Synthesis of fluorine-containing heterocycles based on polyfluorooxiranes and O,N,S-dinucleophiles

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The methods of synthesis of fluorine-containing O, N, S-heterocyclic compounds, such as diazines, oxazines, thiazolines, oxazolines, quinoxalines, benzoxazines, benzothiazines, imidazolidines, and glycolurils, based on the reactions of perfluoro- and polyfluorooxiranes with bifunctional nucleophilic reagents, are presented in the review. Significant influence of the solvent nature on the composition and structure of the obtained compounds is demonstrated.

Key words: polyfluorooxiranes, diazines, oxazines, thiazolines, oxazolines, quinoxalines, benzoxazines, benzothiazines, imidazolidines, glycolurils.

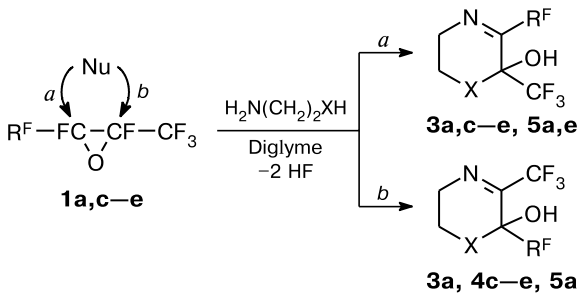
Intensive development of chemistry of N,O,S-heterocycles, including fluorine-containing compounds, is due to their high physiological activity.[1—4] Compounds containing imidazoline, oxazoline, imidazole, thiazole, and thiazine cycles are the basis of known drugs, namely hypotensive and anti-inflammatory drugs, tranquilizers and neuroleptics.[5—7] Additionally, heterocyclic moieties are part of antibiotics, e.g. there is thiazine cycle in the structure of penicillin. Among the derivatives of imidazole, thiazole, oxazole, and diazine there are compounds possessing pesticidal, fungicidal, and herbicidal activities.[8—11]

One way to create fluorine-containing heterocyclic compounds is the introduction of fluorine atom and fluorine-containing groups by reaction of fluorine-containing precursors with nucleophilic reagents. It has been shown previously[12—18] that the hexafluoropropylene oxide (HFPO), possessing a pronounced electrophilic center (C(2) atom of oxirane cycle) is a convenient precursor for the synthesis of O,N,S-heterocyclic compounds containing perfluoroalkyl substituent.

In the present review the work on the creation of perfluoroalkyl- and polyfluroalkyl-containing O,N,S-heterocyclic compounds based on internal (**1a—e**)[19] and terminal (**2a**,**b**)[20] perfluoro- and polyflurooxiranes and bifunctional nucleophilic reagents is considered.

It is known that the reaction of HFPO with ethylendiamine (EDA) and 2-aminoethanol (2-AE) lead to non cyclic product of the oxirane cycle opening, namely *N*,*N*′-bis(pentafluoropropanoyl)ethylenediamine and *N*,*O*-bis(pentafluoropropanoyl)-2-aminoethanol.[18] In contrast to HFPO internal perfluorooxiranes **1a**,**c—e** upon reaction with EDA and 2-AE form heterocyclic compounds, namely fluoroalkyl-containing diazines and oxazines.[21] The reaction of unsymmetrical oxiranes **1c**,**d** lead to the mixtures of regioisomer products. At that the nucleophilic attack is directed predominantly onto C(3) atom of the oxirane ring (Scheme 1, direction *a*).[21] The oxirane **1e** is of special interest, while it interacts regiospecifically with EDA exceptionally according to direction *a* with formation of diazine **5e** (see Scheme 1).

Scheme 1



X = O: R^F = CF_3 (**3a**), C_3F_7 (**3c**, **4c**), C_5F_{11} (**3d**, **4d**), $H(CF_2)_3$ (**3e**, **4e**);
X = NH: R^F = CF_3 (**5a**), $H(CF_2)_3$ (**5e**)
Yield (*a* + *b*) ~20—62%.

The direction of interaction of internal perfluorooxiranes with *o*-phenylenediamine (OPDA) and 2-aminophenol (2-AP) depends on the polarity of the solvent. Thus, in dioxane the interaction of oxiranes **1a—c** with OPDA leads to the formation of quinoxalines **6a—c** and some amount of isomeric ketones **7** (Scheme 2).[22]

* Based on the materials of the IV all-Russian Conference on Organic Chemistry and the XVIII Youth School-Conference on Organic Chemistry (November 22—27, 2015, Moscow, Russia).

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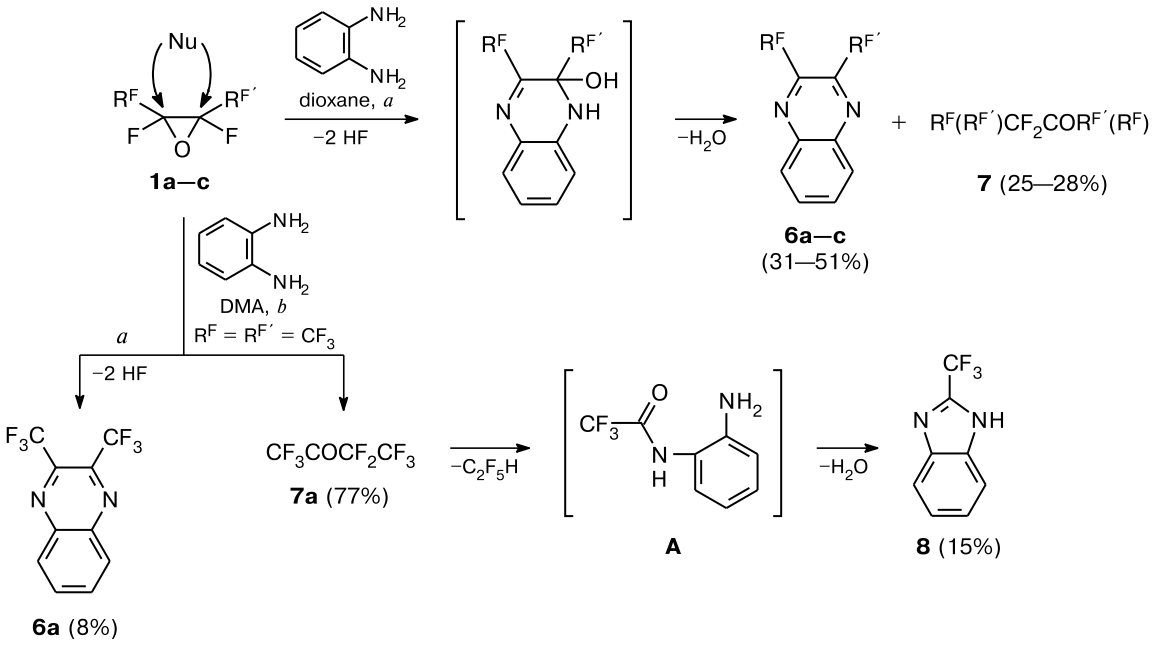
Scheme 2

