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SYNTHESIS OF SULFUR-CONTAINING HETEROCYCLIC COMPOUNDS BASED ON ISOTHIOCYANATE DERIVATIVES OF PERFLUOROOLEFINS (REVIEW)*

G. G. Furin[1] and E. L. Zhuzhgov[2]

The paper reviews data on the synthesis of heterocyclic compounds with perfluoroalkyl groups based on the reaction of thiocyanate and isothiocyanate derivatives of perfluoroolefins with mononucleophilic reagents (C-, O-, S-, P-, and N-nucleophiles). It was shown that such derivatives are prospective synthons for the production of 1,3-thiazoles and 1,3-thiazolines. The factors affecting the formation of the heterocyclic system are identified.

Keywords: 3-methyl-2-methylamino-6-pentafluoroethyl-5-trifluoromethyl-3H-pyrimidine-4-thione, nucleophilic reagents, perfluoro(3-isothiocyanato-2-methyl-2-pentene), 4,5-dihydrothiazole derivatives, 6H-1,3-thiazine, nucleophilic addition, intramolecular cyclization.

The unique characteristics of fluorine compounds have given rise to the appearance of new fields of application [1-5]. The regioselective substitution of hydrogen in aromatic or heterocyclic systems by a perfluoroalkyl group substantially changes the physical and biological characteristics of such molecules, and in many cases the biological activity of an existing product is increased by the introduction of a fluorine atom or perfluoroalkyl group [6-8]. Considerable efforts have therefore been directed toward the development of methods for the synthesis of heterocyclic compounds containing perfluoroalkyl groups [9-15].

The synthesis of heterocyclic compounds containing fluorine atoms is one of the most important parts of organofluorine chemistry [10-12]. Its development arises from the strong biological activity found in certain functional derivatives of fluorine-containing heterocycles and also from the possibility of using them for the synthesis of other compounds of practical use.

The key methods for the synthesis of various heterocyclic compounds containing perfluoroalkyl groups are based on two types of chemical transformations [9, 10]. The first includes processes taking place at a ready-made heterocyclic system, into which a perfluoroalkyl group is inserted. Direct methods for the insertion of perfluoroalkyl groups into heterocyclic compounds involve the generation of perfluoroalkyl radicals as intermediate and reactive particles.

The second, most interesting and most widely studied, group of methods includes processes based on intramolecular cyclization under the influence of heteronucleophiles and on the condensation of several

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molecules having appropriate functional groups. We note that the construction of heterocyclic systems by condensation has been studied well, while the use of intramolecular cyclization has been characteristic just for polyfluorinated unsaturated compounds. This new method in synthetic organic chemistry has been used in the production of various heterocyclic compounds employing bidentate nucleophilic reagents. A significant number or researches have been carried out on the synthesis of heterocyclic compounds with perfluoroalkyl substituents from perfluoroolefins as the main "building" blocks, which act as electrophiles in reactions with bidentate nucleophiles. This makes it possible to realize intramolecular nucleophilic cyclization, affecting both the existing multiple bond in the initial substrate and a new multiple bond generated in the course of the process, particularly if the system contains a sufficiently strong base [11]. These investigations have substantially extended the possibilities of synthesizing fluorinated heterocyclic compounds that may prove to be of interest in the production of biologically active compounds for medicine and agriculture. The development of this approach to the formation of a heterocyclic system using readily obtainable fluoroolefins as synthons is promising for the synthesis of heterocycles and for the development of the new compounds essential to pharmacological research.

The presence of the fluorine atoms in the starting materials provides the basis for the development of new procedures for the formation of double bonds in the molecule and for the construction of the heterocyclic system and also in the search for new ways of inserting fluorine-containing groups into the rings of the heterocycle.

One such method could be to use mononucleophilic reagents in reaction with derivatives of perfluoroolefins that contain at the double bond functional groups with multiple bonds at which nucleophilic addition occurs, resulting in the possibility of generation of a new nucleophilic center. The heterocyclic nucleus here will be formed as a result of intramolecular nucleophilic cyclization involving the double bond of the olefin and the new nucleophilic center. During the fluorination of the multiple bond such groups could be, for example, SCN, N=C=S, and C=O. The presence of the multiple bond in the initial substrate is not essential – the most important thing in the course of the reaction of the polyfluorinated compound with the nucleophilic reagent is the generation of a multiple bond at the α-position to the functional group. The presence of the nucleophilic center in the inserted fragment and of the multiple bond then ensures the occurrence of intramolecular nucleophilic cyclization.

Aromatic aminothiocyanates and aliphatic enamino thiocyanates are widely used for the synthesis of thiazoles and benzothiazoles. Effective pesticides have been found among these compounds [15].

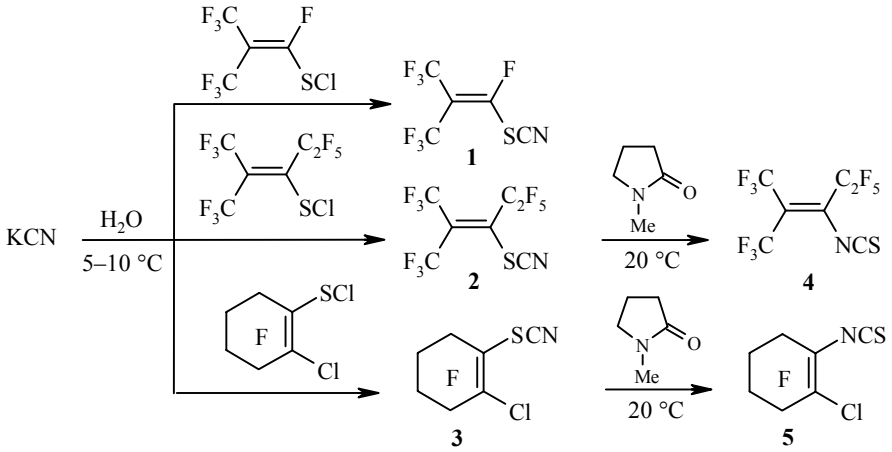
The paper [16] was devoted to the creation of heterocyclic systems by cycloaddition and cyclocondensation based on α,β-unsaturated isothiocyanates. The addition of C- and N-nucleophiles to these compounds takes place regiospecifically with the formation of thioamides and derivatives of thiourea. Thus, fluorine-substituted α,β-unsaturated isothiocyanates have the highly electrophilic C=C double bond, which is capable of nucleophilic attack, and the mobile fluorine atoms at the allylic position. This significantly extends the synthetic potential of this type of compound [17-19].

In the present review data on the formation of the 1,3-thiazole skeleton with perfluoroalkyl groups based on the reaction of mononucleophilic reagents with isothiocyanate derivatives of perfluoroolefins are examined and analyzed [10, 17, 20].

1. METHODS OF PRODUCTION OF ISOTHIOCYANATE DERIVATIVES OF PERFLUOROOLEFINS

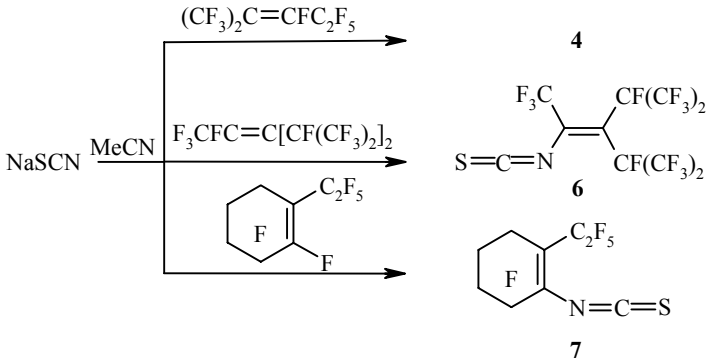
The isothiocyanate derivatives of perfluoroolefins can be synthesized by: 1) Isomerization of thiocyanate derivatives by the action of bases; 2) direct substitution of fluorine at the multiple bond by the action of sodium or potassium thiocyanate.

The synthesis of α,β-unsaturated perfluorothiocyanates both with linear and with cyclic structure can be realized successfully by substituting the halogen at a sulfur atom by a nitrile group in the readily obtainable α,β-unsaturated perfluorinated sulfenyl chlorides [21, 22].

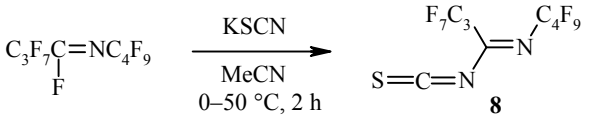


The α,β-unsaturated thiocyanates **1-3** are stable and do not isomerize spontaneously to the corresponding isothiocyanates either at 20°C in polar solvents (sulfolane, benzonitrile) or when heated (autoclave, 6-7 h, 150°C). This distinguishes the compounds from the unfluorinated analogs. Such isomerization is initiated by aprotic weak bases such as N-methylpyrrolidone at 20°C, diethyl ether at 230°C (in an autoclave), and CsF or KSCN in benzonitrile and leads to compounds **4** and **5**. The thiocyanate **2** is thermodynamically less stable than the isomeric isothiocyanate **4** [22].

The reaction of potassium thiocyanate with perfluoroisobutylene leads to the formation of perfluoro-2-methylallyl isothiocyanate with a small yield [21, 23, 24]. However, the reaction is complicated by the formation of bis(trifluoromethylthioketene) as the main product [21]. The thiocyanates of alkali metals act as ambident nucleophilic reagents, as a result of which the formation of the corresponding thiocyanates or isothiocyanates is possible. It was suggested [21] that the perfluoro-2-methylallyl isothiocyanate is formed through perfluoro-2-methylallyl thiocyanate, although its isomerization to the isothiocyanate under the influence of bases gives a low yield. At the same time 3-isothiocyanatoperfluoro-2-methyl-2-pentene (**4**) was obtained during the reaction of perfluoro-2-methyl-2-pentene with sodium thiocyanate in acetonitrile (acetone, tetrahydrofuran, sulfolane, monoglyme) at 50°C (yield 80%) [25] or with potassium thiocyanate in benzonitrile at 0°C (yield 93%) [26]. Perfluoro-3-isopropyl-4-methyl-2-pentene and perfluoro-1-ethylcyclohexene react similarly with sodium thiocyanate giving the corresponding isothiocyanate derivatives **6** and **7**.



