

Heteroatomic Chloroalkylation of Arenes and N-hetarenes

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Abstract

Promising methods are reviewed for obtaining N-, O- and S-derivatives of arenes and N-hetarenes useful from synthetic and applied standpoint (both substituted and unsubstituted) via direct heteroatomic chloroalkylation, those contain either mono-, di- or trichloroalkyl group in the α -position with respect to the heteroatom. The chloroalkylation reactions are systematized according to a particular reaction mechanism (free radical, carbene, nucleophilic or electrophilic one).

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1. INTRODUCTION

The reactions of halogenoalkylation those allow halogenoalkyl or polyhalogenoalkyl group to be introduced into the molecule of a compound, for a long time draw attention of researchers owing to synthetic and biological importance of the products obtained. These reactions can proceed either with respect to a carbon atom of or with respect to a heteroatom, if the latter is present in the structure of the compound. As an example of the first type reactions a Friedel–Crafts chloroalkylation in the arene series [1, 2] as well as similar reactions of fluorinated olefines [3, 4] could be considered.

For the last years an increasingly important part is played by the processes of perfluoroalkylation, in particular of trifluoromethylation since fluoroalkyl derivatives represent the compounds interesting from the point of physiological activity, which was reflected in a number of publications including reviews [5–8] and a monograph [8a]. On the contrary, the reactions heteroatomic halogenoalkylation those be-

long to the second type have not been systematized till now, though for the last years the works on heteroatomic polyfluoroalkylation of hetarenes [9–11] actively came into carrying out, and heteroatomic chloroalkylation of arenes and hetarenes is already actively studied and used by chemists for a long time.

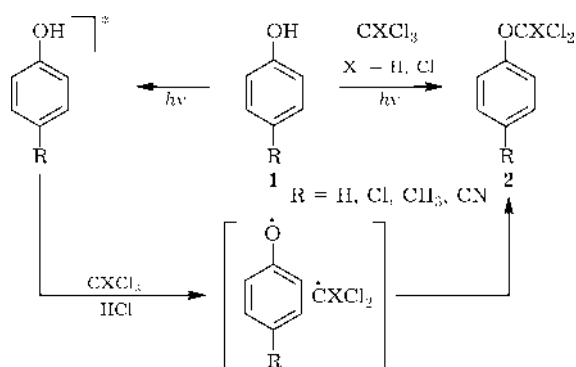
The importance of the reactions of heteroatomic chloroalkylation is first of all determined by the fact that they enable a ready chloroalkyl group to be introduced into a molecule, avoiding the process of chlorination of an alkyl derivative with the use of elementary chlorine or other hazardous chloridizing reagents. Such reactions are not only a source of additional data on the reactivity of compounds under investigation, but also provide obtaining the substances with the properties interesting both from the point of synthesis and of applications. Indeed, due to the presence of the E-CClXY fragment (where E = N, O, S; X = Y = Cl; X = Cl, Y = R; X = R, Y = R') these substances can be used as initial products for the synthesis of various types of derivatives, including fluoroalkyl compounds, too [12–14].

On the other hand, the compounds with such fragments could themselves exhibit an appreciable physiological activity as well as other properties useful for practice. So, the presence of SCCl_3 group may cause the substances to exhibit fungicidal, insecticidal and herbicidal properties [15, 16]. In the synthesis of herbicides and insecticides the derivatives containing OCCl_3 or OCCl_2 are also used [17–19]. The compounds containing SCCl_3 and SCCl_2 groups are intermediate species in the synthesis of medical products [20, 21] as well as of azo and cyanine dyes [22, 23]. High biological activity is exhibited by heterocyclic compounds containing N-CCl_3 fragment [24, 25].

In the present review the chloroalkylation reactions at the heteroatomic position of N-, O- and S-containing derivatives of arenes and N-heteroarenes (both substituted and unsubstituted) are considered those occur with the formation of compounds containing α chloro- or polychloroalkyl fragment in the α -position with respect to a heteroatom. For the most part, the works have been analysed those were accomplished within the last 15 years. The systematisation has been carried out according to the mechanism proposed. It should be noted that the final result of the reaction of chloroalkylation depends on the stability of formed the chloroalkyl derivative formed: either it is stable it can be isolated, or it is unstable under treatment, or it is formed only as an intermediate species resulting in the formation of the substances of another structure as the end products.

2. FREE RADICAL POLYCHLOROALKYLATION

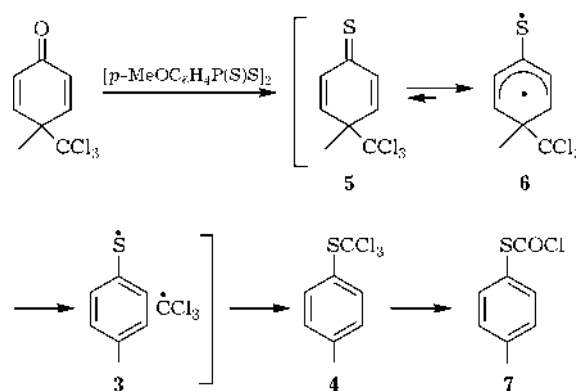
Free radical polychloroalkylation at the heteroatomic position in the series of N-, O- and S-containing derivatives of arenes and N-heteroarenes usually occurs due to the action of trichloromethyl or dichloromethyl radical generated from CCl_4 and CHCl_3 or from the other sources with the use of photochemical or thermal technique. Since such radicals are capable for reacting not only with a heteroatomic fragment, but also with a carbon atom of the ring, in a number of cases complicated mixtures of products are formed with a rather low content of the necessary compounds.



Scheme 1.

A notable example of free radical polychloroalkylation in a number of O-containing compounds is a Reimer–Tiemann photoreaction of substituted phenols in the absence a base [18]. The photolysis of phenols **1** in CHCl_3 or CCl_4 media results in the formation of corresponding di- and trichloromethyl ethers **2** as main products (Scheme 1).

The reaction with CCl_4 proceeds more efficiently, though in both the cases the conversion level as a whole is rather high (55–95 % for CHCl_3 , 66–100 % for CCl_4); electron donating substituents promote its increase, and electron accepting ones promote its decrease. Due to the absence of bases under the conditions of such photolysis, dichloromethylaryl ethers were obtained, unstable in the basic media. For the formation of polychloroalkylaryl ethers a mechanism of electron transfer is postulated including electron detachment from radiation-excited phenol, electron transfer to solvent, reductive cleavage of a solvent to produce dichloro- or trichloromethyl radical and then the inter-

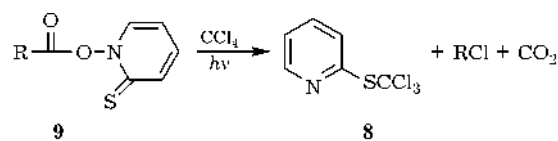


Scheme 2.

