Reinvestigation of the Two-step Synthesis of Sevoflurane

Abolghasem Moghimi\textsuperscript{a}, Mostafa Vojdani\textsuperscript{a,b}*\textsuperscript{*}, Ali R. Banan\textsuperscript{a}, Ahmad Mollaei\textsuperscript{a}, Mojtaba Mahmoodian\textsuperscript{a} and Sayyed Mojtaba Moosavi\textsuperscript{a}

\textsuperscript{a}Department of Chemistry, Imam Hossein University, Tehran, Iran. \textsuperscript{b}Department of Nuclear Medicine, The Educational, Research and Clinical Center, Dr. Masih Daneshvari Hospital, Tehran, Iran.

Abstract

Improvements in the two-step synthesis of 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane (Sevoflurane) that result in the product cost reduction, safety level enhancement and positive environmental impacts are described. This process consists of chloromethylation reaction of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) followed by a halogen-exchange fluorination. This is the first synthesis of Sevoflurane in Iran which was successfully scaled up. During this work, several improvements have been achieved by optimization of the reaction time, the amount of consumed starting materials and solvents and work up procedure while keeping the yield and purity intact. The reaction time of the first step (24 h) was diminished to 4 h. \textsuperscript{19}F NMR spectroscopy was used to investigate the rate of the reaction in the first step and to evaluate the influence of different parameters mentioned on the achieved improvements.

Keywords: Inhalation anesthetic; Sevoflurane; Halogen-exchange fluorination; Hexafluoro-2-propanol.

Introduction

Sevoflurane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-propane, is an important and widely used nonflammable general inhalation anesthetic in the world. Although a number of methods have been introduced by different research groups (1-4), three methods have gained more interest for the industrial production of Sevoflurane (Scheme 1). The single-step synthetic process involves the reaction of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and stoichiometric excess of paraformaldehyde and HF in the presence of fuming sulfuric acid. In this one pot method, a large quantity of chemically aggressive species may cause corrosion of the plant during the process and would also circumvent the problems associated with the handling of highly toxic HF. The three-step method involves, i) reaction of HFIP with a methylating agent such as dimethylsulfate to form sevomethyl ether (1), ii) photochemical chlorination of sevomethyl ether 1 to form Sevochlorane (2), and iii) substitution of the chlorine of Sevochlorane through a Halogen-exchange reaction. In this process, dimethylsulfate and chlorine gas must be handled which are both toxic. In addition, the low yield of the second step was the other disadvantages of this process.

The third process has been introduced by C. Bieniarz \textit{et al.} as a two-step, efficient, safe and amenable method. The overall yield has been differently reported from 65 to 70\% with purity in the range of 99.40-99.95\% depending on the procedure (2, 3).

Our investigations on this process, clarified some disadvantages that could be partially or
734 h, the reaction mixture was cooled to 0 ºC and the careful dropwise addition of cooled water (40 g) started. When adding water was completed, and the exothermic reaction was subsided, 6 N HCl (40 mL) was added rapidly in one portion. Then, the bath temperature was increased to ambient temperature and stirrer rate was increased to dissolve all the remaining aluminate salts. Consequently, three clear layers appeared. The bottom layer (Sevochlorane phase) was separated and washed twice with water and then dried over MgSO₄ to afford 45 g (87.2%) highly pure Sevochlorane.

Data for 1,1,1,3,3,3-hexafluoro-2-(chloromethoxy)-propane (1): bp = 76 °C; 1H NMR (250.1 MHz, CDCl₃): δ 5.57 (s, 2H) 4.54 (septet, 1H, 3JHF = 5.7 Hz); 19F NMR (235.4 MHz, CDCl₃): δ -74.14 (d, 3JHF = 5.9 Hz); 13C NMR (62.9 MHz, CDCl₃): δ 121.0 (q, 1JFC = 283.0 Hz) 80.4 (s), 73.8 (septet, 2JFC = 31.4 Hz).

