The Synthesis of 4-Fluorolutidines and 4-Fluoropyridine

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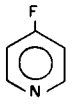
In a study of acid-base equilibria using fluorine-19 nmr we needed a fluorine tagged base in which the fluorine would have great sensitivity, yet be removed from the site of acid-base interaction. Such a base is 4-fluoropyridine, in which the fluorine is in direct conjugation with the basic ring nitrogen.

Wibaut and Holmes-Kamminga (1) have reported the synthesis of 4-fluoropyridine (**1**) by the diazotization of 4-aminopyridine in concentrated hydrofluoric acid. Their yield was very poor and the liquid compound decomposed rapidly. Profft and Richter (2) prepared 4-fluoro-2-picoline by the diazotization of 4-amino-2-picoline in 48% fluoboric acid. They found that the methyl group in the 2-position gave added stability to the compound which could be kept for long periods of time without decomposition.

Since one methyl group gave added stability we decided to synthesize three isomeric 4-fluorolutidines having even greater stability and base strength due to the additional methyl group. We report here both the synthesis



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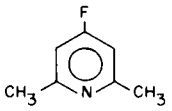

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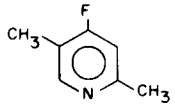

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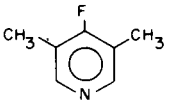

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of these three new 4-fluorolutidines as well as a method for the synthesis of 4-fluoropyridine such that it may be obtained in solution and stored without decomposition.

The fluorolutidines were synthesized by the Schiemann reaction, *e.g.*, the diazotization of the corresponding amine in fluoboric acid. It was possible to steam distill 4-fluoro-2,6-lutidine (**2**) and 4-fluoro-2,5-lutidine (**3**) from the reaction mixture. However, the desired product could not be obtained when 4-fluoro-3,5-lutidine (**4**) was steam distilled. For this compound, it was, however, possible to isolate it by extraction with chloroform from the reaction mixture followed by fractional distillation.

The instability of 4-fluoro-3,5-lutidine upon steam distillation led us to examine conditions which would favor stability. Under weakly basic conditions all of the compounds were stable. However, they could all be easily hydrolyzed with dilute acid. The order of stability observed toward acid hydrolysis was found to be:

4-Fluoro-2,6-lutidine (**2**) > 4-fluoro-2,5-lutidine (**3**) > 4-fluoro-3,5-lutidine (**4**). Clearly the placement of the methyl groups is vitally important in the stabilization of the 4-fluoro group. Methyl groups adjacent to the ring nitrogen appear to stabilize the fluorine more than methyl groups adjacent to the fluorine itself. In the 2- and 6-positions, the methyl groups can donate charge to the electron withdrawing ring nitrogen decreasing the activating influence toward nucleophilic attack at the 4-position.

It also appears that for these compounds acid hydrolysis is much more important than base hydrolysis. This has been observed for other halopyridines (3). With this in mind, we were able to synthesize 4-fluoropyridine (**1**) itself by taking advantage of its stability toward weak base. After diazotization of 4-aminopyridine in fluoboric acid, the mixture was made basic with sodium bicarbonate and extracted with methylene chloride which was then dried over sodium sulfate. This solution was then stored in the refrigerator and appears to be indefinitely stable. (We have kept one sample for over two months without change).

The fluoropyridines thus prepared can be stored and their ^{19}F-nmr taken. Acid-base equilibria studies are being investigated with these compounds.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The proton nmr spectra were determined with a Varian A-60 spectrometer. Fluorine-19 nmr were determined with a Varian HA-60 operating at 56.45 MHz. Analyses were performed by Spang Micro-Analytical Laboratory, Ann Arbor, Michigan.

4-Fluoropyridine (**1**).

Twenty g. (0.21 mole) of 4-aminopyridine was dissolved in 80 ml. of 48% fluoboric acid and cooled to 0°. Keeping the temperature below 10°, the amine was diazotized by adding 14.7 g. (0.21 mole) of sodium nitrite in small portions with constant stirring. After the addition was complete, the solution was allowed to stand at ice bath temperature for one hour. It was then warmed slowly to room temperature to decompose the diazonium salt. After evolution of nitrogen ceased, the solution was quickly cooled to 0° and neutralized with solid sodium bicarbonate. The resulting solution was then extracted with 100 ml. of methylene chloride and dried over anhydrous sodium sulfate. The resulting solution was 0.54 *M* in 4-fluoropyridine and was stable when kept in the refrigerator. No attempt was made to isolate the pure 4-fluoropyridine due to its instability in the pure state; ^{1}H nmr: $\delta_{3,5}$ = 7.53 ppm; $\delta_{2,6}$ = 9.16 ppm; $J_{H(2)\text{-}F}$, $J_{H(3)\text{-}F}$ = 8.5 cps; ^{19}F-nmr: 8.78 ppm downfield from internal fluorobenzene (methylene chloride).

