Contribution from Olin Mathieson Chemical Corporation, Chemicals Division

New Synthesis Routes to 2-Halopyridines. III. 2-Fluoropyridine

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The solvent-free fluorination of 2-chloropyridine (III) with alkali metal fluorides and bifluorides was investigated. While complete degradation occurred with potassium fluoride at 315°, the use of potassium bifluoride under identical conditions provided a 74% yield of 2-fluoropyridine (II). Sodium bifluoride gave only a 3.5% yield of the desired product. These results are discussed in the light of: activation of the substrate, properties of the fluorinating agents, and the stability of 2-fluoropyridine.

Prior to 1962, the conventional route to 2-fluoropyridine (II) involved the diazotization-fluorination of 2-aminopyridine (I) (1). Other 2-fluoropyridine processes (unspecified yield) include the fluorination (free fluorine) of pyridine (2) and the reaction of 2-pyridone with cyanuric fluoride (3).

Recently, a novel route involving the potassium fluoride exchange technique with 2-chloropyridine (III) in polar solvents, e.g., dimethylsulfone and tetramethylene sulfone ("sulfolane"), gave 49.5-58.0% yields of 2-fluoropyridine (II) (4,5). The reaction proceeded sluggishly as evidenced by long reaction times (510 hours/210°). With other polar solvents, dimethylsulfoxide or dimethylformamide, 2-chloropyridine was resistant to fluorination with potassium fluoride (6).
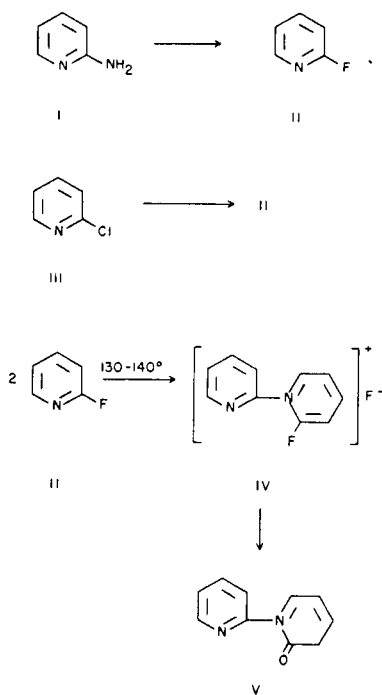
The potassium fluoride exchange technique was recently applied to pentachloropyridine under solvent-free conditions to give pentafluoropyridine (7,8). Such non-solvent conditions with potassium fluoride also effected conversion of o-chloronitrobenzene to o-fluoronitrobenzene (9). Since aza-activation (polar effect) of halogen in 2-chloropyridine is qualitatively of the same type as exerted by the exocyclic nitro group in o-chloronitrobenzene, the corresponding solvent-free fluorination (potassium fluoride) of 2-chloropyridine was investigated. The results were disappointing. At 375-420°, reductive dehalogenation of 2-chloropyridine to give pyridine (24.1% yield) occurred; the bulk of the 2-chloropyridine was converted to a carbonaceous mass. Carbonization also predominated at 315°; minor quantities (< 1% yield) of 2-fluoropyridine and pyridine were obtained. At lower temperatures (250°), 2-chloropyridine was relatively inert (> 90% recovery); trace quantities of 2-fluoropyridine and pyridine were formed. However, the use of potassium bifluoride in the above reaction at 315° provided a 74% yield of 2-fluoropyridine; under the same conditions, sodium bifluoride furnished a 3.5% yield of this product.

The above observations may be interpreted in light of several factors: activation of the substrate, properties of the fluorinating agents, and the stability of 2-fluoropyridine.

A. Activation of the Substrate.

Since Finger (5,6) and Hamer (4) demonstrated that the carbon-chlorine bond in 2-chloropyridine either resisted fluorination with potassium fluoride in polar solvents or proceeded sluggishly (510 hours), competitive side reactions under solvent-free conditions can be envisaged. For example, self-condensation of 2-chloropyridine to give unknown product(s) has been reported when successively heated at 160-170° (10 days) and 200-220° (18 days) (10).

It has been suggested that the degradation encountered in the solvent-free fluorination (potassium fluoride) of the tetrachloropyridines above 420° might be attributed to hydrogen in the latter (7); structural considerations may also be a factor in the degradation encountered in the comparable fluorination (potassium fluoride) of 2-chloropyridine at 315°.

