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"According to the review of Associate Professor Q.O. Zohidov from Sharof Rashidov Samarkand State University"

SYNTHESIS OF (E)-7-(4-CHLOROPHENYL)-3-(3,4,5-TRIMETHOXYBENZYLIDENE)-2,3-DIHYDROPYRROLO[2,1-b]QUINAZOLINE-9(1H)-ONE

Annotation

In this study, a three-step synthesis method for 7-(4-Chlorophenyl)-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one was developed, and its structure was confirmed using spectroscopic techniques. The synthesis was performed under acidic conditions in the presence of various solvents, and the optimal reaction parameters were established.

Keywords: Quinazolinone, boronic acids, cesium carbonate, toluene, palladium catalyst, 3,4,5-trimethoxybenzaldehyde, acetic acid.

(E)-7-(4-XLORFENIL)-3-(3,4,5-TRIMETOKSIBENZILIDEN)-2,3-DIGIDROPIRROLO[2,1-b]XINAZOLIN-9(1H)-ONNING SINTEZI

Annotatsiya

Ushbu tadqiqotda 7-(4-Xlorofenil)-3-(3,4,5-trimetoksibenziliden)-2,3-digidropirrol[2,1-b]xinazolin-9(1H)-onning uch bosqichli sintez usuli ishlab chiqildi va uning tuzilishi spektroskopik usullar yordamida tasdiqlandi. Sintez kislotali muhitda va turli erituvchilar ishtirokida amalga oshirilib, optimal reaksiya parametrlari belgilandi.

Kalit so'zlar: Xinazolinon, boronik kislotalar, seziy karbonat, toluol, palladiy katalizatori, 3,4,5-trimetoksibenzaldegid, sirka kislotasi.

СИНТЕЗ (E)-7-(4-ХЛОРФЕНИЛ)-3-(3,4,5-ТРИМЕТОКСИБЕНЗИЛИДЕН)-2,3-ДИГИДРОПИРРОЛО[2,1-b]ХИНАЗОЛИН-9(1H)-ОНА

Аннотация

В данном исследовании был разработан трехстадийный метод синтеза 7-(4-Хлорфенил)-3-(3,4,5-триметоксибензилиден)-2,3-дигидропирроло[2,1-b]хиназолин-9(1H)-она, и его структура была подтверждена с помощью спектроскопических методов. Синтез проводился в кислых условиях в присутствии различных растворителей, и были установлены оптимальные параметры реакции.

Ключевые слова: Хиназолинон, бороновые кислоты, карбонат цезия, толуол, палладиевый катализатор, 3,4,5-триметоксибензальдегид, уксусная кислота.

Introduction. 2-Amino-5-bromobenzoic acid is an important precursor in the synthesis of various heterocyclic compounds. It reacts with lactams in solvents such as benzene, toluene, or 1,4-dioxane, and in some cases, the reactions can proceed in solvent-free conditions at elevated temperatures [1, 2]. This initial step is crucial as it forms intermediate structures necessary for cyclization. Subsequent addition of reagents like thionyl chloride or phosphorus oxochloride facilitates cyclization, forming tri- and tetramethylenequinazolinones [3]. These compounds are key building blocks in pharmaceutical and material science applications.

The synthesis of halogen-containing quinazolin-4-one analogs has gained significant interest due to their diverse biological and chemical properties [4]. Researchers have developed various methods to introduce and modify halogen functional groups within these molecules to enhance their activity. One of the most effective strategies for replacing halogens at the 6-position with carbon-nitrogen (C-N) bonds is through palladium-catalyzed amination reactions [5]. These reactions enable efficient bond formation while maintaining the quinazoline scaffold, making them valuable in medicinal chemistry.

