Journal "Fluorine Notes", Volume # 5(54), September - October 2007

The Synthesis of Low-Fluorinated Compounds Based on Polyfluoroaromatic Compounds

G. G. Furin

Siberian Branch of Russian Academy of Sciences Novosibirsk N.N. Vorozhtsov Institute of Organic Chemistry of SB RAS

Abstract

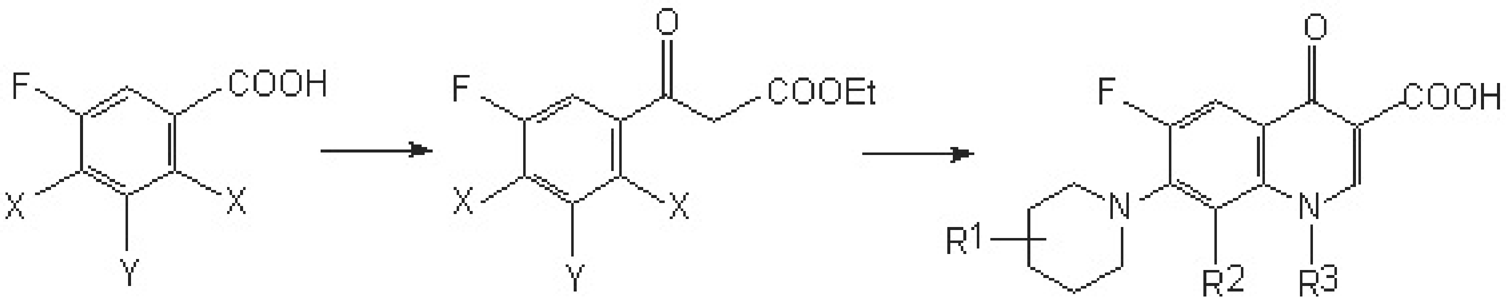
The analysis of obtaining methods for low-fluorinated derivatives of aromatic row including processes of transformation of polyfluoroaromatic compounds had been carried out: using reducing hydrogenolysis of C-F, C-Cl bonds , electrochemical transformation and protodehalogenation by the influence of zinc, copper, nickel in different media. Here the examples on using that processes with the yield of significant semi-products and materials are given.

Table of Contents

1. Introduction

Mono- and difluoroderivatives of aromayic and heterocyclic series are important semi-products for creating of medicals and herbicides. That's why it is not surprising that the attention, which many researchers pay to the development of obtaining methods for them, especially applicable for commercial implementation [1].

Here the key methods are the processes based on the Balz-Schiemann reaction [2] and the forming of benzene system with fluorine atoms with use of intermediate fluorocarbenes reactions [3]. The demand for partly fluorinated benzoic acids were originated by creating a new generation of antibiotics on their base, which action is more selective and has no or little side and harmful effect on human body. The antibiotics of the fluoroquinolone series, for example, pefloxacin, norfloxacin, ziprofloxacin, levofloxacin and others are considered to be among of the most promising for today. According to their characteristics they are close to real antibiotics and their spectrum action is rather wide. Some of fluoroquinolones are not only antibacterial but also antitumoral and anti-AIDS active. Synthesis of compounds of fluoroquinolones' series is carried out according to the scheme:



X = F, Cl

Y = H, Cl

As the development and upgrading of hexafluorobenzene and a number of benzene pentafluoroderivatives obtaining technology was going on the real opportunity for carrying out the purposeful synthesis of partly fluorinated benzenes based on them had appeared.

Purposeful and systematic study of these processes can be subdivided into two groups. The processes of fluorine or chlorine atoms substitution of benzene ring for hydrogen atoms are referred to the first group. These reactions are characterized by a quite deep variation of different structure factors, by the development and working out of reduction systems. The methods based on functional groups preliminary introduction into polyfluoroaromatic ring, that groups later are easily replaced by hydrogen atom are referred to the second group.

For example, in case of hydrazogroup [4-7] introduction the further oxidation of pentafluorophenylhydrazine using copper compounds (II) [5-6] or its decomposition in the main media during heating [6, 8] results in forming of products of reduction. This process is studied quite well and we will mark its rather high positional and substructural selectivity.

