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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 benzoylacetone 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 CH_2 reactive compound. The ratio of the products formed depends on the base, the temperature, and the acidity of the reactive CH_2 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 acetylacetone and acetoacetic 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 equilibrium and the wide variation of substituents introducible into them.

The present work is devoted to 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. acetylacetone, ethyl cyanoacetate, acetoacetic acid ester, and ethyl benzoylacetate.

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 $CDCl_3$, DMSO-D_6, and acetone-D_6 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 $CDCl_3$,

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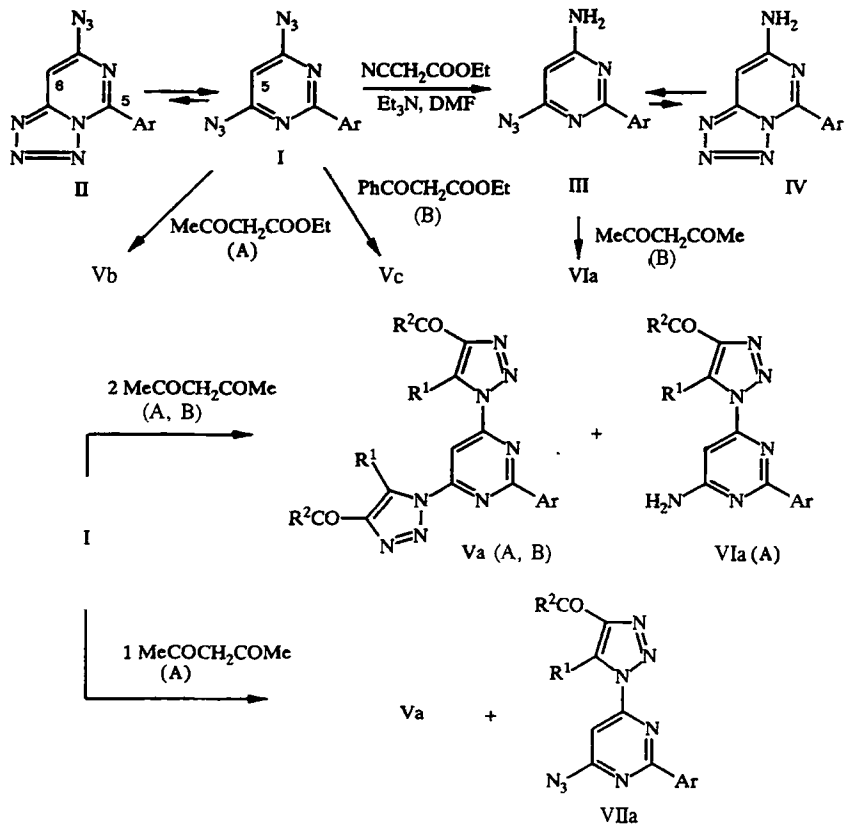
acetone-D_6, and DMSO-D_6 respectively. The presence of compound (II) was indicated by the signal of the 8-H atom being displaced by more than 1 ppm towards low field relative to the 5-H signal in diazide (I) (see diazido–tetrazole equilibrium of 4,6-diazidopyrimidine in [11, 12]).

Scheme 1



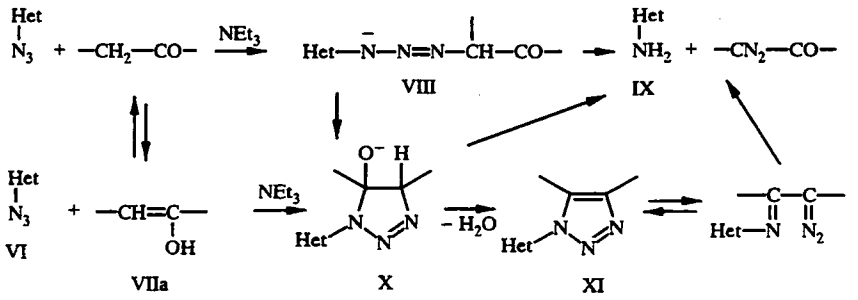
I–VII Ar = 4-$MeOC_6H_4$; a $R^1 = R^2 = Me$; b $R^1 = Me$, $R^2 = EtO$; c $R^1 = Ph$, $R^2 = EtO$

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 aminoazidipyrimidine (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).

The reaction of heteroaromatic azides with CH_2-reactive compounds may be represented by the general Scheme 2 on the basis of literature data [2, 4, 8, 13].

Scheme 2



According to this scheme, the reaction of diazide (I) with cyanoacetic ester comprises the intermediate formation of the corresponding low-stability triazene (VIII), the subsequent spontaneous decomposition of which with transfer of proton leads to amine (III) [general formula (IX) in Scheme 2]. The presence of a strong electron-donating amino group in the latter reduces the electrophilicity of the terminal nitrogen of the remaining azide group, which slows further reaction with cyanoacetic ester and provides the selectivity in the conversion of (I) → (III).