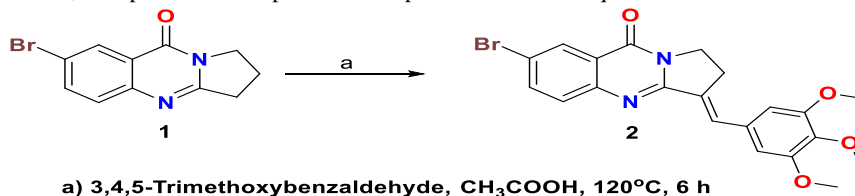
The primary objective in the synthesis of 6-halogen-substituted bicyclic quinazolinones is to develop novel analogs with carbon-carbon (C-C)[6], C-N, and C-O bonds at the 6-position [7-9]. Researchers modify the chemical structure to improve biological activity, aiming to develop new therapeutic agents. Several synthetic methods have been explored for bicyclic quinazolin-4-ones [10], involving reagents such as aryl boronic acids, arylamines, and tricyclic aromatic alkynes. These compounds have shown potential pharmacological applications [11].

Extensive research has been conducted on quinazoline-containing compounds, and this area remains active [12]. In addition to structural modifications, the synthesis of new derivatives often involves base catalysts like potassium carbonate, cesium carbonate, sodium tetrabutoxide, and potassium phosphate. Palladium catalysts, along with ligands such as DavePhos and XantPhos[13], are widely used to optimize reaction conditions and improve yields [2, 5, 7]. Deoxyvasicinones and mackinazolinones have also garnered attention due to their ability to be isolated from natural sources, particularly plants [14-16].

These biologically active compounds hold significant potential for drug discovery and development. Extensive research in this field has led to the synthesis of novel derivatives, highlighting the ongoing importance of quinazoline-based compounds in chemical and pharmaceutical sciences [14, 17-19].

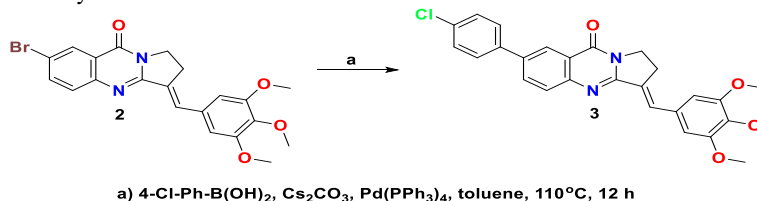
Research methodology. Compound **2** was synthesized by condensing 7-bromo-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**1**) with 3,4,5-trimethoxybenzaldehyde in an acidic medium. The reaction mechanism follows an aldol condensation pathway, where 3,4,5-trimethoxybenzaldehyde is protonated to form an electrophilic center, subsequently reacting with the carbonyl group on the quinazolinone ring to create a new C=C bond. This process results in a conjugated π -electron system.

The synthesis conditions were optimized, yielding the highest amount of product in CH_3COOH at 120 °C for 6 hours. The final product was isolated by precipitation and recrystallized from ethanol. Compound **2** exhibits high reactivity, interacting with various electrophilic and nucleophilic reagents. In particular, it can participate in Suzuki or Sonogashira coupling reactions via the bromine atom. Additionally, the carbonyl group enables condensation with hydrazines, thiols, and amines, forming new heterocyclic systems. Thus, Compound **2** holds potential as a precursor for novel quinazolinone derivatives.



Scheme 1. Synthesis of (E)-7-bromo-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one

Quinazolin-4-one derivative (**3**) was synthesized by reacting 7-bromo-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**2**) with various bases and the tetrakis palladium $[\text{Pd}(\text{PPh}_3)_4]$ catalyst. The Suzuki coupling reaction efficiently functionalized the aromatic rings. To optimize the reaction, different bases (such as cesium carbonate and potassium carbonate) and solvents (including toluene, 1,4-dioxane, and a water-toluene mixture) were tested. Temperature ranges were examined to establish optimal conditions and evaluate reaction efficiency. According to the reaction scheme, the Suzuki coupling was performed in the presence of a borate derivative (phenylboronic acid derivative) and a halogenated quinazolin-4-one substrate, using a palladium catalyst and a base. The optimal conditions were achieved using a water-toluene (3:1) solvent system, Cs_2CO_3 base, and a temperature of 110 °C, resulting in a maximum yield of 71%.



Scheme 2. Synthesis of (E)-7-(4-chlorophenyl)-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one

Below is a more extensive optimization table for the Suzuki coupling reaction. This table examines the effects of various catalysts, bases, and solvents, and helps determine the optimal conditions.

