Reactions of regioisomeric 3,3-dimethyl- and 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with N-nucleophiles

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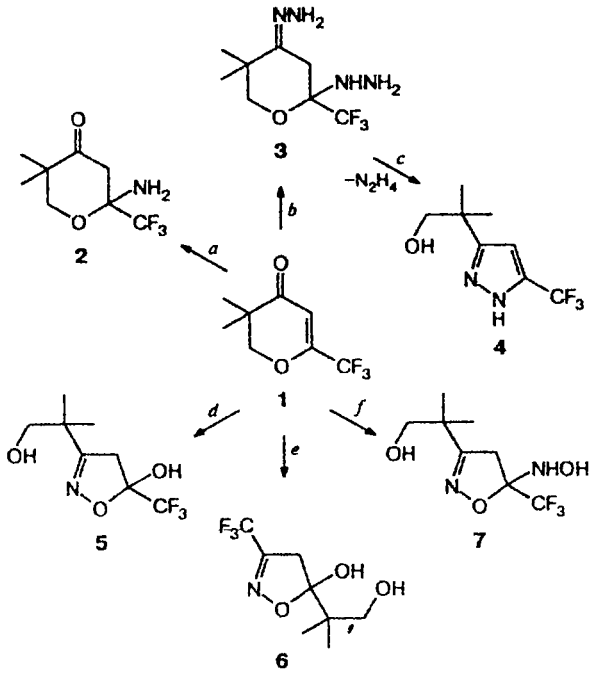
Reactions of 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone with ethylenediamine, hydrazine, or hydroxylamine yield 5-methyl-7-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepine, 3(5)-(2-hydroxy-2-methylpropyl)-5(3)-trifluoromethylpyrazole, and 5-hydroxy-3-(2-hydroxy-2-methylpropyl)-5-trifluoromethyl-Δ^2-isoxazoline, respectively. The same compounds were obtained from 2-amino-1,1,1-trifluoro-6-hydroxy-6-methylhept-2(*Z*)-en-4-one and 2-hydroxy-6,6-dimethyl-2-trifluoromethyltetrahydro-4-pyrone.

Key words: substituted 2,3-dihydro-4-pyrones, substituted tetrahydro-4-pyrones, CF_3-containing aminoenones, pyrazoles, Δ^2-isoxazolines.

Recently,[1–3] we have described the reactions of 3,3-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone (**1**) with ammonia, hydrazine hydrate, and hydroxylamine (Scheme 1), which yield 2-aminotetrahydropyrone **2**, hydrazone **3** (when heated, the latter undergoes recyclization into pyrazole **4** with elimination of the hydrazine molecule), and regioisomeric 5-hydroxy-Δ^2-isoxazolines **5**, **6** and 5-hydroxyamino-Δ^2-isoxazoline **7**.

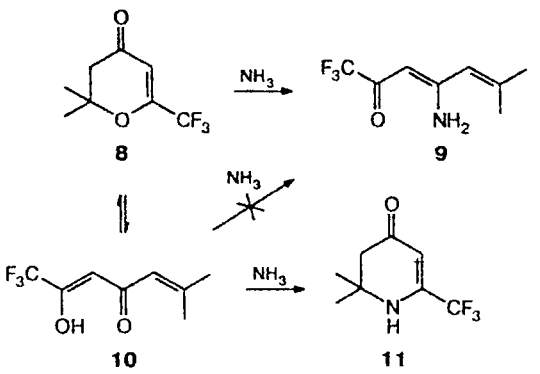
Scheme 1



Reagents and conditions : *a*. NH_3; *b*. N_2H_4; *c*. Δ; *d*. $NH_2OH \cdot HCl$, EtOH, H_2O, Δ; *e*. $NH_2OH \cdot HCl$, Et_3N, MeOH; *f*. $NH_2OH \cdot HCl$, KOH, MeOH.

