

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 .

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3.2. Opening nitrogen-containing three-membered heterocycles.

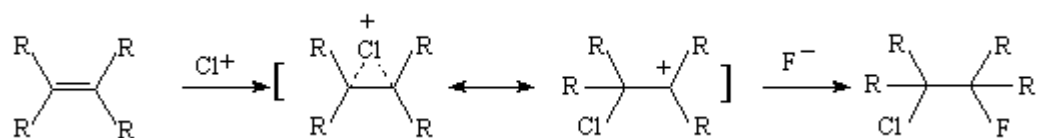
Conclusion.

1.1.5. Fluorination of unsaturated compounds by hydrogen fluoride in the presence of electrophilic reagents.

Addition of a positive particle X^+ (Cl^+ , Br^+ , I^+) of a halogen in the presence of a fluoride-ion source to form a product of trans-addition of X-F elements to the double bond of the olefin is a selective reaction for a wide range of unsaturated compounds. The source of X^+ cation is mainly such reagents as halogen-amides (N-bromosuccinamide, N-bromoacetamide etc.) or free halogen (I_2 or Br_2). The fluoride-ion source is usually anhydrous hydrogen fluoride or its complexes with bases.

Above there were mentioned examples of the use of anhydrous hydrogen fluoride and its complexes for implementation of the hydrofluorination process. The latter runs in two stages: at first hydrogen fluoride as an acid protonates an unsaturated organic compound or a substrate containing a heteroatom with unpaired electron couple to generate a cationoid particle. Further an attack of fluoride ion towards the carbon atom with the greatest positive charge takes place. This process scheme may be realized otherwise. At first due to interaction of electrophilic agents with the multiple bond or due to a different influence on the bond a carbanion is generated and hydrogen fluoride or its complex with a base then becomes the fluoride-ion source. Introduction of fluorine into the organic molecule takes place in this case also but a different functional group is involved. It should be noted that this approach was found very productive and was widely used. This review presents only examples illustrating opportunities of using hydrogen fluoride and its complexes with bases in such a way.

