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*N.V. Toropin, Y.V. Trush, B.V. Murashevich, K.S. Burmistrov***SYNTHESIS OF 1-(HYDROXYLPHENYL)-3-ARYL-5-MERCAPTO-1,2,4-TRIAZOLES FROM ARENALAZINE QUINONES**

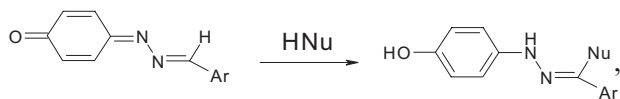
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New reactions of arenalazines 1,4-benzoquinones with potassium thiocyanate in acetic acid were investigated. It was established that the reactions proceed via the 1,8-addition scheme, similar to that described earlier for hydrohalogens and amines of different nature and in contrast to other type of quinoneimines which react with hydrochloric acid, potassium thiocyanate and other nucleophilic agents according to the 1,4-, 6,3-, 1,6- or 6,1-addition scheme. The addition product of potassium thiocyanate is spontaneously cyclized with the formation of the derivatives of 5-mercapto-1,2,4-triazoles with a good yield. The alkylation of these triazoles with equimolar quantity of dimethylsulfate leads to S-methyl derivative; a threefold excess of dimethylsulfate yields dimethylated product. The structures of the obtained compounds were confirmed by ^{13}C , ^1H NMR and IR spectroscopies. The synthesized mercaptotriazoles can be used as inhibitors of metal corrosion, as well as components of drugs with cytostatic, antibacterial, immunopotentiating and hepatoprotective activities.

Keywords: arenalazine, 1,2,4-triazole, potassium thiocyanate, alkylation, cyclization.

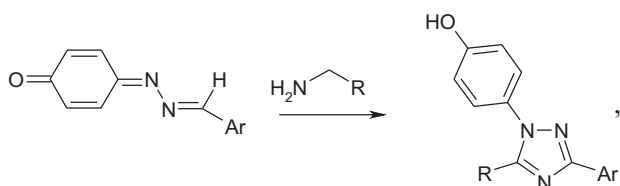
Introduction

Earlier we have discovered the following reaction of 1,8-addition between nucleophilic agents and arenalazines [1]:



where Nu=Cl, Br, (Alk) $_2$ N, AlkNH, ArNH.

It was established that hydrohalogens, amines (aromatic, primary amines, N,N-dialkylamines) also react according to this scheme. Additionally, primary monoalkylamines, which contain $-\text{CH}_2-\text{NH}_2$ fragments, undergo cyclization with the formation of 1-aryl-2-(p-hydroxyphenyl)-5-alkyl-1,2,4-triazoles [2–4] as follows:



where R= H, CH $_3$, C $_2$ H $_5$, Ph, CH $_2$ OH.

However, the reaction of arenalazine quinones with thiocyanic acid has not been studied yet. Therefore, the purpose of this research was to investigate the reaction of thiocyanic acid with 4-[(4-chloro-benzylidene)-hydrazono]-cyclohexa-2,5-dienon.

Theory

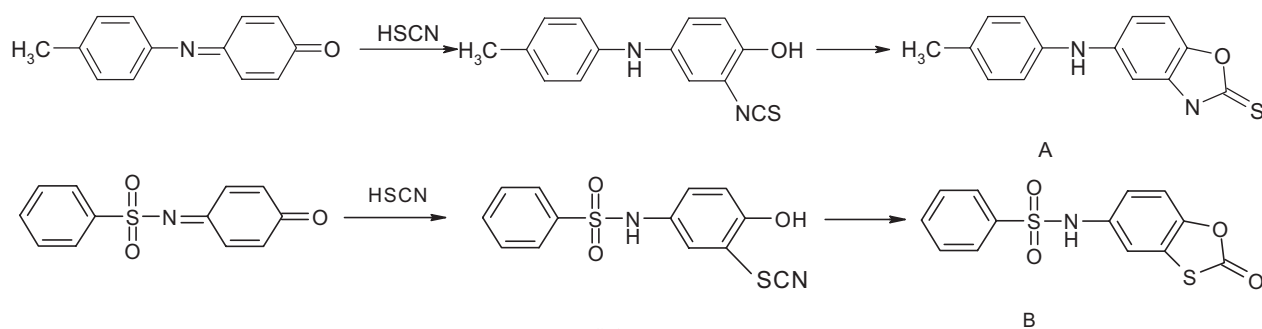
It is known that quinone compounds, depending of their structure and reaction condition, react with thiocyanic acid, resulting in 1,4-addition products of different structure; these products can form corresponding heterocyclic systems (Schema 1) [5,6].

