

Synthesis of [^{14}C]Methylphosphonic Difluoride

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SUMMARY

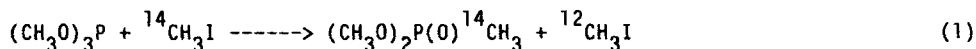
The synthesis of [^{14}C] methylphosphonic difluoride is described. First, [^{14}C]methyl iodide was used to catalyse the conversion of trimethyl phosphite to dimethyl [^{14}C]methylphosphonate by the Arbusov reaction. The dimethyl methylphosphonate was then chlorinated with PCl_5 and fluorinated with SbF_3 . Radiochemical yield from the reaction was 25%.

Key words: [^{14}C]Methylphosphonic Difluoride, [^{14}C]Methyl Iodide,
 Inhalation Toxicology

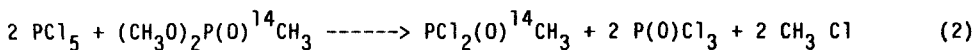
INTRODUCTION

Methylphosphonic difluoride (DF) is an intermediate in the formation of several anticholinesterases. Production and storage of DF could lead to the exposure of workers to fugitive emissions. The relatively high vapor pressure of DF (bp $\sim 100^\circ\text{C}$) makes inhalation a probable route of exposure. To study absorption, distribution, and elimination of DF after inhalation, radiolabeled DF was needed. Synthesis of radiolabeled DF has not been described previously, although its precursor, methylphosphonic dichloride (DC), has been synthesized with both [^{32}P] and [^{14}C] labels.^{1,2}

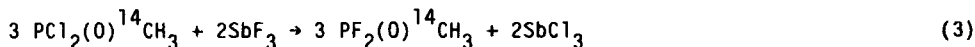
Synthesis using a [^{14}C] label is appealing because of the availability of [^{14}C]methyl iodide, and the possibility of introduction with the Arbusov reaction:



followed by chlorination of the dimethyl methylphosphonate with PCl_5 :



The methylphosphonic dichloride is converted to the difluoride with SbF_3 :



When several grams of starting material is used, reactions according to equations 1 and 2 proceed virtually quantitatively. Introduction of radiolabeled alkyl groups by the Arbusov reaction in a semimicro synthesis has recently been questioned on the grounds that one of the products, unlabeled CH_3I , can compete for available trimethyl phosphite (TMP).² However, we have successfully used this reaction for the introduction of the label.

EXPERIMENTAL

The radiolabeled starting material was 2.0 mCi of [^{14}C] methyl iodide purchased from New England Nuclear with a specific activity of 40-60 mCi/mole. TMP and PCl_5 were obtained from Aldrich, and were purified by distillation and sublimation, respectively, immediately before use. Antimony trifluoride was made from antimony trioxide (Fisher) and 50% aqueous HF. Excess aqueous HF was added to the Sb_2O_3 and vaporized by heating. The resulting SbF_3 was dried in an oven at 180°C overnight. For use as standards, methylphosphonfluoridic acid and methylphosphonic acid were acquired by the hydrolysis of DF and characterized by their NMR spectra. All purifications were by vacuum line distillation. Proton, [^{31}P], and [^{19}F] NMR spectra were obtained using a Varian FT80A NMR Spectrometer. Gas phase IR spectra were obtained using a Perkin Elmer 283B. Ion chromatography was performed using a Dionex Model 16 ion chromatograph. Specific activities of [^{14}C] were determined using a Packard Model 460c liquid scintillation counter. The automatic external standard method was used for quench correction.

For syntheses using unlabeled materials, complete characterization of all intermediates was by NMR, IR, and vapor pressure measurements. Only the final product, DF, was characterized for the synthesis of [^{14}C] labeled materials.

[^{14}C]Dimethyl Methylphosphonate

The [^{14}C]methyl iodide was (2.0 mCi) added to 7.0 mmoles of TMP in a single-neck 100-ml round bottom flask. About 100 μl of unlabeled methyl iodide was used to rinse the [^{14}C] methyl iodide container and was added in turn to the 100-ml flask. The flask was then equipped with an efficient condenser, and the mixture was refluxed for 24 hrs with stirring by a magnetic stirrer. The reflux condenser was removed, and the product was heated to 45°C to vaporize remaining methyl iodide. Trial runs with unlabeled methyl iodide and TMP showed the yield of dimethyl methylphosphonate (DMMP) to be greater than 90% based on TMP. A small aliquot (1 μl) was removed for determination of specific activity; the remainder was quantitatively used in the following step. The specific activity of the [^{14}C]DMMP was 0.24 mCi/mole.

[^{14}C]Methyl Phosphonic Dichloride

To the [^{14}C]DMMP was added 4.1 g (20 mmoles) PCl_5 incrementally over 5 min. The flask was fitted with a drying tube, and the mixture was placed in an oil bath at 60°C. The contents were stirred with a stirring bar for about 1 hr and were transferred to a vacuum line. The products of the reaction were collected in two cryogenic traps. The first, held at -24°C (dichlorobenzene slush), effectively retained DC, but allowed passage of the reaction byproduct, phosphorus oxychloride (POC). The second trap, held at liquid nitrogen temperature, trapped the POC. Time for the distillation was 90 min. A second distillation was performed to ensure the purity of DC. The repurified DC readily crystallized in the trap. With use of unlabeled DMMP, yields of DC were about 80%.

