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Scale-up of sevoflurane synthesis: selection of chemical route and influence of reagent characteristics

David Lokhat*, Ajij Golandaj and D. Ramjugernath

Reactor Technology Research Group, School of Engineering,
University of KwaZulu-Natal, Durban 4041, South Africa
**Author to whom correspondence should be addressed,*

Abstract

The general anaesthetic sevoflurane was prepared from chlorosevo ether using two fluorinating agents, potassium fluoride dihydrate in the presence of a phase transfer catalyst and potassium fluoride in the presence of a complexing solvent. A pure sevoflurane product could not be recovered via conventional distillation from the crude reaction mass obtained using the dehydrate (at 72% purity), due to the existence of a maximum boiling azeotrope at 368 K. The efficacy of the potassium fluoride reagent allowed for a more complete reaction and bypassing of the azeotrope. Scale-up tests showed that the quality of the potassium fluoride directly affects the selectivity and yield of sevoflurane. The salt undergoes morphological changes upon exposure to moisture that results in significantly lower yield of the target compound even after reprocessing and drying, from 73% to 28% respectively.

Keywords: sevoflurane, chlorosevo ether, fluorination, scale-up

1. INTRODUCTION

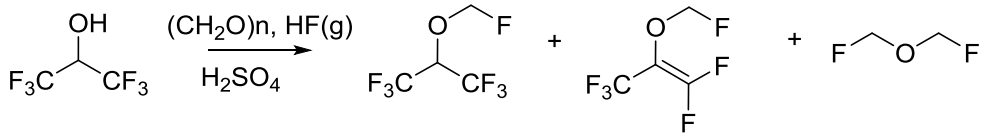
Sevoflurane ($C_4H_3F_7O$) is a chemical compound widely used as an anaesthetic agent in the health industry [1]. Sevoflurane is preferred over other available anaesthetic agents as it is volatile, non-flammable and possesses a pleasant odour. In addition to this, it has a low blood/gas partition coefficient, which facilitates the precise control over the depth of anaesthesia and also results in smooth induction and rapid recovery of the patient from unconsciousness [2,3]. Overall, these characteristics make sevoflurane a strong candidate for clinical use to treat out-patients i.e. adults and especially children,

since the introduction of sevoflurane via inhalation is more pleasant than through intravenous administration [3].

In terms of the anaesthetic action of sevoflurane, the detailed mechanism is still not clear. Some reports have shown that sevoflurane interacts with the nicotinic acetylcholine receptors as well as affects the reversible modulation of gamma-amino butyric acid and glycine receptors [4,5]. These interactions were claimed to be involved in the generation of anaesthetic action.

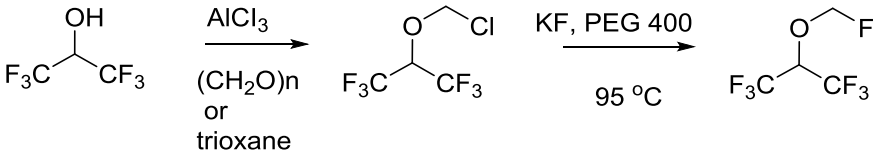
The first synthesis of aliphatic anaesthetic gas was disclosed by Croix and Szur in 1969, using a photosynthetic method [6]. Further, Ryan and Burges [7] invented a synthesis route for sevoflurane, using bisfluoromethyl ether and sulphuric acid as reagents which gave a 55% sevoflurane yield. Later Baker et al. [8] prepared sevoflurane using methoxy-malononitrile as a starting material and carried out fluorination using BF_3, but in this process the formation of the side product (1,1,1,3,3,3-hexafluoroisopropyl ether) was found to be excessive with a ratio of 1:1 to the target compound. Bieniarz et al. [9] patented a three step synthesis route for sevoflurane (final yield 28%) through fluoromethylation of alcohols via halogenative decarboxylation using lead acetate.

The synthesis of sevoflurane was later achieved in high yields (> 75%) using hexafluoroisopropyl alcohol (HFIP) and paraformaldehyde in presence of excess hydrofluoric acid (HF) (Scheme 1). However, the use of toxic HF at large scale raised questions on the feasibility and the safety of the process [10].



Scheme 1

Moreover, this process (Scheme 1) also required an extensive purification system (acid-base treatments) to remove side-products such as bisfluoromethyl ether, various chain lengths polyacetals, and toxic fluoromethyl 2,2-difluoro-1-(tri-fluoromethyl) vinyl ether, which also contributes to the lower yield of the target molecule by degrading it into the unwanted by-products. Together these aspects rendered the process complicated and environmentally unfriendly. To overcome these problems Bieniarz et al. [11] developed a non-toxic, two-step process for the synthesis of sevoflurane using HFIP as a starting material (Scheme 2).