When using magnesium in methyl alcohol adding N,N- dimethylformamide the reduction of C-F bonds in hexafluorobenzene forming pentafluorobenzene with the yield of 60% goes on [9]. The oxidation of polyfluoroarylhydrazines by copper salts (II), the decarboxylation of polyfluoroarenecarboxylic acids or substitution of fluorine using lithium aluminium hydride result in forming of partly fluorinated aromatic compounds as well [2].

It was reported that [10] N,N-dimethyl-4-iodo-tetrafluoraniline had transformed into 2,3,5,6-tetrafluoro-N,N-dimethylaniline with the yield of 7% by triphenylphosphene. Protodehalogenation of 4-iodo(bromo)-

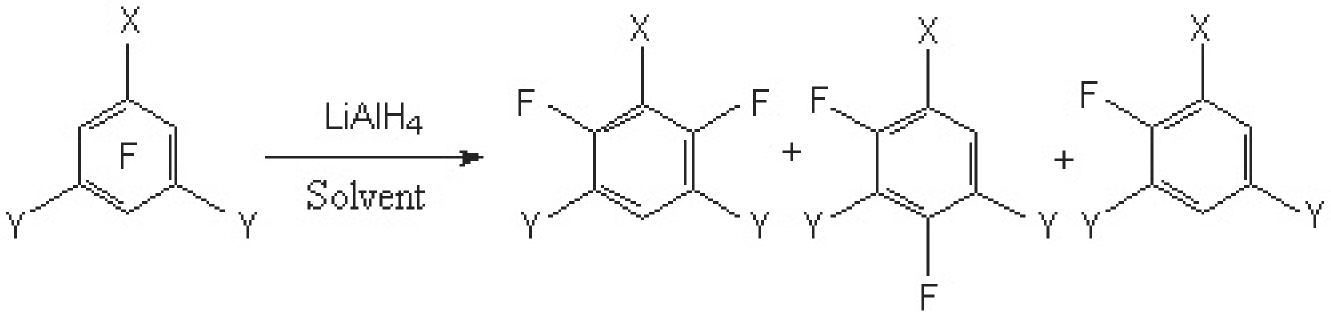
tetrafluorophenyltrimethylammonium triphlate goes on resulting with higher yields, but in case of $[C_6F_5NMe_3]^+$ * OTf^- we obtain the demethylation and not the substitution of fluorine for hydrogen. Iodonepentaflurobenzene is smoothly reduced by ($HOCH_2SO_2Na$ * $2H_2O$) rongalite, sulphite or sodium dithionite into pentafluorobenzene, while the chloropentafluorobenzene doesn't react with these reagents and transfoms into the 3-chloro-1,2,4,5-tetraflurobenzene [11] under the influence of rongalite. In the review presented we will speak mainly on the new approaches to reductive dehalogenation and only in brief we will draw a reference on the old tested by the time reductive systems and their opportunities [2].

2. Approaches to Synthesis of Partly Fluorinated Benzene Derivatives

The reduction of chlorine and fluorine containing arenes allows getting closer to the precious incompletely fluorinated benzenes, which are semi-products for the synthesis of the whole range of essential medicals and materials for agriculture.

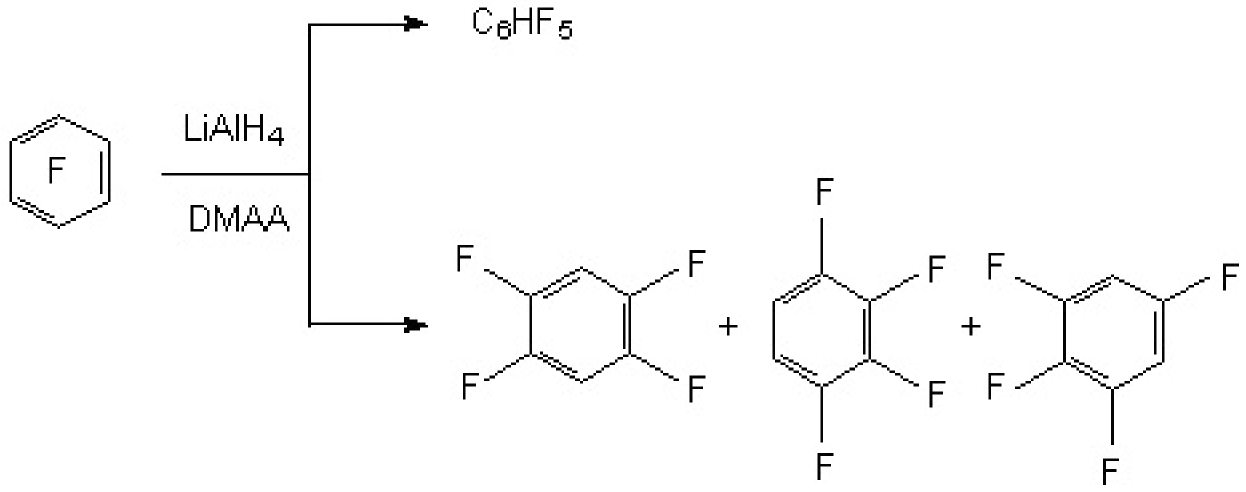
2.1. Reductive Dehalogenation of Polyfluorochloroarenes by Lithium Aluminium Hydride