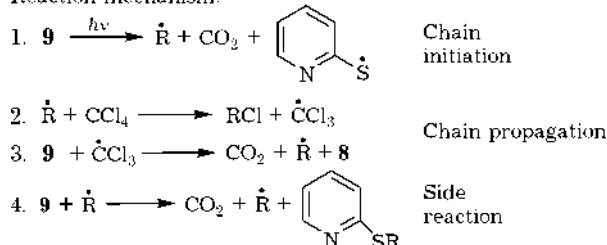
action of these radicals with a radical or radical cation of phenol (see Scheme 1).

The recombination of the radical pair **3** (Scheme 2) results also in the formation of *p*-tolyltrichloromethylsulphide **4** during a skeleton rearrangement of thioketone **5**, proceeding with a 1,5-shift of the substituent and aromatisation [26]. It seems reasonable to believe that the reaction proceeds through a biradical state like *p*-semiquinoid thioketone species **6** transforming into a radical pair **3**. The compound **4** was isolated with the yield of 84 %, but being unstable it was partially undergone to hydrolysis to produce *p*-tolylthiochloroformate **7**.

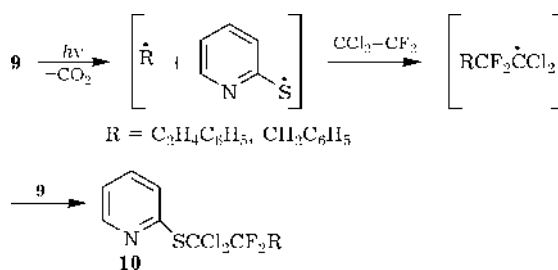
2-Pyridyl trichloromethylsulphide **8** is formed as one of the products during the process of free radical halogenation of the esters of aromatic and aliphatic acids, accompanied by decarboxylation reaction (that is an analogue of a Hunsdiecker reaction), which is carried out in the presence of halogene donors such Cl-CCl₃, Br-CCl₃, I-CHI₂ [27]. The essence of this method consists in the fact that the esters **9** (see Scheme 3), obtained from the acids and N-oxy-2-thiopyridone, at heating or under irradiation with visible light are capable of undergoing to a free radical chain transformation with a loss of CO₂ and then in the presence of CCl₄ to produce sulphide **8** alongside with aryl- or alkylchlorides and other products. The yield of the compound **8** ranges from 50 to 90 %. As for the method suggested, the range of initial



Reaction mechanism:



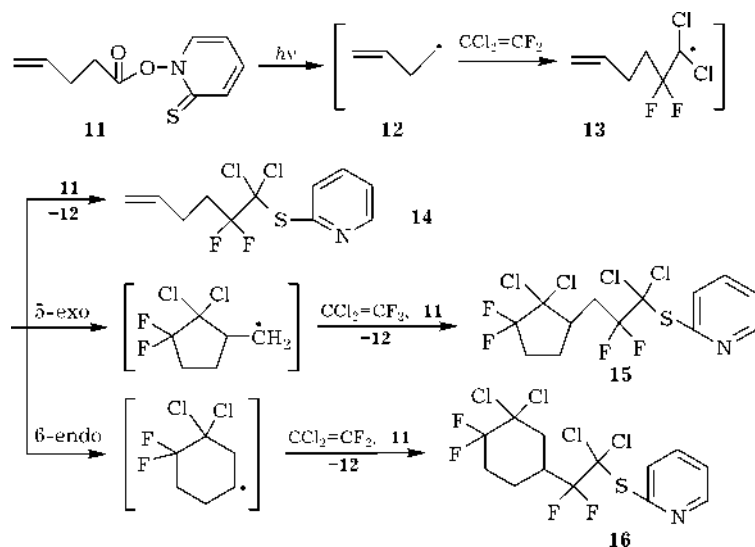
Scheme 3.



Scheme 4.

esters such as **9** obtained from the acids of various classes of compounds is essentially extended [28–31].

Besides the thermolysis and photolysis, the reaction was initiated also using an ultrasonic technique [32]. The results obtained have demonstrated that the advantage of such initiation consists in more mild conditions the reaction proceeds. The use of 1,1-dichlorodifluoro-

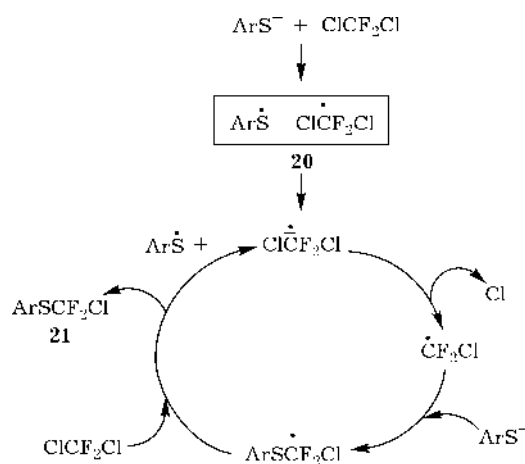


Scheme 5.

ethylene as a spin trap for free radicals made it possible to obtain sulphides **10**, the analogues of the compound such as **8** containing a more complicated radical at the atom of sulphur with an α -dichloromethylene fragment (Scheme 4) [30, 31]. In such a way, for example, corresponding sulphides **10** were obtained from the esters such as **9** (where $R = C_2H_4C_6H_5, CH_2C_6H_5$) with the yield of ~45 %.

In the case of the esters of aliphatic unsaturated acids (see, for example, compound **11**, Scheme 5) free radicals such as **12** formed during irradiation, interact with a spin trap to produce radicals like **13** capable of undergoing an intramolecular cyclization resulting in the formation of new cyclic radicals those participate in the reaction, too. As the result a mixture of compounds like **10** is formed, with a non-cyclized functional group R (**14**, the yield of 35 %) as well as with a cyclized functional group R' (**15** and **16**, the yield of 8 and 4 %, respectively) (see Scheme 5). In the presence of substituents at the double bond of compound **11** the ratio between non-cyclized and cyclized products is determined by the nature of these substituents [31].

