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CONVENIENT SYNTHESIS OF 2-METHYLQUINAZOLIN-4-THIONE BASED ON ANTHRANYL ACID

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Abstract

The synthesis of intermediate products based on anthranilic acid, the reactions of excess amides are justified in the article, and optimal synthesis methods of 2-methylquinazolin-4-thione are well studied. The reaction mechanism was proved on the basis of the corresponding spectra.

Keywords: *Anthranilic acid, intermediate product, synthon, 2-methylquinazolin-4-thione, "structure-activity", 2-methylquinazolin-4-one, N-acetylanthranilic acid, ammonium chloride*

Introduction

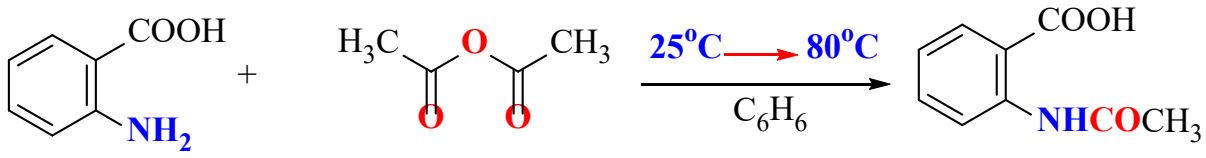
The targeted synthesis of low-toxic biologically active substances based on the study of the "structure-activity" relationship is an important task of organic chemistry. In recent years, priority has been given to the study of substances that are close in structure to natural ones. Anthranilic acid is 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. The search for compounds with a hypoglycemic effect is also relevant. In organic synthesis, anthranilic acid derivatives are used as sources for obtaining various heterocyclic compounds, among which substances with antiviral, antitumor, tuberculostatic and other types of activity have been found (Saitkulov, F.E., Tashniyazov, A.A., Mamadrahimov, A.A., & Shakhidoyatov, K.M., 2014; Sapaev, B., Saitkulov, F.E., Tashniyazov, A.A., & Normurodov, O.U., 2021; Sapaev, B., Sapaev, I.B., Saitkulov, F.E., Tashniyazov, A.A., & Nazaraliev, D., 2022; Saitkulov, F., Farhodov, O., Olisheva, M., Saparboyeva, S., & Azimova, U., 2022; Saitkulov, F.E., Elmuradov, B.J., & Giyasov, K., 2023). Equally

important is the establishment of a quantitative dependence of biological action on structure, since the use of computational methods allows to significantly reduce material costs for the targeted synthesis of biologically active substances (Saitkulov, F.E., Giyasov, K., & Elmuradov, B.J., 2022; Saitkulov, F.E., Elmuradov, B.Z., Giyasov, K., Ruziboev, D.M., & Sultonova, S.X., 2023; Sapayev, B., Saitkulov, F.E., Normurodov, O.U., Haydarov, G., & Ergashyev, B., 2023).

For this purpose, we would like to propose the most convenient and easy method of synthesis of 2-methylquinazlin-4-thione based on anthranilic acid.

Methods and results

N-acetylanthranilic acid is used as the main raw material in the synthesis of 2-methylquinazolin-4-one. In the literature, this compound was synthesized by various methods and the product yield was 65–72%. Anthranilic acid (AA), which we obtained in an equivalent amount, was first completely dissolved in benzene by heating the mixture until boiling (80 °C), then 1 equivalent amount of acetic anhydride was added dropwise. The mixture is cooled and white N-acetylanthranilic acid is obtained:



N-acetylanthranilic acid is formed with a high yield (92%).