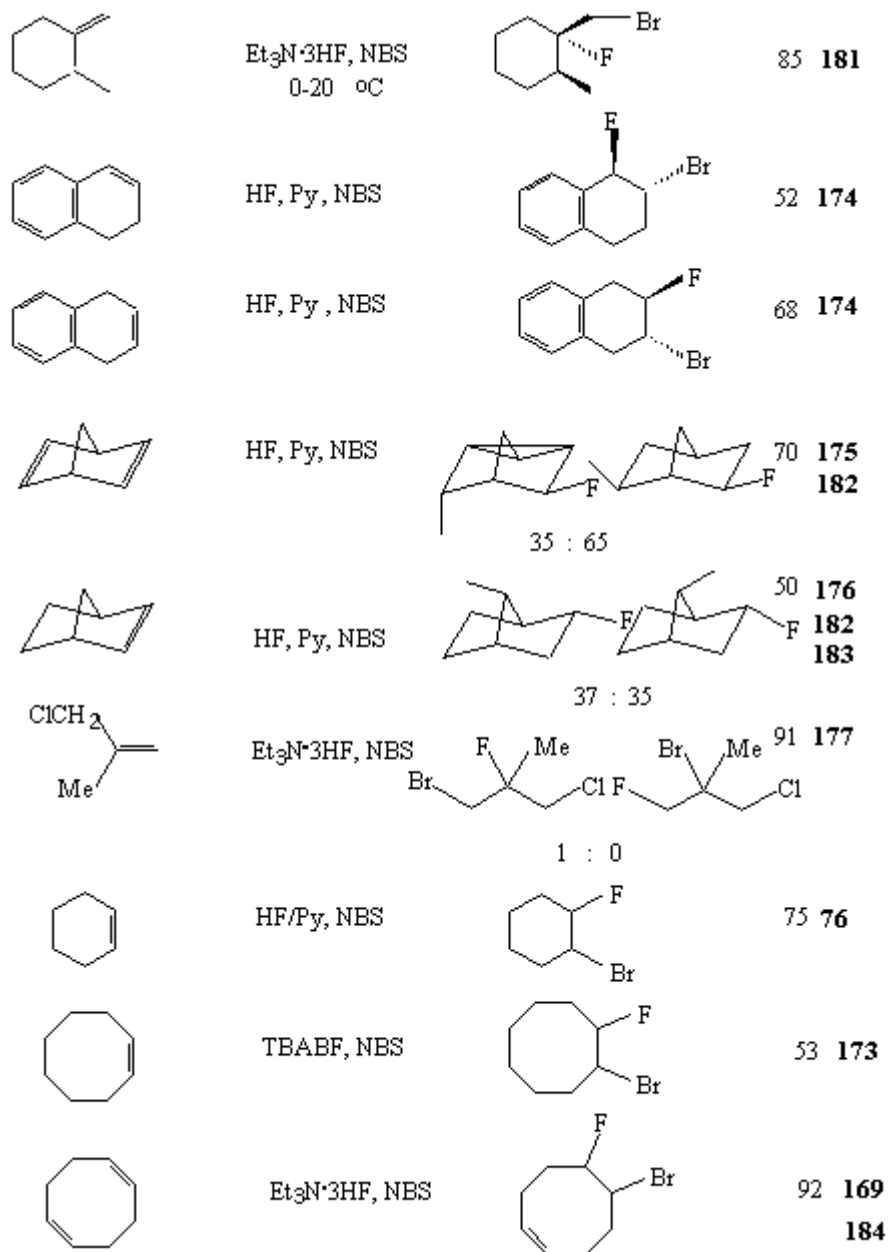
Generally the reaction runs according to the following scheme. At first the cationoid particle reacts with the multiple bond to form halogenoid cation which is subjected to the attack of the fluoride-ion to give, as a rule, a product of *anti-addition*. So, in case of interaction of N-chlorosuccinamide in a medium of anhydrous hydrogen fluoride with alkenes there is formed α -chloro- β -fluoroalkane.



AgF, BF₃ etc. are often used in these processes as catalysts. Et₃N/3HF system is an universal source of fluoride-ion in reactions of halogenfluorination of unsaturated hydrocarbons [168]. Table 10 presents the examples of stereo- and regio-selective synthesis of organic compounds by chlorofluorination and bromo-fluorination of alkenes.

Table 10. Halogenfluorination of alkenes

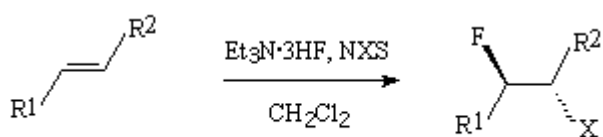
Substance	Conditions	Products	Yield,% Ref.
	Et ₃ N·3HF, NCS 0-20 °C		82 169
	TBABF, NCS 20 °C		47 173
	Et ₃ N·3HF, NCS 0-20 °C		96 169
	Et ₃ N·3HF, NCS 0-20 °C		92 169
	HF, Py, NCS 20 °C		48 174
	HF, Py, NCS 20 °C		60 174
	HF, Py, NCS 0-15 °C		60 175
	HF, Py, NCS 0-15 °C		52 176
	Et ₃ N·3HF, NCS 0 °C		94 177
	HF/Py, NCS CCl ₄ , THF		60 188



