Reviews

Polyfunctional fluoroalkyl-containing carbonyl compounds in the synthesis of heterocycles*

K. I. Pashkevich, V. I. Filyakova, V. G. Ratner, and O. G. Khomutov*

Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343 2) 74 5944. E-mail: tantra@tantra.ural.ru

Efficient procedures for the regioselective synthesis of fluoroalkyl-containing three-, five-, six-, and seven-membered heterocycles as well as of related fused compounds, namely, α,β-epoxyketones, α,β-aziridinylketones, pyrazoles, pyrazolines, isoxazolines, 1,2-dithiolenes, amino- and mercaptopyrimidines, $\Delta^{3,5}$-2-thioxo-1,3,2-thiazaphosphorines, $\Delta^{3,5}$-2-thioxo-1,3,2-oxazaphosphorines, 2,3-dihydro-1,4-diazepines, azirino[1,2-*a*]quinoxalines, benzo[*b*]- and naphtho[2,3-*b*]-1,4-diazepines, and triazolopyridazines, which have been developed by the authors and coworkers, are summarized. The α- and β-functionalized fluoroalkyl-containing carbonyl compounds (β-diketones, β-ketoesters, their salts, regioisomeric β-aminovinyl ketones, β-aminovinylthiones, β-hydroxyketones, α,β-enones, and their halogen derivatives) were used as synthons in the processes of formation of the above-mentioned heterocycles.

Key words: α- and β-functionalized fluoroalkyl-containing carbonyl compounds; fluoroalkyl-containing α,β-epoxyketones, α,β-aziridinylketones, pyrazoles, pyrazolines, isoxazolines, 1,2-dithiolenes, aminopyrimidines, mercaptopyrimidines, $\Delta^{3,5}$-2-thioxo-1,3,2-thiazaphosphorines, $\Delta^{3,5}$-2-thioxo-1,3,2-oxazaphosphorines, 2,3-dihydro-1,4-diazepines, azirino[1,2-*a*]quinoxalines, benzo[*b*]- and naphtho[2,3-*b*]-1,4-diazepines, triazolopyridazines.

In recent years, fluorine-containing heterocyclic compounds have attracted growing interest as potent biologically active compounds. This interest was aroused by their unusual combination of electronic and steric factors, unexpected aspects of the reactivity of fluorine-containing compounds, and their enhanced lipophility, which improves permeability through cell membranes. The introduction of fluorine atoms into biologically active molecules often leads to an increase in the activity or to a change in the spectrum of action. Generally, procedures for the synthesis, which are most widely used for compounds of the hydrocarbon series, are not suitable for the preparation of fluorinated analogs. The regio- and stereoselectivity of the processes of direct fluorination of biologically active heterocycles is poor, which necessitates the involvement of additional stages associated with protection of functional groups, which should not be converted. Because of this, fluorine-containing synthons are finding increasing use for intro-

*Dedicated to the memory of Academician I. Ya. Postovskii on his 100th birthday.

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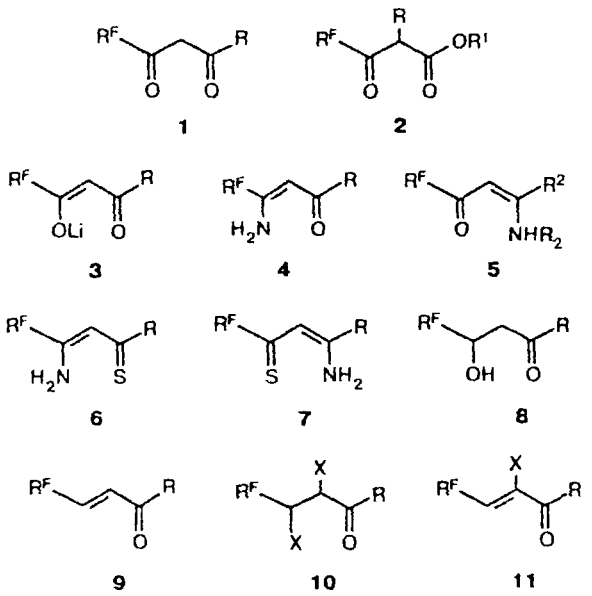
ducing fluorine-containing fragments. However, available fluorine-containing synthons, particularly, polyfunctional synthons, are few in number.[1,2]

