Reactions of 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrones with hydroxylamine. Synthesis and structures of 5-(1,1-dialkyl-2-hydroxyethyl)-5-hydroxy-3-trifluoromethyl-Δ^2-isoxazolines

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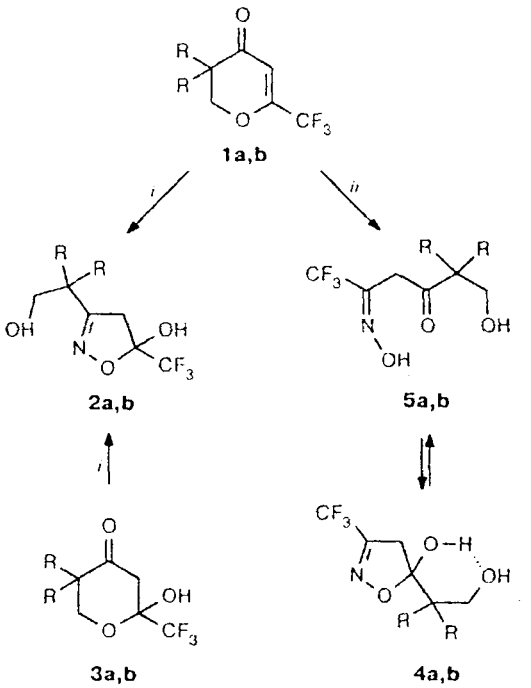
The reactions of 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrones with hydroxylamine hydrochloride afforded regioisomeric 3(5)-(1,1-dialkyl-2-hydroxyethyl)-5-hydroxy-5(3)-trifluoromethyl-Δ^2-isoxazolines depending on the reaction conditions. The title compounds were also prepared from 2,2-dialkyl-5-amino-1-hydroxy-6,6,6-trifluorohex-4-en-3-ones. The above dihydropyrones reacted with hydroxylamine (base) to yield 3-(1,1-dialkyl-2-hydroxyethyl)-5-hydroxyamino-5-trifluoromethyl-Δ^2-isoxazolines.

Key words: CF_3-containing 2,3-dihydro-4-pyrones, hydroxylamine, (hydroxyalkyl)-enaminones, regioisomeric Δ^2-isoxazolines; X-ray diffraction analysis.

The development of new efficient procedures for the synthesis of trifluoromethylated heterocycles is of great interest because many of these compounds exhibit high biological activity. However, procedures for regiospecific synthesis, which allow one to prepare CF_3-containing heterocyclic compounds in good yields, are still few in number.[1]

Recently,[2] we reported the reaction of 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrones (**1a,b**) with hydrazine hydrate, which proceeded simultaneously at two electrophilic centers to form hydrazones of 5,5-dialkyl-2-hydrazino-2-trifluoromethyltetrahydro-4-pyrones. These compounds are stable in storage, but they lose a hydrazine molecule upon heating or in an acidic medium and are converted into the corresponding pyrazoles or azines through dihydropyrone hydrazones **1a,b**.

The aim of the present work is to study the reactions of dihydropyrones **1a,b** with hydroxylamine and to establish the structures of the products obtained. We found that these reactions followed two different pathways depending on the reaction conditions, to yield regioisomeric CF_3-containing Δ^2-isoxazolines. Thus, boiling of compounds **1a,b** with hydroxylamine hydrochloride in aqueous alcohol afforded 5-trifluoromethyl-Δ^2-isoxazolines **2a,b**, which have been prepared previously[3] under analogous conditions from 5,5-dialkyl-2-hydroxy-2-trifluoromethyltetrahydro-4-pyrones (**3a,b**). Treatment of dyhydropyrones **1a,b** with $NH_2OH \cdot HCl$ in the presence of Et_3N



a: R = Me; **b**: R + R = $(CH_2)_5$

i. $NH_2OH \cdot HCl$, EtOH, H_2O, ~80 °C; *ii*. $NH_2OH \cdot HCl$, MeOH, Et_3N, ~20 °C

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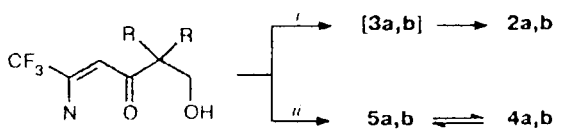
in methanol at room temperature afforded regioisomeric 3-trifluoromethyl-Δ^2-isoxazolines **4a,b** in 48—53% yields.

Since hydration of dihydropyrones **1a,b** to form tetrahydropyrones **3a,b** proceeds even upon storage and is catalyzed by acids,[4] it can be assumed that the formation of compounds **2a,b** from **1a,b** in an acidic medium proceeds through the addition of water at the double bond followed by the attack of hydroxylamine on the carbonyl group of tetrahydropyrones **3a,b** and recyclization of intermediate oximes to isoxazolines **2a,b**. The formation of regioisomeric isoxazolines **4a,b** in a non-aqueous medium in the presence of Et_3N is associated with a change in the direction of the nucleophilic attack. In this case, the hydroxylamine molecule added at the double bond of compounds **1a,b**, which was accompanied by opening of the tetrahydropyrone ring to form monooximes **5a,b**. The latter compounds underwent further cyclization to isoxazolines **4a,b**.

