REACTION OF ARYL-SUBSTITUTED AZIDOPYRIMIDINES WITH 1,3-DICARBONYL COMPOUNDS

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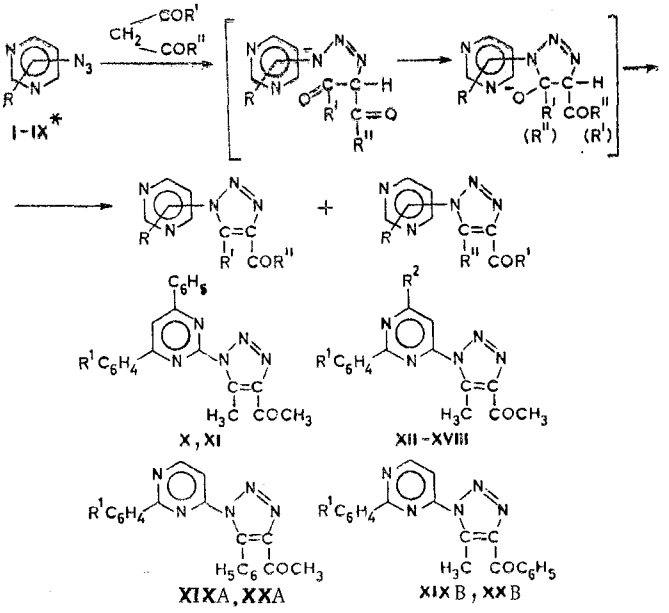
UDC 546.171.8:547.855.3.7'791'442.3:542.953:543.422

Substituted 1-pyrimidyl-4-acyl-1,2,3-triazoles were obtained by the reaction of 2- and 4-azidopyrimidines with aryl substituents with acetyl- or benzoylacetone. An accelerating effect of an o-hydroxyphenylpyrimidine fragment in this reaction, which was explained by the effect of an intramolecular hydrogen bond, was observed.

In a continuation of our research on the synthesis and reactivities of azidopyrimidines that contain an o-hydroxyphenyl group [1] we studied the reaction of substituted 2- and 4-azidopyrimidines with 1,3-dicarbonyl compounds.



X R^1=H; XI R^1=*o*-HO; XII R^1=R^2=H; XIII R^1=*o*-HO; R^2=H; XIV R^1=H, R^2=C_6H_5; XV R^1=*o*-HO, R^2=C_6H_5; XVI R^1=*p*-Br, R^2=H; XVII R^1=*p*-CH_3O, R^2=H; XVIII R^1=*o*-CH_3O, R^2=H; XIX R^1=*o*-HO.

The reaction of organic azides with 1,3-dicarbonyl compounds is widely used in the synthesis of substituted 1,2,3-triazoles [2-6]. In addition to triazoles amines, diazo ketones, or diazo esters are formed in some cases in this reaction [4, 5]. It is known that the reaction of azides with 1,3-dicarbonyl compounds takes place in the presence of bases; the terminal nitrogen atom of the azido group initially adds to the carbanion of the CH_2-active compound to give an intermediate triazene, after which the intermediate undergoes cyclization and aromatization to give the triazole [2, 7]. The rates of the reactions of organic azides with CH_2-active compounds depend both on the acidity of the CH_2 group and on

*See the experimental section for the R substituents in the azidopyrimidines.

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 0009-3122/83/1910-1116$07.50

TABLE 1. PMR Spectra of 1-Pyrimidyl-4-acetyl(or benzoyl)-5-methyl(or phenyl)-1,2,3-triazoles in $CDCl_3$[a] [ppm (J, Hz)]

