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FLUORINATION OF NITROGEN-CONTAINING AROMATICS WITH XENON DIFLUORIDE

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To Professor George H. Cady on his 70th birthday

SUMMARY

Pyridine reacts with xenon difluoride to give a mixture of 2-fluoropyridine, 3-fluoropyridine, and 2,6-difluoropyridine, while 8-hydroxyquinoline is converted to 5-fluoro-8-quinolinol. Aniline and benzylamine react vigorously with XeF_2 to yield mixtures of monofluoro isomers derived from the parent amines.

INTRODUCTION

Xenon difluoride serves as an excellent reagent for the direct introduction of fluorine into the aromatic nucleus. In earlier papers we described the reaction of XeF_2 with benzene and substituted benzenes [1,2], aryl oxygen compounds [3], and polycyclic aromatic compounds [4] to afford monofluoro compounds, many of which are not readily accessible by more conventional methods, e.g., the Balz-Schiemann reaction. We report here our observations on the fluorination of pyridine, aniline, 8-hydroxyquinoline, and benzylamine.

RESULTS AND DISCUSSION

Pyridine

Pyridine reacts with xenon difluoride in methylene chloride solution with or without external initiation by hydrogen fluoride, to give a mixture

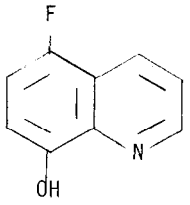
containing 2-fluoropyridine (35% yield), 3-fluoropyridine (20%), and 2,6-difluoropyridine (11%). The components were separated by gas chromatography and identified by comparison with the gas chromatograms and mass spectra of authentic samples. The mass spectrum of the reaction mixture also revealed the presence of a very small amount of pentafluoropyridine, but this compound could not be detected by gas chromatographic analysis.

The ease with which pyridine reacts with XeF_2 and the nature of the products are somewhat surprising. We had anticipated that pyridine would be less reactive than benzene, which requires initiation by externally added HF. More readily oxidized aromatics react with XeF_2 without initiation [3,4]. Once reaction commences, HF is generated in situ, the strongly oxidizing, electrophilic species $[XeF]^+$ is rapidly formed, and fluorination proceeds normally [3]. Although the reaction apparently involves electron transfer to $[XeF]^+$ and participation of cation radicals [5], the product distribution is characteristic of electrophilic substitution [2]. Usually, such substitution on the pyridine nucleus can be accomplished only under drastic conditions, in contrast to the relative ease of nucleophilic displacement. We would certainly expect initial formation of the kinetically favored pyridinium salt. It has been shown that replacement of the =CH- of benzene by $=\overset{+}{N}H$ results in a 10^{-12} to 10^{-18} fold deactivation toward electrophilic attack [6]. Finally, the product distribution is inconsistent with electrophilic substitution on both pyridine and pyridinium ion. Thus, attack usually occurs preferentially at the 3- position, since 2- and 4-substitution involves an energetically unfavorable transition state in which a partial positive charge is localized on the positively charged nitrogen. In nucleophilic substitution, however, the 2- and 6- positions are strongly favored. We conclude that the reactivity and product distribution are not readily accommodated by a simple electrophilic process, nor are the reaction conditions and the appreciable yield of 3-fluoropyridine consistent with nucleophilic substitution. The reaction merits additional study, including the relative susceptibility of the benzene and pyridine rings in quinoline.

8-Hydroxyquinoline

Although we have not examined quinoline as a substrate, we did study the reaction of 8-hydroxyquinoline with XeF_2. In this case, activation of the benzene ring leads to 5-fluoro-8-hydroxyquinoline (I) (35% yield) as

the only identifiable product. Additional material was obtained, but could not be characterized.



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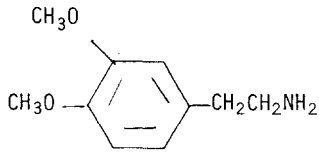

(II)

Aniline and Benzylamine

We have demonstrated previously [3] and above that phenolic hydroxyl groups do not interfere with ring fluorination. In order to determine whether primary amino groups interact with xenon difluoride, we examined an aromatic amine (aniline) and an aralkylamine (benzylamine). In both cases, vigorous reactions occurred, but the amino functions were unreactive and remained intact. Thus, aniline reacts with XeF_2 in acetonitrile, in the absence of added HF, to give a mixture of fluoroanilines containing 37% ortho, 3% meta, and 16% para isomers.

Benzylamine in CH_2Cl_2 behaved similarly to give 40% of o-fluorobenzylamine and only 2% of the para isomer. No meta fluoro compound could be detected by gas chromatography.

As part of our studies on the synthesis of fluoro analogs of pharmacologically active compounds, we also briefly examined the reaction of XeF_2 with the dimethyl ether of dopamine (II). While no pure product was isolated, we obtained definitive mass spectral evidence for incorporation of one nuclear fluorine atom, whose position could not be established. This reaction deserves further study, since monofluoro analogs of biogenic amines are not readily synthesized by other routes.