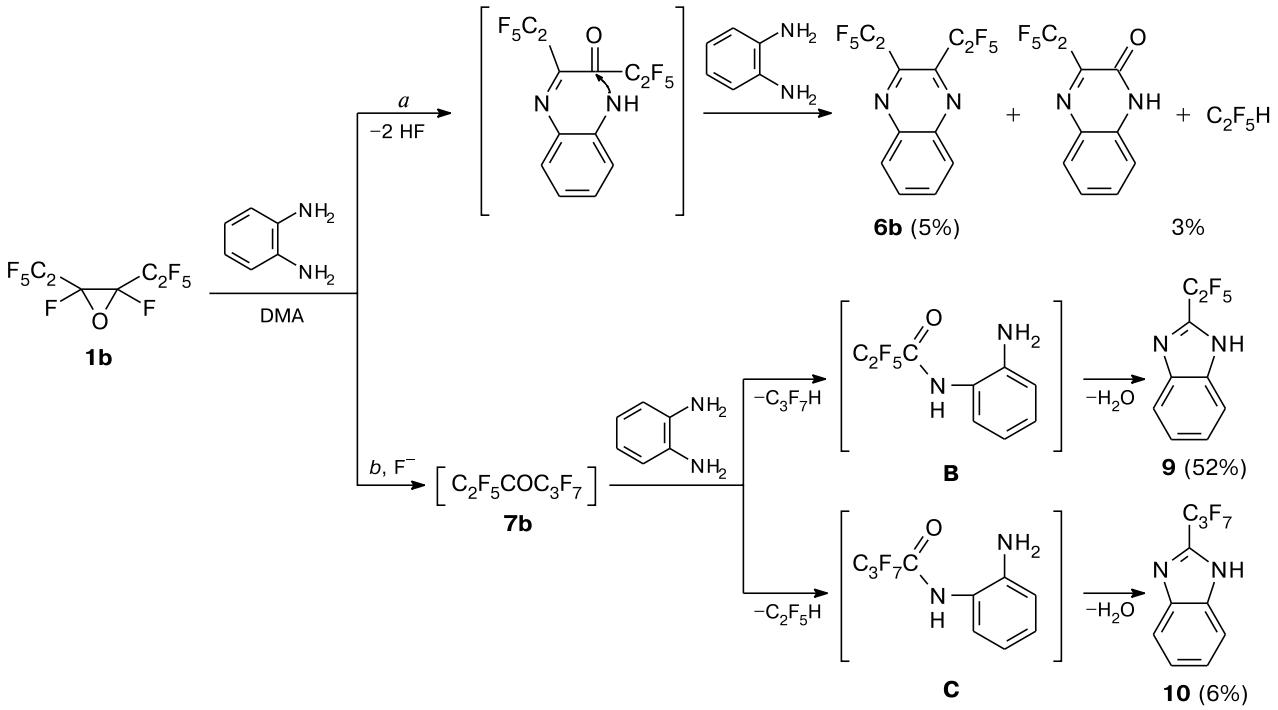


DMA is dimethylacetamide.
7, 8: $R^F = R^{Fr'} = CF_3$ (**a**); $R^F = R^{Fr'} = C_2F_6$ (**b**); $R^F = CF_3$, $R^{Fr'} = C_3F_7$ (**c**)

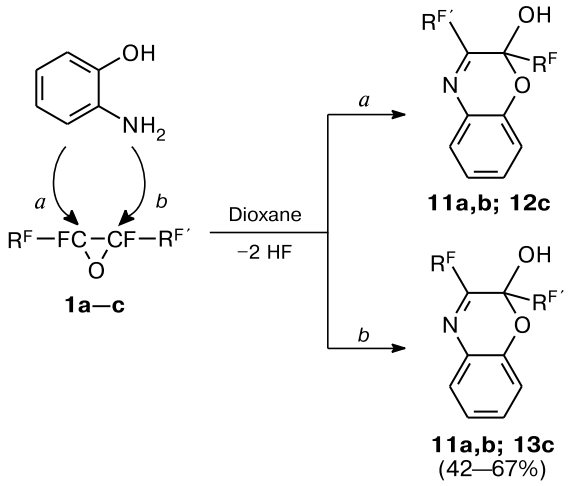
A decrease of quinoxalines **6** yield and increase of proportion of isomeric ketones **7** is observed by using more polar DMA. The ketones **7** are split to the amides **A**—**C** followed by the formation of benzimidazoles **8**—**10** (direction *b*); at that quinoxalines **6** (direction *a*) are the minor products (Schemes 2 и 3).

The reaction of symmetric perfluorooxiranes **1a**,**b** with 2-AP in dioxane is realized with high selectivity and yields

Scheme 3



Scheme 4



$R^F = R^{F'} = CF_3$ (**1a**, **11a**); $R^F = R^{F'} = C_2F_5$ (**1b**, **11b**); $R^F = CF_3$, $R^{F'} = C_3F_7$ (**1c**, **12c**, **13c**)
12c : **13c** ≈ 1 : 1, yield (**12c** + **13c**) 62%, yield **13c** is 23% (from isomers mixture).

the cyclic products, namely 2,3-bis(perfluoroalkyl)-2*H*-1,4-benzoxazine-2-ols **11a,b**. Nucleophilic opening of the oxirane ring of unsymmetrical perfluoro-2,3-epoxyhexane **1c** upon action of 2-AP is going in two possible directions (Scheme 4, directions *a*, *b*) with formation of regioisomeric benzoxazinoles **12c** and **13c** (~1 : 1). Individual compound **13c** was separated by fractional crystallization (Scheme 4).[22]

