Ring-Chain Tautomerism of Acetone *N*-Methylated Thiosemicarbazones

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Ring-chain tautomerism of acetone *N*-methylated thiosemicarbazones was studied by nmr spectroscopy. Acetone thiosemicarbazone, acetone 2-methylthiosemicarbazone, and acetone 4-methylthiosemicarbazone exist as chain forms in DMSO-d_6 and ring forms in deuteriotrifluoroacetic acid. However, the compound obtained by reaction of acetone with 2,4-dimethylthiosemicarbazide exists only as the ring form 3,5,5-trimethyl-1,3,4-thiadiazolidine-2-methylimine both in DMSO-d_6 and in deuteriotrifluoroacetic acid, due to steric hindrance of the three methyl groups.

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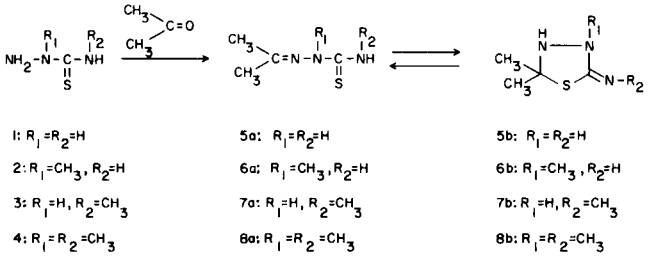
Aldehyde thiosemicarbazones (1) and ketone thiosemicarbazones (2) generally exist as ring forms in acidic solution, whereas they exist as chain forms in neutral solution. However, we recently found that the product obtained by reaction of 2,4-dimethylthiosemicarbazide with acetone exists as only the cyclic isomer, 3,5,5-trimethyl-1,3,4-thiadiazolidine-2-methylimine, even in neutral solution. Previously we reported that some aldehyde *N*-methylated semicarbazones cyclize in trifluoroacetic acid and that the presence of substituents at the N^2-position in aldehyde semicarbazone is of primary importance for their cycloisomerization (3). This finding and the results obtained previously prompted us to study the effect on *N*-substituents on cycloisomerization of various acetone *N*-methylated thiosemicarbazones.

It has been reported that the nmr signal of the six *C*-methyl protons of 5,5-dimethyl-1,3,4-thiadiazolidine-2-thione appears as one singlet, while the signal of those of methyl 3-isopropylidenedithiocarbazate appears as two singlets, because of the C=N bond (4). Thus it is possible to determine whether acetone thiosemicarbazones exist in ring or chain forms from the signal patterns of their *C*-methyl protons.

Chart I



1: R_1=R_2=H
2: R_1=CH_3, R_2=H
3: R_1=H, R_2=CH_3
4: R_1=R_2=CH_3

5a: R_1=R_2=H
6a: R_1=CH_3, R_2=H
7a: R_1=H, R_2=CH_3
8a: R_1=R_2=CH_3

5b: R_1=R_2=H
6b: R_1=CH_3, R_2=H
7b: R_1=H, R_2=CH_3
8b: R_1=R_2=CH_3

Table I shows that the signals of *C*-methyl protons of acetone thiosemicarbazone (**5a**), acetone 2-methylthiosemicarbazone (**6a**) and acetone 4-methylthiosemicarbazone (**7a**) appeared as two singlets (each 3H) in DMSO-d_6, while they appeared as a singlet (6H) in deuteriotrifluoroacetic acid. This indicates that compounds **5a**, **6a**, and **7a** exist as chain forms in DMSO-d_6, but that they are cyclized to the 1,3,4-thiadiazolidine derivatives (**5b**, **6b**, and **7b**, respectively) in deuteriotrifluoroacetic acid. However, the signal of the *C*-methyl protons of the compound obtained by reaction of 2,4-dimethylthiosemicarbazide (**4**) with acetone appeared as a singlet (6H) in both DMSO-d_6 and deuteriotrifluoroacetic acid. This suggests that it can exist only as the ring form, 3,5,5-trimethyl-1,3,4-thiadiazolidine-2-methylimine (**8b**).

To examine the stability of the ring isomer (**8b**), we measured the nmr spectra of this compound in various alkaline media, which seem to favor ring-opening. The nmr spectral data on **8b** in these alkaline solutions are shown in Table II. The signal of the six *C*-methyl protons of **8b** appeared as a singlet, suggesting that **8b** remained unchanged in alkaline solution.

In DMSO-d_6 the difference between the chemical shifts of the two *C*-methyl peaks of 2-methylthiosemicarbazone (**6a**) was about 18 Hz, whereas the differences between the two chemical shifts of other thiosemicarbazones (**5a** and **7a**) without a methyl group at position 2 were much smaller. The relatively large value for **6a** is ascribed to the anisotropic effects of its thiocarbonyl group, because the steric hindrance of the *C*-methyl groups with the N^2-methyl group seems to favor the conformation in which the C=S group is near to one of the two *C*-methyl groups. These data and the fact that the signal of the *C*-methyl protons of **8b** still appeared as a singlet in alkaline solution indicate that there is no tautomeric change in **8b**. The high stability of **8b** in alkaline solutions is in contrast to the fact that the 5-monosubstituted 1,3,4-thiadiazolidine-2-thions (1) and 5,5-disubstituted 1,3,4-thiadiazolidine-2-thiones (4,5) are readily converted to their chain isomers in alkaline solutions.

