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POLYFLUORINATED CYCLOHEXADIENONES: SUITABLE INTERMEDIATES FOR THE SELECTIVE SYNTHESIS OF COMPLEX ORGANOFLUORIC SUBSTANCES

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Abstract: *The article summarizes the results of studies on the reactivity of polyfluorinated cyclohexadienones: nucleophilic reactions, cycloadditions, and photochemical transformations. The use of polyfluorinated cyclohexadienones for synthons in the synthesis of a wide range of earlier inaccessible fluorinated organic substances (derivatives of polyphenolic esters, arylacetic acids, naphthalene, and anthraquinone) containing carboxylic groups, cyclohexene carboxylic acids, and some fluorinated heterocyclic substances are discussed.*

Keywords: *Organofluoric substances, cyclohexadienones, nucleophilic reactions, cycloaddition, polyphenyl esters, arylacetic acid.*

The functionalization of fluorinated compounds is of fundamental importance both because of the limited possibility for the synthesis of such derivatives by direct introduction of fluorine atoms into organic compounds containing functional groups, and because of the difficulties related with the introduction of functional groups into fluorinated compounds, that requires multistage synthesis process [1]. We disclose a novel promising approach to the synthesis of multifunctional organofluoric substances through the conversion of some comparatively easy accessible polyfluoroaromatic compounds to highly reactive and easily modifiable polyfluorinated cyclohexadienones [2].

The great interest in polyfluorinated cyclohexadienones is because of their high and diverse reactivity due to the presence of numerous reactive centres in those molecules: mobile fluorine atoms linked to their double bonds, 1,3-diene systems in 2,4-cyclohexadienones, carbonyl groups, and reactive substituents at sp^3-hybridized carbon atoms.

Nucleophilic or photochemical reactions and cycloaddition were shown to be the most effective methods for the modification of polyfluorinated cyclohexadienones.

Synthesis of polyfluorinated cyclohexadienones

Polyfluorinated cyclohexadienones with various substituents in their geminal units are producible with good yields from polyfluorinated phenols, naphthols or their salts by halogenation [3] or oxidation [4-10]. (Figure 1)

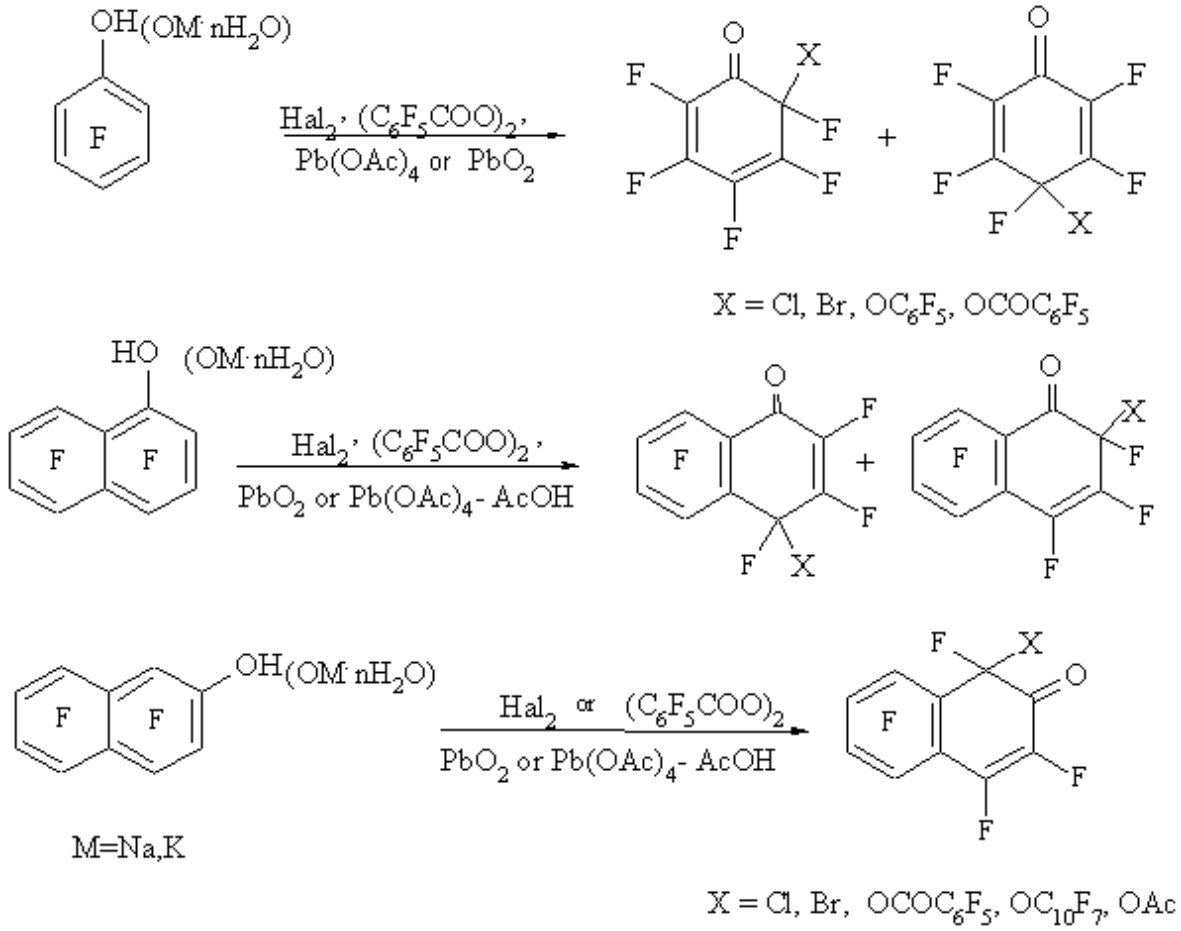


Figure 1

For the manufacture of polyfluorinated cyclohexadienones with phenyl groups at their saturated carbon atoms a new convenient method was proposed that was based on the selective oxidative *ortho*-arylation of perfluorinated phenols or naphthols [11], and involved the interaction of appropriate alkali metal phenolates or naphtholates with $PhPb(OAc)_3$.

In the case of sodium pentafluorophenolate the reaction does not stop at the stage of cyclohexadienone 1 formation, and nucleophilic-mobile fluorines at position 3 are substituted by pentafluorophenoxy or hydroxy groups resulting eventually in cyclohexadienone 2 or 3 [11] (Figure 2).

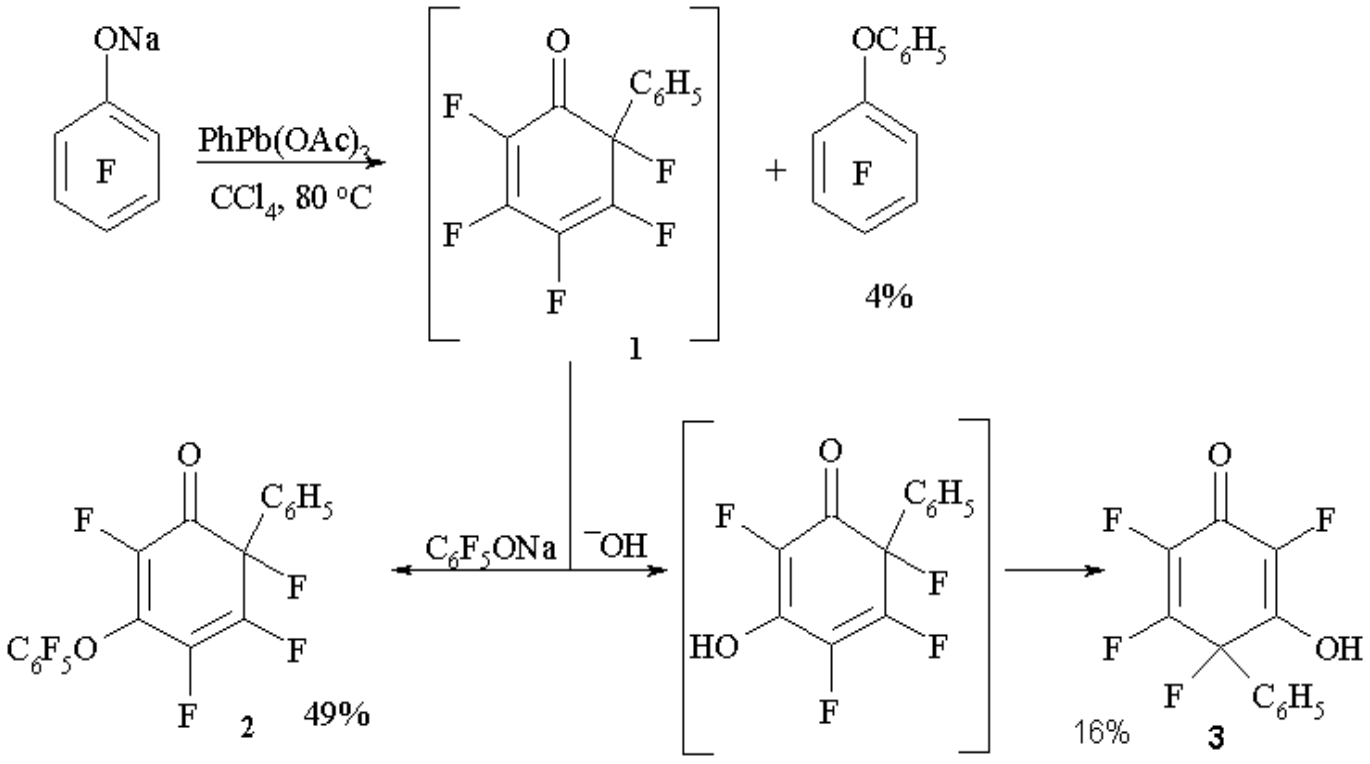


Figure 2

The reactions between sodium or potassium heptafluoro-1-naphtholate and ArPb $(OAc)_3$ or Ph_2Pb $(OAc)_2$ result in corresponding 2-aryl-1-oxoheptafluoro-1,2-dihydronaphthalene 4. (Figure 3)

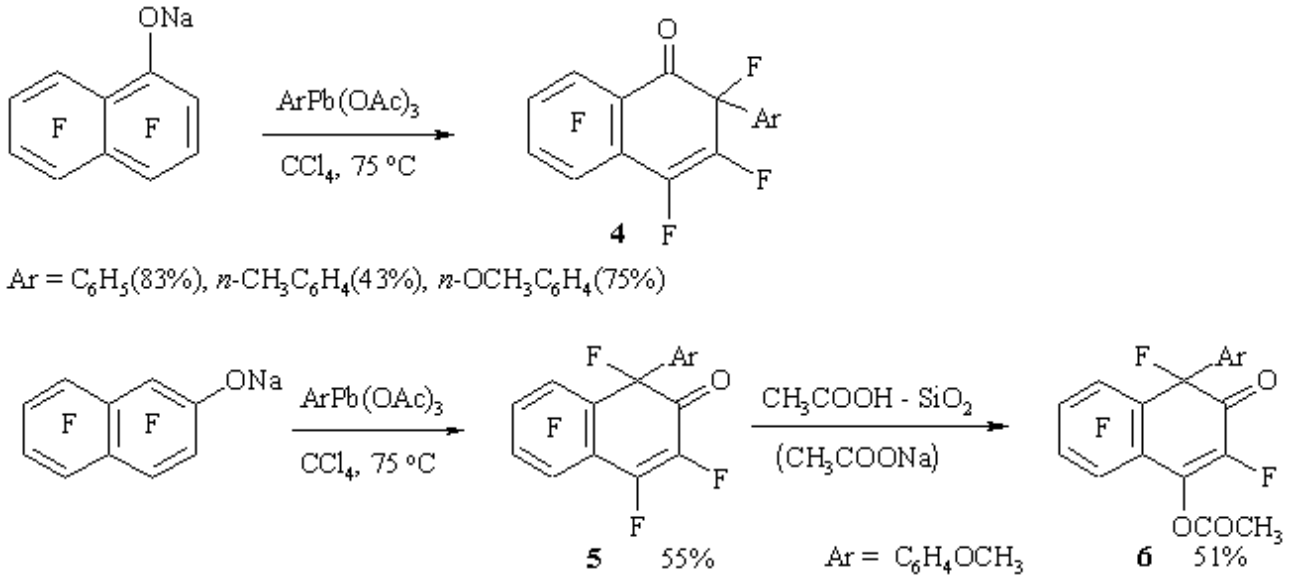


Figure 3

Sodium heptafluoro-2-naphtholate reacts with lead p-anisyltriacetate to form a mixture with predominant content of substance 5; and its chromatography on silica gel deactivated by acetic acid, results in 2-oxodihydronaphtalene 6 with yield 51%.

Nucleophilic substitution and reduction

The reactions between nucleophilic reagents and cyclohexadienones, that contain halogens at their saturated carbon atoms only, result, as a rule, in their reduction to phenol derivatives or in halogen substitution, and formation of corresponding substituted cyclohexadienones [12,13].

In contrast, polyfluorinated cyclohexadienones react easily with nucleophiles and one or two fluorines at their double bond are then replaced as a consequence both of very B high reactivity in nucleophilic reactions of fluorinated compounds with double bonds, and B as well of the double bond activation due to its conjugation with carbonyl groups [14].

Due to the carbonyl group effect, the fluorine at position 3 of polyfluorinated 2,4-cyclohexadienone is substituted much easier than that at position 5, and this result is consistent with MO calculations of charge distribution in polyfluorinated 2,4-cyclohexadienone [15]. Such reactions, usually with high yields, are exemplified in Figure 4 [16-19]. (Figure 4)

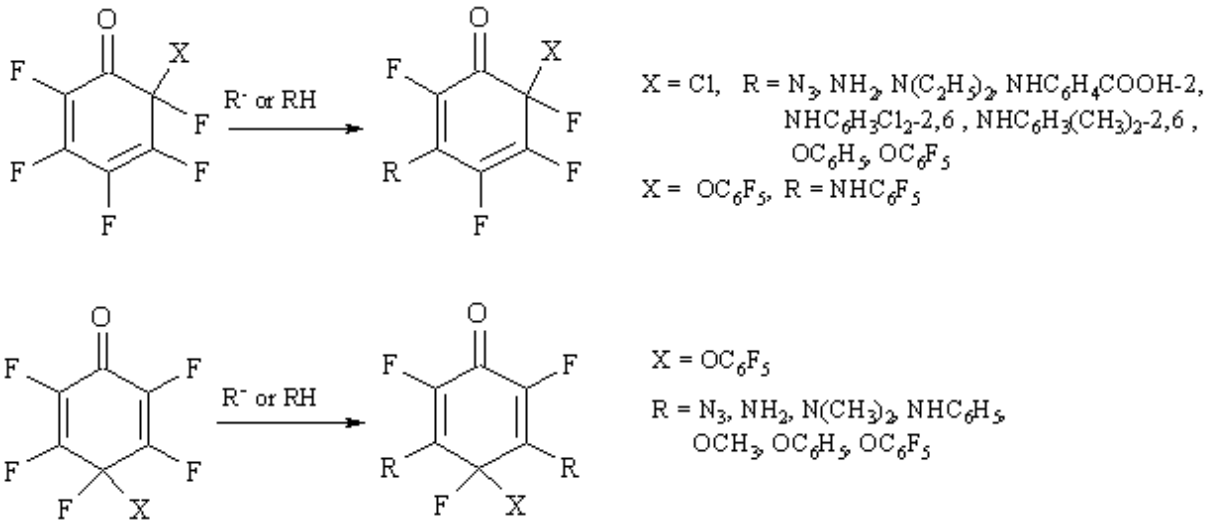


Figure 4

It should be noted that pentafluorophenoxyl group at position 3 of polyfluorinated 2,4-cyclohexadienonea 2 is easily substituted for a nucleophile at mild conditions. For example, cyclohexadienone 2 boiling with methanol results in the formation of the corresponding methoxy derivative 7 [19]. (Figure 5)

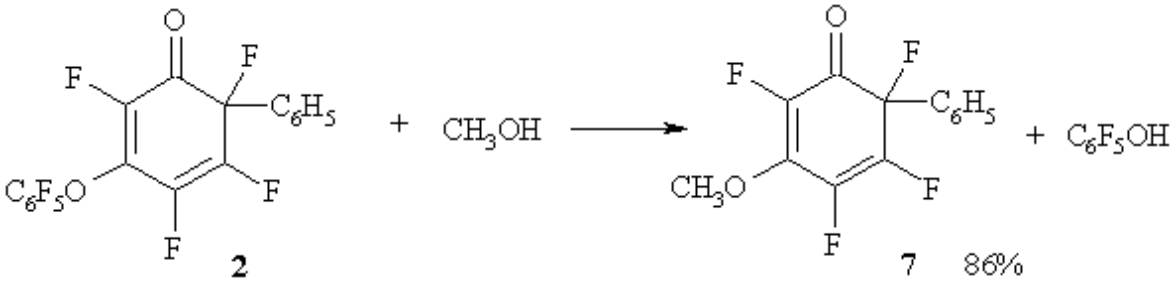


Figure 5

It is common for cyclohexadienones containing halogen at their saturated carbon atoms that being reduced they convert to phenols. When two different halogens, e.g. fluorine and chlorine, are bound to a saturated carbon atom, chlorine is always the first to be split-off under reduction. The use of this method in the synthesis of polyfluorinated phenols is the most advantageous when combined with the initial nucleophilic substitution of fluorine atom at the double bond of polyfluorinated cyclohexadienone as illustrated by examples [11,16,17,20] in Figure 6.

