HETEROCYCLIZATION REACTION OF ANTHRANILIC ACID WITH ALLYL ISOCYANATE

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Annotation: By synthesizing compounds containing various functional groups within the heterocyclic structure, optimal reaction conditions were proposed. To optimize the reaction parameters, a series of experiments were carried out, in which factors such as the type of solvent (DMF, DMSO), the nature of the main heterocyclizing reagent (substituted isocyanates, substituted isothiocyanates), temperature, and reaction time were studied. Among the synthesized compounds, promising samples with high biological activity were identified. It was established that the proposed synthesis method is relatively simple and cost-effective. The structures of the synthesized benzyl derivatives were confirmed using modern physicochemical methods (IR and NMR spectroscopy).

Keywords: substituted isocyanate, substituted isothiocyanate, DMF, DMSO, 3-allyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one, IR, ^{1}H and ^{13}C NMR spectra.

Аннотация: Посредством синтеза соединений, содержащих различные функциональные группы в структуре гетероцикла, предложены оптимальные условия проведения реакций. С целью оптимизации реакционных условий проведены различные эксперименты, в ходе которых изучались такие

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факторы, как тип растворителя (ДМФА, ДМСО), вид основного гетероциклизирующего реагента (замещённый изоцианат, замещённый изотиоцианат), температура и время реакции. Среди синтезированных соединений выявлены перспективные образцы с высокой биологической активностью. Установлено, что предложенный метод синтеза отличается относительной простотой и низкими затратами. Строение синтезированных бензильных производных подтверждено современными физико-химическими методами (ИК, ЯМР-спектроскопия).

Ключевые слова: замещённый изоцианат, замещённый изотиоцианат, ДМФА, ДМСО, 3-аллил-2-тиоксо-2,3-дигидрохиназолин-4(1H)-он, ИК спектры, ^{1}H ЯМР и ^{13}C ЯМР спектры

Annotatsiya: molekula geterohalqasida turli xil funksional guruh saqlagan moddalar sintez qilish orqali optimal reaksion sharoitlar tavsiya qilish. Reaksiya sharoitlarini optimallashtirish maqsadida turli tajribalar o‘tkazish. Erituvchi turi (DMFA, DMSO), asos gertohalqalovchi reagent turi (almashingan izosianat, almashingan izotiosianat), harorat va reaksion vaqt kabi omillar o‘rganish. Sintez qilingan moddalarining biologik faolligi yuqori bo’lgan istiqbolli namunalar aniqlanshdan iborat. Olingan moddaning sintez usuli kam xarajat va nisbatan oson usul ekanligi o’rganilgan. Sintez qilingan benzil hosilalarining tuzilishi zamonaviy fizik kimyoviy usullar (IQ, YMR) yordamida aniqlangan.

Kalit so’zlar. Almashingan izosianat, almashingan izotiosianat, DMFA, DMSO, 3-allyl-2-tiokso-2,3-digdroxinazolin-4(1H)-on, *IR* spektr, ^{1}H NMR, va ^{13}C NMR spektr.

Introduction

Quinazolin-4-one and its derivatives are important heterocyclic compounds that occupy a special place in pharmaceuticals, agrochemistry, and the chemistry of biologically active substances. Their molecular structure underlies a wide range of pharmacological properties, including antimycotic, antiviral [1], antibacterial [2], anti-inflammatory [3], and antiparasitic [3–4] activities. Particularly, the introduction of functional groups into different positions of the quinazolin-4-one nucleus can significantly enhance the biological activity of the molecules. In this regard, the study of quinazolin-4-one benzylation reactions provides an opportunity to create new promising derivatives [1–5,6].

The incorporation of a benzyl group may increase the lipophilicity of molecules, improve their ability to penetrate biomembranes, and positively influence their pharmacokinetic profile. Benzylated derivatives can also serve as intermediates in catalytic reactions and in the synthesis of coordination compounds. Therefore, an in-depth investigation of the mechanism of quinazolin-4-one

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benzylation reactions, optimization of their conditions, and structural characterization of the resulting products is of both scientific and practical significance [6–7].

A review of the literature shows that benzylation of quinazolin-4-one is usually carried out in the presence of strong bases or catalysts. Polar aprotic solvents, such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), are commonly employed. In some cases, ultrasonic or microwave activation is used to increase the efficiency of benzylation reactions. However, these methods do not always provide high selectivity or purity of the resulting products. Moreover, the dependence of the reaction conditions on the molecular structure, the nature, and the position of substituents has not yet been fully investigated.

In the present work, benzylation reactions of quinazolin-4-one were studied under various conditions (temperature, solvent, type and amount of catalyst). The structures of the synthesized derivatives were confirmed by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. Based on the obtained data, the optimal conditions for the reactions were determined, and the preliminary prospects of their biological activity were evaluated [8].

