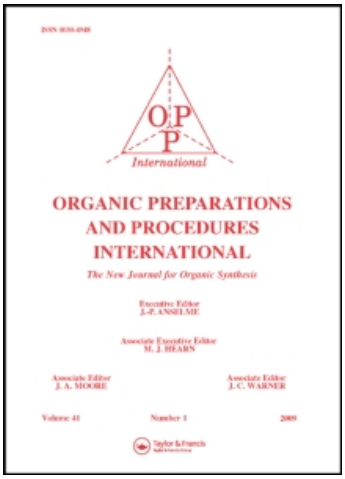

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IMPROVED PROCEDURES FOR PREPARATION OF 4-HYDROXY- AND 2-AMINO-4-METHOXY-2-AMINOPYRIDINES

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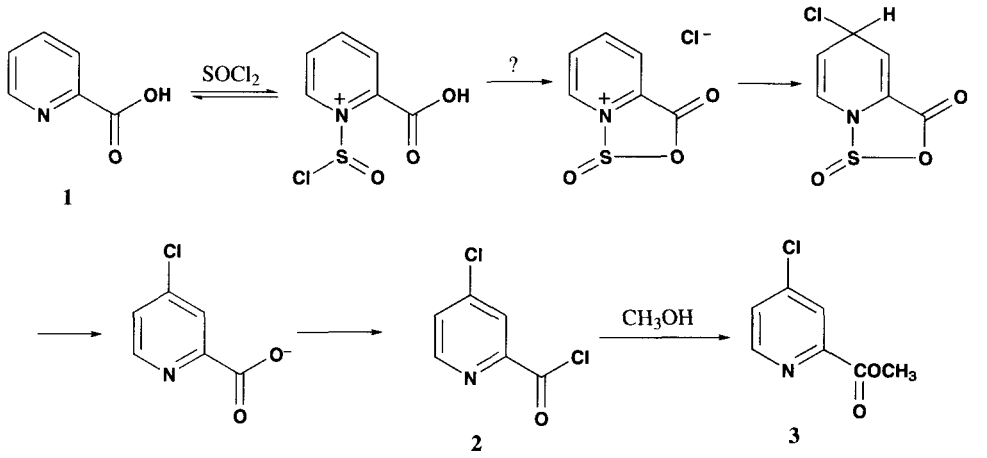
There are few synthetic approaches to 4-alkoxy and/or 4-hydroxy derivatives of 2-aminopyridine.[1] The most direct route begins with the conversion of picolinic acid (**1**) to 4-chloropicolinyl chloride (**2**) by reaction with thionyl chloride.[2] However, the original procedure involves a 10 day reflux period. In 1955, the use of thionyl chloride saturated with sulfur dioxide was reported to reduce the reaction period to 4 days.[3] Most subsequent reports, however, have used the older procedure,[4] with one exception.[5] Consideration of the mechanism by which this reaction occurs suggested that it must involve a nucleophilic addition and a redox process, perhaps involving a cyclic anhydride (**Scheme 1**).



Scheme 1

It was reasoned that the addition of sodium bromide or sodium iodide might facilitate the reaction. This proved to be the case as indicated by yields of the methyl ester **3** given in Table 1. Upon the addition of a catalytic amount (10 mol %) of sodium bromide, the reaction time decreased dramatically from 10 days to less than one day (Entry 1). Increasing the amount of sodium bromide to two equivalents resulted in the reaction being complete in 4 hours (Entry 2). Interestingly, no bromo

substituted product was found. The failure to observe of addition of bromide to the pyridine ring may be attributed to the presence of excess of chloride (about 4.8 fold), the likelihood that halide exchange can occur at the dihydropyridine stage and the presumed greater thermodynamic stability of the chloro adduct. Similarly, addition of catalytic amount of thionyl bromide also accelerated the reaction (Entry 3). This suggested that the active catalytic species might be thionyl bromide. However, use of neat thionyl bromide as reaction media produced little product.[6] Addition of sodium iodide to the reaction did not result in improvement for the reaction in terms of yield and efficiency (Entries 4 and 5). However in this case, a significant amount (37%) of methyl 2,4-dichloropicolinate was obtained in addition to the monochloro substituted product.