The method proposed for the manufacture of fluorinated phenols by the above mentioned sequence of reactions, is an example of a general strategy for the synthesis of polyfunctional aromatic compounds. At the first stage polyfluorinated phenols are converted to corresponding cyclohexadienones, which are easily and selectively modified by nucleophilic substitution of fluorines, and the cyclohexadienones thus modified are then reduced to polyfluorinated phenols containing various substituents.

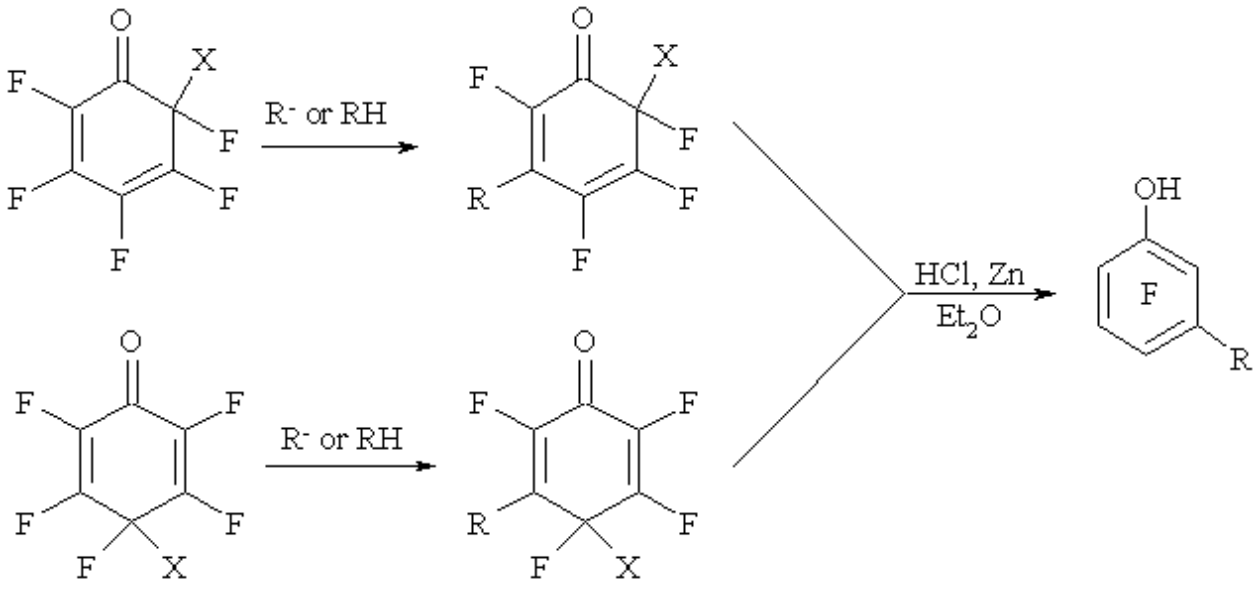


Figure 6

Nucleophilic reactions between cyclohexadienone 8 and phenols [21] or tetrafluororezorcin [22] were used in the synthesis of some polyfluorinated polyphenyl esters with nitro-, amino-, or carboxyl groups, branched or linear polyfluorinated polyphenyl esters with five or eight carbocyclic fragments in their molecules.

Cyclohexadienone 8 reacts with two equivalents of sodium pentafluorophenolate at room temperature with the formation of 3,5-substituted cyclohexadienone **9**. The latter undergoes isomerisation at 50-70B°C resulting in dienone **10a**. Using four equivalents of phenol in the presence of potassium carbonate at 70B°C, one can produce cyclohexadienone **11a-f** with phenoxy groups both in aromatic

and dienone parts of the molecule (Figure 7). The rearrangement of cyclohexadienone **9** probably follows intramolecular mechanism. An indirect argument in favour of such mechanism is the absence of reaction products with the *ortho*-quinoid structures (quite stable under those conditions [23]), which were to be formed, would the mechanism of isomerisation involve dissociation-recombination of phenoxyl radicals.

Cyclohexadienone **11a-f** can be reduced to 3,5-diaryloxy phenols **12a-f** that form polyfluorinated polyphenyl esters **13a-c** in reactions with hexafluorobenzene, or **13d-f** in the reactions with octofluorotoluene [22].

Two equivalents of 2,3,4,5,6-pentafluoro-6-chloro-2 ,4-cyclohexa-dienone **14** react with tetrafluororezorcin at room temperature resulting in 1,3-bis(4-chlorotetrafluoro-3-oxo-1,5-cyclohexadienyloxy)-tetrafluorobenzene **15** with the yield 90%.

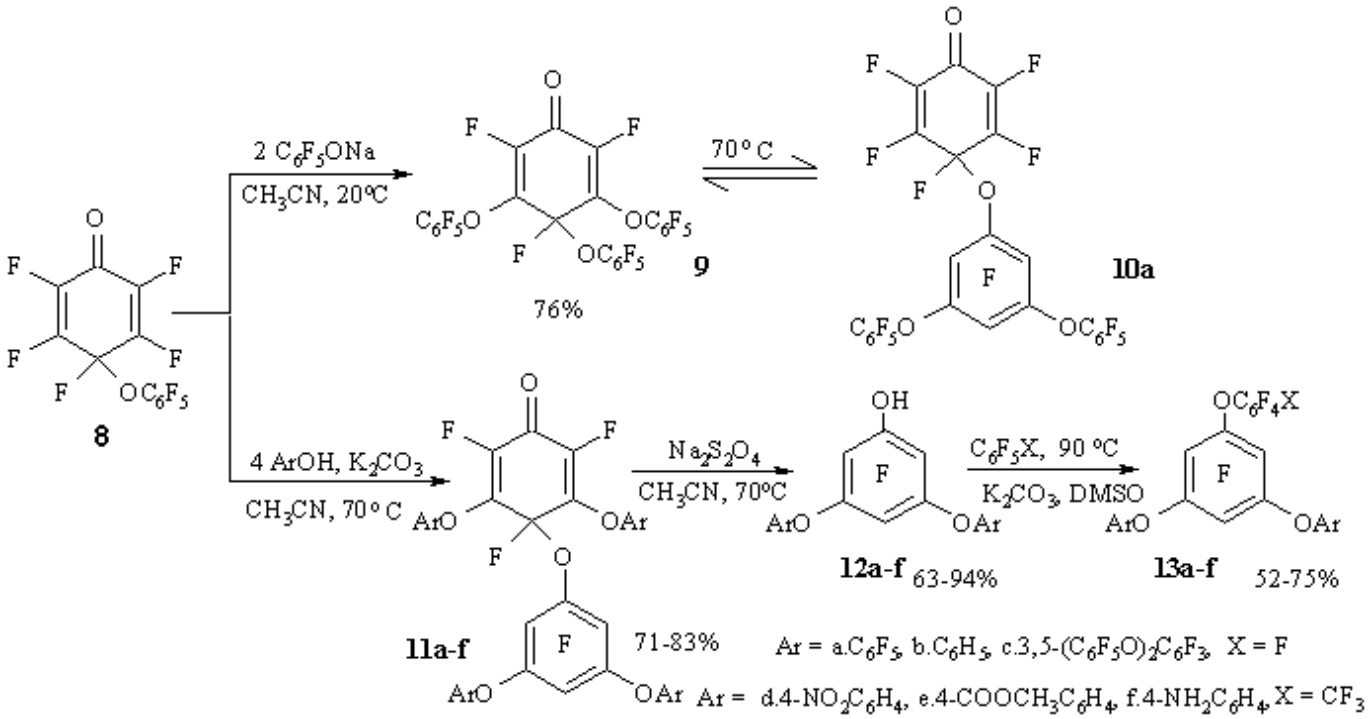
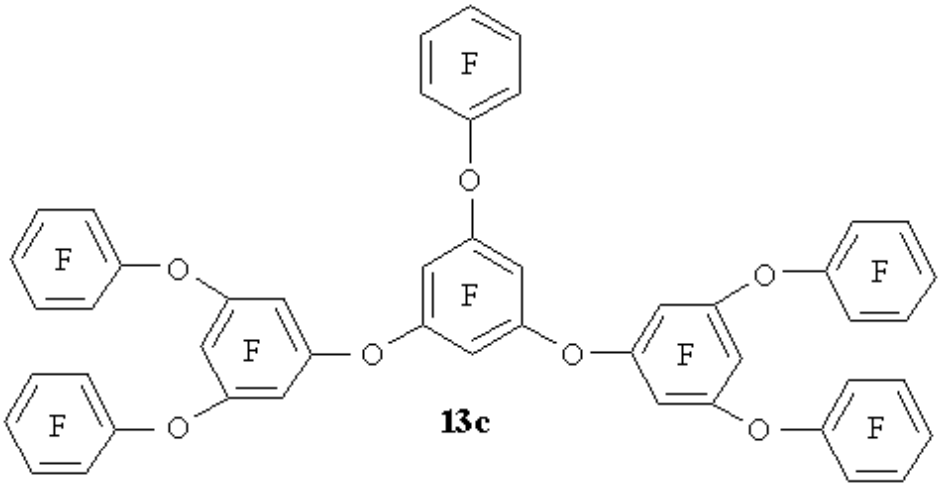


Figure 7



The reduction of **15** with sodium dithionite results in tetrafluoro-1,3-bis-(tetrafluoro-3-hydroxyphenoxy)benzene 16 [21], the former being also produced by the reaction of cyclohexadienone **8** with tetrafluororezorcin. The step-by-step reduction of **15** to **16**, the formation of disodium salt of the latter, and its reaction with polyfluorinated octafluorotoluene result in polyfluorinated polyphenyl ether **17**. (Figure 8)

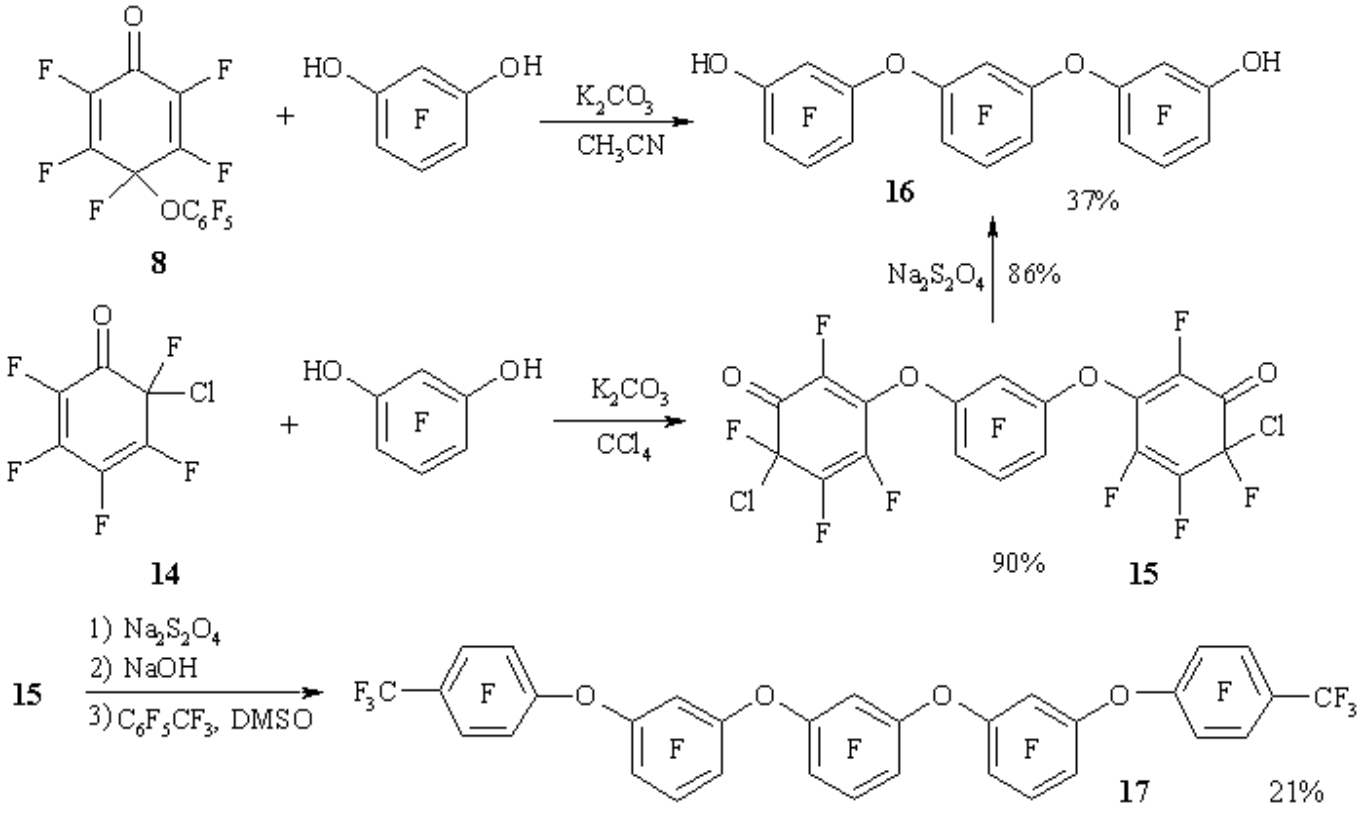


Figure 8

The reaction of a nucleophile, such as triphenylphosphine, withB polyfluorocyclohexadienone **2** leads to an interesting and unexpected result [24]. The main product of this reaction is cyclohexenedione **19**, with structure that according to X-ray diffraction (XRD), contains CF_2 and two carbonyl groups. Besides, in this compound phenyl group and pentafluorophenoxyl are in neighbouring positions, while in the original cyclohexadienone **2**, they occupy positions 6 and 3, respectively. (Figure 9)

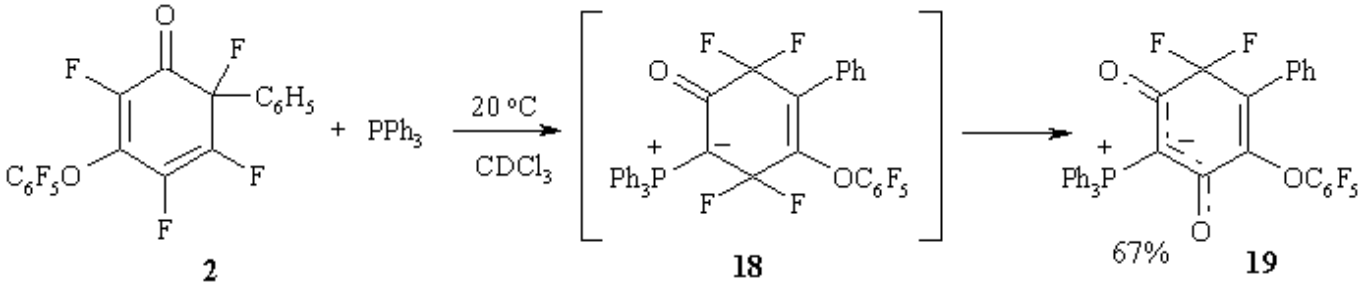


Figure 9

Figure 10 illustrates the likely sequence of reactions leading to the formation of compound **19**.

