

## Synthesis of 1,2,4-triazoline-5-thione derivatives

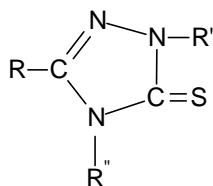
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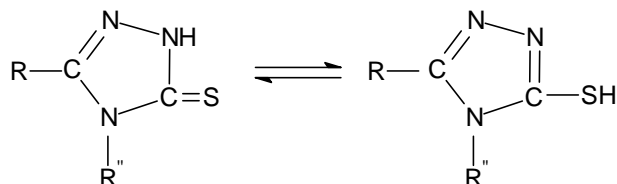
This paper is a review of the methods used for preparation of 1,2,4-triazoline-5-thione derivatives. The initial products were thiosemicarbazide, thiosemicarbazone, amidrazones salts, aminoguanidine salts and their derivatives.

### 1. INTRODUCTION

1,2,4-Triazoline-5-thione derivatives have the general formula:



were: R, R', R'' can be hydrogen, alkyl, aryl, amine group. In the case when R' = H or R'' = H, in this type of compounds tautomerism is likely to occur as can be seen in the formulae.

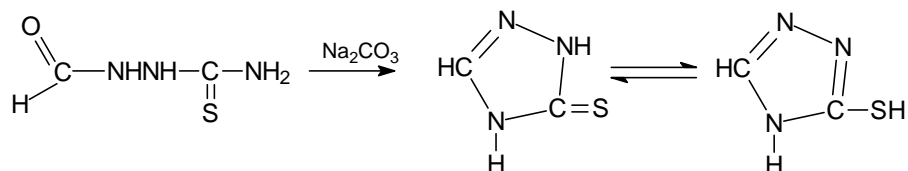


This paper is a review of the methods used for preparation of 1,2,4-triazoline-5-thione derivatives .

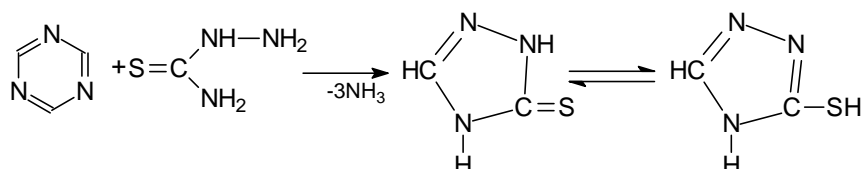
## 2. SYNTHESIS OF 1,2,4-TRIAZOLINE-5-THIONE

## 1. 1,2,4-Triazoline-5-thione

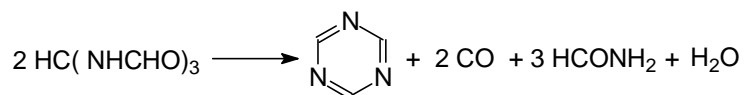
1,2,4-Triazoline-5-thione can be obtained by cyclization 1-formylthiosemicarbazide in a 2M sodium carbonate solution [1]. The reaction yield was 73%.



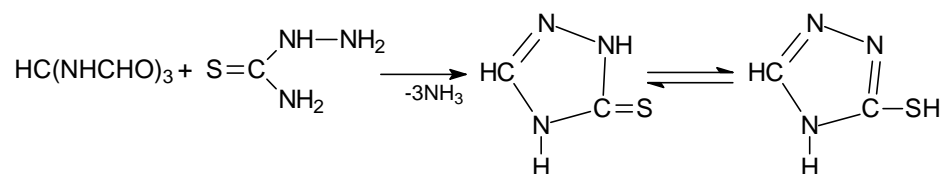
While studying chemical properties of s-triazine, Grundmann [2] carried out the reaction with thiosemicarbazide according to the scheme.



This reaction was carried out with little yield and became quite problematic because of a complicated synthesis of s-triazine. As follows from the literature reports s-triazine is formed during the thermal decomposition of triformylaminomethane [3].



The method of obtaining 1,2,4-triazoline-5-thione was therefore shortened by means of heating thiosemicarbazide direct from triformylaminomethane at the temperature of its decomposition (about 180–190°C). The reaction was carried out without the formation of s-triazine [4]. The reaction yield was about 90%.

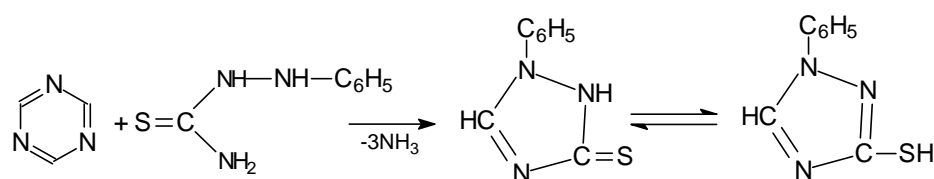


## 2. Monosubstituted 1,2,4-triazoline-5-thione

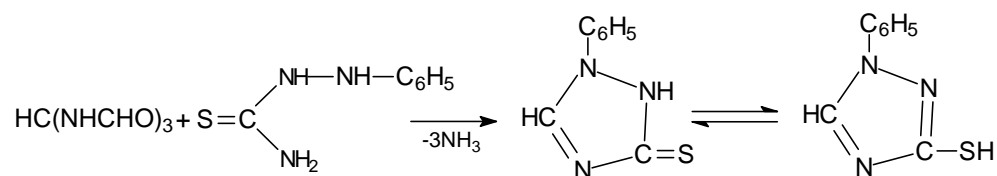
Derivatives of thiosemicarbazide, thiosemicarbazone, amidrazones salts, aminoguanidine salts and their derivatives were the initial products used for preparation of alkyl, aryl or amine derivatives of 1,2,4-triazoline-5-thione.

2-Substituted-1,2,4-triazoline-5-thione derivatives was obtained using the above mentioned methods.

Cyclization of 1-phenylthiosemicarbazide with s-triazine led to 2-phenyl-1,2,4-triazoline-5-thione [2]. The reaction yield was about 80 %.

