Synthesis and reactions of 2-hydroxy-5,5-dimethyl- and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranones with N-nucleophiles

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Condensation of 4-hydroxy-3,3-dimethyl- and 4-hydroxy-3,3-pentamethylenebutan-2-ones with ethyl trifluoroacetate in the presence of LiH in hexane afforded 2-hydroxy-5,5-dimethyl- and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranones, whose behavior in reactions with N-nucleophiles is analogous to that of unsymmetrical polyfluorinated β-diketones.

Key words: condensation, β-hydroxyketones, ethyl trifluoroacetate, tetrahydro-4-pyranones; aminoenones, CF₃-containing pyrazoles and Δ²-isoxazolines.

Recently,¹ we have demonstrated that intramolecular cyclization of 2,2-dimethyl- and 2,2-pentamethylene-3-hydroxobutyl trifluoroacetates under the action of N-phenyl-N-ethylammonium magnesium bromide afforded 2-hydroxy-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyranone (1a) and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranone (1b), respectively. These compounds were also obtained by acid hydrolysis of the corresponding 2-amino-6-hydroxy-5,5-dialkyl-1,1,1-trifluorohex-2-en-4-ones (2a, b), which were the products of condensation of trifluoroacetamide with 4-hydroxy-3,3-dialkylbutan-2-ones (3a, b).²

Because tetrahydroxypropyrazole 1a, b are cyclic hemiketals of the corresponding β-hydroxy-1,3-diketones, it is reasonable to suggest that in the reactions with N-nucleophiles these compounds will behave analogously to the previously described unsymmetrical fluorine-containing 1,3-diketones, which react with ammonia and amines at the carbonyl group of the nonfluorinated substituent³ and give pyrazoles⁴ and Δ²-isoxazolines⁵ in the reactions with hydrazine and hydroxylamine, respectively. We studied the reactions of tetrahydroxypropyrazoles 1a, b with ammonia, benzylamine, hydrazine, and hydroxylamine and found that the reactions of the compounds under consideration with N-nucleophiles are accompanied by cleavage of the tetrahydroxypropyrazole ring and occur at the β-diketone fragment to form analogous products containing hydroxyalkyl groups.

When tetrahydroxypropyrazoles 1a, b were treated with a methanol solution of ammonia at room temperature,
Hydroxyaminoenones $4a,b$ were isolated in yields of no more than 70% due to partial decomposition of compounds $1a,b$ to corresponding $\beta$-hydroxyketones $3a,b$ and $\text{CF}_3\text{COONH}_2$. In an aqueous medium, this direction of the reaction predominated and the yields of compounds $4a,b$ decreased to 20–25%. The reaction of tetrahydropyranones $1a,b$ with benzylamine afforded $N$-benzyltrifluoroacetamide and $\beta$-hydroxyketones $3a,b$ regardless of the nature of the solvent (methanol or benzene).

Hydroxyaminoenones $4a,b$ are isomeric to compounds $2a,b$, which have been prepared previously from trifluoroacetonitrile and $\beta$-hydroxyketones $3a,b$, and differ substantially from $2a,b$ in the spectral characteristics. At the same time, the $^1H$ NMR spectra of compounds $4a,b$ and $5$ have much in common. Thus, the $^1H$ NMR spectrum of compound $4a$ has singlets of the gem-dimethyl and methylene groups at $\delta$ 1.23 and 3.66, respectively, a broadened singlet of the hydroxyl group at $\delta$ 3.06, and a doublet of the vinyl proton ($J = 1.6$ Hz) at $\delta$ 5.46. In aminone $5$, this proton is observed in the form of a doublet ($J = 2.1$ Hz) at $\delta$ 5.52, and in aminone $6$, in which one hydrogen atom of the NH$_2$ group is replaced by the benzyl fragment, this proton occurs as a singlet at $\delta$ 5.75. These data suggest that in compounds $4a,b$ and $5$, the splitting of the signal of the vinyl proton into a doublet is associated with long-range spin–spin interaction with the proton of the NH group, which is not involved in intramolecular hydrogen bonding with the carbonyl oxygen atom. The signals of the protons of the amino group of compound $4a$ occur as two significantly broadened singlets at $\delta$ 7.3 (the hydrogen atom involved in intramolecular hydrogen bonding with the oxygen atom of the OH group) and 10.5 (the hydrogen atom involved in intramolecular hydrogen bonding with the oxygen atom of the C=O group) (Table 1), which suggests that the double bond has the $Z$ configuration. The presence of two signals of the nonequivalent protons of the amino group is indicative of a stronger intramolecular hydrogen bond in the aminone fragment of compound $4a$ compared to that in compound $2a$, in which the hydrogen atoms of the NH$_2$ group are observed in the form of a broadened two-proton singlet at $\delta$ 7.3.$^2$

Treatment of tetrahydropyranone $1a$ with an excess of hydrazine hydrate at room temperature or upon heating afforded a mixture of $5$-hydroxy-$\Delta^2$-pyrazoline $7$ and pyrazole $8a$ in a ratio of 2 : 1, which was determined based on the $^1H$ NMR spectral data. Boiling of this mixture in alcohol in the presence of concentrated HCl gave pyrazole $8a$ without an admixture of pyrazoline $7$, which indicates that the latter compound readily undergoes dehydration. The reaction of tetrahydropyranone $1b$ with hydrazine hydrate yielded only pyrazole $8b$. Most probably, conversion of compounds $1a,b$ into pyrazoles $8a,b$ proceeds through initial formation of hydrazones at the carbonyl group that is not bonded to the trifluoromethyl substituent followed by cyclization at the carbonyl carbon atom of the CF$_3$CO group to form the corresponding pyrazolines, which then undergo dehydration to give pyrazoles $8a,b$.

The $^1H$ NMR spectrum of pyrazole $8a$ has three singlets at $\delta$ 1.32, 3.64, and 6.32, which correspond to the gem-dimethyl group, the methylene group, and the hydrogen atom of the pyrazole ring, respectively. The signals of the labile protons of the OH and NH groups are not observed in the $^1H$ NMR spectrum. In the IR spectrum, these protons are observed at 3075, 3130,