A SIMPLE ACCESS TO KEY PYRIDINE BUILDING BLOCKS

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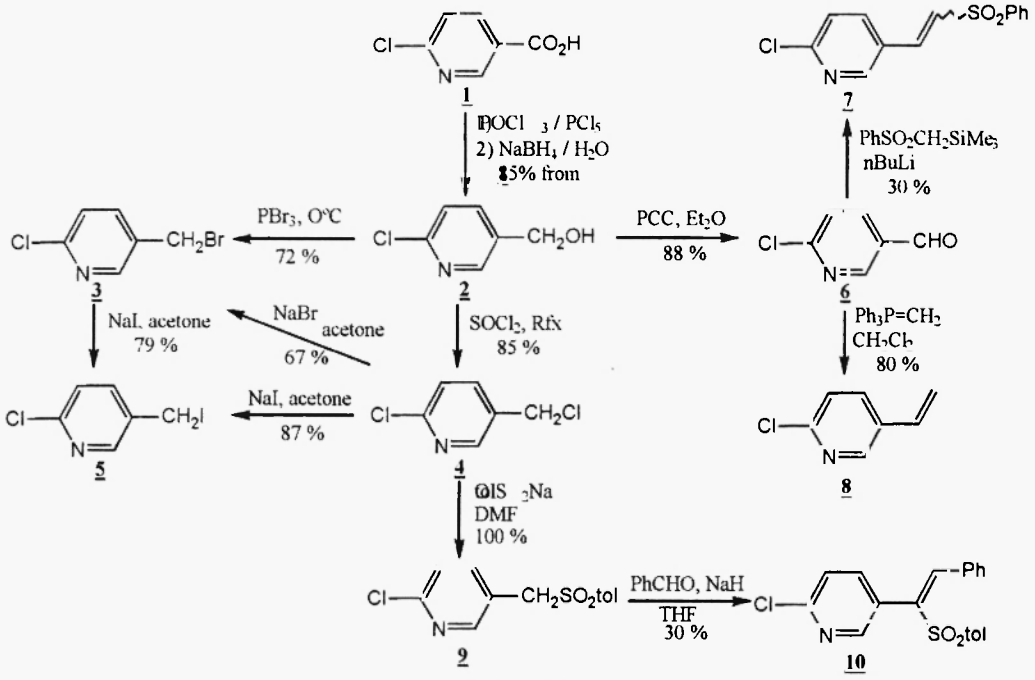
Abstract : A wide variety of 2,5-disubstituted pyridines were synthetized in good yield, using 6-chloronicotinic acid 1 as starting material. These pyridines are useful in the field of the pesticide industry, as well as in medicinal chemistry.

Introduction : Substituted pyridines can be considered as key building blocks because of their wide use in heterocyclic chemistry, complex chemistry and industrial chemistry. Furthermore, 2,5-disubstituted pyridines are useful precursors to pharmacological compounds (1,2) and recently retained much attention as taking part of natural products syntheses like epibatidine (3,4), nicotinic derivatives (5,6) or aritenoids (7). They can also be use in industrial chemistry (e.g. pesticides), as well as in the field of liquid crystals depending on their physicochemistry (8).
We describe herein a simple access to many different 2,5-disubstituted pyridines. While many routes to 2,4- or 2,6-disubstituted pyridines are often described in the literature (9,10), syntheses of 2,5-disubstituted pyridines have been far less developed. Some 2,5-disubstituted pyridines have already been described in the literature (4,6,7,11,12,13,14). However most of these compounds require for their preparation many steps with no yields mentioned for some of them. We present now alternative routes with improved yields and very easy access.

Results : Using 6-chloronicotinic acid 1 as starting material, we have been able to build many 2,5-disubstituted pyridines (compounds 2 - 16), which are potentially useful tools because of their diversity. We can classify the pyridine derivatives synthetized here into two categories, having either a chloro or a methoxy function at position 2. Position 5 encompasses many different functions like halogenomethyl, carbonyl, carboxyl and ethylenyl.
For the 2-chloropyridine series (Scheme 1), 6-chloronicotinic acid 1 was efficiently transformed into the corresponding acylchloride with $POCl_3/PCl_5$ and then reduced with $NaBH_4$ to give the methylalcohol 2 in 85% overall yield.