Substance	Conditions	Products	Yield,%	References
CH ₂ =CH ₂	HF/Py, NBS	CH ₂ FCH ₂ Br	30	179
MeCH=CH ₂	HF/Py, NBS	MeCHFCH ₂ Br	40	179
Me ₂ C=CH ₂	HF/Py, NBS	Me ₂ CFCH ₂ Br	85	179
BuCH=CH ₂	HF/Py, NBS	BuCHFCH ₂ Br	90	179
(Z)MeCH=CHMe	HF/Py, NBS	MeCHFCHBrMe	46	180
(Z)EtCH=CHEt	HF/Py, NBS	EtCHFCHBrEt	58	180
PhCH=CH ₂	HF/Py, NBS	PhCHFCH ₂ Br	53	185
BnCH=CH ₂	HF/Py, NBS	BnCHFCH ₂ Br	74	186
Ph ₂ C=CH ₂	HF/Py, NBS	Ph ₂ CFCH ₂ Br	78	182,187
Ph ₂ C=CHMe	HF/Py, NBS	Ph ₂ CFCHBrMe	68	185
MePhC=CH ₂	HF/Py, NBS	PhCMeFCH ₂ Br	72	185

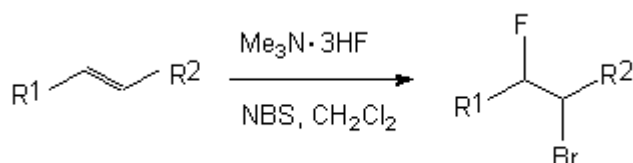
MePhC=CH ₂	Et ₃ N·3HF, NBS	PhCMeFCH ₂ Br	97	185
CICH=CMeCOOMe	HF, NBS	CHCIFCBrMeCOOMe	57	186
CICH=CFCOOMe	HF, NBS	CHFClCBrFCOOMe	39	186
CICH=CCICOOMe	HF, NBS	CHFClCBrCICOOMe	41	186
PhCCI=CHCOOEt	HF/Py, NBS	PhCCIFCHBrCOOEt		188
BzCH=CHPh	HF/Py, NBS	BzCHBrCHPh	40	189

A combination of Et₃N/3HF system and N-halosuccinimides was found an effective halofluorinating reagent of alkenes [169,170]. The reaction runs at room temperature in glassware. The anti-addition has a stereospecific character.



X = Cl, Br, I

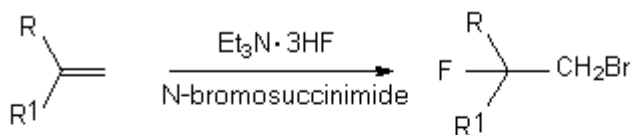
It has been shown [171] that the fluorinating agent being a complex of trialkylamine/HF (for example Me₃N/3HF in combination with N-bromosuccinimide (NBS)) in reactions with styrenes is more effective in comparison with Et₃N/3HF and gives bromofluorination products according to Markovnikov law with high regioselectivity.



R1	Ph	4-ClPh	Ph	C ₄ H ₉
R2	H	H	Me	H
Yield, %	96	98	92	95
Regioisomers	>99:1	>99:1	>99:1	95:5

In case of terminal aliphatic alkenes, hexene for example, the regioselectivity decreases a little at transition from Me₃N/ 3HF (95:5) system to Et₃N/3HF (87:13) system.

The high regioselectivity takes place in bromofluorination of terminal olefins when Et₃N 3HF complex is used in the presence of N-bromosuccinimide [172] The yield of the products is almost quantitative.

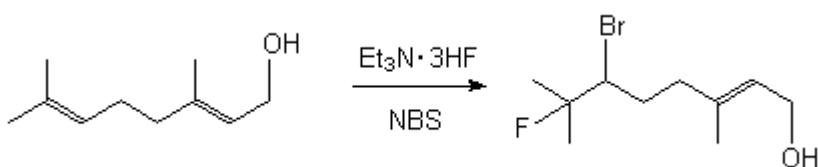


R	C ₈ H ₁₇	Ph	Me	Me ₃ CCH ₂	C ₈ H ₁₇	Ph
R1	H	H	Me	Me	F	F
Yield, %	92	97	86	93	85	90

Regioisomers 9:31* 84:16**

- 1-bromo-2-fluoro-3,3-dimethylbutane: 2-bromo-1-fluoro-3,3-dimethylbutane
- 1-bromo-2-fluoro-2,4,4-trimethylpentane: 2-bromo-1-fluoro-2,4,4-trimethylpentane

In case of cis- and trans-6-dodecene there are formed threo- and erythro-6-bromo-7-fluorododecenes respectively in a quantitative yield. (E)-6-bromo-7-fluoro-3,7-dimethyl-2-octen-1-ol was obtained in a similar way in 96% yield [172].



