[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of Heterocyclic Fluorine Compounds by the Schiemann Reaction. I. The Monofluoropyridines

BY ARTHUR ROE AND G. F. HAWKINS

The Schiemann reaction has been used with considerable success in the preparation of aromatic fluorides, but there seems to be no record in the literature of the preparation of any heterocyclic fluorides by this method. Elderfield[1] and co-workers report an unsuccessful attempt to prepare 5-fluoro-6-methoxyquinoline using this procedure; they obtained an 83% yield of the diazonium fluoborate, but were unable to obtain anything but a tar by thermal decomposition of the fluoborate. Smith, Elisberg and Sherrill[2] report that the diazonium fluoborate of 6-amino-4-quinazolone was obtained in almost quantitative yield from the amine; they were interested in the preparation of 6-methoxy- rather than 6-fluoro-4-quinazolone, however, and did not try the Schiemann reaction. Steck, Hallock and Holland[3] indicate that some quinolines containing fluorine and other substituents will be discussed in an article to be published in the near future. Another point of interest in this connection is the statement of Whaley and Starkey[4] that pyridine causes decomposition of diazonium fluoborates.

An attempt to extend the scope of the Schiemann reaction by investigating its usefulness in the preparation of heterocyclic fluorine compounds is being carried out in this Laboratory. The first compounds studied were the three aminopyridines. Preparation of 2- and 3-fluoropyridine from the corresponding amines in over-all yields of 34 and 50%, respectively, was achieved. Both of these compounds had been previously prepared from the amines by diazotization in hydrofluoric acid; Chichibabin[5] reported a 25% yield of 2-fluoropyridine, and Binz and Räth[6] prepared 3-fluoropyridine in 22% yield.

In contrast to the diazonium fluoborates of most aromatic compounds, which are quite stable, both 2- and 3-pyridinediazonium fluoborate are quite unstable, thus necessitating some modification of the usual Schiemann technique. Attempts to isolate 2-pyridinediazonium fluoborate were unsuccessful because the compound decomposes as fast as it is formed; a 34% yield of 2-fluoropyridine was obtained by diazotization of 2-aminopyridine in fluoboric acid solution, followed by neutralization with sodium carbonate and steam distillation.

Isolation of 3-pyridinediazonium fluoborate was accomplished by diazotizing 3-aminopyridine with ethyl nitrite in ethanol–fluoboric acid solution; addition of ether when diazotization was complete caused precipitation of 3-pyridinediazonium fluoborate. This substance is stable when moist with ether below about 10°, but decomposes spontaneously and with considerable violence when the last trace of ether is removed. It decomposes smoothly, however, when a suspension of it in high-boiling petroleum ether is allowed to stand at 15–20°; a 50% yield of 3-fluoropyridine is obtained in this manner.

Apparently 4-pyridinediazonium fluoborate is unstable; isolation of it was accomplished only one time among many attempts. Solutions containing it start to decompose at about 15°. Efforts to isolate 4-fluoropyridine from these solutions in which decomposition had occurred were not successful; the compound apparently is quite unstable, as indicated by the appearance of a red color in the solution or ether extracts. A solid hydrochloride of 4-fluoropyridine was isolated, but its orange-red color and low fluorine content indicate that it was impure.

The instability of 4-fluoropyridine is not surprising in view of the fact that 4-chloropyridine starts to decompose a few hours after its formation, and 4-bromopyridine is even less stable. Wibaut and Broekman[7] present evidence showing that 4-chloropyridine reacts with itself forming N-(4′-pyridyl)-4-chloropyridinium chloride; 4-bromopyridine forms a comparable compound. Both these compounds hydrolyze easily to form N-(4′-pyridyl)-4-pyridone, the picrate of which melts at 195.5–196°. It seems likely that N-(4′-pyridyl)-4-pyridone is also formed by the decomposition of 4-fluoropyridine, as a picrate m.p. 193–5° was obtained in several of the attempted preparations of 4-fluoropyridine.

