SYNTHESIS OF 4,6-BIS(1H-1,2,3-TRIAZOLYL)PYRIMIDINES BY
THE REACTION OF 4,6-DIAZIDO-2-(4-METHOXYPHENYL)-
PYRIMIDINE WITH COMPOUNDS CONTAINING A
REACTIVE METHYLENE GROUP

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The reaction of 4,6-diazido-2-(4-methoxyphenyl)pyrimidine with cyanoacetic ester in the presence of triethylamine leads only to 4-azido-6-amino-1-(4-methoxyphenyl)pyrimidine. The main product in reactions with 1,3-dicarbonyl compounds (acetylacetone, acetoacetic and benzoylacetic esters) is the corresponding substituted 4,6-bis(1H-1,2,3-triazolyl)pyrimidine. The formation of 4-azido-6-(1H-1,2,3-triazolyl)pyrimidine and 4-amino-6-(1H-1,2,3-triazolyl)pyrimidine as minor products was also recorded.

We showed previously [1] that the reaction of 2- and 4-azidopyrimidines with acetylacetone and benzoylacetonate in the presence of triethylamine may be used as a method of obtaining substituted 1-(2-pyrimidinyl)- or 1-(4-pyrimidinyl)-4-acyl-1H-1,2,3-triazoles in good yield. In addition, 2,4- and 4,6-diazidopyrimidines did not participate in this reaction. Consequently, the possibility of forming bis(1H-1,2,3-triazolyl)pyrimidines remained vague, as did the probable special features of the process linked with the presence in the molecule of two tautomerizing azido groups. On studying the reactions of 1,3-dicarbonyl compounds with other diazidodiazines such as 6-azidotetrazolo[1,5-b]pyridazine [2-4], 6-azidotetrazolo[5,1-a]phthalazine [4,5], 5-azidotetrazolo[1,5-a]quinazoline [4], 6-azidopyrido[3,2-d]-, 6-azidopyrido[2,3-d]-, 6-azidopyrido[4,3-d]-, and 6-azidopyrido[3,4-d]tetrazolo[1,5-b]pyridazine [2,4,6], it was established that one azido group participates in the reaction with the formation of the corresponding mono(1H-1,2,3-triazolyl)- and/or amino derivatives, although in certain cases azidotetrazole isomerization precedes reaction with a CH₂ reactive compound. The ratio of the products formed depends on the base, the temperature, and the acidity of the reactive CH₂ group.

It has been shown possible [7] to reduce an azido group to an amino group in a series of 2,4-diazido-6-alkoxy- or 2,4-diazido-6-amino-1,3,5-triazines by a diazo transfer reaction [8] using cyanoacetic ester, but 2-amino-4-(1H-1,2,3-triazolyl)-1,3,5-triazines were formed on reacting these compounds with acetylacetonate and acetooacetic ester. It should be noted that esters of cyanoacetic acid are also used for the synthesis of substituted 5-amino-1H-1,2,3-triazoles by condensation in the presence of base with hetaryl and aryl azides such as 4-azidopyridine and its N-oxide [9], 5-azido-2-trifluoromethylpyrimidine [10], 4-nitrophenyl azide [9, 10], etc. The 2,4- and 4,6-diazidopyrimidines are in our view convenient models for such investigations because of the relative ease (low activation barrier) of azide—tetrazole isomerism and the wide variation of substituents introducible into them.

We investigated the synthesis and an investigation of the reactivity of 4,6-diazido-2-(4-methoxyphenyl)pyrimidine (I) with compounds containing a reactive methylene group, viz. acetylacetonate, ethyl cyanoacetate, acetoacetic acid ester, and ethyl benzoylacetonate.

Diazidopyrimidine (I) was synthesized under mild conditions by the reaction of the corresponding dichloropyrimidine with lithium azide in DMF solution obtained in situ. The equilibrium of diazide (I) and its tetrazole tautomer (II) (Scheme 1) was recorded in the PMR spectrum of the product in CDCl₃, DMSO-D₆, and acetone-D₆ with a strong displacement towards the diazide form. Under equilibrium conditions at room temperature, the ratio (I):(II) = 99:~ 1, 95:5, and 85:15% in CDCl₃.
acetone-$D_6$, and DMSO-$D_6$ respectively. The presence of compound (II) was indicated by the signal of the 8-H atom being displaced by more than 1 ppm towards low field relative to the 5-H signal in diazide (I) (see diazido-tetrazole equilibrium of 4,6-diazidopyrimidine in [11, 12]).

Assuming that both azido groups may be involved in the reaction of cyanoacetic ester with diazidopyrimidine (I), we condensed these reactants with a twofold excess of ester in DMF solution in the presence of triethylamine. However, according to the analytical and spectral data (see Experimental section) the process stopped at the formation of aminoazidopyrimidine (III). A strong absorption band for the azide group was observed at 2100-2200 cm$^{-1}$ in the IR spectrum of the obtained product, which indicates the presence of azide (III) unequivocally. Only signals for compound (III) were recorded in the PMR spectra in CDCl$_3$ and acetone-$D_6$. This implies that the tetrazole tautomer (IV) is not formed under these conditions and the equilibrium is practically completely displaced to the side of the azide form (III).

The reaction of diazide (I) with two equivalents of 1,3-dicarbonyl compounds (acetylacetone, ethyl esters of acetoacetic and benzoylacetic acids) in the presence of triethylamine proceeds differently both at room temperature in DMF (procedure A) and on boiling in ethanol (procedure B). Under these conditions, the main product is the corresponding bis(triazolyl)pyrimidine (Va-c), according to analytical and spectral data (see Experimental section). It should be noted that ethyl benzoylacetate reacts significantly more slowly than the other compounds containing a reactive methylene group. A small quantity of amino(triazolyl)pyrimidine (Via) was isolated from the reaction of (I) with acetylacetone. On using one equivalent of acetylacetone in DMF solution in this reaction, we successfully isolated a minor quantity of azido(triazolyl)pyrimidine (VIIa) in addition to the main bis(triazolyl)pyrimidine. The reduced reactivity of the azide group in aminoazidopyrimidine (III) compared with diazidopyrimidine (I) attracted attention. The reaction of the former with acetylacetone on boiling in ethanol leads, according to TLC and IR spectral data, to the formation of triazolyl-pyrimidine (Via) but the process requires several days (see with cyanoacetic ester).