Use of hydrogen fluoride and its complexes with bases for introduction of fluorine atoms into organic molecules

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Annotation

The review summarizes and systematizes up-to-date data on fluorinating ability of anhydrous hydrogen fluoride and its complexes with bases of unsaturated organic compounds, alcohols, diazoketones, hydrazones and oximes of ketones, 3,3-dialkyl-1-aryltriazenes, aryldiazosulfides etc.. It contains an analysis of main achievements in use of anhydrous hydrogen fluoride as a fluorinating agent to produce ozone-friendly freons in gas and liquid phases both without catalysts and in the presence of latter. There has been examined factors influencing opening three-membered cycles containing oxygen and nitrogen atoms. The review contains examples of practical application of different groups of fluoroorganic compounds, rational methods of their production and their role in development of modern industry .

Contents

Introduction. Hydrogen fluoride as a basic stock substance in chemical industry.

1. Fluorination with anhydrous hydrogen fluoride and its complexes with bases of compounds from different classes.

1.1.Hydrofluorination of unsaturated compounds
1.1.1. Influence of anhydrous hydrogen fluoride on unsaturated compounds
1.1.2. Hydrofluorination of unsaturated compounds by hydrogen fluoride complexes with bases
1.1.3. Reactions of anhydrous hydrogen fluoride and its complexes containing bases with acetylene derivatives
1.1.4. Fluorination of alkenes with hydrogen fluoride in the presence of catalysts
1.1.5. Fluorination of unsaturated compounds with hydrogen fluoride in the presence of electrophilic reagents

2. Processes of replacement of functional groups with fluorine atoms.

2.2. Reactions with hydroxylamines, hydrazones and oximes of ketones.

The Bamberger rearrangement of N-arylhydroxylamine or arylazide under the effect of anhydrous hydrogen fluoride results in formation of 4-fluoroaniline [251,252].
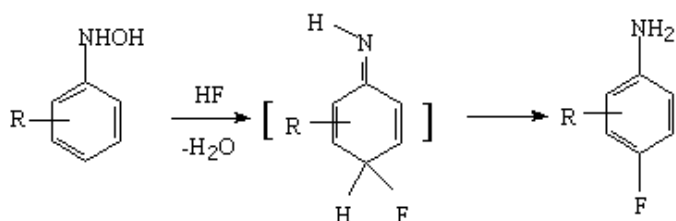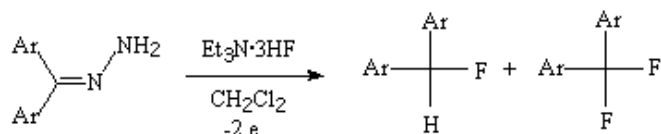

R = H (43%), 2-Me (40%), 3-Me (61%), 2-Cl (39%),
2-COOEt (29%)

The reduction of nitrobenzene (with bismuth or lead) in a medium of anhydrous hydrogen fluoride runs through an intermediate formation of arylhydroxylamines which convert to fluoroanilines in the hydrogen fluoride medium [253-255].

R	H	2-Me	3-Me	2-Cl	3-Cl	2-F	3-CF$_3$	3-CF$_3$
M	Bi	Pb	Pb	Pb	Pb	Bi	Bi	Bi
Yield, %	45	48	44	35	34	65	12	13

Hydrazones of ketones under the influence of 60% HF/Py or 59% HF/poly-4-vinylpyridine in the presence of N-bromsuccinimide convert to hem-difluoro-derivatives [256]. In case of oximes of ketones the presence of chlorine is necessary, therefore a mixture of products is obtained (hem-dichloro-, chlorofluoro- and difluoro-derivatives) [257].

An electrochemical process (1.3 mA/cm2) can be used for hydrazones of diarylketones that makes possible to obtain a monofluoro-derivative only [258].

$$Ar_2C=N-NH_2 \xrightarrow[\substack{CH_2Cl_2 \\ -2e}]{Et_3N \cdot 3HF} Ar-\underset{H}{\overset{Ar}{C}}-F \ + \ Ar-\underset{F}{\overset{Ar}{C}}-F$$

Ar	Yield, %	
$4\text{-}ClC_6H_4$	40	0
$4\text{-}FC_6H_4$	63	8
Ph	95	3
$4\text{-}Tol$	16	1