Work is continuing in this Laboratory on the introduction of fluorine into other heterocyclic nuclei.

Experimental

Preparation of the Amines.—The 2-aminopyridine was obtained from Eastman Kodak Co., m. p. 58–60°. The 3-aminopyridine was obtained from nicotinamide; 50 g. of nicotinamide treated with a solution of 65.6 g. of bromine and 92 g. of potassium hydroxide in 450 cc. of water upon being worked up in the usual manner formed 23 g. of 3-aminopyridine, m. p. 64°. The method of Koenigs and Greiner[8] was employed for the preparation of 4-aminopyridine; it was also made from isonicotinamide by a method similar to the one described above for 3-aminopyridine.

2-Fluoropyridine.—Of the several methods tried, the following proved to be the most satisfactory. A cold

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(1) Elderfield, Gensler, Williamson, Griffing, Kupchan, Maynard, Kreysa and Wright, THIS JOURNAL, **68**, 1584 (1946).

(2) Smith, Elisberg and Sherrill, *ibid.*, **68**, 1301 (1946).

(3) Steck, Hallock and Holland, *ibid.*, **68**, 1241 (1946).

(4) Whaley and Starkey, *ibid.*, **68**, 793 (1946).

(5) Chichibabin and Rjazancev, *J. Russ. Phys.-Chem. Soc.*, **47**, 1571 (1915).

(6) Binz and Räth, *Ann.*, **486**, 95 (1931).

(7) Wibaut and Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

(8) Koenigs and Greiner, *Ber.*, **64**, 1049 (1931).

solution of 30 g. of 2-aminopyridine in 125 cc. of 40% fluoboric acid was diazotized by the addition of 22.5 g. of sodium nitrite, the solid being added slowly in small portions with vigorous stirring. Since the diazonium salt decomposes almost immediately with liberation of heat, it is necessary to add the sodium nitrite slowly to keep the temperature below 10°. After an hour of standing in the ice-bath, the solution was warmed to 37° to complete the decomposition. A dark oil separated when the solution, cooled to 5°, was neutralized with sodium carbonate; the solution was steam-distilled and the 2-fluoropyridine was separated from the water layer; ether extraction at this point is not advisable because much of the product is lost on evaporation of the ether. When dried over sodium sulfate and distilled at 758 mm., the product (10.6 g., 34.2%) boiled at 125°; n^{20}_D 1.4674 (*cf.* ref. (5), b. p. 125.8° (752 mm.); n^{20}_D 1.4678). Decomposition of 2-fluoropyridine was indicated by the appearance of a yellow color after several days, and the formation of a white precipitate on longer standing.

3-Fluoropyridine.—The following procedure was the best of several tried: 12.5 g. of 3-aminopyridine was dissolved in a mixture of 50 cc. of 40% fluoboric acid and 100 cc. of 95% ethanol. The solution was cooled to 0° and a stream of ethyl nitrite[9] was passed in until no more of the diazonium fluoborate precipitated. Fifty cc. of cold ether was added to complete the precipitation, and the mixture was filtered while cold, washed once with cold ether and then once with cold petroleum ether. Care was taken not to allow the precipitate to become completely dry, for the dry diazonium salt will undergo spontaneous decomposition. The salt was then dampened with petroleum ether and transferred to a beaker containing cold high-boiling petroleum ether. The temperature of the mixture was kept below 25°; above this point the decomposition is uncontrollable, whereas from 15–25° the decomposition takes place slowly.

After the decomposition was complete a few cc. of conc. hydrochloric acid was added to assure salt formation, and the solvent removed under reduced pressure. The residue was made alkaline with sodium hydroxide solution, keeping the solution cold during the process. The solution was then distilled, and solid sodium hydroxide added to the distillate, whereupon an oil separated. The oil was dried with sodium hydroxide; the resulting 3-fluoropyridine boiled at 105–107° (752 mm.), n^{20}_D 1.4700 (*cf.* ref. (6), b. p. 106–108° (750 mm.)). The yield so obtained was 6.2 g. (48%); another 0.2 g. was recovered by reworking the mother liquor, bringing the total yield to 50%.

