[Contribution from the Department of Chemistry and Chemical Engineering, Stanford University]

HETEROCYCLIC BASIC COMPOUNDS. XVI. 4-CHLOROPICOLINIC ACID AND SOME OF ITS DERIVATIVES

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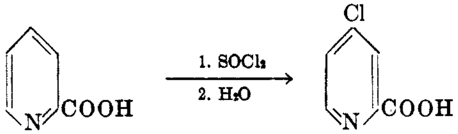
Received June 21, 1954

The object of this investigation was to develop a good method of preparation for 4-chloropicolinic acid, which would be a useful intermediate because of its active halogen. 4-Chloropicolinic acid has been synthesized previously from lutidone (1) and picolinic acid (2, 3). The method of Sedgwick (1) involved partial oxidation of lutidone, decarboxylation, and oxidation of the side chain; the yields in some of these steps were quite small. Seyfferth (2) reported the fusion of picolinic acid with phosphorus pentachloride and hydrolysis with sulfuric acid; however, yields and other data were unspecified. Meyer and Graf (3) obtained 4-chloropicolinic acid by the prolonged action of thionyl chloride on picolinic acid.



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Of the methods previously tried, the one of Meyer and Graf appeared to be the most promising, as their reported yields were high and their procedures were the least complicated. Graf reported the synthesis of 4-chloropicolinic acid in 50–55% yields by refluxing thionyl chloride with picolinic acid hydrochloride for ten days. In numerous attempts to follow his procedures, we have found the yields of 4-chloropicolinic acid to be low and erratic. Moreover, the product was obtained as both the free acid and the hydrochloride salt in several stages of the isolation procedure. The isolation of the products was also complicated by the formation of large amounts of polysubstituted chloropicolinic acids and tar. Therefore a thorough study of this reaction was undertaken in order to increase its preparative value and to clarify its mechanism.

The chlorination of picolinic acid hydrochloride was shown to be due to thionyl chloride and not the impurities, such as sulfuryl chloride, ordinarily present in the reagent, by the use of extremely pure thionyl chloride and picolinic acid hydrochloride; subsequent trials were then made with commercial grade thionyl chloride. It was found that the use of air-dried picolinic acid hydrochloride in the reaction gave a higher yield of 4-chloropicolinic acid under comparable conditions than when anhydrous starting material was used. This lead to the observation that the presence of sulfur dioxide in the chlorination mixture increased the rate of chlorination and yield of product. If the thionyl chloride

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[1] From the thesis submitted by M. Look in partial fulfillment of the requirements of the degree of Master of Science, Stanford University, 1954. See *J. Org. Chem.*, **19**, 357 (1954) for paper XV.

was saturated with sulfur dioxide in the beginning, the chlorination period was reduced from ten days to less than four days. The problem of isolation of the products was simply solved by converting the chlorinated products to their methyl esters and distilling the latter.

The ease of substitution of chlorine for hydrogen by thionyl chloride on the normally resistant pyridine nucleus of picolinic acid seems surprising. Moreover, the reaction appears to be general since chlorination with thionyl chloride has been reported for nicotinic acid and isonicotinic acid (3). The mechanism may be similar to that of Koenigs and Greiner for the formation of 4-pyridylpyridium chloride hydrochloride from pyridine (4). Whether the role of sulfur dioxide in the chlorination is that of an ionization media for thionyl chloride (5) or as a complexing agent for the picolinic acid hydrochloride [similar to pyridine (6)] is still obscure.

In order to check the other synthetic possibilities and to secure an authentic sample of 4-chloropicolinic acid from another source, 4-chloropicolinic acid was made starting with chelidonic acid, which was partially decarboxylated and treated with ammonium hydroxide and then phosphorus oxychloride. However, the over-all low yield (10%) made this method impractical from a synthetic viewpoint.

With the discovery of isonicotinic hydrazide as a tuberculostatic agent, it became of interest to prepare the hydrazide derivatives of 4-chloropicolinic acid. The synthesis of 4-chloro-, 4-amino-, 4-hydrazino-, and 4-methoxy-picolinic hydrazides is described in the experimental section.

