Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[a0082]

SYNTHESIS OF 4-AMINOPYRIDINE AND 4-ACETYLAMINOPYRIDINE BY REDUCTION OF 4-NITROPYRIDINE-N-OXIDE WITH IRON AND MINERAL ACIDS

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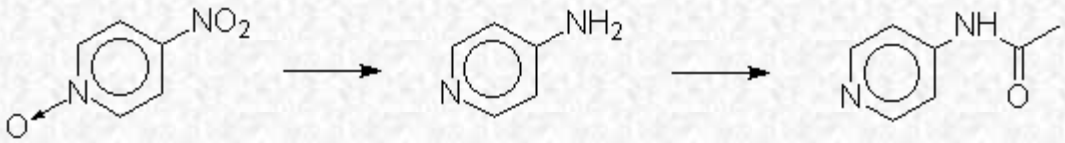
Received: 9 August 2000 / Uploaded: 16 August

The usual way of commercial 4-aminopyridine preparation is a two-stage synthesis starting from pyridine and including 1-(4-pyridyl)pyridinium chloride hydrochloride as an intermediate. The total yield is 36-40% [1, 2, 3].

A semipreparative scale three-stage synthesis including pyridine-N-oxide and 4-nitropyridine-N-oxide as an intermediates is preferable. At the third stage 4-nitro-pyridine-N-oxide was reduced with iron and acetic acid at reflux temperature to produce 4-aminopyridine in quantitative yield. The reaction demands continuous extraction with diethyl ether of the title compound. The total yield is 65% [4].



In order to avoid the use of special equipment for continuous extraction with diethyl ether (or a large amount of diethyl ether for ordinary extraction) we tried to minimize the acid excess. All our attempts to minimize the amount of acetic acid or replace its excess with water failed. The precipitation of basic ferric acetates and/or extensive 4-aminopyridine hydrolysis to 4-pyridone were observed.

We studied the reduction of 4-nitropyridine-N-oxide with iron and aqueous mineral acids. The reduction with iron and hydrochloric acid gives mainly 4-aminopyridine (80-85%), and as by-products 4-aminopyridine-N-oxide, 4-pyridone, and 4,4'-azopyridine. The reduction with iron and 25-30% sulphuric acid proceeds slowly, but the yield of the desired 4-aminopyridine is better. The isolation of the reaction product after reduction, subsequent neutralization with sodium carbonate, and filtration was carried out by two methods. The first method was extraction with ethyl acetate. After removal of the solvent 4-aminopyridine was obtained in 85-90% yield. The second method was the concentration of the filtrate on

the rotatory evaporator, extraction with ethanol, and after evaporation of ethanol reextraction with hot benzene to give a title compound after cooling (85%).

After evaporation of the solvent, crude 4-aminopyridine, if desired, was acetylated with acetic anhydride to produce 4-acetylaminopyridine in 80-85% yield [5].

When the neutral or basic aqueous solutions containing of 4-aminopyridine were heated for concentration, partial hydrolysis to 4-pyridone was observed. It caused some decreased yields of desired compound.

References

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4. den Hertog, H. J., Overhoff, J. Pyridine and quinoline derivatives. LXXXII. Pyridine-N-oxide as an intermediate for the preparation of 2- and 4-substituted pyridines. *Rec. trav. chim.*, 1950, **69**, 468-473.

5. 4-Acetylaminopyridine monohydrate, m. p. 145-147^{o}C (from 96% ethanol);
MS ("Selmi" TOF-spectrometer, +25kV), (m/z): M^{+} 136,8.
PMR (Bruker AC-300), (CCl_4 and $(D_3C)_2SO$) (p. p. m.): 3,02 (3H, s, CH_3);
7,52 (2H, d, 3- and 4-H); 8,33 (2H, d, 2- and 5-H); 10.05 (1H, bs, NH).
