The electrolytic method of fluorination in the medium containing the complexes of anhydrous hydrogen fluoride and trialkylamines.

G.G.Furin

Novosibirsk Institute of organic chemistry named after N.N.Vorozhtsov

Siberian branch of the Academy of Science of Russian Federataion

Fax: +7-3822-344752

e-mail: **furin@nioch.nsc.ru**

ABSTRACT

The review generalizes and systematizes the latest date on fluorination of the various classes of organic compounds by the electrolytic anodic oxidation method in the medium of electrolyte the complexes of anhydrous hydrogen fluoride and trialkylamines. An analysis was performed of the basic achievements of the method of one atom fluorine introduction. The facts having an influence on the process and influence of electron-seeking substitutes arranged by CH-fragment and by heteroatoms of VIA group are shown. The examples are given of the useful applications of this method for the synthesis of aromatic and heterocyclic compounds as well as compounds having XCHF fragments, where X=S, Se, Te, as the potential intermediate products for synthesis of the preparations possessing a biological activity. The new efficient production methods of monofluorine containing organic compounds and their role in organic synthesis are discussed.

Contents

Introduction

1. Electrolytic fluorination of organic compounds in the presence of the electrolyte containing the complexes of anhydrous hydrogen fluoride and trialkylamines.

1.1 Anodic monofluorination of aromatic compounds

1.2 Electrolytic fluorination of heterocyclic compounds.

1.3. Anodic fluorination of the organic compound with CH-fragment containing electron-seeking substitutes.

2. Behavior of organic derivatives of the VI group elements, having CH-fragment in alpha position to heteroatom in the electrolytic solutions containing hydrogen fluoride.

Conclusions

References

1.2. Electrolytic fluorination of heterocyclic compounds

Partly fluorinated heterocyclic compounds are in focus of researchers due to their high biological activity. They are used as intermediate products when creating preparations for medicine and agriculture. Their synthesis is rather non-selective and limited in many cases. Continuous search for fluorinating reagents for introduction of the fluorine atoms and reagents for introduction of perfluoroalkyl groups into organic molecules [56,57] is going on because of this. Unlike this electrochemical fluorination method is the ideal method of direct fluorination and can be carried out at one go when conditions are mild [58]. However there are few examples of such fluorination, though high yield and selectivity make this method rather attractive [34,43,59-61].

Having a carbonyl group in α-position to nitrogen atom N-methylpyrazoles are subject to electrolytic fluorination in the Py/9HF system at 20 $^{\circ}$C with formation of fluoropyridizinone [62].Et$_3$N*3HF system can also be used as electrolyte [63].

In the case of 4-thiazolydinone **10** Et$_3$N*3HF/MeCN system proved to be rather effective and convenient. The formation of monofluoroderivative **11** with high regioselectivity occurs when carrying out anodic fluorination. These are the first examples of effective anodic fluorination of sulfur-containing heterocyclic compounds [64,65]. Subsequent oxidization using peracids affected sulfur atom and compound **12**was formed.
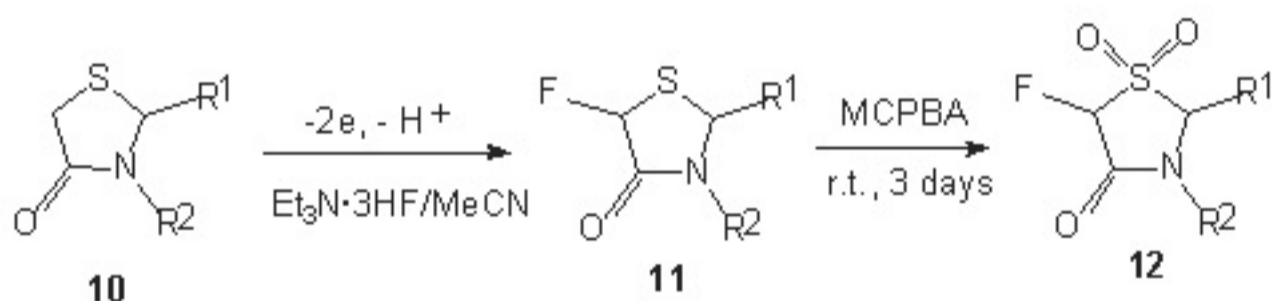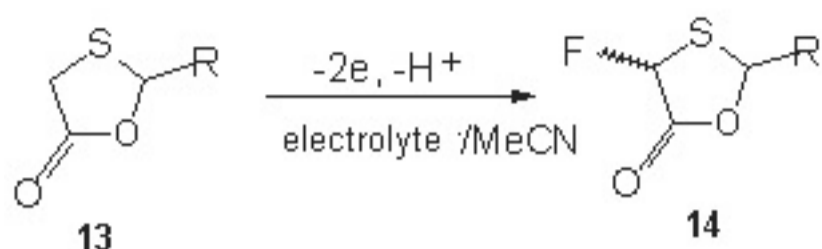

R^1	R^2	Yield **11**, %	*cis:trans*	Yield **12**, %	*cis:trans*
1-naphthyl	Me	79	29:71		
Ph	H	14	35:65		
Ph	Me			42	35:65
Ph	CMe$_3$			59	45:55
Ph	Ph	84	43:57		
PhCH$_2$	Ph			65	46:54

Other heterocyclic compounds react similarly.
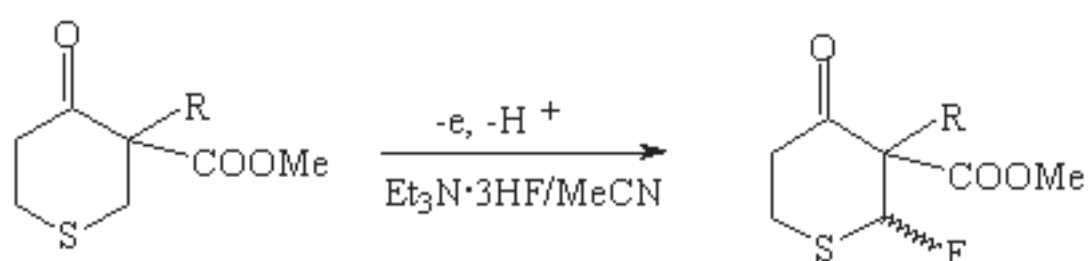
R	Yield,%	Stereoselectivity,%
Me	7	100
CH2Ph	27	76

So, during anodic fluorination of 1,3-dithiolane-4-ones [66] and 1,3-oxathiolan-5-ones **13,** which have the substitutes in position 2, appropriate fluoroderivatives are formed [67].

In table 4 there is information on anodic fluorination of 2-substituted 1,3-oxothiolane-5-ones, during which monofluoroderivative **14** [67] is formed. We'll notice, that fluoride-ion matters a lot in this process.

Table 4. Anodic monofluorination of 2-substituted 1,3-oxothiolane-5-ones [67].

| R	E^{ox}_p/B vs SSSE*	Electrolyte	Potential of oxidation, V	F/mol	Yield of **14**, %	cis/trans
Et	2.34	Et3N*3HF	2,3	3,4	0	
		Et4NF*4HF	2,1	2,6	86	47/53
n-Pr	2,32	Et3N*3HF	2,2-2,3	3,6	5,4	d
		Et4NF*4HF	2,1	2,2	67	45/55
i-Pr	2,44	Et3N*3HF	2,2	2,2	0	
		Et4NF*4HF	2,1	2,4	78	43/57
Ph	1,88	Et3N*3HF	1,6	4,0	0	
		Et4NF*4HF	2,0	2,3	70	45/55
4-CNC6H4	2,17	Et3N*3HF	2,2	3,4	0	
		Et4NF*4HF	2,0	3,2	66	39/61

* Pt- electrodes, 0,1 M NaClO4/MeCN

Taking into attention the data listed in the table 4 the system Et3N*3HF is unusable for carrying out of the anodic fluorination processes for this heterocycle.

