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

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Abstract

In the article a new method of reaction formylation of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (thione) with Vilsmeier-Haack reagent is carried out. It is established that from 2,3-tetramethylene-3,4-dihydroquinazolin-4-one α -formyl-2,3-tetramethylene-3,4-dihydroquinazolin-4-one is formed, and from 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione α -hydroxymethylidene-2,3-tetramethylene-3,4-dihydroquinazolin-4-thione. Reactions of nucleophilic substitution of the obtained products are studied. Representatives of selenium-containing tricyclic quinazolin-4-ones and their thioanalogues with hydrogenated pyridine ring are synthesized for the first time.

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-thione, α -chloromethylidene-2,3-tetramethylene-3,4-dihydroquinazolin-4-one (thione) and their hydrochloride, α -hydroxymethylidene-2,3-tetramethylene-3,4-dihydroquinazolin-4-one (thione)

Introduction

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, anticholinesterase (deoxypeganine) and anticancer drugs (erlotinib, lapatinib gefitinib, etc.)

are especially successfully accepted. Therefore, it is very important to carry out targeted synthesis and chemical transformations of biologically active substances with a pharmacophoric (quinazoline ring) in the molecule, determine their biological properties, create promising medicinal and pesticide preparations based on the obtained substances.

It is known that the formylation reaction is widely used to introduce an aldehyde group in organic chemistry. With the help of the formylation reaction, a highly reactive formyl group ($-\text{CH}=\text{O}$) is introduced into the substrate. The existence of this group in the molecule enables the substrate to react with electrophilic and nucleophilic reagents. Thus, it creates conditions for the synthesis of various derivatives of the original compound. And the existence of compounds with a formyl group in various tautomeric forms (aldehyde, enol, amide, enamine) is of theoretical interest (Gordon A., Ford R., 1976; 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., Til-

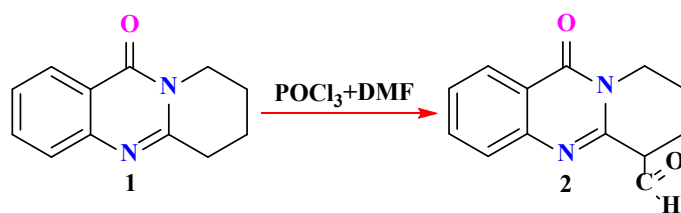
laev S. U., Tukhtaev D. B., Gaibullaev Sh.Sh., Zakhidov K. A., 2023).

Methods and results

The aim of this work is to study the formylation reaction of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and -thione using the Vilsmeier-Haack reagent (phosphorus oxychloride + dimethylformamide), and to study the reaction of the obtained products with nucleophilic reagents.

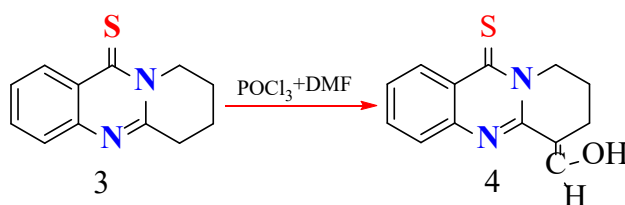
Continuing the research in this direction, we decided to study the formylation reactions of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and its thioanalogue, as well as to study the nucleophilic substitution reactions of the resulting formylation products.

When 2,3-tetramethylene-3,4-dihydroquinazolin-4-one is formylated with the Vilsmeier-Haack reagent (phosphorus oxychloride + dimethyl formamide), α -formylmethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one is formed.



The existence of the obtained product (2) in a stable aldehyde form was proven using chemical methods and physical methods of analysis. In particular, using X-ray structural analysis it was established that the obtained compound exists in the enamine aldehyde form. Unlike 2,3-tetramethylene-3,4-dihydroquinazolin-4-one,

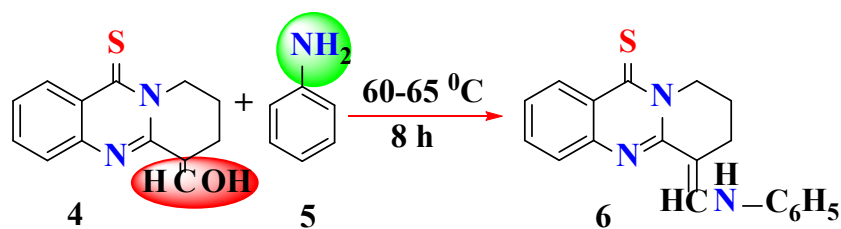
the formylation of its thioanalogue 2,3-tetramethylene-3,4-dihydroquinazolin-4-one with the Vilsmeier-Haack reagent proceeds with the formation of α -hydroxymethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione (3) instead of the expected α -formyl product.



