REDUCTION OF 1-ACYLPYRAZOLINIUM SALTS

L. A. Sviridova, G. A. Golubeva,
A. V. Dovgilevich, and A. N. Kost*

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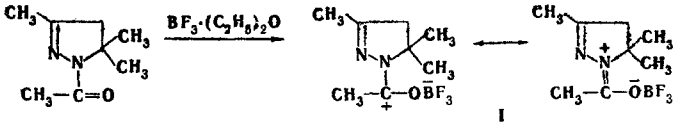
Activation of the C=N bond in the 1-acetylpyrazoline molecule may take place during the formation of a complex with boron trifluoride (coordination at the oxygen atom of the acetyl group) or in the case of protonation at the N_2 atom of the pyrazoline ring. Activated 1-acetylpyrazolines are readily reduced with lithium aluminum hydride to 1-ethylpyrazolidines. The hydrochlorides of 1-acetylpyrazolidines undergo reaction without prior deprotonation. Aluminum hydride reduces 1-acetylpyrazoline bases to 1-ethylpyrazolidines also through prior complexing at the N_2 atom of the pyrazoline ring.

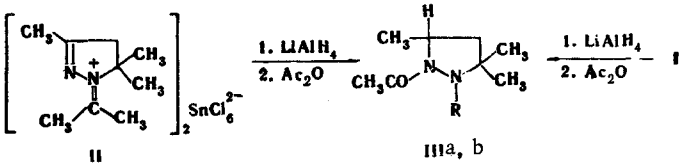
The polarization of the C=N bond in the 2-pyrazoline molecule is insufficient in most cases for nucleophilic attack at the C_3 atom. The reaction with organolithium compounds, which add to the multiple bond [1], constitutes an exception. Activation of the C=N–N fragment in the pyrazoline molecule can be achieved in two ways: by increasing the positive charge on the N_1 atom, or by polarization of the C=N bond itself. In the case of protonation of 1-alkyl(aryl)-pyrazolines the electrophilicity of the C_3 atom is increased, and this made it possible to increase the number of nucleophilic reagents ($LiAlH_4$ and RMgX) [2, 3]. The presence of an electron-acceptor trifluoroacetyl or formyl group attached to the N_1 atom has the same effect — these compounds are reduced by lithium aluminum hydride to the corresponding 1-alkylpyrazolidines. However, other 1-acylpyrazolines are reduced only to 1-alkylpyrazolines under these conditions, and the C=N bond is not involved in this case [4].

Continuing our search for methods for the activation of the pyrazoline molecule we obtained a complex (I) of 1-acetyl-3,5,5-trimethylpyrazoline with boron trifluoride. During the formation of the complex, the absorption band of an amide carbonyl group (1640-1680 cm^{-1}) vanishes in the IR spectrum, and the absorption band at 1600-1620 cm^{-1} becomes more intense; a 0.6-ppm shift of the signal of the protons of the acetyl group to weak field is observed in the PMR spectrum.



I

Coordination of the oxygen and boron atoms leads to an increase in the conjugation along the multiple bonds in the pyrazoline molecule, and this in turn should lead to an increase in the partial positive charge on the C_3 atom and, consequently, to facilitation of nucleophilic attack. The structure of complex I is similar to that of the known isopropylidenepyrazolinium salt II [5], which is readily reduced with lithium aluminum hydride to



II IIIa, b

III a R = $(CH_3)_2CH$; b R = C_2H_5

*Deceased.

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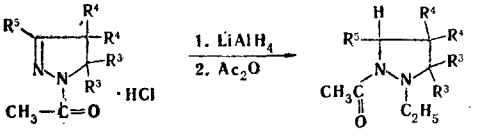
TABLE 1. 1-Acetylpyrazolidines

