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Reaction of Thiosemicarbazide with 1,3-Dibromopropyne

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Abstract—Thiosemicarbazide reacted with an equimolar amount of 1,3-dibromopropyne in aqueous ethanol (1:1) to give (4-bromomethylidenethiazolidin-2-ylidene)hydrazine hydrobromide. The reaction of thiosemicarbazide with 2 equiv of 1,3-dibromopropyne in ethanol on heating resulted in the formation of 3,6-bis(bromomethylidene)-3,4,6,7-tetrahydro-2*H*-thiazolo[2,3-*c*][1,2,4]triazine hydrobromide. The corresponding free base was obtained when the reaction performed in the presence of triethylamine.

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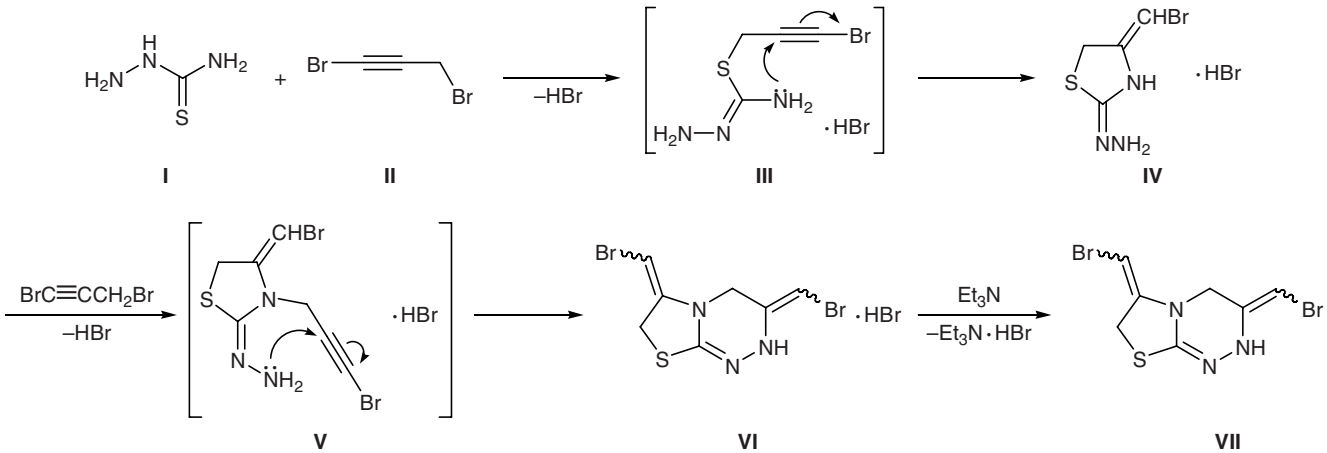
It is known that reactions of 1-hetaryl-4-arylthiosemicarbazides with dimethyl acetylenedicarboxylate in methanol lead to the formation of thiazolidine derivatives in good yields [1]. Thiosemicarbazide reacts with bromoethynyl ketones in methanol or acetonitrile in the presence of triethylamine at –30°C to give substituted 1,3,4-thiadiazoles via replacement of bromine at the triple-bonded carbon atom [2]. 7-Hydroxy-2-phenylamino-6*H*-1,3,4-thiadiazepines were obtained in good yields by reaction of 4-phenylthiosemicarbazide with 1-acyl-2-phenylacetylenes in glacial acetic acid at 20°C [3]. Substituted thiazole hydrochlorides were isolated in reactions of thiosemicarbazones with chloro(organylsulfanyl)acetylenes in acetone or methyl ethyl ketone at 20°C [4, 5].

In continuation of our studies on reactions of activated acetylenes with sulfur- and nitrogen-containing polyfunctional nucleophiles [6–8], we examined the reaction of thiosemicarbazide (**I**) with 1,3-dibromopropyne (**II**). When the reaction was performed with equimolar amounts of the reactants in aqueous ethanol (1:1) at 70°C, we isolated 52% of (4-bromomethylidenethiazolidin-2-ylidene)hydrazine hydrobromide (**IV**) (Scheme 1). Presumably, the process involves intermediate formation of prop-2-yn-1-yl sulfide **III**, and intramolecular attack by the amino group on the triple-bonded carbon atom in **III** leads to cyclization with formation of substituted thiazolidine hydrobromide **IV**. The IR spectrum of **IV** lacks absorption band assignable to stretching vibrations of triple C≡C bond, but

Scheme 1.



I II III IV V VI VII

a band at 1600 cm^{-1} appears due to vibrations of the exocyclic C=C bond. In the ^1H NMR spectrum of **IV**, the =CHBr proton gives a singlet at δ 5.06 ppm, and the corresponding carbon nucleus resonated in the ^{13}C NMR spectrum at δ_C 100.1 ppm .

The reaction of thiosemicarbazide (**I**) with 2 equiv of 1,3-dibromopropyne (**II**) in ethanol at 75°C gave 65% of substituted thiazolo[2,3-*c*][1,2,4]triazine hydrobromide (**VI**). Presumably, alkylation of initially formed thiazole **IV** with the second 1,3-dibromopropyne (**II**) molecule leads to acetylenic intermediate **V**, and intramolecular attack by the primary amino group of the hydrazone fragment at the activated triple bond is accompanied by cyclization to fused structure **VI**. The IR spectrum of **VI** contained no triple bond absorption, but bands assignable to the exocyclic double bonds (C=CHBr) were observed. In the ^1H NMR spectrum of **VI**, the CHBr protons resonated at δ 5.06 and 5.22 ppm. By reaction of thiosemicarbazide (**I**) with dibromide **II** in methanol at 50°C in the presence of a slight excess of triethylamine we obtained free base **VII** in 62% yield.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX-400 instrument at 400.13 and 100.61 MHz, respectively, using DMSO-d_6 as solvent and hexamethyldisiloxane as internal reference. The mass spectrum was measured on a Shimadzu GCMS-QP5050A instrument (SPB-5 ms capillary column, 60 m×0.25 mm, film thickness 0.25 μm; injector temperature 250°C; carrier gas helium, flow rate 2.7 ml/min; quadrupole mass analyzer; electron impact, 70 eV; ion source temperature 250°C; mass range 34–650 a.m.u.); total ion current chromatograms were recorded.