Such a feature of the reaction of quinone systems with thiocyanic acid is related to the fact that thiocyanic ion is ambidentate. The results of quantum-chemical calculation showed that sulfur atom is «soft» nucleophilic center and the nitrogen atom is a «hard» one [7].

We assumed that the interaction with sulfur atom proceeds under the orbital control, whereas the interaction with nitrogen atom occurs under charge control. Thus, the formation of 1,8-addition products C or D could be expected.

Results and discussion

When arenalazines react in acetic acid with



potassium thiocyanate, we obtained a white product with an 80% yield, the NMR spectrum (Fig. 1) of which shows signals of two para-substituted phenyls.

However, in the IR-spectrum of the resulting product (Fig. 2), the absorption at $2130\text{--}2140\text{ cm}^{-1}$, which is typical of $-\text{SCN}$ and $-\text{NCS}$ groups, has

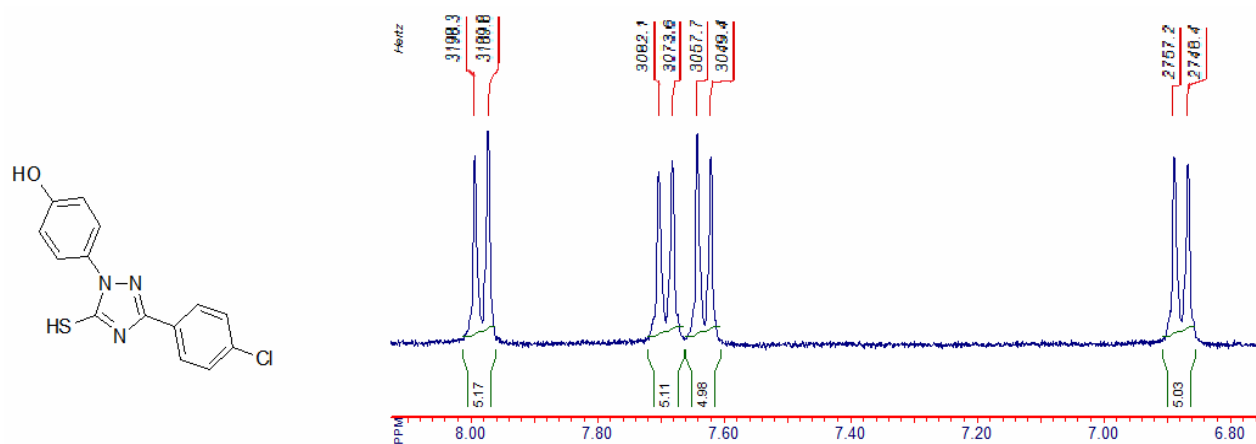


Fig. 1. NMR spectrum of 4-[3-(4-chlorophenyl)-5-mercapto-1,2,4-triazole-1-yl]-phenol

