Contribution from Olin Mathieson Chemical Corporation, Chemicals Division

New Synthesis Routes to 2-Halopyridines. I. 2-Chloropyridine

Max M. Boudakian (1), F. F. Frulla (2), David F. Gavin and Joel A. Zaslowsky (3)

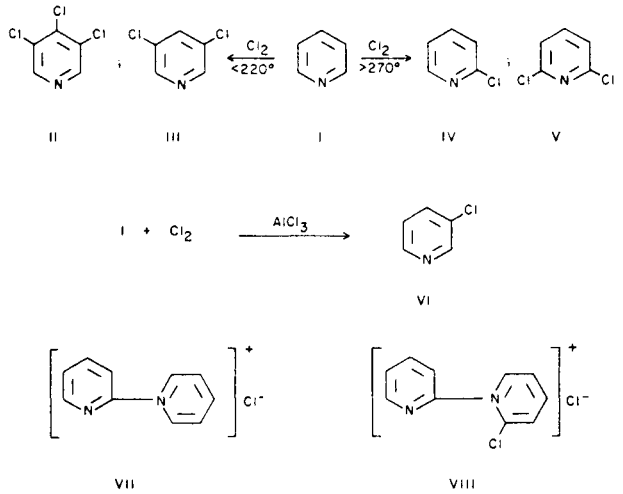
In contrast to the wide variety of products previously reported from the non-photolytic liquid or vapor phase chlorination of pyridine (I), it has been demonstrated that the corresponding photochemical chlorination of I in carbon tetrachloride under reflux conditions gave 2-chloropyridine (IV) in 62-78 percent yield.

Depending on temperature and other environmental conditions, the chlorination of pyridine (I) follows different reaction paths. Thus, chlorination of I at 0-117° gave 3,4,5-trichloropyridine (II) (4). At 170-220°, 3,5-dichloropyridine (III) and, to a lesser extent, II, were formed (5); while, above 270°, 2-chloropyridine (IV) and smaller quantities of 2,6-dichloropyridine (V) were the main products (5).

When I and chlorine were allowed to react in the presence of aluminum chloride ("swamping catalyst" effect) at 80-115°, 3-chloropyridine (VI) was the main product (6).

Likewise, in different solvent media, the chlorination of I took different paths. For example, Williams isolated a crystalline compound, $C_5H_5N{\cdot}Cl_2$, m.p. 47°, when the chlorination of I was conducted in carbon tetrachloride (7). In aqueous media, the chlorination of I gave nitrogen, carbonic acid and dichloroacetic acid (8).

No studies on the photochlorination of I have been reported. When I was photochlorinated in carbon tetrachloride, 2-chloropyridine (IV) was obtained in 62-78 percent corrected yield (based on 41-66 percent conversion of I (9). A brief discussion of reaction parameters of the previously unknown photolytic route to IV is presented below.



Effect of Light.

That the reaction is truly promoted by light was illustrated by the chlorination of I in carbon tetrachloride in the presence of laboratory daylight ("dark" process) at reflux temperatures (80°) to give unidentified dark solids and tarry residues; no IV was detected. Similar unknown nonvolatile materials were noted by others (4,7). When the same reaction was conducted in the presence of ultraviolet light, 2-chloropyridine (IV) was the main product. Thus, light intensity as low as 0.72 watt (black fluorescent lamp) increased both the conversion of I (from 13.2 to 34.2%) and yield of IV (from 0 to 34.7%). Further increase of light intensity to 5.6 watts (same light source), did not improve the conversion of I; however, the yield of IV rose to 61.9%.

Solids deposition (light-colored, in this instance) arising from the photochemical reaction was less than in the "dark" process. Chloride ion analysis indicated that these white solids were primarily pyridine hydrochloride. This would be expected on the basis of the significant basicity differences of I and IV (10): *p*Ka pyridine, 5.17; 2-chloropyridine, 0.72.

Solvent Systems.

A comparison of several solvent systems such as water, excess pyridine and carbon tetrachloride demonstrated that the latter was the most satisfactory solvent for the photolytic process. The use of water was based on the possible removal of pyridine hydrochloride deposits thus permitting more efficient light utilization.