According to physical analysis methods, it was established that the obtained compound (4) exists in the enol form.

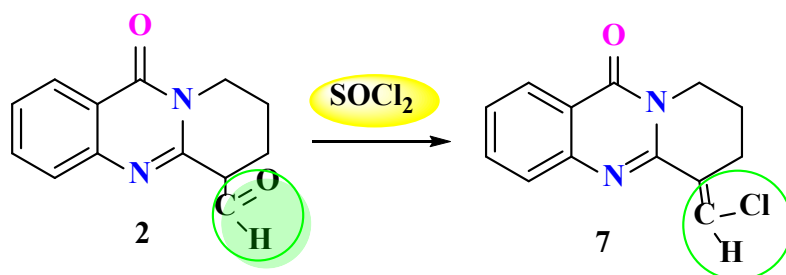
When the obtained α -hydroxymethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione interacted with aniline (5) in an amount of (1: 9) at a tem-

perature of 60–65 °C for 8 hours, α -anilinomethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione (6) was obtained with a good yield (73%).



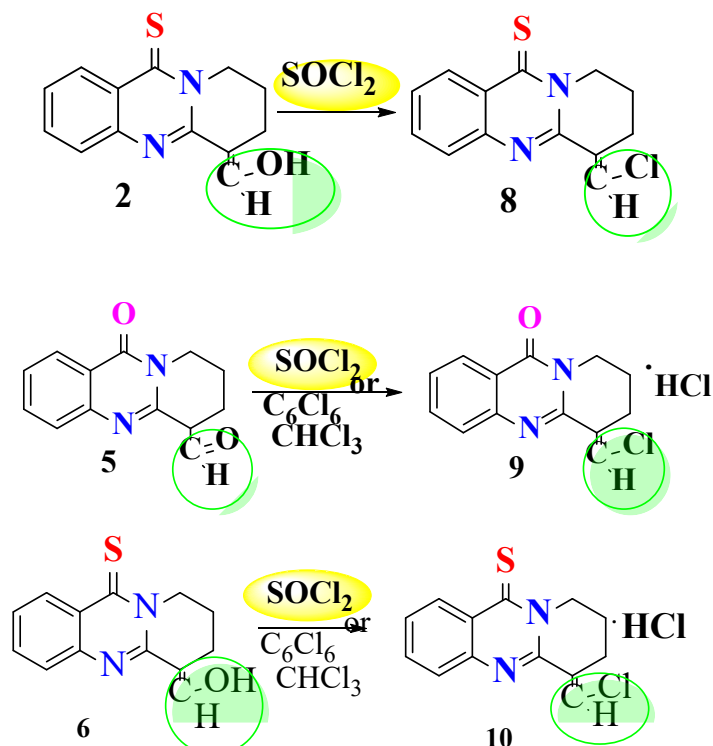
When α -formyl-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one (5) reacts with an excess of thionyl chloride, nucleophilic substitution of the hydroxyl group by

a chlorine atom occurs to form α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one (7).



When α -hydroxymethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one (6) reacts with an excess of thionyl chloride, nucleophilic substitution of the hydroxyl group by a chlorine atom also occurs,

resulting in the formation of α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione (10):

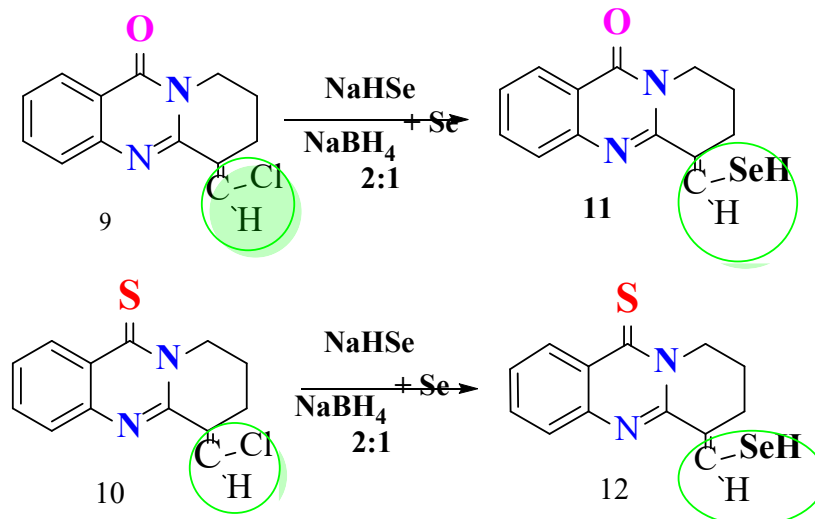


In this case, α -chloromethylidene is formed with good yields. Since the obtained compounds are unstable and can decompose during storage with the release of hydrogen chloride. Therefore, in order for the obtained compound

