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Practical preparation of potentially anesthetic fluorinated ethyl methyl ethers by means of bromine trifluoride and other methods

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Dedicated to Professor Paul Tarrant on the occasion of his 85th birthday

Abstract

Synthetic methods, especially those that use bromine trifluoride as a fluorinating agent, are described for the preparation of a number of fluorinated ethyl methyl ethers in good yield and high purity. In all cases, medium-scale syntheses (8–22 g) of potentially anesthetic compounds have been accomplished. The compounds are of sufficient purity (>99%) for biological evaluation.

Keywords: Fluorinated ethyl methyl ethers; Bromine trifluoride; Potentially anesthetic

1. Introduction

The 1846 demonstration by William Morton of the anesthetic effects of diethyl ether at the Massachusetts General Hospital constitutes one of the great discoveries in medicine. Diethyl ether remained the mainstay of anesthetic practice in North America for the next century, giving way in the 1950s to anesthetics halogenated with fluorine. The move to halogenation was animated by the need to supply anesthetics that did not burn or explode. Explosions were a concern because of the increasing application of electrical equipment, including electrocautery, in surgery. Although halogenated anesthetics had been used for nearly as long as diethyl ether (the anesthetic effects of chloroform were discovered by Simpson in 1847), toxicity limited their application. Indeed, chloroform is a classical hepatotoxin [1].

The blossoming of fluorine chemistry during and after the Second World War permitted the development of fluorinated anesthetic compounds that displayed far greater stability (resistance to degradation), and thus less toxicity, than their chlorinated analogs [2]. The first of these, fluroxene ($CF_3CH_2OCH{=}CH_2$), was a fluorinated ethyl vinyl ether that enjoyed a limited success, limited because it remained flammable (albeit, a flammability so diminished that no explosion with it was ever reported, despite its widespread use). A far greater success was halothane, a fluorinated alkane anesthetic ($CF_3CHBrCl$) invented by Suckling in 1951 [3]. Within a few years of its introduction [4], halothane displaced diethyl ether and chloroform as the primary anesthetic worldwide. But halothane soon was found to be imperfect. Although far less toxic than chloroform, it could cause fatal hepatic injury [5]. It caused cardiac arrhythmias that, if not dangerous to the patient, were disturbing to the anesthetist.

Thus, the search for a better halogenated anesthetic resumed in the 1960s under the direction of Terrell [6]. His work resulted in the synthesis of over 700 halogenated, mainly fluorinated, compounds. He found that ethers were more desirable anesthetics than alkanes because alkanes predisposed to cardiac arrhythmias. But not all ethers were equally useful; most dimethyl and diethyl ethers possessed undesirable properties (e.g., producing convulsions). The most useful appeared to be methyl ethyl and methyl isopropyl ethers [7]. Methoxyflurane ($CH_3OCF_2CHCl_2$) and enflurane (CHF_2OCF_2CHClF) were the first of these to be developed, replacing halothane in the 1960s and 1970s.

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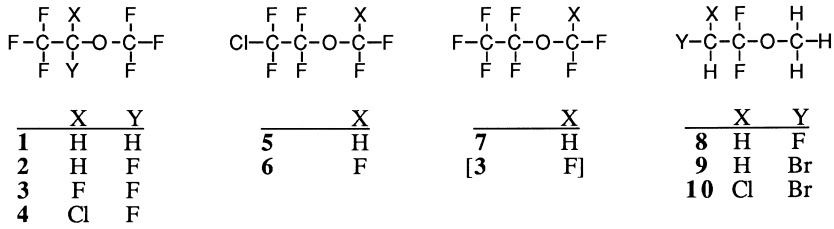

Fig. 1. Fluorinated ethyl methyl ethers.

Isoflurane ($CHF_2OCHClCF_3$) in turn became the mainstay of anesthetic practice in the 1980s and early 1990s. And today, desflurane ($CHF_2OCHFCF_3$) and sevoflurane ($CH_2FOCH(CF_3)_2$) are the leading anesthetics in North America.

An examination of the history of anesthesia reveals an increasing reliance on halogenation with fluorine (the most recent anesthetics have no other halogens), and a focus on the ether structure, particularly methyl ethyl ethers. Although much is known about the compounds that are widely used (i.e., enflurane, isoflurane, desflurane), the pharmacology of the other diverse compounds synthesized by Terrell and others was usually limited to crude measurements of potency and toxicity. We considered that more might be learned with detailed studies, and that the resulting information might lead to a better understanding of the characteristics of ideal anesthetics. This thought led to the preparations of the several methyl ethyl ethers, described in the present paper, and an examination of their anesthetic effects [8].