The mechanism of forming bis(triazolyl)pyrimidines (Va-c) on condensing diazidopyrimidine (I) with 1,3-dicarbonyl compounds probably comprises the corresponding intermediate trazoline (X), the thermal decomposition of which leads to amine (IX), but aromatization of which leads to the stable triazole [general formula (XI) in Scheme 2]. We have shown that bis(triazolyl)pyrimidine (Va) is practically unchanged under the conditions of its synthesis (according to TLC and IR spectral data) and consequently is not the source of aminotriazolylpyrimidine (VIa).

On investigating the reactivity of 4,6-diazidopyrimidine (I) it has been shown that the corresponding bis(1,2,3-triazolyl)pyrimidine (V) is formed on condensation with 1,3-dicarbonyl compounds and a regioselective conversion of one azide group to an amino group [(I) → (III)] is effected on reaction with ethyl cyanoacetate under mild conditions.

EXPERIMENTAL

The IR spectra were drawn on UR 20 and Specord M 80 instruments in KBr disks (concentration 0.25%). The PMR spectra were drawn on a Bruker AC 200 (200, 13 MHz) spectrometer. Chemical shifts were measured relative to the residual protons of the solvent ($CDCl_3$, δ 7.24 ppm; DMSO-D_6, δ 2.50 ppm; acetone-D_6, δ 2.04 ppm). The mass spectra were recorded on a Finnigan MAT 8200 spectrometer. A check on the progress of reactions and the homogeneity of products was carried out by TLC on Silufol UV 254 plates. Silicagel 60 (0.063-0.100 mm) from Merck was used for preparative column chromatography.

4,6-Diazido-2-(4′-methoxyphenyl)pyrimidine (I) and 7-Azido-5-(4′-methoxyphenyl)tetrazolo[1,5-*c*]pyrimidine (II). A solution of purified 4,6-dichloro-2-(4′-methoxyphenyl)pyrimidine (0.55 g, 2.2 mmole), NaN_3 (0.34 g, 5.2 mmole), and anhydrous LiCl (0.22 g, 5.2 mmole) in dry DMF (20 ml) was stirred at room temperature for 2 days. The reaction mixture was poured into water, the precipitated product was filtered off, washed with water, and dried. The product (0.56 g, 96%) was obtained as a mixture of tautomers (I) and (II) used subsequently without further purification. It had mp 136-137°C. IR spectrum: 2125, 2160 cm^{-1} (N_3). PMR spectrum of tautomer (I) in $CDCl_3$: 8.38 (2H, d, J = 9 Hz, 2′-H, 6′-H); 6.96 (2H, d, J = 9 Hz, 3′-H, 5′-H); 6.05 (1H, s, 5-H); 3.87 ppm (3H, s, 4′-CH_3O); in acetone-D_6: 8.39 (2H, d, J = 9 Hz, 2′-H, 6′-H); 7.06 (2H, d, J = 9 Hz, 3′-H, 5′-H); 6.24 (1H, s, 5-H); 3.89 ppm (3H, s, 4′-CH_3O); in DMSO-D_6: 8.30 (2H, d, J = 9 Hz, 2′-H, 6′-H); 7.11 (2H, d, J = 9 Hz, 3′-H, 5′-H); 6.48 (1H, s, 5-H); 3.85 ppm (3H, s, 4′-CH_3O); for tautomer (II) in $CDCl_3$; 8.81 (2H, d, J = 9 Hz, 2′-H, 6′-H); 7.10 ppm (2H, d, J = 9 Hz, 3′-H, 5′-H)*; in acetone-D_6: 8.80 (2H, d, J = 9 Hz, 2′-H, 6′-H); 7.34 (1H, s, 8-H); 7.25 (2H, d, J = 9 Hz, 3′-H, 5′-H); 3.98 ppm (3H, s, 4′-CH_3O); in DMSO-D_6: 8.61 (2H, d, J =

*Assignment of the other signals was difficult.

9 Hz, 2'-H, 6'-H); 7.65 (1H, s, 8-H); 7.29 (2H, d, J = 9 Hz, 3'-H, 5'-H); 3.92 ppm (3H, s, 4'-CH_3O). High-resolution mass spectrum, m/z: M^+ 268.0821, calculated for $C_{11}H_8N_8O$ M 268.0821.

