

AlCl₃ in modern chemistry of polyfluoroarenes

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Summary

AlCl₃ is one of the most important and widely used catalysts known a long ago in laboratory and industrial practice. This review informs of AlCl₃ application in a relatively new field of organic chemistry, chemistry of polyfluoroaromatic compounds, since 1995y. Conversions of aromatic compounds containing two and more fluorine atoms on one aromatic ring have been under consideration. Systematization was made according to the type of running conversions. The list of literature for the period under consideration is not exhaustive, but illustrates completely all directions of using AlCl₃ in this field.

Key words: AlCl₃, catalysis, Friedel-Crafts alkylation, acylation, cyclization, intermediates

Introduction

Long ago AlCl₃ has become a classic reagent in organic chemistry and its role as a catalyst in organic reactions promoted by Lewis acids is well known [1-3]. Chemical activity, accessibility and cheapness of aluminum chloride are of constant attention of researchers in different fields of chemistry. It was used in organofluorine chemistry as well [4,5]. Recently for acid-catalyzed reactions of different type compounds along with traditional mineral acids and Lewis acids new type catalysts were started to use, for example solid acids and solid super acids [6 and references], metal complexes (Hf, Sc, Ga, Bi, Yb) with -N(SO₂C₈F₁₇)₂ and -OSO₂CF₃ ligands, including Al(OSO₂CF₃)₃ [7], as well as aluminum chlorofluorides of general formula AlCl_xF_y [8-10].

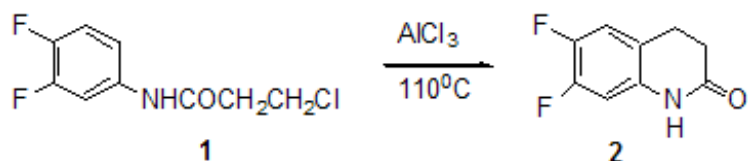
Nevertheless, in spite of appearance of new catalytic reagents, the use of AlCl₃ is continued. Chemistry of polyfluoroarenes is one of comparatively new fields in which possibility of using AlCl₃ has been demonstrated. This report presents a data review of AlCl₃ application in the chemistry of polyfluoroarenes beginning since 1995y. As substrates or reagents there are given fluorinated compounds containing two and more fluorine atoms in one aromatic ring and the transformations are systematized according to the type of the reactions taking place.

1. Friedel-Crafts alkylation and acylation reactions

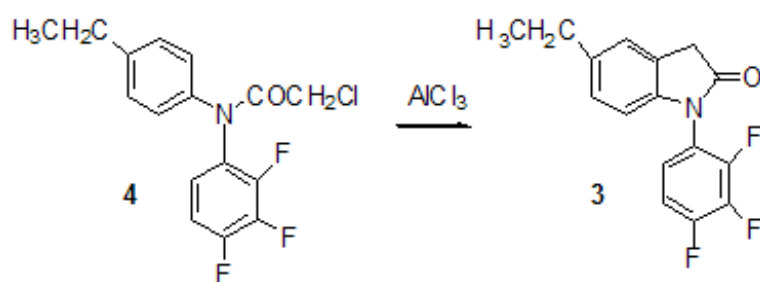
Among the reactions catalyzed by AlCl₃, both in series of polyfluoroarenes and for non-fluorinated compounds the most common are Friedel-Crafts alkylation and acylation reactions. Substitution of hydrogen atoms for fluorine in the aromatic ring of polyfluoroarenes reduces reactivity of such compounds towards electrophilic alkylating and acylating agents, but activation of these agents under the action of AlCl₃ is sufficient for successful course of these reactions. At that a polyfluorinated compound may act both as a substrate and as a reagent and the process itself may proceed with participation of the polyfluorinated ring and with another molecule moiety as well. Thus, AlCl₃ immobilized on a substrate was used for monoisopropylation of metha-difluorobenzene [11].

Chlorometylation of 1,3,5-trifluorobenzene in the presence of AlCl₃ by the action of

chloro(methoxy)methane in carbon bisulfide affords 1,3,5-tris-(chloromethyl)-2,4,6-trifluorobenzene in 80% yield [12]). The interaction of 1-bromo-2,3,5,6-tetrafluorobenzene with CHCl_3 and AlCl_3 results in tris(4-bromo-2,3,5,6-tetrafluorophenyl)methane in 22.4% yield [13]. The multi-stage synthesis of antibacterial agents of benzo[b]naphthiridones series includes the stage of intramolecular alkylation of 3-chloro-N-(3,4-difluorophenyl)-propionamide (1) in the presence of AlCl_3 to give 6,7-difluoro-3,4-dihydro-1H-quinolin-2-one (2) in 78% yield [14](Scheme1).

