# Six-membered cyclic semiaminal as intermediate in the synthesis of thiazoles from thiosemicarbazide and α-haloketones

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Cyclization of thiosemicarbazide with methyl 3-chloro-2-oxo-3-phenylpropionate in MeCN results in 5-hydroxy-2-imino-5-methoxycarbonyl-6-phenylperhydro-1,3,4-thiadiazine. The structure of the product has been confirmed using spectral (IR, $^1H$, $^{13}C$, $^{13}C\{^1H\}$ NMR) methods and chemical transformations.

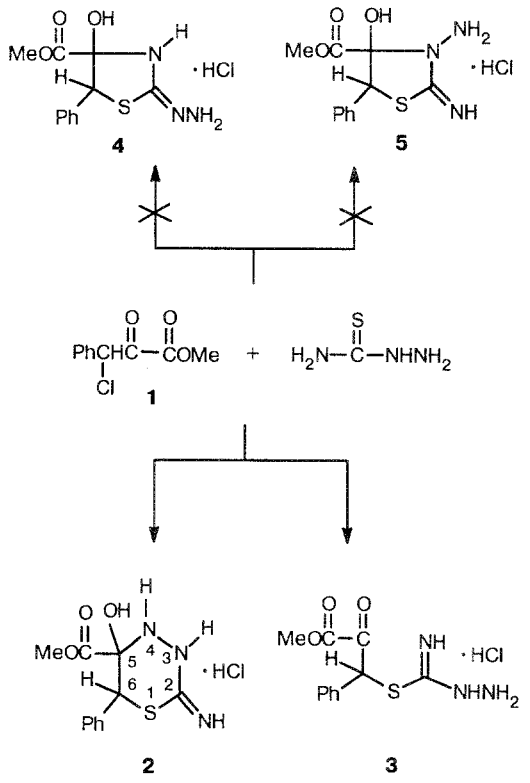
**Key words:** cyclic hemiaminals, thiadiazine, 2-amino- and 2-hydrazinothiazoles.

Although a large number of works[1,2] deal with the reactions of thiosemicarbazide (TSC) with α-haloketones, it is practically impossible to predict the structure of condensation products for newly obtained α-haloketones. The analysis of literature data shows that in such reactions possible products are thiadiazines,[3] thiazoles,[4] thiazolines,[5] pyrazoles,[6] and other compounds,[1,2] depending on the nature of the substituents both in the α-halocarbonyl compound and in TSC, as well as on the reaction conditions, *i.e.*, temperature, solvent, reagent addition order, *etc.* In a number of cases, variation of medium acidity enabled isolation and identification of the first stage products: isothiocarbohydrazides formed by sulfur alkylation in a neutral medium,[7] and α-halothiocarbazones[8] formed by the Shiff reaction of the carbonyl group in a weak acid medium. Nevertheless, until recently in the literature there were no data on the isolation of cyclic hemiaminals as intermediates, possibly, because of the instability of these compounds.

It could be expected that varying the nature of the substituent in an α-halocarbonyl compound might affect the stability of intermediates. With this in mind in the present work methyl 3-chloro-3-phenyl-2-oxopropionate (**1**)[9] was used as an α-halocarbonyl compound for the first time. We have shown that the reaction of α-chloroketone **1** with TSC in MeCN results in a crystalline product with a fixed melting point. According to the mass-spectrum and microanalysis data it is possible to assert that the reaction product has one of the four structures (**2**—**5**) (Scheme 1).

The absence of signals for the carbonyl and C=N groups in the $^{13}C$ NMR spectrum makes it possible to confidently exclude structure **3** from consideration. The product of the reaction of **1** with TSC when treated with

**Scheme 1**

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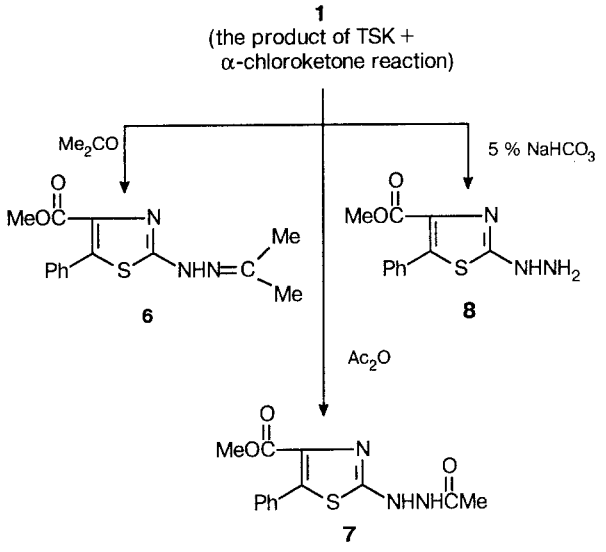
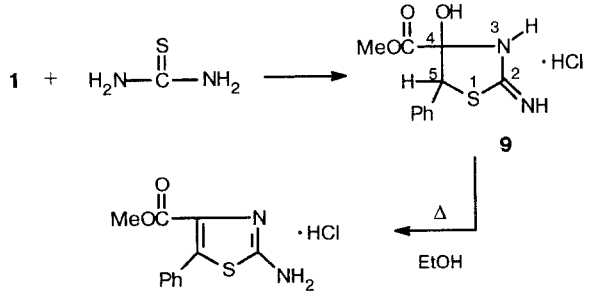
$Me_2CO$, $Ac_2O$, and an aqueous solution of $NaHCO_3$ (Scheme 2) is converted to 2-hydrazinothiazole derivatives[10] (**6**—**8**) (*cf.* Ref. 10).