Compound	Pyrimidine ring protons		Aromatic substituent in the pyrimidine ring		Substituent in the triazole ring
	4'-H	5'-H	H_{arom}	OH	
X	—	—[b]	8,40—7,97m, 7,73—7,38m, 5 : 6	—	CH_3, 2,93s; CH_3CO, 2,70s
XI	—	8,37 s	8,17—7,73 m, 7,60—7,17 m, 7,17—6,77 m, 3 : 4 : 2	12,77 s	CH_3, 3,00s; CH_3CO, 2,53s
XII	8,93 d (7)	8,43 d (7)	8,20—7,80 m, 7,67—7,20 m, 2 : 3	—	CH_3, 2,97s; CH_3CO, 2,53s
XIII	8,83 d (6)	7,77 d (6)	8,37—8,07 m, 7,47—7,13 m, 7,13—6,80 m, 1 : 1 : 2	12,80 s	CH_3, 3,10s; CH_3CO, 2,70s
XIV	—	8,30 s	8,63—8,40 m, 8,40—8,07 m, 7,73—7,30 m, 2 : 2 : 6	—	CH_3, 3,10s; CH_3CO, 2,70s
XV	—	8,27 s	8,47—7,83 m, 7,73—7,33 m, 7,10—6,73 m, 3 : 4 : 2	13,07 s	CH_3, 3,07s; CH_3CO, 2,70s
XVI	8,90 d (7)	8,43 d (7)	7,87 d (8), 7,50 d (8), 2 : 2	—	CH_3, 2,95s; CH_3CO, 2,53s
XVII	8,92 d (6)	7,83 d (6)	8,37 d (9), 6,97 d (9), 2 : 2	—	CH_3, 3,10s; CH_3CO, 2,70s
XVIII	8,97 d (5,5)	7,93 d (5,5)	8,10—7,70 m, 7,70—6,83 m, 1 : 3	—	CH_3, 3,07s; CH_3CO, 2,70s
XIXA	8,87 d (6)	7,80 d (6)	8,60—8,10m, 7,70—7,30 m	—	CH_3CO, 2,67s[c], C_6H_5[b]
XIXB	8,90 d (6)	7,90 d (6)			CH_3, 3,10s., C_6H_5CO[b]
XXA	8,77 d (6)	7,90 d (6)	7,60—6,40 m	12,63 s	CH_3CO, 2,67s[c]; C_6H_5, 7,40 s
XXB	8,87 d (6)	8,03 d (6)		12,70 s	CH_3, 3,17 s; C_6H_5CO, 8,63—8,20 m[b]

[a]In the case of XI, XII, and XVI the spectra of solutions in CF_3COOH were recorded. [b]The signal coincides with the region of absorption of the phenyl protons of the pyrimidine ring. [c]The A/B isomer ratios in the reaction mixtures were 1/1 for XIX and 3/2 for XX.

the electronic nature of the organic residue of the azides; an increase in the electron-acceptor character of this residue accelerates the reaction [2, 5, 7].

The reaction of 2- and 4-azidopyrimidines I-IX with acetylacetone and benzoylacetone was carried out in the presence of triethylamine in ethanol or dioxane.

As one should have expected [7], the reaction products had the 1-(R-pyrimidyl)-4-acetyl-5-methyl-1,2,3-triazole structure (X-XVIII) in the case of acetylacetone, whereas two isomers, viz., 4-acetyl-5-phenyl- (XIXA and XXA) and 4-benzoyl-5-methyl-1-(R-pyrimidyl)-1,2,3-triazoles (XIXB and XXB) in a ratio of ∿1:1 (Table 1), were obtained in the case of benzoylacetone. The compositions of the mixtures of isomers for XIX and XX (Table 2) were determined from the PMR spectral data.

The IR spectra of X-XVIII contain an intense absorption band of a C=O bond at 1690-1700 cm^{-1}. The signals of the protons of the CH_3 and CH_3CO groups in the PMR spectra differ by 0.4-0.5 ppm (Table 1); the signal of the protons of the acetyl group is found at stronger field [3].

In contrast to X-XVIII, two absorption bands of a carbonyl group were observed in the IR spectra of products XIX and XX (mixtures of A and B isomers) at 1650-1720 cm^{-1}. Product XX was separated by chromatography to give individual XXA and XXB. The absorption bands of the carbonyl group in their IR spectra are found at 1690 and 1660 cm^{-1}, respectively, which indicates the presence of an acetyl group in the A isomer and a benzoyl group in the B isomer (see [6]). The structure of the XXA and XXB isomers are confirmed by the PMR spectra, in which the signals of the protons of the methyl groups are located at, respectively, 2.67 (4-CH_3CO group) and 3.17 ppm (5-CH_3 group), in good agreement with the positions of the signals in the spectra of X-XVIII. In addition, in the PMR spectrum of XXA the signal of the protons of the phenyl group of the triazole has the form of a singlet; this was previously noted for the protons of the phenyl group in 1-substituted 5-phenyl-1,2,3-triazoles [8].