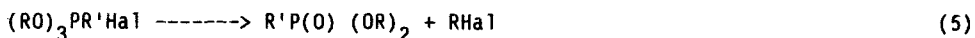
[^{14}C]Methylphosphonic Difluoride

The above [^{14}C]DC was quantitatively transferred under vacuum to a flask containing 3.2 g of SbF_3 . The mixture was carefully brought to atmospheric

pressure by opening the vacuum so that outside air first passed through a liquid nitrogen trap. This ensured that moisture in the air would not pass to and hydrolyze the highly reactive DC. The mixture was immersed into a 60°C oil bath for 30 min. The vacuum line was closed and evacuated, and the products were collected in three traps held at -45°C (chlorobenzene), -65°C (CHCl₃), and -208°C (liquid nitrogen). After 30 min, the DF remained in the -65°C trap. The DF was further purified by redistillation through the same series of traps. A total of 0.21 g of DF was collected, with a specific activity of 0.24 mCi/mmole, for an overall yield of 30% and a radiochemical yield of \approx 25%. The IR and NMR spectra from unlabeled reaction products synthesized on the same scale consistently matched those of standard samples of DF (IR: ν P-F, 932 cm⁻¹; ν P=O, 1335 cm⁻¹, NMR: J_{H-P} , 19.8 Hz; J_{F-P} , 1103 Hz). Ion chromatography of the hydrolysis products of unlabeled samples showed only the components of methylphosphonfluoridic acid, methylphosphonic acid, and fluoride, all products of hydrolysis of DF.

DISCUSSION

This communication describes a convenient three-step synthesis of [¹⁴C]methylphosphonic difluoride. Several previous syntheses of DF have been described.⁴⁻⁶ The scheme used here was chosen because it allows the easy introduction of a ¹⁴C-label by methyl iodide by the Arbusov reaction. Recently, some question has been raised concerning the applicability of the Arbusov reaction in the synthesis of [¹⁴C] DC.² The Arbusov reaction is formally catalytic when the alkyl groups of both the halide and the phosphite ester are the same.² Thus, the product of the reaction, unlabeled methyl iodide, could in principle, compete with [¹⁴C] labeled material for available trimethyl phosphite. However, the Arbusov reaction probably proceeds through a two-step mechanism:⁷



Experimental evidence indicates that the second step is rate determining.⁷ As a result, virtually all of the original alkyl halide becomes incorporated to form the "quasi-phosponium" compound, $(\text{RO})_3\text{P}^+\text{R}'\text{Hal}$, before the generation of new alkyl halide, RHal .⁷ For example, the reaction of methyl iodide with triethyl phosphite quantitatively produces diethyl methylphosphonate.⁷ Our results are consistent with this mechanism, as a significant fraction of the [^{14}C]methyl iodide was incorporated. The reduction of radiochemical yield observed could be due to some competitive catalysis by unlabeled methyl iodide, but more likely was due to the loss of some of the volatile [^{14}C]methyl iodide in transfer to the reaction flask.

Reaction of dialkyl phosphonates with chlorinating agents can sometimes lead to by-products that cannot be separated from the dichloride². The ^{31}P NMR spectra of the reaction products of unlabeled DMMP with 2 molar equivalents of PCl_5 showed only peaks caused by DC and POC in the expected 1:2 ratio. The two were separated because the desired product of the subsequent step, DF, has a boiling point close to that of POC (106° and 100°C, respectively). Yields of the reaction were slightly reduced in the process. The only other by-product of the reaction, chloromethane, has a boiling point much lower than DC (-24°C), and was thus quantitatively removed.

Whereas the first two steps of our synthesis have been previously described, we are unaware of any report of the use of SbF_3 as a fluorinating agent in the preparation of DF. SbF_3 has often been used as a fluorinating agent for various other chlorophosphorus compounds, including ethylphosphonic dichloride.⁸ The use of SbF_3 in this synthesis offers one or more advantages over other fluorinating agents, including:

- 1) Because of its low vapor pressure (bp 376°C), SbF_3 is less hazardous than some volatile agents such as HF and AsF_3 , and only standard laboratory precautions are needed;
- 2) SbF_3 does not etch glass. Thus, no special apparatus is needed for reaction or purification;
- 3) The reactant SbF_3 and product SbCl_3 have boiling points that

differ markedly from DF (376°C, 224°C, and 100°C respectively). This makes vacuum line distillation a convenient method for purification. Extended periods of exposure of SbF_3 to high vacuum showed no loss of material. During purification of DF, the $\text{SbCl}_n \text{F}_{(3-n)}$ did show some volatility. This material was easily separated by passing the reaction products through a -45°C trap.

A disadvantage of using SbF_3 instead of HF as a fluorinating agent is reduced yields. Use of HF on the gram scale as a fluorinating agent gives quantitative yields. In unlabeled syntheses using SbF_3 , yields were consistently low (30-70%). The low yield may be due to a) absorption of the DF to the remaining SbF_3 and SbCl_3 , and b) wall loss to the vacuum distillation apparatus.

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