Synthesis and Reactions of Fluoroether Anesthetics

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Abstract: New and recent work by the author and colleagues will be presented. Six methods for functionalizing halogenated ethers will be presented: (1) a new regent for halogen-exchange fluorination of chloromethyl ethers, (2) a selective photochemical or thermal reduction of poly-chlorinated substrates, (3) new organic sources of fluoride for antiomny-pentachloride-catalyzed halogen-exchange fluorination, (4) a chemoselective methanolation reaction of the trifluoromethyl group, (5) a stereoselective decarboxylation reaction, and (6) the use of bromine trifluoride for fluorination with inversion of configuration. The reactions are applied to the synthesis of individual enantiomers of fluoroether anesthetics.

Key words: fluorine, halogenation, drugs, halogenated ethers, halogen-exchange fluorination

This article will review recent work from the author’s lab and also disclose new results. The direction of our research has been toward a new synthesis of the anesthetic sevoflurane, and syntheses of individual enantiomers of the anesthetics isoflurane and desflurane. Along the way, we have either discovered new synthetic chemistry or adapted existing reactions to our particular substrates. A proposed and partially completed route to the isoflurane and desflurane enantiomers demonstrates the reactions used (Scheme 1):

![Scheme 1 Proposed route to isoflurane and desflurane enantiomers.](image)

Reaction II – A known photochemical reduction of chlorinated ethers allowed us to prepare chlorofluoromethyl ether 3 from dichlorofluoromethyl ether 2, the product of unavoidable over-chlorination of sevoflurane. We showed that the reaction is selective for mono-reduction on this substrate, and related substrates, and based on a mechanistic study, also found conditions for performing the reaction thermally.

Reaction III – The conversion of chlorofluoromethyl ether 3 to difluoromethyl ether 4 was done by either the traditional Swarts-type inorganic reagents, or by employing new organic sources of fluoride discovered in our lab. When applied to poly-chlorinated substrates, the new reagents have the advantage of selectivity for mono-fluorination.

Reaction IV – We have found conditions for chemoselective methanolation of the trifluoromethyl group, exemplified by the conversion of difluoromethyl ether 4 to ester 5. The structural requirements of the substrate and the reaction mechanism were both studied.

Reaction V – The proposed stereoselective decarboxylation reaction, which will transform acid 6 into isoflurane has close precedent in our work. In related substrates, we have shown that the reaction proceeds with clean retention of configuration.

Reaction VI – This highlights the use of bromine trifluoride as a nucleophilic fluorinating reagent. The chlorine atom of isoflurane was displaced with clean inversion of configuration, giving an enantiomer of desflurane.

Reaction I

The complexes of triethylamine and hydrogen fluoride are well established as nucleophilic fluorinating reagents. When we applied triethylamine mono(hydrogen fluoride) to the conversion of chloromethyl ether 1 to sevoflurane however, we found that part of the starting material had reacted with free triethylamine to give a quaternary ammonium salt. This led us to substitute the more sterically hindered diisopropylethylamine for triethylamine in the complex. This completely suppressed quaternization, and raised the yield of sevoflurane from 79% to 95%. The reaction has been used to prepare multi-kilogram quantities of sevoflurane for commercial use, and has the practical advantage of solventless conditions, plus the diisopropylethylamine can be recycled.
The new reagent is advantageous for fluorination of highly halogenated chloroethers, but its scope is not limited to that structural type. For example, we found that fluoromethyl ethyl ether (8) cannot be prepared using triethylamine mono(hydrogen fluoride), because the starting material chloromethyl ethyl ether (7) was almost completely consumed by the quaternization reaction. However, when the new reagent was employed, the product was isolated by simple distillation from the reaction flask in good yield (Scheme 2).

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\begin{align*}
7 \quad \text{CH}_3\text{CH}_2\text{OCH}_2\text{Cl} \quad \text{CH}_3\text{CH}_2\text{OCH}_2\text{F} \\
\text{H} \quad \text{3} \quad \text{CH}_2\text{OCH}_2\text{Cl} \quad \text{CH}_3 \quad \text{CH}_2\text{OCH}_2\text{Cl} \quad \text{CH}_3 \quad \text{CH}_2\text{OCH}_2\text{Cl}
\end{align*}
\]

Scheme 2 Use of disopropylethylamine mono(hydrogen fluoride) in a halogenation reaction.

