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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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Fluoroalkenes

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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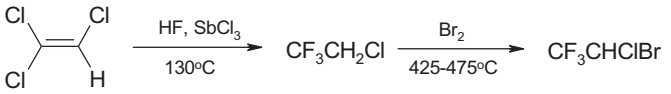


Since 1956, followed by clinical investigations by J. Raventos and M. Johnstone [3], halothane became popular as a low-cost non-flammable inhalation anaestetic replacing old volatile anaestetics such as diethyl ether and cyclopropane. From its introduction to clinical practice in 1956 through 1980s, 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].

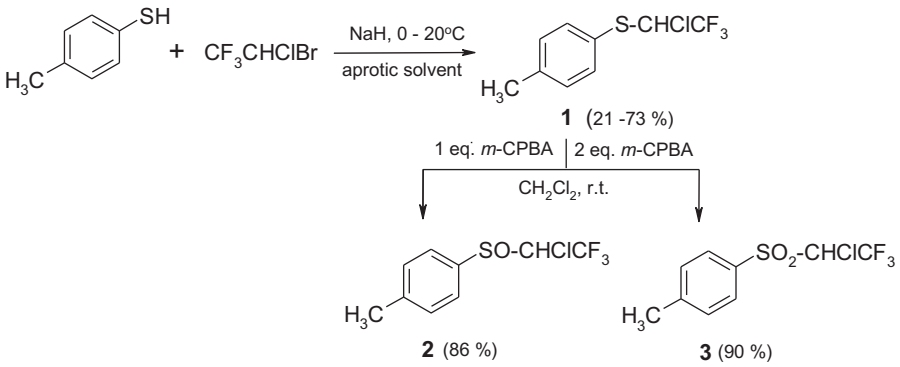
Halothane has a number of advantages to be useful building block for the synthesis of fluorine, and especially, trifluoromethyl group containing compounds. They are:

- 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.

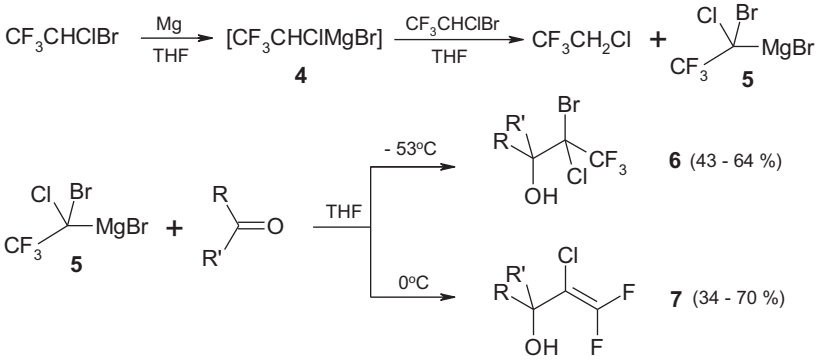
2. Nucleopilic substitution of bromine in $CF_3CHClBr$

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].



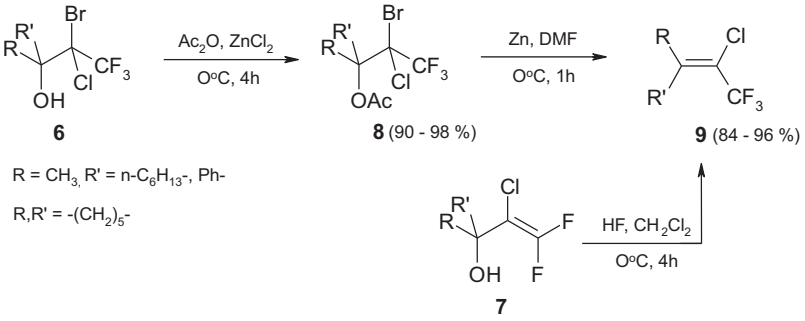
3. Grignard reactions of $CF_3CHClBr$

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**.



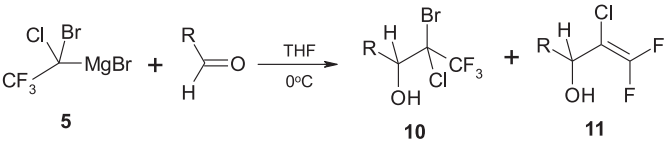
R = CH_3, R' = n-C_6H_{13}-, Ph-; R,R' = -$(CH_2)_5$-

Alcohols **6** and **7** were found to be useful intermediates for a number of fluorinated alkenes. Acetylation of **6** with acetic anhydride and $ZnCl_2$ gave acetoxy derivatives **8** which, by reductive debromoacetoxylation with zinc, were converted to 1-chloro-1-(trfluoromethyl)-alkenes **9** in high yields [11]. Alkenes **9** were also obtained by treatment of **7** with anhydrous hydrogen fluoride [10].



