SYNTHESIS AND PURIFICATION OF METHYL-^{13}C FLUORIDE*

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SUMMARY

A 20 mmole quantity of methyl-^{13}C fluoride at a ^{13}C-enrichment level of 90% was prepared by a two-step synthesis starting with methanol-^{13}C. The overall yield was 60% of methanol used. A series of gas-chromatographic treatments using Ascarite, silica gel, and Chromosorb-102 columns yielded a highly purified methyl fluoride in which the major impurities were less than 10 parts per million of carbon dioxide and 10 parts per million of methyl chloride.

Key Words: Methyl fluoride, carbon-13, methyl p-toluenesulfonate-^{13}C

INTRODUCTION

Methyl fluoride has been prepared in low yields (below 60%) from methane$^{(1)}$, methyl iodide$^{(2)}$, and methyl chloride$^{(3)}$ by chemical and electrochemical methods. Preparations with higher yields have been reported, which used methyl formate$^{(4)}$, methyl potassium sulfate$^{(5)}$, tetramethylsilane$^{(6)}$, and methoxyamine hydrochloride$^{(7)}$ as starting materials. These are, however, not suitable for a synthesis of ^{13}C-labelled methyl fluoride.

The method used in our synthesis is based on, and represents an improvement of, the procedures of Patterson and Frew$^{(8)}$, Edgell and Parts$^{(9,10)}$, Pattison$^{(11)}$, and Tipson$^{(12)}$. It is a two-step procedure in which methanol is initially reacted, at low temperature, with p-toluenesulfonyl chloride (tosyl chloride) in the presence of pyridine to produce methyl tosylate. The methyl tosylate is then reacted with potassium fluoride at reduced pressure to form gaseous methyl

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fluoride:

$$CH_3OH + p\text{-}CH_3C_6H_4SO_2Cl \xrightarrow[-42^\circ C]{\text{pyridine}} p\text{-}CH_3C_6H_4SO_2OCH_3 \tag{1}$$

$$p\text{-}CH_3C_6H_4SO_2OCH_3 + KF \xrightarrow[230^\circ C]{150\ \text{torr}} CH_3F\ (\text{gas}) + [p\text{-}CH_3C_6H_4SO_3]^-K^+ \tag{2}$$

The yield reported for Step (1) varies between 85% and 99% on the basis of the amount of methanol used, while the yield for Step (2) typically is 65%.

The synthesis of sulfonic esters from the reaction of alcohols and sulfonyl chlorides has been studied in the absence of solvent(13) and in various bases such as sodium hydroxide(14-17), sodium carbonate(18-19), diethylaniline(19), 2,6-dimethylpyridine (2,6-lutidine)(9), and pyridine(8-12), but high yields have been reported only when the esterification was run in an organic solvent. For the purpose of minimizing the amount of ^{13}C-labelled alcohol required, pyridine seemed best suited as the solvent for Reaction (1). Pyridine shifts the equilibrium in favor of the tosylate by removing HCl. The rate-determining step is believed to be the formation of p-toluenesulfonyl pyridinium chloride, the latter subsequently being attacked nucleophilically by the alcohol to produce methyl tosylate. Since the labelled methanol is not involved in the rate-determining step, Step (1) will not cause any significant isotope fractionation. Use of 2,6-lutidine in the place of pyridine causes a marked decrease in the rate of tosylate formation(9), and this can be viewed as evidence supporting the mechanism mentioned above: One would expect formation of the complex by 2,6-lutidine to be sterically hindered.

As the concentration of methyl tosylate increases, the reaction of this product with additional pyridine to form methylpyridinium p-toluenesulfonate would become significant(20,21):

$$p\text{-}CH_3C_6H_4SO_2OCH_3 + C_5H_5N \longrightarrow [C_5H_5N{:}CH_3]^+[p\text{-}CH_3C_6H_4SO_3]^- \tag{3}$$

Subambient temperatures have been used to minimize this side reaction(22). The optimum temperatures for the best yield of methyl tosylate have been reported to be between -40°C and -44°C. Below this temperature range tosyl chloride crystallizes out of solution, reducing the methyl tosylate yield.