**Reaction II**

The next intermediate we required was chlorofluoromethyl ether 3. When sevoflurane was subjected to free-radical chlorination, a mixture of 3 and dichlorofluoromethyl ether 2 resulted unavoidably (Scheme 3). When this mixture was treated with excess 2-propanol and irradiated with UV light, smooth conversion of 2 to 3 took place, resulting in a useful synthesis of 3.4

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\begin{align*}
\text{CF}_3\text{OCH}_2\text{F} \quad \text{CF}_3\text{OCH}_2\text{F} \\
\text{hv} \quad \text{hv} \\
\text{Cl}_2 \quad \text{Cl}_3
\end{align*}
\]

Scheme 3 Photoreduction of dichlorofluoromethyl ether 2.

This reaction is a well-established method for the reduction of chlorinated substrates.5–9 We have applied this reaction to a high-yielding synthesis of isoflurane from the over-chlorinated dichloroether 9 (Scheme 4).10,11 Other examples which demonstrate the selectivity for mono-reduction are the conversion of 10 to 11 (needed in connection with a chiral GC study13), and 12 to 13.13 Noteworthy in the latter example is the lack of epimerization at the chiral center. Our contribution to the area is a mechanistic study, which suggested that the reaction could be performed thermally with common free-radical initiators.10

**Reaction III**

Another way we attempted to synthesize sevoflurane was to treat chloromethyl ether 1 with hydrogen fluoride and a catalytic amount of antimony pentachloride, common conditions for halogen-exchange (halex) fluorination.14 We were never able to obtain complete conversion because the antimony pentachloride was apparently reacting with the product sevoflurane to give back the starting material and a mixed antimony halide species. We then found that in the absence of hydrogen fluoride, the reaction between sevoflurane and one equivalent of antimony pentachloride gave quantitatively chloromethyl ether 1 and a mixed antimony halide species – presumably antimony monofluorotetrachloride – which can deliver one fluoride atom to poly-chlorinated substrates (Scheme 5).15 The reaction is most conveniently run with a catalytic amount of antimony pentachloride under solventless conditions. For example, treatment of chlorofluoromethyl ether 3 with one equivalent of sevoflurane and a catalytic amount of antimony pentachloride gave difluoromethyl ether 4. Alternatively, 4 can be obtained in high yield by treatment of dichloromethyl ether 14 with two equivalents of sevoflurane. The conversion of trichloromethyl ether 15 to either dichlorofluoromethyl ether 2 or difluorochloromethyl ether 16 by simply adjusting the amount of sevoflurane demonstrates the selectivity of the process. This selectivity is difficult to obtain using the traditional Swarts-type fluorinating reagents. Using the new reagent combination, we have also demonstrated that carbon tetrachloride can be monofluorinated to give chlorofluoromethane selec-

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\begin{align*}
\text{CF}_3\text{OCHClF} \quad \text{CF}_3\text{OCHClF} \\
\text{cat. SbCl}_5 \quad \text{cat. SbCl}_5 \\
\text{sevoflurane} \quad \text{sevoflurane}
\end{align*}
\]

Scheme 5 Selective halex reactions using sevoflurane as fluoride source.
tively, an indication that the reaction can be applied to substrates other than haloethers.

The reaction can be run in the reverse direction if needed, that is, a fluorine atom in the substrate can be exchanged for a chlorine atom. For example, treatment of alkene 17 (known as ‘compound A’ within the anesthesiology community\(^1\)) with antimony pentachloride and carbon tetrachloride to supply the chlorine atoms resulted in production of alkene 18 (Scheme 6).\(^2\)

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**Scheme 6** Reversing the direction of halogen-exchange.

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One major drawback of using sevoflurane as a source of fluorine atoms is that the by-product of every reaction is chloromethyl ether 1. Compound 1 is sometimes difficult or impossible to separate from the desired products. This led us to develop new organic sources of fluoride that give by-products, which are easily separable from the product. Based on the known\(^3\)–\(^5\) instability of 1,1-difluoroalkyl methyl ethers, we have found that 1,1-difluoroethers such as 19 decompose in the presence of antimony pentachloride to give methyl halides and acid fluorides. When the decomposition reaction is run in the presence of one equivalent of a chloroether such as trichloromethyl ether 15, selectivity for monofluorination can be achieved (Scheme 7).\(^2\) Alternatively, dichloromethyl fluor ether 2 can be prepared by exchanging halogen atoms with acid fluoride 20. In the former case, the by-products are extremely volatile methyl halides and an acid fluoride, which readily reacts with water during the aqueous work-up to give a water-soluble acid. In the latter case, the by-product is an acid chloride, which can also react with water to give a water-soluble acid. Thus, the by-products in both cases are easily separated from the desired product.

