Comparative reactivity of hydroxyketones and their derivatives in the reactions with *N*,*S*-nucleophiles

E. Kh. Pulatov, M. D. Isobaev, B. G. Mavlonov, and T. Kh. Abdullaev*

V. I. Nikitin Institute of Chemistry, Academy of Sciences of the Republic of Tajikistan, 299/2 ul. Aini, 734063 Dushanbe, Tajikistan.
Fax: +992 (37) 225 8095. E-mail: coordin@yandex.ru

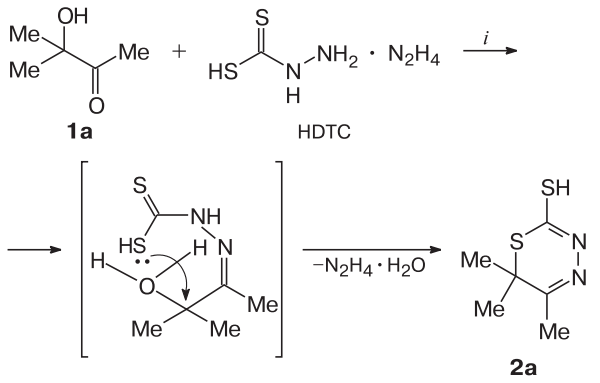
The reactions of thiosemicarbazide (TSC), thiocarbohydrazide, and hydrazine thiocarbamate with oxyketones, haloketones, and derivatives of acetylenic alcohols were studied. Thiadiazines bearing exocyclic thio and hydrazo groups were synthesized. Acetylenic alcohols react with TSC to give the corresponding thiazolidines. The reactions of halo derivatives of acetylenic alcohols with TSC are complicated by side reactions.

Key words: monohalo- and dihalo-substituted acetylenic alcohols, oxyketones, thiosemicarbazide, thiocarbohydrazide, thiocarbamic acid.

At present, there are data showing promise for application of the six-membered heterocycles as anticoagulant agents.[1,2] This prompted the development of new synthetic approaches towards these type of compounds. We believe that derivatives of acetylenic alcohols are the promising building blocks to solve this problem. Earlier,[3] we have shown that hydroxy ketones react with thiosemicarbazide to give 2-amino- and 5-alkoxy-substituted thiadiazine derivatives. With the aim to extend the scope of this reaction, in the present work we studied the reactions of 3-hydroxy-3-methylbutan-2-one (**1a**) and 1-bromo-3-hydroxy-3-methylbutan-2-one (**1b**) with thiocarbohydrazide (TCH) and hydrazine dithiocarbamate (HDTC).

Acid-catalyzed reaction of ketone **1a** with HDTC in dioxane at room temperature produces six-membered heterocyclic compound, 5,6,6-trimethyl-3,6-dihydro-2*H*-1,3,4-thiadiazine-2-thiol (**2a**) (Scheme 1).

Scheme 1



Conditions: *i*. H^+, dioxane.

The structure of compound **2a** was established by IR and ^{1}H NMR spectroscopy. ^{1}H NMR spectrum of compound **2a** exhibits a broadened singlet at δ 13.04 with integral intensity of 1 H attributed to the SH group proton. A singlet signal at δ 2.10 was ascribed to the C(5) methyl group protons. A signal of the C(6) methyl group protons appeared at δ 1.35.

Ketone **1a** reacts with TCH in the presence of CF_3COOH to give thiadiazine **2b** bearing an endocyclic hydrazo group. Thiadiazine **2b** is likely formed by the mechanism described by us earlier[3] (Scheme 2).

Analysis of the directions of the competitive reactions of bifunctional reagents with the compounds bearing simultaneously hydroxy and haloalkyl groups is of special interest. If the compound contains hydroxy and bromomethyl groups that can compete upon the reaction, the latter group is generally more reactive. Bromo-substituted derivatives of oxyketones were synthesized by known procedures.[4,5]

It follows from the analysis of the reaction products that cyclization of 1-bromo-3-hydroxy-3-methylbutan-2-one (**1b**) upon the reaction with TCH proceeds *via* substitution of the bromine atom to give 2-hydrazinyl-5-(2-hydroxypropan-2-yl)-3,6-dihydro-2*H*-1,3,4-thiadiazine (**2c**) (Scheme 3).

To reliably explain this reaction pathway, we calculated the electron density distribution and minimum-energy geometries for molecules **1a**, **1b**, and **1b′** at the DFT/B3LYP/3-21G level of theory using Gaussian software[6,7] (Fig. 1).

