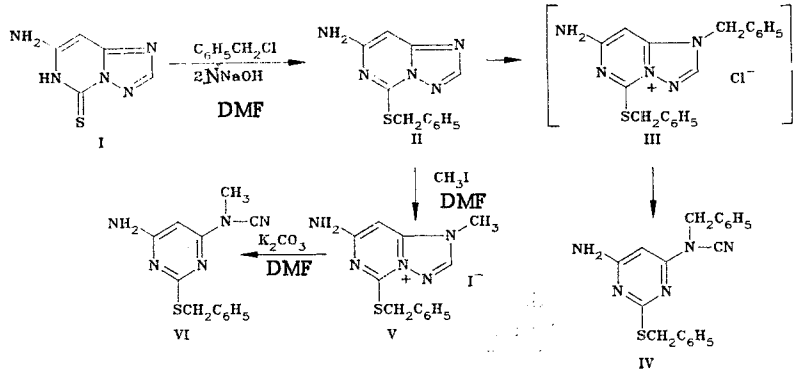
AMINONITRILE REARRANGEMENT OF s-TRIAZOLO[1,5-c]PYRIMIDINES UPON REACTION WITH ARYL (ALKYL) HALIDES

V. N. Konyukhov, L. N. Dianova,
T. G. Koksharova, N. V. Volkova,
V. A. Bakulev, and O. S. Anisimova

UDC 547.792.9'853.04

Aminonitrile cleavage of the cyclic system was observed in the reaction of s-triazolo[1,5-c]pyrimidine derivatives with aryl (alkyl) halides in an alkaline medium or in dimethylformamide. It is shown that this transformation proceeds through the formation of intermediate quaternary salts. The effect of electron-acceptor and electron-donor substituents on their stability was ascertained. The structures of the substances were established by means of IR, UV, PMR, and mass spectroscopy.

Two new products were detected in the reaction of equimolar amounts of our previously synthesized [1] s-triazolo[1,5-c]pyrimidine (I) and benzyl chloride in 2 N NaOH at 90-95°C after 0.5 h; these new products were detected, along with the starting compound, by thin-layer chromatography (TLC). An increase in the reaction time led to the disappearance of one of them; however, we found that the reaction proceeded only to the extent of 50%. Further studies showed that a twofold excess of benzyl chloride is required for the completion of the reaction. We also observed that the same reaction product is formed from I and benzyl chloride in refluxing dimethylformamide (DMF). According to the TLC data, the substance obtained was an individual compound, and the results of elementary analysis were in agreement with the values calculated for the dibenzyl derivative. We initially assumed that benzyl chloride reacts with I both at the mercapto group and at the amino group; however, absorption bands of a primary amino group at 3400 and 3335 cm^{-1} and an intense absorption band at 2240 cm^{-1}, which attests to the presence of a nitrile group in the molecule, were present in the IR spectrum of the reaction product.



It is apparent from the structure of I that the formation of a nitrile group is possible in the case of cleavage of the triazolopyrimidine heterocyclic system at the N–N bond, which evidently proceeds in analogy to the aminonitrile cleavage observed for derivatives of aliphatic and aromatic aldohydrazones [2-4], a number of their five-membered analogs [5], and, in a unique example, for a six-membered condensed heteroring [6].

On the basis of the literature data, as well as the results of elementary analysis and data from IR, PMR, and mass spectroscopy, we proposed, for the product of the reaction under investigation, a structure that corresponds to structure IV.

This transformation is evidently realized in the following way: I reacts with benzyl chloride to give initially benzylthio derivative II, which is then converted to quaternary

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 421-425, March, 1985. Original article submitted May 17, 1984.

0009-3122/85/2103-0355$09.50

salt III with a strongly polarized N—N bond. Then, in an aqueous alkali medium, as a result of the influence of two factors, viz., polarization of the N—N bond and the nucleophilic reagent, the quaternary salt is cleaved to give IV. The studies showed that the conversion of I to product IV in an alkaline medium takes place commencing at 40°C; the reaction rate increases as the temperature is raised. In DMF the reaction mechanism evidently remains the same, and the solvent acts as the nucleophilic reagent.