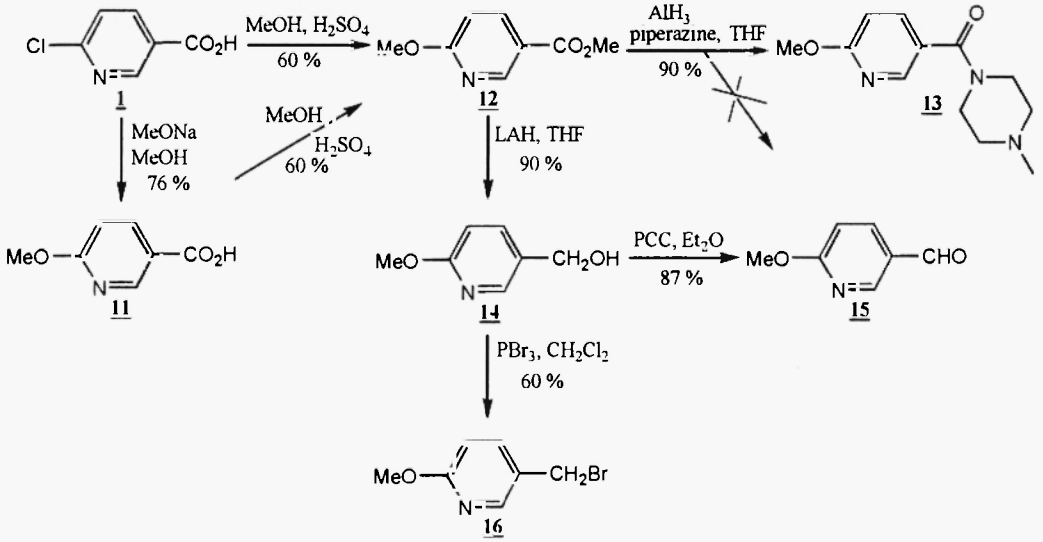
Methylalcohol 2 was converted into the corresponding bromomethylpyridine 3 with PBr_3 in CH_2Cl_2 in 72% yield. It could also be made from chloromethylpyridine 4 (synthesized from alcohol 2 using $SOCl_2$ in 85% yield) by treating it with NaBr in acetone in 67% yield. The iodomethyl analogue 5 was formed in good yield by treatment of either the bromomethyl derivate 3 (79%) or the chloromethyl 4 (87%) with NaI in acetone. Iodomethylpyridine 5 has not been described in the literature so far while bromomethylpyridine 3 has been prepared in 5 steps from β-picolin with no yield mentioned (13). Chloromethyl derivative 4 is of much interest and is used in the chemistry of pesticides. Its structure has been already described in two patents (15), but in more steps and lower yields. We propose here a very facile access to halogenomethylpyridines which are known to polymerize under other experimental conditions.
We also have developed access to the tolylsulfone building block 9 not described in the literature so far by treating chloromethylpyridine 4 with para-toluene sodium sulfinate in DMF, in quantitative yield.

The methylalcohol **2** was oxidized with PCC/Et_2O to give the aldehyde **6** in 88% yield. This aldehyde has already been described in the literature made either by chlorination of nicotinic acid **1**, using (i) $PCl_5/POCl_3$, (ii) $NaBH_4$, (iii) DMSO, TFA (33% yield) (16) or MnO_2 (70% yield) (10) , either by reduction of acid **1** followed by oxidation of the resulting alcohol using a sequence (i) LAH, (ii) PCC (55% yield) (17). Thus the route we describe here gave a superior yield (76% overall yield), which makes it competitive compared with other syntheses.



SCHEME 1

The aldehyde **6** can be transformed into a vinylsulfone by a Peterson like reaction (18) to give **7** in 30% yield (mixture of 2/1 *trans/cis* isomers). Although the yield was not excellent even after numerous attempts, it was the only method which would gave the desired product. Such compounds have not been described so far in the literature, probably because of the competitive substitution of the chlorine with lithiated bases (19).



SCHEME 2

The aldehyde 6 reacted with $Ph_3P=CH_2$ to give vinylpyridine 8 by a Wittig reaction (18,20) in 80% yield. Synthesis of compound 8 from 1 has been described in the literature using a sequence (i) LAH, (ii) PCC, (iii) Ph_3PCH_3Br, but the yield was not as high (33%) (21).
Tosylmethylchloropyridine 9 was deprotonated with NaH in THF and reacted with benzaldehyde to give after spontaneous deshydratation the olefine 10 as a single isomer in 30% yield. Configuration of the double bond in 10 have not been determined. Once again, the preparation of this kind of olefine proved to be very critical, because of numerous side reactions. In this case, the success of the reaction closely depended on the choice of reactants and solvents.

