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A GAS-SOLID-PHASE MICROCHEMICAL METHOD FOR THE SYNTHESIS OF ACETYL HYPOFLUORITE

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SUMMARY

The useful electrophilic fluorinating agent, acetyl hypofluorite, was obtained by passing F_2 diluted in N_2 through columns containing complexes of alkali metal acetates with acetic acid. Acetyl hypofluorite obtained from $KOAc(HOAc)_{1.5}$ and 0.14% F_2 in N_2 was reacted with tri-O-acetyl-D-glucal in CCl_3F to obtain tetra-O-acetyl-2-deoxy-2-fluoro-D-glucose in 68% yield based on F_2. These conditions are appropriate to the radiosynthesis of ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose for positron emission tomography. Important variables were the metal cation used, the ratio of HOAc to MOAc and the water content of the complex.

INTRODUCTION

Acetyl hypofluorite (1, AcOF) has been found to be an efficient, stereoselective reagent for electrophilic fluorination [1,2,8]. Of particular interest is the use of $AcO^{18}F$ in the radiosynthesis of ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose (2, FdG), an important imaging agent for positron emission tomography [3,4]. Currently, the most satisfactory preparation of $AcO^{18}F$ involves bubbling ^{18}F-labeled F_2 in neon through a solution of NH_4OAc in HOAc and adding the resulting dilute solution of $AcO^{18}F$ to a solution of tri-O-acetyl-D-glucal (3, TAG) in acetic acid [4]. Since AcOF is highly volatile [8], we thought that the generation of $AcO^{18}F$ by a gas-solid-phase reaction might have the following advantages: a separate step for the generation and

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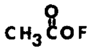
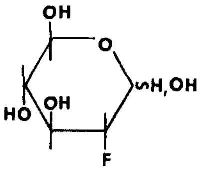


$CH_3\overset{O}{C}OF$

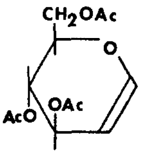
1

Acetyl hypofluorite



2

FdG



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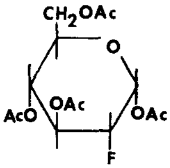
TAG



4

FTAG

transfer of a liquid reagent could be eliminated. The subsequent reaction could be done in a more volatile solvent than HOAc, eg., CCl_3F, allowing a simpler apparatus to be used in an automated system. Finally, the $^{18}F^-$ formed by the reaction: $F_2 + M^+OAc^- \rightarrow M^+F^- + AcOF$, instead of being carried along to the next step as a contaminant, might be easily recovered for another simultaneous synthesis. While such considerations would usually not apply to the synthesis of non-radiolabeled compounds, they become important in remote radiochemical syntheses where the simplicity of operations and the 110 min half-life of ^{18}F are important constraints.

We therefore attempted to generate AcOF by passing dilute F_2/N_2 through columns of NaOAc. The yield of AcOF, based on F_2, measured by GLC after reaction with TAG (3) to form tetra-O-acetyl-2-deoxy-2-fluoro-D-glucose (FTAG, 4) was too low to be of practical use for radiochemical syntheses. We thought that F^- formed by the reaction might be reacting with the product to reduce the yield [5], and that acidic conditions might suppress such a reaction.We found that anhydrous NaOAC or KOAc reacted with up to 2 equivalents of HOAc to give crystalline complexes after standing several days. Passing dilute F_2 (0.1 to 0.2% in N_2) through columns containing these complexes gave AcOF in sufficient yield and purity to allow the method to be considered for radiochemical syntheses. Further, given a constant flow of F_2/N_2, the production of AcOF was uniform for several hours, permitting simple, precise metering of the reagent for microchemical methods.

We have determined several variables which affect the yield of AcOF. Significantly, attempts to produce the reagent on a larger scale from 10% F_2 did not succeed.

EXPERIMENTAL

Potassium acetate and acetic acid were analytical reagent grade (Mallinckrodt) used as purchased. A standard sample of tetra-O-acetyl-2-deoxy-2-fluoro-D-glucose was obtained by the method of Adam [3]. The concentration of F_2 in N_2 was determined by iodometric titration [6].

