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HETEROCYCLIC AROMATIC FLUORIDES BY A MODIFIED SCHIEMANN METHOD (1)

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INTRODUCTION

The Schiemann Reaction (2) has long been employed by organic chemists as the most efficient means of introducing flourine into aromatic systems. The method is basically simple (equation 1) and involves diazotization of a primary aromatic amine in hydrochloric acid followed by the addition of fluoboric acid (HBF_4) to the cold solution of the diazonium chloride. The precipitated diazonium fluborate is then filtered from the reaction mixture and thermally decomposed to yield the aromatic flouride. The success of

$$(1)\quad ArNH_2 \xrightarrow[NaNO_2\ 0^\circ]{HCl} ArN_2^+Cl^- \xrightarrow{HBF_4} ArN_2^+BF_4^- \xrightarrow{\Delta} ArF + N_2 + BF_3$$

the method lies in the fact that the diazonium fluborates are usually formed in good yields and their stability permits thorough washing and purification before thermal decomposition. Furthermore, these diazonium salts decompose smoothly without violence to generally give good yields of the desired fluoride.

Rutherford and co-workers have shown that replacement of fluoboric acid with hexafluorophosphoric acid (HPF_6) in the Schiemann Reaction (equation 2) results in much improved yields of aromatic fluoride from aromatic amine (3). The following significant yield increases were realized over the classical Schiemann method:

$$(2)\quad ArNH_2 \xrightarrow[NaNO_2 0^\circ]{HCl} ArN_2^+Cl^- \xrightarrow{HPF_6} ArN_2^+PF_6^- \xrightarrow{heat} ArF + N_2 + PF_5$$

o-fluorobenzoic acid from anthranilic acid (+52%); *p*-fluorobenzoic acid from *p*-aminobenzoic acid (+ 49%); *p*-bromofluorobenzene from *p*-bromoaniline (+27%); and *p*-fluoroanisole from *p*-aminoanisole (+23%). Small yield increases were noted in numerous other cases. The success of the HPF_6 method was attributed to the increased insolubility of the diazonium hexafluorophosphates ($ArN_2^+ PF_6^-$) which would permit more efficient isolation and purification before decomposition. Furthermore, phosphorus pentafluoride, a weaker Lewis acid than boron trifluoride, would be expected to promote less polymerization during decomposition.

RESULTS AND DISCUSSION

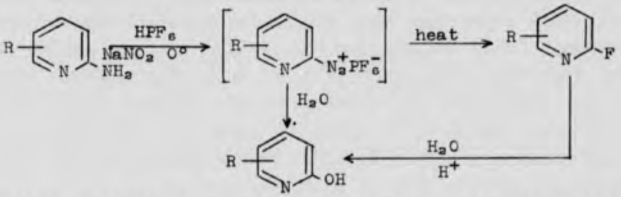
Our extension of this modified method to several aromatic amines in the heterocyclic series, i.e. pyridines and quinolines has surprisingly revealed a predominant inferiority of HPF_6 to HBF_4

(see Table I; the HBF_4 yield data are taken from the literature). The rather large differences in yields of fluorides from the 2-aminopyridines may be experimentally accounted for. In these instances it was necessary to diazotize the amines directly in the presence of HPF_6 since the resulting diazonium hexafluorophosphates are too unstable to be isolated before decomposition (8) (equation 3).

$$(3)\quad ArNH_2 \xrightarrow[NaNO_2 0^\circ]{HPF_6} ArN_2^+PF_6^- \longrightarrow ArF + N_2 + PF_5$$

The amine hydrohexafluorophosphates ($ArNH_3^+$ PF_6^-) which precipitate at the low temperature required for diazotization require rather large quantities of water for dissolution before diazotization. Thus, diazonium hexafluorophosphate hydrolysis would appear to be a probable competitive side reaction to normal diazonium salt decomposition. In addition, acid-catalyzed hydrolysis of the initially formed fluoroderivative could be operative to a large extent (9). Either of these side reactions would result in pyridol side products as depicted in Scheme I.

Scheme I



As indicated in Table I pyridols were indeed observed in addition to the fluorides in the series of 2-aminopyridines studied. That acid-catalyzed fluoride hydrolysis could be at least partially responsible for the pyridol formation was established by independent experiment. Under the conditions of the formation of 2-fluoro-3-methylpyridine, pure 2-fluoro-3-methylpyridine was converted to 2-hydroxy-3-methylpyridine in 31% yield. It is assumed that similar results would be obtained in other specific cases. The pyridols were identified by mixed melting point determinatons with authentic samples prepared by diazotization (and subsequent hydrolysis) of the appropriate 2-aminopyridine.

In those cases (i.e., 3-aminopyridine and 3-aminoquinoline) where the stability of the diazonium hexafluorophosphate permitted their isolation before decomposition, the resulting yields of aromatic fluorides more nearly paralleled those obtainable by the HBF_4 method, with no accompanying pyridol formation.

