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Review Article

Some Aspects of Getting and Conversion Among the New 3-Thio- and 3-Thio-4-Amino Derivatives of 1,2,4-Triazole (Literature Review)

Prytula R.L [1], Shmatenko O.P [2], Bushuyeva I. V [3]*, Parchenko V.V. [3]

[1] National Military Medical Clinical Center "Main Military Clinical Hospital", Ukraine.

[2] Ukrainian Military Medical Academy, Ukraine.

[3] Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.

***Corresponding Author:** Bushuyeva I. V. Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.

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Abstract

In terms of the number of industrial injuries in the world over the past 20 years, there has been a positive trend; occupational safety is increasing. At the same time, the mechanization of domestic work has led to a significant increase in the number of domestic injuries. The rate of growth in the number of domestic injuries outpaces the rate of decline in the number of industrial injuries. Among household injuries, combined injuries, which can combine signs of two or more types of injuries, become dominant. This determines the difficulty in their treatment and the frequent occurrence of severe complications. The goal is to evaluate and determine the effectiveness of the ointment and suspension we developed in the treatment of combined wounds.

Key words: 3-thio- and 3-thio-4-amino derivatives of 1,2,4-triazole; physicochemical properties; synthesis; chemical modification

Introduction

For a long time, synthetic drugs have been widely used for the prevention and treatment of various diseases. Derivatives of 1,2,4-triazole are structural fragments of compounds that make up a significant proportion of the substances of well-known effective drugs. 1,2,4-Triazole is a kind of "framework" for the new molecules' getting. Publications of domestic and foreign authors convincingly prove the prospect of finding new substances in a number of substituted 1,2,4-triazoles [1-3]. Among new optical materials and photosensitizers, 1,2,4-triazole derivatives account for a significant share. They are also used in the practice of manufacturing various dyes, antioxidants, fuel and lubricant additives, some of them have found a use as corrosion inhibitors, etc. Most often, they are a perspective for the creation of new original medicines for both humane medicine and veterinary practice. The continuous searching process of new promising molecules among 1,2,4-triazole derivatives, which includes stages starting from the initial compounds' synthesis and certain transformations and ending with the study of biological properties, inspires scientists to continue research in this direction. It should be noted that despite the sufficient amount of information on the synthesis and transformations of a number of 1,2,4-triazole derivatives, some synthetic issues of new 3-thio- and 3-thio-4-amino derivatives of the 1,2,4-triazole are not sufficiently explained.

The aim

of our work was to summarize the available literary sources, the material which relates to the synthesis methods, studies of the physicochemical properties of 3-thio- and 3-thio-4-amino derivatives of the 1,2,4-triazole.

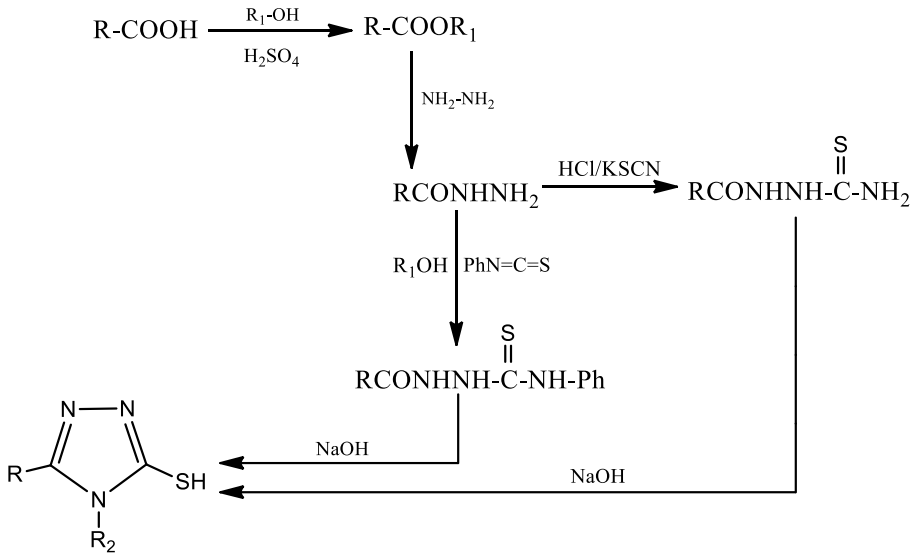
Research materials and methods.