Halogen-exchange fluorination
PEG-400 (50 mL) was placed into a jacketed glass reactor. KF (12.9 g, 0.22 mol) was added thereafter while stirring. Then, Sevochlorane (40 g, 0.18 mol) was added to the mixture and the reaction mixture was heated at 90 ºC for 2 h, and then cooled down to room temperature. Water (50 mL) was added to the mixture. Two clear phases had formed. The bottom phase was separated, dried over MgSO₄, and distilled to afford 27 g (72%) of highly pure Sevoflurane (99.9%). Data for 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane (Sevoflurane, 3): bp = 58.5 °C; 1H NMR (250.1 MHz, CDCl₃): δ 5.42 (d, 2H, 3JHF = 5.3 Hz) 4.42 (septet, 1H, 3JHF =

Scheme 1. The single, two and three-step synthetic methods of Sevoflurane from hexafluoroisopropanol.
5.7 Hz); $^{19}$F NMR (235.4 MHz, CDCl$_3$): $\delta$ -75.13 (dd, $^3$J$_{HF}$ = 4.7 Hz, $^5$J$_{HF}$ = 2.4 Hz), -155.65 (septet of t, $^2$J$_{HF}$ = 54.13 Hz, $^5$J$_{HF}$ = 2.4 Hz); $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ 121.1 (q, $^1$J$_{CF}$ = 283.0 Hz), 103.1 (d, $^1$J$_{CF}$ = 226.4 Hz), 74.24 (septet, $^2$J$_{CF}$ = 33.4 Hz).

### Results and Discussion

The first modification applied for the two-step process was the first step reaction time that was decreased to 4 h by changing the ratio of the starting materials. The next modification was reducing the amount of solvent and KF, in the second step, with no change on the yield and purity of the product. These modifications would change the original two-step method into a real cost-effective process.

The chloromethylation reaction of HFIP has been reported to take 24 h and a 1:1:0.3 molar ratio for HFIP, AlCl$_3$, and trioxane, respectively, has been used (2, 3). In order to decrease the full conversion time for the first step, the solvent effect was initially investigated. The application of chloroform and dichloromethane resulted in the synthesis of sevochlorane in low yield. Tetrachloroethene led to the formation of bis (HFIP) acetal by-products. Therefore, this solvent has been proposed for the preparation of bis-acetal. Afterwards our attention was shifted to the effect of reagent ratios on the reaction kinetics and reaction yield. It was found out that increasing the amount of AlCl$_3$ (only 10 mol%) would sharply accelerates this reaction within the first 2 h and approximately 100% conversion was achieved after 4 h. Increasing the excess value of AlCl$_3$ by more than 10% or increasing the amount of trioxane, didn’t show further acceleration (Figures 1 and 2).

The next issue was the high volume of water and acid used for quenching. The addition of 6 N HCl solution to interrupt the reaction, increases the reaction temperature violently, and consequently results in partial product loss by decomposition, evaporation, and polymerization which decreases the first step yield. Considering these disadvantages the aqueous acid and water addition sequence was changed and the bath temperature was increased to dissolve the aluminate salts sufficiently. The HCl gas was directed to a water bath and, after pH adjustment, was used for quenching the chloromethylation step. The aqueous phase contains some SVC that was extracted by a solvent. The quenching time depends on the reaction scale.
Figure 1. Monitoring the Chloromethylation Reaction by $^{19}$F NMR Using 10% Excess of AlCl$_3$. 
A: Sevochlorane, B and C: by-products such as bis(HFIP) acetals and HFIP-methylacetal, D: HFIP

Figure 2. Kinetics of HFIP chloromethylation reaction followed by $^{19}$F NMR spectroscopy.
Sevoflurane Synthesis Improvements

conducted to a water vessel and this aqueous HCl, after pH adjustment, was used at the end of the first step (quenching) to dissolve the aluminate salt. The applied changes would certainly reduce environmental pollution and costs.

An important question in relation to the separation of the organic phase in the first step is whether there is any Sevochlorane in the aqueous phase. This question was positively answered by $^{19}$F NMR analyzing of aqueous phases using 2,2,2-trifluoroethanol, as an internal standard. Thus, all the aqueous phases (used for quenching or washing the organic phase, which were all siphoned off by Bieniarz et al.) were recycled and reused in the next batches.

Halogen-exchange (Halex) fluorination is an important method in preparing fluorinated compounds. Different reagents such as KF, HF, BrF$_3$, Bu$_4$N$^+$F$^-$, F$_2$, and CsF have been used for this purpose (4-8). Among them, KF, which presents the best ratio between cost and reactivity, is the most popular reagent to perform the «Halex» reaction on a large scale (5). In order to increase the efficiency of KF, several phase-transfer catalysts such as 18-crown-6, poly (ethylene glycol) (PEG-400) and polar aprotic solvents such as DMSO, DMF and sulfolane have been reported (5-10). Among these, the best result has been obtained when using PEG-400 as the solvent in the case of Sevochlorane (2, 3).

