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ADVANCES IN FLUORINATION OF ORGANIC COMPOUNDS WITH SULPHUR TETRAFLUORIDE

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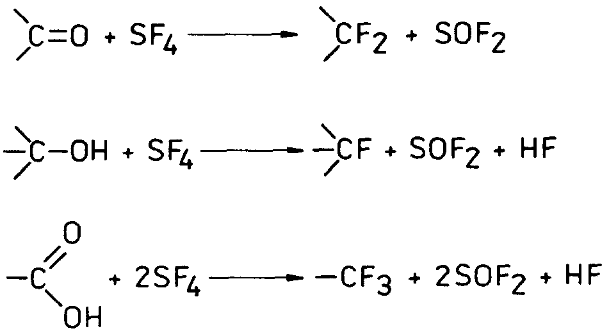
SUMMARY

Sulphur tetrafluoride has been known since 1958 as an efficient fluorinating agent for replacing oxygen atoms in carbonyl groups by fluorines. In the past fifteen years a number of new reactions of sulphur tetrafluoride with carbonyl compounds have been discovered. These include formatio of bis(1,1-difluoroalkyl) ethers from alkanecarboxylic acids, bis(1-fluoroalkyl) ethers from aliphatic aldehydes, and cyclic fluoroethers from difunctional carboxylic acids and aldehydes. In the reactions with branched aldehydes rearrangements of hydrogen and fluorine atoms and also of the carbon skeleton were observed. Tertiary amides were successfully converted to 1,1-difluoroamines and tertiary formamides to trifluoromethylamines. This last reaction involves simultaneous fluorination of the carbon-oxygen and carbon-hydrogen bonds.

Participation of carbocations in the mechanism of fluorination of carbonyl groups has been proved and a revised mechanism proposed. Evidence for a reduction-oxidation mechanism for the replacement of formyl hydrogen by fluorine has also been found.

INTRODUCTION

The use of sulphur tetrafluoride in organic chemistry as a fluorinating agent was pioneered at the turn of fifties by the DuPont group [1,2] . Their work showed that it is an efficient and versatile reagent for the replacement of oxygen functions by fluorine atoms. Thus, hydroxyl, carbonyl, and carboxylic groups when acted upon by sulphur tetrafluoride are converted to mono-, di- and trifluoromethyl groups, respectively. Since this discovery, hundreds of successful applications of sulphur tetrafluoride for synthesis of fluoroorganic compounds, even compounds as complex as steroids and terpenes, have been reported.



Two excellent reviews, one in Russian [3] and one in English [4] summarise the literature on fluorination of organic compounds with SF_4 thro 1971. Therefore, reactions of SF_4 with the oxygen functions, particularly with carbonyl and carboxyl groups, became well established as convenient laboratory methods for the selective introduction of fluorine atoms in organic molecules. However, in the past fifteen years a number of new results involving reactions of SF_4 with organic compounds, particularly, with carbonyl compounds, have been discovered and many of these have come out of our laboratory. The most important of these discoveries are:

- improved synthesis of SF_4 ;
- formation of symmetric α -fluoroethers from carboxylic acids and from carboaldehydes ;
- rearrangements in the reactions with branched aldehydes;
- the role of hydrogen fluoride as a catalyst;
- trapping of intermediates ;
- synthesis of α ,α -difluoroamines from tertiary amides;
- direct conversion of tertiary formamides to trifluoromethylamines ;
- increasing number of examples of fluorination of the carbon-hydrogen bond.

These results have advanced our knowledge of the nature of the reaction of SF_4 with carbonyl groups and have given experimental evidence for mechanism of this reaction. A mechanism for the carbon-hydrogen bond fluorination involved in the reactions with formamides has also been found experimentally.

SYNTHESIS OF SF_4

The general method for the synthesis of SF_4 consists of the halogen exchange between sulphur dichloride, SCl_2, and sodium fluoride[5] . A few versions of this synthesis are possible:

- reactions in an aprotic solvent, best of all in acetonitrile ;
- reactions without a solvent, conducted at elevated temperatures in an autoclave under autogenous pressure of about one hundred atmospheres. Either sulphur dichloride SCl_2, sulphur monochloride S_2Cl_2, or elemental sulphur and elemental chlorine may be used for the synthesis of SF_4.

$$3SCl_2 + 4NaF \xrightarrow[60°]{MeCN} SF_4 + S_2Cl_2 + 4NaCl$$

$$SCl_2 + 4NaF + Cl_2 \xrightarrow[300°]{autoclave} SF_4 + 4NaCl$$

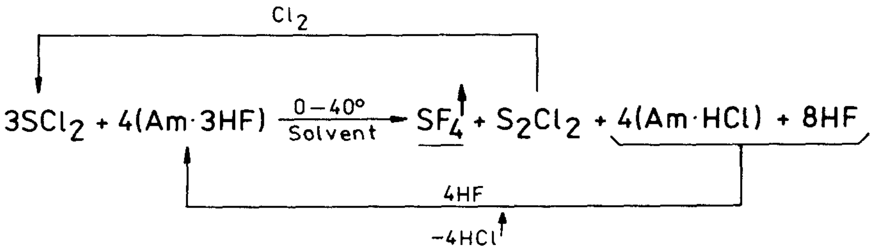
$$S_2Cl_2 + 8NaF + 3Cl_2 \xrightarrow[300°]{autoclave} 2SF_4 + 8NaCl$$

$$S + 4NaF + 2Cl_2 \xrightarrow[300°]{autoclave} SF_4 + 4NaCl$$

Yields: 80 – 90%

In these reactions, sulphur or sulphur monochloride are chlorinated 'in situ to sulphur dichloride. We have adopted the last method, from elemental sulphur and chlorine, and have found it very convenient for 200-300 g scale preparations. This method, however, is not convenient for technical scale preparation.

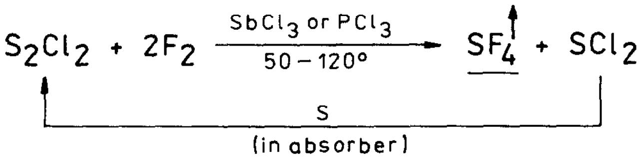
Recently a number of patents and papers describe another version in which SF_4 is obtained under very mild conditions by the halogen exchange between sulphur dichloride SCl_2 and amine-hydrogen fluoride complexes [6-10]. Pyridine and trialkylamine complexes of HF were mostly used. The reactions were conducted at temperatures ranging from 0 to 40° using halogenated hydrocarbons or acetonitrile as solvents. SF_4 was removed from the reaction mixture by vacuum distillation and, as the authors claim, all by-products may be recycled thus making the process inexpensive. Sulphur monochloride is chlorinated back to sulphur dichloride and an amine-hydrogen chloride complex on treatment with additional amount of HF releases HCl to reproduce the amine–HF complex. A 40 kg scale synthesis of SF_4 by this method has been reported.



Am : Pyridine, Me_3N, Et_3N,...

Solvent : CH_2Cl_2, CCl_4, $C_2Cl_3F_3$, CH_3CN

Synthesis of SF_4 by fluorination of sulphur monochloride, S_2Cl_2, with elemental fluorine in the presence of a catalyst has also been reported [11,12]. Sulphur dichloride, SCl_2, which is formed as the byproduct, is converted back to sulphur monochloride in an absorber filled with granulated sulphur and then recycled.



