Some tendencies in application of reagents containing O-F bonds in organic synthesis

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This paper summarizes and systemizes up-to-date information on synthesis of organofluorine compounds of different classes with use of new reagents as fluorine carriers including organic compounds containing O-F bonds (hypofluorites of perfluorinated alcohols and carbonic acids) and cesium fluorooxysulfate. Fluorinating ability of these reagents is comparatively analyzed in dependence on their structure and the solvent nature. A feasibility to fluorinate unsaturated organic, heterocyclic and hetero-organic compounds is discussed. Matters of a mechanism of fluorination with compounds containing O-F bonds are examined. Specific features of carrying out the processes of fluorination, their merits and demerits in comparison with reactions using elemental fluorine, xenon difluoride and other fluorinating agents are revealed. Availability of methyl- and tret-butylhypofluorites as reagents able to introduce the alkoxy- group into unsaturated organic compounds and their opportunities are shown. Examples of application of HOF/MeCN system as an oxidizer of unsaturated compounds to carry out processes of epoxidation and hydroxylation of olefins are under review. This oxidizer advantages, its specific peculiarities and application in organic synthesis are discussed.

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5.1. Fluorinating properties of cesium fluorooxysulfate containing the O-F ionic bond .

After the development of the method to produce cesium salt of fluoroxysulfate by Appelman the interest to this compound is steadily increasing [92-94]. Appelman isolated and completely described $CsSO_4F$ and $RbSO_4F$ [92,93]. The structure of the rubidium salt was analyzed by the X-ray structure analysis [95]. The oxidizing properties of $CsSO_4F$ were described in [96,97]. Zoopan's team in Yugoslavia executed the main work. Cesium fluoroxysulfate $CsSO_4F$ is the most stable among the class of compounds containing the O-F bond and may be successfully used in practice provided safety regulations. The organic chemistry of $CsSO_4$ has been intensively studied for the last ten years that brought to the understanding of uniqueness of this ionic electrophilic fluorinating reagent used at present for selective fluorination of organic compounds (see 98,99). The reactions with aromatic, heterocyclic compounds [93,94,99], organometallic derivatives [100], β-diketones [101], alkenes [102,106] etc. have been studied.

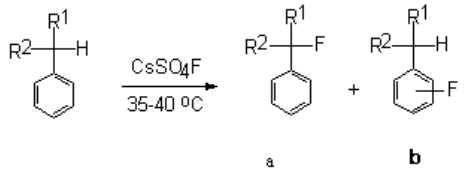
Its reactions with organic substrates depend strongly on the type of the organic molecule and the character of a functional substituent in it. It was determined that even small changes in the substrate nature and reaction conditions are sufficient for another way of the process passing. Capabilities of this reagent have not been determined completely but even the existing data allow characterizing it as a very perspective and convenient reagent in laboratory practice. It

is important that it may be successfully used for the synthesis of mono fluoro-derivatives of the aromatic series among which compounds the high biological activity have been found.

5.1.1. Aromatic and unsaturated compounds in the reactions with cesium fluorooxysulfate.

The investigation of the reactions of aromatic compounds with $CsSO_4F$ have revealed the character of behavior of this fluorinating agent . It has been found that $CsSO_4F$ in acetonitrile at 35^oC is a mild reagent fluorinating mono-alkylbenzenes to the benzene main body and to the side chain (Table 3)[49,107,108]. Functional orientation of mono- and di-substituted benzene derivatives under the influence of $CsSO_4F$ depends on the nature of the substituent in the benzene ring and the process may be directed either to the fluorination of the benzene ring itself or to involve the substituent [109]. In this process the conditions are of great importance (Table 3). The process proceeds regioselectively. When BF_3 is used as a catalyst, the fluorination affects only the benzene ring [101].