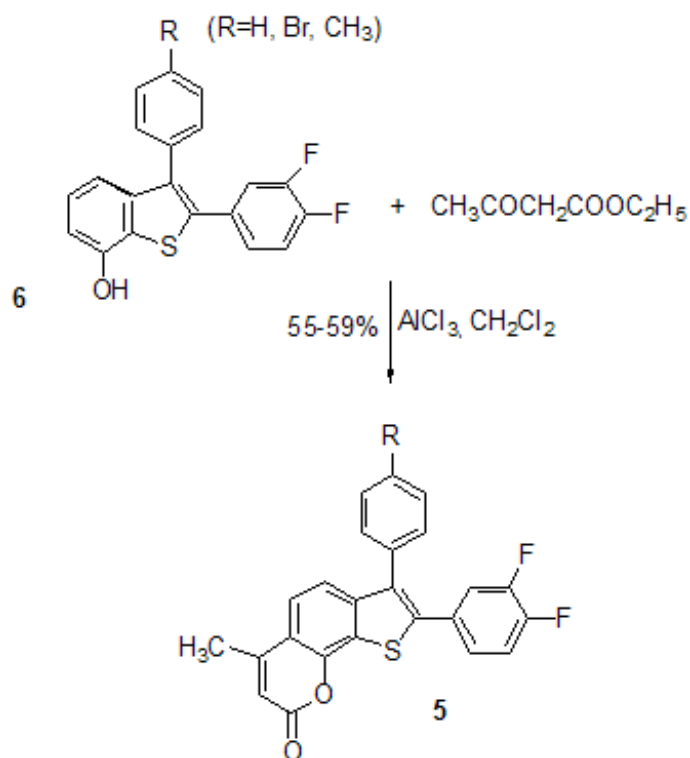


Scheme 1



Scheme 2

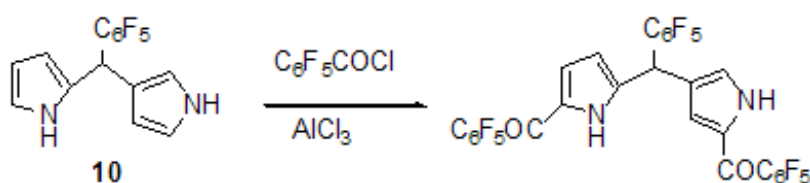
An example of the intramolecular alkylation reactions with cyclization in which course the polyfluorinated phenyl ring does not undergo transformations is obtaining 5-ethyl-1-(2,3,6-trifluorophenyl)-1,3-dihydroindol-2-one (3) from 2-chloro-N-(4-ethylphenyl)-N-(2,3,6-trifluorophenyl)acetamide (4) (48% yield) [15] (Scheme 2) and formation of 7,8-diaryl-4-methylcoumarinobenzo[b]thiophenes 5 in the interaction of 7-oxy-2-(3,4-difluorophenyl)-3-aryl-benzo[b]thiophenes 6 with acetoacetic ether and AlCl_3 [16] (Scheme 3).



Scheme 3

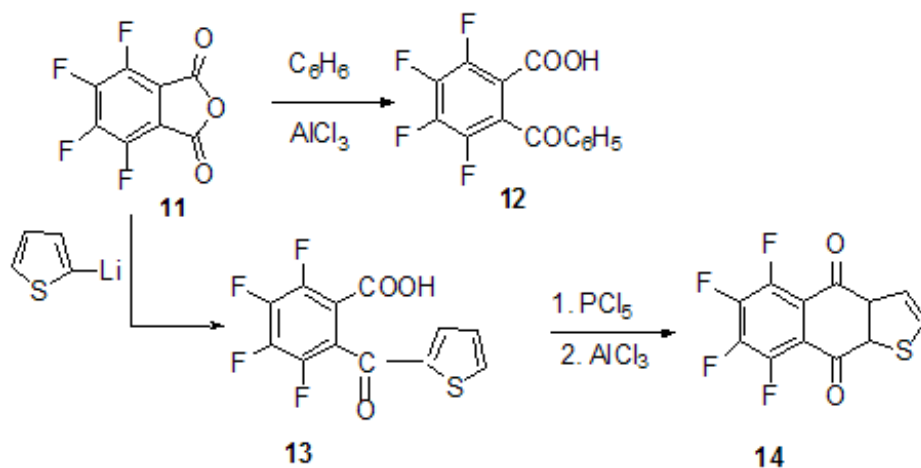
The acylation of 1,2,4-trifluorobenzene with acetyl chloride runs to 1-(2,4,5-trifluorophenyl)ethanone [20]. A similar process proceeds also in the case of 1,2,3-trifluoro-2-methylbenzene when 1-(2,3,4-trifluoro-5-methylphenyl)ethanone is formed [40]. Analogously there were produced accordingly 1-(4,8-difluoronaphthalen-1-yl)ethanone from 1,8-difluoronaphthalene [41], 1-(4,5-difluoronaphthalen-1-yl)ethanone from 1,8-difluoronaphthalene [42], 1-(1,3-difluoro-5,6,7,8-tetrahydro-5,5-dimethyl-2-naphthalenyl)ethanone from 5,7-difluoro-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene [43]. The acylation of 1,3-difluorodiphenyl with succinic aldehyde led to the formation of 4-(2'4'-difluorobiphenyl-4-yl)-4-oxobutyric acid [44].

Polyfluoroarenes may act as acylating agents themselves. For example, 2,6-difluorobenzoyl chloride in the presence of AlCl_3 acylates 1-benzosulfonylpyrrole to position 3 [45]. The acylation reaction of 3-methoxythiophene by 3,5-difluorobenzoyl chloride runs to position 2 along with demethylation of 3-methoxy group [46]. 2,4-Difluorophenylacetyl chloride acylates methylsulfide in position 4 [47], and pentafluorobenzoyl chloride in the presence of AlCl_3 allows insertion of the pentafluorobenzoyl group in the both pyrrole rings of pentafluorophenyl-substituted dipyrrolmethane **10** [48] (Scheme 7) and in position 5 in 2-bromothiophene [49]