B. Fluorinating Agent.

The 2-chloropyridine-potassium fluoride system represents a heterogeneous mixture involving liquid-solid phases (m.p. potassium fluoride, 858° (11)). Replacement of potassium fluoride by potassium bifluoride, a relatively neglected fluorinating agent (12), provides a system consisting of two liquid phases (m.p. potassium bifluoride, 239° (13)). Thus, the 2-chloropyridine-potassium bifluoride reaction mixture (presumably as a dispersion of two liquids) proceeded smoothly at 315° to give a 74% uncorrected yield of 2-fluoropyridine (II). The solvent-free process with potassium bifluoride provides higher yields of this product and shorter reaction times than the corresponding reaction with potassium fluoride in polar solvents as summarized in Table I.

Sodium bifluoride was not as effective as potassium bifluoride. Under the same conditions (315°; 4 hours), a 3.5% yield of 2-fluoropyridine was achieved; the bulk of the 2-chloropyridine was converted to water- and ether-insoluble solids. The difference in behavior of potassium bifluoride and sodium bifluoride might be sought in their respective physical properties at 315°. While potassium bifluoride is a liquid at this temperature; its dissociation pressure at 315° is approximately 150 mm (13). Potassium bifluoride must be heated to about 400° to cause the vapor pressure of hydrogen fluoride to be one atmosphere (14). In contrast, this pressure (1 atmosphere) is achieved at lower temperatures (278°) with sodium bifluoride (15). Thus, for the sodium bifluoride-2-chloropyridine system at 315°, the fluorinating agent is a solid (m.p. sodium fluoride, 992° (11)), similar to that encountered in the corresponding reaction with potassium fluoride.

C. Stability of 2-Fluoropyridine.

The reported thermal instability of 2-fluoropyridine could also play a critical role in the high temperature fluorination of 2-chloropyridine. For example, 2-fluoropyridine has been self-condensed at 130-140° (glass ampoules; 240 hours) to give N-(2-pyridyl)-2-fluoropyridinium fluoride (IV) in approximately 46% yield (10, 16). (Compound IV was characterized by hydrolysis to N-(2-pyridyl)-2-pyridone (V)). The successful isolation of 2-fluoropyridine with the potassium bifluoride fluorination system at 315° might be attributed to a rate factor (4 hours). The effect of longer reaction times was not investigated.

Several mechanisms may be considered.

a) Bifluoride ion as the nucleophile: potassium bifluoride might exhibit sufficient solubility in 2-chloropyridine to effect fluorination. Alternatively, the physical state of potassium bifluoride at 315° provides a dual liquid system, thereby permitting halogen displacement by potassium bifluoride at the interface of the two liquid phases.

b) Fluoride ion as the attacking species: Since partial dissociation of potassium bifluoride to potassium fluoride and hydrogen fluoride occurs at 315°, the following alternative sequences could be envisaged:
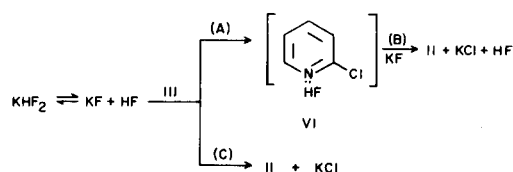
By one sequence (Steps A and B), 2-chloropyridine may be activated by in situ formation of 2-chloropyridinium hydrofluoride (VI), followed by displacement with potassium fluoride to give 2-fluoropyridine. Alternatively, fluorination of 2-chloropyridine may be achieved through displacement by potassium fluoride (presumably soluble in the potassium bifluoride melt) (Step C).

It should be noted that the weak basicity of 2-fluoropyridine (17,18) permitted its isolation as the free base. Therefore, the preferred mechanism for the conversion of 2-chloropyridine to 2-fluoropyridine by potassium bifluoride need not designate the product as the hydrofluoride salt.

EXPERIMENTAL

1. Analytical.

VPC was employed to monitor the extent of fluorination: F and M Chromatograph, Model 200: 2 meter; 15% XF 1150 General Electric Nitrile Silicone on Chromosorb W (80-100 mesh); temperature, 100° isothermal for 6 minutes, then programmed to 150° at 13°/minute; sample size, 5 μl; helium flow, 5.7 sec./10 ml.; injection port temp., 140°; block temp., 225°.

The following retention times were noted: 2-chloropyridine, 13.5 cm.; 2-fluoropyridine (Columbia Organics), 6.0 cm.; and, pyridine, 4.7 cm.

