Recyclization of 2-amino- and 2-methylamino-2-trifluoromethyl-5,5-dimethyltetrahydro-4-pyrone oximes to 5-amino- and 5-methylamino-5-trifluoromethyl-3-(2-hydroxy-1,1-dimethylethyl)-Δ²-isoxazolines

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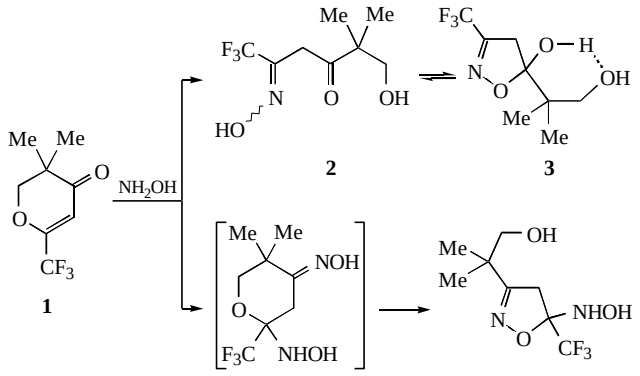
The reactions of hydroxylamine with 2-amino- and 2-methylamino-2-trifluoromethyl-5,5-dimethyltetrahydro-4-pyrones yield 2-amino- and 2-methylamino-2-trifluoromethyl-5,5-dimethyltetrahydro-4-pyrone oximes, which can be converted to 5-amino- and 5-methylamino-5-trifluoromethyl-3-(2-hydroxy-1,1-dimethylethyl)-Δ²-isoxazolines, respectively, by heating in ethanol.

Previously[1] we described the interaction of 6-trifluoromethyl-3,3-dimethyl-2,3-dihydro-4-pyrone **1** with hydroxylamine hydrochloride and hydroxylamine base. We found that the reaction with $NH_2OH·HCl$ in the presence of Et_3N in methanol proceeded at the C(6) atom and was accompanied by ring opening to form monoxime **2**. This compound exists as cyclic isoxazoline species **3** in the solid state and in $CDCl_3$ solution or as a mixture of monoxime **2** and isoxazoline **3** (in the ratio 40:60) in DMSO solution. Dihydropyrone **1** with an excess of hydroxylamine base yielded 5-hydroxyamino-Δ²-isoxazoline **4**. To explain the formation of **4**, we suggested that the reaction proceeds simultaneously at two electrophilic sites *via* a step of formation of 2-trifluoromethyl-2-hydroxyamino-5,5-dimethyltetrahydro-4-pyrone oxime **5**, which immediately undergoes recyclization to isoxazoline **4** under the reaction conditions.



To test this hypothesis, we decided to examine the interaction of hydroxylamine with 2-amino- and 2-methylamino-2-trifluoromethyl-5,5-dimethyltetrahydro-4-pyrones **6a**,**b** prepared by reactions of dihydropyrone **1** with ammonia[2] and methylamine.† Because tetrahydropyrone **6a** is a cyclic form of 5-amino-6,6,6-trifluoro-1-hydroxy-2,2-dimethylhex-4-en-2-one **7**, which was synthesised previously by condensation of 4-hydroxy-3,3-dimethyl-2-butanone with trifluoroacetonitrile,[2] it was also of interest to compare the behaviour of aminoenone **7** and its cyclic isomer **6a** in reactions with hydroxylamine. Note that **7** cannot transform into **6a** either spontaneously or in the presence of bases.

We found that tetrahydropyrones **6a**,**b** with hydroxylamine base in methanol at room temperature formed oximes **8a**,**b**‡ in high yields. These oximes undergo recyclization to thermodynamically more stable 5-amino- and 5-methylamino-Δ²-isoxazolines **9a**,**b**§ on heating in ethanol. The transformation **8** → **9** supports a scheme that was suggested previously[1] for the formation of isoxazoline **4** and makes it possible to prepare 5-amino derivatives of 5-trifluoromethyl-Δ²-isoxazolines. This transformation can be considered as a new example of ring-chain isomerisation (see ref. 3 and references therein) that proceeds *via* unstable open-chain imino-oxime species **10**, which cannot be detected in ^{1}H NMR spectra. Note that a mixture of compounds **8b** and **9b** in the ratio 55:45 was formed when deuterioacetic acid was added to an oxime **8b** solution in $CDCl_3$, whereas oxime **8a** remained unchanged under similar conditions (according to ^{1}H NMR spectral data).

