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A Safe and Efficient Process for the Synthesis of the Inhalation Anesthetic Sevoflurane

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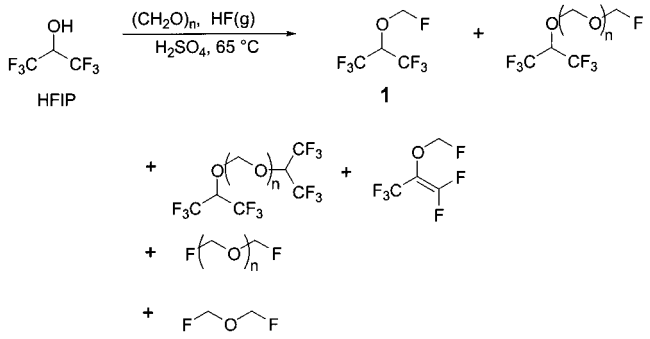
Abstract:

A novel method for the synthesis of 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane (sevoflurane) is described. Starting from commercially available 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), the process involves a novel, safe and efficient fluoromethylation protocol in a two-step, one-vessel procedure. The method avoids many of the hazards and complications of the current process for sevoflurane manufacture. The new method is easily scaled up to afford 10-kg batches of 99.4% pure sevoflurane.

Introduction

Sevoflurane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-propane (**1**, Scheme 1), is one of the most widely used inhalation anesthetics. In addition to being essentially nonflammable, sevoflurane has many desirable properties, including patients' rapid induction and recovery from the anesthesia, minimal irritation to the respiratory system, low metabolic rate, and rapid elimination.[1] Sevoflurane is currently manufactured in a one-step process, which reportedly produces the crude anesthetic in yields of up to 71%.[2] Thus, commercially available 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is treated with paraformaldehyde in the presence of large molar excesses of sulfuric acid and hydrogen fluoride gas. HF gas is extremely corrosive and highly toxic and requires that special precautions be taken for its handling and use. Due to the caustic nature of HF, special reactors must be used that resist degradation by the action of this reagent. In addition to the chemical hazards posed by the current process, the crude material requires extensive purification. As shown in Scheme 1, this synthesis of sevoflurane is accompanied by the formation of various higher molecular weight fluoromethyl polyacetals of HFIP, bis(hexafluoroisopropoxy) polyacetals and bis(fluoromethyl) polyacetals, fluoromethyl ether, and toxic fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether. The polyacetals are removed by acid hydrolysis to formaldehyde and HFIP, and the HFIP is then extracted by washing with base. Several cycles of acid and base treatment are necessary to remove all of the polyacetals, and some of the sevoflurane product is degraded in the process. The fluoromethyl ether remains through the washes and, since it codistills with sevoflurane, must be removed by passing the mixture through molecular sieves. We sought a method which would circumvent the problems associated with the handling of HF and the difficulties in purifying the product of the reaction. We also required that the method be cost-effective and amenable to large-scale manufacture. The new method presented here represents a safe and efficient as well as commercially viable alternative to the current process for the manufacture of sevoflurane.

Scheme 1



Results and Discussion

Our process involves a two-step sequence, consisting of a chloromethylation of HFIP followed by a halogen exchange reaction. We discovered that the chloromethylation could be effected through the use of aluminum trichloride, a reagent uniquely suited to our purpose, and a polymeric formaldehyde source, such as paraformaldehyde or 1,3,5-trioxane. Fluorination of the intermediate chloromethyl ether was found to proceed smoothly under relatively mild conditions in the presence of potassium fluoride in poly(ethylene glycol). While these reactions were developed on a small (10−100 mmol) scale, the reaction sequence was readily adapted to furnish 10-kg lots of high-purity sevoflurane with minimal optimization.

Chloromethylation of Hexafluoro-2-propanol

Our initial procedure for the synthesis of the intermediate chloromethyl ether involved the reaction of equimolar amounts of HFIP, paraformaldehyde, and $AlCl_3$ at 0 °C (Scheme 2.A). The reaction was, however, very rapid and exothermic and resulted in the concomitant formation of a dense chlorohydroxyaluminate polymer which invariably stopped the stirring and complicated the isolation of the product. The use of a mechanical stirrer did alleviate the

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(1) Longnecker, D. E.; Murphy, F. L. *Introduction to Anesthesia*; W. B. Saunders: Philadelphia, PA, 1992.
(2) Coon, C. L.; Simon, R. L. U.S. Patent 4,469,898, 1984.

