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SYNTHESIS AND METHYLATION OF SOME DERIVATIVES OF 2,3-TETRAMETHYLENE-3,4- DIHYDROQUINAZOLIN-4-ONE AND -THIONE

Nasrullaev Azizbek Ozodovich¹, **Tukhtaev Davlat**¹, **Samiev Rajab Akbarovich**¹,
Kodirov Khakim Iskandarzoda², **Karimov Ilyasbek**²,
Zohidov Kasim Akilovich¹, **Saitkulov Foziljon Ergashevich**³

¹ Samarkand State University

² Uzbek-Finnish Pedagogical Institute

³ Tashkent State Agrarian University

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Abstract

Formylation reactions of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (thione) with Vilsmeier-Haack reagent were carried out. It was found that 2,3-tetramethylene-3,4-dihydroquinazolin-4-one yields α -formyl-2,3-tetramethylene-3,4-dihydroquinazolin-4-one, and 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione yields α -hydroxymethylidene-2,3-tetramethylene-3,4-dihydroquinazolin-4-thione.

Keywords: *Vilsmeier-Haack reagent, 2,3-tetramethylene-2,3-dihydroquinazolin-4-one (thione), α -formyl-2,3-tetramethylene-3,4-dihydroquinazolin-4-one, α -hydroxymethylidene-2,3-tetramethylene-3,4-dihydroquinazolin-4-one (thione)*

Introduction

Currently, one of the urgent tasks in the agricultural, medical and veterinary fields is the development of new high-quality and safe for humans and the environment drugs. One of the important approaches to the creation of these drugs is the synthesis of candidate compounds with bioactive groups in their molecules or the introduction of new pharmacophoric groups using appropriate modification methods among heterocyclic compounds, tricyclic substituted quinazolo-

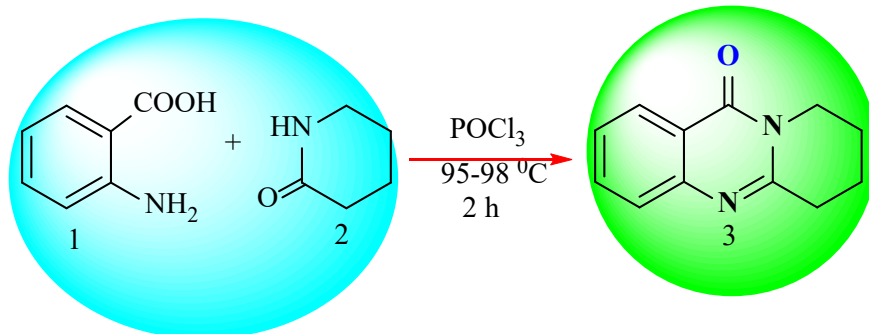
nes and their thioanalogues occupy an important and interesting place. The synthesis of new derivatives of these compounds, the identification of biologically active substances among them will make a significant contribution to the development of chemistry and biology of this class of compounds. In the world, drugs based on tricyclic quinazolones and quinazolinethiones are widely used in agriculture (anthelmintics, stimulants and pesticides) in medicine (against cancer and viruses). Among these compounds, anticho-

linesterase (deoxypeganine) and anticancer drugs (erlotinib, lapatinib, gefitinib, etc.) are especially successfully accepted. Therefore, it is very important to conduct targeted synthesis and chemical transformations of biologically active substances with a pharmacophoric (quinoxaline ring) in the molecule, determine their biological properties, and create promising medicinal and pesticide preparations based on the obtained substances (Gordon A., Ford R., 1976). The aim of this work is to synthesize the reaction of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and -thione using phosphorus pentasulfide reagent (Nasrullaev A. O., Tillaev S. U., Tukhtaev D. B., Gaibullaev Sh. Sh., Kadyrov Kh. I., Zakhidov K. A., 2023; Elmuradov B. Zh., Yakubov U. M., Zhurayev B. B., Tadjimukhamedov K. S., Zakhidov K. A., 2017; Samarov Z. U., Urazov T. S., Urinov I. O.,