At the first step triphenylphosphine replaces pentafluorophenoxyl group at position 3 of the original cyclohexadienone **2**. After that pentafluorophenoxyl anion replaces fluorine at position 5 of the new cyclohexadienone with the formation of phosphonium fluoride **A,** that B undergoes isomerisation (via the formation of oxirane) to phosphonium salt **B**, further converted to zwitterion **18** with two CF_2 groups. This compound appears to be unstable, it adds water and splits-off HF resulting in stable dione **19**. (Figure 10)

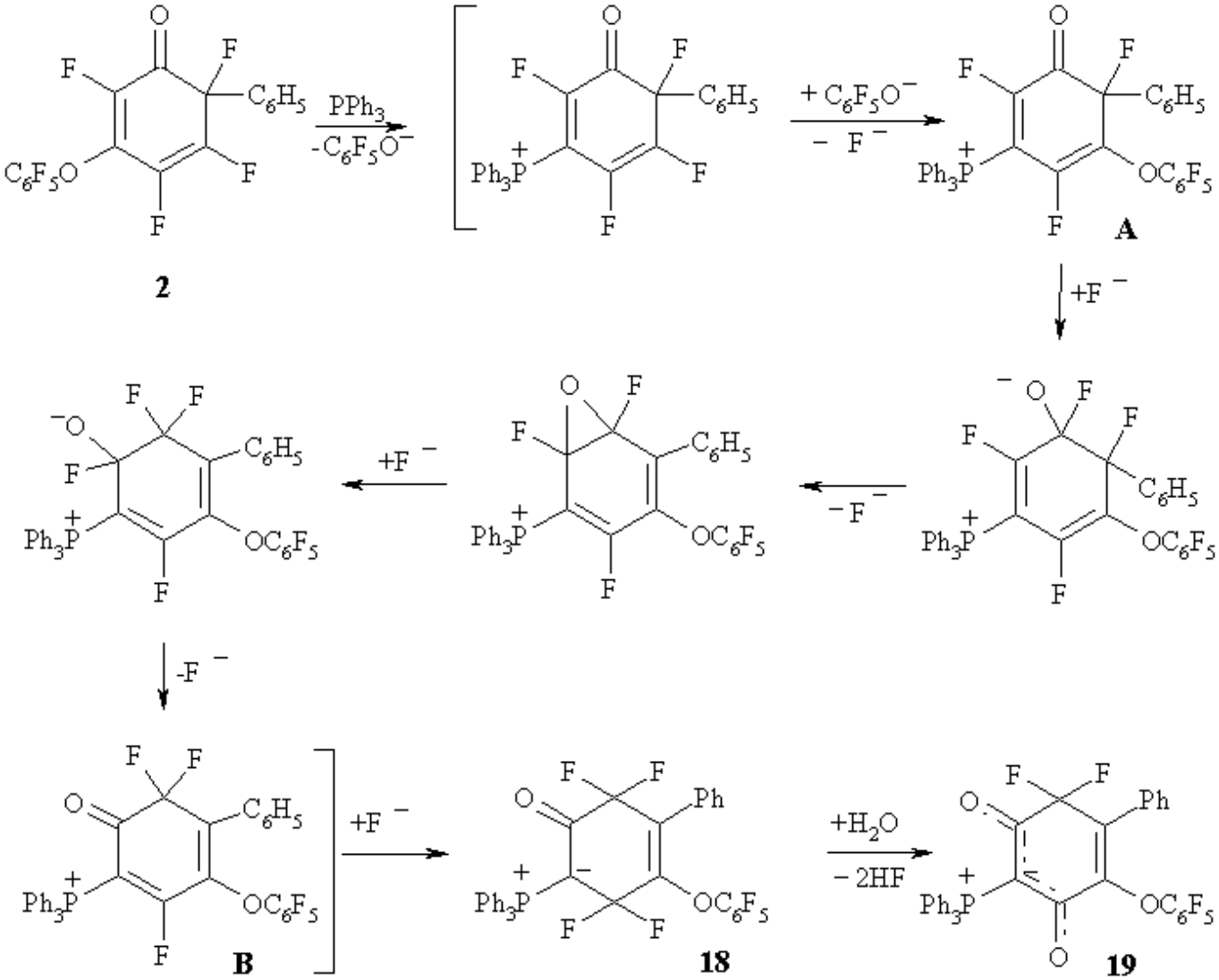


Figure 10

Reactions involving carbonyl groups

Reactions with phenylhydrazines

It is well-known that the reactions of non-fluorinated cyclohexadienone with nucleophiles occur with the participation of double bonds and carbonyl groups [25].

The transformations of cyclohexadienones by their carbonyl groups are represented, best of all, by their reactions with hydrazine derivatives [26], or with organometallic compounds [25.27].

The study on reactions between polyfluorinated cyclohexadienones and hydrazine derivatives, or organometallic compounds make it possible to evaluate the relative reactivity of two electrophilic centres available in those compounds, i.e. fluorinated double bond and carbonyl group.

Cyclohexadienone **8** in acetonitrile reacts with phenyl- or pentafluorophenylhydrazine resulting in cyclohexadienone 20 that is a product of nucleophilic substitution of fluorine atom at the double bond in the original dienone **8**, then it disproportionates resulting in a mixture of corresponding 3-arylazotetrafluoro-phenols 21a, b and pentafluorophenol at equal ratio. The carbonyl group of polyfluorinated cyclohexadienone obviously does not participate in this reaction. (Figure 11)

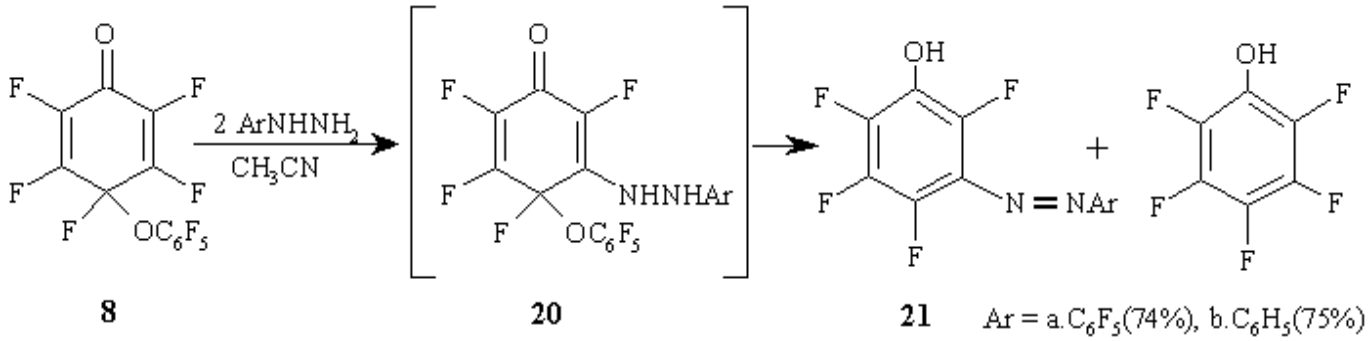


Figure 11

Since the acids are known to catalyze the reactions of arylhydrazines by carbonyl groups of cyclohexadienones [28, 29], a study was made on the interaction of polyfluorinated cyclohexadienones with complexes of phenyl- or pentafluorophenylhydrazine and aluminium chloride.

Cyclohexadienone **8** reacts with those reagents only with the participation of the carbonyl group to give the corresponding azobenzenes **22-24** [30]. During the azobenzene formation either fluorine or pentafluorophenoxyl group perform as groups leaving the cyclohexadienone geminate node. In the reactions with aluminium chloride/pentafluorophenylhydrazine complex the main reaction product is formed by the elimination of fluorine atom, while with the complex of phenylhydrazine both reaction paths are realized at nearly equal proportions. (Figure 12)

Such difference in the behaviour between phenyl- and pentafluorophenylhydrazine is probably due to the interaction of aromatic dienone substituent and hydrazine aromatic ring in the transition state. It is very likely [30], that initially formed complexes dienone/arylhydrazine/aluminium chloride have "sandwich" structure where arylhydrazine is possibly placed either on the side of aromatic fragment located in the cyclohexadienone geminate node **A**, or on its opposite side **B**. Those **A** and **B** complexes form relevant intermediates of type **C** and **D**. In the first case **C** pentafluorophenoxyl group will be leaving, and in the second **D** fluorine atom will be leaving [30].

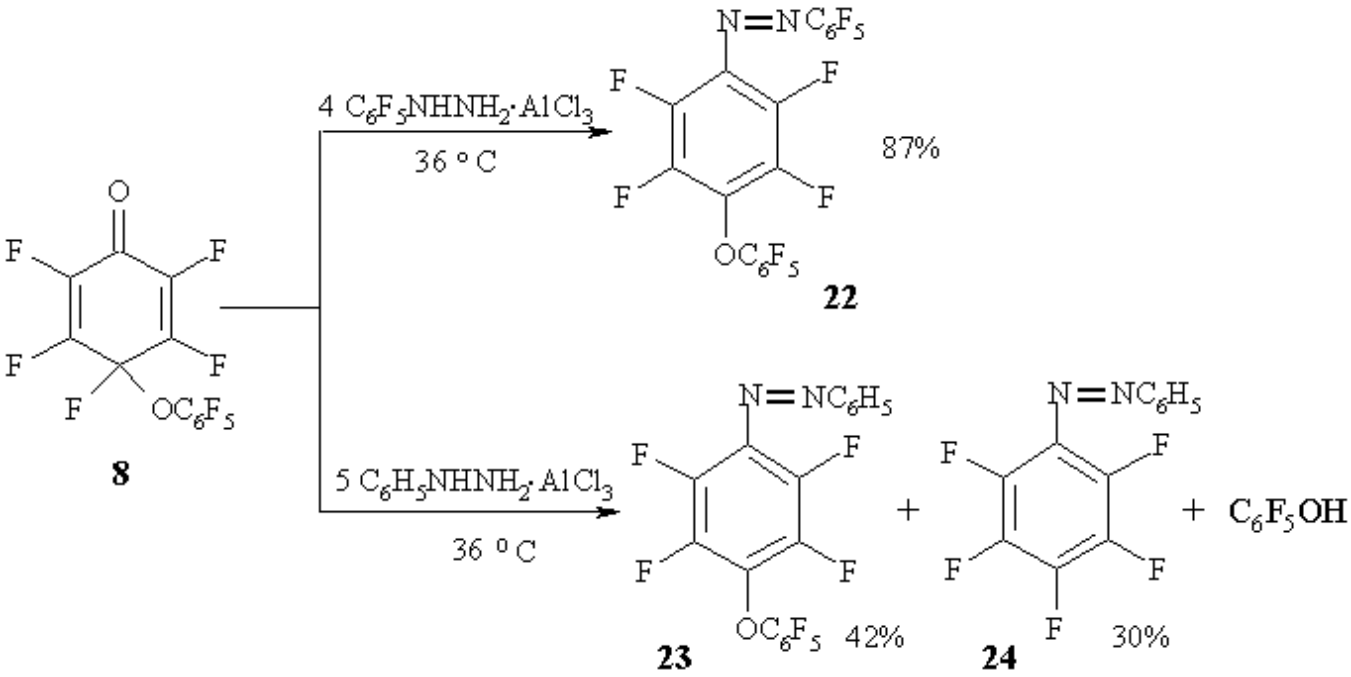


Figure 12

Intermediates with non-fluorinated phenylhydrazine type **C** can be further stabilized by *p*-interaction between the fluorinated and non-fluorinated aromatic rings (formation of *p*-complexes between fluorinated and nonfluorinated aromatic compounds is well known [31]), resulting, ultimately, in the splitting off pentafluorophenoxyl group from the dienone geminate node. In the case of fluoroarylhydrazine the interaction between hydrazine and dienone fluorinated aromatic rings results in the destabilization of complex C and formation of transient state D, B more favourable for the fluorine atom split-off. (Figure 13)

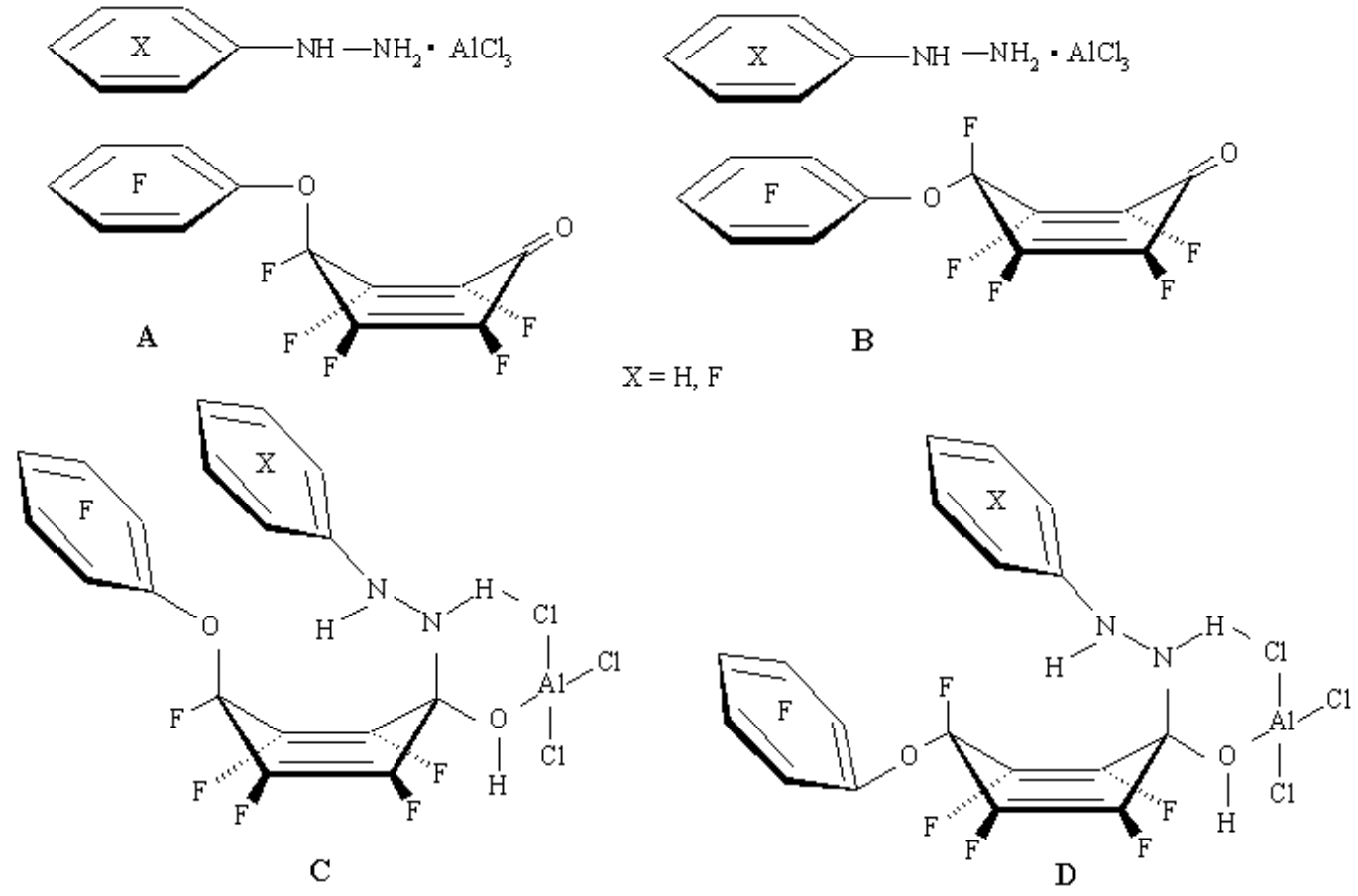


Figure 13

Arylhydrazine/aluminium chloride complexes can be used in the synthesis of various fluorinated azocompounds **25-27**, as shown in Figure 14.