In the middle 70s, a new trend of investigations, "Chemistry of functional fluoroalkyl-containing carbonyl compounds," was initiated under the direction of Academician I. Ya. Postovskii. These works were undertaken as a logical part of continuing studies devoted to the chemistry of fluorine, which were carried out by the Sverdlovsk school. As a result of these studies, β-diketones (**1**) and β-ketoesters (**2**) became available. Moreover, lithium salts of β-diketones (**3**), regioisomeric β-aminovinyl ketones (**4**) and (**5**), β-aminovinylthiones (**6**) and (**7**), β-hydroxyketones (**8**), α,β-enones (**9**), and their halogen derivatives (**10**) and (**11**) (Scheme 1) were brought into practical use in organic synthesis as fluoroalkyl-containing reagents.[3—19]

Scheme 1

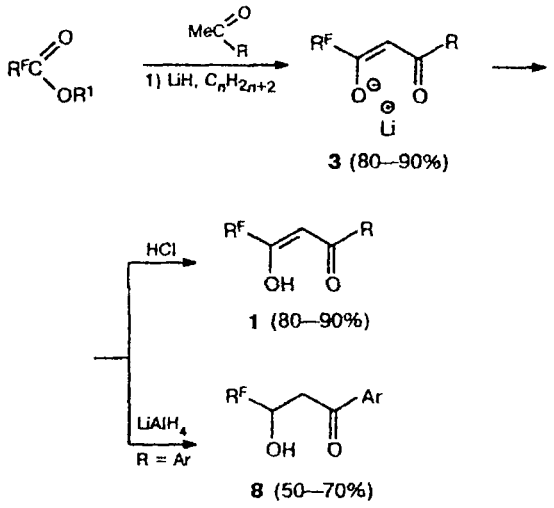


R^F = CF_3...C_8F_{17}; $H(CF_2)_n$ (n = 1, 2, 4, or 6).
R = Me, Et, Bu^n, Bu^t, or 4-YC_6H_4
(Y = H, Cl, Br, Me, OMe, or NO_2)
R^1 = Me or Et
R^2 = H, MeH, or Ph; X = Br or Cl

Of the above-mentioned compounds, lithium salts **3** are the most readily available reagents. They are readily obtained by the version of the Claisen condensation suggested by us[16,17] and are used without purification (sometimes even without isolation) in the synthesis of compounds **1**, **2**, and **4**—**11** as well as in the synthesis of heterocycles as such (Scheme 2).

The use of salts **3** as synthetic equivalents of β-diketones **1** allows one to do without stages of isolation and purification. It appeared that mercaptopyrimidines and triazolopyridazines can be synthesized only starting from salts **3** (see Schemes 14 and 23, respectively).

Scheme 2



Below are given the most typical examples of the use of compounds **1**—**10** as "building blocks" in the synthesis of fluoroalkyl-containing three-, five-, six-, and seven-membered heterocycles: α,β-epoxyketones (**12**), α,β-aziridinylketones (**13**), pyrazoles (**14**), pyrazolines (**15**), isoxazolines (**16**), 1,2-dithiolenes (**17**), aminopyrimidines (**18**), mercaptopyrimidines (**19**), $\Delta^{3,5}$-2-thioxo-1,3,2-thiazaphosphorines (**20**), $\Delta^{3,5}$-2-thioxo-1,3,2-oxazaphosphorines (**21**), 2,3-dihydro-1,4-diazepines (**22**), azirino[1,2-*a*]quinoxalines (**23**), 1,5-benzo- and naphtho[2,3-*b*]-1,4-diazepines (**24** and **25**, respectively), and triazolopyridazines (**26**).

All the above-mentioned heterocycles are of interest as potent synthons, biologically active compounds, comonomers, and admixtures for polymeric compositions. However, these compounds are poorly studied because of the lack of efficient procedures for their preparation.

We have developed a number of procedures for the synthesis of a series of heterocycles, which allow one to vary the set of substituents in the above-mentioned compounds within wide limits and give a relative freedom in choosing the synthetic pathway.

