HNUE JOURNAL OF SCIENCE
Natural Sciences 2024, Volume 69, Issue 2, pp. 110-117
This paper is available online at http://hnuejs.edu.vn/ns
DOI: 10.18173/2354-1059.2024-0025

SYNTHESIS AND STRUCTURE OF SOME 8-METHOXY-2-ARYLQUINOLIN-7-OL DERIVATIVES FROM VANILLIN

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Received May 24, 2024. Revised June 13, 2024. Accepted June 20, 2024.

Abstract. The key compound, 4-hydroxy-3-methoxy-2-nitrobenzaldehyde (**3**), was synthesized from vanillin by esterification, nitration, and hydrolysis. The aldol condensation reaction of compound **3** was performed with aryl methyl ketones to obtain two chalcones **4a** and **4b**. The reduction reactions of these chalcones **4a** and **4b** were performed using $SnCl_2$ in HCl to obtain two 8-methoxy-2-arylquinolin-7-ol derivatives **5a** and **5b**. The structures of the two quinoline derivatives were confirmed by ^{1}H-NMR, ^{13}C-NMR spectroscopic methods and MS and HRMS spectrometry.

Keywords: vanillin, arylquinolin-7-ol, chalcone.

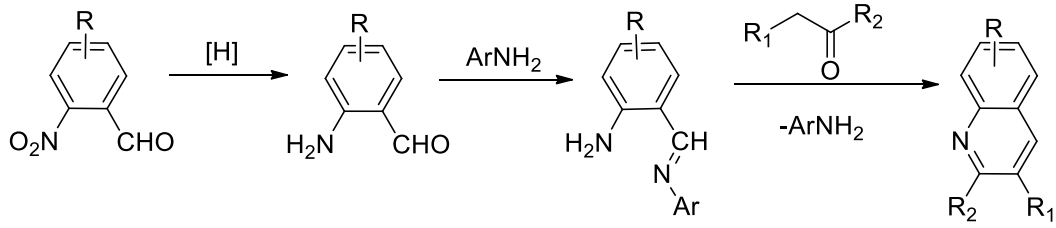
1. Introduction

Quinoline is a class of heterocyclic compounds of paramount importance to humankind. There are a large number of quinoline derivatives occurring in nature. They are compounds with good pharmacological activity and have long been known for their many biological [1] and chemotherapeutic activities [2]. The quinoline framework is found in many antimalarial, antibacterial, and anticancer agents [3]. In addition, quinoline derivatives are also used in dyes and as a photosensitizer [4] and are a valuable precursor for the synthesis of nanostructures and structures with electrical and optical properties [5].

One of the most important uses of 2-arylquinoline derivatives used as medicine is brequinar, a human dihydroorotate dehydrogenase (DHODH) inhibitor, which has been prepared and evaluated as a DHODH inhibitor from the malaria parasite *Plasmodium falciparum* [6]-[10].

Quinoline is synthesized by many different methods from various starting materials, including 2-nitrobenzaldehyde derivatives. Among those, the Friedländer reaction is a prominent method in which the 2-nitrobenzaldehyde derivative is reduced to the 2-

aminobenzaldehyde derivative and then condensed with an aromatic amine and finally cyclocondensed with a carbonyl compound to form a quinoline heterocycle according to the Scheme 1 [11]-[14]:



Scheme 1. The formation of a quinoline heterocycle

In the last two decades, one of the most popular methods to synthesize quinoline derivatives was that the 2-nitrobenzaldehyde derivative was condensed with aryl methyl ketone to produce chalcone and then reduced with different agents to produce the derivative containing the quinoline ring [15]-[19].

Vanillin is a natural compound used as a flavoring additive in food technology. There are many different derivatives synthesized from vanillin and have valuable biological activity. Our studies reported the synthesis of azomethine derivatives [20], chalcone [21], and thiazolidine-4-one heterocycles [22]. In our previous article, the synthesis and structural research of some chalones from vanillin was presented [21]. In this paper, we present the reduction process of two 1-aryl-3-(2-nitrophenyl)prop-2-en-1-one derivatives of vanillin using $SnCl_2$/HCl to form 8-methoxy-2-arylquinolin-7-ol derivatives and confirmation of their structures.