It should be noted that attempts to synthesize two regioisomeric 5-hydroxy-Δ^2-isoxazolines based on unsymmetrical β-diketones were unsuccessful. In all cases, either a mixture or only one of the possible regioisomers were obtained.[5] In this respect, unsymmetrical fluorine-containing β-diketones are no exception. These compounds reacted with hydroxylamine to form, generally, only 5-hydroxy-5-trifluoromethyl-Δ^2-isoxazolines regardless of the reaction conditions.[6,7] The only exception is the 5-trifluoroacetyl derivative of 4-homoadamantanone. Based on the latter compound, regioisomeric 3- and 5-trifluoromethylisoxazolones were synthesized.[8]

Acid hydrolysis of 2,2-dialkyl-5-amino-1-hydroxy-6,6,6-trifluorohex-4-en-3-ones (**6a,b**) followed by dehydration afforded dihydropyrones **1a,b**.[4] We found that the reactions of compounds **6a,b** with hydroxylamine hydrochloride performed under the same conditions also gave regioisomeric isoxazolines **2a,b** and **4a,b**, the latter being obtained in higher yields (70—77%).



6a,b

a: R = Me; *i*. $NH_2OH \cdot HCl$, EtOH, H_2O, ~80 °C;
b: R + R = $(CH_2)_5$ *ii*. $NH_2OH \cdot HCl$, MeOH, Et_3N, ~20 °C

These reactions are the first examples of regiospecific synthesis of 5-hydroxy-Δ^2-isoxazolines in the series of β-aminovinyl ketones, which are aza analogs of the corresponding CF_3-containing β-diketones and synthetic equivalents of trifluoroacetylacetylenes, based on which the regiospecific synthesis of 3- and 5-trifluoromethylisoxazoles was described.[1]

Heating of 5-amino-2,2-dimethyl-6,6,6-trifluorohex-4-en-3-one, which is a compound related to aminoenones **6a,b**, with $NH_2OH \cdot HCl$ in aqueous alcohol afforded 3-*tert*-butyl-5-hydroxy-5-trifluoromethyl-Δ^2-isoxazoline. The latter has been prepared previously from pivaloyltrifluoroacetone under the same conditions.[3] However, we failed to perform transamination at the double bond to obtain regioisomeric 5-*tert*-butyl-5-hydroxy-3-trifluoromethyl-Δ^2-isoxazoline.

Unlike compounds **2a,b**, whose cyclic forms are stable due to the CF_3 group at the hemiketal carbon atom,[9,10] regioisomers **4a,b** in a $CDCl_3$ solution exist in the cyclic form stabilized *via* an intramolecular hydrogen bond between the more acidic hydrogen atom of the hemiketal hydroxyl group and the more basic oxygen atom of the alcohol group. In a DMSO-d_6 solution, compounds **4a,b** exist as mixtures of the open monooxime form **5** and isoxazoline form **4**, which agrees with the results reported in Refs. 5 and 11 and allows one to consider the **4** ⇌ **5** conversion as a new example of ring-chain tautomerism in the 5-hydroxy-Δ^2-isoxazoline series.[12]

In the solid state, the products prepared by the reactions of dihydropyrones **1a,b** or aminoenones **6a,b** with $NH_2OH \cdot HCl$ in the presence of Et_3N exist in the cyclic isoxazoline form **4**. This is evident from the fact that the IR spectra recorded in Nujol mulls do not contain a C=O stretching band but have an absorption band of the azomethine group at 1630 cm^{-1} and two intense bands of the hydroxyl groups in the 3210—3555 cm^{-1} region.

The above conclusion was confirmed by X-ray diffraction analysis of isoxazoline **4a**. It was demonstrated that there are two crystallographically independent molecules per asymmetric unit. These molecules adopt similar conformations, which can be described as envelopes with the C(4) and C(12) atoms deviating from the planes through the remaining four atoms of the ring by 0.24 and 0.30 Å, respectively (Fig. 1).

The corresponding bond lengths and bond angles in both molecules coincide to within the experimental error and have standard values. The F(3)—C(1)—C(2)—N(1), O(1)—C(4)—C(5)—C(8), and C(4)—C(5)—C(8)—O(3) torsion angles differ from the corresponding angles in the second molecule by no more than 2°.

An interesting feature of the crystal packing is the formation (in addition to an intramolecular hydrogen

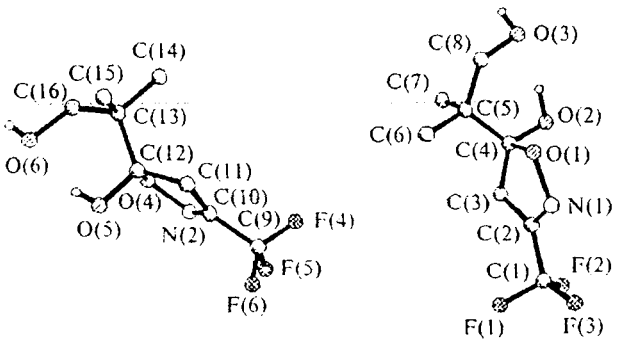


Fig. 1. Overall view of the molecules of compound **4a**. The H atoms of the CH_2 and CH_3 groups are omitted.