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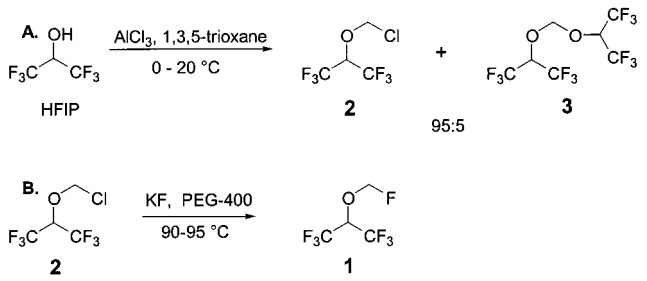
Scheme 2



problem somewhat, but the yield was lower due to the loss of material occluded within the polymeric mass. It was then discovered that substituting 1,3,5-trioxane for paraformaldehyde gave a much smoother, more controlled reaction, and the chlorohydroxyaluminate byproduct formed as a granular precipitate rather than a solid mass. The crude product was distilled directly from the reaction flask. However, this method of recovering the product proved rather inefficient since at some point the polymeric aluminate would begin to decompose, emitting dense fumes of HCl and preventing further product isolation. This problem was solved by instead dissolving the aluminate salts with cold 6 N HCl. The addition of aqueous acid did not have any deleterious effect on the product, and the reaction mixture cleanly partitioned into two clear layers, an upper layer of water and dissolved aluminum salts and a lower phase consisting of 95% pure chloromethyl ether **2**. This general protocol was easily implemented on larger scales. Pilot runs starting with 200, 600, and 1000 g of HFIP were conducted uneventfully. One concern throughout the process was the minimization of evaporative losses, due to the high volatility of HFIP (bp = 59 °C), HFIP chloromethyl ether **2** (bp = 76 °C), and sevoflurane **1** (bp = 58.5 °C). Another immediate concern was the efficient mixing of the reaction, which was quite thick to begin with and became very difficult to stir during the acid quench. The reaction apparatus therefore included a carefully enclosed system equipped with cold water condensers to limit losses due to volatility and an efficient mechanical stirrer for proper mixing. Upon scale-up, using 50-L and then 100-L reactors (5.4 and 10.9 kg of HFIP, respectively), maintaining the appropriate reaction temperature through the moderately exothermic chloromethylation reaction and the very exothermic quenching of the chlorohydroxyaluminate byproduct became more critical. During the 50-L process, the temperature of the chloromethylation reaction mixture was measured at 15 °C after 1 h and then observed to return to 0 °C within 2 h. The conversion to the chloromethyl ether (Figure 1) was recorded as over 60% at 1 h and approaching 80% at 2 h. In the standard protocol, the reaction was allowed to warm to ambient temperature while being stirred overnight. After 24 h, GC analysis revealed that the conversion had proceeded to afford over 96% of the desired product **2**, with less than 4% of the acetal **3** and only a minuscule amount of diacetal **4**. The product ratios and reaction times were very consistent from batch to batch and did not vary with scale. Since the bis(HFIP) acetals **3** and **4** were present in much higher concentrations in the early stages of the reaction, they appeared to be converted

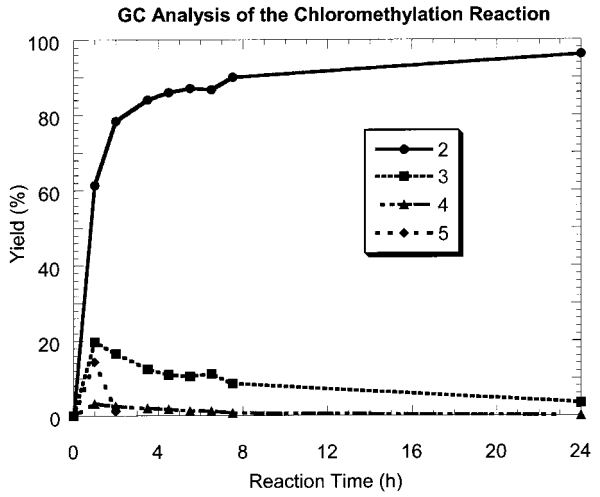
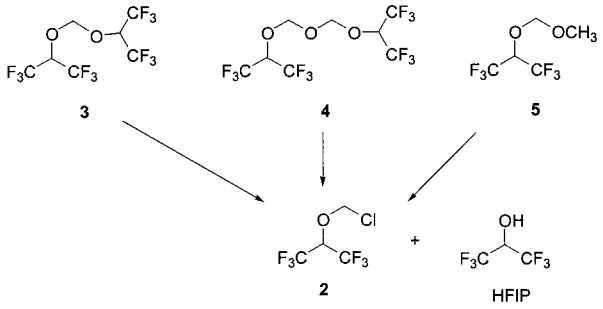


Figure 1.