Two methods were described for direct fluorination of elemental sulphur to SF_4:

- low-temperature fluorination of powdered sulphur suspended in trichloro-fluoromethane [13], and
- fluorination of melted sulphur at elevated temperature using ten-fold excess of sulphur with respect to fluorine [14].

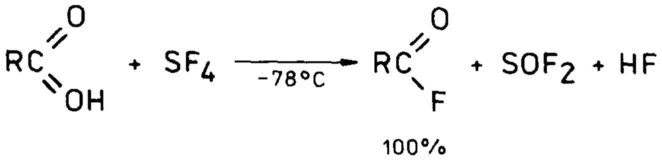
$$S(\text{susp. in } CCl_3F) \xrightarrow[-78°]{F_2/N_2\,(1:3)} SF_4$$

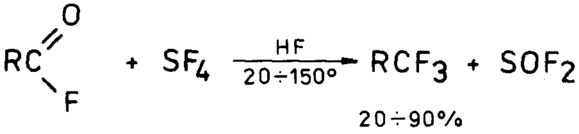
$$S(\text{liquid}) \xrightarrow[120-200°]{F/S\,(1/10)} SF_4$$

However, by our experience, for the laboratory scale preparation of SF_4, the simplest method is the synthesis from sulphur, chlorine, and sodium fluoride in an autoclave. This method does not involve such aggressive materials as hydrogen fluoride or elemental fluorine.

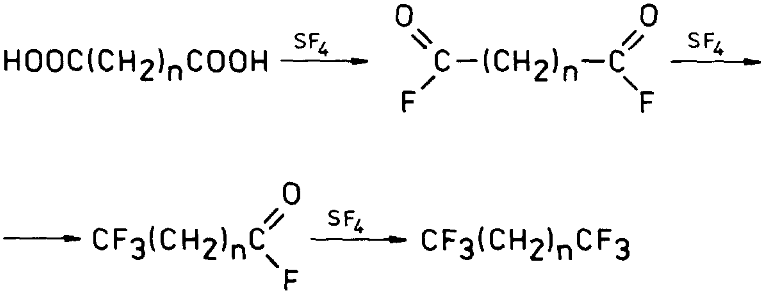
REACTIONS WITH ALKANECARBOXYLIC ACIDS. FORMATION OF LINEAR BIS(1 , 1 -DIFLUOROALKYL) ETHERS

From amongst numerous applications of SF_4, the reactions with carboxylic acids, aliphatic, aromatic, and heterocyclic, are of particular importance as general, simple routes to trifluoromethyl derivatives[2-4] .





R = alkyl, Ar

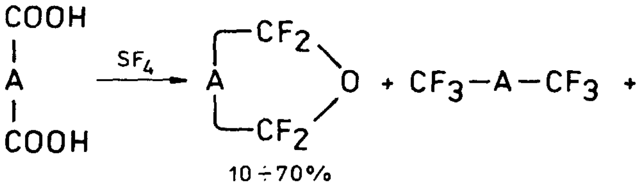


The reaction proceeds in two steps, via acyl fluorides; HF which is released in the first step catalyses the second step of the reaction. The reaction is also catalysed by Lewis acid type fluorides like BF_3, TiF_4, AsF_3 and others. Formation of acyl fluorides proceeds readily even at low temperature, while the second step, fluorination of the carbonyl group, usually requires a temperature range of 20 to 200°, depending on the nature of the acid fluoride. In reactions with di- and polycarboxylic acids, products with the corresponding number of the trifluoromethyl groups are formed in a stepwise manner.

However, formation of trifluoromethyl derivatives is not the only direction for the reaction of SF_4 with carboxylic acids and acyl fluorides. Under correctly choosen conditions, the reaction of SF_4 with alkanecarboxylic acids affords, in addition to trifluoromethylalkanes, symmetric bis(1 , 1-difluoroalkyl) ethers in up to 35 % yields [15-17] . With alkane-dicarboxylic acids, particularly 1,2-dicarboxylic acids, high yields of cyclic tetrafluoroethers, together with bis(trifluoromethyl)alkanes, linear ethers and polyethers are formed [18] .

$$RCOOH \xrightarrow{SF_4} RCF_3 + \underset{5\div 35\%}{RCF_2-O-CF_2R}$$

R = alkyl, cycloalkyl



$$+ CF_3-A-CF_2-O-CF_2-A-CF_3 \;+$$

$$+ CF_3-A-CF_2-(-O-CF_2-A-)_n-CF_3$$

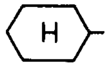
A = alkylene, cycloalkylene n = 2,3

Yields of the ethers are related to the nature of the starting acids and to the reaction conditions; typical examples are shown in Table 1.

TABLE 1

Reactions of SF_4 with some alkanecarboxylic acids

$$RCOOH \xrightarrow{SF_4} RCF_3 + RCF_2{-}O{-}CF_2R$$

RCOOH	Reaction conditions		Yield, mol %	
	temp, °C	time, h	RCF_3	$RCF_3{-}O{-}CF_2R$
CH_3COOH	-10	48	28	16
	4	48	78	0
	20	24	90	0
CH_3CH_2COOH	-15	48	26	16
	20	20	96	0
$CH_3(CH_2)_4COOH$	15	16	48	7
	70	3	74	0
COOH	40	10	36	14
CH_2ClCH_2COOH	70	3	45	20
$CH_3CHClCOOH$	170	3	48	21

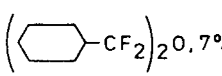
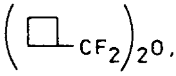
From simple unsubstituted acids like acetic and propionic, the ethers are formed only at low temperatures, -10 and -15°, while longer chain and cycloaliphatic acids give the corresponding ethers also at higher temperatures, +15 and +40°. With halo-substituted acids the ethers are formed in reasonable yields even at the much higher temperatures which are necessary for these reactions to proceed. The optimum conditions for the formation of the ethers are dependent on their stability in highly acidic reaction media and on the reactivity of the acids towards SF_4.

The influence of negative substituents like halogens is twofold: they stabilise the resulting ethers but at the same time they limit the reactivity of the acids. The best compromise of these two factors has been found for 3-halosubstituted ethers (in the frame) which were obtained in more than 30 % yields.

On the basis of numerous examples we have found that formation of bis(1,1-difluoroalkyl)ethers is general in nature and constitutes a second direction for the reaction of SF_4 with alkanecarboxylic acids. Yields of the ethers are listed below. No ethers were obtained from the acids which were not sufficiently reactive to also afford trifluoroalkanes, such as trihaloacetic acids and trimethylacetic acid; in this latter case presumably because of steric hindrance. Reactions with alkoxyacetic, allylic, and aromatic acids also did not give the expected ethers, possibly because of their instability under the reaction conditions.