TABLE 2. Reaction Conditions and Characteristics for 1-Pyrimidyl-4-acetyl(or benzoyl)-5-methyl(or phenyl)-1,2,3-triazoles

Compound	Solvent	Reaction time, h	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
X	Ethanol	30	210—213	71,3	5,0	19,9	$C_{21}H_{17}N_5O$	71,0	4,8	19,7	70
XI	Ethanol	2,5	236—238	68,2	4,4	18,7	$C_{21}H_{17}N_5O_2$	67,9	4,6	18,9	78
XII	„ „	8	166—168	64,3	4,9	25,3	$C_{15}H_{13}N_5O$	64,5	4,7	25,1	95
	Dioxane	8									
XIII	Ethanol	0,5	180—181	60,7	4,4	23,6	$C_{15}H_{13}N_5O_2$	61,0	4,4	23,7	89
	Dioxane	1									
XIV	Ethanol	6	202—204	70,7	4,6	19,7	$C_{21}H_{17}N_5O$	71,0	4,8	19,7	77
XV	Ethanol	1,5	185—187	67,7	4,5	18,6	$C_{21}H_{17}N_5O_2$	67,9	4,6	18,9	94
XVI	„ „	3	218—220	50,3	3,4	19,5	$C_{15}H_{12}BrN_5O$	50,3	3,4	19,6	96
	Dioxane	3									
XVII	Ethanol	15	213—215	62,3	4,8	22,8	$C_{16}H_{15}N_5O_2$	62,1	4,9	22,6	87
	Dioxane	>20									
XVIII	Ethanol	7	132—134	62,4	4,7	22,7	$C_{16}H_{15}N_5O_2$	62,1	4,9	22,6	78
XIX(A+B)	Ethanol	30	122—132	70,7	4,4	20,7	$C_{20}H_{15}N_5O$	70,4	4,4	20,5	92
XX(A+B)	„ „	2	180—186	67,2	4,2	19,6	$C_{20}H_{15}N_5O_2$	67,2	4,2	19,6	83

In analogy with triazole XX, in the case of XIX, without additional separation to give individual isomers, the signals of the protons of the methyl groups are assigned as follows: the signal at 2.67 ppm was assigned to the CH_3CO group in isomer XIXA, and the signal at 3.10 ppm was assigned to the CH_3 group in isomer XIXB.

When one examines the experimental data on the reaction of azidopyrimidines with 1,3-diketones, one's attention is drawn to the increased reactivities of azidopyrimidines that contain an o-hydroxyphenyl group as compared with unsubstituted phenyl analogs (Table 2, compare X and XI, XII and XIII, XIV, and XV, and XIX and XX).

We carried out the condensation of acetylacetone with 4-azido-2-R-phenylpyrimidines with donor and acceptor substituents in the phenyl ring under comparable conditions. The reactivities of the azidopyrimidines were judged qualitatively from the times required for the starting azidopyrimidines to disappear in the reaction media by thin-layer chromatography (TLC); these times were found to be 8 h for III (R = H), 0.5 h for IV (R = o-OH), 3 h for VII (R = p-Br), 15 h for VIII (R = p-CH_3O), and 7 h for IX (R = o-CH_3O). It follows from these data that the introduction of an acceptor group (p-Br) in the phenyl substituent accelerated the reaction, and the introduction of a donor group (p-CH_3O) slows down the reaction; the effect produced by the o-CH_3O group is very slight, whereas an o-hydroxy group has a stong accelerating effect.