2.3. Reactions with diazoketones, hydrazones and oximes of ketones.

Reactions of diazoketones with 70% HF/Py system in the presence of a source of cations of a haloid give appropriate fluoroketones or fluoroparaffines [2]. Diazaalkanes, diazaketones and diazaacetates can be fluorinated at 0^oC under the effect of this system in 30-95% yield [2,259].
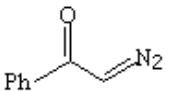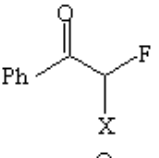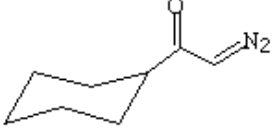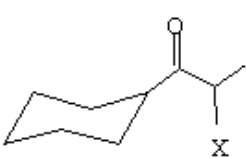
$R = Et, C_6H_{11}, Ph, OEt$
$x = H, Cl, Br, I$
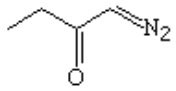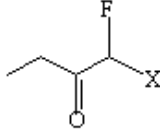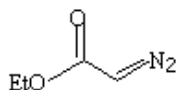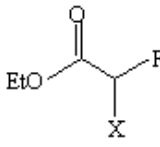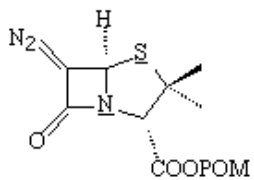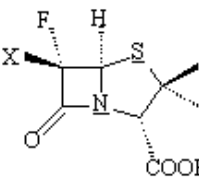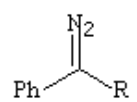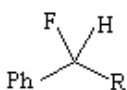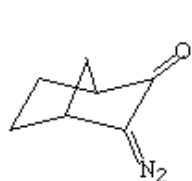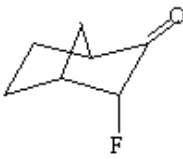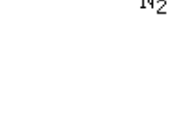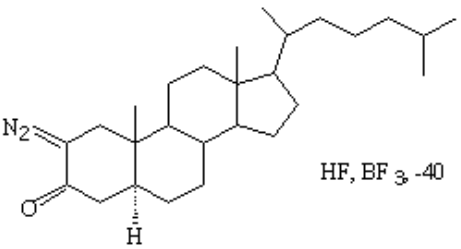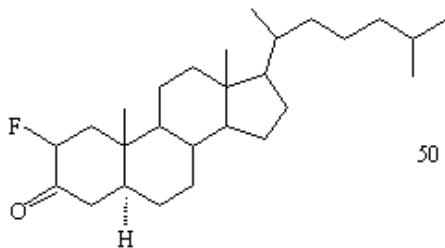
R	X	Conditions	Yield, %
Ph	H	$Et_2O, 0^oC$	51
Ph	Br	$NBS, -15^o\tilde{N}$	63
OEt	Br	$NBS, Et_2O, 0^oC$	50

where **NBS**- bromosuccinamide

The process α,-hydrofluorination in the presence of a source of haloid cations, N-bromosuccinamide for example, in HF/Py system runs according to the halofluorination type (Table19) [2,259]. α-Fluoro-α-haloethers, α-fluoroketones, α-fluoroethers are obtained. So, benzyl fluoride was produced in 70% yield according to this method.

β-Bromo- and β-chloro-α-fluoro*penicilates* were obtained from appropriate diazo-compounds and present interesting products (Table 19). A mixture of endo-3-fluorobornan-2-one (30%) and a product of exo-2-fluorobornan-7-one (52%) was obtained from norbornane diazo-compound. 2-Diazocholestan-3-one under the effect of HF/Py system converts to an appropriate fluoride in 50% yield (table 19).

Table 19. *Reaction of diazo compounds with 70% HF/Py in the presence of N-halosuccinimides.*

