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MECHANISM OF SYNTHESIS OF QUINAZOLIN-4-THIONE IN A NEW METHOD

Elmuradov Chori Juraevich [1], ***Qayumova Maftuna Ilxom qizi*** [3], ***Saitkulov Foziljon Ergashevich*** [2], ***Isaqulova Marxoba Ne'mat qiz*** [3], ***Muminova Nigora Kilichovna*** [3]

[1] Karshi State University, Republic of Uzbekistan, Uzbekistan

[2] Tashkent State Agrarian University of Uzbekistan, Uzbekistan

[3] Institute of Biochemistry of Samarkand State University named after Sh. Rashidov, Uzbekistan

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Abstract

In the article, the preparation of quinazolin-4-thione in the presence of quinazolin-4-one by various methods was thoroughly studied, and for the first time, the thionation reaction was carried out in the presence of Lavesson's reagent.

The structure of the quinazoline-4-thione molecule has be en proven using modern physical and chemical research methods.

Keywords: *quinazolin-4-thione, quinazolin-4-one, various methods, thionation reaction, Lavesson's reagent, P_2S_5, in an inert atmosphere (argon), cycloreversion (opposite process to cycloaddition!)*

Introduction

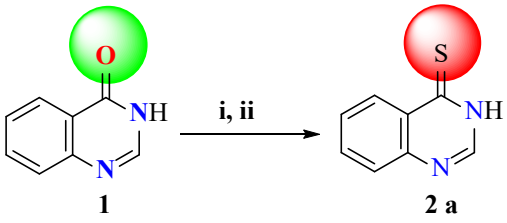
Usually, organic reactions involve step-by-step formation of individual bonds of the target molecule. It is often necessary to isolate and purify intermediate substances, change reaction conditions at subsequent stages of synthesis. Tandem reactions have a number of advantages. Firstly, they allow creating complex structures in a small number of stages. Moreover, the process is often accompanied by high chemo-, regio- and stereoselectivity. It also eliminates the need for purification at each stage. Targeted synthesis of low-toxic biologically active substances based on the study of the "structure-activity" relationship is an important task of organic chemistry. In recent years, priority has been given to the study of substances that are close in structure to natural ones. Anthranilic acid is a product of the metabolism of natural substances in a living organism, and its derivatives exhibit a wide range of pharmacological activity. The search for substances with high anti-inflammatory, analgesic activity and low toxicity is relevant, untimely use of anti-inflammatory agents in systemic inflammatory diseases of connective tissue with a

chronic progressive course can lead to disability of patients (Saitkulov F.E., Elmuradov B. Zh., Sapaev B., 2024; Saitkulov F.E., Elmuradov B.J., Giyasov K., 2023; Saitkulov F.E., Elmuradov B.J., 2024; Saitkulov F. E., Elmuradov B. J., 2022; Saitkulov F., Sapaev B., Nasimov K., Kurbanova D., Tursunova N., 2023).

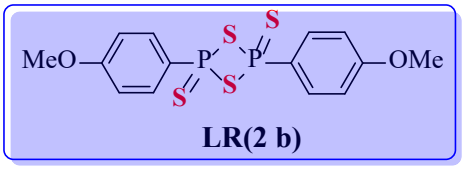
Finally, tandem reactions allow saving on the cost and quantity of reagents, solvents, adsorbents, reducing the amount of waste generated, energy costs and the number of laboratory operations (Saitkulov F.E., Elmuradov B. Zh., Giyasov K., 2023; Saitkulov F. E., Giyasov K., Elmuradov B. J., 2022; Saitkulov F.E., Tashniyazov A.A., Mamadrahimov A.A., Shakhidoyatov Kh.M., 2014).