The reaction of I with benzyl chloride in 2 N NaOH at room temperature made it possible to obtain 5-benzylthio-7-amino-s-triazolo[1,5-c]pyrimidine (II). In the mass spectrum of this compound one observes intense peaks of a molecular ion (257)* and the benzyl cation $C_6H_5CH_2^+$, which indicate the introduction of a benzyl grouping into the molecule. The fragmentation of the molecular ion was characterized by the elimination of HCN (230), SH (224), C_6H_5 (180), $SCHC_6H_5$ (135), and $NCSCH_2C_6H_5$ (108) particles; this is in agreement with the structure of product II. It was also established by TLC that one of the two substances formed in the reaction of triazolopyrimidine I with benzyl chloride at high temperatures, which vanishes with an increase in the reaction time, corresponds to benzylthio derivative II.

The next step in our research involved a study of the possible pathways for the synthesis of quaternary salt III. Heating equimolar amounts of II and benzyl chloride in dimethylformamide (DMF) at 90-100°C made it possible to observe the slow conversion of benzylthiotriazolopyrimidine to product IV, which was accelerated significantly in a refluxing solvent, but hypothetical salt III was not detected. However, when we used methyl iodide instead of benzyl chloride, we obtained a substance that contained iodine and, according to the results of elementary analysis, corresponded to 5-benzylthio-7-amino-s-traizolo[1,5-c]pyrimidine methiodide (V).

A signal of protons of a methyl group attached to a nitrogen atom at 3.8 ppm is observed in the PMR spectrum of V; the position of this signal constitutes evidence for the absence of a positive charge on the nitrogen atom. The structure of the compound obtained can evidently be represented by formula V with localization of the positive charge on the common $N_{(4)}$ atom, which should give rise to polarization of the N—N bond. In fact, refluxing of quaternary salt V in DMF in the presence of K_2CO_3 leads to cleavage of the N—N bond to give VI, in the IR spectrum of which an absorption band of a nitrile group at 2250 cm^{-1} appears. It should be noted that potassium carbonate is evidently a catalyst for the cleavage process, since ring opening is not observed when it is not present. Thus it is extremely likely that the cleavage of the ring under the conditions of benzylation takes place through the formation of an intermediate quaternary salt; however, it is very unstable by virtue of its structure — that is to say, the presence of an electron-acceptor benzyl group attached to the nitrogen atom in the 1 position, which significantly increases the lability of the proton in the β position relative to the quaternary nitrogen atom and facilitates deprotonation and, thereby, cleavage of the salt. The stability of quaternary salt V is evidently associated with replacement of the electron-acceptor benzyl group by the electron-donor methyl group, which decreases the lability of the proton attached to the $C_{(2)}$ atom. This conclusion was confirmed by subsequent transformations.

5-Methylthio-7-amino-s-triazolo[1,5-c]pyrmidine (VII) [1] reacts with benzyl chloride in DMF to give VIII, which contains a nitrile group. As one might have expected, as a consequence of the electronic effect of the benzyl residue, we did not detect a quaternary salt but isolated only its cleavage product VIII. However, as a result of the reaction of VII with methyl iodide under the same conditions, we obtained and isolated quaternary salt IX, which, upon refluxing in DMF with the addition of potassium carbonate, is converted to product X, which contains a nitrile group (see following page).

The results of quantum-chemical calculations by the MO LCAO method within the Pariser—Paar—Pople (PPP) approximation exclude the addition of benzyl and methyl residues in salts III, V, and IX to the $N_{(6)}$ atom.

The results of calculations of the charges and the π-electron density in the highest occupied molecular orbital (HOMO) of 5-methylthio-7-amino-s-triazolo[1,5-c]pyrimidine (VII) (the π-electron density in the HOMO is presented in parentheses) show that the negative charge in the molecule is localized on the $N_{(1)}$, $N_{(3)}$, and $N_{(6)}$ atoms, which will be attacked by "hard" nucleophilic reagents. An examination of the π-electron density on the HOMO is

*Here and subsequently, the m/z values are given in parentheses.

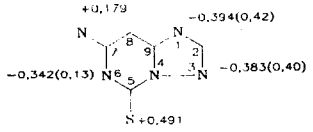


Fig. 1. Data from the quantum-chemical calculation of the charges and π-electron densities on the HOMO of 5-methylthio-7-amino-s-triazolo[1,5-c]pyrimidine.

