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

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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 aldehydrazones [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
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 C6H5CH2+, 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), C6H5 (180), SCH2C6H5 (135), and NCSCH2C6H5 (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 benzylthio-triazolopyrimidine 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-triazolo[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(6) atom, which should give rise to polarization of the N–N bond. In fact, refluxing of quaternary salt V in DMF with the presence of K2CO3 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 benzylolation 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 8 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]pyrimidine (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.

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