As shown in Table 2, it is possible to affirm that a decrease of 4 times in the PEG amount (entries 3 and 4) lead to a decrease of less than 1% of sevoflurane conversion and the same is observed when the KF amount is decreased (entries 2 and 3). Accordingly, the amount of KF was decreased to 1.2 mol per each mol of Sevochlorane and the solvent volume was decreased to 3.7 times that of Sevochlorane. An experiment was also carried out using catalytic amount of PEG but the result was not satisfactory because reaching the desired yield required a much longer time (Table 2).

Finally, Sevoflurane was simply isolated from the reaction mixture by the addition of water to the reaction mixture and the organic phase was separated and dried. Analysis of the aqueous phase showed the presence of Sevoflurane. Therefore this phase was used instead of distilled water in subsequent batches. After several batches, tetrachloroethane was added to the accumulated aqueous phases and Sevoflurane was extracted and then the organic phase was distilled to get even more Sevoflurane.

**Conclusion**

The two-step synthesis of Sevoflurane has been reinvestigated. Accordingly, the reaction time of the first step was lowered to 4 h and the amount of KF and PEG-400 used in the second step was optimized to minimize the product cost and environmental pollutions. As the solvents were investigated in the first step, tetrachloroethane was found to be a good solvent to direct the chloromethylation step to the bis-HFIP-acetal product. All the aqueous phases, which were all siphoned off by the previous works, were analyzed for the first time and it
was found out that these phases contain some product (Sevochlorane and Sevoflurane) that could be recycled. Therefore all these phases together with HCl gas, produced during the first step, were reused in the next batches to decrease the environmental pollutions. Finally all the reactions were monitored by $^{19}$F NMR for the first time. This process could be easily implemented on larger scales.

References

(1) Baker MT. Sevoflurane: are there differences in products? *Anesth. Analg.* (2007) 104: 1447-1451.
(2) Ramakrishna K, Behme C, Schure RM and Bieniarz C. A safe and efficient process for the synthesis of the inhalation anesthetic sevoflurane. *Org. Proc. Res. Dev.* (2000) 4: 581-584.
(3) Bieniarz C, Behme C and Ramakrishna K. An efficient and environmentally friendly synthesis of the inhalation anesthetic sevoflurane . *J. Fluorine Chem.* (2000) 106: 99-103.
(4) Bin-Dong L and Chun-Xu L. Synthesis of Sevoflurane in Ionic Liquids by Halogen-exchange Fluorination. *Chinese J. Applied Chem.* (2009) 26: 1126-1128.
(5) Langlois B, Gilbert L and Forat G. A new family of delocalized lipophilic cations. *Indust. Chem. Library* (1996) 8: 244-248.
(6) Yoneda N. Progress in the preparation of organofluorine compounds using HF or HF–base molten salts. *J. Fluorine Chem.* (2000) 105: 205-207.
(7) Marjan Esfahanizadeh, Koroush Omidi, Joel Kauffman, Ali Gudarzi, Shahram Shahraki Zahedani, Salimeh Amidi and Farzad Koharfard. Synthesis and evaluation of new fluorinated anti-tubercular compounds. *Iran. J. Pharm. Res.* (2014) 13: 115-126.
(8) Ahmad Mohammadi-Farani, Neda Heidarian and Alireza Alibadi. N-(5-Mercapto-1,3,4-thiadiazol-2-yl)-2-phenylacetamide derivatives: synthesis and *in-vitro* cytotoxicity evaluation as potential anticancer agents. *Iran. J. Pharm. Res.* (2014) 13: 487-492.
(9) Luo J, Li CX and Wu W. A polymer onium acting as phase-transfer catalyst in halogen-exchange fluorination promoted by microwave. *J. Fluorine Chem.* (2004) 125: 701-704.
(10) Zheng Yong Liang, Chun Xu Lu, Jun Luo and Li Bin Dong. A polymer imidazole salt as phase-transfer catalyst in halex fluorination irradiated by microwave. *J. Fluorine Chem.* (2007) 128: 608-611.

This article is available online at http://www.ijpr.ir