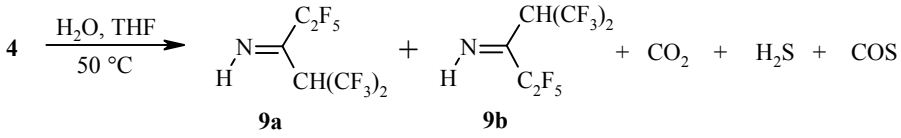
The action of potassium thiocyanate on perfluoro-5-aza-4-nonene in acetonitrile under the same conditions leads to the corresponding isothiocyanate derivative **8**.



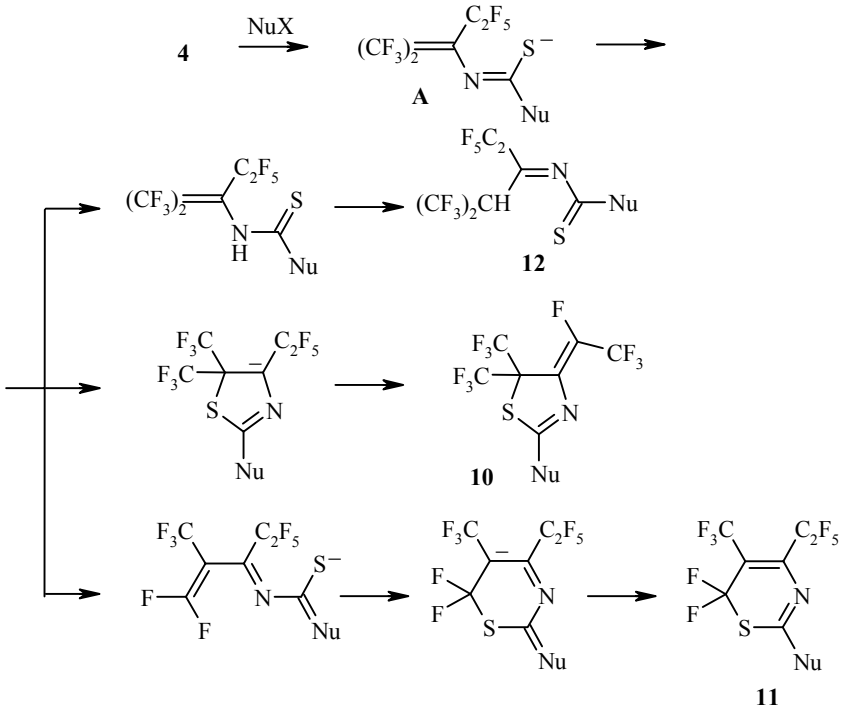
2. REACTIVITY OF ISOTHIOCYANATE DERIVATIVES OF PERFLUOROOLEFINS IN REACTIONS WITH NUCLEOPHILES

Compound **4** was used as model on account of its availability.

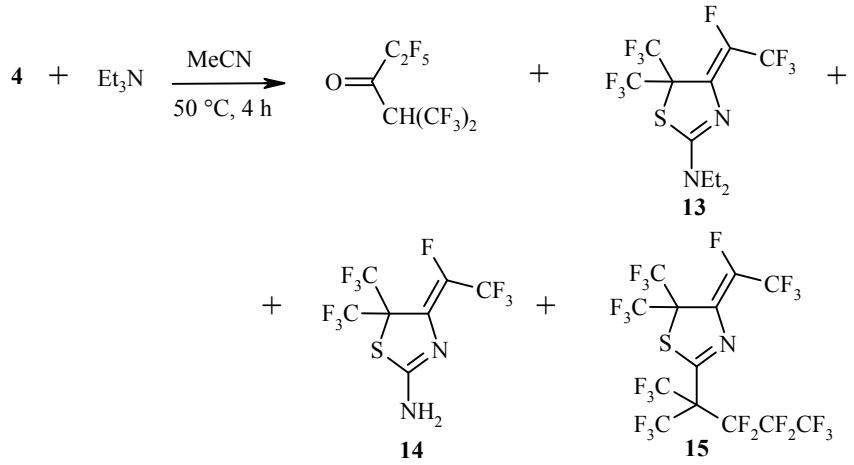
It is known [24] that the isothiocyanate group is extremely reactive and enters vigorously into reaction with nucleophiles, giving the products from addition at the N=C bond. Even extremely weak nucleophiles (e.g., water, alcohols) enter into reaction with alkyl isothiocyanates. In the case of the reaction of compound **4** with water in THF at 50°C on account, probably, of the effect of the electron-withdrawing perfluoroalkenyl group gaseous products are released (H_2S, CO_2, COS), and the isomeric imines of perfluoro(2H-isopropyl) perfluoroethyl ketone **9a**,**b** (1:1) are formed [25]. Therefore, it is necessary to use the absolute solvents for the reaction of compound **4** with nucleophilic reagents.



The presence of the N=C=S group, directly attached to the double bond, in the perfluoroolefin leads to initial attack by the nucleophile at the carbon atom of the N=C bond. This results in the generation of the charged S-nucleophile **A**, which can undergo cyclization with the formation of the five-membered **10** or six-membered **11** heterocycle [27, 28]. If the generated S-nucleophile is not sufficiently active, the derivatives of dithiocarbonic acid **12** are formed.



It could be supposed that the nature of the nucleophilic reagent would play a determining role in the direction of formation of the heterocyclic system. Realization of the whole process requires the presence of a base, which takes part in the elimination of the fluoride ion. Triethylamine (solvent acetonitrile) and potassium carbonate (solvent DMF) were mainly used as bases. Triethylamine is an active nucleophile, capable of reacting at the carbon atom of the N=C=S group. This must lead to the formation of a mixture of products [29]. The reaction of compound **4** and triethylamine results in the formation of a mixture, the main components of which are the 4,5-dihydrothiazole derivatives **13**-**15** [29].

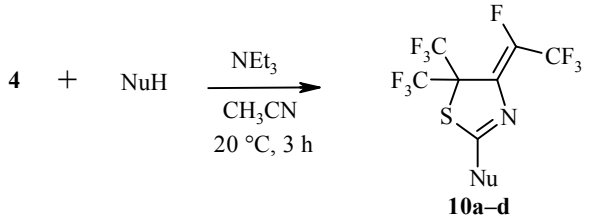


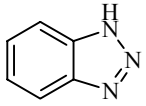
However, such a process takes place at a low rate and requires elevated temperatures.

2.1. Reactions of Isothiocyanate Derivatives of Perfluoroolefins with N-Nucleophiles

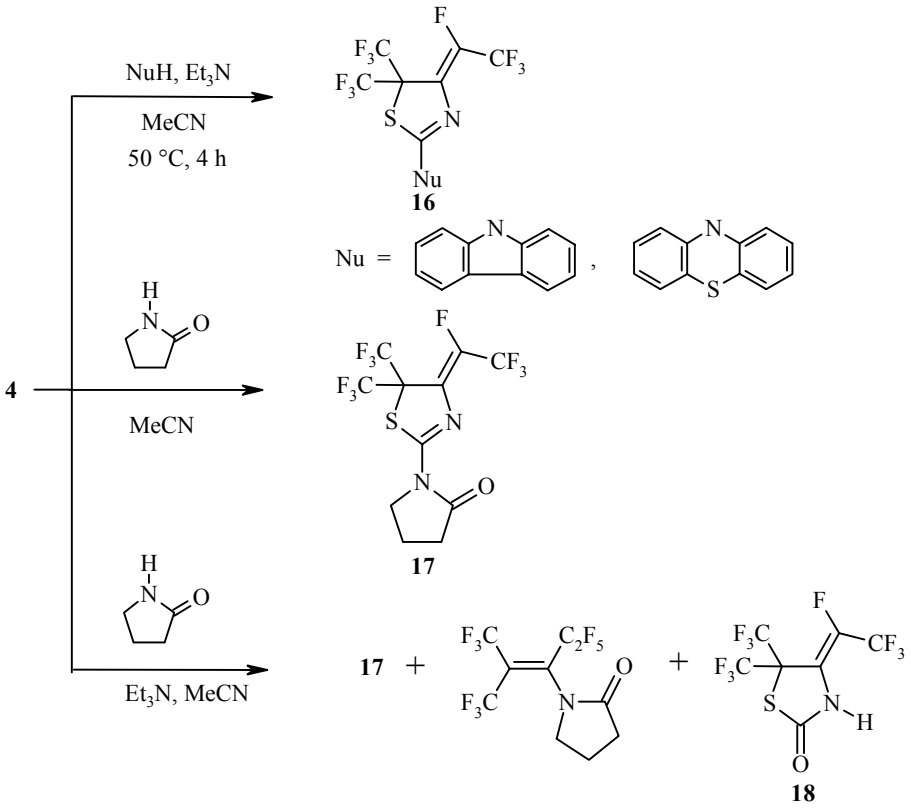
The reaction of compound **4** with a typical N-nucleophilic reagent – triethylamine – indicates the formation of a five-membered heterocycle, which was also to be expected for other nucleophilic agents.

The reactions of compound **4** with azoles in acetonitrile in the presence of an equimolar amount of triethylamine lead exclusively to the five-membered heterocycles **10a-d** (derivatives of Δ^2-1,3-thiazoline) [30]. The structure of 1-[4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydro-2-thiazolyl]-1H-[1.2.4]triazole (**10b**) was confirmed by X-ray crystallographic analysis [28].

