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The Preparation of Methyl 5-Chloro-6-Fluoronicotinate by Fluoride-Chloride Exchange

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Several chloro and fluoronicotinic acids have been examined for hypolipidemic activity in dogs (Carlson et. al., 1972). It was demonstrated that 5-fluoronicotinic acid, 6-fluoronicotinic acid, and 5-chloronicotinic acid were effective for the supresssion of elevated free fatty acid levels, with the fluoroacids having longer duration. A few simple alkyl esters of these acids also showed some activity, presumably due to in vivo hydrolysis to the acids. While it would seem feasible to study possible hypolipidemic activities of nicotinic acids and esters with a dual combination of fluorine and chlorine on the pyridine ring, such studies have been limited by the relative nonavailability of these compounds.

In connection with our previous studies involving exchange of fluorine for chlorine in the pyridine 2- or 6-position by nucleophilic displacement (Setliff and DeFoggi, 1978), we saw the opportunity to prepare methyl 5-chloro-6-fluoronicotinate (a heretofore unknown compound) from methyl 5,6-dichloronicotinate, which is readily accessible. It has been known for decades that chlorine in the 2-or 6-position of pyridine is displaced easily by fluoride in boiling anhydrous dimethylformamide (DMF), provided a very strong electron withdrawing group (e.g. nitro or ammonium) is located at the *para* position (Finger and Starr, 1959). However, the more weakly electron withdrawing carbomethoxy group, although shown to be sufficiently activating to induce displacement of chloride by fluoride in the benzene system if a nitro group is also present (Finger and Cruse, 1956), had not been tested in a pyridine system. Thus, we attempted and were successful in the conversion of methyl 5,6-dichloronicotinate to methyl 5-chloro-6-fluoronicotinate as depicted in Fig. 1.

We previously attempted the fluoride exchange with various chloronicotinic acids, but the results were totally unrewarding. Only tars or intractable resins were obtained (Coop, 1996).

Melting points were determined on a Mel Temp II apparatus and are uncorrected. Elemental analysis was performed by Desert Analytics Organic Microanalysis, Tuscon, AZ. Proton NMR spectra were determined on a Bruker AC-F 200 MHz superconducting FT spectrometer with chloroform-d as solvent and tetramethylsilane as internal standard. Infrared spectra were obtained on a Nicolet 500 Magna FT-IR spectrophotometer, with samples deposited as films evaporated from chloroform onto a KBr plate. Methyl 5,6-dichloronicotinate was prepared as described previously (Setliff and Huie 1981). Potassium fluoride (fine powder) was purchased from Aldrich Chemical Company and was oven-dried at 110°C for several days prior to use. Dimethylformamide (Aldrich) was dried over neutral alumina for several days and distilled immediately before use (b.p. 158°C.)

The synthesis of methyl 5-chloro-6-fluoronicotinate was accomplished as follows. Methyl 5,6-dichloronicotinate 0.0049 mole) was placed in a 25 mL round-bottom flask and dissolved in DMF (2.5 mL). Dry potassium fluoride powder (0.6 g, 0.0098 mole) was quickly added, and a reflux condenser equipped with a calcium chloride drying tube was attached to the flask. The reaction mixture was stirred under gentle reflux for 1 hr with oil bath heating. The oil bath temperature was maintained at 155-158°C. The dark reaction mixture was cooled and transferred to a 250 mL 3-necked

Fig. 1. Nucleophilic displacement of chloride by fluoride at 158°C

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flask, 10 mL of water was added, and the mixture was indirectly steam distilled. A white solid (0.30 g, m.p. 47-57°C) was filtered from the steam distillate. This material, shown by proton NMR to be a mixture of starting material and product, was returned to the reflux flask and once again heated with potassium fluoride (0.6 g) in DMF (2.5 mL) for an additional hour. Indirect steam distillation yielded the pure chlorofluoro ester as a fluffy white solid, 0.22 g , 24% yield, m.p. 66-68°C. IR: ν 1724 (C=O), 1068 (C-O) cm^{-1}.

^1H NMR: δ 8.75 (m), H_2 ; [8.45, 8.44 and 8.41,8.40] (d of d), H_4; 3.97 (s) CH_3. The pyridine ring proton signals of the starting dichloro ester [H_2 at 8.89 ppm (d) and H_4 at 8.36 ppm (d)] were not visible at high amplification, indicating reasonable purity. Anal. Calcd. for $C_7H_5NO_2FCl$: C, 44.35; H. 2.66; N, 7.39. Found: C, 44.13; H, 2.51; N. 7.41.

Although methyl 5-chloro-6-fluoronicotinate was sucessfully prepared and characterized, the low yield could not be improved upon due to a competitive reaction of the dichloroester with DMF. After the initial reflux of 1 hr and after the volatile solid was removed by steam distillation, cooling of the steam distillation pot afforded a nonvolatile organic material (0.20 g) of m.p. 147-150°C. Preliminary indications based on infrared and ^1H NMR data suggest a possible imminium salt structure (Fig. 2).

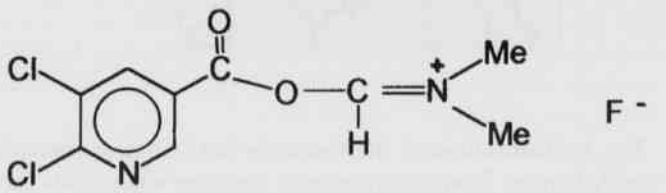

Fig. 2. Likely structure of the imminium salt formed competitively.

This material was not characterized further. Reaction times longer than 1 hr led to increased amounts of the presumed imminium salt and virtually no steam volatile ester; whereas shorter reaction times and lower reaction temperatures resulted in recovery of mostly unconverted starting material.

Although Finger (Finger et al., 1963) had demonstrated the superiority of dimethyl sulfone over DMF as a solvent in fluoride-chloride exchanges in pyridine systems, no examples of chloroester substrates were mentioned. With the hope that the use of dimethyl sulfone would eliminate our competitive reaction, we employed this solvent under a variety of conditions. However, no pure steam volatile products could be isolated.

In conclusion it appears that the ester group offers only very weak activation to chloride displacement in the absence of strongly electron withdrawing groups. Actually, the chlorine in the 5- position significantly aided activation since in a control experiment we observed that methyl 2-chloronicotinate gave only spectral traces of the fluoroester.

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