2. Content

2.1. Experiments

2.1.1. Chemicals and laboratory equipment

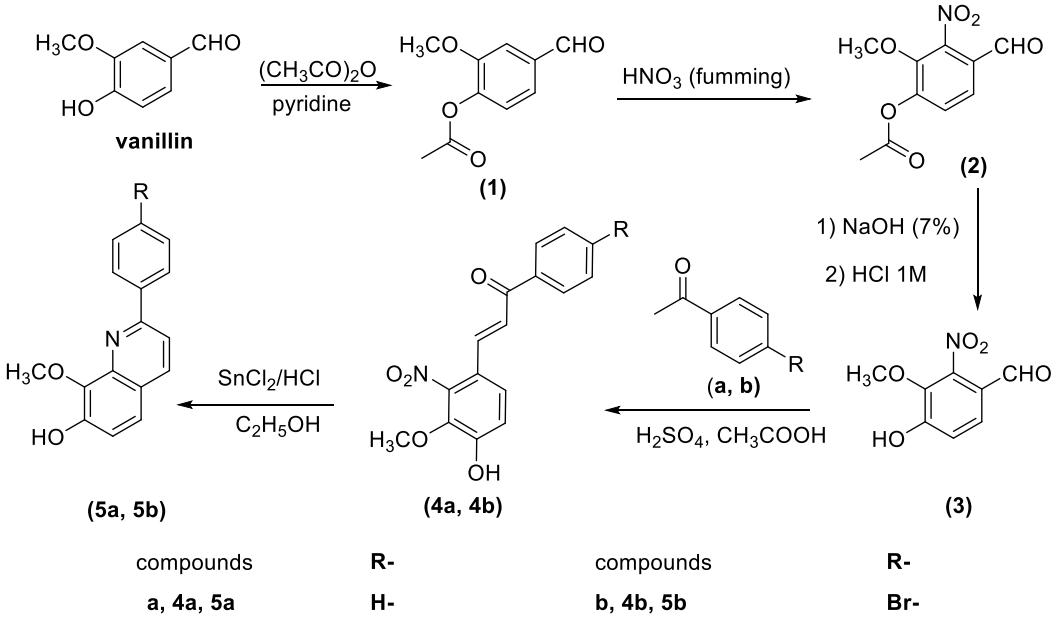
**** Chemicals***

Vanillin, pyridine, HNO_3, NaOH, acetophenone, *p*-bromacetophenone, ethanol, $SnCl_2.2H_2O$, *n*-hexane, and HCl were purchased from China, ethyl acetate was bought from Viet Nam. $(CH_3CO)_2O$ was from the UK.

**** Laboratory equipment***

Magnetic heating stirrer, flasks, condensers, and chromatography columns are required. Thin layer chromatography plates and silicone beads were bought from Merck. An ultraviolet lamp with two wavelengths 254 nm and 365 nm was used. Bruker Avance magnetic resonance spectrometer (Germany) with TMS standard in DMSO-d_6 solvent was used to record NMR spectra. MS was measured on an LC-MSD-Trap-SL and HRMS was measured on a SCIEX X500 QTOF with *+IDA TOF MS/MS* method.

2.1.2. Synthesis of 2-arylquinoline derivatives



Scheme 2. Synthesis of derivatives containing quinolines

2.1.3. Synthesis of chalcone derivatives from vanillin

Chalcones **4a** and **4b** were synthesized from vanillin according to reference [21]. Intermediate products **(1)**, **(2)**, **(3),** and chalcones **4a**, and **4b** were tested with thin-layer chromatography and compared with standards, Scheme 2.

2.1.4. Synthesis of 2-arylquinoline derivatives

General procedure

Tin chloride hydrate ($SnCl_2.2H_2O$, 0.76g (3.5 mmol) and concentrated HCl (0.5 mL) were dissolved in ethanol (10 mL). The resulting solution was stirred and heated at about 70°C to which the chalcone (1 mmol) was slowly added. The reaction solution was refluxed at 70°C for 7 hours. The reaction mixture was cooled to room temperature and added ice to obtain a dark brown mixture. The product mixture was extracted with ethyl acetate (3 x10 mL). The organic layer was dried with anhydrous Na_2SO_4, and then filtered. The solvent of the mother liquid was removed in a vapor to obtain a solid residue. The products were purified with a flash column in eluent of *n*-hexane: ethyl acetate to obtain pure **5a** and **5b**.

Compound 5a: **5a** was as a yellow-brown needle-shaped crystals, eluent for the flash column: *n*-hexane: ethyl acetate = 2 : 1 (v/v), yield = 45.3%.