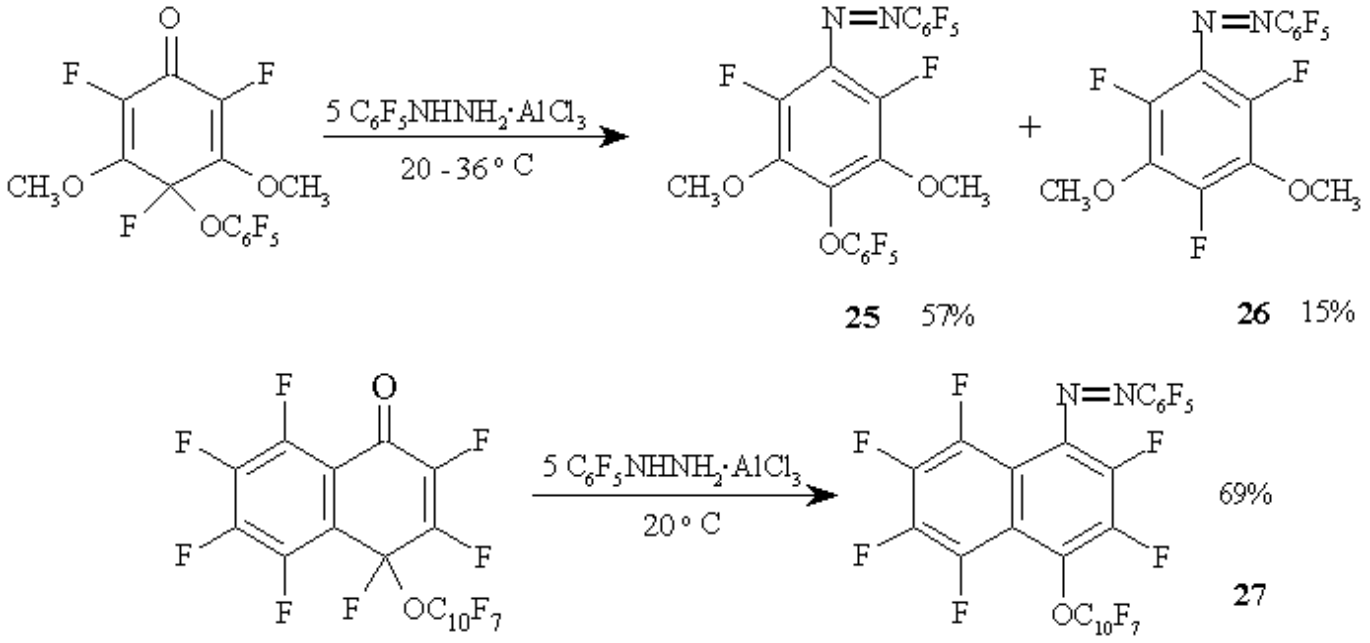


Figure 14

Reactions with organometallic compounds

The reactions between cyclohexadienone 8 and n-butyl lithium or n-butyl magnesium-bromide also occur by the carbonyl group resulting in 1-butyl-4-pentafluoro-phenoxy-2,3,4,5,6-pentafluoro-cyclohexa-

2,5-diene-1-ol **28** [30]. (Figure 15)

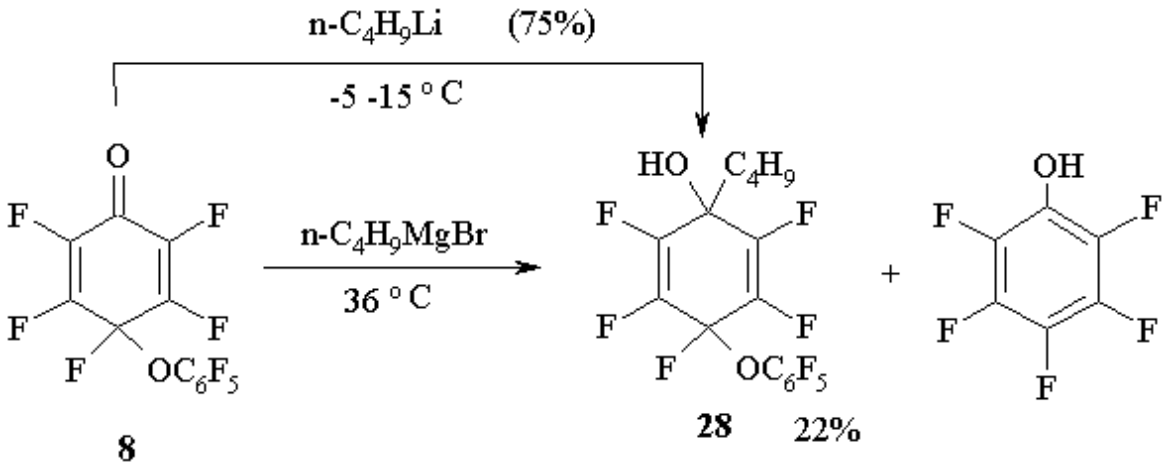


Figure 15

Therefore, polyfluorinated 2,5-cyclohexadienones react with nucleophiles exclusively by the carbonyl group, despite the presence of nucleophilic-mobile fluorine atoms at the double bond of polyfluorinated cyclohexadienone.

Photochemical transformations

Unlike the photolysis of non-fluorinated phenylcyclohexadienones, that occurs with transformations not involving carbonyl groups [32-35], photochemical reactions of polyfluorinated phenylcyclohexadienones in hexane solution proceed with the participation of both carbonyl group and phenyl fragment located in the geminate node, they result in the formation of polyfluorinated furan derivatives: dibenzofuran **29** and benzonaphthofuran **30** [36]. (Figure 16)

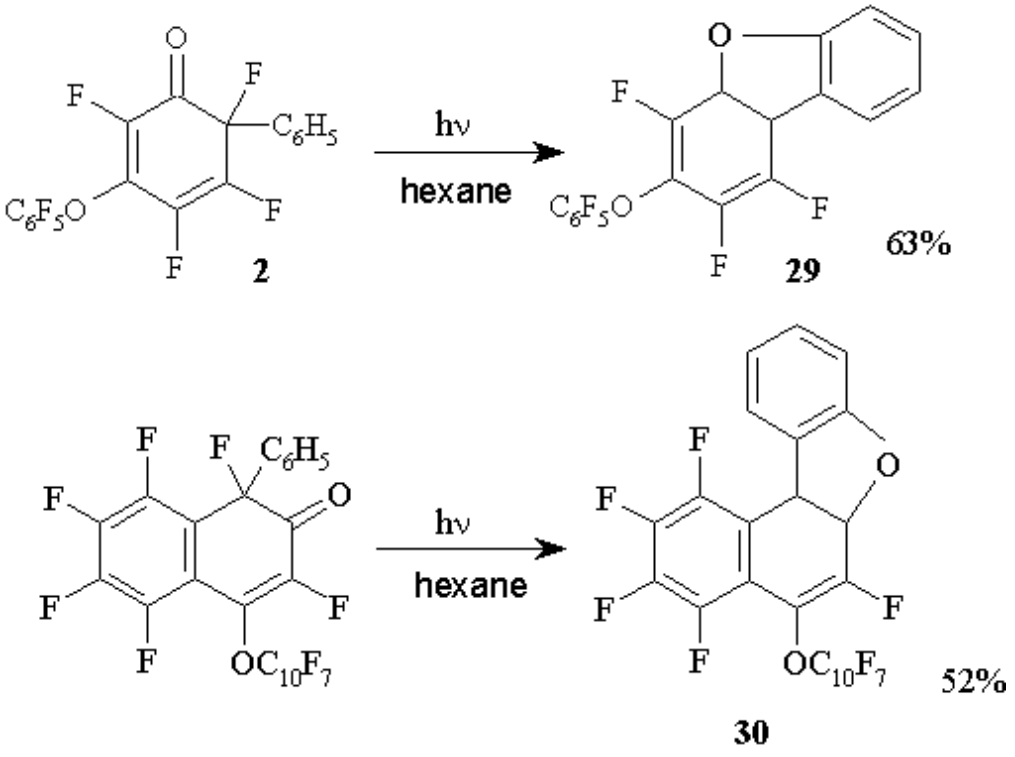


Figure 16

The main product of the photolysis of 2-tolyl-1-oxoheptafluoro-1,2-dihydronaphthalene **31** in chloroform solution is fluorinated derivative of benzonaphtofuran **32**.B Moreover, the product of fluorine atom migration that is 2-tolyl-1-oxoheptafluoro-1,4 -dihydronaphthalene **33** is also produced though in small quantity. Besides, for the studied polyfluorocyclohexadienes this is the only reaction where the formation of cyclopropane derivative 6a-tolilheptafluoro-1,1a-dihydro-cyclopropane [a] indenone (**34**) is observed, typical however, for their hydrocarbon analogues. (Figure 17)

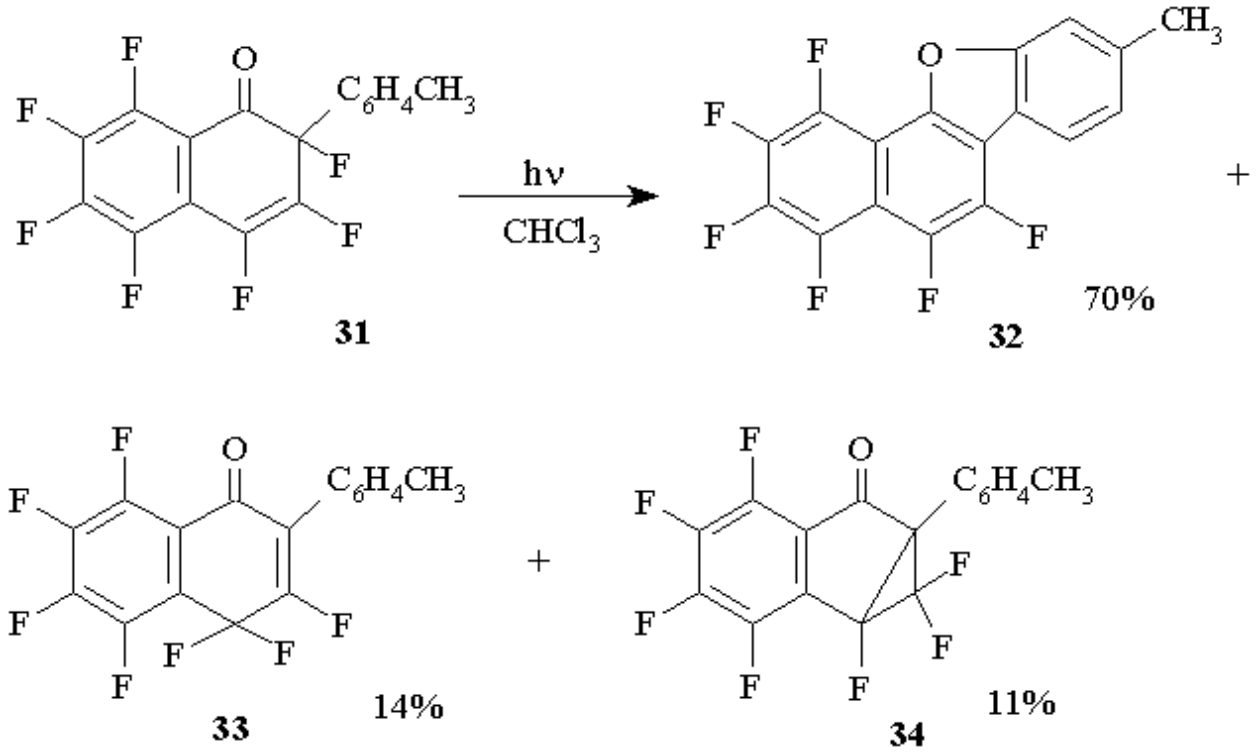


Figure 17

Cycloaddition reactions of polyfluorinated cyclohexadienones

1,3-cycloaddition of diazomethane and its derivatives

Alkyl-substituted 2,4-cyclohexadienoneB is known to react with diazomethane and alkyl-or phenyldiazomethanes only by their carbon-carbon double bonds, thus forming polycyclic pyrazoles and cyclopropanes [37-40].

The main products of the reaction between cyclohexadienone **14** and phenyldiazomethane in acetonitrile (phenyldiazomethane solution is added to the solution of dienone **14**) are isomeric 3-chloro-1,3,4,5,6-penta-fluoro-7-phenylbicyclo-[4.1.0] hepta-4 -en-2-ones (**35a** and **35b**, 62:38), formed with the participation of their double bonds only. In addition, isomeric 6-chloro-3a,4,5,6,7a-penta-fluoro-3,3вЂ™-diphenyl-3a,6,7,7a-tetrahydro-spiro[3H-indazol-7,2вЂ™-oxiranes] (**36a** and **36b**, 67:33) were obtained with very low yield (5%)

In contrast, 6-chloro-2 ,3,4,5,6-pentafluoro-2 ,4-cyclohexadienone **14** reacts with diazomethane in ether at 0B°C, both by its carbonyl group and by its double bond resulting in a mixture of two isomers (58:42) **37a, b** with the yield 52% [41]. (Figure 18)

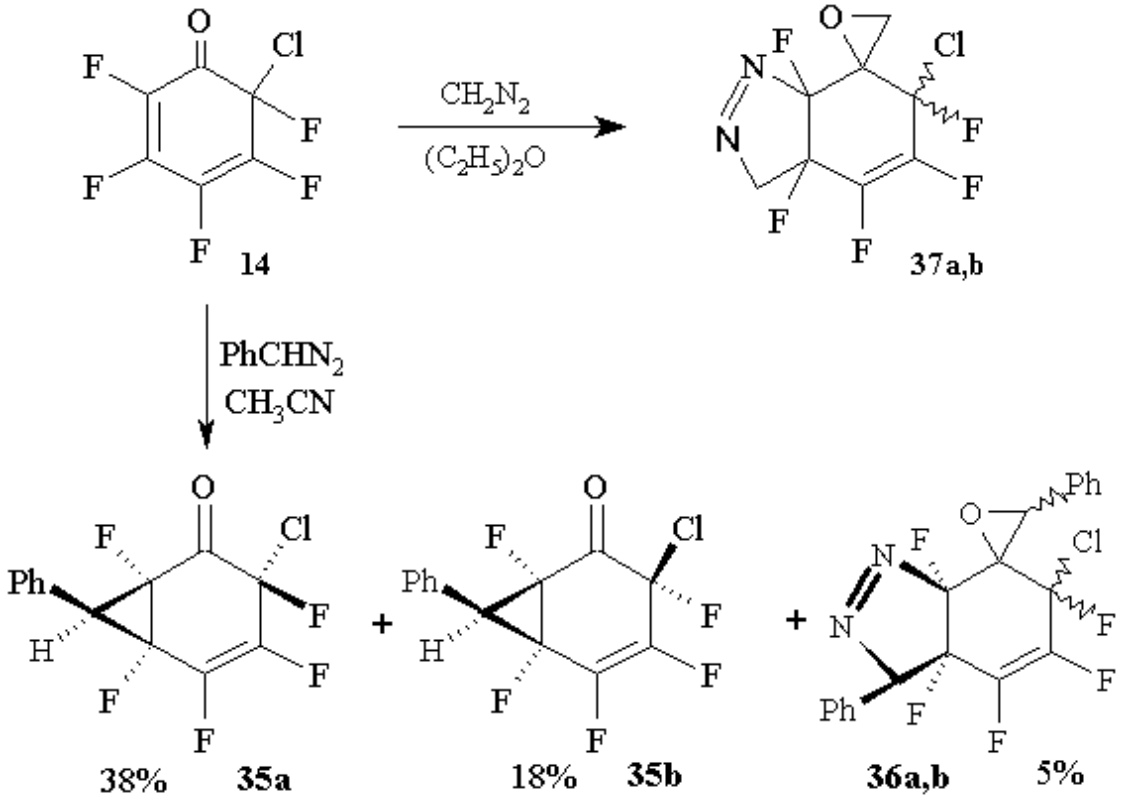


Figure 18

Bicyclotetrahydroindazols of type **36 or 37** were not detected in those reactions. (Figure 19) The reactions of 6-chloro-3-(pentafluorophenoxy)-2,4,5,6-tetrafluoro-2,4-cyclohexadienone **38** or cyclohexadienone **2** with phenyldiazomethane in acetonitrile also result in cyclopropane derivatives **39a** and **39b** (67:33), or **40a** and **40b** (83:17), respectively, and in pentafluorobenzylphenyl ether **41** (10%). At the same time (Z) - and (E)-stilbenes **42** are produced in significant amounts being the products of competitive reactions. Bicyclotetrahydroindazols of type **36** or **37** were not found among the reaction products (Figure 19).

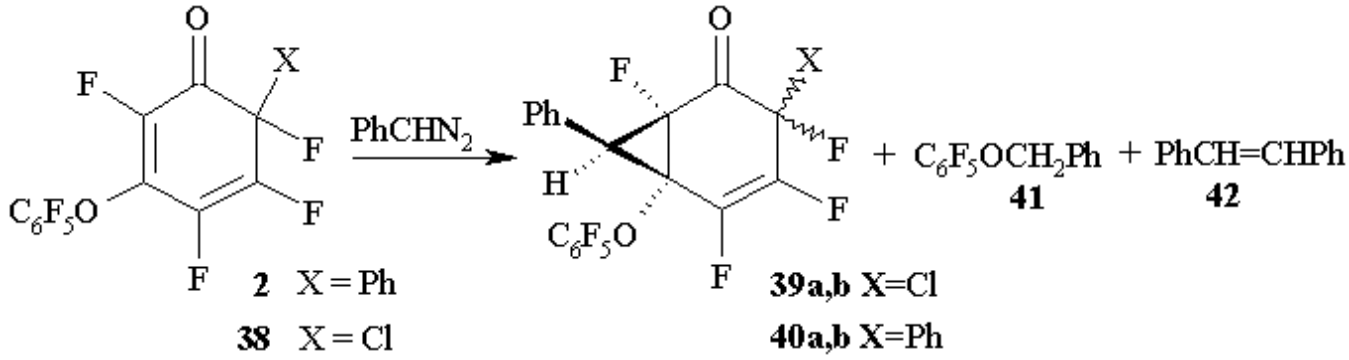


Figure 19

For the formation of cyclopropane derivatives in the reactions of polyfluorinated cyclo-hexadienones **2**, **14** and **38** phenyldiazomethane the following mechanism was suggested (Figure 20)

Zwitter-ion **44**, formed at the first step from dienones **2**, **14** or **38**, via a transition state similar to 43, is stabilized either by nitrogen elimination followed by cyclisation, resulting in the formation of cyclopropane derivatives **35a**, **b**, **39a**, **b** and **40a**, **b** or by the elimination of pentafluorophenol, that interacts with phenyldiazomethane resulting in the formation of pentafluorophenylbenzyl ether **41**. The probability of the latter reaction was verified in an independent experiment. In addition, it is known that pentafluorophenoxyl group at position 3 of polyfluorinated cyclohexadienone is easily substituted by various nucleophiles [24].