EXPERIMENTAL[2]

4-Chloropicolinic acid from thionyl chloride and picolinic acid hydrochloride. The following experimen t is the description of one out of several attempts to duplicate Graf's work (3)

In a flask, well protected from moisture, was placed 20 g. (0.125 mole) of water-free picolinic acid hydrochloride[3] (7). Thionyl chloride (50 cc.) was added; if the hydrochloride was dried, there was no exothermic reaction. The mixture was heated for ten days in an oil-bath maintained at 80–90°. A 10-cc. portion of thionyl chloride was added one hour after the start of the refluxing, and another 10-cc. portion was added three hours after the first. At the end of the reflux period, the excess thionyl chloride was removed by vacuum-distillation. Benzene (80 cc.) was added to the residue, and the solid that formed was filtered and washed with benzene. The solid was then hydrolyzed with 75 cc. of water. Recrystallization of the solid gave 2.4 g. (12%) of 4-chloropicolinic acid, m.p. 175–176° (uncorr.).

Upon evaporation of the water of hydrolysis, 5 g. of a pale brown solid was collected. This solid was recrystallized from water, and an insoluble, brown polymer containing elemental sulfur was removed. The recrystallized solid (1.7 g.) was added to the 4-chloropicolinic acid collected above. The total yield of 4-chloropicolinic acid was 4.1 g. (21%); Graf (3) reported a 50–55% yield.

The original benzene filtrate and washings with subsequent treatment yielded a tarry residue (14 g.) containing, among other things, higher chlorinated picolinic acids.

4-Chloropicolinic acid from sulfur dioxide, thionyl chloride, and picolinic acid hydrochloride. The reaction was run according to the same procedures as given above using 100 g.

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[2] Melting points, except when noted, were taken on a Kofler microblock. Boiling points are uncorrected. Microanalysis by Microchemical Specialties Co., Berkeley, Calif.

[3] Further experiments were run on the hydrochloride of picolinic acid acquired from Reilly Tar and Chemical Co.

of picolinic acid hydrochloride and 400 ml. of thionyl chloride; however, in this case sulfur dioxide was bubbled into the reaction mixture in the beginning until the thionyl chloride was saturated. The heating was continued without interruption for four days instead of ten days. The thionyl chloride was evaporated under a vacuum, about 100 cc. of dry benzene was added, and the solvent was taken off by vacuum-distillation to remove the last traces of thionyl chloride. The brown syrupy residue (4-chloropicolinoyl chloride) was hydrolyzed by stirring in 300 cc. of an ice-water mixture, for one-half hour. The yellow solid which formed was filtered and recrystallized from water (1300 cc.). A mass of brown residue containing sulfur was removed and 4-chloropicolinic acid, 7.7 g. (8%), was collected upon cooling of the solution, m.p. 181–182° (dec.).

The mother liquor of the hydrolysis water was evaporated to dryness, and 45 g. of a yellow solid was collected (m.p. 174–181° dec.). A sublimed sample of the solid melted at 185–187° and proved to be identical to the hydrochloride of 4-chloropicolinic acid made by passing hydrogen chloride in a solution of 0.1 g. of 4-chloropicolinic acid, 1 cc. of ethanol, and 20 cc. of ethyl ether. The yield of 4-chloropicolinic acid and its hydrochloride was about 50%. A similar reaction which was heated under reflux for two days gave a 25% yield of 4-chloropicolinic acid.

Methyl 4-chloropicolinate from picolinic acid hydrochloride. 4-Chloropicolinyl chloride was prepared from 100 g. (0.625 mole) of picolinic acid hydrochloride with thionyl chloride and sulfur dioxide, following the procedures given above. However, the product was subjected to alcoholysis instead of hydrolysis as follows: to the dark residue cooled in an ice-bath was added slowly 300 cc. of absolute methanol. A sticky, insoluble residue was removed by filtering through Celite, and the filtrate was neutralized with a concentrated solution of sodium methoxide in methanol (70 g. in 300 cc.). In order to aid precipitation of the sodium chloride, 200 cc. of ethyl ether was added. Any excess sodium methoxide was neutralized with acetic acid and the finely divided sodium chloride then was removed by filtering through a fritted funnel. The product, which solidified upon cooling, distilled at 105–111° (2–3 mm.) giving 75.7 g. (71%) of methyl 4-chloropicolinate. There was a forerun of methyl picolinate (4 g.) and a higher-boiling fraction of methyl 4,6-dichloropicolinate (7 g., b.p. 125°, 2–3 mm.). A residue of about 20 g. of a red polymer was left. The melting point of recrystallized methyl 4-chloropicolinate from petroleum ether (b.p. 35–55°) was 51–54° (Graf reported 57-58°).

