Hydroxyketones in the thiadiazine cycle formation

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Cyclocondensation of 1-hydroxyketones with thiosemicarbazide resulted in thiadiazines. Nitrate ester of 1-hydroxyketone reacted under similar conditions to give the corresponding thiosemicarbazone. In the case of bromoacetyl-substituted nitrate ester of 1-hydroxyketone, condensation proceeded *via* intramolecular reaction between the thiol and bromomethyl groups.

Key words: cyclocondensation, thiosemicarbazones, 1-hydroxyketones, aminothiadiazine ring.

One of the modern approaches towards five- and six-membered heterocycles is a condensation of thiosemicarbazide (TSC) with carbonyl compounds. The main advantages in this filed are summarized in the review.[1] It has been shown that the reaction course depends on the reaction conditions to give either five-membered thiazolidines or six-membered 1,2,4-triazines and 1,3,4-thiadiazines as the major products.

For instance, reaction of TSC with acetylenedicarboxylates in anhydrous dichloromethane gives the corresponding thiazolidines in high yields,[2] while the same reaction carried out either solvent-free under microwave irradiation or in refluxing low alcohols produces six-membered triazinones.[3]

Reaction of TSC with aromatic carbonyl compounds in acidic alcohol solutions leads to the corresponding thiosemicarbazones, which undergo condensation with α-halocarboxylic acids to yield five-membered thiazolidinones.[4]

1,3,4-Thiadiazines can be also synthesized by the reaction of TSC with α-halocarbonyl compounds.[5—7]

Synthesis of vicinal 2-amino-1,3,4-thiadiazines by the reaction of acyloins with thiosemicarbazides in TFA has been described earlier.[8] The thiadiazine ring system is formed *via* an intermediate carbocation.

In the present work, we report on the reactions of TSC with 3-hydroxy-3-methylbutan-2-one (**1**), 1-(1-hydroxycyclohexyl)ethanone (**2**), and 3-methyl-3-nitrooxybutan-2-one (**3**). Analysis of the reaction products indicates that in all cases compounds of the Schiff base type are initially formed. This conclusion is based on a comparison of the reactivity of structural analogs of 1-hydroxy ketones and directions of their reactions with TSC.

Thus, cyclization of thiosemicarbazones of 3-hydroxy-3-methylbutan-2-one (**4**) and 1-(1-hydroxycyclohexyl)ethanone (**5**) to give thiadiazines **6** and **7** can be enabled by catalytic amounts of sulfuric acid (Scheme 1). Note that thiosemicarbazone **8** (Scheme 2) bearing protected hydroxy group is stable under these conditions.

Apparently, the reaction is initiated by protonation of the hydroxy group as described,[8] leading to a water molecule elimination and subsequent bonding of the thiol group to the adjacent carbon atom.

Formation of six-membered thiadiazine ring of **6** was also confirmed by the counter synthesis, namely, by the reaction of TSC with isopropenyl methyl ketone (**9**). Compound **9** was prepared from dimethylacetylcarbinol by dehydration with phosphorous anhydride in anhydrous chloroform as earlier described.[9]

Total similarity of the cyclizations involving compound **1** and its dehydrated derivative **9** suggests that in the case of compound **1** the water molecule elimination at the intermediate stage is essential for finalizing the cyclization.

^{1}H NMR spectra of compounds **6** and **7** lack the proton signals at δ 6.30 characteristic of the OH groups of the starting thiosemicabazones of 3-hydroxy-3-methylbutan-2-one (**4**) and 1-(1-hydroxycyclohexyl)ethanone (**5**).

In the case of 3-methyl-3-nitrooxybutan-2-one (**3**), the nitro ester group apparently impedes the cyclization and the Schiff base becomes the major reaction product (see Scheme 2).

IR spectrum of 3-methyl-3-nitrooxobutan-2-one (**8**) exhibits new absorptions at 1170, 1275, 1650, 1520, and 3200 cm^{-1} attributed to the N—C(S)—N, O—NO_2, C=N, N—N, and NH_2 groups, respectively.