To achieve the goal, theoretical methods were used: bibliographic, information search, review, generalization. The scientific material was the results of fundamental and applied research by domestic and foreign specialists, namely: leading scientists' articles, thesis studies, analytical reports and reviews on the above-mentioned issue.

Results and their discussion

A well-known classic method for the synthesis of 3-thioderivatives of 1,2,4-triazole is the method described in the monograph [4-7]. Other

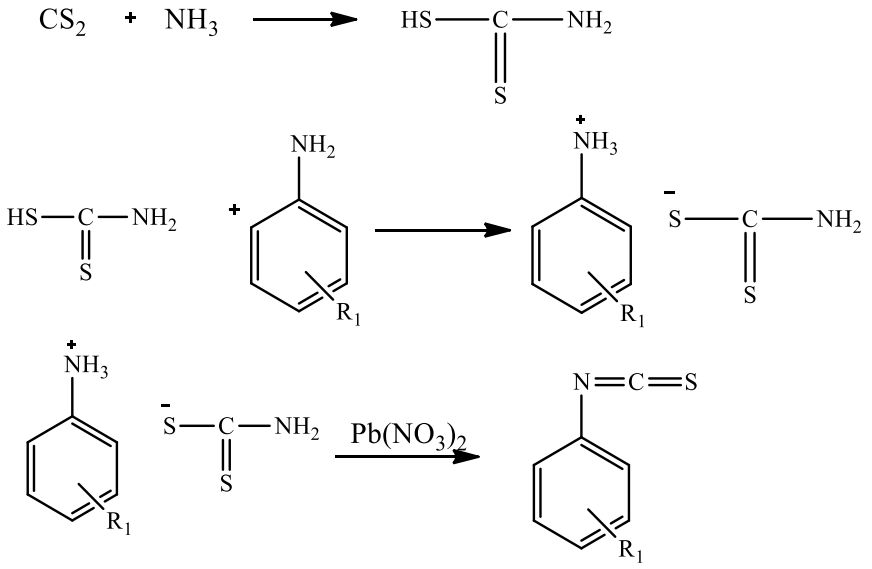
sources convincingly prove that various alkyl-, aryl-, heterylcarboxylic acids can be used as starting compounds for the synthesis of 3-S-derivatives of 1,2,4-triazoles [4, 6] [8-10]. In future, 2-acylhydrazinocarbothioamides are obtained from hydrazides [11]. The presented methods of synthesis are united by a common stage of cyclization of the corresponding 2-acylhydrazinocarbothioamides in an alkaline medium (Figure. 1).



R=Alk, Ar, Het, R_1=Alk, R_2=Ar (Ph)

Figure 1: Synthesis scheme of S-derivatives of the 1,2,4-triazole

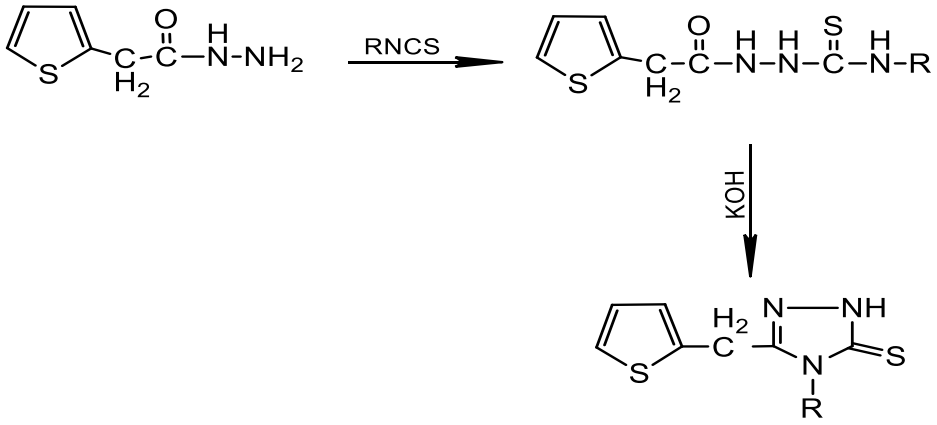
The arylisothiocyanates use in the synthesis of the 1,2,4-triazole derivatives has been devoted to a large number of works [12-15], but the simple method described in the work [5] deserves the most attention. The corresponding aryl isothiocyanates are synthesized through the intermediate stage of obtaining the corresponding arylammonium dithiocarbamates using aniline, 2-methylaniline, 2-methoxyaniline, or 4-bromoaniline as starting amines (Fig. 2).