Scheme 7

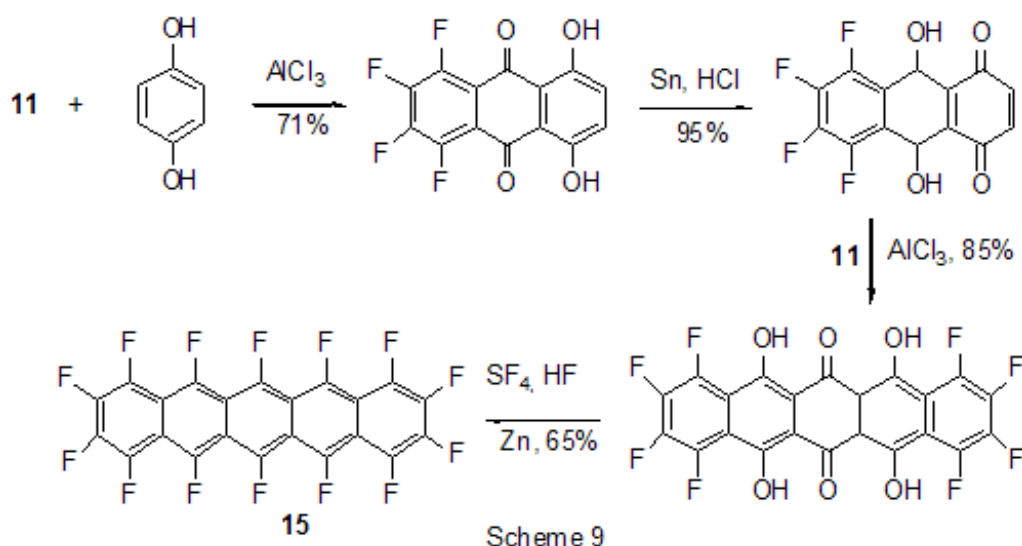
Pentafluorophenyl ethers of N^α -substituted amino acids are used as acylating agents in interaction with free amino acids in peptide synthesis [50]. Aluminum chloride is used in this process as one of the component of AlCl_3 -DMF (or another aprotic solvent)-pyridine system that promotes better solubility of the amino acid and correspondingly more complete reaction. The yield of di- and tripeptides under such conditions is over 90%. 3,6-Difluorophthalic anhydride in the reaction with para-xylene affords 2-(2,5-dimethylbenzoyl)-3,6-difluorobenzoic acid [51], and tetrafluorophthalic anhydride (11) reacts with benzene according to Friedel-Crafts to give 2-benzoyl-3,4,5,6-tetrafluorobenzoic acid (12) in 70% yield [52] (Scheme 8). Anhydride 11 was also used for the synthesis of 2-(2-thienylcarbonyl)-3,4,5,6-tetrafluorobenzoic acid (13). The intramolecular acylation of the latter under the action of PCl_5 and AlCl_3 brings to the formation of 5,6,7,8-tetrafluoro-4,9-dihydrohaphtho[2,3-b]thiopen-4,9-dione (14) [52] (Scheme 8).



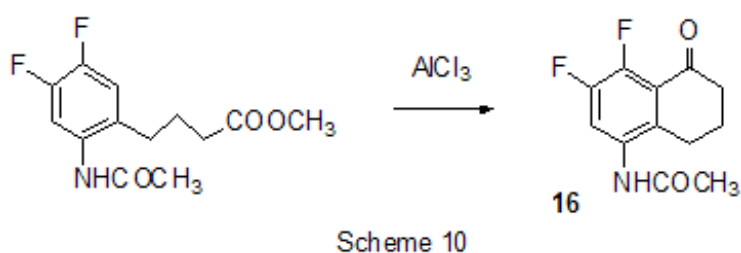
Scheme 8.

Cyclization in the process of intramolecular acylation occurs also when anhydride 11 is used as the acylating agent in multi-stage synthesis of perfluoropentacene (15) which is

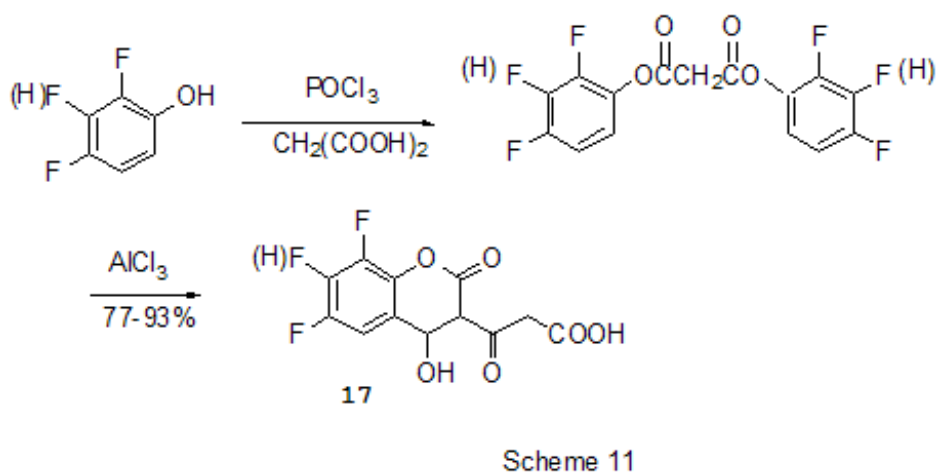
of interest as a n-semiconductor for organic FET transistors [53,54] (Scheme 9).



In production of novel liquid crystal materials of tetrahydronaphthalene structure there has been used a reaction of formation of 5,7-difluoro-3,4-dihydro-1H-naphthalen-2-one from ethylene and 3,5-difluorophenylacetic acid in the presence of AlCl_3 [55]. Difluoronaphtoic acids which are used to obtain biologically active carboxamides have also been synthesized by Friedel-Crafts acylation and intramolecular cyclization of appropriate difluoroacetophenones and difluorophenylethylacetates[42]. The latter reaction was used for synthesis of difluoro-3,4-dihydronaphthalenones (for example, 16 (Scheme 10), intermediates in the production of biologically active hexacyclic analogues of camptothecine [56].