4-Arylthio-1,3-dioxalane-2-one in dimethoxyethane undergoes the fluorodesulfurization and fluorination with formation of 4-fluoro-1,3-dioxolane-2-one [68].
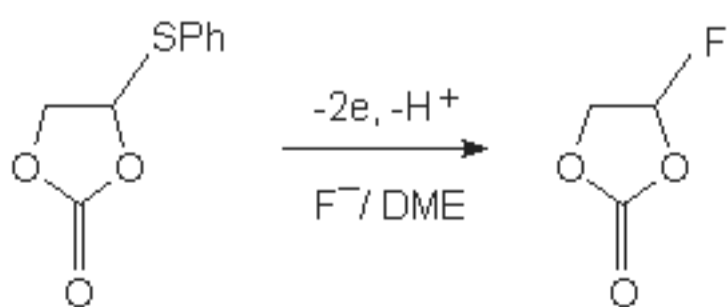
Electrochemical oxidization of 2,2,-diphenyl-1,3-dithiane in Et3N*4HF system results in formation of difluorodiphenylmethane [69].

$$PhCF_2Ph \quad 49\%$$
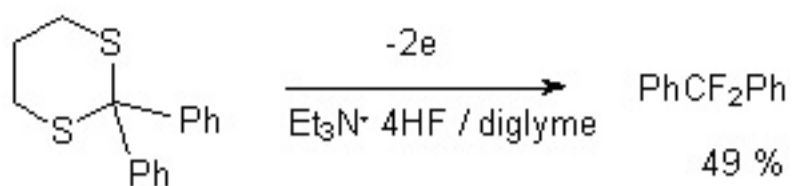
Monofluorinated β-lactams are of interest of fluorocontaining antibiotics synthesis as intermediate products and they also are of interest of creating amino-acids and sugars as block. Thus, regioselective anodic monofluorination of 3-phenylthio-2-azetidinones and 4-phenylthio-2-azetidinones results in formation of 3-and 4-substituted derivatives of 2-azetidinones[60]. The product yield of monofluorination essentially depends on electrolyte used. It is interesting that in case Py/(HF)n system doesn't really work [70].
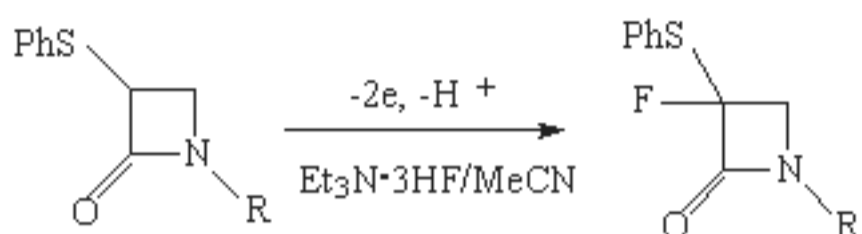
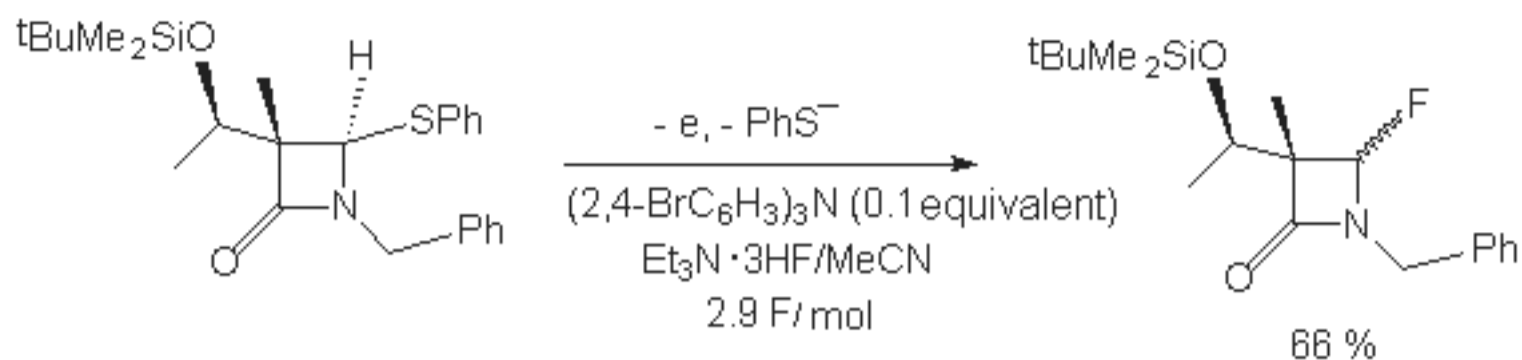| R	Electrolyte	B, vs. SCE	F/mol	Yield,%
Et			2,5	65
	Et$_3$N . 3HF	1,8	2,3	77
Pr^i	Et$_4$NF*4HF	1,5	2,0	64
	Py(HF)n	1,9	2,2	traces
	Et$_3$N . 2HF	1,7	13,2	33
Bu^n		1,8	2,4	92
Bu^t		1,9	2,5	67
c-C$_6$H$_{11}$		1,8	2,5	84
PhCH$_2$		2,0	4,0	68

In general case electrochemical fluorination of N-substituted lactams in electrolyte Et$_3$N*3HF/MeCN goes selectively and affects the carbon atom, being i α-position to nitrogen atom of lactam. In this case the monofluoroderivative product was formed, moreover the yield is rather high [71].