$(CH_3CF_2)_2O$, 16% ; $(CH_3CH_2CF_2)_2O$, 16% ; $(CH_3/CH_2/_2CF_2)_2O$, 15%

$(CH_3/CH_2/_3CF_2)_2O$, 15% ; $(CH_3/CH_2/_4CF_2)_2O$, 7% ; $(CH_3/CH_2/_7CF_2)_2O$, 7%

$(/CH_3/_2CHCF_2)_2O$, 18% ; , 7% ; , 15%

$(CH_2FCF_2)_2O$, 11% ; $(CH_3CHClCF_2)_2O$, 20% ; $(CH_2ClCHClCF_2)_2O$, 9%

$(CH_2ClCF_2)_2O$, 24% ; $(CH_3CHBrCF_2)_2O$, 20% ; $(CH_2Cl/CH_2/_2CF_2)_2O$, 11%

$(CH_2BrCF_2)_2O$, 24% ; $(CH_2ClCH_2CF_2)_2O$, $\underline{34\%}$; $(CF_3/CH_2/_2CF_2)_2O$, 22%

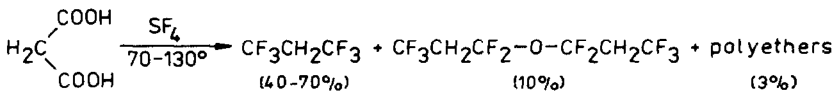
$(CH_2ICF_2)_2O$, 17% ; $(CH_2BrCH_2CF_2)_2O$, $\underline{28\%}$

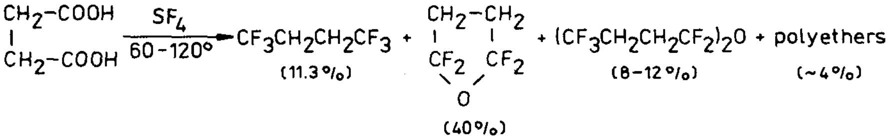
$(CHCl_2CF_2)_2O$, 8% ; $(CH_2ICH_2CF_2)_2O$, $\underline{33\%}$

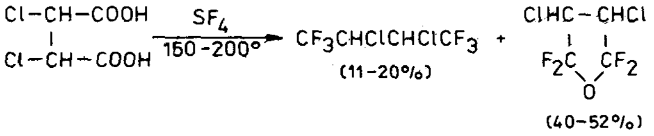
REACTIONS WITH DICARBOXYLIC ACIDS. FORMATION OF CYCLIC TETRAFLUOROETHERS

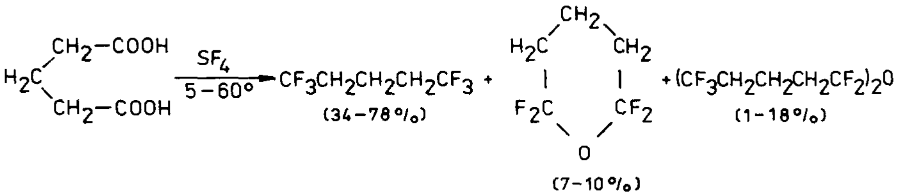
Formation of cyclic tetrafluoroethers from dicarboxylic acids is governed mainly by steric factors in the acids, that is, by mutual distance and spatial configuration of the carboxylic groups.

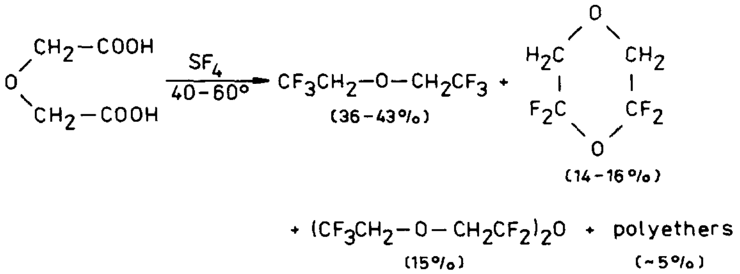
Good yields of cyclic five-membered ethers were obtained from 1,2-dicarboxylic acids, such as succinic and halosuccinic acids, but from 1,3-dicarboxylic acids such as glutaric and diglycolic, yields of the six-membered ethers were only one-forth as high as the former. 1,1- and 1,4-Dicarboxylic acids, malonic and adipic, gave only linear products[18] .

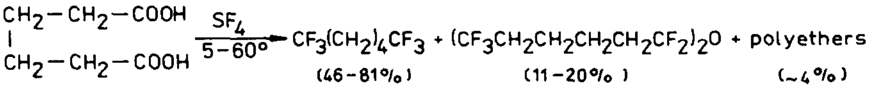




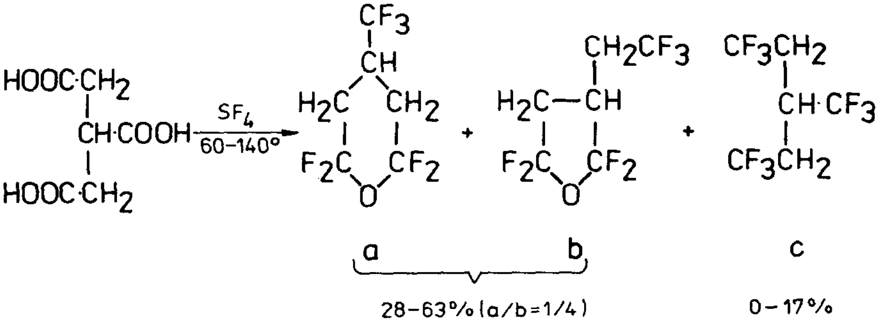




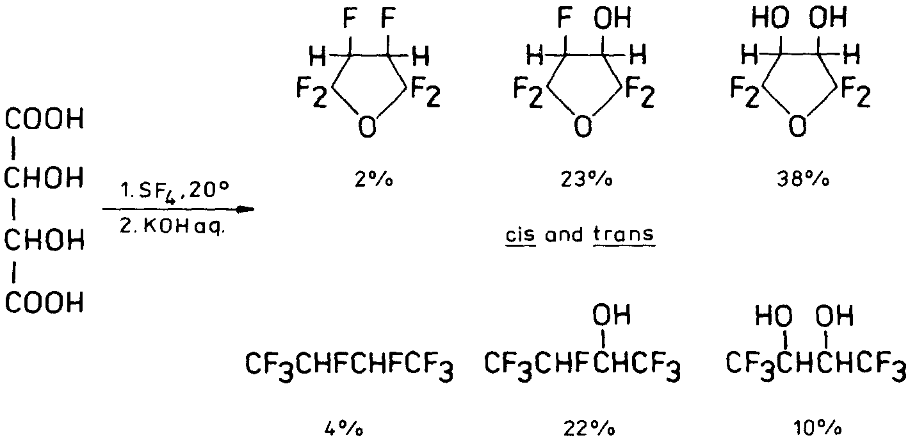




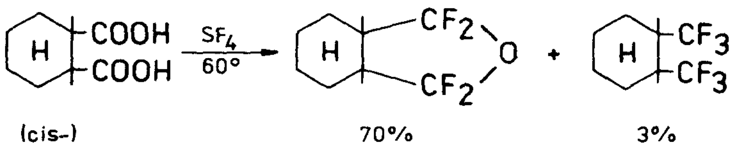
A clear illustration of the tendency of 1,2- and 1,3-dicarboxylic acids to a ring closure during the reaction with SF_4 is the reaction with 1,2,3-propane-tricarboxylic acid; the corresponding six- and five-membered fluoroethers are formed in a 1 : 4 ratio, independently of the reaction conditions [18] .