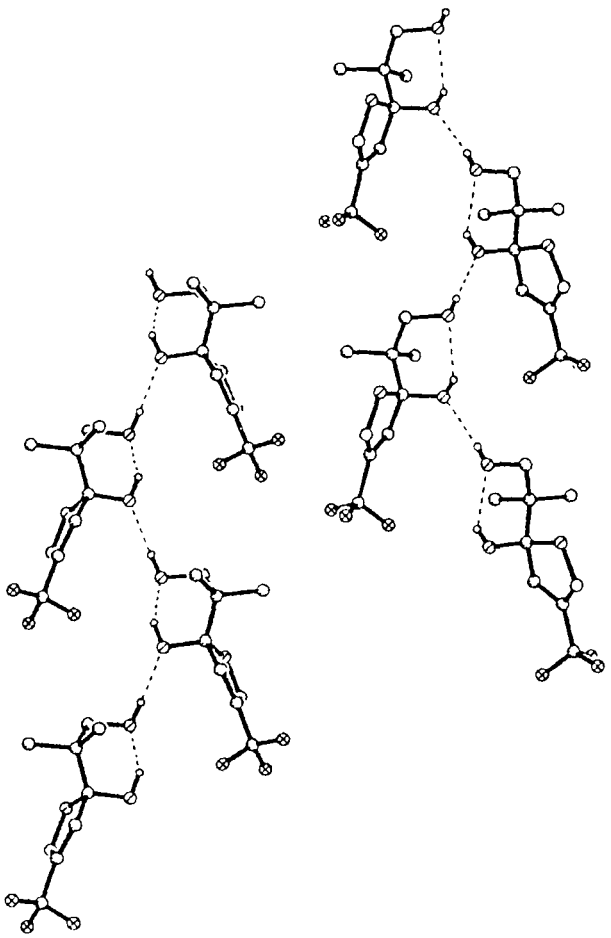


Fig. 2. Molecular packing in the crystal structure of **4a**.

bond between the hemiketal hydrogen atom and the alcoholic oxygen atom) of chains of weak O(3)...H(2′)—O(2)...H(3′A)—O(3A) and O(6)... H(5′)—O(5)...H(6′B)—O(6B) intermolecular hydrogen bonds between the alcohol hydrogen atoms and the oxygen atoms of the hemiketal hydroxyl groups. The O...H—O angles are close to 180°. The O(2)...O(3), O(3)...O(2A), O(6)...O(5), and O(5)...O(6B) distances are 2.619, 2.799, 2.619, and 2.779 Å, respectively. The O...H distances in the chains vary in the range of 1.78—2.10 Å (Fig. 2).

Based on the ^{1}H and ^{19}F NMR spectral data, it was established that the **4a** : **5a** and **4b** : **5b** ratios in a DMSO-d_6 solution are approximately 60 : 40 and 10 : 90, respectively. We believe that, unlike nonfluorinated analogs, for example, 5-*tert*-butyl-5-hydroxy-3-methyl-Δ^2-isoxazoline, which exists only in the cyclic form in solutions both in $CDCl_3$ and pyridine-d_5,[5,11] the stability of 5-hydroxy-3-trifluoromethyl-Δ^2-isoxazolines **4a,b** is substantially affected by intramolecular hydrogen bonds because the CF_3 group at the imine carbon atom decreases the nucleophilicity of the oxygen atom of the oxime group and hinders the transformation of open forms **5a,b** to the cyclic forms, while an intramolecular hydrogen bond that exists in compounds **4a,b** promotes this process. Apparently, the formation of open tautomers **5a,b** in a DMSO solution is associated with the cleavage of the intramolecular hydrogen bonds in cyclic tautomers **4a,b** under the action of this solvent, which forms with OH groups rather stable associates through intermolecular hydrogen bonds. Moreover, monooximes **5a,b** are more efficiently solvated by polar dimethyl sulfoxide molecules. This phenomenon is most pronounced in the case of isoxazoline **4b**, in which the presence of the spirocyclohexane fragment hinders the formation of associates with the cyclic form and leads to almost complete opening of isoxazoline **4b** to form monooxime **5b**. In this case, the proton exchange slows down, which makes it possible to observe the spin-spin coupling in the CH_2OH group.