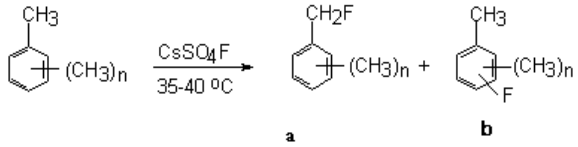
Table 3. *Results of fluorination of monoalkyl-substituted of benzene under the influence of $CsSO_4F$ [101]*



Substrate		Solvent	Content in the reaction products, %		
R^1	R^2		a	b	Total yield,%
H	H	MeCN	90	10	68
H	Me	MeCN	100	traces	73
Me	Me	MeCN	100	traces	70
H	Ph	MeCN/O_2	traces	100	12
		MeCN	85	15	70
Ph	Ph	MeCN/O_2	25	75	20
		MeCN	100	traces	70

The presence of some alkyl groups in the benzene ring does not change the character of the forming products (Table 4) [109]. The fluorination of di- and trialkylbenzenes takes place according to the same scheme: compounds with fluorine are formed both in the benzene ring and in the alkyl fragment (Table 4)[109].

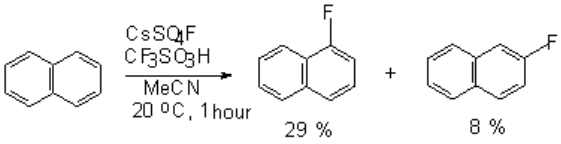
Table 4. *Fluorination of dialkyl- and trialkyl-derivatives of benzene under the influence of $CsSO_4F$ in MeCN (60% excess of $CsSO_4F$)*



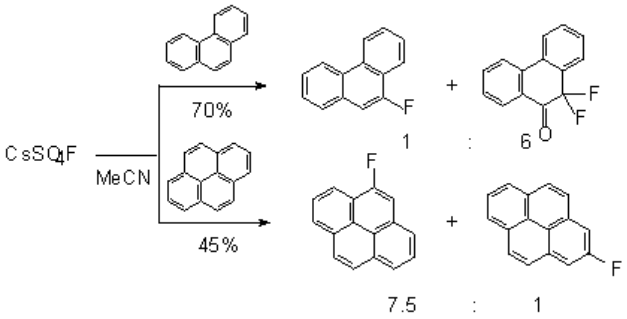
Substrate	Solvent	Content in the reaction products, %		
		a	b	Total yield,%
o-xylene	MeCN	90	10	76
m-xylene	MeCN	62	38	75
	MeCN/CH_2Cl_2(1:1)	36	64	63
	MeCN/CH_2Cl_2(1:9)	32	68	50
	CH_2Cl_2	-	traces	<2
	MeCN/$PhNO_2$	50	50	72
	MeCN/O_2	37	63	68
p-xylene	MeCN	90	10	75
	MeCN/CH_2Cl_2(4:1)	87	13	70
	MeCN/CH_2Cl_2(1:1)	73	27	53
	CH_2Cl_2	-	traces	<2
	MeCN/O_2	58	42	42
1,2,3,-trimethylbenzene	MeCN	90	10	75
1,2,3,-trimethylbenzene	MeCN	85	15	74
1,2,3,-trimethylbenzene	MeCN/$PhNO_2$	33	67	70
	MeCN/O_2	32	68	70

In case of polycyclic aromatic compounds the yield of the fluorination products is slightly less in comparison with the benzene derivatives though the ratio of the isomeric products remains the same and an increase of the *ortho*-isomer takes place [108].

In case of polyaromatic compounds (naphthalene[103,109], phenanthrene, pyrene [108]) mixtures of isomeric mono fluoroderivatives and also difluoroderivatives can be formed [101].



Zoopan used $CsSO_4F$ for the fluorination of nonactivated polyaromatic compounds, naphthalene, phenanthrene and pyrene, at room temperature for 4 hours [108].

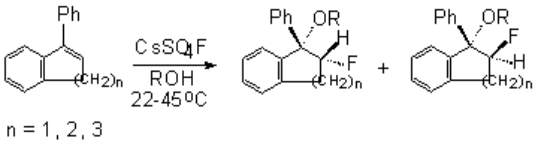


In case of the fluorination of pyrene, there is a need in a solvent in which pyrene would be easily dissolved. In this case 1-fluoro- and 4-fluoropyrones are formed in the ratio of 7.5:1 in a total yield of 40-45%.