EXPERIMENTAL

The synthesis of methyl tosylate was carried out in a 500 ml round-bottomed flask fitted with a Teflon-coated stirring rod. The temperature of -40°C was maintained by a Dry Ice/acetone slurry bath and monitored by using a copper-constantan thermocouple. Spectrophotometric grade tosyl chloride was purchased from Aldrich Chemical Co., and pyridine was purified by storage over potassium hydroxide pellets and distilled over anhydrous potassium carbonate immediately before use.

Approximately 100 mmoles of methanol-^{13}C was mixed with 120∿130 mmoles of tosyl chloride in the reaction vessel maintained at -40°C to -45°C. About 85∿90 ml of pyridine was then added slowly over a period of two hours while providing rapid stirring. The stirring at -44°C was continued for one more hour after the completion of the addition of pyridine. Excess pyridine was then neutralized with 300 ml of ice-cold 5N-H_2SO_4. The temperature of the product mixture was maintained below 20°C during the neutralization. The crystallized methyl tosylate was vacuum-filtered and stored in a cold chest of Dry Ice to prevent decomposition. Starting with 3.0 grams (91 mmoles) of $^{13}CH_3OH$, 16.8 grams (89.7 mmoles) of methyl tosylate-^{13}C were recovered, which corresponds to a yield of 99%. The infra-red spectrum of the product in carbon tetrachloride compared well to a standard spectrum(23).

The apparatus used for the synthesis of methyl fluoride from methyl tosylate is shown in Figure 1. The internal pressure of the system was maintained at about 150 torr by bleeding the gaseous product through a needle valve into a series of traps which are connected to a mechanical pump at the other end. About 22 mmoles of methyl tosylate were mixed with approximately 50 mmoles of anhydrous potassium fluoride in the reaction flask, which was heated to and maintained at 230°C for seven hours. The bulk of the product was formed during the first one and half hours. Methyl fluoride was trapped at liquid nitrogen temperature. Bulb-to-bulb distillation was performed several times to remove the bulk of very high-boiling and very low-boiling impurities. The yields of $^{13}CH_3F$ obtained in three runs were as follows: In Run No. 1, 4.10 grams (21.9 mmoles) of methyl tosylate-^{13}C (MeTs) produced 13.8 mmoles of $^{13}CH_3F$, as determined from the

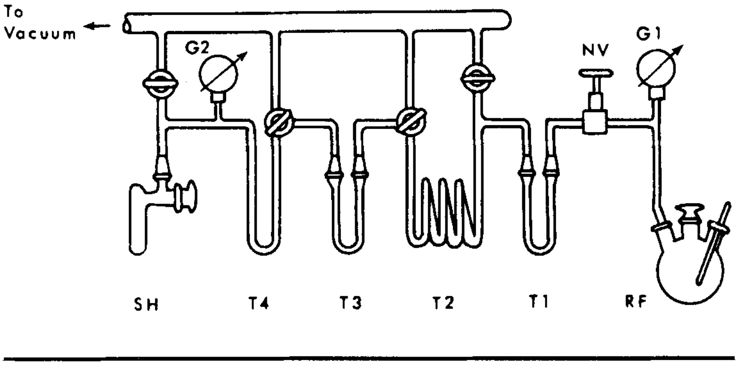

Figure 1. Apparatus for synthesis of methyl fluoride:

RF = Reaction flask; G1 and G2 = Diaphragm gauges; NV = Needle valve;
T1 = Silica gel tube; T2 = Dry Ice-acetone trap; T3 = Ascarite tube;
T4 = Liquid nitrogen trap; SH = Product sample holder.

pressure in a known volume and the ideal gas law. This corresponds to a yield of 63%. In Run No. 2, 4.116 grams (22.0 mmoles) of MeTs produced 14.1 mmoles of the product for a yield of 64%. In Run No. 3, 4.163 grams (22.1 mmoles) of MeTs led to 9.82 mmoles of the product, which corresponds to a yield of 44%. The low yield for the last run is attributable to a difficulty we experienced in controlling the pressure in the reaction flask. The average yield of the first two runs is 64%, while the average of all three runs is 57%. The identity of the product was confirmed by IR spectroscopy of the gas.