It was of interest to compare the behavior of dihydropyrone **1** with that of isomeric 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone (**8**) in reactions with N-nucleophiles. In the preliminary communication,[4] it was shown that dihydropyrone **8**, which can be easily obtained by condensation of mesityl oxide with ethyl trifluoroacetate, undergoes ring opening under the action of an aqueous solution of ammonia to give 4-amino-1,1,1-trifluoro-6-methylhepta-3,5-dien-2-one (**9**) (Scheme 2). Similar transformation of dihydropyrone **8** in the reaction with methylamine was also described.[5]

Scheme 2



At first glance, the formation of aminodienone **9** can be explained by ring opening of dihydropyrone **8** into β-diketone **10**, which further reacts with NH_3 at the

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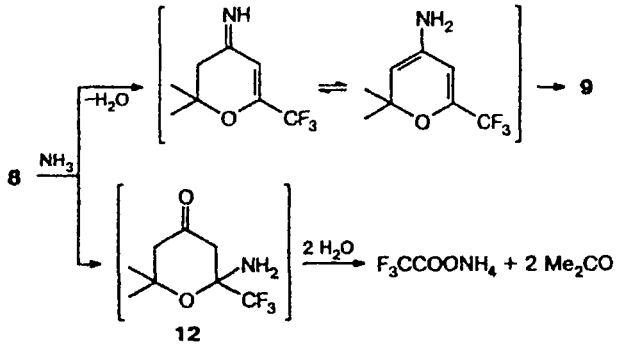
keto group remote from the trifluoromethyl substituent (such a site of attack in the reaction of unsymmetrical fluorine-containing β-diketones with ammonia or amines has long been established[6]). However, this explanation has little force here because it has been previously reported[4] that diketone **10** reacts under similar conditions with NH_3 to give 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyridone (**11**) (see Scheme 2). That is why the following mechanism seems to be more probable. An ammonia molecule attacks the carbonyl group of dihydropyrone **8** to give an imine that is in tautomeric equilibrium with an amino derivative of 2*H*-pyran, which further undergoes valence isomerization[7] with the formation of acyclic aminodienone **9** (Scheme 3).

Scheme 3

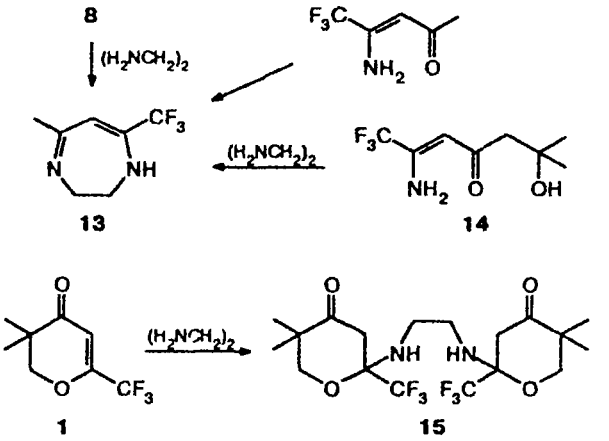


A low yield (46%) of aminodienone **9** is due to an alternative attack at the CF_3-bonded carbon atom resulting in the formation of unstable tetrahydropyrone **12**, which undergoes scission *in situ* to give $F_3CCOONH_4$ and acetone (see Scheme 3).

Apparently, compounds **1** and **8** react with ammonia so differently because of the different characters of substitution in the dihydropyrone system, *viz.*, dislocation of *gem*-dimethyl group from the C(3) atom to C(2) increases the mobility of hydrogen atoms in dihydropyrone **8** and hence allows them to participate in the ring opening. This dislocation is also responsible for the stability of addition products **2** and **12**. The latter is less stable because its decomposition is accompanied by elimination of acetone.

The present work is devoted to the study of reactions of dihydropyrone **8** with ethylenediamine, hydrazine hydrate, and hydroxylamine hydrochloride. We found that the reaction of **8** with ethylenediamine at room temperature yields 5-methyl-7-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepine (**13**), obtained earlier from products of condensation of trifluoroacetonitrile with acetone[8] or diacetone alcohol (**14**).[9] The reaction involves both reaction centers of dihydropyrone **8** and, as in the case of aminoenone **14**, is accompanied by elimination of acetone (Scheme 4).