The computations indicate that the difference in the energies for molecules **1a**, **1b**, and **1′b** does not explain their reactivity. Apparently, the formation of the intramolecular H-bond between the OH-group proton and the lone electron pair of the intermediate hydrazone nitrogen

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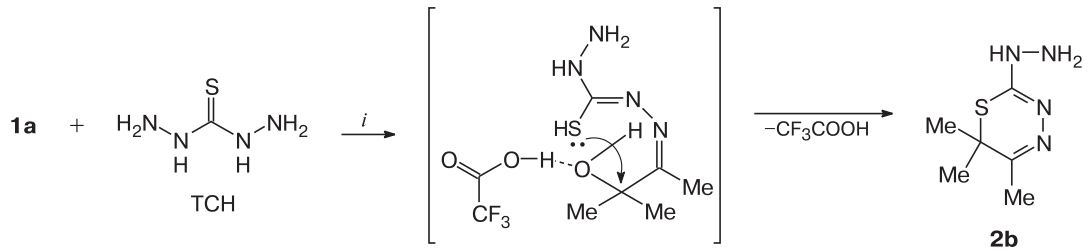
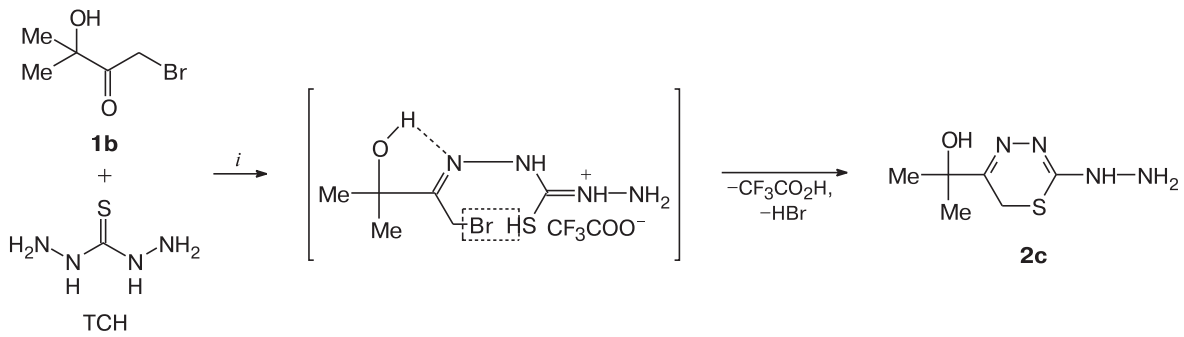
Scheme 2



Reagents and conditions: *i*. CF_3COOH, H_2O, reflux.

Scheme 3



Reagents and conditions: *i*. CF_3COOH, H_2O, reflux.

atom has a greater effect (see Scheme 3). This conformation favors spatial proximity of the thiol group and the bromomethyl group carbon atom.

The structures of compounds **2b,c** were established by ^{1}H NMR and IR spectroscopy. IR spectra of compounds **2b,c** show new absorption bands at 3385 and 3088 cm^{-1} characteristic of the vibrations of the NH_2 group of the hydrazino moiety. Absorption band at the 600—700 cm^{-1} range characteristic of the C—SH bond was observed only in the IR spectrum of compound **2a** but not in the IR spectrum of compounds **2b,c**. In the IR spectra of compounds **2a**—**c**, the absorptions at the ranges of 1701—1650 (**2a**,**b**) and 1701—1628 cm^{-1} (**2c**) were attributed to the endocyclic N=C bond vibrations and the intense absorption at the 1520—1504 cm^{-1} range was ascribed to the vibrations of endo- and exocyclic N—N bond. In the case of compound **2c**, a broadened absorption band at 3358 cm^{-1} was ascribed to the OH group vibrations.