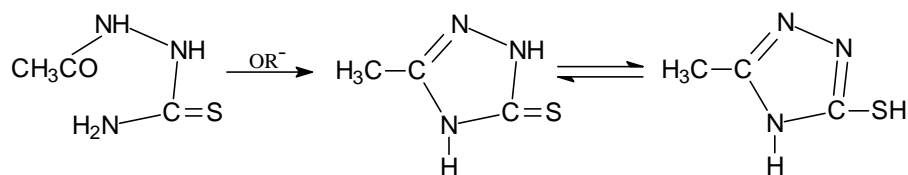


A better yield ( 93 % ) of this compound was obtained by means of a shortened method of direct cyclization of 1-phenylthiosemicarbazide with trimethylaminomethane which was a product used for the synthesis of s-triazine [4]. The reaction proceeded at 170–180 °C.



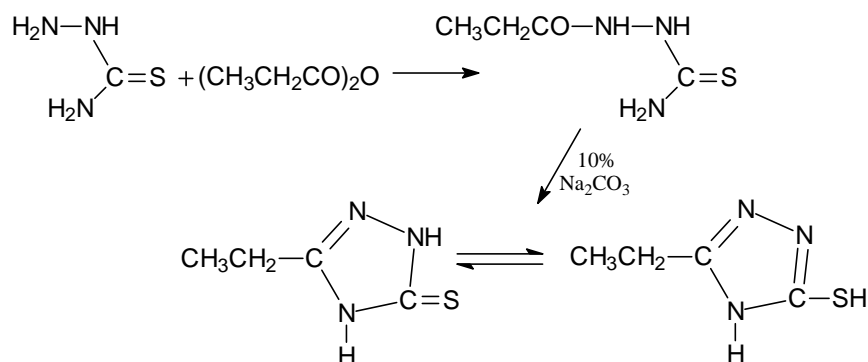
Thiosemicarbazide was also used as an initial product to prepare 3-substituted-1,2,4-triazoline-5-thione.

Thus, 1-acetylthiosemicarbazide may be cyclize with sodium methoxide in methanol to 3-methyl-1,2,4-triazoline-5-thione [5].



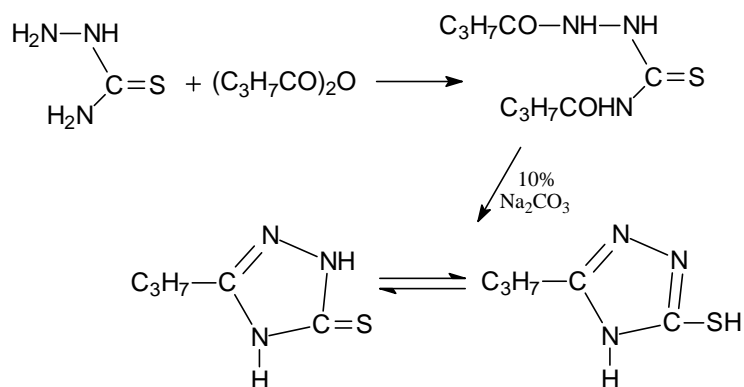
Alternatively, the cyclization can be effected by heating to about 185<sup>0</sup>C [6,7] although yields of the product are often inferior.

Another route to the acylthiosemicarbazide is offered by the reaction of thiosemicarbazide with aliphatic anhydrides. With one mole of propionic anhydride, 1-propionylthiosemicarbazide is formed [8] and cyclization to 3-ethyl-1,2,4-triazoline-5-thione is effected by boiling with 10% sodium carbonate solution for 1 hour.

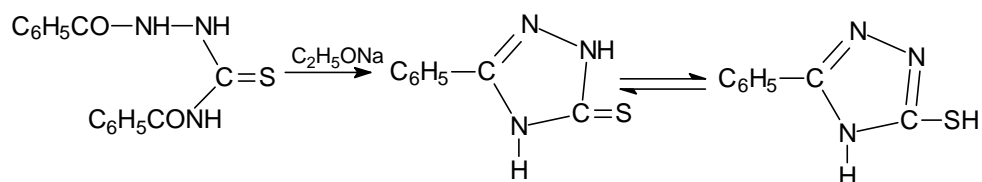


The reaction of cyclization 1-acetylthiosemicarbazide can be performed in sodium hydroxide[9-12]. The reaction yield is about 70%.

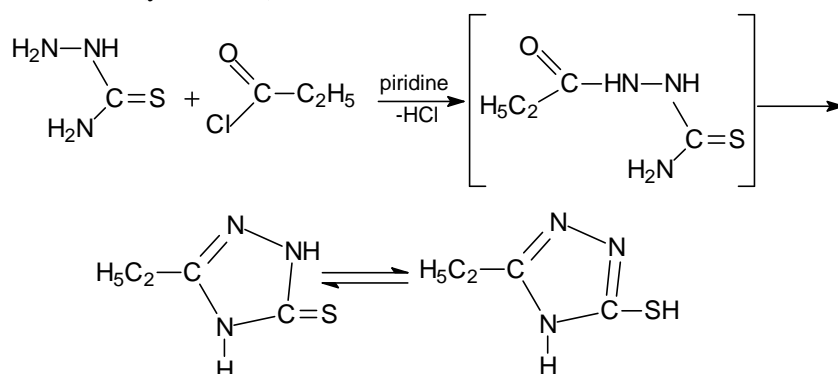
However, with an excess of butyric anhydride diacylation occurs to give the 1,4-dibutyryl-thiosemicarbazide, which cyclize with 10% per sodium carbonate solution at 100<sup>0</sup>C, forming 3-propyl-1,2,4-triazoline-5-thione. The reaction yield was about 60%.



A similar yield can be obtained for 3-phenyl-1,2,4-triazoline-5-thione in the cyclization reaction of 1,4-dibenzoylthiosemicarbazide with sodium ethoxide or hydrazine in boiling ethanol [13,14].