We can name two processes as synthesis methods for partly fluorinated benzenes among the approaches, resulting in exchange of fluorine for hydrogen in polyfluoroarenes. One of which is based practically on nucleophilic substitution of fluorine directly for hydrogen under the influence of $LiAlH_4$ [4,9,12-15]. In this case, as a rule, the fluorine atom is affected, which is in *para*-position to the substituent in benzene ring.



X = CF_3, Cl, Br
Y = F, Cl
Solvent = MeCN, DMF, DMAA
Yield = 85-100 %

The application of bipolar aprotonic solvent like N,N,-dimethylacetamide results in substitution of several fluorine atoms in hexafluorobenzene at reducing of $LiAlH_4$ [13]. For example, during the reaction of hexafluorobenzene and sodium borane in N,N-dimethylacetamide isomeric tetrafluorobenzenes are formed along with pentafluorobenzene [9].



The reduction of polyhalogentoluols and benzenes by sodium borane in polar solvents results in forming of a mixture of products with the common yield equal to 90% with the predominance of para-isomer [9]. The rate of products depends on the selection of the solvent and reaction conditions.

2.2. Catalytic Hydration of Polyfluoroaromatic Compounds

Catalytic hydration of polyfluoroaromatic compounds using hydrogen over the noble metals, for example palladium, is one of the variants for obtaining of partly fluorinated benzenes [16,17]. However, the hydration of hexafluorobenzene over the palladium coated coal at 300 ^{o}C goes without any selection forming a mixture of products containing different number of fluorine atoms [18].

Especially this process works very well during the substitution of haloides different from fluorine atom. Thus, hydrodechlorination is carried out when palladium influences 2-chlorine-3,5-difluoroaniline at coal over triethylamine [19], 3-chlorine-a,a,a,4,5-pentafluorotoluole in methyl alcohol [20] and 2,3-difluorochlorobenzene in ethyleneglycole [21]. If there is a nitro-group in benzene ring it will become possible to substitute two chlorine atoms for hygrogen. Thus, during the reduction of 2,6- dibrome [22] and 2,6-dichloro-3,5-difluoronitrobenzenes [22, 23] using hydrogen over palladium and over the base not only do we have the substitution of haloid for hydrogen but we get the reduction of nitro-group as well.

3,5-dichlorotrifluorobenzoic acid is introduced into the process; the following conditions are being applied: the solvent- the alcohol at 40 ^{o}C [24], 3,5-dichlorotrifluorobenzonitrile in acetonitrile over the natrium carbonate at 82 ^{o}C [25] and dichloro-2,4,6-trifluorobenzene in aqueous NaOH at 100 ^{o}C [26]. At that the two chlorine atoms have been exchanged for hydrogen at the total yield of final products no less than 80 %.

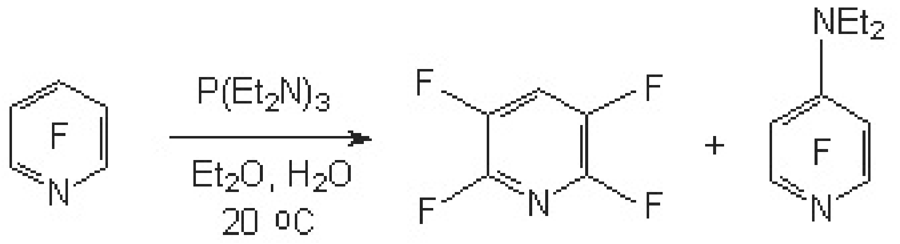
In the work [27] the information on hydration of mixture containing a- and b-chloroheptafluoronaphtalenes above palladium is given, in this case the mixture containing 30% of a-heptafluoronaphtalene and 70% of b-heptafluoronaphtalene was obtained with the yield of 80%.