R_1= H, 2- methyl, 2- methoxy, 4-bromine

Figure 2: Obtaining scheme of arylisothiocyanates' number

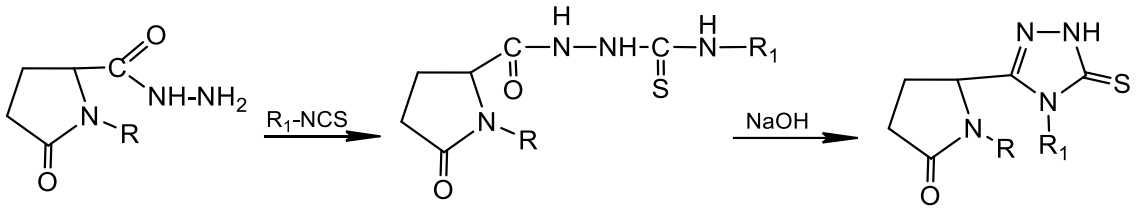
It has been proven that combinations of various typical pharmacophores in the form of five- and six-membered heterocycles' fragments and the 1,2,4-triazole can lead to the appearance of a structure with high biological activity [16-19]. The introduction of the thiophene fragment and various alkyl or aryl derivatives in the 4-position of the 1,2,4-triazole ring leads to the appearance of molecules with high activity indicators [20]. The thus obtained 4-R-3-(thiophen-2-ylmethyl)-1*H*-1,2,4-triazole-5(4*H*)-thion has antifungal activity (Figure. 3).



R=C_2H_5, C_6H_5, CH_2-C_6H_5, 4-CH_3-C_6H_4, 4-BrC_6H_4, 4-ClC_6H_4

Figurea 3: Synthesis scheme of 4-R-3-(thiophen-2-ylmethyl)-1*H*-1,2,4-triazole-5(4*H*)-thions

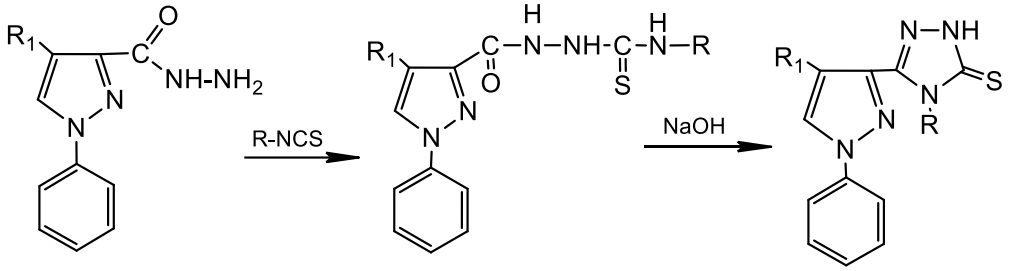
The synthesis of 5-(4-methyl-(phenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-3-yl)-pyrolidin-2-ones by a team of French scientists proves the prospects of new substituted 1,2,4-triazole [21]. 1-R-5-oxo-pyrrolidine-2-carbohydrazide was used as the starting compound (Figure. 4).



R=H, $C_6H_5CH_2$, R_1 = H_3C, C_6H_5

Figure 4: Synthesis scheme of 5-(4-R_1-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-3-yl)pyrrolidin-2-ones

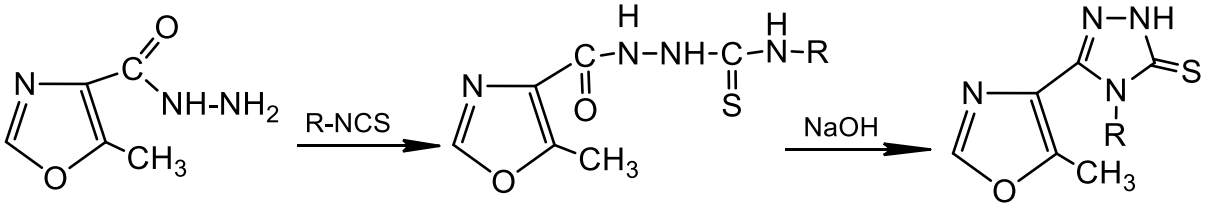
The combination of 1,2,4-triazole-3-thione and pyrazole derivatives resulted in compounds with potential anti-inflammatory, analgesic, and antipyretic activity [20-22]. Scientists have synthesized 4-R-3-(4-R_1-1-aryl-1*H*-pyrazole-3-yl)-1*H*-1,2,4-triazole-5(4H)-thions in high yields (Figure. 5) .