Compound	1-Acetylpyrazolidine	bp, °C (mm)	n_D^{20}	PMR spectra, δ, ppm					Mass spectrum, m/e (relative intensity, %)	Yield, %
				N—C_2H_5	R^3	R^4	R^5	5-H		
IVa	2-Ethyl-3,3,5-trimethyl-	138—140 (13)	1,4610	1,13 (t, 3H), 2,76 (q, 2H) J=7 Hz	1,00 (s, 3H), 1,30 (s, 3H)	1,93 (m 2H)	1,33 (d, 3H), J=7 Hz	4,20 (m, 1H)	184 (6), 142 (19), 141 (100), 113 (10), 98 (5), 97 (6), 85 (46), 84 (11), 83 (17), 59 (17), 56 (11)	80
IVb	2-Ethyl-3-phenyl-5-methyl-	204—209 (10)	1,5300	0,97 (m, 3H), 2,55 (m, 2H)	2,90 (m 1H), 7,20 (m 5H)	1,87 (m, 2H)	1,27 (d, 3H), J=8 Hz	4,20 (m, 1H)	232 (0,5), 189 (100), 161 (3), 176 (5), 131 (15), 117 (6), 104 (9), 91 (22), 85 (31), 83 (8)	60
IVc	2-Ethyl-3-isopropyl-4,4-dimethyl-	156—158 (10)	1,4668	1,04 (t, 3H), J=7 Hz 2,71 (m, 2H)	0,95 (d, 6H), J=9Hz., 1,65 (m 1H), 2,71 (m 1H)	0,85 (s, 3H) 1,15 (s, 3H)		3,90 (s, 1H) 4,01 (s, 1H)	212 (4), 169 (100), 141 (4), 128 (9), 113 (11), 99 (12), 98 (13), 97 (42), 85 (7), 73 (13), 71 (12)	52
IVd	2,3-Diethyl-4-methyl-	149—152 (10)	1,4649	1,30 (t, 3H), J=8 Hz 2,80	1,10 (t, 3H), J=6 Hz (m, 4H)	1,04 (d, 3H), J=7 Hz, 1,98 (m, 1H)		4,22 (m, 2H)	184 (1), 183 (5), 141 (100), 113 (38), 84 (27), 83 (17)	60
IVe	2-(1,1-Dideuteroethyl)-3,3,5-trimethyl-5-deutero-	138—140 (13)	1,4600	0,98 (s, 3H)	1,30 (s, 6H)	1,70 (d, 1H), 1,99 (d, 1H)	1,15 (s, 1H)		187 (1), 172 (1), 145 (9), 144 (100), 114 (9), 99 (9), 97 (5), 86 (21), 84 (14)	80*
IIIa	2-Isopropyl-3,3,5-trimethyl-								198 (0,1), 155 (38), 114 (10), 113 (100), 99 (18), 98 (3), 70 (12), 58 (12), 56 (36)	87†

*The compound was obtained by reduction with lithium aluminum hydride.
†The substance was analyzed by chromatographic mass spectrometry.

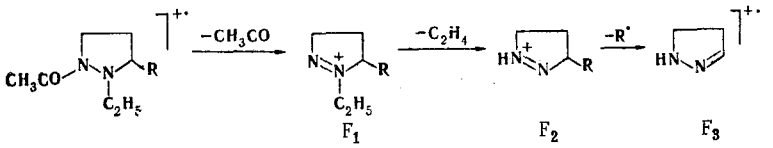
pyrazolidine IIIa. Complex I is reduced in precisely the same way to IIIb. Thus activation of the C=N bond of 1-acetylpyrazoline is achieved in the formation of a complex with BF_3.

In contrast to the reaction with boron trifluoride, protonation of the acetylpyrazoline molecule takes place at the N_2 atom,* and this leads to the formation of an immonium system, which also has a rather electrophilic C_3 atom. Experiments showed that the hydrochlorides of 1-acetylpyrazolines are reduced by lithium aluminum hydride to the corresponding 1-ethylpyrazolidines, which were isolated in 50-80% yields in the form of N-acetyl derivatives IV (Table 1).



IV

The IR spectra of the compounds obtained contain intense absorption at 1665-1685 cm^{-1} (C=O), but vibrations of the C=N bond are absent. As compared with the spectrum of the starting substance, a multiplet of a newly developed 5-H proton at 4 ppm is observed in the PMR spectra, while the signal of the 5-CH_3 group at 1.2 ppm becomes a doublet (J = 7 Hz). The signal of the protons of the acetyl group appears in the form of a characteristic singlet at 2.0-2.1 ppm. Low-intensity molecular-ion peaks (1.5-2% relative to the maximum peak), the fragmentation of which involves the successive splitting out of the substituents from the 1, 2, and 3 positions of the pyrazolidine ring with the formation of pyrazolinium ions, which subsequently undergo the fragmentation that is characteristic for them [6], are observed in the mass spectra. The sum of the intensities of the F_1, F_2, and F_3 ions constitutes 50-70% of the total ion current, and this indicates the high specificity and directed character of the fragmentation of acetylpyrazolidines IV, as well as the common character of the structures of all of the compounds obtained.