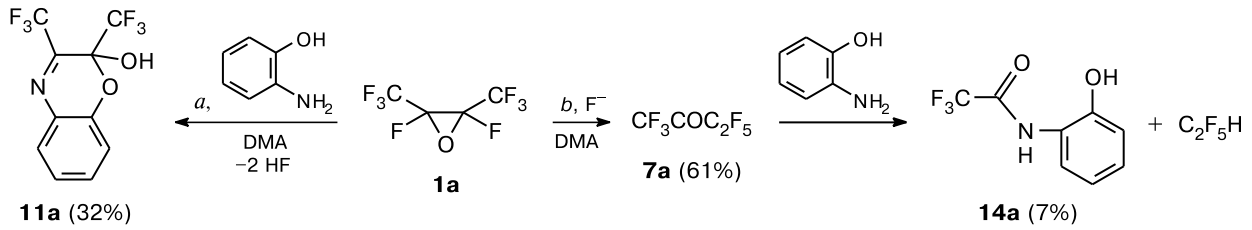
An application of polar solvent (DMA) in the reaction of perfluoro-2,3-epoxybutane **1a** with 2-AP leads to the decrease of benzoxazine **11a** yield (Scheme 5, direction *a*). In this case, main direction of the reaction leads to the isomeric perfluoro-2-butanone **7a** (as a results of ionic isomerization of oxide in the presence of F^- anion), which is partially decomposed upon action of 2-AP with formation of small amount of 2-hydroxy-*N*-trifluroacetylaniline **14a** (Scheme 5, direction *b*).[22]

Unexpected reaction direction is observed by interaction of perfluoro-3,4-epoxyhexane **1b** with 2-AP in DMA medium: the formation of benzoxazolidine **15** and *o*-hydroxyanilides **16**, **17** (Scheme 6).[22]

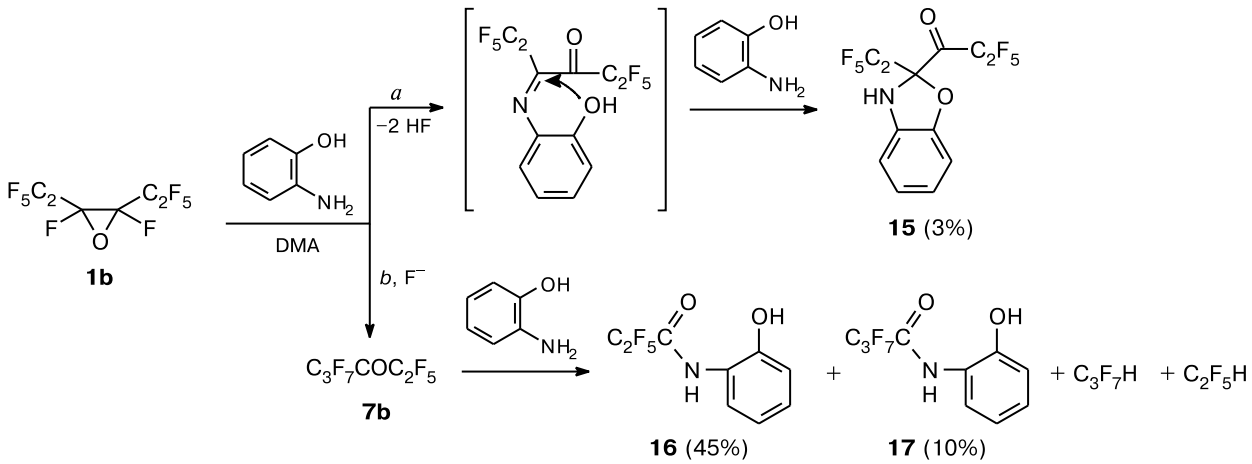
An interaction of compounds **1a**,**c**,**e** with thiourea (TU) in MeOH or DMSO yields 1,3-thiazolines **18a**,**c**,**e** and **19c**,**e** (Scheme 7).[23,24]

Unsymmetrical oxiranes **1c,e** yield the mixture of regioisomeric thiazolines (**18c**, **19c** and **18e**, **19e**), and an opening of the epoxy ring from the side of more bulky fluoroalkyl group dominates (see Scheme 7, direction *a*). According to ^{19}F NMR spectroscopy regioisomers are formed as *trans*- and *cis*-isomers with domination of *trans*-isomers, which were separated in individual form and characterized by IR spectroscopy, ^{19}F and ^1H NMR spectro-

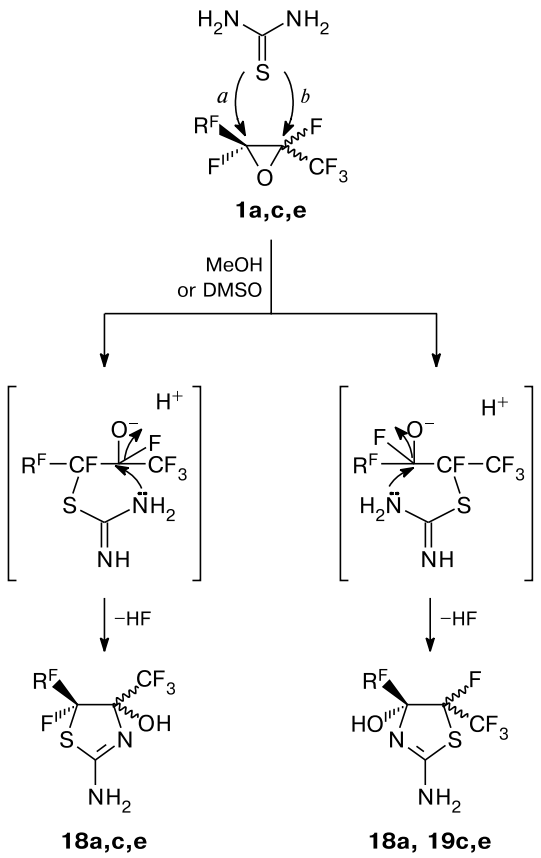
Scheme 5



Scheme 6



Scheme 7



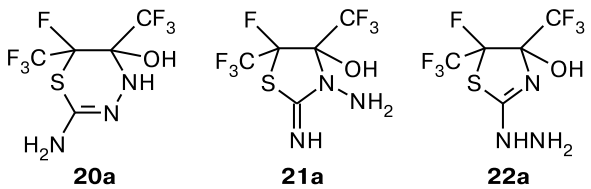
1a,c,e **18a,c,e** **18a, 19c,e**

$R^F = CF_3$ (**a**), C_3F_7 (**c**), $H(CF_2)_3$ (**e**)
Yield (*a* + *b*) 50—64%.

scopy, mass spectrometry, elemental analysis, and X-ray crystallography.[23,24]

The character of the solvent has a significant influence on the ratio of stereoisomers: in DMSO total molar ratio in obtained thiazolines was approximately equal to corresponding value for starting epoxide, while in MeOH the ratio of *trans* : *cis*-thiazolines changed in the direction of increased portion of *trans*-isomers.

