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# Reductive Dechlorination of a 2-Chloronicotinic Acid Under Finkelstein Conditions

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We reported previously the preparation of 5-fluoro-6-iodonicotinic acid and 5-bromo-6-iodonicotinic acid (Setliff, F., *J. Chem. Eng. Data* 18: 449-450, 1973) as well as 5-chloro-6-iodonicotinic acid (Setliff, F., *J. Chem. Eng. Data* 21: 246-247, 1976) by the Finkelstein Reaction (Klingsberg, E., *J. Am. Chem. Soc.* 72:1031, 1950). The process involves nucleophilic displacement of chloride by iodide (as sodium or potassium iodide) in refluxing acetone or methyl ethyl ketone (MEK), and the reaction is driven by the insolubility of the resultant sodium or potassium chloride in the ketone solvent. The aforementioned 5-halo-6-iodonicotinic acids were thus generated from their respective 6-chloro derivatives in acceptable yields. Although these reactions are presumably catalyzed by autoprotonation of the ring nitrogen, it was found that our conversions proceeded more efficiently when a small amount of hydroiodic acid was added. The electron withdrawing carboxyl group para to the 6-chloro, together with the halogen in the five position, and the protonated ring nitrogen all serve to activate the 6-chloro for nucleophilic displacement by iodide.

Reasoning that an ortho carboxyl group and a para bromo should also promote chloride displacement, we attempted the preparation of 5-bromo-2-iodonicotinic acid from 5-bromo-2-chloronicotinic acid by the Finkelstein technique, but the expected bromoiodoacid was not formed. Surprisingly, 5-bromonicotinic acid was the only product isolated, and the reaction was accompanied by the formation of copious amounts of molecular iodine. Evidently, reductive dechlorination occurred at the expense of displacement, possibly due to steric interference by the ortho carboxyl group. The overall reaction is shown in Fig. 1.

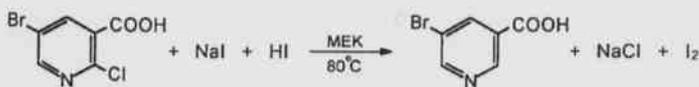


Fig. 1. Reductive dechlorination of 5-bromo-2-chloronicotinic acid.

Although iodide-induced reductive dechlorinations of

several 4-chloro-2-pyridinecarboxylic acids (4-chloropicolinic acids) have been reported (Graf, H., *J. Prakt. Chem.* 148:13-19, 1937), high concentrations of hydroiodic acid together with red phosphorus and extremely elevated temperatures were required. To our knowledge, this note represents the first example of a reductive dechlorination of a 3-pyridinecarboxylic acid (nicotinic acid) and more significantly, under such mild conditions.

No exact mechanism for reactions of this type is described in the literature, but the process could involve initial iodide attack on chlorine of the N-protonated substrate yielding iodine monochloride and a 2-pyridyl anion, which could subsequently undergo protonation to afford the reduction product. Further reaction of iodine monochloride with iodide ion could then produce molecular iodine, which we observed.

The experiment was conducted as follows. A mixture of 5-bromo-2-chloronicotinic acid (Setliff, F., *J. Chem. Eng. Data* 590-591, 1970), (0.9 g, 0.0038 mole), sodium iodide (2.0 g, 0.013 mole), 57% hydroiodic acid (2 ml), water (1 mL), and methyl ethyl ketone (25 mL) was stirred under reflux for 48 hr. The reaction mixture was cooled to room temperature, and the sodium chloride which had precipitated (0.16 g, 72% of the theoretical) was removed by suction filtration. The reddish-brown filtrate was evaporated leaving a dark brown solid, which was washed with 10 mL of 10% sodium bisulfite to remove the iodine. The resulting light yellow powder was recrystallized from water, yielding light tan leaflets of 5-bromonicotinic acid (0.25 g, 32%), mp 180-182° C. The infrared spectrum was superimposable on that of an authentic sample obtained from Aldrich Chemical Co., Milwaukee, WI. A mixture melting point with an authentic sample showed no depression. The 200 MHz proton NMR spectrum in DMSO-d<sub>6</sub> with tetramethylsilane as the internal standard showed three aromatic protons: δ 9.04 (H-2), 8.96 (H-6), and 8.42 (H-4) ppm, all singlets in the area ratio of 1:1:1. The carboxyl proton appeared in the water signal at 3.42 ppm as a result of exchange with the water present in the DMSO.

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