РОЗДІЛ 8. ХІМІЯ НАВКОЛИШНЬОГО СЕРЕДОВИЩА, ПРИРОДНИХ ТА БІОАКТИВНИХ СПОЛУК

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SYNTHESIS, STRUCTURE AND ANTIMICROBIAL PROPERTIES OF 5-ARYLSUBSTITUTED 2-AMINOTHIAZOL-4(5*H*)-ONES WITH TWO THIAZOLE FRAGMENTS

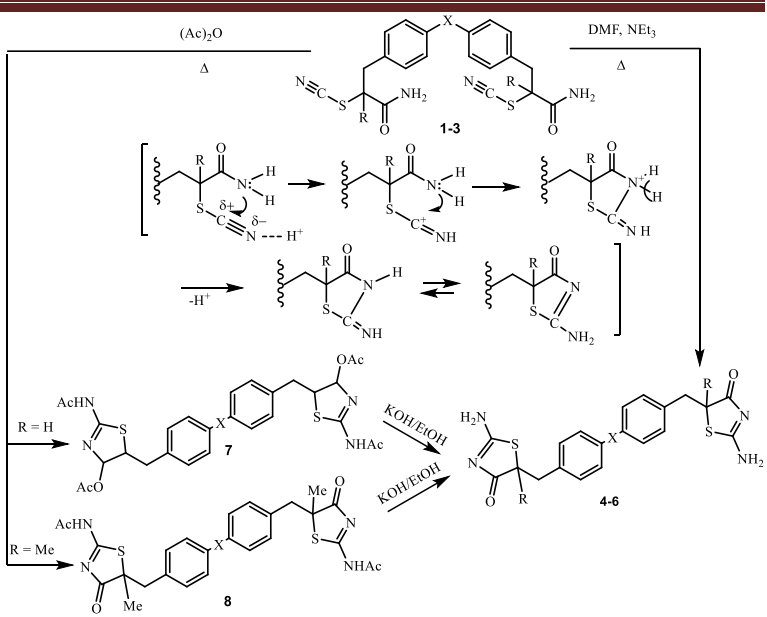
[1]Tulaidan H. M., [1]Symchak R. V., [2]Yatsiuk V. M., [1]Baranovskyi V. S.

[1] Ternopil Volodymyr Hnatiuk National Pedagogical University
[2] Ternopil Scientific Research Forensic Center of the Ministry of Internal Affairs of Ukraine
E-mail: baranovsky@tnpu.edu.ua

The expansion of the synthetic possibilities of the anionarylation reaction is possible in several directions: the study of new unsaturated substrates, anionoid reagents and diazo compounds. Promising in this aspect is the use of arylbisdiazonium salts as arylating reagents, which contain two highly reactive diazo groups in the molecular structure.

The interaction of aromatic bisdiazonium salts based on benzidine and its derivatives with unsaturated acid amides under thiocyanatoarylation reaction conditions has previously been used to obtain 3,3'-[4,4'-diphenyl(methane, sulfonyl)]bis[(2-methyl)-2-thiocyanatopropanamides] 1a,b-3a,b [1].

The presence of thiocyanate and amide groups in the molecular structure of compounds 1-3 opens up possibilities for the design of new heterocyclic systems, in particular 5-substituted derivatives of thiazol-4(5*H*)-one. We have investigated the cyclization of bisthiocyanatoarylation products – 3,3'-[4,4'- diphenyl(methane, sulfonyl)]bis[(2-methyl)2-thiocyanatopropanamides)] 1a,b-3a,b upon boiling in a mixture of dimethylformamide and triethylamine, which occurs with the formation of 5,5'-[1,1'-diphenyl(methane, sulfonyl)-4,4'-diylbis(methylene)]bis[2-amino-5-(methyl)thiazol-4(5*H*)-ones] 4-6. The synthesis of compounds 4a,b-6a,b was carried out according to the following scheme:



The cyclization of the starting bisthiocyanatoamides **1-3** occurs by boiling in a mixture of dimethylformamide and triethylamine (10:1) for 6-8 hours. The yields of bis(2-aminothiazol-4(5*H*)-ones 4-6 are 74-92%.

The synthesized 5,5'-[1,1'-diphenyl(methane, sulfonyl)-4,4'-diylbis(methylene)]-bis[2-amino-5-(methyl)thiazol-4(5*H*)-ones] 4a,b-6a,b are colorless crystalline substances that melt at sufficiently high temperatures (217-249ºC) without decomposition and are soluble in most polar organic solvents (methanol, ethanol, acetone, dimethylsulfoxide, etc.).