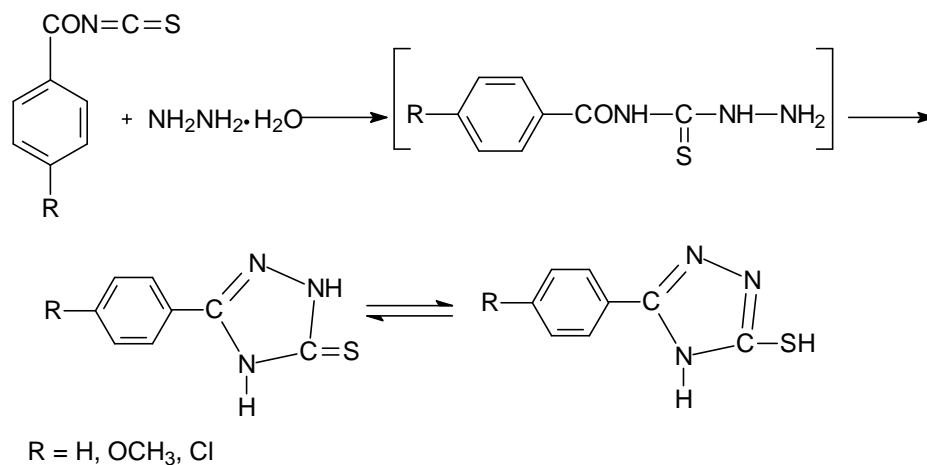


3-Ethyl-1,2,4-triazoline-5-thione was obtained in the reaction of thiosemicarbazide with appropriately substituted acid chlorides in the presence of pyridine [15] (yield 71%).

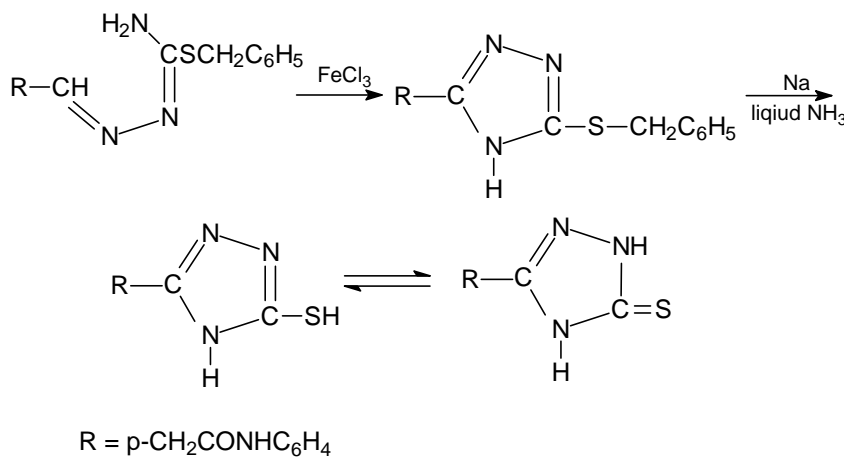


3-Substituted-1,2,4-triazoline-5-thione derivatives were obtained in the reaction of aroyl isothiocyanate with an excess of hydrazine hydrate too. The course of these reaction includes formation of intermediate thiosemicarbazide

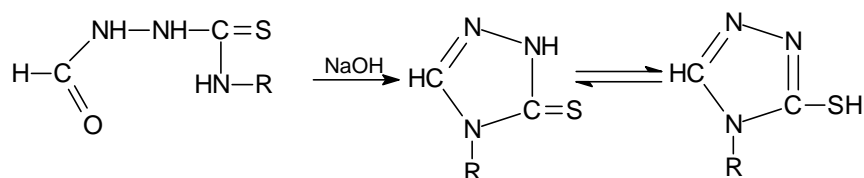
derivatives which cyclize spontaneously to the 3-aryl-1,2,4-triazoline-5-thione [16] and yields varying from 23 to 37%.



Thiosemicarbazone was used as an initial product to prepare 3-aryl-1,2,4-triazoline-5-thione [17,18].

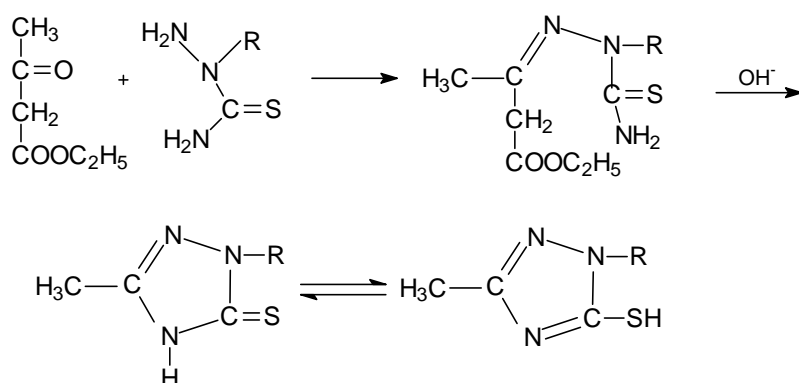


4-Substituted-1,2,4-triazoline-5-thione can be obtained in the process of cyclization of 1-formyl-4-substituted thiosemicarbazide. This reaction is carried out in alkaline medium [19] with the yield varying from 71 to 80%.

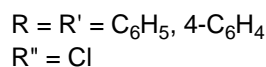
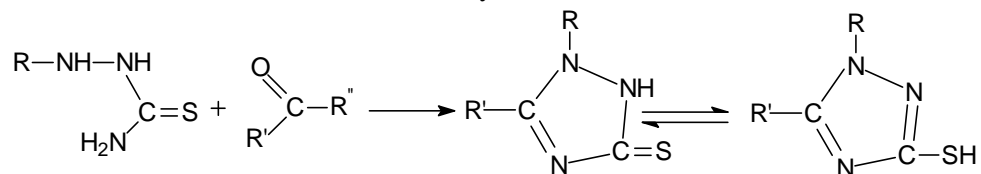


### 3. Disubstituted 1,2,4-triazoline-5-thione

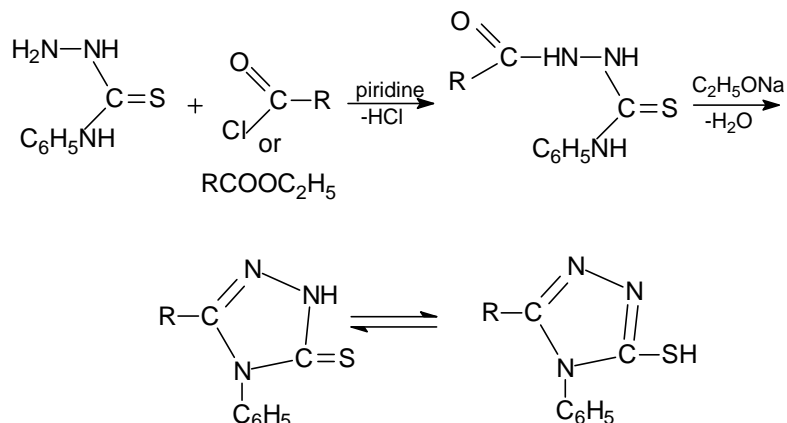
1,3-Disubstituted-1,2,4-triazoline-5-thione can be obtained in the reaction of thiosemicarbazide with aldehydes and ketones. The cyclization of obtained thiosemicarbazones leads to the formation of suitable derivatives of 1,2,4-triazoline-5-thione. The course of the reaction of esters of  $\beta$ -ketone acids and  $\beta$ -ketones with thiosemicarbazide includes the formation of disubstituted-1,2,4-triazoline-5-thione with good yield [20].