By-Products.

Only trace quantities of 3-chloropyridine (VI) and 3,5-dichloropyridine (III) were formed in the photochemical process. Tars were noted but not identified. Since 2-pyridyl-*N*-pyridinium chloride (VII) was formed from I and IV (11), the tars isolated in the photolytic process may contain VII, and possibly the corresponding condensation product VIII formed from two molecules of IV.

The photochlorination of I represents a more convenient laboratory route than the following known routes to 2-chloropyridine (IV):

(a) Thermal chlorination of pyridine above 270° (5).
(b) Diazotization of 2-aminopyridine (12).
(c) Treatment of pyridine-*N*-oxide with sulfuryl chloride (13).
(d) Reaction of pyridine hydrochloride with cupric chloride or cupric chloride-chlorine (14).
(e) Chlorination of *N*-methyl 2-pyridone (15) or 2-pyridinol (16) with phosphorus pentachloride and/or phosphorus oxychloride.

EXPERIMENTAL

Analytical.

A direct calibration VPC procedure based on known reference standards dissolved in carbon tetrachloride was employed for product analysis.

Beckman Gas Chromatograph, Model GC-2A: 1 meter, 6 mm. O.D. aluminum column, packed with 15% poly-*m*-phenyl ether on Chromosorb W (80-100 mesh); column temperature, 130°; helium inlet pressure, 49.5 psi; sample size, 3 μl.; detector current, 350 m.a. The following peak retention times (minutes) were noted; carbon tetrachloride, 0.7; pyridine, 0.9; 3- and 4-chloropyridine, 2.4; 2-chloropyridine, 3.5; 3,5-dichloropyridine, 5.1; 2,5-dichloropyridine, 8.3; 2,3-dichloropyridine, 10.7; 2,6-dichloropyridine, 11.5 (Except for I and carbon tetrachloride, the above reference standards were obtained from the Aldrich Chemical Co.).

Typical Photochlorination Conditions.

A. In a typical experiment, I (16.4 g.; 0.2 mole: Mallinckrodt, A. R.) and carbon tetrachloride (323 g.; 2.1 moles; Mallinckrodt, A. R.) were placed in a 1 liter 3-necked Pyrex 7740 flask equipped with a stirrer. The chlorine inlet tube was placed 1 inch below the surface of the liquid reactants. A 100 watt high-pressure mercury vapor, sealed beam spot-type lamp (E. H. Sargent Co., No. S-44260), equipped with a filter (No. 19057) to permit transmission at 3665 Å, was located 4 inches from the reactor. An aluminum foil reflector was employed for more efficient light utilization.

The reaction mixture was heated to reflux (78-81°) and chlorine (8.0 g.; 0.11 mole; Matheson Co.) introduced over a 35 minute period. (Titration of unconverted chlorine collected in an aqueous potassium iodide scrubber (20 percent) indicated 89.5 percent chlorine consumption). The reaction mixture was cooled and the white solids filtered, wt. 18.7 g. Analysis of the diethyl ether-washed solids for ionizable chloride indicated: % Cl^-: Found: 28.0. Calcd. for $C_5H_5N{\cdot}HCl$, 30.7%; $C_5H_4ClN{\cdot}HCl$, 23.7. The solids were neutralized with 100 ml. portions of aqueous potassium hydroxide (20 percent) and extracted with 100 ml. and 50 ml. portions each of carbon tetrachloride. VPC assay of the combined carbon tetrachloride extract (wt. 224.5 g.) of the neutralized solids showed 1.78 wt. % (I) and 0.02 wt. % (IV). VPC analysis of the original organic filtrate (wt. 359.7 g.) assayed: (I), 0.06 wt. %; (IV) 2.67 wt. %; and, (V), 0.07 wt. %. These combined analyses indicated 63.3% corrected yield of IV based on 65.9% conversion of I. At least 92% of IV could be isolated in 98.5% purity (VPC) by distillation through a 4 in. column filled with 316 stainless steel Goodloe packing: b.p., 169.5°; 73.5°/23 mm; n_D^{25} 1.5309. (Reported for 2-chloropyridine (5): b.p. 171°; n_D^{20} 1.5322).