Diazo compound	Reagent/conditions	Product	Yield,%	Ref.
Ph–CO–CH=N₂ (PhCOCHN₂)	HF/Py, 0 °C	Ph–CO–CHF–X	X = Cl 49; Br 63; I 62; H 32	2,3
cyclohexyl–CO–CH=N₂	HF/Py, 0 °C	cyclohexyl–CO–CHF–X (with CH₃)	X = Cl 95; Br 38; I 80; H 50	2
CH₃CH₂–CO–CH=N₂	HF/Py, 0 °C	CH₃CH₂–CO–CHF–X	X = Cl 50; Br 32; I 80; H 40	2
EtO–CO–CH=N₂	HF/Py, 0 °C	EtO–CO–CHF–X	X = Cl 30; Br 50; I 50; H 40	2,259
Ph–CH₂–CH=N₂ (Ph~N₂)	HF/Py, 0 °C	Ph–CH₂–CH₂F (Ph~F)	70	2,259
penam diazo, H, S, N, O, COOPOM (N₂=)	70% HF/Py, 0 °C NBS, CH₂Cl₂, Bu₄N⁺HF₂⁻, −40 °C r.t., 4 h; −23 °C r.t., 48 h	penam, F, H, S, X, N, O, COOPOM	X = Br 40; X = Cl 25	260-262; 261
Ph–C(=N₂)–R	aq. KHF₂ Bu₄N⁺ClO₄⁻ CH₂Cl₂, H₂O, r.t., 48 h	Ph–CF(H)–R	R = Ph 52; H 14	263
bicyclic diazo ketone (N₂)	H₂O, CH₂Cl₂, −10 °C	bicyclic fluoro ketone (F)	30	264
		bicyclic fluoro ketone (F) isomer	52	
steroid 2-diazo-3-one (N₂=, O, H)	HF, BF₃, −40 °C	2-fluoro steroid-3-one (F, O, H)	50	265

POM = (CH₃)₃CCOCH₂

3,3-Dialkyl-1-aryltriazenes have been known for a long time. They are obtained by condesation of aryldiazonium salt with secondary dialkylamines. It has been found that under the further influence of hydrogen fluoride in an anhydrous medium there was generated aryldiazonium salt which composition runs smoothly to for appropriate fluorobenzenes [266-268].

$$ArNO_2 \longrightarrow ArNH_2 \longrightarrow ArN_2^+ \cdot Cl^- \xrightarrow{R_2NH} ArN=N\text{-}NR_2$$

$$ArN=NNR_2 \xrightarrow{HF} [ArN_2^+ \cdot F^- + R_2NH_2^+ \cdot F^-] \longrightarrow ArF$$
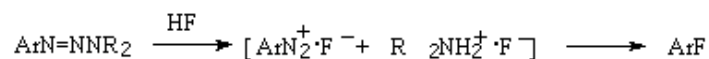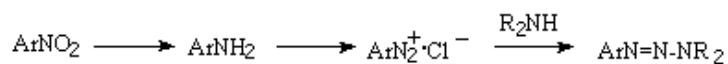
For the first time this approach was proposed by Wallach. But only now it has become an important method to produce fluoroaromatic compounds and fluorine-containing natural compounds. In case of using anhydrous hydrogen fluoride for decomposition of 3,3-dialkyl-1-aryltriazenes the nature of the solvent used is of great importance. So, a mixture of products is obtained in tetrahydrofuran, radical processes (dimerization, reduction) are realised in methene chloride, products of fluorination are obtained in acetic acid (table 20)[269].

Table 20. *Conversion of 3,3-dialkyl-1-aryltriazenes to fluoroaromatic compounds under the influence of HF/Py system [269].*
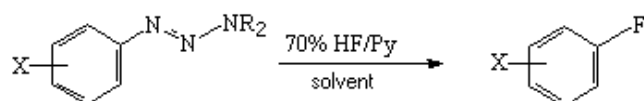
X	R_2	Solvent	T°C	Time, min	Yield, %
H	-(CH$_2$)$_5$-	HOAc	18	15	97
4-OMe	-(CH$_2$)$_5$-	HOAc	18	60	75
2-COOH	Me$_2$	HOAc	45	20	89
3-COOH	-(CH$_2$)$_5$-		45	60	96
4-COOH	-(CH$_2$)$_5$-		18	30	95
4-COOH	Me$_2$	HOAc, Et$_2$O	18	20	90
2,4,6-Me$_3$	Me$_2$		30	60	97
2,4-Me$_2$	-(CH$_2$)$_5$-	DME	60	120	20
2-OMe	-(CH$_2$)$_5$-	HOAc	18	15	0
2-OTs	Me$_2$		18	60	79
4-Cl	-(CH$_2$)$_5$-		50	60	35
4-NO$_2$	Me$_2$		18	120	0
3-CH$_2$C(COOEt)$_2$NHAc	Me$_2$	HOAc	18	60	76
d	Me$_2$	HOAc	18	30	20
c	Me$_2$	HOAc	18	20	85
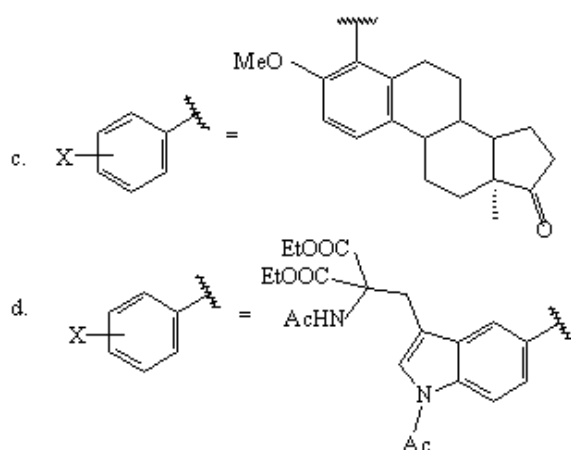
Aromatic and haloaromatic compounds are found the best solvents for this reaction [270]. Against a background of N=N-NH$_2$ group the presence of the OH group in the 4-position of the benzene ring does not impede the fluorination process followed by thermal or photochemical decomposition resulting in formation of 4-fluorophenol.