For the 2-methoxypyridine series (Scheme 2), some of these reactions were applied similarly using 6-methoxynicotinic acid 11. This compound derived from 6-chloronicotinic acid 1, with NaOMe in MeOH in 76% yield. By refluxing the acid 11 in MeOH with H_2SO_4, the methyl ester 12 was obtained in 60% yield. The methyl ester 12 can also be obtained in one single step by refluxing chloronicotinic acid 1 in a solution of 5% H_2SO_4/MeOH in 60% yield. We first wanted to synthetize aldehyde 15 in one single step by treating ester 12 with aluminium hydride and piperazine. Instead, the amide 13 was obtained in almost quantitative yield as a competitive reaction. So the ester 12 was then reduced with lithium aluminium hydride in THF to give the corresponding alcohol 14 in 90 % yield, and oxidation with PCC gave aldehyde 15 in 87% yield. Compounds 11, 12 and 14 have been described in the literature but to our knowledge with more steps and lower yields (14). Compound 15 has been described in the literature using 2,5-dibromopyridine as starting material following the sequence (i) MeONa/MeOH and (ii) DMF/BuLi (12). Following this procedure and despite many attempts, it was not possible to isolate the desired aldehyde in good yields. The alternative method we propose is of easy access and reproductible.
Also, bromination of alcohol 14 with PBr_3 in CH_2Cl_2 at 0°C afforded the bromomethyl pyridine 16 in 60% yield. All these compounds constitute useful tools for heterocyclic chemistry because of their methoxy function which allows many transformations of the pyridine ring.
However, halogenomethyl pyridines 3 to 5 and 16 are very irritant due to a similarity to nicotinic derivatives.

Experimental: Melting points were taken on a Kofler Hot Stage apparatus and are corrected. Mass spectra were measured on AEI MS-50 instrument. Evaporations were carried out on a rotary vacuum evaporator. 6-chloronicotinic acid was purchased from Fluka.

2-Chloro-5-hydroxymethyl pyridine 2 :
6-chloronicotinic acid 1 (1g, 6.34 mmoles, 1 eq) was introduced into a 10 ml flask and a solution of 1.45 g (7 mmoles, 1.1 eq) of PCl_5 in 10 ml of $POCl_3$ was then added. The reaction was heated under reflux during 1 hour until gas evolution ceased. The solvent was evaporated under reduced pressure and the corresponding acylchloride was obtained as a yellow brown solid. The solid was added slowly to a 40 ml cold aqueous solution of 880 mg of $NaBH_4$ and stirred overnight at room temperature. The slurry was then saturated with brine and the aqueous phase extracted three times with 20 ml CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure to give 775 mg of 2 as colourless crystals which can be crystallized from heptane (85% yield).
^1H nmr ($CDCl_3$, δ, ppm) : 8.30 (d, 1H, J = 2.1 Hz), 7.65 (dd, Ja = 2.3 Hz, Jb = 8.7 Hz), 7.20 (d, J = 8.6 Hz, 1H), 4.65 (s, 2H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 150.3, 148.0, 137.8, 135.4, 124.2, 61.6. ms (EI) m/z : 146/144 (M^+, 65/100) ; 110 (58). ir (ν, cm^{-1}) : 3400, 1620.
2-chloro-5-bromomethyl-pyridine 3 :
In a 10 ml flask under argon were introduced 517 mg (3.6 mmoles, 1 eq) of hydroxymethylpyridine 2, and 3 ml of dry CH_2Cl_2. The solution was cooled to 0°C and 0.24 ml (0.7 eq) of PBr_3 were slowly added. The slurry was then allowed to warm up to room temperature. Stirring was maintained for 12 hr. The reaction was quenched by adding 2 ml of a aqueous solution of saturated Na_2CO_3. The organic layer was separated and the aqueous phase extracted twice with 5 ml of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. After filtration through a plug of silica, (eluent CH_2Cl_2), 534 mg of 3 as a white solid were obtained (72% yield).
The same procedure was used starting with 5-chloromethyl-2-chloro-pyridine 4, and 2-bromomethylpyridine 3 was obtained in 67% yield.
mp : 49°C (heptane). ^1H nmr ($CDCl_3$, δ, ppm): 8.35 (d, J = 3.0, 1H), 7.50 (dd, Ja = 3.1 Hz, Jb = 9.5 Hz, 1H), 7.35 (d, J = 9.4 Hz, 1H), 4.44 (s, 2H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 149.6, 149.0, 139.5, 133.6, 124.5, 28.5. ms (CI) m/z = 264 (M + 58) ; 206/208. ir (ν, cm^{-1}): 3070, 2320. Analyses. Calcd for C_6H_5NBr : C 34.90, H 2.44, N 6.78. Found C 34.99, H 2.36, N 6.78.
2-chloro-5-chloromethyl pyridine 4 :
570 mg (4 mmoles, 1eq) of 2 were introduced under argon in a 10ml flask and dissolved in 2 ml of anhydrous toluene. Then, 1.5 ml (6 eq) of thionylchloride was added at 0°C and the mixture stirred at room temperature for 24 h. Solvent was evaporated under reduced pressure and the resulting solid was crystallized from heptane to give 560 mg of 4 as white crystals (85% yield).