to be in a stable form, the reactions were carried out with substrate + thionyl chloride in equimolar quantities in absolute solutions of benzene or chloroform with the formation of the corresponding hydrochlorides (9, 10):

Since the chlorine atom in the obtained α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one and -thione (9,10) is very active and can interact with other nucleophilic reagents, we decided to study reactions with sodium hydroselenide. The reaction of α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one (8) and α -chloromethylidene-2,3-tetrame-

thylidene-3,4-dihydroquinazoline-4-thione (9) with sodium hydroselenide (at the time of isolation from sodium borohydride and selenium) gave the corresponding α -hydroselenylmethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one (10) and α -hydroselenylmethylidene-2,3-tetramethylidene-3,4-dihydroquinazoline-4-thione (11) in good yield:



The obtained compounds (11, 12) are the first representatives of selenium-containing tricyclic and quinazolin-4-ones and thioanalogues with a hydrogenated pyridine ring.

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 with the Vilsmeier-Haack reagent. Then, the reactions of nucleophilic substitution of the obtained products with aniline, thionyl chloride and sodium hydroselenide were studied.

Synthesis of α -formyl-2,3-tetramethylene-3,4-dihydroquinazolin-4-one

0.68 ml (8.25 mmol) of dimethylformamide was placed in a 100 ml three-neck flask and cooled in an ice bath. The flask was stirred mechanically for 10–15 minutes. Then, 0.8 ml (8.25 mmol) of phosphorus oxychloride was added dropwise with stirring. Then, 0.5 g (2.5 mmol) of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one was added with stirring for 15 minutes. The reaction mixture was stirred for 1 hour at room temperature and left overnight. On the second day, the reaction mixture was heated in a wa-

ter bath at 95–98 °C for 2 hours, then cooled to room temperature and POCl₃ was decomposed with water. The mixture was neutralized with a saturated sodium acetate solution to pH=7. The formed precipitate was filtered, washed with water and dried. Product yield 0.51 g (90%). IR spectrum (ν , cm⁻¹): 1630 (ν C=N), 1675 (ν C=C), 3300–3600 (ν OH). Molecular weight = 228 (mass spectrometric).

Synthesis of α -hydroxymethylidene-2,3-tetramethylene-3,4-dihydroquinazolin-4-thione

1.49 g (4.6 mmol) of dimethylformamide were placed in a 100 ml three-neck flask and the flask was cooled in an ice bath. The contents of the flask were stirred mechanically for 10–15 minutes. Then, 1.54 g (10 mmol) of phosphorus oxychloride were added dropwise with stirring. Then, 1 g (4.6 mmol) of 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione was added with stirring for 10–15 minutes. The reaction mixture was stirred for 2 hours at room temperature and left overnight. The next day, the reaction mixture was heated in a water bath (95–98 °C) for 2 hours, then cooled to room temperature and decomposed into

5–10 g of ice, neutralized with an ammonia solution (10%) to a weak alkaline medium (pH=8). The yellow precipitate that formed was filtered off, washed with water (3–4 times) and dried. Product yield 0.88 g (78%). IR spectrum (ν , cm^{-1}): 3435 (νOH), 1563 ($\nu\text{C}=\text{N}$), 1488 ($\nu\text{C}-\text{N}$), 1283 ($\nu\text{C}=\text{S}$).