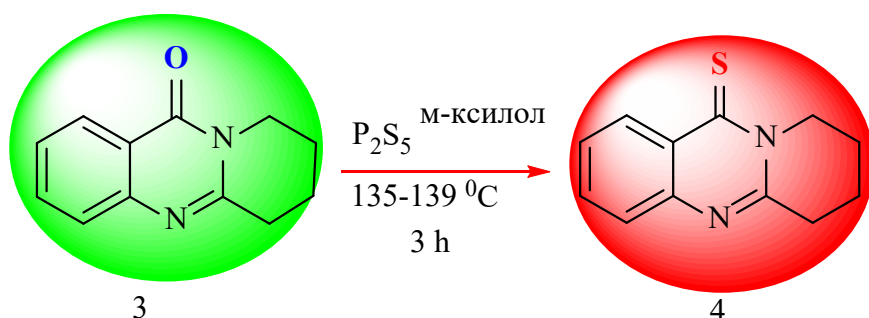
Ravshanov A. S., Zakhidov K. A. 2017; Samarov Z. U., Urinov I. O., Zhavkharov Zh. Zh. 2018; Gaibullaev Sh. Sh., Tukhsanov F. S., Asrorov D. A., Nasrullaev A. O., Tillaev S. U., Zakhidov K. A., 2022; Nasrullaev A. O., Tillaev S. U., Tukhtaev D. B., Gaibullaev Sh. Sh., Zakhidov K. A., 2023).

Methods and results

Continuing the research in this direction, we decided to study the reactions of formylation of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and its thioanalogue, as well as to study the reactions of nucleophilic substitution of the obtained formylation products. The first synthesized compound 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (3) was obtained by condensation of anthranilic acid (1) with valerolactam (2) in the presence of chloroxyphosphorus.



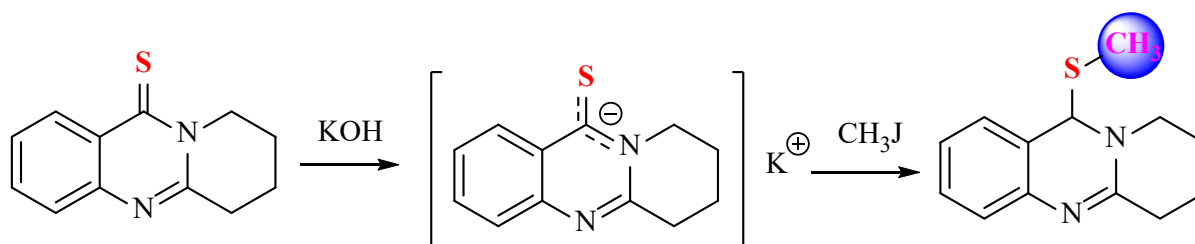
The reaction of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (3) with phosphorus pentasulfide in *m*-xylene yielded the second compound 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione (4)



It should be said that the methylation reactions in the corresponding 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione (4) in relation to 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (3) take place mainly on the sulfur atom

Methylation reactions of 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione (4) in different organic solvents (absolute alcohol, dioxane-1,4, DMFA, DMSO) with three different methylating agents (methyl iodide,

methyl tosylate, dimethylsulfate) was carried out in the presence of an alkaline catalyst (KOH). Reactions were carried out at room temperature for 24 hours or heated at 70–75 °C (85–90 °C) for 3–4 hours.



Experimental Part

To achieve the set goal, we carried out reactions of formylation of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and its thioanalogue using the Vilsmeier-Haack reagent.

For this purpose, the following operations were carried out: Solvents and reagents: m-xylene, DMF, ether, thionyl chloride, chloroform, benzene were anhydrous by the known method (Gordon A., Ford R., 1976). Identification of substances using thin-layer chromatography (TLC) was carried out on Sorbfil (Russia), Whatman UV-254 (Germany) and G60F-254 (Qingdao Haiyang Chemical) plates. Eluents: benzene: methanol = 5: 1 (system A) and benzene: methanol = 3:1 (system B).