4-Fluoro-3,5-lutidine (**4**).

Ten g. (0.082 mole) of 4-amino-3,5-lutidine (4) was diazotized in the same manner described for 4-fluoropyridine in 50 ml. of 48% fluoboric acid with 5.65 g. (0.082 mole) of sodium nitrite. After neutralization, the solution was extracted with chloroform, dried, and then fractionally distilled to yield 1.75 g. (9%) of product, b.p. 160°; ^{1}H nmr: δ_{CH_3} = 2.20 ppm; $\delta_{2,6}$ = 8.19 ppm; J_{CH_3F} = 1 cps; $J_{H(2)\text{-}F}$ = 10 cps; ^{19}F nmr: 2.55 ppm upfield from internal fluorobenzene (carbon tetrachloride); picrate, m.p. 187°.

Anal. Calcd. for $C_{13}H_{11}FN_4O_7$: C, 44.08; H, 3.13; N, 15.82. Found: C, 44.15; H, 3.03; N, 15.80.

4-Fluoro-2,6-lutidine (**2**).

4-Amino-2,6-lutidine (5) 5.4 g. (0.045 mole) was diazotized by the same procedure used for 4-fluoropyridine in 30 ml. of 48% fluoboric acid with 3.05 g. (0.045 mole) of sodium nitrite. After neutralization, the solution was subjected to steam distillation, the distillate was then cooled, and the solid product was filtered off, yield 1 g., (18%), m.p. 28°; ^{1}H nmr: δ_{CH_3} = 2.46 ppm; $\delta_{2,6}$ = 6.63 ppm; $J_{H(2)\text{-}F}$ = 9.5 cps; ^{19}F nmr: 6.40 ppm downfield from internal fluorobenzene (carbon tetrachloride); picrate, m.p. 184-185° (lit. (7) m.p. 191°).

Anal. Calcd. for $C_{13}H_{11}FN_4O_7$: C, 44.07; H, 3.12; N, 15.81. Found: C, 44.08; H, 3.13; N, 15.78.

4-Fluoro-2,5-lutidine (**3**).

4-Amino-2,5-lutidine (6) 9.5 g. (0.078 mole) was diazotized using the same method for 4-fluoropyridine in 60 ml. of 48% fluoboric acid with 5.4 g. (0.078 mole) of sodium nitrite. After neutralization the solution was subjected to steam distillation. The oily layer was separated from the distillate, dried over potassium hydroxide pellets and distilled to yield 3.5 g. (36%) of product, b.p. 133°; ^{1}H nmr: δ_{CH_3}(5) = 2.16 ppm; δ_{CH_3}(2) = 2.38 ppm; δ_3 = 6.58 ppm; δ_6 = 8.00 ppm; $J_{H(3)\text{-}F}$ = 10 cps; $J_{H(6)\text{-}F}$ = 10.5 cps; F nmr: 2.23 ppm downfield from internal fluorobenzene (carbon tetrachloride); picrate, m.p. 185°.

Anal. Calcd. for $C_{13}H_{11}FN_4O_7$: C, 44.07; H, 3.12; N, 15.81. Found: C, 44.10; H, 3.12; N, 15.63.

REFERENCES

(1) J. P. Wibaut and W. J. Holmes-Kamminga, *Bull. Soc. Chim. France*, 424 (1958).

(2) E. Profft and H. Richter, *J. Prackt. Chem.*, **9**, 164 (1959).

(3) H. L. Bradlow and C. A. Vander Werf, *J. Org. Chem.*, **14**, 509 (1949).

(4) J. M. Essery and K. Schoefield, *J. Chem. Soc.*, 4953 (1960).

(5) T. Kato and F. Hamaguchi, *Pharm. Bull.*, **4**, 174 (1956).

(6) J. Koncewicz and Z. Skrowaczewska, *Rocz. Chem.*, **42**, 1873 (1968).

(7) T. Talik and Z. Talik, *ibid.*, **44**, 1249 (1970).