

Synthesis of [2-¹⁴C]Perfluorohexane

M. Haddach, J. Sapienza and C.M. Sharts
Department of Chemistry, San Diego State University
5500 Campanile Drive
San Diego, CA 92182-1030

SUMMARY

A general synthesis of [2-¹⁴C]perfluoroalkanes from 1-iodoperfluoroalkanes and ethyl acetate was developed by synthesis of unlabeled perfluorodecane from 1-iodoperfluorooctane. Using the general synthesis, [2-¹⁴C]perfluorohexane was synthesized from ethyl [1-¹⁴C]acetate and 1-iodoperfluorobutane as illustrated in Scheme 1.

Keywords: [1-¹⁴C]Ethyl acetate, [2-¹⁴C]perfluorohexane, [2-¹⁴C]perfluorononane, perfluorodecane, perfluoroalkane, Grignard, sulfur tetrafluoride, xenon difluoride

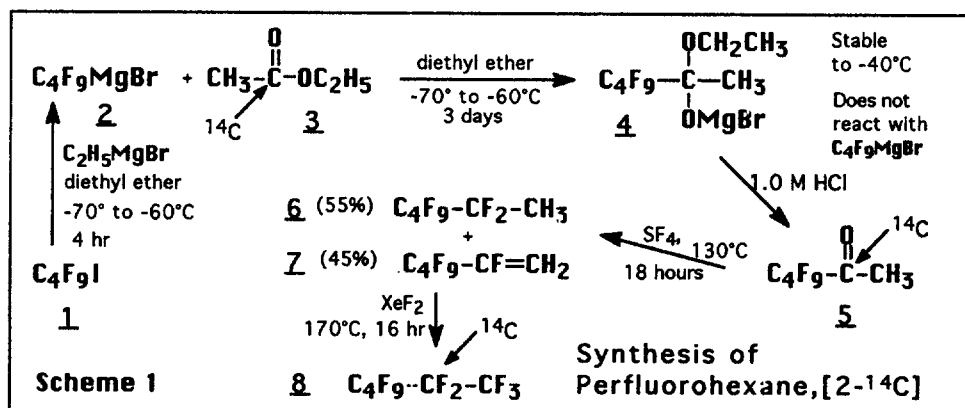
Introduction

Perfluorohexane is the major component of an ultrasound imaging agent (Imagent US®) currently under development. ¹⁴Carbon-labeled perfluorohexane was required for distribution studies of perfluorohexane in animal tissues. The low boiling point (57-58 °C) and very low surface tension (12 dynes/cm) of perfluorohexane make it extremely volatile and difficult to handle at room temperature (27 °C) in San Diego. To minimize problems during the development of a synthetic route, the first target was perfluorodecane. The synthetic scheme for perfluorodecane was then applied to synthesis of [2-¹⁴C] perfluorononane and finally to [1-¹⁴C] perfluorohexane. As our source of ¹⁴carbon we chose the moderately expensive but synthetically convenient [¹⁴C]carbonyl-labeled ethyl acetate, CH₃¹⁴COOC₂H₅. The reaction of a perfluoroalkyl Grignard reagent with [1-¹⁴C]ethyl acetate is a general synthesis for perfluoroalkyl methyl ketones labeled at the carbonyl carbon and is similar to work by Tamborski and co-workers with diethyl carbonate and diethyl oxylate⁽¹⁾. Although it is cheaper, we chose to avoid gaseous ¹⁴carbon dioxide from [¹⁴C]barium carbonate as our ¹⁴carbon source; we anticipated difficulties in the synthesis of [1-¹⁴C]perfluorohexanoic acid from ¹⁴carbon dioxide⁽²⁾. We were also concerned about converting the carboxylic acid group of perfluorohexanoic acid to a trifluoromethyl group^(3,4,5,6) to give [1-¹⁴C]perfluorohexane.