EXPERIMENTAL SECTION

General Information. Hexafluorophosphoric acid is available as a 65% aqueous solution from the Ozark-Mahoning Co., Tulsa, Oklahoma. All diazotizations were carried out in a polyethylene beaker and measured quantities of hexafluorophosphoric acid were added from a polyethylene graduate cylinder. A positive qualitative test for fluorine (10) was obtained on each fluoride, and a positive ferric chloride test (11) on each pyridol. Melting points and boiling points are uncorrected.

The 2-fluoropyridines.

2-Aminopyridine or the appropriately substituted 2-aminomethylpyridine (aminopicoline); (0.28 mole) was dissolved in a mixture of water (110 ml.) and 65% hexafluorophosphoric acid (125 ml.). The solution was cooled at -5°, and solid, finely-divided sodium nitrite (0.281 mole) was added in small portions over a period of 1.5 hr. with efficient magnetic stirring and rigorous temperature control (-5 to 0°) being maintained. At the end of the nitrite addition the solution was stirred at room temperature for 30 minutes followed by warming to 45° for 30 minutes to insure complete decomposition of the diazonium hexafluorophosphate. The crude fluoride was obtained by cooling the solution to 5-10°, followed by careful neutralization with sodium carbonate and steam distillation. The oil which separated from the steam distillate was removed, and the aqueous distillate was saturated with sodium sulfate and extracted with ether (50 ml.). The oil and ether extract were combined and dried over anhydrous sodium sulfate. After removal of the ether the appropriate fluoropyridine was distilled at atmospheric pressure. Physical data are summarized in Table II.

The 2-pyridols.

The residues from the steam distillation of the fluoropyridines were cooled and the solid material filtered and recrystallized from benzene to yield the appropriate pyridols. Yield and physical data are reported in Table III.

Preparation of authentic pyridol samples:

The appropriate aminopyridine (0.10 mole) was dissolved in a mixture of sulfuric acid (30 ml.) and water (50 ml.) and the resulting solution diazotized at 0° by the dropwise addition of a solution of sodium nitrite (.11 mole) in water 25 ml.). The solution was then warmed to 70° for 1 hr., cooled to 10°, and made basic with aqueous ammonia. The crude pyridols which precipitated were recrystallized from benzene.

HPF_6 Hydrolysis of 2-fluoro-3-methylpyridine.

2-Fluoro-3-methylpyridine (5.0 g.) was dissolved in a mixture of water (20 ml.) and 65% hexafluorophosphoric acid (20 ml.), and the resulting solution warmed at 45° for 40 min. The solution was cooled to 10°, made basic with sodium carbonate, and the resulting mixture subjected to steam distillation. The steam distillate yielded

2.7 g. (54% recovery) of starting material. The pot residue from the steam distillation deposited 1.52 g. (31%) of 2-hydroxy-3-methylpyridine, m.p. 138°.

3-Fluoropyridine.

3-Aminopyridine (18.8 g.; 0.2 mole) was dissolved in a mixture of water (100 ml.) and concentrated hydrochloric acid (75 ml.) and cooled to 0° with stirring. Sodium nitrite (15.4 g.; 0.22 mole) dissolved in water (30 ml.) was added slowly to the cold, acid solution over a period of twenty minutes, maintaining the temperature below 5°. Hexafluorophosphoric acid (70 ml.) was then added to the cold solution causing instant precipitation of the diazonium hexafluorophosphate. Complete precipitation of the diazo compound was insured by added a few pieces of ice to the suspension and allowing the mixture to stand in an ice bath for thirty minutes. The salt was filtered and washed with 50 ml. portions of ice-cold water, methanol, and ether respectively. A small portion of the slightly moist salt was found to decompose at 45°. If this diazonium salt is allowed to become dry, it will decompose spontaneously at room temperature. Thus, it is necessary to proceed directly to the decomposition step without drying and weighing the salt.

The slightly moist salt was transferred to a three-necked, round-bottomed flask equipped with two condensers and covered with petroleum ether (150 ml.; b.p. 60-90°). Decomposition began at room temperature, and the flask was heated gently in order to facilitate smooth decomposition. When gas evolution subsided, the mixture was refluxed gently for one hour to insure complete decomposition. The solution was then cooled, concentrated hydrochloric acid (10 ml.) was added, followed by removal of petroleum ether at reduced pressure. The petroleum ether distillate was extracted with 25% hydrochloric acid (25 ml.) and the acid extract returned to the residue in the boiler. The acid solution was cooled to 10°, made basic with sodium hydroxide solution, and the alkaline solution steam distilled. Solid sodium hydroxide was added to the steam distillate and the oil which separated removed. Ether extraction at this point is not desirable since the product azeotropes with ether (4). The oil was dried over sodium hydroxide and distilled to give 7.5 g. (38.5%) of clear, colorless 3-fluoropyridine, b.p. 107-108° (763 mm.), n_D^{25} 1.4689 (lit. (4) b.p. 105-107° at 752 mm.; n_D^{25} 1.4700).