2. Processes of replacement of functional groups with fluorine.

2.1. Replacement of oxy-groups with fluorine under the influence of hydrogen fluoride complexes with bases.

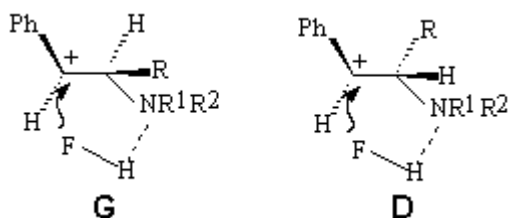
Replacement of OH groups with fluorine in alcohols under the influence of anhydrous hydrogen fluoride is not a very smooth reaction due to formation of a variety of side products such as ethers, alkenes, polymers. Besides, aqueous hydrogen fluoride is a highly corrosive substance and only a special apparatus may be used in this case. Under common conditions primary alcohols do not react with anhydrous hydrogen fluoride, but at elevated temperatures or in the presence of catalysts they can be converted to fluoroalkyls [220-224]. For example, methyl fluoride can be obtained in a reaction of methyl alcohol with hydrogen fluoride in gas phase in the presence of aluminium trifluoride (at a temperature of 375-425^oC [225]) or of chromium trifluoride (260^oC). At the same time interaction of primary alcohols (hexanol-1, octanol-1, 2,2-dimethylpropanol-1) with HF/Py complexes or with Et₃N/3HF in the presence of fluorides of alkali metals results in formation of appropriate 1-fluoroalkanes in 30-55% yield [226].

The complexes of HF with bases are used as fluorinating agents for replacement of alcohol oxy-group for alcohols of relatively low reactivity, i.e. for secondary and tertiary alcohols or for benzyl alcohol [2, 227]. The review on using Py* 9HF system (the Ohle reagent) for replacement of a hydroxy-group in secondary and tertiary alcohols with fluorine has been given in [228].

Secondary and tertiary alcohols interact with anhydrous hydrogen fluoride already at low

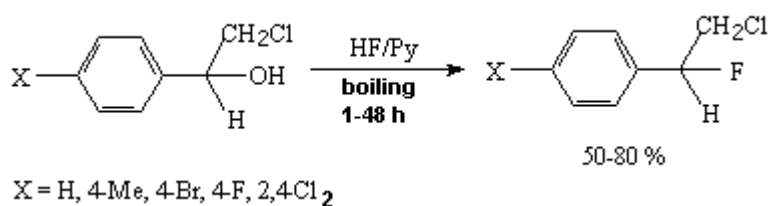
polymerisation. If the reaction is carried out in the presence of formaldehyde then ethers are formed. So, interaction of $(CF_3)_2CHOH$ with CH_2O in a medium of HF at 60-60°C results in formation of fluoromethylhexafluoroisopropyl ether $FCH_2OCH(CF_3)_2$ in 90% yield which is used as anaesthetic [229]. The use of HF/Py complex in a reaction with secondary and tertiary alcohols gives better results (table 16) [2,38,230].

Hydrofluorination of amino-alcohols of $PhCH(OH)CHRNR^1R^2$ type (where $R=H,D,Me$; $NR^1R^2=$ piperidino; $R=Me$, $NR^1R^2=$ morpholino; $R=R^1=R^2=Me$, $R=Ph$, $NR^1R^2=$ piperidino) under effect of HF/Py system results in formation of a mixture of threo- and erythro-fluoroamines $PhCHFCHRNR^1R^2$, in which the threo-isomer prevails independently on the configuration of the initial aminoalcohol [231]. In hydrofluorination by HF/Py system there is possible rotation around the C-C bond in the carbocation generating followed by hydrogen fluoride attack from the amino-group side to form intermediate carbocations **G** and **D** being in dynamic equilibrium.