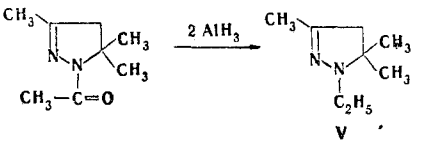
F_1 F_2 F_3

The reduction of salts of 1-acetylpyrazolines with lithium aluminum hydride can be conceived of in several variants. It is known, for example, that 1,2-dialkylpyrazolinium salts are readily converted under the influence of bases to 3-pyrazolines, which in turn are readily reduced to pyrazolidines [7]. However, the reduction of 1-acetyl-4,4-dimethyl-5-isopropylpyrazoline to the corresponding pyrazolidine IVc evidently excludes this reaction pathway or in any case constitutes evidence that the reduction of salts of 2-pyrazolines may take place without prior conversion to the Δ^3 isomer.

Another possible pathway for this reaction is irreversible neutralization of the salt with lithium aluminum hydride, i.e., a process that leads to the liberation of the pyrazoline base, aluminum hydride, and hydrogen. To ascertain the possibility of deprotonation during the reduction of the hydrochlorides of 1-acetylpyrazolines and to definitively verify the hypothesis of the isomerization of salts of 1-acetylpyrazolines to the corresponding 3-pyrazolines under the influence of the reducing agent we reduced 1-acetyl-3,5,5-trimethylpyrazoline deuterochloride with lithium aluminum chloride and did not observe the liberation of deuterohydrogen in this case. Consequently, prior deprotonation does not occur during reduction, i.e., precisely the 1-acetylpyrazolinium salt undergoes the reaction. This result is in conformity with principle, since proton exchange in ammonium salts of tertiary amines proceeds quite rapidly only with the participation of proton solvents [8], whereas we carried out the reaction in absolute ether.

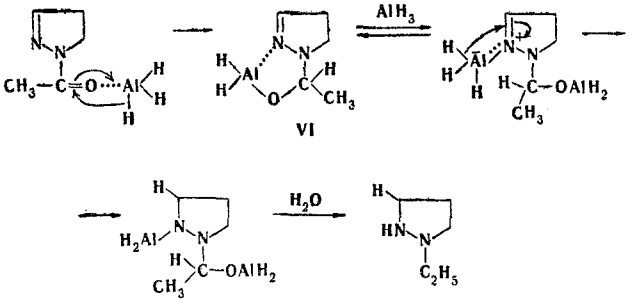
The special properties of aluminum hydride, which is a reducing agent and simultaneously a complexing agent (a Lewis acid), made it possible to assume that the 2-pyrazoline base can be subjected to reaction with it. However, only 1-ethylpyrazoline V was present as the chief component in the reaction mixture in the reduction of 1-acetylpyrazolines with aluminum hydride in a ratio of 1:2, although 1-alkylpyrazolines are reduced with aluminum hydride to pyrazolidines in 70-80% yields at a reagent ratio of 1:1.

*A study of the protonation of 1-acylpyrazolines will be the subject of a separate communication.



V

If, however, the ratio of 1-acetylpyrazoline and aluminum hydride is 1:4, the reduction leads completely to 1-ethylpyrazolines. Aluminum hydride evidently adds initially to the C=O bond to give VI, in which the N_2 atom of the pyrazoline ring is coordinated with the aluminum atom.



VI

Thus aluminum hydride is a unique reducing agent that converts the C=N bond in pyrazolines to a single bond. The mechanism of its action is determined in this case by its ability to complex with the N_2 atom of the pyrazoline ring.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with Varian T-60 and XL-100 spectrometers (in CCl_4 with hexamethyldisiloxane as the internal standard). The mass spectra were obtained with a Varian MAT 111 (Gnom) spectrometer with an ionizing voltage of 70 eV; the column was 3 m by 4 mm and was filled with SE-30 silicone.

1-Acetyl-3,3,5-trimethyl-2-ethylpyrazolidine. A 2.8-g (0.02 mole) sample of boron trifluoride etherate was added in portions to a solution of 3.0 g (0.02 mole) of 1-acetyl-3,5,5-trimethylpyrazoline in dry ether, and the resulting precipitate was washed with ether to give 4.4 g (100%) of complex I with mp 133°C (dec.). IR spectrum: 1620 cm^{-1} (C=N). PMR spectrum (in $CHCl_3$): 1.57 (s, 6H, 5-CH_3), 2.10 (s, 3H, 3-CH_3), 2.60 (s, 3H, CH_3CO), and 2.97 ppm (s, 2H, 4-H). Found: C 43.6; H 6.3%. $C_8H_{14}N_2O \cdot BF_3$. Calculated: C 43.3; H 6.3%. A suspension of 1.5 g (0.04 mole) of $LiAlH_4$ in ether was added to a suspension of 2.2 g (0.01 mole) of complex I in 30 ml of absolute ether, and the mixture was refluxed for 3 h. It was then decomposed with 1 ml of water, and the precipitate was removed by filtration and washed with ether. A mixture of 3.0 g (0.03 mole) of acetic anhydride was added to the filtrate, the ether was evaporated, and the mixture was refluxed for 2 h. It was then distilled to give 1.4 g (74%) of 1-acetyl-2-ethyl-3,3,5-trimethylpyrazolidine with bp 138-140°C (13 mm) and n_D^{20} 1.4612. The IR spectra of this compound and the compound obtained by reduction of 1-acetyl-3,5,5-trimethylpyrazoline hydrochloride are identical.