HO—⟨benzene⟩—N=N—NMe2 →(60 % HF/Py) HO—⟨benzene⟩—F

140 °C, 1 h, yield 29 %
UV, 20 °C, 6 h, yield 45 %
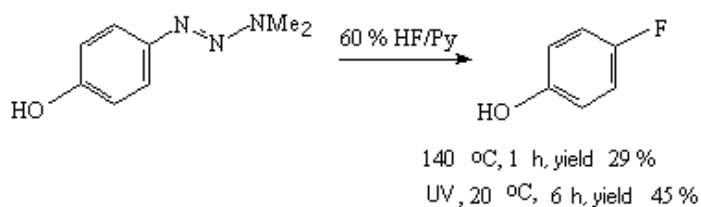
If hydrogen fluoride labeled with ^{18}F isotope is used in the stage of decomposition of intermediate diazo-salt then fluoroaromatic compounds labelled with ^{18}F isotope are obtained, [^{18}F] haloperidol for example. It is particularly important for production of preparations for positron tomography [271].
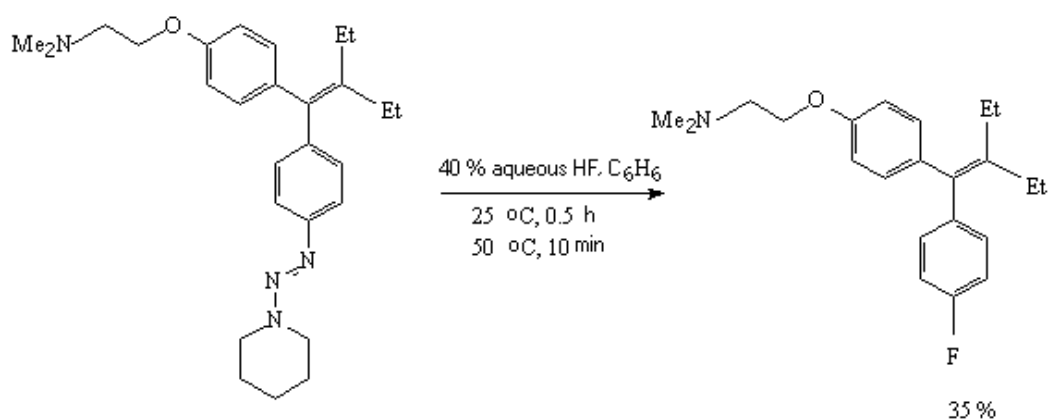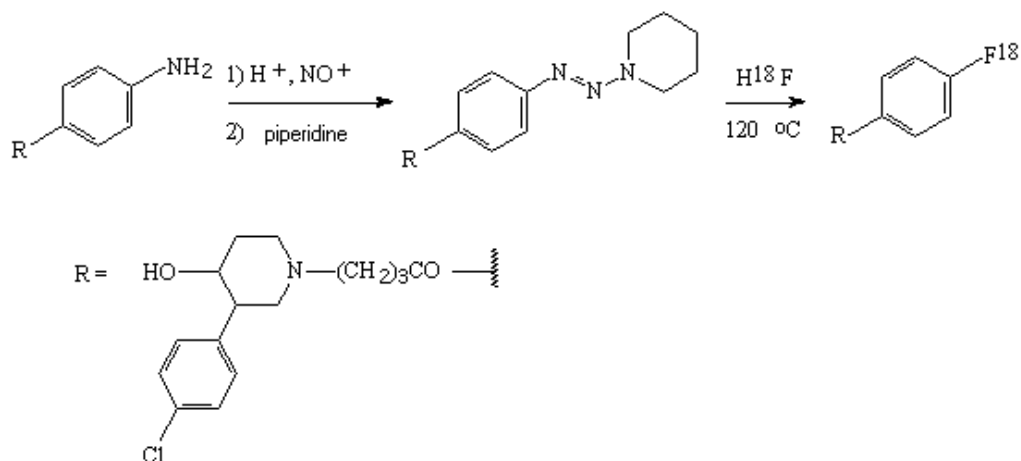
Also, aqueous hydrogen fluoride can be used for decomposition of aromatic triazenes, here fluoro-derivatives are obtained in a low yield.