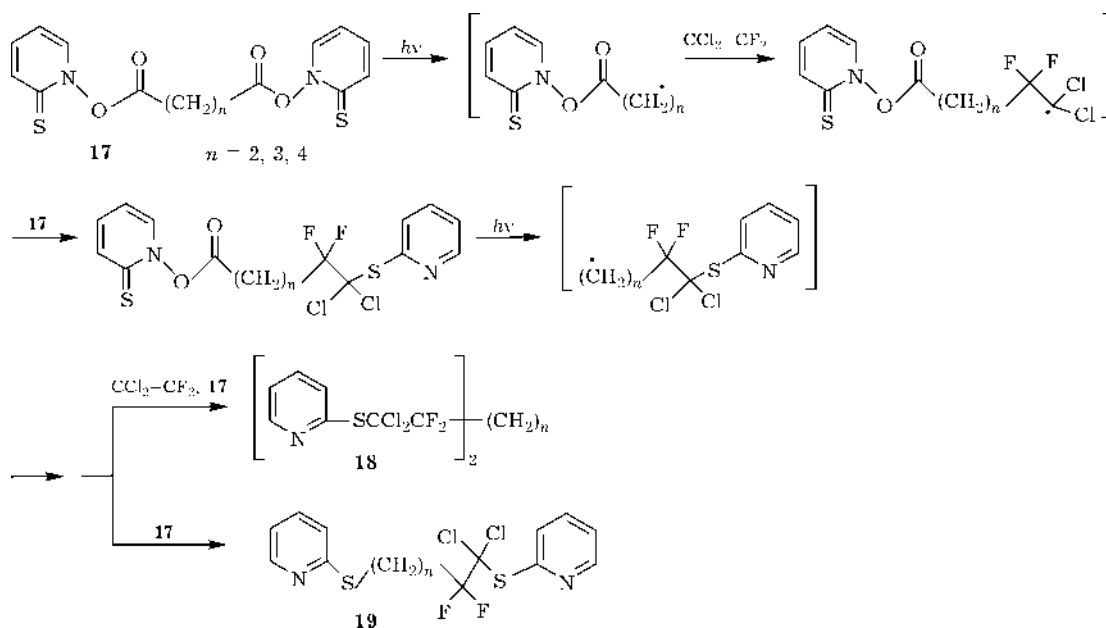
From the esters of aliphatic dibasic acids like **17** and 1,1-dichlorodifluoroethylene under irradiation, the compounds such as **18** result with the yields amounting to 50, 62 and 48 %



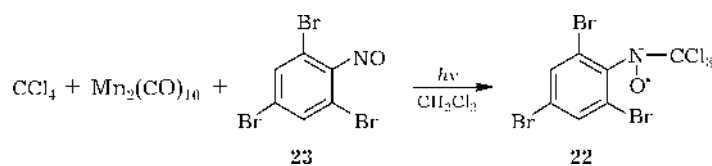
Scheme 7.

for $n = 2, 3, 4$, respectively and **19** with the yield ranging from 10 to 28 % (Scheme 6) [30].

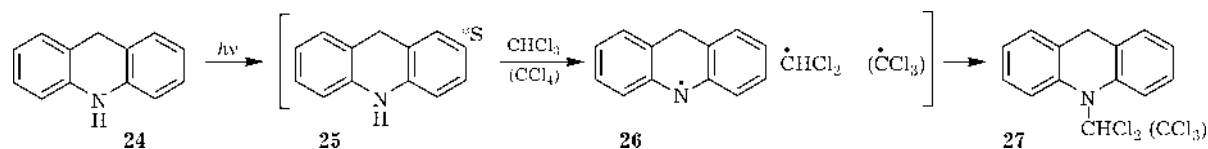
The free radical chain mechanism was postulated for the formation of chlorodifluoromethylaryldisulphides in the reactions of arylthiolates with dichlorodifluoromethane in DMF media. When carrying out the reaction under increased pressure the yield of a sulphide such as **21** (Scheme 7) ranges from 40 to 60 % [33]. It is supposed that during the course of the transformation a single-electron transfer from thiophenolate ion to polyhalogenomethane occurs with the formation of a radical/radical-anion pair such as **20** in the cage of solvent



Scheme 6.



Scheme 8.



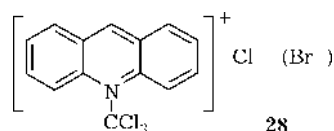
Scheme 9.

which pair transformation then results in the formation of sulphide like **21** (see Scheme 7). As distinguished from thiophenolates, phenolates do not enter into similar reaction in DMF media, which, probably, is connected with the fact that phenolate ion is incapable of electron transfer and then of further formation of a radical/radical anion pair [34].

In the reaction of potassium thiophenolate with trichlorofluoromethane in DMF media under increased pressure, dichlorofluoromethanesulphide is formed with a low yield (~21 %), but the mechanism of this reaction was not discussed by the authors [35].

Free radical trichloromethylation of nitrogen heteroatom was used in order to study various photochemical or thermal radical reactions proceeding in CCl_4 or CHCl_3 media by means of ESR method. In this case in order to confirm the formation of trichloromethyl radical basing on ESR spectra, its radical adduct **22** is detected resulting from the reaction with a spin trap such as tetramethylnitrobenzene [36] or 1,3,5-tribromonitrobenzene **23** [37] (Scheme 8).

Using the method of chemically induced dynamic nuclear polarization (CIDNP) it has been demonstrated [38] that under the photolysis of alcoholic solutions of acridane **24** and its 9-derivatives (C_6H_5 , $\text{CH}_2\text{CH}_2\text{OH}$) in the presence CHCl_3 or CCl_4 , N-dichloromethyl and N-trichloromethyl acridane derivatives are

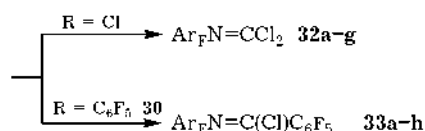
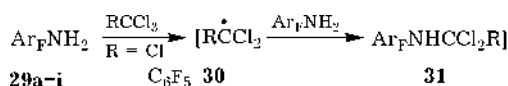


formed, respectively. It is supposed (Scheme 9) that the singlet acridane **25** formed during the process of irradiation due to the interaction with polyhalogenomethane produces a radical pair **26**, one of the pathways of the transformation of the latter resulting in the formation of compounds such as **27**.

Under UV or γ -irradiation of acridine or 9-methylacridine solutions in CCl_4 or CBrCl_3 , solid products were obtained to which the products the structure of salts such as **28** have been attributed.

The pathways of their formation are not unequivocally established, but one suppose the participation of trichloromethyl radical [39] in the process.