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**Scheme 7** Selective halogen reactions using other organic fluoride sources.

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### Reaction IV

When taken together, many of the reactions shown thus far showcase various routes to the key intermediate difluoromethyl ether 4 (see Scheme 1). The next step was to selectively convert a trifluoromethyl group to obtain ester 5, which turned out to be a difficult task. This type of conversion has been successful for a limited range of substrates,\(^6\)–\(^8\) but none of the suggested conditions worked in our case. Based on a hint in the literature,\(^9\) we have found conditions for the conversion of 4 to 5 that also work for a wide variety of compounds that contain one or two trifluoromethyl groups. Treatment of difluoromethyl ether 4 with 3 equivalents of sodium methoxide followed by an aqueous acidic work-up gave the ester 5 (Scheme 8).\(^10\) The reaction shows signs of being general for compounds that contain an appropriately positioned active hydrogen atom, and electron-withdrawing groups. Other examples of less highly fluorintated substrates include the conversions of isoflurane to ester 21, and 22 to 23. The extension of the reaction conditions to the latter types of substrates was made possible by a mechanistic study, which suggested a dehydrofluorination-addition-elimination sequence is operative.

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**Scheme 8** Selective methanolysis of the trifluoromethyl group.

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Currently, our next intermediate goal is the transformation of ester 5 into the key racemic acid 6 (see Scheme 1). Hydrolysis of ester 5 gives acid 24, which is converted to its acid chloride 25 by treatment with phthaloyl dichloride (Scheme 9). Thus far, we have not been able to chlorinate 25 efficiently, either by free-radical or ionic methods. The free-radical method did give some of the desired acid chloride 26, but as a mixture with the bischlorinated acid chloride 27.\(^11\) When the chlorination reaction does become successful, the acid derivative of 26, rac-6, will be resolved. Further down the road is an asymmetric synthesis of acid 6. Once an enantiomer of 6 is obtained, then heating of its potassium salt in a protic solvent should cause decarboxylation, giving an enantiomer of isoflurane with clean retention of configuration.

Another approach to isoflurane enantiomers that we have been pursuing, uses ester 21 (Scheme 8) as a key intermediate. Hydrolysis of 21 furnishes acid 28 (Scheme 10).\(^12\) Eventually, an asymmetric synthesis of acid 28 will be attempted, but for now, treatment of 28 with \(\alpha\)-methylbenzylamine gives the mixture of diastereomers 29. We have found that the diastereomers of salt 29 differ so greatly in solubility that the resolution process is very easy. The dextrorotatory diastereomer is nearly in-
soluble in methylene chloride at room temperature, while the levorotatory diastereomer dissolved completely. Simply dissolving the mixture as thoroughly as possible in this solvent followed by suction filtration gives nearly complete separation and nearly quantitative yield of individual diastereomers. What remains to be done is the conversion of enantiomers of acid 28 into (R)- and (S)-isoflurane.

Scheme 9  Progress in conversion of ester 5 to isoflurane enantiomers.


doesn't ground “Reaction V”.

Reaction V

We predict the successful outcome of Scheme 9 based on precedents from the work of others31–33 and our own work.13,34–37 Efforts at the synthesis of highly halogenated enantiomers and their pharmacology have been summarized in two reviews.38,39 The two most important results relating to Scheme 9 are the preparation of the enantiomers of ether 30, an intermediate in the synthesis of anesthetics, and of halothane, another of the fluorinated enantiomers of ether 30, an intermediate in the synthesis of anesthetics, and of halothane, another of the fluorinated

Scheme 10  Progress in conversion of ester 21 to isoflurane enantiomers.

Reaction VI

It is expected that large amounts of enantiomerically pure isoflurane will eventually result from the above routes, allowing possible testing on human subjects for differences in potency and recovery time. We have found that the isoflurane enantiomers can be used as starting material for a synthesis of the enantiomers of desflurane, another of the fluoroether anesthetics (Scheme 12).40,41 For example, treatment of (S)-isoflurane with bromine trifluoride gives (R)-desflurane, the product of inversion of configuration.

Scheme 11  Stereoselective decarboxylations.

Scheme 12  Stereoselective synthesis of desflurane from isoflurane.

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References