(4-Bromomethylidenethiazolidin-2-ylidene)hydrazine hydrobromide (IV). A solution of 1.0 g (0.011 mol) of thiosemicarbazide (**I**) in 20 ml of aqueous ethanol (1:1) was slowly added under stirring to a solution of 2.38 g (0.012 mol) of 1,3-dibromopropyne (**II**) in 30 ml of aqueous ethanol (1:1), and the mixture was heated for 7 h at 70°C. The solvent was partially distilled off, the remaining solution was cooled to 0°C, and the precipitate was filtered off and washed on a filter with cold diethyl ether. Yield 1.75 g (52%), dark red crystals, mp 97–99°C. IR spectrum, ν, cm^{-1}: 3390, 3090 (NH, NH_2); 1600 (C=C, C=N), 1390 (δCH_2), 1220 (C–N), 750 (C–S), 590 (C–Br). ^1H NMR spectrum, δ, ppm: 4.29 s (2H, CH_2S), 5.05 s (1H, =CHBr), 7.08 s (1H, NH), 7.38 s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 39.3 (C^5), 100.1 (=CHBr), 142.6 (C^4), 168.5 (C^2). Found, %: C 16.40; H 2.39; Br 55.44; N 14.51; S 10.97. $C_4H_7Br_2N_3S$. Calculated, %: C 16.61; H 2.42; Br 55.36; N 14.53; S 11.07.

4,6-Bis(bromomethylidene)-3,4,6,7-tetrahydro-2*H*-thiazolo[2,3-*c*][1,2,4]triazine hydrobromide (VI). A solution of 1.0 g (0.011 mol) of thiosemicarbazide (**I**) in 20 ml of ethanol was slowly added under stirring to a solution of 4.75 g (0.024 mol) of 1,3-dibromopropyne (**I**) in 30 ml of ethanol, and the mixture was slowly heated to 75°C, stirred for 5 h at that temperature, and cooled to 0°C. The precipitate was filtered off, washed on a filter with cold diethyl ether and chloroform, and dried under reduced pressure. Yield 3.48 g (65%), mp 158–159°C. IR spectrum, ν, cm^{-1}: 3380 (NH); 2950, 2935 (CH_2); 1610, 1605 (C=C, C=N); 1465, 1440 (δCH_2); 1280 (C–N); 730 (C–S); 660, 645 (C–Br). ^1H NMR spectrum, δ, ppm: 4.16 s (2H, CH_2S), 4.85 s (1H, NH), 5.06 s and 5.22 s (2H, =CHBr), 5.68 s (2H, CH_2N). ^{13}C NMR spectrum, δ_C, ppm: 39.3 (C^7), 44.5 (C^4), 99.8 and 108.7 (=CHBr), 128.9 and 137.6 (C^3, C^6), 163.3 (C^{8a}). Found, %: C 20.44; H 1.90; Br 59.40; N 10.24; S 7.76. $C_7H_8Br_3N_3S$. Calculated, %: C 20.69; H 1.97; Br 59.11; N 10.34; S 7.88.

When the reaction was carried out in anhydrous methanol, the yield of **VI** was 62%. In the reaction of 1.0 g (0.011 mol) of thiosemicarbazide (**I**) with 2.4 g (0.012 mol) of 1,3-dibromopropyne (**II**) in 30 ml of DMF, compound **VI** was isolated as the only product; yield 1.41 g (48%).

4,6-Bis(bromomethylidene)-3,4,6,7-tetrahydro-2*H*-thiazolo[2,3-*c*][1,2,4]triazine (VII). A solution of 0.5 g (5.5 mmol) of thiosemicarbazide (**I**) and 1.0 ml (7.3 mmol) of triethylamine in 25 ml of methanol was slowly added under stirring to a solution of 1.2 g (6.1 mmol) of 1,3-dibromopropyne (**II**) in 20 ml of methanol, and the mixture was heated to 50°C and stirred for 3 h at that temperature. A part of the solvent was distilled off, the remaining solution was cooled to 0°C, and the precipitate was filtered off, washed on a filter with water and diethyl ether, and dried under reduced pressure. Yield 1.33 g (62%), yellow crystals, mp 240–243°C. IR spectrum, ν, cm^{-1}: 3405 (NH); 2955, 2930 (CH_2); 1600 (C=C, C=N); 1470, 1420 (δCH_2); 1275 (C–N); 730 (C–S); 660, 650 (C–Br). ^1H NMR spectrum, δ, ppm: 4.16 s (2H, CH_2S), 4.72 s (2H, CH_2N), 5.20 s and 5.35 s (2H, =CHBr). Mass

spectrum, *m*/*z* (I_{rel}, %): 232 (15), 199 (62), 153 (46), 117 (18), 82 (15), 79 (18), 72 (24), 71 (28), 69 (14), 45 (58), 44 (40), 39 (100), 38 (62). Found, %: C 25.91; H 2.20; Br 49.20; N 12.70; S 9.82. $C_7H_7Br_2N_3S$. Calculated, %: C 25.85; H 2.15; Br 49.23; N 12.92; S 9.85.

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