Results and Discussion

Our initial goal was to develop a synthesis for perfluoroalkanes. We did so through the synthesis of unlabeled perfluorodecane. To hone our skills, we used the synthetic scheme for perfluorodecane to synthesize $[2-^{14}\text{C}]$ perfluorononane from $[1-^{14}\text{C}]$ ethyl acetate and 1-iodoperfluoroheptane. Only then did we begin the more difficult synthesis of our target compound, $[2-^{14}\text{C}]$ perfluorohexane.

At -70°C to -60°C , ethylmagnesium bromide in diethyl ether underwent exchange with 1-iodoperfluorobutane (**1**) to form perfluorobutylmagnesium bromide (**2**). The ethereal Grignard reagent **2** at -70°C to -60°C reacted slowly with $[1-^{14}\text{C}]$ ethyl acetate (**3**) over a minimum 72-hour period. The intermediate magnesium salt of perfluorobutyl methyl ketone- $[^{14}\text{C}]$ ethyl hemiacetal (**4**) precipitated slowly from solution, paralleling earlier observations by C. Tamborski's group⁽²⁾. Intermediate **4** did not react further with Grignard reagent **2**. No methyl-bis-(perfluorobutyl)-methanol was isolated. Hydrolysis of the reaction mixture with hydrochloric acid gave $[2-^{14}\text{C}]$ -1H,1H,1H-perfluorohexan-2-one (**5**). Reaction of ketone **5** with sulfur tetrafluoride under autogenous pressure at 130°C gave a mixture of $[2-^{14}\text{C}]$ -1H,1H,1H-perfluorohexane (**6**, 55%) and $[2-^{14}\text{C}]$ -1H,1H-perfluoro-1-hexene (**7**, 45%). The mixture of **6** and **7** was fluorinated completely when heated slowly with xenon difluoride in a high-pressure reactor from 130°C to 150°C over a two-hour period as shown in Scheme 1. No proton signals were observed in the NMR spectrum of $[2-^{14}\text{C}]$ perfluorohexane (**8**).



The synthesis steps for $[2-^{14}\text{C}]$ perfluorohexane presented in Scheme 1 can be used to synthesize $[2-^{14}\text{C}]$ perfluoroalkanes containing from five to twelve carbons.

Experimental

General: Organometallic reactions were carried out under a N₂ atmosphere. Ethyl acetate was distilled from P₂O₅ and stored under a N₂ atmosphere. The various spectra were recorded on spectrometers as specified: ¹H-NMR, Varian EM-300 90MHz; ¹⁹F-NMR, recorded on a Varian Gemini 300 MHz; IR, Perkin Elmer Model 1600; GC, Carlo Erba HRGC Series 4160. Chemicals were the best available reagent grade and were purchased from the vendors cited. American Radiolabeled Chemicals: [1-¹⁴C]ethyl acetate; Aldrich: 1-iodoperfluorobutane, ethyl acetate, ethylmagnesium bromide, phosphorus pentoxide; Peninsular Chemical Research: xenon difluoride, sulfur tetrafluoride; VWR scientific: anhydrous ether. Reactions of sulfur tetrafluoride and xenon difluoride were carried out in a high-pressure stainless-steel minireactor fabricated in our laboratories from Whitey® Valves, Swagelok® Fittings and thick-walled tubing. The reactor design is our own and has not been publically described.

1H,1H,1H-Perfluoro-2-hexanone (5)

A one-liter oven-dried three-necked flask was fitted with a mechanical stirrer, a septum with nitrogen inlet/outlet needles and a low-temperature thermometer. Dry diethyl ether (0.70 L), 50.00 g (0.1445 mol) of 1-iodoperfluorobutane (1) and 0.10 g of magnesium shavings [Mg(s)] were added. Stirring was started and the flask cooled to -75°C under a dry nitrogen atmosphere. A 3-M solution of ethylmagnesium bromide (48.2 mL, 0.144 mol) was added through the septum. The mixture was stirred for 2 hours (-70°C to -60°C) after which time ethyl acetate (10.75 g, 12.0 mL, 0.122 mol) containing 1.0 mCi of [1-¹⁴C]ethyl acetate was added. The reaction mixture was maintained at -60° ± 10°C during normal working hours over a 5-day period. At night the reaction vessel was packed in well insulated solid carbon dioxide (-78°C). After 5 days the reaction contents were allowed to warm to -20°C and concentrated hydrochloric acid (25 mL) was added. At 0°C, 125-mL water was added and the reaction mixture then allowed to warm to room temperature. The ether layer was separated and washed with three 100-mL portions 5% sodium bicarbonate solution, one 100-ml portion of sodium thio-sulfate, and finally with two 100-mL portions of brine. The ether was slowly and carefully distilled adiabatically at 34-35°C through a vacuum-jacketed well insulated column packed with glass helices. A mixture of ethyl iodide, ethanol and the product were fractionally distilled to give 19.4 g (60%), of [2-¹⁴C]-C₄F₉C(O)CH₃ (5), bp=83°-87°C. ¹H-NMR (ppm, CDCl₃): 2.4 (s, 3H). ¹⁹F-NMR (ppm, CFCl₃): -81.46 (CF₃), -121.04 (α-CF₂), -123.83