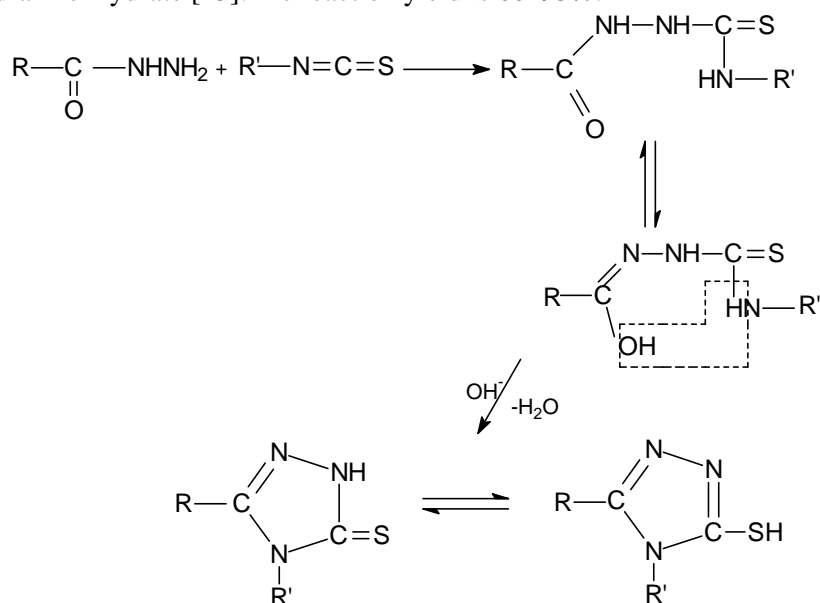
2,3-Disubstituted-1,2,4-triazoline-5-thione derivatives are prepared by the cyclization of the thiosemicarbazide with the acid halides. A mixt was stirred at  $80-90^\circ\text{C}$  for 90 minutes [21]. The reaction yield is 60–80%.



3,4-Disubstituted-1,2,4-triazoline-5-thione was obtained in the reaction of 4-alkyl- or 4-aryl thiosemicarbazide with aliphatic or aromatic acids chlorides or esters in the presence of a sodium alkoxide [22] with good yield.

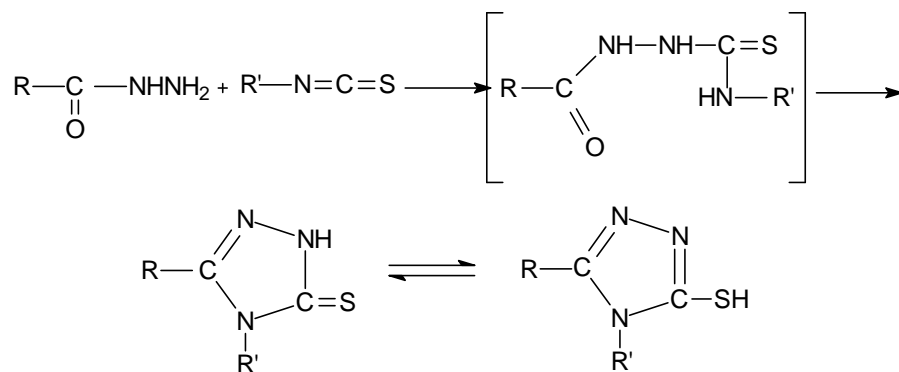


The same derivatives were obtained in the reaction of cyclization of 1-acyl derivatives of thiosemicarbazide in alkaline medium [19,23-42]. This reaction was carried out with sodium methanol or sodium ethanol [43,44] sodium carbonate [8] sodium hydroxide [23] sodium hydroxide with methyl iodide [43] or hydrazine hydrate [45]. The reaction yield is 60–95%.





Similarly, 3,4-disubstituted-1,2,4-triazoline-5-thione derivatives were obtained in the reaction of hydrazide of carboxylic acid with isothiocyanate.

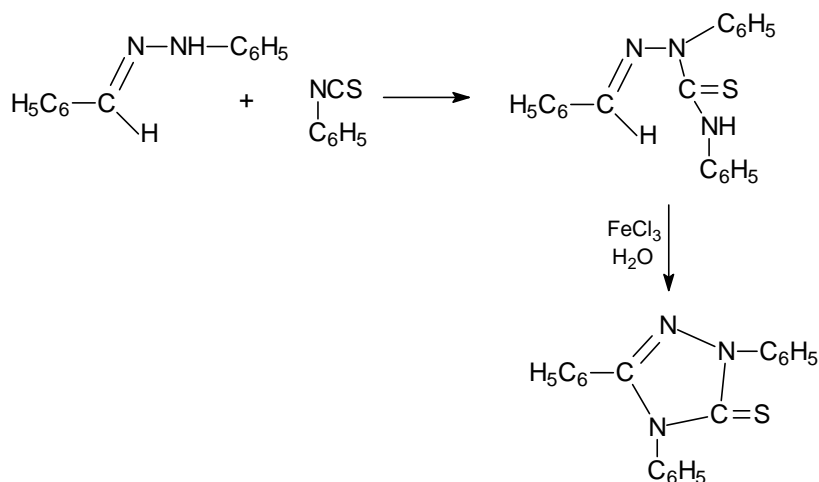


The reactions were performed in alloy at the temperature higher than formation of thiosemicarbazide derivatives. The reactions of cyclization were proceeding immediately without separation of thiosemicarbazide derivatives [19]. Yield 75–80%.