Preparation of $KOAc(HOAc)_n$

Potassium acetate, 1.0 mole, was mixed with 1.5 moles acetic acid, and the resulting slurry was allowed to stand 24 h. The solid which formed was mixed and crushed with a spatula, and the powder was allowed to stand another 48 h before use. Other samples containing different ratios of HOAc/MOAc were prepared in the same way. NH_4OAc and CsOAc failed to yield solids with HOAc, but powders were obtained by mixing 0.1 mole KOAc with solutions of .04 mole NH_4OAc or CsOAc in .16 mole HOAc, in order to study the effect of these cations on the yield of AcOF.

Gas-solid-phase generation of acetyl hypofluorite

Fluorine in N_2 (.14%) was passed at the rate of 20 to 25 ml/min through a stainless steel column (4 mm by 108 mm) containing 1.0 g of $KOAc(HOAc)_{1.5}$. The effluent was bubbled into the bottom of a cylindrical reaction vessel with downward-directed indentations similar to those in a Vigreaux column [7], containing 40 mg TAG (stoichiometric excess) in 15 ml Freon-11 (CCl_3F) at room temperature. Solvent was added occasionally to replace that lost by evaporation. After introduction of the gas stream at a constant rate for a measured time, the sample was allowed to stand 5 min. The solvent was removed, and the residue was dissolved in a measured amount of MeCN and analyzed by GLC (DEGS, 200°, thermal conductivity detector).

RESULTS

Since the reaction of AcOF with TAG (3) proceeds with high yield and stereospecificity [2,3], results are based on the measurement of FTAG (4) by GLC. This method is capable of distinguishing AcOF from other oxidizing species such as F_2, and is directly relevant to the synthesis of radiolabeled FdG. The GLC profiles obtained from the reaction mixtures were the same whether the latter were obtained by the gas-solid-phase method or by previously reported liquid-phase methods [3,4], indicating that the purity of the AcOF made by various methods was similar. In addition to unreacted TAG, GLC of the reaction mixture detected FTAG (90% of product), and 3 unidentified peaks (total 6.2% of product). Peaks possibly assignable to products of the direct reaction of TAG with F_2 were detected (3.8%) showing that some F_2 may have passed through the column without reacting with the complex. Careful removal of the $KOAc(HOAc)_2$ from a column exposed to ^{18}F-labeled F_2 showed almost all of the radioactivity concentrated in the first 2 mm of the column, indicating that the reaction between F_2 and the acetate complex is rapid at room temperature.

Effect of the cation

Table 1 shows the effect on the yield of FTAG of substituting different cations in the complex $MOAc(HOAc)_n$. Partial replacement of K^+ in KOAc $(HOAc)_2$ by Cs^+ or NH_4^+ was the only way we could obtain solids for these cations. Because of the higher yield obtained with K^+, potassium complexes were used for all subsequent experiments. Except for NH_4^+ the order and approximate yields for the various cations follow those already published for the liquid-phase reaction in HOAc [4].

TABLE 1

Effect of the cation on the yield of acetyl hypofluorite as determined indirectly by measurement by GLC of the FTAG produced

Complex	Moles FTAG formed / mole F_2[a]
$KOAC(HOAc)_2$	.64
$NaOAc(HOAc)_2$	.46
$(KOAc)_{.7}(CsOAc)_{.3}(HOAc)_2$	.57
$(KOAc)_{.7}(NH_4OAc)_{.3}(HOAc)_2$	.15
$Mg(OAc)_2(HOAc)_2$	.18

[a] .14% F_2 in N_2 at 20 ml/min for 20 min

Effect of the ratio of HOAc to KOAc on the yield of FTAG

Table 2 shows the effect on the yield of FTAG of increasing the molar ratio of HOAc to KOAc in the solid phase. Acidic conditions could be expected to suppress nucleophilic attack by F^- on AcOF [5]. Another explanation for the enhancement of the yield of AcOF by HOAc is given by Rozen and Lerman [8]. The drop in yield when HOAc is increased above 2 equivalents results from a delay in the time for the production of AcOF to reach a steady state.

TABLE 2

Effect of the molar ratio of HOAc to KOAc in the solid phase on the yield of acetyl hypofluorite as determined indirectly by measurement by GLC of the FTAG produced.