R—⟨benzene⟩—NH2 →(1) H+, NO+ 2) piperidine) R—⟨benzene⟩—N=N—N⟨piperidine⟩ →(H^{18}F, 120 °C) R—⟨benzene⟩—F^{18}

R = HO—⟨piperidine ring with 4-chlorophenyl⟩—N—(CH2)3CO—

Me2N—CH2CH2—O—⟨benzene⟩—C(=C(Et)Et)—⟨benzene⟩—N=N—N⟨piperidine⟩ →(40 % aqueous HF, C6H6; 25 °C, 0.5 h; 50 °C, 10 min) Me2N—CH2CH2—O—⟨benzene⟩—C(=C(Et)Et)—⟨benzene⟩—F

35 %

For example, dimethyl ether of 2-fluorohexestrol **18** [270] is obtained under the effect of hydrogen fluoride (anhydrous HF, aqueous HF, HF/Py system) on piperidintriazene **19** in various solvents (tetrahydrofuran, benzene, methene chloride, acetic acid) [270].

→(40 % aqueous HF, C6H6; 25 °C, 0.5 h; 50 °C, 10 min)

19   **18**   41 %

An important alternative for fluorobenzene production is decomposition of 3,3-dialkyl-1-aryltriazenes **20** and decomposition of aryldiazosulfides **21** in the presence of silver ions (AgF or AgNO$_3$) which is realised at a

NaNO₂ — shown as $NaNO_2$
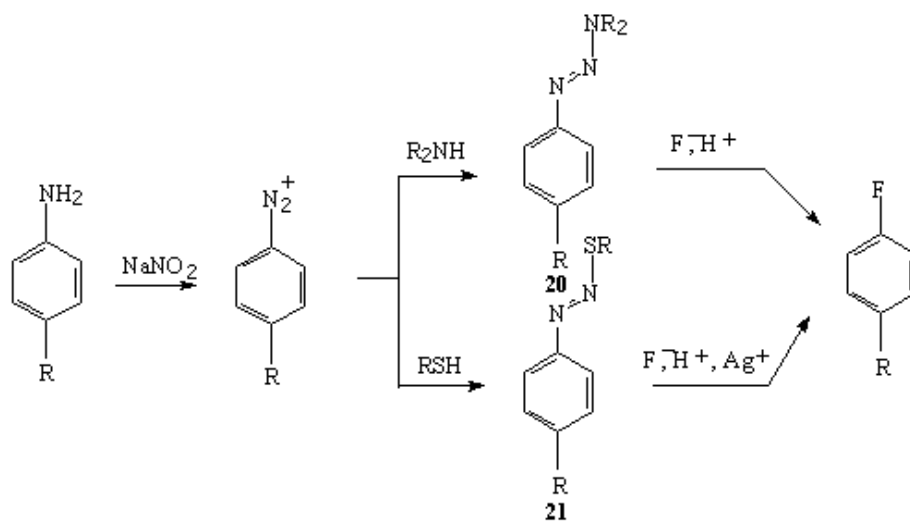
Table 21. *Decomposition of aryldiazosulfides to fluorobenzenes promoted by salts of monovalent silver [272].*

HF/Py, AgNO₃
PhMe, 90 °C, 30 min

27 → 28 + 29 + another products
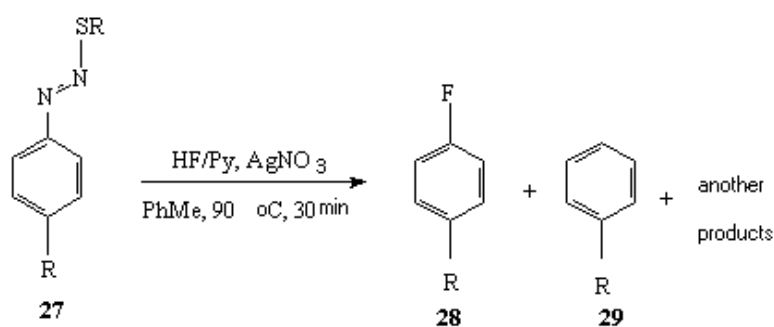
F⁻(equivalent)	Yield, %					
	R=Ac		R=Bu		R=OMe	
	28	**29**	**28**	**29**	**28**	**29**
20	71	4	39	54	14	-
5	44	10	38	42	11	9
1	29	22	17	29	9	8
0,5	39	22	25	27	12	7
0,1	52	25	32	24	21	8