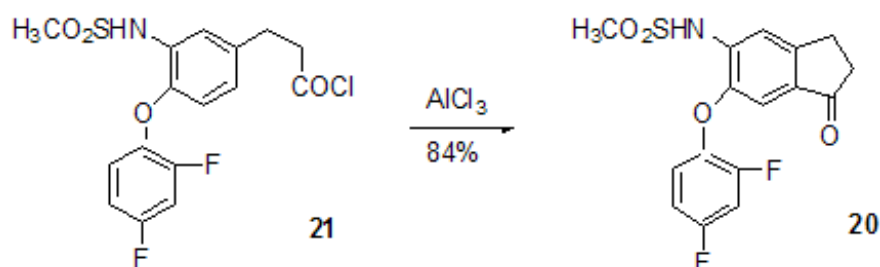
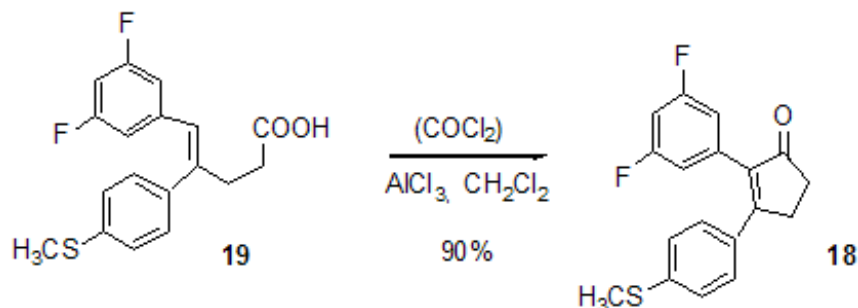


Analogously, 2,4-difluorophenylpropionic acid was converted into 4,6-difluoro-1-indanone which is used for the synthesis of fluorinated 1-indanylidene acetamide, a potential miorelaxant of central action [57]. The intramolecular cyclization was also used in the synthesis of biologically active fluorinated 4-oxycoumarins 17 derived from available fluorinated phenols [58] (Scheme 11).

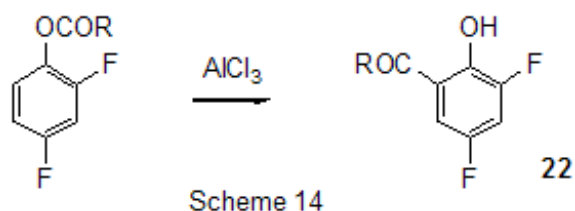


At last, acylation reactions with intramolecular cyclization and without it were described for substrates containing a polyfluoroaromatic fragment when the acylation did not

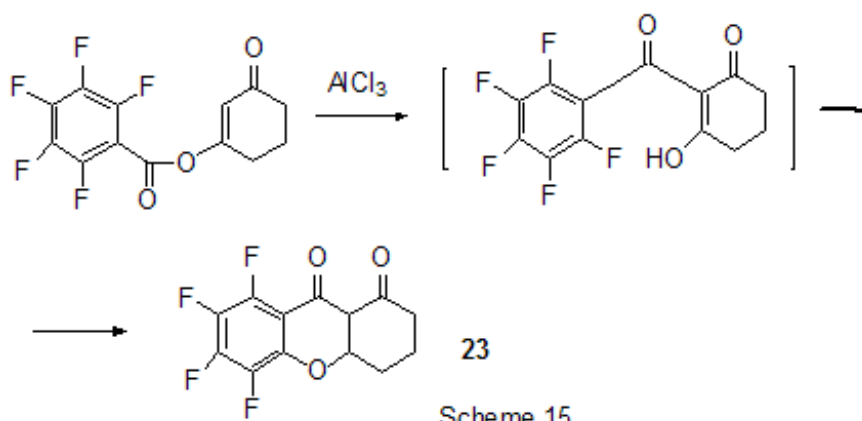
involve the polyfluorinated ring. The acylation of such type with cyclization was used in the multi-stage synthesis of potential inhibitors of cyclooxygenase (COX-2), in particular in obtaining 2-(3',5'-difluorophenyl)-3-(4'-methylthiophenyl)cyclopenta-2-en-1-one (18) from 5-(3',5'-difluorophenyl)-4-(4'-methylthiophenyl)pentenic acid (19) [59] (Scheme 12), in producing 5-(2',4'-difluorobiphenyl-4-yl)-5-oxy-4-methyl-5H-furan-2-one in the acylation of 1,3-difluorobiphenyl with methylmaleic acid anhydride [44] and to form N-[6-(2,4-difluorophenoxy)-1-oxoindan-5-yl]methanesulfonamide (20) from 3-[4-(2,4-difluorophenoxy)-3-methanesulfonylaminophenyl]propionyl chloride (21) [60] (Scheme 13).



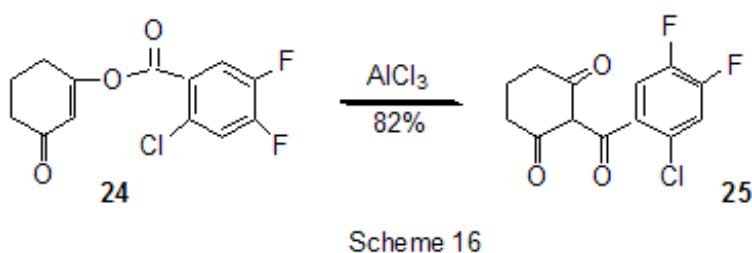
The acylation without cyclization illustrates conversion of N-[3-(2,4-difluorophenoxy)-2-thienyl]methanesulfonamide into N-[5-(3-chloro-1-oxopropyl)-3-(2,4-difluorophenoxy)-2-thienyl]methanesulfonamide [61] and conversion of 2,6-difluoro-4-pyrrol-1-ylphenyl ether of benzoic acid into an appropriate compound with the benzoyl group at position 3 of the pyrrole ring [62]. The acylation reaction variant by Fries rearrangement was also realized, i.e. conversions of esters, phenols under the action of AlCl_3 into ortho- and para-acylphenols. Thus, esters of 2,4-difluorophenol with acetic [63] or benzoic [64] acids are rearranged into stable (2'-oxy-3',5'-difluorophenyl)aceto- and -benzophenones 22 accordingly (Scheme 14)



The rearrangement of 3,4-difluorophenylacetate results in 1-(4,5-difluoro-2-oxyphenyl)ethanone [65] and the rearrangement of 2,6-difluorophenyl ester of propionic acid results in (3,5-difluoro-4-oxyphenyl)propiophenone [66]. In contrast to that the reactions of 3-oxocyclohex-2-enyl-2,6-difluoro-, -2,4-difluoro or 2,3,4,5,6-pentafluorobenzoates run with the formation of non stable products of the Fries rearrangement which are readily converted into appropriate derivatives of 2,3,4,9-tetrahydro-1H-xanten-1,9-dione 23 [67] (Scheme 15).