It has been shown previously[10] that the activated methyl group bonded to the carbonyl group is rather readily undergoes bromination and the products of cyclocondensation of these α-bromo derivatives with 4-substituted thiosemicarbazides inhibit human platelet aggrega-

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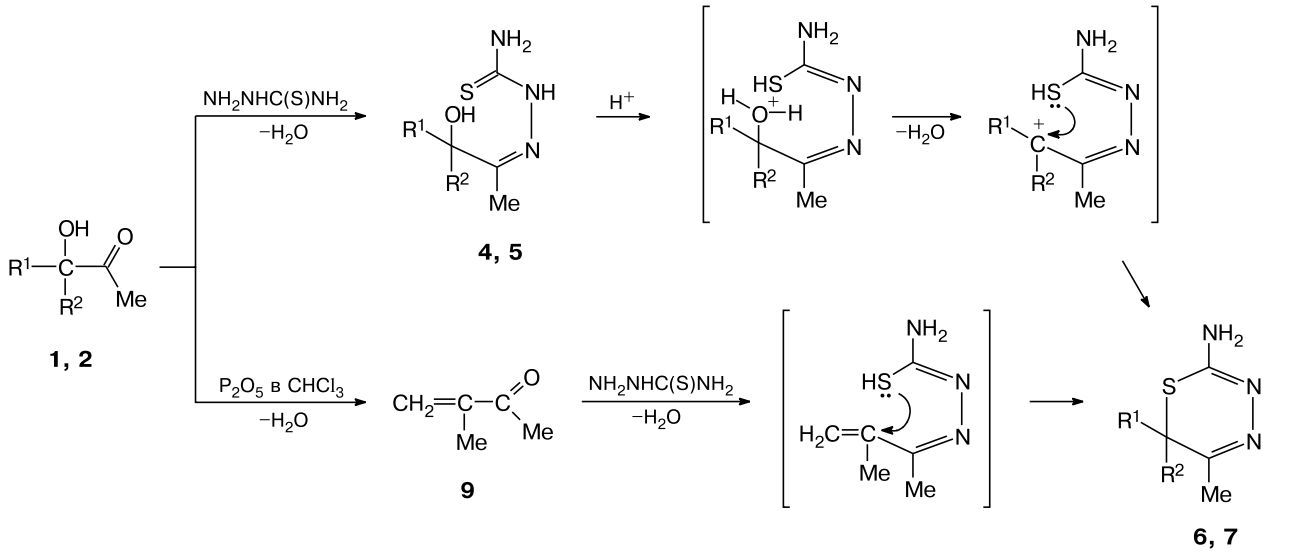
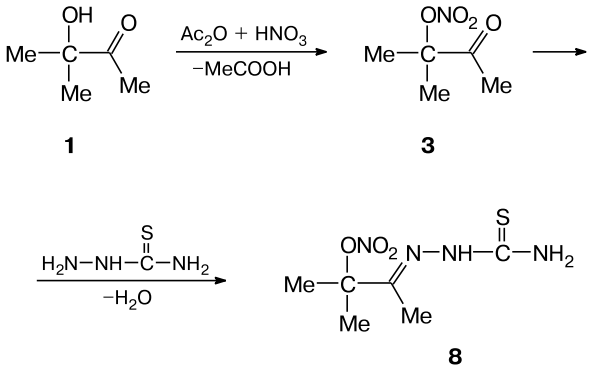
Scheme 1



$R^1 = R^2 = Me$ (**1**, **4**, **6**), $R^1 + R^2 = (CH_2)_5$ (**2**, **5**, **7**)

Scheme 2



tion induced by ADP. Taking these facts into account, we synthesized the corresponding bifunctional brominated derivatives **10—12** from 3-hydroxy-3-methyl-1-butanone (**1**) and 1-(1-hydroxycyclohexyl)-2-ethanone (**2**) (Scheme 3).

We believed that bromo-substituted 1-hydroxy ketones **10** and **11** can serve as the starting material in the synthesis of six-membered aminothiadiazines since the C atom of the bromomethyl group will participate in the reaction.

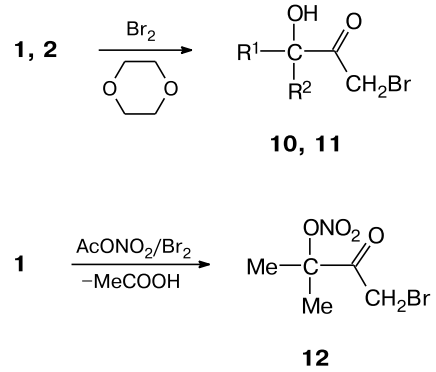
3-Hydroxy-3-methylbutan-2-one (**1**) was treated one-pot with acetyl nitrate ($AcONO_2$) and bromine in AcOH to give 1-bromo-3-methyl-3-nitrooxybutan-2-one (**12**) in 75% yield (see Scheme 3).