On the basis of these results, a convenient procedure for the preparation of 4-chloropicolinyl chloride was devised. For reactions on a 0.2 mole scale, picolinic acid was heated to reflux in excess thionyl chloride in the presence of 5-10 mol % of sodium bromide for 16-24 hours. Evaporation of excess thionyl chloride gave the product as a reddish solid. These conditions provided product which could be used in subsequent steps without further purification.

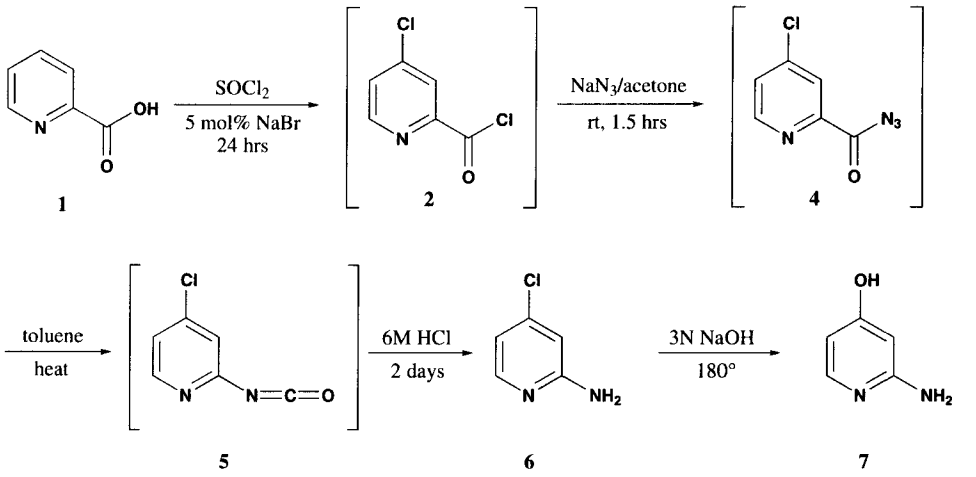
Table 1. Chlorination of Picolinic Acid with Thionyl Chloride

Entry	Catalyst	Amount (equiv.)[a]	Time (hrs)	Yield **3** (%)[b]	Unreacted **1** (%)[b]
1	NaBr	0.10	21	82	6
2	NaBr	2.00	4	88	4
3	$SOBr_2$	0.10	27	77	5[c]
4	NaI	0.05	76	36	4[d]
5	NaI	2.00	27	21	22

a) Molar equivalent. b) Isolated as the methyl ester. c) 5% methyl 2,4-dichloropicolinate was isolated. d) 37% methyl 2,4-dichloropicolinate was isolated.

The second step in the original sequence to 4-hydroxy-2-aminopyridine is a Curtius rearrangement of the azide obtained by nitrosation of 4-chloropicolinoylhydrazide.[2] We found that the acid chloride from the first step is sufficiently pure to be reacted directly with sodium azide. The acyl azide was then rearranged to isocyanate upon heating in toluene. Hydrolysis of the isocyanate in acidic media produced 4-chloro-2-aminopyridine in 61% overall, which is sufficiently pure for the final step in the sequence, the displacement of the chloride by hydroxide according to the procedure reported by Barlin and Pfleiderer.[4a] 4-Methoxy-2-aminopyridine can be prepared using same method.[1]

