1; Cl, 12.8. Calc. for $C_{14}H_{10}NO_3Cl$: C, 61.0; H, 5.6; N, 5.1; Cl, 12.8%); IR ($CHCl_3$) 1790 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 8.7 (1H, d, J 5Hz, 5-H), 7.5 (1H, d, J 5Hz, 6-H), 7.0 - 6.6 (4H, m, Ph-H), 6.4 (1H, s, 1-H), 3.7 (3H, s, OMe-H).

4-Chloro-3-(p-methoxyphenyl)-furo[3,4-c]pyridine-1(3H)-one (12b), (59.4%) m.p. 160-162°C (ethanol); (Found: C, 61.7; H, 6.6; N, 5.2; Cl, 12.8. Calc. for $C_{14}H_{10}NO_3Cl$: C, 61.0; H, 3.6; N, 5.1; Cl, 12.8%); IR ($CHCl_3$) 1780 $cm^{-1}$ (C=O); $^1H$ - NMR ( $CDCl_3$) 8.6 (1H, d, J 5Hz, 6-H), 7.7 (1H, d, J 5Hz, 7-H), 7.3 - 6.8 (4H, m, Ph-H), 6.3 (1H, s, 3-H), 3.7 (3H, s, OMe-H).

7-Chloro-1-hydroxy-2-phenyl-pyrro[3,4-b]pyridine-3(1H)-one (13), (46.0%) m.p. 196-198°C (benzene); (Found: C, 59.7; H, 3.7; N, 10.5; Cl, 13.5. Calc. for $C_{13}H_9N_2O_2Cl$: C, 59.9; H, 3.5; N, 10.7; Cl, 13.6%); IR (KBr) 1700 $cm^{-1}$ (C=O); $^1H$ - NMR (DMSO) 8.7 (1H, d, J 5Hz, 5-H), 8.0 - 6.9 (7H, m, 6-, OH- and Ph-H), 6.6 (1H, d, J 10Hz, 1-H).

4-Chloro-3-hydroxy-2-phenyl-pyrro[3,4-c]pyridine-1(3H)-one (14), (80.6%) m.p. 145-146°C (benzene); (Found: C, 60.2, H, 3.6; N, 10.5; Cl, 13.7. Calc. for $C_{13}H_9N_2O_2Cl$: C, 59.9; H, 3.5; N, 10.7; Cl, 13.6%); IR (KBr) 1680 $cm^{-1}$ (C=O); $^1H$ - NMR (DMSO) 8.7 (1H, d, J 5Hz, 6-H), 8.0 - 7.0 (7H, m, 7-, OH- and Ph-H), 6.6 (1H, d, J 10Hz, 3-H).

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

The methylated anilide (9b) or (10c) was heated to reflux in 58% sulphuric acid for 4h. On when the mixture cooled, the whole lot was poured on to ice.

(a) Hydrolysis of the anilide (9b); The mixture was adjusted with $Na_2CO_3$ to pH = 3.6 and continuously extracted with $CHCl_3$, then the layers were separated. From the organic layer the solvent was evaporated and the formed residue after crystallization from heptane gave colourless crystals of 4-chloro-3-methylpicolinic acid (17), (71%) m.p. 164-166°C; (Found: C, 49.3; H, 3.6; N, 8.3; Cl, 20.8. Calc. for $C_7H_6NO_2Cl$: C, 49.0; H, 3.5; N, 8.2; Cl, 20.6%); IR (KBr) 1700 $cm^{-1}$ (C=O); $^1H$ - NMR ($CDCl_3$) 9.8 (1H, br.s, COOH-H), 8.4 (1H, d, J 5Hz, 6-H), 7.6 (1H, d, J 5Hz, 5-H), 2.8 (3H, s, Me-H).

(b) Hydrolysis of the anilide (10c); The mixture was made alkaline with $Na_2CO_3$ and impurity was filtered off. The filtrate was acidified (pH = 3.6). The precipitated solid after crystallization from ethanol gave colourless crystals of 2-chloro-3-methylisonicotinic acid (18), (65%) m.p. 230-232°C; (Found: C, 49.2; H, 3.6; N, 8.3; Cl, 20.3. Calc. for $C_7H_6NO_2Cl$: C, 49.0; H, 3.5; N, 8.2; Cl, 20.6%); IR (KBr) 1720 $cm^{-1}$ (C=O); $^1H$ - NMR (DMSO) 8.6 (1H, d, J 5Hz, 6-H), 7.8 (1H, d, J 5Hz, 5-H), 2.6 (3H, s, Me-H).

Proto - desilylation of the Silylated Anilides (9d) and (10d)

The appropriate silylated anilide (9d) or (10d) (0.001 mol) and 0.3g of potassium fluoride in methanol (10 ml) was heated till boiling for 10h. Then the solvent was removed and the formed residue washed with water to give the anilides (1) or (2). The m.p., mixed m.p., IR and $^1H$ - NMR spectra indicated for the anilide (1) or (2), respectively.

Acknowledgment. We are grateful to the Polish Academy of Sciences for support of this work (Grant CPBP 01.13).

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