Scheme 4



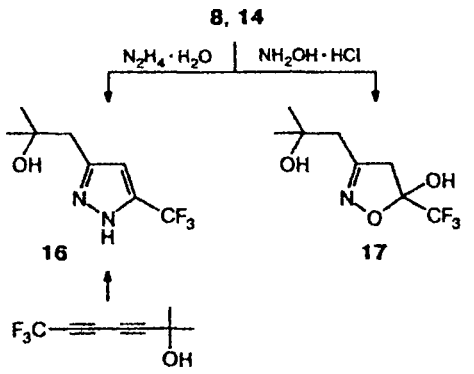
It is interesting to note that the reaction of dihydropyrone **1** with ethylenediamine at room temperature yields *N,N'*-ethylenebis(2-amino-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyrone) (**15**, see Scheme 4). This is additional evidence that the products of addition of amines at the double bond of compound **1** are more stable than similar adducts obtained from isomeric dihydropyrone **8**. Bistetrahydropyrone **15** is formed as a 1 : 1 mixture of two diastereomers (^{1}H NMR). The spectrum of this compound exhibits two singlets at δ 1.02 and 1.29 (each 6 H) corresponding to the equatorial and axial Me groups; a broadened singlet for the protons of two NH groups at δ 1.72; a triplet at δ 2.24 (2 H) formed by superposition of two doublets (with J_{AX} = 15.0 Hz) from the C(3)H_2 equatorial protons belonging to different diastereomers; a narrow multiplet of the ethylene bridge at δ 2.77; two doublets at δ 2.98 and 2.99 for the C(3)H_2* axial protons of two diastereomers; and also two AB systems with centers at δ 3.70 and 3.72 and J_{AB} = 11.3 Hz corresponding to the protons of the C(6)H_2 groups of two diastereomers.

Dihydropyrone **8** reacts with hydrazine hydrate in boiling ethanol to give 3(5)-(2-hydroxy-2-methylpropyl)-

* Assignment of the protons of the C(3)H_2 group was based on our unpublished data on such compounds as 2-hydroxy-2-trifluoromethyl-5,5-dimethyltetrahydro-4-pyrone and 2-amino-2-trichloromethyl-5,5-dimethyltetrahydro-4-pyrone, which are related to bistetrahydropyrone **15**. In their ^{1}H NMR spectra, it is the low-field doublet of the AX system of the C(3)H_2 protons that is split into a doublet of doublets and a doublet of triplets with J_{AX} ≈ 15.0 Hz and ^4J = 1.8 and 1.6 Hz, respectively, which is due to a long-range spin-spin coupling of the proton corresponding to the low-field signal with the OH and NH_2 protons. This attests to a rigid chair conformation where the above-mentioned groups and the low-field proton are *trans*-diaxial, which allows the *W* conformation necessary for the observed stereospecific splitting through four σ bonds to be possible.

5(3)-trifluoromethylpyrazole (**16**), obtained earlier from not easily available 7,7,7-trifluoro-2-methylhepta-3,5-diyn-2-ol and hydrazine hydrate,[10] while the reaction of compound **8** with hydroxylamine hydrochloride yields 5-hydroxy-3-(2-hydroxy-2-methylpropyl)-5-trifluoromethyl-Δ^2-isoxazoline (**17**), which had not been reported earlier (Scheme 5). We failed to isolate in individual state the products of reaction of dihydropyrone **8** with free hydroxylamine, probably, because of rapid decomposition of the initially formed intermediate of type **12**.

Scheme 5

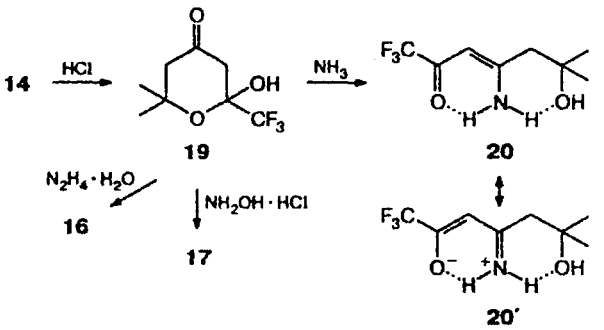


The reactions of aminoenone **14**, whose acid hydrolysis gives dihydropyrone **8**,[11] with hydrazine and hydroxylamine also yield pyrazole **16** and isoxazoline **17**, respectively (see Scheme 5). The ^{1}H NMR spectrum of isoxazoline **17** (recorded in DMSO-d_6 because of its poor solubility in deuterochloroform) exhibits two singlets at δ 1.10 and 1.17 for the methyl groups (they are nonequivalent because the molecule bears a chiral center); a singlet at δ 2.42 for the protons of the CH_2 group of the alkyl substituent; the AB system of the CH_2 protons of the isoxazoline ring with a center at δ 3.30 and J_{AB} = 18.8 Hz; and two singlets at δ 4.64 and 8.20 corresponding to the alcoholic and hemiketal hydroxyl group, respectively.