Purification of anthranilic acid. 10 g of technical anthranilic acid were placed in a 500 ml flat-bottomed flask and 250 ml of distilled water were poured in. The suspension was boiled until the starting material was completely dissolved. 2–3 g of activated carbon were added to the resulting brown solution and mixed. The undisclosed precipitate was separated by filtering the hot solution under vacuum. When cooled in a water bath with cold water, pure crystals of anthranilic acid precipitated from the filtrate solution. The precipitate was separated by filtration, washed with water and dried in a drying cabinet. Recrystallization was carried out until the required amount of anthranilic acid was accumulated.

Obtaining phosphorus oxychloride.

A mixture of 61 g of benzoic acid and 105 g of phosphorus pentachloride was prepared in a 0.5 l flask. The reaction mixture was left for 30 minutes and boiled. The resulting phosphorus oxychloride was distilled in the range of 105–120 °C. The yield of the product was 70.5 ml (72 g, 94%).

Synthesis of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one. A mixture of 30 g (0.219 mol) of anthranilic

acid and 32.9 g (0.332 mol) of δ -valerolactam was placed in a 250 ml round-bottomed flask equipped with a reflux condenser, and 122 g (73 ml) ($\rho = 1.675 \text{ g/cm}^3$) (0.794 mol) of phosphorus oxychloride were added from a dropping funnel over 1 hour. The reaction mixture was then heated in a water bath (95–98 °C) for 2 hours. The reaction mixture was cooled and poured onto ice. The temperature of the reaction mixture was maintained at 0–2 °C. After complete decomposition of the reaction mixture, it was neutralized with a 25% ammonia solution to pH = 8–9. The alkaline solution was extracted three times with chloroform (3×100 ml), the extract was washed with water and dried over anhydrous sodium sulfate. The extract was filtered and the chloroform was distilled off in vacuum. The yield of the residue was 41.5 g. Recrystallization from the reaction residue yielded 35 g (80%) of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (3).

Synthesis of 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione.

In a 100 ml round-bottomed flask equipped with a reflux condenser and stirrer, a solution of 7.2 g (0.036 mol) of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and 8.3 g (0.037 mol) of phosphorus pentasulfide in 40 ml of m-xylene was prepared. The reaction mixture was boiled at a temperature of 135–139 °C for 3 hours. Then the reaction mixture was cooled, 80 ml (10%) sodium hydroxide solution was added and left for 1 hour. The formed precipitate was filtered, washed with water until neutral reaction and dried. Product yield 5.45 g (70%). Mass spectrum: m/z (I, %): 217([M+1]⁺, 52.6), 201 (10.5), 183 (26.3), 176 (100), 169 (23.7), 162 (10.5), 149 (15.8), 143 (21), 129 (24), 102 (5.3).

Methylation of some derivatives of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and -thione. A solvent (absolute ethanol/1,4-dioxane/DMFA/or DMSO) is poured into a three-necked round-

bottom flask equipped with a reflux condenser, a calcium chloride tube, a thermometer, a separatory funnel, and a mechanical stirrer, and 0.01 mol of 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione and 0.01 mol KOH are added, then a solution of 0.01 mol methylating agent (methyl iodide/methyltosylate/ or dimethylsulfate) in 5 ml solvent is added dropwise. The mixture is heated at room temperature for 24 hours or 4 hours (70–75 °C or 85–90 °C), then decomposed with water, extracted with chloroform, the extract is dried

over dry Na₂SO₄. After removal of the solvent, the residue is purified by recrystallization or column chromatography.

Conclusion

Thus, the direction of the methylation reaction is significantly affected by the nature of the alkylating agent, solvent and temperature. In the case of methylation with methyl iodide, the reaction is selective for the sulfur atom, regardless of the nature of the solvent and temperature.

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Contact: z.qosim2019@g.mail.com