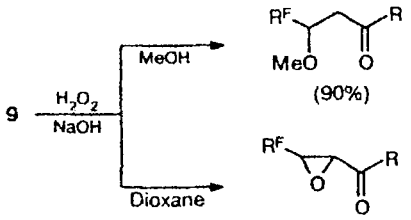
Synthesis of three-membered heterocycles

Until our studies have been carried out, fluoroalkyl-containing α,β-epoxyketones **12** and α,β-aziridinylketones **13** were virtually unavailable. We succeeded in developing several efficient procedures for their preparation and demonstrated some synthetic possibilities.[20—21]

Synthesis of α,β-epoxyketones. Numerous attempts to use fluorinated aldehydes in the Darzens reaction (the major procedure for the synthesis of nonfluorinated α,β-epoxyketones) and in various modifications of this reaction led to complex mixtures containing only traces of epoxyketones **12**. In our opinion, this is because fluorine-containing aldehydes are sensitive to bases, in particular, because of the known ability of these compounds to immediately undergo polymerization under the action of compounds of basic character.[13]

The use of fluorine-containing α,β-enones in the Weitz—Scheffer reaction (epoxidation of H_2O_2 in an alkaline medium) afforded fluorine-containing α,β-epoxyketones in high yields[20] (Scheme 3). However, careful purification of initial α,β-enones and control of the pH of the medium and the reaction temperature (0—5 °C) are necessary for the reaction to occur successfully. The reaction proceeded in the required way only in dioxane, while in methanol (which is commonly used as the solvent for preparing nonfluorinated analogs), the addition of methanol at the C=C bond competed with epoxidation.

Scheme 3

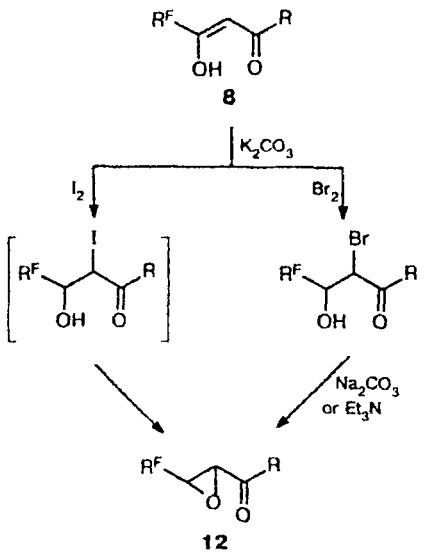


We have developed two efficient procedures for the synthesis of α,β-epoxyketones based on β-polyfluoroalkyl-β-hydroxyketones, which are more readily available and convenient in use compared to the corresponding α,β-enones.[15]

β-Hydroxyketones **8** are readily oxidized by iodine to give the corresponding α,β-epoxyketones **12**. The reaction proceeds through intermediate formation of α-iodo-β-hydroxyketone, which readily undergoes dehydroiodination accompanied by the cleavage of the epoxide ring.[21] The slight decrease in the yield compared to that obtained in the syntheses of compounds **12** using epoxidation of α,β-enones with hydrogen peroxide in an alkaline medium[20] is offset by the simple and fast procedure for the synthesis and by the use of starting reagents that are more readily available (fluoroalkyl-containing α,β-enones are prepared by dehydration of the corresponding β-hydroxyketones[12]).

When bromine was used instead of iodine, dehydrobromination did not occur under analogous conditions: α-bromo-β-hydroxyketones are stable products. Dehydrobromination with the formation of α,β-epoxyketone occurred upon boiling in an inert solvent with a fivefold molar excess of Na_2CO_3 or NEt_3 (Scheme 4).

Scheme 4



Rigid control over the pH of the medium and over the temperature of the reaction mixture is not necessary for the above-mentioned reactions to proceed. Due to simple experimental conditions (room temperature, low-polarity solvent, and the presence of K_2CO_3 or $CaCO_3$) and clear visual indication of completion of the reaction (decoloration of the reaction mixture), these reactions can be considered as the most efficient procedures for the preparation of fluoroalkyl-containing α,β-epoxyketones.

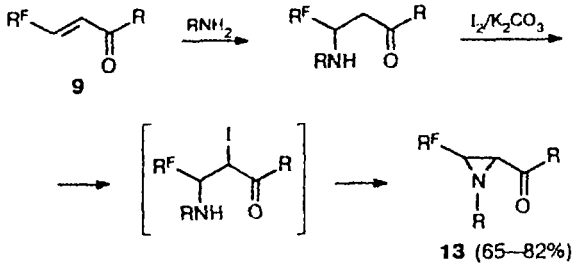
The formation of the epoxide ring in the reactions of β-polyfluoroalkyl-β-hydroxyketones with an equimolar amount of iodine or bromine is a specific pathway of the reaction of fluorine-containing β-hydroxyketones, which is not typical of nonfluorinated analogs. Under the above-mentioned conditions, the latter compounds underwent dehydration to form α,β-enones.[13]

α,β-Epoxyketones, which were prepared by the above-described methods, have a *trans* configuration, as shown by the values of the spin-spin coupling constant of the protons of the ring (1.4—1.9 Hz[22]).