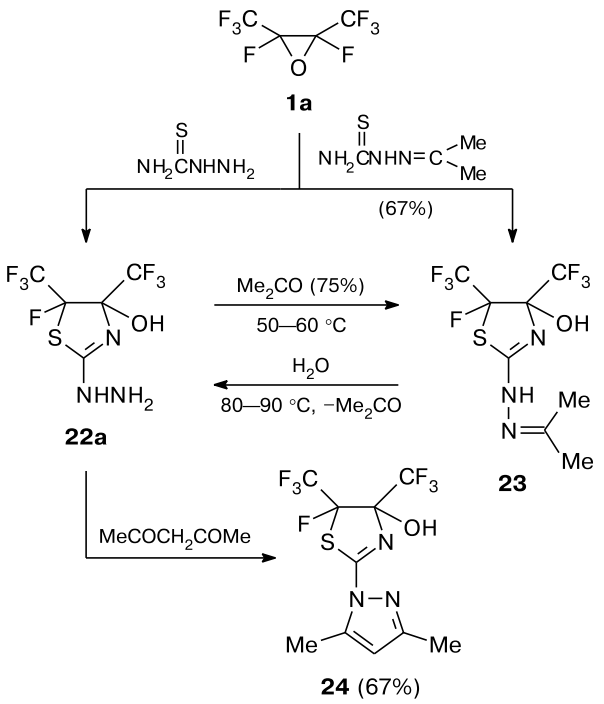
By interaction of perfluoroepoxybutane **1a** (*trans* : *cis* ≈ ≈ 9 : 1) with thiosemicarbazide (TSC) the product with one of the three structures **20a**, **21a** or **22a** was obtained. The assignment was made on the basis of data of IR spectroscopy, ^1H, ^{19}F, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. It was proved by chemical way that the compound has a structure of **22a**:



20a **21a** **22a**

a treatment of the product with acetone led to hydrazone **23**, and its condensation with acetylacetone to thiazolinepyrazole **24** (Scheme 8).[24]

Scheme 8

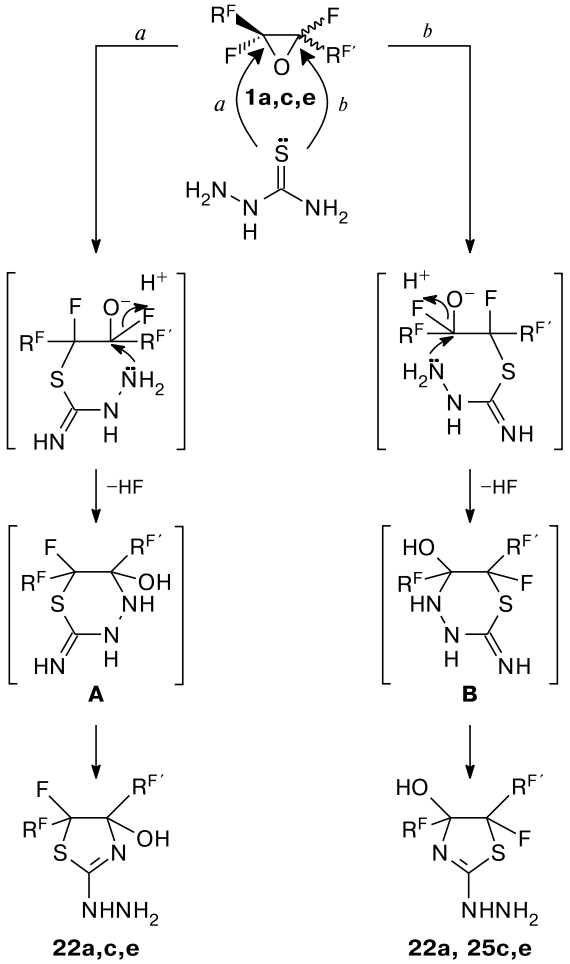


1a **22a** **23** **24** (67%)

By interaction of oxiranes (**1c**, *trans* : *cis* ≈ 9 : 1; **1e**, *trans* : *cis* ≈ 85 : 15) with TSC the mixtures of regioisomeric 2-hydrazino-1,3-thiazolines **22c**, **25c**, **22e**, **25e** (Scheme 9) were obtained. Evidently, in this reaction TSC acts similarly to TU leading to thiadiazines **A** and **B**, which rearrange into 2-hydrazinothiazolines **22a**,**c**,**e** and **25c**,**e**. It is evident that the formation of final products undergoes as the result of hydrolytic splitting of N(4)—C(5) bond in intermediate thiadiazines **A**, **B** followed by closing of thiazoline cycles with participation of nitrogen atom of the imine group.[24,25]