If SR group is not i α-position to C=O heterocycle group, then during anodic fluorination its replacement for fluorine atom occurs [72].
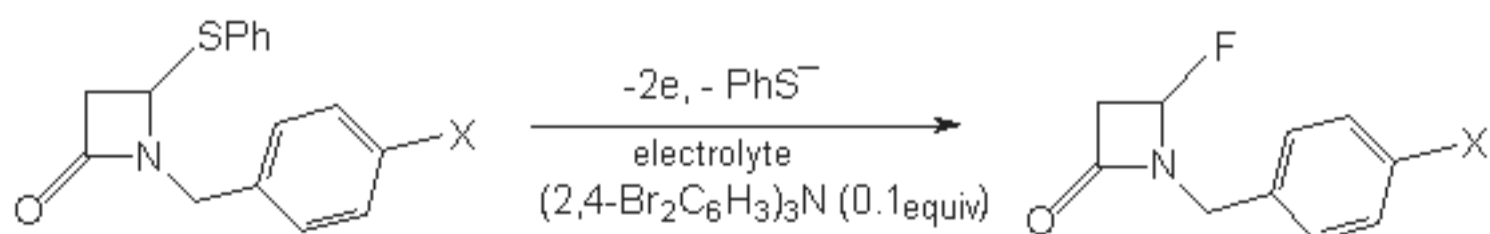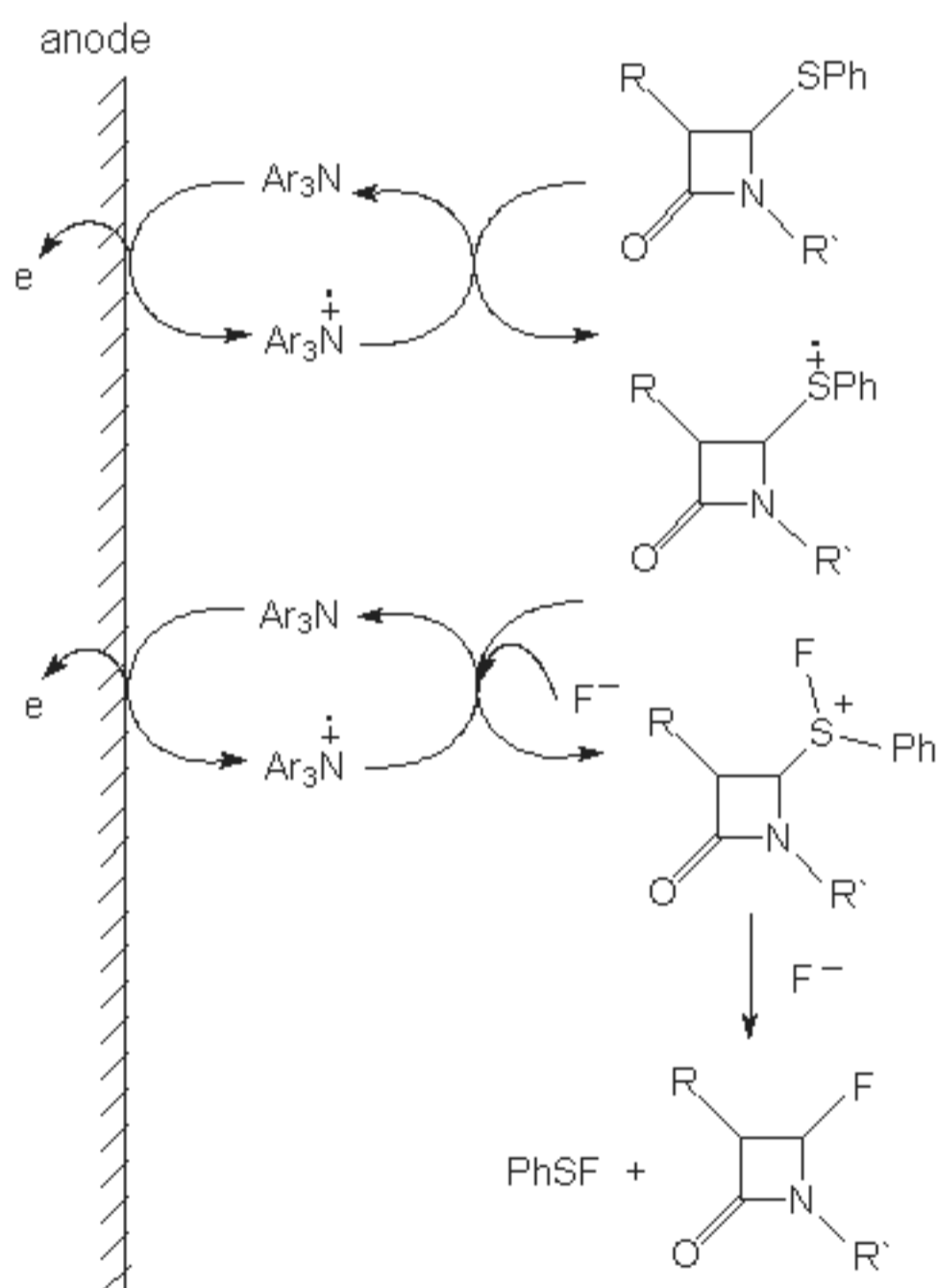

X	Electrolyte	Yield,%
H	Et$_3$N . 3HF/MeCN	83
Me	Et$_3$N . 3HF/MeCN	71
Br	Et$_3$N . 3HF/MeCN	quantitatively

H   Et$_4$NF . 3HF/MeCN 43

The presence of other substituents in heterocyclic ring doesn't change the reaction direction - fluorodesulfurization occurs[72].

tBuMe$_2$SiO   H   SPh   — e, - PhS$^-$ tBuMe$_2$SiO   F

(2,4-BrC$_6$H$_3$)$_3$N (0.1 equivalent)
Et$_3$N ·3HF/MeCN
2.9 F/mol

Ph   O   N   Ph
66 %

The authors of article [53a] represent the mechanism of this process as follows.

anode

Ar$_3$N

e

Ar$_3$N

R   SPh

O   N   R`

R   SPh

O   N   R`

Ar$_3$N

e

Ar$_3$N

F$^-$ R   S$^+$—Ph   F

O   N   R`

F$^-$

PhSF +   R   F

O   N   R`

If in position 4 of azetidine-2-one there is SiMe$_3$ group, then the formation of 4-substituted fluoroderivative also takes place (table. 5) [73].

Heterocyclic compounds with carbonyl groups are subject to selective fluorination too. For example, the formation of mono- and difluoro- derivatives of (4-methoxyphenyl)acetone, ethyl(4-methoxyphenyl)acetate [74,75] and fluoroderivatives of indan [76] is observed when carrying out anodic fluorination of hydrocarbon substrate in electrolyte-complex Et$_3$N*3HF. Anodic fluorination of 1-naphthalene derivatives in Et$_3$N*3HF system, oxyindole and 3-oxy-

1,2,3,4-tetrahydroisoquinoline in $Et_4NF \cdot 3HF$ system goes without problems when groups CN, COOEt or SPh [77,78] are available.

**Table 5.** *Electrochemical obtaining of 4-fluoroazetidine-2-one derivatives [73].*

Substrate		Electrolyte	F/mol	Product	Yield,%
X | R					
SiMe$_3$	Ph	Et_3N 3HF	8.0		80
SiMe$_3$	Ph	$Et_3N \cdot 2HF$	20.0		49
SiMe$_3$	Ph	Py$\cdot$nHF	4.0		66
SiMe$_3$	Ph	$Bu_4N \cdot BF_4$	4.0		смола
SiMe$_3$	Pr	$Et_3N \cdot 3HF$	18.0		78
E- Z-		$Et_3N \cdot 3HF$	10 6	E- Z-	68 80
trans-		$Et_3N \cdot 3HF$	14	cis/trans = 1/1	88
trans-		$Et_3N \cdot 3HF$	10	trans-	75

	n	R	R^1	Electrolyte	F/mol	Yield,%
	0	H	Ph	$Me_4NF*4HF$	3,5	64
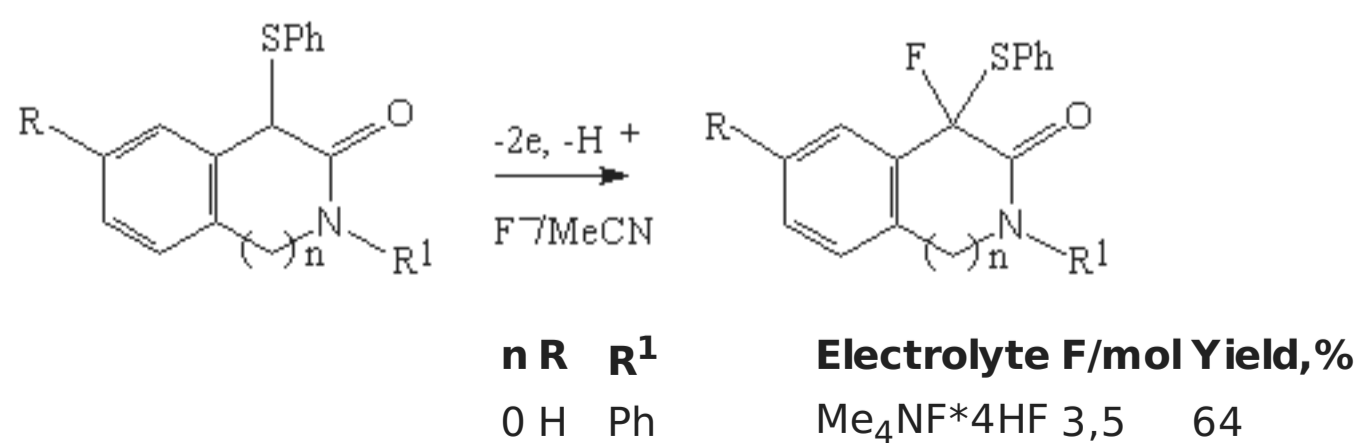
0	Me	4-MeC$_6$H$_4$	Me$_4$NF*4HF	3	50
1	H	Ph	Et$_4$NF*3HF	2,6	71
1	H	PhCH$_2$	Et$_4$NF*3HF	2	70