Nonbenzene aromatic derivatives, porphyrins, react with $CsSO_4F$ to form 5-fluoropophyrins together with di-,tri- and tetrafluoro derivatives [111].

The processes of addition and elimination take place in the reaction of substituted benzene and norbornene at an excess of $CsSO_4F$ in methene chloride. It has been found that using $CsSO_4F$ in alcohols it is possible to fluorinate successfully conjugated olefins , for example indene, acenaphthylene, stilbene and substituted phenanthrene. Stereoselectivity of the reaction of 1-phenyl-1-benzocyclene with $CsSO_4F$ in alcohols was studied in papers [105,112,113]. The results are given in Table 5.

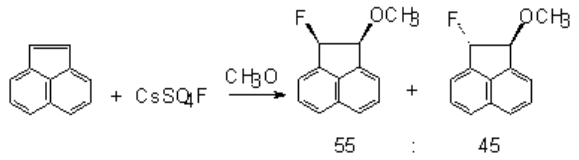
Table 5. *Influence of structure of benzocyclene and the nature of ROH alcohol on stereoselectivity of the formation of vicinal fluoroethers in the reaction with $CsSO_4F$ [105]*

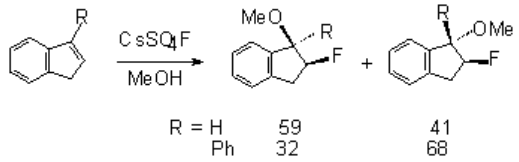


n	R	Stereoselectivity *syn/anti*	Yield,%
1	Me	2,00:1	94
	Et	2,03:1	91
	i-Pr	1,19:1	68
2	Me	0,63:1	79
	Et	0,65:1	95
	i-Pr	0,31:1	65
3	Me	1,15:1	72
	Et	2,94:1	72
	i-Pr	9,00:1	82

The stereochemistry of the process was also studied in fluorination of acenaphtene, stilbene, indene and 1-phenylidene with $CsSO_4F$. Thus, the interaction of $CsSO_4F$ with acenaphthylene leads to the formation of products of fluoromethoxylation syn:anti in a ratio of 55:45. In case of elemental fluorine at –78 °C the ratio is 35:11 and it is 16:84 for xenon difluoride.As it is evident from the data of table 5, the transition from methyl to isopropyl alcohol results

in a considerable increase in the content of syn-isomer in case of the 7-member cycle, that points to an increase of stereospecificity of the process, whereas it is not observed for small cycles.



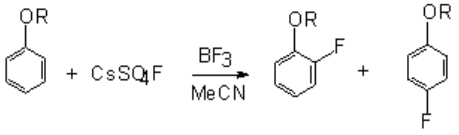


R = H 59 41
Ph 32 68

If alkyl-substituted benzenes in a reaction with $CsSO_4F$ form mixtures in different ratios of isomeric mono-fluoro-derivatives, then oxy- and alkoxy-derivatives give ortho-substituted fluorobenzenes preferably. The nature of the alkoxy-group influences the ratio of isomeric ortho- and para- fluoroalkoxybenzenes [49,107,108].Table 6 shows the data on fluorination of anisole with various fluorinating reagents.