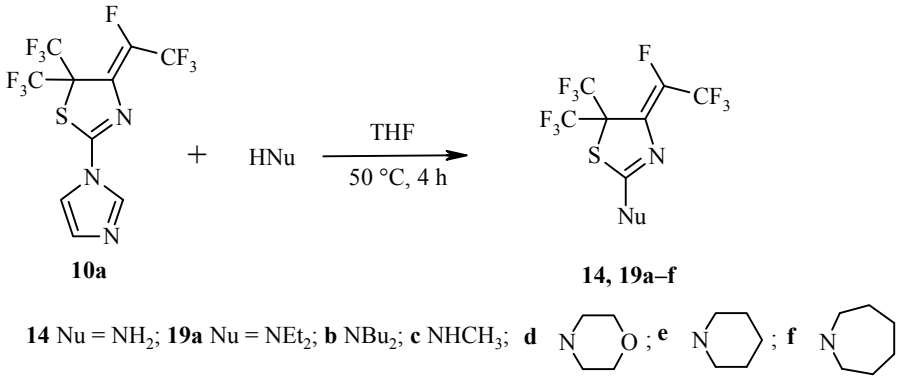


a NuH =  ; **b**  ; **c**  ; **d** 

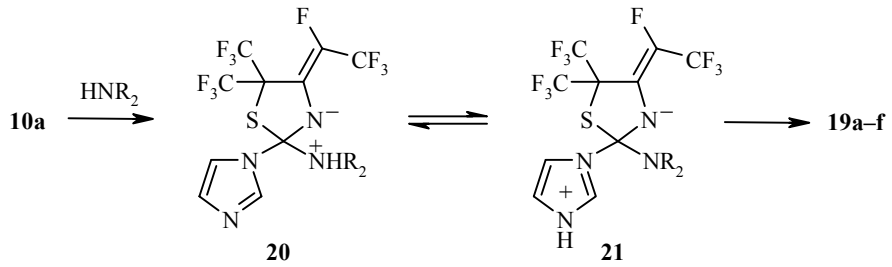
By the reaction of compound **4** and carbazole, phenothiazine, and 2-pyrrolidone it is possible to obtain various 2-substituted derivatives of perfluoro(4-ethylidene-5,5-dimethyl-4,5-dihydrothiazole) **16-18** [28]. This opens up the prospect of comprehensive investigations into the biological activity of this type of compound.



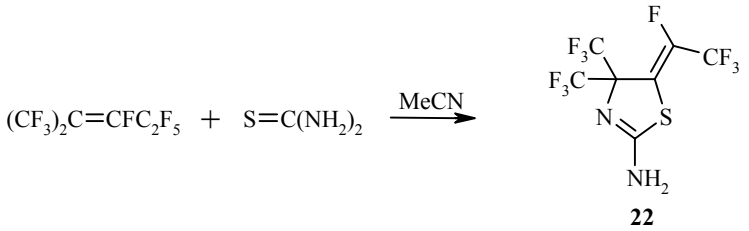
The reaction of certain 2-substituted 4,5-dihydrothiazoles (e.g., **10a-d**) with nitrogen-containing nucleophilic reagents leads to 2-substituted derivatives [31]. Thus, compounds **14**, **19a-f** were obtained from compound **10a** by the action of nucleophiles. The structure of 2-amino-4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazole (**14**) was confirmed by X-ray crystallographic analysis [28].



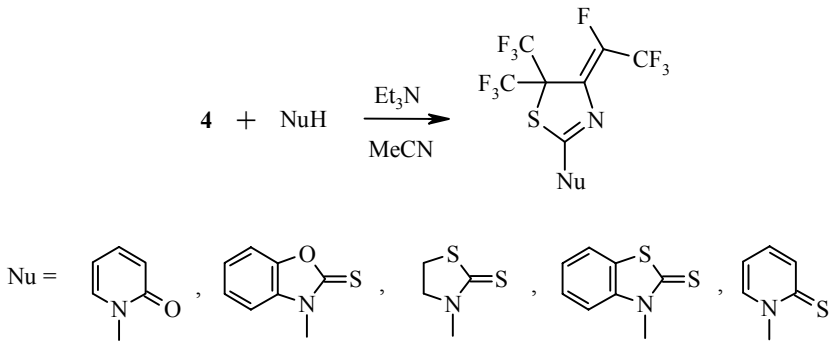
Addition of the N-nucleophile at the C=N bond of compound **10a** with the formation of the zwitterion **20** evidently takes place initially. The transformation of **20** into the zwitterion **21** by transfer of a proton then leads to the reaction products **19a-f** as a result of the elimination of imidazole.



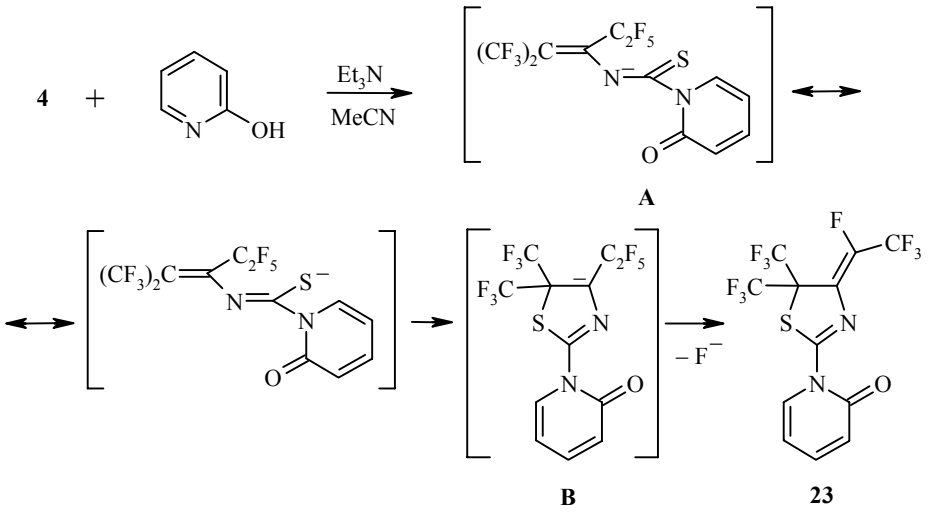
In the case of the reaction with ammonia the 2-amino derivative **14** is formed [28]. Its isomer **22** was obtained by the reaction of perfluoro-2-methyl-2-pentene with thiourea [18, 32]. The structure of both compounds was confirmed by X-ray crystallographic analysis.



With the use of binucleophilic reagents the main object is to determine correctly the nucleophilic center responsible for the initial formation of the product that precedes the intramolecular nucleophilic cyclization. In [33] this was studied for the reactions of N,S- and N,O-binucleophiles with compound **4** – in all cases initial attack was by the N-nucleophilic center.

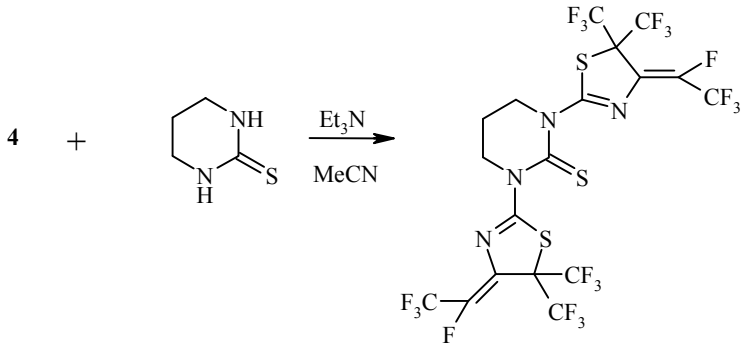


The reaction of compound **4** with 2-hydroxypyridine in the presence of triethylamine in acetonitrile gave the N-substituted derivative of thiazoline 2-[4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydro-2-thiazolyloxy]pyridine (**23**), the structure of which was studied by X-ray crystallographic analysis. Attack by the N-nucleophilic center of the 2-hydroxypyridine at the carbon of the N=C=S group evidently occurs initially with the formation of the anion **A**, and the reaction then proceeds according to the scheme:



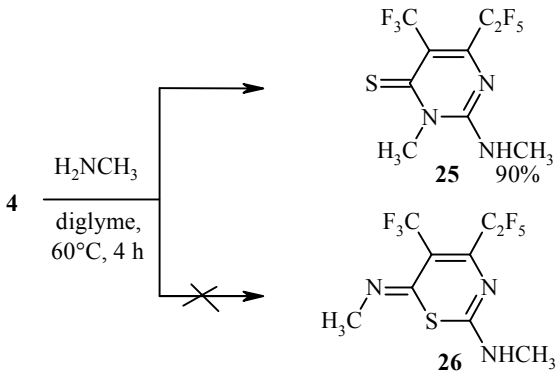
The key element of these transformations is intramolecular nucleophilic cyclization, leading through the carbanion **B** to the heterocyclic compound **23**.

The reaction of compound **4** with 2-mercaptobenzothiazole and 2-mercaptobenzoxazole in the presence of triethylamine in acetonitrile leads to the formation of thiazoline derivatives, the structure of which was confirmed by X-ray crystallographic analysis. It was established [33] that the reaction of compound **4** with 2-mercaptothiazole and 2-mercaptopyridine in the presence of triethylamine in acetonitrile at -10°C leads to the formation of 2-N-substituted 2-[4-(tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazoles. At the same time the reaction of perfluoro-2-methyl-2-pent-3-yl isothiocyanate with 3,4,5,6-tetrahydro-2-mercaptopyrimidine in the presence of triethylamine in acetonitrile at -20°C gives the product **24**, the structure of which indicates that compound **4** attacks through both N-nucleophilic centers.