Scheme 2

In this method, HFIP was chloromethylated using 1,3,5-trioxane/paraformaldehyde in the presence of aluminium trichloride ($AlCl_3$) to yield 1,1,1,3,3,3-hexafluoro-2-

chloromethoxy-propane (chlorosevo ether). Further, the fluorination of chlorosevo ether was achieved using high molecular weight polyethylene glycol (PEG-400) as a solvent and potassium fluoride (KF) as a fluorine source to yield sevoflurane. This was the first method to report high sevoflurane yield (>70%) without the use of hazardous HF. Following these developments, Terrell et al. [12] described a new method for sevoflurane synthesis using an organic tertiary amine with 69% conversion of chlorosevo ether and 83% yield of sevoflurane. The same authors later patented a new synthetic method for sevoflurane using chlorosevo ether as a starting material with aliquat HTA-1 as a phase transfer catalyst and potassium difluoride (KHF_2) as the fluorine source [13]. The method achieved both a chlorosevo ether conversion and sevoflurane yield of 83%.

Although some of these patents and papers report high sevoflurane yields (> 70%), the separation of the product from the residual starting material is often difficult and the reagents themselves are problematic to work with in larger quantities. In this study we compare the performance of two synthesis methods using chlorosevo ether as starting material, and interrogate their applicability to large-scale production with respect to the ease of purification and influence of reagent characteristics on scale-up.

2. EXPERIMENTAL

2.1 Materials and analytical procedures

In this work, fluorination of chlorosevo ether to sevoflurane was performed using the procedures described by Terrell et al. [13] and Bieniarz et al. [11]. For the approach reported by Terrell et al. [13], the chlorosevo ether was acquired from Manchester Organics (98%), KHF_2 was sourced from Alfa Aesar (99%) and HTA-1 was obtained from Sigma Aldrich (99%). For the Bieniarz et al. [11] approach, the KF was received from Merck Millipore LTD (99%) and the PEG-400 was obtained from Sigma Aldrich. Analyses of the reaction products were performed on a Shimadzu 2010 gas chromatography equipped with a Restek Rxi-5Sil MS fused column (0.25 μm × 0.25 mm × 30m) and a flame ionization detector with helium as the carrier gas (linear velocity 6.5 $cm \cdot s^{-1}$). The column was held isothermal at 313 K. The detector was calibrated using authentic standards of sevoflurane (98%) and hexafluroisopropyl alcohol (99%) from Sigma Aldrich. Selected samples of the product were analysed by a Shimadzu GCMS QP 2010 equipped with an ultra-alloy-5 capillary column (0.25 μm × 0.25 mm × 30m) operating in SCAN mode (30-500 *m/z*). The temperature program for the oven was 323 K for 5 min, 323 K to 523 K at 5 $K \cdot min^{-1}$ and 523 K for 5 min. NMR of the purified product was recorded on a Bruker 400 MHz instrument using $CDCl_3$ as a solvent.

2.2 Methods applied for the synthesis of sevoflurane

2.2.1 Terrell et al. [13] approach

The reaction was carried out in a sealed 300 ml Parr high pressure reactor fabricated from Monel 400 alloy. The reaction vessel was charged with 43.2 g (0.2 mole) of chlorosevo ether, 18.8 g (0.2 mole) of potassium fluoride dihydrate, 1.56 g (0.02 mole) of KHF_2 and 1 g of Aliquat HTA-1 phase transfer catalyst. The reaction mixture was

stirred and heated to 373 K for 6 hours to yield a brown coloured solution. The brown coloured reaction mass was then washed several times with distilled water. The organic layer was dried over sodium sulphate (Na_2SO_4) and then subjected to distillation. The distillation was carried out in a conventional laboratory distillation apparatus consisting of a 250 ml flask, distillation head, condenser and vacuum tube. The distillation of the brown reaction mass yielded a colourless distillate that weighed 18 g.

2.2.2 Bieniarz et al. [11] approach

The reaction was also carried out in the high pressure reactor apparatus. To a solution of 13 g (0.059 moles) of chlorosevo ether in 60 ml of PEG-400, 13.92 g (0.239 moles) of oven dried KF was added at room temperature (Prior to the use, KF was dried in an oven at 373 K for 72 hours). The reaction vessel was then heated to 371 K for 1.5 hours and then cooled down to room temperature. The reactor contents were diluted with 20 ml of water followed by distillation to afford 8.6 g of product.

3. RESULTS AND DISCUSSION

3.1 Results for Terrell et al. [13] approach

The GC analysis of the crude reaction mass showed that the purity of the sevoflurane obtained after reaction and extraction with water was approximately 72%. Several attempts were made to distil the reactor contents and obtain pure sevoflurane. In all cases the initially brown reaction mass yielded a colourless distillate that distilled at 368 K. This is very close to the boiling point of pure chlorosevo ether. Analysis of the distilled product and distillation residue showed that the composition did not change appreciably upon distillation. In fact it proved impossible to recover the sevoflurane at its normal boiling point of 332 K. It is likely that the system exhibits a maximum boiling azeotrope and that the crude reactor contents are very close to this azeotropic composition. In order to achieve a pure sevoflurane product via distillation the reaction mass would have to contain a higher proportion of sevoflurane, at least higher than the azeotropic composition.