To determine, which one of two possible directions of the attack of the thiol group on the C atom is realized (C—OH (intermediate **A**) or C—Br (intermediate **B**)), we studied the reactions of bromo ketones **10—12** with TSC in refluxing ethanol (Scheme 4).

It was found that these reactions produce 2-aminothiadiazines **13a—c**. This indicates that intramolecular attack on the thiol group is directed on the C atom of the bromomethyl group.

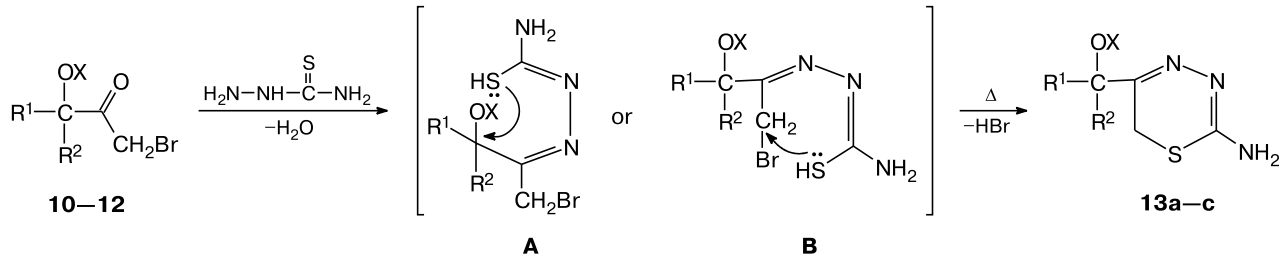
Formation of six-membered aminothiadiazines **13a—c** was confirmed by IR and ^1H NMR spectroscopy. IR spectra of compounds **13a—c** lack the absorptions characteristic of the C—Br bonds. This spectral change can be attributed to the involvement of the Br atom in the cyclization. New bands at 1325—1175, 1425, 3250, and 760, 675, 1520, 1650 cm^{-1} were ascribed to the vibrations of the exocyclic (C—C, C—N, C—O) and endocyclic (C—S, N—N, C=N) bonds, respectively.

Scheme 3



$R^1 = R^2 = Me$ (**1**, **10**), $R^1 + R^2 = (CH_2)_5$ (**2**, **11**)

Scheme 4



$R^1 = R^2 = Me$, X = H (**10**, **13a**); $R^1 = R^2 = Me$, X= NO_2 (**12**, **13c**); $R^1 + R^2 = (CH_2)_5$, X = H (**11**, **13b**)

^{1}H NMR spectra of compounds **13a—c** show two singlets at δ 4.42 and 4.82 with the 4 H integral intensity. These signals were assigned to the protons at the 6-position and the exocyclic amino group, respectively. Note that in the ^{1}H NMR spectrum of compound **13a** a singlet signal of the OH group proton of the starting bromo derivative **10** is retained and appeared at δ 6.30.

Experimental

^{1}H NMR spectra were recorded on a XTIPC VARIAN MR-400 instrument with the working frequency of 400 MHz. The chemical shifts are given in the δ scale relative to $SiMe_4$ (internal standard).

IR spectra were recoded with a Perkin—Elmer Spectrum-65 spectrophotometer. Elemental analysis was performed with a Perkin—Elmer 2400 analyzer. Melting points were measured on a Boetius apparatus; heating range was 4 °C min^{-1}.

3-Hydroxy-3-methylbutan-2-one (1) and 1-(1-hydroxycyclohexyl)ethanone (2) were synthesized by the Kucherov reaction from the corresponding acetylene alcohols.[11] **Isopropenyl methyl ketone (9)** was synthesized following the known procedure.[9] **1-Bromo-3-hydroxy-3-methylbutan-2-one (10)** and **2-bromo-1-(1-hydroxycyclohexyl)ethanone (11)** were synthesized by the described procedure.[10].

3-Methyl-3-nitrooxybutan-2-one (3). To a stirred solution of dimethyl acetyl carbinol (**1**) (10.2 g, 0.1 mol) in a mixture of Ac_2O (10.2 g, 0.1 mol) and glacial AcOH (20 mL), a solution of 98% HNO_3 (6.5 g, 0.1 mol) in glacial AcOH (10 mL) was added dropwise at −5 °C. The reaction mixture was stirred for 2 h with cooling and then Ac_2O was distilled off at 70 °C (water bath) under vacuum. The product was purified by vacuum distillation at 45 °C (20 Torr). Yield 10 g (68%), n_D^{20} = 1.4580.