Method and results

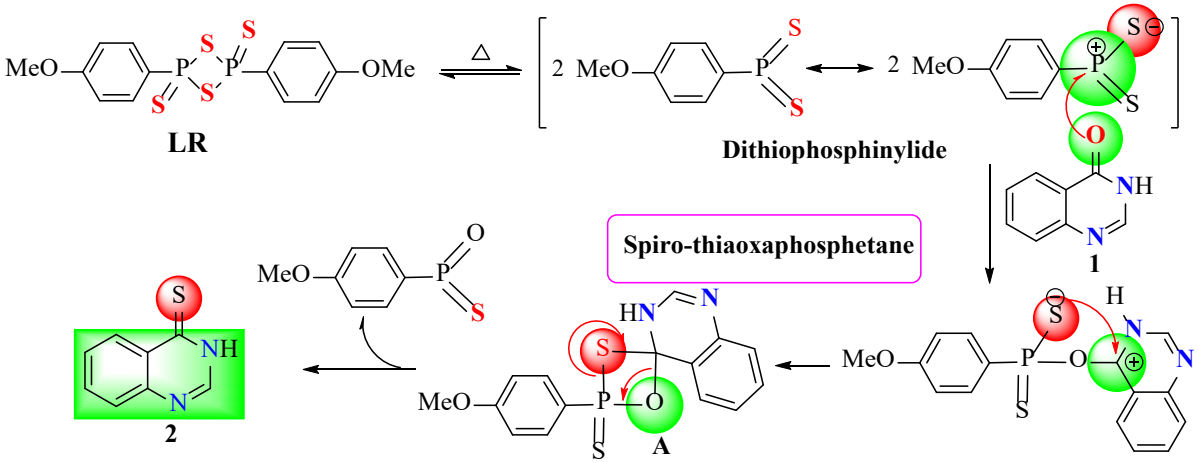
It is known that heterocyclic compounds containing a thione group are of great interest both theoretically and practically. The reason for this is the high synthetic potential of this group and the abundance of biologically active substances among compounds of this class. Therefore, we considered it appropriate to carry out our dissertation studies on a comparative study of selective methylation reactions with quinazolin-4-thione (2) and its various substituted derivatives. Thionation reactions of quinazolin-4-one (1) were carried out in two ways: in the presence of P_2S_5 and Lawesson's reagent (Lawesson's reagent (LR), 2). Reactions with P_2S_5 are carried out by heating the reagents in an equimolar amount at the boiling temperature of m-xylene for 4 hours, and with LR (2) at the boiling temperature of absolute toluene in an inert atmosphere (argon):



1 2 a



The approximate mechanism of the reaction carried out with Lavesson's reagent (LR) can be described as follows:

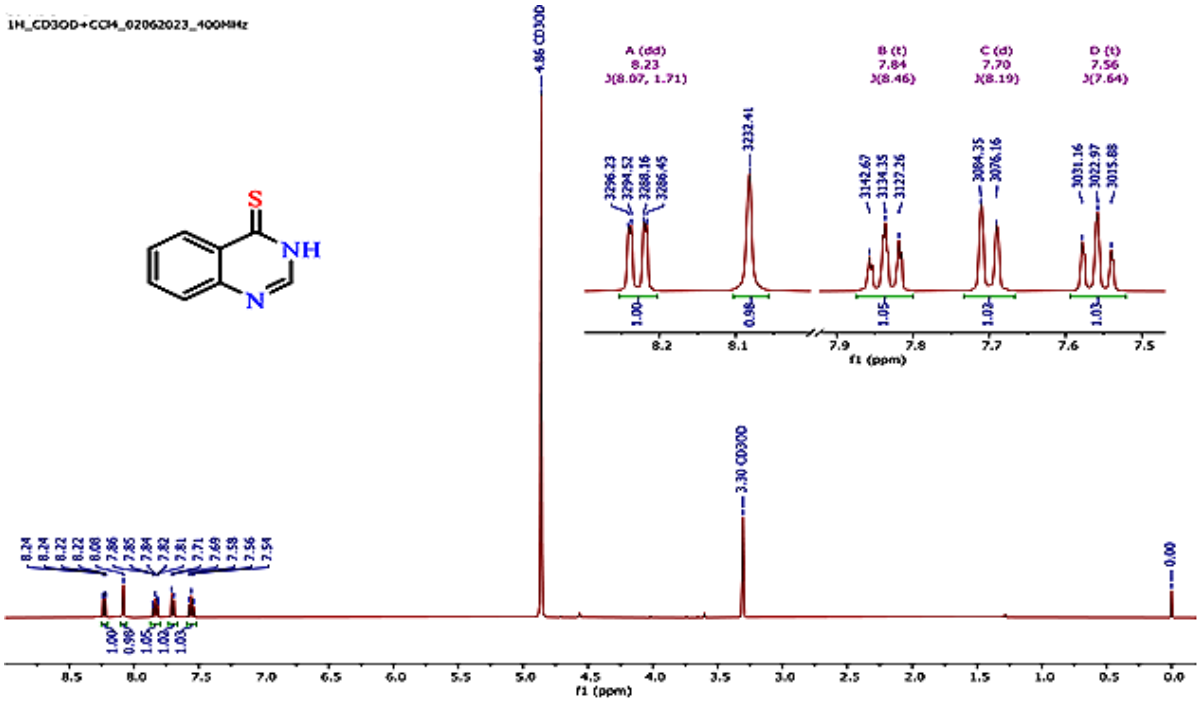


Usually RL is in equilibrium with dithiophosphinylide, which has high reactive activity when heated in an organic solvent. Its reaction with carbonyl compounds can lead to the formation of the intermediate spiro-thioxaphosphetane (A). As a result of thermal cycloreversion (reverse process to cycloaddition!) this cyclic compound (A) leads to the formation of (4-methoxyphenyl)(thioxo)phosphine oxide with a stable P=O bond and the desired thione (2). In the IR spectrum of thione (2) the presence of the absorption frequency corresponding to the C=S bond at 1302 cm^{-1}, in the ^1H NMR spectrum, the one-proton singlet of the NH group at 13.86 ppm, the one-proton doublet signal of the N-2 proton at 8.59 ppm, doublet and triplet signals of 4 aromatic protons of benzene ring appear at 7.62 (t),

7.74 (d), 7.90 (t) and 8.59 (d) ppm (fig-1). In the mass spectrum (M=162), the protonated molecular ion m/z = 163 [M + H]+ was identified, confirming its structure.

Quinazolin-4-one (3) and quinazolin-4-thione (2) contain C=O, C=S, C=N bonds and aromatic ring chromophores. Therefore, their UV spectrum has absorption frequencies specific to these groups. These molecules have absorption frequencies at 220, 311, 330 nm. The longest absorption line at 311 nm corresponds to the n → p* transition. It should be noted that the position of the main absorption lines increases during the transition to the derivatives of quinazolin-4-one (1) and quinazolin-4-thione (2).

Figure 1. *^{1}H NMR spectra of quinazolin-4-thione*



It should be said that the thiolation reactions with LR occur at a relatively low temperature and in a short time, and the product (2) is formed in quantitative yields, as a result, an easy and highly efficient thionation method of quinazolin-4-one (1) was developed.

Experimental part

Quinazolin-4-thione (2). **Method A** (in the presence of P_2S_5): A mixture of 1.46 g (0.01 mol) of quinazolin-4-one (1) and 2.22 g (0.01 mol) of P_2S_5 in 50 ml of absolute m-xylene was refluxed for 4 hours, the mixture was cooled and the reaction mixture was filtered, the filter residue was washed with m-xylene and treated with 7 ml (10%) NaOH. The precipitate was filtered, washed with water and dried under normal conditions, and the substance was recrystallized from hexane. As a result, 1.26 g (78%) of quinazolin-4-thione (2) was obtained, melting point 288–289 °C.

Method B (with Lesson's reagent (LR)): A mixture of 1.46 g (0.01 mol) of quinazolin-4-one and 2.02 g (0.005 mol) of LR in 30 ml of absolute toluene was refluxed for 1 hour (inert gas, Ar). It was cooled to 20–25 °C, the precipitate was filtered and dried. As a result, 1.57 g (97%) of quinazolin-4-thione (2) was obtained, melting point 288–289 °C.

IR (ν, cm^{-1}): 1621 (C=N), 1566 (C=C), 1302 (C=S). ^{1}H NMR (δ, ppm., Gz): 13.86 (1H,.c., NH), 8.59 (1H, d, J = 8.0, H-5), 8.19 (1H, s, H-2), 7.90 (1H, t, J = 7.5, H-7), 7.74 (1H, d, J = 8.0, H-8), 7.62 (1H, t, J = 7.1, H-6). LC–MS: m/z = 163 $[M + H]^+$.

UV spectrum (nm); ethanol 216, 284, 359; ethanol + acid 205, 357; ethanol + acid + base 216, 274, 357; $C_8H_6N_2S$.

Conclusion

A chemical reaction was carried out from quinazolin-4-one with the corresponding quinazolin-4-thione phosphorus V-sulfide and Lavesson's reagent. Reaction mechanisms were studied.

Thionation reactions with Lavesson's reagent occur at relatively low temperature and in a short time, and the product (2) is formed in quantitative yields, resulting in the development of a facile and highly efficient method for thionation of quinazolin-4-one (3).

UF Spectra were first obtained in ethanol, then a shift in the spectral lines was observed when 1–2 drops of 0.1 N HCl solution were added. Then 0.1 N alkali (NaOH) was added and compared with the original spectrum lines, it was found to be compatible.

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Contact: fsaitkulov@bk.ru