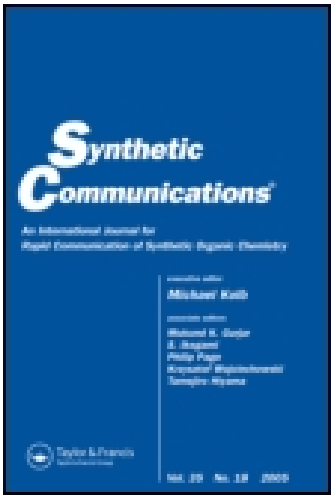

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Improved Large-Scale Preparation of 4-Iodopicolinic Acid

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IMPROVED LARGE-SCALE PREPARATION OF 4-IODOPICOLINIC ACID

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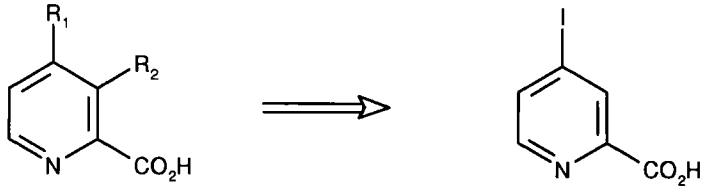
Abstract - Dimethylformamide showed a dramatic catalytic effect in the chlorination of picolinic acid with thionyl chloride. Methyl 4-chloropicolinate was directly transformed to 4-iodopicolinic acid in a good yield.

During the past few years, 4-halopyridines have proven to be useful intermediates for the synthesis of natural products[1] as well as for the preparation of medicinal drugs[2]. We recently became interested in the preparation of 3,4-disubstituted picolinic acids and required large amounts of 4-iodopicolinic acid (Scheme 1) as a starting material.

The chlorination of picolinic acid had been previously described in 1928 by Meyer and Graf[3] and later on by Mosher and Look[4]. Their procedure required refluxing picolinic acid in thionyl chloride in the presence of a large excess of sulfur dioxide for 4 days. Due to the slow decomposition



Scheme 1

of thionyl chloride at reflux and to the enormous volume of gases to be handled, we found this reaction problematic for scale-up and the published yield (65%[2]) could not be reproduced. During the search of a catalyst for this reaction, we found that dimethylformamide (DMF) had an extreme accelerating effect (Figure 1). Therefore, reaction of picolinic acid **1** with thionyl chloride and 0.16 eq. DMF at 72 °C over 24 hours afforded, after quenching with methanol[5], methyl 4-chloropicolinate hydrochloride **2** in a good yield (Scheme 2). The product, contaminated by the 2,4-dichlorinated derivative and by methyl picolinate, could be efficiently purified by recrystallization in acetone and yielded 55% of pure material (>98% by GC).

We found that inverse addition of the intermediate acid chloride to a toluene solution of methanol was necessary to ensure good product quality and to avoid problems during the crystallization[6].

In order to replace the chlorine atom by an iodine[3,7], we submitted directly

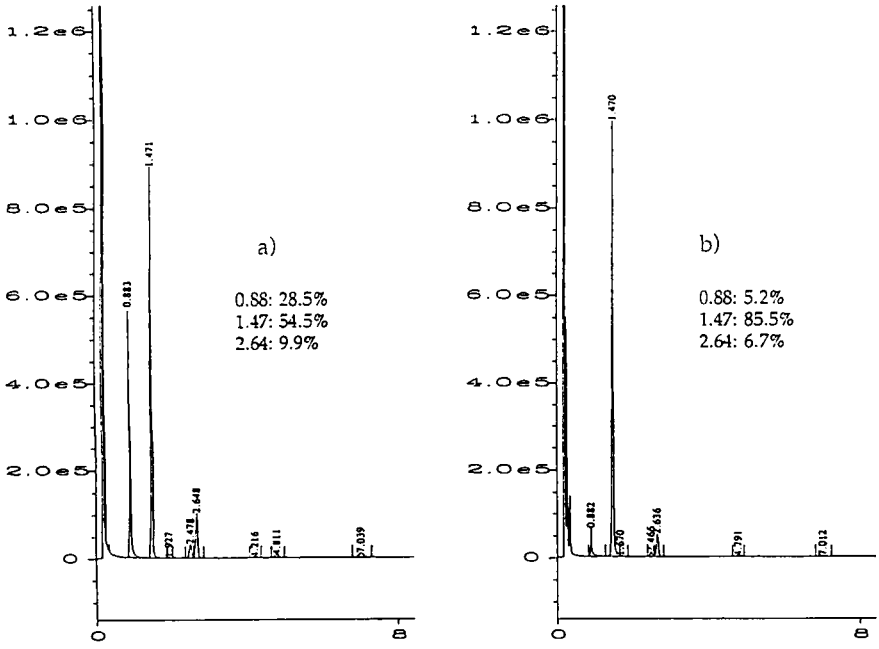
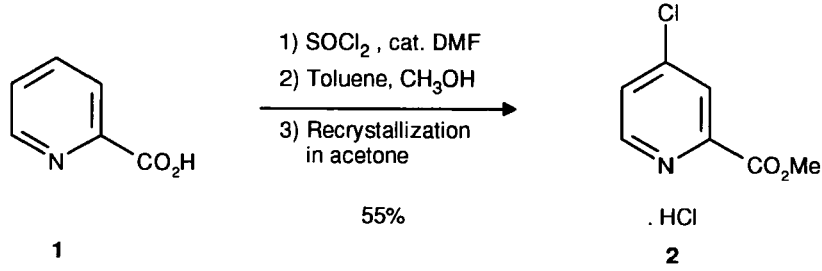