Under the same conditions the hydrodechlorination of pentafluorochlorobenzene was carried out till the obtaining of pentafluorobenzene and the same process was accomplished with the mixture of tetradichlorobenzenes till the obtaining of isomeric tetrafluorobenzenes.

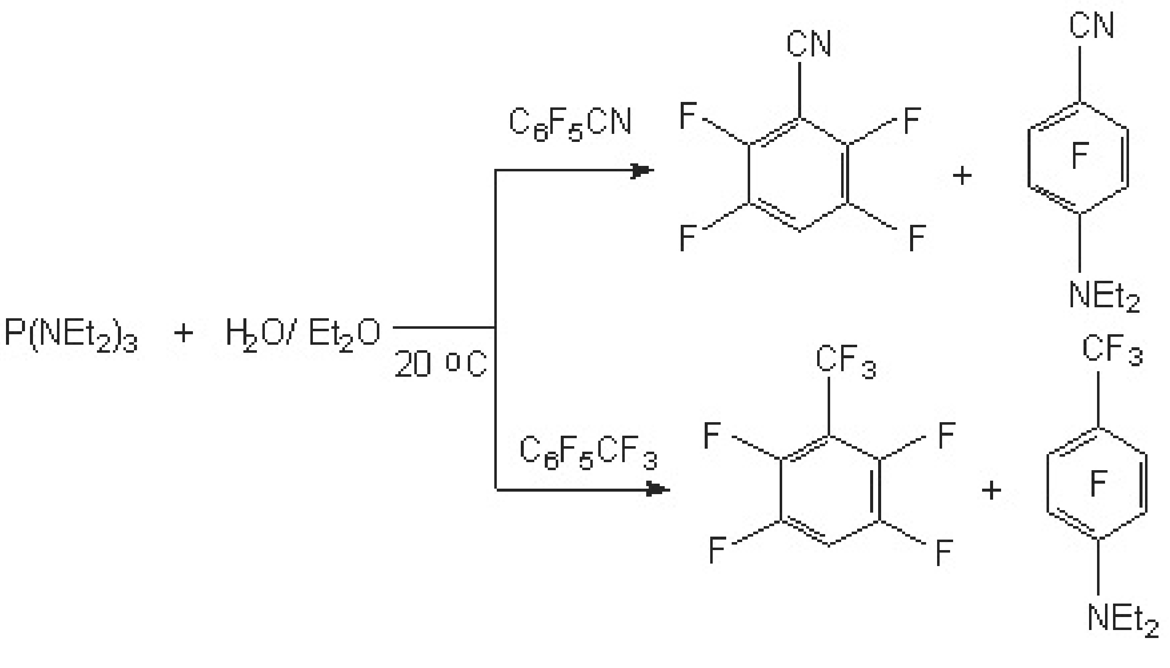
Thus, the catalytic hydration of polyfluorochlorobenzenes can be a rather convenient obtaining method of partly fluorinated fluorobenzenes, it can be implemented at a commercial scale.

2.3. Reductive Dehalogenation of Polyfluoroarenes by P(NEt2)3 in Aqueous Media

The reactions of polyfluoroarenes selective hydrodehalogenation are of synthetic interest for obtaining of partly fluorinated benzene derivatives. One of the new approaches to carrying out of this process is using of hexaethylphosphotriamide in aqueous organic solvents. It is stated [28], that under the influence of $P(NEt_2)_3$ on polyfluoroaromatic compounds over the water the substitution of fluorine atom for hydrogen takes place with the orientation corresponding to one at nucleophilic substitution. For example, in aqueous diethyl ester the influence of $P(NEt_2)_3$ on pentafluoropyridine results in forming of 2,3,5,6-tetrafluoropyridine and 4-diethylamino-2,3,5,6-tetrafluoropyridine. The use of more polar solvents for example dimethylformamide gives us exclusively 4-diethylamino-2,3,5,6-tetrafluoropyridine [28,29].



