Synthesis of [1-^{14}C]-2,2-Difluoroethene from [^{14}C]-Formaldehyde

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Summary

[1-^{14}C]-2,2-Difluoroethene was synthesized from [^{14}C]-formaldehyde using a modification of the Wadsworth-Emmons reaction, *via* formation of the intermediate $(EtO)_2P(O)CF_2{}^{14}CH_2OSiMe_3$. This highly volatile product was collected in a liquid nitrogen trap at a purity of >97% and specific activity of 0.2 mCi/mmol, with yields of 10 -15%.

Key Words: [1-^{14}C]-2,2-difluoroethene, vinylidene fluoride, olefination

Introduction

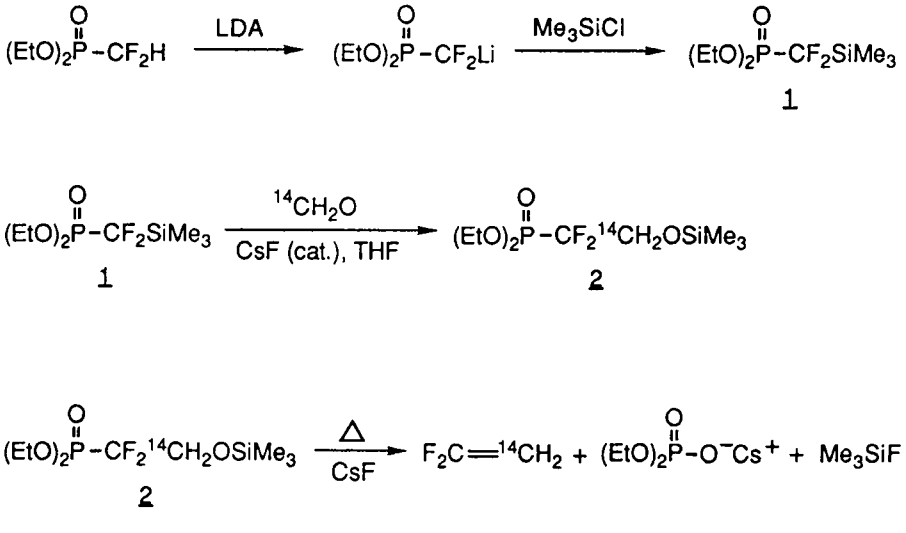
1,1-Difluoroethene (DFE) is a highly volatile industrial monomer (bp, -82° C) widely used in the production of a variety of polymers (1). While the large volume of DFE produced warrants a thorough knowledge of its metabolism and toxicity, studies to date are incomplete and somewhat conflicting. DFE has been reported to be of low toxicity (2, 3). However, studies in the rat have detected DFE-induced hepatotoxicity (4,5) and acetonemia (6). Numerous compounds structurally similar to DFE (*e.g.* vinyl chloride) are susceptible to cytochrome P450-dependent biotransformation (7-10), which may be a pivotal step leading to the metabolic species actually responsible for eliciting any observed toxicity. Although DFE metabolism is slow compared to that of vinyl chloride (3), it is known to release fluoride *in vivo* (11) and *in vitro* (12), and we have preliminary evidence that microsomal DFE metabolism is

0362–4803/94/010059–07$08.50

Received 10 June, 1993
Revised 9 August, 1993

accelerated by the anesthetic isoflurane. The metabolic fate of the carbon fragment(s) of DFE, however, is unknown.

In order to expedite study of DFE metabolism, we desired a ^{14}C-radiolabelled form of this compound. No methods of [^{14}C]-DFE synthesis have been reported. The synthetic approaches used industrially, dehydrochlorination of CH_3CClF_2 and dechlorination of $CH_2ClCClF_2$ at high temperature (1), were impractical as these starting materials are not commercially available in radiolabelled form. This necessitated a synthesis procedure for DFE which encompassed formation of the carbon-carbon bond from a radiolabelled single carbon compound. We have developed a method of synthesizing [^{14}C]-DFE using [^{14}C]-formaldehyde and diethyl difluoro-(trimethylsilyl)methylphosphonate (1) (13,14) a reagent capable of introducing the difluoromethylene moiety into a variety of organic compounds (Scheme 1).



Scheme 1

Materials

[^{14}C]-Formaldehyde (1 mCi, 43.6 mCi/mmol) was purchased from Sigma (St. Louis, MO). Formaldehyde (36.5-38%) was obtained from EM Science (Gibbstown, NJ) and DFE was from PCR (Gainesville, FL). Cesium fluoride was

purchased from Ozark-Mahoning (Tulsa, OK). If the CsF showed evidence of caking, it was stirred with dry acetone followed by solvent removal *in vacuo* and heating at 120° C. Tetrahydrofuran (THF) was freshly distilled over sodium.

Diethyl difluoro(trimethylsilyl)methylphosphonate (1), which is stable for several months when stored at room temperature in a sealed container, was prepared by a literature procedure (13) from (diethylphosphinyl)difluoromethyllithium in 68% yield.

[^{14}C]-Formaldehyde was diluted with cold formaldehyde to a specific activity of 0.2 mCi/mmol and polymerized to a dry solid on a lyophilizer.

Experimental

[^{14}C]-Paraformaldehyde (1.0 mmol) was taken up in THF (2-3 mL) in a 25 mL 2-neck round bottom flask, a catalytic amount of CsF (1-3 mg) was added, and the flask was flushed with nitrogen and sealed with a septum. Phosphonate (1, 1.2 equiv.) was added *via* syringe and the mixture was stirred overnight at room temperature.