3-Fluoroquinoline.

3-Aminoquinoline (28.8 g.; 0.20 mole) was dissolved in a mixture of water (250 ml.) and concentrated hydrochloric acid (85 ml.) and cooled to 0° with stirring. Diazotization of the cold solution was performed by the dropwise addition of sodium nitrite (15.4 g.; 0.22 mole) in water (35 ml.). The amine hydrochloride, which began to separate, disappeared as the diazotization proceeded. Precipitation of the yellow 3-quinoline-diazonium hexafluorophosphate was accomplished by addition of 65% hexafluorophosphoric acid (90 ml.), to the cold, diazotized solution. After allowing the slurry to stand in the ice bath for one hour, the yellow salt was filtered and washed with cold 100 ml. portions of water, methanol, and ether respectively. The air-dried salt weighed 58.7 g. (97.5% from the amine). The decomposition point was found to be 96°.

The dry salt (30 g.) was transferred to a round-bottomed flask and covered with dry toluene (150 ml.). A spiral condenser was attached, and the flask was heated gently under the hood to facilitate smooth decomposition. Once decomposition began, it was rapid, as evidenced by expulsion of white phosphorous pentafluoride fumes. After gas evolution had moderated, the solution was gently refluxed for one hour. The toluene was decanted and extracted with 50 ml. portions of 30% hydrochloric acid, with the acid extracts being returned to the decomposition flask. The acid solution was steam distilled to remove a small amount of toluene, then cooled to 15° and neutralized with a 50% sodium carbonate solution. The steam distillation was continued whereupon white solid collected in the condenser and receiving flask. The solid, evidently a hydrae of 3-fluoroquinoline (7), was separated and the aqueous dstillate saturated with sodium sulfate and extracted twice with ether (75 ml.). The white solid was added to the ether extracts and dissolved; the resulting solution was dried over anhydrous sodium sulfate. After removal of ether at atmospheric pressure, 3-fluoroquinoline (7.0 g.; 45% from the amine) dstilled, b.p. 96-97° (10 mm.), n_D^{25} 1.5900 (lit. (7) b.p. 102° at 15 mm.; n_D^{25} 1.5902).

In another experiment, the diazonium salt (58.7 g.) was decomposed in heavy mineral oil (350 ml.) preheated to 100°. The product, which was isolated by steam distillation and worked up as above, weighed 14.1 grams (48%), b.p. 96-97° (10 mm.).

TABLE I

Aromatic Amine	Aromatic Fluoride	% yld. (HBF_4 method)	Lit. Ref.	% yld. (HPF_6 method)	% yld. pyridol (HPF_6 method)
2-aminopyridine	2-fluoropyridine	34	(4)	20	39
2-amino-3-methyl-pyridine	2-fluoro-3-methyl-pyridine	48	(5)	32	28
2-amino-4-methyl-pyridine	2-fluoro-4-methyl-pyridine	36	(6)	24	27
2-amino-5-methyl-pyridine	2-fluoro-5-methyl-pyridine	46	(5)	39	22
2-amino-6-methyl-pyridine	2-fluoro-6-methyl-pyridine	34	(6)	25	33
3-aminopyridine	3-fluoropyridine	50	(4)	39	—
3-aminoquinoline	3-fluoroquinoline	53	(7)	48	—

TABLE II

Fluoropyridine	yld. grams (%)	obs. b.p.	obs. ref. ind.	rept'd b.p.	rept'd ref. ind.	lit. ref.
2-fluoropyridine	5.4 (20)	126°	n_D^{26}1.4706	125°	n_D^{25}1.4700	(4)
2-fluoro-3-methyl-pyridine	9.9 (32)	149-150°	n_D^{26}1.4686	150-151°	not rept'd	(5)
2-fluoro-4-methyl-pyridine	8.4 (24)	155°	n_D^{25}1.4692	157°	n_D^{25}1.4690	(6)
2-fluoro-5-methyl-pyridine	12.0 (39)	156°	n_D^{24}1.4680	155-156°	not rept'd	(5)
2-fluoro-6-methyl-pyridine	7.7 (25)	142-144°	n_D^{25}1.4675	142°	n_D^{25}1.4673	(6)

TABLE III

Pyridol	yld. gms. (%)	obs. m.p.	reported m.p.	lit. reference
2-hydroxypyridine	2.7 (39)	104-105°	106°	(12)
2-hydroxy-3-methyl-pyridine	3.0 (28)	138°	140°	(13)
2-hydroxy-4-methyl-pyridine	2.9 (27)	127-128°	130°	(14)
2-hydroxy-5-methyl-pyridine	2.4 (22)	182°	183-184°	(15)
2-hydroxy-6-methyl-pyridine	3.6 (33)	159°	158°	(16)

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