Chemistry of Heterocyclic Compounds, Vol. 38, No. 8, 2002

REACTION OF ACETONE CYANOHYDRIN WITH THIOSEMICARBAZIDE

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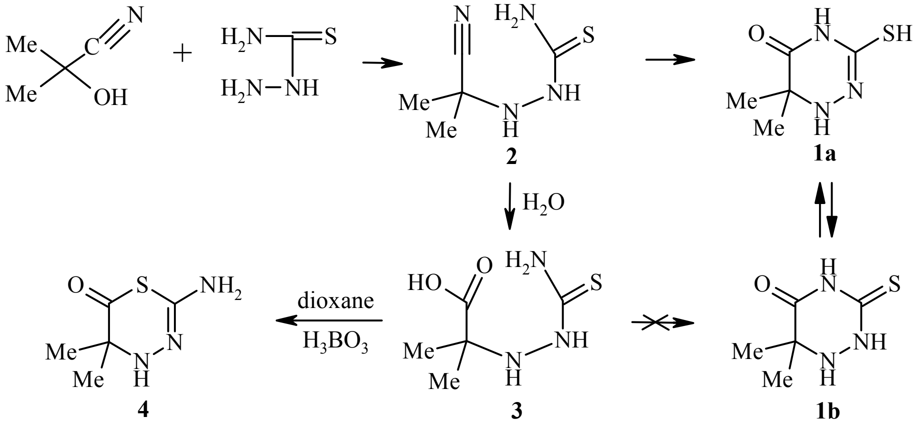
We have established that when acetone cyanohydrin is heated with thiosemicarbazide in aqueous medium, 3-mercapto-6,6-dimethyl-1,2,4-triazin-5-one and 2-methyl-2-thiosemicarbazidopropanoic acid are formed. Cyclization of the latter in dioxane in the presence of H_3BO_3 leads to 2-amino-5,5-dimethyl-1,3,4-thiadiazin-6-one.

Keywords: acetone cyanohydrin, 1,3,4-thiadizin-6-one, thiosemicarbazide, 1,2,4-triazin-5-one.

A two-step synthesis of 3-mercapto-6,6-dimethyl-1,2,4-triazin-5-one (**1**) has been described previously, starting from acetone cyanohydrin and thiosemicarbazide [1]. The authors of that paper suggested that in the first step of the reaction (heating the reagents in water at 95-100°C), an intermediate 2-methyl-2-thiosemicarbazidopropanoic acid nitrile (**2**) is formed which in the second step (holding at 95-98°C in a potassium carbonate solution) undergoes ring closure to form mercaptotriazinone **1a**. Filtering off the precipitate falling out of the reaction mixture after the second step, the authors isolated the target product **1a** with mp 170-172°C by acidification of the filtrate.



We attempted to reproduce the described procedure, with the goal of studying the reactivity of mercaptotriazinone **1a** in heterocyclization reactions. In this case, we observed (monitoring by TLC) that even in the first step, instead of nitrile **2** two products are formed, one of which is compound **1a**. An increase in the heating temperature leads to a decrease in the yield of the latter and an increase in the fraction of the second product. Heating the mixture with potassium carbonate in the aqueous solution in the second step does not lead

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Voronezh State University, Voronezh 394693, Russia; e-mail: shikh@online.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1133-1134, August, 2002. Original article submitted December 17, 1999; revision submitted September 19, 2000.

0009-3122/02/3808-0992$27.00©2002 Plenum Publishing Corporation

to chemical modifications, but makes it possible to separate the products: mercaptotriazinone **1a** precipitates from the cooled alkaline solution (it was discarded by the authors of [1] as an impurity) and has mp 191-192°C; the second product with mp 172-173°C (coinciding with that indicated in [1] for compound **1a**) precipitates from the strongly acidified filtrate. According to ^{1}H NMR and mass spectroscopy data, the latter product can be definitely assigned the structure of 2-methyl-2-thiosemicarbazidopropanoic acid (**3**). Thus in [1], the structure of mercaptotriazinone **1a** was erroneously assigned to acid **3**, and the reaction of acetone cyanohydrin with thiosemicarbazide in aqueous medium occurs differently than assumed. Although formation of the intermediate nitrile **2** is obvious, it is doubtful that it can survive in hot aqueous medium. More likely, under the reaction conditions it is either hydrolyzed with formation of the corresponding acid or undergoes ring closure to form 5-imino-3-mercapto-6,6-dimethyltriazine, the hydrolysis of which also leads to the final mercaptotriazinone **1a**. The poor solubility of the latter in basic medium is obviously explained by the predominance of the thione form **1b**.