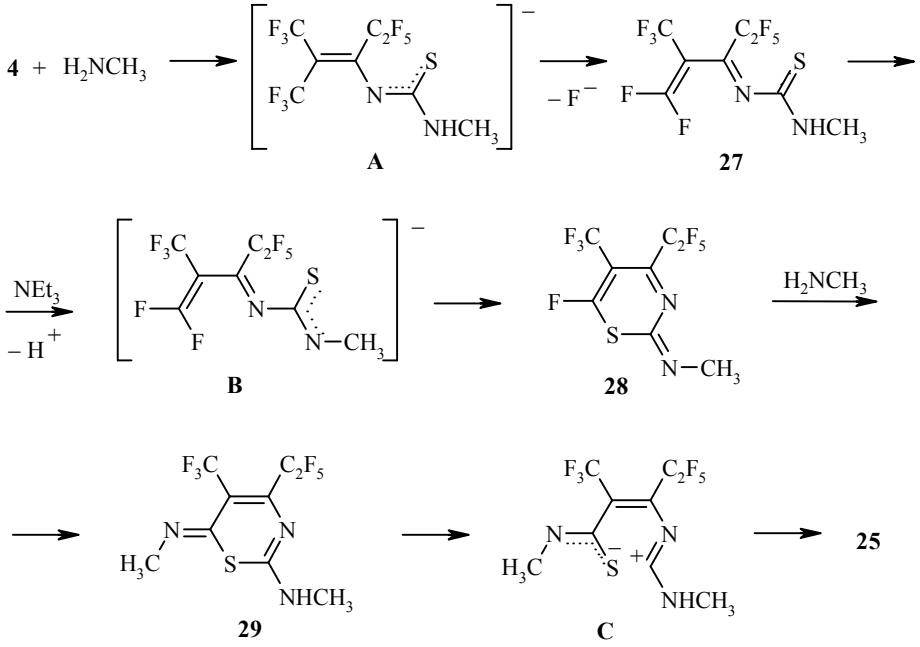


Thus, 2-N-substituted derivatives of thiazoline are obtained exclusively in the reactions of N,O- and N,S-ambident nucleophiles with compound **4**.

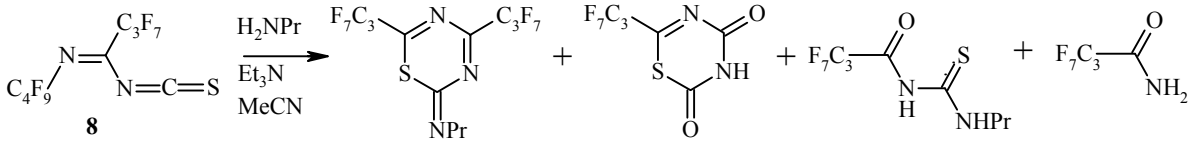
The reaction of compound **4** with an excess of methylamine in diglyme leads to the formation of 3-methyl-2-methylamino-6-pentafluoroethyl-5-trifluoromethyl-3H-pyrimidine-4-thione (**25**) and not 2-methylamino-6-methylimino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazine (**26**) [34]. The structure of compound **25** was confirmed by X-ray crystallographic analysis [34].



The following path can be proposed for the formation of compound **25**. Attack by the methylamine at the carbon atom of the N=C=S bond takes place initially with the formation of the anion A, which is stabilized by the elimination of a fluoride ion and is converted into compound **27**. The anion **B** is generated from compound **27** under the conditions of base catalysis (triethylamine) and then undergoes intramolecular nucleophilic cyclization with the elimination of a fluoride ion, leading to compound **28**. In this compound there is a very mobile fluorine atom at the double bond. The action of methylamine leads to compound **29**, the recyclization of which through the intermediate **C** leads to compound **25**.

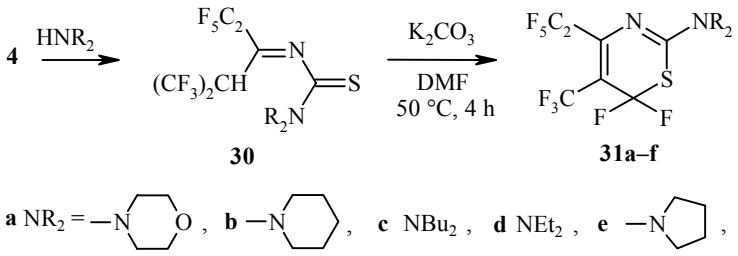


In the reaction of compound **8** and propylamine in the presence of triethylamine in acetonitrile a mixture of products with a small content of heterocyclic compounds is formed, and the main product is a derivative of thiocarbonic acid.

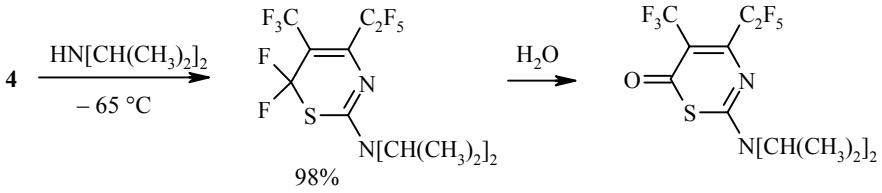


This can be explained by the more extensive transformations of the intermediately generated N-anions, including cleavage at the N–C bond.

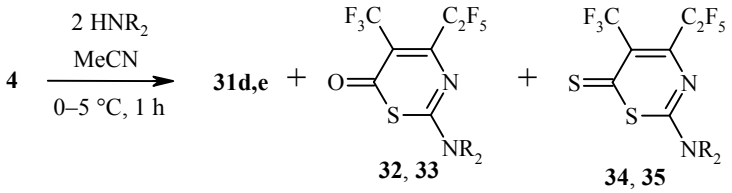
It was noticed that process takes place in an unusual way with secondary amines, when a six-membered ring is formed instead of a five-membered ring. In the reaction of compound **4** with morpholine, pyrrolidine, piperidine, butylamine, and dimethylamine in acetonitrile addition products are formed initially. The more stable under these conditions are not the propenylureas but the propylideneureas **30**, heating of which in DMF with potassium carbonate at 50°C leads to the formation of six-membered 1,3-thiazines **31** [27, 35-37]. Triethylamine has a similar effect on the cyclization process.



For example, in the presence of triethylamine the reaction of compound **4** with morpholine gives 6,6-difluoro-2-morpholino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazine (**31a**) [35]. With dimethylamine it gives 6,6-difluoro-2-dimethylamino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazine (**31e**) [36]. The formation of 2-isopropylaminoperfluoro-5-methyl-4-ethyl-6H-[1,3]thiazine with a 98% yield in the reaction of compound **4** with isopropylamine was described in [17]. In this compound the CF_2 group readily undergoes hydrolysis to a keto group.



The reaction of compound **4** with diethylamine and pyrrolidine leads to the formation of other derivatives of 6H-thiazine. In particular, 2-diethylamino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazin-6-one (**32**) and 2-pyrrolidino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazin-6-one (**33**) and also, unexpectedly, 2-diethylamino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazine-6-thione (**34**) and 2-pyrrolidino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]thiazine-6-thione (**35**) are formed as a result of hydrolysis. The structure of compounds **32** and **35** was confirmed by X-ray crystallographic analysis [36].

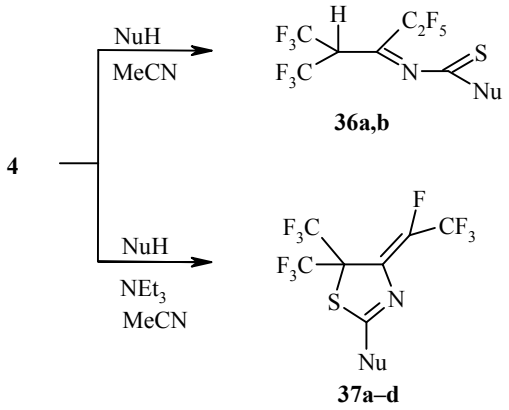


32, **34** R = Et; **33**, **35** $R_2 = (CH_2)_4$

2.2. Reaction of 3-Isothiocyanatoperfluoro-2-methyl-2-pentene with S-Nucleophiles

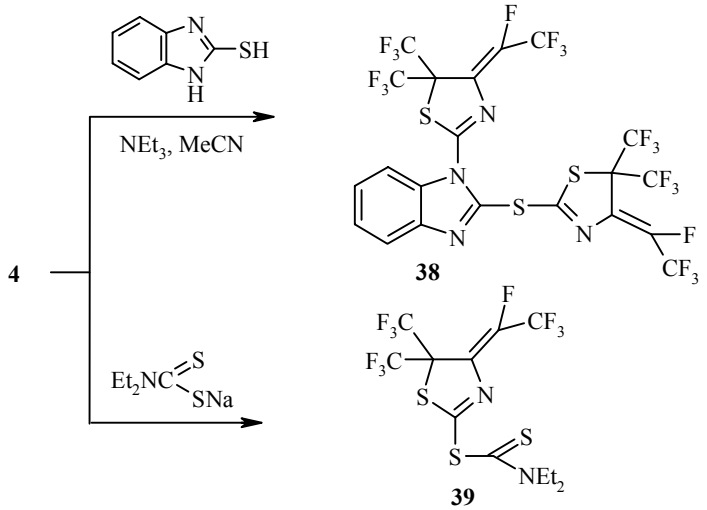
The action of S-nucleophilic reagents on compound **4** leads smoothly to 2-substituted derivatives of 4,5-dihydrothiazole. The S-nucleophiles enter into the reaction both in neutral form (alkanethiols, pentafluorothiophenol, 2-mercaptobenzimidazole) and in charged form (sodium N,N-diethyldithiocarbamate, potassium ethyl- and methylxanthates). Alkanethiols and pentafluorothiophenol also react in the presence of bases (triethylamine and potassium carbonate) [38].

Compound **4** reacts smoothly with isopropyl mercaptan and pentafluorothiophenol in acetonitrile at 40-50°C, forming the isopropyl and pentafluorothiophenyl esters of N-(perfluoro-2-methyl-2H-pent-3-ylidene)dithiocarbamic acid (**36a**,**b**). In the presence of triethylamine or potassium carbonate the derivatives of 4,5-dihydro-1,3-thiazole **37a-d** are formed.