Alcohols **7** were also converted in good yields to β,β-difluoro-γ,δ-unsaturated carboxylic esters by the Claisen rearrangement of the corresponding orthoesters and by the reactions with methanesulphonyl chloride to 2-chloro-1,1-difluoroalkenyl mathanesulphonates [12].

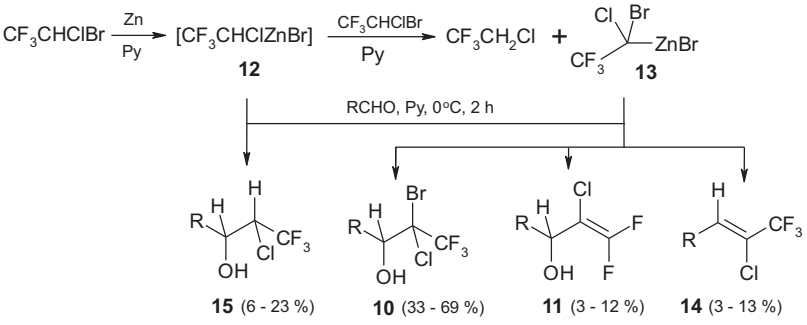
Aldehydes were found to be much less reactive towards abnormal Grignard reagent of halothane [5] than the ketones. The reactions of halothane with magnesium and aldehydes conducted at −20 °C or below gave only low yields of alcohols **10** and **11**, but at 0 °C mostly the dehalogenated compounds **11** were obtained. Vinyl alcohols **11** were also converted to alkenes of the type **9** by treatment with hydrogen fluoride [13].



4. Reactions of $CF_3CHClBr$ *via* zinc intermediates

Halothane, similarly to the reaction with magnesium, reacts with zinc to give predominantly 1-bromo-1-chloro-2,2,2-trifluoroethylzinc bromide [13], however, primary zinc reagent **12** was also trapped by the reactions with aldehydes. The reactions with aldehydes were preferentially carried out in pyridine in the presence of catalytic amount CuCl. Four type of products were formed, independently of an aldehyde used. Alcohols of the type **10**, formed by the addition of **13** to the carbonyl group, were always major components of the reaction mixture together with alkenes **11** and **14** and compound **15,** deriving from the reaction of the primary zinc reagent **12**, as minor components [14].

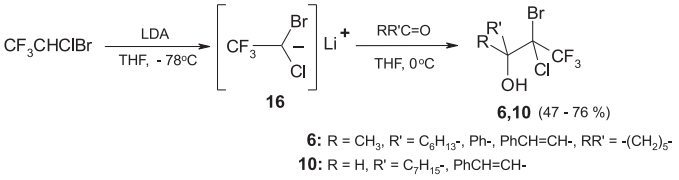
The above procedure gives better yields of alcohols **10** than that involving Grignard reagents but because of the complicity of the reaction mixtures seems to be of little preparative value.



5. Alkyllithium promoted reactions of $CF_3CHClBr$

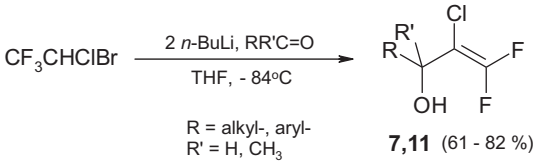
Early attempts the generate a carbanion from halothane by the reaction with ethylmagnesium bromide failed; only decomposition products were obtained which suggested α- or β-elimination of the supposed carbanion [15]. Successful generation of the carbanion **16** was achieved by treatment of halothane with lithium diisopropylamide (LDA) in THF at −78 to 0 °C.

This carbanion was trapped with both ketones or aldehydes to give good yields of alcohols of the type **6** and **10** as the only or main products of the reaction [16].

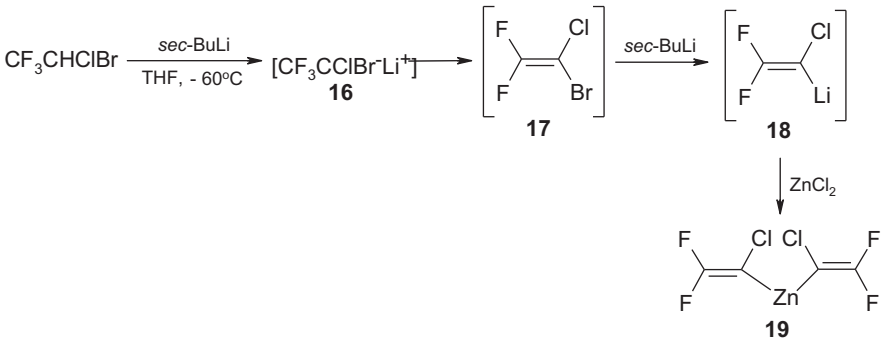


Saturated secondary and tertiary 1-(1-bromo-1-chloro-2,2,2-trifluoroethyl) alcohols (**6**) and (**10**) were obtained selectively and in high yields (up to 96%) when, instead of LDA, lithium or sodium hexamethyldisilazide (Li/NaHMDS) was used as a base for the reactions of halothane with carbonyl compounds [17].