4-Chloropicolinic hydrazide. To a solution of 20 g. (0.12 mole) of methyl 4-chloropicolinate in 50 cc. of methanol was added slowly with swirling 15.5 g. of 64% hydrazine solution. There was an immediate precipitation in the now pink solution; the precipitate was filtered and washed with water. Recrystallization from water (500 cc.) gave 7.5 g. (37%) of white 4-chloropicolinic hydrazide, m.p. 166.5–168°. Graf (3), who prepared the compound by a different route, reported m.p. 167–168°. Further treatment of the mother liquor gave more hydrazide but the product was impure.

4-Aminopicolinic hydrazide. 4-Aminopicolinic acid was prepared according to the method of Graf (3) in 49% yield, m.p. 265°, reported 260°.

Dry hydrogen chloride was bubbled into a mixture of 0.46 g. (0.0037 mole) of 4-aminopicolinic acid in 40 cc. of dry methanol which was cooled to 0°. As the methanol became saturated with hydrogen chloride, the 4-aminopicolinic acid went into solution. The solution then was heated under reflux for one hour with the gas continuing to be passed in. The excess methanol was removed by vacuum distillation, the residue dissolved in 25 cc. of water, and the solution made basic with solid sodium carbonate. The aqueous solution was extracted with four 15-cc. portions of chloroform, the extracts were dried with magnesium sulfate, and the chloroform was evaporated on a steam-bath. The residue weighed 0.29 g. (57%), m.p. 129–132° (Reported by Graf: 129°). Further extractions of the aqueous solution yielded very minute amounts of ester.

A mixture of 0.21 g. (0.0014 mole) of methyl 4-aminopicolinate, 4 cc. of methanol, and 0.2 cc. of 64% hydrazine solution was evaporated to dryness, and the residue was crystallized from methanol-water. The fine, white needles of 4-aminopicolinic hydrazide weighed 0.11 g. (52% from ester) m.p. 194.5–196°.

Anal. Calc'd for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.83.
Found: C, 47.32; H, 5.23; N, 37.18.

4-Hydrazino picolinic hydrazide.[4] With continual shaking 125 cc. of a 64% hydrazine solution was added to 30 g. (0.175 mole) of methyl 4-chloropicolinate. To the solution now was added 35 cc. of ethanol and the pink solution was heated under reflux for 4.5 hours on a steam-bath. The white solid which precipitated in the beginning (4-chloropicolinic hydrazide) went back into solution upon the first hour of heating. The excess hydrazine, water, and alcohol were removed by vacuum-distillation and the dark solid residue was crystallized from 500 cc. of boiling water. The solid that formed upon cooling was recrystallized from methanol giving 8.1 g. (28%) of 4-hydrazinopicolinic hydrazide, m.p. 186.5–188.5°.

Anal. Calc'd for $C_6H_9N_5O$: C, 43.10; H, 5.43; N, 41.90.
Found: C, 43.34; H, 5.36; N, 42.45.

4-Methoxypicolinic hydrazide.[5] To 13 g. (0.076 mole) of methyl 4-chloropicolinate was added a solution of 1.74 g. (0.076 mole) of sodium in 40 cc. of methanol. There was an immediate precipitation; after the mixture was heated under reflux for eight hours, the sodium chloride was collected (3.7 g.) and washed with methanol. Sodium methoxide that was left in solution was removed by heating the solution for 30 minutes with 2.5 cc. of *tert*-butyl chloride and collecting the precipitate of sodium chloride. The solvents were removed under reduced pressure; without further purification, the grey crystals were treated with 15 cc. of hydrazine hydrate (85%) and 6 cc. of methanol to effect a solution. The mixture was heated under reflux for 1.5 hours, and the solid which formed upon cooling was collected and recrystallized from water giving 4.8 g. (26%) of 4-methoxypicolinic hydrazide, m.p. 152–154° (uncorr.).

Anal. Calc'd for $C_7H_9N_3O_2$: C, 50.30; H, 5.42; N, 25.15.
Found: C, 50.17; H, 5.33; N, 25.28.

Acknowledgment. We wish to thank Parke, Davis and Co. for a fellowship which made this investigation possible.

SUMMARY

The reaction of chlorination of picolinic acid hydrochloride with thionyl chloride forming 4-chloropicolinic acid was studied. By the use of sulfur dioxide in the reaction mixture, the period of chlorination was cut substantially and the yield was raised materially. Several hydrazides were synthesized from the 4-chloropicolinic acid and its methyl ester.

STANFORD, CALIFORNIA

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[4] The mixture melting point with a sample previously made by Frank J. Welch of these Laboratories by treating methyl 4-chloropicolinate (made by diazomethane on 4-chloropicolinic acid) with hydrazine was undepressed.

[5] Experimental work by Robert Bernard.