Synthesis of 3-hydroxy-3-methylbutan-2-one thiosemicarbazone (4). To a stirred suspension of TSC (0.91 g, 0.01 mol) in H_2O—EtOH (60 mL, 2 : 1), 3-hydroxy-3-methylbutan-2-one (**1**) (1.02 g, 0.01 mol) was added and the clear solution was formed (thiosemicarbazide completely dissolved). After 10—15 min, a white precipitate was formed. The precipitate was collected by filtration, dried and recrystallized from aqueous EtOH. Yield 1.43 g (82%), m.p. 179 °C (from EtOH). Found (%): C, 41.08; H, 7.35; N, 23.92; S, 18.21. $C_6H_{13}N_3OS$. Calculated (%): C, 41.14; H, 7.42; N, 24.00; S, 18.28. IR (KBr), ν/cm^{-1}: 1160 (N—C(S)—N); 3370 (OH); 1520 (N—N); 1645 (C=N); 3245—3065 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 0.96 (s, 6 H, 2 Me); 1.80 (s, 3 H, Me); 6.30 (s, 1 H, OH); 7.26 (s, 2 H, NH_2); 8.54 (s, 1 H, NH).

Thiosemicarbazones **5** and **8** were synthesized similarly.

1-(1-Hydroxycyclohexyl)ethanone thiosemicarbazone (5). Yield 1.63 g (76%), m.p. 164 °C (from EtOH). Found (%): C, 50.16; H, 7.85; N, 19.48; S, 14.81. $C_9H_{17}N_3OS$. Calculated (%): C, 50.23; H, 7.90; N, 19.53; S, 14.88. IR (KBr), ν/cm^{-1}: 1165 (N—C(S)—N); 3365 (OH); 1515 (N—N); 1640 (C=N); 3240—3060 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.62 (s, 3 H, Me); 0.92—2.25 (m, 10 H, $C(CH_2)_5$); 6.32 (s, 1 H, OH); 7.30 (s, 2 H, NH_2); 8.60 (s, 1 H, NH).

3-Methyl-3-nitrooxybutan-2-one thiosemicarbazone (8). Yield 1.78 g (81%), m.p. 187 °C (from EtOH). Found (%): C, 32.68; H, 5.38; N, 25.37; S, 14.48. $C_6H_{12}N_4O_3S$. Calculated (%): C, 32.72; H, 5.45; N, 25.45; S, 14.54. IR (KBr), ν/cm^{-1}: 1170 (N—C(S)—N); 1275 (O—NO_2); 1520 (N—N); 1650 (C=N); 3240—3060 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 0.98 (s, 6 H, 2 Me); 1.90 (s, 3 H, Me); 7.38 (s, 2 H, NH_2); 8.72 (s, 1 H, NH).

2-Amino-5,6,6-trimethyl-1,3,4-thiadiazine (6). Thiosemicarbazone **4** (1.75 g, 0.01 mol) was dissolved in concentrated sulfuric acid (10 mL) with heating at 60—70 °C and the mixture was kept at room temperature for 24 h. Then the reaction mixture was poured by portions into ice-water (100 mL) and carefully neutralized with 25% aqueous ammonia until low basic mixture was obtained. The precipitate formed was collected by filtration, washed and purified by refluxing in EtOH with activated charcoal. Recrystallization from aqueous EtOH afforded the title product in the yield of 1.16 g (74%), m.p. 196 °C (from EtOH). Found (%): C, 41.31; H, 5.69; N, 16.02; S, 36.71. $C_6H_{11}N_3S$. Calculated (%): C, 41.38; H, 5.75; N, 16.09; S, 36.78. IR (KBr), ν/cm^{-1}: 1325, 1170 (C—C); 1425 (C—N); 1520 (N—N); 1650 (C=N); 750 (C—S); 3240—3060 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.39 (s, 6 H, 2 Me); 2.16 (s, 3 H, Me); 4.80 (s, 2 H, NH_2).