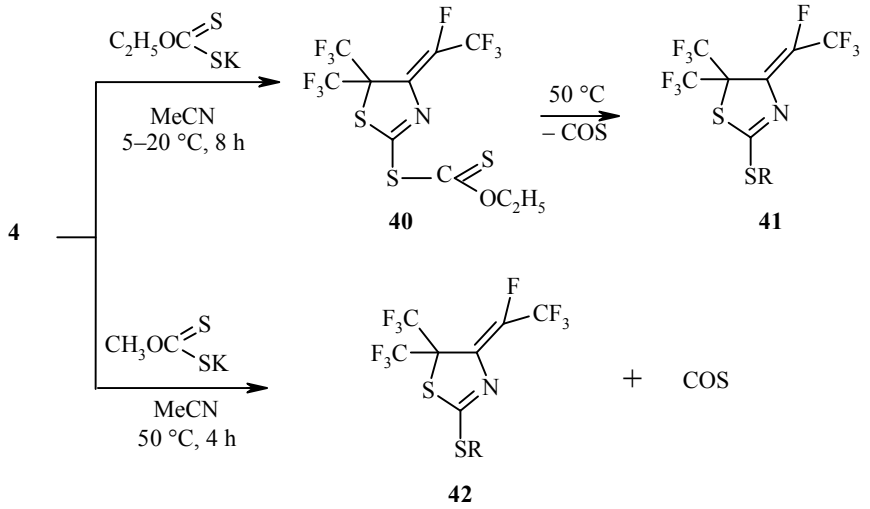
36 a Nu = *i*-PrS, **b** C_6F_5S; **37 a** *i*-PrS, **b** BuS, **c** $C_8H_{17}S$, **d** C_6F_5S

The reaction of compound **4** with the ambident reagent 2-mercaptobenzimidazole in the presence of triethylamine in acetonitrile leads to the formation of two dihydrothiazole rings. 1-(Perfluoro-5,5-dimethyl-4-ethylidene-4,5-dihydro-2-thiazolyl)-2-(perfluoro-5,5-dimethyl-4-ethylidene-4,5-dihydro-2-thiazolylthio)benzimidazole (**38**) is formed [38].

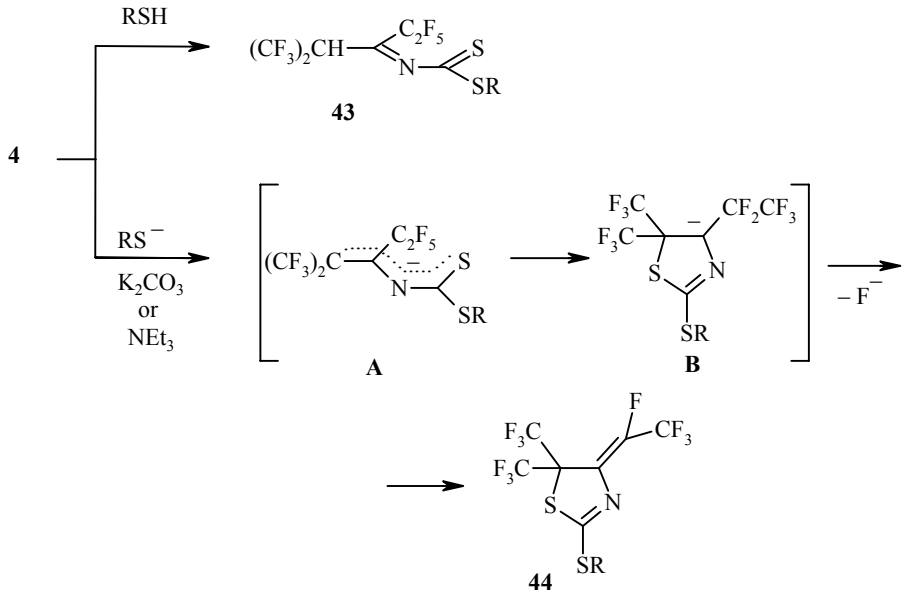


In reaction with compound **4** charged S-nucleophiles and sodium N,N-diethyldithiocarbamate and potassium ethylxanthate, in particular, form the 2-substituted derivatives of 4,5-dihydrothiazole **39** and **40**. At elevated temperature (with the reaction mixture heated to 50°C) or during distillation compound **40** is converted

into compound **41**. It was found that the thermal stability of dihydrothiazole containing the SC(S)OAlk group at position 2 is affected by the structure of the alkoxyl group. In the reaction of compound **4** with potassium methylxanthate under these conditions it is not possible to isolate the corresponding derivative of 2-(O-methylxanthato)-4,5-dihydrothiazole – the O-ester of S-(perfluoro-5,5-dimethyl-4-ethylidene-4,5-dihydro-1,3-thiazol-2-yl)dithiocarbonic acid (**42**) is formed exclusively.



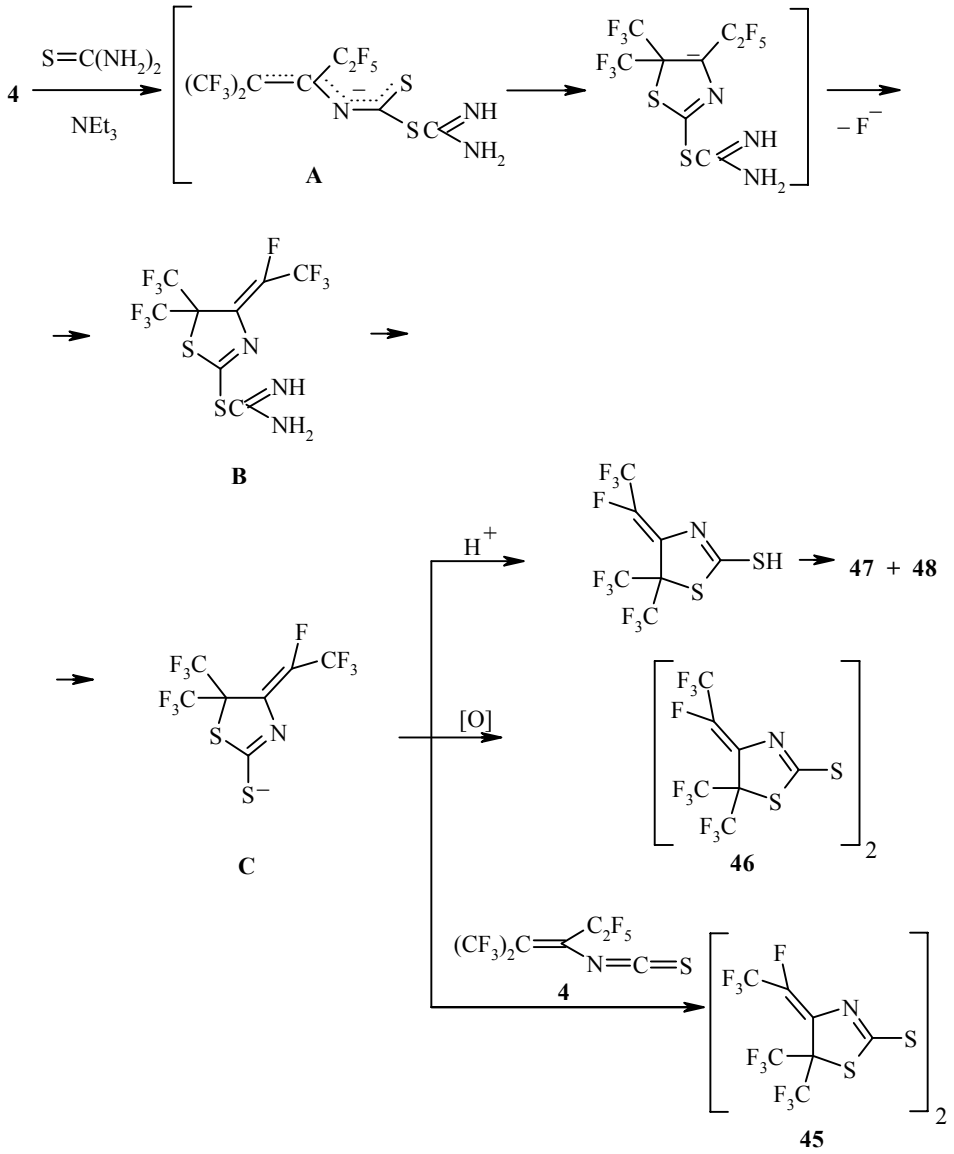
The following path can be proposed for the reactions of compound **4** with S-nucleophilic reagents. In the absence of bases alkanethiols react with compound **4** to form the addition product **43**. In the presence of bases (triethylamine, potassium carbonate) the charged nucleophile attacks the carbon atom of the N=C bond of compound **4**, and the anion **A** is formed. Intramolecular cyclization of the anion **A** leads to the carbanion **B**, which is transformed into the 4,5-dihydrothiazole derivative **44** as a result of the elimination of a fluoride ion from the CF_2 fragment.



The reaction of compound **4** with thiourea in the presence of triethylamine leads to a mixture containing both the expected 4,5-dihydrothiazole derivatives **45** and **46** and compounds **47** and (**48**) [39]. The 2-substituted derivative – the thioether **B** – is probably formed initially through the anion **A**. The S-anion **C** is generated by

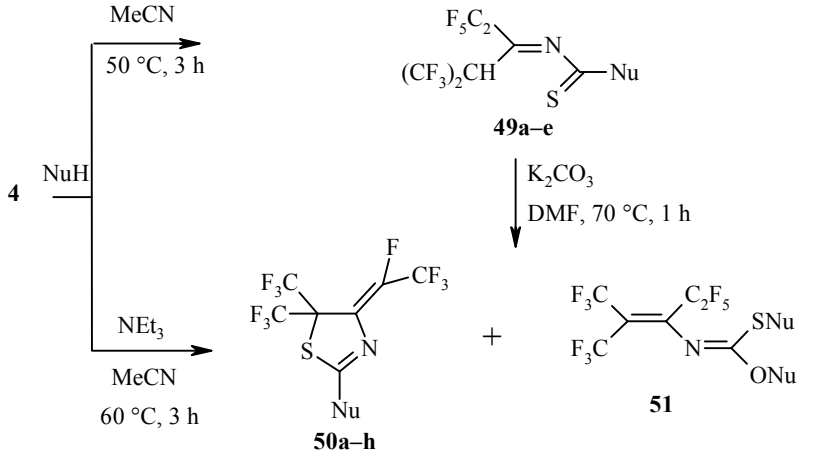
the action of bases as a result of cleavage of the C–S bond. The reaction of **C** with the initial compound **4** leads to the sulfide **45**, while reaction with a proton from the system gives a thiol, which is then oxidized to the disulfide **46** or isomerizes to the more stable thione **48**. Compound **47** is probably produced by intramolecular nucleophilic cyclization of the anion **A** at the CF_2 fragment.