R=H, $C_6H_5CH_2$, R_1 = H_3C, C_6H_5

Figure 5: Synthesis scheme of 4-R-3-(4-R_1-1-phenyl-1*H*-pyrazole-3-yl)-1*H*-1,2,4-triazole-5(4*H*)-thions

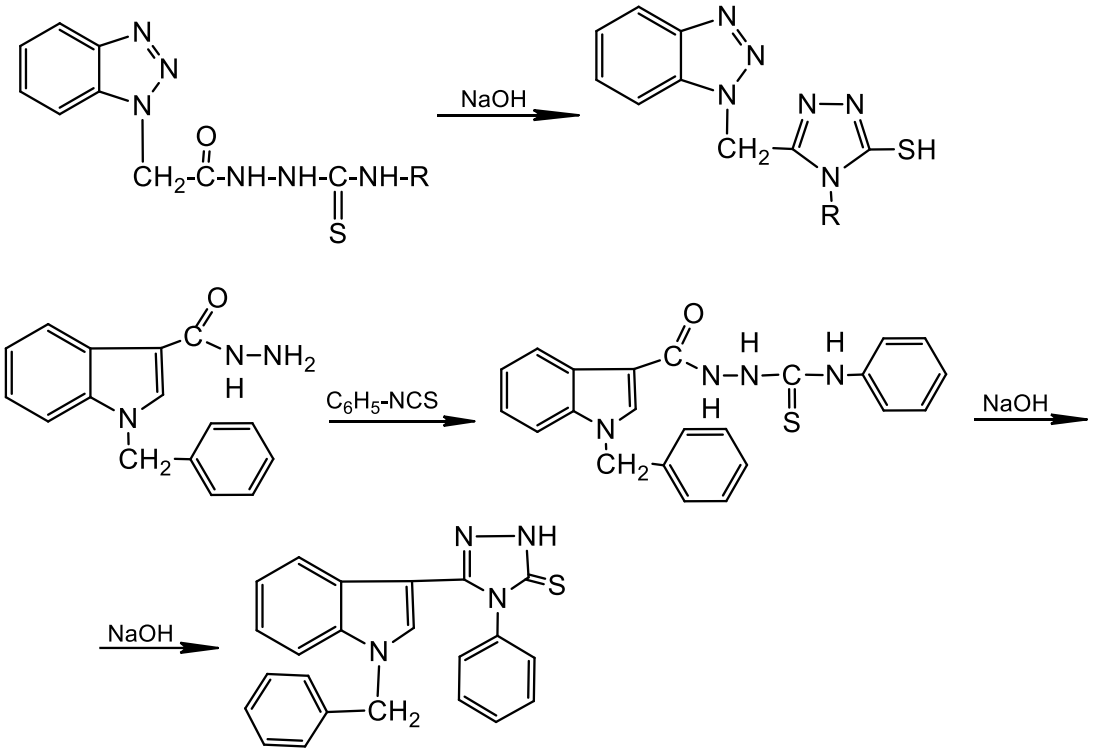
Another group of scientists has managed to combine 1,2,4-triazole-3-thion and imidazole, obtaining compounds with antiparasitic action [23-24]. The authors have also succeeded in synthesizing molecules with oxazole and 1,2,4-triazole residues, which possess psychostimulant activity (Figure. 6).