The relevance of this research lies in the synthesis of a new series of quinazolin-4-one derivatives, expanding their potential applications in pharmaceutical and agrochemical industries. The newly obtained benzylated quinazolin-4-ones are considered promising candidates for use as plant growth stimulators, pathogen control agents, or novel antitumor agents [9–10]. Furthermore, a deeper study of the chemical properties of these derivatives creates a basis for future developments in molecular design.

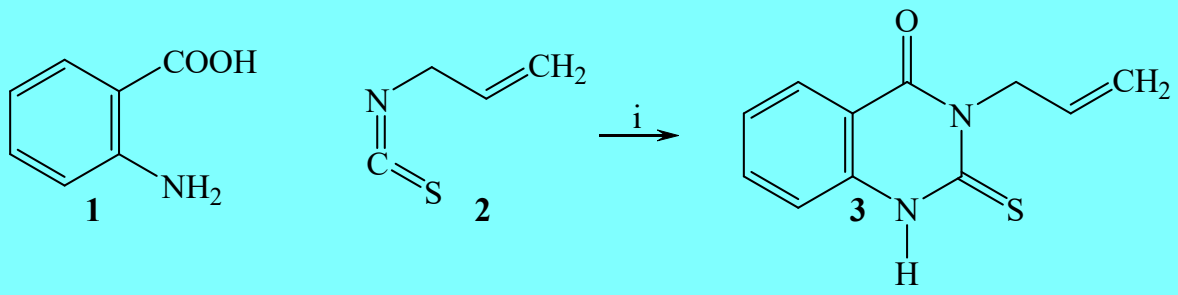
Thus, this paper aims to thoroughly investigate the benzylation reactions of the quinazolin-4-one molecule, to determine their mechanisms, to analyze the structures of the synthesized products, and to assess their practical potential. The results obtained are of great importance for the development of new bioactive substances and for applications in industrial chemistry [11–12].

Method and Materials. Solvents: chloroform, hexane, cyclohexane, benzene, ethyl alcohol, methyl alcohol were dried and purified according to literature data [14]. IQ spectra of the compounds were recorded on a Perkin-Elmer IR -Fourier System 2000 spectrometer on KBr pellets, ^{1}H NMR spectra were recorded on a UNITY-400+ spectrometer (GMDS internal standard, δ -scale) with an operating frequency of 400 MHz, in deuterated solvents (CD_3Cl, DMSO-d6+CCl_4, Piridin-d_5), were checked by thin layer chromatography (YuQX) on «Sorbfil» (Russia) and « Whatman® UV-254» (Germany) plates, and as eluents benzene: acetone - 3:1, chloroform:methanol was used in the ratio of 8:1. The

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liquefaction temperature of the synthesized compounds was determined using «Boetius» (Germany) and «MEL-TEMP» (USA) instruments.

During the study, each reaction experiment was repeated at least three times. The obtained results were recorded as average values. The error margin for each experiment was maintained within the range of 2–3%. Special attention was given to the aforementioned methods to ensure the isolation of synthesized products in pure form and the correct determination of their structures. As a result, high-quality derivatives of allyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one were synthesized, and their structures were thoroughly investigated.



i) DMF, *o*-aminobenzoic acid allyl isocyanate (1:1.1 ratio), 70 °C, 12 h.

Into a 100 ml round-bottom flask were placed 1.37 g (0.01 mol) of anthranilic acid **(1),** 15 ml of DMF, and 0.672 g (0.012 mol) of potassium hydroxide (KOH). The mixture was gently heated and stirred until complete dissolution of the components. After cooling, 2.16 ml (1.09 g, density 1.011 g/ml; 0.011 mol) of allyl isothiocyanate **(2)** was added. The reaction was carried out at 88–90 °C for 12 hours. Upon completion, the reaction mixture was poured into a beaker containing cold water. The precipitated white solid was filtered off. The obtained product — 3-allyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one **(3)** was dried and purified by recrystallization from a DMSO : water mixture (30 : 70). The melting point of the compound was 189–191 °C. R_f = 0.56 (system: benzene : acetone, 1:2).

Conclusion

Based on the reaction of anthranilic acid with allyl isothiocyanate, 3-allyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one was obtained. The melting point and R_f values of the synthesized compound were determined. During the study, each reaction experiment was repeated at least three times. Based on the obtained results, the optimal reaction conditions were established and evaluated. It is planned that these findings will serve as a basis for the synthesis of new compounds containing pharmacophore fragments in place of various functional groups. The synthesized compound was submitted for further investigation of its biological activity, including toxicological studies and determination of toxicity level.

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