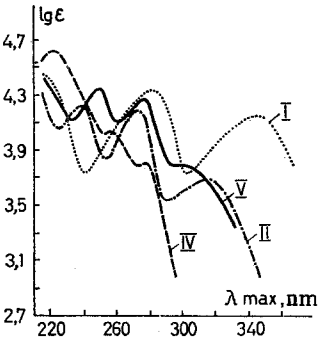
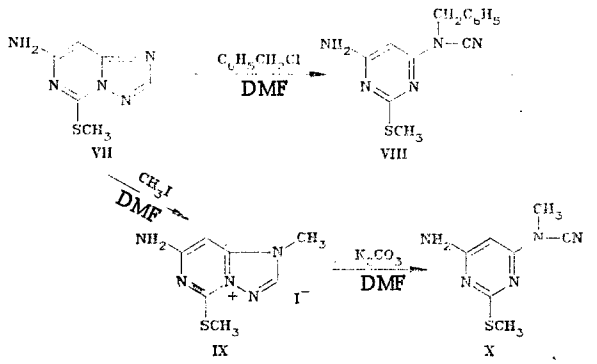


Fig. 2. UV spectra of I-IV recorded in solution in ethanol:

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	R_f,* (system)	Found, %				Empirical formula	Calc., %				Yield, %
			C	H	N	S		C	H	N	S	
II	195	0,68	56,4	4,4	26,8	12,4	$C_{12}H_{11}N_5S$	56,0	4,3	27,2	12,5	92
IV	185	0,79	65,8	4,5	20,2	9,5	$C_{19}H_{17}N_5S$	65,7	4,9	26,2	9,2	79
V	146	0,53	38,8	3,9	17,5	7,9	$C_{13}H_{14}IN_5S$	39,1	3,6	17,5	8,0	71
VI	176	0,54	57,3	4,7	25,6	12,1	$C_{13}H_{13}N_5S$	57,6	4,8	25,8	11,8	75
VIII	202	0,64	57,9	4,6	25,3	11,6	$C_{13}H_{13}N_5S$	57,6	4,8	25,8	11,8	81
IX	256	0,49	25,6	3,6	21,4	9,8	$C_7H_{10}IN_5S$	26,0	3,2	21,7	9,9	82
X	203	0,52	43,1	4,6	35,9	16,4	$C_7H_9N_5S$	43,4	4,5	36,2	16,6	87

*The R_f values for the various compounds were determined as follows: in chloroform—ethanol (9:1) for II, IV, VI, VIII, and X and in ethanol—water—acetic acid—sodium acetate (8:6:2:1) for V and IX.



more important for the prediction of the site of attack on VII by "soft" nucleophilic reagents such as benzyl chloride and methyl iodide. For the $N_{(1)}$ and $N_{(3)}$ atoms these values are 0.42 and 0.40, respectively, and 0.13 for the $N_{(6)}$ atom. Consequently, the most probable sites of attack will be the nitrogen atoms of the triazole ring. In addition, in the case of the attachment of substituents to the $N_{(6)}$ atom one would not observe that they have an effect on the stabilities of the salts.

The methyl and benzyl groups evidently cannot be attached to the nitrogen atom in the 3 position, since in this case the formation of a nitrile is impossible.

In order to confirm the structure of the product of the reaction of triazolopyrimidine with benzyl chloride (viz., IV) we investigated its PMR and mass spectra. The same intense peaks in the mass spectrum belong to the molecular ion (347) and the benzyl cation (91). There is also an intense peak of an $[M - CH_2C_6H_5]^+$ fragment (256). The absence of this fragmentation pathway in the case of benzylthiothriazolopyrimidine II provides a basis for the assumption that the $[M - CH_2C_6H_5]^+$ ion in the mass spectrum if IV is formed through the elimination of an N-benzyl group; the benzyl group is not bonded to the nitrogen atom of the

amino group, since absorption bands of a primary amino group are present in the IR spectrum. The presence of $[M - S{=}CHC_6H_5]^+$ (225) and $[M - CN]^+$ (321) peaks constitutes proof for the presence in the molecule of s-benzyl and nitrile groups. The spectrum also contains peaks of $[M - SH]^+$ (314) and $[M - C_6H_5]^+$ (270) fragments.