Synthesis of fluoroalkyl-containing α,β-aziridinylketones. The conditions of formation of the epoxide ring by iodination—dehydroiodination of fluorine-containing β-hydroxyketones **8** appeared to be suitable also for the formation of the aziridine ring based on β-polyfluoroalkyl-β-aminoketones (Scheme 5). However, this reaction is of limited usefulness. Because of the instability of *N*-alkyl-substituted β-aminoketones, we succeeded in preparing the corresponding aziridinylketones **13** only directly from a mixture of α,β-enones **9**, amine, and I_2.

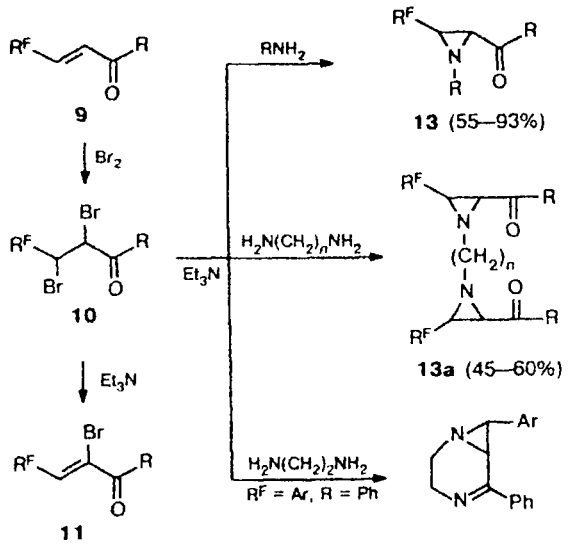
Besides, *N*-phenyl-substituted β-aminoketones do not enter into this reaction.[23]

Scheme 5



The more versatile procedure for the synthesis, which allows one to vary the substituents at the nitrogen atom of the aziridine ring within wide limits, involves the reactions of bromine derivatives **10** and **11** with NH_3, primary amines, and diamines.[24—26] Aziridinylketones **13** and bis(aziridinyl)ketones **13a** can be synthesized without isolation and purification of intermediate bromine derivatives **10** and **11** (Scheme 6). It should be noted that nonfluorinated α,β-dibromoketones react with ethylenediamine to form 1,4-diazabicyclo[4.1.0]hept-4-enes.[27]

Scheme 6

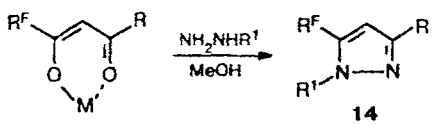


Unlike nonfluorinated analogs, which exist generally as a mixture of *cis* and *trans* isomers, fluoroalkyl-containing aziridinylketones and bis(aziridinyl)ketones are formed exclusively as *trans* isomers, which is evidenced by the values of the spin-spin coupling constant of the protons of the three-membered ring (2.30—2.50 Hz; the constant for the *cis* isomer is ~6 Hz).[27] X-ray diffraction study of one of aziridinylketones (**13**; $R^F = CF_3$ and R = R^1 = Ph) confirmed the suggested configuration.[28]

Synthesis of five-membered heterocycles

Synthesis of pyrazoles. The conventional procedure for the synthesis of pyrazoles involves condensation of β-diketones with hydrazines. The reaction of fluorinated β-diketones **1** with hydrazines afforded hydroxypyrazolines or mixtures of regioisomeric pyrazoles.[29] We have developed several alternative syntheses of fluorinated pyrazoles **14** based on the reactions of different salts of β-diketones **1** with hydrazine hydrochlorides (Scheme 7). The procedures are characterized by simplicity and high yields of pyrazoles. An important point is that these reactions are carried out with the use of stable hydrazine hydrochlorides instead of readily oxidized (and sometimes dangerously explosive) hydrazines.

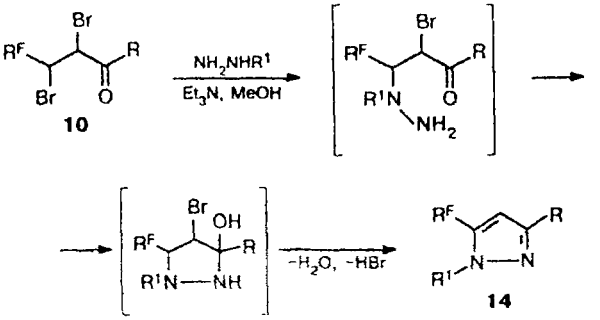
Scheme 7



M = Li, Na, K, NH_4^+, $NHEt_3^+$

Fluorine-containing pyrazoles can be prepared also starting from α,β-dibromoketones **10** (Scheme 8). The reactions of the latter with hydrazines afford the pyrazole rather than the aziridine ring as in the reactions of α,β-dibromoketones **10** with mono- and diamines[24—26] (see Scheme 4).