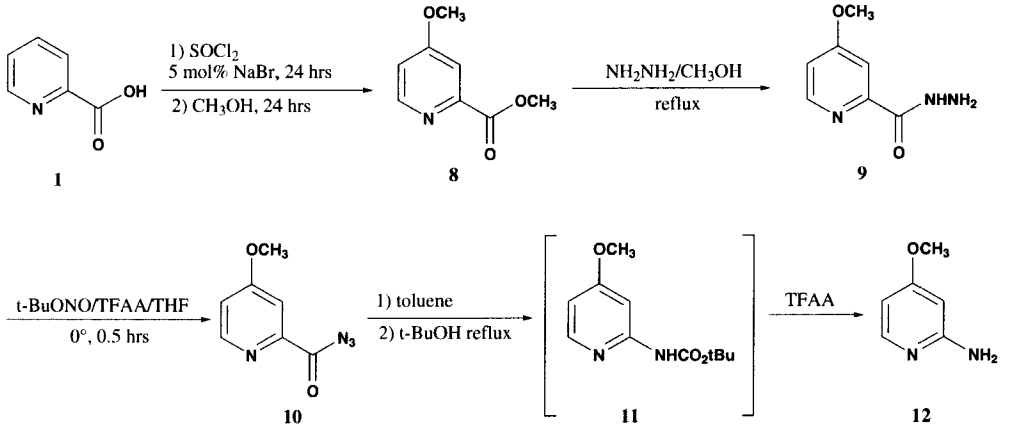
Although these procedures provide a satisfactory method for the preparation of 4-hydroxy/alkoxy-2-aminopyridines, the last step requires the use of a pressure reactor which limits its application. Conceivably, if the displacement of chloride with the alkoxy group was performed prior to the conversion of the carboxylic acid group to the amino group, the displacement might proceed more readily because of the nucleophilic nature of the substitution. Therefore, we explored a different approach for the preparation of 4-alkoxy-2-aminopyridines (**Scheme 3**). The 4-chloropicolinyl chloride



1 2 4 5 6 7

Scheme 2

was converted to methyl 4-methoxypicolinate (**8**) in refluxing methanol, and the resulting methyl ester was then converted to an acyl hydrazide. Nitrosation of the acyl hydrazide using *t*-butyl nitrite,[7] followed by Curtius rearrangement produced 4-methoxy-2-aminopyridine in 67% overall yield. Similarly, ethyl 4-ethoxypicolinate was prepared from picolinic acid in 52% yield, and conveniently transformed to 4-ethoxy-2-aminopyridine[1b] using the above procedure.



1 8 9 10 11 12

Scheme 3

In summary, the 4-chlorination of picolinic acid has been improved dramatically in this work. The reaction product was used to prepare 4-alkoxy and/or 4-hydroxy derivatives of 2-aminopyridines efficiently.

EXPERIMENTAL SECTION

Except for THF, solvents and reagents were used as supplied from commercial sources. THF was distilled from benzophenone sodium ketyl. Chromatography was performed using 230-400 mesh

silica gel. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were determined at 75 MHz. Chemical shifts are relative to TMS.

Chlorination of Picolinic Acid and Isolation Methyl 4-Chloropicolinate 3.- A mixture of picolinic acid (1.23 g, 10 mmol) and of the catalyst (Table 1) in thionyl chloride (5 mL) was heated to reflux for 4-76 hours. The solvent was evaporated under aspirator pressure. Absolute methanol (10 mL) was added and the mixture was stirred at rt for 0.5 hr. The methanol was evaporated, and the residue was taken up in 5% $NaHCO_3$ (25 mL) and extracted with EtOAc (3x25 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 to 10% acetone in CH_2Cl_2). The yields are given in Table 1. The product can further purified by recrystallization from ether to give white crystals, mp. 58-59.5°, lit.[3] mp. 57-58°. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, J = 5.4 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.44 (dd, J = 1.8, 5.4 Hz, 1H), 4.01(s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 165.1, 151.1, 149.7, 145.9, 127.6, 126.1, 53.7; IR (KBr): 1719 cm^{-1}; MS (Cl, methane): 172 (100, m+1), 174 (45).

