

Medical Academy in Lublin

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*Synthesis of 3-amino-1,2,4-triazole  
derivatives*

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Synteza pochodnych 3-amino-1,2,4-triazolu

3-Amino-1,2,4-triazole called Amitrol or Amizol is widely used in practice because of its pesticide properties [1–4]. Its presence in soil influences the increase of amount of carbohydrates contained in plants [5]. Amitrol has also an inhibitive effect on development of some bacteria [5,6]. The presence of 3-amino-1,2,4-triazole in *Ochromonas denica*, *Euglena gracilis* and *Spirodella digoriza* cultures inhibits the multiplication processes owing to inhibition of photosynthesis process [5,6].

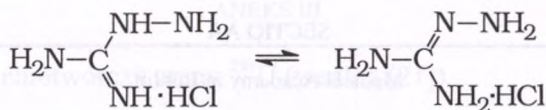
Bacteriostatic action have shown derivatives of 3-amino-1,2,4-triazole, containing thiocyanate group [7,8] and 3-heteroamino-1,2,4-triazole derivatives [9,10]. 3-Amino-1,2,4-triazoline-5-thione and 3-amino-4-substituted-1,2,4-triazoline-5-thione derivatives are widely used in photography [11–25].

Regarding practical significance of 3-amino-1,2,4-triazole derivatives this paper presents the review of methods of their synthesis.

The starting material to synthesis of 3-amino-1,2,4-triazole and its derivatives is aminoguanidine, which because of its instability [26–28] is used in chemical reactions in the salt form usually as hydrochloride, sulphate or carbonate:

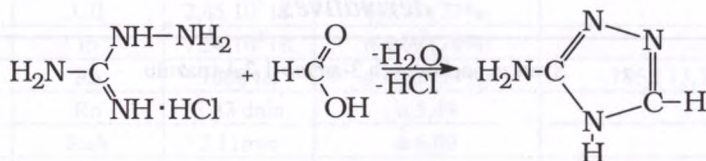
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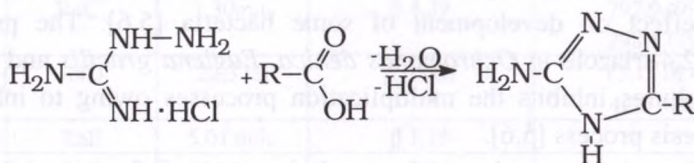


In chemical reactions there can participate hydrazine and amidine group. From the literature data it results that the hydrazine group is a more reactive group which gives 1,2,4-triazole derivatives or corresponding linear products, which are then cyclized and form the derivatives of the same system.

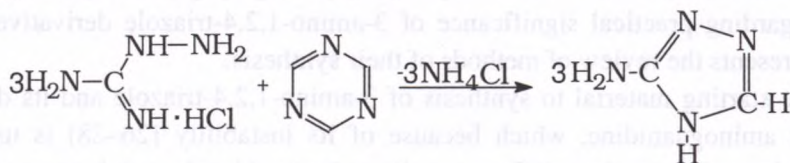
3-Amino-1,2,4-triazole was obtained in the reaction of aminoguanidine salt with formic acid [29,30]:



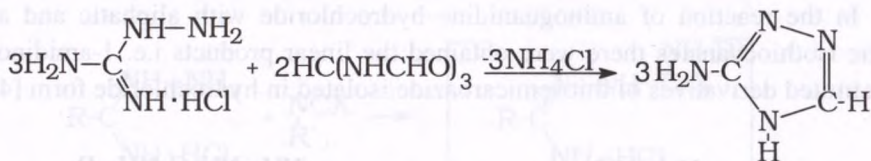
Cyclization with other acids led to formation of corresponding 3-amino-5-substituted derivatives of 1,2,4-triazole [31–39]:



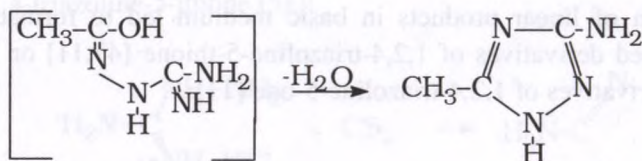
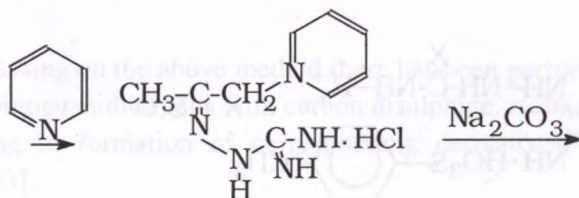
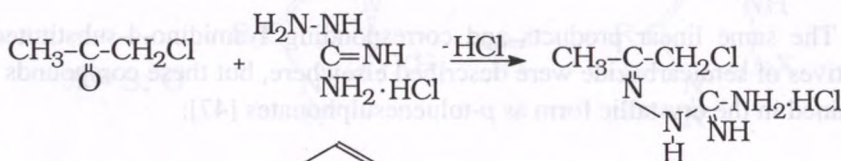
The other authors have obtained 3-amino-1,2,4-triazole in the reaction of aminoguanidine salt with s-triazine [40]:



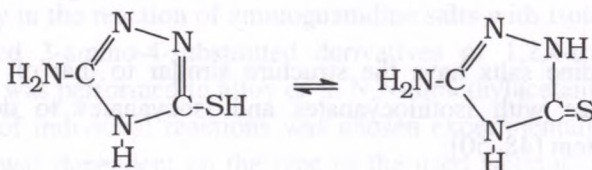
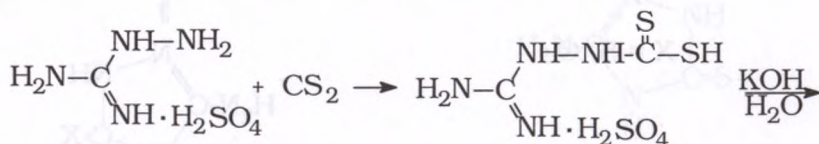
This method was later shortened owing to the use of triformylamino methane being the starting product for the synthesis of s-triazine [41]:



In the reaction of aminoguanidine hydrochloride with chloroacetone there was obtained 3-amino-5-methyl-1,2,4-triazole [42–44]:

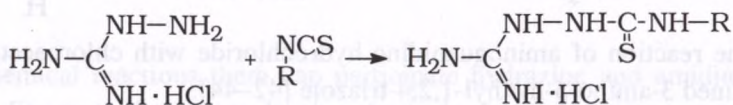


According to British patent aminoguanidine sulphate reacts with carbon disulphide giving the sulphate of 1-guanidinodithiocarbamic acid [45], which is then cyclized in basic medium and convert to 3-amino-1,2,4-triazoline-5-thione [12]:

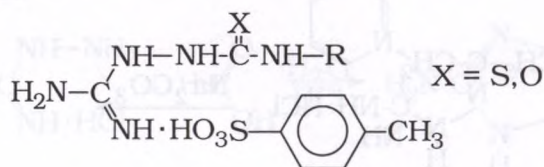




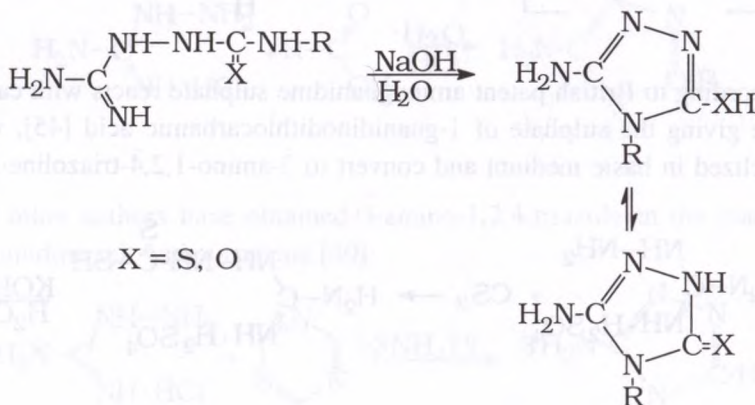
In the reaction of aminoguanidine hydrochloride with aliphatic and aromatic isothiocyanates there were obtained the linear products i.e. 1-amidino-4-substituted derivatives of thiosemicarbazide isolated in hydrochloride form [46]:



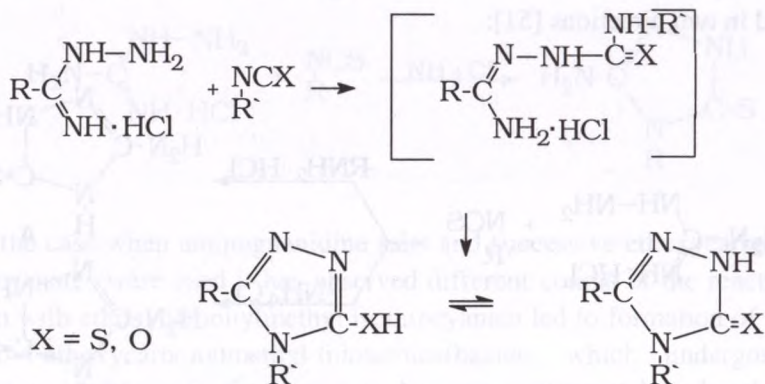
The same linear products and corresponding 1-amidino-4-substituted derivatives of semicarbazide were described elsewhere, but these compounds were obtained in the crystalline form as *p*-toluenesulphonates [47]:



The cyclization of linear products in basic medium led to formation of 3-amino-4-substituted derivatives of 1,2,4-triazoline-5-thione [47,11] or 3-amino-4-substituted derivatives of 1,2,4-triazoline-5-one [11]:

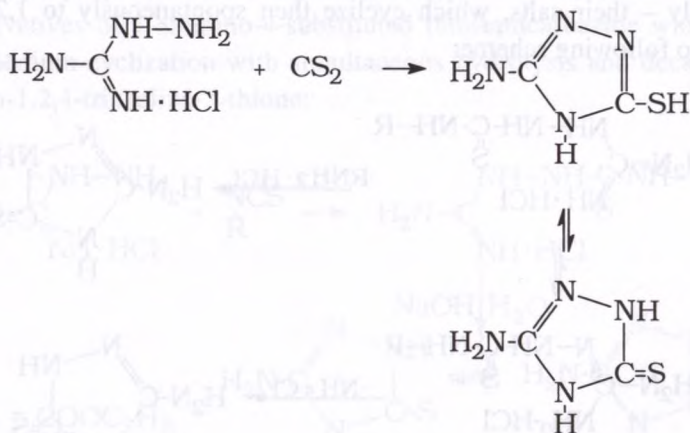


Aminoguanidine salts have the structure similar to that of amidrazones, which can cyclize with isothiocyanates and isocyanates to derivatives of 1,2,4-triazole system [48–50]:



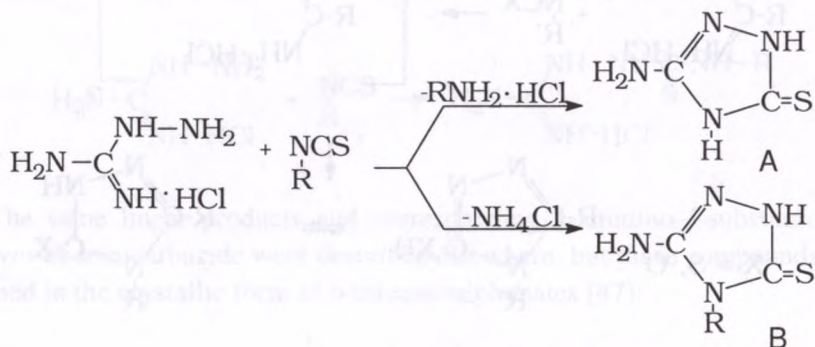
Basing on the above method there has been performed the direct cyclization of aminoguanidine salts with carbon disulphide, isothiocyanates and isocyanates leading to formation of corresponding derivatives of 3-amino-1,2,4-triazole [51–53].