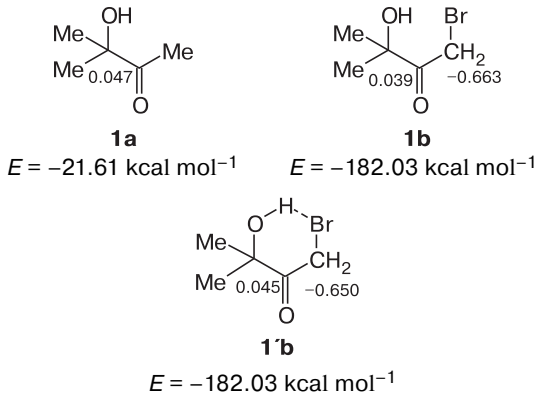
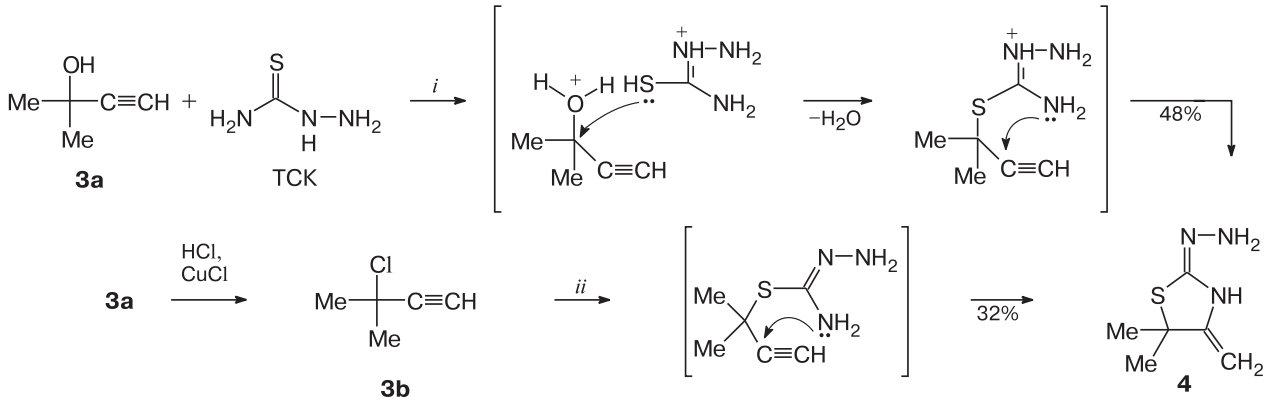


Fig. 1. Quantum-chemical calculations of the molecules of oxyketone (**1a**) and bromo-substituted oxyketone (**1b**). Charges on the carbon atoms of the carboxyl and bromomethyl groups are given in a.u.

^{1}H NMR spectra of compounds **2b**,**c** exhibit the broadened singlets of the NH and NH_2 group protons at about δ 7.05 and 7.35, respectively. In ^{1}H NMR spectrum of compound **2b**, the C(5) and C(6) methyl group protons resonate at δ 2.05 and 1.33, respectively. ^{1}H NMR spectrum of compound **2c** shows a new signal at δ 4.40 attributed to the CH_2S group protons, a signal of the C(6) methyl group protons at δ 1.39, and a broadened signal of the OH group at δ 6.28.

The reaction of 1,3-dibromopropyne with TSC in aqueous EtOH to give thiazolidines is known.[8] Hennion and Boisselle[9] described the synthesis of functionalized iminodihydrofurans by the reaction of chloro derivative of cyanoacetylenic alcohols with TSC under mild conditions. To compare the reaction pathways, we involved 3-hydroxy-

Scheme 4



Reagents and conditions: *i*. CF_3COOH (2 equiv.), dioxane, H_2O, 70 °C, 8 h; *ii*. TSC, Et_3N, dioxane, 70 °C, 8 h.

3-methylbut-1-yne (**3a**) and 3-chloro-3-methylbut-1-yne (**3b**) in the reactions with TSC.

It was found that 3-hydroxy-3-methylbut-1-yne (**3a**) reacts with TSC in aqueous CF_3CO_2H to produce 2-hydrazono-5,5-dimethyl-4-methylene-1,3-thiazolidine (**4**). At the same time, the same product **4** was obtained by the reaction of chloro-substituted acetylenic alcohol, 3-chloro-3-methylbut-1-yne (**3b**), with TSC in the presence of triethylamine in refluxing dioxane (Scheme 4).

In the case of 3-hydroxy-3-methylbut-1-yne (**3a**), the reaction is initiated by the protonation of the OH group of CF_3CO_2H *via* the known mechanism[3,10] that involves elimination of the water molecule; while, in the case of 3-chloro-3-methylbut-1-yne (**3b**), the abstraction of HCl in the presence of Et_3N occurs. In both cases, the reaction involves nucleophilic attack of the thiol group of TSC on an electron-deficient C(3) carbon atom to give intermediate *S*-alkylation product and subsequent intramolecular addition of the thiosemicarbazide amino group to the triple bond to produce thiazolidine **4**.