Preparative Procedure for 4-Chloro-2-aminopyridine (6).- A mixture of picolinic acid (24.6 g, 0.2 mol), sodium bromide (1.03 g, 0.01 mol) and thionyl chloride (70 mL, 0.96 mol) in a 250 mL round bottom flask equipped with a calcium chloride drying tube was heated to reflux in an oil bath. A rapid evolution of HCl and SO_2 occurred. After 24 hrs, the ^{1}H NMR of a reaction sample (the acyl chloride was converted to its methyl ester) indicated the completion of the reaction. The excess thionyl chloride was distilled off under reduced pressure. The reddish liquid was dissolved in anhydrous ether (30 mL) and added slowly to a stirred suspension of sodium azide (14.31 g, 0.22 mol) in dry acetone (500 mL) in 15 min at 0°. After being stirred at rt for 1.5 hrs, the mixture was filtered, and the filter cake was washed with dry acetone. Acetone was evaporated under reduced pressure at rt to afford the acyl azide as a yellow solid (38.5 g). **CAUTION**: ***While we have experienced no problems with normal handling of this azide, it should be presumed to be potentially explosive***. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.68 (d, J = 5.1 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.85 (dd, J = 1.8, 5.1 Hz, 1H).

The crude acyl azide was heated in toluene (200 mL) at 55° for 15 hrs and then refluxed for 2 hrs. The toluene was removed by vacuum distillation. The dark residue was refluxed with 6M HCl (200 mL) for 2 days. The reaction was cooled to rt, and solid NaOH (approximately 60 g) was added portionwise to adjust pH > 12. The brown solid was collected, dried *in vacuo* and triturated several times with ether and the ether was evaporated to give **6** as a yellow solid (15.1 g). The aqueous filtrate from the original isolation was extracted with ether (4x50 mL). The ether was dried over $MgSO_4$, and evaporated to give an additional 0.6 g of product (overall 61% from picolinic acid). The crude product is pure enough for the next step. The pure product can be obtained as a white solid, mp. 133-134°, lit.[2] 130-131° by purification using column chromatography (silica gel, ether). IR (KBr): 3450, 3290, 3250, 1628, 1599, 1586, 1543, 1485, 1431, 1253, 1097, 987, 910, 850, 796, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 5.4 Hz, 1H), 6.65 (dd, J = 1.8, 5.4 Hz, 1H), 6.50 (d, J = 1.8 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 149.5, 145.5, 115.0, 108.7.

4-Hydroxy-2-aminopyridine (7).- Crude 4-chloro-2-aminopyridine (7.71 g, 60 mmol) in 3N NaOH solution (300 mL) was heated in a stainless steel autoclave at 180° for 20 hrs. The reaction was cooled to rt and neutralized to pH = 7 using concentrated HCl (approximately 80 mL). The reaction mixture was concentrated to about 100 mL, and the salt was filtered out and washed with methanol. The filtrate was then evaporated to dryness. The white residue was triturated with absolute ethanol (300 mL, and 2x100 mL) with vigorously stirring, filtered and the ethanol was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% MeOH in CH_2Cl_2) to afford **7** (5.61 g, 85 %) as white needles from ethanol, mp 187-188°C, lit. 181.5-182.5°.[4a] ^{1}H NMR(300 MHz, DMSO-d_6): δ 7.42 (d, J = 6.3 Hz, 1H), 5.81 (dd, J = 2.4, 6.3 Hz, 1H), 5.70-5.50 (m, 3H), 3.26 (s, OH); ^{13}C NMR (75 MHz, CD_3OD) δ 180.0, 134.8, 132.2, 110.8, 95.9.

Methyl 4-Methoxypicolinate (8).- A mixture of picolinic acid (24.6 g, 0.2 mol), sodium bromide (2.06 g, 0.02 mol) and thionyl chloride (70 mL, 0.96 mol) in a 250 mL round bottom flask equipped with a calcium chloride drying tube was heated to reflux in an oil bath for 13 hrs. The excess thionyl chloride was distilled off under aspirator pressure. Methanol was added cautiously to the reddish residue (40 mL) at 0° and the mixture was then heated to reflux. After 36 hrs, the methanol was evaporated and residue was neutralized with saturated $NaHCO_3$ (approximately 100 mL), and the aqueous solution was extracted with EtOAc (3x75 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by the flash column (SiO_2, first eluted with ether then 5% CH_3OH in CH_2Cl_2) to offer 12.93 g (73%) of product as a light yellow solid, mp 48-50°, lit.[8] 47-50°. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 2.4, 5.5 Hz, 1H), 4.01 (s, 3H), 3.92(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 166.2, 151.4, 150.1, 113.6, 111.7, 56.0, 53.5; MS (CI, methane) 168 (m+1).