According to the above-indicated scheme of the reaction of azides with CH_2-active compounds, the reaction is a stepwise process, and the rate-determining step is evidently the formation of unstable intermediate triazenes [7]; the accelerating effect of the p-BrC_6H_4 substituent or the slowing effect of the p-$CH_3OC_6H_4$ group as compared with the phenyl group is associated with a change in the electrophilic properties of the terminal nitrogen atom of the azido group. Since the o-hydroxyphenyl group forms a strong intramolecular hydrogen bond (IHB) with the nitrogen atom of the pyrimidine ring, the negative charge on the azido group that develops as the transition state is approached should promote strengthening of the hydrogen bond. In analogy with [9, 10], the latter may evidently lead to a decrease in the energy of activation and acceleration of the formation of a triazene.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Varian A56/60 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The course of the reactions and the individuality of the compounds were monitored by means of TLC on Silufol UV-254 plates.

The starting azidopyrimidines were previously described: 2-azido-4,6-diphenyl- (I), 2-azido-4-(o-hydroxyphenyl)-6-phenyl- (II), 4-azido-2-phenyl- (III), 4-azido-2-(o-hydroxyphenyl)- (IV), and 4-azido-2-(o-hydroxyphenyl)-6-phenylpyrimidine (VI) were described in [1], and 4-azido-2,6-diphenylpyrimidine (V) was described in [11].

2-(p-Bromophenyl)-4-hydroxypyrimidine. A solution of 3 g (20 mmole) of ethyl formylacetate sodium salt in 10 ml of water was added with stirring to a solution of 4 g (19 mmole) of p-bromobenzamidine hydrochloride and 5 g of NaOH in aqueous ethanol, and the mixture was maintained at room temperature for 5 days. The solution was partially evaporated, and the residual mixture was neutralized with acetic acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 3.1 g (74%) of a product with mp 247-249°C (from methylcellosolve). Found: C 47.5; H 2.7; N 11.1%. $C_{10}H_7BrN_2O$. Calculated: C 47.8; H 2.8; N 11.2%.

2-(p-Methoxyphenyl)-4-hydroxypyrimidine. A mixture of 1.8 g (9.7 mmole) of p-methoxybenzamidine hydrochloride and 1.7 g (12.6 mmole) of ethyl formylacetate sodium salt in 30 ml of absolute ethanol was refluxed for 5 h, after which the ethanol was evaporated, and the reaction mixture was diluted with water and neutralized with acetic acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 1.1 g (44%) of a product with mp 214-215°C (from methylcellosolve). Found: C 65.2; H 5.2; N 13.7%. $C_{11}H_{10}N_2O_2$. Calculated: C 65.3; H 5.1; N 13.9%.

2-(p-Bromophenyl)-4-chloropyrimidine. A 2.6-g (10 mmole) sample of 2-(p-bromophenyl)-4-hydroxypyrimidine was refluxed in 20 ml of $POCl_3$ for 4 h, after which the mixture was cooled and poured over ice. The resulting precipitate was removed by filtration, washed with water, dried, and passed through a column packed with silica gel by elution with benzene to give 1.9 g (69%) of a product with mp 120-121°C (from ethanol). Found: C 44.1; H 2.4; N 10.2%. $C_{10}H_6BrClN_2$. Calculated: C 44.4; H 2.2; N 10.4%.

2-(p-Methoxyphenyl)-4-chloropyrimidine. This compound was similarly obtained in 85% yield and had mp 112-114°C. Found: C 59.9; H 4.3; N 12.4%. $C_{11}H_9ClN_2O$. Calculated: C 59.7; H 4.1; N 12.7%.

2-(p-Bromophenyl)-4-azidopyrimidine (VII). This compound, with mp 97-98°C (from ethanol), was obtained in 82% yield from 2-(p-bromophenyl)-4-chloropyrimidine by method B described in [1]. Found: C 43.4; H 2.2; N 25.5%. $C_{10}H_6BrN_5$. Calculated: C 43.1; H 2.2; N 25.4%.

2-(p-Methoxyphenyl)-4-azidopyrimidine (VIII). This compound, with mp 78-80°C (from hexane), was obtained in 87% yield from 2-(p-methoxyphenyl)-4-chloropyrimidine by method B described in [1]. Found: C 58.1; H 3.9; N 30.6%. $C_{11}H_9N_5O$. Calculated: C 58.1; H 4.0; N 30.8%.