The structure of the synthesized compound **4** was confirmed by ^{1}H NMR and IR spectroscopy. IR spectrum of compound **4** exhibits the absorptions at 1668, 1574, and 1510 cm^{-1} attributed, respectively, to the vibrations of the exocyclic C=C, C=N, and N—N bonds. The absorptions at 3181 and 2973 cm^{-1} were ascribed to the stretching vibrations of the endo- and exocyclic amino groups. In ^{1}H NMR spectrum of compound **4**, the protons of the C(5) dimethyl groups resonate at δ 1.83 and two signals of the geminal protons of exocyclic $=CH_2$ groups at the C(4) appear at δ 5.88 and 7.47 with integral intensity of 1 H each. The signals observed at δ 11.02 and 8.04 were attributed to the protons of the endocyclic NH and exocyclic NH_2 groups.

We failed to involve TSC in the reaction with acetylenic halo derivatives, *e.g.*, 1-bromo-3-hydroxy-3-methylbut-1-yne (**3c**) and 1,3-dibromo-3-methylbut-1-yne (**3d**). These compounds were synthesized as earlier described[11—13] by the replacement of the terminal hydrogen atom of 3-hydroxy-3-methylbut-1-yne (**1a**) with molecular bromine in aqueous basic medium followed by the replacement of the α-hydroxy group of a newly formed derivative **3c** with the bromine atom in acetic medium. The reactions of acetylenic halo derivatives **3c**,**d** with TSC were unsuccessful due to resinification of the reaction mixture.

In summary, the present work reveals that the reactions of acetylenic alcohols and oxy- and halo-substituted ketones with thiosemicarbazide, thiocarbohydrazide, and hydrazine dithiocarbamate result in cyclic products — thiazolidines and thiadiazines. In contrast, the same reactions with halo-substituted acetylenic alcohols failed to give the desired products due to resinification.

Experimental

^{1}H NMR spectra were recorded with an XTIPC VARIAN MR-400 instrument (working frequency of 400 MHz) in DMSO-d_6. The chemical shifts are given in the δ scale relative to Me_4Si (internal standard).

IR spectra were obtained on a Perkin—Elmer Spectrum-65 instrument. Elemental analysis was performed with a Perkin—Elmer-2400 analyzer. Melting points were measured on a Boetius apparatus at heating rate of 4 °C min^{-1}.

3-Chloro-3-methylbut-1-yne (1d) was synthesized from the corresponding acetylenic alcohol as earlier described.[11—13]

1-Bromo-3-hydroxy-3-methylbutan-2-one (1b) was synthesized following known procedures.[4,5]

1-Bromo-3-hydroxy-3-methylbut-1-yne (3c) and **1,3-dibromo-3-methylbut-1-yne (3d)** were synthesized similarly to known procedures.[11—13]

5,6,6-Trimethyl-3,6-dihydro-2*H*-1,3,4-thiadiazine-2-thiol (2a). To a solution of 3-hydroxy-3-methylbutan-2-one (**1a**) (1.02 g, 0.01 mol) in water (100 mL), hydrazine dithiocarbamate (1.40 g, 0.01 mol) in water—dioxane (1 : 1, 20 mL) was added

and the reaction mixture was refluxed for 8 h in the presence of catalytic amounts of H_2SO_4. After three-fourth of the solvent was removed, the residue was neutralized with a $NaHCO_3$ solution. The light yellow precipitate formed was collected by filtration and recrystallized from water—dioxane (1 : 1). Yield 1.07 g (62%), m.p. 115 °C (from water—dioxane, 1 : 1). Found (%): C, 41.31; H, 5.69; N, 16.02; S, 36.71. $C_6H_{10}N_2S_2$. Calculated (%): C, 41.38; H, 5.75; N, 16.09; S, 36.78. IR (KBr), ν/cm^{-1}: 1325, 1170 (C—C); 1565 (C—N); 1520 (N—N); 1650 (C=N); 750 (C—S); 1265 (C=S). ^{1}H NMR, δ: 1.35 (s, 6 H, 2 Me); 2.10 (s, 3 H, Me); 13.05 (s, 1 H, SH).