Moles HOAc per mole KOAc	Moles FTAG formed / mole F_2[a]
0.0	.04
0.5	.25
1.0	.64
1.5	.68
2.0	.65
2.7	.22

[a] .14% F_2 in N_2 at 20 ml/min for 20 min

Effect of the water content of the solid phase on the yield of AcOF

Table 3 shows the effect on the yield of AcOF of adding small amounts of water to $KOAc(HOAc)_{1.5}$. When the KOAc was dried over P_2O_5 and the HOAc dried by refluxing with .1 mole % acetic anhydride, the results were the same as when the reagents were used as obtained. Distillation of the dried HOAc from CrO_3 in an attempt to remove possible impurities reactive toward F_2 [9] resulted in markedly lowered yields of FTAG.

TABLE 3

Effect of water added to the solid phase on the yield of acetyl hypofluorite as determined by measurement of the TAG produced.

Mole % H_2O added to $KOAc(HOAc)_{1.5}$	Moles FTAG formed / mole F_2
0.0	.66
0.2	.74
0.4	.74
1.0	.64
2.0	.67
3.0	.53
5.0	.53
7.5	.58
10.0	.35

[a].14 % F_2 in N_2 at 20 ml/min for 20 min.

Effect of the amount of solid phase in the column on the yield of AcOF

We considered that excess solid phase in the column over that needed for the complete conversion of F_2 to AcOF might react with the product or irreversibly adsorb it, resulting in a reduced yield. However, increasing the length of a column containing $KOAc(HOAc)_2$ from 14 mm (.125 g complex) to 108 mm (1.0 g) increased the yield slightly.

Effect of the temperature of the solid phase on the yield of AcOF

The yield of FTAG was the same whether the column of $KOAc(HOAc)_2$ was maintained at 0° or 20°C. When the column was maintained at -40°, the yield of FTAG was halved, and significant amounts of the products of the direct reaction of F_2 with TAG were detected by GLC.

Effect of the reaction vessel shape on the formation of FTAG from TAG

For the reaction of AcOF in N_2 with TAG in CCl_3F, a vessel consisting of a vertical column (1 cm diameter) with downward-directed indentations similar to those in a Vigreaux column gave better yields than a simple tubular column, even when the gas was supplied to the latter through a fine frit.

A schematic drawing of such an apparatus has been published by Ido et al. [7]. However, as not well shown in the schematic, the indentations should extend well into the lumen of the tube in order to interact as much as possible with the rising gas bubbles.

Effect of gas flow rate on the yield of FTAG

While we did not study systematically the effect of flow rate, we observed that yields decreased with flow rates of F_2/N_2 above 25 ml/min. We did not determine whether the decrease was the result of a decreased yield of AcOF in the solid phase reaction or of inadequate gas-liquid exchange in the subsequent reaction with TAG.

Uniformity of delivery of AcOF

When .14% F_2/N_2 was passed through a column containing 1.0 g of $KOAc(HOAc)_2$ for 5 h at 25 ml/min, and 20 min aliquots of the effluent gas stream were reacted with TAG in CCl_3F, the yield of FTAG was constant over the first 4 hours. Thus, multiple reactions using micromolar amounts of AcOF can be done after only a single standardization of the reagent.

Solvents usable for the reaction of AcOF with TAG

We found that, at least when a stoichiometric excess of TAG was present, CCl_3F (from -70° to $+20^\circ C$), HOAc (20°), hexane (-70°) and $MeCl_2$ (-70°) all gave approximately the same yield of FTAG. Thus, the use of a gas-solid-phase reaction for the generation of AcOF allows considerable flexibility in the choice of solvent for reactions using the reagent.

DISCUSSION

When we attempted to extend the gas-solid-phase method to the synthesis of millimolar amounts of AcOF by using 10% F_2/N_2, the yield of FTAG was only a few percent of that expected. While products other than FTAG were present, most of the TAG did not react, indicating that neither F_2 nor AcOF were present in the effluent gas from the column. We thought that the reaction might be too exothermic, and therefore cooled the F_2/N_2 entering the column to -70° or $-100^\circ C$ while maintaining the outlet at room temperature, in order that the F_2 might react at the minimum possible temperature. However, the yield of AcOF was again very small. We suspect that the condition of the surface of the solid phase may be important. When we have attempted to use $KOAc(HOAc)_2$ for the microchemical generation of AcOF before the material has been allowed to stand for several days, the yields have been lower. Insufficient time for aging of the complex was indicated by a damp material which was more difficult to pour or pack into columns than the material aged for 96 hours. It may be that F_2 introduced at too high a rate consumes some essential surface species faster than it can be regenerated.

ACKNOWLEDGMENT

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