**Scheme 2**

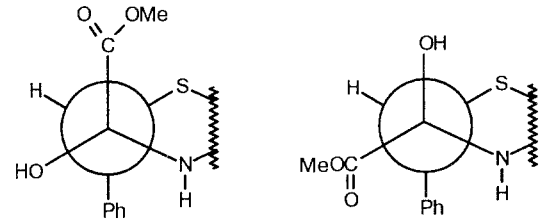



Although the formation of compounds **6**—**8** could be explained by recyclization of molecules like **4** and **5**, the latter can not be the products of the reaction considered (α-chlorocarbonyl compound **1** with TSC) because an authentic sample of 2-iminothiazolidine **9**, which was synthesized from thiourea and α-chloroketone **1** and has a structure similar to those of **4** and **5**, is unstable and readily transforms to 2-aminothiazole **10** by heating in ethanol (Scheme 3). On the other hand, the product of the reaction of TSC with α-chloroketone **1** is stable and can be recrystallized from ethanol (scheme 3).

**Scheme 3**




Proton and carbon spectra of the product of the reaction of TSC with α-chloroketone **1** do not contradict to structure **2**. In the $^1H$ NMR spectra, besides phenyl ring proton signals and those of the protons connected with the nitrogen atom, there are two pairs of singlet signals corresponding to the resonance of methoxyl and methyne protons at 3.5 and 5.5 ppm, respectively. We believe that the duplication of the signals is caused by the existence of two diastereomers (**2**α and **2**β) of 5-hydroxy-2-imino-5-methoxycarbonyl-6-phenylperhydro-1,3,4-thiadiazine **2** in a ratio of 1 : 1, as follows from the signal intensities in both pairs.




The $^{13}C$ and $^{13}C\{^1H\}$ NMR spectra also have double the number of resonance signals for each $^{13}C$ nucleus (Fig. 1). The location of the signals and their multiplicity, caused by spin-spin $^{13}C$ and $^1H$ interaction through one bond as well as by long distance couplings, permitted us to assign the chemical shifts unequivocally in the hydrochloride **2** structure.

The inversion of the chemical shifts of the atoms C(6), C(7) (methoxyl group carbon atom), $C_m$, $C_p$, and $C_o$ (phenyl ring *meta*-, *para*-, and *ortho*-carbon atoms correspondingly) of one diastereomer relative to the other one draws attention. For example, in one diastereomer the C(6) atom signal is located in a higher field than that of the C(7) atom, while in the other diastereomer $\delta C(6) > \delta C(7)$. Analogously, in one diastereomer the signals of the $C_m$ atom and the $C_p$ atom lie in a lower field relative to the signal of the $C_o$ atom, but in the other diastereomer this regularity is reversed. In addition, the signal of the quaternary C(5) carbon atom is split into a doublet ($^2J_{CH}$ = 6.6 Hz) in only one of the diastereomers. The last fact indicates a different spatial disposition of the substituents at the C(6) and C(5) atoms in the diastereomers.

Thus, on the grounds of the data mentioned above, we believe that the product of the reaction of α-chloroketone **1** with TSC has the structure of the six-membered cyclic hemiaminal **2**, and exists as a mixture of two diastereomers (**2**α and **2**β).