The reaction of free radical polychloroalkylation in the series of polyfluoroaromatic amines was carried out in the course of high-temperature joint pyrolysis (500–620 °C) of polyfluorinated primary amines of benzene series **29a-g**, naphthalene **29h** and pyridine **29i** in flow system with CCl_4 and pentafluorobenzenetrichloro-



$\text{Ar}_F = \text{C}_6\text{F}_5$ (**29a**, **32a**, **33a**); 4- $\text{CF}_3\text{C}_6\text{F}_4$ (**29b**, **32b**, **33b**);
4- HC_6F_4 (**29c**, **32c**, **33c**); 4- BrC_6F_4 (**29d**);
4- ClC_6F_4 (**29e**, **32d**, **33d**); 4- CNC_6F_4 (**29f**, **32e**, **33e**);
2, 6, 4- $(\text{CF}_3)_3\text{C}_6\text{F}_2$ (**29g**, **33f**);
2-heptafluoronaphthyl (**29h**, **32f**, **33g**);
4-tetrafluoropyridyl (**29i**, **32g**, **33h**).

Scheme 10.

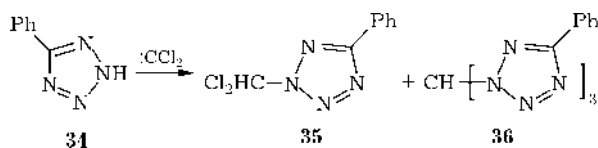
ride **30**. The polychloroalkylpolyfluoroarylamines **31** (Scheme 10) expected to be produced, are apparently formed as intermediate species being transformed into polyfluoroarylcarbonimidoyl chlorides **32a-g** (with the yield of 21–37 %) or polyfluoroarylimidoyl chlorides **33a-h** (with the yield of 50–77 %) [40]. An attempt to involve fluorinated amines, for example aniline into the reaction, was unsuccessful, which could be connected with thermal instability of hydrocarbon compounds under the conditions of high temperatures [40].

3. REACTIONS WITH THE PARTICIPATION OF DICHLOROCARBENE

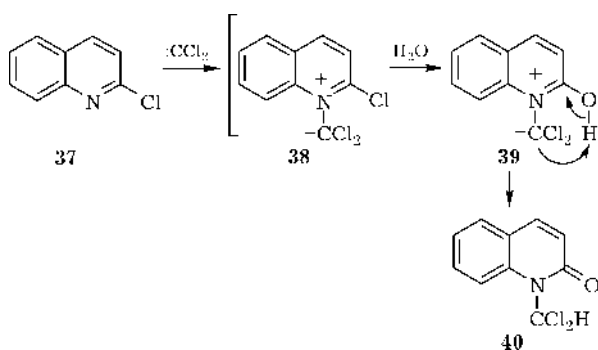
A prevailing number of polychloroalkylation reactions with the participation of dichlorocarbene was carried out in the series of N-containing compounds. The generation of dichlorocarbene was carried out from CHCl_3 under the conditions of interphase transfer catalytic reaction. Thus, from 2-*tert*-butyl-1H-benzimidazole [41] alongside with other products a small amount of 2-*tert*-butyl-1-dichloromethyl-1H-benzimidazole has been obtained. Low content of this compound in the reaction mixture might be, apparently, connected with the fact, that being a primary product of the reaction it could transform further to give di- and tribenzimidazolyl-methanes. The reaction with 5-phenyltetrazole **34** proceeds in a similar manner

to result in the formation of 2-dichloro-5-phenyltetrazole **35** (with the yield of 4 %) and tris(5-phenyltetrazole-2-yl) methane **36** (with the yield amounting to 23 %) (Scheme 11) [42].

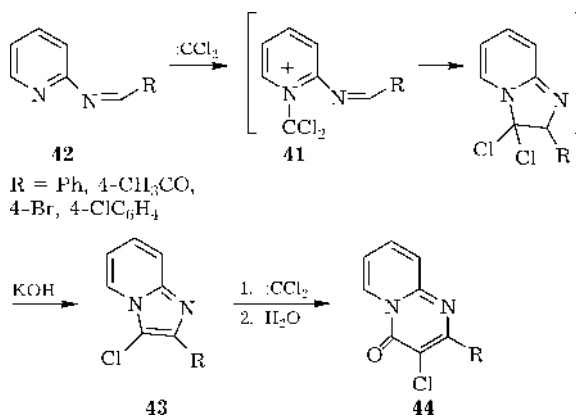
2-Chloro derivatives of quinoline, pyridine and benzotriazole under the conditions of interphase transfer catalytic reaction are subjected to the attack by dichlorocarbene and to the replacement of chlorine, which results in the formation of corresponding N-dichloromethyl-2-oxo derivatives with the yields amounting to 25, 13 and 19 % [43]. The mechanism of the reaction is presented by the example of 2-chloroquinoline **37** (Scheme 12). The first stage could consist in the formation of ylide **38** further interacting with water with the substitution of active chlorine. Then a proton migration would occur through 5-membered transition state **39** to result in the formation of N-dichloromethyl-2-quinolone **40**. According to [44], the reaction of dichlorocarbene with 2-chlorobenzothiazole proceeds in much the same manner as the reaction described above and results in the formation of N-(dichloromethyl)benzothiazole-2-one with the yield of 60 %. Quinoline, 4-cyanopyridine, 2-chloro-6-methoxypyridine, 2-methylbenzothiazole do not react with dichlorocarbene. In the case of 2-chloro-6-methylpyridine, 2-bromopyridine, 2-cyanopyridine and 4-chloro-2-methylquinoline, labile products were observed to appear not identified by the authors of [43].



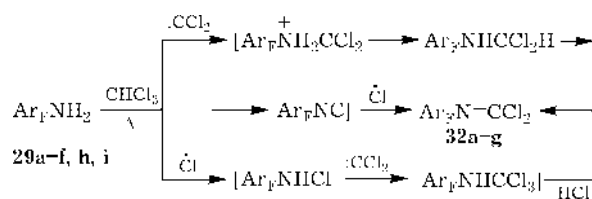
Scheme 11.



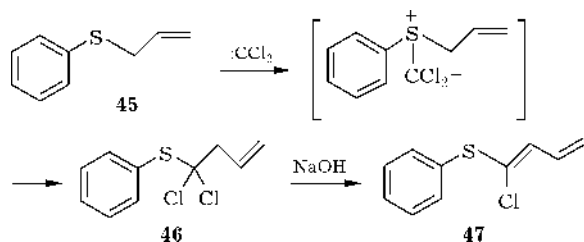
Scheme 12.



Scheme 13.



Scheme 14.

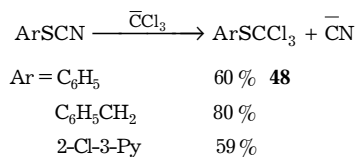


Scheme 15.