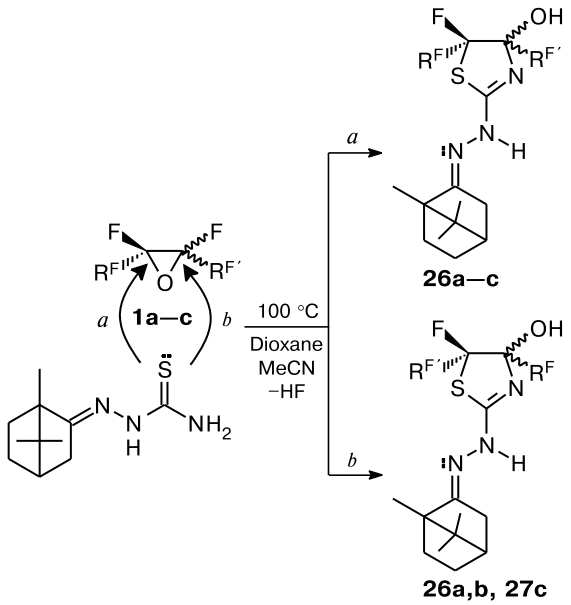
Thiazolinyl-2-hydrazones (1*S*)- and (*rac*)-camphores **26a**,**b** (*trans* : *cis* ≈ 9 : 1) were obtained by the reaction of oxiranes **1a**,**b** (*trans* : *cis* ≈ 9 : 1) with (1*S*)- and racemic camphor thiosemicarbazone (CTSC) in dioxane and acetonitrile (Scheme 10).[26] ^1H, ^{13}C, and ^{19}F NMR spectra of *trans*-bis(trifluoromethyl)thiazolinylhydrazone (1*S*,4*S*)-CTSC **26a**, separated as individual compound exhibited the presence of two diastereomers [(1*S*,4*S*,4′*S*,5′*S*) and (1*S*,4*S*,4′*R*,5′*R*)] (1 : 1). It was established by studing of the monocrystal of **26a** by X-ray crystallography that instead of expected separation the co-crystallization of two diastereomers (1*S*,4*S*,4′*R*,5′*R*)-**26a** and (1*S*,4*S*,4′*S*,5′*S*)-**26a** (ratio 1 : 1) takes place. These diastereomers have *anti*-configuration in chiral crystal; the substituent at atom N_{sp^2} is directed in opposite direction from Me(10) (space group $P2_1$).

Scheme 9



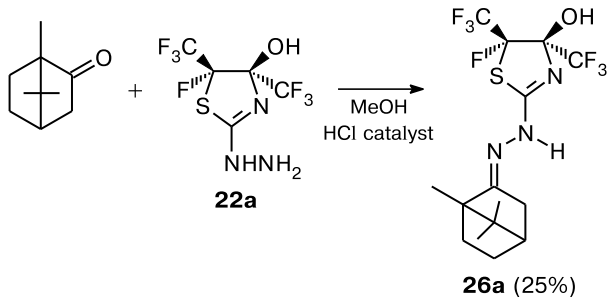
$R^F = R^{F'} = CF_3$ (**1a**, **22a**); $R^F = CF_3$, $R^{F'} = C_3F_7$ (**1c**, **22c**, **25c**); $R^F = CF_3$, $R^{F'} = H(CF_2)_3$ (**1e**, **22e**, **25e**)
Yield (*a* + *b*) ~10%

Scheme 10



$R^F = R^{F'} = CF_3$ (**a**); $R^F = R^{F'} = C_2F_5$ (**b**); $R^F = CF_3$, $R^{F'} = C_3F_7$ (**c**)
Yield (*a* + *b*) 50—70%.

Scheme 11



An opening of epoxy cycle of unsymmetrical perfluoro-2,3-epoxyhexane **1c** (*trans* : *cis* ≈ 9 : 1) under action of (1*S*,4*S*)-camphor in similar conditions is undergoing in both possible directions (see Scheme 10, directions *a* and *b*) with formation of regioisomeric thiazolinylhydrazones of (1*S*)-camphor **26c** and **27c** (44 : 56).[26]

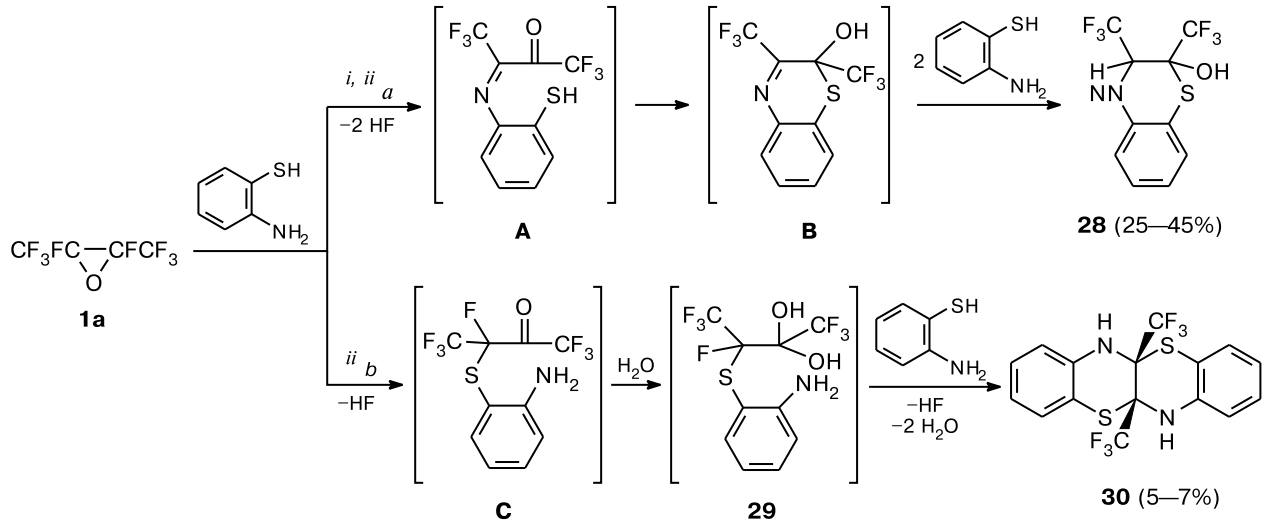
Alternative method of hydrazones **26** and **27** synthesis could be reaction of camphor with hydrazines **22** and **25**. Compound **26a** (1*S*,4*S*,4′*RS*,5′*RS*) was obtained using this method (Scheme 11). However, this method appeared to be less successful compared with described above due to the formation of side products and moderate yield of starting hydrazines.[26]

The direction of interaction of oxiranes **1a** with 1-aminothiophenol (2-ATP) is determined by the reactivity of SH- and NH_2-groups of dinucleophile and depends on a nature of solvent. Thus, the reaction in the medium of low polar solvents with low ionization and dissociation ability, such as toluene, dioxane, THF, and dimethoxyethane, as a result of primary attack of amino group of 2-ATP leads mainly to benzothiazine **28** (*cis* : *trans* ≈ 1 : 4) (Scheme 12, direction *a*).[27]