(β -CF₂), -126.31 (γ -CF₂). IR (cm⁻¹), 1764.1 (C=O, vs); no absorptions that might be assigned as carbon-carbon double bonds were observed in the 1650-1750 region.

1H, 1H, 1H-perfluorohexane (6) and 1H, 1H-perfluorohexene (Z)

Using vacuum-line techniques, sulfur tetrafluoride was condensed into a (304)-stainless-steel high-pressure reactor which contained 9.0 g (34.3 mmol) of [2-¹⁴C]-1H, 1H, 1H-per-fluoro-2-hexanone, [2-¹⁴C]-C₄F₉C(O)CH₃ (5). The pressure reactor was permitted to warm in a high flow hood and checked for leaks during the period of warming to room temperature. The pressure reactor was heated to 130°C for 18 hours and permitted to cool to ≈25°C. The valve on the pressure vessel was opened and gasses vented to a sodium hydroxide solution. A water aspirator was used to give a continuous flow and to destroy any noxious gases not absorbed by the sodium hydroxide solution. A black liquid (6 g) was poured out of the reactor. The crude product was distilled without additional work up, bp 56-58°C, to give 5.5 g of a colorless mixture containing two major components as determined by gas chromatography. From the ¹H-NMR spectrum the products were assigned as [2-¹⁴C]-C₄F₉CF₂CH₃ (6) and [2-¹⁴C]-C₄F₉CF=CH₂ (Z). ¹H-NMR (ppm, CDCl₃): 6, 1.8 (t, 3H, J_{H-F} 19 Hz); Z, 5.2 (multiplet, not first order, 2H). Amount 6/Z = 47%/53% from ¹H-NMR integrals. IR (cm⁻¹) 1689.7 (C=C,s). There was no absorption in the carbonyl region near 1764 cm⁻¹; all 5 was consumed.

Perfluorohexane (8)

To an 18-mL high-pressure stainless-steel reactor under a nitrogen atmosphere, was added 3.5 g (12.7 mmol) of the preceding mixture of 6 and Z and 8.6 g (50.7 mmol) of xenon difluoride. The reactor was sealed and heated 2 hr at 130°C and 16 hr at 170°C. The reactor was cooled in a solid CO₂-acetone bath and vented to a sodium hydroxide solution while warming to room temperature. A black liquid amounting to 3.8 g was poured out of the reactor. Product was distilled without additional work up to give 2.1 g (6.2 mmol, 49%) of [2-¹⁴C]perfluorohexane (8), bp = 58-60°C. ¹⁹F-NMR (ppm, CDCl₃): -81.4 (CF₃), -123.4 (β -CF₂), -127.6 (α -CF₂). All physical properties of synthesized 8 were identical with those of authentic samples of perfluorohexane obtained from Peninsular Chemical Research Corporation and from Exfluor Corp.. The pot residue from the distillation of 8 afforded 1.5 g of perfluorododecane (9) (2.3 mmol, 38%, mp 74-76°C) identical with an authentic sample of perfluorododecane (mp 75-77°C), purchased from Peninsular Chemicals Research Corporation. Presumably, 9 is formed by dimerization of intermediate C₆F₁₃ radicals.

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