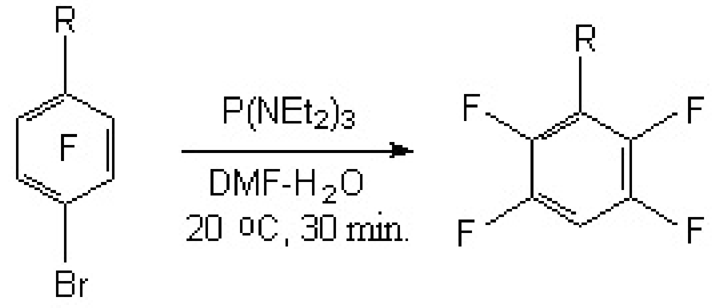
For pentafluorosubstituted benzenes derivatives containing electron seeking groups the following picture is observed - along with product of substitution of fluorine atom, which is in *para*-position to substituent we get the forming of product of substitution of fluorine atom for diethylamino-group as well. At that by the increasing of temperature and transforming into more polar solvent the share of fluorine substitution for diethylamino-group increases [29].



Pentafluorochlorobenzene remains constant at room temperature for 5 days at holding with aqueous $P(NEt_2)_3$, while the bromopentafluorobenzene and iodopentafluorobenzene are reduced under these conditions in a few minutes [30]. Instead of water methyl alcohol can be used. Thus, pentafluorobenzene is formed with a quantitive yield out of bromopentafluorobenzene at room temperature in 5-10 minutes.

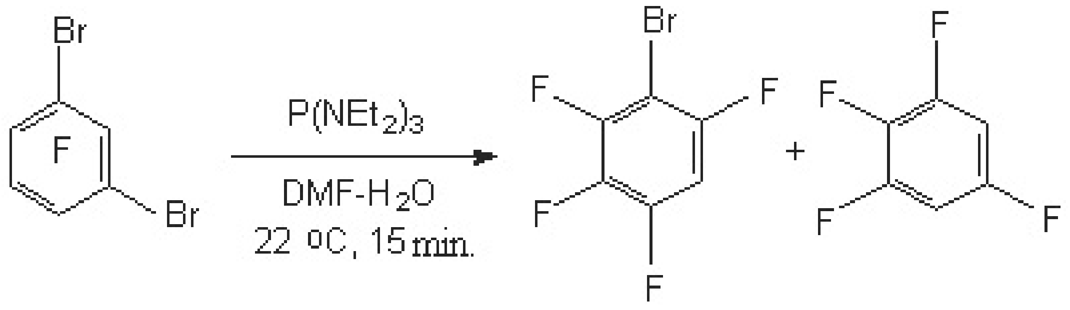
$$C_6F_5Br \xrightarrow[\substack{MeOH \\ 22\ ^oC,\ 5\text{-}10\ min.}]{P(NEt_2)_3} C_6HF_5$$

The presence of both electrone-acceptor and electrone-donor substituents in benzene ring under the influence of $P(NEt_2)_3$ in aqueous organic solvents does not tell upon the character of the products formed, influencing only the target product yield. At that only the bromine atom is being substituted.



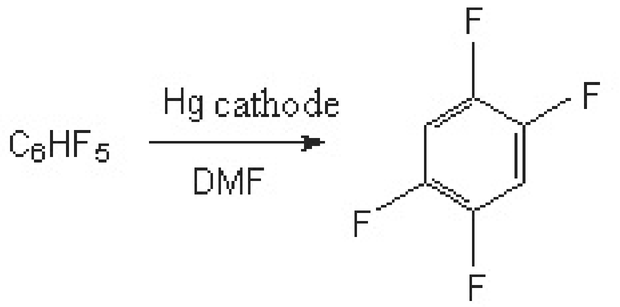
R = CF_3, OMe, NC_5H_{10}

If in the molecule of perfluoroarene there is more than one bromine atom then the process of their successive substitution for the hydrogen atom is possible. Thus, when the equivalent of $P(NEt_2)_3$ influences 1,3-dibromotetrafluorobenzene the mixture of 1-bromo-2,4,5,6-terafluorobenzene and 1,3,4,5-tetrafluorobenzene is formed while in the excess of $P(NEt_2)_3$ the both bromine atoms are being substituted for hydrogen.