Pyridinium dichloromethides **41**, the hypothetical intermediate species formed in the reaction of dichlorocarbene with 2-(benzylidene-amino)-pyridines **42**, undergo intramolecular 1,5-cyclization to give 2-aryl-3-chloroimidazo [1,2a] pyridines **43** (the yield of 35–40 %) those under the conditions of the reaction are partially transformed to produce 2-aryl-3-chloro-4H-pyrido[1,2a]pyrimidine-4-ones **44** (Scheme 13) [45]. The reaction with dichlorocarbene affects only a pyridine nitrogen atom, which may be caused by a decrease in nucleophilic properties of azomethyne nitrogen atom due to the electron accepting influence of the pyridine ring and the polarization of chemical bonds in the CH=N–C=N system. The prevailing route of the reaction of a quinoline analogue of the compound **42** (R = Ph) with dichlorocarbene is similar to that shown in Scheme 13 [45].

From polyfluoroaromatic amines **29a–f, h, i** at high-temperature joint pyrolysis (620–670 °C) with CHCl₃ that acts the part of dichlorocarbene source, polyfluoroarylcarbonimidoyl dichlorides **32a–g** are formed with the yield ranging within 14–34 % [40], identical to those obtained as the result of free radical joint pyrolysis of these amines with CCl₄ mentioned above (see Section 2). As well as for the free radical variant of the process, it is supposed that polyfluoroarylpolychloroalkylamines are formed as intermediate species. Possible pathways of the reaction course are presented in Scheme 14.

The products of the attack of heteroatom by dichlorocarbene were not isolated, but they



Scheme 16.

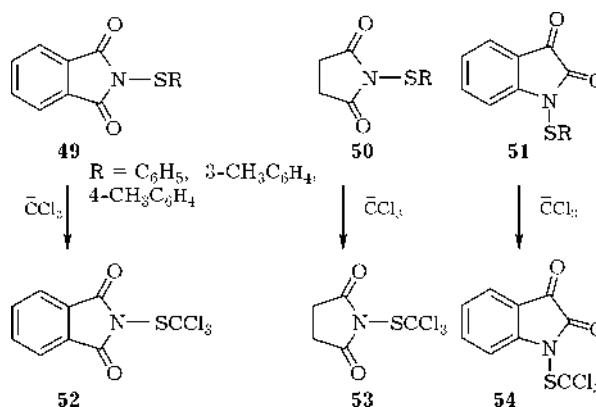
were also postulated in the carbene scheme of reactions with aromatic secondary amines [46], sodium thiophenolates [47], pentafluorophenol [48] resulted in the producing of arylorthoamides, arylorthothioformates and arylorthoformates, respectively (with the yield of 80–90 %).

The interaction of dichlorocarbene with phenylallylsulphide **45** results in the formation of unstable (1,1-dichloro-3-butenyl)-phenylsulphide **46** with the yield of 64 % (Scheme 15) [49] that readily turns into (1-chloro-1,3-butadienyl) phenylsulphide **47**.

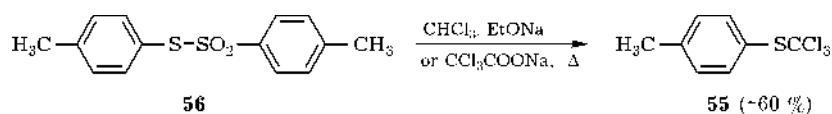
4. NUCLEOPHYLIC ROUTES OF CHLOROALKYLATION

It is possible to use trichloromethyl anion generated from CHCl₃ in biphasic system for trichloromethylation of atom sulphur in S-containing compounds, for example arylthiocyanates [50] and het arylthiocyanates [51] (Scheme 16).

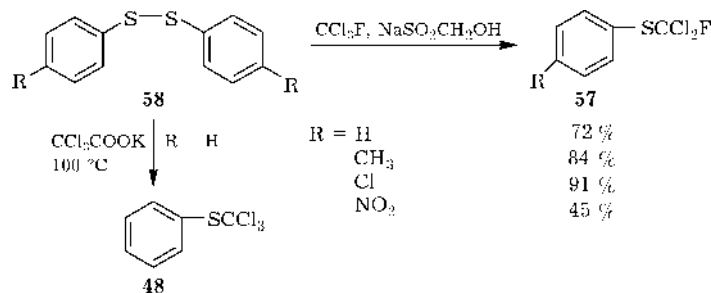
Trichloromethyl anion as a rather soft base attacks mainly the atom of sulphur. This attack is favourable also due to the ability of sulphur to stabilize a negative charge at the expense of unoccupied 3d-orbitals. The formation of sulphides with a good yield is testimony to high reaction rate for the interaction of trichloromethyl anion with thiocyanates (being higher than for the decomposition of this anion pro-



Scheme 17.



Scheme 18.



Scheme 19.

ducing dichlorocarbene). However, the data obtained do not make it possible to determine unequivocally the mechanism of cyano group replacement: the reaction might occur either through the formation of an intermediate anionic adduct, or according to a synchronous mechanism such as S_N2 via a transition state.

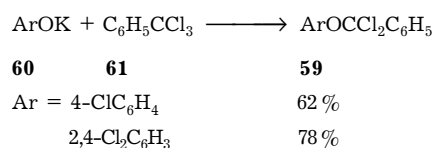
Due to the availability of source thiocyanates, the simplicity of the procedure, high yields as well as the purity of products obtained the present method for the synthesis of trichloromethylarylsulphides offers some advantages over other known methods for such compounds to obtain.

The obtaining of trichloromethylsulphides **52–54** from *N*-thio-substituted phthalimides **49**, succinimides **50** and isatins **51** (the yield amounting to 24–42 %, Scheme 17) [52], as well as of *p*-tolyltrichloromethyl sulphide **55** from (*p*-tolyl)-*p*-toluenetiosulphonate **56** is also based on the principle of nucleophilic substitution of the residue at bivalent sulphur atom by trichloromethyl group (Scheme 18) [53]. In the latter case, the results did not differ from each other both for the process of trichloromethyl anion generation from CHCl_3 and for the thermolysis of sodium trichloroacetate.