2-Amino-5-methyl-1-thia-3,4-diazaspiro[5.5]undeca-2,4-diene (7) was synthesized similarly. Yield 1.53 g (78%), m.p. 169 °C (from EtOH). Found (%): C, 50.16; H, 7.85; N, 19.48; S, 14.81. $C_9H_{15}N_3S$. Calculated (%): C, 50.23; H, 7.90; N, 19.53; S, 14.88. IR (KBr), ν/cm^{-1}: 1065, 1290 (C—C); 1440 (C—N); 1500 (N—N); 1600 (C=N); 740 (C—S); 2850 (O—C); 3185 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.62 (t, 3 H, Me); 0.95—2.30 (m, 10 H, $C(CH_2)_5$); 4.75 (s, 2 H, NH_2).

1-Bromo-3-methyl-3-nitrooxybutan-2-one (12). To a stirred solution of compound **1** (10.2 g, 0.1 mol) in a mixture of Ac_2O (10.2 g, 0.1 mmol) and glacial AcOH (20 mL), a solution of 98%

HNO_3 (6.5 g, 0.1 mol) in glacial AcOH (10 mL) was added dropwise at −5 °C. The reaction mixture was stirred for 2 h with cooling, treated dropwise with bromine (9.6 g, 0.06 mol), and stirred for 2 h. Then the reaction mixture was heated at 60 °C (water bath) for 4 h, cooled down, and poured into cold water (300 mL). Precipitated heavy liquid was separated and subjected to vacuum distillation at 55 °C (20 Torr). Yield 9.9 g (73%, based on nitro ester **3**), $n_D^{20} = 1.4500$.

2-Amino-5-(1-hydroxy-1-methylethyl)-6*H*-1,3,4-thiadiazine (13a). To a stirred solution of 1-bromo-3-hydroxy-3-methylbutan-2-one (**10**) (3.62 g, 0.02 mol) in 96% EtOH (30 mL), a solution of TSC (1.82 g, 0.02 mol) in aqueous EtOH (150 mL) was added followed by addition of concentrated HBr (1 mL). The mixture was heated for 2 h and concentrated to 1/4 of the initial volume. The residue was neutralized with NH_4OH. The precipitate was recrystallized from EtOH (70 mL per 1 g of the compound) with activated charcoal, washed with aqueous EtOH, and dried at 40—50 °C. Yield 2.45 g (70.8%), m.p. 125 °C (from EtOH). Found (%): C, 41.55; H, 6.27; N, 24.20; S, 18.41. $C_6H_{11}N_3OS$. Calculated (%): C, 41.62; H, 6.35; N, 24.27; S, 18.49. IR (KBr), ν/cm^{-1}: 1059, 1284 (C—C); 1438 (C—N); 1508 (N—N); 1607 (C=N); 739 (C—S); 3200 (NH_2), 3360 (OH). ^{1}H NMR ($CDCl_3$), δ: 0.98 (s, 6 H, 2 Me); 4.42 (s, 2 H, CH_2); 4.82 (s, 2 H, NH_2); 6.30 (s, 1 H, OH).

Thiadiazines **13b,c** were synthesized similarly.

2-Amino-5-(1-hydroxycyclohexyl)-6*H*-1,3,4-thiadiazine (13b). Yield 2.81 g (66%), m.p. 66 °C (from EtOH). Found (%): C, 50.63; H, 6.96; N, 19.65; S, 14.95. $C_9H_{15}N_3OS$. Calculated (%): C, 50.70; H, 7.04; N, 19.72; S, 15.02. IR (KBr), ν/cm^{-1}: 1063, 1288 (C—C); 1441 (C—N); 1510 (N—N); 1610 (C=N); 740 (C—S); 3200 (NH_2). ^{1}H NMR ($CDCl_3$), δ 0.94—2.26 (m, 10 H, $C(CH_2)_5$); 4.40 (s, 2 H, CH_2); 4.80 (s, 2 H, NH_2); 6.34 (s, 1 H, OH).

2-Amino-5-[1-methyl-1-(nitrooxy)ethyl]-6*H*-1,3,4-thiadiazine (13c). Yield 3.4 g (78%), m.p. 198—99 °C (from EtOH). Found (%): C, 32.96; H, 4.51; N, 25.61; S, 14.62. $C_6H_{10}N_4O_3S$. Calculated (%): C, 33.02; H, 4.58; N, 25.68; S, 14.68. IR (KBr), ν/cm^{-1}: 1065, 1290 (C—C); 1443 (C—N); 1513 (N—N); 1611 (C=N); 741 (C—S); 3200 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.06 (s, 6 H, 2 Me); 4.46 (s, 2 H, CH_2); 4.92 (s, 2 H, NH_2).

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