3' -fluorophenylalanine **22** [269], 5' - fluorotryptophan **23** [269], 4-fluoroestron **24** [269], 2' - fluorohexestrol **25** [270] and fluoro*tamoxyphen* **26.**The following biologically active compounds can be obtained according to this way:

22   23   24

25 **26**
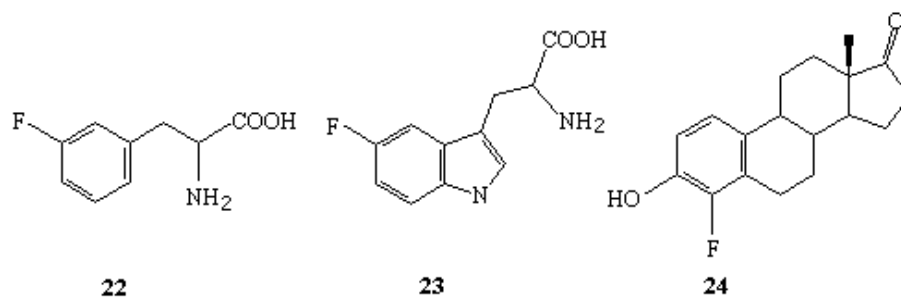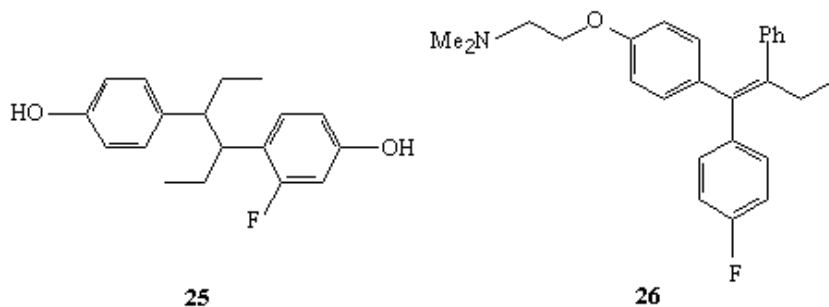
The action of Bu$_4$NF*2HF and HF/Py systems on aryl and alkyl ethers of xanthic acid in CH$_2$Cl$_2$ in the presence of N-bromosuccinimide results in formation of trifluoromethyl ethers [273-275].

$$X = 4\text{-Me},4\text{-}^nPr,4\text{-Br},4\text{-MeO},4\text{-PhCH}_2O,$$
$$3\text{-MeOOC},$$
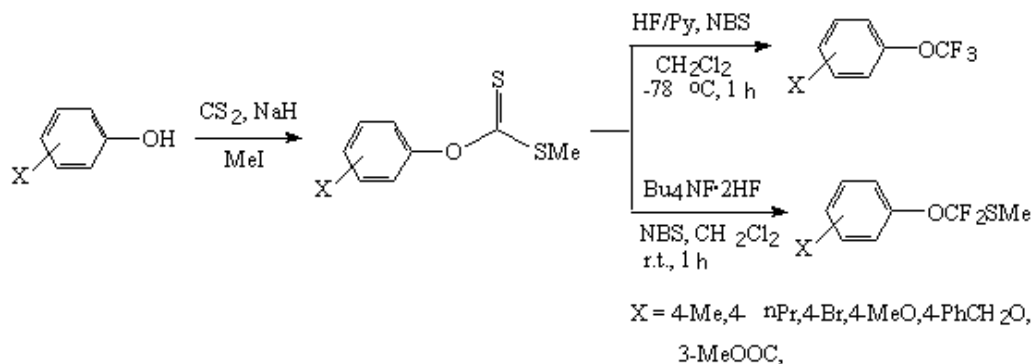
In case of ethers of dithiocarbamic acid these systems result in formation of tertiary amines containing one trifluoromethyl group [274].