Scheme 8

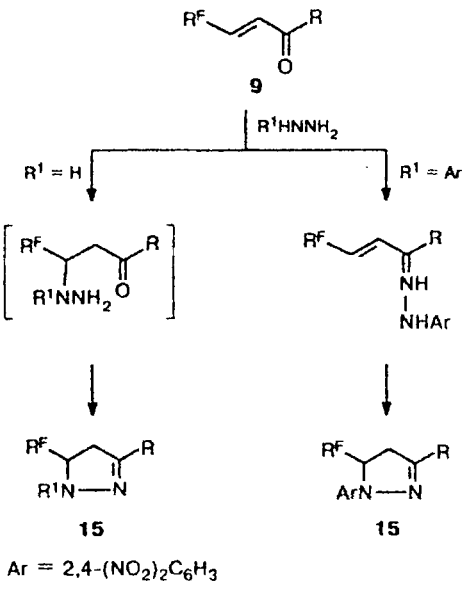


Presently, the most efficient procedure for the synthesis of pyrazoles is based on the reaction of lithium

salts **3** (intermediates in the synthesis of the corresponding β-diketones) with hydrazine hydrochlorides because salts **3** are more readily available as well as because the synthesis of pyrazoles is simple to carry out.[19]

Synthesis of Δ^2-pyrazolines. 3,5-Disubstituted Δ^2-pyrazolines (**15**) were readily obtained by the reaction of β-polyfluoroalkyl-α,β-enones (**9**) with hydrazine (Scheme 9). However, the resulting compounds were readily oxidized in air to form a complex mixture of unidentified products. The introduction of the bulky electron-withdrawing 2,4-dinitrophenyl substituent into the hydrazine molecule afforded a mixture of Δ^2-pyrazoline and hydrazone (when R = Me) or only hydrazone (when R = Ph).

Scheme 9

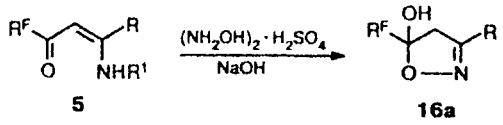


Synthesis of Δ^2-isoxazolines. Owing to the fact that the formation and cleavage of the isoxazole ring are sterically controlled, derivatives of isoxazole are widely used in the synthesis of natural products and their analogs.[30,31]

Unlike nonfluorinated analogs, which gave isoxazoles in the reactions with hydroxylamines, fluorine-containing β-diketones gave 5-hydroxy-5-fluoroalkyl-Δ^2-isoxazolines.[3,32] This is associated with the fact that the fluorinated substituent has a strengthening effect on the adjacent C—O bond.[33]

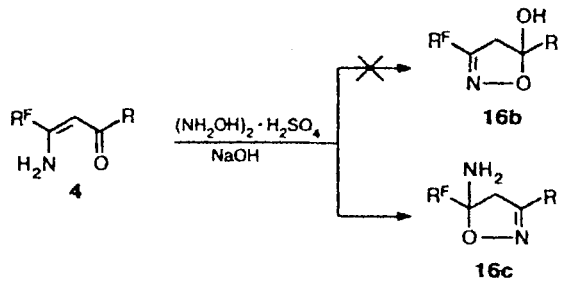
It was expected that the use of regioisomeric β-aminovinyl ketones **4** and **5** as aza analogs of two enol forms of β-diketones **1** would make possible the target synthesis of isomeric fluoroalkyl-containing isoxazolines. However, it appeared that only the reaction of β-aminovinyl ketone **5** with hydroxylamine, which was generated *in situ* from hydroxylamine sulfate, gave the expected 5-hydroxy-5-fluoroalkyl-Δ^2-isoxazoline (**16a**) (Scheme 10).

Scheme 10



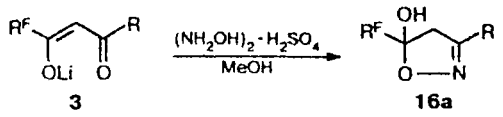
Under analogous conditions, isomeric β-aminovinyl ketone **4** unexpectedly gave the previously unavailable 5-amino-5-fluoroalkyl-Δ^2-isoxazoline (**16c**)[34] (Scheme 11) rather than regioisomeric 3-hydroxy-5-fluoroalkyl-Δ^2-isoxazoline (**16b**).