Figure 1: reaction mixture after 22.5h at 72°C, quenched with methanol and injected in GC. a) without DMF; b) with 0.16 eq. DMF. *retention times:* 0.88, methyl picolinate; 1.47, methyl 4-chloropicolinate; 2.64, methyl 4,6-dichloropicolinate.



1 2

Scheme 2

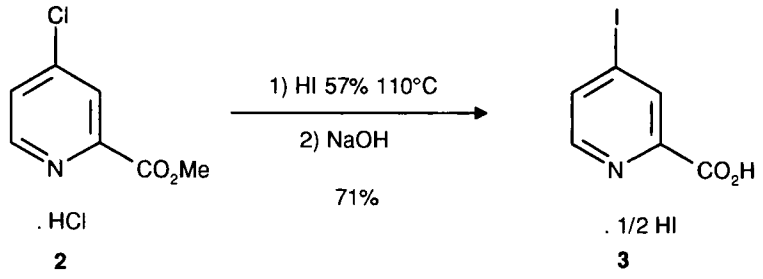
the ester **2** to aqueous 57% HI at 110 °C for 6 hours (Scheme 3). Partial neutralization of the reaction mixture with NaOH was necessary to obtain a good yield (71%) of **3**. Red phosphorus[3] was advantageously replaced by phosphonic acid to avoid the formation of I_2. Titration[8] of the 4-iodopicolinic acid **3** confirmed that it contained half an equivalent of HI per pyridine[3]. Eventually, the free base could be obtained by recrystallization of **3** in methanol/water (60% yield) but we used directly the salt form for the next step.

Finally, transformation of the acid function into an ester or an amide could be easily achieved by activation of **3** with 1,1'-carbonyldiimidazole in DMF[9].

Experimental

Methyl 4-chloropicolinate hydrochloride 2 :

A 4-L, 4-necked round bottomed flask, equipped with a mechanical stirrer, addition funnel, gas bubbler, condenser, distillation head, thermometer and heating bath was charged with thionyl chloride (1050 mL, 14.47 mol, 5 eq.). The solution was heated at 40-45 °C and dimethylformamide (35 mL, 0.452 mol, 0.16 eq.) was added slowly dropwise. Picolinic acid (350 g, 2.843 mol, 1 eq.) was added in small portions over 30 minutes and the mixture kept at 40-45 °C for 15 minutes (***evolution of SO_2 !***). The temperature was



Scheme 3

slowly (2 hours) raised to 72 °C and the mixture kept at the same temperature for 21 hours[10] (***relative strong evolution of gases at the beginning !***). The temperature of the oil-bath was raised and the excess of thionyl chloride was distilled off while at the same time toluene (1225 mL) was added. The resulting acid chloride solution was then allowed to stand at 40 °C (crystallization occurred at lower temperature). A 4.5-L, 4-necked round bottomed flask, equipped with a mechanical stirrer, addition funnel, gas bubbler, condenser, thermometer and cooling-bath was charged with toluene (210 mL) and methanol (250 mL) and heated to 35-40 °C. The above acid chloride solution was transferred via a canula during 30 minutes to the methanol solution. The resulting suspension, after reaching room temperature (RT) and stirring for 1 hour, was cooled and kept at 10 °C with stirring for 15 minutes and subsequently filtered. The product was washed with toluene (2x 200 mL) and with cold acetone (3x 200 mL). 510g