mp : 34-35°C (heptane). ^{1}H nmr ($CDCl_3$, δ, ppm) : 8.40 (d, J = 2.5 Hz, 1H), 7.70 (dd, Ja = 2.4 Hz, Jb = 12.0 Hz, 1H), 7.30 (d, J = 2.5, 1H), 4.55 (s, 2H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 151.3, 149.2, 139.2, 132.4, 124.5, 42.0. ms (EI) m/z = 160/162 (M^+, 87/56), 124/126 (M^+ - Cl, 100/96). ir (ν, cm^{-1}): 1650, 701. Analyses. Calcd for $C_6H_5NCl_2$: C 44.48, H 3.11, N 8.64. Found C 44.26, H 3.25, N 8.47.

2-chloro-5-iodomethyl-pyridine 5 :

470 mg of 4 (2.9 mmoles, 1 eq), and 652 mg (4.35 mmoles, 1.5 eq) of sodium iodide were introduced in a 25 ml flask, and dissolved in 10 ml of acetone. The mixture was maintained with vigourous stirring at 40°C during 24 h. The solvent was then evaporated under reduced pressure and the residue dissolved in 10 ml CH_2Cl_2. The organic layer was washed twice with 5 ml H_2O, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. After filtration over silica gel, 645 mg of 5 as a light yellow solid (87% yield) were obtained.

^{1}H nmr ($CDCl_3$, δ, ppm): 8.40 (d, J = 2.1 Hz, 1H), 7.60 (dd, Ja = 2.0 Hz, Jb = 9.6 Hz, 1H) , 7.24 (d, J = 9.5 Hz), 4.35 (s, 2H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 151.3, 149.2, 139.3, 134.5, 124.5, 29.7. ms (CI) m/z = 254/256 (M + H) ; 142/144 ; 128/130 (M - 127).

The same procedure can be used starting with compound 3 to obtain 5 (79% yield)

2-chloro-pyridine-5-carbaldehyde 6 :

In a 100 ml flask was introduced under argon 11.6 g (54 mmoles, 1.5 eq) of PCC and 50 ml of anhydrous Et_2O. After 5 minutes of vigourous stirring, 5.165 g (36 mmoles, 1 eq) of methylalcohol 2 in 20 ml anhydrous Et_2O was added. The suspension was stirred for another 5 hours at room temperature (until completion of reaction followed by TLC) and the upper layer was decanted from the black thick gum. The gum was extracted four times with Et_2O, the organic layers combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. After purification by flash chromatography (eluant heptane/ethyl acetate 7/3) and further crystallization from hexane, 4.52 g of 6 was obtained (88% yield).

mp : 70°C (heptane/ethyl acetate 8/2). ^{1}H nmr ($CDCl_3$, δ, ppm): 10.14 (d, J = 2.4 Hz, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.15 (dd, Ja = 8.3 Hz, Jb = 2.4 Hz, 1H), 7.50 (dd, Ja = 8.3 Hz, Jb = 2.4 Hz, 1H). ms (EI) m/z = 140/142 (M^+, 100/50). ir (ν, cm^{-1}): 1708.