The ^{1}H NMR spectrum of isoxazoline **4a** recorded in $CDCl_3$ has an ABX_3 system (with the center at δ 3.04, J_{AB} = 18.3 Hz, $^4J_{HA,F}$ = 1.6 Hz, and $^4J_{HB,F}$ = 1.4 Hz) formed by the protons of the CH_2 group of the isoxazoline ring and the fluorine atoms of the trifluoromethyl substituent. This is indicative of the symmetrical arrangement of the CF_3 group with respect to the hydrogen atom at position 4 of the ring. This arrangement can be realized if the CF_3 group is attached to an unsaturated carbon atom and the inequality of the spin-spin coupling constants (J are 1.6 and 1.4 Hz for the low-field and high-field portions, respectively) is associated with the nonplanar conformation of the ring. It should be noted that in the spectrum of isomer **2a**, only the high-field doublet of the AB system of the cyclic CH_2 group is split into a quartet with $^4J_{H,F}$ = 1.3 Hz; this doublet belongs to the proton in the *cis* position with respect to the CF_3 group (the proton in the *cis* position with respect to the hydroxyl group is deshielded to a greater extent[5]). The signals of the methyl groups of compound **4a** appear as singlets at δ 0.86 and 1.20 (in isomer **2a**, as singlets at δ 1.19 and 1.22) and the protons of the CH_2OH group give two doublets of an AX system (J_{AX} = 10.2 Hz) at δ 3.50 and 4.18 (in isomer **2a**, a singlet at δ 3.62). Isomers **2a** and **4a** can also be readily distinguished by the chemical shift of the signal of the CF_3 group. In the spectra of compounds **2a** and **4a**, this signal is observed at δ 79.15 and 95.22, respectively.

The diastereotopism of the methylene protons and the methyl groups of the alkyl substituent in isoxazoline **4a** is associated with the presence of the adjacent asymmetrical carbon atom. The substantial differences in their chemical shifts are due to the formation of the six-membered ring through a rather strong intramolecular hydrogen bond between the oxygen atom of the alcohol group (a broadened singlet at δ 2.39) and the hydrogen atom of the hemiketal hydroxyl group (a broadened singlet at δ 6.18). As a result of the cleavage of the intramolecular hydrogen bond under the action of DMSO-d_6 molecules, the singlets of the CH_3 groups approach each other (δ 0.90 and 0.93) and the protons

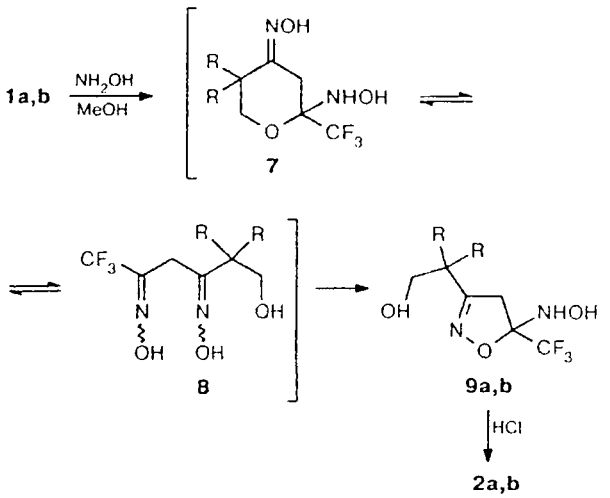
of the CH_2OH groups give an AB system (J_{AB} = 10.5 Hz; δ H_A and H_B are 3.45 and 3.27, respectively) rather than an AX spectrum, each signal of the AB system being split into a doublet due to spin-spin coupling with the hydroxyl proton, which gives a triplet at δ 4.87 (J = 5.2 Hz). In the spectrum in a DMSO-d_6 solution, the doublet (J_{AX} = 18.9 Hz) of the proton of the cyclic CH_2 group, which is in the *cis* position with respect to the hemiketal hydroxyl group, is shifted downfield by 0.42 ppm (observed at δ 3.60 instead of 3.18 in $CDCl_3$). An analogous situation has been observed previously on going from chloroform to a more polar solvent that forms an intermolecular hydrogen bond with the hydroxyl group.[5] The chemical shift of the proton in the *cis* position with respect to the alkyl group changes only slightly (a doublet at δ 2.81 instead of 2.90 in $CDCl_3$) and the hemiketal hydroxyl group gives a low-field singlet at δ 7.27.

As mentioned above, 40% of isoxazoline **4a** in a DMSO-d_6 solution opened to give monooxime form **5a**. The ^{1}H NMR spectrum of **5a** has a singlet of two equivalent methyl groups at δ 1.05, a doublet of the methylene protons (at δ 3.49, J = 5.0 Hz), and a triplet of the hydroxyl group (at δ 4.93) of the CH_2OH group as well as singlets of the CH_2 group and the oxime hydroxyl group at δ 3.81 and 12.42, respectively. The addition of CD_3CO_2D led to the disappearance of the signals of the hydroxyl protons, while the percentage composition of the mixture of compounds **4a** and **5a** remained virtually unchanged.

Unlike 5-aryl-5-hydroxy-Δ^2-isoxazolines, which exist in deuterochloroform or pyridine-d_5 solutions as mixtures of *Z*/*E* isomers of the corresponding monooximes and the cyclic form,[5,11] isoxazolines **4a,b** (judging from the presence of one set of signals of the linear form) undergo stereospecific opening to monooximes **5a,b**. Based on a comparison of the chemical shifts of the CH_2 groups of monooximes **5a,b** and nonfluorinated monooximes and taking into account that compounds containing an intramolecular hydrogen bond between the oxime hydroxyl group and the carbonyl group are more stable,[11] preference was given to the *E* form of compounds **5a,b**. However, the available data do not allow definite conclusions about the configuration of the C=N bond in the compounds under consideration.