The GC chromatogram of the crude product after extraction did not show the presence of any impurities other than the unreacted chlorosevo ether. The water extraction was able to remove practically all of the hexfluoroisopropyl alcohol byproduct. However it appears that at least a trace amount of a second unidentified byproduct survived the extraction and is responsible for the brown colour of the product mixture. This byproduct was retained in the distillation residue. Unfortunately the separation was unsuccessful and thus the method of Terrell et al. [13] was deemed unsuitable for large-scale production of medical-grade sevoflurane.

3.2 Results for the Bieniarz et al. [11] approach.

The crude reaction mass obtained using the method proposed by Bieniarz et al. [11] was not discoloured. After combining with water to extract any possible alcohol byproduct the reaction mixture was distilled. After distillation, the distilled product was characterised by GC-FID and was found to be relatively pure (> 98%). In this case the reaction proceeded almost to completion and the composition of the crude product was

above the azeotropic composition. Upon distillation the lighter sevoflurane was fully recovered in the distillate and the heavier residual chlorosevo ether, water and hexalfluoroisopropyl alcohol was retained in the distillation residue. The presence and purity of the sevoflurane product were confirmed by mass spectrometry and ^{1}H NMR measurements, respectively. Fragmentations of the ether product were *m/z* 199 ([M-H]$^{+}$), 181, 113, 69, 33. The ^{1}H NMR of the distilled product confirmed that the sevoflurane obtained via the Bieniarz et al. [11] method was chemically pure (1H NMR data: δ=5.40 (d, 2H) and δ=4.40 (m, 1H)).

3.3 Scale-up of sevoflurane synthesis

Based on the above results, all subsequent tests were based only on the Bieniarz et al. [11] approach for the synthesis of sevoflurane. The reactions were progressively scaled up from 4 g to 40 g of starting material. The quantity of sevoflurane obtained from each reaction and its yield is reported in Table 1. As depicted in Table 1, the synthesis of sevoflurane was achieved in 4 different batches, in which the first two batches gave >70% yield to sevoflurane, consistent with the yield reported by Bieniarz et al. [11]. However, the yield towards the final product was found to decrease as the reactions were progressively scaled up. The synthesis attempt with 40 g starting material gave the lowest sevoflurane yield (28%), whereas, the following synthesis attempt (16 g of starting material) also failed to reproduce the previous yield (>70%) and gave < 45% yield to sevoflurane. The poor yield of sevoflurane for the latter two batches could be attributed to the quality of the KF used in the reaction. For the first two syntheses, the small quantity of KF used was present in a finely divided powdered form, which was dried for 72 hours and then used in the reaction. On the other hand, the larger quantity of KF used in the last two batches was present in the form of large lumps having been exposed to moisture during storage. These larger lumps were crushed and then dried in an oven for 72 hours before being used in the reaction. Due to its hygroscopic nature KF can rapidly absorb moisture from the air, which causes the salt to agglomerate and form large clumps. It is difficult to remove this moisture and obtain a finely divided solid. The latter is important since a high surface area is required for the KF to be sufficiently active in the main reaction. Bieniarz at al. [11] used spray-dried KF, which has a significantly higher surface area than normal precipitated KF, for their syntheses. However, special equipment is required to produce sprayed-dried KF and commercially it is much more expensive. This would impact negatively on its suitability for large-scale production.

Table 1. Results of scale-up experiments for the synthesis of sevoflurane

Experiment number	Chlorosevo ether (g)	Obtained mass of sevoflurane (g)	Practical yield %	Sevoflurane Purity in % (by GC-FID)
1	4	2.7	73	95.5
2	13	8.5	71	98.4
3	40	10.3	28	98.3
4	16	6.5	44	99.4

CONCLUSIONS

Large-scale synthesis of sevoflurane can be carried out via fluorination of chlorosevo ether. This method offers satisfactorily high yield of the target compound to ensure economic viability of the process. Potassium fluoride dihydrate as the fluorinating agent gives a crude product consisting of approximately 72% sevoflurane after water extraction. The purity of this mixture is impossible to upgrade via conventional distillation due to the presence of a maximum boiling azeotrope and the method is thus unsuited for large-scale operation.

When potassium fluoride is applied in the presence of a complexing solvent (high molecular weight polyethylene glycol) the reaction goes almost to completion allowing for the recovery of pure sevoflurane via simple distillation. The quality of the potassium fluoride is an important factor. KF exposed to air during storage does not have sufficient surface area for efficient complexation of the potassium ion and concomitant release of fluoride ion into the solvent. This has a dramatic effect on the selectivity and yield of the main reaction.

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