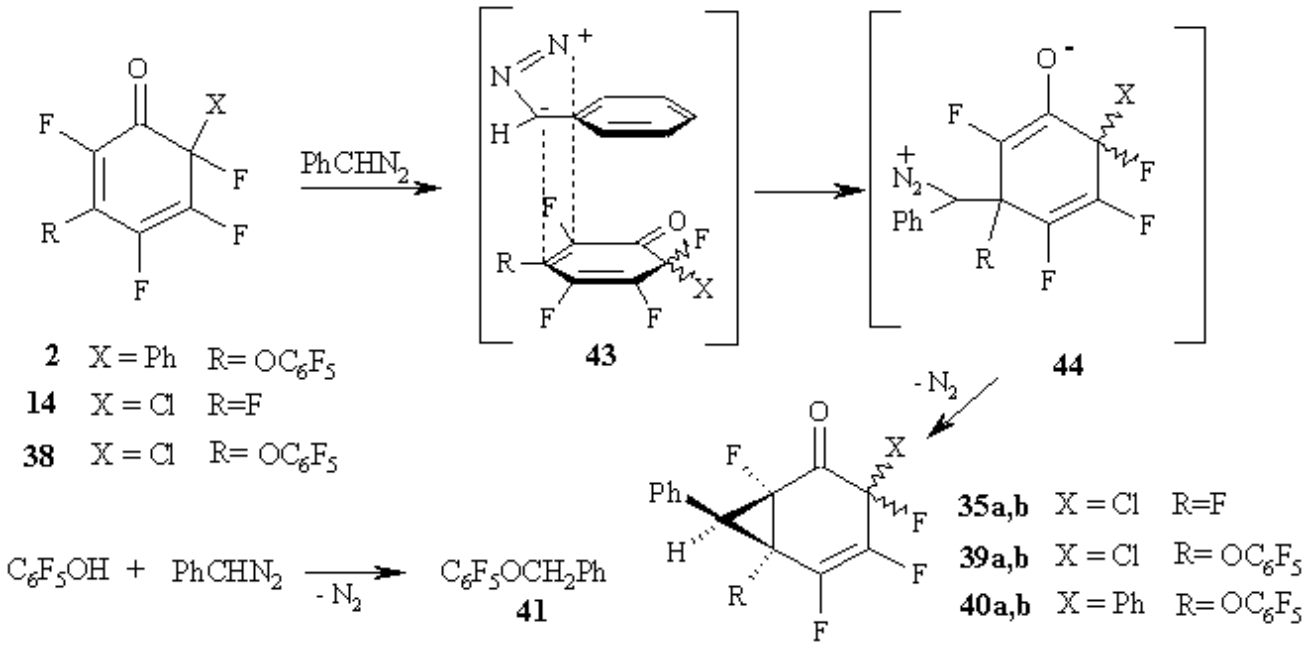


Figure 20

X-ray structure analysis of bicycloheptenons **35a** and **35b** show that the cycloaddition of cyclohexadienone **14** or phenyldiazomethane occurs with high selectivity: both isomers **35a** and **35b** have *endo*-configurations, which is consistent with the above proposed scheme.

It is interesting [42] that the tetrafluoro-*n*-benzoquinone reacts with diazomethane only by its carbonyl group resulting in tetrafluoro-2 ,5-cyclohexadiene-1-one-4-spiro-2 '-oxirane **45**, along with a small amount of pentacyclic compound **46** that is a product of the reaction with the participation of both double bonds and carbonyl groups of tetrafluoro-*n*-benzoquinone. (Figure 21)

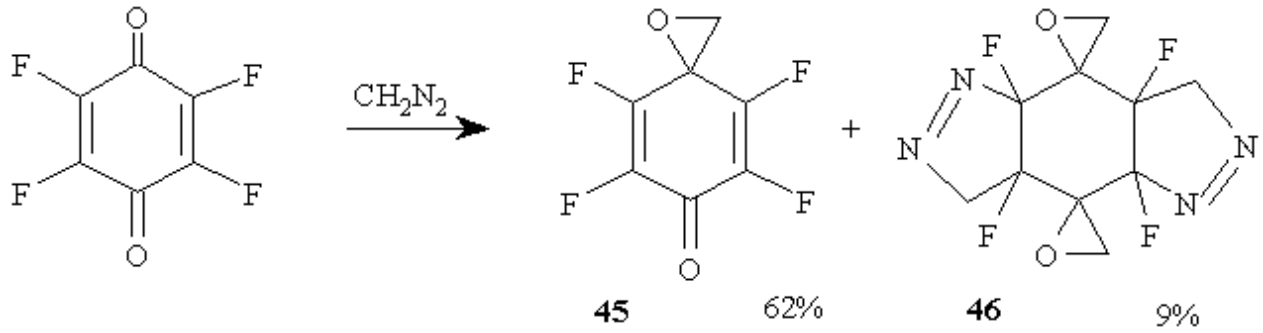


Figure 21

B Polyfluorinated 2,5-cyclohexadienones **8, 47-49**, being rather similar to tetrafluoro-*n*-benzoquinone react with diazomethane by its carbonyl group resulting in high yield (70 вЂ“ 98%) of a mixture containing two diastereomeric polyfluorinated 1-oxaspiro[2.5]octa-4,7-dienones **50a-52a** and **50b-52b,** and **53** as well **B [**43] (Figure 22).

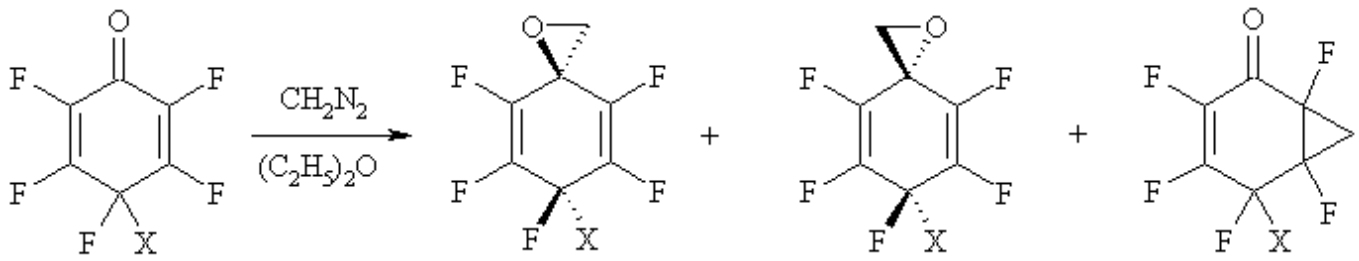


Figure 22

The product of diazomethane addition by the double bond of polyfluorinated 2,5-cyclohexadienone **54** is formed in trace quantity only.

Therefore, polyfluorinated 2,4-cyclohexadienones unlike non-fluorinated cyclohexadienones react with diazomethane both by their double bonds and by carbonyl groups resulting in the formation of isomeric fluorinated tetrahydro-spiro[indazol-oxiranes] that differ in the steric position of halogens in their CFCl-groups. PolyfluorinatedB 2,4-cyclohexadienones react with phenyldiazomethane mostly by their fluorinated double bonds resulting, with high stereoselectivity, in isomeric fluorinated phenylbicyclo[4.1.0]heptenones in *endo*-configuration. B While so doing polyfluorinated 2,5-cyclohexadienones react with diazomethane by its B carbonyl group mostly.

For polyfluorinated 2,5-cyclohexadienones the replacement of carbonyl groups for reactive oxirane cycles expands considerably their synthetic potentialities. The addition of alkyl- or arylisocyanates resulting in the formation of 2-oxazolidinones [44, 45] is an interesting and well-known reaction of oxiranes.

Polyfluorinated spiro-oxiranes **50,51** react with aryl- or alkyl- isocyanates in the presence of lithium or sodium salts resulting in the formation of fluorinated dihydro-1,3-benzoxazol-2(3Pќ)-ones **55** [43] (Figure 23).

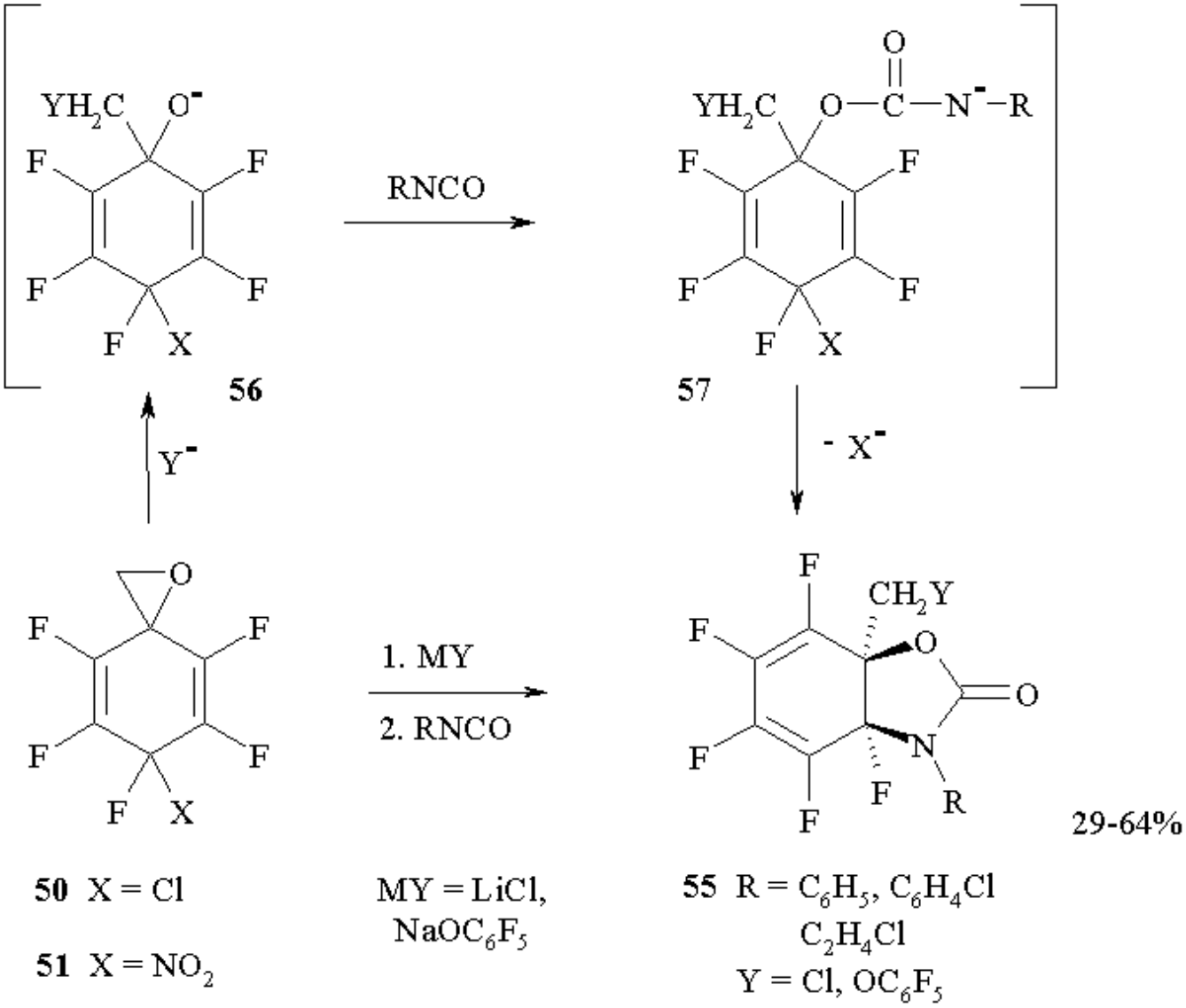
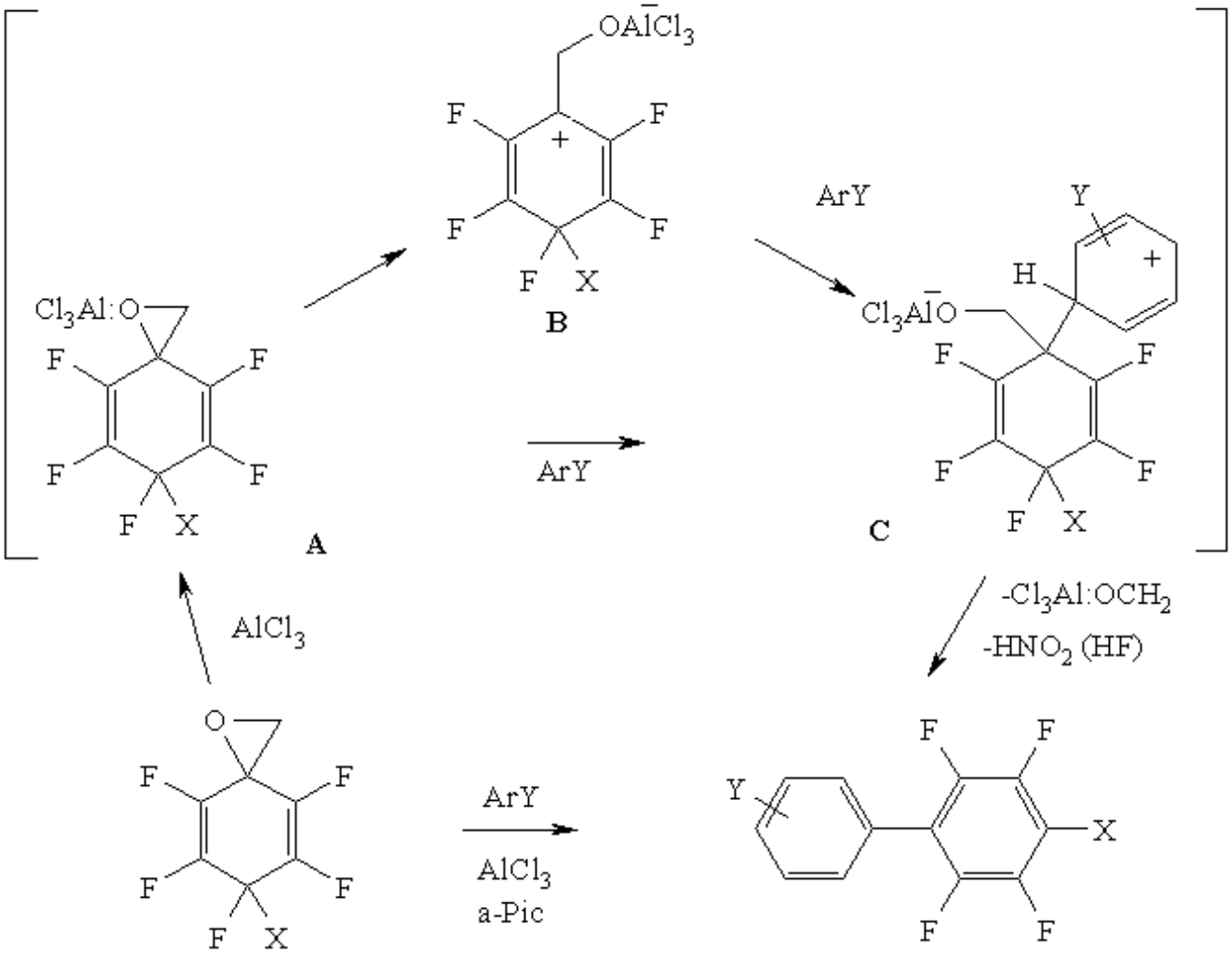


Figure 23

It should be marked that spirooxirane **50** reacts in the presence of catalytic amounts of LiCl, while in the reactions of oxirane **51** lithium or sodium salts perform as reagents and consumed in equimolar quantities. This is in conformity with the assumption about primary cleavage of CH_2-O bond under the action of a nucleophile (ClBÏ or BÏOC_6F_5), resulting in the formation of alcoholate **56**. Addition of anion

56 to isocyanate results in ambident ion **57**, that undergoes cycling by РЎ=РЎ bond exclusively followed by the elimination of РґВЇ from geminal CFX nod and the formation of benzoxazolones **55**.

