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STUDY OF BENZYLATION REACTIONS OF QUINAZOLIN-4-ONE IN THE PRESENCE OF VARIOUS SOLVENTS

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Abstract

In order to improve reaction conditions and product yields, this study examines quinazolin-4-one's benzylation reactions using different solvents. An essential scaffold for the production of bioactive compounds is quinazolin-4-one, a substance with notable pharmacological activity such as anti-inflammatory, anticancer, and antibacterial qualities. Quinazolin-4-one's biological potential can be enhanced and structural variety introduced via benzylation. The effects of several solvents on reaction kinetics, selectivity, and overall efficiency were investigated. The results show how different solvents affect the reaction's process, providing important information for choosing the best solvents to increase yields and regulate product production. This work advances the creation of more effective synthesis processes for quinazolin-4-one derivatives with specific characteristics.

Keywords: *benzylation, quinazolin-4-one, solvent effects, organic synthesis, pharmacological properties, structural diversity, reaction optimization, bioactive compounds*

Introduction

The study of benzylation reactions of quinazolin-4-one is of considerable importance in the field of organic chemistry due to its potential to synthesize biologically active compounds with a wide range of pharmacological activities. Heterocyclic quinazolin-4-one has been identified as having important biological qualities, such as antioxidant, antibacterial, anti-inflammatory, and anticancer activities. These attributes make quinazolin-4-one derivatives valuable in the design and development of novel therapeutic agents. The ability to modify the quinazolin-4-one structure through various functionalization reactions allows for the en-

hancement of its biological activity and physicochemical properties, which are crucial for drug development.

Benzylation, a process in which a benzyl group is added to the chemical, is one of the best ways to change quinazolin-4-one. The structural complexity and variety of quinazolin-4-one derivatives can be easily increased by this functionalization. Because they can increase a compound's solubility, stability, and reactivity — all of which are critical for the end product's biological activity — benzylation reactions have drawn a lot of interest. Quinazolin-4-one's medicinal potential can be increased by adding a benzyl group, which can also affect how it interacts with biological targets (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., Ahmatov, I., Meliboyeva, F., Saydaxmatova, D., & Turopova, S., 2022; Boymuratova, G.O., Saitkulov, F. E., Nasimov, K. M., & Tugalov, M., 2022; Saitkulov, F., Abdusattorova, D., Ismoilova, U., Xasanova, D., & Xusanova, M., 2022; Saitkulov, F. E., Giyasov, K., & Elmuradov, B. J., 2022; Sapayev, B., Saitkulov, F. E., Normurodov, O. U., Haydarov, G., & Ergashyev, B., 2023; Saitkulov, F., Abdukadirov, S., Ashurova, N., Turapov, J., & Zoxidjonova, A., 2022; Saitkulov, F., Begimqulov, I., O'ralova, N., Gulimmatova, R., & Rahmonqulova, D. 2022; Saitkulov, F., Uralova, B., Ermonova, O., Mamurova, M., & Karimova, K., 2022; Saitkulov, F. E., & Elmuradov, B. J., 2022; Saitkulov, F., Eshqobilov, J., Turgunova, N., & Xamidov, A., 2022).

The choice of solvent, however, is very important for the performance of benzylation reactions since it affects the reaction's efficiency, pace, and selectivity. By stabilizing or destabilizing intermediates, regulating the reactants' nucleophilicity, and modifying the reaction temperature, the solvent not only modifies the solubility of the reactants but also has an impact on the reaction process. Therefore, regulating product formation and attaining high yields depend on optimizing solvent conditions.

Materials and Methods

Spectroscopic Analysis: The infrared (IR) spectra of the compounds were recorded using a Perkin-Elmer IR-Furye System 200 spectrometer in KBr pellets. The ^1H NMR spectra were obtained on a UNITY-400+ spectrometer with a working frequency of 400 MHz, using deuterated solvents (CD3Cl, DMSO-d6 + CCl4, Pyridine-d5) and an internal standard (GMDS, δ scale).