The reaction of oxiranes **1a** with 2-ATP in polar DMA and DMSO yields mainly benzothiazolidine **31** (*RS*,*SR*/*RR*,*SS* ≈ 1 : 1) and small amount of diol **29**, which probably is formed from intermediate **C** after treatment of the reaction mass with water. The diol **29**, included in raw product, in the presence of 2-ATP and solvent during few weeks at room temperature transforms into dithiadiazanaphtazene **30**. Apparently, the formation of compounds **29**—**31** is the result of primary attack of SH-group of dinucleophile (Schemes 12 and 13). In both types of solvents 2-ATP serves not only as nucleophilic reagent, but also as reducing agent for C=N and C=O groups.[27]

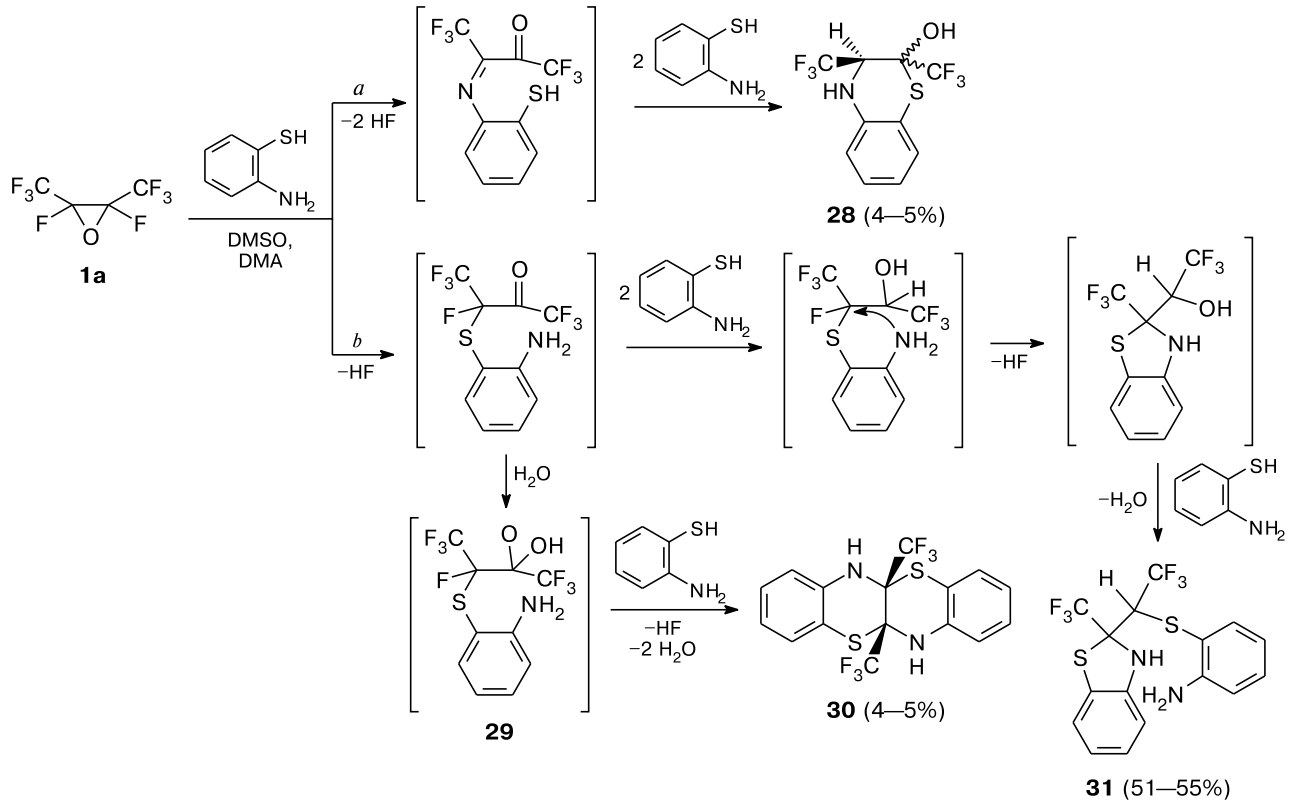
The structure of compound **29** was proved by the data of GC-MS, and also by ^1H and ^{19}F NMR spectroscopy. Molecular structure of *RS*,*SR*-benzothiazine **28**, dithia-

Scheme 12



i. Dioxane, $PhCH_3$; *ii*. THF, dimethoxyethane, MeCN.

Scheme 13

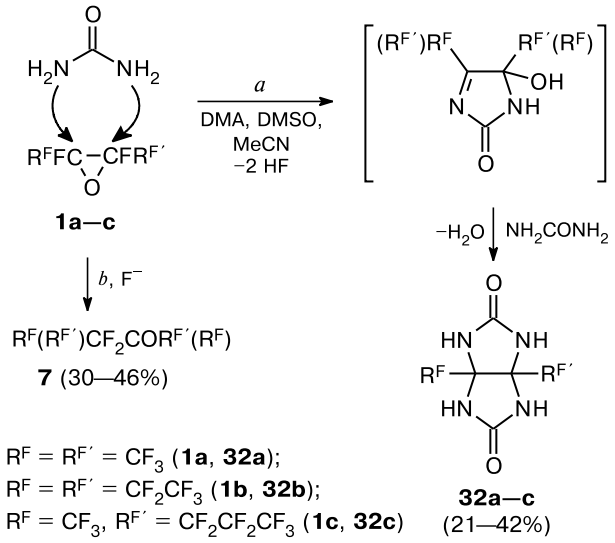


diazanaphtazene **30**, and *RS*,*SR*-benzothiazolidine **31** was solved by X-ray crystallography.

Interaction of internal perfluorooxiranes **1a—c** with urea in bipolar aprotonic solvents (DMSO, DMA, and MeCN) leads to glycoluriles **32a—c** (Scheme 14, direction *a*),[28] which are formed apparently as a result of primary nucleophilc attack of urea NH_2 group onto one of the carbon atoms of epoxide. The reaction is accompanied by the formation of isomeric ketones **7** (30—46%) (see Scheme 14, direction *b*). Using of amine in deficiency the ketones **7** become to be main reaction products, glycouriles **32a—c** are obtained with small yields.