In reactions of hemiaminal **2** with electrophilic reagents, *i.e.*, $Me_2CO$, $Ac_2O$, and sodium bicarbonate, the initial splitting of the N(4)—C(5) bond in hydrochloride **2** and consequent ring closure with participation of

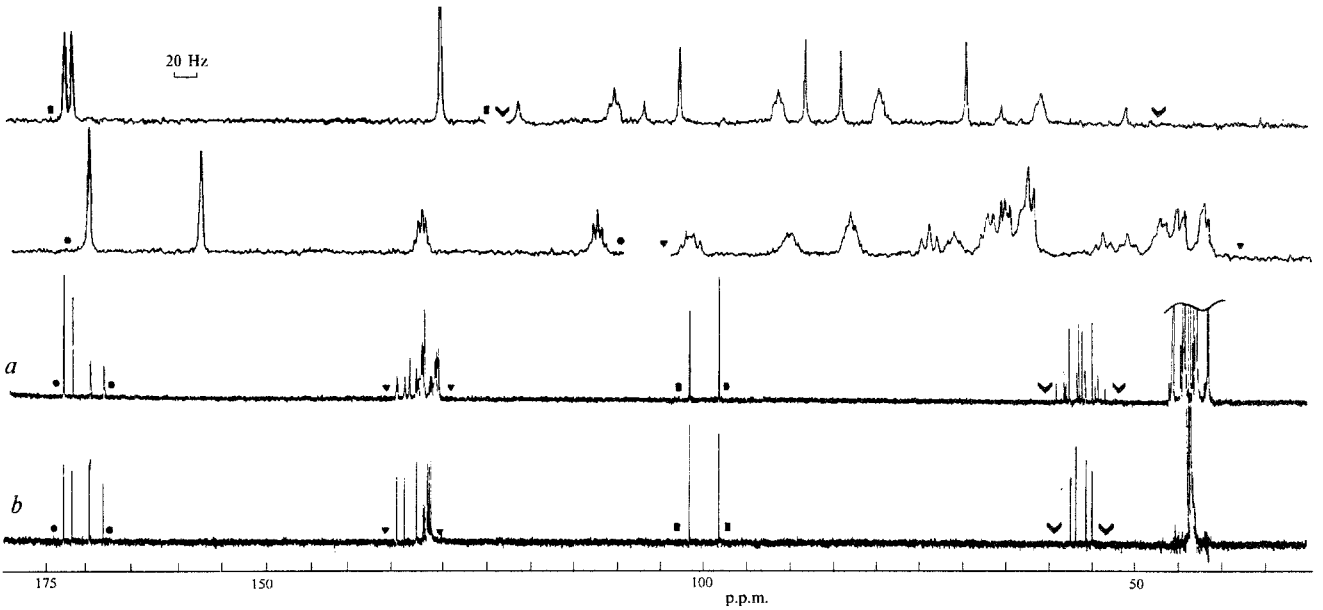



**Fig.1.** $^{13}C$ (*a*) and $^{13}C\{^1H\}$ (*b*) NMR spectra of 5-hydroxy-2-imino-5-methoxycarbonyl-6-phenylperhydro-1,3,4-thiadiazine hydrochloride (**2**).

imine nitrogen should preceed the formation of 2-hydrazinothiazoles derivatives **6—8**.

## Experimental

Melting points were measured on a«Boetius» table. $^1H$ and $^{13}C$ NMR spectra of compound **2** were recorded on a «Bruker MSL-400» spectrometer with working frequency 400.13 MHz for $^1H$ and 100.6 MHz for $^{13}C$; samples were dissolved in $(CD_3)_2SO$. Chemical shifts are reported in δ-scale and measured relative to $(CD_3)_2SO$. $^1H$ NMR spectra of the compounds **6—9** were recorded on a «Varian-60» (60 MHz) spectrometer; chemical shifts are reported relative to TMS. IR spectra were registered on a UR-20 spectrophotometer (paste in vaseline). Mass-spectra were obtained on an MX-1310 instrument with ionization power 70 eV; a sample was injected into ion emitter with the use of an SVP-5 syringe at ion emitter temperature 50°C and current in electron collector $I_c$ = 30 μA.

**5-Hydroxy-2-imino-5-methoxycarbonyl-6-phenylperhydro-1,3,4-thiadiazine hydrochloride (2).** 4.2 g (0.02 mol) of methyl 3-phenyl-3-chlor-2-oxopropionate **1** was added to a suspension of 1.8 g (0.02 mol) of TSC in 100 ml of $CH_3CN$ at ~20°C. The reaction mixture was heated at 60°C for 6 h. The crystals that formed were filtered off to give 5.05 g (83%) of compound **2**, m.p. 154—156°C (EtOH). Found (%): C 43.39; H 4.42; Cl 11.55; N 14.01; S 10.80. $C_{11}H_{14}ClN_3O_3S$. Calculated (%): C 43.51; H 4.61; Cl 11.68; N 13.83; S 10.56. IR spectrum, (ν, $cm^{-1}$): 705, 730, 858, 975, 1050, 1135, 1155, 1300, 1450, 1550, 1660, 1795, 3090, 3170, 3320. $^1H$ NMR spectrum, (δ, ppm): 7.45 (m, 10 H, 2 $C_6H_5$); 5.57 (s, 1 H, CH); 5.47 (s, 1 H, CH); 3.88 (s, 3 H, $CH_3O$); 3.38 (s, 3 H, $CH_3O$). $^{13}C\{^1H\}$ NMR spectrum (δ, ppm): 173.16 and 172.16 ($C_2$); 170.15 and 168.54 (C=O); 135.29 and 134.37 ($C_i$); 131.73 and 131.57 ($C_o$); 133.01 and 131.34 ($C_m$); 132.27 and 132.00 ($C_p$); 101.63 and 98.26 ($C_5$); 57.50 and 55.06 ($C_5$); 56.88 and 55.73 ($CH_3O$). Mass spectrum, *m/z* ($I_{отн}$, %): 267 $[M]^+$ (2.2); 249 $[M-H_2O]^+$ (2.5); 218 $[M-H_2O-CH_3OH]^+$ (6); 91 $[M-176]^+$ (21); 60 $[M-207]^+$ (23); 36 $[HCl]^+$ (100).