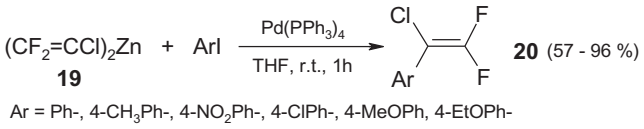
It has been reported that the reaction of halothane with two equivalents of n-butyllithium in the presence of carbonyl compounds in THF at −84 °C provides the most efficient method for preparation of 1-(1-chloro-2,2-difluorovinyl) alcohols (**7**) and (**11**). This reactions proceeded with both ketones and aldehydes with high selectivity and gave better yields than those of the corresponding Grignard reactions [17].



The reaction of halothane with an excess of secondary butyllithium and zinc chloride in THF at −60 °C gave a clear solution, the ^{19}F NMR spectra of which suggested that it contained bis(1-chloro-2,2-difluorovinyl)zinc (**19**). It has been postulated that the carbanion **16** loses lithium fluoride to give ethene **17** which is again lithiated to **18** and the reaction of the latter with $ZnCl_2$ provides **19** [18].

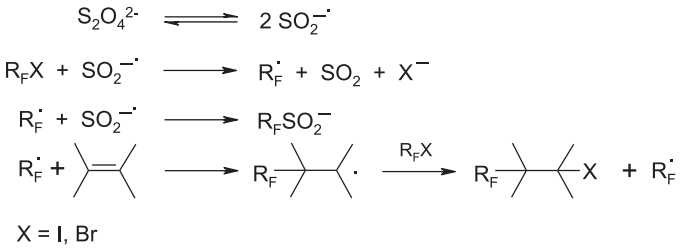


The solution of the vinylzinc reagent **19** is stable enough to be kept in a refrigerator for several month. When aryl iodides and catalytic amount of tetrakis-(triphenylphosphine)palladium were added to this solution, the cross-coupling reactions occurred to give, in most cases, high yields of (1-chloro-2,2-difluorovinyl)arenes (**20**) [18].



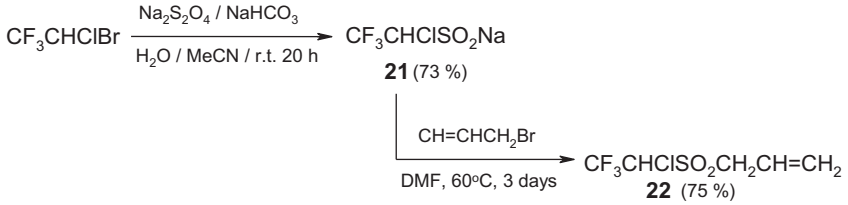
6. Radical reactions involving sulphinatodehalogenation of $CF_3CHClBr$

The most convenient and general way of generating perfluoroalkyl radicals from the corresponding perfluoroalkyl halides (I, Br), known as sulphinatodehalogenation, has been developed in early 1990s by W.Y. Huang and co-workers [19]. Water solutions of sodium dithionite or related reagents (e.g. Rongalite) are used as the free radical initiators. In this reaction systems, dithionite anions ($S_2O_4^{-2}$) exist in equilibrium with radical-anions $SO_2^{\bullet-}$, which by a SET process abstract halogens from perfluoroalkyl halides (iodides, bromides) to generate perfluoroalkyl radicals $R_F^{\bullet}$. These electron deficient radicals could be effectively trapped by electron rich substrates like alkenes, alkynes, arenes and heteroarenes to give addition or substitutions products [20]. In the absence of such reagents, recombination of perfluoalkyl radicals and radical-anions $SO_2^{\bullet-}$ occurs to give perfluoroalkyl sulphinates $R_FSO_2^-$ [19,21]. Usually, $NaHCO_3$ is added to the reaction system to neutralise evolved SO_2.



Sulphinatodehalogenation procedure has a number of advantages over other methods of generation of perfluoroalkyl radicals: the reactions are carried out in aqueous media under mild reaction conditions (in most cases at ambient temperature), inexpensive and safe initiators ($Na_2S_2O_4$, $HOCH_2SO_2Na$) are used, and usually good yields of the addition products are obtained. Since 1990s through 2005s numerous papers, mostly by W.Y. Huang and his co-workers, report successful application of this procedure to perfluoroalkylation of a variety of the electron rich unsaturated substrates.