2-(6-chloro-3-pyridyl)ethen-1-yl phenyl sulfone 7 :

To a 1 ml solution of 0.161 ml (0.742 mmoles, 1 eq) of phenyltrimethylsilyl methylsulfone in DME, at -78°C under argon was added 0.556 ml (1.2 eq) of *n*BuLi (1.6 M in hexane). After half an hour stirring, 105 mg (0.742 mmole, 1eq) of aldehyde 6 in 1 ml DME was added. After 3 hours stirring at -78°C, the reaction was quenched with 5 ml saturated aqueous solution of NH_4Cl. The aqueous phase was extracted three times with 10 ml CH_2Cl_2 portions, dried with Na_2SO_4, and the solvent evaporated. After purification by flash chromatography (eluant heptane/ethyl acetate : 7/3), 40 mg of *trans* 7 as a soft solid and 20 mg of *cis* 7 (30% yield) as an oil were obtained.

^{1}H nmr ($CDCl_3$, δ, ppm): 8.55 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.75 (dd, Ja = 2.3 Hz, Jb = 8.3 Hz, 1H), 7.62 (d, J = 15.6 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.25-7.20 (m, 2H), 6.91 (d, J = 15.4 Hz, 1H), 2.40 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 149.8, 149.0, 145.4, 139.8, 137.0, 136.6, 134.2, 130.6, 130.1, 127.9, 124.7, 21.2.

2-chloro-5-vinyl-pyridine 8 :

To a suspension of methyltriphenylphosphonium bromide (2.150 g, 6.01 mmoles) in 25 ml anhydrous THF was added *n*butyl lithium (5.3 mmoles), under argon at -78°C. The cold bath was then removed and the reaction was allowed to reach room temperature for one hour. To the resulting suspension was added very slowly at 0°C a solution of aldehyde 6 (500 mg, 3.53 mmoles) dissolved in 12.5 ml THF. Stirring was maintained at room temperature for 4 hours under argon. Reaction was quenched by adding 8 ml H_2O and the aqueous layer extracted three times with CH_2Cl_2. The resulting organic layers were combined, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. After purification by flash chromatography (eluant heptane/ethyl acetate 95 : 5), 394 mg of the olefin 8 was obtained in 80% yield.

^{1}H nmr ($CDCl_3$, δ, ppm): 8.42 (s, 1H), 7.70, (d, J = 7.0 Hz, 1H), 7.30 (d, J = 7.1 Hz, 1H), 6.7 (dd, Ja = 10.0 Hz, Jb = 17.1 Hz, 1H), 5.85 (d, J = 17.1 Hz, 1H), 5.47 (d, J = 10.0 Hz, 1H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 148.8, 135.2, 131.8, 128.4, 128.2, 123.9, 121.9.

(6-chloro-3-pyridyl)methyl tolyl sulfone 9 :

320 mg (2.0 mmoles, 1 eq) of chloromethylpyridine 4 was dissolved under argon in 5 ml of recently distilled DMF and 356 mg (1 eq) of sodium tosylsulfinate was added. The mixture was stirred at room temperature for 24 hours, then 150 ml of H_2O was then added, and the white precipitate filtered, and washed several times with H_2O. This was then dried by azeotropic removal with toluene and crystallization from heptane afforded 534 mg of 9 as a white solid (95 % yield).

mp : 43°C (heptane). ^{1}H nmr ($CDCl_3$, δ, ppm): 7.90 (d, J = 2.3 Hz, 1H), 7.65 (dd, Ja = 2.4 Hz, Jb = 8.3 Hz, 1H), 7.5-7.2 (m, 5H), 4.30 (s, 2H), 2.5 (s, 3H) ` ^{13}C nmr ($CDCl_3$, δ, ppm) : 152.5, 151.1, 145.4, 140.9, 139.9, 134.2, 130.1, 128.6, 124.4, 59.3, 21.8. ms (EI) m/z = 281/283 (M^+, 21/8), 126/128 (100/37). ir (ν, cm^{-1}): 1750. Analyses. Calcd for $C_{13}H_{12}NO_2ClS$: C 55.42, H 4.29, N 4.97. Found C 55.57, H 4.59, N 4.78.