2. Potassium Bifluoride as a Fluorinating Agent.

A monel rocking microautoclave containing 2-chloropyridine (1.0 mole; 113.6 g.; Olin Mathieson, assay (VPC): 98.9%) and potassium bifluoride (1.5 moles; 117.0 g.; Baker and Adamson; assay 99.6%) was purged with nitrogen and the contents heated to 315° (550 p.s.i.g.) for 4 hours. The reaction mixture was cooled to room temperature and extracted with diethyl ether. The insoluble inorganic salts were filtered and dissolved in water. Analysis of the aqueous solution showed 0.937 g.-atom chloride ion, corresponding to 93.7% conversion of 2-chloropyridine. The ether extract was dried (magnesium sulfate) and concentrated to give 77.0 g. of a liquid. VPC revealed: 2-fluoropyridine, 93.2%

TABLE I

Solvent	Fluorinating Agent	Time (hours)	Temp. (°C)	% Yield 2-Fluoropyridine	Ref.
None	KHF_2	4	315	74%	This Study
None	$NaHF_2$	4	315	3.5%	This Study
None	KF	4	315	< 1%	This Study
$DMSO_2$	KF	510	210	49.5%	(5)
Sulfolane	KF	510	210	58%	(5)

(or 74% uncorrected yield); 2-chloropyridine, 6.2% (or 96% conversion). Only trace quantities of pyridine could be detected. Distillation provided 63.7 g. (65.8% in-hand yield) of a center-fraction, b.p. 126-128°, n_D^{27} 1.4662. (Reported for 2-fluoropyridine: b.p. 125° (1a); 126-127° (5); n_D^{20} 1.4678 (1a); $n_D^{23.5}$ 1.4663 (5)). The infrared spectrum was identical with that of a reference standard sample of 2-fluoropyridine (Columbia Organics). The unidentified water- and ether-insoluble solids, m.p. > 320°, weighed 3.05 g.

3. Sodium Bifluoride as a Fluorinating Agent.

Under similar conditions, a mixture of 2-chloropyridine (1 mole; 113.6 g.) and sodium bifluoride (1.5 moles; 91.0 g.; Baker and Adamson; assay, 98%) was heated at 315° for 4 hours (525 p.s.i.g.). The aqueous layer contained 0.09 g.-atom of chloride ion, which corresponded to 9% conversion of 2-chloropyridine. Concentration of the ether extract gave 6.6 g. of a liquid, which was found by VPC to contain: 2-fluoropyridine, 51.4% (3.5% uncorrected yield); 2-chloropyridine, 41.5% (97.4% conversion). The bulk of the consumed 2-chloropyridine can be accounted for as water- and ether-insoluble solids, m.p. > 350°, wt. 90.0 g.

4. Potassium Fluoride as a Fluorinating Agent.

A mixture of 2-chloropyridine (1.0 mole; 113.6 g.) and potassium fluoride (1.5 moles; 87.5 g.; Baker and Adamson, dried at 100°/0.5 mm. for 18 hours) was heated at 375-420° for 4 hours (350 p.s.i.g.). Considerable degradation had occurred. Without extracting inorganic salts, the carbonaceous mass was distilled to give a liquid, b.p. 105-120°, n^{20} 1.4909, which was primarily pyridine (VPC) (wt. 18.75 g.; 0.241 mole); no 2-fluoropyridine was found. The distillation residue (180 g.) was a black porous solid.

The above reaction was also conducted at 315° for 4 hours (150 p.s.i.g.). The inorganic salts were extracted with water (0.753 g.-atom of chloride). The black water-insoluble carbonaceous reaction product was extracted with diethyl ether; concentration of this extract provided 3.3 g. of a liquid which assayed (VPC): 2-fluoropyridine, 48.3% (0.4% uncorrected yield); pyridine, 50.7% (0.5% uncorrected yield); and 2-chloropyridine, 1% (99.3% conversion).

When the above reaction was conducted at 250° (4 hours) with 2-chloropyridine (1 mole; 113.6 g.) and potassium fluoride (1.2 moles; 69.7 g.), negligible fluorination resulted. Analysis of the aqueous extract revealed 0.055 g.-atom of chloride ion had been liberated. VPC analysis of the organic layer revealed: 2-fluoropyridine (0.011 mole; 1.1% uncorrected yield); pyridine, (0.005

mole; 0.5% yield); 2-chloropyridine (0.91 mole; 9% conversion).

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