Anesthetic activity cannot be reliably predicted from molecular structure; it must be deduced from actual experiments. Based on a series of experimental studies, it has been found that: (1) as the molecular weight of the compound increases (such as a saturated straight chain halogenated ether), the potency and toxicity also increase; (2) as the boiling point of the compound increases, the margin of safety decreases; (3) the higher the boiling point of the compound, the longer the recovery time; and (4) compounds containing an asymmetric terminal carbon seem to produce good anesthesia [9].

The reason for introducing fluorine into a potential anesthetic is to reduce its boiling point. The presence of other halogens such as chlorine and bromine causes an increase in the boiling point. Compounds with several halogens must contain a fluorine atom in order to keep the boiling point low (and vapor pressure sufficiently high) in order to utilize these agents as volatile anesthetics [10]. Addition of chlorine to a fluorinated compound usually enhances its anesthetic activity, while addition of bromine renders the compound more chemically stable and less toxic. Fluorinated ethers are usually characterized by volatility, low toxicity, and high anesthetic activity; therefore, they are ideal for study as anesthetics.

There has been an increased demand for high levels of purity for compounds before they are actually tested on laboratory animals. Traces of impurities in anesthetics can render the formulation toxic. Among the approaches taken to ensure high levels of purity of the final product is to use highly selective reagents in their preparation or rigorous purification and lengthy synthesis. In this paper we reinforce the case for bromine trifluoride as a suitable fluorinating agent. Bromine trifluoride is a fluorinating agent that effects substitution for hydrogen or halogen in aliphatic compounds with high levels of specificity.

Fig. 1 shows several compounds grouped according to structural similarities. These compounds are all known to be general anesthetics. The present report describes the preparation of several fluorinated ethyl methyl ethers previously known in the literature, synthesized for the first time by means of bromine trifluoride on a practical scale.

2. Results and discussion

Several fluorinated ethyl methyl ethers were synthesized by means of bromine trifluoride. Because of the specificity of the reagent, the products are free of contamination by unwanted side-reactions. The reaction produces excellent yields, and its use allows gentle reaction conditions [11] for the substitution of fluorine for hydrogen or other halogens in aliphatic compounds. Although it has a limited utility in the introduction of CF_2 and CF_3 groups, its advantage as a fluorinating agent lies in its high regiospecificity [12,13]. For example, in compounds which contain both halogen and hydrogen, the reagent selectively displaces only the halogen. From the point of view of developing a synthetic methodology, the preparation of a single product avoids tedious separations that are at times nearly impossible to achieve, even by distillation through a spinning-band apparatus. Because bromine trifluoride has a highly specific reactivity, the reaction product is clean and the yields are excellent.

Although all are known compounds, many of the reported preparations are not practical, often producing a mixture of products, with low yield of the desired product. Other preparations require reagents not readily available. The syntheses reported here are convenient for medium-scale syntheses and provide the desired compounds with good yield and in high purity. Compounds **8–10** were prepared by methods other than bromine trifluoride.

Compound **1** was previously prepared by Johri and DesMarteau [14] by the reaction (2–3 mmol scale) of trifluoromethyl hypofluorite with CH_2=CF_2, in 76% yield (97.5% purity). By the same method on a slightly larger scale (5 mmol), Sekiya and Ueda obtained 83% yield [15]. In our laboratory, on multigram scale, treatment of chlorodifluoromethyl 2,2,2-trifluoroethyl ether with bromine trifluoride yielded **1** as the exclusive product in 85% yield (99.8 % purity).

In 1964, Russian workers prepared compound **2** by addition of HF to perfluoromethyl perfluorovinyl ether [16]. A decade later it was identified by another Russian group as a component of a complex mixture obtained from electrochemical fluorination of methyl 3-methoxypropionate [17]. Sekiya and Ueda obtained **2** from the reaction of trifluoromethyl hypofluorite and CHF=CF_2 as a 2 : 1 mixture with its regioisomer (75% yield of the mixture) [15]. We were able to obtain **2** from $CF_3CHClOCClF_2$ in 70% yield with 99.5% purity.