A comparison of the chemical properties of dihydropyrones **1** (see Scheme 1) and **8** (see Schemes 2, 4, and 5) shows that, unlike their reactions with ammonia and ethylenediamine, those with hydrazine hydrate and hydroxylamine hydrochloride proceed similarly and are accompanied by opening of the pyrone ring to give isomeric pyrazoles **4** and **16** and isoxazolines **5** and **17**. The single difference is that, in the case of compound **8**, our attempts to isolate intermediate products of types **3**, **6**, and **7** failed.

It is known[1] that dihydropyrone **1** easily undergoes hydration to give 2-hydroxy-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyrone (**18**), whose properties were recently described.[12] However, we failed to add a water molecule at the double bond of compound **8**, though its hydration product, 2-hydroxy-6,6-dimethyl-2-trifluoromethyltetrahydro-4-pyrone (**19**), had been obtained earlier[11] by mild acid hydrolysis of aminoenone **14**. Under the action of ethylenediamine or an aqueous solution of ammonia, tetrahydropyrone **19** undergoes scission to form salts and acetone, while its reaction with a methanolic solution of ammonia at room temperature gives in low yield (25%) the expected hydroxyaminoenone **20**, which is isomeric to the known[11] compound **14**. The reactions with $N_2H_4 \cdot H_2O$ and $NH_2OH \cdot HCl$ also yield pyrazole **16** and isoxazoline **17**, respectively (Scheme 6).

Scheme 6



The ^{1}H NMR spectrum of aminoenone **20** exhibits singlets at δ 1.34 and 2.41 corresponding to the *gem*-dimethyl and methylene groups, respectively; a broadened singlet at δ 1.9 for the hydroxyl group; and a doublet at δ 5.27 (J = 1.2 Hz) for the vinyl proton. This doublet is split on the NH_2 proton that is not involved in the formation of an intramolecular hydrogen bond (IMHB) with the oxygen atom of the carbonyl group. The protons of the NH_2 group in compound **20** manifest themselves as two broadened singlets at δ 7.3 (the hydrogen atom involved in IMHB with the OH oxygen atom) and δ 9.9 (the hydrogen atom involved in IMHB with the C=O oxygen atom), which allows one to assign a Z configuration to the double bond. In contrast to isomeric aminoenone **14**, whose spectrum exhibits a broadened two-proton singlet at δ 7.5 corresponding to the hydrogen atoms of the amino group,[11] the presence of two signals for the nonequivalent protons of the amino group in the spectrum of aminoenone **20** suggests a significant contribution of the zwitterionic resonance structure (**20'**), which is responsible for the partially doubled C—N bond and a correspondingly slower rotation of the NH_2 group.

A comparison of the data on transformations of compound **19** (see Scheme 6) with the results obtained from the study[12] of reactions of 2-hydroxy-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyrone (**18**) with amines, hydrazine, and hydroxylamine shows that isomeric tetrahydropyrones **18** and **19** behave in reactions with N-nucleophiles as the corresponding fluorine-containing 5-hydroxy-1,3-diketones, because they are the cyclic

forms of the latter. Note that tetrahydropyrone **19** is less resistant to the action of ammonia than tetrahydropyrone **18**, which gave[12] the corresponding hydroxyaminoenone, 4-amino-1,1,1-trifluoro-6-hydroxy-5,5-dimethylhex-3(*Z*)-en-2-one, in 70% yield.

Thus, because of their availability, dihydropyrone **8** and related aminoenone **14** and tetrahydropyrone **19** are convenient starting compounds for the synthesis of pyrazole **16** and isoxazoline **17**, which have the 2-hydroxy-2-methylpropyl substituent and hence can be used in the preparation of more complex systems, including polymers. However, a comparison of the chemical properties of dihydropyrones **1** and **8** (in particular, the pyrone ring of **8** tends more strongly to opening and scission) suggests that the synthetic capabilities of the latter in reactions with N-nucleophiles are poorer than those of dihydropyrone **1**.

Experimental

IR spectra were recorded on an IKS-29 instrument (Vaseline oil). ^{1}H NMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz) with Me_4Si as the internal standard.

5-Methyl-7-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepine (13) was obtained in 40% yield from dihydropyrone **8** according to the known procedure.[13] Its properties had been studied earlier (see Refs. 8 and 9).