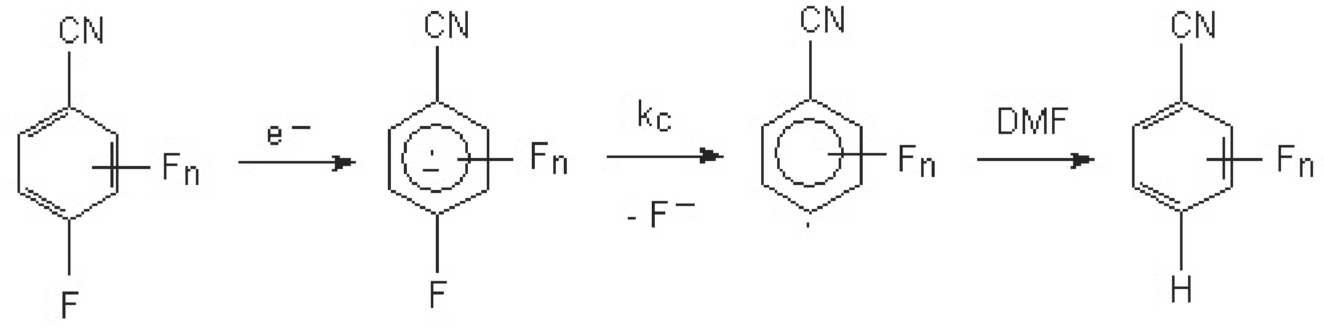


2.4. Electrochemical Reduction of Fluorine Containing Benzene Derivatives.

Selective reduction using electrochemical method is an important component of the obtaining method for partly fluorinated aromatic compounds. The using of mercury electrode for these purposes allows the reducing of pentafluorobenzene, 1,2,3,5-tetrafluorobenzene, 1,2,4,5-tetrafluorobenzene, 1,3-difluorobenzene and also 4,4'-difluorodiphenyl and decafluorodiphenyl [31, 32] in the solution of dimethyl-formamide. At that, the fluorine atom is affected, which is in para-position to the hydrogen cycle and partly fluorinated benzene derivatives are formed. Here we should notice that the total reduction of benzene fluorine derivatives is possible. Thus, *meta*-difluorobenzene [33] and hexafluorobenzene [34] are reduced to benzene.



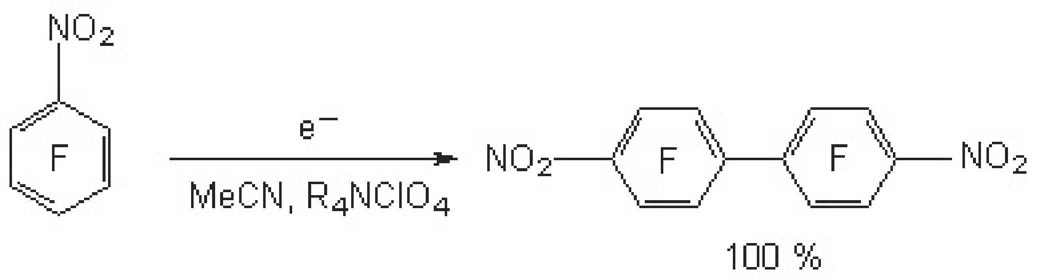
The electrochemical reduction of fluorine containing benzene derivatives stands at a very important place, what is caused by the intensive study of the electron structure and reactivity of anion-radicals of halogen-aromatic compounds [35]. In the framework of this project we have carried out the reduction of fluorinated benzonitriles in dimethylformamide and we have obtained very good resolution spectra of electron paramagnetic resonance (EPR). It is supposed, that the reduction process goes through the intermediate generation of anion-radical of benzene derivative, which during the reaction process is being decomposed forming the aryl radical and ion fluoride. Such anion-radicals were settled by EPR method for the compounds, containing electron acceptor substituents in benzene ring. In case of fluorine containing benzonitriles the reduction leads to the forming of products of fluorine atom substitution, which is in para-position to CN-group, for hydrogen atom [36-38].



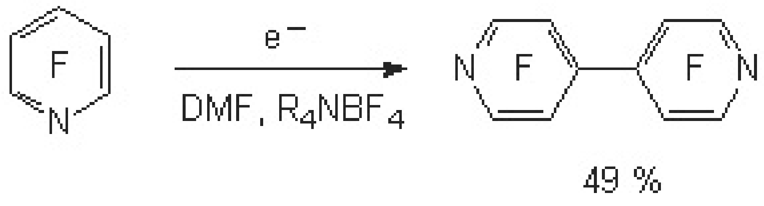
As it is stated in the works [39,40] the constant of anion-radicals fragmentation rate depends on the number and disposition of the fluorine atoms in benzene ring.