1-(6-chloro-3-pyridyl)-2-phenylethenyl tolyl sulfone 10 :

In a 100 ml flask was introduced under argon at room temperature 210 mg (2 eq) of NaH and 10 ml of dry THF. Then 1.17 g (4.15 mmoles, 1 eq) of 9 dissolved in 10 ml THF was slowly added and stirring was maintained for half an hour. Benzaldehyde (2.4 eq, 1 ml) was then added to the preformed anion and the temperature raised gradually until reflux was obtained. After two hours, TLC monitoring showed an equilibrium and the reaction was quenched by adding 5 ml of a saturated solution of NH_4Cl. The organic layer was evaporated under reduced pressure and the resulting aqueous phase was extracted three times with 10 ml CH_2Cl_2. The

organic layers were combined, dried over Na_2SO_4 and the solvents evaporated under reduced pressure. After purification by flash chromatography (eluant heptane/ethyl acetate 15/5), 450 mg of **10** (30% yield) was obtained as a white powder.
mp : 148°C (heptane/ethyl acetate). ^1H nmr ($CDCl_3$, δ, ppm): 8.05 (s, 1H), 7.8 (d, J = 2.2 Hz, 1H), 7.60 (dd, Ja = 2.2 Hz, Jb = 8.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.55-7.05 (m, 9H), 2.4 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 152.4, 151.0, 144.9, 139.7, 137.5, 135.3, 132.2, 130.7, 130.5, 130.0, 129.0, 128.6, 127.0, 124.6, 21.6 5. ms (EI) m/z = 369/371 (M^+, 100/39), 230/232 (60/21). ir (ν, cm^{-1}): 3000, 1100. Analyses. Calcd for $C_{20}H_{16}NO_2ClS$: C 63.40, H 4.49, N 3.69. Found C 63.75, H 4.53, N 3.80.

2-methoxy-5 pyridine-carboxylic acid 11 :

In a 25 ml flask, 460 mg (20 mmoles, 16.6 eq) of sodium metal and 5 ml of anhydrous MeOH were introduced under argon. After complete dissolution of Na, 190 mg (1.2 mmoles, 1eq) of 6-chloronicotinic acid **1** dissolved in 2 ml of 1:1 MeOH/dioxane was added. After three hours refluxing, the white precipitate was filtered off. The resulting layer was evaporated under reduced pressure and the white powder was solubilized in 10 ml 10% HCl. The aqueous layer was extracted with 3 portions of 10 ml CH_2Cl_2, the organic phases were combined, dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. After crystallization from a solution of MeOH/H_2O, 140 mg of **11** as needles was obtained (76% yield).
mp : 175°C (H_2O/MeOH 9/1). ^1H nmr (CD_3OD, δ, ppm): 8.80 (d, J = 2.0 Hz, 1H), 8.05 (dd, Ja = 2.0 Hz, Jb = 9.1 Hz, 1H), 6.8 (d, J = 9.0, 1H), 4.05 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 168.3, 153.4, 151.0, 141.5, 141.1, 111.5, 58.35. ms (CI) m/z = 154 ($M+H^+$). ir (ν, cm^{-1}): 1696, 1266. Analyses. Calcd for $C_7H_7O_3N$: C 54.90, H 4.60, H 9.14. Found C 54.54, H 4.71, N 9.07.

5-methoxy-pyridine-2-carboxylic acid methyl ester 12 :

To 25 ml of a 5% methanolic solution of sulfuric acid, 4.685 g (29.72 mmoles) was added 6-chloronicotinic acid **1**. The resulting slurry was heated under reflux for 3 and after cooling, the solution was neutralized with a saturated aqueous solution of Na_2CO_3 until pH 10 was obtained. The aqueous phase was extracted twice with 20 ml CH_2Cl_2. The resulting organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. After flash chromatography through silica gel, (eluant CH_2Cl_2), 2.913 g of methyl ester **12** as a white solid was obtained (60% yield).
mp : 53°C (cyclohexane). ^1H nmr ($CDCl_3$, δ, ppm): 8.75 (d, J = 2.1 Hz, 1H), 8.11 (dd, Ja = 2.2, Jb = 10.9), 1H), 6.85 (d, J = 8.9, 1H), 4.05 (s, 3H), 3.90 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 166.5, 165.5, 149.7, 139.0, 119.3, 110.2, 53.6, 51.6. ms (EI) m/z = 167 (M^+, 100), 136 (M^+ - OMe, 58). ir (ν, cm^{-1}): 2880, 1721.