Scheme 3



slowly into the chloromethyl ether as the reaction progressed (Scheme 3 and Figure 1). This hypothesis was subsequently confirmed by reacting a neat solution of **3** with anhydrous $AlCl_3$ at ambient temperature and monitoring the reaction by GC. Over a period of several hours, the acetal was converted to equimolar amounts of HFIP and the HFIP−chloromethyl ether. In the presence of a formaldehyde equivalent, as in the chloromethylation reaction, liberated HFIP from acetal cleavage is then free to undergo further reaction, yielding additional product. The only other component observed in the reaction mixture was a compound identified on the basis of NMR and mass spectral analysis as HFIP−methylacetal **5**. Although **5** was detected in a significant quantity in the early stages of the reaction, it was never isolated as a product. At the completion of the reaction, the resultant chlorohydroxyaluminate polymer was most effectively neutralized by slow quenching with cold 6 N hydrochloric acid. Acetic acid and sulfuric acid were also effective but did not appear to offer any advantage over the use of 6 N HCl. The reaction was very exothermic, which in itself was not detrimental to the product, but the heat caused the volatile chloromethyl ether product to evaporate. Thus, 6 N HCl was added slowly, and dry ice/acetone condensers were added to the system to prevent any vaporized product from escaping. The initial addition of the acid also caused the granular solid aluminate to coagulate into a thick, gummy mass, necessitating the use of an efficient high-torque stirrer. Fortunately, the quenching reaction gradually became much less exothermic and much

easier to stir after about one-third of the required amount of acid was added. When the addition of acid was complete, the reaction mixture consisted of two clear layers, the bottom containing the neat product and the upper containing an aqueous solution of aluminate salts. The upper layer was siphoned off and the product washed twice with water, followed by siphoning of the washes. The crude chloromethyl ether product was suitable for use directly in the subsequent fluoride exchange.

Fluoride Exchange

An earlier method for the conversion of the HFIP−chloromethyl ether into sevoflurane required the use of KF under supercritical conditions.[3] We discovered that the fluoride exchange could be effected under much milder conditions, without the need for high temperatures and pressures (Scheme 2B). In a typical procedure, the crude product of the chloromethylation reaction was dissolved in a suitable solvent, dry KF was added, and the mixture was stirred at 90−95 °C for 1−2 h. When NMP, DMF, or DMSO was used as solvent, GC/MS analysis of the crude reaction mixture revealed quantitative conversion to sevoflurane in each case. However, these solvents tended to darken as the reaction progressed, and more problematic was the tendency for the highly fluorinated product to form intractable complexes with these polar aprotic solvents, making product isolation difficult. The use of glyme or diglyme as solvent resulted in very little (<1%) product formation. The most successful method incorporated poly(ethylene glycol) (PEG) as the solvent. The fluoride exchange by this method is remarkably tolerant of a small percentage of water in the reaction mixture, and since the crude product of the chloromethylation does not need to be rigorously dried, the entire process can be performed in a single vessel. Indeed, a water content as high as 20% afforded the product, although in lower (37%) yield. Thus, to the crude product of the chloromethylation, in the same reaction vessel, was added PEG-400. The water content of the resultant solution was determined as 3.2% by Karl Fischer titration. Spray-dried KF was added in portions, and the reaction mixture was heated to an internal temperature of 78 °C for 2.5 h, at which time GC analysis showed the reaction to be complete. The crude sevoflurane was then distilled directly from the reaction vessel by gradually heating the mixture from an internal temperature of 78 to 125 °C. Although sevoflurane boils at 58.5 °C, heating is necessary to decomplex the product from the solvent. The addition of water to the reaction mixture aids in breaking this complex to maximize product recovery. The crude sevoflurane, as distilled directly from the reaction vessel, is very pure, containing only a small quantity of water and the bis(HFIP) acetal as contaminants. After being dried over $MgSO_4$ and distilled through a short (1 ft) Vigreux column, sevoflurane was obtained in 64% overall yield and at a purity of 99.4%. We believe that with minor improvements in the reaction apparatus, a yield in excess of 80% and a purity of greater than 99.95% can easily be attained.[4]

(3) Halpern, D. F.; Robin, M. L. U.S. Patent 4,874,901, 1989; *Chem. Abstr.* **1990**, *112*, 157680a.