Thus, during investigation of the reactions of compound **4** with S-nucleophiles the following relationships were discovered: 1) Reaction with thiols leads to addition products without the formation of a heterocycle. 2) The action of charged nucleophiles (sodium N,N-diethyldithiocarbamate, potassium ethyl- and methylxanthate) leads to 2-substituted 4,5-dihydrothiazoles. 3) Reactions with thiols in the presence of bases take place in various ways depending on the nature of the base. In the presence of triethylamine derivatives of 2-substituted 4,5-dihydrothiazole are formed exclusively. With potassium carbonate in DMF, as demonstrated in the case of butanethiol, the formation of the product from formal substitution of the isothiocyanate group in compound **4** by an alkylthio group is possible in addition to the formation of the 2-substituted 4,5-dihydrothiazole.



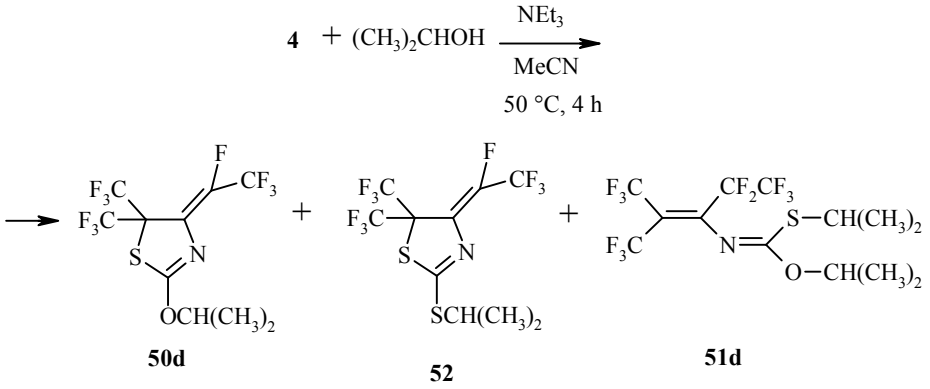
2.3. Reactions of 3-Isothiocyanatoperfluoro-2-methyl-2-pentene with O-Nucleophiles

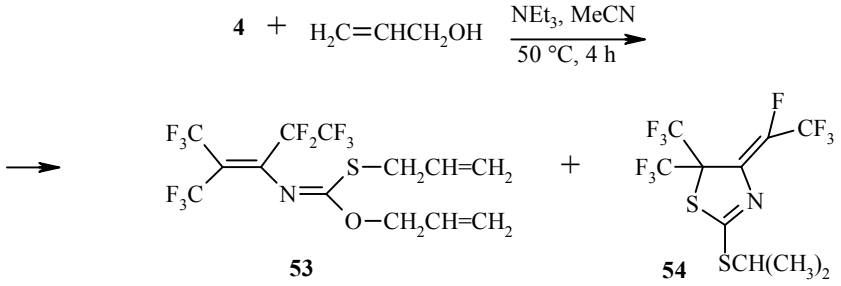
The reaction of compound **4** with alcohols in the absence of bases leads to the addition products **49**. In the presence of potassium carbonate or triethylamine 2-alkoxy-5,5-bis(trifluoromethyl)-4-perfluoroethylidene-4,5-dihydrothiazoles **50** and alkoxy(alkylthio)methylene(1,1,1,4,4,5,5,5-octafluoro-2-trifluoromethyl-2-penten-3-yl)amines **51** are formed [29, 40, 41]. In addition, 4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)thiazolin-2-one, the structure of which was confirmed by X-ray crystallographic analysis, is formed during the reaction [40].



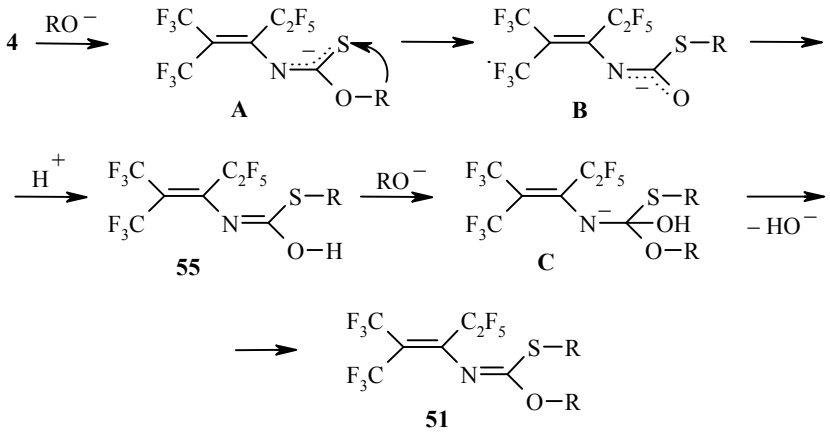
a Nu = MeO, **b** BuO, **c** EtO, **d** *i*-PrO, **e** $C_2H_5CHCH_2O$ (CH$_3$), **f** CF_3CH_2O, **g** C_6H_5O, **h** C_6F_5O

In addition to the expected product **50d**, the reaction of compound **4** and isopropyl alcohol in acetonitrile in the presence of triethylamine gives compounds **51d** and **52**. The action of allyl alcohol under these conditions gives a mixture of the products **53** and **54** [29].

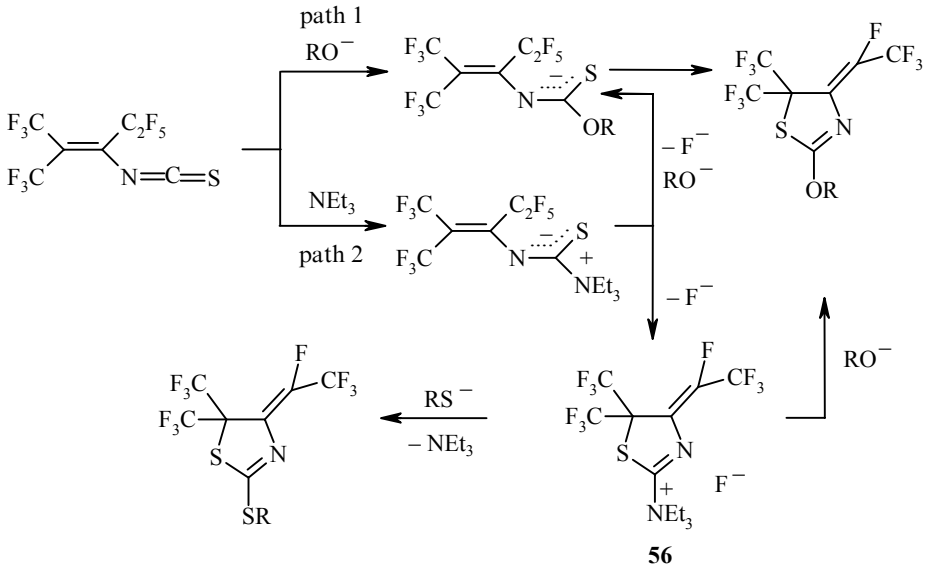




The formation of compounds of the **51** type can be represented by the following scheme. Initially, the O-nucleophile attacks the carbon atom of the C=N bond, leading to the anion **A**, in which rearrangement with participation of the allyl cation (or rearrangement in an intermediate complex) occurs. This results in the formation of the anion **B**, which in reaction with a proton from the medium gives compound **55**. Further action of the O-nucleophile on this anion at the carbon of the C=N bond leads to the anion **C**, which is transformed into the reaction product **51**.



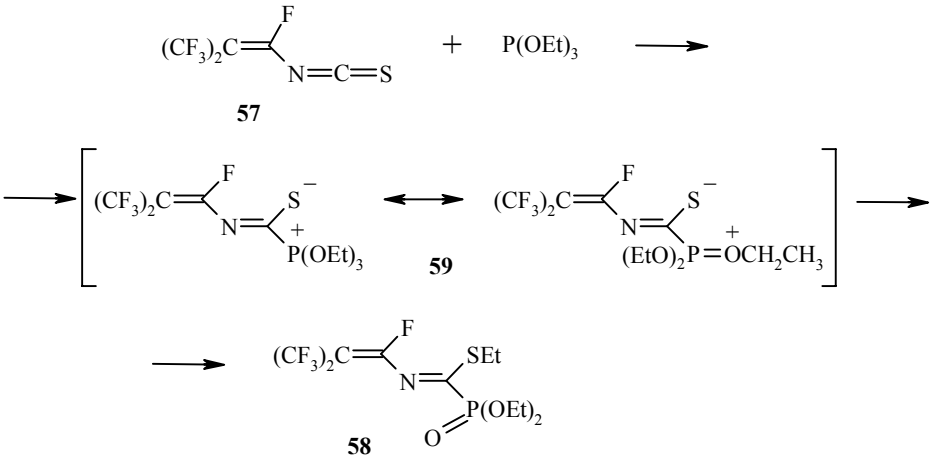
The 2-substituted derivatives of 4,5-dihydrothiazoles are probably formed in the same way as for the S-nucleophiles. The main feature is the generation of the S-nucleophilic center against the background of the formation of the terminal double bond.