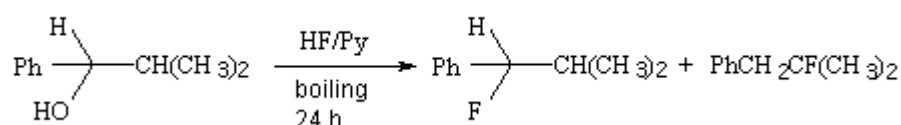


Preferable formation of the threo-product is caused by the equilibrium shift to the side of the more stable intermediate carbocation **D** in which steric interactions of substituents are minimal.

The hydroxyl group in the benzyl position is replaced with fluorine by 50-80% under the influence of 70% HF/Py system [232]. Thus, 1-chloro-2-hydroxy-2-phenylethane reacts with HF/Py at room temperature to give 1-chloro-1-fluoro-2-phenylethane.



In case α -isopropylbenzyl alcohol in dependence on the mole ratio of HF and pyridine in HF/Py system the formation α - and β -fluorides takes place [233].



X_{HF}

0,82 100% 0%

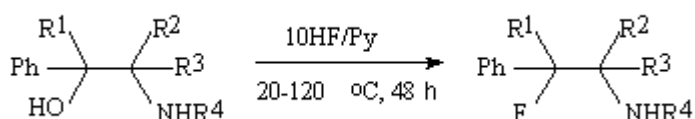
0,85 50 50

0,87 0 100

The interaction of benzylo β -aminoalcohol and HF/Py system results in the formation of $\alpha\beta$ -fluoroamines [234].

Table 16. Production of alkyl fluorides from secondary and tertiary alcohols under the influence of HF/Pr [2].

R	T ^o C	Time,h	Yield,%
Pr ⁱ	50	3	30
Bu ^s	20	3	70
Bu ^t	0	1	50
CEt ₃ Me	0	0,5	95
CEtMeBu	0	2	35
CPr ₂ Me	-70	0,5	85
Cy	20	2	99
Norborn-2-yl	20	1	95
Adamant-2-yl	20	1	95
Adamant-2-yl	20	1	98
CHPhMe	20	0,5	65
CPh ₃	20	1	76



