RECYCLIZATION OF 5-CARBETHOXY-4-METHYL-2-MERCAPTO(AMINO, HYDROXY)PYRIMIDINES TO GIVE 5-ACETYL-2-MERCAPTO(AMINO, HYDROXY)-4-HYDROXYPYRIMIDINES

R. S. Vartanyan, Zh. V. Kazaryan, and S. A. Vartanyan

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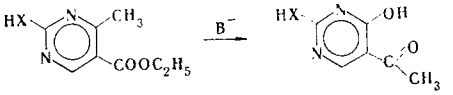
Conditions for the selective preparation of 5-carbethoxy-4-methyl-2-substituted pyrimidines or 5-acetyl-4-hydroxy-2-substituted pyrimidines by condensation of ethoxymethyleneacetoacetic ester with 1,3-binucleophiles are proposed. It is shown that under the influence of sodium ethoxide 5-carbethoxy-4-methyl-2-substituted pyrimidines undergo rearrangement to 5-acetyl-4-hydroxy-2-substituted pyrimidines.

The published data on the reaction of ethoxymethyleneacetoacetic ester with 1,3-binucleophiles make it possible to make certain generalizations. Thus the thermal reaction of guanidine carbonate with hydroxymethyleneacetoacetic ester leads to the formation of 2-amino-6-methyl-4-hydroxypyrimidine, i.e., the reaction proceeds as the reaction of the acetoacetic ester itself with guanidine [1], whereas the reaction with ethoxymethyleneacetoacetic ester in alcohol solution leads to 2-amino-5-carbethoxy-4-methylpyrimidine [2]. Depending on the conditions, either 5-acetyl-2-mercapto-4-hydroxypyrimidine [3] or 5-carbethoxy-4-methyl-2-mercaptopyrimidine [4] is formed in the reaction of thiourea with ethoxymethyleneacetoacetic ester. However, the reaction of ureidomethyleneacetoacetic ester with potassium hydroxide gives 5-acetyl-2,4-dihydroxypyrimidine, whereas the reaction with sodium ethoxide gives 5-carbethoxy-4-methyl-2-hydroxypyrimidine [5]. 5-Acetyl-2,4-dihydroxypyrimidine was isolated when 5-carbethoxy-4-methyl-2-hydroxypyrimidine was heated in aqueous potassium hydroxide [5].

It seemed of interest to make a detailed study of this rearrangement and to ascertain the possibility of a similar transformation for other substituted carbethoxypyrimidines. For this, we studied the synthesis of the corresponding 2-amino(mercapto)-5-carbethoxy-4-methylpyrimidines. We demonstrated that 2-amino-5-carbethoxy-4-methylpyrimidine is obtained in the reaction of ethoxymethyleneacetoacetic ester with guanidine hydrochloride in the presence of bases.

Attempts to synthesize cyclic products under acidic conditions for this pair of reagents were unsuccessful. However, 5-carbethoxy-4-methyl-2-hydroxy- and 5-carbethoxy-2-mercapto-4-methylpyrimidines, respectively, were obtained in the reaction of urea and thiourea with ethoxymethyleneacetoacetic ester in glacial acetic acid.

Attempts to recyclize 2-amino(mercapto)-5-carbethoxy-4-methylpyrimidines under the conditions of the rearrangement of the corresponding 2-hydroxy analog (with an aqueous solution of potassium hydroxide) were unsuccessful. The reactions were subsequently carried out in alcohol solutions of sodium ethoxide, which led to the expected rearrangements:



X = O, S, NH

The recyclization is, in all likelihood, similar to the known Dimroth [6] and Kost–Sagitullin [7] rearrangements.

It should be noted that the alternatively possible 2-mercapto(amino, hydroxy)-6-methyl-4-hydroxy-5-formylpyrimidines were not detected in the reaction products. However, the absence in the PMR spectrum of the signal of an aldehyde proton and the presence of the signal

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of a proton of the pyrimidine ring (8.4 ppm), just like the detachment of [M–43] in the mass spectra of the compounds obtained, constitute evidence for the formation of exclusively a 5-acetyl derivative. It is evident that the thermodynamic stability of the 5-acetyl derivative predetermines the direction of recyclization.