The nature of electrodes matters within certain limits. The increase of anhydrous hydrogen fluoride results in increment of fluorination product. As example, it was shown by anodic fluorination of oxyindole [77,78].
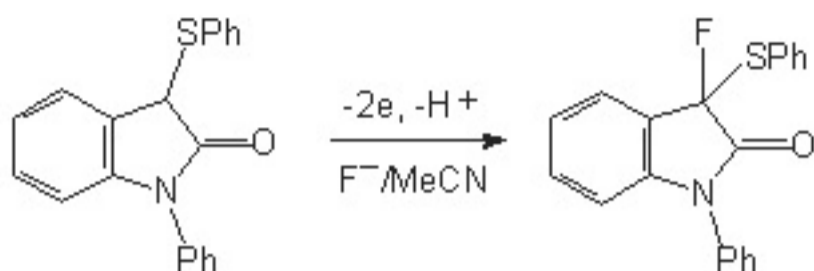

Anode	Yield,%	
	Et$_4$NF*3HF	Me$_4$NF*4HF
Pt	58	64
Carbon	28	60
C-steel	36	59
C-felt	21	42

At the same time anodic fluorination of oxyindole in Et$_4$NF*3HF/MeCN system with absence of SPh group results in fluorination of benzene ring without affecting of heterocyclic system [79].

This example shows the importance of SPh group in anodic fluorination of different derivatives.

During anodic fluorination of ethyl isonicotinate [80], pyrazole (table 6) [61,81], pyridine [60,82], 1,10-phenanthroline [42,83,84] the fluorination products containing fluorine in heterocycle and in methyl group were formed. However the yield of fluoroderivatives is not very high.

It was shown [61], that during electrochemical fluorination of 1-methylpyrazole-4-carboxylic acid ethyl ester **15** the using of 70 % HF/Py/Et$_3$N complex on platinum anode results in formation of 1-methyl-5-fluoropyrazole-4-carboxylic acid ethyl ester **16** and 1-fluoromethyl-5-fluoropyrazole-4-carboxylic acid ethyl ester **17.** The highest yield was 40 % and selectivity of fluorine attack *in position 5* was 83% .
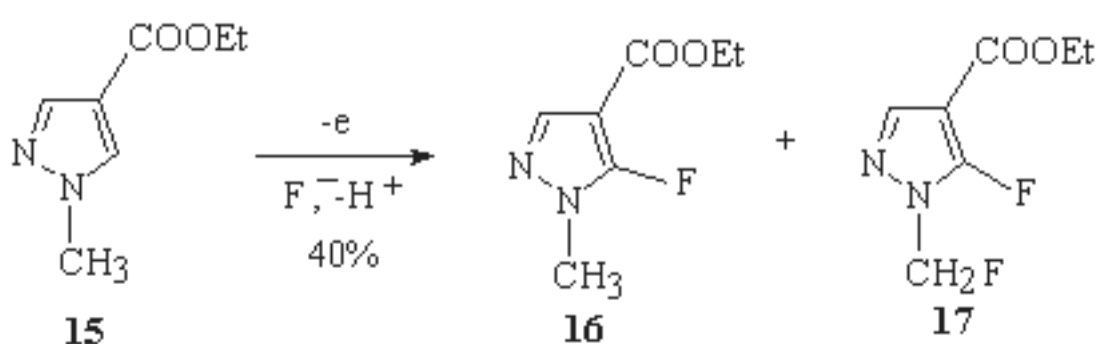

Anodic fluorination of pyridinein Et$_3$N*3HF system gives 2-fluoropyridine with 22 % yield

[60]. Heterocyclic ring containing electron-seeking substituents complicate the direct fluorination of cycle and the yield of 2-fluorosubstituted derivative is low [80]. For example, 2-fluoro-iso-nicotinic acid ethyl ester with high conversion is obtained using electrolysis of iso-nicotinic acid ester in $Et_3N*3HF/MeCN$ system with 30 % yield and 76% conversion [80].

**Table 6.** *Anodic fluorination of 2-methylpyrazole-4-carboxylic acid ethyl ester [61].*

Anode	System		Solvent	Voltage, V	Products 16:17 ratio	Yield,%
Pt	Pt	HF/Py	MeCN	2,5	25:75	16
		HF/Py/Et3N(0.3)			57:43	23
		HF/Py/Et3N(0.6)			83:17	40
		HF/Py/Et3N(1.0)		3	100:0	18
		HF/Py/Et3N(0.6)	THF	2,7	100:0	2
		HF/Py/Et2NPh	MeCN	2,5	92:8	39
C		HF/Py/Et3N	MeCN	2,1	97:3	31
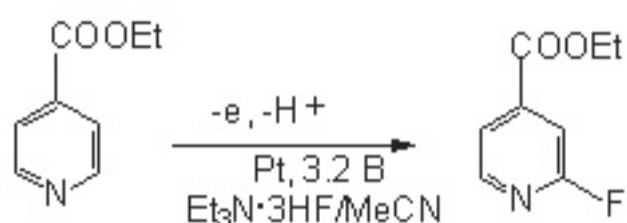
Nitrogen-containing heterocyclic compounds in electrolytes mentioned are subject to fluorination and as a rule hydrogen atoms are displaced i α-position to nitrogen atom of the cycle. For example, anodic fluorination of pyridazininone-3-onaderivative **18** in the medium 70 % HF/Py/MeCN at Pt electrodes at room temperature gives monofluoroderivative **19** [85].
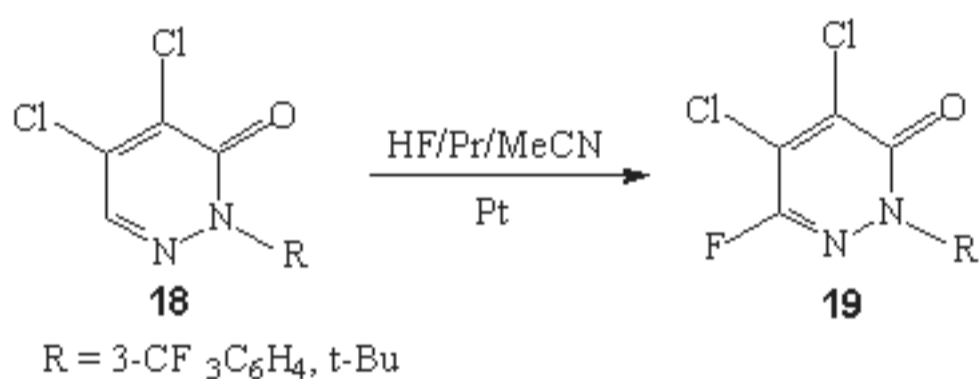

Anodic fluorination of 2H-1,4-benzothiazine-3(4)-ones derivatives **20** in acetonitrile in the presence of Et_3N*3HF results in formation of monofluoroderivatives **21**, moreover fluorine displaces hydrogen i α-position to sulfur atom of ring [86].
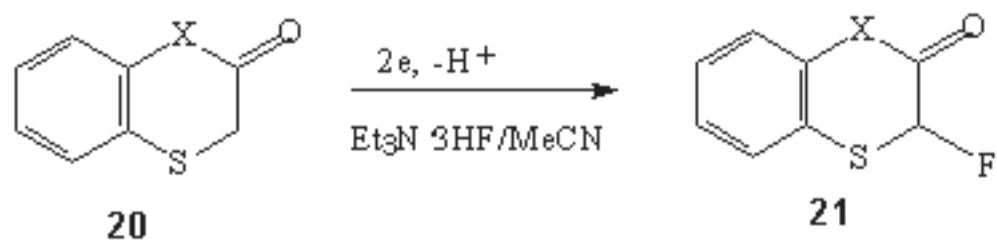
X	Potential of anode, V	F/mol	Yield of 21,%
NH	3.0	15	0
NHCOPh	2.0	2.2	77