The reactions of dihydropyrones **1a,b** with an excess of free base NH_2OH in methanol at room temperature (procedure proposed by Wislicenus[13]) followed the third pathway to yield substituted 5-hydroxyamino-5-trifluoromethyl-Δ^2-isoxazolines **9a,b**.

In this case, due to the high concentration of free NH_2OH molecules, the reaction proceeded analogously to the reaction with hydrazine hydrate[2] with attack on the double bond and the carbonyl carbon atom but it was not terminated in the stage of formation of oximes **7**. The latter, apparently, immediately underwent recyclization to thermodynamically more stable isoxazolines **9a,b** through the open dioxime form **8**. Functionalized



a: R = Me; **b**: R + R = $(CH_2)_5$

isoxazolines were synthesized according to this procedure for the first time. These compounds owe their existence to the presence of the electron-withdrawing trifluoromethyl group at the C(5) atom, which is able to stabilize not only hemiacetals but also hemiaminals.[14] When heated in an aqueous-alcoholic solution in the presence of catalytic amounts of hydrochloric acid, 5-hydroxyamino-Δ^2-isoxazolines **9a,b** were converted into 5-hydroxy-Δ^2-isoxazolines **2a,b**, and, consequently, the possibility of formation of these compounds as intermediates in the course of conversions of dihydropyrones **1a,b** into compounds **2a,b** under the action of $NH_2OH \cdot HCl$ in aqueous alcohol must not be ruled out.

An interesting feature of the ^{1}H NMR spectra of compounds **9a,b** is the fact that the signals of the low-field portion of the AB system of the cyclic CH_2 group are each split into quartets with $^4J_{H,F}$ = 1.3 Hz. As mentioned above, in the NMR spectra of isoxazolines **2a,b** (which differ from compounds **9a,b** by the presence of the hydroxyl group instead of the NHOH group), the high-field doublet, which was assigned to the hydrogen atom in the *cis* position with respect to the CF_3 group, is split into a quartet with $^4J_{H,F}$ = 1.4 Hz. According to our data,[15] in the NMR spectra of isoxazolines containing the CF_3 or NH_2 group at the C(5) atom, the high-field doublet of the AB system is also split into a quartet. The replacement of the hydroxyl group by the amino group has virtually no effect on the chemical shift of the proton in the *cis* position with respect to these groups (at δ 3.36 and 3.33 for isoxazoline **2a** and its amino analog, respectively). Based on these data, it can be concluded that the *cis*-proton (with respect to the CF_3 group) in compounds **9a,b** is sterically close to the hydroxyl group of the NHOH fragment, which causes an additional downfield shift due to the electrostatic deshielding effect,[16] as a result of which the paramagnetic shift of this proton is larger than that of the proton in the *cis* position with respect to the nitrogen atom of the NHOH

fragment. The IR spectra of compounds **9a,b** have a broad nonresolved absorption band of the NH and OH groups at 3300 cm^{-1} and a band of the azomethine group at 1630 cm^{-1}.

To summarize, the reactions of dihydropyrones **1a,b** and aminoenones **6a,b** with hydroxylamine hydrochloride described in the present work allow one to synthesize regioisomeric 3- and 5-trifluoromethyl-Δ^2-isoxazolines. The reactions of dihydropyrones **1a,b** with the base NH_2OH afforded the previously unknown Δ^2-isoxazolines containing the NHOH group at position 5 of the ring.

Experimental

The ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ and DMSO-d_6 operating at 250 MHz with Me_4Si as the internal standard. The ^{19}F NMR spectra were recorded on a Tesla BS-587A instrument operating at 75.3 MHz with C_6F_6 as the internal standard.

The X-ray diffraction data for compound **4a** were collected on a Siemens P3/PC diffractometer (λMo-Kα radiation, θ/2θ scanning technique, $2\theta_{max} = 50°$, 3525 measured reflections). Colorless crystals of **4a** are monoclinic, at 293 K, $a = 10.539(6)$, $b = 20.299(13)$, $c = 9.739(6)$ Å, $\beta = 90.05(5)°$, $V = 2084(2)$ Å^3, $d_{calc} = 1.449$ g cm^{-3}, $Z = 8$ ($C_8H_{12}NO_3F_3$), space group $P2_1/c$ (two crystallographically independent molecules per symmetric unit). The structure was solved by the direct method and refined by the least-squares method based on F^2 with anisotropic thermal parameters for nonhydrogen atoms (287 refinable parameters). The positions of the H(2'), H(3'), H(5'), and H(6') atoms were located from difference electron density syntheses and refined anisotropically. The remaining H atoms were placed in calculated positions and included in the refinement using the riding model with fixed C—H distances and thermal parameters $U = 1.5U_C$ and $1.2U_C$ (U_C is the equivalent isotropic thermal parameter of the corresponding C atom) for the methyl groups and for the remaining fragments, respectively. The absorption coefficient $\mu = 1.42$ cm^{-1}. The final values of the R factors were as follows: $R_1 = 0.084$, $wR_2 = 0.134$, GOOF = 1.112 based on 1781 reflections with $I > 2\theta(I)$. All calculations were carried out on an IBM PC/AT computer with the use of the SHELXTL program packages (versions 4.0[17] and 5.0[18]). The atomic coordinates are given in Table 1. The bond lengths and bond angles are listed in Tables 2 and 3, respectively.