MS: $[M+1]^+$, m/z = 251.8;^{1}H-NMR (500 MHz, DMSO-d_6, δ (ppm), *J* (Hz)): 4.09 (3H, s), 7.22 (1H, d, *J* = 8.5 Hz), 7.49 (1H, d, *J* = 7.5 Hz), 7.58 (1H, d, *J* = 9.0 Hz), 7.55 (2H, d, *J* = 8.5 Hz), 7.92 (1H, d, *J* = 8.5 Hz), 8.28 (2H, d, *J* = 8.5 Hz), 8.30 (1H, d, *J* = 8.5 Hz), 9.68 (1H, s).

^{13}C-NMR (125 MHz, DMSO-d_6, ppm): 61.2, 119.4, 122.3, 123.3, 127.1, 127.1, 128.8, 128.8, 129.4, 137.2, 139.1, 140.1, 143.0, 154.9.

Compound 5b: **5b** was as a yellow-brown needle-shaped crystals, eluent for the flash column: *n*-hexane : ethyl acetate = 6:1 (v/v), yield = 46.1%.

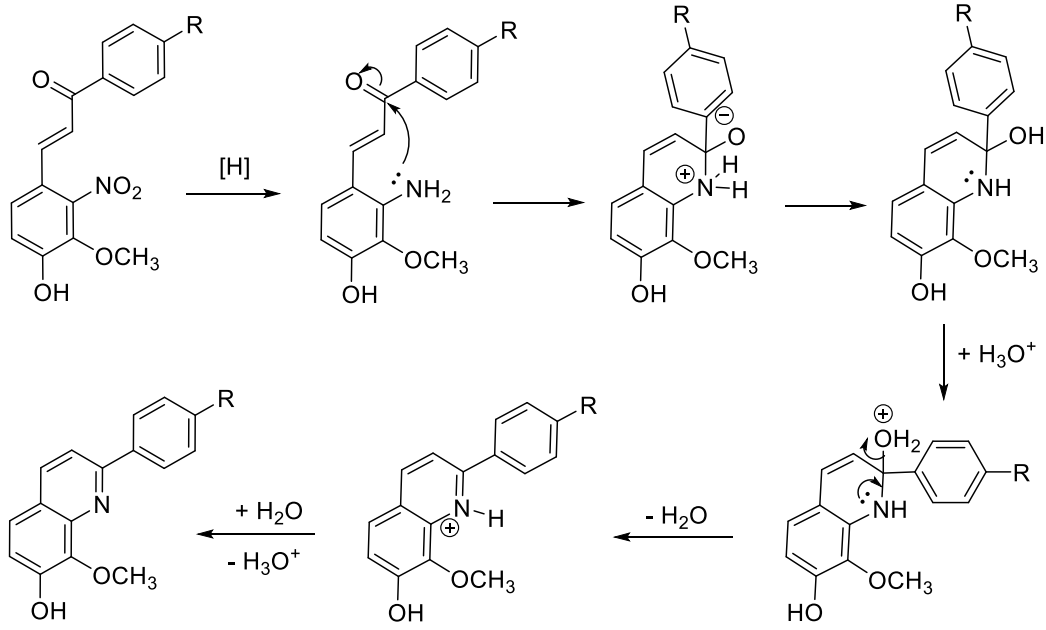
HRMS: calcd. $C_{16}H_{13}{}^{80}BrNO_2^+$, 330.0124, found. 329.9781 and 331.9760, ^{1}H-NMR (500 MHz, DMSO-d_6, δ (ppm), J (Hz)): 4.07 (3H, s), 7.24 (1H, d, J = 8.5 Hz), 7.59 (1H, d, J = 8.5 Hz), 7.75 (2H, d, J = 8.5 Hz), 7.94 (1H, d, J=8.5 Hz), 8.24 (2H, d, J = 8.5 Hz), 8,32 (1H, d, J = 8.5 Hz), 9.71 (1H, s).

^{13}C-NMR (125 MHz, DMSO-d_6, ppm): 61.2, 119.7, 122.4, 123.1, 123.3, 129.0, 129.0, 131.7, 131.7, 137.0, 138.2, 140.0, 142.9, 153.8.

2.2. Results and discussion

The intermediates and two chalcones **4a** and **4b** were synthesized according to the reference [21]. The obtained products were tested by thin-layer chromatography and the R_f of the products coincided with R_f of known compounds.