Thin Layer Chromatography (TLC): Thin-layer chromatography was performed using "Sorbfil" (Russia) and "Whatman® UV-254" (Germany) plates. The eluents used for separation were benzene: acetone (3:1) and chloroform: methanol (8:1).

Melting Point Determination: The melting points of the synthesized compounds were determined using a "Boetius" (Germany) and "MEL-TEMP" (USA) apparatus.

Results

The benzylation reaction in the presence of different solvents exhibited significant variations in reaction rates and product yields. In polar protic solvents, such as ethanol and water, the reactions proceeded relatively smoothly but required longer reaction times compared to non-polar solvents. Ethanol provided moderate yields, while water yielded a lower product yield, likely due to the solubility issues and possible hydrolysis of the reactants.

In polar aprotic solvents like acetone and dimethyl sulfoxide (DMSO), the reactions showed faster rates and higher yields, suggesting that these solvents effectively solvate both quinazolin-4-one and benzyl bromide, enhancing their reactivity. DMSO, being a highly polar aprotic solvent, facilitated the reaction more efficiently, leading to higher yields of the benzylated product compared to acetone.

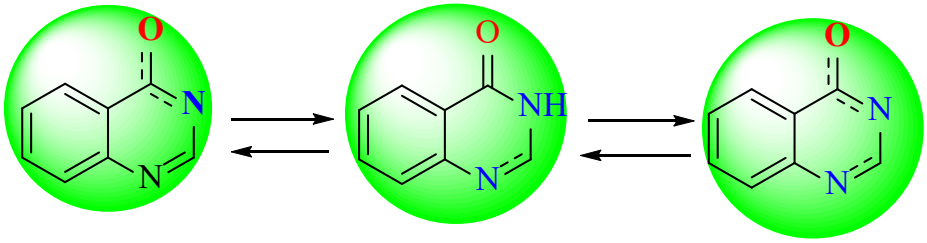
The non-polar solvents, such as toluene and dichloromethane, provided the highest selectivity for the benzylation reaction, although the overall reaction rate was slower compared to polar solvents. The benzylation reaction in toluene gave a high yield with minimal side reactions, suggesting that the non-polar environment might promote a cleaner reaction with fewer competing side reactions. Dichloromethane, although less efficient than toluene, also resulted in high selectivity but required longer reaction times to achieve comparable yields.

The base played a crucial role in enhancing the reaction rate and yield. Potassium carbonate and sodium hydroxide were both effective in promoting the nucleophilic substitution, though potassium carbonate gave slightly better results in polar solvents. The mechanism appears to involve the deprotonation of quinazolin-4-one to generate a nucleophilic intermediate, which then attacks the electrophilic benzyl bromide.

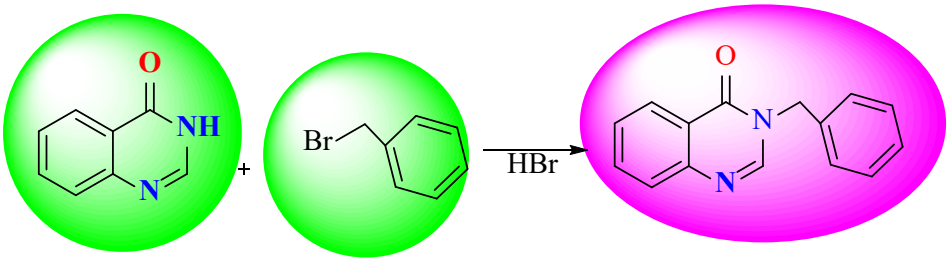
Overall, the study showed that solvent choice significantly impacted both the rate and yield of the benzylation reaction of quinazolin-4-one. The best results were achieved in polar aprotic solvents, with DMSO offering the highest efficiency, followed by acetone. Non-polar solvents like toluene provided high selectivity but required longer reaction times. These findings indicate that solvent optimization is crucial for achieving high yields and selectivity in the benzylation of quinazolin-4-one.