6-Amino-4-azido-2-(4'-methoxyphenyl)pyrimidine (III). A solution of the mixture of tautomers (I) and (II) (see above) (0.1 g, 0.4 mmole), ethyl cyanoacetate (0.1 ml, 0.9 mmole), and triethylamine (0.15 ml, 0.9 mmole) in dry DMF (10 ml) was stirred at room temperature for ~5 h, then left at the same temperature for ~16 h. The mixture was diluted with water and cooled. The precipitate of product which formed gradually was filtered off, washed with water, and dried. Compound (III) (0.07 g, 78%) was obtained and was purified by column chromatography in chloroform. Mp 142-144°C. IR spectrum: 2140 cm^{-1} (N_3). PMR spectrum ($CDCl_3$): 8.33 (2H, d, J = 9 Hz, 2'-H, 6'-H); 6.94 (2H, d, J = 9 Hz, 3'-H, 5'-H); 5.75 (1H, s, 5-H); 4.82 (2H, br.s, NH_2); 3.85 ppm (3H, s, 4'-CH_3O). PMR spectrum (acetone-D_6): 8.33, (2H, d, J = 9 Hz, 2'-H, 6'-H); 6.99 (2H, d, J = 9 Hz, 3'-H, 5'-H); 6.33 (2H, br.s, NH_2); 5.88 (1H, s, 5-H); 3.86 ppm (3H, s, 4'-CH_3O). High-resolution mass spectrum, m/z: M^+ 242.0917, calculated for $C_{11}H_{10}N_6O$ M 242.0916.

Reaction of 4,6-Diazido-2-(4'-methoxyphenyl)pyrimidine (I) with 1,3-Dicarbonyl Compounds. A. A solution of diazide (I) (1 mmole), 1,3-dicarbonyl compound (2.5 mmole), and triethylamine (2.5 mmole) in DMF (15 ml) was stirred at room temperature for 2-3 days. The resulting precipitate was filtered off, washed with water and with ethanol, and dried. The corresponding bis(triazolyl)pyrimidine (V) was obtained.

B. A mixture of diazidopyrimidine (I) (1 mmole), 1,3-dicarbonyl compound (2.5 mmole), and triethylamine (2.5 mmole) in ethanol (10 ml) was boiled until the initial diazide has disappeared. The solid which separated on cooling was treated as described above (see A).

4,6-Bis(4"-acetyl-5"-methyl-1"H-1",2",3"-triazolyl)-2-(4'-methoxyphenyl)pyrimidine (Va) was obtained by methods A and B using acetylacetone and was purified by column chromatography with chloroform. Yield was 56% of mp 280-282°C. IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 8.67 (1H, s, 5-H); 8.34 (2H, d, J = 9 Hz, 2'-H, 6'-H); 7.04 (2H, d, J = 9 Hz, 3'-H, 5'-H); 3.90 (3H, s, 4'-CH_3O); 3.18 (6H, s, 2 × 5"-CH_3); 2.78 ppm (6H, s, 2 × 4"-$COCH_3$). High-resolution mass spectrum, m/z: M^+ 432.1641, calculated for $C_{21}H_{20}N_8O_3$ M 432.1658; $[M-56]^+$ 376.1534, calculated for $C_{21}H_{20}N_4O_3$ [M−56] 376.1535.

4,6-Bis(4"-ethoxycarbonyl-5"-methyl-1"H-1",2",3"-triazolyl)-2-(4'-methoxyphenyl)pyrimidine (Vb) was obtained by method A using ethyl acetoacetate. Yield was 65%, mp 227-229°C (from ethanol−DMF). IR spectrum: 1735 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 8.65 (1H, s, 5-H); 8.32 (2H, d, J = 9 Hz, 2'-H, 6'-H); 7.02 (2H, d, J = 9 Hz, 3'-H, 5'-H); 4.47 (4H, q, J = 7 Hz, 2 × 4"-O$\underline{CH_2}CH_3$); 3.89 (3H, s, 4'-CH_3O); 3.16 (6H, s, 2 × 5"-CH_3); 1.45 ppm (6H, t, J = 7 Hz, 2 × 4"-$OCH_2\underline{CH_3}$). High-resolution mass spectrum, m/z: M^+ 492.1871, calculated for $C_{23}H_{24}N_8O_5$ M 492.1870.

4,6-Bis(4"-ethoxycarbonyl-5"-phenyl-1"H-1",2",3"-triazolyl)-2-(4'-methoxyphenyl)pyrimidine (Vc) was obtained by method B using ethyl benzoylacetate. Yield was 43%, mp 265-267°C (from ethanol−DMF). IR spectrum: 1730 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 8.61 (1H, s, 5-H); 7.42-7.50 (10H, m, 2 × 5"-C_6H_5); 6.75 (2H, d, J = 9 Hz, 2'-H, 6'-H); 6.53 (2H, d, J = 9 Hz, 3'-H, 5'-H); 4.32 (4H, q, J = 7 Hz, 2 × 4"-O$\underline{CH_2}CH_3$); 3.78 (3H, s, 4'-CH_3O); 1.26 ppm (6H, t, J = 7 Hz, 2 × 4"-$OCH_2\underline{CH_3}$). High-resolution mass spectrum, m/z: $[M-56]^+$ 560.2070, calculated for $C_{33}H_{28}N_4O_5$ [M−56] 560.2060.