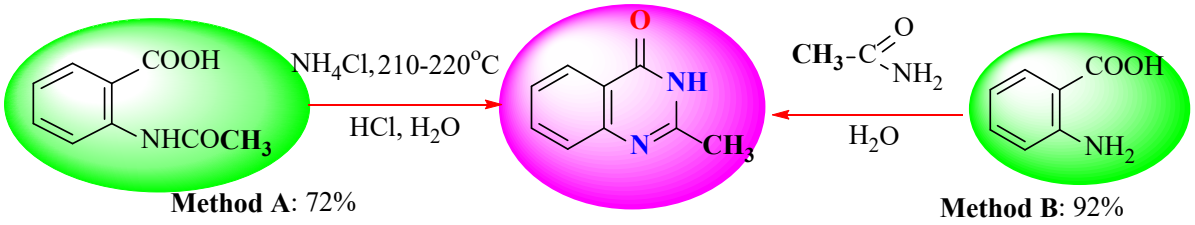
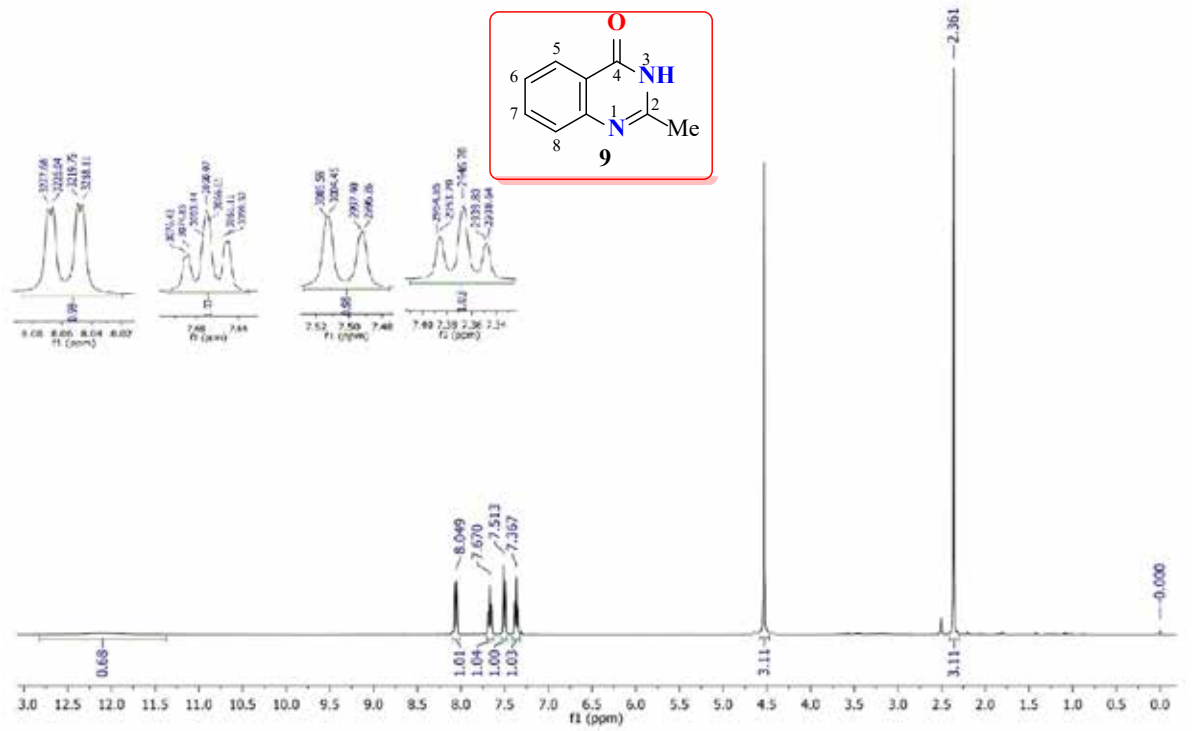


Figure 1. *1P NMR spectrum of 2-Methylquinazolin-4-one.(CD_3OD, 400 MHz)*



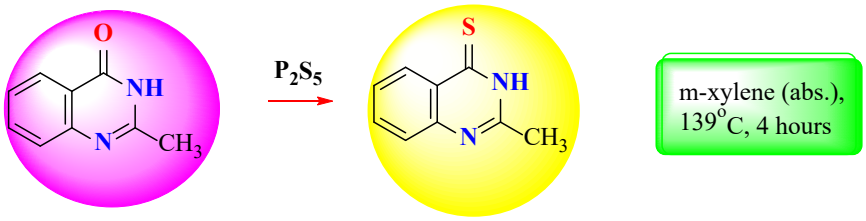
The synthesis of 2-methylquinazolin-4-one needed for research is carried out in two ways (A and B). According to method A: a mixture of initial N-acetylanthranilic acid and ammonium chloride reagents in a ratio of 1:8 is heated at 210–220 °C for 4–5 hours. The yield of 2-methylquinazolin-4-one is 72%:

According to method B: anthranilic acid and acetamide were used as starting raw materials. In this case, a mixture of reagents in a ratio of 1:1 is heated at 210–220 °C for 2 hours. As a result, 2-methylquinazolin-4-one was obtained with a yield of 92%. In the 1H NMR spectrum of the compound, the methyl group is a three-proton singlet (3H, s) at 2.61 parts ppm, 4 aromatic protons in the benzene ring.: 7.33–7.54 ppm. one-proton multiplet at 7.69 ppm. and has one-proton doublets at 7.78 ppm. and one-proton doublet signals at 8.29 ppm., while the N^3-H proton exhibits a singlet signal in the weak region (12.03 ppm.), and these results confirm its structure.