Table 6. *Results of fluorination of anisole with different reagents*

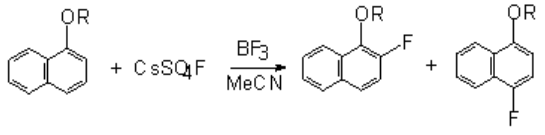
F-reagent	Conditions	o-	p-	m-	di-substituted
XeF_2	CH_2Cl_2,20°C	50	42	8	-
F_2	$CFCl_3$,-78°C	50	24	9	17
CH_3COOF	CH_2Cl_2,$CFCl_3$,-78°C	57	29	7	7
$CsSO_4F$	MeCN, 20°C	5	3	-	92
	MeCN, BF_3,20°C	87	13	-	-



R = H 6.2 : 1
Me 2.8 : 1
n-Bu 1.8 : 1
i-Bu 1.2 : 1

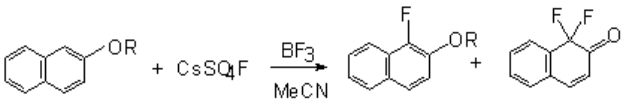
It is evident from the data that only $CsSO_4F$ falls out from a common pattern and gives practically completely ortho-isomeric product. It is most preferable to carry out such processes in the presence of polar solvents and catalysts, strong proton acids or BF_3. The yield of the products is 70-80%[114].

Appelman and collaborators studied the effect of acid catalysis (HF,H_2SO_4, BF_3, CF_3SO_3H, FSO_3H and SbF_5-FSO_3H) on the reaction of $CsSO_4F$ with toluene, nitrobenzene and naphthalene in acetonitrile [110,114]. In a general case an increase in acidity of the catalytic system results in a catalytic effect increase. These results are interpreted in terms of electrophilic fluorination catalyzed with acids. A similar picture takes place in the interaction of CsO_4F with 1-naphtol and 1-alkoxynaphthalene in the presence of BF_3 as a catalyst [49]. The yield of alkoxynaphthalenes is above 50%.



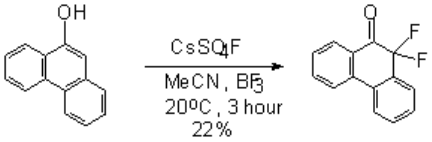
R = H 4.9 : 1
Me 2.8 : 1
Et 2.6 : 1
i-Pr 1.6 : 1

At the same time 2-naphtol and 2-alkoxynaphthalenes in the reaction with $CsSO_4F$ in the presence of BF_3 give 1,1-difluoro-2-oxa-1,2-dihydrohaphthalene together with the fluorination product in the ortho-position in a total yield of 60-80% [114]. For the first time the tendency to form α-difluoroketones was shown exactly in the reaction of $CsSO_4F$ with 1-alkoxy- and 2-alkoxynaphthalenes [100,107].



R = H	4.9	:	1
Me	2.8	:	1
Et	2.6	:	1
i-Pr	1.6	:	1

In a number of cases difluoro derivatives are the main products of the reaction [102].



9-Acetamidophenanthrene under the influence of this reagent gives 10,10-difluorophenanthrene 9(10H)-one in 22% yield , whereas 9-hydroxy- or 9-methoxy- and 9-acetoxy-derivatives give 9-fluoro-1-hydroxyphenanthrene or 10-fluoro-9,9-dimethoxy-9,10-dihydrophenanthrene [108].The fluorination of aniline with $CsSO_4F$ results in the formation of a mixture of 2- and 4-fluoroanilines. The use of the reagent labeled with ^{19}F gives a possibility to obtain important diagnostic preparations for medical purposes.

The reaction of styrene with $CsSO_4F$ in acetonitrile gives two vicinal fluorosulfates with anti-Markovnik regioselectivity[115].

Norbornene under the influence of $CsSO_4F$ reagent gives a mixture of 7-fluoro-nortricyclane and 7-syn-fluorononborn-2-ene [104].

The interaction of $CsSO_4F$ with unsaturated compounds is in general an occurence of several reactions: substitution of the hydrogen atom at the multiple bond with fluorine, addition to the double bond, conjugated fluorination with participation of the external nucleophile which source is a solvent. The completeness of the latter is influenced by the quantitative ratio of solvent/substrate [115,116]. In methyl alcohol fluoromethoxylation of the multiple bond takes place [102,103]. These ways are exhibited in the mentioned below scheme and data of Table 7.

