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The Synthesis and Nucleophilic Displacement Reactions of Fluoropyrazine

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Sir:

We wish to report the synthesis of fluoropyrazine from aminopyrazine by a Schiemann reaction. The isolation of this compound in 23% yield (2) via a diazonium salt was surprising in view of the reported failure of aminopyrazine to undergo Sandmeyer reactions with the formation of chloro or bromopyrazine (3). Preliminary results indicate that fluoropyrazine exhibits considerably greater reactivity towards nucleophilic agents than 2-fluoropyridine, chloro- or iodopyrazine.

Fluoropyrazine was prepared from aminopyrazine (25 g.) in 40% fluoroboric acid (150 ml.) at -5 to 0° by slow addition of a slight excess of solid sodium nitrite (19 g.). In the presence of a small amount of copper powder (1 g.) the initially formed heavy suspension of diazonium salt gradually dissolved with evolution of nitrogen. After brief warming to room temperature the reaction mixture was cooled to 0-5°, carefully neutralized with solid sodium carbonate (4), and extracted exhaustively with ether. Double fractionation afforded 6.0 g. (23%) of fluoropyrazine, a colorless, mobile liquid, b.p. 108-109.5°/atm., $n_D^{24} = 1.4661$.

Anal. Calcd. for $C_4H_3FN_2$: C, 48.98; H, 3.08; N, 28.56; F, 19.38. Found: C, 48.86; H, 3.17; N, 28.44; F, 19.21.

Infrared spectrum: 1265 cm^{-1} strong (C-F).

Ultraviolet spectrum: λ max (95% EtOH), 261 and 266 $m\mu$ (ϵ , 5,300); λ max (0.01 N NaOH or HCl), 264 $m\mu$ (ϵ , 5,200).

Fluoropyrazine slowly hydrolyzed in 0.01 N sodium hydroxide solution at room temperature ($t_{1/2}$, 5-6 days), more rapidly in excess 1.07 sodium hydroxide solution at 26.0 ($t_{1/2}$, 43 minutes) following pseudo-first-order kinetics. Under the latter conditions chloropyrazine had a half-life of 18 days while iodopyrazine and 2-fluoropyridine remained unchanged. Hydrolysis in 6 N hydrochloric acid solution at room temperature proceeded at a much slower rate ($t_{1/2}$, 4 days) in contrast to 2-fluoropyridine (5) and 2-fluorohypoxanthine (6) which are reported to hydrolyze more readily in acid media, an effect attributed to N-protonation and resultant weakening of the C-F bond. Absence of this effect and a lack of a shift in the λ max in 6 N hydrochloric acid solution suggest low basicity of fluoropyrazine.

Hydrolysis of fluoropyrazine with N sodium hydroxide solution on a preparative scale produced pyrazinol which was isolated in 93% yield by sublimation. Ammonolysis of fluoropyrazine in 28% aqueous ammonia at room temperature for one week yielded aminopyrazine, m.p. (sublimed): 116-118° (lit. m.p.: 117-118°) (7), in 70% yield. Methanolic ammonia at room temperature or anhydrous ammonia in boiling benzene failed to react. Similar yields had been obtained with chloropyrazine at 200° (3). Benzylamine (2.2 moles) in methanol at room temperature for 3 days afforded a 74% yield of benzylaminopyrazine, m.p. (sublimed): 71-71.5°, m.p. of picrate (EtOH): 139.5-140° (lit. m.p. 67-68° and 140-141°, respectively) (8). Refluxing fluoropyrazine with aqueous sodium sulfite (1.5 moles) for 2 hours gave sodium pyrazine sulfonate in 75% yield, m.p. (95% EtOH): 290-292° dec. (lit. m.p. 295° dec.) (9,10), while reaction of chloropyrazine at 150° for 12 hours with the same reagent resulted in a 44% yield (11). The significantly greater reactivity of fluoropyrazine towards nucleophiles is currently under further investigation.

REFERENCES

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