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UNUSUAL COURSE OF THE REACTION OF N-(TOSYLMETHYL)THIOUREA AND N-(AZIDOMETHYL)THIOUREA WITH SODIUM ENOLATE OF DIMEDONE

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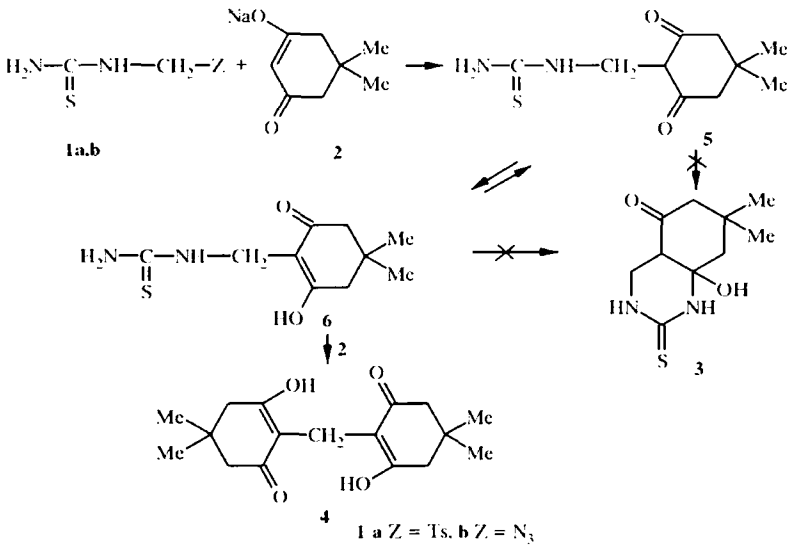
The end product of the reaction of N-(tosylmethyl)thiourea or N-(azidomethyl)thiourea with sodium enolate of dimedone is bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methane (methylenebis-dimedone) instead of the expected 8a-hydroxy-7,7-dimethyl-2-thioxoperhydroquinazolin-5-one.

Keywords: N-(tosylmethyl)thiourea, N-(azidomethyl)thiourea, dimedone, methylenebisdimedone.

Earlier [1,2] we developed a new convenient and general method for synthesis of hydrogenated pyrimidine-2-thiones, based on the reaction of α-azido- and α-tosyl-substituted thioureas with sodium enolates of acyclic 1,3-dicarbonyl compounds. We suggested that it would be advisable to use cyclic 1,3-dicarbonyl compounds in this reaction, which might lead to synthesis of condensed heterocyclic compounds containing a pyrimidine ring. In this paper, the results of our study of the reaction of N-(tosylmethyl)thiourea (**1a**) and N-(azidomethyl)thiourea (**1b**) with the sodium enolate of dimedone **2** are described.



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We established that the end product of the reaction of tosylmethylthiourea **1a** with compound **2** (obtained by reaction of dimedone with sodium hydride) in acetonitrile is bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methane (**4**) (methylenebisdimedone) instead of the expected 8a-hydroxy-7,7-dimethyl-2-thioxoperhydroquinazolin-5-one (**3**). We should note that the reaction between compounds **1a** and **2** proceeds quite slowly at room temperature: the yield of methylenebisdimedone **4** is 27.2% in 4 h, and 44.1% in 46 days. The reaction rate increases significantly with an increase of temperature. So at boiling of compounds **1a** and **2** in acetonitrile for 4 h, compound **4** was obtained in 86.4% yield.

The reaction of N-(azidomethyl)thiourea (**1b**) with sodium enolate of dimedone **2** proceeds just a little faster, and also leads to formation of methylbisdimedone **4**. So carrying out the reaction in acetonitrile at room temperature for 5 h, compound **4** was isolated in 46.7% yield.

The results obtained can probably be explained by the fact that the heterocyclization rate of the intermediate **5** to perhydroquinazoline **3** is significantly slower than the rate of its enolization with formation of compound **6**. The latter in turn, due to the low electrophilicity of the carbonyl group, does not undergo cyclization to perhydroquinazoline **2** but rather undergoes nucleophilic attack by a second molecule of sodium enolate of dimedone with formation of methylenebisdimedone **4** and thiourea. We can consider the results of [3,4] to bear a certain analogy to the conversions described. In those papers, it was shown that in reaction of N-(chloromethyl)phthalimide or (trimethyl)(phthalimidomethyl)ammonium iodide with sodium enolate of cyclohexane-1,3-dione, the expected 2-(phthalimidomethyl)cyclohexane-1,3-dione .is not formed but rather the products of its subsequent reaction with the enolate (a mixture of bis(2,6-dioxocyclohex-1-yl)methane and phthalimide) is obtained.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker MSL-200 (200 MHz) spectrometer for $CDCl_3$ solutions. The course of the reactions and the purity of the products were monitored by TLC on Silufol or Kieselgel 60 F254 (Merck) plates in chloroform–methanol systems, 9:1 and 20:1; the spots were visualized by iodine vapors.