R = CH_3, C_4H_9, C_6H_5, 4-$CH_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$4-OCH_3, naphthyl

Figure 6. Synthesis scheme of 1,2,4-triazole and oxazole derivatives

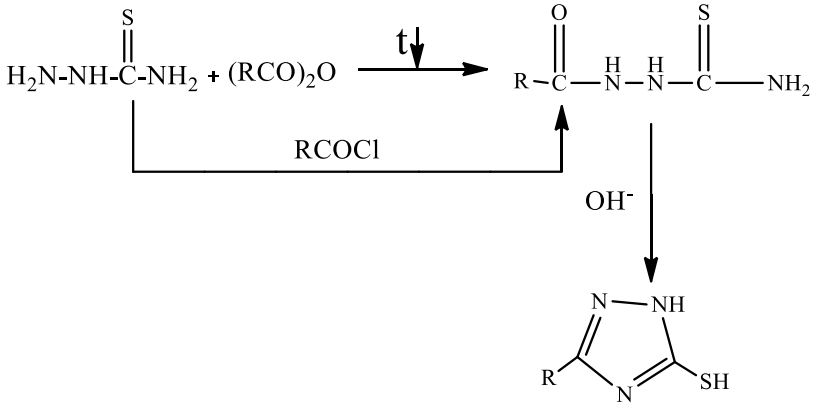
The condensed derivatives' synthesis of 1,2,4-triazole is gaining popularity [20]. Thus, for biological research, a number of 5-((1H-benzo-1,2,3-triazole-1-yl)methyl)-4-R-4H-1,2,4-triazole-3-thiols and 3- (1-benzyl-1H-indol-3-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thion (Figure. 7).



R = C_6H_5, 2-, 3- та 4-$CH_3C_6H_5$

Figure 7: Synthesis scheme of 5-((1H-benzo-1,2,3-triazole-1-yl)methyl)-4-R-4*H*-1,2,4-triazole-3-thiols and 3-(1-benzyl-1*H*-indol-3-yl)-4-phenyl-1*H*-1,2,4-triazole-5(4H)-thion

In some works, there are alternative, simple and effective obtaining methods of 2-acylhydrazinocarbothioamides by the interaction of thiosemicarbazide with anhydrides or haloanhydrides of carboxylic acids [25-27]. Closure of the 1,2,4-triazole cycle takes place as in the previous cases in an alkaline medium (Figure. 8).



R=Alk, Ar, Het

Figure 8: Synthesis of 5-R-1,2,4-triazole-3-thiols

Another group of authors has proved the closure of the 1,2,4-triazole cycle by catalytic amounts of Cu^{2+} salts [28]. Similar processes are caused by the fact that 2-R-hydrazinocarbothioamides contain a fragment of an unsaturated hydrocarbon and an increase in temperature in the presence of sodium or potassium hydroxide excess can lead to the unsaturated bonds' breaking (Figure. 9).

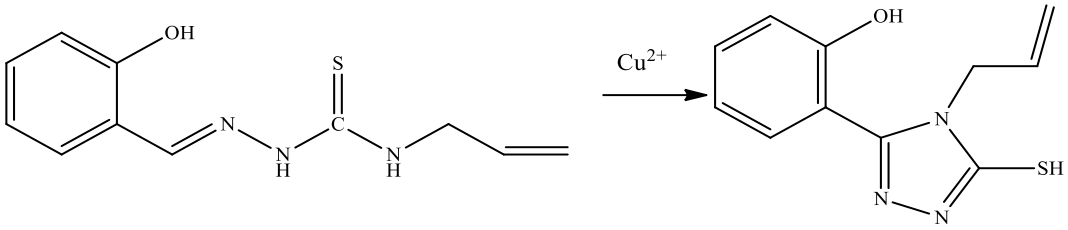
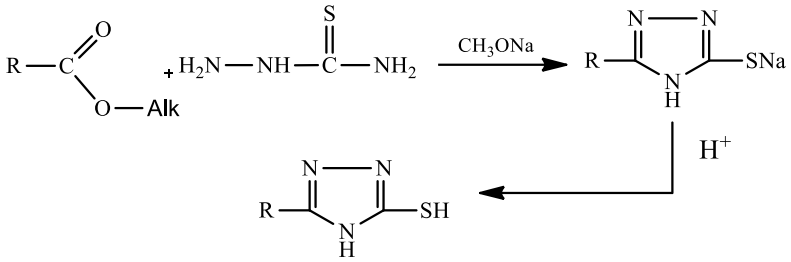