EXPERIMENTAL

Materials

Xenon difluoride was prepared photosynthetically according to a procedure described previously [3]. Purified solvents and reagents of AR

grades were used and handled under a dry nitrogen atmosphere. Melting points were determined on a Fisher-Johns block and are uncorrected. All gas chromatographic data were recorded on a Perkin Elmer Model-900 instrument equipped with a flame ionization detector. Mass spectra were recorded on a Bendix time-of-flight instrument and some gc-ms data were obtained on a Finnegan Model 3000 instrument. All reactions were carried out in Kel-F tubes of about 30 ml capacity fitted with 1/4" brass valves and under reduced pressure (10^{-5} to 10^{-6} torr). A small portion of the reaction mixture, when removed for gc or ms analysis, was always treated with sodium fluoride pellets to remove hydrogen fluoride produced during the course of the reaction. The remainder of the reaction mixture was dried under reduced pressure at room temperature to remove the solvents as well as HF.

Reaction of Pyridine with XeF_2

Xenon difluroide (0.76 g., 4.5 mmol) was treated at -196° with a threefold excess of pyridine (0.95 g., 12 mmol) in 20 ml. of methylene chloride which was degassed at $5x10^{-6}$ torr, to give a 4% solution. The reaction mixture was gradually warmed to room temperature by means of a series of baths during a period of 1.5 hr to give a yellow-orange solution and a small amount of insoluble material. The solution was distilled in vacuo and a small sample of the distillate was chromatographed at 80° on a 6'x1/8" column packed with Carbowax 750 on Chromosorb G (80/100 mesh), which had been pretreated with 5% potassium hydroxide. Three major identifiable components were detected, in addition to some unreacted pyridine, viz., 2-fluoropyridine (35% yield), 3-fluoropyridine (20%), and 2,6-difluoropyridine (11%). The isomers were identified by comparison with the gas chromatograms of authentic samples. The mass spectrum of the reaction mixture also indicated the presence of a small amount of pentafluoropyridine (m/e 169), but it could not be detected from g.c. studies.

Reaction of 8-hydroxyquinoline with XeF_2

A degassed solution of 2.3 g (16 mmol) of 8-quinolinol in 10 ml of methylene chloride at 10^{-5} torr was poured onto 2.7 g (ca. 16 mmol) of xenon difluoride contained in an evacuated ($5x10^{-6}$ torr) Kel-F tube at -196°. The contents were warmed gradually to 5°, at which temperature the reaction was complete to give a thick red-brown mixture which was filtered

at room temperature and the residue washed with methylene chloride. The filtrate and washings were combined, the solvent removed in vacuo and the residue dried and sublimed in vacuo to give 0.9 g (35%) of colorless, crystalline 5-fluoro-8-hydroxyquinoline, mp 110° (lit. mp 110.5-111° [7]). An insoluble brown solid of indefinite composition was also extracted from the residue, mp 150-152° dec.

Reaction of aniline with XeF_2

A solution containing 1 g (10.7 mmol) of aniline in 11 ml of acetonitrile was degassed at $5x10^{-6}$ torr and allowed to react with 1.3 g (7.7 mmol) of xenon difluoride in a Kel-F tube evacuated to 10^{-6} torr at -196°. Instantaneously, orange-red icy traces started appearing, which intensified by raising the temperature of the reaction mixture up to 0°, at which time the reaction was complete to give a dark brown solution. The course of reaction as followed by gc showed the absence of any unreacted aniline. The contents were filtered in vacuo through a glass wool plug. Gas chromatographic analysis (on a 2'x1/8" column packed with 2% Carbowax-KOH on Chromosorb G 80/100 mesh at 90°), mass spectrometry, and comparative data of authentic samples, indicated a 37% yield of o-fluoroaniline, 16% of p-fluoroaniline, and 3% of m-fluoroaniline.

Reaction of benzylamine with XeF_2

The interaction of a degassed solution of 0.54 g (5 mmol) of benzylamine in 7 ml of methylene chloride at 10^{-5} torr with 0.42 g (2.5 mmol) of xenon difluoride in a Kel-F tube was carried out by a procedure similar to that used for other reactions. A spontaneous and vigorous reaction occurred even at -78°. A large volume of xenon gas evolved at -20°, which had to be collected and condensed in a separate container in order to control the mounting pressure in the reaction tube.* The reaction was essentially complete at 10° after standing overnight, but was warmed to 60° to insure complete reaction. The resulting thick orange contents were filtered and the solvent was removed to give a red-brown solution and a gray-white residue, presumably the amine salt. The gas chromatographic a-

* In an earlier experiment, 2.2 g (12.5 mmol) of XeF_2 reacted with 3.78 g (35 mmol) of benzylamine in 18 ml. of CH_2Cl_2. When the temperature was raised to -20°, a violent explosion occurred.

nalysis of the reaction products on a 6'x1/8" column packed with 5% Carbowax-KOH on Chromosorb G 80/100 mesh at 105° indicated the formation of the o-fluoro derivative (40% yield), a very small p-fluoro component (2%) and no evidence of m-fluorobenzylamine, by comparison with authentic samples.

3,4-Dimethoxy-β-phenylethylamine with XeF_2

The mass spectrum of the reaction mixture indicated a peak of low intensity at m/e=199, which corresponds to the molecular ion of a monofluoro product. The presence of a peak at m/e=170 (M^+-$CHNH_2$) confirmed this assignment since the starting material exhibited corresponding peaks at m/e=181 and 152.

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