B Some interesting results followed from the efforts to open oxirane cycles in substances **51**, **52** under the action of Lewis acids [46, 47]. It is well-known that the interaction between oxiranes and aromatic substances in the presence of Lewis acids results in electrophilic oxyalkylation [48, 49]. We found that the reactions of polyfluorinated spirooxiranes **51**,**52** with B benzene, toluene, mesitulene, or anisole in the presence of $AlCl_3$ and O±-picoline resulted in the formation of fluorinated biaryls. At the same time oxirane **51** loosing nitrogroup performs as a pentafluorophenylating agent, producing biphenyls **58a-58d**. At the same time, oxirane **52**, with OC_6F_5 group in its geminal nod reserves it untouched in the reaction products, therefore resulting in biaryls **59a,b**. In fact, in the reactions of electrophilic substitution in aromatic nucleus oxiranes **51, 52** perform as "synthetic equivalent" of polyfluorinated aryl cations. (Figure 24)



51 $X = NO_2$

52 $X = OC_6F_5$

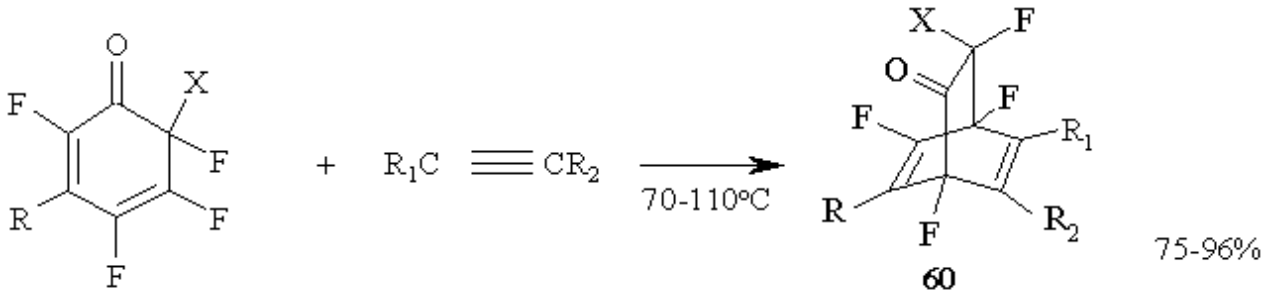
58a	Y = H; X = F	30%
b	Y = 2,4,6-CH_3; X = F	51%
c	Y = CH_3 (***o,m,p***); X = F	58%
	(***o:m:p*** 24:15:61)	
d	Y = OCH_3 (***o,p***); X = F	52%
	(***o:p*** 48:52)	
59a	Y = H; X = OC_6F_5	28%
b	Y = 2,4,6-CH_3; X = OC_6F_5	49%

Figure 24

B One may assume that complex **"A"** formed by oxirane (**51 or 52)** with $AlCl_3$ at the first step is opened with the formation of arenonium ion **"B"**. The latter interacts with aromatic substrate probably via transient zwitter-ion **"C"** resulting finally in the formation of polyfluorinated biaryls **58a-d, 59a,b**, though the possibility of direct interaction between complex "**A"** and aromatic substrate is not ruled out..

Reactions [4+2] of cycloaddition with acetylene derivatives

Polyfluorinated 2,4-cyclohexadienones easily enter into a reaction of [4+2] cycloaddition with dienophiles such as acetylene derivatives containing aryl- , alkyl-, or hydroxyalkyl groups, resulting in high yield (75-96%) of bicyclo[2,2,2]octadienes **60** [19,50-52]. Those reactions proceed under soft conditions on boiling in benzene, toluene, or carbon tetrachloride. The cycloaddition occurs with high regio- and stereo- specificity resulting in the formation of isomers **60** only, where R_1=H for the reactions with non-symmetric acetylenes, the fact being in conformity with the distribution of electronic density within the diene fragment of original 2,4-cyclohexadienone and acetylene (Figure 25)



$R = F, OCH_3, OC_6F_5$ $\quad R_1 = H, Et, Ph$

$X = Cl, OC_6F_5, C_6H_5$ $\quad R_2 = Et, n\text{-}Bu, CH_2OH, CMe_2OH, Ph$

Figure 25

The results of x-ray structural analysis confirm [52] high stereoselectivity of Diels-Alder reaction of polyfluorinated cyclohexadienones with acetylenes. The configuration of sp^3- Sp3-hybridized carbon atom with a fluorine atom and substituent X does not depend on the nature of the said substituent: the fluorine atom is always oriented towards the bond formed due to the dienophile addition. The computation by the molecular mechanical method (MM) [52] of two epimeric adducts with different positions of fluorine and chlorine atoms at sp^3-hybridized carbon atom demonstrated that high stereoselectivity of the reaction is due to the thermodynamic stability of thus formed adducts, but is likely a result of less hindered attack by the dienophile on the cyclohexadienone from fluorine side as to compare with those from other geminal substituents, i.e. B chloro-, phenyl-, or pentafluorophenoxyl groups [52].

An interesting result was obtained for the cycloaddition of 3-azidoPs-tetrafluoro-6-chloro-2,4-cyclohexadiene-1-on **61**. The main product of this dienone heating with phenylacetylene in CCl_4 at 70B°C was 4-oxo-2-phenyl-3,5,6,7-tetrafluoro-5-chloro-bicyclo[4.1.0]hepto-2-en-7- carbonitrile **62**[19]. Cyclopropane derivative **62** is a product of cycloadduct **63** conversion, its formation being confirmed by ^{19}F NMR spectra during the reaction conducted at room temperature. (Figure 26)

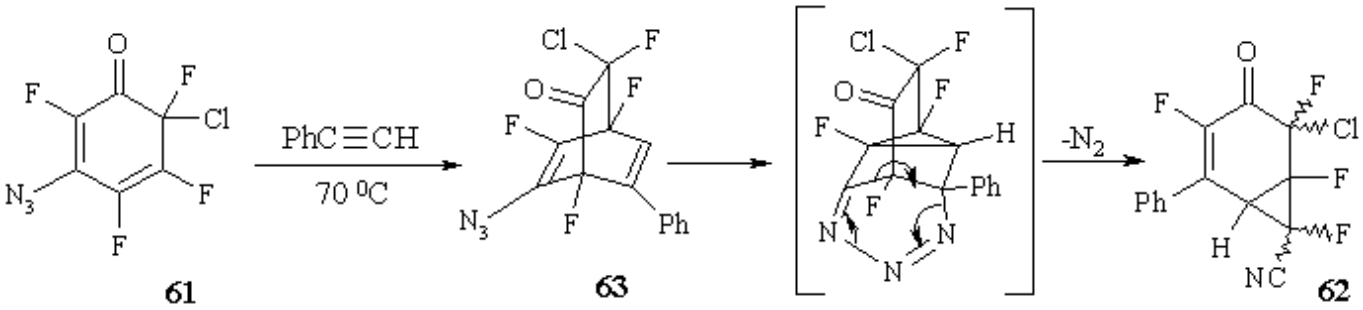


Figure 26

Phosphaalkynes are hetero-analogues of acetylene that also enter the reaction [4+2] of cycloaddition with polyfluorinated cyclohexadienones [53]. Earlier the reactions [4+2] of phosphaalkyne cycloaddition to cyclic 1,3-dienes were applied in the synthesis of cyclic phosphaalkenes, particularly, of phosphoaromatic substances [54, 55]. Usually, the researchers failed to isolate the intermediate bicyclic adducts in those reactions [56].

Heating cyclohexadienone **2** with bis(isopropyl)aminophosphaethine in $P\breve{Y}H_2Cl_2$ solution from -196 B°C to room temperature we succeeded to produce with quantitative yield only one isomeric bicyclic adduct **64** [53]. (Figure 27)

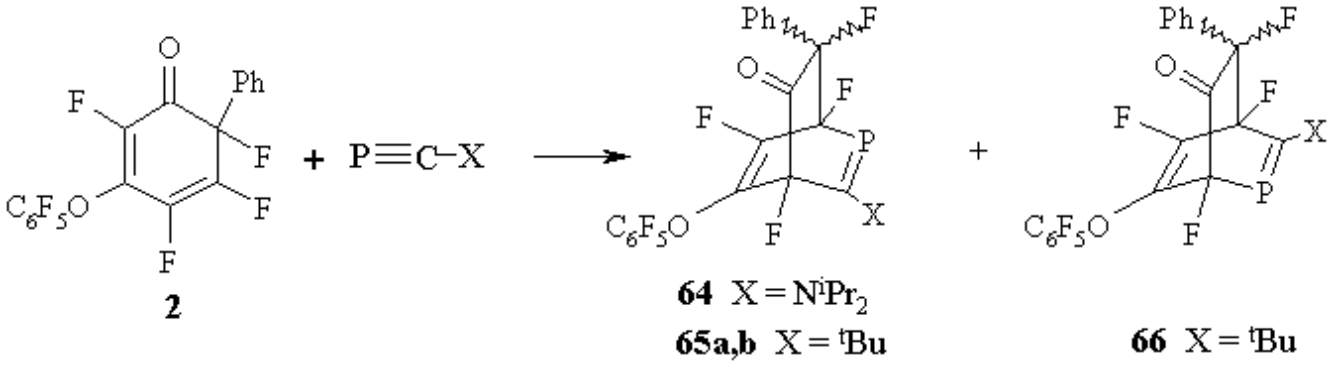


Figure 27

Both chemical composition and structure of adduct **64** were determined by elemental analysis and spectral studies (MS, NMR ^1H, ^{19}F, ^{31}P, ^{13}C).

It is interesting that unlike the above reaction the interaction of cyclohexadienone **2** with B *tert*-butylphosphaethine results in the formation of a tree-component mixture of substances **65a,b** and **66** at ratio 90:4:6. The results of ^{31}P NMR spectroscopy allow for concluding that in the product blend of this reaction regioisomer **65** is present in the form of two **different** stereomers, while regioisomer **66** is present in a single form only. The rate of reaction with *tert*-butylphosphaethine is markedly less, because the conversion of cyclohexadienone **2** is completed only after two days of heating the reagent mixture at 60 B°C. (Figure 27)

Bicyclic adducts **64, 65a,b** and **66** are stable in solid state or in usual organic solvents, and with surplus phosphaalkyne they do not enter DielsвЂ“Alder homo-reaction so typical for 2-phosphabicyclo [2.2.2] octa-2, 5-diene [57]. However, in chloroform solution substance **65a** undergoes intramolecular [2+2] cycloaddition initiated probably by diffused daylight. Adduct **65P°** after aging for a week at room temperature is 60% isomerised to substance **67**. (Figure 28)

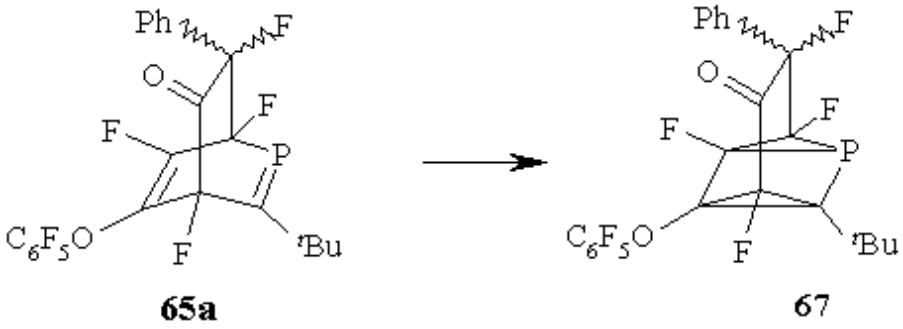
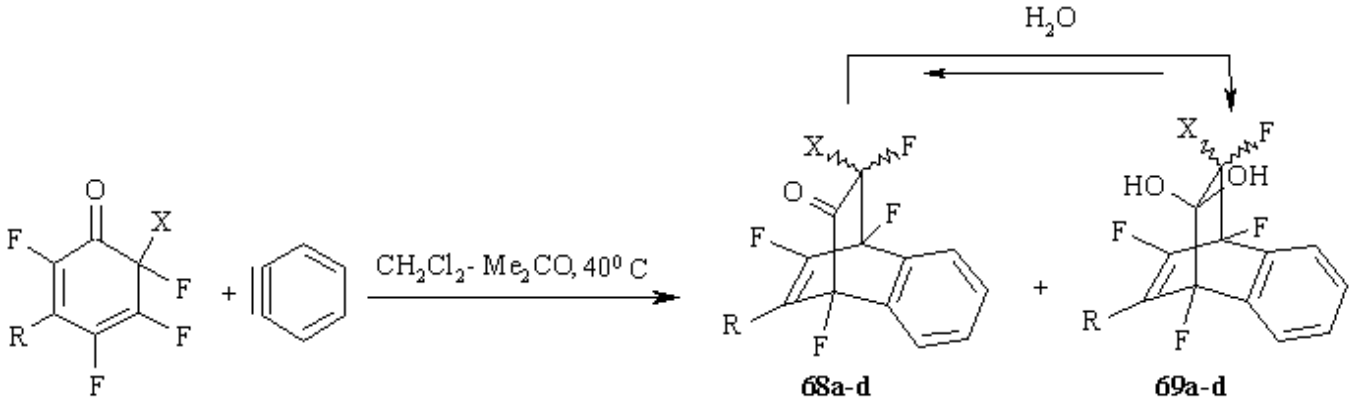


Figure 28

B B The tetracyclic structure of substance **67** was assumed reasoning from the analysis of NMR spectroscopy data. The observed considerable shift towards strong field of signal ^{31}P ($\Delta\delta_p$ 304.1 m.d.) caused by valent isomerisation of substance **65a** (δ_p = 217.7 m.d.) to **67** (δ_p = -86.4 m.d.), is in conformity with the shift value $\Delta\delta_p$ 445 m.d., observed during the photochemical transformation of 2-dewar-phosphine to corresponding derivative of phosphoprismane [58].

Polyfluorinated cyclohexadienones enter the reactions of [4+2] cycloaddition with such dienophile as dehydrobenzene [59]. The former was produced *in situ* from *Ps*-aminobenzoic acid and isoamylnitrite [60-62]. (Figure 29)



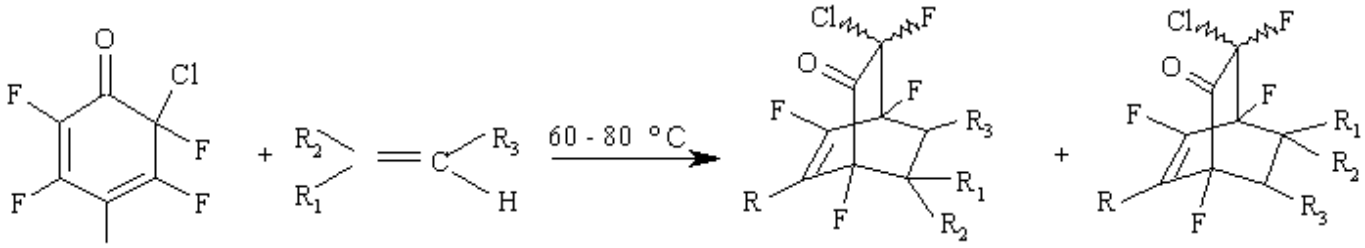
a.R = F, X=Cl b.R=OC_6F_5, X=Cl c. R=OCH_3, X=Cl d.R=F, X=OC_6F_5

Figure 29

The low-yield (26-37%) reaction products are a mixture of two substances **68a-d** and **B 69a-d**. From the analysis of their NMR^{19}F and NMR ^{13}C spectra one may conclude that substances **69a-d are in fact hydrated** cycloadducts **68a-d**, formed probably with the participation of water available in the solvent.

Reactions of [4+2] cycloaddition to alkenes

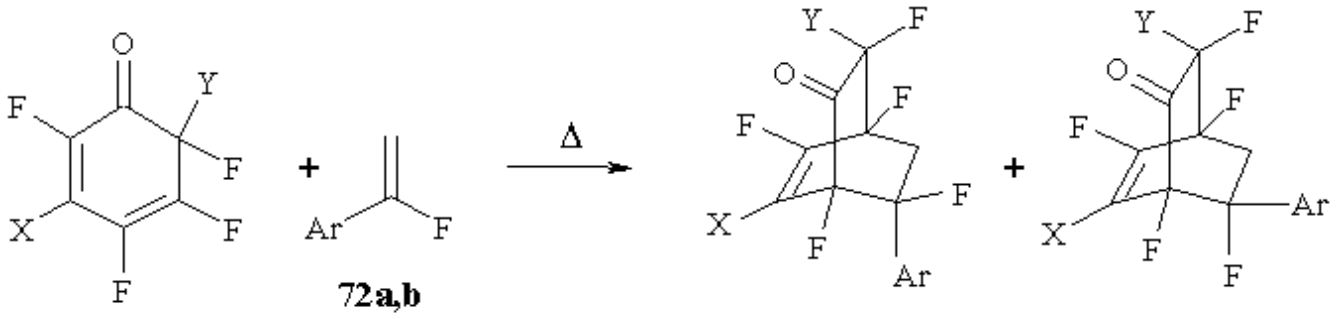
The reactions of polyfluorinated cyclohexadienones with alkenes [63] result in the high-yield (84-97%) formation of bicyclic adducts **70a-f**. With most of alkenes those reactions proceed with high regioselectivity, like those with acetylenes [52], except the reactions with 1-hexene or allylbenzene that result in a equal mixture of two isomeric cycloadducts **70a,b** and **71a,b**, probably in consequence of slight polarization of the double bond in those alkenes. (Figure 30)



a.R_1=H, R_2=Bu, R_3=H
b. R_1=H, R_2=CH_2Ph, R_3=H
c.R_1=H, R_2R_3=o-$C_6H_4CH_2$
d.R_1=Me, R_2=COOBu, R_3=H
e.R_1=Me, R_2=Ph, R_3=H
f.R_1=H, R_2=COOH, R_3=H
g.R_1=H, R_2=Ph, R_3= H

B Figure 30

The reactions between cyclohexadienone **14** and *a*-fluorostyrene **72a** or *a*-fluoro-4-chlorostyrene (**72b**) in boiling benzene result in the products of [4+2] cycloaddition that is an equal mixture of isomer: *endo*-**73a,b** and *exo*-**73a,b** [64]. The reaction between cyclohexadienone **2** and *a*-fluorostyrene **72a** proceeds in similar manner though under more drastic conditions (toluene, 110°C), resulting in a couple of isomeric bicyclic adducts (*endo*-**74** and *exo*-**74**) in nearly equal proportion.B (Figure 31)



14 X = F, Y = Cl	Ar = C_6H_5 (70%)	*endo*- **73a**	53:47	*exo*- **73a**
	Ar = p-ClC_6H_4 (78%)	*endo*- **73b**	42:58	*exo*- **73b**
2 X = OC_6F_5, Y = C_6H_5	Ar = C_6H_5 (90%)	*endo*- **74**	43:57	*exo*- **74**

Figure 31

High stereoselectivity is observed in the reactions between cyclohexadienones **2** or B **14** and B *a*-fluorostyrenes **72a,b,** as well as in those with acetylenes: fluorine of CFX group in bicyclo[2.2.2]octenones **73** and **74** is oriented towards the new bond, formed due to the addition of *a*-fluorostyrene **72a** (X-ray analysis of *endo*-**73a,** *endo*- and *exo*-**74**) **[**64].