Compound **3** was reported in the literature as components of complex product mixtures produced by electrochemical fluorinations [18,19]. Sekiya and Ueda prepared **3** on millimolar scale by direct fluorination (F_2, NaF) of several trifluoromethyl ethers (85–94% yield) [15] and by similar fluorination (F_2, SnF_2) of $CHClFCHClOCF_3$ (51% spectroscopic yield) [20]. Bardin and coworkers prepared **3** in 40% yield by reacting perfluoromethyl vinyl ether with vanadium pentachloride [21]. We prepared **3** from $CF_3CF_2OCClF_2$ (obtained by photochlorination of $CF_3CF_2OCHF_2$, **7**), whose treatment with bromine trifluoride with a catalytic amount of SbF_5 gave **3** in 76% yield (99% purity).

Compound **4** was reported as a component of a complex product mixture from the reaction of C_2F_3Cl with CF_3OOF [22]. Our treatment of $CClF_2OCCl_2CF_3$ with bromine triflouride produced **4** in 84% yield and 99% purity.

Terrell et al. [23] obtained compound **5** in 80% yield by photochlorination of $CHF_2OCF_2CHF_2$. Okazaki and coworkers obtained **5** as a component of complex mixtures during the electrochemical fluorination of chlorine-containing methyl ethyl ethers [24]. Recently **3** was identified in a mixture produced by fluorination of 2-chloroethyl methyl ether by potassium tetrafluorocobaltate [25]. We prepared compound **5** from the reaction of $CHF_2OCF_2CCl_2F$ and bromine trifluoride (90% yield, with >98% purity).

The literature reports several preparations of **6**. Decarboxylation of silver perfluoro-2-methoxypropionate in the presence of Cl_2 yielded **6** [26]. It was prepared on small scale by the reaction of CF_3OCl with CF_2=CF_2 [27], by electrochemical fluorination [24], and by treatment of $CF_3OCH_2CFCl_2$ or $CF_3OCHClCHClF$ with F_2 and SnF_2 [20]. We obtained **6** by the reaction of $CClF_2OCF_2CClF_2$ with bromine trifluoride in a yield of 92% and purity >99.5%.

Compound **7** was reported by England as a byproduct (27% yield) of the reaction of $CF_3CF_2OCHFCF_2OCH_3$ with SbF_3 [28]. We prepared the compound in a 81% yield (purity >99.5%) by the reaction of $CHF_2OCCl_2CF_3$ with bromine trifluoride.

In 1911 Swarts reported the preparation of **8** by the reaction of $CBrF_2CH_2F$ with NaOMe [29]. Yakubovich and coworkers obtained **8** in low yield (8%) by reacting trifluoroethene with sodium methoxide. We prepared **8** in 78% yield (purity 99.8%) by the reduction of CH_3OCF_2-CFHBr with triethylsilane in the presence of $PdCl_2$.

Compound **9** was obtained by Demiel's method [30], by reaction of 1-bromo-2,2-difluoroethylene with sodium methoxide. Its NMR data is reported for the first time in this paper.

Compound **10** has been prepared in modest yield by reaction of Fluothane ($CF_3CHBrCl$) with sodium methoxide [23,31]. We prepared **10** in three steps with good overall yield and excellent purity of the final product (99.5%).

3. Experimental

NMR spectra were recorded on a 300 MHz Varian spectrometer; all samples were dissolved in $CDCl_3$. For ^{1}H-NMR spectra, chemical shifts are reported relative to internal tetramethylsilane ($\delta = 0.00$); for ^{19}F-NMR spectra they are reported relative to external $CFCl_3$ ($\delta = 0.00$). Boiling points are uncorrected. Starting materials are commercially available except for the starting material for **3**, chlorodifluoromethyl perfluoroethyl ether, which was prepared by photochlorination of compound **7**.

3.1. General procedure for preparation of ethers with bromine trifluoride

The starting material was placed in a dry 100 ml two-necked round-bottomed flask equipped with a dry-ice condenser, a stir bar, and a Teflon-wrapped flange septum. In the case of compound **3** the starting material was dissolved in perfluorodecalin. After bromine trifluoride was added at room temperature by means of a Teflon syringe, the reaction mixture was stirred at the given temperature. (see Table 1) In two cases (**3**, **5**) a catalytic amount of SbF_5 was added to the reaction mixture. When the reaction was complete, the condenser was removed and the product was collected in a trap cooled with a mixture of dry ice and isopropanol. The contents in the trap were bubbled through 10% aqueous KOH then 10% sodium sulfite into another trap cooled with a mixture of dry ice and isopropanol.