It has been proved by the present author that, not only perfluoroalkyl halides, but also halothane undergoes sulphinatodebromination to generate the corresponding radical $CF_3CHCl^{\bullet}$. Thus, treatment of $CF_3CHClBr$ with sodium dithionite and $NaHCO_3$ in a water acetonitrile-solution gave 1-chloro-2,2,2-trifluoroethanesulphinate (**21**) in over 70% of isolated yield. The sulphinate **21** is stable white crystalline salt which on prolonged reaction with allyl bromide afforded 1-chloro-2,2,2-trifluoroethyl-3-propenyl sulphone (**22**) [22].

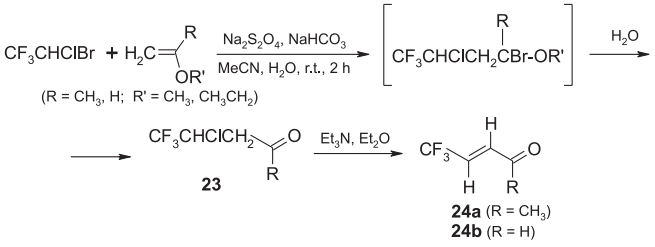


Bromination of **22** followed by dehydrobromination gave isomeric α,β-unsaturated sulphone, which was shown to be active dienophile [22].

6.1. Reactions with enol ethers

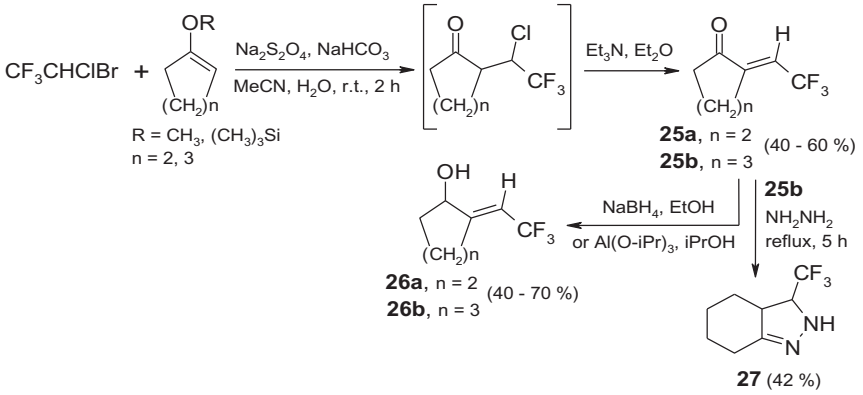
Perfluoroalkyl radicals generated from perfluoroalkyl iodides under sulphinato-dehalogenation conditions were reported to

react with alkyl vinyl ethers to form unstable adducts which in the water reaction medium immediately undergo hydrolysis and elimination of an alcohol molecule to afford high yields of 2-perfluoroalkyl aldehydes or ketones [23,24]. Similar results were obtained from the reactions of halothane with alkyl vinyl ethers. However, in this case the resulted 2-(2-chloro-3,3,3-trifluoropropyl) ketones or aldehydes, because of their instability, were not isolated but by treatment *in situ* with a base they were dehydrochlorinated to α,β-unsaturated carbonyl compound. Thus, the sodium dithionite promoted reactions of halothane with 2-methoxypropene and ethyl vinyl ether, followed by treatment of the reaction mixture with triethylamine afforded, respectively, 5,5,5-trifluoro-3-penten-2-one (**24a**) and 4,4,4-trifluorocrotonaldehyde (**24b**) in reasonable yields [25].



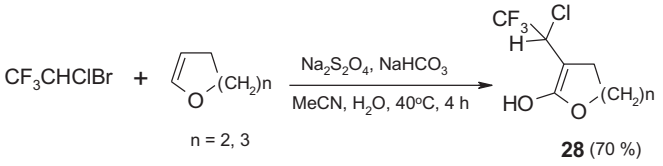
The unstable intermediate carbonyl compounds **23** were isolated from the crude reaction mixtures as the corresponding hydrazones in over 70% yields (after recrystallisation) which gave evidence for high efficiency of the reaction of $CF_3CHClBr$ with enol ethers. Ketone **24a,** by reduction with aluminium isopropoxide, was further converted to 5,5,5-trifluoro-3-penten-2-ol, and aldehyde **24b**, by oxidation with CrO_3, to 4,4,4-trifluorocrotonic acid [25].