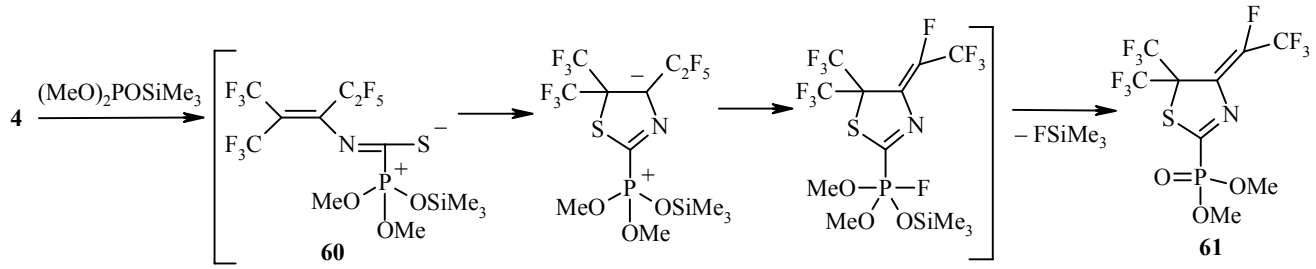
The triethylamine in these processes may behave as an active nucleophile, reacting at the carbon atom of the N=C=S bond [29]. Thus, triethylamine reacts with compound **4** to form the triethylammonium salt of substituted 4,5-dihydrothiazole **56**. The action of the S- and O-nucleophiles then results in substitution of the triethylammonium group, and this leads to the reaction products.

2.4. Reactions of 3-Isothiocyanatoperfluoro-2-methyl-2-pentene with P-Nucleophiles

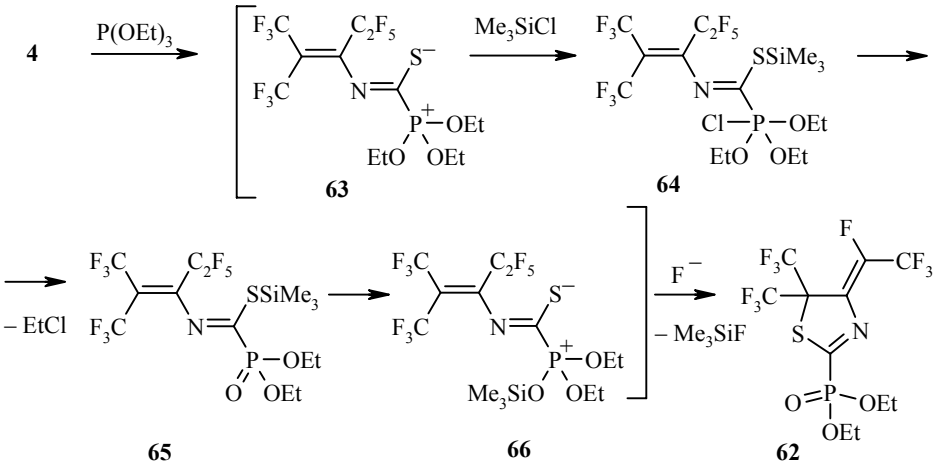
The production of 2-phosphorus-substituted fluorinated thiazolines by the reaction of compound **4** and derivatives of trivalent phosphorus is extremely interesting since on the one hand it is possible to expect enhanced bioactivity from such compounds on account of the presence of the P–C=N–C=CF fragment; on the other, the obtained phosphonium salts and phosphonates could be good extractants and phase-transfer catalysts on account of the presence of the superlipophilic groups. During the production of such compounds at least two obstacles were to be expected. The first is the fact that the most typical reaction of isothiocyanates with compounds of trivalent phosphorus is desulfurization of the isothiocyanate group [42-44]. The second, particularly for compounds with a P–O bond, is the thermodynamic favorability of the formation of the P–F bond. For this reason the reactions taking place with the release of fluoride ion give complex mixtures of products in which part of the oxygen atoms at the phosphorus atom are substituted by fluorine atoms [45]. Moreover, it was shown [46] that the replacement of oxygen atoms by fluorine can take place right up to the formation of PF_6. Nevertheless, the reaction of 1-isothiocyanatoperfluoro-2-methyl-1-propene (**57**) with triethyl phosphite can take place without desulfurization. The formation of the heterocycle was not observed in this case, and the authors explained the formation of the product **58** by intramolecular alkylation of the sulfur atom by the zwitterion **59** that forms [24].



The desulfurization could be expected to decrease in the case of the reaction of dimethyl trimethylsilyl phosphite with compound **4**, since the trimethylsilyl group stabilizes the positive charge at the oxygen atom in the supposed intermediate **60** better than the alkyl group. In order to avoid van der Waals repulsion of the sulfur atom and the pentafluoroethyl group the =C–N=C–S fragment adopts the cisoid conformation preferentially, and this favors the formation of the heterocycle. On account of the repulsion of the $SiMe_3$ and C_2F_5 groups the transoid conformation is more favorable for the S–C–P–OMe fragment, and this must prevent desulfurization and intramolecular alkylation. After ring closure trimethylfluorosilane and the dimethyl phosphonate **61** are formed with high yields as a result of the great strength of the Si–F bond [47].



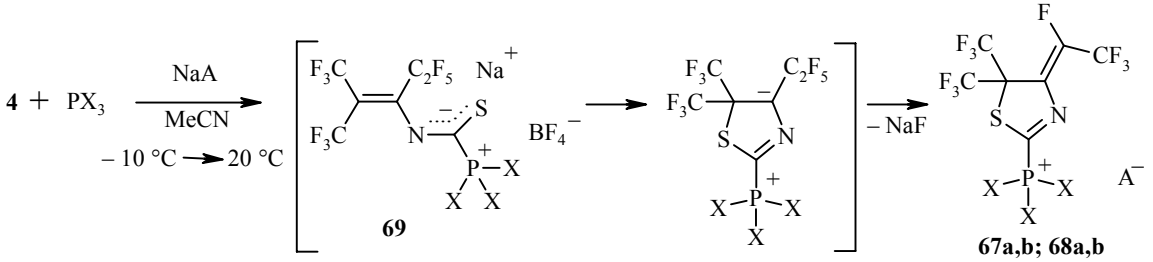
If the electrophilic trimethylchlorosilane and triethyl phosphite (which do not react with each other under the reaction conditions) are brought into reaction with compound **4**, the trimethylchlorosilane can temporarily block the S-nucleophilic center and serve as an acceptor of the fluoride ion. In fact, the reaction takes place smoothly, leading to the diethyl phosphonate **62** with almost quantitative yield [47]. The proposed reaction path is the following:



The initially formed zwitterion **63** reacts with the trimethylchlorosilane, giving the phosphorane **64**, which after decomposition with the release of EtCl leads to the phosphonate **65**. On account of the great strength of the Si–O bond the phosphonate **65** most likely isomerizes to compound **66**, completely analogous with the intermediate **60**. After attack by the S-nucleophile at the double bond of the olefin and elimination of the trimethylfluorosilane the phosphonate **62** is formed.

Another tactic was chosen for the production of phosphonium salts by the action of triphenylphosphine and tris(dimethylamino)phosphine [47]. In this case as a result of the high solubility of the phosphonium salts in acetonitrile the released fluoride ion makes the reaction reversible.

The relatively lipophilic salts KI and $NaBF_4$, the cations of which form insoluble fluorides, were used to stabilize the zwitterion and combine with the fluoride ion. Here compound **4** reacts smoothly with the triphenylphosphine and tris(dimethylamino)phosphine, forming the respective phosphonium salts **67a**,**b**, **68a**,**b** with a perfluorinated thiazolinyl substituent [47]. These salts withstand heating of their solutions in acetonitrile to at least 50°C. The reaction of compound **4** with tris(tetrafluorophenyl)phosphine does not lead to the corresponding salt.



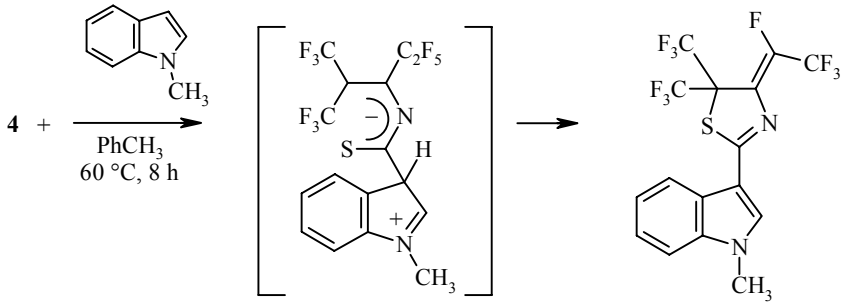
67 a X = Ph, A = BF_4 ; **b** X = Ph, A = BPh_4 ; **68 a** X = NEt_2, A = BF_4; **b** X = NEt_2, A = I

After attack by the P-nucleophile at the carbon atom of the N=C=S group a zwitterion stabilized by the corresponding counterions BF_4^-, I^-, or BPh_4^- is probably formed and then undergoes intramolecular cyclization. After closure of the heterocycle the fluoride ion is withdrawn from the reaction in the form of NaF or KF.

In view of the common nature of the methods it can be expected that they will be used successfully with other P-nucleophilic reagents and with different electrophiles of the hydrocarbon and fluorocarbon series. Such compounds may be of interest from the standpoint of their biological activity.

2.5. Reactions of 3-Isothiocyanatoperfluoro-2-methyl-2-pentene with C-Nucleophiles

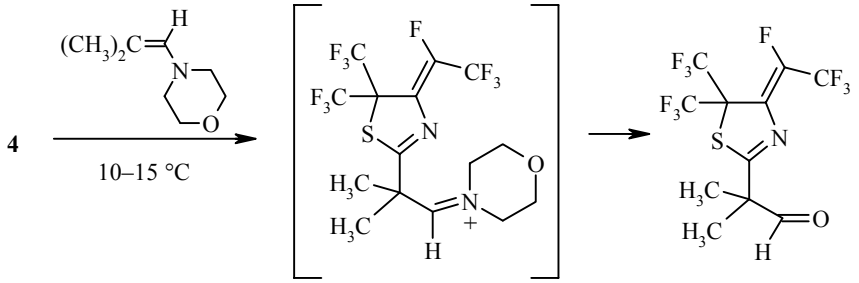
In the reaction of compound **4** and the C-nucleophile generated from 1-methylindane (or 1-morpholino-1-cyclohexene, 1-morpholinocyclopentene, 2-methyl-1-morpholinopropene) isomeric derivatives of 4,5-dihydrothiazole are formed [48]. Thus, the reaction with 1-methylindole in toluene at 60°C (8 h) gives a 78% yield of *E*-3-[5,5-bis(trifluoromethyl)-4-tetrafluoroethylidene)-4,5-dihydro-2-thiazolyl]-1-methyl-1H-indole (**70**). In energy terms the formation of the *E*-isomers is more favorable, since in this case the steric arrangement of the $(CF_3)_2C$ and CF_3 groups secures maximum separation of these functions from each other.



