



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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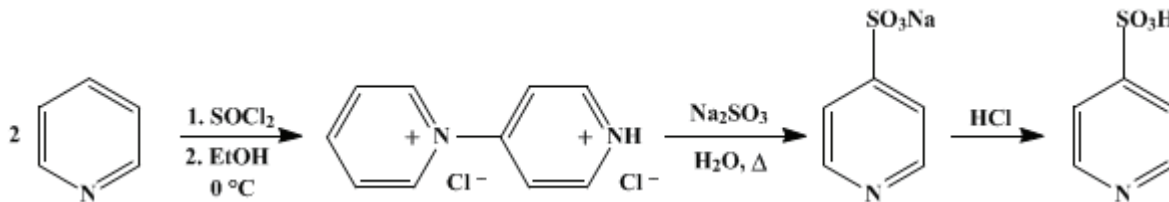
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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4-PYRIDINESULFONIC ACID



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Checked by James Cason and Taysir Jaouni.

1. Procedure

A. *N*-(4-Pyridyl)pyridinium chloride hydrochloride. In a 2-l. round-bottomed flask equipped with a ground joint (Note 2) is placed 395 g. (5.00 moles) of dry pyridine (Note 3). As this flask is cooled by swirling in a bath of cold water (Note 4), there is added during a few minutes 1190 g. (10.0 moles) of a good commercial grade of thionyl chloride (Note 1). After completion of the addition, the flask is protected by a drying tube, and the reaction mixture is allowed to stand at room temperature under a hood for 3 days. During this period, the color of the mixture changes from deep yellow through brown to black.

The flask is fitted with a Claisen head, and excess thionyl chloride is distilled at reduced pressure (water pump) and collected in a receiver cooled in a mixture of dry ice and acetone (Note 5). The flask is heated with a water bath that is slowly raised from room temperature to about 90°, then held at that temperature until no more distillation occurs and a black residue remains.

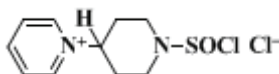
The black residue is cooled to 0°, and 100 ml. of ice-cold ethanol is added very cautiously to react with residual thionyl chloride. An additional 400 ml. of ice-cold ethanol is added, and the solid mass left at the bottom of the flask is broken up with the aid of a rod (Note 2). The resultant light-brown powder is collected by suction filtration, preferably on a sintered glass funnel, and washed with five 150-ml. portions of ethanol. The yield of crude *N*-(4-pyridyl)pyridinium chloride hydrochloride is 230–257 g. (40–45%). This product is very deliquescent and should be used immediately or stored over phosphorus pentoxide.

B. *4-Pyridinesulfonic acid*. A 115-g. (0.50 mole) quantity of *N*-(4-pyridyl)pyridinium chloride hydrochloride is dissolved in 750 ml. of water in a 2-l. round-bottomed flask, and 378 g. (1.50 moles) of solid sodium sulfite heptahydrate is added cautiously. After the evolution of sulfur dioxide has ceased, the solution is gently heated under reflux in a nitrogen atmosphere for 24 hours. After slight cooling, 20 g. of charcoal is added to the mixture, and it is heated under reflux for an additional hour. The resultant mixture is filtered through a fluted paper, the filtrate is evaporated to dryness on a steam bath under reduced pressure, and the residue is air-dried at 100–110° (Note 6). This solid is now continuously extracted with absolute ethanol for 24 hours in a Soxhlet apparatus. The alcohol is distilled from the extract on a steam bath, and the crude sodium 4-pyridinesulfonate is dissolved in about 160 ml. of hot water. After 320 ml. of 12*N* hydrochloric acid has been added with mixing, the solution is cooled to room temperature. The precipitate of sodium chloride is filtered, and the filtrate is evaporated to dryness under reduced pressure on a steam bath. Crystallization of the residue from 600 ml. of 70% aqueous ethanol yields 27–30 g. of colorless crystals of 4-pyridinesulfonic acid, m.p. 313–315° (dec.). Concentration of the mother liquor affords about 10 g. of additional product which is less pure. The total yield is 36–40 g. (45–50%) (Note 7). Recrystallization from 70% aqueous ethanol affords a purer specimen, m.p. 317–318° (dec.). (Note 8).