2-Hydrazinyl-5,6,6-trimethyl-6*H*-1,3,4-thiadiazine (2b). To a solution of 3-hydroxy-3-methylbutan-2-one (**1a**) (1.02 g, 0.01 mol) in 1.5% aqueous CF_3CO_2H (100 mL), TCH (1.06 g, 0.01 mol) in water (20 mL) was added. The mixture was refluxed for 8 h, cooled down, and neutralized with a chilled aqueous $NaHCO_3$. The precipitate formed was collected by filtration and crystallized from water. Yield 1.27 g (74%), m.p. 124 °C (from water). Found (%): C, 41.78; H, 6.90; N, 32.49; S, 18.54. $C_6H_{12}N_4S$. Calculated (%): C, 41.86; H, 6.97; N, 32.56; S, 18.60. IR (KBr), ν/cm^{-1}: 1323, 1167 (C—C); 1564 (C—N); 1517 (N—N); 1650 (C=N); 750 (C—S). ^{1}H NMR, δ: 1.33 (s, 6 H, 2 Me); 2.05 (s, 3 H, Me); 7.05 (s, 1 H, NH); 7.35 (s, 2 H, NH_2).

2-Hydrazinyl-5-(1-hydroxy-1-methylethyl)-6*H*-1,3,4-thiadiazine (2c). To a stirred solution of 1-bromo-3-hydroxy-3-methylbutan-2-one (**1b**) (1.81 g, 0.01 mol) in 1.5% aqueous CF_3CO_2H (30 mL), TCH (1.06 g, 0.01 mol) in hot water (20 mL) was added. The mixture was refluxed for 8 h and neutralized with a $NaHCO_3$ solution. The precipitate formed was refluxed in water (70 mL per 1 g of the precipitate) with activated charcoal, filtered, and precipitated. Yield 1.55 g (82%), m.p. 112 °C. Found (%): C, 37.81; H, 5.18; N, 14.66; S, 33.61. $C_6H_{10}N_2OS_2$. Calculated (%): C, 37.89; H, 5.26; N, 14.73; S, 33.68. IR (KBr), ν/cm^{-1}: 1056, 1280 (C—C); 1434 (C—N); 1504—1512 (N—N); 1628—1701 (C=N); 736 (C—S); 3340—3200 (NH—NH_2), 3358 (OH), 1262. ^{1}H NMR, δ: 1.39 (s, 6 H, 2 Me); 3.20 (s, 1 H, OH); 4.40 (s, 2 H, CH_2); 7.06 (s, 1 H, NH); 7.36 (s, 2 H, NH_2).

2-Hydrazono-5,5-dimethyl-4-methylenethiazolidine (4). *A*. To a solution of 3-hydroxy-3-methylbut-1-yne (**3a**) (0.84 g, 0.01 mol) and CF_3CO_2H (3 mL) in water, a solution of TSC (0.91 g, 0.01 mol) in water—dioxane (1 : 1) was added portionwise. The mixture was heated at 70 °C for 8 h and concentrated *in vacuo*. The residue was cooled to 0 °C, the precipitate formed was collected by filtration and crystallized from water. Yield 0.9 g (48%), m.p. 168—169 °C (from water—ethanol, 1 : 1). Found (%): C, 45.79; H, 6.93; N, 26.68; S, 20.31. $C_6H_{11}N_3S$. Calculated (%): C, 45.86; H, 7.00; N, 26.75; S, 20.38. IR (KBr), ν/cm^{-1}: 3182, 2973 (NH, NH_2); 1668 (C=C, C=N); 1368 ($C(CH_3)_2$); 1268 (C—N); 1574, 1510 (N—N). ^{1}H NMR, δ: 1.83 (s, 6 H, 2 Me); 5.88 and 7.47 (both s, 1 H each, $=CH_2$); 11.02 (s, 1 H, NH), 8.04 (s, 2 H, NH_2).

B*.** To a solution of TSC (0.91 g, 0.01 mol) in dioxane (20 mL), a solution of 3-chloro-3-methylbut-1-yne (**3b**) (1.02 g, 0.01 mol) in dioxane was added portionwise and the reaction mixture was heated at 70 °C for 8 h in the presence of triethylamine as a catalyst. The mixture was cooled down to 0 °C and neutralized with an HCl solution. The precipitate formed was collected by filtration and crystallized from water—ethanol (1 : 1). Yield 0.6 g (32%). Physicochemical properties of compound **4** obtained by methods ***A and ***B*** are identical.

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