2-(o-Methoxyphenyl)-4-azidopyrimidine (IX). A 1-g (5 mmole) sample of azide IV was added with stirring to a solution of 0.12 g (5 mmole) of NaH in 10 ml of dry DMSO, 3.5 g (25 mmole) of CH_3I was added dropwise with stirring to the resulting solution, and the mixture was allowed to stand for 30 min. It was then poured into water, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.76 g (70%) of IX with mp 122-124°C (from ethanol). Found: C 57.9; H 3.9; N 30.6%. $C_{11}H_9N_5O$. Calculated: C 58.1; H 4.0; N 30.8%.

Reaction of 2- and 4-Azidopyrimidines with 1,3-Diketones. A 1-mmole sample of the azidopyrimidine was added to a solution of 2 mmole of the 1,3-diketone and 2 mmole of triethylamine in 5 ml of the solvent, and the mixture was refluxed until the starting azide vanished. The resulting precipitate was removed by filtration, washed with ethanol, dried, and recrystallized from ethanol—DMF.

Isomers XXA and XXB were separated preparatively on a plate coated with silica gel by elution with benzene.

The characteristics of the 1-pyrimidyl-1,2,3-triazoles are presented in Table 2, and data from the PMR spectra are presented in Table 1.

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INTRAMOLECULAR CYCLIZATION OF 5-AMINO-4-BIS(β-CHLOROETHYL)AMINO-PYRIMIDINES

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UDC 547.853.7:542.953.5

4-R-5,6,7,8,9,10-Hexahydroimidazo[1,2,3-i,j]pteridinium chlorides and 4-R-7-(β-chloroethyl)-7,8-dihydroimidazo[1,2-c]pyrimidinium chlorides were obtained in the reaction of 6-R-5-amino-4-bis(β-hydroxyethyl)aminopyrimidines (R = H, Cl) with $SOCl_2$ or $POCl_3$. The pteridinium chlorides are formed through cyclization of the intermediately formed 4-R-8-(β-chloroethyl)-5,6,7,8-tetrahydropteridines, which, for R = Cl, were obtained independently by reduction of 4-chloro-6-bis-(β-chloroethyl)amino-5-nitropyrimidine. The conditions for the cyclization of imidazopyrimidinium chlorides to give imidazopteridinium chlorides were investigated.

It has been shown that the cyclization of N,N-bis(β-chloroethyl)-o-phenylenediamine leads to benzo[b]-1,4-diazabicyclo[2.2.2]octene [1], whereas N-haloalkyltetrahydroquinoxalines are converted under similar conditions either to benzodiazabicycloalkenes [2, 3] or to tetrahydropyridoquinoxalines through intramolecular C alkylation [3]; the formation of condensed heterocyclic systems that contain five-membered rings was not observed. In this connection, it seemed of interest to investigate the possibility and direction of the intramolecular cyclization of 5-amino-4-bis(β-chloroethyl)aminopyrimidines that contain a heteroatom adjacent to a chloroethylamino group. The literature contains a rather large amount of data on the chemical properties of 4(6)-haloalkylaminopyrimidines, and the case of cyclization at the pyrimidine nitrogen atom to give dihydroimidazo[1,2-c]- [4-14] and tetrahydropyrimido[1,2-c]pyrimidine [12-14] systems is particularly noted. However, in individual cases [15] in the cyclization of compounds that contain two nucleophilic centers for attack by the chloroethylamino group, viz., ring (pyrimidine) and exocyclic (5-amino group) nitrogen atoms, the formation of a 5,6,7,8-tetrahydropteridine system occurs exclusively due to the presence of a bulky substituent in this group.

We realized the synthesis of the starting diaminopyrimidines for the preparation of previously undescribed 4-bis(β-chloroethyl)aminopyrimidines with an amino group in the 5 position via the scheme presented above.

The amination of 4,6-dichloro-5-nitropyrimidine (I) [16, 17] with a stoichiometric amount of diethanolamine proceeds smoothly to give 4-chloro-6-bis(β-hydroxyethyl)amino-5-nitropyrimidine (II), the reduction of which on Raney nickel leads to 4-chloro-5-amino-6-

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1406-1413, October, 1983. Original article submitted January 10, 1983; revision submitted April 19, 1983.

 0009-3122/83/1910-1120$07.50