In the case of compound **5** the product was distilled as it formed into a dry-ice trap. The product was washed with 10% aqueous KOH then 10% sodium sulfite, then dried over KOH. The product was subsequently flash distilled.

2,2,2-Trifluoroethyl trifluoromethyl ether (**1**). ^{1}H NMR δ 4.29 (q, $J = 7.80$ Hz, 2H). ^{19}F NMR δ −62.31 (S, 3F), −75.10 (t, $J = 9.11$ Hz, 3F).

1,2,2,2-Tetrafluoroethyl trifluoromethyl ether (**2**). ^{1}H NMR δ 5.89 (d, $J = 24$ Hz, ^{1}H). ^{19}F NMR δ −60.47 (d, $J = 9.5$ Hz, 3F), −84.29 (q, $J = 9.5$ Hz, 3F), −146.5 (S, 1F).

Table 1
Preparation of ethers by bromine trifluoride

	Product	Starting material (mmol)	BrF_3 (mmol)	Temperature, °C (h)	Yield	Purity (GC)	bp (°C)
1	$CF_3CH_2OCF_3$	$CClF_2CH_2OCF_3$ (65)	70	35–45 (6)	8.9 g, 85%	>99.8	11
2	$CF_3CHFOCF_3$	$CF_3CHClOCClF_2$ (66)	102	40–45 (5)	8.6 g, 70%	>99.5	−5
3	$CF_3CF_2OCF_3$	$CF_2CF_2OCClF_2$ (136)	112[a]	20–30 (3)	22 g, 76%	99	−20
4	$CF_3CClFOCF_3$	$CF_3CCl_2OCClF_2$ (50)	75	40–50 (4)	9.2 g, 84%	>99	−4
5	$CClF_2CF_2OCHF_2$	$CCl_2FCF_2OCHF_2$ (150)	71[b]	50 (5)	10 g, 33%[c]	98.6	28
6	$CClF_2CF_2OCF_3$	$CClF_2CF_2OCClF_2$ (51)	41	30–35 (2)	10 g, 92%	99.5	10
7	$CF_3CF_2OCHF_2$	$CF_3CCl_2OCHF_2$ (83)	102	30–40 (5)	13 g, 81%	>99.5	−12

[a] With perfluorodecalin as solvent and a catalytic amount of $SbCl_5$.
[b] Catalytic amount of $SbCl_5$ was added after 1 h.
[c] After flash distillation.

Perfluoroethylmethyl ether (**3**). ^{19}F NMR δ −55.72 (t, $J = 9.6$ Hz, 2F), −87.16 (s, 3F), −96.06 (q, $J = 9.8$ Hz, 2F).

1-Chloro-1,2,2,2-tetrafluoroethyl trifluoromethyl ether (**4**). ^{19}F NMR δ −55.17 (d, $J = 9.90$ Hz, 3F), −81.25 (q, $J = 9.90$ Hz, 3F), −86.02 (S, 1F).

2-Chloro-1,1,2,2-tetrafluoroethyl difluoromethyl ether (**5**). ^{1}H NMR δ 6.70 (t, $J = 69.5$ Hz, ^{1}H). ^{19}F NMR δ −74.20 (s, 2F), −85.10 (s, 1F), −85.30 (t, $J = 4.90$ Hz, 1F), −88.00 (s, 2F).

2-Chloro-1,1,2,2-tetrafluoroethyl 1,1,1-trifluoromethyl ether (**6**). ^{19}F NMR δ −55.75 (t, $J = 7.3$ Hz, 3F), −74.35 (S, 2F), −89.52 (q, $J = 7.3$ Hz, 2F).

Difluoromethyl 1,1,2,2,2-pentafluoroethyl ether (**7**). ^{1}H NMR δ 6.71 (t, $J = 69.0$ Hz, ^{1}H). ^{19}F NMR δ −85.01 (dt, $J_1 = 68.30$ Hz, $J_2 = 4.8$ Hz, 2F), −86.98 (s, 3F), −89.32 (s, 2F).