$$R^1 = XC_6H_4 \ (X = 4\text{-Cl}, 4\text{-F}, 4\text{-MeO}, 4\text{-CN}, 4\text{-NO}_2, 3\text{-MeO}), PhCH_2$$
$$R^2 = PhCH_2, Me, 3\text{-MeC}_6H_4$$

2.4. Exchange reactions of haloids running under the influence of hydrogen fluoride in the presence of catalysts.
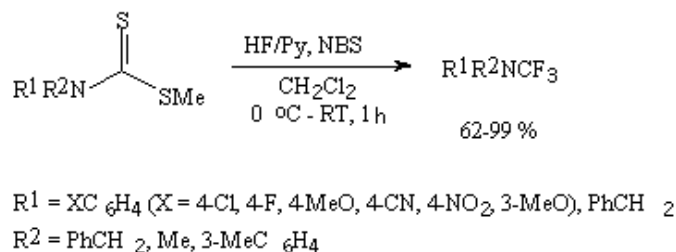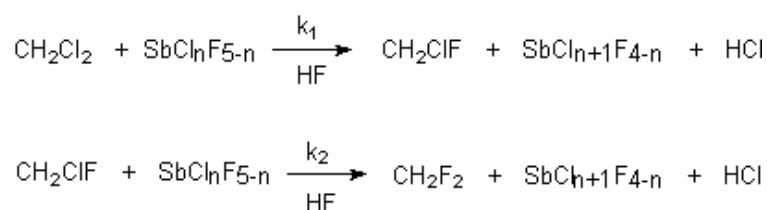
An important aspect of synthesis of ozone-safety freons are processes of fluorinaton of halogenated hydrocarbons by means of anhydrous hydrogen fluoride in the presence of the following substances: oxides or fluorides of indium, chromium at 300-500^{0}C [276], chrome-gallium catalysts [277], chromium oxide treated with Ru and Pt [278], chromium precipitated on aluminium oxide [279, 280], zinc, its oxide and fluoride [281], chromium chloride [282]. The process is carried our in gas phase over catalyst.. But catalysts based on chloro-fluorides of antimony were found the most effective [283-286a]. A method to obtain difluoromethane by fluorination of methylene chloride with anhydrous HF in the presence of antimony chlorides runs according to the following scheme:

$$CH_2Cl_2 + SbCl_nF_{5-n} \xrightarrow[HF]{k_1} CH_2ClF + SbCl_{n+1}F_{4-n} + HCl$$

$$CH_2ClF + SbCl_nF_{5-n} \xrightarrow[HF]{k_2} CH_2F_2 + SbCl_{n+1}F_{4-n} + HCl$$

The reaction rate is described by the equation:

$$-rCH_2CH_2 = 2.2 \times 10^5 \exp(5.8 \times 10^7/RT) \times C_{CH2Cl2} \times C_k$$

$-rCH_2CH_2 = 8.3*10^6 \exp(6.2*10^7/RT) * C_{CH2ClF} * C_k$

Where C_{CH2Cl2}, C_{CH2ClF}, C_k are concentrations of CH_2Cl_2, CH_2ClF and catalysts accordingly.

Processes of production CH_2F_2 from CH_2Cl_2 by the effect of HF over catalyst are carried out at a temperature of 250^oC and above it, the yield is 80% at a contact time >20sec {186a, 286b].

Similarly under effect of HF on chloroform in the presence of fluorides of Cr, Al, In, Bi at 100-150^oC a mixture of products CHF_2Cl, CHF_3, $CHFCl_2$ is obtained, the conversion is above 98% [287]. The following compounds as CF_3CH_2Cl, CCl_4, CH_2Cl_2, CH_3Cl, CCl_2F_2, C_2Cl_4 under the influence of anhydrous hydrogen fluoride in the presence of catalyst (partially fluorinated chromium oxide which is treated with Ru or Pt in amount of 0.61-10 mole%) at 290-380^oC and a mole ratio of HF/halogenated hydrocarbon within a range of 1:10 to 10:1 give partially fluorinated hydrocarbons [288]. For example, 1,1,1,2-tetrafluoroethane is obtained, it is used as a refrigerant.

1,1,1,3,3,3-Hexafluoroisopropylfluoromethyl ether, an important inhalation anesthetic, is obtained under the influence of $Et_2NMe*HF$ [228a] or ($^iPr)_2(Et)N$ HF [288b,c] complexes on 1,1,1,3,3,3-hexafluoroisopropylchloromethyl ether at a temperature of 40-80^oC. Similarly other subfluorinated ethers are obtained [288d].