The overall yield for the combination of the two steps was 60% of methanol used. The product collected was analyzed in a Perlein-Elmer Model 990 gas-chromatograph with a six-foot column packed with 60/200 mesh silica gel and maintained at 100°C. It contained 1.5% carbon dioxide and 1% methyl chloride. The impurities were reduced to a level below 10 ppm by a combination of treatments with Ascarite and Chromosorb-102 columns and a preparative gas-chromatographic procedure.

First, the product of Step (2) was passed three times through a short

Ascarite tube (15 mm O.D. x 60 cm), which was conditioned by heating at 150°C for 48 hours under vacuum.

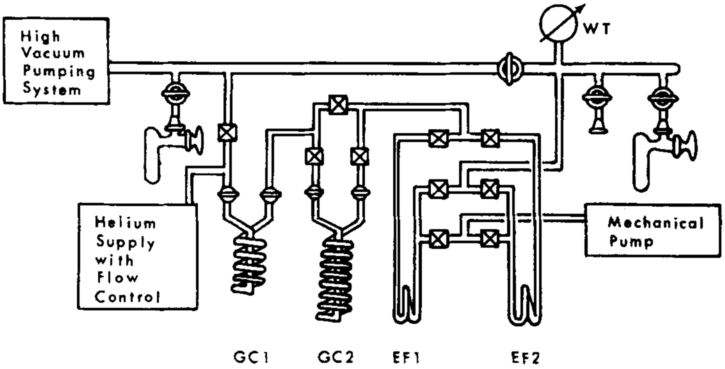

Figure 2. Preparative Gas Chromatograph:

GCC1 = Gas chromatograph column, short; GCC2 = Gas chromatograph column, long; EC1 and EC2 = Effluent collector coils, Pyrex; SH1 = Gas sample holder, feed; SH2 = Gas sample holder, effluent; WT = Wallace-Tiernan diaphragm gauge, 0-800 torr.

The preparative gas-chromatograph shown in Figure 2 consisted of two columns of 3/8 inch O.D. copper tubing packed with silica gel, one being six foot long and the other of 20 foot length, twin effluent collector coils, a helium flow control system (a flow-meter, needle valves, and a roughing pump), and a service high-vacuum line. Except for the chromatographic columns, which are copper, and the valves attached directly to the columns, which are made of stainless steel, the system was constructed entirely out of Pyrex. The short column was used primarily for adsorbing the input gas, but it also functioned as a preliminary separator. The twin effluent collector was designed to facilitate transfer of an effluent fraction without disturbing the flow of carrier gas. While a fraction was transferred from one of the collector coils to a sample holder, the next fraction was collected in the other coil. After the transfer was completed, the first coil is evacuated and readied for collection of the subsequent fraction.

A portion of gaseous methyl fluoride (500∿1000 ml NTP) which had been treated by the Ascarite column was condensed onto the short column submerged in liquid nitrogen. The column was then rapidly warmed up to room temperature by using a hot water bath around it. It is further heated to approximately 60°C by means of a heating mantle that replaced the water bath. Flow of carrier gas, helium, was started and maintained at about 20 ml/min through both columns connected in series. Emergence of methyl fluoride was visually detected by a purple discharge by a Tesla coil, which was clearly distinguishable from the pink discharge of helium. The effluent fractions were collected alternately in one or the other of the two collector coils and transferred to separate sample holders. Twenty five fractions were collected in seven hours, and the contents of each sample holder were later analyzed by the analytical GC to determine the levels of impurities. The fractions with acceptable purity levels were then combined. At a yield of 70%, the impurity level in the purified, combined portion was 10 ppm for CO_2 and 50 ppm for CH_3Cl.

The combined portion was then passed very slowly, i.e., two passes in 7 hours, through a tube packed with Chromosorb-102 and maintained at -50°C. This brought the methyl chloride level down to less than 10 ppm.

Thus the purification procedure described above brought the levels of all impurities below 10 parts per million.

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