SYNTHESIS OF 3,4-DIAMINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES

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The reaction of 4-(amino-substituted)-2-methylthio-6-chloropyrimidine-5-carbonitriles with hydrazine and methylhydrazine was used to synthesize 3,4-diamino-6-methylthio-1H-pyrazolo[3,4-d]pyrimidines. It was shown that the formation of pyrazolopyrimidines proceeds through intermediate 6-hydrazinopyrimidine-5-carbonitriles.

Pyrazolo[3,4-d]pyrimidines, as isoanalogs of biogenic purines, are of considerable interest from the standpoint of searching for biologically active substances. In this respect, derivatives of 3- and 4-aminopyrazolo[3,4-d]pyrimidines are especially interesting; substances possessing valuable pharmacological properties have been found among them [1-7]. 3-Aminopyrazolo[3,4-d]pyrimidines can also serve as useful intermediates for the production of more complex heterocycles [8, 9]. However, 3,4-diaminopyrazolo[3,4-d]pyrimidines have been insufficiently studied. In the literature there are only a few examples of the synthesis of compounds of this type [10]. Recently we reported on the synthesis of 4,5-diaminothieno[2,3-d]pyrimidines and their use for the production of 1-thia-3,4,6,8-tetraaza- and 1-thia-3,4,5,6,8-pentaazaacenaphthylenes [11-13]. Continuing investigations along this line, this work presents the results obtained in the development of the synthesis of 3,4-diamino-1H-pyrazolo[3,4-d]pyrimidines.

An analysis of the literature data showed that one of the methods of producing 3-aminopyrazolo[3,4-d]pyrimidines is the reaction of pyrimidine-5-carbonitriles possessing groups sensitive to nucleophiles in the 4- or 6-position of the pyrimidine ring with hydrazine [7, 10, 14]. Therefore, N-substituted 4-amino-2-methylthio-6-chloropyrimidine-5-carbonitriles (IIa-f), which are readily synthesized by the reaction of 2-methylthio-4,6-dichloropyrimidine-5-carbonitrile (I) with an excess of the corresponding amine, were selected as starting materials for the synthesis of the target compounds.

A study of the interaction of the carbonitriles IIa-e with hydrazine hydrate showed that when 4-alkylamino-2-methylthio-6-chloropyrimidine-5-carbonitriles (IIa,b) are heated in methanol solution with hydrazine hydrate, the corresponding 3-aminopyrazolo[3,4-d]pyrimidines (IIIa,b) are formed in yields of 69 and 64%, respectively. However, the reaction of compounds IIId,e with hydrazine hydrate proceeds with the formation of 4-arylamino-6-hydrazino-2-methylthio pyrimidine-5-carbonitriles (IVd,e). The reaction was observed to stop at the step of hydrazinopyrimidine formation in the series of 4-aryl-6-chloropyrimidine-5-carbonitriles as well [15-17]. After brief heating of the hydrazinopyrimidine IVd in dioxane solution in the presence of a catalytic amount of hydrochloric acid, this compound was converted to the corresponding 3-aminopyrazolo[3,4-d]pyrimidine IIIId. To bring out cyclization between the hydrazino and cyano groups in compound IVe, sodium ethylate was used as a reagent activating the cyano group [18].

The interaction of compounds IIa,c-f with methylhydrazine leads to the formation of 3,4-diaminopyrazolo[3,4-d]pyrimidines (Va,c-f), regardless of the nature of the substituent in the 4-position of the pyrimidine ring. The reaction of 6-chloropyrimidine-5-carbonitriles with methylhydrazine, depending on the intermediate formed (hydrazinopyrimidine or amidrazone), may lead to isomeric 1-methyl-1H- (V) or 2-methyl-2H-pyrazolo[3,4-d]pyrimidines (VI). The possibility that the reaction may proceed through the corresponding amidrazones is indicated by the data of [19, 20], according to which certain pyrimidine-5-carbonitriles are capable of adding amines or hydrazine at the cyano group. Therefore, an attempt was made to isolate the intermediate product of the reaction between the carbonitrile IIa and methylhydrazine. However, despite variation

of the temperature system of the reaction, its duration, the solvents (dioxane, methanol, water), and the reagent ratio, only the pyrazolopyrimidine was isolated in all cases. Then the interaction of 2-methylthio-4,6-dichloropyrimidine-5-carbonitrile (I) with methylhydrazine was studied. It was established that conducting the reaction at room temperature leads to the formation of 4-(1-methylhydrazino)-2-methylthio-6-chloropyrimidine-5-carbonitrile (VII). The structure of compound VII was confirmed by the spectral data (Table 1). The IR spectrum has an absorption band of the cyano group at 2208 cm⁻¹, and a singlet of the amino group at 4.12 ppm was observed in the ¹H NMR spectrum together with the singlets of CH₃S and the CH₃N groups, indicating that replacement of the chlorine atom involves the substituted nitrogen atom of methylhydrazine. In an attempt to purify compound VII by crystallization, it was noted that it is converted to the pyrazolopyrimidine VIII, which was also obtained with a yield of 56% by heating compound VII in dioxane solution for 6 h. The IR spectrum of compound VIII does not contain the absorption band of the cyano group, while the signals of the CH₃N and NH₂ groups in the ¹H NMR spectrum are shifted 0.3 ppm in the weak-field direction in comparison with those of the hydrazinopyrimidine VII. We should mention that carrying out the reaction between the carbonitrile I and methylhydrazine at 65°C (10 min) leads to the formation of a mixture of compounds VII and VIII in a 2:3 ratio (according to the data of the ¹H NMR spectra).

When the pyrazolopyrimidine VIII was heated with an excess of butylamine, 3-amino-4-butylamino-1-methyl-6-methylthio-1H-pyrazolo[3,4-d]pyrimidine (Vc) was isolated; in its physical characteristics and ¹H NMR and IR spectral data it is identical with the compound obtained by the reaction of the carbonitrile IIIc with methylhydrazine. These data permit us to conclude that the formation of 3,4-diamino-1-methyl-6-methylthio-1H-pyrazolo[3,4-d]pyrimidines in the reaction of the corresponding 6-chloropyrimidine-5-carbonitriles with methylhydrazine proceeds through intermediate 4-(2-methylhydrazino)pyrimidine-5-carbonitriles.