#### 4. Trisubstituted 1,2,4-triazoline-5-thione

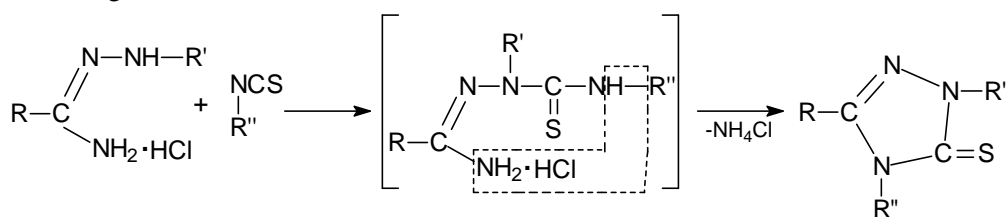
1,3,4-Trisubstituted-1,2,4-triazoline-5-thione can be obtained by means of heating 1,2,4-trisubstituted thiosemicarbazide and pyridine hydrochloride in sodium hydrogen carbon solution [46]. The reaction is carried out with the yield of 73%.

1,3,4-Triphenyl-1,2,4-triazoline-5-thione is obtained in the reaction of phenylhydrazone of benzoic aldehyde with phenylisothiocyanate and then in cyclization of the obtained compound with iron chloride in the aqueous solution [47]. The reaction yield varies from 60 to 72%.



### 5. Synthesis from amidrazones salts

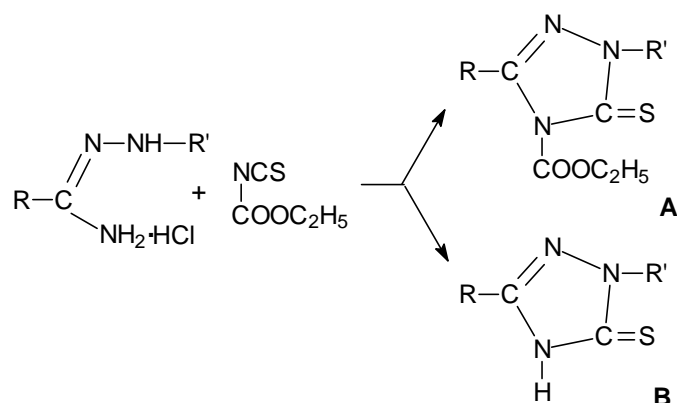
The basic method involving the formation of derivatives of 1,2,4-triazoline-5-thione was introduced by T. Bany [48]. The reaction consists in the condensation of amidrazones salts with aliphatic and aromatic isothiocyanates, according to the scheme:



R, R', R'' = H, alkyl, aryl

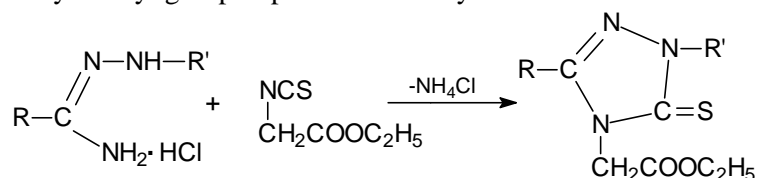
This method contributes to the formation of 3,4-disubstituted- and 1,3,4-trisubstituted 1,2,4-triazoline-5-thione.

Following the method the reactions of amidrazones hydrochloride with ethyl isothiocyanatoformate were performed [49]. These reactions were carried out by heating the substrates in the alloy. Depending on the temperature the reaction occurred in two directions.



The condensations were carried out without the separation of the intermediate products. The temperature of reaction in which the A product was formed was established for every amidrazone. The heating above this temperature led to the formation of B product, and the cyclization was accompanied by the thermal decomposition and decarboxylation.

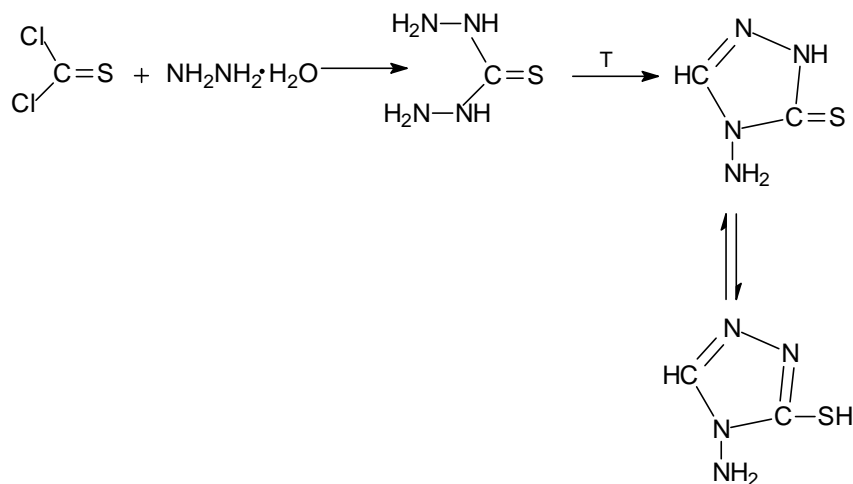
What is more, the reactions of amidrazone hydrochlorides and ethoxycarbonylmethyl isothiocyanate [50] were performed and resulted in obtaining of derivatives of 1,2,4-triazoline-5-thione which have ethoxycarbonylmethyl group in position 4. The yield varies from 53 to 70%.



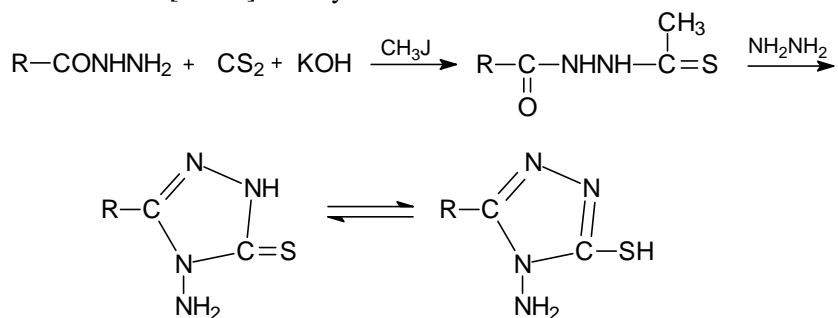
Many alternations on the ester group were performed and the compounds of different pharmacological activities were obtained: e.g. tranquilizing [51] antibacterial [52] and analgesic, anticonvulsant, anti-inflammatory [53,54]. The groups of compounds characteristic for the  $\beta$ -adrenal, hypotensive, spasmolytic medicines were also introduced [55].

