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An efficient and environmentally friendly synthesis of the inhalation anesthetic sevoflurane

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Abstract

We report a new, high yield, single vessel synthesis of the general anesthetic sevoflurane. The new synthesis consists of a two-stage fluoromethylation of hexafluoroisopropanol. In the first stage, hexafluoroisopropanol is chloromethylated using aluminum trichloride and trioxane. In the second stage fluorine exchange is carried out using potassium fluoride and poly(ethylene glycol). Sevoflurane is distilled directly from the reaction vessel yielding material of 99.95% purity. The overall yield of the process is 65–70%.

Keywords: Anesthetic; Sevoflurane; Fluoromethyl ether; Aluminum trichloride; Chloromethylation; Fluoromethylation

1. Introduction

Sevoflurane, (**1**), [1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy) propane] is today one of the most important and widely used general anesthetics. Seroflurone anesthetic combines various characteristics that are most desirable in an inhalation anesthetic including the lowest blood/gas partition coefficient of 0.63, smooth induction and recovery from anesthesia, minimal irritation to the upper respiratory tract, low metabolic rate and rapid elimination. In addition, sevoflurane is suitable for out-patient surgery use.

Although the definitive mechanism of action has not been elucidated, it has recently been shown that sevoflurane interacts with nicotinic acetylcholine receptors, by affecting the open and closed state of the ion channels at clinical and lower concentrations [1,2]. Sevoflurane may also effect reversible modulation of GABA and glycine receptors as recently reported [3]. The above suggests that at least part of the anesthetic action of sevoflurane may be due to interactions between sevoflurane and specific voltage-gated ion channels.

Sevoflurane (**1**) is currently synthesized (Scheme 1) by reacting 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) with paraformaldehyde in the presence of a large molar excess of hydrogen fluoride in fuming sulfuric acid [4,5]. Although the yield is reported to exceed 70%, the crude product requires extensive purification to remove side-products including bisfluoromethyl ether, various chain length polyacetals, and toxic fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether. The use of toxic and caustic reagents, particularly hydrogen fluoride gas, make this synthesis environmentally unfriendly and complicates large scale manufacture. The drawbacks of the current synthesis prompted us to devise a new synthetic route to sevoflurane with several goals in mind. The process should be environmentally safe, without hazardous reagents or toxic by-products, cost-effective, and manufacturable in industrial quantities.

In this note we describe a new synthetic route to sevoflurane which meets these goals. The synthesis involves a novel method for the chloromethylation of HFIP followed by fluorination of the intermediate chloromethyl ether. This two-step procedure can be run in a single vessel and affords high yields of very pure sevoflurane.

2. Results and discussion

Simply put, the synthesis of sevoflurane involves fluoromethylation of HFIP. However, direct fluorination did not appear possible without the use of hydrogen fluoride gas or expensive fluorinating agents such as diethylaminosulfur trifluoride, or XeF_2 [6,7]. We therefore turned our attention toward a two-step procedure, specifically a chloromethyla-

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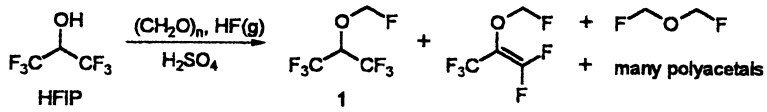
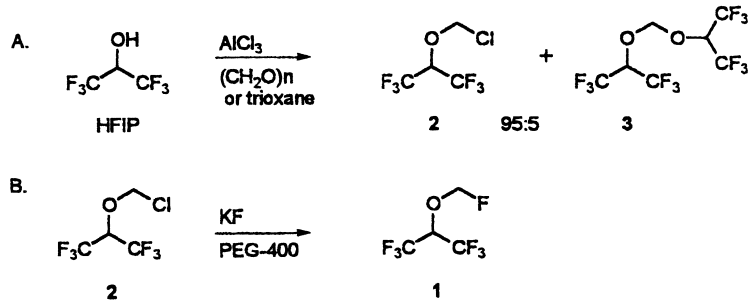


Scheme 1.



Scheme 2.

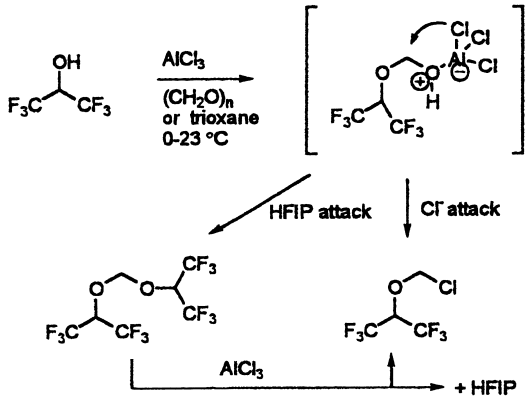
tion of HFIP followed by fluorination of the intermediate HFIP chloromethyl ether.