N-Pr^i	1.5		2.5	88
n-Me	1.6		2.1	68

Anodic fluorination of biologically active flavone derivatives, having first potential E_p^{ox} within 2.36 - 2.52 V, results in formation of difluoro- and trifluoroderivatives [84].
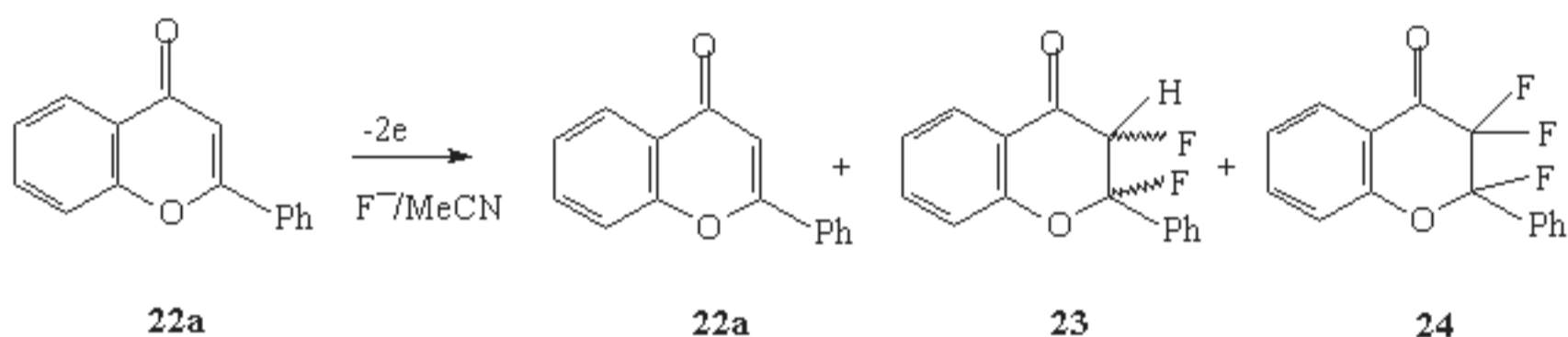

22 a-c
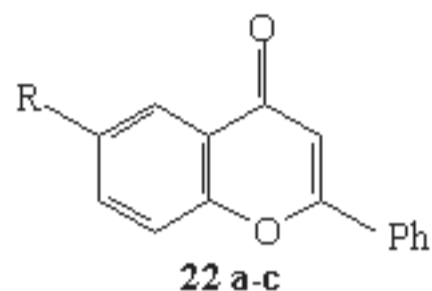
R   =   H(a) Me(b) Cl(c)

E_p^{ox} = 2.50 2.36 2.52

B vsSSCE

Anodic fluorination of flavone and 6-chloroflavone in Et$_3$N *3HF and Et$_4$NF*4HF systems mainly produced 3-monofluoroderivative with small quantity of 2,3-difluoroderivative. The process was carried out at 30 ^{o}C [27,87] and the ratio of products in reaction mixture depended on electrolyte used [84].

Electrolyte	Yield, %		
	22a	**23 (cis:trans)**	**24**
Et$_3$N.3HF	43	0	6
Et$_3$N.5HF	9		4
Et$_4$NF.3HF	3	54(2:1)	6
Et$_4$NF.4HF	7	68(2:1)	9

At that the temperature has a key influence:

Temperature, ^{o}C	-10	0	10	20	30
Yield **22a**,%	9	27	31	43	58
Yield **24**,%	traces	3	4	6	19

Electrochemical oxidization of caffeine, guanosine tetra-acetate and uridine tri-acetate, proceeding in electrolyte Et$_3$N . 3HF, results in formation of monofluoroderivatives with small yield (table 7) [88].

It should be noted that there is the high regioselectivity during anodic fluorination o α-

phenylsulpho phenyl substituted lactams **25** in Et$_3$N .3HF/MeCN medium (Pt electrodes) when hydrogen is substituted by fluorine α-position to Sph-group independently of ring size **26** [86].
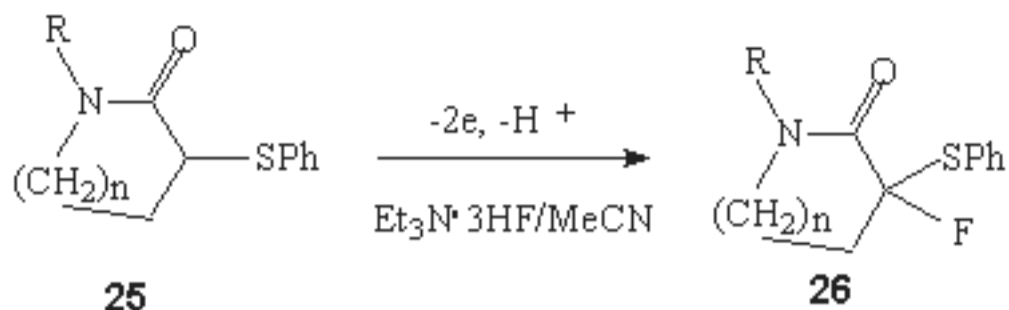
n	R	Potential of anode (V), relative to SSCE	F/mol	Yield of 26,%,
1	Me	1,8	2,5	85
1	cyclohexyl	1,8	2,5	84
2	Me	2,0	2,2	69
3	Me	1,9	4,0	compounds mixture

1.3. Anodic fluorination of the organic compound with CH-fragment containing electron-seeking substitutes.

High yield of fluoroderivatives is achieved by anodic fluorination of substituted derivatives both aromatic and heterocyclic compounds, having protons movable enough α-position to the main cycle. As a rule, most effective Et$_3$N* 3HF system and platinum electrode are used [89,90].

1.49 B, X = H, R = COOEt (99 %)
1.80 B, X = H, R = CN (94 %)

1.70 B, X = PhS, R = COOEt (55 %)
2.00 B, X = PhS, R = CN (56 %)
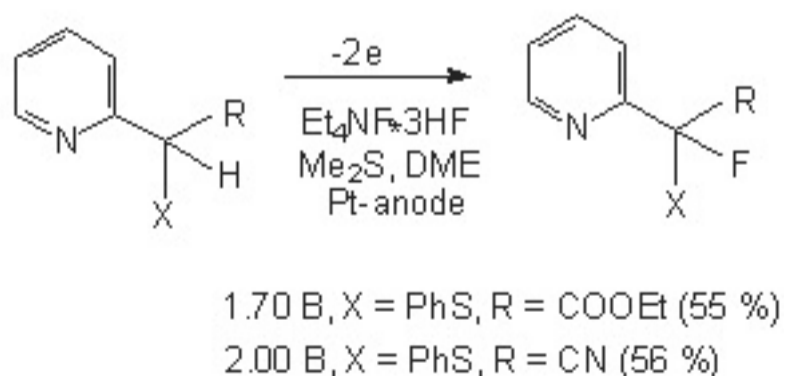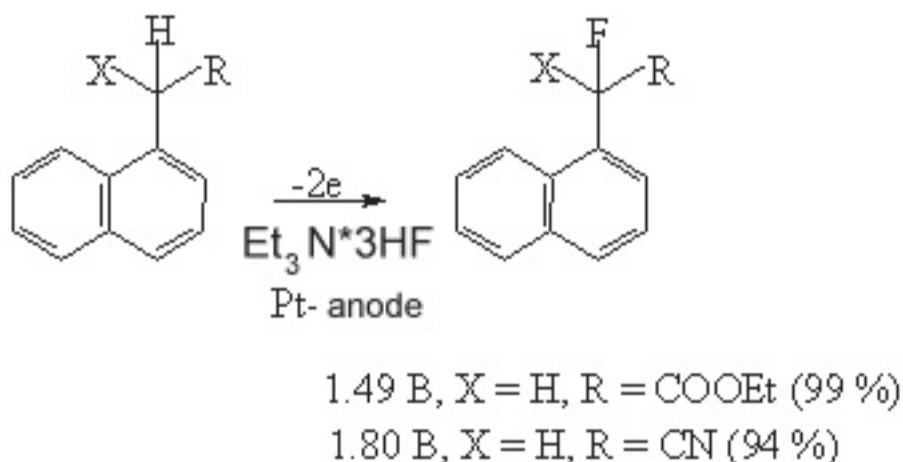
Table 7. Electrochemical oxidization of caffeine and similar compounds (MeCN, Et$_3$N * 3HF) [88].