(6-methoxy-3-pyridyl)(4-methyl-piperazin-1-yl)-methanone 13 :

N-methylpiperazine (1.1 ml, 10 mmoles, 4 eq) was added to 7.94 ml of a 0.63 M solution of AlH_3 in THF at 0°C. The solution was stirred for 90 minutes under argon, and 420 mg (2.5 mmoles, 1 eq) of **12** dissolved in 3 ml of THF was added. The cold bath was removed, and the solution refluxed for two hours. Once the reaction cooled, 20 ml of H_2O was added, and the mixture filtered. The residue was extracted with THF (100 ml total). The organic layer was evaporated under reduced pressure. The oil obtained was dissolved in 15 ml CH_2Cl_2, and washed with 10 ml H_2O. The solvent was dried with Na_2SO_4, and evaporated under reduced pressure. The crude amine **13** was obtained as a oil which could be purified by flash chromatography (eluant CH_2Cl_2/MeOH : 9/1) (90% yield).
^1H nmr ($CDCl_3$, δ, ppm): 8.20 (d, J = 2.2 Hz, 1H), 7.65 (dd, Ja = 2.0 Hz, Jb = 8.2 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 4.05 (s, 3H), 3.60 (bs, 4H), 2.40 (bs, 4H), 2.20 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 167.8, 164.3, 146.1, 138.0, 124.4, 110.5, 54.8, 53.4, 45.7. ms (EI) m/z = 235 (M^+, 76), 191 (24), 178 (32), 136 (100). ir (ν, cm^{-1}): 1625, 1275.

2-methoxy-5-hydroxymethylpyridine 14 :

118 mg of 6-chloronicotinic acid **1** was dissolved in 5 ml of a 5 % solution of H_2SO_4 in MeOH. After two hours refluxing, the solution was basified to pH 11 with a saturated solution of Na_2CO_3. The aqueous solution was extracted three times with 15 ml CH_2Cl_2 portions. The resulting organic layers were combined, dried with Na_2SO_4 and the solvent evaporated. The crude product **12** was dissolved in 2 ml of anhydrous THF and cautiously added under argon at 0°C to a solution of lithium aluminium hydride (1.4 eq) in 1 ml THF. The solution was stirred for one hour until completion of reaction, then 5 ml of H_2O was added. The aqueous phase was extracted twice with 10 ml CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated to give 85 mg of a yellow paste **14** (90% yield).
^1H nmr ($CDCl_3$, δ, ppm): 8.05 (d, J = 2.2 Hz, 1H), 7.55 (dd, Ja = 2.2 Hz, Jb = 8.7 Hz, 1H), 6.75 Hz (d, J = 8.5 Hz, 1H), 4.90 (s, 3H), 4.55 (s, 2H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 163.8, 145.6, 138.5, 129.1, 62.1, 53.5. ir (ν, cm^{-1}). 3300, 1618, 1300.

2-methoxy-5-pyridine carbaldehyde 15 :

178 mg (0.825 mmoles, 1.5 eq) of PCC was introduced in a 10 ml flask and 1.5 ml of anhydrous CH_2Cl_2 was added under argon. After 5 minutes stirring, 77 mg (0.55 mmoles, 1 eq) of **14** was added. After three hours, the upper layer was decanted and the remaining black gum was extracted four times with 10 ml CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. After filtration through a plug of silica (eluant heptane/ethyl acetate 1:1), 68 mg of **15** as a white solid was obtained (87% yield).
mp = 50.5 - 51.5 °C (heptane). ^1H nmr ($CDCl_3$, δ, ppm): 9.95 (s, 1H), 8.65 (d, J = 1.9 Hz, 1H), 8.05 (dd, Ja = 2.0 Hz, Jb = 8.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 4.1 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 188.6, 166.6, 151.8, 136.5, 125.8, 111.0, 53.3. ms (EI) m/z = 137 (M^+, 70) ; 109 (M^+ - 18, 100). ir (ν, cm^{-1}) : 1695.

2-methoxy-5-bromomethyl-pyridine 16 :
330 mg (2.37 mmoles, 1 eq) of alcohol 14 was dissolved in 5 ml of anhydrous CH_2Cl_2 under argon. The solution was cooled to -40°C and 0.156 ml (0.7 eq) of PBr_3 was slowly added. The cooling bath was then removed and stirring was continued for three hours before 2 ml of H_2O was added. The organic phase was separated and the aqueous phase was extracted three times with 10 ml CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4 and then evaporated under reduced pressure. 2-methoxy-5-bromomethyl-pyridine 16 was obtained as a crystalline solid (290 mg, 60% yield).
^1H nmr ($CDCl_3$, δ, ppm): 8.15 (d, J = 1.3 Hz, 1H), 7.60 (dd, Ja = 1.5 Hz, Jb = 7.8 Hz, 1H), 6.75 (d, J = 8.75 Hz, 1H), 4.45 (s, 2H), 3.90 (s, 3H). ^{13}C nmr ($CDCl_3$, δ, ppm) : 163.9, 146.8, 139.4, 126.5, 53.6, 30.4. ms (EI) m/z = 201/203 (M^+, 17/17), 122 (M^+ - 80, 100).