Similar reaction of oxiranes **1a—c** in low polar dioxane leads to unexpected heterocyclic compounds (oxazolines **33a—c** and **34c**), probably due to primary nucleophilic attack by oxygen atom of urea carbonyl group onto ox-

Scheme 14



irane. The compounds **33a**—**c** and **34c** are obtained in high yields (Scheme 15).[28]

Nucleophilic opening of epoxide cycle of unsymmetrical epoxide **1c** upon action of urea leads in both possible directions (directions *a* and *b*) with formation of regioisomeric oxazolines **33c** and **34c** (predominatly in *trans*-form) (see Scheme 15).

An application of aqueous dioxane in the reaction of oxiranes **1b**,**c** with urea exhibits low yields of oxazolines **33b**,**c** and **34c** (direction *b*), while the main reaction direction turn to be the formation of dihydroxyimidazolidines **35b**,**c** and glycouriles **32b**,**c** (Scheme 16, direction *a*). Molecular structure of *trans*-isomer of imidazolidine **35b** was studied by X-ray crystallography.[28]

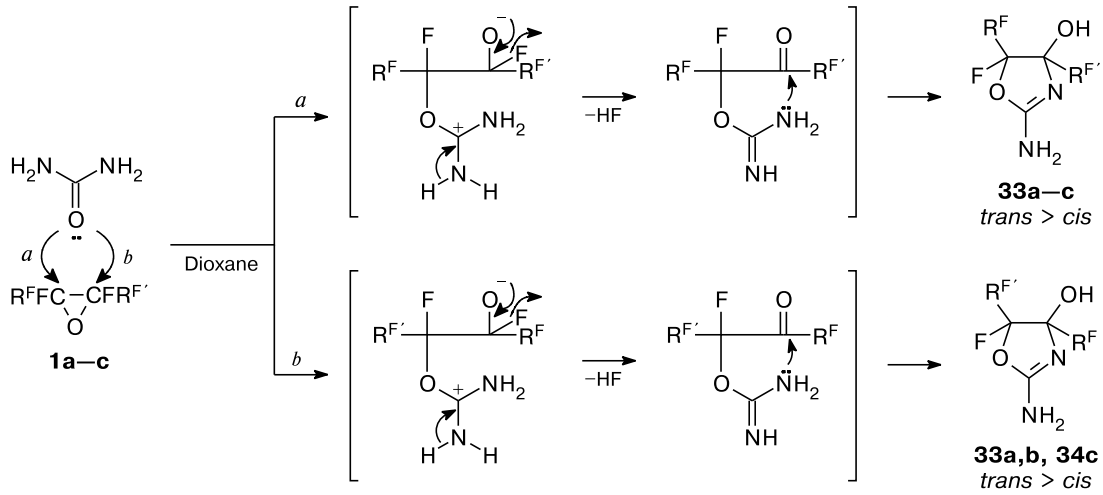
Another example of influence of type of solvent on the composition and structure of products is interaction of terminal perfluorooxiranes **2a**,**b** with urea. Conducting the reaction of octafluoro-1,2-epoxybutane **2a** with urea in DMSO, aqueous DMSO, dioxane, and acetonitrile, as well as of hexafluoro-1,2-epoxyoctane **2b** with urea in aqueous DMSO perfluoroalkylhydantoins **36a**,**b** were obtained. As a result of interaction of oxirane **2b** with urea in DMSO and aqueous DMSO perfluoroalkylallantoin **37b**, *N*-(1-hydroxy-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)urea **38b**, and in small amount oxyacid **39b** (Scheme 17)[29] are formed.

The reaction of oxiranes **2a**,**b** with urea in aqueous dioxane and aqueous acetonitrile leads to heterocyclic compounds of another type, namely to perfluoroalkyloxazolones **40a**,**b** (Scheme 18, direction *a*), and in aqueous dioxane and aqueous acetonitrile to the mixture of oxazolones **40a**,**b** and hydantoins **36a**,**b** (Scheme 18, directions *a* and *b*) is formed.[29]

The compositions and structures of compounds **36a**,**b**, **37b**—**39b**, and **40a**,**b** are proved by the data of IR spectroscopy, ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, and elemental analysis. The structure of hydantoin **36a** is studied by X-ray crystallography.

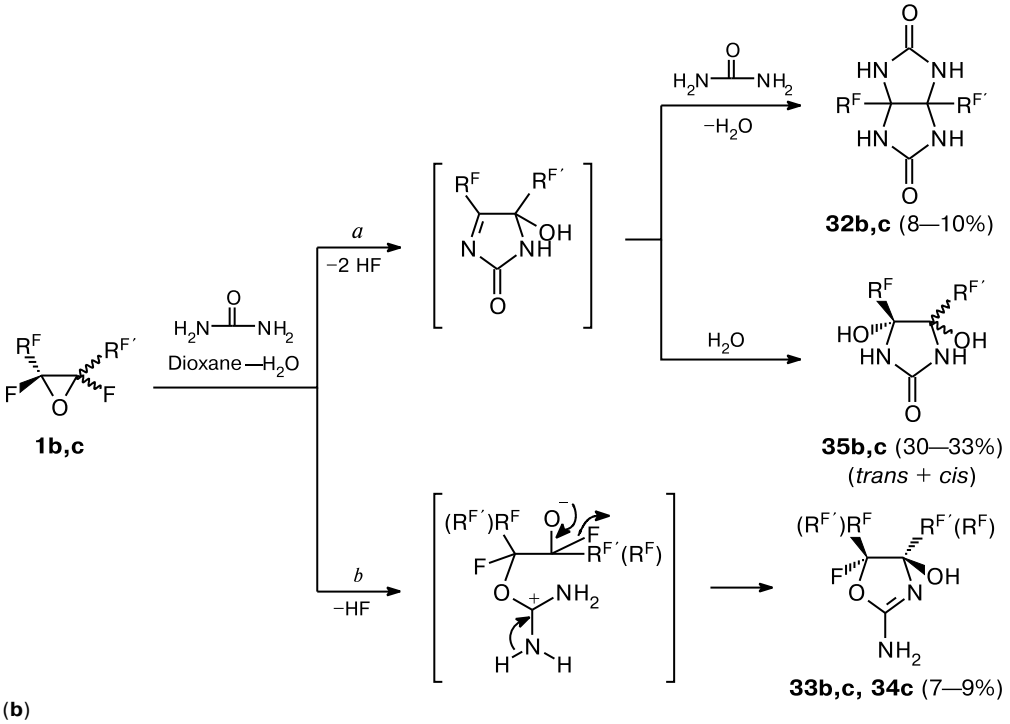
As a summary, the directions of formation of fluorocontaining O,N,S-heterocyclic compounds based on the reactions of internal and terminal perfluoro- and polyfluoroxiranes with bifunctional nucleophilic reagents are analyzed. It is shown that such approach allows the formation of perfluoro- и polyfluoroalkyl substituted diazines, oxazines, thiazolines, oxazolines, benzothiazines, quinoxalines, benzoxazines, imidazolidines, glycolurils, and other heterocyclic compounds. The compounds described in the