Reaction of N-(Tosylmethyl)thiourea 1a with Sodium Enolate of Dimedone. A. Dimedone (0.538 g, 3.84 mmol) was added to a suspension of sodium hydride (0.092 g, 3.83 mmol) in dry acetonitrile (24 ml). The reaction mixture was stirred at room temperature for 24 h while protected from air moisture, then tosylmethylthiourea **1a** (0.938 g, 3.84 mmol) was added [1]. The reaction mass was stirred for 1 h at room temperature and then boiled for 4 h. Then the solvent was evaporated under vacuum to dryness and the solid residue was extracted with boiling heptane (12 × 5 ml). The combined extract was filtered hot, the solvent was distilled off, and the solid residue was washed with cold heptane (2 ml). Obtained 0.484 g (86.4%) of compound **4**; mp 189.5-190°C (acetonitrile). Literature mp 187-188°C [5]. Found, %: C 70.04; H 7.99. $C_{17}H_{24}O_4$. Calculated, %: C 69.84; H 8.27. PMR spectrum ($CDCl_3$): 11.56 (2H, br. s, OH); 3.14 (2H, s, CH_2); 2.27 (8H, s, ring CH_2); 1.03 ppm (12H, s, CH_3).

B. Tosylmethylthiourea **1a** (2.769 g, 11.33 mmol) was added to a suspension of sodium enolate of dimedone, obtained from dimedone (1.593 g, 11.36 mmol) and sodium hydride (0.272 g, 11.33 mmol), in dry acetonitrile (31 ml). The reaction mass was stirred for 4 h at room temperature, and then evaporated under vacuum to dryness. Water (9 ml) was added to the solid residue and then the mixture was stirred and cooled down to 0°C. The residue was filtered, washed with ice water (7 × 15 ml), and dried. Obtained 1.879 g of solid material which then was extracted with boiling heptane (10 × 10 ml). The combined extract was boiled for 5 min with silica gel 100-400 μm, filtered, evaporated down to a volume of 2 ml, and cooled down to 0°C. The precipitated crystals were filtered. Obtained 0.093 g of compound **4**. When the aqueous mother liquor was allowed to stand at room temperature for 6 days, an additional 0.358 g of product was isolated. Total yield of compound **4** was 0.451 g (27.2%).

C. Tosylmethylthiourea **1a** (0.877 g, 3.59 mmol) was added to a suspension of sodium enolate of dimedone, obtained from dimedone (0.503 g, 3.59 mmol) and sodium hydride (0.086 g, 3.59 mmol), in dry acetonitrile (24 ml). The reaction mass was allowed to stand for 46 days at room temperature, and then evaporated

under vacuum to dryness. The solid residue was extracted with boiling heptane (10 × 10 ml). The combined hot extract was filtered, evaporated down to a volume of 2 ml, and cooled down to 0°C. The residue was filtered, washed with cold heptane and acetonitrile, and dried. Obtained 0.231 g (44.1%) of compound **4**.

Reaction of N-(Azidomethyl)thiourea 1b with Sodium Enolate of Dimedone. Dimedone (1.464 g, 10.44 mmol) was added to a suspension of sodium hydride (0.251 g, 10.46 mmol) in dry acetonitrile (20 ml). The mixture obtained was stirred at room temperature for 24 h while protected from air moisture. Then azidomethylthiourea **1b** (1.369 g, 10.44 mmol) was added [1]. The reaction mass was stirred for 5 h at room temperature, and then evaporated under vacuum to dryness. Water (6 ml) was added and then the mixture was extracted with hot chloroform (12 × 5 ml). A small amount of silica gel 100-400 μm was added to the combined extract. The mixture was stirred for 5 min with heating, then filtered hot, and the solvent was evaporated. Obtained 0.713 g (46.7%) of compound **4**.

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