2. Notes

1. Although *N*-(4-pyridyl)pyridinium chloride hydrochloride is formed by reaction of pyridine with

thionyl chloride, followed by treatment with ethanol, the intermediates involved in the reaction have not been well established. It has been suggested^{4,5} that 1 mole of thionyl chloride converts 2 moles of pyridine to the compound. This intermediate would be further oxidized by thionyl chloride and solvolyzed by ethanol to the pyridinium chloride hydrochloride. According to this reaction route, the stoichiometric ratio of pyridine to thionyl chloride for the overall process would be about 1:1. Varying ratios of thionyl chloride have been used^{6,7,8} and varying yields of the product have been reported, ranging from 60% of crude product⁷ to 48% of recrystallized product.⁸ In one run in which the checkers used one-half the specified amount of thionyl chloride, the yield was unaffected. The submitters report yields in the range 58–62% by the procedure described here.



2. Thionyl chloride attacks rubber so rapidly that all-glass apparatus is highly desirable for this procedure. Since breaking up the residual product in a flask results in a high mortality of flasks, the checkers preferred a distilling vessel with a removable top of the type used with vacuum desiccators (e.g., Corning Glass Works, No. 3480).
3. Since moisture reacts with thionyl chloride to give hydrogen chloride, which forms the salt of pyridine and thus inactivates it, the pyridine should be dried over barium oxide for 24 hours, then distilled under anhydrous conditions shortly before use.
4. Provided that this addition is carried out rapidly, ingress of moisture is not significant, and more complicated apparatus is not recommended.
5. Since thionyl chloride ruins all rubber tubing with which it comes in contact, efficient cooling of the receiver is recommended.
6. Alternatively, to decrease the time required to complete drying at 100–110°, the moist solid residue may be triturated with chloroform and the chloroform distilled from the steam bath. The checkers used a vacuum oven for drying.
7. The submitters report yields in the range 63–70%.
8. Because the sulfonic acid melts with decomposition, the value observed for the melting point is highly dependent on the rate of heating of the sample.^{9,10,11,12}

3. Discussion

The preparation of N-(4-pyridyl)pyridinium chloride hydrochloride follows the procedure of Koenigs and Greiner,⁶ while the preparation of the sulfonic acid is a modification of a patent procedure.¹³

4-Pyridinesulfonic acid has been prepared by oxidation of 4-pyridinethiol with hydrogen peroxide in barium hydroxide solution,⁹ with hydrogen peroxide in glacial acetic acid,¹⁰ with nitric acid-chlorine or nitric acid-chlorine-hydrochloric acid mixtures,¹¹ and with nitric acid alone.^{10,12,14} The latter reaction gives a mixture of 4-pyridinesulfonic acid and other products, e.g., di-4-pyridyl disulfide dinitrate, and this has led to some confusion in the literature.^{10,11,12,14} 4-Pyridinesulfonic acid has also been obtained from its N-oxide derivative by reduction of the N-oxide group with iron and acetic acid¹⁵ or catalytically.¹⁶

Sodium 4-pyridinesulfonate has been formed by the oxidation of 4-pyridinethiol with hydrogen peroxide in sodium hydroxide solution,^{17,18} and from the reaction of 4-chloropyridine with aqueous sodium sulfite.¹⁹ The salt has been converted to the free acid by treatment with a cation-exchange resin^{10,11} or with sulfuric acid.¹¹

4. Merits of the Preparation

This is the most convenient preparation of 4-pyridinesulfonic acid, a useful intermediate for the synthesis of various pyridine derivatives.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

nitric acid-chlorine-hydrochloric acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride,
hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

iron (7439-89-6)

nitric acid (7697-37-2)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

barium oxide

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

hydrogen peroxide (7722-84-1)

barium hydroxide (17194-00-2)

4-Pyridinesulfonic acid (5402-20-0)

N-(4-Pyridyl)pyridinium chloride hydrochloride (5421-92-1)

sodium sulfite heptahydrate

sodium 4-pyridinesulfonate

4-pyridinethiol (4556-23-4)

nitric acid-chlorine (14545-72-3)

4-chloropyridine (626-61-9)

phosphorus pentoxide (1314-56-3)

di-4-pyridyl disulfide dinitrate