## 6. Amine derivatives of 1,2,4-triazoline-5-thione

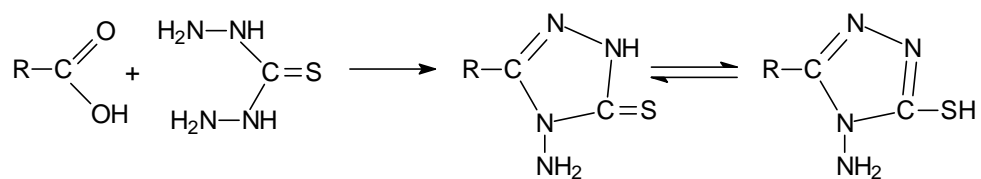
Amine derivatives of 1,2,4-triazoline-5-thione are a large group of compounds. Treatment thiophosgene with hydrazine in ether to give thiocarbonylhydrazide and heating this in a sealed tube at  $100^\circ C$  gives 4-amino-1,2,4-triazoline-5-thione [56] with good yield.



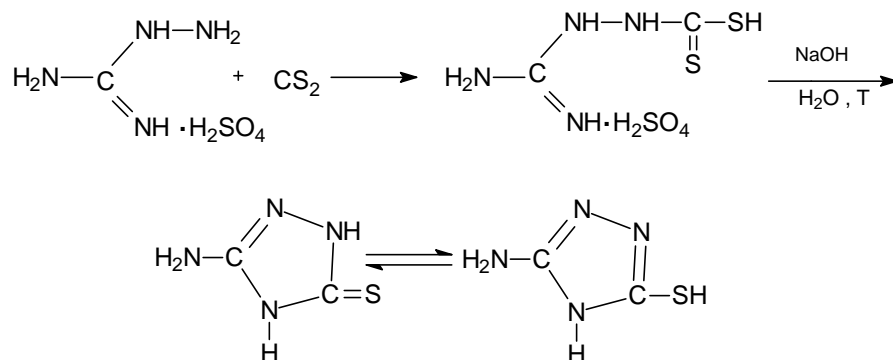
The second important method involves the reaction of an acid hydrazide with carbon disulphide and potassium hydroxide, giving the potassium salt of a 2-acyl-dithiocarbamic acid, which is converted into its methyl ester with methyl iodide. This reacts readily with hydrazine to form 4-amino-3-substituted-1,2,4-triazoline-5-thione [57-59] with yield about 69%.



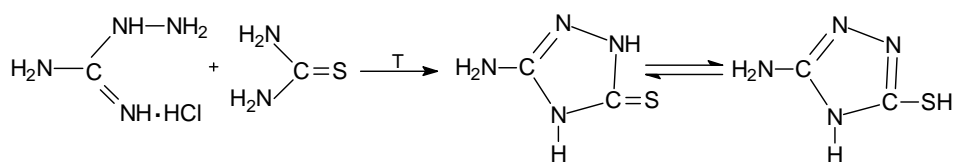
The same compounds can be obtained in the reaction of thiocarbamic acid dihydrazide with carboxylic acid [60].



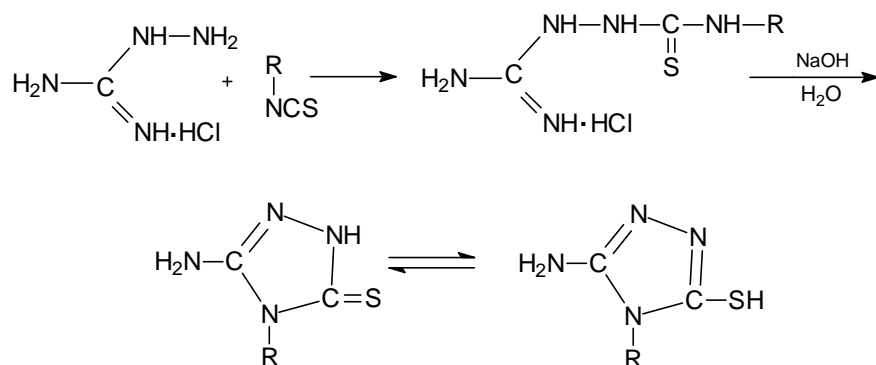
Aminoguanidine salts were the products used to obtain 3-amino-1,2,4-triazoline-5-thione derivatives. According to British patent aminoguanidine sulphate reacts with carbon disulphide giving the sulphate of 1-guanidinodithiocarbamic acid [61] which is then cyclized in basic medium and converted to 3-amino-1,2,4-triazoline-5-thione [62].



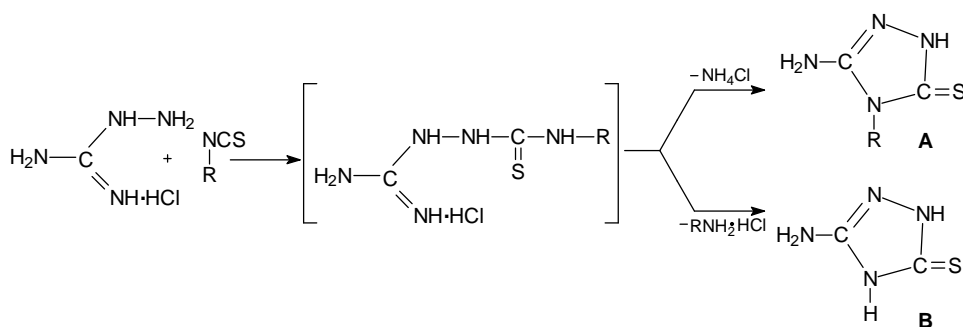
The same derivatives can be obtained in the reaction of aminoguanidine salts with thiourea in a melt at the temperature 195–210°C [63].