The sodium dithionite promoted reactions of halothane with methyl or trimethylsilyl ethers of cyclopentanone and cyclohexanone enols, followed by dehydrochlorination gave, respectively, 2-(2,2,2-trifluoroethylidene)cyclopentanone (**25a**) and 2-(2,2,2-trifluoroethylidene)-cyclohexanone (**25b**) in a 40–60% yields. These α,β-unsaturated ketones were reduced either with $NaBH_4$ or aluminium isopropoxide to 2-(2,2,2-trifluoroethylidene)cycloalkanols (**26a)** and (**26b).** Condensation of **25b** with hydrazine gave 3-trifluoromethyl substituted indazole derivative **27** [26].



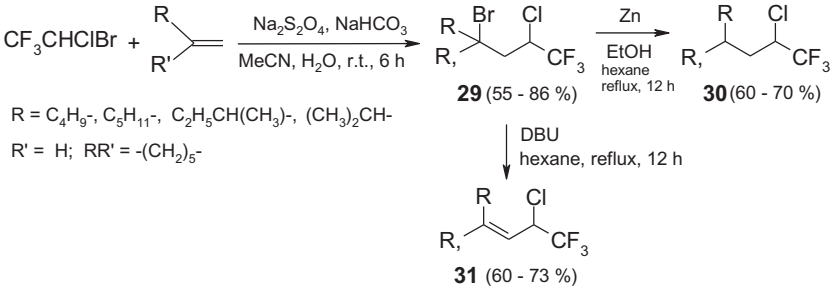
The above described reactions of halothane with enol ethers, however give not very high isolated yields of the final compounds **24** or **25**, nevertheless, they provide an easy and environmentally friendly way, more convenient that conventional Wittig-type or Knoevenagel reactions, to valuable trifluoromethyl substituted α,β-unsaturated ketones and aldehydes.

Addition of halothane to unsaturated cyclic ethers, 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran, gave stable cyclic hemiacetals **28** which were isolated with 70% yields. Attempted dehydrochlorination or dehydration of these compounds resulted in decomposition [27].

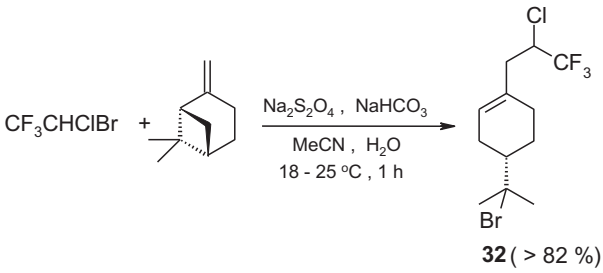


6.2. Reactions with alkenes

The carbanion generated from $CF_3CHClBr$ easily adds to linear and cyclic terminal alkenes to give good yields of simple addition products, 4-bromo-2-chloro-1,1,1-trifluoroalkanes **29** as a mixture of diastereoisomers. Debromination with zinc or dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) of **29** gave, respectively, 2-chloro-1,1,1-trifluoroalkanes (**30)** or 2-chloro-1,1,1-trifluoroalk-3-nes (**31**). Numerous such reaction were successfully carried out [27].

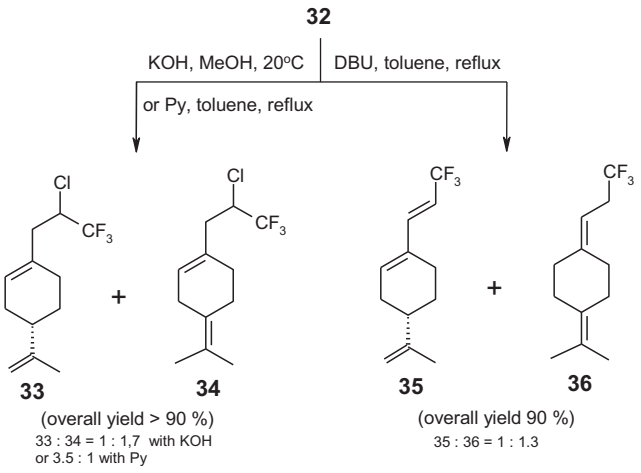


Sulphinatodehalogenation conditions were found to be particularly effective for the addition of 1-bromo-1-chloro-2,2,2-trifluoroethane to the exocyclic double bond of β-pinene. The reaction proceeded spontaneously to give almost quantitatively a 1:1 mixture of diastereoisomers of 4-(2-bromopropan-2-yl)-1-(2-chloro-3,3,3-trifluoropropyl)-cyclohexene (**32**) which, after purification, was obtained in a 82% yield and of 99% purity [28].