Our initial attempts to chloromethylate HFIP using traditional methods met with failure. Infusing a slurry of paraformaldehyde in HFIP with anhydrous HCl gas afforded a complex mixture of polyacetals. The addition of Lewis acid catalysts, i.e. $AlCl_3$ or anhydrous $SnCl_4$ and/or lowering the reaction temperature had little effect on the product distribution. The use of other Lewis acid chlorides, including BCl_3 and $FeCl_3$, gave complex mixtures of chloromethyl polyacetals. Phosphorous trichloride furnished the chloromethyl ether in low (7%) yield in addition to numerous polyacetals and unreacted HFIP. A successful high yielding synthesis of the chloromethyl ether of HFIP was finally achieved with the use of $AlCl_3$ (Scheme 2A). When paraformaldehyde was added to a neat slurry of $AlCl_3$ in HFIP, a rapid exothermic reaction took place, generating the desired chloromethyl ether **2** as the major product. Several modifications of our initial attempts led to a facile, high yielding protocol. In the optimized procedure, equimolar amounts of HFIP and anhydrous $AlCl_3$ were cooled to 0°C for the addition of 1/3 equivalent of trioxane. The latter reagent gave a more controlled, less exothermic reaction than paraformaldehyde. The mixture was stirred overnight at ambient temperature, then carefully quenched with cold 6N HCl to decompose the hydroxydichloroaluminate gel which forms during the reaction. The addition of water caused the mixture to separate into a clear aqueous phase containing the dissolved low molecular weight aluminum salts and a lower phase consisting of 95% pure HFIP chloromethyl ether **2**. In addition, 4.5% of the bis-acetal of HFIP (**3**) and about 0.5% of higher molecular weight polyacetals were present as side products.

After separation of the aqueous phase the chloromethyl ether was washed repeatedly with water to remove remaining aluminum salts. In the second stage of the process (Scheme 2B), the crude chloromethyl ether was dissolved in PEG 400 and 4 equivalents of spray-dried KF were added. The reaction mixture was then heated at 95°C for 1–2 h. Smooth halide exchange yielded sevoflurane, which after distillation gave a 71% yield of 99.95% pure anesthetic. Other solvents, including DMF, NMP, and DMSO likewise afforded the product, but in lower yields and product isolation was difficult. The use of glyme or diglyme furnished only traces of the desired product. Since the conversion of the chloromethylated intermediate to sevoflurane is essentially quantitative as determined by GC–MS, the evaporative loss of sevoflurane, which boils at 59°C, undoubtedly lowered the yield. Although we used spray-dried KF, less expensive commercial grade KF gave a product of comparable purity and yield.

The two component reactions of our procedure deserve further comment. The chloromethylation protocol appears to have little if any direct precedent in the chemical literature. For example, $AlCl_3$ has previously been used as a chlorinating agent in the preparation of β-chloroglycosides [8], and in *para*-chloromethylation of thioanisole [9]. In our synthesis, $AlCl_3$ plays a triple role, as illustrated in Scheme 3. First, it serves as a Lewis acid in the complexation to trioxane and hydroxymethylation of HFIP, probably through intermediate formation of $^{+}CH_2O{-}AlCl_3^{-}$. Second, it functions as a chlorinating agent. And third, it acts as a dehydrating agent, a role which is fulfilled by fuming sulfuric acid in the previous synthesis. Although we did not study the mechanism of the reaction in detail, we depict the mechanism of halogenation in Scheme 3 as SNi. Other mechanisms involving intermolecular chloride attack may also be operative.[1] Alternatively, attack of a second molecule of HFIP on the putative intermediate aluminate affords instead the bis-HFIP-acetal. Indeed, increasing the ratio of $AlCl_3$ to 2:1

[1] For instance, it is possible that $AlCl_3$ initially coordinates with the oxygen of HFIP followed by electrophilic attack of the protonated formaldehyde on the oxygen of HFIP.