***N,N'*-Ethylenebis(2-amino-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyrone) (15)** was obtained by the reaction of dihydropyrone **1** with a 25% ethanolic solution of ethylenediamine as described for 2-amino-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyrone.[1] Yield 70%, m.p. 99—100 °C (CCl_4). Found (%): C, 48.14; H, 5.94; N, 6.30. $C_{18}H_{26}F_6N_2O_4$. Calculated (%): C, 48.22; H, 5.84; N, 6.25. IR, ν/cm^{-1}: 1725 (C=O); 3360, 3410 (NH). ^{1}H NMR spectrum of a 1 : 1 mixture of two diastereomers (250 MHz, $CDCl_3$), δ: 1.02 (s, 6 H, 2 CH_3); 1.29 (s, 6 H, 2 CH_3); 1.72 (br.s, 2 H, 2 NH); 2.21 (d, 1 H, $CH_{eq}H$, J_{AX} = 15.0 Hz); 2.28 (d, 1 H, $CH_{eq}H$, J_{AX} = 15.0 Hz); 2.77 (m, 4 H, CH_2CH_2); 2.98 (d, 1 H, CHH_{ax}, J_{AX} = 15.0 Hz); 2.99 (d, 1 H, CHH_{ax}, J_{AX} = 15.0 Hz); 3.70 (AB system, $\Delta\delta$ = 0.21, 2 H, CH_2O, J_{AB} = 11.3 Hz); 3.72 (AB system, $\Delta\delta$ = 0.21, 2 H, CH_2O, J_{AB} = 11.3 Hz).

3(5)-(2-Hydroxy-2-methylpropyl)-5(3)-trifluoromethylpyrazole (16) was obtained from compounds **8**, **14**, and **19** as described for pyrazole **4**.[12] Yields 65—74%, m.p. 100—101 °C (aqueous EtOH) (*cf.* Ref. 10: m.p. 100 °C). IR, ν/cm^{-1}: 1505, 1585, 3085, 3120, 3165, 3200, 3420. ^{1}H NMR ($CDCl_3$), δ: 1.28 (s, 6 H, 2 CH_3); 2.0 (br.s, 2 H, OH, NH); 2.83 (s, 2 H, CH_2); 6.33 (s, 1 H, =CH).

5-Hydroxy-3-(2-hydroxy-2-methylpropyl)-5-trifluoromethyl-Δ^2-isoxazoline (17) was obtained from compounds **8**, **14**, and **19** as described for isoxazoline **5**.[12] Yields 52—62%, m.p. 137—138 °C (aqueous EtOH). Found (%): C, 42.09; H, 5.03; N, 6.15. $C_8H_{12}F_3NO_3$. Calculated (%): C, 42.30; H, 5.32; N, 6.17. IR, ν/cm^{-1}: 1630 (C=N); 3140, 3330 (OH). ^{1}H NMR (DMSO-d_6), δ: 1.10 (s, 3 H, CH_3); 1.17 (s, 3 H, CH_3); 2.42 (s, 2 H, CH_2); 3.30 (AB system, $\Delta\delta$ = 0.30, 2 H, CH_2, J_{AB} = 18.8 Hz); 4.64 (s, 1 H, $Me_2C\underline{O}H$); 8.20 (s, 1 H, OH).

4-Amino-1,1,1-trifluoro-6-hydroxy-6-methylhept-3(*Z*)-en-2-one (20) was obtained from tetrahydropyrone **19** as described for 4-amino-1,1,1-trifluoro-6-hydroxy-5,5-dimethylhex-3(*Z*)-en-2-one[12] and isolated in the form of copper chelate, which was further decomposed by treatment with H_2S in ether. Yield 25%, m.p. 111—112 °C (hexane). Found (%): C, 45.70; H, 5.62; N, 6.74. $C_8H_{12}F_3NO_2$. Calculated (%): C, 45.50; H, 5.73; N, 6.63. IR, ν/cm^{-1}: 1560, 1620 (C=C, NH_2); 1645 sh. (C=O); 3155, 3310, 3410 (NH_2, OH). ^{1}H NMR ($CDCl_3$), δ: 1.34 (s, 6 H, 2 CH_3); 1.9 (br.s, 1 H, OH); 2.41 (s, 2 H, CH_2); 5.27 (d, 1 H, =CH, J = 1.2 Hz); 7.3 (br.s, 1 H, NH); 9.9 (br.s, 1 H, NH).

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