The attempts to conduct the reaction of 2,4,5,6-tetrafluoro-3-metoxy-6-phenyl-2,4-cyclohexadienone **7** with B *O*±-fluorostyrene **72a** failed. Instead of bicyclic adducts the reaction resulted only in a product of 1,3-shift of fluorine: 2,4,4,5-tetrafluoro-3-metoxy-6-phenyl-2,5-cyclohexa-dienone **75**. (Figure 32)

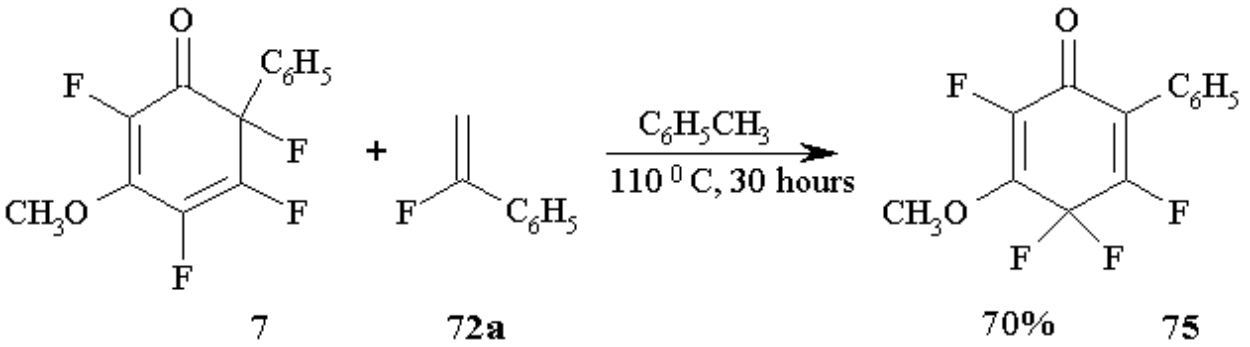


Figure 32

It is well-known that *OI*-fluorostyrene in the reaction with 1,3-diphenylisobenzofuran perform as a dienophile less active than *O*±-fluorostyrene[65]. The reactions of *trans*-*OI*-fluorostyrenes **76a-d** with polyfluorinated 2,4-cyclohexadienones proceed slower than those with *O*±-fluorostyrenes. However, boiling of cyclohexadienone **14** with *trans*-*OI*-fluorostyrenes **76a-d** in toluene result in the formation, with yield 75-79%, of two bicyclicB adducts, those being *endo-trans*-**77** and *exo-trans*-**77** isomers, with predominance of *endo-trans*-isomers in all cases. (Figure 33)

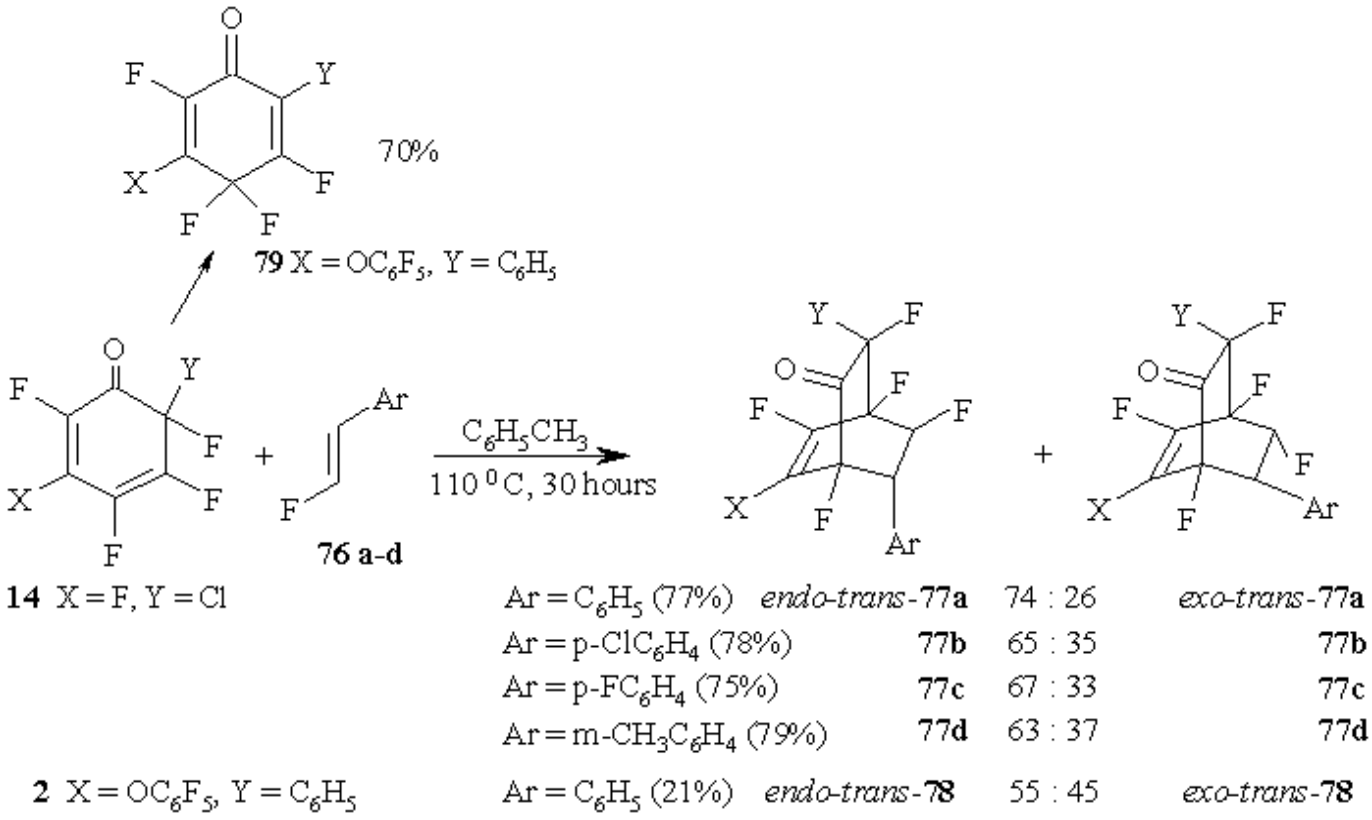


Figure 33

Cyclohexadienone **2** demonstrates low reactivity in the interaction with *trans-OI*-fluorostyrene **76a** and it isomerizes predominantly into 2,4,4,5-tetrafluoro-3-(pentafluorophenoxy)-6-phenyl-2,5-cyclohexadienone **79**; the products of cycloaddition (*endo-trans*-**78** and *exo-trans*-**78**) were produced with small yields. (Figure 33)

Under similar conditions the isomerisation of cyclohexadienone **7** results in one product only **75**, as if in the reaction with *O*±-fluorostyrene. (Figure 32)

Quantum-mechanical calculations [64] using PM3 method [66] are in conformity with the results on the interaction of 2,4-cyclohexadienones with α- or β-fluorostyrenes. The comparison between HOMO and LUMO energies, and between orbital coefficients of cyclohexadienone - styrene pairs that participate in the process, demonstrates that their interaction is an agreed process with reverse electronic request. Thus, for cyclohexadienone **14** - styrene **72a** pair the interaction $HOMO_{styrene}$ - $LUMO_{dienone}$ (O”=6.94 Ev) is more profitable as to compare with $HOMO_{dienone}$ - $LUMO_{styrene}$ (O”=10.33 Ev). In addition, the orbital coefficients demonstrate very effective overlapping. For reaction between substance **14** and **76a** the observed picture is similar: $HOMO_{styrene}$ - $LUMO_{dienone}$ (O”=6.76 Ev) and $HOMO_{dienone}$ - $LUMO_{styrene}$ (O”=10.33 Ev). However, in this case the orbital overlapping is less efficient. For the reactions of substance B **2** with B **72a** and **76a** the differences between $HOMO_{styrene}$ and $LUMO_{dienone}$ energies are larger (7.30 Ev and 7.12 Ev, correspondingly) and, more than that, in the reactions of substance **2** with **72a** the involved orbitals overlap less, and even more less in the reactions of substance **2** with **76a**. As a consequence, in this case under thermal conditions partial isomerisation of substance B **2** to **79** is a more probable by-process (see Figure 33).

At last, in the reactions of methoxy-substituted cyclohexadienone **4** with **72a** or **76a** the difference in the energy of participating orbitals reaches its maximum (7.60 Ev or 7.42 Ev, correspondingly) and cycloaddition at those conditions is not observed, but only the isomerisation of **4** to **75** takes place (see Figure 32).

All attempts to conduct Diels-Alder reaction of polyfluorinated 2,4-cyclohexadienones with the participation of *a*-fluoro-*a*,*b*-unsaturated ketones, e.g., 4-fluoroocto-4-en-3-on, were resultless. At the same time, cyclohexadienone **14** easily enters the reaction of diene synthesis with such dienophile as naphthoquinone, resulting in high yield of stable adduct **80** [67]. (Figure 34)

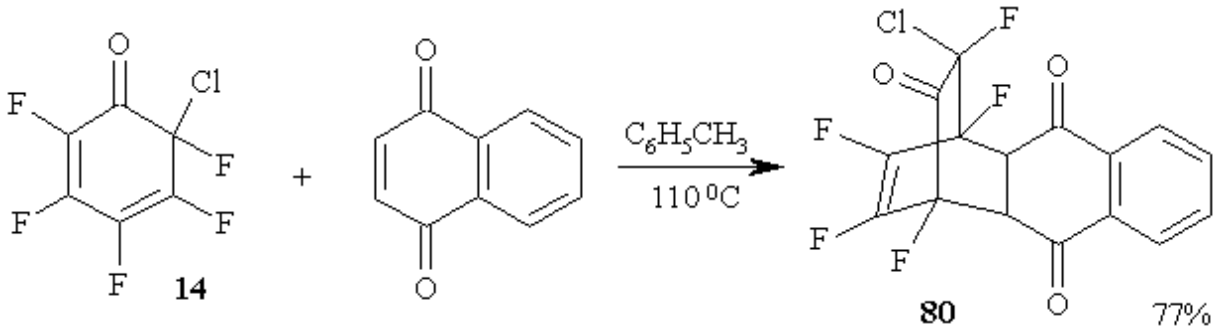


Figure 34

Conversion of fluorinated bicyclo[2.2.2]octadienones

Photochemical reactions

The photolysis of fluorinated bicyclo[2.2.2]octadienones **60**, **68a** with CFCl group in the position adjacent to carbonyl group at room temperature in chloroform solution results in the formation of, mainly, tetrafluoroaromatic substances **81**, probably, due to the elimination of fluorochloroketene (FClC=C=O) [68]. The observed conversion of bicyclo[2.2.2]octadienones is 100-75%, and the yield of fluoroaromatic substances vary between 50 and 86%, as recalculated to non-reacted bicyclo[2.2.2]octadienone. (Figure 35)

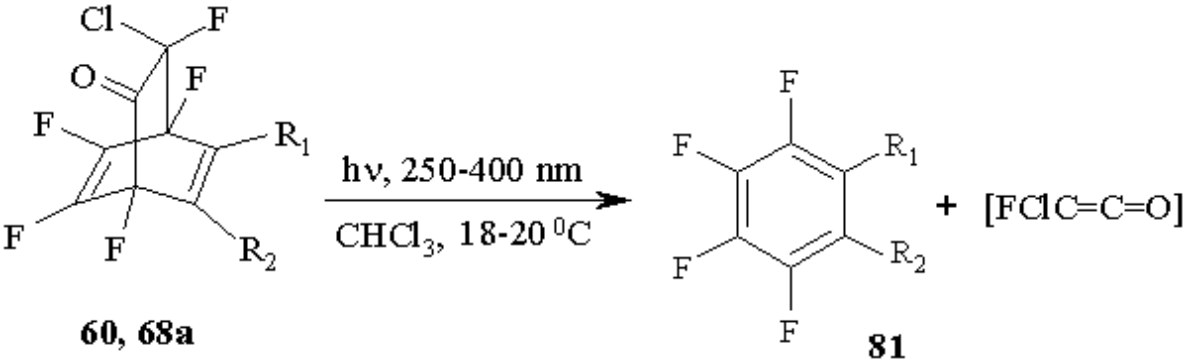
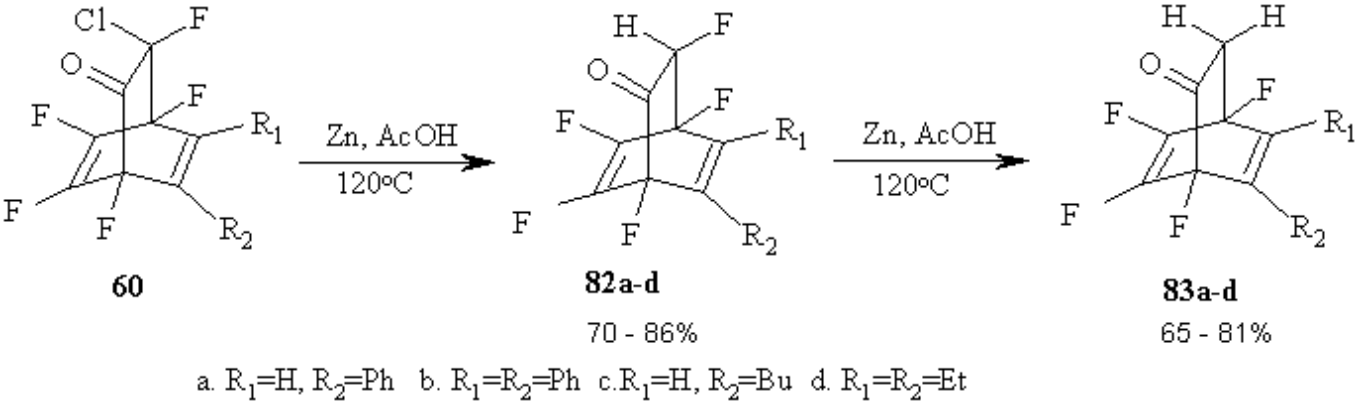


Figure 35

Selective reductive dehalogenation of halogen atoms at sp^3-hybridized carbon atom

The reaction of bicyclic adducts of 8-chloro-1,2,3,4,8-pentafluoro-bicyclo[2.2.2]octa-2,5-dienones **60** with Zn in acetic acid allows step-by-step replacement of chlorines for hydrogens, and further for fluorines at sp^3-hybridized carbon atom [69]. The structure of new bicyclic adducts **82a-d** and **83a-d** was ascribed to them reasoning from the spectral and analytical data. The fluorines in other positions stay untouched. (Figure 36)



a. R_1=H, R_2=Ph b. R_1=R_2=Ph c.R_1=H, R_2=Bu d. R_1=R_2=Et

Figure 36

It should be marked that though the replacement of chlorine for hydrogen in *a*-position to carbonyl group, particularly in cyclic ketones, is well-known [70], but no published data were found about similar replacement of fluorine atoms [71].