In one experiment, the above mercury vapor lamp was augmented by another light source (Hanovia, No. 616A; 100 watts). Treatment of 0.2 mole of I with 0.099 mole chlorine in 2.1 moles carbon tetrachloride at 78° gave a 77.6% yield of IV based on 49.6% conversion of I.

The effect of light intensity was studied with a black fluorescent lamp (15 watts, General Electric) which was taped to give different light intensities. In each example, chlorine (0.2 mole) was introduced into a solution of I (0.4 mole) dissolved in 4.13 moles carbon tetrachloride at 78°:

Light Intensity (watts)	10.5	5.6	0.72	0
% Conversion (I)	48.7	34.5	34.2	13.2
% Corrected Yield (IV)	55.5	61.9	34.7	0.0

B. Solvent Systems.

1. Excess Pyridine.

Chlorine (18.0 g.; 0.253 mole) was introduced into I (791 g.; 10.0 moles) during a 61 minute period at 116-119°. Illumination was provided by a mercury vapor lamp (Hanovia No. 616A). By the product isolation procedure described above, the following data was obtained: conversion of I, 19.0%; corrected yields: (IV), 28.5%; (V), 0.1%; (VI), 0.2%; and, (III), 1.6%.

2. Water-Pyridine Systems.

In a similar manner, chlorine (7.0 g.; 0.099 mole) was introduced during a 25 minute period into I (24.7 moles; 1950 g.) and water (1.1 moles; 20 g.) at 98.5-102°. Illumination was provided by a Hanovia No. 616A mercury vapor lamp. VPC analysis showed 16.3% conversion of I and 12.8% corrected yield of IV.

By use of a large quantity of water (11.1 moles; 200 g.), the reaction of I (0.2 mole; 15.8 g.) and chlorine (14.0 g.; 0.198 mole) at 94-101° during a 39 minute period (mercury vapor lamp, Sargent No. 44260) gave an 8.2% conversion of I and 7.3% corrected yield of IV.

REFERENCES

(1) To whom inquiries should be addressed.
(2) Present Address: The Upjohn Company; North Haven, Connecticut.
(3) Present Address: Alcolac Chemical Corporation, Baltimore, Maryland.
(4) W. J. Sell and F. W. Dootson, *J. Chem. Soc.*, 73, 442 (1898).
(5) J. P. Wibaut and G. R. Nicolai, *Rec. Trav. Chim.*, 58, 709 (1939).
(6) D. E. Pearson, W. W. Hargrove, J. K. T. Chow and B. R. Struthers, *J. Org. Chem.*, 26, 789 (1961).
(7) D. M. Williams, *J. Chem. Soc.*, 2783 (1931). Removal of the solvent from the 1:1 adduct liberated chlorine, hydrogen chloroide and gave an oil containing pyridine and an unidentified compound. This 1:1 adduct was also obtained upon passage of chlorine into a chloroform solution of I. (See reference 8.)
(8) O. Bally, *Ber.*, 21, 1772 (1888).
(9) M. M. Boudakian and J. A. Zaslowsky, U. S. Patent 3,297,556 (Jan. 10, 1967).
(10) D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, 77, 3756 (1955).
(11) G. Koller and H. Ruppersberg, *Monatsh. Chem.*, 50, 436 (1928).
(12) A. E. Tschitschibabin and M. D. Rjazancev, *J. Russ. Phys. Chem. Soc.*, 46, 1571 (1915); *J. Chem. Soc. Abstr.*, i, 224 (1916). W. Marckwald, *Ber.*, 27, 1317 (1894); *J. Chem. Soc. Abstr.* i, 381 (1894).
(13) B. Bobranski, L. Kochanska and A. Kowalewska, *Ber.*, 71, 2385 (1938).
(14) W. G. Tucker, Ph.D. Thesis, University of Oklahoma, 1962. (See *Dissertation Abstracts*, 23, 1522 (1963).
(15) O. Fischer, *Ber.*, 32, 1297 (1899); *ibid.*, 32, 1307 (1899).
(16) H. V. Pechmann and O. Baltzer, *ibid.*, 24, 3144 (1891).

Received June 2, 1967 New Haven, Conn. 06504