Synthesis of α -(Anilino)methylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione

A solution of 0.2 g (0.82 mmol) of α -hydroxymethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione and 0.7 ml (7.7 mmol) of aniline was prepared in a 100 ml round-bottomed flask. The reaction mixture was heated in a water bath (60–65 °C) for 8 hours and left overnight while cooling. The reaction mixture was treated with ether, the precipitate that fell was filtered off and recrystallized from methanol. The yield of the product was 0.19 g (73%). Tm 152 °C (methanol) Rf=0.85 (A). ^1H NMR (400 MGs, CCl_4+DMSO , δ , ppt J/Gs): 12.3 (1H, c, $J = 7.5$, NH). 7.4–8.1 (4H, m, H-5,6,7,8), 7.35 (1H, d, $J = 7.5$, CH), 6.6–7.3 (5H, m, H-Ph),

Synthesis of α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one

450 mg (1.9 mmol) of α -formyl-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one and 4 ml (56.2 mmol, $\rho = 1.66 \text{ g / cm}^3$) of freshly distilled thionyl chloride were placed in a 100 ml round-bottomed flask and the reaction mixture was heated in a water bath (70–75 °C) for 1.5–2 hours. Cooled, decomposed with distilled water (100 ml). The formed precipitate was filtered, washed 3–4 times with water and dried. Product yield 336 mg (70%). Tm 172 °C (benzene).

Synthesis of α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione

595 mg (2.44 mol) of α -hydroxy-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione and 3.5 ml (48.8 mmol, $\rho = 1.66 \text{ g / ml}$) of freshly distilled thionyl chloride were placed in a 100 ml round-bottomed flask. After 5 minutes, a precipitate began to fall out. The reaction mixture was stirred for another 30 minutes at room temperature. The precipitate was filtered off with chloro-

form and dried. Yield 0.9 g (78.4%). IR spectrum (ν , cm^{-1}): 1567 ($\nu\text{C}=\text{N}$), 1484 ($\nu\text{C}-\text{N}$), 1284 ($\nu\text{C}=\text{S}$), 757 ($\nu\text{C}-\text{Cl}$).

Synthesis of α -hydroselenylmethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one.

In a four-necked round-bottomed flask with a capacity of 250 ml, equipped with a mechanical stirrer, thermometer, reflux condenser, glass gas conductor were placed 25 ml of distilled water, 720 mg (9 mmol) of selenium and the suspension was stirred for 15–20 minutes by passing molecular nitrogen (N_2) through it. Then 430 mg (13.4 mmol) of sodium borohydride were added in portions and the reaction mixture was stirred for 15–20 minutes, after which it was heated in a water bath at 35–40 °C for 1 hour. During this process, the color of the solution changed from colorless to brown-burgundy. Then the reaction mixture was cooled and 1.66 g (7.3 mmol) of α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-one were added. The reaction mixture was stirred for 1 hour at room temperature, then with heating in a water bath (90–95 °C) while passing molecular nitrogen (N_2) through it. The reaction mixture was cooled, the residue was filtered, the filtrate was neutralized with glacial acetic acid. The resulting red precipitate was filtered, washed with a sufficient amount of water, and dried. Product yield 882 mg (45%).

Synthesis of α -hydroselenylmethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione

In a 150 ml four-neck round-bottomed flask equipped with a mechanical stirrer, thermometer, reflux condenser, glass gas conductor were placed 15 ml of distilled water, 235 mg (3 mmol) of selenium and the suspension was stirred for 15–20 minutes by passing molecular nitrogen (N_2) through it. Then 160 mg (4.2 mmol) of sodium borohydride were added in portions and the reaction mixture was stirred for 15–20 minutes. Then it was heated in a water bath (35–40 °C) for 1 hour. During this time, the color of the solution changed from colorless to brown burgundy. Then the reaction mixture was cooled and 0.6 g (2.3 mmol) of α -chloromethylidene-2,3-tetramethylidene-3,4-dihydroquinazolin-4-thione was added. The reaction mixture was stirred for 1 hour at room tempera-

ture, then with heating in a water bath (90–95 °C) while passing molecular nitrogen (N₂) through it. The reaction mixture was cooled, the residue was filtered, the filtrate was neutralized with glacial acetic acid. The resulting red precipitate was filtered, washed with a sufficient amount of water, dried. The yield of the product is 288 mg (41%). IR spectrum (ν , cm⁻¹): 2795 (ν Se-H), 1563 (ν C=N), 1474 (ν C-N), 1283 (ν C=S).

Conclusion

The formylation reactions of 2,3-tetramethylene-3,4-dihydroquinazolin-4-one and its thioanalogue were studied, as well as the nucleophilic substitution reactions of the formed formylation products. The first synthesized compound 2,3-tetramethylene-3,4-dihydroquinazolin-4-one (3) was synthesized in high yield by condensation of anthranilic acid with valerolactam in the presence of chlorooxyphosphorus. For the first time, selenium-containing tricyclic heterocyclic compounds were synthesized.

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