4-Fluoropyridine.—Methods similar to the ones which proved successful in the preparation of 2- and 3-fluoropyridine were tried without success. Diazotization of 4-aminopyridine appeared to take place rapidly at 0°; the fluoborate of the amine is less soluble than the diazonium fluoborate, so the precipitate dissolved as the diazotization progressed. When the diazotized solution was warmed to about 15° decomposition began, as evidenced by the evolution of nitrogen. When the decomposed diazotized solution was neutralized a red oil appeared, which turned more or less rapidly to a brown solid. When the neutralized solution was distilled the distillate had a pyridine-like odor which disappeared rapidly, the solution becoming amber in color. Treatment of any of the decomposition products with picric acid produced a solid picrate, m. p. 193–195°. This agrees with the melting point reported[7] for the picrate of N-(4′-pyridyl)-4-pyridone.

Summary

2-Fluoropyridine has been prepared in 34% yield and 3-fluoropyridine in 50% yield from the corresponding amines by the Schiemann reaction. Attempts to isolate the unstable 4-fluoropyridine by this method were unsuccessful.

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(9) Semon and Damerell, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 204.

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Ketene Dimers from Acid Halides

BY J. C. SAUER

Diketene, the first member of the ketene dimer series, is readily prepared in good yield by dimerizing ketene.[1] However, no satisfactory method for the synthesis of monosubstituted ketenes[2] ($RCH{=}C{=}O$) and, accordingly, the dimers from them, has been reported. The dehydrohalogenation of acid chlorides, either by pyrolysis[3] or by means of aliphatic tertiary amines,[4] has given low yields of ketene trimers. In the latter case, 2,4-pyranones were obtained but ketene dimers were not identified.

This paper describes a practical synthesis of dimers of monoalkyl ketenes.[5] The reaction involves the dehydrohalogenation of acid halides of the type RCH_2COX by aliphatic tertiary amines. The dehydrohalogenation of the acid halide is assumed to involve the formation of an intermediate ketene monomer which rapidly undergoes self-addition, probably under the catalytic influence of tertiary amine and tertiary amine hydrohalide, as indicated in the equations[6]

$$RCH_2COX + R'_3N \longrightarrow [RCH{=}C{=}O] + R'_3N\cdot HX$$
$$2[RCH{=}C{=}O] \longrightarrow RCH_2COCR{=}C{=}O$$

No evidence for the transitory existence of the ketene monomers was obtained, the lowest boiling product isolated in every case being the dimer.

The dehydrohalogenations were usually carried out by adding an equivalent amount of tertiary

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(1) Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).

(2) Hurd, Cashion and Perletz, *J. Org. Chem.*, **8**, 367 (1943); **9**, 557 (1944).

(3) Bistrzycki and Landtwing, *Ber.*, **42**, 4720 (1909).

(4) Wedekind, *ibid.*, **34**, 2070 (1901); *Ann.*, **323**, 246 (1902); *ibid.*, **378**, 261 (1910); Wedekind and Haeussermann, *Ber.*, **41**, 2297 (1908).

(5) Sauer, U. S. Patent 2,369,919; Adams, "Organic Reactions," Vol. III, p. 129 (1946).

(6) The dimers are represented as having linear structures for the purposes of this paper. For leading references dealing with the structure of diketene, the first member of the ketene dimer series, see Taufen and Murray, THIS JOURNAL, **67**, 754 (1945); Rice and Roberts, *ibid.*, **65**, 1677 (1943); Hurd and Abernethy, *ibid.*, **62**, 1147 (1940); and ref. 1.