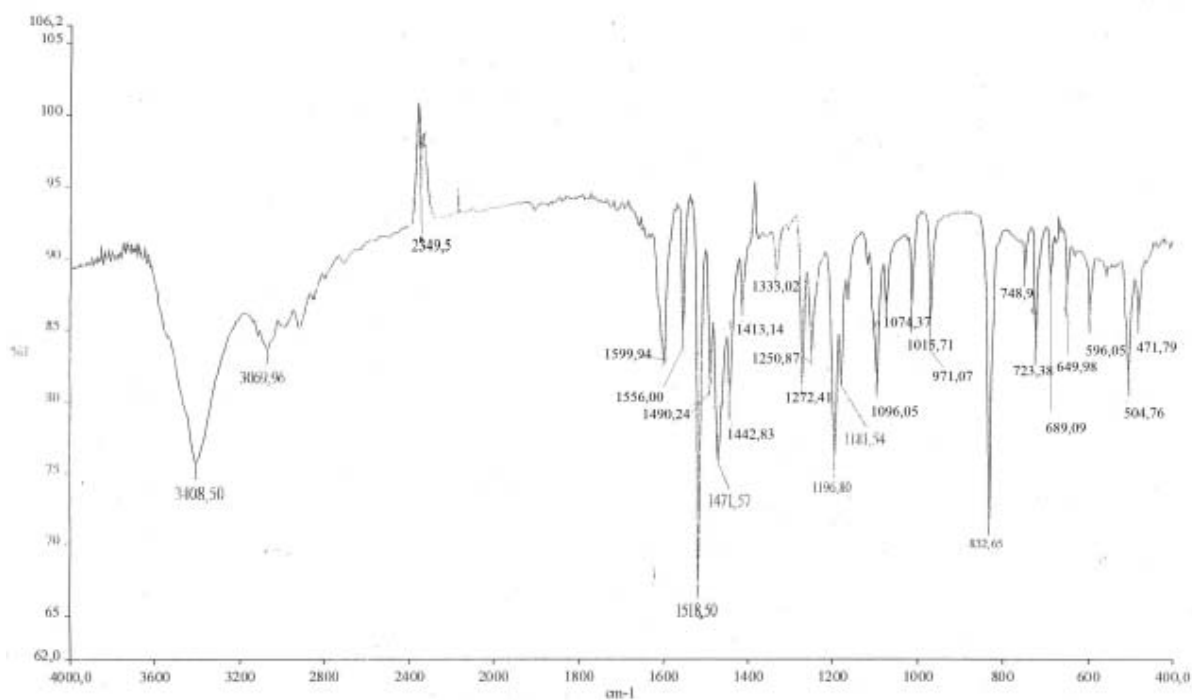


Fig. 2. IR-spectrum of 4-[3-(4-chlorophenyl)-5-mercapto-1,2,4-triazole-1-yl]-phenol

not been observed.

In order to determine the structure, we have methylated this product with dimethylsulfate in a ratio of 1:1.2. The singlet at 2.7 ppm in the NMR-spectrum of the resulting product is characteristic of S-CH₃ group. With an excess of dimethylsulfate (1:3), we obtained dimethylated product. A singlet at 3.85 ppm, which is characteristic of O-CH₃, is observed in the NMR-spectrum of this product (Fig. 3).

Thus we have established that 4-[3-(4-chlorophenyl)-5-mercapto-1,2,4-triazole-1-yl]-phenol (II) is formed in the reaction of (I) with potassium thiocyanate (Scheme 2). The data of NMR ¹³C spectrum confirms this structure.

It is obvious that the reaction occurs through the formation of an intermediate product (C), which we failed to isolate, probably due to its fast cyclization into triazole (II). The absence of other products, except (II), indicates that the reaction on sulfur atom of thiocyanic ion (an intermediate D) does not occur.

This unexpected result allows us to simply synthesize 1-aryl-2-(4-hydroxyphenyl)-5-thiol-1,2,4-triazoles. According to the analysis performed by using PASS software, the compounds of such a structure are promising as interleukin 1 and 2 antagonists, insulin inhibitors, histidine kinase inhibitors etc.