Scheme 11



However, the simplest procedure for the synthesis of 5-hydroxy-Δ^2-isoxazolines (**16a**), which we have suggested recently,[19] is based on lithium salts of fluorine-containing β-diketones (Scheme 12).

Scheme 12

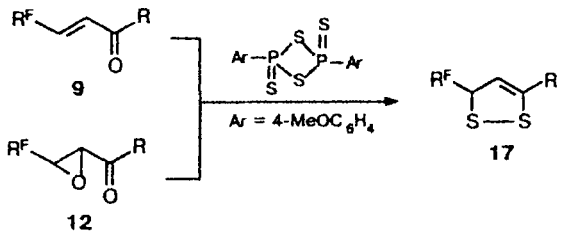


Fluoroalkyl-containing hydroxy- and aminoisoxazolines are promising polyfunctional synthons. Taking into account the data reported previously,[29—32] the nucleophilic replacement of OH and NH_2 groups can be expected for these compounds in addition to the cleavage of the ring.

Synthesis of polyfluoroalkyl-containing 1,2-dithiolenes. Boiling of fluorine-containing α,β-enones **9** and α,β-epoxyketones **12** in acetonitrile, toluene, or xylene with 2,4-bis(4′-methoxyphenyl)2,4-dithioxo-P^V,P^V-1,3,2,4-dithiadiphosphetane (Lawesson's reagent) as a thionating agent gave the corresponding 3-alkyl(aryl)-5-polyfluoroalkyl-1,2-dithiolenes (**17**) in low or moderate yields. We obtained the best results when the reaction was carried out in xylene with the use of α,β-epoxyketone **12** as the initial reagent (Scheme 13). The length of the fluoroalkyl substituent and the charac-

ter of the hydrocarbon substituents have virtually no effect on the direction of the reaction.[35]

Scheme 13

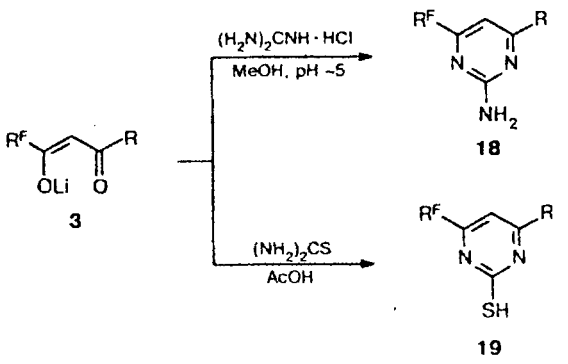


It should be noted that the participation of the carbonyl and olefin (or epoxide) groups in the reaction is not typical of hydrocarbon analogs. Thus, the reaction of epoxychalcone, which does not contain fluoroalkyl substituents, with Lawesson's reagent was accompanied by the cleavage of the epoxide ring to form 1,3,2-oxathiaphospholane. In this case, the carbonyl group did not participate in the reaction.[35]

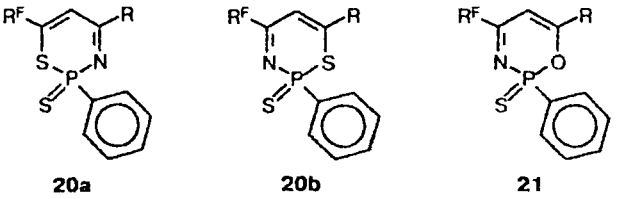
Synthesis of six-membered heterocycles

Synthesis of amino- and mercaptopyrimidines. We have established that lithium salts of fluorine-containing β-diketones **3** serve as convenient synthons for preparing 2-amino- and 2-mercaptopyrimidines **18** and **19** (Scheme 14). The reactions of salts **3** with guanidine hydrochloride and thiourea occurred under mild conditions to give the target products in high yields. It should be noted that the synthesis of mercaptopyrimidines appeared to be possible only based on salts **3**. The use of the corresponding β-diketones **1** necessarily afforded complex mixtures of products.[19]