Scheme 15



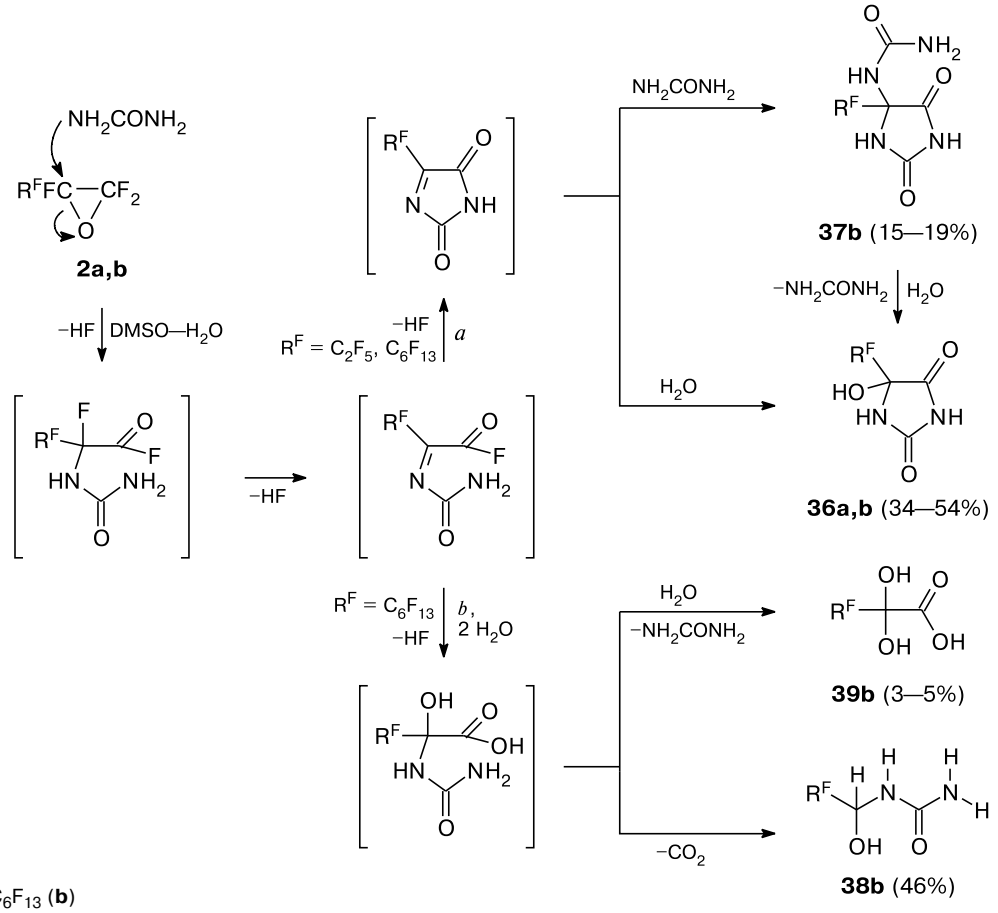
$R^F = R^{F'} = CF_3$ (**a**); $R^F = R^{F'} = C_2F_5$ (**b**); $R^F = CF_3$, $R^{F'} = C_3F_7$ (**c**)
Yields (*a* + *b*) 60—66%.

Scheme 16



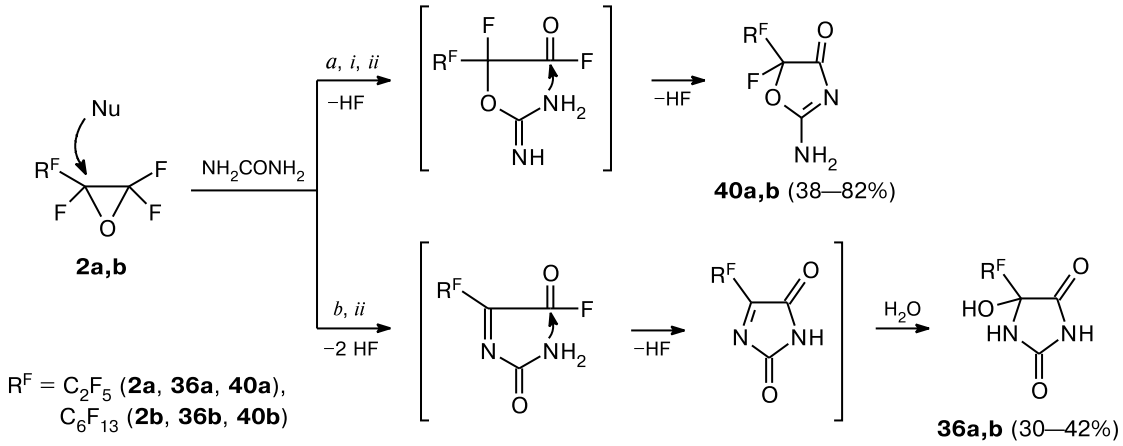
$R^F = R^{F'} = C_2F_5$ (**b**)
$R^F = CF_3$, $R^{F'} = C_3F_7$ (**c**)

Scheme 17



$R^F = C_2F_5$ (**a**), C_6F_{13} (**b**)

Scheme 18



i. Dioxane, MeCN; *ii*. Dioxane—H_2O, MeCN—H_2O.

review are of interest for the application as biologically active compounds.

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