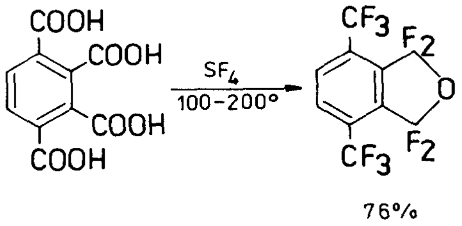
It has also been reported [19] that treatment of d-tartaric acid with SF$_4$, followed by hydrolysis, gave a complex mixture of cyclic and linear products with the preferential formation of five-membered ethers, derivatives of 2,2,5,5-tetrafluorotetrahydrofuran.

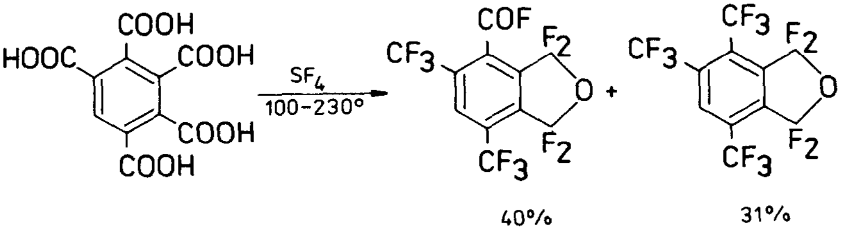


Particularly high yields of cyclic tetrafluoroethers were obtained from acids in which the carboxylic groups were fixed in cis-positions relative to one another. For example, the reaction with 1,2-cis-cyclohexanedicarboxylic acid gave 70 % yield of the cyclic ether with very limited formation of bis (trifluoromethyl) derivative [18] .

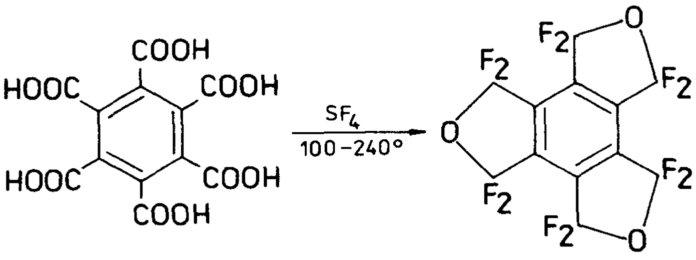


In the series of benzene-polycarboxylic acids, only sterically crowded tetrakis- and pentakis-carboxylic acids gave the expected ethers, fluorinated derivatives of phthalan. No ring closure occured in the case of ortho-phthalic acid [20,21] .





The reaction of SF_4 with benzene-hexacarboxylic acid leads to the closure of three rings to give tris-tetrafluorophthalan as the only product in 90 % yield [21] .



REACTIONS WITH ALDEHYDES. REARRANGEMENTS AND FORMATION OF BIS(1-FLUOROALKYL) ETHERS AND CYCLIC FLUOROETHERS

It has been found that reactions of SF_4 with aliphatic aldehydes, which were previously known to give difluoromethyl derivatives, are much more complex and, in general, afford three types of products: the expected 1,1-difluoroalkanes, rearranged 1,2-difluoroalkanes, and bis(1-fluoroalkyl)ethers[22]

$$R.CH_2.CHO \xrightarrow[-20,+40^\circ]{SF_4} \underset{I}{R.CH_2CHF_2} + \underset{II}{R.CHF.CH_2F}$$

$$+ \underset{III}{(R.CHF)_2O} + \underset{trimer}{[(R.CH_2.CHO)_3]}$$

$$(R.CH_2.CHO)_3 \xrightarrow{SF_4} I + II + III$$

In some cases, at low reaction temperature, high yields of cyclic trimers of the aldehydes were also obtained, but these trimers reacted further with SF_4 in the same manner as monomeric aldehydes to give products I, II, and III. The trimerisation is evidently induced by trace amounts of HF usually present in standard quality SF_4. Formation, or not, of particular products I, II, and III and their ratios strongly depends on the properties of individual aldehydes and on the reaction conditions.

Most of straight-chain aldehydes, acetic, propionic, valeric, and caproic, reacted with SF_4 in the usual manner to give the expected 1,1-difluoroalkanes as the only isolable products. Reasonable yields were obtained in rather narrow ranges of reaction temperature.
An exception in this series was n-butylaldehyde which, in addition to 1,1-difluoro-n-butane, also gave bis (1-fluoro-n-butyl) ether . Since this ether is rather unstable, reasonable yields (15-38 %) were obtained only at reaction temperatures below $0^\circ C$.

$$CH_3.CH_2.CH_2.CHO \xrightarrow[18hrs]{SF_4} CH_3.CH_2.CH_2.CHF_2 + (CH_3.CH_2.CH_2.CHF)_2O$$

The ethers were also formed in the reaction of SF_4 with formaldehyde [2] and with perhaloacetaldehydes [23] . It is interesting to note that chloral reacts with SF_4 with a chlorine-fluorine rearrangement to give the asymmetric ether and 1,1,2-trichloro-1,2-difluoroethane as the main reaction product. Symmetric polyhalodiethyl ethers were obtained by treatment of haloacetaldehydes with diethylamino-sulphur trifluoride (DAST) [23] .

$$(CH_2O)_n \xrightarrow[150^\circ]{SF_4} \underset{21\%}{CH_2F{-}O{-}CH_2F} + \underset{49\%}{CH_2F_2}$$

$$CF_3CHO \xrightarrow[30^\circ]{SF_4} \underset{16\%}{CF_3CHF{-}O{-}CHF.CF_3} + \underset{58\%}{CF_3CHF_2}$$

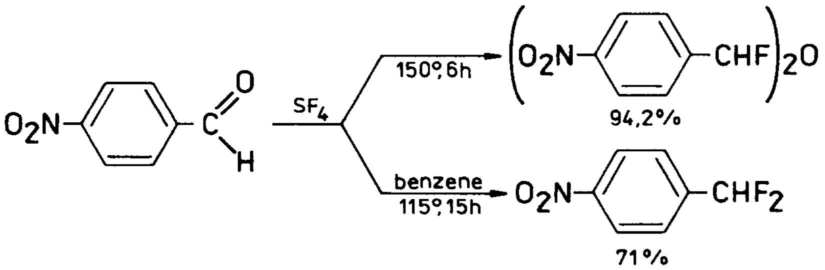
$$CCl_3CHO \xrightarrow[20^\circ]{SF_4} \underset{1.3\%}{CCl_3CHF{-}O{-}CHFCCl_3} + \underset{57\%}{CFCl_2CHFCl} +$$

$$+ \underset{12.7\%}{CCl_3CHF{-}O{-}CCl_2CHFCl}$$

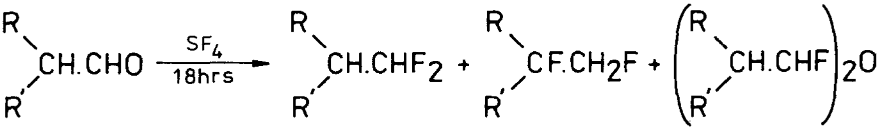
$$RCHO \xrightarrow[-20 \div 60^\circ]{Et_2NSF_3} \underset{33 \div 80\%}{RCHF{-}O{-}CHFR}$$

$R = CCl_3, CF_3, CHBr_2, CHCl_2, CH_2Cl$

From a number of benzaldehydes investigated, only p-nitrobenzaldehyde gave the corresponding ether, surprisingly enough, as the sole product and in greater than 94 % yield. This same reaction, however, when conducted in a benzene solution, gave exclusively p-nitrobenzylidene fluoride [24] .