Tetrahydropyrone **6a** reacted with NH_2OH at the carbonyl group with the retention of the cyclic structure; this fact suggests that this compound is reasonably stable despite the hemiaminal character of the C–O bond. In contrast, open-chain species **7** exhibited a much different behaviour in this reaction. Aminoenone **7** underwent a nucleophilic attack on the carbon atom adjacent to the CF_3 group and, *via* a transamination step, resulted in monoxime **2**, which exists predominantly as isoxazoline **3**, which was prepared previously from dihydropyrone **1**.[1]

Judging from the ^{1}H NMR spectral data for oximes **8a**,**b** (only a single set of signals was observed in the spectra), the reaction resulting in these compounds is highly stereoselective and leads to products with the *E*-configuration of the C=N bond. A comparison between the ^{1}H NMR spectra for compounds **6b** and **8b** indicates that replacing a carbonyl oxygen by an oxime functional group primarily affected the positions of doublets of

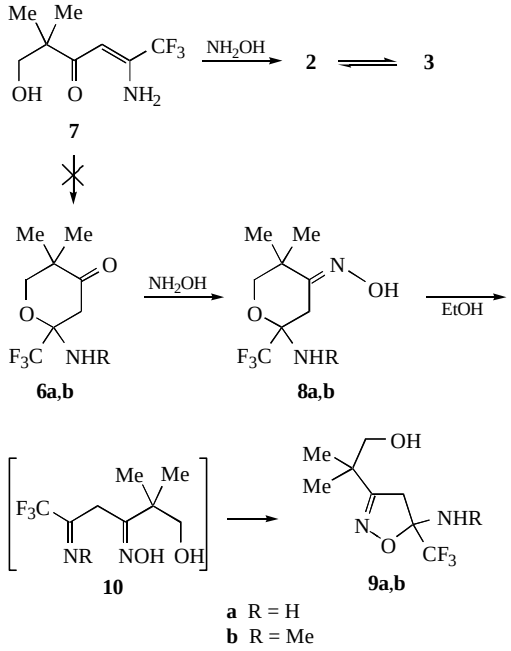
† *2-Trifluoromethyl-2-methylamino-5,5-dimethyltetrahydro-4-pyrone* **6b**: yield 84%, mp 87–88 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.01 (s, 3H, Me), 1.30 (s, 3H, Me), 1.58 (br. s, 1H, NH), 2.27 (d, 1H, CH_eH, J_{AX} 15.0 Hz), 2.42 (s, 3H, NMe), 2.97 (d, 1H, CHH_a, J_{AX} 15.0 Hz), 3.72 (AB system, δ 0.22, 2H, CH_2–O, J_{AB} 11.0 Hz). IR (Vaseline oil, ν/cm^{-1}): 3390 (NH), 1720 (C=O). Found (%): C 48.00; H 6.49; N 6.14. Calc. for $C_9H_{14}F_3NO_2$ (%): C 48.00; H 6.27; N 6.22.

‡ *2-Amino-2-trifluoromethyl-5,5-dimethyltetrahydro-4-pyrone oxime* **8a**: yield 63%, mp 126–127 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.11 (s, 3H, Me), 1.29 (s, 3H, Me), 1.80 (s, 2H, NH_2), 2.43 (d, 1H, CH_eH, J_{AX} 15.0 Hz), 3.34 (d, 1H, CHH_a, J_{AX} 15.0 Hz), 3.46 (d, 1H, C*H*H–O, J_{AX} 11.2 Hz), 3.93 (d, 1H, CH*H*–O, J_{AX} 11.2 Hz), 8.43 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3425, 3385, 3280 (br.), 3120 (OH, NH_2), 1660, 1625 (C=N, NH_2). Found (%): C 42.40; H 5.82; N 12.09. Calc. for $C_8H_{13}F_3N_2O_2$ (%): C 42.48; H 5.79; N 12.38.