1-Acetyl-2-isopropyl-3,3,5-trimethylpyrazolidine. A suspension of 3.7 g (0.1 mole) of $LiAlH_4$ was added to a suspension of 11.5 g (0.019 mole) of 1-isopropylidene-3,5,5-trimethylpyrazoline hexachlorostannate [9] in 50 ml of absolute ether, and the mixture was refluxed for 3 h. It was then worked up as in the preceding experiment. Vacuum distillation gave 1.6 g (36%) of 1-acetyl-2-isopropyl-3,3,5-trimethyl-pyrazolidine (Table 1).

Reduction of 1-Acetylpyrazoline Hydrochlorides. A strong stream of dry hydrogen chloride was passed into a solution of 0.1 mole of acetylpyrazoline in absolute ether for 15-20 min, after which the ether was evaporated, and absolute benzene was distilled from the residue four to five times. A suspension of 11.4 g (0.3 mole) of $LiAlH_4$ in 50 ml of ether was added to a suspension of the hydrochloride in 100 ml of absolute ether or tetrahydrofuran (THF), and the mixture was refluxed for 2-3 h. The mixture was then worked up as in the preceding experiment. The spectral characteristics and constants are presented in Table 1.

Reduction of 1-Acetyl-3,5,5-trimethylpyrazoline Deuterochloride. A strong stream of dry deuterium chloride was passed into a solution of 7.7 g (0.05 mole) of 1-acetyl-3,5,5-trimethylpyrazoline in absolute ether, and the resulting suspension was transferred to a

filter by means of dry argon, washed four to five times with absolute ether, blow-dried with dry argon, and dried in vacuo (with an oil pump). The salt was suspended in absolute ether and transferred by means of dry argon to a flask that had been previously dried in a stream of argon at 110-115°C. A 7.6-g (0.2 mole) sample of $LiAlH_4$ was sprinkled into the flask that had been previously dried in a stream of argon at 110-115°C. A 7.6-g (0.2 mole) sample of $LiAlH_4$ was sprinkled into the flask with stirring, and the liberated gases were passed through a trap cooled to −70°C. A total of 50 ml of a gas with m/e 39 (argon) was isolated. The usual workup gave 7.2 g (80%) of 1-acetyl-2-ethyl-3,3,5-trimethylpyrazolidine.

Reduction of Pyrazolines with Aluminum Hydride. A solution of aluminum hydride was obtained by the method in [10] from 31.2 ml of a 1.6 M solution of $LiAlH_4$ in THF and 2.45 g (0.025 mole) of 100% H_2SO_4 dissolved in 20 ml of absolute THF. The resulting solution was used without additional purification. A solution of 1-alkyl(acetyl)pyrazoline in the necessary ratio (see the text) was added to the solution of AlH_3, and the mixture was refluxed for 3 h in an argon atmosphere. The subsequent workup was similar to that described above.

LITERATURE CITED

1. A. N. Kost, G. A. Golubeva, M. A. Lapitskaya, and A. G. Popova, Zh. Org. Khim., 8, 1320 (1972).
2. G. A. Golubeva, L. A. Sviridova, N. Yu. Lebedenko, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 4, 547 (1973).
3. M. A. Lapitskaya, Author's Abstract of Master's Dissertation, Moscow State Univ. (1972).
4. A. N. Kost, G. A. Golubeva, M. A. Lapitskaya, and S. M. Sernikova, Zh. Org. Khim., 5, 752 (1969).
5. E. B. Rathbone, A. M. Stefen, J. Schwersenski, and J. B. Tyler, S. Af. Chem. Inst., 28, 287 (1975).
6. R. A. Khmel'nitskii, A. N. Krasnoshchek, A. A. Polyakova, and I. I. Grandberg, Zh. Org. Khim., 3, 1540 (1967).
7. A. V. El'tsov and N. M. Omar, Zh. Org. Khim., 4, 1294 (1968).
8. R. Bell, The Proton in Chemistry, Cornell Univ. Press (1973).
9. M. Lamchen, W. Pugh, and A. M. Stefen, J. Chem. Soc., No. 7, 2429 (1954).
10. H. C. Brown and N. M. Yoon, J. Am. Chem. Soc., 88, 1416 (1966).