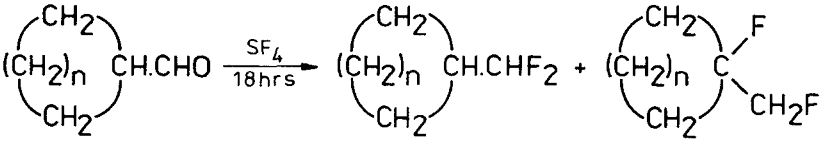


Fluorine-hydrogen rearrangements are typical for the reactions of SF_4 with aldehydes branched at the carbon atom α to the formyl group. The reactions with iso-butyraldehyde, α-ethyl-butyraldehyde, and α-methyl-butyraldehyde gave "normal" 1,1-difluoroalkanes and rearranged 1,2-difluoroalkanes in comparable amounts and, with the exception of the most branched α-ethylbutylaldehyde, good yields of the corresponding bis (1-fluoroalkyl) ethers were obtained [22] . However, in contrast to the reaction with chloral, which has already been described, these ethers have the predicted structure with no fluorine-proton rearrangement.



R_1R'=Me,Et

Rearrangements occur also in the reactions with cycloaliphatic aldehydes; cyclopentane and cyclohexane carboaldehydes gave mixtures of difluoromethylcycloalkanes and 1-fluoro-1-fluoromethylcycloalkanes [22] . Thus, the reactions of SF_4 with cyclic aldehydes results also in substitution of a hydrogen atom in the cycloalkane ring by fluorine to give ring-fluorinated products. No ethers were formed from cycloalkane carboaldehydes, presumably because of steric hindrances.



The reaction of SF_4 with trimethylacetaldehyde proceeds in a very unexpected way: none of the expected 1,1-difluoroalkane was detected, however, 2,3-difluoro-2-methyl-butane was formed in high yield as the only fluoroalkane along with a reasonable yield of bis (1-fluoro-2,2-dimethylpropyl) ether [22] . In this reaction, migration of one of the methyl groups takes place.

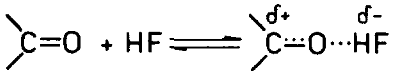
$$(CH_3)_3C\cdot CHO \xrightarrow[18hrs]{SF_4} (CH_3)_2CF\cdot CHF\cdot CH_3 + [(CH_3)_3C\cdot CHF]_2O$$

MECHANISM OF THE REACTION OF SF_4 WITH CARBONYL GROUPS

Observed rearrangements in the reactions with aldehydes and the formation of fluoroethers from carboxylic acids and from aldehydes called for a revision of the mechanism of the reactions of SF_4 with carbonyl compounds which was proposed 25 years ago by the DuPont group. The key problem in this mechanism rests with the role of hydrogen fluoride or Lewis acid type fluorides. Do these catalysts activate carbonyl groups or the sulphur tetrafluoride molecule? Results of our studies on the effect of the HF concentration on the rate of the reaction with acid fluorides gave experimental evidence that, in contrast to the previous concept, co-ordination of HF to a carbonyl group inhibits its reaction with SF_4 [25] . Therefore, the catalytic activity of HF must result from activation of the sulphur tetrafluoride molecule by forming a strongly polar or ionic HF-SF_4 complex. Such a concept is supported by spectral and conductometric measurements by Gillespie and co-workers, which have shown the existence of the ionic species SF_3^+ and HF_2^- in the HF-SF_4 system [26] . Competitive complexation of HF by a carbonyl group decreases the rate of its reaction with SF_4, firstly by lowering the effective concentration of HF required for the activation of SF_4, and secondly by blocking the carbonyl group.

$$SF_4 + HF \rightleftharpoons \overset{\delta+}{SF_4}\cdot\overset{\delta-}{HF} \rightleftharpoons SF_3^+ + HF_2^-$$

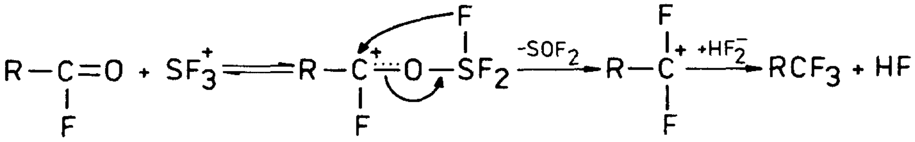
Competitive reaction:

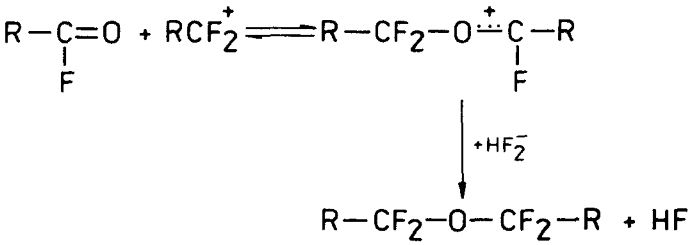


$$>C{=}O + HF \rightleftharpoons >\overset{\delta+}{C}{\cdots}O\cdots\overset{\delta-}{HF}$$

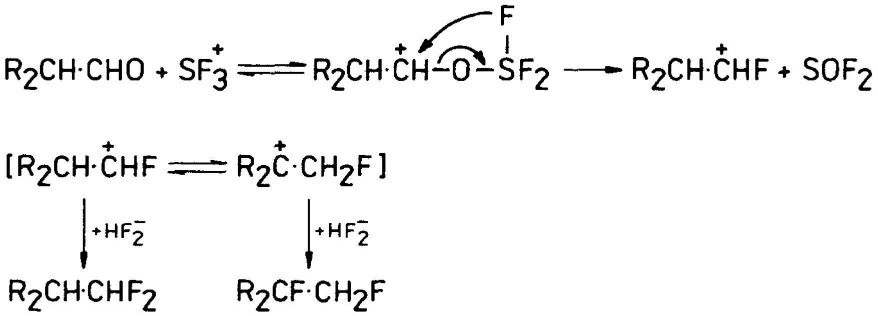
Consequently, we proposed a new mechanism [25] for the reaction of SF_4 with carbonyl compounds which involves electrophilic attack by the SF_3^+ cation on the oxygen atom of a carbonyl group to form a mesomeric cation which undergoes intramolecular rearrangement with subsequent elimination of thionyl fluoride to give fluorocarbonium ion. Neutralisation of this ion by fluoride yields a product in which the carbonyl oxygen has been replaced by two fluorines. When the carbonyl compounds is an acid fluoride, the corresponding trifluoromethyl derivative is formed.

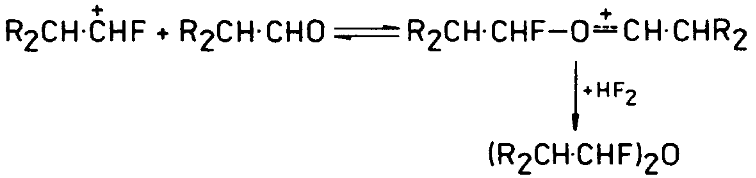
Furthermore, electrophilic attack of the fluorocarbonium ion on the second molecule of the carbonyl compound and neutralisation of the subsequent catio leads to the formation of fluoroethers.