Hydrolysis of bicyclic adducts in the presence of various alcohols and amines

One interesting property of bicyclic adducts produced by the reactions of polyfluorinated cyclohexadienones with acetylene derivatives is their easy splitting under the action of nucleophilic reagents with the formation of fluorine-containing derivatives of arylacetic acids **80-83**. The peculiarity of those reactions is the retention in those aromatic substances of bridge bond structural elements with CFCl and carbonyl group [51]. Bicyclic adducts resulting from the replacement of geminal chlorines or fluorines for hydrogens **82,83** [69] are easily aromatised with high yield (85-95%) of corresponding fluorinated arylacetic acids **88,89**. (Figure 37)

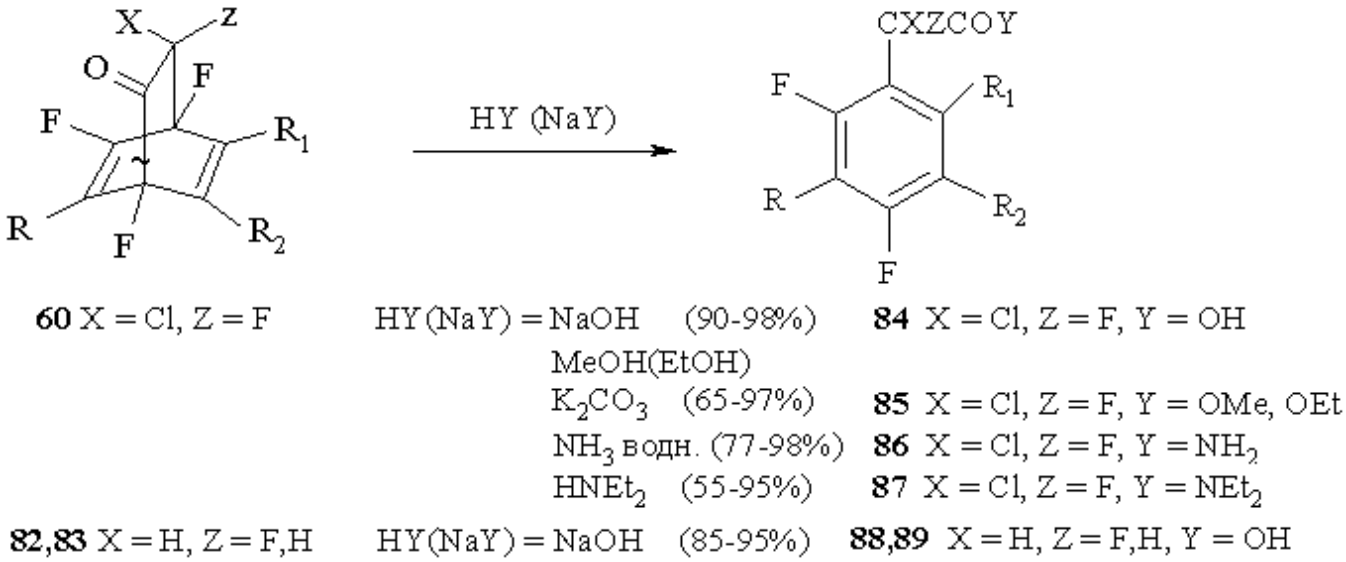
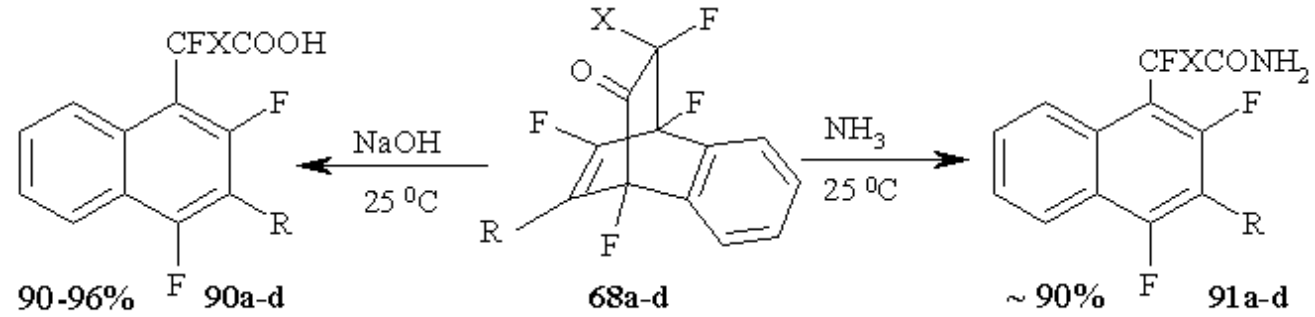


Figure 37

The treatment of cyclic adducts **68a-d** produced from polyfluorinated 2,4-cyclohexadienones and dehydrobenzene, with a base or ammonia in water dioxane solution results in the formation of fluorine-containing naphthylacetic acids **90a-d** or their amides **91a-d** [59] with high yields. It should be marked that in those cases the aromatization occurs with conserving of the structural elements of bridges containing carbonyl groups. (Figure 38)



a. R=F, X=Cl **b**. R=OC$_6$F$_5$, X=Cl **c**. R=OCH$_3$, X=Cl **d**. R=F, X=OC$_6$F$_5$

Figure 38

Unlike those reactions some fluorinated or non-fluorinated analogues of the said adducts are aromatised only under the action of strong bases followed by the elimination of the bridge [72] involving a carbonyl group, or they are unclosed with the formation of non-aromatic cyclic B substances [73], or do not react with water base [72].

The mechanism of Diels-Alder aromatisation of the polyfluorinated adducts involves evidently the split of C(4)-C(7) bond (path Pђ) under the action of a nucleophile and the formation of a stable anionic *Пґ*-complex **92**, that undergoes aromatisation eliminating fluoride-ion from the geminal nod of the cycle. (Figure 39)

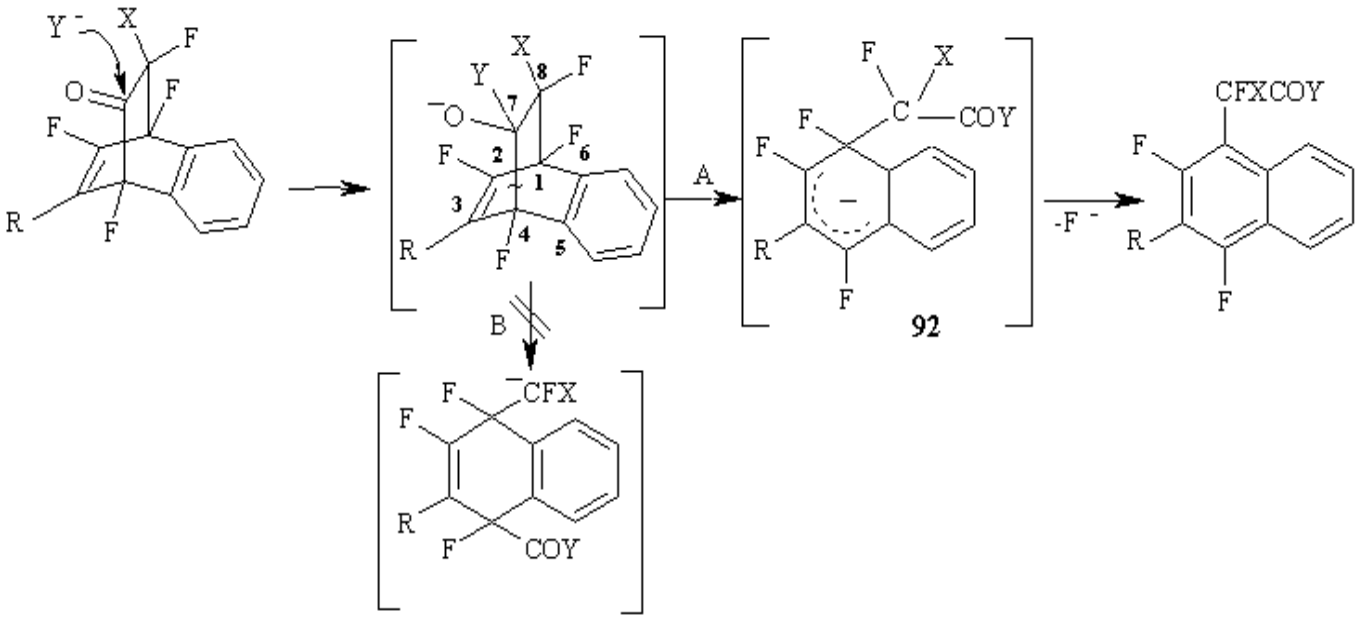


Figure 39

One may see that the alkaline cleavage of bicyclic adducts of polyfluorinated cyclohexadienones produced by Diels-Alder reaction is a convenient method for the synthesis of B fluorinated derivatives of arylacetic acids. With variable substituents in acetylene, in geminal and 3 positions of polyfluorinated 2,4-cyclohexadienone, using different alcohols and amines at the stage of adduct aromatization one may produce various derivatives of arylacetic acids, containing functional groups along with fluorine atoms. It is difficult to produce this type of promising biologically active substances by another method.

Cycloadducts formed in the reactions between polyfluorinated cyclohexadienones and alkenes **70** easily undergo alkaline cleavage in water dioxane solution resulting in fluorine вЂ“containing cyclohexenecarbonic acids **93** with rather high yields (65-95%) [63]. The configuration of those substances was confirmed by x-ray structure analysis of two samples of cyclohexenecarbonic acid. (Figure 40)

The most interesting aspect of the reaction is that under the action of hydroxide anion on the adducts of the reactions between polyfluorinated cyclohexadienones and alkenesB it is bond C(7)-C(8) (path P') undergoes cleavage, but not bond C(4)-C(7) (path Pђ), as it has place for bicyclic adducts, formed through the interaction of polyfluorinated cyclohexadienones with acetylenes or dehydrobenzene (see Figure 39). When so doing, the intermediate anion **94** with negatively charged carbon atom linked with fluorine and chlorine is stabilized due to the addition of proton and formation of cyclohexenecarbonic acid [63].

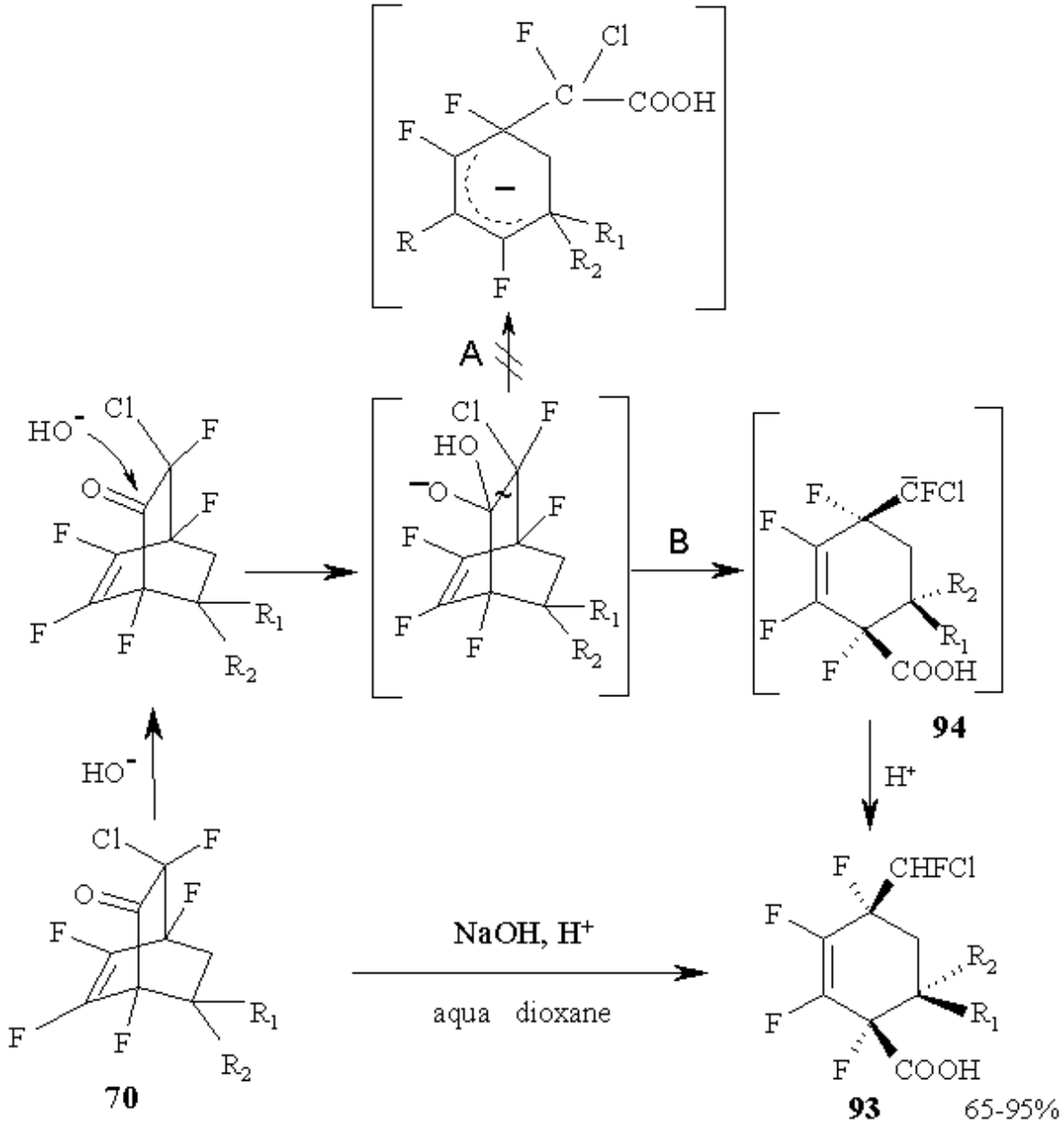


Figure 40

Cycloadduct **80** produced through the interaction of polyfluorinated cyclohexadienone B **14** with 1,4-naphtoquinone under the action of sodium hydroxide at room temperature undergoes the cleavage of C-C bond in its O=C-CFCl fragment and simultaneous elimination of B hydrogen fluoride resulting in the formation of fluorinated anthraquinonecarbonic acid **95**. This new method is a convenient way to functional derivatives of fluorinated anthraquinones [67]. (Figure 41)

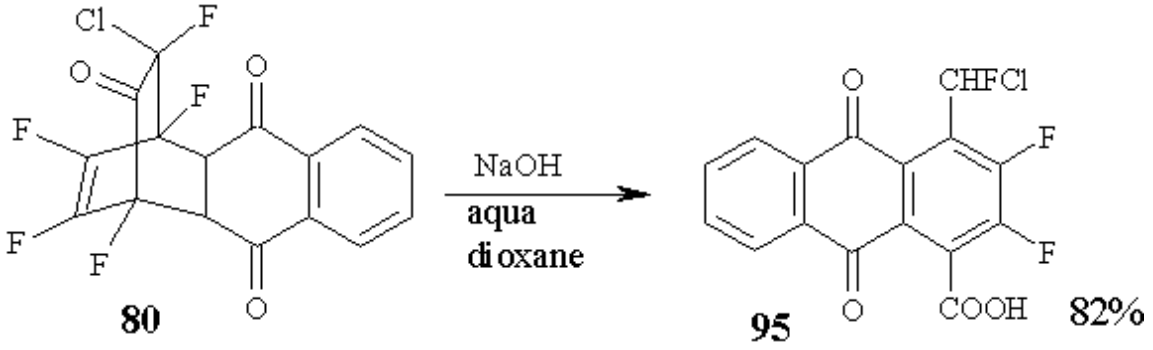


Figure 41

Conclusion

The synthetic conversions here reviewed are based on the use of polyfluorinated cyclohexadienones for synthons and allow the production by the methods of photolysis, nucleophilic reactions, cycloaddition and simple conversion of those reactions products a wide range of fluorinated substances: derivatives of polyphenyl ethers, biphenyls, arylacetic acids, derivatives of naphthalene or anthraquinone, containing carboxyl groups, cyclohexenecarbonic acids, fluorinated heterocyclic substances, cyclopropane derivatives and bicyclic phosphorus-containing substances. The further transformation and modification of those reactions products make it possible to manufacture various structured organofluoric substances earlier inaccessible.

The new approach is particularly important as a method for the synthesis of fluorinated derivatives of aryl- or diarylacetic acids, because the representatives of this substance category provide the basis for many drugs (propanidid, diclofenac, spazmolitin, pafentsil, aprofen). It is well-known that the presence of fluorine atoms in pharmaceutical preparations enforces their activity, improves their metabolic stability, prolongs their active life time, and frequently decreases their toxicity [74-76].

The approach in what polyfluorinated cyclohexadienones may be used for highly reactive synthons, opens promising perspectives for the synthesis of earlier inaccessible physiologically active fluorinated arylacetic acids that contain functional groups. Those synthetic processes are realizable due to the possibility of introduction of the required functional groups at any step of the process of the acid synthesis: nucleophilic substitution of fluorine atom t position 3 of B polyfluorinated cyclohexadienones; using of various substituted acetylenes in the reactions of cycloaddition; selective replacement of halogens for hydrogen atoms at sp^3-hybridized carbon atom in bicyclic adducts; hydrolysis of bicyclic adducts with various alcohols or amines resulting in the formation of derivatives of arylacetic acids.

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