R-O-CHXCl $\xrightarrow[\text{iPr}_2\text{EtN}\cdot \text{HF}]{\text{Et}_3\text{N}\cdot \text{HF}}$ R-O-CHXF

(или)
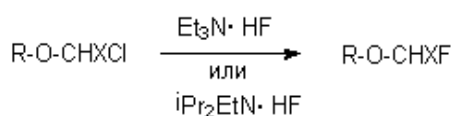
Reagent	R	X	Yield, %
$^iPr)_2(Et)N^* HF$	$(CF_3)_2CH$	H	95
	CF_3CHF	H	78
	CF_3CHCF_2	H	81
	CH_3CH_2	H	65
	CCl_2FCF_2	H	65
	$CHClFCF_2$	H	66
	$(CF_3)_2CH$	F	66
	CF_3CHCl	F	67
$Et_{23}N^*HF$	CF_3CHF	H	52
	CF_3CHFCF_2	H	35
	CH_3CH_2	H	traces

This method was extended for ethane series, for example for synthesis of 1,1-difluoroethane, 1,1,2-trifluoroethane, 1,1,1,2-tetrafluoroethane, pentafluoroethane. They have been found wide application in modern industry as refrigerants, propellents, fire extinguishing agents, reagents for plasmochemical manufacturing super-large integrated circuits, gas dielectrics etc.. Thus, chromomagnesium catalyst was found effective in producing 1,1,1,2-tetrafluoroethane from 1,1,1-trifluoro-2-chloroethane in gas phase [289], 1,1,1,2,2-pentafluoroethane from 1,1,1-trifluoro-2,2-dichloroethane [290], pentafluoroethane from tetrachloroethane [291], 1,1,1,2-tetrafluoroethane and pentafluoroethane from 2-chloro-1,1,1-trifluoroethane [292]. Cr_2O_3 may be used as a catalyst, the process runs at 300-500^oC resulting in hexafluoroethane in high yield and selectivity [293]. $SbCl_5$ acts similarly in liquid phase giving 1,1,1-trifluoroethane from 1-chloro-1,1-difluoroethane [294]. In these cases a role of catalyst reduces to HCl elimination and formation of a derivative of ethylene which is subjected to hydrofluorination under the effect of anhydrous hydrogen fluoride. $SnCl_4$-$B(OEt)_3$ system may be used as a catalyst [295].

If the molecule contains several chlorine atoms then the process may be carried out under conditions of replacement of one chlorine atom only. So, 1,1,1-trichloroethane and HF at 80-100^oC and pressure of 10.5-12 kg/cm^2 give 1,1-dichloro-1-fluoroethane [296].

It is of interest that in case of fluorine-containing ethanes carrying out the process with HF in the presence of chromium compounds results in an increase of the number of fluorine atoms in the molecule. Thus, interaction of

1,1,1,2-tetrafluoroethane with HF at $302^{\circ}C$ gives 1,1,1,2,2-pentafluoroethane. But the yield of the desired product is too low (1.3%)[297].

The method has been also extended for propane and butane series. So, from hexachloropropane under the effect of HF and in the presence of catalyst $SbCl_nF_{5-n}$ (n=1-5) at $50-100^{\circ}C$ there were produced 1-chloro-1,1,3,3,3-pentafluoropropane and 1,1,1,3,3-pentafluoropropane [298]. Similarly when the following substances as halides of molybdenum, tantalum, niobium [299,300], $TiCl_4$ [301], halides of the IV B and V B groups [302,303], $SbCl_5$ [304] were used as catalysts in a reaction with 1,1,1,3,3-pentachloeopropane (freon 240fa) at $100-150^{\circ}C$ there was obtained 1,1,1,3,3-pentafluoropropane (freon 245 fa) in a yield above 90%. 1,1,1,2,3,3,3-Heptafluoropropane was obtained in hydrofluorination of 1,1,1,2,3,3,3-heptachloropropane over catalyst [305] and also in hydrofluorination of hexafluoropropane in gas phase over a fluorinated catalyst (fluorides of aluminium and chromium) [306].

Hydrofluorination of chlorofluorobutanes $CCl_aCF_{3-a}CH_2CCl_bF_{2-b}CH_3$under the influence of HF results in formation of 1,1,1,3,3-pentafluorobutane [307,308].

The given examples show that the parameters determining the course of hydrofluorination processes are caused by a wider interaction spectrum than interaction of organic substrate with hydrogen fluoride, in particular by processes of generation of unsaturated compounds and their interaction with anhydrous hydrogen fluoride [309-314].