Figure 9: Synthesis of 2-(4-allyl-5-thio-1,2,4-triazole-3-yl)phenol

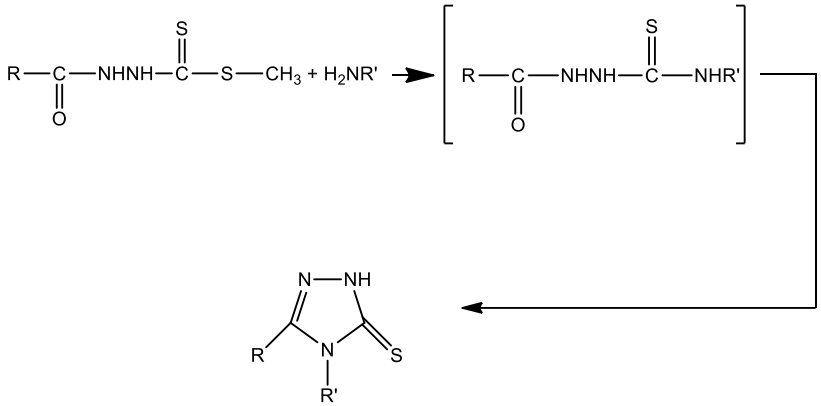
In the articles, scientists also present a synthesis scheme of the 5-heteryl-substituted 1,2,4-triazole-3-thion by the interaction of esters of heterylcarboxylic acids with thiosemicarbazide in the presence of sodium methanolate [29-30]. The corresponding thiols were isolated by adding the 5-R-1,2,4-triazole-3-thiolate acids to sodium (Figure. 10).



R=Het

Figure 10: Synthesis scheme of 5-substituted 2,4-dihydro-1,2,4-triazole-3-thiols

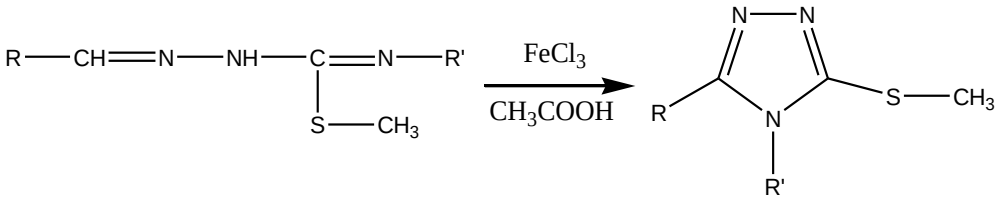
Polish scientists have described in details the synthesis of the 1,2,4-triazole-3-thions by the interaction of 2-acylhydrazinocarbodithioates with aliphatic amines [31]. At the same time, 3,4-disubstituted 1,2,4-triazole-3-thions are formed in one stage (Figure. 11).



R = R’ = Alk, Ar

Figure 11: Synthesis of 5,4-disubstituted 1,2,4-triazole-3-thions

Cyclocondensation of the 1,2,4-triazole-3-thions and R-(aminomethylthiomethyl)-2-benzylidene hydrazides in the presence of ferrum (III) chloride in concentrated acetic acid takes place at a temperature of 90°C with short heating (Figure. 12).



R = R’ = Ar

Figure 12: Cyclocondensation of R-(aminomethylthiomethyl)-2-benzylidene hydrazides

3-Thioderivatives of 1,2,4-triazoles can also be synthesized by thionation of 1 or 4 substituted 1,2,4-triazoles [32-34]. There is also a well-known method of thionation of 1-R-1,2,4-triazole-3-ones under stricter conditions - by heating the starting substances in dimethylformamide for 16 hours at a temperature of 150°C (Figure. 13).