of solvent-wet product were obtained (89.4% pure by GC). The crude product was charged in a 2-L flask with acetone (1400 mL), stirred at 52 °C for 1 hour, allowed to reach RT, stirred for 1 hour, cooled down to 5 °C, stirred for 1 hour and filtered. The resulting white solid was washed with cold acetone (3x 100 mL) and dried (25-30 mm Hg, 22-23 °C for 24 hours) 324 g (54.7%) of pure **2** (98.5% by GC) were so obtained. ^{13}C NMR (90 MHz) δ (DMSO d6): 163.6, 150.7, 148.4, 144.1, 127.2, 124.64, 52.6 ppm . ^{1}H NMR (360 MHz) δ (DMSO d6): 8.72 (d, 1H, J=5.2 Hz), 8.08 (d, 1H, J=2.1 Hz), 7.85 (dd, 1H, J=5.2, 2.1 Hz), 3.93 (s, 3H) ppm. IR (KBr, cm^{-1}): 3085, 3013, 2599, 1743, 1615, 1600, 1442, 1301, 1096. MS (CH_4/DCI): m/z = 172 (free base +1). $C_7H_6NO_2Cl.HCl$ Calc. C: 40.41; H: 3.39. Found: C: 40.14; H: 3.43 ; m.p.= 146.5-147 °C.

4-iodopicolinic acid (hemi-hydroiodide, hydrate) 3 :

During this reaction, traces of H_2S (150 ppm) could be detected, resulting from the reduction of particles of sulfate present in 2. Therefore, this reaction should be performed in an efficiently ventilated hood.

A 4-L, 4-necked round bottomed flask, equipped with a mechanical stirrer, gas bubbler, distillation head, thermometer and heating bath was charged with 357g (1.71 mol) of ester **2**, 1610 mL of 57% hydriodic acid and 80 mL of 50% aqueous hypophosphorous acid. The mixture was heated to 85 °C where iodomethane started distillating. ~96 mL CH_3I were collected in 1

hour. The solution was then stirred for 6 hours at 107 °C and allowed to reach 95 °C. At this temperature were added in 30 minutes 508 mL of a 10M NaOH aqueous solution followed by water (1840 mL). The orange solution was allowed to reach RT and stirred at this temperature for 1 hour. Crystallization began at ~75 °C. The solid was filtered, washed with cold water (3x 200 mL) and dried (25-30 mm Hg, 22-23 °C for 24 hours). 400 g (71%) of pure **3** (>95% by NMR, ~2-4% of the 4-chloroderivative) were so obtained. ^{13}C NMR (90 MHz) δ (DMSO d6): 163.7, 148.1, 146.8, 136.2, 133.7, 111.1 ppm . ^{1}H NMR (360 MHz) δ (DMSO d6): 8.43 (d, 1H, J=6.3 Hz), 8.41 (d, 1H, J=1.4 Hz), 8.13 (dd, 1H, J=6.3, 1.4 Hz), 7.45 (br., 1.5H) ppm. IR (KBr, cm^{-1}): 3440, 3065, 2650, 1741, 1600, 1435, 1174, 789.MS (CH_4/DCI): m/z = 249 (free base +1). $C_6H_4NO_2I.1/2HI.H_2O$ Calc. C: 21.77; H: 1.98; N: 4.23; I: 57.51 Found: C: 21.87; H: 1.99; N: 4.11; I: 57.1; m.p.= 190-190.5 °C (lit.[3]:185-190 °C).

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5) In Graf's[3] synthesis, the reaction mixture was quenched with water and the free picolinic acid was obtained. It was shown by Mosher[4] that isolation of the free ester was much more convenient and that it could be purified by distillation. Our synthesis is simpler because the ester hydrochloride salt is isolated and purified by crystallization and it does not need to be hydrolyzed before the halogen exchange reaction.

6) When the methanol was added to the toluene solution of the acid chloride, the mixture separated in two phases with an oily residue. Inverse addition allowed the formation of fine and soft crystals.

7) Graf, R., *Chem. Ber.* **1931**, *64*, 21

8) Titration with $AgNO_3$ (19% HI), $HClO_4$ (75.6% base) and NaOH (19.3% HI), as well as CHN-analysis, confirmed a salt structure of 1/2 HI per picolinic acid. **3** contained 5.8% H_2O.

9) **3** reacted sluggishly with methanol-H_2SO_4 and afforded only a moderate yield of ester. Transformation of the acid into its acid chloride with thionyl chloride was reported to replace the iodine atom by a chlorine in the pyridine nucleus[3]. We found that the use of oxalyl chloride at 0 °C gave the same side reaction to a lower extent (15% chloro-derivative for the preparation of N,N-diisopropyl

4-iodopicolinamide; the compound was obtained pure after recrystallization in hexanes).

10) At that time, an aliquot of the solution was quenched with methanol and injected in GC. The chromatogram revealed the presence of the product (79%), methyl picolinate (8.4%) and by-products (10.6%).

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