3.2. Preparation of other ethers by other methods

1,1,2-Trifluoroethyl methyl ether (**8**). A dry 100 ml two-necked round-bottomed equipped with dry ice condenser, stir bar, and a septum port was charged with $PdCl_2$ (0.55 g, 3.1 mmol), CH_3OCF_2CFHBr (30.0 g, 155 mmol), and $HSiEt_3$ (21.6 g, 186 mmol). The reaction mixture was stirred for 3 h at room temperature, then it was heated at 60°C for 30 min. The reaction mixture was distilled, then the distillate was washed with water. Another distillation gave 15 g of **8** (GC purity 99.8%) plus another 1.5 g of slightly less pure product (97.5%) for a total yield of 77.8%. bp 36.5°C. ^{1}H NMR δ 4.4 (dt, $J = 46.0$, 8.5 Hz, 2H), 3.6 (S, 3H). ^{19}F NMR δ −87.9 (dt, $J = 14.6$, 8.5 Hz, 2F), −236.6 (tt, $J = 46.4$, 15.9 Hz, 1F).

2-Bromo-1,1-difluoroethyl methyl ether (**9**) [30]. bp 27°C (60 mm). ^{1}H NMR δ 3.6 (S, 3H), 3.5 (td, $J = 8.8$, 0.7 Hz, 2H). ^{19}F NMR δ −79.6 (t, $J = 8.5$ Hz, 2F).

3.3. Preparation of 2-bromo-2-chloro-1,1-difluoroethyl methyl ether (*10*)

2-Chloro-1,2-dibromo-1,1-difluoroethane, $CBrF_2CHBrCl$. A dry 250 ml two-necked round-bottomed flask equipped with a stir bar, a septum port, and a dry-ice condenser was charged with bromine (5 g, 310 mmol). 2-Chloro-1,1-difluoroethylene (88.1 g, 895 mmol) was condensed into the flask. Additional bromine was added until the color of the bromine persisted (total Br_2 added: 147 g, 920 mmol). The reaction mixture was washed with a solution of sodium thiosulfite to remove the excess bromine. The organic layer was collected and distilled to give 225 g (yield 97.2%) of 1,2-dibromo-2-chloro-1,1-difluoroethane, purity by GC > 98%. Distillation at room temperature gave 110 g (yield 47.5%) of pure compound (GC > 99.5%) and 105 g (yield 45.4%) of less pure material (GC 95–98%). bp 100–105°C. ^{1}H NMR δ 5.9 (dd, $J = 8.5$, 5.9 Hz, 1H). ^{19}F NMR δ −53.5 (dd, $J = 161.1$, 7.3 Hz, 1F), −56.9 (dd, $J = 161.1$, 7.3 Hz, 1F).

1-Bromo-1-chloro-2,2-difluoroethylene, CF_2=CBrCl. A dry 250 ml two-necked, round-bottomed flask equipped with a septum port and a distillation head was charged with 40 g (710 mmol) of potassium hydroxide. After the reaction flask was heated at 50–70°C, 1,2-dibromo-2-chloro-1,1-difluoroethane (37.5 g, 145 mmol) was added dropwise. The crude product (23.3g, 90.5% yield, GC purity 99.4%) was distilled as it formed. Another distillation yielded 99.8% pure (GC) product (20 g, 78% yield); the remainder had a GC purity of 98%. bp 41–43°C. ^{19}F NMR δ −83.7 (d, $J = 29.3$ Hz, 1F), −84.6 (d, $J = 29.3$ Hz, 1F).

2-Chloro-2-bromo-1,1-difluoroethyl methyl ether, $CH_3OCF_2CHBrCl$ (**10**). A dried 250 ml two-necked, round-bottomed flask, equipped with a stir bar, a septum port, and a dry-ice condenser, was charged with sodium methoxide (2.7 g, 50 mmol) in 50 ml methanol. 1-Bromo-1-chloro-2,2-difluoroethylene (20 g, 110 mmol) was added to the stirred reaction mixture. After 4 h, water (150 ml) was added. The organic layer was separated and distilled to give 20.2 g (yield 85%, purity by GC > 98.5%) of the desired product. As the product decomposed below 100°C, it was distilled at reduced pressure (90°C) to give 8.5 g (purity by GC > 99.5%) of **10**. The remainder of the product was of lesser purity (<98%). bp 112–114°C. ^{1}H NMR δ 5.7 (t, $J = 5.0$ Hz, 1H), 3.7 (s, 3H). ^{19}F NMR δ −85.2 (dd, $J = 43.9$, 4.9 Hz, 2F).

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