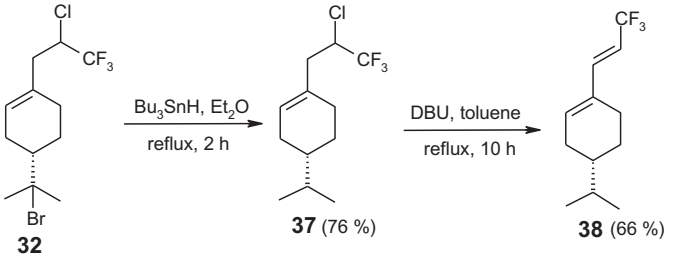


32 (> 82 %)

Compound **32** forms white, soft crystals stable at ambient temperature but the attempted distillation resulted in evolution of HBr and tar formation. Compound **32** was converted to a number of the CF_3 group containing terpenoids. Thus, treatment with strong bases resulted in chemoselective dehydrobromination to give a mixture of regioisomeric dienes, 1-(2-chloro-3,3,3-trifluoropropyl)-4-(isopropenyl)cyclohexene (**33**) and 1-(2-chloro-3,3,3-trifluoropropyl)-4-(isopropylidene)cyclohexene (**34**), in a ratio depending on the base used; no dehydrochlorinated products were found. Total dehydrohalogenation of **32** was achieved by DBU in refluxing toluene to give a mixture of trienes, 4-isopropenyl-1-(*trans*-3,3,3-trifluoropropenyl)cyclohexene (**35**) and 1-isopropylidene-4-(3,3,3-trifluoropropylidene)-cyclohexane (**36**) [28].

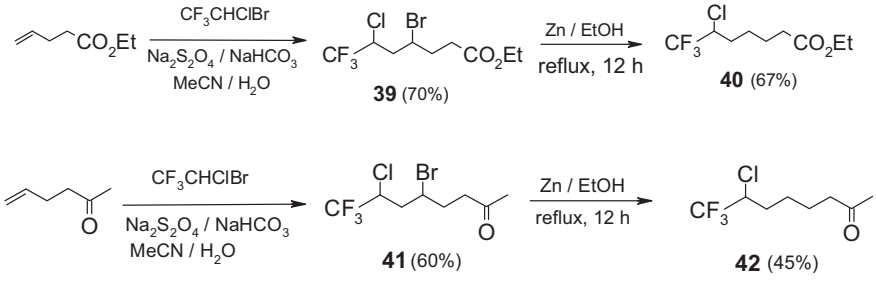


The reduction of the bromine atom in **32** with Bu_3SnH gave the menthene like compound **37** which on dehydrochlorination with DBU in refluxing toluene afforded conjugated diene, 4-isopropyl-1-(*trans*-3,3,3-trifluoropropenyl)cyclohexene (**38**). Diene **38** exhibited high optical activity and the same sign of the optical rotation coefficient as the starting β-pinene; this suggested that all the transformations leading to **38** proceeded with the retention of absolute configuration at carbon atom C-4 [28].



32 **37** (76 %) **38** (66 %)

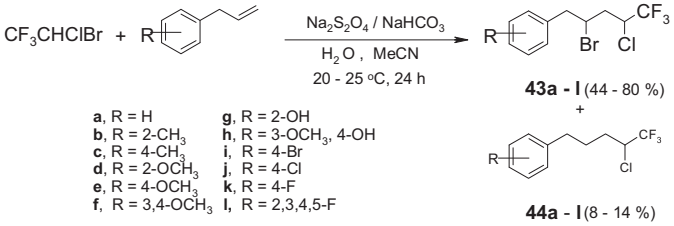
The presence of electron withdrawing substituents, like halogens, CN, SO_2, or a carbonyl group in allylic position of alkenes totally prevents addition of the $CF_3CHCl^{\cdot}$ radical. However, when such a group is separated from the double bond by the $-CH_2CH_2-$ bridge, the addition proceeded normally; reactions of halothane with ethyl ester of 4-pentenoic acid and with 5-hexen-2-one gave the expected adducts **39** and **41** which after debromination afforded, respectively, ethyl 6-chloro-7,7,7-trifluoroheptanoate (**40**) and 7-chloro-8,8,8-trifluorooctan-2-one (**42**) [27].