Attempts to make acid **3** undergo ring closure in aqueous acid, neutral or basic medium were unsuccessful. However, heating it in dioxane with boric acid makes it possible to obtain a compound isomeric to **1**, 2-amino-5,5-dimethyl-1,3,4-thiadiazin-6-one (**4**).

EXPERIMENTAL

The course of the reaction and the purity of the substances obtained were monitored by TLC on Silufol UV-254 plates; the eluent was chloroform–ethyl acetate, 3:1. The ^{1}H NMR spectra were taken on a Bruker AC-300 (300 MHz) in DMSO-d$_6$ relative to TMS; the mass spectra were taken on an LKB 9000, ionizing electron energy 70 eV.

Reaction of Acetone Cyanohydrin with Thiosemicarbazide. A mixture of acetone cyanohydrin (0.1 mol) and thiosemicarbazide (0.1 mol) was held for 3 h in water (50 ml) at 95-100°C. The crystals that precipitated after cooling were filtered out, washed with cold water, and dried. The crystals obtained (15 g) were mixed with potassium carbonate (12 g) and water (40 ml), and held for 3 h at 95-98°C. After cooling from basic solution, triazinone **1a** precipitated, which was filtered out, washed with water, and recrystallized from alcohol. Acid **3** precipitated from the filtrate acidified with HCl (pH 3-4), and was filtered out, washed with water, and crystallized from alcohol.

3-Mercapto-6,6-dimethyl-1,2,4-triazin-5-one (1a). Yield 20%; mp 191-192°C. ^{1}H NMR spectrum, δ, ppm: 2.0 (6H, s, 2CH$_3$); 7.2 (1H, s, NH); 7.8 (1H, s, NH); 9.7 (1H, s, SH). M 159 (mass spectrometrically). Found, %: C 37.85; H 5.82; N 26.25; S 20.02. $C_5H_9N_3OS$. Calculated, %: C 37.73; H 5.66; N 26.42; S 20.13.

2-Methyl-2-thiosemicarbazidopropanoic Acid (3). Yield 55%; mp 172-173°C. ^{1}H NMR spectrum, δ, ppm: 1.2 (6H, s, 2CH$_3$); 5.5 (1H, s, NH); 7.4 (1H, s, NH); 7.6 (1H, s, NH$_2$); 7.9 (1H, s, NH$_2$); 12.7 (1H, s, COOH). M 177 (mass spectrometrically). Found, %: C 34.15; H 6.52; N 23.45; S 18.22. $C_5H_{11}N_3O_2S$. Calculated, %: C 33.90; H 6.21; N 23.73; S 18.08.

2-Amino-5,5-dimethyl-1,3,4-thiadiazin-6-one (4). A mixture of acid **3** (3.5 g) and anhydrous H_3BO_3 (1.2 g) was refluxed in dioxane (20 ml) for 10 h. After cooling, the boric acid was filtered out and the filtrate was poured into water. The precipitate was filtered out, dried, and recrystallized from dioxane. Yield 60%; mp 270-272°C. ^{1}H NMR spectrum, δ, ppm: 1.2 (6H, s, 2 CH$_3$); 5.8 (1H, s, NH); 10.4 (1H, s, NH$_2$); 10.7 (1H, s, NH$_2$). M 159 (mass spectrometrically). Found, %: C 38.15; H 5.52; N 26.85; S 19.75. $C_5H_9N_3OS$. Calculated, %: C 37.73; H 5.66; N 26.42; S 20.13.

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