CYCLIZATION OF SUBSTITUTED 1,3-ALKENYNES WITH THIOUREA

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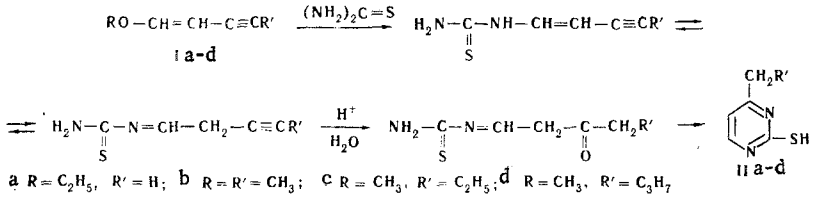
UDC 547.854.1

2-Mercapto-4-methylpyrimidine was obtained by the reaction of 1,3-butenyne ethers, thioethers, and amines with thiourea. The corresponding 2-mercapto-4-alkylpyrimidines were obtained for the first time by analogous cyclization of 1-methoxy-1-buten-3-yne homologs ($CH_3OCH{=}CHC{\equiv}CR$, where R = CH_3, C_2H_5, and C_3H_7) with thiourea. The effect of the nature of the substituents in the 1,3-enyne system on the capacity for cyclization with thiourea was investigated.

In previous papers [1-3] we studied the cyclization of 1,3-enyne ethers, amines, and thioethers with formamide and guanidine. The task of this research was to investigate the possibility of the cyclization of the indicated enyne compounds with thiourea. There is information in the literature regarding the preparation of 2-mercapto-4-methylpyrimidine from 1-methoxy-1-buten-3-yne and thiourea [4].

By an analogous reaction we also obtained 2-mercapto-4-methylpyrimidine (IIa) from 1-ethoxy-1-buten-3-yne (Ia). The structure of IIa was proved by alternative synthesis from acetoacetaldehyde dimethylacetal and thiourea [5]. Under the same conditions, 1-butoxy- and 1-amyloxy-1-buten-3-ynes did not give cyclization products.

We propose that the cyclization with thiourea proceeds like the reaction with guanidine in acid media [3].



Thiourea, by reacting with the potential β-dicarbonyl compound, forms a derivative at the aldehyde group that undergoes ring closure after hydration of the triple bond. The fact that 1-butoxy- and 1-amyloxy-1-buten-3-ynes, which are not hydrolyzed under the reaction conditions [6], did not give cyclization products confirms our assumption regarding the intermediate hydrolysis of the enyne compound.

1-Ethylthio-1-buten-3-yne (III) reacts with thiourea to form 2-mercapto-4-methylpyrimidine (IIa) in very low yield. This fact also confirms our assumption concerning the occurrence of the reaction in acid media through aminolysis and hydration of the starting enyne compound, since 1-ethylthio-1-buten-3-yne is much less inclined to undergo the indicated transformations [7].

We also obtained IIa by the reaction of 1-diethylamino- (IV) and 1-piperidino-1-buten-3-yne (V) with thiourea in alkaline media. The enynamine is hydrolyzed and hydrated in acid media, and triacetylbenzene is formed at a much greater rate.

Lensovet Leningrad Engineering Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 843-845, June, 1971. Original article submitted December 16, 1970.

TABLE 1. Constants and Results of Elementary Analysis of 2-Mercapto-4

Comp.	Mp, °C	Empirical formula	Found,%		Calc.,%		Yield, %
			S	N	S	N	
IIa	220—221	$C_5H_6N_2S$	25,6; 25,3	21,8; 21,9	25,4	22,2	72
IIa·HCl	250 (dec.)	$C_5H_6N_2S \cdot HCl$	17,0; 17,3	17,0; 17,5	19,7	17,2	94 (from IV. V) 32 (from III) 94 (from Ia)
IIb	217—218	$C_6H_8N_2S$	22,6; 22,7	19,9; 19,9	22,8	20,0	65
IIb·HCl	244	$C_6H_8N_2S \cdot HCl$	18,0; 18,3	16,2; 16,0	18,1	15,9	80
IIc	213—215	$C_7H_{10}N_2S$	20,3; 20,6	18,2; 17,9	20,8	18,2	57
IIc·HCl	239	$C_7H_{10}N_2S \cdot HCl$	16,5; 16,8	14,5; 14,8	16,8	14,7	72
IId·HCl	230	$C_8H_{12}N_2S \cdot HCl$	15,4; 15,3	13,5; 13,7	15,7	13,7	52

We also investigated the behavior of 1-methoxy-1-buten-3-yne homologs in the reaction under discussion. 1-Methoxy-1-penten-3-yne (Ib), 1-methoxy-1-hexen-3-yne (Ic), and 1-methoxy-1-hepten-3-yne (Id) react with thiourea almost quantitatively to give 2-mercapto-4-ethyl- (IIb), 2-mercapto-4-propyl- (IIc), and 2-mercapto-4-butylpyrimidines (IId), respectively.

$$RX{-}CH{=}CH{-}C{\equiv}CH \;+\; NH_2{-}C(=S){-}NH_2 \;\longrightarrow\; \text{II a}$$

III-V

III $RX = C_2H_5S$; IV $RX = (C_2H_5)_2N$; V $RX = (CH_2)_5N$

Pyrimidines IIb-d, which we have obtained for the first time, were isolated as the hydrochlorides and, in the case of IIb and IIc, also as the free bases. Polymerization was observed during an attempt to isolate pyrimidine IId from its hydrochloride. The constants, results of elementary analysis, and yields of the cyclization products are presented in Table 1.

2-Mercapto-4-methylpyrimidine was previously obtained from acetoacetaldehyde 1,3-bisdimethylacetal and thiourea [8]. Somewhat later, this synthesis was described for acetoacetaldehyde dimethylacetal and β-aryloxyvinyl aldehydes [9, 10]. 2-Mercapto-4-alkylpyrimidines are obtained in higher yields (almost quantitative) via our synthetic method.

EXPERIMENTAL

The methoxy- and ethoxybutenynes were obtained by the addition of methanol and ethanol to diacetylene [10]. The methoxybutenyne homologs were obtained by alkylation of the sodium derivative of the methoxybutenyne; the constants and spectra of the products were in agreement with the data in [10, 11]. 1-Ethylthio-1-buten-3-yne was obtained from diacetylene and ethyl mercaptan [12], while 1-diethylamino- and 1-piperidino-1-buten-3-ynes were obtained from diacetylene and the appropriate amines [13, 14].

2-Mercapto-4-alkylpyrimidines. A 0.05-mole sample of the enyne ether or thioether was added slowly to a solution of 0.05 mole of thiourea in 100 ml of ethanol. The reaction mass was heated to 50-60°, and 9 ml of concentrated hydrochloric acid was added dropwise with vigorous stirring. The mixture was heated on a boiling-water bath for 6 h, and the precipitated hydrochloride was filtered, washed with alcohol, and dried.

Isolation of the Base from the Hydrochloride. The salt was dissolved in 0.1 M potassium hydroxide, and the base was obtained by neutralization of this solution with 40% acetic acid. The crystals were filtered, dried, and recrystallized from alcohol.

2-Mercapto-4-methylpyrimidine from Enynamines. Thiourea (0.05 mole) was added to a solution of 0.05 mole of sodium ethoxide in 70 ml of ethanol, the mixture was heated to 70-75°, 0.05 mole of the enynamine was added to the reaction mass, and the mixture was heated on a boiling-water bath for 10 h. The addition of 50 ml of water and neutralization with acetic acid gave 40% of 2-mercapto-4-methylpyrimidine.

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