Quinoline heterocycles were synthesized by reduction of the 3-(2-nitroaryl)-1-arylprop-2-en-1-one derivative with the selected reducing agent $SnCl_2$/HCl due to its selective reduction of -NO_2 group only. Therefore, the proposed reduction mechanism is performed in Scheme 3. Initially, the -NO_2 group is reduced in an acidic medium to form a primary amine, then the primary amine condensed with a ketone to form an aromatic imine called a quinoline heterocycle:



Scheme. 3. Proposed mechanism of reduction-cyclization of quinoline derivative

When R = H, product **5a** is obtained in 45.3% yield. When R = Br, product **5b** is obtained in 46.1% yield. Previous authors used basic agents such as N_2H_4, Sn/NH_4Cl, etc., so most of the products obtained were quinoline *N*-oxide or mixtures with quinoline. Meanwhile, the Zn/H_2O agent required harsh conditions of pressure and temperature. On the other hand, the agent $SnCl_2$/HCl is a selective reducing reagent that only reduces NO_2 in acidic environments, so it rarely stops at intermediate products, therefore byproducts will not be generated.

MS spectra were used to confirm the molecular formula of compounds **5a** and **5b**. Compound **5b** recorded the HRMS spectrum and the results are presented in Figure 1.

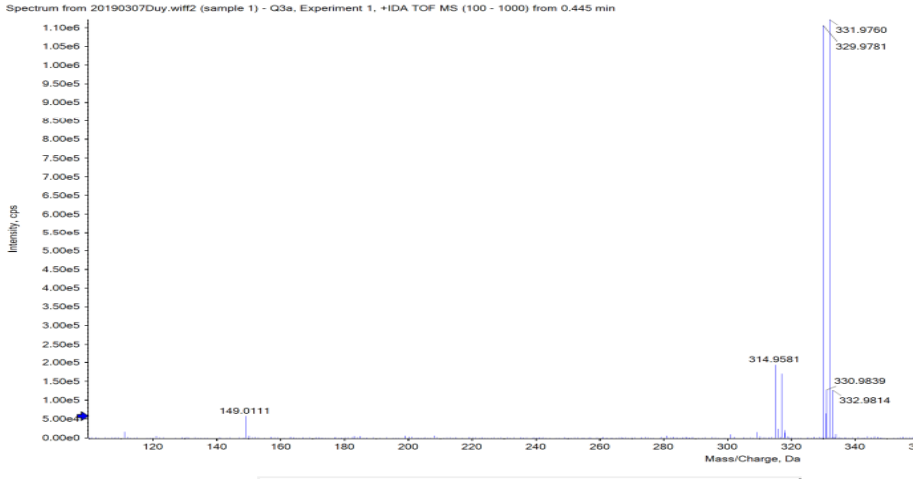


Figure 1. HRMS spectrum of compound 5b

On the high resolution mass spectrum of **5b**, there is a pseudomolecular ion peak $[M+H]^+$ with m/z = 329.9781 and an isotopic pseudomolecular ion peak $[M+H+2]^+$ with m/z = 331.9760. Two pseudomolecular ion peaks with nearly equivalent intensity are consistent with monobromine derivatives with isotopes ^{79}Br and ^{81}Br. The molecular formula of the compound is $C_{16}H_{12}NO_2Br$, consistent with the above pseudomolecular ion peaks.

The pseudomolecular ion peak $[M+H]^+$ in the +MS spectrum of compound **5a** has *m/z*=251.8, consistent with the compound with the molecular formula $C_{16}H_{13}NO_2$ with M = 251.

*** ^{1}H-NMR spectrum**

^{1}H-NMR spectrum analysis of **5a** and **5b** are presented in Figure 2.

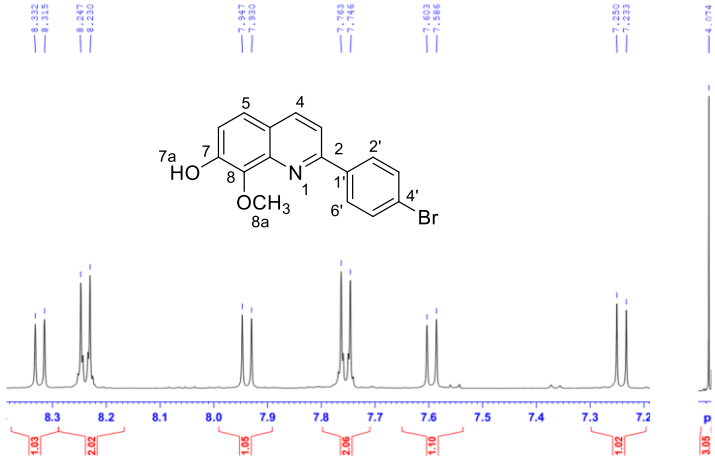


Figure 2. ^{1}H-NMR spectrum of compound 5b

The ^{1}H-NMR spectrum of compounds **5a** and **5b** has spectral peaks consistent with the resonance signals of protons in the expected formulas (number of peaks, chemical

shift, spectral peak intensity, and multiplicity). In particular, the spectral peak characteristic of the resonance signal of the unsaturated *α,β*-ketone group no longer exists.