Experimental Section

Hexafluoro-2-propanol, $AlCl_3$, 1,3,5-trioxane, KF, and PEG-400 were purchased from commercial sources and used as received. GC/MS data were acquired using an HP 6890 gas chromatograph in tandem with an HP 5973 mass-selective detector and using a Quadrex cyanopropyl methyl phenyl silicone column. GC analysis was performed using a Varian 3800 gas chromatograph with a flame ionization detector (FID) at 300 °C, 280 °C injection, and a helium gas flow of 2.4 mL/min through a 30-m × 0.55-mm-i.d. fused silica RTX-1301 capillary GC column. ^{1}H NMR spectra were recorded at 300 or 400 MHz on Varian NMR specrometers; ^{13}C spectra were recorded at 75 or 100 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ 0.00).

Synthesis of 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)-propane (Sevoflurane, 1). Into a 100-L glass reaction vessel equipped with an efficient mechanical stirrer, temperature probe, water-cooled condenser, and cooling coils was placed anhydrous $AlCl_3$ (8.63 kg, 64.54 mol). Scrubbers containing water were attached to the reactor to absorb residual HCl gas produced during the reaction. The reaction vessel was cooled to 0 °C, and 1,1,1,3,3,3-hexafluoro-2-propanol (11.08 kg, 6.72 L, 64.54 mol) was added in a single portion with stirring. The mixture was stirred at 0 °C until HCl gas evolution ceased. To the homogeneous slurry of HFIP and $AlCl_3$ was added 1,3,5-trioxane (1.94 kg, 21.58 mol) in a single portion, and the temperature of the reaction was observed to increase to 8 °C. Stirring was continued for 2 h, at which point the reaction exotherm had subsided and the mixture was shown to contain approximately 80% of the chloromethyl ether **2**. The reaction mixture was then allowed to warm to ambient temperature with stirring overnight. After 24 h of reaction, the yield of **2** had increased to over 96%, as assayed by GC. The reaction mixture was cooled to 0 °C and stirred vigorously for the careful addition of 26.6 L of ice-cold 6 N HCl. Stirring became difficult during the highly exothermic quench, and the aqueous acid was added at such a rate that the reaction temperature was maintained between 40 and 60 °C. When the exotherm had subsided, the remainder of the acid was added rapidly. Water (10 L) was added and the solution stirred until two clear phases were formed. The aqueous portion was siphoned off, and the organic layer was washed twice with water (10 L). A distillation receiver was attached to the reaction vessel, and PEG-400 (32 L) was added to the crude chloromethyl ether **2** with stirring. The water content of the solution was measured as 3.2% by Karl Fischer titration. Spray-dried KF was then added in portions to the reaction mixture. The reaction was heated to an internal temperature of 78 °C for 2.5 h, at which time all of the chloromethyl ether had been consumed. The crude sevoflurane **1** (8.73 kg) was distilled

(4) Sevoflurane purity was redetermined at 99.43% by GC. Proposed yield improvements include the minimization of evaporative losses throughout the procedure and the maximization of product recovery from the PEG solvent. Product purity can be improved by distillation using an increased number of theoretical plates. The fluoride exchange works well in glass reactors, although with some etching of the glass by KF. A stainless steel reactor is more suitable for the process and may also result in increased yield and purity.

directly from the reaction vessel by gradually increasing the internal temperature from 78 to 125 °C. The reactor was cooled, and 15 L of water was added. The mixture was heated at 100−110 °C, and an additional 0.85 kg of crude product was collected. The combined crude product was dried over $MgSO_4$, filtered, and distilled through a 1-ft Vigreux column to afford 8.29 kg (64%) of 99.4% pure sevoflurane. Data for 1,1,1,3,3,3-hexafluoro-2-(chloromethoxy)-propane (**2**): bp = 76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.55 (s, 2H), 4.54 (septet, 1H, J_{FCCH} = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 121.3 (dq, J_{FC} = 283 Hz, J_{FCCC} = 3.0 Hz), 80.2 (s), 73.1 (septet, J_{FCC} = 33.4 Hz). Data for 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane (Sevoflurane, **1**): bp = 58.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.39 (d, 2H, J_{HF} = 53.4 Hz), 4.40 (septet, 1H, J_{FCCH} = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 121.1 (q, J_{FC} = 282 Hz), 103.0 (d, J_{FC} = 225 Hz), 74.2 (septet, J_{FCC} = 33 Hz). Characterization and NMR data are consistent with literature values.[2]

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