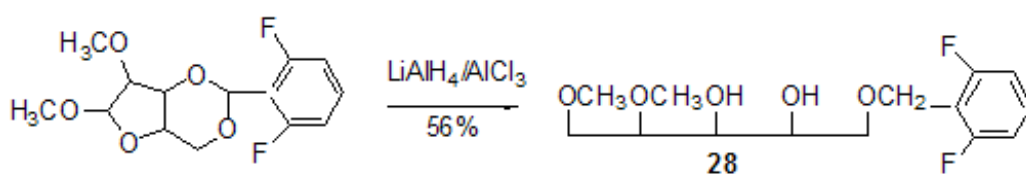
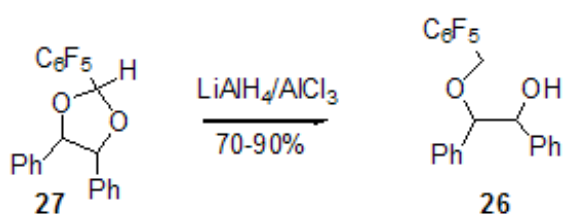


Analogous cyclization runs also in case of 3-(2,4,5-trifluorobenzoyloxy)-2-cyclohexen-1-one, while appropriate 2-chloro-4,5-difluorophenylbenzoate (24) under the action of AlCl_3 gives 2-(2-chloro-4,5-difluorobenzoyl)-1,3-cyclohexandione (25) [68] (Scheme 16).



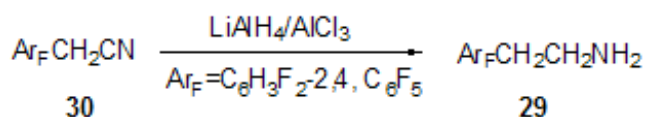
2. Dealkylation reaction (cleavage of the C-O bond)

A known cleavage reaction of phenol ethers under the action of AlCl_3 was used in obtaining 7-oxy-2-(3,4-difluorophenyl)-3-arylbenzo[b]thiophenes from 7-methoxy derivatives [16], 4-(4',5'-difluoro-2'-oxy-phenoxy) derivative of 2-substituted tetrahydropyran-3-ol from appropriate 2'-methoxy derivative [69] as well as in producing a 3-methoxyphenyl fragment of complex porphyrin compound with pentafluorophenyl groups in positions 10,20 [70]. Cleavage of O-C ether bond in cycles is achieved by reduction with $\text{LiAlH}_4/\text{AlCl}_3$ (1:2) system, as addition of AlCl_3 weakens reductive ability of LiAlH_4 in the system and thereby makes possible to avoid side reactions [71]. This procedure was used for producing (1R,2R)-1,2-diphenyl-2-(2,3,4,5,6-pentafluorobenzoyloxy)ethanol (26) from (4R,5R)- α -(2,3,4,5,6-pentafluorophenyl)-4,5-diphenyl-1,3-dioxolane (27) [72] (Scheme 17) and for 1-(2,6-difluorobenzoyloxy)-4,5-dimethoxypentan-2,3-diol (28) from 2-(2,6-difluorophenyl)-6,7-dimethoxytetrahydrofuro[3,2-d][1,3]dioxane [73] (Scheme 18).



It should be noted that $\text{LiAlH}_4/\text{AlCl}_3$ system was also used for reduction of compounds of

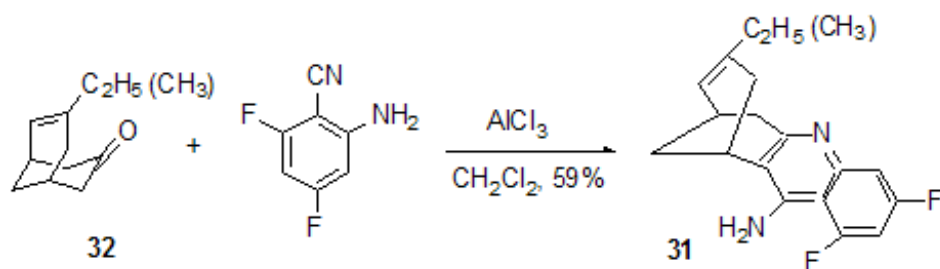
different types. In this was, for example, were obtained polyfluorophenyl ethylamines 29 from polyfluorophenyl acetonitriles 30 in 50-75% yield [74,75] (Scheme 19).



Scheme 19

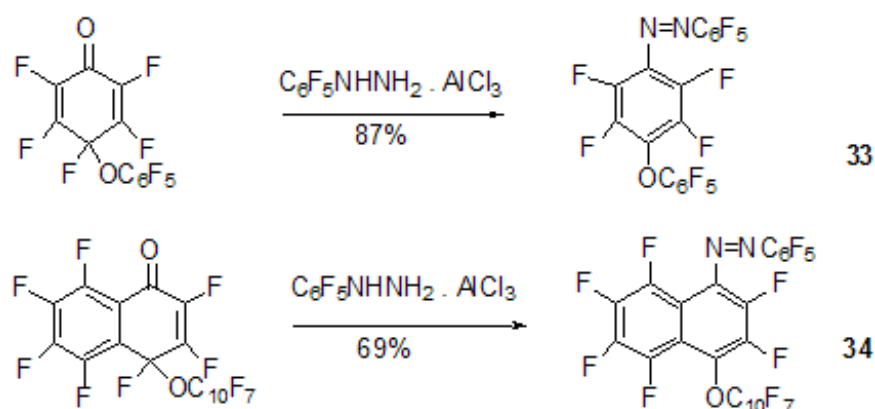
3. Condensations, isomerisations and reactions with nucleophiles

New chlorohydrates of 12-amino-6,7,10,11-tetrahydro-7,11-methanocycloocta[b]quinolines (huprines) of 31 type containing a methyl or ethyl group as well as two fluorine atoms in positions 1,3 as potential inhibitors of acetylcholinesterase were synthesized by the interaction of bicycloenones 32 with 2-amino-4,6-difluorobenzonitrile according to the Friedländer reaction type with participation of carbonyl group [76](Scheme 20).