Optimal Synthesis of 2-Methylquinazolin-4-Thione

Theoretically, the introduction of electron-donating or electron-withdrawing substituents into state 2 can affect the direction of the reaction and the yield of the products.

Therefore, in order to synthesize 2-methylquinazolin-4-thion, which has an electron-donating (methyl) group, the reaction of an equimolar mixture of 2-methylquinazolin-4-one and P_2S_5 was carried out. For this, the mixture was boiled in absolute m-xylene for 4 hours.



The reaction mixture was filtered, the residue was washed with m-xylene on the filter and treated with aqueous NaOH (10%). The precipitate was filtered, washed with distilled water and dried.

The structure of the synthesized 2-methylquinazolin-4-thione was confirmed by spectral methods. In particular, in its 1H NMR spectrum, the three-proton singlet signal of the methyl group at 2.48 ppt, the aromatic protons H-5, 6, 7, 8 of the benzene ring are 8.55 (d), 7.54 (t), 7.87 (t), 7.64 (d) ppt. presence of doublet and triplet signals, broad singlet signal of endocyclic NH proton at 13.72 ppt. Also, the absorption frequency of the C=S bond at 1292 cm^{-1} is shown in the IR spectrum of the substance, and in the mass spectrum, the detection of the protonated molecular ion m/z 177 $[M^+H]^+$ confirms its structure.

Excremental part

Method A: a mixture of 0.1 mol of N-acetylanthranilic acid with 0.8 mol of NH_4Cl was heated at 210–220 °C for 4–5 hours with the help of a reverse cooler, and then cooled. It was then dissolved in boiling water, adjusted to pH-7.8 (NH_4OH) and cooled. The precipitate was filtered, dried at 20–25 °C. 15.48 g (72%) of 2-methylquinazolin-4-one was obtained, melting point 231 °C.

Method B: a mixture of 0.1 mol of anthranilic acid and 0.1 mol of acetamide was heated at 210–220 °C for 2 hours using a reverse cooler. The mixture was cooled, the precipitate was filtered and dried. 15.48 g (92%) of 2-methylquinazolin-4-one was obtained, melting point 231 °C. 1H NMR (400 MHz, d, $CDCl_3$): 2.61 (s, 3H), 7.33–7.54 (m, 1H), 7.69 (d, 1H, J=7.8), 7.78 (t, 1H, J=7.7), 8.29 (d, 1H, J=7.8), 12.03 (s, 1H). 13C NMR (75 MHz, d, DMSO-d6): 22.4, 120.5, 127.6, 133.4, 138.5, 147.9, 154.9, 163.8. IR spectrum (KBr, cm^{-1}): 1665 (C=O), 3137 (NH); UV spectrum (nm); ethanol 205, 223, 262; ethanol + acid 209, 207, 279; ethanol + acid + base 207, 271.

2-Methylquinazolin-4-thione. 1.6 g (0.01 mol) of 2-methylquinazolin-4-one was refluxed with 2.22 g (0.01 mol) of P_2S_5 in absolute m-xylene for 4 h. The reaction mixture was filtered, the residue was washed with m-xylene on the filter and treated with 7 mL of NaOH (10%). The precipitate was

filtered off, washed with distilled water and dried at room temperature and recrystallized from hexane. 1.58 g (90%) of 2-methylquinazolin-4-thione was obtained, melting point 218 °C. IR (ν, cm^{-1}): 2977 (CH_3), 1607 (C=N), 1568 (C=C), 1292 (C=S). 1H NMR (d, ppt, Hz): 13.72 (1H, broad s., NH), 8.55 (1H, d, J = 8.1, H-5), 7.87 (1H, t, J = 7.6, H –7), 7.64 (1H, d, J = 8.0, H-8), 7.54 (1H, t, J = =7.6, H-6), 2.48 (3H, s, CH_3).

LC–MS: m/z = 177 $[M^+ H]^+$; UV spectrum (nm); ethanol 204, 224, 263, 315; ethanol + acid 211, 221, 281, 310; ethanol + acid + base 202, 226, 263, 315; $C_9H_9N_2S$.

Conclusion

In order to synthesize 2-methylquinazolin-4-thione with an electron-donating (methyl) group, the reaction of mixtures of 2-methylquinazolin-4-one and P_2S_5 in an equimolar ratio of 1:1, 1:2, 1:3, 1:4 was carried out, in which we consider the optimal ratio to be a mixture of 1:1 ratio.

The methyl group in the second position increases the electron density on the pyrimidine ring, which in turn occurs relatively easily in 2-methylquinazolin-4-thione compared to the corresponding 2(H)quinazolin-4-thione.

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