Figure 2 is the ^{1}H-NMR spectrum of **5b** showing 8 spectral peaks, of which: the characteristic peak of the resonance signal of the -OCH_3 group has δ = 4.07 ppm (3H, s). The typical peak for the resonance signal of the -OH group has δ = 9.71 ppm (1H, s). The 6 peaks represent resonance signals of aromatic protons with δ ranging from 7.24 ppm to 8.32 ppm.

Compound **5a** has 9 spectral peaks, of which: the peak characteristic of the resonance signal of the -OCH_3 group has δ = 4.10 ppm (3H, s). The typical peak for the resonance signal of the -OH group has δ =9.69 ppm (1H, s). The 7 peaks represent resonance signals of aromatic protons with δ ranging from 7.23 ppm to 8.30 ppm.

Thus, ^{1}H-NMR spectrum analysis shows that the two compounds **5a** and **5b** are quinoline derivatives as expected.

^{13}C-NMR spectrum results are presented in Figure 3.

Figure 3 is the ^{13}C-NMR spectrum of compound 5b with 14 peaks representing 14 equivalent carbon groups, in which the peak with δ=61.2 ppm is the resonance signal of carbon of group -OCH_3 at position 8. There are 13 peaks with chemical shifts in the region from 115.3 ppm to 153.8 ppm, which are the resonance signal of aromatic carbons of the quinoline nucleus and phenyl nucleus. These peaks are consistent with the expected formula.

Similar to compound **5b**, compound **5a** also has spectral peaks consistent with the expected formula.

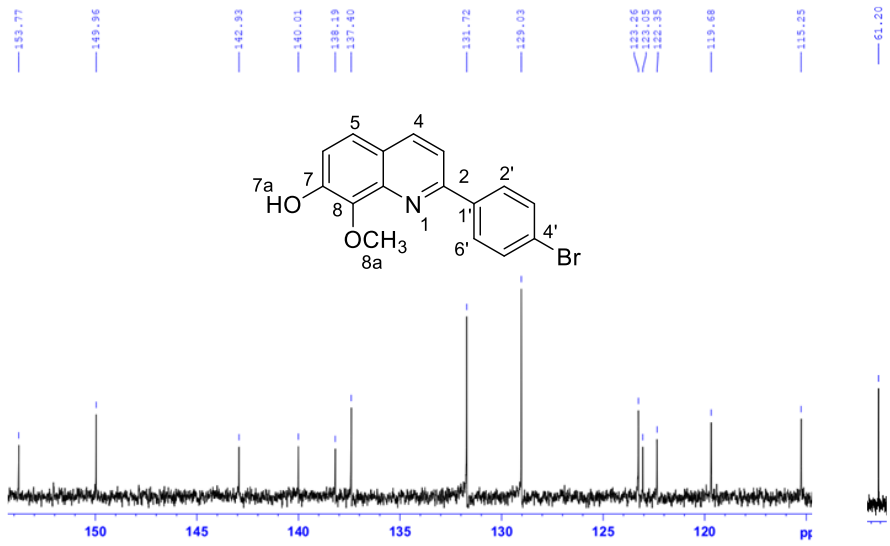


Figure 3. ^{13}C NMR spectrum of compound 5b

The results of the ^{13}C-NMR spectrum analysis confirmed that the two formed compounds are aryl quinoline derivatives.

Thus, based on the reaction diagram and the results of MS, HRMS, ^{1}H-NMR, and ^{13}C-NMR spectra, it has been confirmed that compound **5a** is 8-methoxy-2-phenylquinolin-7-ol and compound **5b** is 2-(4-bromophenyl)-8-methoxyquinolin-7-ol.

3. Conclusions

Two new quinoline derivatives 8-methoxy-2-phenylquinolin-7-ol (**5a**) and 2-(4-bromophenyl)-8-methoxyquinolin-7-ol (**5b**) were synthesized from vanillin via a 5-step route in moderate reaction yields. Their structures were confirmed by MS, HRMS, ^{1}H-NMR, and ^{13}C-NMR spectra.

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