Scheme 20

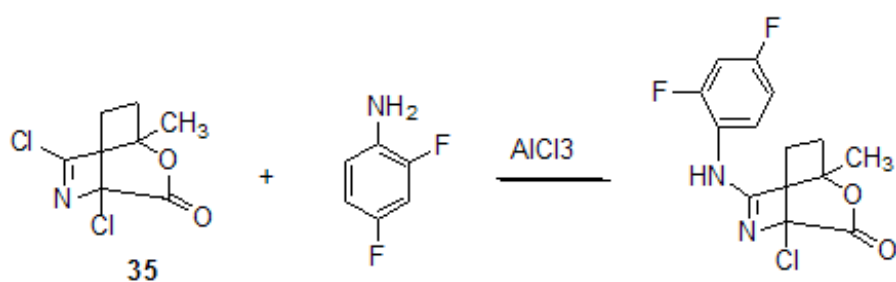
The interaction of polyfluorinated 2,5-cyclohexadienes and 1-oxo-1,4-dihydronaphthalenes, containing pentafluorophenoxy- and perfluoronaphthoxy-fragments, with a complex of pentafluorophenylhydrazine and AlCl₃ also involves the carbonyl group according to 1,2-addition reaction type in spite of the presence of fluorine atoms, sensitive to the action of nucleophilic agents, at the double bond in the cyclohexadienone fragment. The end products of these conversions as a result of aromatization are perfluoroaryloxy derivatives of nitrocompounds of benzene series 33 and naphthalene series 34 [77] (Scheme 21).



Scheme 21

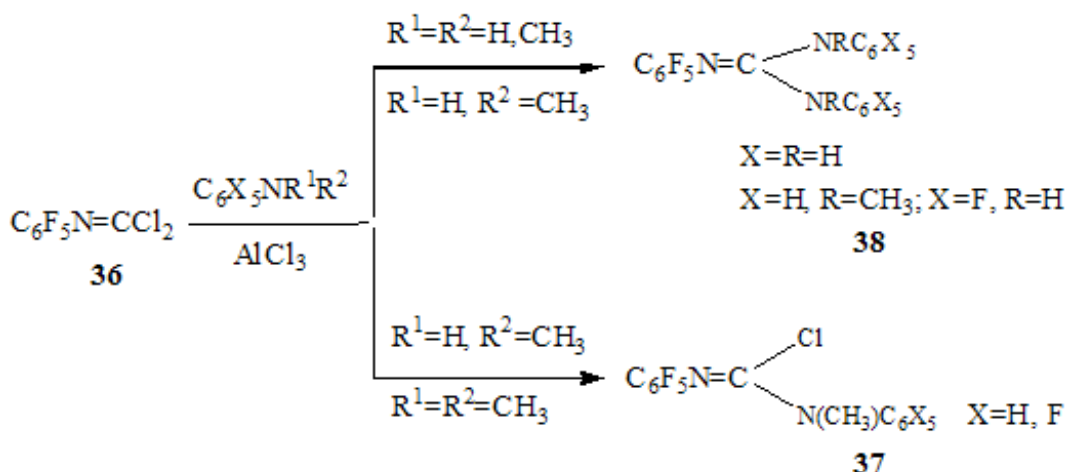
The absence of reactions involving fluorine atoms of the ring may be connected with reduced basicity of pentafluorophenylhydrazine including due to complexation with AlCl₃. Reactions of nucleophilic agents in the presence of AlCl₃ run smoothly enough if activation of the substrate is possible at the expense of formation of cationoid intermediates in the interaction of this substrate with AlCl₃. Thus, activation of chloroimine function in 4,6-dichloro-1-methyl-2-oxa-5-azabicyclo[2,2,2]oct-5-en-3-one (35) by the action of AlCl₃ allows realization of the reaction of this compound with 2,4-

difluoroaniline [78] (Scheme 22).