Consequently, the rearrangement of 5-carbethoxypyrimidines to 5-acetylpyrimidines is general in character and can be regarded as a new convenient method for the synthesis of 5-acetylpyrimidines.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained with an MKh-1320 spectrometer.

2-Amino-5-carbethoxy-4-methylpyrimidine. Sodium ethoxide prepared by dissolving 0.5 g (22 mmole) of sodium metal in 10 ml of absolute ethanol was added to a solution of 1 g (5 mmole) of ethoxymethyleneacetoacetic ester and 0.5 g (5 mmole) of guanidine hydrochloride in 5 ml of absolute ethanol, and the mixture was allowed to stand overnight. The precipitated crystals were removed by filtration, washed with water, and air dried to give 0.8 g (82%) of a product with mp 212-213°C. IR spectrum: 1715 (ester C=O), 3200-3300 (NH_2), and 1600 cm^{-1} (pyrimidine aromatic ring). PMR spectrum: 8.6 (1H, s, CH=C), 7.2 (2H, s, NH_2), 4.3 (2H, q, J = 6 Hz, CH_2), 2.66 (3H, s, CH_3), and 1.2 ppm (3H, t, J = 6 Hz, CH_3). Found: C 53.1; H 6.2; N 23.2%; M^+ 181. $C_8H_{11}N_3O_2$. Calculated: C 53.0; H 6.1; N 23.2%; M 181.

5-Carbethoxy-4-methyl-2-hydroxypyrimidine. A mixture of 1 g (5 mmole) of ethoxymethyleneacetoacetic ester and 0.35 g (5 mmole) of urea in 15 ml of glacial acetic acid was refluxed for 4-5 h (until the color of the solution darkened), after which the acetic acid was removed partially in vacuo, and the residue was poured over ice. The precipitated crystals were remived by filtration, washed with water, and air dried to give 0.8 g (82%) of 5-carbethoxy-4-methyl-2-hydroxypyrimidine with mp 248-249°C (mp 248-250°C [5]).

5-Carbethoxy-2-mercapto-4-methylpyrimidine. This compound was similarly obtained from 1 g (5 mmole) of ethoxymethyleneacetoacetic ester, 0.4 g (5 mmole) of thiourea, and 15 ml of glacial acetic acid. Workup gave 0.8 g (76%) of a product with mp 188-189°C.

2-Amino-5-acetyl-4-hydroxypyrimidine. A 1.8-g (10 mmole) sample of 2-amino-5-carbethoxy-4-methylpyrimidine was added to sodium ethoxide, prepared by dissolving 0.5 g (22 mmole) of sodium in 10 ml of absolute ethanol, and the mixture was evaporated to dryness on a boiling-water bath. The residue was dissolved in 10 ml of water, 1.2 ml of glacial acetic acid was added with stirring, and the mixture was stirred until room temperature was reached. The precipitated crystals were removed by filtration, washed with water, and air dried to give 1.2 g (79%) of a product with mp 301-302°C. IR spectrum: 1600 (pyrimidine aromatic ring), 1665 (ring C=O), 1690 (keto C=O), and 3200-3300 cm^{-1} (NH, NH_2). PMR spectrum: 8.6 (1H, s, CH=C), 7.2 (1H, s, NH), 6.0 (2H, s, NH_2), and 2.7 ppm (3H, s, CH_3). Found: C 47.1; H 4.6; N 27.4%; M^+ 153. $C_6H_7N_3O_2$. Calculated: C 47.1; H 4.6; N 27.4%; M 153.

5-Acetyl-2-mercapto-4-hydroxypyrimidine. This compound was similarly obtained from 2 g (10 mmole) of 5-carbethoxy-2-mercapto-4-hydroxypyrimidine. Workup gave 1.5 g (87%) of a product with mp 310-311°C.

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