| Substrate	Oxidation potential B v SSCE	Time, h	Product	Yield, %
	5	17		40.3
	3	10		6.3
	C.C.E. 100 mA	5.5		4.6

If in benzene ring there are electron-donating substituents, then during anodic fluorination active methene group of substituent will be affected mostly [75,91-94].
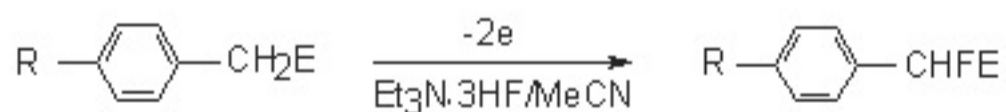

R	E	Potential, V	Conversion	Yield,%
MeO	COMe	1,2	100	72
MeO	COC$_6$H$_4$OMe	1,2	99	72
Cl	COOEt	1,7	75	36
MeO	COOEt	1,28	100	69
3,4(MeO)$_2$	COOEt	0,8	92	73
CH$_2$=CHCH$_2$O	COOEt	1,49	100	51
H	CN	2,33	44	22
MeO	SO$_3$Et	1,37	96	71
Cl	CN	1,88	65	64
MeO	CN	1,37	97	67

It is shown, that the reaction goes via initial generation of cation-radical of substituent atom neighboring to $-CH_2-$ fragment with following fluoride-ion attack of cationoid centre of intermediate carbcation, which is α-position to carbonyl group [92,94].
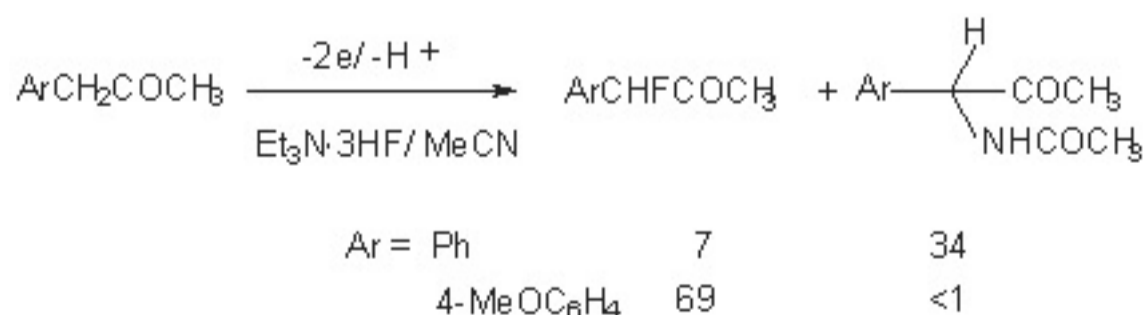
Anodic fluorination of sulfides in Et_3N*3HF medium results in formation of monofluoro- and hem-difluoroderivatives [95]. At that elimination of SPh group occurs .


84 %

-e
E = 1.6 B

PhSSPh +

73 %
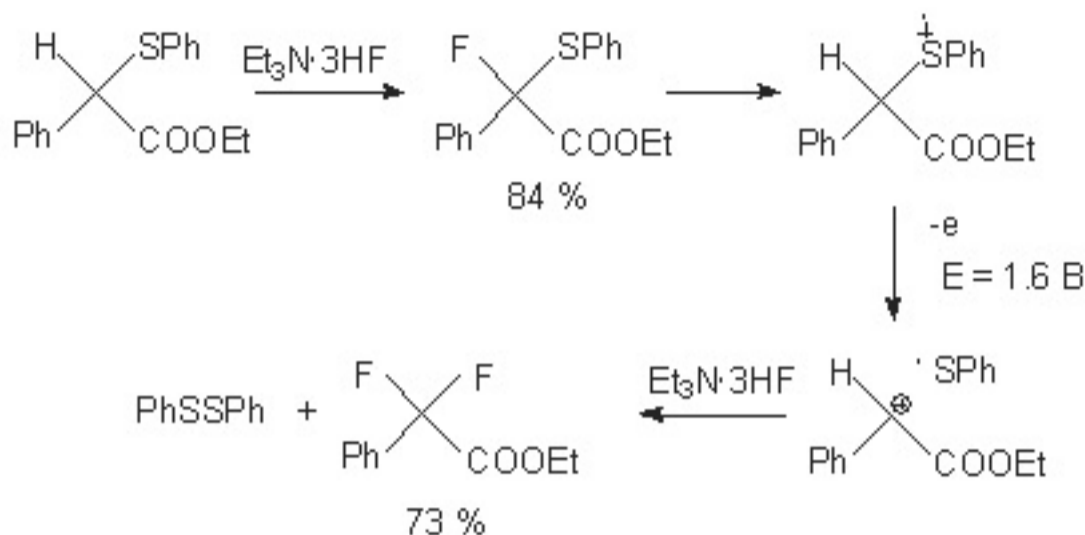
$Et_3N \cdot 3HF$

Anodic oxidization of benzylalkyl ketones, carboxylic acids esters, nitriles, benzyl derivatives in the system $Et_3N*3HF/MeCN$ at platinum anode enables to obtain monofluoroderivatives, some of which are biologically active [64,70,91,96-100].

-2e /-H +
$Et_3N \cdot 3HF/MeCN$

65-71 %

E = COR, COOEt, CN,

R = 4-MeO , Me
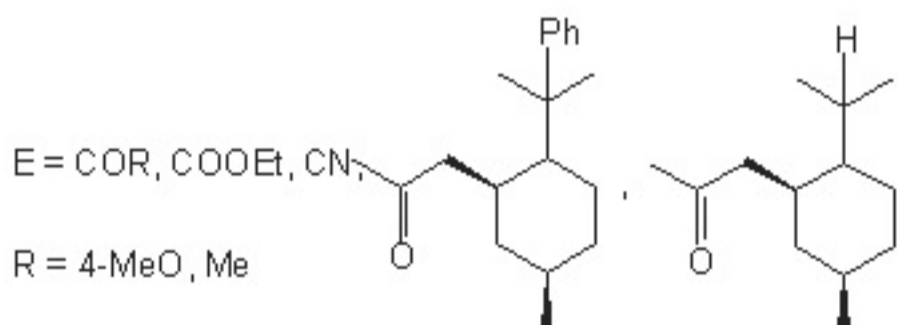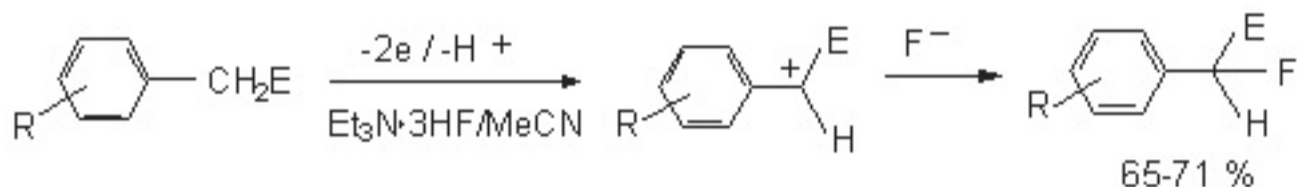
Substituent in benzene ring influences greatly on the ratio of resulting products [91].