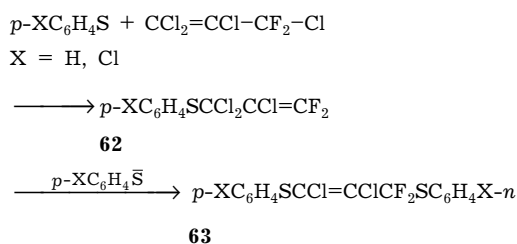
Dichlorofluoromethylarylsulphides **57** are formed with a good yield from diarylsulphides **58** and CCl_3F in the presence of sodium hydroxymethanesulphinate in aqueous DMF under increased pressure (Scheme 19) [35]. Sulphide **48** with the yield of 80 % was obtained from disulphide **58** (R = H) due to interaction with trichloromethyl anion formed during the process of thermal decomposition of potassium trichloroacetate in DMF media at 100 °C (see Scheme 19) [54]. An attempt to obtain phenylchlorodifluoromethylsulphide in much the same manner in the reaction compound **58** (R = H) with potassium salt of chlorodifluoroacetic acid was unsuccessful, which seems to be connected with a worse stability of chlorodifluoromethyl anion under the conditions of this reaction in comparison with other anions.

Chlorine-containing benzylphenyl ethers **59** as potential insecticides were synthesized through the interaction of potassium phenolates **60** with benzotrichloride **61** (Scheme 20) [19].

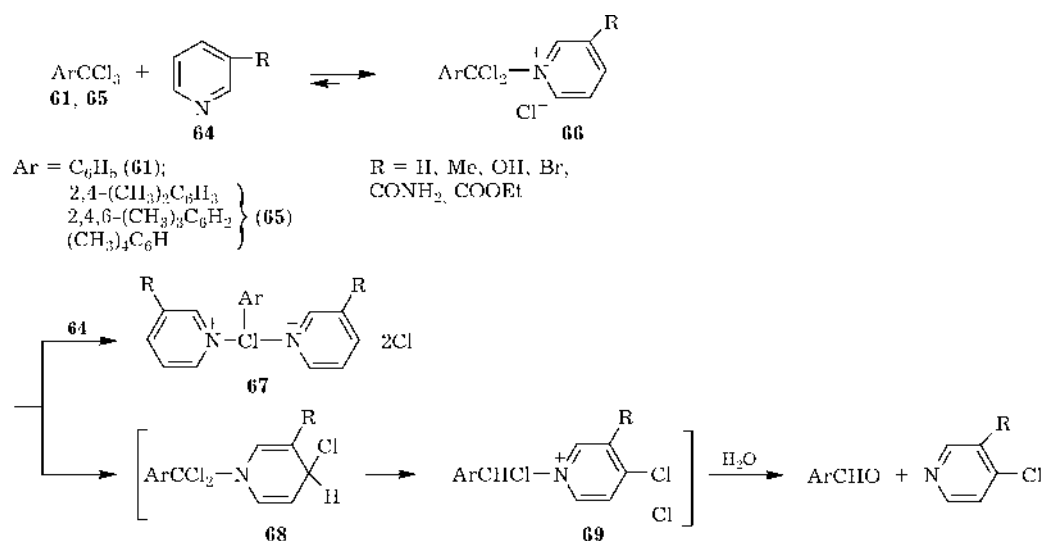
The studies of the possibility to obtain *O*- and *S*-chloroalkyl derivatives in the reactions of phenolates and thiophenolates with chlorine-



Scheme 20.



Scheme 21.



Scheme 22.

containing olefins by the example of polyhalogenated propenes demonstrated that the reaction with 1,1,2,3-tetrachloro-3,3-difluoropropene in alcoholic media results in the formation of 1,1-difluoro-2,3,3-trichloro-3-arylthiopropene **62** (as the result of the substitution of one chlorine atom and allylic rearrangement) and the products such as **63** (as the result of the substitution of two chlorine atoms and allylic rearrangement) (Scheme 21) [55]. In regard to similar reaction with phenolates, it was not possible to isolate individual compounds [55].

For the further transformation into biologically active compounds through the action of 4-chloro-4'-oxybenzophenone on dichlorodifluoromethane in the presence of NaOH and potassium *tert*-butylate, 4-chloro-4'-(chlorodifluoromethoxy)benzophenone was synthesized (with the yield up to 40 %) [56].

The reaction of 5-methoxy-2,3-diphenylindole with sodium hydride and ethyltrichloroacetate results in the formation of 1-dichloromethyl-5-methoxy-2,3-diphenylindole with the yield amounting to 50 %. From the standpoint of the authors of [57], this process may occur as the result of decarboxylation of a primary formed derivative species such as ethyl-dichloro(1H-indole-1-yl)acetate.

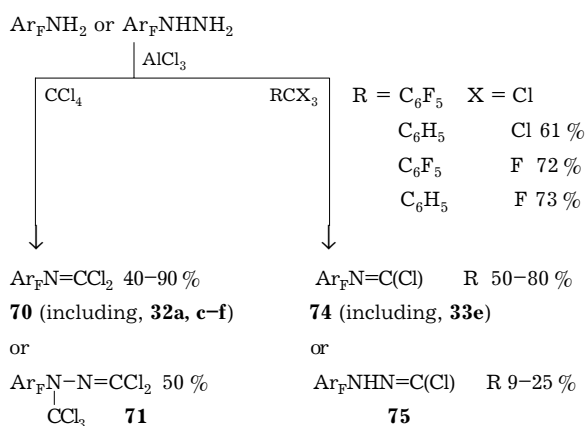
The nucleophilic attacking by substituted pyridines **64** on trichloromethylarenes **61**, **65** results in the formation of corresponding N-(α,α -dichloromethylaryloxy)pyridinium chlorides **66**, some of those were isolated as hexachloroanti-

monates with a satisfactory yield (up to 86 %) (Scheme 22). Chlorides **66** could either react with the second molecule of pyridine **64** to produce salts **67**, or undergo addition of chloride anion into the position 4 with the formation of corresponding 4-chloro substituted 1,4-dihydropyridines **68** [58, 59]. The latter are subject to oxidation-reduction transformation with a proton transfer from the position 4 to benzyl dichloromethylene group and aromatisation of the ring.

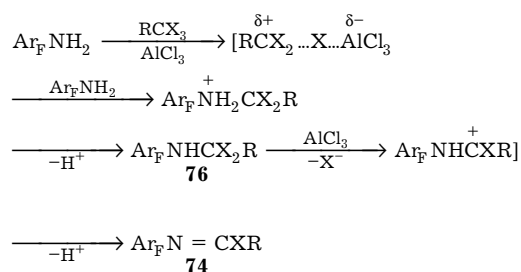
N-(α -chloromethylaryloxy)-4-chloropyridinium chlorides **69** produced in this process can be readily decomposed by water to give arylaldehydes and 4-chloropyridines. Antimonate **69** (Ar = 2,4,6-(CH₃)₃C₆H₂, R = H) was isolated with the yield amounting to 6 %.