In the reaction of aminoguanidine salt with disulphide was obtained 3-amino-1,2,4-triazoline-5-thione [51]:

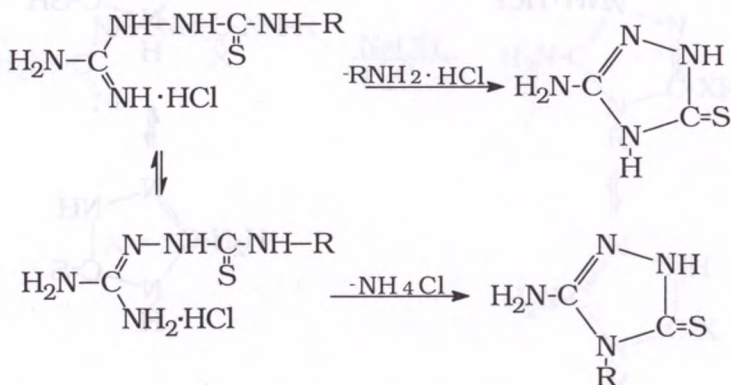


Similarly in the reaction of aminoguanidine salts with isothiocyanates there were obtained 3-amino-4-substituted derivatives of 1,2,4-triazoline-5-thione. The reaction was performed in alloy or in *N,N*-dimethylacetamide medium. The temperature of individual reactions was chosen experimentally. The course of the reaction was dependent on the type of the used isothiocyanate. Depending

on the temperature the reaction of aminoguanidine salt with isothiocyanates occurred in two directions [51]:

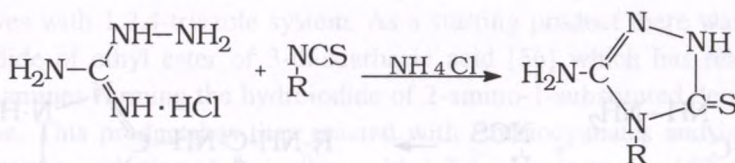


For each isothiocyanate there was established the appropriate temperature below which there was formed the product B. The heating above this temperature led always to formation of the product A. This was the same compound as the one obtained in the reaction of aminoguanidine salts with carbon disulphide [51]. The course of these reactions may be explained by the formation of intermediate linear 1-amidino-4-substituted derivatives of thiosemicarbazide and more strictly – their salts, which cyclize then spontaneously to 1,2,4-triazole according to following scheme:



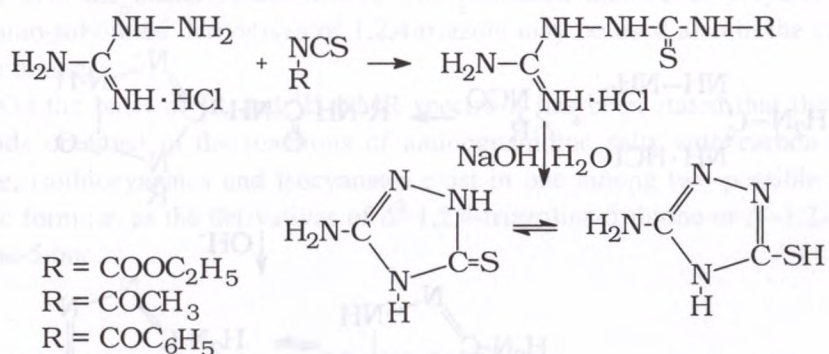
In the reaction of aminoguanidine salts with aliphatic isothiocyanates there were formed only 3-amino-4-substituted derivatives of 1,2,4-triazoline-5-thione [51]:





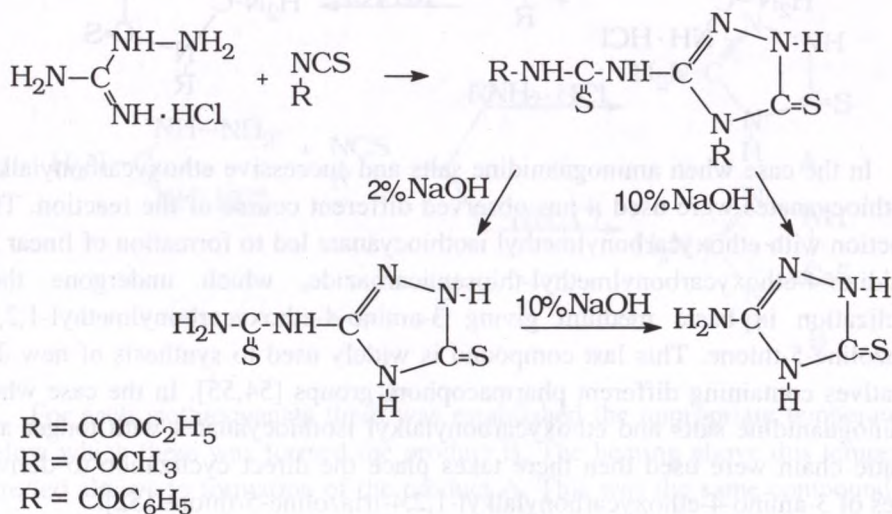
In the case when aminoguanidine salts and successive ethoxycarbonylalkyl isothiocyanates were used it has observed different course of the reaction. The reaction with ethoxycarbonylmethyl isothiocyanate led to formation of linear 1-amidino-4-ethoxycarbonylmethyl-thiosemicarbazide, which undergone then cyclization in basic medium giving 3-amino-4-ethoxycarbonylmethyl-1,2,4-triazoline-5-thione. This last compound is widely used to synthesis of new derivatives containing different pharmacophore groups [54,55]. In the case when aminoguanidine salts and ethoxycarbonylalkyl isothiocyanates with longer aliphatic chain were used then there takes place the direct cyclization to derivatives of 3-amino-4-ethoxycarbonylalkyl-1,2,4-triazoline-5-thione [52].

There were also performed the reactions of aminoguanidine salts with more reactive isothiocyanates such as ethyl isothiocyanofornate or acetyl and benzoyl isothiocyanate [53]. At room temperature there were obtained corresponding linear derivatives of 1-amidino-4-substituted thiosemicarbazide which undergo in basic medium cyclization with simultaneous hydrolysis and decarboxylation to 3-amino-1,2,4-triazoline-5-thione:

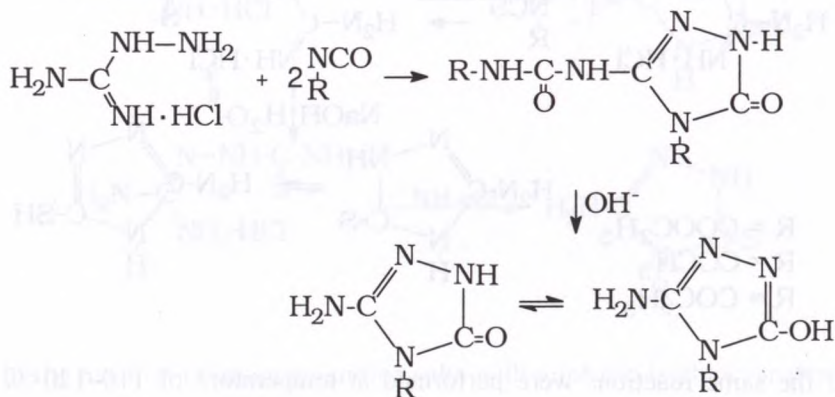


If the same reactions were performed at temperature of 110–120 °C then there reacted either hydrazine or amidine group. In this case it has obtained corresponding thiourea derivatives containing 1,2,4-triazole system and the basic

hydrolysis of these compounds led to formation of 3-amino-1,2,4-triazoline-5-thione:

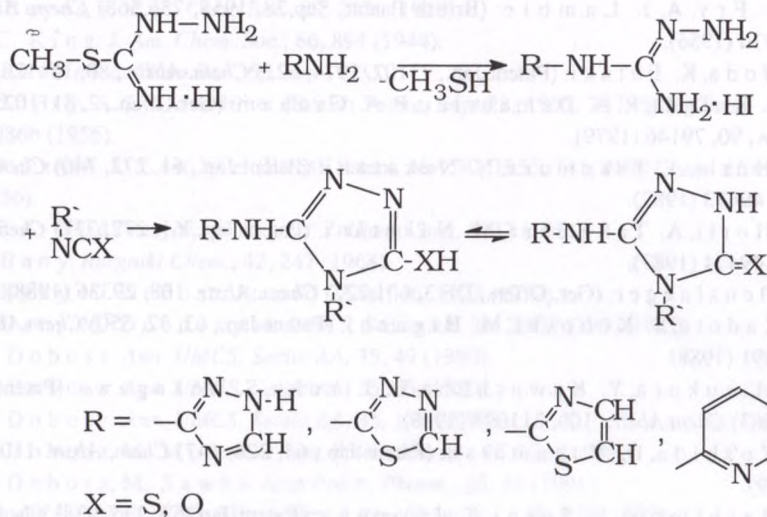


Examining the cyclization reactions of aminoguanidine salts occurring in the presence of isocyanates it has been stated that in such case there reacts either hydrazine or amidine groups, which leads to formation of corresponding urea derivatives containing 1,2,4-triazole system. Hydrolysis of these compounds in basis medium led to formation of 3-amino-4-substituted derivatives of 1,2,4-triazoline-5-one [53]:





On the basis of above reactions there can be obtained 3-amino-substituted derivatives with 1,2,4-triazole system. As a starting product there was used the hydroiodide of ethyl ester of 3-thiocarbazic acid [56] which has reacted with primary amines forming the hydroiodide of 2-amino-1-substituted derivatives of guanidine. This product has then reacted with isothiocyanates and isocyanates giving 3-amino-substituted derivatives with 1,2,4-triazole system [57–60]:



Similarly as the derivatives of 3-amino-1,2,4-triazole these compounds can show also the bacteriostatic action. The presented method of preparation of 3-amino-substituted derivatives of 1,2,4-triazole may be used also in the case of other amines.

On the basis of IR and  $^1\text{H}$  NMR spectra it has been stated that the compounds obtained in the reactions of aminoguanidine salts with carbon disulphide, isothiocyanates and isocyanates exist in one among two possible tautomeric form i.e. as the derivatives of  $\Delta^2$ -1,2,4-triazoline-5-thione or  $\Delta^2$ -1,2,4-triazoline-5-one.

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## STRESZCZENIE

3-Amino-1,2,4-triazol oraz jego pochodne mają duże zastosowanie jako herbicydy. Wiele pochodnych 3-amino-1,2,4-triazolu znalazło również szerokie zastosowanie w fotografice. Produktem wyjściowym służącym do otrzymywania 3-amino-1,2,4-triazolu i jego pochodnych jest aminoguanidyna w postaci soli, w której są dwie grupy reaktywne: amidynowa i hydrazynowa. Pochodne 3-amino-1,2,4-triazolu otrzymano metodą cyklizacji – w środowisku zasadowym – produktów liniowych 1-amidyno-4-podstawionych tiosemikarbazydu lub semikarbazydu. Metody te były skrócone przez bezpośrednią cyklizację soli aminoguanidyny i jej pochodnych disiarczkiem węgla, izotiocyjanianami i izocyjanianami. Wydajności tych reakcji były dobre.