Substituted benzonitrile	k_c (c^{-1})
4-fluoribenzonitrile	11
2,4-difluoribenzonitrile	$0.5 \cdot 10^2$
2,4,6-trifluoribenzonitrile	$0.8 \cdot 10^3$
2,3,4,6--tetrafluoribenzonitrile	10^3
pentafluoribenzonitrile	10^3

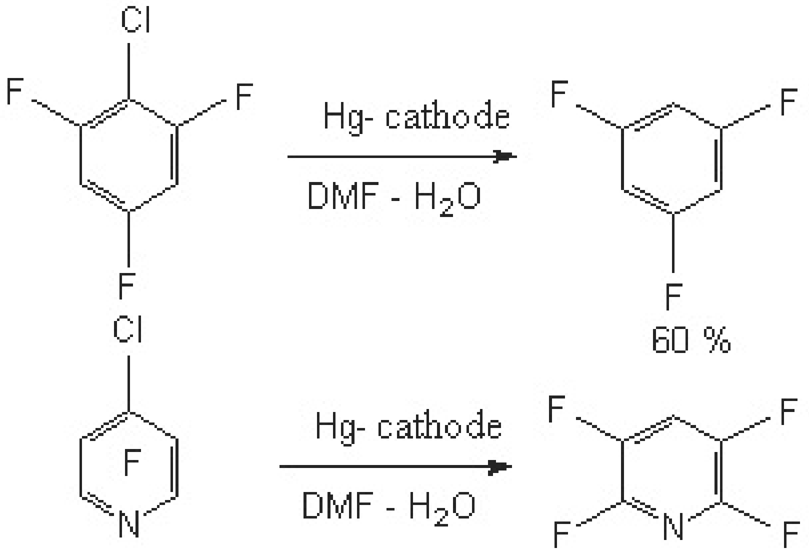
This data shows us the increasing of fragmentation rate by the increasing of the fluorine atoms number in benzene ring. In this row we also observe the increasing of anion-radicals stability by the increasing of fluorine atoms number in benzene ring for the corresponding nitrobenzenes [41, 42]. However, it should be noted, that during the electrochemical reduction of pentafluoronitrobenzene, for example in acetonitrile, dimethylformamide and at the absence of proton donor in system in the generated intermediate anion-radical we do not see the substitution of fluorine atom for hydrogen and we see forming of 4,4'-dinitrooctafluorodiphenyl with practically quantitive yield [43].



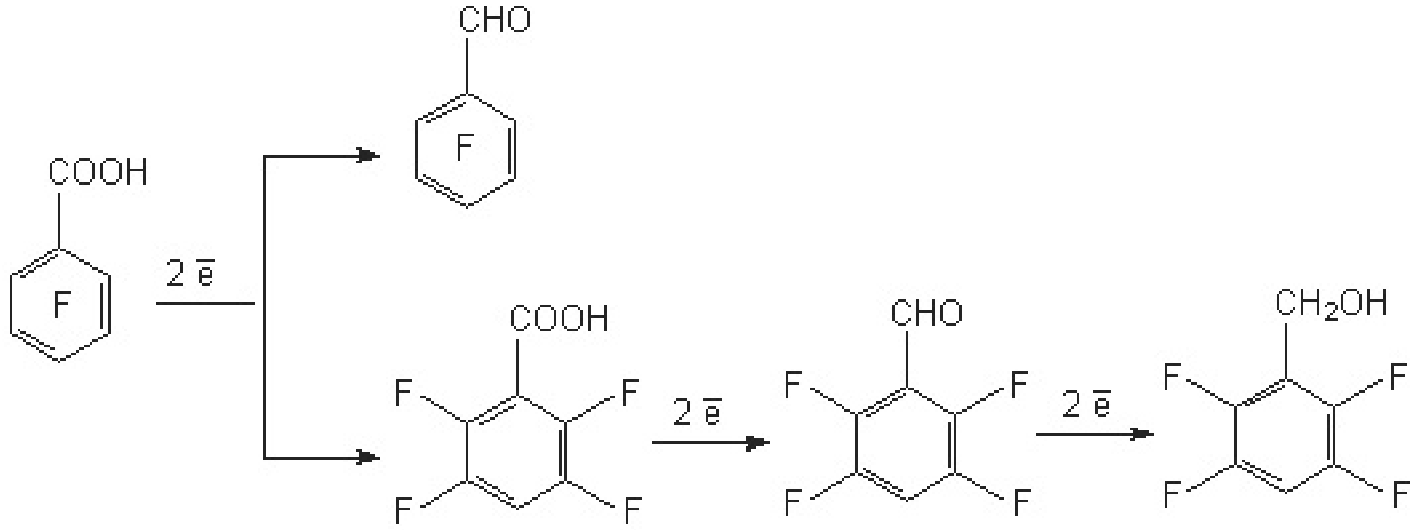
The situation like that is observed as well at the electrochemical reduction of pentafluorpyridine [44] and at the same time the presence of a rather strong proton donor in the system, which hydroquinone is ,the product of substitution of fluorine atom for hydrogen i$^{\gamma}$ -position of pyridine ring is formed [45].