The presence of active functional groups (-OH, -NH and -SH) in the compounds of type

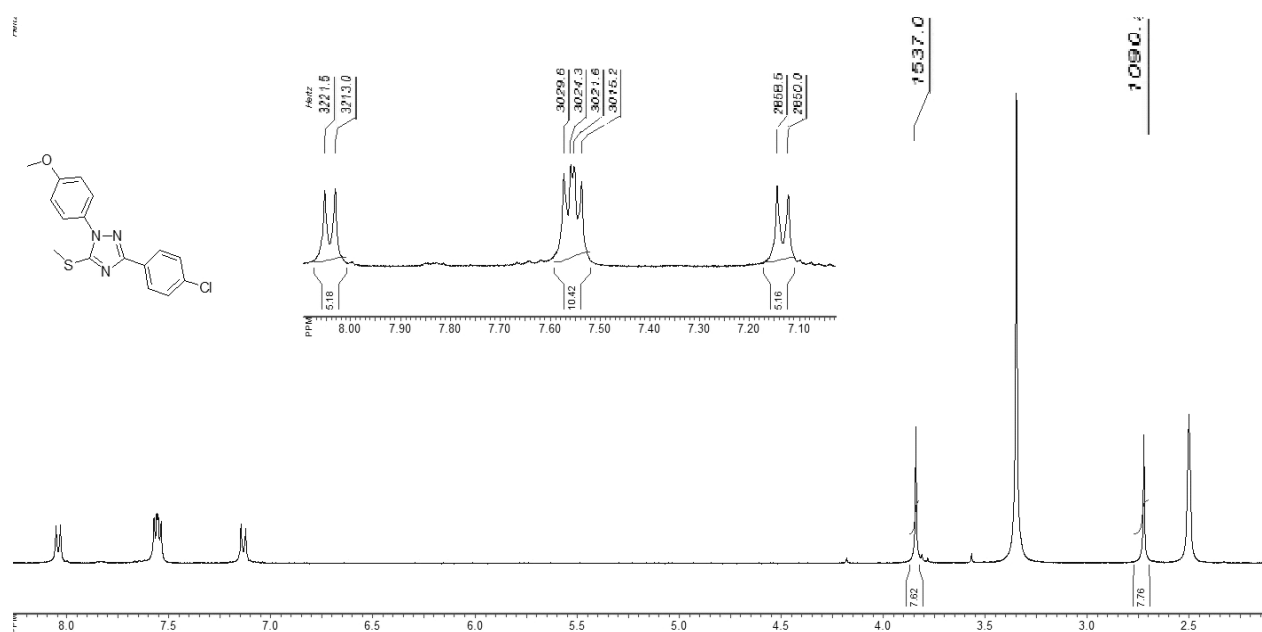
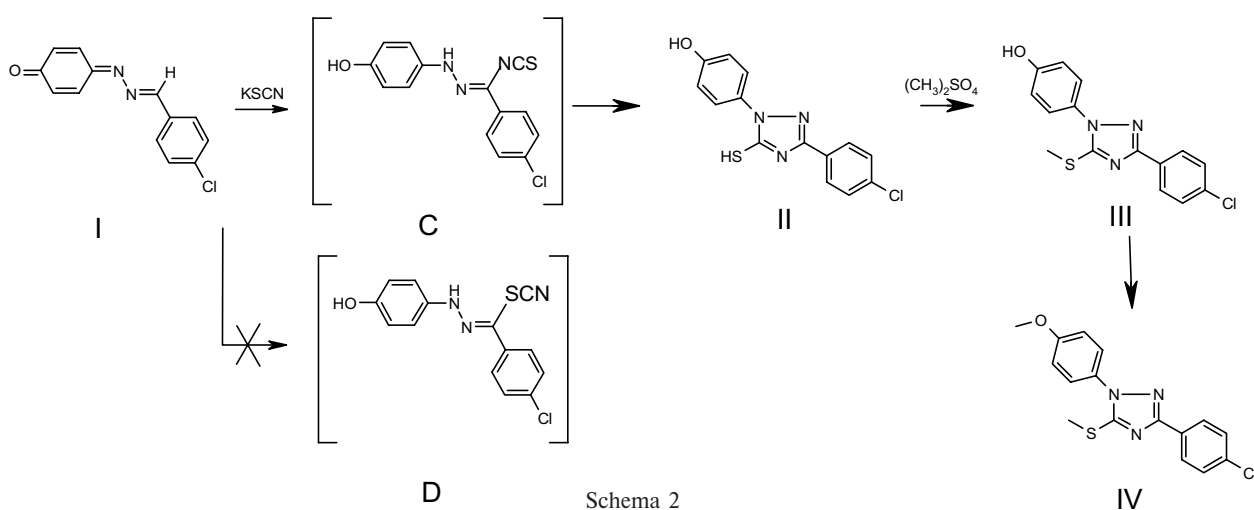


