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Review

1-Bromo-1-chloro-2,2,2-trifluoroethane (Halothane) as a building block for fluorine compounds

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ABSTRACT

This review provides an overview of several synthetic applications of the first fluorinated anaestetic, 1-bromo-1-chloro-2,2,2-trifluoroethane, leading to convenient preparation of numerous fluorine, and particularly, CF_3 group containing compounds *via* organometallic (Mg, Zn) and free radical "sulphinatodehalogenation" reactions.

Contents

1. Introduction

1-Bromo-1-chloro-2,2,2-trifluoroethane, $CF_3CHClBr$, trademarked as **Halothane** or **Fluothane**, is colourless, inflammable, volatile liquid (b.p. 50.2 °C) of low toxicity and pleasant smell. This highly halogenated hydrocarbon was developed by C.W. Suckling of Imperial Chemical Industries (ICI) in 1951 [1]. The commercial synthesis starts from, trichloroethylene, which is reacted with anhydrous hydrogen fluoride in the presence of antimony trichloride at 130 °C to form 2-chloro-1,1,1-trifluoroethane and treatment of the later with bromine at *ca.*450 °C produces halothane [2].

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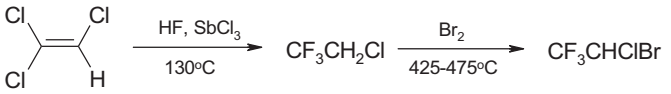


Since 1956, followed by clinical investigations by J. Raventos and M. Johnstone [3], halothane became popular as a low-cost non-flammable inhalation anaestetic replacing old volatile anaestetics such as diethyl ether and cyclopropane. From its introduction to clinical practice in 1956 through 1980s, halothane was given to many millions of patients worldwide. However, the use of this anaestetic was phased out during the 1980s and 1990s and replaced by newer anaestetics, like Isoflurane (CHF_2–O–$CHClCF_3$), Sevoflurane (CH_2F–O–$CH(CF_3)_2$ and others. This was due to the risk of liver injury on repeated exposure to halothane. The resulting syndrome was referred as 'halothane hepatitis', which is thought to result from the metabolism of halothane to trifluoroacetic acid *via* oxidative reactions in the liver [4]. Complete optical resolution of racemic halothane on *n*-pentylated α-cyclodextrin (Lipodex A) has been achieved [5] and numerous papers, e.g. [6,7] deal with pharmacokinetic differences between them. Synthetic approach to (+)-(S)-halothane *via* decarboxylation of a salt of optically enriched 1-bromo-1-chloro-2,2,2-trifluoropropionic acid has also been reported [8].

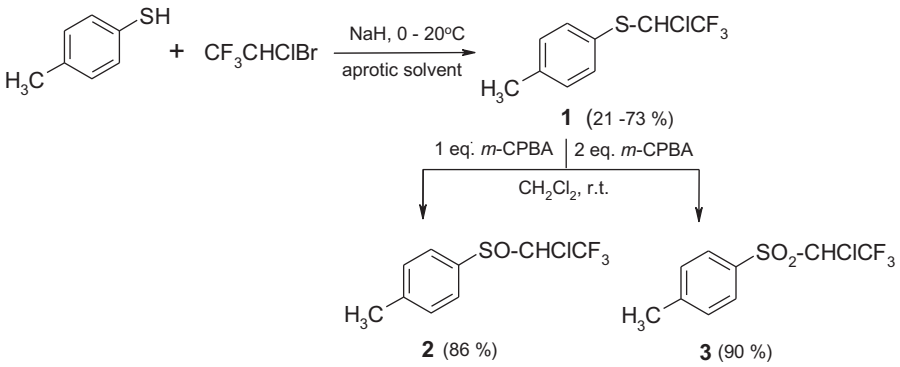
Halothane has a number of advantages to be useful building block for the synthesis of fluorine, and especially, trifluoromethyl group containing compounds. They are:

- active, removable bromine and, in some consecutive reactions, also chlorine atoms,
- conveniently low boiling point which allows easy removal of an excess of the reagent from the reaction mixture,
- non-flammability and relatively low toxicity are important factors for the safety of its application in any laboratory,
- low cost, relatively to typical trifluorinating reagent like $(CH_3)_3SiCF_3$, CF_3I.

The above factors caused an interest of halothane as a reagent in organofluorine chemistry; organometallic and free radical reactions of halothane were the most successful ones, which have been reported till nowadays.

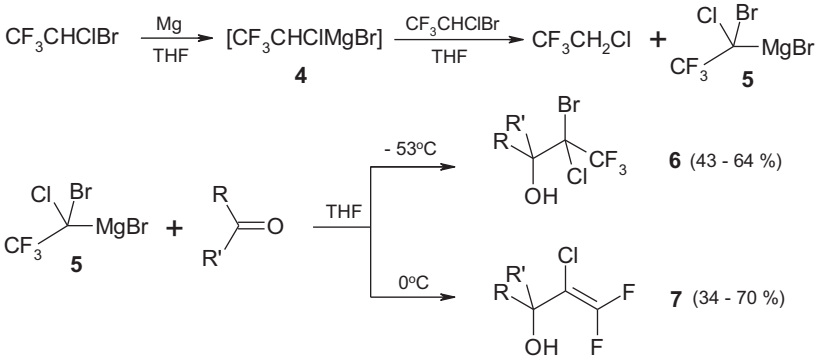
2. Nucleopilic substitution of bromine in $CF_3CHClBr$

The bromine atom in halothane is rather resistant to typical nucleophilic substitution. The only successful reaction was that with 4-methylbenzenethiol in the presence of sodium hydroxide in aprotic solvents to give 1-[(1-chloro-2,2,2-trifluoroethyl)sulphanyl]-4-methylbenzene (**1**). The yield of **1** varied from 21 to 73% depending on the solvent used; *N*-methylpyrrolidone gave the best results. Oxidation of (**1**) with one or two equivalents of *m*-chloroperbenzoic acid gave selectively the corresponding sulphoxide (**2**) or diastereoisomeric mixture of sulphone (**3**) in high yields [9]. Compounds **1** and **3** on treatment with tributyltin hydride in the presence of AIBN or titanium(IV) chloride form the radical intermediates which react with allylbutyltin to give the corresponding allyl derivatives [9].



3. Grignard reactions of $CF_3CHClBr$

The reactions of halothane with magnesium and carbonyl compounds proceeds readily, even at low temperature, but give abnormal adducts. When the reaction with ketones was carried out at −53 °C, 1-(1-bromo-1-chloro-2,2,2-trifluoroethyl) alcohols **6**, while at 0 °C the debromofluorination products, 1-(1-chloro-2,2-difluorovinyl) alcohols **7**, were obtained as the main products. The compounds expected from the normal Grignard reaction, 1-(1-chloro-2,2,2-trifluoroethyl) alcohols, were not found [10]. It has been proved that the primary Grignard reagent **4** is unstable and immediately reacts with an excess of $CF_3CHClBr$ to give 1-chloro-2,2,2-trifluoroethane and 1-bromo-1-chloro-2,2,2-trifluoroethylmagnesium bromide (**5**). The reactions of **5** with ketones provided **6** or/and **7**.



R = CH_3, R' = n-C_6H_{13}-, Ph-; R,R' = -$(CH_2)_5$-