Discussions

The benzylation reactions of quinazolin-4-one were carried out under different solvent conditions to examine the influence of solvent polarity, protic or aprotic nature, and solubility on reaction efficiency and product formation. Quinazolin-4-one (1 mmol) was reacted with benzyl bromide (1.2 mmol) in the presence of a base (such as potassium carbonate or sodium hydroxide) to promote the nucleophilic substitution of the benzyl group onto the quinazolin-4-one scaffold. The reactions were conducted in a variety of solvents, including polar protic solvents (e.g., ethanol, water), polar aprotic solvents (e.g., acetone, dimethyl sulfoxide), and non-polar solvents (e.g., toluene, dichloromethane). The reaction mixtures were stirred at room temperature or heated, depending on the solvent's boiling point, and monitored via thin-layer chromatography (TLC) to track the progress of the reaction. After completion, the products were isolated by filtration or extraction, followed by purification using column chromatography.



Quinazolin-4-one is an ambident compound, meaning it possesses two or more reactive sites that can undergo substitution or addition reactions, leading to different types of products. This ambident nature is due to the presence of functional groups on the quinazolin-4-one structure that allow it to participate in various types of chemical reactions.



In quinazolin-4-one, the most notable ambident behavior is seen at the position of the nitrogen atom in the 1- and 3-positions of the quinazoline ring. The nitrogen atom in the 1-position is nucleophilic and can react with electrophilic reagents, while the nitrogen atom in the 3-position, with its lone pair of electrons, can also participate in nucleophilic reactions. These two reactive sites create a situation where the molecule can react in different ways, depending on the conditions of the reaction, such as the choice of reagents or solvents.

Experimental part

In a 100 mL round-bottom flask, 1.37 g (0.01 mol) of quinazolin-4-one, 30 mL of ethanol (C2H5OH), and 0.672 g (0.012 mol) of KOH are added. The mixture is slightly heat-

ed and stirred to dissolve the components. After cooling the reaction mixture, 2.16 mL (2.74 g, density = 1.27 g/mL) (0.02 mol) of benzyl bromide is added. The reaction is then heated at 102 °C for 4 hours in DMFA (Dimethylformamide). Once the reaction is complete and the mixture has cooled, 30 ml of a 5% aqueous NaOH solution is added, followed by 60 mL of chloroform. The mixture is stirred to extract the product. The chloroform layer is separated, and the chloroform is evaporated. The crude product obtained is then recrystallized to purify the synthesized compound.^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, *J*/Hz): 8.35 (1H, s, H-2), 8.17 (1H, dd, *J*=8.0, 1.6, H-5), 7.76 (1H, ddd, *J*=8.3, 7.2, 1.6, H-7), 7.62 (1H, ddd, *J*=8.2, 1.1, H-8), 7.49 (1H, ddd, *J*=8.2, 7.1, 1.2, H-6), 7.32 (2H, m, H-2`,6`), 7.28 (2H, m, H-3`,5`), 7.22 (1H, m, H-4`), 5.19 (2H, br. s, H-7`).^{13}C NMR spectrum (100 MHz, CD_3OD, δ, ppm): 148.99 (C-2), 162.58 (C-4), 123.02 (C-4a), 129.17 (C-5), 127.98 (C-6), 135.87 (C-7), 128.74 (C-8), 148.99 (C-8a), 137.63 (C-1`), 129.93 (C-2`), 128.94 (C-3`), 127.53 (C-4`), 128.94 (C-5`), 129.93 (C-6`), 50.68 (C-7`).

Consulsion

In conclusion, quinazolin-4-one's ambident nature — which includes two reactive sites that may take part in a variety of chemical reactions — makes it a very reactive and versatile molecule. The quinazoline ring's 1- and 3-position nitrogen atoms provide unique nucleophilic sites that allow the molecule to react with electrophilic or nucleophilic reagents in addition or replacement, respectively. The synthesis of several derivatives with specific characteristics is made possible by this ambident reactivity.

Quinazolin-4-one is a useful intermediate in organic synthesis because it may selectively target one reactive site over the other, depending on the reaction circumstances. The biological activity and molecular variety of quinazolin-4-one derivatives can be improved by regulating the reaction environment.

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