$$ArCH_2COCH_3 \xrightarrow[Et_3N \cdot 3HF/MeCN]{-2e/-H+} ArCHFCOCH_3 + Ar-C(H)(COCH_3)(NHCOCH_3)$$

| Ar = Ph | 7 | 34 |
| 4-MeOC_6H_4 | 69 | <1 |

At the same time electrophilic substituents in α-position to methene group have a light influence on the anodic fluorination process, while the increasing of voltage results in increasing of difluoro-derivative yield.
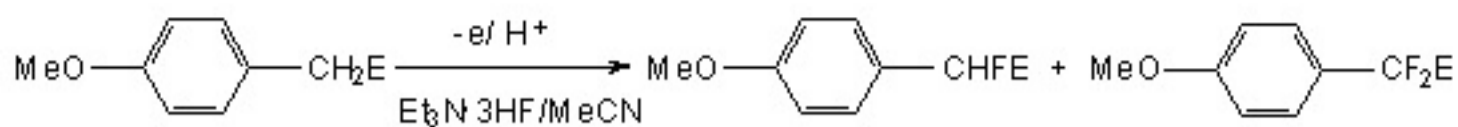
| E	Voltage,V	Yield,%	Voltage,V	Yield,%
CH_3CO	1,2	69	1,6	61
$4\text{-}MeOC_6H_4CO$	1,2	71	1,55	50
COOEt	1,28	69	1,45	55
CN	1,35	65	1,60	50

The presence of methyl group in benzene ring results in its fluorination. Thus, *p*-methylbenzylsulfonate during anodic fluorination in $Et_3N*3HF/MeCN$ system forms the mixture of electrolysis products **27-30** [93].
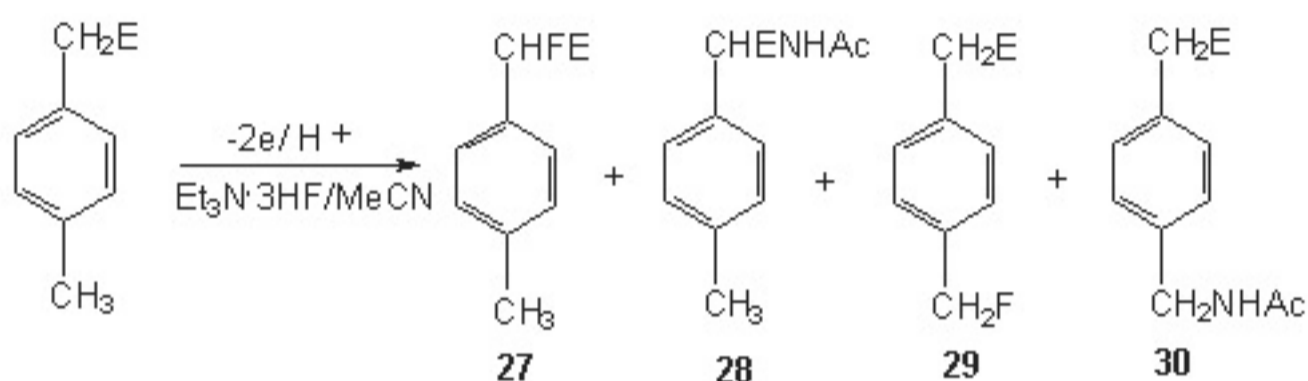

E	Voltage, V	Yield,%		
		27	**28**	**29**	**30**
COOEt	1,65	40	14 8	18
CN	1,73	58	<1 3	6
SO3Et	1,78	15	0 21	30
H	1,80		10	25

Electrochemical oxidization of aliphatic aldehydes in Et_3N*5HF or $Py* nHF$ (n = 3-6) in acetonitrile or sulpholane results in formation of corresponding carboxylic acids fluoroanhydrides with high yield [101,102].

2,2-disubstituted cyclic ketones in Et_4N*5HF at anodic fluorination produce fluoroanhydrides of appropriate fluorocontaining carboxylic acids due to selective splitting of C-C bond between carbonyl atom of carbon and α-substituted carbon atom (table 8) [103-105]. Thus, electrolysis of 2,2-dimethylcyclohexanone in electrolyte Et_4N*5HF at 0°C with subsequent addition of methyl alcohol produces methyl 6-fluoro-6-methylheptanoic acid ester.
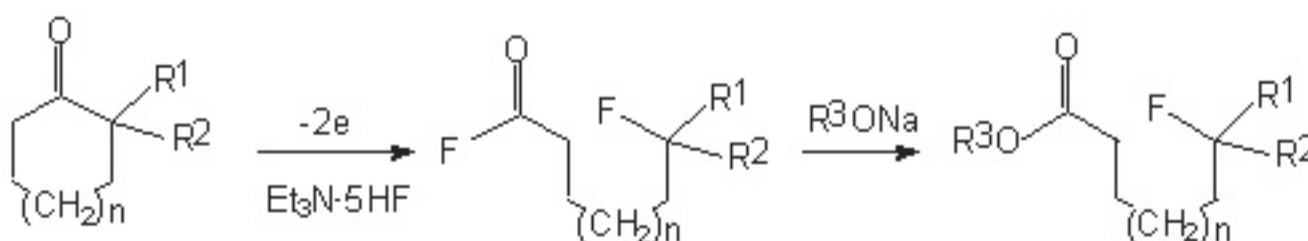
Probably, the reaction path is the following:
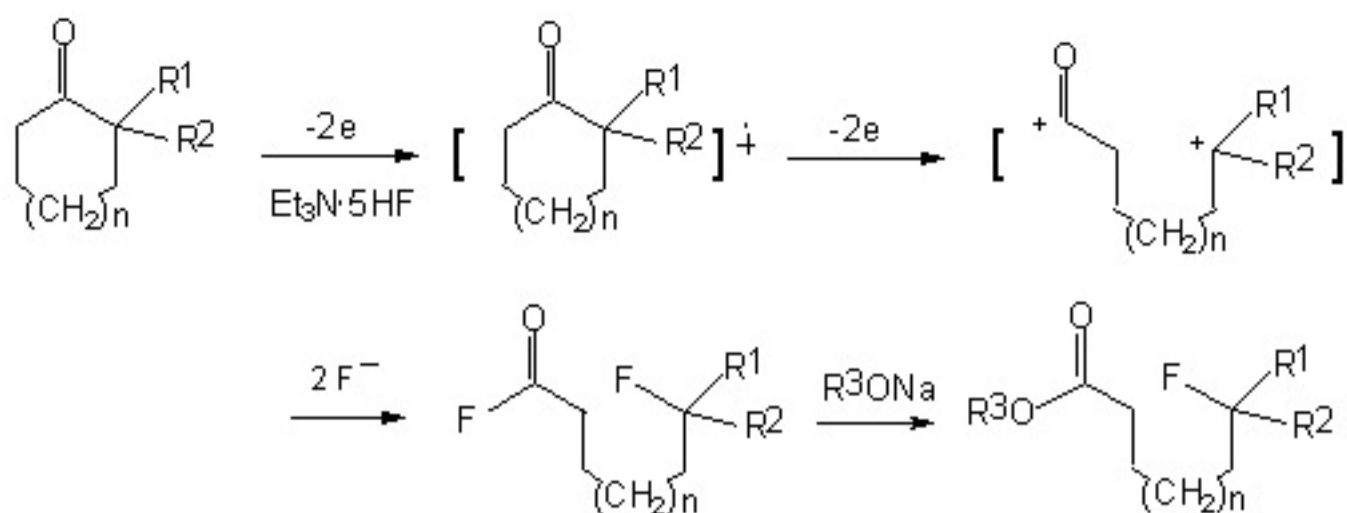
At the same time anodic fluorination of unsaturated carboxylic acids esters having cylcopentane and cyclohexane fragments in Et_3N*5HF system results in forming of expanded by one carbon atom cycle. 2-2-Difluorocycloalkanecarboxylic acids esters with high selectivity and good yield are produced (table. 9) [106,107].
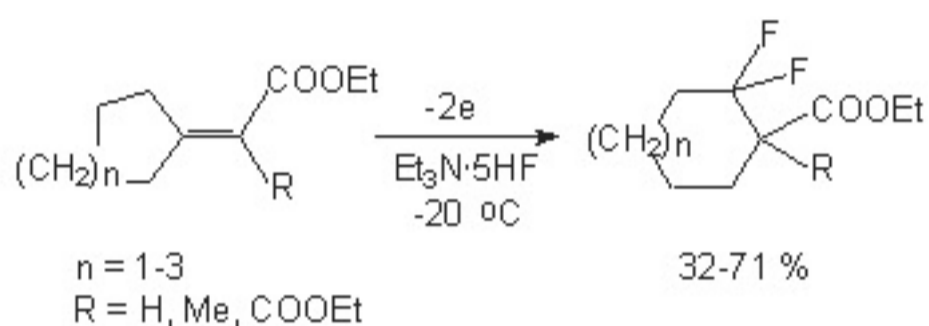