^{1}H NMR spectra of thiazol-4(5H)-ones 4a,b-6a,b are characterized by signals of protons of two phenyl nuclei of diphenyl (diphenylsulfone) fragments in the form of two doublets at 7.86-7.56 and 7.44-7.26 ppm or a singlet for the diphenylmethane fragment at 7.14-7.11 ppm, protons of methylene groups of benzyl fragments (doublets of doublets in the region of 3.3-3.0 ppm). Protons of amino groups in position 2 of thiazole rings are shifted to the weak field region and resonate at 9.4-8.6 ppm, forming two singlets (in the case of

compound 6b – a broad singlet).

Carrying out the cyclization of bisthiocyanatoamides 1-3 in acetic anhydride allows obtaining acylated derivatives **7** and 8, which as a result of deacylation are converted into 2-aminothiazol-4(5*H*)-ones 3-6. The cyclization of bisthiocyanatoamides based on acrylamide 1-3a is accompanied by additional acylation at position 4 of the thiazole ring, due to the migration of a hydrogen atom from position 5 by the mechanism of keto-enol tautomerism.

Thus, under the conditions found by us for the cyclization of bisthiocyanatoamides 1-3, the closure of the thiazole ring occurs with the participation of thiocyanate and amide groups. In this case, triethylamine plays a crucial role in the process, in the absence of which cyclization does not occur. In our opinion, the main properties of triethylamine contribute to additional polarization of the CN-group with the subsequent interaction of the lone electron pair of the nitrogen atom of the amide group with the carbon atom of the thiocyanate and the formation of the iminothiazolidine ring. The latter as a result of the tautomeric imide-amide rearrangement is stabilized into a stable aminothiazol-4(5*H*)-one ring.

Thus, arylalkyl bisthiocyanatoamides are convenient bicenter synthons for obtaining difficult-to-access 5-arylsubstituted 2-aminothiazol-4(5*H*)-ones, which are of interest as building blocks in the synthesis of new sulfur- and nitrogen-containing heterocyclic systems. The use of bisthiocyanatoamides for cyclizations involving thiocyanate and amide groups opens up wide possibilities for obtaining complex heterocycles with two thiazole fragments – potential bioactive substances with a wide spectrum of action [2].

We investigated the antimicrobial properties of thiazol-4(5*H*)-ones 4a,b-6a,b against test cultures of bacteria (*S. aureus* ATCC 6538, *B. subtilis* ATCC 6633, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 9027), and yeast fungi (*C. albicans* ATCC 885-653). Derivatives of 2-aminothiazol-4(5*H*)-one **4-6** have a slight antifungal effect on yeast fungi culture at concentrations of 62.5-250 μg/ml, which indicates their moderate activity. The exception is compounds 6a,b for which the MIC is at the level of 31.2 μg/ml. Compounds 4-6 are completely indifferent to cultures of gram-positive spore-forming bacteria *B. subtilis*. With

regard to gram-negative bacteria - intestinal *(E. coli*), pseudomonas (*P. aeruginosa*) rods and gram-positive bacteria (*S. aureus*), the most effective were compounds 6a,b whose MIC was 62.5-125.0 μg/ml, and compounds 4a,b, 5a,b showed low antimicrobial activity (MIC 125.0-500.0 μg/ml).

Reference

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2-HALOGENO(THIOCYANATO, O-ETHYLDITHIOCARBONATO)BENZO[d]THIAZOLES. SYNTHESIS AND ANTIMICROBIAL ACTIVITY

Symchak R. V., Pidgurska D.V., Tulaidan H. M., Baranovskyi V. S.

Ternopil Volodymyr Hnatiuk National Pedagogical University
E-mail: baranovsky@tnpu.edu.ua

In recent decades, a number of studies have been conducted on the introduction of various arylating reagents into anionarylation reactions – aryldiazonium salts with specific functional groups, bisdiazonium salts based on aromatic diamines, aromatic triazenes, which resulted in the development of methods for the regioselective modification of unsaturated compounds with the formation of functionalized mono- and bisanionarylated derivatives. At the same time, the synthesis of a similar type of compounds can be carried out using heteryl(hetaryl)diazonium salts as arylating reagents, in particular based on 2-aminobenzothiazole. Such arylating reagents, due to the