Compounds **2a,b** have been described previously.[3]

5-Hydroxy-3-(2-hydroxy-1,1-dimethylethyl)-5-trifluoromethyl-Δ^2-isoxazoline (2a). ^1H NMR ($CDCl_3$), δ: 1.19 (s, 3 H, Me); 1.22 (s, 3 H, Me); 2.95 (br.s, 1 H, CH_2—OH); 3.13 (dq, 1 H, CHH, $J_{AB} = 18.3$ Hz, $^4J_{H,F} = 1.3$ Hz); 3.36 (dq, 1 H, CHH, $J_{AB} = 18.3$ Hz); 3.62 (s, 2 H, CH_2—OH); 5.04 (br.s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: 79.15 (s, CF_3).

5-Hydroxy-5-(2-hydroxy-1,1-dimethylethyl)-3-trifluoromethyl-Δ^2-isoxazoline (4a). A solution (4 mL) prepared from $NH_2OH \cdot HCl$ (1.20 g, 17.3 mmol), triethylamine (0.8 mL, 0.58 r, 5.7 mmol), and ethanol (20 mL) was added to dihydropyrone **1a** (0.45 g, 2.3 mmol). The reaction mixture was allowed to stand at ~20 °C for three days. Then the solvent was evaporated and the crystalline precipitate that formed was treated with water. Undissolved crystals of compound **4a** were filtered off, dried, and recrystallized from ethanol. The yield was 53%, m.p. 73—74 °C. Isoxazoline **4a** was also prepared from aminoenone **6a** under analogous conditions in 70% yield. Found (%): C, 42.32; H, 5.60; N, 6.28. $C_8H_{12}F_3NO_3$. Calculated (%): C, 42.30; H, 5.32; N, 6.17. ^1H NMR ($CDCl_3$), δ: 0.86 (s, 3 H, Me); 1.20 (s, 3 H, Me); 2.39 (br.s, 1 H, CH_2—OH); 2.90 (dq, 1 H, CHH, $J_{AB} = 18.3$ Hz, $^4J_{H,F} = 1.4$ Hz); 3.18 (dq, 1 H, CHH, $J_{AB} = 18.3$ Hz, $^4J_{H,F} = 1.6$ Hz); 3.50 (d, 1 H, CHH—OH, $J_{AX} = 10.2$ Hz); 4.18 (d, 1 H, CHH—OH, $J_{AX} = 10.2$ Hz); 6.18 (br.s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: 95.22 (s, CF_3) ^1H NMR (DMSO-d_6), δ, for **4a** (60%): 0.90 (s,

Table 1. Atomic coordinates (×10^4) and equivalent isotropic thermal parameter U_{eq} (×10^3/Å^2) in the structure of **4a**

Atom	x	y	z	U_{eq}
F(1)	7685(6)	4608(2)	5927(6)	103(3)
F(2)	8059(6)	3663(2)	6676(5)	104(3)
F(3)	9536(8)	4391(4)	6725(7)	103(4)
O(1)	10182(7)	3780(3)	2844(7)	75(3)
O(2)	9295(8)	2766(3)	2623(6)	91(4)
O(3)	10173(10)	2757(3)	107(7)	84(4)
N(1)	10092(9)	4025(3)	4229(10)	67(5)
C(1)	8604(12)	4160(6)	6006(11)	67(6)
C(2)	8921(11)	3920(4)	4567(11)	56(6)
C(3)	8096(11)	3640(4)	3557(10)	64(5)
C(4)	9025(12)	3434(4)	2459(11)	72(6)
C(5)	8754(9)	3620(4)	987(9)	38(4)
C(6)	8576(11)	4362(4)	855(10)	105(7)
C(7)	7552(10)	3261(5)	510(12)	94(5)
C(8)	9875(9)	3440(4)	70(9)	72(5)
F(4)	7300(7)	5428(3)	−1584(7)	131(4)
F(5)	5411(7)	5547(4)	−977(7)	160(4)
F(6)	6630(9)	6312(3)	−903(6)	137(5)
O(4)	4818(8)	6109(3)	−4904(7)	73(4)
O(5)	5495(9)	7178(3)	−4923(6)	82(3)
O(6)	4751(9)	7233(3)	−7476(6)	82(3)
N(2)	4926(11)	5876(4)	−3514(15)	90(6)
C(9)	6377(14)	5808(5)	−1605(13)	99(7)
C(10)	5973(13)	5998(5)	−3112(17)	64(6)
C(11)	6861(9)	6352(4)	−4026(9)	39(4)
C(12)	5930(10)	6542(4)	−5134(10)	49(4)
C(13)	6315(11)	6425(4)	−6647(10)	55(5)
C(14)	6732(11)	5709(4)	−6856(10)	97(6)
C(15)	7469(8)	6877(4)	−6933(9)	74(4)
C(16)	5257(12)	6578(5)	−7577(10)	72(5)
H(2')	9480(80)	2620(30)	1760(90)	80(20)
H(3')	9900(100)	2590(40)	−630(80)	60(30)
H(5')	5500(100)	7350(50)	−5500(100)	90(40)
H(6')	4800(100)	7370(50)	−8100(100)	100(40)