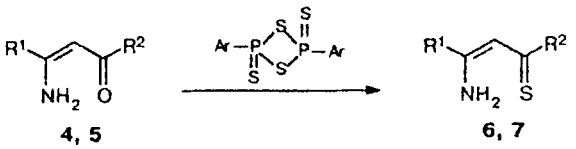
Scheme 14



Synthesis of $\Delta^{3,5}$-2-thioxo-1,2,3-diheteraphosphorines. The reactions of regioisomeric β-aminovinylthiones **6** and **7** with Lawesson's reagent afforded the previously unknown $\Delta^{3,5}$-2-thioxo-1,3,2-thiazaphosphorines (**20a,b**) and $\Delta^{3,5}$-2-thioxo-1,3,2-oxaazaphosphorines (**21**), respectively, in moderate yields. These heterocycles were already formed at the stage of the synthesis of regioisomeric β-aminovinylthiones from the corresponding β-aminovinyl ketones **6** and **7** (Scheme 15).[36]



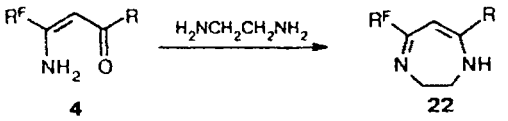
Scheme 15



Synthesis of seven-membered heterocycles

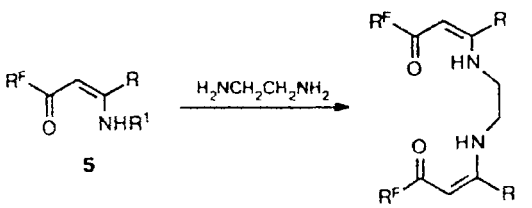
The condensation reactions between ethylenediamine and β-aminovinyl ketones **4** with the *gem* arrangement of the amino group and the fluoroalkyl substituent afforded 2,3-dihydro-1,4-diazepines (**22**), which occurred as a mixture of three tautomeric forms, namely, two enamine forms and one diimine form[37] (Scheme 16).

Scheme 16



Under analogous conditions, regioisomeric β-aminovinyl ketones **5** gave exclusively *N,N'*-ethylenebis(β-aminovinyl ketones)[37] (Scheme 17).

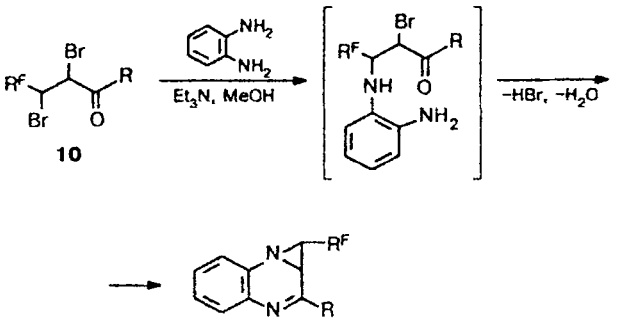
Scheme 17



Synthesis of fused heterocycles

Synthesis of dihydroazirinoquinoxalines. A series of the previously unknown fluoroalkyl-containing dihydroazirinoquinoxalines **23** was obtained in the reactions of dibromocarbonyl compounds **10** with *o*-phenylenediamine[38,39] (Scheme 18).

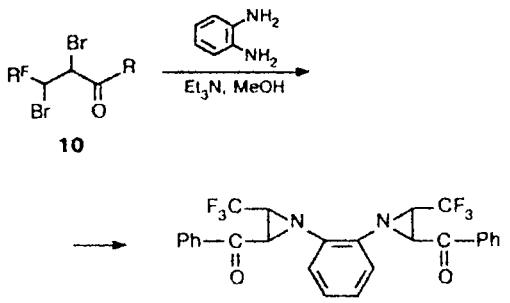
Scheme 18



23 (45–65%)

In the case of $R^F = CF_3$, the reaction proceeded anomalously to form bis(aziridinyl)ketone. Apparently, this is not dictated by steric factors (when $R^F = HCF_2$, dihydroazirinoquinoxaline was formed) but can be explained by the specific electron-withdrawing effect of the CF_3 group due to which dehydrobromination with the formation of the three-membered ring is sharply accelerated compared to dehydration (Scheme 19).

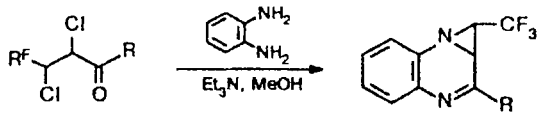
Scheme 19



(68%)

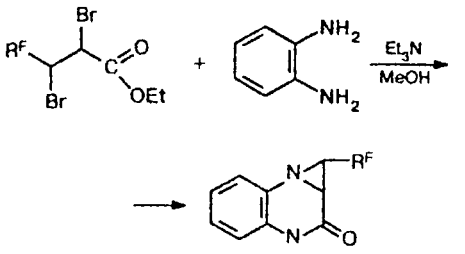
The process can be directed toward the formation of dihydroazirinoquinoxaline **23** when the bromine atom in initial compound **10** is replaced by the chlorine atom, which is a poorer leaving group. We succeeded in preparing 1-trifluoromethyl-2-phenyl-1,1a-dihydroazirino[1,2-*a*]quinoxaline (**23a**) by the reaction of α,β-dichloroketone **10a** with *o*-phenylenediamine (Scheme 20) but the yield of the product was only 13.6%. In this case, bis(aziridinyl)ketone was not formed but a large number of colored products, apparently, acyclic Schiff bases and diazepines, was obtained.