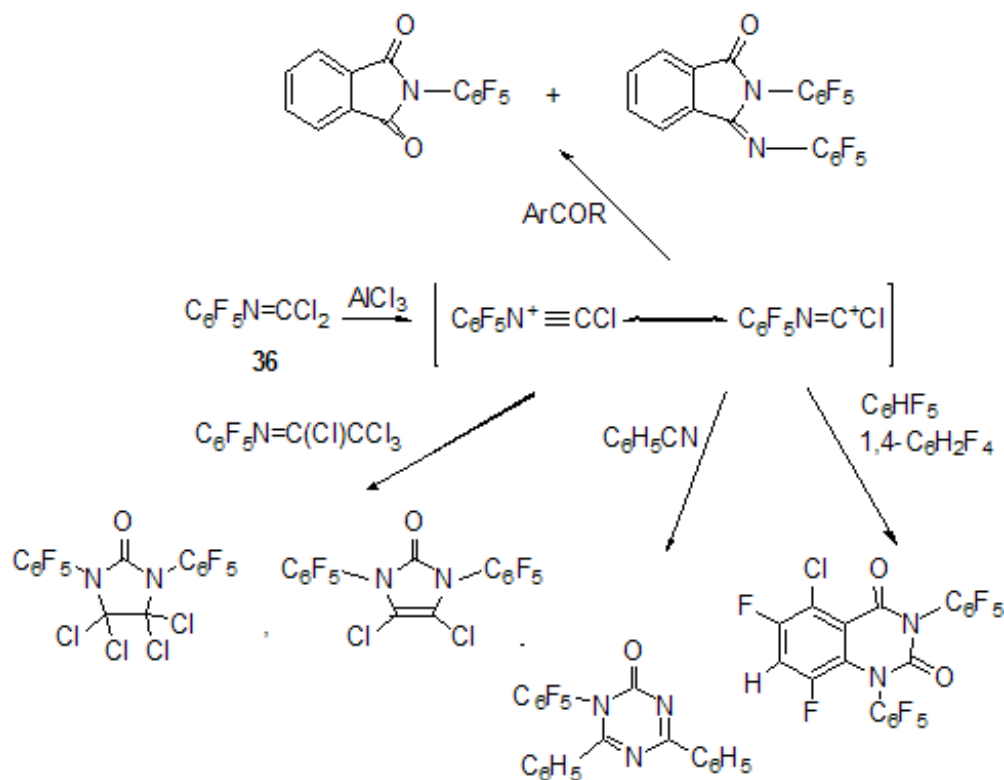
Scheme 22

The reactions of polyfluoroarenes of such type, containing imidoylchloride group, run with polarization of C-Cl bond under the action of AlCl_3 and formation of cationoid intermediate of nitrile- cation type. The interaction of positively charged intermediate with a nucleophile results in products of substitution of chlorine atoms for a nucleophile residue or in products of more complete conversions. For example, reactions of N-pentafluorophenylcarbonimidoyl dichloride (36) with aromatic amines (aniline, N-methyl-, N.N-dimethylaniline and their pentafluorophenyl analogues) in the presence of AlCl_3 and without it involve the amine nitrogen atom to form the same chloroformamidines 37 and guanidines 38 [79] (Scheme 23), but the conversion is higher in the reactions with aluminum chloride.



Scheme 23

It is explained by different mechanisms of the reactions in both cases. The reactions in the presence of AlCl_3 run with participation of nitrile cation, whereas in the absence of AlCl_3 a stage mechanism of bimolecular nucleophilic addition-detachment to form tetrahedral intermediate is realized [80,81]. The reactions of dichloride 36 and AlCl_3 with other arenes acting as the donor component (compounds with multiple bond nitrogen-carbon [82], fluorinated benzenes [83], aromatic acids and their derivatives [84]) run with intramolecular heterocyclization. So, polyfluoroaromatic compounds containing - $\text{N}=\text{CClR}$ group may be promising starting compounds for synthesis of fluorinated 5- and 6-membered N-heterocyclic systems (Scheme 24).

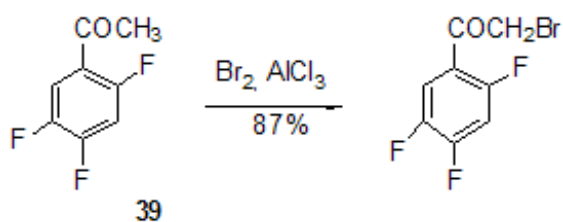


Scheme 24

Stereoselective isolation of trans-2-(3',4'-difluorophenyl)-6-propyldecahydronaphthalene from a mixture of isomers is realized by the mixture treatment with AlCl_3 [85].

4. Halogenation and hydrodefluorination reactions

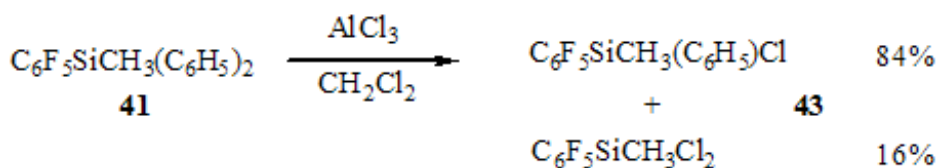
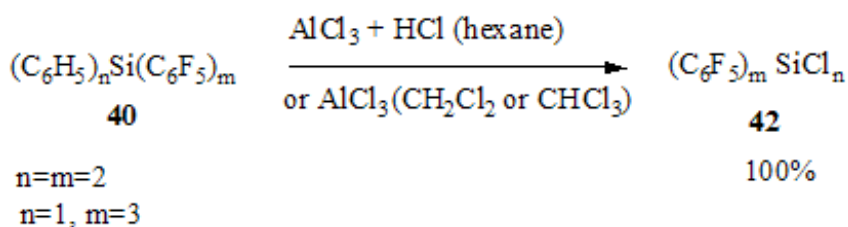
Conventionally AlCl_3 has been used as a catalyst in halogenation reactions. In particular bromination of the methyl group of 2,4,5-trifluoroacetophenone (39) in the presence of AlCl_3 is one of the stages in the multi-stage synthesis of 4-cyclopropyl-7-fluoro-6-(4-methylpiperazin-1-yl)-1,2,4,9-tetrahydrothiazol[5,4-b]quinolin-2,9-dione [86](Scheme 25).



Scheme 25

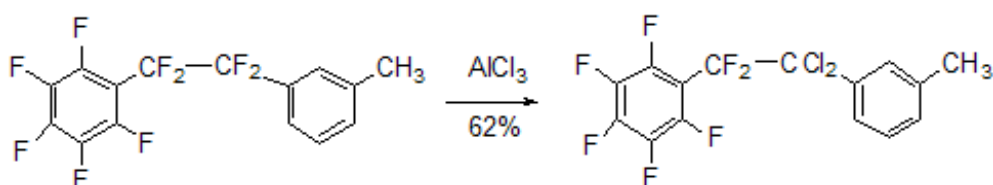
Catalysis by AlCl_3 was also used for halogenation of the ring to produce halotetrafluorobenzenes $\text{C}_6\text{F}_4\text{XH}$ ($\text{X}=\text{Cl}, \text{Br}$) in high yields from tetrafluorobenzenes [87].