5. ELECTROPHILIC CHLOROALKYLATION

The method of electrophilic polychloroalkylation was developed for the series of polyfluorinated aromatic N-, O- and S-containing functional derivatives basing on the action of RCX₃/AlCl₃ system (X = Cl, F). Primary amines and hydrazines [40 and references therein], pentafluorophenol [60], pentafluorobenzaldehyde [61], thiophenoles [62] were used as substrates. The RCX₃ compounds included CCl₄, aromatic derivatives with one or several CX₃ groups including poly- and perfluorohalogenated, as well as perhalogenated olefines with a terminal group such as CCl₃ (CClX=C₂YCl₃, X = Cl, C₆F₅; Y = Cl, F).

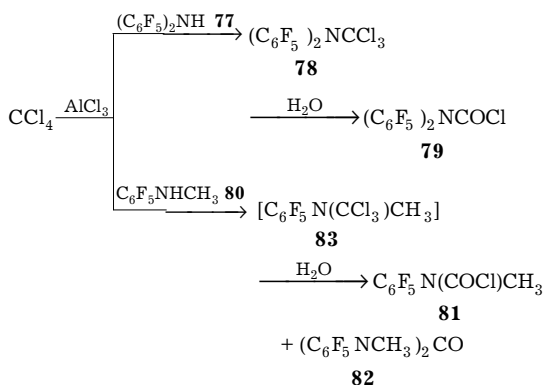


Scheme 23.



Scheme 24.

Successful development of this method was forwarded due to substitution of hydrogen atoms by fluorine in the aromatic ring of a substrate, which prevented an electrophilic attacking the $\text{C}_{\text{aryl}}\text{-H}$ bond and thus provided an alternative reaction pathway to be excluded. The method is based on the fact that an intermediate complex formed due to the interaction of trihalogenomethyl reactant with AlCl_3 attacks on the donor N, O or S heteroatom of a functional group resulting in the formation of a N, O or S polyhalogenomethyl derivative.

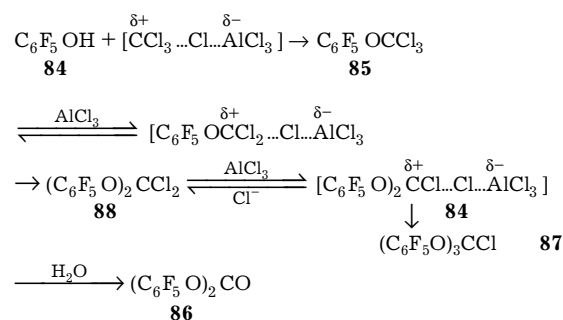


Scheme 25.

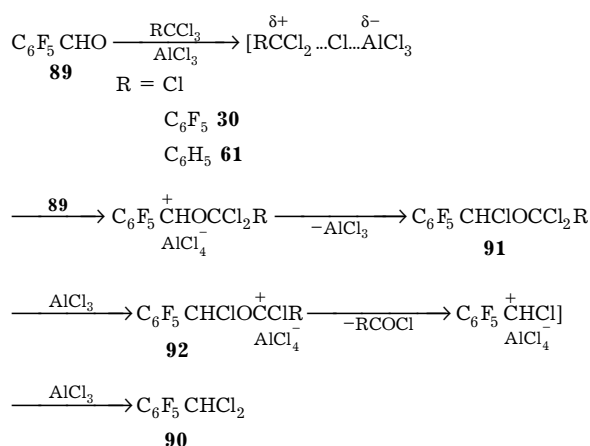
The latter could be isolated or subject to further transformations into the compounds of various types. So, the reaction of polyfluorinated aromatic amines (**29a, c-f, h, etc.**) or hydrazines with CCl_4 and AlCl_3 results in the formation of N-trichloromethyl derivatives those under the conditions of the reaction could form polyfluoroarylcarbonimidoyl dichlorides **70** (including **32a, c-f**) or N-trichloromethyl-N-polyfluoroarylhydrazonodichloromethanes **71**, respectively (Scheme 23) [40]. In the reactions with aromatic trichloromethyl and trifluoromethyl derivatives (**30, 61, 72, 73**), N-polyfluoroarylimidoyl chlorides **74** (including, **33e**) or N-polyfluoroarylhydrazono chlorides **75** are formed.

A possible route of the reaction by the example of amines is presented in Scheme 24. An intermediate N-polychloroalkylamine species such as **76** can be detected when its transformation into carbonimidoyl dichloride or imidoyl chloride is impossible. So, N-trichloromethylamine **78** was identified among the reaction products of decafluorodiphenylamine **77**, however the former product can quickly undergo hydrolysis resulting in the formation of compound **79** (Scheme 25) [40]. The heating of N-methylpentafluoroaniline **80** together with CCl_4 and AlCl_3 resulted in the formation of chloroanhydride of N-methyl-N-pentafluorophenylcarbamic acid **81** and bis(N-methyl-N-pentafluorophenyl)urea **82**, those are, obviously, the products of further transformations of N-trichloromethylamine **83** formed initially (Scheme 25) [40].

The reaction of polyhalogen alkylation of NH_2 -containing polyfluoroaromatic compounds is quite general one occurring with the partici-



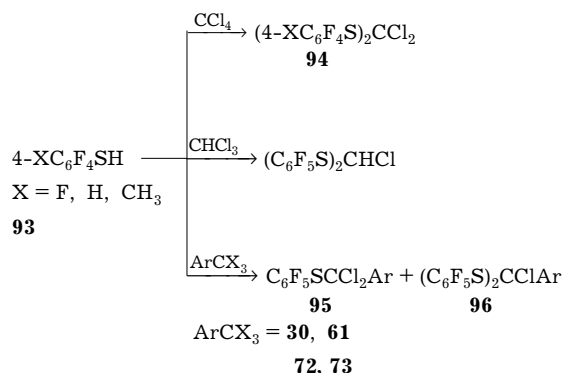
Scheme 26.



Scheme 27.

pation of benzene, naphthalene and diphenyl series of compounds. Fluorinated aromatic amines and hydrazines with electron accepting nitro group can be also involved in this reaction, which, apparently, is connected with their reduced basicity and, as a result, is caused by a weakening of nitrogen atom to AlCl_3 coordination that could interfere with the course of the main reaction. Negative results obtained in the experiments with aniline and phenylhydrazine [40] point out this fact, too.