Fig. 3. NMR spectrum of 3-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-(methylmercapto)-1H-1,2,4-triazole



Scheme 2

(II), provides their application as synthones for synthesis of drugs with expected biological activity. Thus, for instance, the activity of compound (II) as interleukin antagonist is 0.540, but mono methyl derivative and dimethyl derivative increase the possibility coefficient of activity presence (P_a) up to 0.798 and 0.8, respectively (according to the PASS calculations).

Experimental

The purity of the synthesized substances was controlled by thin layer chromatography with SORBFIL plates. The eluent is a mixture of 1,2-dichloroethane with propanol-2 (9:1). ^{13}C , ^1H NMR spectra were recorded on Varian Gemini 2000 radiometer spectrometer (400 MHz) in DMSO - d_6 . IR spectra were obtained in tablets with potassium bromine by means of Spectrum BX11FT-IR Perkin Elmer.

Synthesis of 4-[3-(4-chlorophenyl)-5-mercapto-1,2,4-triazole-1-yl]-phenol (II)

The solution of 0.5 g (2 mmol) 4-[(4-chlorobenzylidene)-hydrazono]-cyclohexa-2,5-dienon (I) in 10–12 ml of acetic acid was prepared at 25–30°C. Then 0.6 g (6 mmol) of potassium thiocyanate was added. The solution was stirred for 1.5–2.0 h and left overnight. The formed precipitate was filtered, washed with water and dried. It looked like a white crystalline powder with yellow tint. The yield was 0.6 g (85%).

$T_m > 285^\circ\text{C}$.

NMR spectrum, δ , ppm. (DMSO- d_6): 6.87 d (2H, 4- ClC_6H_4 , J 8.6 Hz), 7.99 d (2H, 4-OHC $_6\text{H}_4$, J 8.5 Hz), 7.63 d (2H, 4-OHC $_6\text{H}_4$, J 8.3 Hz), 7.7 d (2H, 4- ClC_6H_4 , J 8.6 Hz), 9.85 s (1H, OH).

IR spectrum, ν , cm^{-1} : 3409, 3070, 1600, 1556, 1520, 1272, 1197, 1096, 833, 723.

^{13}C spectrum, δ , ppm. (DMSO - d_6): 114.9, 123.9, 125.8, 127.5, 129.2, 135.4, 156.8, 165.8.

Synthesis of 4-[3-(4-chlorophenyl)-5-(methylmercapto)-1H-1,2,4-triazol-1-yl]-phenol (III)

The solution of 0.3 g 4-[3-(4-chlorophenyl)-5-mercapto-1,2,4-triazole-1-yl]-phenol (II) (1 mmol), 0.1 g potassium hydroxide and 1.2 mmol of dimethylsulphate in 80 ml of 1, 4-dioxane was boiled with condensation for 2–3 h. The reaction was controlled using TLC method.