n = 1-3
R = H, Me, COOEt

32-71 %

Table 8. Synthesis of carboxylic acids esters using electrosynthesis (electrolyte Et_3N*5HF, 0^oC) of cyclic ketones [103].
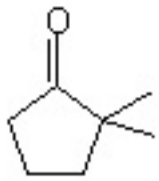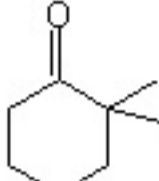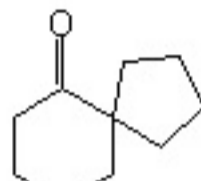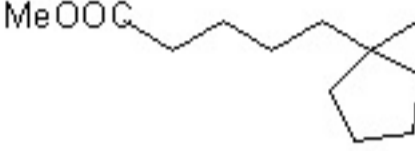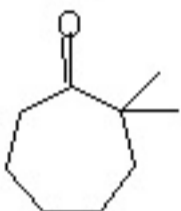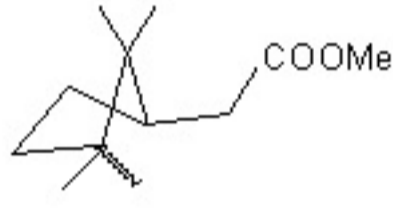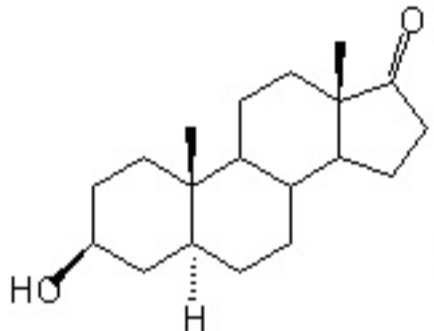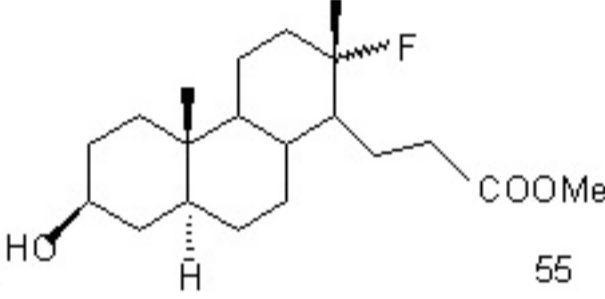
Ketone	V,vs Ag/Ag+	F /mol	Product	Yield,%
	2.0	2.5		80
	2.0	3.1		81
	2.2	3.0		82
	2.3	3.5		81
	2.2	4.0		60
	2.0	8.0		55

Table 9. Electrochemical oxidization of unsaturated cyclic esters [103].

Substrate	V,vs Ag/Ag+	F /mol	Product	Yield,%

Anodic fluorination of different N-substituted lactams using electrolyte Et_3N*3HF results in formation of corresponding monofluorocontaining products, in which fluorine atom is in α-position to nitrogen atom [105].

During electrolysis of β,γ-unsaturated esters the α,β-difluoroderivatives of esters were formed in electrolyte due to rearrangement of alkyl group from α- to β-position [107]. If alkenyl group is in this position, for example in case of carboxylic acids esters of dienes , then the fluorination with formation of vicinal difluoroderivatives will occur (table 10) [102].

Table 10. Anodic fluorination of dienes esters [102].
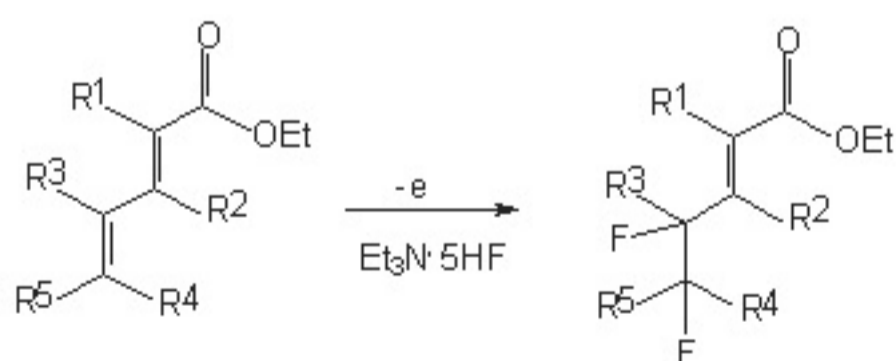
R^1	R^2	R^3	R^4	R^5	Electrolyte	F/mol	Potential of anode, V	Yield, %	Isomer ratio
H	H	H	Me	Me	Et_3N*5HF	2,5	1,6	73	-
H	H	H	H	Ph	$Et_4NF*2HF$	2,5	1,4	35	2,5:1
H	H	H	H	Me	Et_3N*5HF	2,5	1,8	69	2:1
H	H	H	H	n-C_6H_{13}	Et_3N*5HF	2,5	1,8	53	5:1

H	H	Me	H	Me	Et$_3$N*5HF	2,5	1,6	61	1,5:1
H	Me	H	Me	Me	Et$_3$N*5HF	2,5	1,6	16	-
H	Me	H	Me	Me	Et$_3$N*3HF	8	1,6	45	-
Me	H	H	Me	Me	Et$_3$N*5HF	2,5	1,25	86	
COOEt	H	H	Me	Me	Et$_3$N*5HF	2,5	1,6	85	3:1
COOEt	H	H	Me	Me	Et$_3$N*2HF	2,5	1,6	4	3:1

In case of compounds, containing two carb-ethoxy groups at multiple bonds of diene and electron-donating substituents (for example, methyl groups), anodic fluorination produces mixture of hem-difluoro-and vicinal difluoroderivatives (ratio 3:1) [102]. This shows the realization of two fluorination processes pathways.

Olah's reagent (HF/Py) is most widely used as electrolyte, and methylene chloride is used as solvent [49,50]. Another path is connected with use of Et$_3$N*3HF as electrolyte , and acetonitrile as solvent [31]. Carbonyl compounds, containing enol form of -CH$_2$- fragment in α-position are fluorinated with high selectivity into α-position, producing as a rule monofluoroderivatives. It is important, that phenyl substituent should be at carbonyl group or this fragment should be in cyclic system (table 11) [44]. This circumstance results in the fact that anodic fluorination is widely used for selective introduction of fluorine atom into compounds, having electron-seeking groups.

to be continued