Scheme 3.

and 4:1 resulted in the predominant formation of the bis-acetal. The success of the reaction is a result of the very nonnucleophilic character of HFIP, which allows for chloride attack to effectively compete. This reaction is therefore probably best suited for the chloromethylation of low pK_a alcohols, since our attempts at applying this method to chloromethylate other alcohols without electron withdrawing groups failed, giving instead only the bis-acetal of the alcohol. In the chloromethylation of HFIP, the concentration of the bis HFIP-acetal is the highest at the early stages of the reaction and diminishes as the reaction proceeds. We suspected that the bis-acetal was being cleaved by the $AlCl_3$ once it had formed. Indeed, when a solution of pure bis-HFIP-acetal was stirred at 23°C with an equivalent of $AlCl_3$, equimolar amounts of HFIP and HFIP-chloromethyl ether were produced. The second stage of the process, the conversion of the HFIP chloromethyl ether to the corresponding fluoromethyl ether, represents an optimization of previously documented methods for fluorination. In particular, we found that polyethers are excellent solvents in the second stage of the reaction. The use of poly(ethylene glycol) (PEG) as the solvent allows for lower reaction temperature and shorter reaction times and results in a remarkable increase in yield. In addition, the use of PEG afforded the purest crude product in comparison with other solvents. These effects may be due to the reported complexation of potassium ion to the PEGs and the concomitant increase in the nucleophilicity of the fluoride ion [10]. While the use of KF as an inexpensive reagent in chloride to fluoride exchange is well documented [7] there are very few literature examples of the use of PEGs as solvents in these reactions [11–13]. Moreover, the existing fluorination methods which utilize KF in the absence of cation-complexing solvents invariably call for much harsher reaction conditions [7].

In summary, we have developed a new synthesis of sevoflurane, a very important inhalation anesthetic. The new synthesis avoids the use of toxic and environmentally hazardous reagents, and can be carried out in a single vessel in two stages. Purification via a simple distillation affords 99.95% pure sevoflurane in 65–70% overall yield. The minimization of evaporative losses throughout the process will undoubtedly result in a considerably higher yield. We believe that the new synthesis will be used in the future manufacture of sevoflurane.

3. Experimental

3.1. General methods

^{1}H NMR spectra were recorded at 300 or 400 MHz on Varian NMR spectrometers. ^{13}C spectra were recorded at 75 or 100 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ 0.00). Qualitative and semiquantitative analyses of reaction mixtures were performed on an HP 6890 gas chromatograph equipped with an HP 5973 mass selective detector. All reagents were purchased from Aldrich and used without further purification.

3.2. Synthesis of 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-propane

3.2.1. Stage 1: synthesis of 1,1,1,3,3,3,-hexafluoro-2-(chloromethoxy)-propane

To a 100 ml flask containing anhydrous aluminum trichloride (18.56 g, 139.2 mmol) was added cold (0°C) HFIP (14.66 ml, 139.2 mmol) and the resultant slurry was stirred for 10 min in an ice bath. To the reaction mixture was added 1,3,5-trioxane (4.18 g, 46.60 mmol) in a single portion and the flask was capped with a rubber septum and vented through a drying tube. The reaction was allowed to warm to ambient temperature while stirring overnight. The mixture was then cooled to 0°C in an ice bath and an efficient dry ice/acetone condenser was placed on the flask. The reaction was quenched with 50 ml of ice-cold 6N HCl, added in small portions. Water was added, sufficient to dissolve any remaining aluminum salts, and the mixture was partitioned. The bottom layer consisted of 27.0 g of 95% pure chloromethyl ether, for a yield of 90%. The product, 1,1,1,3,3,3-hexafluoro-2-(chloromethoxy)-propane may be further purified by washing with 1N NaOH, drying over $MgSO_4$ and distilling at atmospheric pressure (bp 76°C) to yield pure (99.9%) hexafluoroisopropylchloromethyl ether: ^{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). In the one-vessel procedure, the crude product of the first reaction is simply rinsed with water (2 × 100 ml) to remove residual aluminum salts, and carefully decanted.

3.2.2. Stage 2: fluorination of 1,1,1,3,3,3-hexafluoro-2-(chloromethoxy)-propane

To a solution of 1,1,1,3,3,3-hexafluoro-2-(chloromethoxy)-propane (2.16 g, 10 mmol) in PEG 400 (10 ml) was added spray-dried KF (2.32 g, 40 mmol) at room tem-

perature. The reaction mixture was heated at 95°C, for 1 h, then cooled to room temperature and diluted with water (30 ml). Distillation directly from the reaction vessel afforded 1.42 g (71%) of 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-propane, bp 55°C. The purity of this material was determined at 99.95% by GC analysis). El-MS: *m/z* 199 ([M^+–H], 5%, 181 (30%), 131 (100%), 79 (35%), 69 (50%), and 51 (27%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.42 (d, 2H, $J_{HF} = 53.4$ Hz, 4.42 (m, 1H, $J_{FCCH} = 5.7$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 121.1 (q, $J_{FC} = 283$ Hz), 103.0 (d, $J_{FC} = 226$ Hz), 74.2 (septet, $J_{FCC} = 33.8$ Hz).

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