Table 2. Bond lengths (d) in compound **4a**

Bond	d/Å	Bond	d/Å
F(1)—C(1)	1.331(14)	F(4)—C(9)	1.242(14)
F(2)—C(1)	1.332(11)	F(5)—C(9)	1.301(10)
F(3)—C(1)	1.294(13)	F(6)—C(9)	1.259(13)
O(1)—N(1)	1.440(13)	O(4)—N(2)	1.44(2)
O(1)—C(4)	1.46(2)	O(4)—C(12)	1.482(11)
O(2)—C(4)	1.394(9)	O(5)—C(12)	1.385(8)
O(3)—C(8)	1.423(9)	O(6)—C(16)	1.436(11)
N(1)—C(2)	1.294(12)	N(2)—C(10)	1.20(2)
C(1)—C(2)	1.522(13)	C(9)—C(10)	1.58(3)
C(2)—C(3)	1.43(2)	C(10)—C(11)	1.479(12)
C(3)—C(4)	1.511(9)	C(11)—C(12)	1.508(14)
C(4)—C(5)	1.51(2)	C(12)—C(13)	1.547(11)
C(5)—C(6)	1.522(10)	C(13)—C(16)	1.469(14)
C(5)—C(8)	1.526(8)	C(13)—C(14)	1.532(10)
C(5)—C(7)	1.53(2)	C(13)—C(15)	1.550(12)

Table 3. Bond angles (ω) in compound **4a**

Angle	ω/deg	Angle	ω/deg
N(1)—O(1)—C(4)	110.6(6)	N(2)—O(4)—C(12)	106.0(11)
C(2)—N(1)—O(1)	104.2(11)	C(10)—N(2)—O(4)	108.2(9)
F(3)—C(1)—F(2)	109.7(11)	F(4)—C(9)—F(6)	109(2)
F(3)—C(1)—F(1)	109.6(10)	F(4)—C(9)—F(5)	110.7(9)
F(2)—C(1)—F(1)	103.4(7)	F(6)—C(9)—F(5)	103.9(7)
F(3)—C(1)—C(2)	116.6(8)	F(4)—C(9)—C(10)	112.2(8)
F(2)—C(1)—C(2)	107.7(9)	F(6)—C(9)—C(10)	111.3(8)
F(1)—C(1)—C(2)	109.0(11)	F(5)—C(9)—C(10)	109.1(13)
N(1)—C(2)—C(3)	118.0(8)	N(2)—C(10)—C(11)	119(2)
N(1)—C(2)—C(1)	113.1(12)	N(2)—C(10)—C(9)	120.2(12)
C(3)—C(2)—C(1)	128.8(9)	C(11)—C(10)—C(9)	120.6(14)
C(2)—C(3)—C(4)	101.7(9)	C(10)—C(11)—C(12)	98.2(10)
O(2)—C(4)—O(1)	105.7(10)	O(5)—C(12)—O(4)	105.6(7)
O(2)—C(4)—C(5)	113.1(8)	O(5)—C(12)—C(13)	111.8(7)
O(1)—C(4)—C(5)	106.3(7)	O(4)—C(12)—C(13)	105.1(9)
O(2)—C(4)—C(3)	108.7(6)	O(5)—C(12)—C(11)	110.3(9)
O(1)—C(4)—C(3)	103.1(9)	O(4)—C(12)—C(11)	104.7(6)
C(5)—C(4)—C(3)	118.7(10)	C(13)—C(12)—C(11)	118.1(8)
C(4)—C(5)—C(6)	110.6(8)	C(12)—C(13)—C(14)	110.4(7)
C(4)—C(5)—C(8)	110.4(9)	C(12)—C(13)—C(16)	110.8(7)
C(6)—C(5)—C(8)	106.4(6)	C(14)—C(13)—C(16)	109.7(10)
C(4)—C(5)—C(7)	108.9(8)	C(12)—C(13)—C(15)	106.6(9)
C(6)—C(5)—C(7)	110.0(10)	C(14)—C(13)—C(15)	108.2(7)
C(8)—C(5)—C(7)	110.4(7)	C(16)—C(13)—C(15)	111.0(7)
O(3)—C(8)—C(5)	112.9(6)	O(6)—C(16)—C(13)	115.9(10)

3 H, Me); 0.93 (s, 3 H, Me); 2.81 (d, 1 H, CHH, J_{AX} = 18.9 Hz); 3.27 (dd, 1 H, CHH—OH, J_{AB} = 10.5 Hz, J = 5.2 Hz); 3.45 (dd, 1 H, CHH—OH, J_{AB} = 10.5 Hz, J = 5.2 Hz); 3.60 (d, 1 H, CHH, J_{AX} = 18.9 Hz); 4.87 (t, 1 H, CH_2—OH, J = 5.2 Hz); 7.27 (s, 1 H, OH); for **5a** (40%): 1.05 (s, 6 H, 2 Me); 3.49 (d, 2 H, CH_2—OH, J = 5.0 Hz); 3.81 (s, 2 H, CH_2); 4.93 (t, 1 H, OH, J = 5.0 Hz); 12.42 (s, 1 H, N—OH). ^{19}F NMR (DMSO-d_6), δ, for **4a** (61%): 97.36 (s, CF_3); for **5a** (39%): 94.82 (s, CF_3). IR, ν/cm^{-1}: 3425, 3210 (OH); 1630 (C=N).