A comparison of the PMR spectra of the compounds with a triazolopyrimidine structure (I, II, VI, VII, IX) and the cleavage products (IV, VI, VIII, X) revealed the presence in the spectra of all of the compounds of a signal of an 8-H proton at 5.8-6.5 ppm, whereas the signal of the 2-H proton at 8.2-9.4 ppm, which is present in the spectra of triazolopyrimidines, vanishes in the spectra of the cleavage products; this constitutes evidence for their pyrimidine structure.

Compounds I, II, IV, and V display substantial differences in their UV spectra, which are shown in Fig. 2.

EXPERIMENTAL

The individuality of the synthesized compounds was monitored by TLC on Silufol UV-254 plates. The UV spectra of solutions of the compounds in ethanol were recorded with a Beckmann-26 spectrophotometer. The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Perkin-Elmer-12B spectrometer (60 MHz) with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-112 mass spectrometer at an ionizing voltage of 70 eV with direct introduction of the samples into the source; the ionization-chamber temperature was 180°C.

The characteristics of the synthesized compounds are presented in Table 1.

5-Benzylthio-7-amino-s-triazolo[1,5-c]pyrimidine (II). A solution of 0.14 ml (1.2 mmoles) of benzyl chloride in 1 ml of ethanol was added to a solution of 0.2 g (1.2 mmoles) of I in 5 ml of 2 N NaOH, and the mixture was stirred at room temperature for 1 h. The precipitate was removed by filtration and crystallized from aqueous ethanol.

2-Benzylthio-4-amino-6-(N-benzylcyanamino)pyrimidine (IV). A 0.3-ml (2.6 mmoles) sample of benzyl chloride was added to a solution of 0.2 g (1.2 mmoles) of I in 6 ml of DMF, and the mixture was refluxed for 1-2 h. The solvent was evaporated *in vacuo*, and the residue was treated with water. The aqueous mixture was filtered, and the solid material was crystallized from ethanol. 2-Methylthio-4-amino-6-(N-benzylcyanamino)pyrimidine (VIII) was similarly obtained from VII.

5-Benzylthio-7-amino-s-triazolo[1,5-c]pyrimidine Methiodide (V). A 0.1-ml (1.6 mmoles) sample of methyl iodide was added to a solution of 0.3 g (1.17 mmoles) of II in 10 ml of DMF, and the mixture was refluxed on a water bath for 1.5-3 h. The solvent was evaporated *in vacuo*, and the residue was treated with water. The precipitated crystals were removed by filtration, washed with ether, and recrystallized from aqueous ethanol.

Quaternary salt IX was similarly obtained from 5-methylthio-7-amino-s-triazolo[1,5-c]-pyrimidine (VII).

2-Benzylthio-4-amino-6-(N-methylcyanamino)pyrimidine (VI). A 0.15-g (1.1 mmoles) sample of potassium carbonate was added to a solution of 0.3 g (0.75 mmole) of V in 10 ml of DMF, and the mixture was refluxed for 2-3 h. It was then filtered, and the filtrate was evaporated *in vacuo*. The residue was treated with cold ethanol, and the precipitated crystals were removed by filtration and crystallized from ethanol.

2-Methylthio-4-amino-6-(N-methylcyanamino)pyrimidine (X) was similarly obtained from quaternary salt IX.

LITERATURE CITED

1. N. V. Volkova, V. N. Konyukhov, T. G. Koksharova, L. N. Dianova, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 2, 262 (1979).
2. R. F. Smith and L. E. Walker, J. Org. Chem., 27, 4372 (1962).
3. B. V. Ioffe, Z. I. Sergeeva, and K. M. Dervinskaite, Zh. Obshch. Khim., 33, 2794 (1963).
4. I. I. Grandberg, A. N. Kost, and Yu. A. Naumov, Dokl. Akad. Nauk SSSR, 149, 838 (1963).
5. B. V. Ioffe and K. N. Zelenin, Zh. Obshch. Khim., 33, 3231 (1963).
6. R. F. Smith and E. D. Otremba, J. Org. Chem., 27, 879 (1962).