The reaction solution was diluted with 200 ml of water and the precipitate was filtered. It was then washed with 10 ml of hexane, water and dried. It looked like a white crystalline powder. The yield was 0.258 g (86%).

$T_m = 150\text{--}153^\circ\text{C}$.

NMR spectrum, δ , ppm. (DMSO- d_6): 2.7 s (3H, MeS), 6.94 d (2H, 4- ClC_6H_4 , J 8.0 Hz), 8.01 d

(2H, 4- ClC_6H_4 , J 8.0 Hz), 7.51 d (2H, 4-OHC $_6\text{H}_4$, J 8.3 Hz), 7.4 d (2H, 4-OHC $_6\text{H}_4$, J 8.3 Hz), 10.04 s (1H, OH).

IR spectrum, ν , cm^{-1} : 3436, 1646, 1524, 1273, 1092, 830, 746.

Synthesis of 3-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-(methylmercapto)-1H-1,2,4-triazole (IV)

The reaction conditions were similar to the synthesis of compound (III), but an excess of dimethylsulfate was used. 1,4-Dioxane was used as a solvent. The obtained substance is a white crystalline powder. Its yield was 0.264 g (88%).

It decomposes at $T > 280^\circ\text{C}$.

NMR spectrum, δ , ppm. (DMSO- d_6): 2.7 s (3H, MeS), 3.85 s (3H, 4-MeO), 7.14 d (2H, 4- ClC_6H_4 , J 8.7 Hz), 8.04 d (2H, 4- ClC_6H_4 , J 8.3 Hz), 7.57–7.54 dd (4H, 4- ClC_6H_4 , J 8.7 Hz).

IR spectrum, ν , cm^{-1} : 2938, 1523, 1466, 1398, 1252, 1090, 1022, 823, 742.

Conclusions

The reaction of arenalazines 1,4-benzoquinones with potassium thiocyanate in acetic acid was investigated for the first time. It ensures a convenient method of the synthesis of functionalized 1-(4-hydroxyphenyl)-3-aryl-5-mercapto-1,2,4-triazoles with a number of useful properties.

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СИНТЕЗ 1-(4-ГІДРОКСИФЕНІЛ)-3-АРИЛ-5-МЕРКАПТО-1,2,4-ТРИАЗОЛІВ ІЗ АРЕНАЛАЗИНІВ ХІНОНІВ

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Вивчені нові реакції взаємодії ареналязинів 1,4-бензохінонів з роданидом калію. Встановлено, що вони протікають за схемою 1,8-приєднання, аналогічно описаній раніше для галогенводнів та амінів різної природи, на відміну від хінонімінів інших класів, які реагують з соляною кислотою, роданидом калію та іншими нуклеофільними агентами за схемою 1,4-, 6,3-, 1,6- чи 6,1-приєднання. Продукт приєднання з роданидом калію самодовільно циклізується з утворенням похідних 5-меркапто-1,2,4-триазолів. Алкілування отриманих триазолів з еквімолярною кількістю диметилсульфату призводить до S-метильного похідного, а з триразовим надлишком диметилсульфату – до диметильованого продукту. Структуру одержаних речовин підтверджено ¹³C, ¹H ЯМР та ІЧ-спектроскопією. Одержані меркаптотриазоли потенційно можуть бути використані в якості інгібіторів корозії металів. Також можуть бути використані в якості компонентів лікарських засобів, які володіють цитостатичним, антибактеріальним, імуностимулюючим, гепатопротекторним ефектами.

Ключові слова: ареналязин, триазол, роданид калію, алкілування, циклізація.

SYNTHESIS OF 1-(HYDROXYPHENYL)-3-ARYL-5-MERCAPTO-1,2,4-TRIAZOLES FROM ARENALAZINE QUINONES

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Keywords: arenalazine; 1,2,4-triazole; potassium thiocyanate; alkylation; cyclization.

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