Attempts to obtain acetone 2,4-dimethylthiosemicarbazone (**8a**), as the chain isomer of **8b** were unsuccessful. The failure to obtain the chain isomer may be because

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Table I

Chemical Shifts of C^5-Methyl Protons of Acetone Thiosemicarbazones

Compound No.	R_1	R_2	Solvent DMSO-d_6	Solvent Deuteriotrifluoroacetic Acid
5a	H	H	1.87 (3H, s) 1.89 (3H, s)	1.88 (6H, s)
6a	CH_3	H	1.84 (3H, s) 2.02 (3H, s)	1.78 (6H, s)
7a	H	CH_3	1.90 (3H, s) 1.92 (3H, s)	1.88 (6H, s)
8a	CH_3	CH_3	1.24 (6H, s)	1.77 (6H, s)

Table II

Chemical Shifts of C^5-Methyl Protons of 3,5,5-Trimethyl-1,3,4-thiadiazolidine-2-methylimine (**8b**) in Alkaline Solutions

Solvent	Chemical Shift (ppm)
0.3 ml. of 1*N* Sodium Deuteroxide + 0.2 ml. of Methanol-d_4	1.74 (6H, s)
0.3 ml. of 3*N* Sodium Deuteroxide + 0.2 ml. of Methanol-d_4	1.68 (6H, s)
0.1 g. of Sodium in 0.5 ml. of Methanol-d_4	1.40 (6H, s)

large steric hindrance by the three methyl groups in the chain isomer (**8a**) prevents its formation

From these results we concluded that acetone thiosemicarbazone (**5a**), 2-methylthiosemicarbazone (**6a**), and 4-methylthiosemicarbazone (**7a**) exist as chain forms in neutral solution and ring forms in trifluoroacetic acid; the product obtained by reaction of 2,4-dimethylthiosemicarbazide with acetone can exist as only the ring form in both DMSO and trifluoroacetic acid, due to steric hindrance of the three methyl groups.

EXPERIMENTAL

Nmr spectra were recorded with JEOL-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. All melting points were determined by the capillary method and are uncorrected. Acetone thiosemicarbazone (**5a**) was prepared by the method described in the literature (6), m.p. 176-178°.

Acetone 2-methylthiosemicarbazone (**6a**).

A mixture of 2-methylthiosemicarbazide (**2**) (7) (0.63 g., 6 mmoles) and anhydrous magnesium sulfate (0.7 g.) in dry acetone (80 ml.) was refluxed for 6 hours. After magnesium sulfate was removed by filtration, the filtrate was evaporated to dryness. The residue was recrystallized from ethanol to give colorless needles (0.71 g., 81%), m.p. 138-140°; nmr (deuteriochloroform): δ 1.98 (3H, s, CH_3), 2.13 (3H, s, CH_3), 3.44 (3H, s, NCH_3), 6.10 (2H, broad, NH_2); (DMSO-d_6): δ 1.84 (3H, s, CH_3), 2.02 (3H, s, CH_3), 3.23 (3H, s, NCH_3), 7.00 (2H, broad, NH_2); (deuteriotrifluoroacetic acid): δ 1.78 (6H, s, CH_3), 3.44 (3H, s, NCH_3).

Anal. Calcd. for $C_5H_{10}N_3S$: C, 41.35; H, 7.63; N, 28.93. Found: C, 41.35; H, 7.68; N, 28.73.

Acetone 4-Methylthiosemicarbazone (**7a**).

A solution of 4-methylthiosemicarbazide (**3**) (8) (0.32 g., 3 mmoles) in dry acetone (30 ml.) was refluxed for 3 hours, and evaporated to dryness. The residue was recrystallized from chloroform giving colorless needles (0.4 g., 92%), m.p. 115-117°; nmr (DMSO-d_6): δ 1.90 (3H, s, CH_3), 1.92 (3H, s, CH_3), 2.93 (3H, d, J = 6 Hz, NCH_3), 8.14 (1H, broad, NH), 9.90 (1H, s, NH); (deuteriochloroform): δ 1.89 (3H, s, CH_3), 1.99 (3H, s, CH_3), 3.18 (3H, d, J = 4 Hz, NCH_3), 7.54 (1H, broad, NH), 8.46 (1H, broad, NH); (deuteriotrifluoroacetic acid): δ 1.88 (6H, s, CH_3), 3.17 (3H, s, NCH_3).

Anal. Calcd. for $C_5H_{10}N_3S$: C, 41.35; H, 7.63; N, 28.93. Found: C, 41.36; H, 7.69; N, 28.70.

3,5,5-Trimethyl-1,3,4-thiadiazolidine-2-methylimine (**8b**).

(a)

A solution of 2,4-dimethylthiosemicarbazide (**4**) (9) (0.36 g., 3 mmoles) in dry acetone (40 ml.) was refluxed for 1 hour, and evaporated to dryness. The residue was recrystallized from isopropyl ether giving colorless needles (0.33 g., 68%), m.p. 72-74°; nmr (DMSO-d_6): δ 1.24 (6H, s, CH_3), 2.83 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 5.62 (1H, s, NH); (deuteriotrifluoroacetic acid): δ 1.77 (6H, s, CH_3), 3.10 (3H, s, NCH_3), 3.35 (3H, s, NCH_3).

Anal. Calcd. for $C_6H_{12}N_3S$: C, 45.25; H, 8.23; N, 26.39. Found: C, 45.04; H, 8.32; N, 26.58.

(b)

A solution of methylisothiocyanate (2.69 g., 0.037 mole) in ethanol (4 ml.) was added dropwise to a solution of acetone methylhydrazone (3.16 g., 0.037 mole) in ethanol (5 ml.) and the mixture was stirred at room temperature overnight. Evaporation of the solvent gave a solid residue which was recrystallized from isopropyl ether to give colorless needles (1.31 g., 23.3%), m.p. 72-74°.

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