5-Hydroxy-5-(2-hydroxy-1,1-pentamethyleneethyl)-3-trifluoromethyl-Δ^2-isoxazoline (4b) was prepared analogously to compound **4a** from dihydropyrone **1b** and aminoenone **6b** in 48 and 77% yields, respectively, m. p. 96—97 °C (ethanol). Found (%): C, 49.46; H, 5.99; N, 5.18. $C_{11}H_{16}F_3NO_3$. Calculated (%): C, 49.44; H, 6.03; N, 5.24. ^{1}H NMR ($CDCl_3$), δ: 1.1—2.1 (m, 10 H, $(CH_2)_5$); 2.16 (s, 1 H, CH_2—OH); 2.87 (d, 1 H, CHH, J_{AB} = 18.3 Hz); 3.30 (d, 1 H, CHH, J_{AB} = 18.3 Hz); 4.11 (s, 2 H, CH_2—OH); 6.23 (s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: 95.31 (s, CF_3). ^{1}H NMR (DMSO-d_6), δ, for **5b**: (93—95%): 1.2—1.9 (m, 10 H, $(CH_2)_5$); 3.49 (d, 2 H, CH_2—OH, J = 5.2 Hz); 3.81 (s, 2 H, CH_2); 4.90 (t, 1 H, OH, J = 5.2 Hz); 12.40 (s, 1 H, N—OH). ^{19}F NMR ($CDCl_3$+DMSO-d_6, 1:1), δ, for **4b** (59%): 95.63 (s, CF_3); for **5b** (41%): 92.97 (s, CF_3). ^{19}F NMR (DMSO-d_6), δ, for **4b** (13%): 97.35 (t, CF_3, J = 1.37 Hz); for **5b** (87%): 94.88 (s, CF_3). IR, ν/cm^{-1}: 3555, 3240 (OH); 1630 (C=N).

5-Hydroxyamino-3-(2-hydroxy-1,1-dimethylethyl)-5-trifluoromethyl-Δ^2-isoxazoline (9a). A solution (4.5 mL) prepared from hydroxylamine hydrochloride (1.2 g), KOH (1.4 g), and methanol (18 mL) was added to dihydropyrone **1a** (0.45 g, 2.3 mmol). The reaction mixture was allowed to stand at ~20 °C for two days and then the solvent was evaporated. After treatment with water and recrystallization from aqueous alcohol, crystals of compound **9a** were isolated in 63% yield, m.p. 140—141 °C. Found (%): C, 39.76; H, 5.51; N, 11.63. $C_8H_{13}F_3N_2O_3$. Calculated (%): C, 39.67; H, 5.41; N, 11.57. ^{1}H NMR ($CDCl_3$), δ: 1.20 (s, 3 H, Me); 1.21 (s, 3 H, Me); 2.19 (br.s, 1 H, CH_2—OH); 3.26 (d, 1 H, CHH, J_{AB} = 18.1 Hz); 3.40 (dq, 1 H, CHH, J_{AB} = 18.1 Hz, $^4J_{H,F}$ = 1.3 Hz); 3.60 (s, 2 H, CH_2—OH); 4.92 (s, 1 H, NH); 5.72 (br.s, 1 H, OH). IR, ν/cm^{-1}: 3300 (br, NH, OH); 1630 (C=N).

5-Hydroxyamino-3-(2-hydroxy-1,1-pentamethyleneethyl)-5-trifluoromethyl-Δ^2-isoxazoline (9b) was prepared analogously to compound **9a** from dihydropyrone **1b** in a 74% yield, m.p. 109—110 °C. Found (%): C, 46.88; H, 6.25; N, 10.04. $C_{11}H_{17}F_3N_2O_3$. Calculated (%): C, 46.81; H, 6.07; N, 9.92. ^{1}H NMR ($CDCl_3$), δ: 1.2—2.1 (m, 10 H, $(CH_2)_5$); 2.46 (br.s, 1 H, CH_2—OH); 3.25 (d, 1 H, CHH, J_{AB} = 18.1 Hz); 3.43 (dq, 1 H, CHH, J_{AB} = 18.1 Hz, $^4J_{H,F}$ = 1.0 Hz); 3.59 (s, 2 H, CH_2—OH); 5.84 (s, 1 H, NH); 5.91 (s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: 82.45 (s, CF_3). IR, ν/cm^{-1}: 3430, 3345, 3295, 3155 (NH, OH); 1625 (C=N).

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