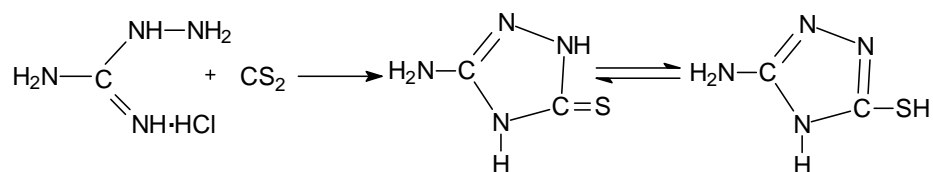
In the reaction of aminoguanidine hydrochloride with aliphatic and aromatic isothiocyanate there were obtained the linear products of 1-amidino-4-substituted derivatives of thiosemicarbazide isolated in hydrochloride form [64] or in the crystalline form as p-toluenesulphonates [65]. The cyclization of linear products in basic medium (3M NaOH) led to formation of 3-amino-4-substituted derivatives of 1,2,4-triazoline-5-thione [65,66].



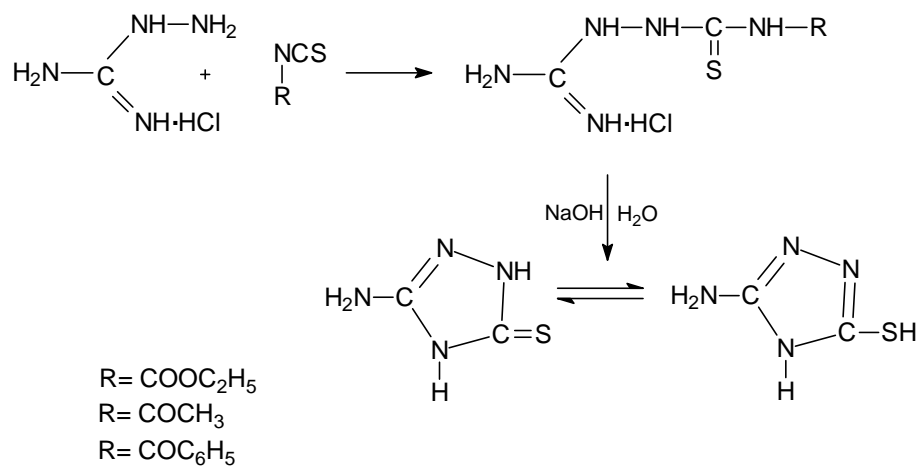
Aminoguanidine salts have a composition similar to amidrazones salts, so they can give the similar reactions as amidrazones salts. The similar course of the reaction cyclization with aromatic isothiocyanates is in the case of use of the salts of aminoguanidine derivatives. The reaction was performed 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 isocyanates occurred in two directions [67].



For each isothiocyanate there was established the appropriate temperature below which there was formed the product A. The heating above this temperature led always to formation of the product B. The course of these reaction 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 (yield 75–81%). Product B resulted from direct cyclization of aminoguanidine with carbon disulphide [67]:

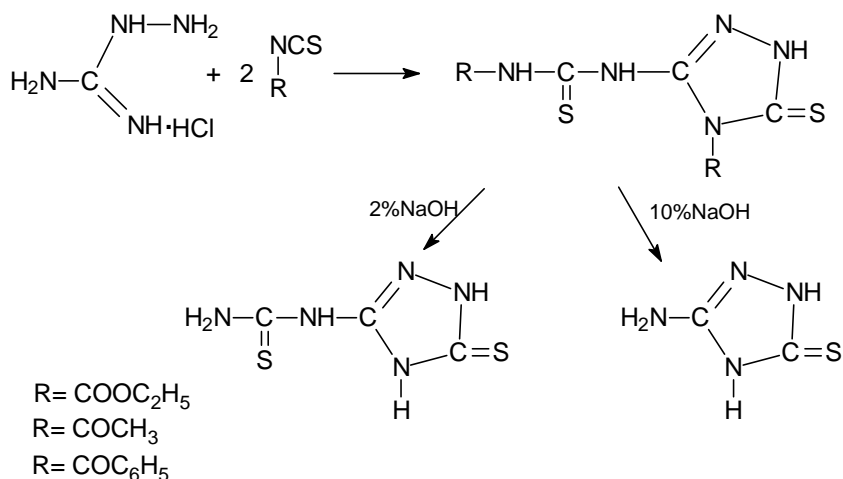


There were also performed the reactions of aminoguanidine salts with more reactive isothiocyanate such as ethyl isothiocyanatoformate or acetyl and benzoyl isothiocyanate [68].



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 the temperature of 110–120<sup>0</sup>C then there reacted either hydrazine or amidine group.



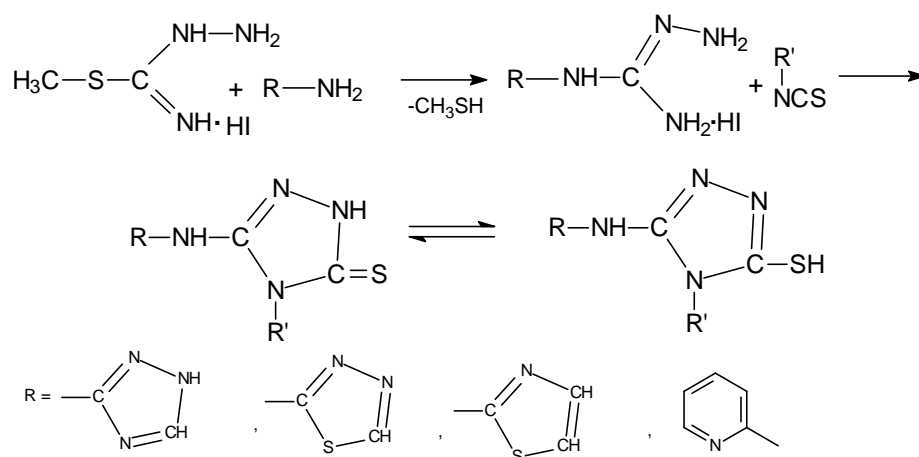
In this case it has obtained corresponding thiourea derivatives containing 1,2,4-triazole system and the basic hydrolysis of these compounds led to formation of 3-amino-1,2,4-triazoline-5-thione.