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Refererences :
1. A. Kleeman, Chem. Ztg., **101**, 389 (1977)
2. H. Beschke, A. Kleeman, W. Claus, W. Kurze, K. Mathes and S. Habersang, Ullmanns Encyclopädie der technischen Chemie, Verlag Chemie, Weinheim, Deerfiled Beach, Florida, Bd. 19, 592-617 (1980)
3. J. W. Daly *et al.*, The Alkaloids, G.A. Cordell (Ed.), Academic Press, San Diego CA, **43**, 255 (1993)
4. T. F. Spande, H. M. Garaffo, M. W. Edwards, H. J. C. Yeh, L. Pannell and J. W. Daly, J. Am. Chem. Soc., **114**, 3475-3478 (1992)
5. C. Qian, T. Li, T. Y. Shen, L. Libertine-Garahan, J. Eckman, T. Biftu and S. Ip., European J. Pharm, R13-R14 (1993)
6. M. Dukat, M. Imad Damaj, W. Glassco, D Dumas, E. L May, B.R. Martin and R. A. Glennon, Med. Chem. Res., 131 (1993)
7. A. Torrado, S. Lopez, R. Alvarez and A. R. De Lera, Synthesis, 285 (1995)
8. S. Kagabu and S. Medej, Biosci. Biotech. Biochem., **59**, 980 (1995)
9. A. J. Boulton and A. McKillop, Reactivity of six membered rings in Comprehensive Heterocyclic Chemistry, **2**, 29-65
10. G. Shi, S. Takagishi and M. Schlosser, Tetrahedron, **50**, 1129 (1994)
11. F. E. Ziegler and J. G. Sweeny, Tetrahedron Lett., 1097 (1969)
12. D. L. Comins and M. O. Killpack, J. Org. Chem., **55**, 69 (1990)
13. P. T. Sullivan and S. J. Norton, J. Med. Chem, **14**, 557 (1971); O. Seide, Ber., **57B**, 1802 (1924)
14. H. Meyer, Mh. Chem., **28**, 47 (1906); A. D. Campbell, E. Chan, S. Y. Chooi, L. W. Deady and R. A. Shanks, Aust. J. Chem., **24**, 377 (1971); N. P. J. Broom, J. S. Elder, P. C. T. Hannan, J. E. Pons, P. J. O'Hanlon, G. Walker, J. Wilson and P. Woodall, J. Antibiotics, 1336 (1995) ; N. M. Chung and H. Tieckelmann, J. Org. Chem., **35**, 2517 (1970); K. Yamano and H. Shirahama, Tetrahedron, **48**, 1457 (1992) ; R. S. Dainter, H. Suschitzky and B. J. Wakefield, J. Chem. Soc. Perkin Trans I, 227 (1988); R. S. Dainter, T. Jackson, A. H. H. Omar, H. Suschitzky, B. J. Wakefield, N. Hughes, A. J. Nelson and G. Varvounis, J. Chem. Soc. Perkin Trans I, 283 (1989); A. P. Kozikowski, Y. Xia, E. R. Reddy, W. Tückmantel, I. Hanin and X. C. Tang, J. Org. Chem., **56**, 4636 (1991) ; G. R. Newkome, D. K. Kohli and T. Kawato, J. Org. Chem., **45**, 4508 (1980)
15. B. Gallenkamp, Ger. Offen, DE, 3,630,046 (1986) ; K. Jelich, Eur. Pat. Appl. EP 393,453 (1989)
16. P.-M. Windscheif and F. Vögtle, Synthesis, 87 (1994)
17. E. J Corey, T.-P. Loh, S. Achyutha Rao, D. C. Daley and S. Sarshar, J. Org. Chem., **58**, 5600 (1993)
18. S. V. Ley and N. S. Simpkins, J. Chem. Soc. Chem.Comm., 1281 (1983)
19. F. Frecourt, F. Marsais, T. Güngor and G. Queguiner, J. Chem. Soc. Perkin Trans 1, 2409 (1990)
20. M. A. Fox, C. A. Triebel and R. Rogers, Synth.Comm, **1055** (1982)
21. S. Y. Ko, J. Lerpiniere, I. D. Linney and R. Wrigglesworth, J. Chem. Soc. Chem. Comm., 1775 (1994)

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