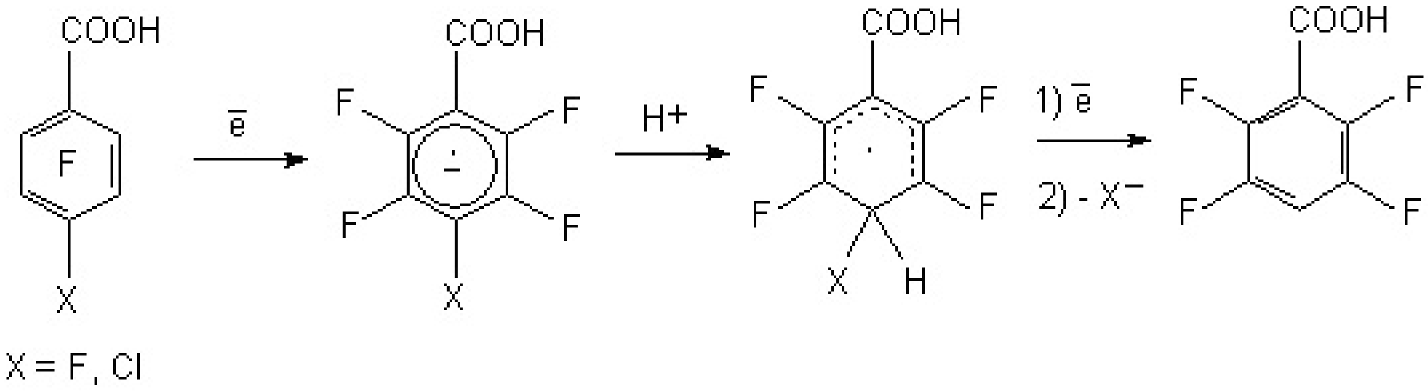
Regioselective reductive dehalogenation at electrochemical reduction of polyfluoro- and polyfluorochloroaromatic compounds was studied in details [41-47]. The authors connect the easiness of reduction with the size of electrochemical reduction potential [32,36-48]. When using aqueous solutions of dimethylformamide we can manage to carry out the hydrodechlorination. Thus, we have obtained 1,3,5-trifluorobenzene [47] out of 1-chlorine-2,4,6-trifluorobenzene, 1,3,5-trifluorobenzene was isolated out of 1,3,5-trifluorotrichlorobenzene with the good yield, and 2,3,5,6-tetrafluoropyridine [45] was isolated out of 4-chlorotetrafluoropyridine [45].



Electrochemical reduction of pentafluorobenzoic acid is carried out at mercury or leaden cathode in aqueous solutions of acids over Et_4NBF_4 electrolyte and several products are obtained, that is pointing out the simultaneously passing processes of hydrogenolysis of C-F bond and reduction of COOH group [46]. At that the hydrogen atom is affected, which is situated in *para*-position towards COOH group. The reduction of pentafluorobenzoic acid in 50% sulphuric acid at electrode potential equal to -1.20 V results in forming of 2,3,5,6-tetrafluorobenzoic acid, which concentration in the reaction mixture is 67%, while in 0.2M solution of Et_4NBF_4 at the potential equal to -2.00 V the total transformation of pentafluorobenzoic acid forming 2,3,5,6-tetrafluorobenzoic acid and 2,3,5,6-tetrafluorobenzyl alcohol (yield equals to 40 and 55% respectively) takes place.



The electrochemical reduction of pentafluorobenzaldehyde, pentafluorobenzoic and 4-chlorotetrafluorobenzoic acid amides take place similarly. The most probable mechanism of these process include initial formation of pentafluorobenzoic acid anion-radical [46].



to be continued