Similarly, in the reaction of derivatives of aminoguanidine salts with isothiocyanate or carbon disulphide, 3-aminosubstituted-1,2,4-triazoline-5-thione was obtained [67]. These reactions were carried out in alloy and *N,N*-dimethylacetamide medium

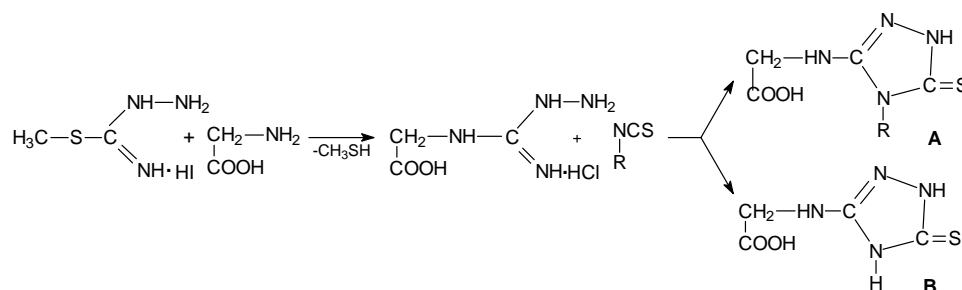
The derivatives of aminoguanidine were obtained in the reaction the hydroiodide of methyl ester of 3-thiocarbazine with amines.

In the reactions the hydroiodide of methyl ester 3-thiocarbazine with heterocyclic primary amines the derivatives of aminoguanidine were obtained with good yield. The obtained 2-amino-1-substituted guanidine hydroiodides reacted with isothiocyanates resulting in 3-aminosubstituted-1,2,4-triazoline-5-thione [69-72].





The course of reactions 2-aminoguanidine-1-acetic acid hydroiodide with aliphatic and aromatic isothiocyanate was carefully examined [73]. Depending on the temperature the reaction of aminoguanidine salt with isocyanates occurred in two directions.

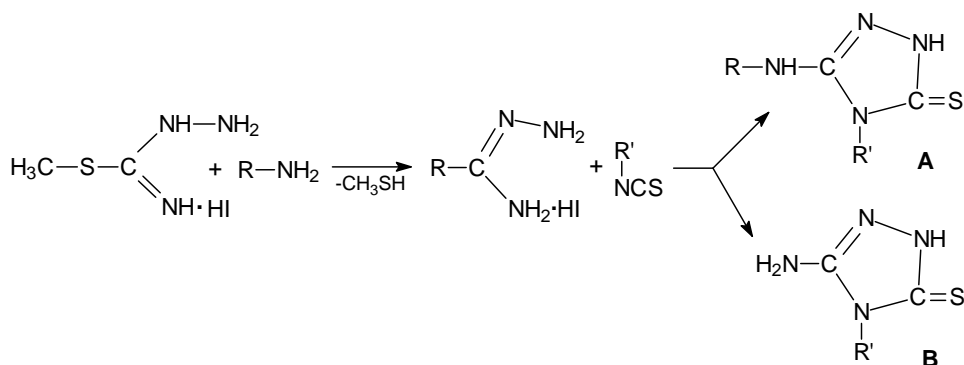


Product A was the result of the reaction carried out at 90–100°C. The heating above this temperature led to formation of the product B. The same products were obtained in the reaction 2-aminoguanidine-1-acetic acid hydroiodide with carbon disulphide [73]. The reaction yield is about 70%.

The mechanism of these reaction can be explained by the formation of transient linear products of 4-substituted-1-amidino-thiosemicarbazone in a form of salts, which undergo a spontaneous cyclization to the 1,2,4-triazole system.

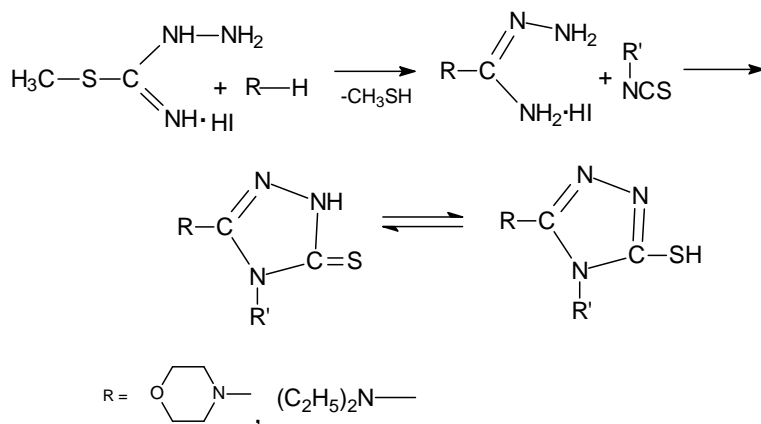
The cyclization of the derivatives of aminoguanidine salts, obtained from methyl ester 3-thiocarbamic acid hydroiodide and aniline, 3-toluidine and benzyl amine, with aromatic isothiocyanates was carried out.

Depending on the temperature the reaction product A or product B was obtained.



Product A was the result of the reaction carried out at 78–90<sup>0</sup>C. The heating at temperature 110–120<sup>0</sup>C led to formation of the product B. There were the same compounds as the ones obtained in the reaction of salts of aminoguanidine with aromatic isothiocyanates [74]. The reaction yield was 64–90%.

Following the scheme above, the reactions of methyl ester 3-thiocarbazine acid hydroiodide with secondary amines were performed, e.g. with morpholine and *N,N*-diethylamine, and then followed the cyclization of the obtained aminoguanidine derivatives with aromatic isothiocyanates [75]. The reaction yield varies from 72 to 87%.



### 3. CONCLUSIONS

1,2,4-Triazoline-5-thione show different biological activity, e.g. tuberculostatic [76-81], analgesic [82], anti-inflammatory [83-85], antimicrobial [86-92] and can be used as herbicides [93] or fungicides [94].

3-Amino-1,2,4-triazoline-5-thione and 3-amino-4-substituted-1,2,4-triazolin-5-thione derivatives are widely used in photography [95-101].

#### 4. REFERENCES

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