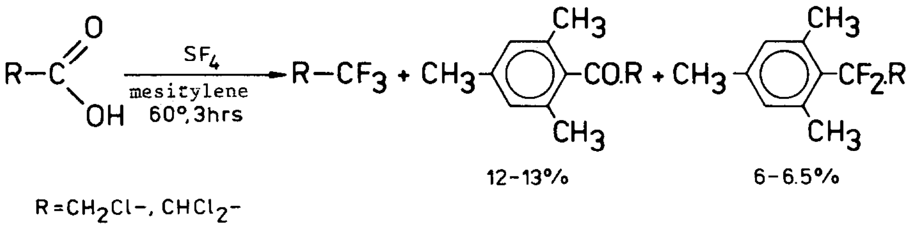


This mechanism easily explains formation of both "normal" and rearranged products in the reactions of SF_4 with aldehydes [22] . The primary fluorocarbonium ion, formed in the first step of the reaction, undergoes reversible isomerisation to a tertiary carbonium ion and neutralisation of both cations by fluoride ion gives 1,1- and 1,2-difluoroalkanes. The ratio of these products depends on the position of the equilibrium between primary and tertiary cations. Reaction of the fluorocarbonium ion with the parent aldehyde leads to the formation of bis (fluoroalkyl) ethers.



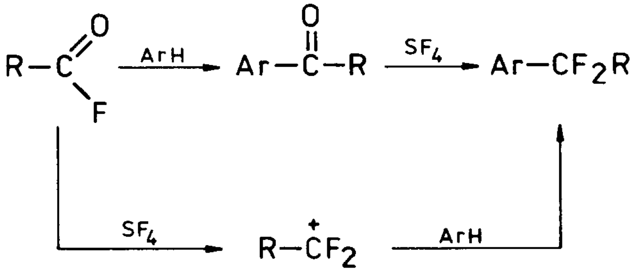


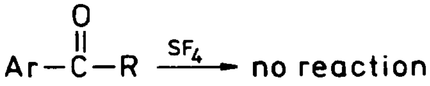
Participation of fluorocarbocations in the reactions of SF_4 with carbonyl compounds has been directly evidenced by trapping them on aromatic hydrocarbons [27] . Thus, reactions of haloacetic acids with SF_4 when carrie out in the presence of mesitylene gave, besides halotrifluoroethanes, the acylation products and fluoroalkylation products.



The ketones resulted simply from the acylation of mesitylene by acyl fluorides, which are formed in the first stage of the reaction of the acids with SF_4, but two ways may be considered for the formation of fluoroalkylated mesitylene.

- consecutive fluorination of the ketones with SF_4, or
- direct alkylation of the aromatic compound by a fluorocarbocation



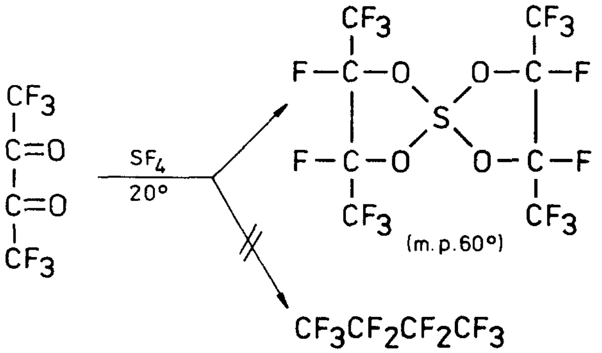


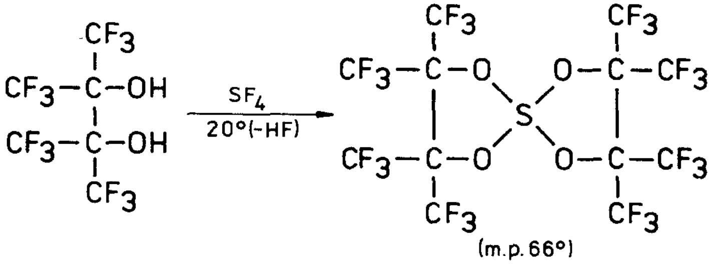
Ar = mesityl

Since, acylated mesitylenes when separately treated with SF_4 remained unaffected, the fluoroalkylated mesitylene must be formed via direct alkylation by the fluorocarbocation. Fluoroalkylated products were also obtained in the reactions of SF_4 with haloacetones and benzene [28

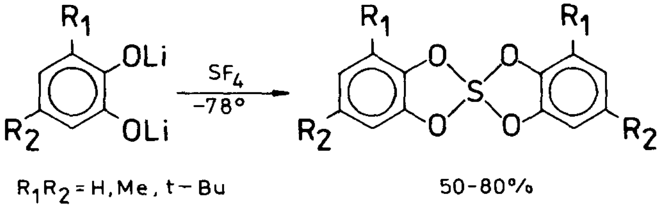
UNCONVENTIONAL REACTIONS WITH KETONES AND PHENOLS

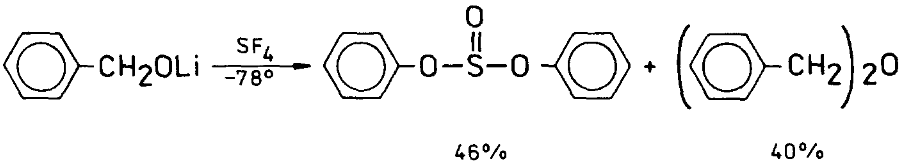
It is interesting to note that some perfluorinated diketones react with SF_4 in rather unconventional ways. Thus, perfluorobiacetyl gives quantitatively the crystalline 2 to 1 adduct, tetraoxyspirosulphurane, instead of the expected perfluoro-n-butane [29] . This reaction involves addition of SF_4 across the carbonyl groups. Similar results were obtained with perfluoropinacol, but in this case the substitution of four fluorine atoms in the SF_4 molecule occurs [30] .



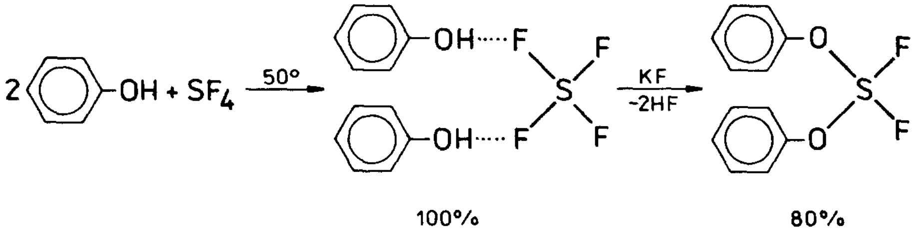


Ortho-phenols react with SF_4 in somewhat similar way to diketones. Low-temperature reactions of SF_4 with lithium salts of catechols provide a general route to non-fluorinated tetraoxysulphuranes. The lithium salts of benzyl alcohol under the some reaction conditions gave dibenzyl sulphite and dibenzyl ether [31] .



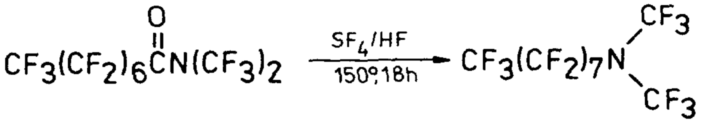


Phenol itself when treated with SF_4 at 50° forms an isolable 2 to 1 adduct, which in the presence of KF eliminates HF to give difluoro-diphenoxy sulphurane. This compound is stable under anhydrous conditions but easily hydrolyses to diphenylsulphite [32] .