39 (70%) **40** (67%)

41 (60%) **42** (45%)

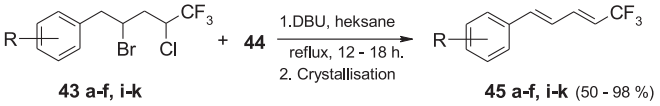
The attempted reactions of halothane with styrene and other alkenes, in which the double bond is conjugated with an aromatic ring, totally failed. In contrast to the latter, allylbenzene and ring substituted allylbenzenes were found to be sufficiently reactive to give the addition products **43** with moderate to high yields together with small amounts of reductively debrominated compounds **44**. No clear evidence was found for the influence of electron donating substituents (Me, OMe, OH) in the aromatic ring on the total yields of **43** and **44** and on their ratio, but electron withdrawing substituents definitely decrease the reactivity of allylbenzenes with increased formation of debrominated products [29].



a, R = H
b, R = 2-CH_3
c, R = 4-CH_3
d, R = 2-OCH_3
e, R = 4-OCH_3
f, R = 3,4-OCH_3
g, R = 2-OH
h, R = 3-OCH_3, 4-OH
i, R = 4-Br
j, R = 4-Cl
k, R = 4-F
l, R = 2,3,4,5-F

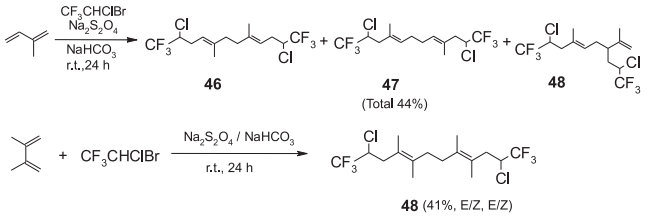
Mixtures of **43** and **44** were converted to **44** by treatment with zinc in methanol and, by refluxing with DBU in hexanes, to conjugated dienes, 1-phenyl-5,5,5-trifluoro-1,3-pentadienes (**45**)

in high yields. Dienes **45** are white crystalline compounds and they were easily separated from the reaction mixtures by simple crystallisation. These dienes were reported to be sufficiently reactive to undergo Diels-Alder condensation with electrophilic dienophiles, like maleic anhydride and diethyl acetylenedicarboxylate, to give trifluoromethylated carbocyles [29].



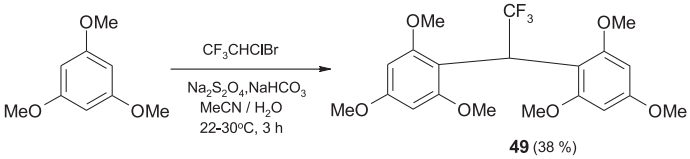
43 a-f, i-k **45 a-f, i-k** (50 - 98 %)

In reactions of halothane with dienes under sulphinatodehalogenation conditions, similarly to such reactions of perfluoroalkyl iodides [30], addition of the $CF_3CHCl^{\cdot}$ radicals occurs to the both sides of a diene to give dimeric products. From the reaction with isoprene a mixture of three regioisomeric compounds **46**,**47** and **48** was obtained, and the reaction with 2,3-dimethyl-1,3-butadiene afforded a mixture of four geometric isomers of 2,11-dichloro-1,1,1,12,12,12-hexafluoro-4,5,8,9-tetramethyl-4,8-diene (**49**) as the only product [27].



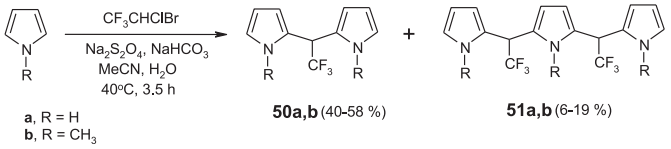
6.3. Reactions with aromatics

The sulphinatodehalogenation reaction system has been successfully applied for perfluoroalkylation of electron rich aromatics, like phenolates and anilines [31,32], aromatic amines [33], methoxybenzenes and alkyl substituted benzenes [34]. Using perfluoroalkyl iodes as alkylating agents, numerous ring-perfluoroalkylated aromatic compounds were obtained in good to excellent yields. All the attempted reactions of $CF_3CHClBr$ with phenoxides, aminobenzenes, toluene, xylenes, mono- and dimethoxybenzenes, both in the CH_3CN/H_2O and DMF/H_2O solutions and at the temperature range of 20–55 °C, totally failed; only unreacted substrates or complex mixtures were obtained. With 1,2,3-trimethoxybenzene and 1,2,4-trimethoxybenzene only low yields of complex mixtures of products, not suitable for separation and indentification, were obtained. However, the reaction with 1,3,5-trimethoxybenzene occurred more cleanly but in quite unusual way to afford, instead of the expected CF_3CHCl substituted derivative, reasonable yield of trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane (**49**) as the only isolable product [35]. Compound **49** is a stable white crystalline solid the structure of which has been confirmed by the X-ray crystal analysis.



49 (38 %)

In a similar way reacts halothane with pyrroles to give 5-(trifluoromethyl) dipyrromethanes methanes **50a** and **50b** as the main products together with small amounts of tripyrranes **51a** and **51b** and trace amounts of higher homologues [36]. The X-ray analysis gave unequivocal evidence for the structure of **50b**.