Table 1. Physicochemical properties of compounds **2-4**.

№	Molecular Formula	Temperature (°C)	Yield (%)	R _f
1	$\text{C}_{11}\text{H}_9\text{BrN}_2\text{O}$	163-164	79	0.33 (PE/EtOAc = 3:1)
2	$\text{C}_{21}\text{H}_{19}\text{BrN}_2\text{O}_4$	225-226	78	0.43 (PE/EtOAc = 1:1)
3	$\text{C}_{27}\text{H}_{23}\text{ClN}_2\text{O}_4$	190-191	71	0.36 (PE/EtOAc = 1:1)

Analysis results

General information

All reagents were of analytical grade and were used directly without further purification. All reactions were monitored by analytical thin-layer chromatography. Visualization was performed using 254 nm UV light, and column chromatography was conducted with 100-200 mesh silica gel. Melting points were determined using a Buchi B-540 melting point apparatus. Hydrogen and carbon spectra were obtained using 400 MHz NMR spectroscopy. High-resolution mass spectra were acquired using an AB SCIEX QSTAR Elite quadrupole time-of-flight mass spectrometer.

General procedure for synthesis of compounds **2-3**.

7-Bromo-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**1**) was dissolved in 10 ml of glacial acetic acid, and an equimolar amount of 3,4,5-trimethoxybenzaldehyde was added. The mixture was heated at 120 °C for 6 hours. Upon completion, the reaction mixture was cooled to room temperature, and the precipitated product was filtered. (E)-7-bromo-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**2**) was obtained in 78% yield and purified by column chromatography.

(E)-7-bromo-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**2**). ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 2.3$ Hz, 1H), 7.80 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.77 (t, $J = 2.8$ Hz, 1H), 7.59 (d, $J = 8.7$ Hz, 1H), 6.80 (s, 2H), 4.32 – 4.27 (t, 2H), 3.91 (s, 9H), 3.34 – 3.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.04, 155.96, 153.37, 148.59, 139.34, 137.40, 131.38, 130.87, 130.09, 128.98, 128.95, 122.20, 119.55, 118.55, 107.33, 61.00, 56.22, 44.16, 25.37.

7-Bromo-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (1 mmol) was mixed with 4-chlorophenylboronic acid (1.2 mmol) in toluene solvent. Then, cesium carbonate (Cs_2CO_3) and tetrakis(triphenylphosphine)palladium $[\text{Pd}(\text{PPh}_3)_4]$ were added. The reaction mixture was heated under inert atmosphere at 110 °C with stirring for 12 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After the reaction was

completed, the mixture was cooled to room temperature, then treated with NH_4Cl solution, then extracted with ethyl acetate and filtered. The resulting product was purified by column chromatography (petroleum ether/ethyl acetate = 3:1). As a result, compound 3 was obtained in high purity.

(E)-7-(4-Chlorophenyl)-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (3). ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 2.4 Hz, 1H), 7.97 (dd, J = 8.6, 2.2 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.25 (s, 2H), 6.83 (s, 2H), 4.38 – 4.32 (t, J = 6.1 Hz, 2H), 3.97–3.92 (s, 9H), 3.35 (t, J = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.60, 157.14, 153.10, 153.03, 144.38, 141.00, 139.44, 137.20, 133.36, 133.24, 130.19, 130.14, 129.93, 128.89, 128.85, 128.55, 128.48, 126.31, 121.29, 120.93, 106.95, 106.90, 60.80, 56.27, 56.24, 46.00, 25.32.

Conclusion. In this research work, methods for the synthesis and modification of new quinazolinone-based compounds were studied. The main attention was paid to two important reactions: aldol condensation and Suzuki coupling. The reaction conditions were optimized, and high efficiency was achieved (78% in aldol condensation, 71% in Suzuki coupling). According to the results of the research, it was found that the bromine atom can participate in various coupling reactions, the carbonyl group allows the formation of new heterocyclic systems, and can be a new direction for the synthesis of biologically active substances. The structure of these compounds was confirmed on the basis of physicochemical research methods.

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