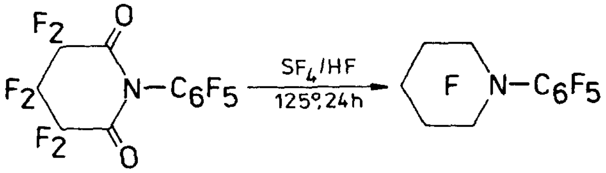


REACTIONS WITH AMIDES AND FORMAMIDES

The next class of compounds for which reactions with SF_4 have been recently developed are the amides and formamides. Using standard quality SF_4 and HF as a catalyst, only perfluorinated tertiary amides and imides could be successfully converted to the corresponding perfluoroamines, under rather drastic conditions [33] .



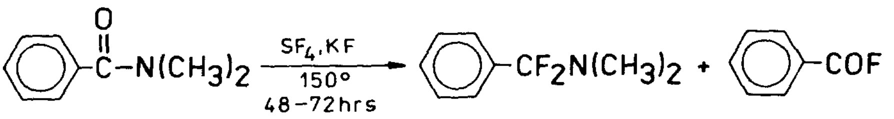
(78%)



(86%)

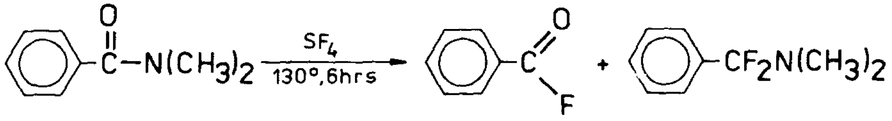
(10%)

Non-fluorinated amides having at least one nitrogen-hydrogen bond when treated with SF_4 undergo nitrogen-carbonyl group bond cleavage to give acyl fluorides and trifluoromethyl compounds. N,N-Dimethylbenzamide, which has no N-H bond, has been reported [2] to give poor and unreproducible yields of a product having the C-H bond retained, namely α,α -difluorobenzyl-dimethylamine. However, when the starting amide was contaminated by small amounts of benzoic acid, only benzoyl fluoride was obtained. It has been suggested that the C-N bond cleavage is catalysed by small amounts of HF which could be formed in the reaction of SF_4 with benzoic acid.



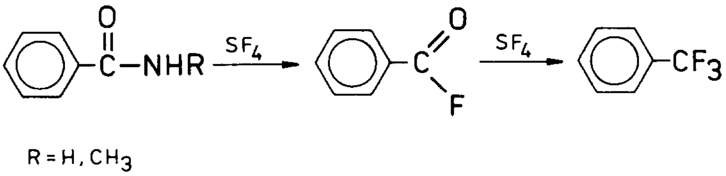
65–72%

minor product

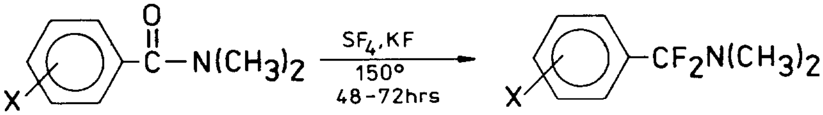


17%

Indeed, we have found [34] that if SF_4 is carefully purified from HF and, in order to bind any amounts of HF which may be formed due to the presence of benzoic acid and moisture, the reaction is conducted in the presence of dry KF, N,N,dimethylformamide gives high and reproducible yields of the expected α ,α -difluorobenzyl-dimethylamine.



Similarly, a number of <u>para</u>- and <u>meta</u>-substituted N,N-dimethylbenzamides were converted to the corresponding α ,α -difluorobenzyldimethylamines [34] . Electron withdrawing substituents in the benzene ring evident lower the yields.

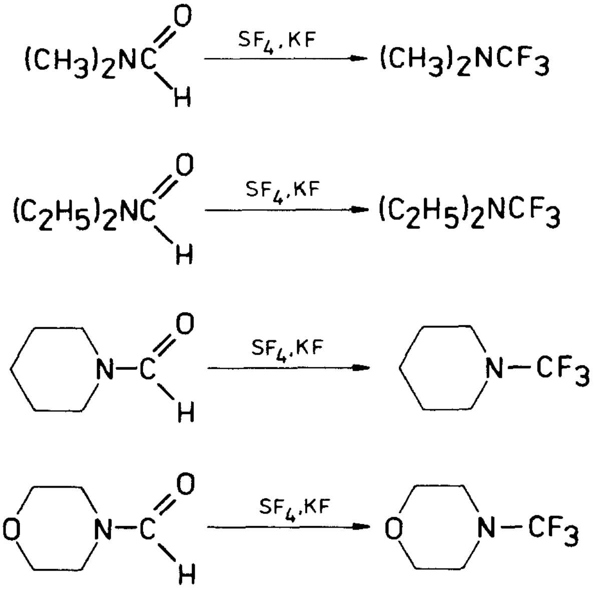


I

II

X	Yield of II (mole%)
p-CH_3O	75.0
p-CH_3	72.0
m-CH_3	90.0
H	71.0
p-Br	33.0
m-Br	31.0
p-CF_3	54.0
m-CF_3	20.0
p-NO_2	16.0

SF_4 reacts in a very unexpected way with formamides: instead of the expected difluoromethylamines, trifluoromethylamines are formed in near quantitative yields [35] . Thus, the formyl group is directly converted to the trifluoromethyl group. The reaction involves, besides fluorination of the carbonyl group, also fluorination of the C-H bond.

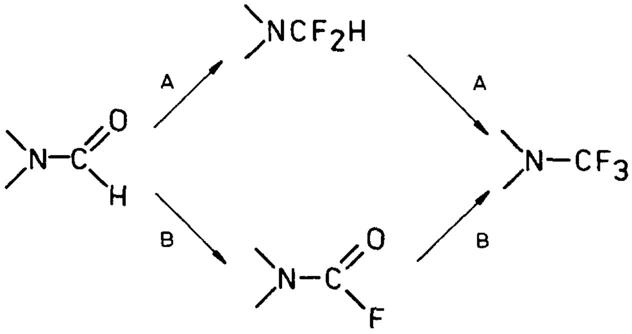


150°,48hrs. Yield~90%

Two alternative reaction pathways for the conversion of the formy group to the trifluoromethyl group may be considered:

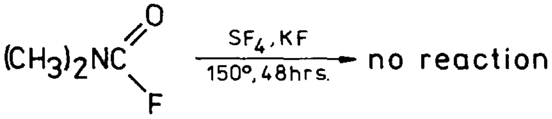
- fluorination of the carbonyl group followed by substitution of hydrogen in the CF_2H group of the intermediate difluoromethylamine (route A), or
- a substitution of the formyl hydrogen by fluorine prior to the fluorination of the carbonyl group in the intermediate N-fluoroformylamine (route B).