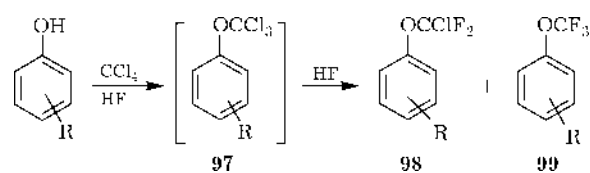
Pentafluorophenol **84** reacts with CCl_4 and AlCl_3 under the conditions similar to the above mentioned reaction with amines to result in the formation of a primary product of trichloromethylation such as trichloromethylpentafluorophenyl ether **85**, bis(pentafluorophenyl) carbonate **86** and tris(pentafluorophenoxy)chloromethane **87** [60]. Through the variation of reaction conditions, either the content of the ether **85** in the mixture of products could be increased up to 40 % or carbonate **86** could be obtained with the yield exceeding 45 %. Scheme 26 demonstrates a possible reaction route for the process. The use of benzotrihalogenides ArCX_3 **30**, **61**, **72**, **73** instead of CCl_4 results in the formation of pentafluorophenyl esters of benzoic acids with the yield amounting to ~50 % those are the products of hydrolysis of ethers such as $\text{C}_6\text{F}_5\text{OCX}_2\text{Ar}$ ($\text{X} = \text{F}, \text{Cl}$; $\text{Ar} = \text{C}_6\text{H}_5, \text{C}_6\text{F}_5$) [63] formed as intermediate species. The formation of the compounds like **85** and **88** as intermediate species was already postulated by Zincke and Suhl [64] for the reactions of polyhalogenated *p*-cresols with CCl_4 and AlCl_3 .



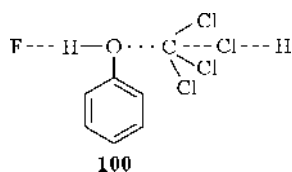
Scheme 28.

Direct polychloroalkylation of the oxygen atom included in the aldehyde group of pentafluorobenzaldehyde **89** via the action of CCl_4 or benzotrichlorides **30** and **61** in the presence of AlCl_3 surplus seems to be rather likely, too. However, in this case among the end products of the reaction, only the products of further transformations of primary polychloroalkyl ethers can be identified or isolated. Pentafluorobenzylidene chloride **90** and corresponding acid chloroanhydrides can be formed with the yield ranging from 55 % up to almost theoretical value (Scheme 27) [61]. It seems reasonable to believe that when $\text{R} = \text{C}_6\text{H}_5$ or C_6F_5 , the intermediate species **91** could more readily transform into **92** as to compare with the case when $\text{R} = \text{Cl}$, since in the two former cases comparatively stabilized intermediate species with a cationic centre at the benzyl position would be generated, which might cause difficulties for the mentioned reaction with CCl_4 as compared with benzoyltrichlorides.

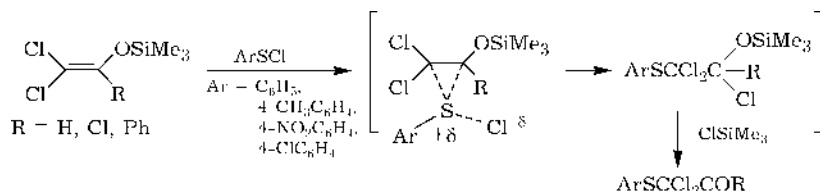
Likewise polyfluorinated phenols, polyfluorinated thiophenols **93** can be also polychloroalkylated with respect to a heteroatom. However, in this case there are no polyfluoroaryltrichloromethylsulphides or polyfluorinated thiocarbonates among the products of reaction with CCl_4 , but polyfluoroarylsulphides containing dichloromethylene group **94** are mainly formed, those are stable with respect to hy-



Scheme 29.



Scheme 30.



Scheme 31.

drolisis (Scheme 28) [62]. Primary products of polychloroalkylation such as **95** were obtained only for benzotrihalogenides, the ratio between the compounds **95** and **96** depending on reaction temperature and the amount of reagents.

The mechanism of polychloroalkylation of polyfluorinated thiophenols is similar to that for polyfluorinated phenols (see Scheme 26). The difference in the reaction proceeding for thio and hydroxy derivatives within the framework of such a scheme may be explained by more pronounced nucleophilic properties of thiophenols in comparison with phenols, as a result of which the conversion of the thio analogue of the compound **85** into the compound **94** would occur much more readily and thus primary thio product such as **85** cannot be detected. On the other hand, the further reactions of the compounds **88** and **94** are determined by the oxygen and sulphur atoms being capable of stabilizing a neighboring carbocationic centre. Since the atom of sulphur is less effective in this sense, the sulphuric analogue would be more stable either against hydrolysis or against the further reaction with another thiophenol molecule and thus can be isolated.

The acid-catalysed reaction of aromatic phenols with CCl_4 [65] or diphosgene [66] in the presence of HF results in the formation of aryltrichloromethyl ethers **97** those; however, represent merely intermediate species (Scheme 29). Under the action of HF the chlorine atoms of the compounds such as **97** are substituted by fluorine so as the end product is presented by the mixture of chlorodifluoromethyl ether **98** and trifluoromethyl ether **99**. The ratio of products, the yield and the features of the re-

action course depend on the nature of substituent R in such a way that electron accepting substituents promote the reaction progress. It is supposed, that in the phenol- CCl_4 -HF system a complex **100** is formed in which the complex a proton promotes the detachment of chloride anion, and the nucleophilic properties of phenol become more pronounced due to a hydrogen bonding with fluorine (Scheme 30).

The reactions of such electrophilic reagents as arylsulphenylchlorides with halogen containing O-silylated enolates [67–69] result in the formation of arylthiodichloroacetic chloroanhydride with a good yield, as well as aldehydes and ketones with α -halogenoalkyl group and arylthio group those are useful multifunctional synthons for organic synthesis difficult to obtain another way. It is supposed, that the reaction may occur via the mechanism of 1,2-addition through episulphonium cation with the subsequent trimethylchlorosilane removal (Scheme 31).

6. CONCLUSION

Nowadays there is no universal method for chloroalkylation of the heteroatoms of N-, O- and S-containing arene or N-heteroarene derivatives. The feasibility of either modification of this reaction is determined by the availability of source compounds, by the influence of substituents therein and by the nature of a heteroatom. In order to introduce CCl_3 group into O and S derivatives it may be useful to apply a one-step process of free radical trichloromethylation. For S-containing compounds good results are obtained also with the use of nucleo-

phylic reactions for the introduction of CCl_3 or CCl_2 groups. With a less success the nucleophilic modification can be used for the series of O and N derivatives. For N derivatives the best results have been achieved with respect to the reactions involving the sources of dichlorocarbene, though in this case the yield is low. The electrophilic pathway of polychloroalkylation was found to be interesting and successful mainly for the series of polyfluoroaromatic N-, O- and S-containing functional derivatives in spite of the fact that in many cases primary products of polychloroalkylation underwent further transformations during the reaction producing the compounds of various types.

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