4-Methoxypicolinic Acid Hydrazide (9).- A mixture of methyl 4-methoxypicolinate (4.45 g, 26.6 mmol) and anhydrous hydrazine (1.25 mL, 39.9 mmol) in methanol (20 mL) was heated to reflux. After 6 hrs, the reaction mixture was cooled to rt, and then in an ice bath. A white precipitate was collected by vacuum filtration and dried (4.14 g, 93%), mp 155-157°, lit.[5] 152-154°. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (s, 1H), 8.33 (d, J = 5.7 Hz, 1H), 7.69 (d, J = 2.7 Hz, 1H), 6.92 (dd, J = 2.4, 5.4 Hz, 1H), 4.07 (s, 1H), 3.91(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 165.1, 151.5, 150.0, 113.6, 108.1, 56.1; IR (KBr): 3306, 3294, 3208, 1677cm^{-1}; MS(CI, methane): 168 (m+1).

4-Methoxy-2-aminopyridine.- To a suspension of 4-methoxypicolinic acid hydrazide (1.67 g, 10 mmol) in THF (20 mL) was added trifluoroacetic acid (0.77 mL, 10 mmol) at 0°, followed by the slow addition of *t*-butyl nitrite (3.6 mL, 30 mmol). The solution became clear and a light yellow precipitate was formed within minutes. After stirring at 0° for 30 min, the solvent was evaporated. Toluene (20 mL) was added and the mixture was refluxed for one hour. *t*-Butanol (2.5 mL, 26 mmol) was added through the top of the condenser and the reaction was refluxed further for 10 hrs. The solvent was evaporated. Toluene (20 mL) and trifluoroacetic acid (1 mL) were added to the dark residue and the mixture was refluxed for 5 hrs. The solvent was evaporated and the residue was purified by flash column (SiO_2, 10-20% CH_3OH in CH_2Cl_2) to offer white crystals (0.83 g, 67%) from ether, mp 119-121°, lit.[4b] 116-

117°: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 5.7 Hz, 1H), 7.27 (dd, J = 2.4, 5.7 Hz, 1H), 5.98 (d, J = 2.4 Hz, 1H), 4.38 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 160.8, 149.7, 103.0, 92.9, 55.3; IR (KBr): 3461, 3298, 3127(OH) cm^{-1}; MS(CI, methane): 125 (m+1).

Ethyl 4-Ethoxypicolinate.- A mixture of picolinic acid (12.3 g, 0.1 mol), sodium bromide (1.03 g, 0.01 mol) and thionyl chloride (35 mL, 0.48 mol) in a 100 mL round bottom flask equipped with a calcium chloride drying tube was heated to reflux in an oil bath for 16 hrs. The excess thionyl chloride was distilled off under aspirator pressure. Absolute ethanol (20 mL) was added cautiously to the reddish residue at 0° and the mixture was then heated to reflux. After 24 hrs, the ethanol was evaporated and residue was neutralized with saturated $NaHCO_3$ and the aqueous solution was extracted with EtOAc (4x75 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by the flash column (SiO_2, ether) to provide 10.24 g (52%) of product as a light yellow oil, lit. bp. 127° (1.3 mm).[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, J = 5.7Hz, 1H), 7.65(d, J = 2.7Hz, 1H); 6.94 (dd, J = 2.7, 5.1 Hz, 1H), 4.47 (q, J = 7.0 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 165.7, 151.4, 150.3, 113.7, 112.1, 64.5, 62.4, 14.8, 14.7; IR (neat): 1719cm^{-1}; MS(CI, methane): 196 (m+1).

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