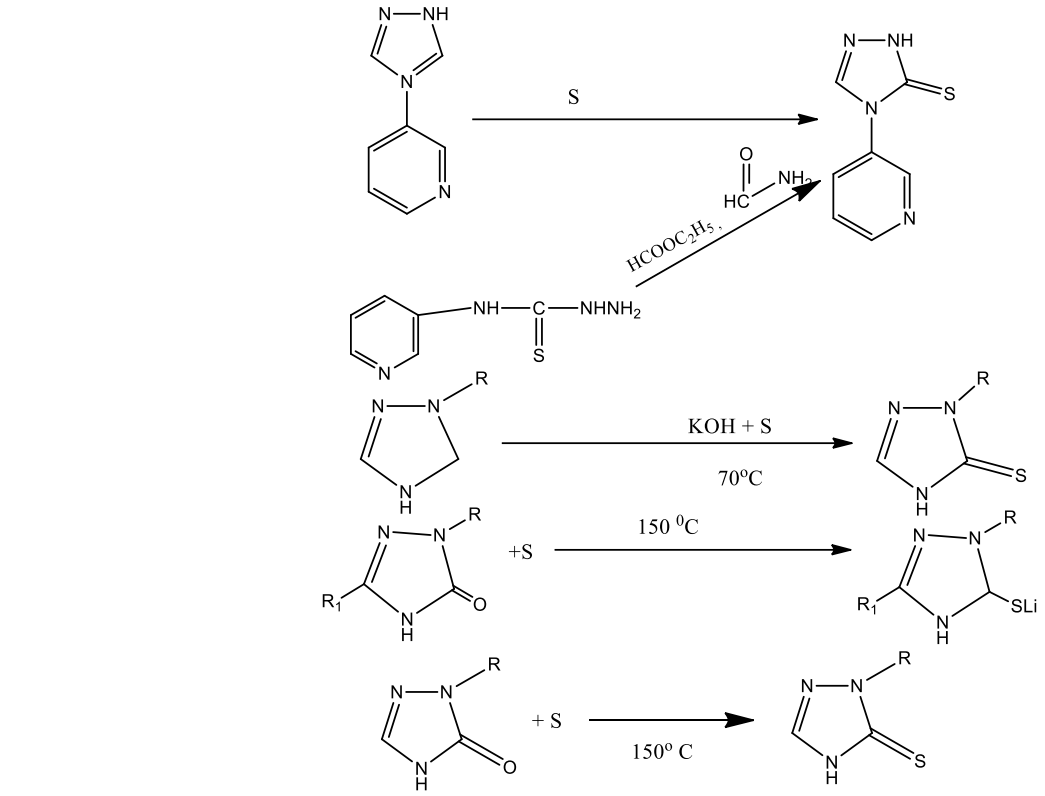


Figure 13. Thionation of substituted 1,2,4-triazole

The original obtaining method of 5,5'-alkylenebis(4H-1,2,4-triazole-3-thions) is proposed by scientists in works [35-36]. It was established that this process can be carried out by two methods (Figure. 14). According to the first method, dicarboxylic acids are used as starting compounds, the second method provides for obtaining esters, hydrazides of alkylenedicarboxylic acids, which, under the action of potassium (or ammonium) thiocyanates in a hydrochloric acid environment, are transformed into alkylbis(hydrazinocarbothioamides).

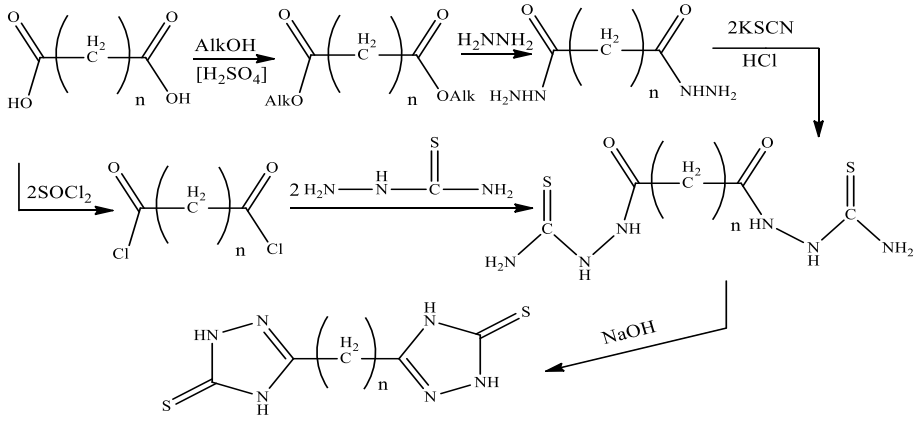


Figure 14: Synthesis scheme of 5,5'-alkylenebis(4H-1,2,4-triazole-3-thions)

Conclusions

The analysis of literary sources shows the prospect of finding new biologically active molecules among the 1,2,4-triazole derivatives. According to the results of the research, a generalization of publicly available literary material on synthesis methods, research of physicochemical properties of the 3-thio- and 3-thio-4-amino derivatives of the 1,2,4-triazole was carried out. A number of new compounds, which are formed during the transformation of the specified derivatives' series, have been studied in detail. The analysis of literary sources has revealed simple and promising methods of obtaining and converting the 3-thio- and 3-thio-4-amino derivatives of the 1,2,4-triazole.

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