2-Trifluoromethyl-2-methylamino-5,5-dimethyltetrahydro-4-pyrone oxime **8b**: yield 70%, mp 129–130 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.08 (s, 3H, Me), 1.28 (s, 3H, Me), 1.58 (br. s, 1H, NH), 2.39 (d, 1H, CH_eH, J_{AX} 15.1 Hz), 2.41 (s, 3H, NMe), 3.31 (d, 1H, CHH_a, J_{AX} 15.1 Hz), 3.56 (AB system, δ 0.22, 2H, CH_2–O, J_{AB} 11.2 Hz), 8.49 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3420, 3250 (br.), 3150 (OH, NH), 1675 (C=N). Found (%): C 44.82; H 6.43; N 11.64. Calc. for $C_9H_{15}F_3N_2O_2$ (%): C 45.00; H 6.29; N 11.66.

§ *5-Amino-5-trifluoromethyl-3-(2-hydroxy-1,1-dimethylethyl)-Δ²-isoxazoline* **9a**: yield 74%, mp 73–74 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.17 (s, 3H, Me), 1.19 (s, 3H, Me), 2.54 (br. s, 3H, NH_2, OH), 2.90 (dq, 1H, C*H*H, J_{AB} 18.3 Hz, $^4J_{H,F}$ 1.1 Hz), 3.33 (d, 1H, CH*H*, J_{AB} 18.3 Hz), 3.58 (AB system, δ 0.02, 2H, CH_2–O, J_{AB} 11.0 Hz). IR (Vaseline oil, ν/cm^{-1}): 3465, 3390, 3320 (OH, NH), 1615 (C=N). Found (%): C 42.56; H 6.02; N 12.04. Calc. for $C_8H_{13}F_3N_2O_2$ (%): C 42.48; H 5.79; N 12.38.

5-Trifluoromethyl-5-methylamino-3-(2-hydroxy-1,1-dimethylethyl)-Δ²-isoxazoline **9b**: yield 82%, mp 41–42 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.18 (s, 6H, 2Me), 2.30 (br. s, 2H, NH, OH), 2.40 (s, 3H, NMe), 3.06 (dq, 1H, C*H*H, J_{AB} 18.6 Hz, $^4J_{H,F}$ 1.1 Hz), 3.18 (d, 1H, CH*H*, J_{AB} 18.6 Hz), 3.59 (s, 2H, CH_2–O). IR (Vaseline oil, ν/cm^{-1}): 3435 (br.), 3310 (OH, NH), 1625 (C=N). Found (%): C 44.93; H 6.30; N 11.36. Calc. for $C_9H_{15}F_3N_2O_2$ (%): C 45.00; H 6.29; N 11.66.



the AX system of CH_2(3) group protons, of which a downfield doublet of the axial proton and an upfield doublet of the equatorial proton exhibited paramagnetic shifts by 0.34 and 0.12 ppm, respectively.¶ At the same time, the chemical shifts of methyl groups changed insignificantly: the δ values are 1.01 and 1.08 ppm for the equatorial methyl or 1.30 and 1.28 for the axial methyl in compounds **6b** and **8b**, respectively.[4] These data count in favour of the *E*-configuration such that protons of the CH_2(3) group spatially approach the oxime hydroxyl to result in a downfield shift primarily due to an electrostatic deshielding effect[5] (this is particularly true for the axial proton). As distinct from the CH_2(3) group protons forming the AX system with J_{AX} ~ 15.0 Hz, hydrogen atoms of the CH_2(6) group appear as the AB spectrum with J_{AB} ~ 11.0 Hz and are shifted to higher field by 0.16 ppm on going from tetrahydropyrone **6b** to oxime **8b**.

Note that in the ^{1}H NMR spectra of both isoxazolines **9a**,**b**, the upfield signal of the AB quartet due to the CH_2 group of the isoxazoline ring (J_{AB} ~ 18.5 Hz) was further split into quartets with $^4J_{H,F}$ = 1.1 Hz. This is due to long-range spin–spin coupling of a proton from this group with fluorine atoms of the trifluoromethyl substituent.

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¶ According to our unpublished data, in compounds related to tetrahydropyrone **6b**, such as 2-trifluoromethyl-2-hydroxy-5,5-dimethyltetrahydro-4-pyrone and 2-amino-2-trichloromethyl-5,5-dimethyltetrahydro-4-pyrone, it is the downfield doublet of the AX system of CH_2(3) group protons that 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. This is due to long-range spin–spin coupling of a downfield proton with the protons of OH and NH_2 groups. This fact is indicative of a rigid chair conformation with the *trans*-diaxial position of these groups and the downfield proton. At this arrangement, the W-conformation, which is required for the observed stereospecific long-range coupling through four bonds,[6] becomes possible.