4-Amino-6-(4"-acetyl-5"-methyl-1"H-1",2",3"-triazolyl)-2-(4'-methoxyphenyl)pyrimidine (VIa). The filtrate obtained in the synthesis of bis(triazolyl)pyrimidine (Va) by method A was diluted with water. The resulting precipitate was filtered off, washed with water, and dried. According to TLC (chloroform) it was a mixture of two products which were separated by column chromatography eluting with chloroform and with chloroform−acetone (9:1). Amino(triazolyl)pyrimidine (VIa) was obtained in <10% yield, mp 254-257°C. IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 8.30 (2H, d, J = 9 Hz, 2'-H, 6'-H); 6.98 (1H, s, 5-H); 6.97 (2H, d, J = 9 Hz, 3'-H, 5'-H); 5.17 (2H, br.s, NH_2); 3.87 (3H, s, 4'-CH_3O); 3.09 (3H, s, 5"-CH_3); 2.74 ppm (3H, s, 4"-$COCH_3$). High-resolution mass spectrum, m/z: M^+ 324.1341, calculated for $C_{16}H_{16}N_6O_2$ M 324.1335.

4-Azido-6-(4"-acetyl-5"-methyl-1"H-1",2",3"-triazolyl)-2-(4'-methoxyphenyl)pyrimidine (VIIa) was obtained by method A using an equimolar ratio of diazidopyrimidine (I) and acetylacetone. The bis(triazolyl)pyrimidine (Va) precipitated as a solid was separated (~30% yield). The filtrate was diluted with water, the resulting solid was filtered off, washed with water, and dried. According to TLC (chloroform−acetone, 9:1) it was a mixture of products from which compound (VIIa) was isolated by column chromatography (with chloroform). Yield was <10%, mp 190-196°C. IR spectrum: 2125, 2160 (N_3), 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 8.37 (2H, d, J = 9 Hz, 2'-H, 6'-H); 7.34 (1H, s, 5-H); 7.00 (2H, d, J = 9 Hz, 3'-H); 3.89 (3H, s, 4'-CH_3O); 3.12 (3H, s, 5"-CH_3); 2.75 ppm (3H, s, 4"-$COCH_3$). High-resolution mass spectrum, m/z: M^+ 350.1241, calculated for $C_{16}H_{14}N_8O_2$ M 350.1240.

REFERENCES

1. V. P. Krivopalov, E. B. Nikolaenkova, V. F. Sedova, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 10, 1401 (1983).
2. A. Gorup, M. Kovacic, B. Kranjc-Skraba, B. Mihelcic, S. Simonic, B. Stanovnik, and M. Tisler, Tetrahedron, **30**, 2251 (1974).
3. A. Kh. Karklinya, L. G. Nikolaeva, O. B. Belkina, and E. Yu. Gudrinietse, Izv. Akad. Nauk LatvSSR, Ser. Khim., No. 4, 436 (1976).
4. B. Stanovnik, M. Tisler, S. Polanc, and J. Zitnik, Synthesis, No. 7, 491 (1977).
5. A. Kh. Kharklinya and E. Yu. Gudrinietse, Izv. Akad. Nauk LatvSSR, Ser. Khim., No. 2, 202 (1974).
6. S. Polanc, B. Stanovnik, and M. Tisler, J. Heterocycl. Chem., **10**, 565 (1973).
7. Y. A. Azev, I. P. Loginova, O. L. Guselnikova, S. V. Shorshnev, V. L. Rusinov, and O. N. Chupakhin, Mendeleev Commun., No. 3, 104 (1994).
8. M. Regitz and G. Maas, Diazo Compounds, Properties and Synthesis, Academic Press, New York (1986), Chap. 13.
9. G. L'abbe and L. Beenaerts, Tetrahedron, **45**, 749 (1989).
10. H. Wamhoff and W. Wambach, Chem. Ztg., **113**, 11 (1989).
11. A. Yu. Denisov, V. P. Krivopalov, V. I. Mamatyuk, and V. P. Mamaev, Magn. Reson. Chem., **26**, 42 (1988).
12. V. P. Krivopalov, A. Yu. Denisov, Yu. V. Gatilov, V. I. Mamatyuk, and V. P. Mamaev, Dokl. Akad. Nauk SSSR, **300**, 115 (1988).
13. G. L'abbe, Ind. Chim. Belg., **34**, 519 (1969).