Scheme 20



Under analogous conditions, the reactions of β-fluoroalkyl-α,β-dibromopropionic esters with *o*-phenylenediamines gave the previously unknown 2-oxo-1-polyfluoroalkyl-1,1a,2,3-tetrahydroazirino[1,2-*a*]quinoxalines (**23b**)[39] (Scheme 21).

Scheme 21

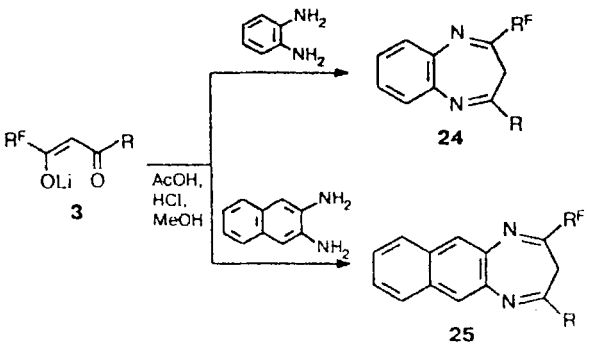


23b

In all derivatives of azirinoquinoxalines, the aziridine ring has a *trans* configuration (J_{H_α,H_β} = 2.3–2.5 Hz). When these compounds are heated or exposed to light, the aziridine ring can be reversibly cleaved at the C—C bond to form intensely colored charged compounds. When irradiated by UV light, azirinoquinoxalines **23** exhibit fluorescence, which changes from blue to yellow-green as the length of the fluoroalkyl substituent increases. Azirinoquinoxalines **23b** do not exhibit fluorescence properties.

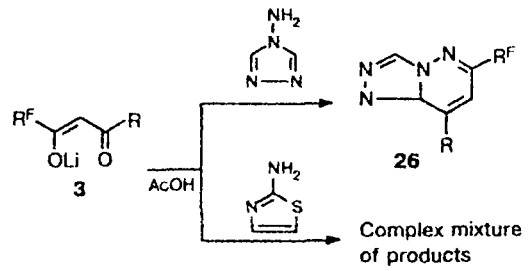
Synthesis of fluorine-containing benzo- and naphthodiazepines. The reactions of salts **3** with *o*-phenylenediamine and *o*-diaminonaphthalene afforded the corresponding 2-difluoromethyl-4-phenyl-3*H*-benzo[*b*]-1,4-diazepines (**24**) and 2-difluoromethyl-4-phenyl-3*H*-naphtho[2,3-*b*]-1,4-diazepines (**25**), respectively[19] (Scheme 22).

Scheme 22



Synthesis of triazolopyridazines. It is known that the reactions of nonfluorinated β-diketones with heterylamines are often accompanied by the disruption of the ring or by recyclization of heterylamine to yield new heterocyclic systems. Our numerous attempts to involve fluorinated β-diketones **1** in the reactions with 4-amino-1,2,4-triazole and 2-aminothiazole have failed. In all cases only complex mixtures of products, which we failed to isolate and identify, were obtained. Apparently, the processes are nonselective because fluorinated β-diketones **1** occur as a mixture of tautomers. We obtained analogous results in the reactions of the corresponding lithium salts **3** with 2-aminothiazole (Scheme 23).

Scheme 23



The use of salts **3** in the reactions with 4-amino-1,2,4-triazole resulted in fluoroalkyl-containing pyridazotriazines **26**, which were virtually unavailable previously.[19]

* * *

To summarize, our studies allowed us to develop efficient procedures for the preparation of fluorine-containing heterocyclic compounds including those previously unavailable. These procedures are characterized by simplicity (as regards both the reagents and equipment), good reproducibility, and rather high yields, which opens up considerable possibilities for studies of chemical properties of compounds synthesized as well as of prospects of their use. The results presented in this review reflect only a small number of synthetic possibilities of the initial "building blocks." We hope that this synthetic potential with time will be unveiled and realized.

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