Separate reactions with both supposed intermediates have ruled out the route B and supported the route A which involves difluoromethylamine as the intermediate.



$$(CH_3)_2NCF_2H \xrightarrow[150^\circ, 48hrs]{SF_4, KF} (CH_3)_2NCF_3$$

100%



$$(CH_3)_2NC\overset{O}{\underset{F}{}} \xrightarrow[150^\circ, 48hrs.]{SF_4, KF} \text{no reaction}$$

Results of studies on the stoichiometry of the reaction of SF_4 with formamides and with the intermediate difluoromethylamines [35] have shown that fluorination of the C-H bond is a redox process as is shown on the scheme below. Hydrogen is abstracted as the hydride ion to form a resonance stabilised carbocation which then reacts with SF_4 to give trifluoromethylamine and SF_3^+ cation. This trifluorosulphuryl cation abstracts hydrogen from the substrate to give HF and sulphur difluoride, SF_2. Sulphur difluoride is known to be very unstable and immediately disproportionates to elemental sulphur and SF_4 [36].

$$2R_2NCHO + 3SF_4 \rightleftharpoons 2R_2NCF_3 + S + 2HF + 2SOF_2$$

$$2R_2NCF_2H + SF_4 \rightleftharpoons 2R_2NCF_3 + S + 2HF$$

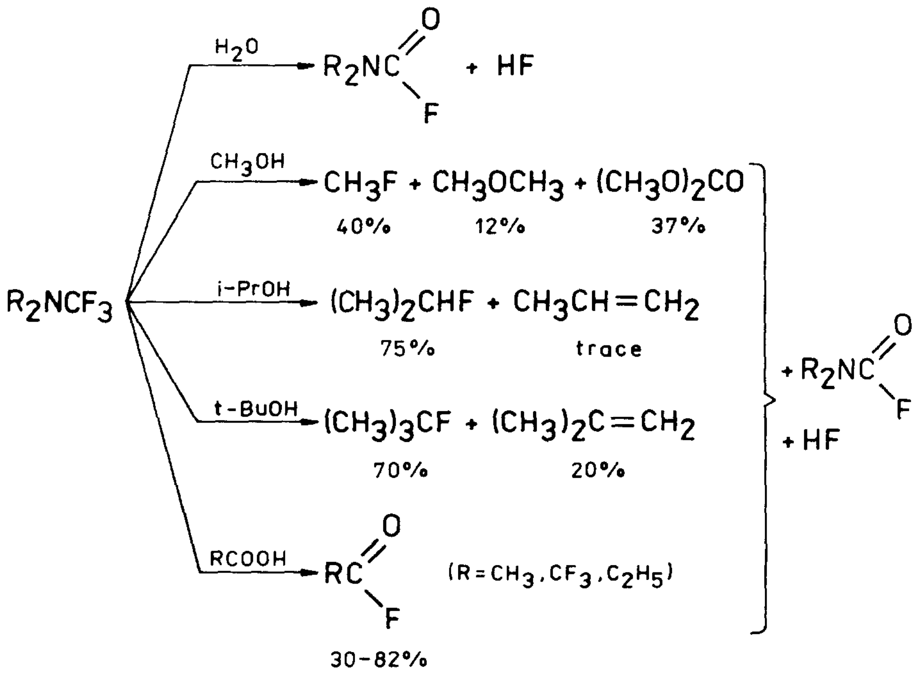
$$R_2NCF_2H \underset{+H^-}{\overset{-H^-}{\rightleftharpoons}} [R_2N\overset{+}{C}F_2 \longleftrightarrow R_2\overset{+}{N}{=}CF_2] \xrightarrow{SF_4}$$

$$\longrightarrow \underline{R_2NCF_3} + SF_3^+$$

$$SF_3^+ + H^-(R_2NCF_2H) \longrightarrow HF + SF_2$$

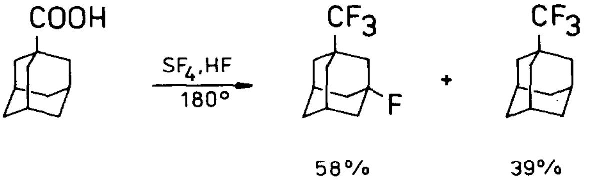
$$2SF_2 \longrightarrow S + SF_4$$

Trifluoromethylamines are useful agents for fluorination of alcohols to alkyl fluorides and carboxylic acids to acyl fluorides [37] . In this respect they resemble DAST and other fluoroalkylamino reagents (Yarovienko, Ishikawa reagents).

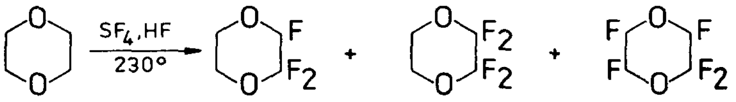


Finally, it is worth mentioning that recently an increasing number of papers have reported the fluorination of the carbon-hydrogen bond with SF_4.

Fluorination of 1-adamantancarboxylic acid gives, besides the expected 1-trifluoromethyladamantan, a high yield of 3-fluoro-1-trifluoromethyladamantan [38, 39] .



Dioxane reacts with SF_4 in the presence of HF to give a mixture of polyfluorodioxanes [40] . Fluorinated dioxane is also formed in the reaction of SF_4 with diglyme [41] .



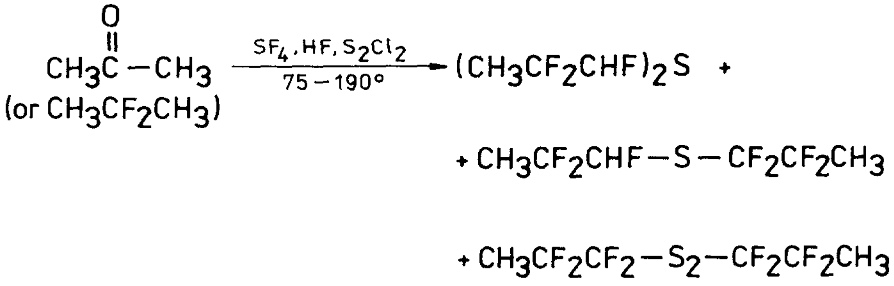
+ $CF_3CHF-O-CH_2CH_2F$

Treatment of bis (β -chloroethyl) ether with SF_4 in the presence of HF and sulphur monochloride, S_2Cl_2, gave a mixture of asymmetric ethers containing from three to five fluorine atom in the molecule [41] . Acetone or 2,2-difluoropropane, under similar conditions gave a mixture of polyfluorosulphides and polysulphides [42] .

$$(ClCH_2CH_2)_2O \xrightarrow[55-200^\circ]{SF_4,HF,S_2Cl_2} CF_2ClCHF-O-CH_2CH_2Cl$$

$$+\ CF_3CHF-O-CH_2CH_2Cl + CF_3CHF-O-CH_2CH_2F$$

Yield: 16÷63%



$$\underset{(\text{or } CH_3CF_2CH_3)}{CH_3\overset{\overset{\displaystyle O}{\|}}{C}-CH_3} \xrightarrow[75-190^\circ]{SF_4,HF,S_2Cl_2} (CH_3CF_2CHF)_2S + CH_3CF_2CHF-S-CF_2CF_2CH_3 + CH_3CF_2CF_2-S_2-CF_2CF_2CH_3$$

Yield: 55-90%

Also, a number of other reactions involving carbon-hydrogen bond fluorination have been reported [43,44] .

CONCLUSION

In this review I have focussed mostly on results which significantly differ from the standard reactions of SF_4 which lead to the well known simple substitution of oxygen functions by fluorine atoms. In conclusion, I would like to express the conviction that SF_4 is the most versatile of all fluorinating agents and that more new and unpredictable reactions involving SF_4 will be found in the future.

ACKNOWLEDGEMENTS

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