71 **70**

The *E*-configuration of the CF_3 group in relation to the exocyclic double bond was established from the ^{19}F NMR spectrum. The reaction takes place through the intermediate formation of the 3-aza-1-thiapentadienyl anion **71** as a result of intramolecular cyclization. Subsequent elimination of hydrogen fluoride gives the isomer **70** with the *E*-configuration less sterically hindered on account of the $(CF_3)_2C$ and CF_3 groups [48].

Similar reaction of compound **4** with 2-methyl-1-morpholino-1-propene leads to the formation of the iminium salt **72** as the product of [1+5] cycloaddition [48]. Hydrolysis of the salt **72** gives the stable 2-[5,5-bis(trifluoromethyl)-4-(tetrafluoroethylidene)-4,5-dihydro-2-thiazolyl]-2-methylpropionaldehyde (**73**), which is extremely interesting as a fluorine-containing building block for the synthesis of heterocyclic compounds through the reactions of the aldehyde group.

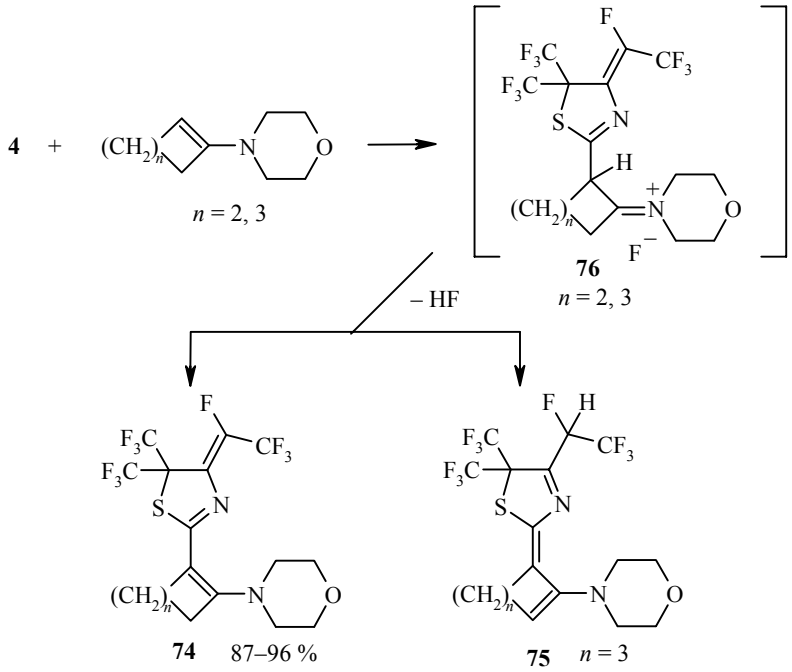


72 **73**

TABLE 1. The Dependence of the Ratio of the Isomers **74** and **75** on the Reaction Conditions

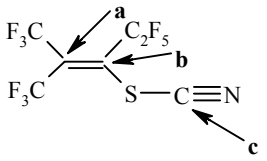
Substrate : enamine	Solvent	Temperature, °C	Ratio, %	
			74	**75**
1	—	2-20	92	8
1 : 2	Hexane	30-35	69	31
1 : 2	Acetonitrile	0-2	84	16
1 : 2	Et_2O	-5-0	13	87
1 : 1	Et_2O	-5-0	100	—

1-Morpholino-1-cyclohexene and 1-morpholino-1-cyclopentene with compound **4** give the individual thiazolines **74** or their mixtures with the isomers **75**, depending on the reaction conditions (Table 1). The isomers are presumably formed through a common intermediate link, i.e., the immonium salt **76**, which has two possibilities of stabilization by deprotonation. (Compounds **74** and **75** are produced.) The structure of compounds **74** and **75** was confirmed by X-ray crystallographic analysis [49].

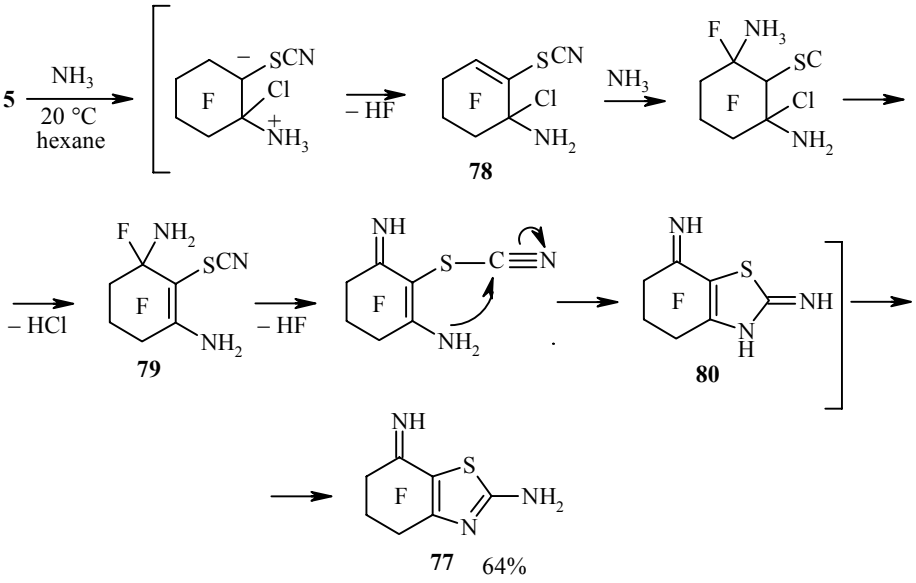


3. REACTIONS OF THE THIOCYANATE DERIVATIVES OF SOME PERFLUOROOLEFINS WITH NUCLEOPHILES

The thiocyanate group is also sensitive to nucleophilic reagents, but in contrast to the isothiocyanates the reaction takes place at the cyclization stage. Fluorine-containing α,β-unsaturated thiocyanates must combine the characteristics of a perfluoroolefin and a thiocyanate. It is easy to see that such a molecule has three potential centers for nucleophilic attack, as shown for compound **2**:



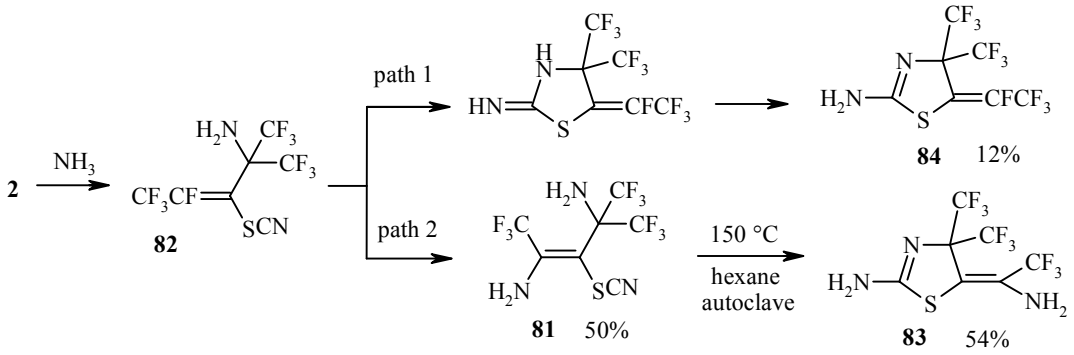
Thus, ammonolysis of 2-chloroperfluoro-1-cyclohexenyl thiocyanate (**5**) is accompanied by intramolecular cyclization of the Thorpe type, leading to 2-amino-7-iminoperfluoro-4,5,6,7-tetrahydrobenzothiazole (**77**) [18].



The addition of ammonia at the double bond leads to compound **78**, then to the intermediate **79**, and finally to the diimine **80**, which is stabilized in the form of the amine **79**. Cyclization takes place spontaneously, and the intermediate products were not isolated.

The ammonolysis of perfluoro-2-methyl-2-penten-3-yl thiocyanate (**2**) takes place by an Ad_E mechanism with simultaneous substitution of the allylic fluorine atoms at the γ position to the sulfur atom by an imino group. It leads to the formation of 2-amino-4,4-diperfluoromethyl-5-perfluoroethylidene-4,5-dihydrothiazole (**84**) and 2,4-diamino-4-perfluoromethyl-2-perfluoropenten-3-yl thiocyanate (**81**) [18]. The reaction is stereospecific with the exclusive formation of the *E*-isomer.

Nucleophilic attack by ammonia at the double bond of compound **2** followed by elimination of HF leads to the formation of the β-aminothiocyanate **82**. Further transformations of the compound can take place by path 1 by intramolecular cyclization through attack by the N-nucleophile at the carbon atom of the thiocyanate group with the formation of compound **24** [50] or by path 2 by the addition of ammonia at the C=C double bond followed by elimination of a fluoride ion, leading to the formation of the thiocyanate **81** [18]. (*E*)-2-Amino-4,4-bis(trifluoromethyl)-4,5-dihydro-5-(1-aminotrifluoroethylidene)thiazole **83** is formed when compound **81** is heated at 150°C in hexane (autoclave, 7 h). The structures of compounds **81**, **83**, and **84** were also confirmed by X-ray crystallographic analysis [18, 19].



The presented data make it possible to conclude that the α,β-unsaturated thiocyanates and isothiocyanates of perfluoroolefins can be used for the synthesis of various substituted fluorine-containing heterocyclic compounds with N and S atoms. Compounds with biological activity have been found among them, and new compounds with such activity can be expected.

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