R¹,R²,R³ = Me, R⁴ = H 82%

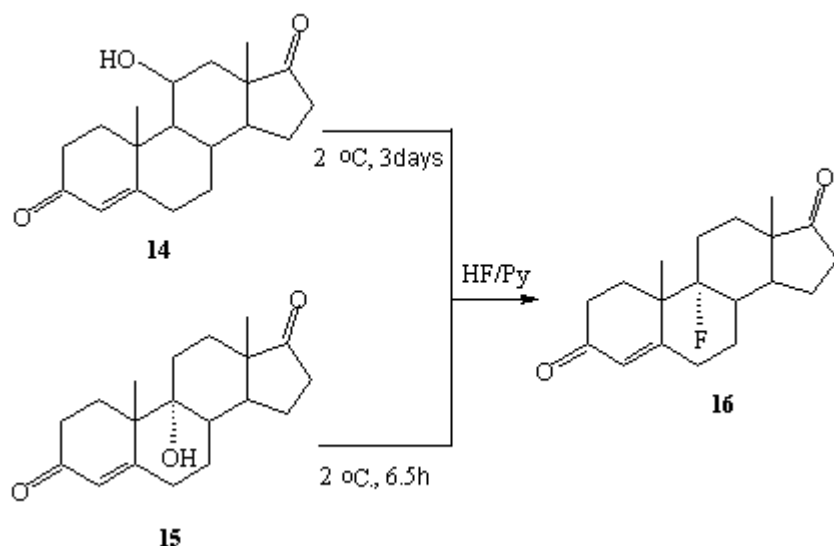
R¹ = Et, R²,R³ = Me, R⁴ = H 100

R¹,R² = H, R³,R⁴ = Me 95

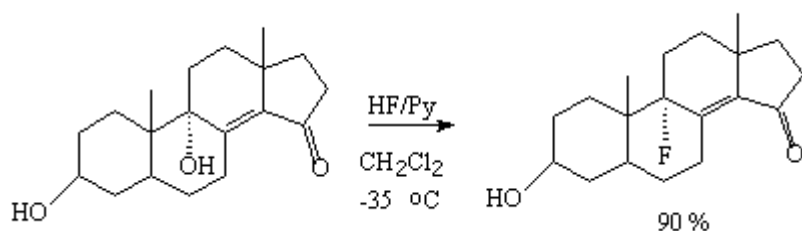
R¹,R² = Et, R³,R⁴ = -(CH₂)- 82

R¹ = H, R² = Et, R³,R⁴ = -(CH₂)- 65

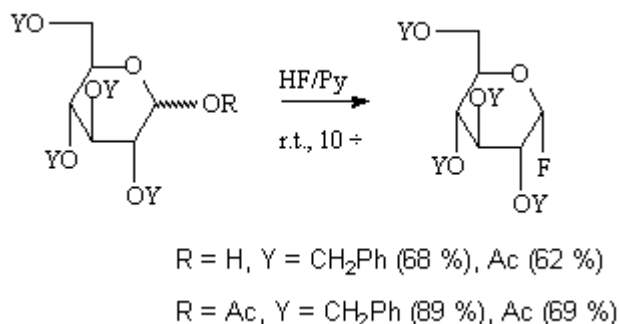
The steroids containing the OH-group, **14** and **15** groups under the effect of HF/Py complex convert to tertiary fluoro- derivatives **16** only (α -fluoro-derivatives) [235].



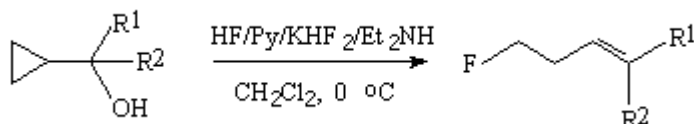
When secondary and tertiary OH groups are present the tertiary group is replaced with a fluorine atom [236-238]. Thus, β -dihydroxy- α -cholest-8(14)-en-15-one under the effect of HF/Py complex in methylene chloride gives α -fluoro- β -hydroxy- α -cholest-8(14)-en-15-one [236].



α -D-Glucopyranoses containing OH or OR groups substitute them with fluorine in position 1 under the effect of HF/Py complex already at room temperature for 10 hours [239,240]. An addition of acetone, methene chloride or collidine brings to an increase of total yield of the reaction product.



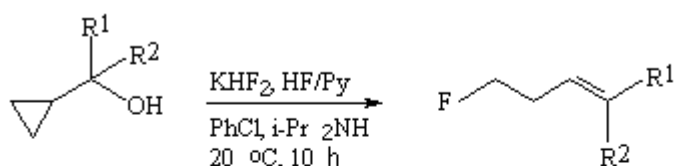
In case of alcohols containing a cyclopropane ring in α -position the influence of HF/Py/KHF₂/Et₂NH system brings not only to replacement of the hydroxyl group with fluorine but to opening the cyclopropane ring also [241].



R ¹	R ²	Yield, %	E/Z ratio
Ph	Me	65	95/5
Ph	Bu	55	85/15
C ₈ H ₁₇	Me	37	65/35
PhCH=CH	H	70	100/0

Table 17 shows the examples of alcohols which have substituents at the cyclopropane ring.

Interaction of alcohols containing the cyclopropane ring β -position with HF/Py complex or with KHF₂/isopropilamine system results in formation of homo-allyl fluorides with prevalence of the product with E-conformation [242-244].



R1	R2	Yield, %	E/Z
Ph	H	73	100/0
Ph	Me	65	95/5
Ph	Bu	55	85/15
C ₈ H ₁₇	Me	37	65/35
PhC≡C	H	70	100/0

To be continued