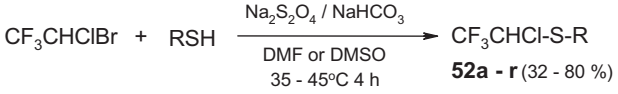
a, R = H
b, R = CH_3

50a,b (40-58 %) **51a,b** (6-19 %)

The reactions with pyrroles seems to be unique, while the attempted reactions of $CF_3CHClBr$ with other heteroaromatics failed.

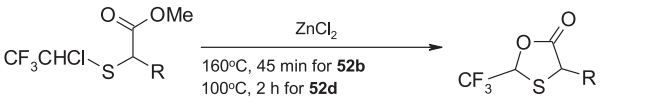
6.4. Reactions with thiols

Recently, it has been reported that thiols undergo fluoroalkylation with halothane under the sulphinatodehalogenation conditions but, instead of the acetonitrinle/water solution, an aprotic solvent like *N*,N-dimethylformamide or dimethylsulphoxide should be applied. The reactions were successfully carried out with a variety of aliphatic, aromatic and heterocyclic thiols yielding structurally diverse 1-chloro-2,2,2-trifluoromethyl sulphides **52** [37]. Although, in this particular case the authors do not fully exclude S_N2 nucleophilic substitution of the bromine with a thiolate, but the detected byproducts and a substantial reduction of the fluoroalkylation product yields in the presence of *p*-dinitrobenzene are supportive of the radical mechanism.



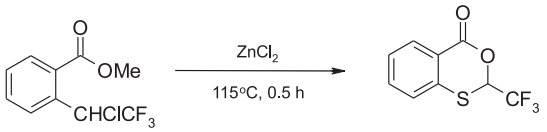
a, R = $HOCH_2CH_2$-; **b,** R = MeO_2CCH_2-; **c,** R = $EtCONHCH_2CH_2$-;
d, R = $MeO_2CCH_2CHCO_2Me$; **e,** R = Ph-; **f,** R = $PhCH_2$-;
g, R = *p*-MePh-; **h,** R = *p*-H_2NPh-; **i,** R = *o*-MeO_2CPh-;
j, R = imidazoyl-; **k,** R = triazoyl-;**l,** R = thiazoyl-; **m,** R = thiophenyl-;
n, R = benzoxazoyl-; **o,** R = benzothoazoyl-; **p,** R = pyridyl-;
r, R = pyrimidinyl-

Some functionalised sulphides **52** were found to be useful for the synthesis of trifluoromethyl substituted heterocycles. Thus, methyl [(1-chloro-2,2,2-trifluoroethyl)-sulphanyl]acetate (**52b**), the corresponding propionate [38], and dimethyl 2-[(1-chloro-2,2,2-trifluoroethyl)sulphanyl]succinate (**52d**) in the presence of Lewis acid catalyst ($ZnCl_2$) undergo heterocyclisation to give a mixture of diastereoisomers of 1,3-oxathiolanones **53** [37,38]. Under similar conditions, methyl 2-[(1-chloro-2,2,2-trifluoroethyl)sulphanyl]benzoate (**52i**) gave rise to a benzoxathianone **54** [37].



52b,d
b, R = H or Me
d, R = -CH_2CO_2Me

53 (65 -81 %)
R = H, Me, -CH_2CO_2Me

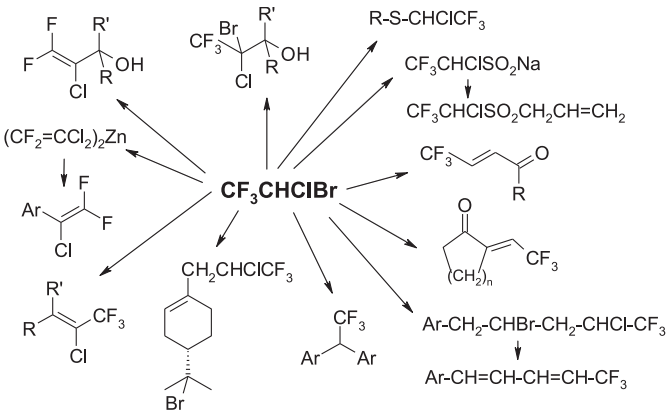


52i **54** (91 %)

7. Summary

1-Bromo-1-chloro-2,2,2-trifluoroethane is a versatile building block for the preparation of numerous fluorine atom and particularly trifluoromethyl group containing compounds like

alkanes, alkenes, dienes, unsaturated alcohols, ketones and aldehydes, sulphides and other derivatives. The reactions are, in most cases, easy to conduct under mild conditions and usually give good yields of the final products. The key types of compounds, syntheses of which have been reported, are depicted in the scheme below.



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