Taken 1,2-diphenylethylene (table 8) and 1,1-diphenylethylene (table 9) as an example, it is possible to compare the data on stereochemistry of the fluorination process with cesium fluorooxysulfate and other reagents. As it is obvious from Table 8 [108], $CsSO_4F$ does not take any representative place in this series. In the reaction with (E)-stilbene it gives preferably syn-isomer whereas the mentioned fluorinating agents with (Z)-stilbene give an identical ratio of syn:anti isomers. Only trifluoroacetylhypofluorite promotes in fact selective process.

As we repeatedly noted, the reaction of $CsSO_4F$ with unsaturated compounds results either in vinyl fluorides or in products of conjugated fluorination with participation of external nucleophiles.

The authors of paper [110] managed to determine conditions under which 1,2-addition of $CsSO_4F$ to the multiple bond occurs to form cesium salts of fluoro-alkylsulfates. For the time being that is the only example of simultaneous introduction of fluorine atom and nucleophilic sulfate group into an organic molecule.

According to the usual scheme $CsSO_4F$ reacts with a group of olefins studied by Zoopan: fluoromethoxylation of the multiple bond takes place in the reaction of $CsSO_4F$ with alkenes in methyl alcohol [117,118].

A complex mixture of products is formed in fluorination of acetylene derivatives with $CsSO_4F$ (table 10). So, the fluorination of 1,2-diphenylacetylene in methanol gives two products: 1,1-difluoro-2,2-dimethoxy-1,2-diphenylethane and 2,2-difluoro-1,2-diphenylethanone [55,118]. Thus, during the course of the reaction, due to transformation of primary reaction products, compounds containing the carbonyl group can be formed [55]. A share of such compounds can be significant (Table 10) and the nature of the substituent at the triple bond does not much affects the ratio of the reaction products, for example in case of substituted phenylacetylene (R=H,Ph,t-Bu).

The authors of papers [109,119,120} developed a new method of regiospecific introduction of a fluorine atom in reactions of $CsSO_4F$ with benzyl alcohols and a-hydroxy-derivatives of aromatic compounds in acetonitrile under rather mild conditions(the yield was 70-86%). In this case the substituent at the benzene ring was replaced with fluorine to form respective aldehydes. $CsSO_4F$ in reactions with aromatic and aliphatic aldehydes in contrast to other fluorinating agents, xenon difluoride for example, gives product of substitution of the proton at the carbonyl group with

formation of fluoroanhydrides of substituted benzoic and alkyl-carbonic acids in a high yield [121]. The rate of these conversions is controlled by the nature of the substituent in the benzene ring.

In case of xenon difluoride, the products of substitution of the carbonyl group with two fluorine atoms are formed[122].

Primary aliphatic alcohols under effect of an excess $CsSO_4F$ give fluoroanhydrides of aliphatic acids, whereas cyclic and acyclic secondary alcohols under the influence of $CsSO_4F$ are converted to respective ketones [123,124]. It should be noted that the presence of a radical initiator, nitrobenzene for example, substantially reduces the yield of the target products.

At the same time phenols are fluorinated on the benzene ring.

Cyclic secondary alcohols , for example 4-tret-butylcyclohexanol under action of CsSO4F gives only 4-tret-butylcyclohexanone [125].

β-Diketones under the influence of CsSO4F give a mixture of monofluoro and difluoroketones [126].

Benzophenone and 5,5-dimethylcyclohexa-1,3-dione under the influence of $CsSO_4F$ also giv α-fluoro- an α,-difluorobenzophenones (in the ratio of 2,3:1) and 2-fluoro-3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one (in 66.5% yield) [100]. At the same time enoles of acetates of cycloalkanes give as a ru α-fluorocycloalkanones [100,126].

This property has been used to obtain fluorine-containing steroids. For example, the synthesis of 2-fluoro-3-cholesterone was done by fluorination of CsSo4F that was an important way to obtain 2-fluorovitamin D [127]. Similarly 16-fluoroestrone was produced [128].

to be continued