To the resulting light brown mixture containing the intermediate 2 was added 2-3 additional milligrams of CsF and the flask was fitted with a water-jacketed condenser. The top of the condenser was vented through two glass traps, connected in series. The first trap was immersed in a dry ice/isopropanol bath, ensuring complete removal of THF and the reaction by-product trimethylfluorosilane (bp,17° C). The second trap (12 mL volume), which was sealable with teflon stopcocks, was immersed in liquid nitrogen and vented through a bubbler containing mineral oil. A check valve between the liquid nitrogen trap and bubbler prevented air from being drawn into the system as the liquid nitrogen was replenished.

The mixture was heated at reflux under a helium atmosphere for 4 h, after which a gentle flow of helium was passed through the system to concentrate DFE in the second trap (use of a nitrogen atmosphere was avoided as nitrogen condenses in the second trap and creates a hazard when the trap is sealed and brought to room temperature).

The [^{14}C]-DFE, under pressure in the sealed trap, was brought to atmospheric pressure by transferring the gas to an inverted 50 mL hypovial submerged in water. The trap was opened so as to allow the escaping gas to displace the water in the vial. The gas remaining in the trap was forced into the vial by displacing it with water, and the vial was sealed with a hycar septum. The purity of the product was determined by gas chromatography using an Alltech NON-PAKD AT-624 capillary column (30 m x 0.53 mm ID, oven temp. 45°C, helium carrier gas flow rate 12.5 mL/min) with flame ionization detection. Yields were determined by packed column GC (Porapak Q) by comparison to a standard curve constructed with authentic DFE. The specific activity of the product was taken as that of the formalin prior to concentration (0.2 mCi/mmol) as DFE exhibits poor solubility in liquid scintillation cocktail, hampering scintillation counting.

Mass-spectral analysis of the synthesized DFE was performed on a Nermag R10-10C mass spectrometer in the electron impact mode. Samples were introduced via a J&W Scientific GS-Q capillary GC column.

Results and Discussion

Using the above method, [^{14}C]-DFE was produced with high purity. Gas chromatographic analysis revealed only one peak, with trace impurities of <3%. Occasionally, significant amounts of trimethylfluorosilane or THF would be present. In this case pure DFE could be withdrawn from the vial when immersed in a dry ice/isopropanol bath. The identity of the product was confirmed by GC/mass spectrometry. In the electron impact mode, the molecular ion (*m/z* 64) was the base peak and abundant fragment ions included *m/z* 45 (loss of F), *m/z* 44 (loss of HF), and *m/z* 31 (loss of CH_2F) (Figure 1).

The yield of radiolabelled DFE was typically 10-15%. This yield may be explained in part by the extreme sensitivity of the reaction to trace amounts of water. In the presence of CsF, both the phosphonate (1) and the key intermediate (2) are destroyed by water or an alternative proton source (Scheme 2).

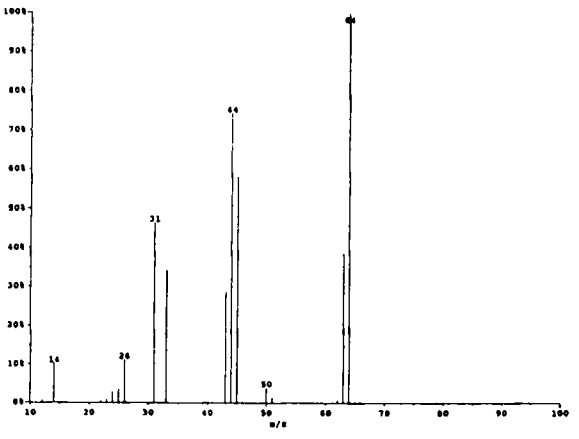
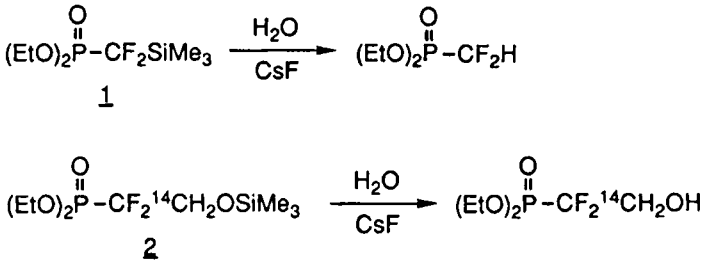


Figure 1 - Electron impact mass-spectrum of DFE.



Scheme 2

The hydroscopic nature of CsF, which must be handled so as to mimimize its exposure to air, complicates this problem. The difficulty of handling small amounts of a gaseous product also undoubtably reduces the yield. These problems were mitigated when the reaction was performed on a larger scale; 12 mmol of (cold) paraformaldehyde gave DFE in 43% yield. However, the present method has proved capable of providing [^{14}C]-DFE in ample quantity and specific activity for further studies.

This synthesis represents an extension of chemistry developed to permit incorporation of a difluoromethylene moiety into organic compounds (14-16). Despite the modest yields, this method proved superior to several related approaches, including the reaction of paraformaldehyde with $(EtO)_2P(O)CF_2CdX$ (15) or $(Me_2N)_3PCF_2Br^+Br^-$ and $(Me_2N)_3P$ (16). It also

constitutes a practical alternative to the high temperature methods of forming DFE from one-carbon fragments (17,18), as the necessary starting materials are not available radiolabelled and due to the need of specialized equipment.

Acknowledgment - The authors thank Mr. Dennis Charkowski for performing the mass-spectral analyses. This work was supported by NIH Grant GM 41121 (M.T.B.).

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