In the presence of AlCl_3 a phenyl group is replaced for fluorine in the synthesis of chloro- and chloro(methyl)pentafluorosilanes 42 and 43 from pentafluorophenyl(phenyl)silanes 40 and methyl(pentafluorophenyl)penylsilanes 41 accordingly [89,90] (Scheme 26).



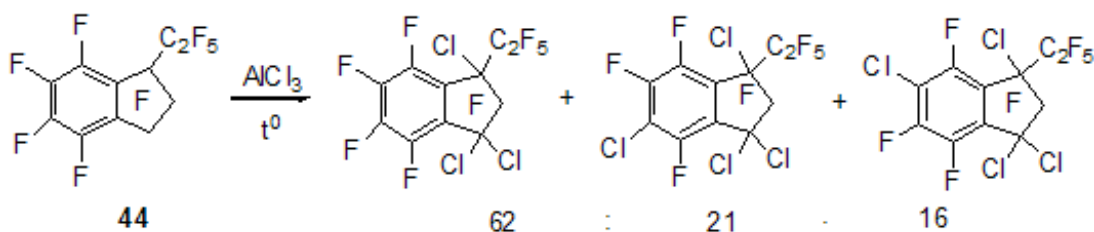
Scheme 26

The reaction is of electrophilic character and proceeds under the action of AlCl_3 itself or AlCl_3/HCl system as well as another electrophiles. The conversion in these reactions depends on the solvent used (preferably halogenated hydrocarbon) and the number of electron-seeking pentafluorophenyl groups in silicon atom (the greater the number the more difficult reaction course). At that $\text{Si-C}_6\text{F}_5$ and Si-Me bond is not cleaved under the action of AlCl_3 . AlCl_3 may be used for substitution of fluorine atoms for chlorine in the benzyl position and in the aromatic ring of polyfluoroarenes containing fluoroaliphatic fragments. Thus, in 2-pentafluorophenyl-1-phenyltetrafluoroethane CF_2 group was converted into CCl_2 by the action of AlCl_3 . The process of substitution of fluorine for chlorine runs only in the benzyl position of $\text{CH}_3\text{C}_6\text{H}_4\text{CF}_2$ - fragment as a result of stabilization by the phenyl group of the forming positively charged center [90] (Scheme 27).



Scheme 27

In case of perfluoro-1-ethylindane (44) under the action of AlCl_3 in dependence on its quantity and reaction temperature, both acyclic fluorine atoms of the 5-membered ring and aromatic fluorine atoms of the 6-membered ring are substituted for chlorine [91] (Scheme 28).



Scheme 28

The observed conversions are explained from point of view of possible formation of intermediate cations of different type and their reactivity. In case of 1,2,4,5-tetrafluoro-3-(2,2,2-trifluoro-1,1-bis-trifluoromethylethyl)-6-trifluoromethylbenzene under the action of AlCl_3 fluorine atoms of the trimethyl group in position 6 are replaced for chlorine (85% yield) [92]. Recently it has been found that substitution of fluorine atoms by hydrogen is possible in polyfluorinated arenes, i.e. it is possible to realize

hydrodefluorination process under certain conditions. Thus, regioselective hydrodefluorination of a trifluoromethyl group in perfluoroalkylbenzenes, for example in octafluorotoluene (48) into 1-methylpentafluorobenzene (49) is realized by heating with AlCl_3 , or with cyclic C_{5-6} compound (for example cyclohexane) or aliphatic C_{5-12} hydrocarbon in a medium of organochlorine solvent, for example CH_2Cl_2 , at 30-80°C [93].

5. Another directions of AlCl_3 using

Complexes of fluorinated derivatives of tris-substituted borane compounds with Lewis bases may be destroyed by the action of strong Lewis acids, including AlCl_3 . In particular, adduct of tris(pentafluorophenyl)borane with TGF, derived from $\text{B}(\text{C}_6\text{F}_5)_3$ and TGF after distillation of solvent excess under vacuum, is destroyed under the action of AlCl_3 in 1,3,5-triisopropylbenzene at 25°C [94].

6. Conclusion

The analysis of publications presented in this report has shown that in spite of appearance of novel effective catalysts like Lewis acids in recent years, AlCl_3 has not lost its importance as a catalyst and reagent in chemistry of polyfluoroarenes. The directions of its application are quite analogous to appropriate directions in non-fluorinated series and mainly come to the processes of Friedel-Crafts alkylation and acylation, that are most often realized as one of stages in complex multi-stage syntheses of promising biologically active substances or different practically important compounds. Also there are different variants of halogenation reactions with participation of AlCl_3 .

An interesting direction of using AlCl_3 appears polychloroalkylation of perfluorinated arenes with N-, O- and S-containing functional groups that unambiguously involves a heteroatom of the functional group, as a possibility of participation of the ring in the reaction is excluded, and results not only in primary products of polychloroalkylation but also in compounds of different types forming as a result of further conversions of these primary products. Activation of derivatives of polyfluorinated arenes by the action of AlCl_3 to form cationoid intermediates is of certain interest as it makes possible to realize a reaction of such arenes with weak nucleophiles, whereas interaction of the latter under conventional conditions of aromatic nucleophilic substitution is rather difficult or does not occur at all. Thereby a scope of conversions with participation of weak nucleophiles is broaden and it makes possible to realize synthesis of compounds difficult to obtain in a different way. At last, the ability of AlCl_3 , earlier found, to reduce reductive properties of such strong reducing agent as LiAlH_4 has been successfully employed in reactions of polyfluoroarenes, that made possible to decrease a probability of side processes and to obtain the desired products in good yields.

References

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