**Reaction of compound 2 with acetone.** A solution of 1.5 g (0.0049 mol) of compound **2** in 15 ml of acetone was refluxed for 45 min. The crystals that formed were filtered off and recrystallized from ethanol to give 1 g (70%) of 2-isopropyliden-hydrazino-4-methoxycarbonyl-5-phenylthiazole **6**, m.p. 184—186 °C (the m.p. of compound **6** reported by us previously[10] was wrong, the corrected value is 185—186 °C).

**Reaction of compound 2 with acetic anhydride.** 1 ml of acetic anhydride was added to a suspension of 1.8 g (0.0042 mol) of compound **2** in 5 ml of pyridine at ~20°C. The reaction mixture was stored for 12 h at this temperature, the solvent was distilled off in vacuo, and the residue was treated with water to give 0.8 g (64 %) of 2-(2′-acethylhydrazino)-4-methoxycarbonyl-5-phenylthiazole **7**, m.p. 240—241°C (MeOH). Found (%): C 53.55; H 4.43; N 14.52; S 11.05. $C_{13}H_{13}N_3O_3S$. Calculated (%): C 53.62; H 4.46; N 14.42; S 11.01. IR spectrum, (ν / $cm^{-1}$): 770, 1210, 1550, 1690, 1720, 3050, 3130. PMR spectrum (DMSO-$d_6$, δ, ppm): 12.36 (br.s, 1 H, NH); 7.33 (s, 5 H, $C_6H_5$); 3.66 (s, 3 H, $CH_3C(O)O$); 2.16 (s, 3 H, $CH_3C(O)$).

**Treatment the compound 2 with $NaHCO_3$.** 50 ml of a 5 % aqueous solution of $NaHCO_3$ was added to a solution of 1.5 g

(0.0032 mol) of the compound **2** in 150 ml $H_2O$ at ~20°C. The reaction mixture was stored for 30 min at 45—50°C, the crystals that formed were filtered off and washed with water to give 0.6 g (46%) of 2-hydrazino-4-methoxycarbonyl-5-phenylthiazole **8**, m.p. 183—185°C (*i*-PrOH) (*cf.* Ref. 10).

**Reaction of methyl 3-chloro-2-oxo-3-phenylpropionate 1 with thiourea.** 4.0 g (0.019 mol) of compound **1** was added at 15°C to a suspension of 1.5 g (0.019 mol) of thiourea in 20 ml of $CH_3CN$, and the reaction mixture was stirred at this temperature for 4 h. The crystals that formed were filtered off and washed with $CH_3CN$ to give 2.1 g (38.8%) of 4-hydroxy-2-imino-4-methoxycarbonyl-5-phenylthiazolidine hydrochloride **9**, m.p. 166—168°C. Found (%): C 45.54; H 4.31; Cl 12.51; N 10.33; S 10.73. $C_{11}H_{13}ClN_2O_3S$. Calculated (%): C 45.78; H 4.50; Cl 12.28; N 9.70; S 11.11. IR spectra, ($\nu$ / $cm^{-1}$): 705, 1050, 1120, 1280, 1660, 1750, 2700, 3080, 3300. $^1H$ NMR spectrum, (DMSO-$d_6$, $\delta$, ppm): 7.28 (m, 5 H, $C_6H_5$); 5.50 (s, 1 H, CH); 3.68 (s, 3 H, $CH_3O$). $^{13}C\{^1H\}$ NMR spectrum, (DMSO-$d_6$, $\delta$, ppm): 172.01 ($C_2$); 167.79 (C=O); 131.20 ($C_i$); 130.55 ($C_o$); 128.34 ($C_m$); 129.1 ($C_p$); 91.88 ($C_4$); 56.79 ($C_5$); 53.54 ($CH_3$).

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