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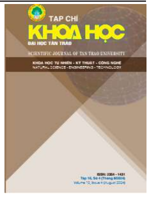

SYNTHESIS OF NOVEL 1,3,4-OXADIAZOLE DERIVATIVES INCORPORATING A BENZOFURAN MOIETY

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Abstract:

To further explore the highly bioactive properties of benzofuran and 1,3,4-oxadiazole derivatives, the synthesis of 1,3,4-oxadiazole derivatives containing a benzofuran moiety was undertaken. A straightforward and efficient four-step synthetic method was employed, utilizing readily available starting materials to prepare novel functionalized 1,3,4-oxadiazole derivatives. As a result, two 1,3,4-oxadiazole derivatives were obtained with moderate yields. The structures of all synthesized compounds were characterized using spectroscopic techniques.

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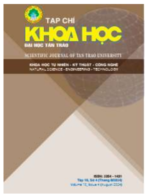

TỔNG HỢP CÁC DẪN XUẤT MỚI CỦA 1,3,4-OXADIAZOLE CHỨA NHÓM BENZOFURAN

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Từ khóa:

Benzofuran, 1,3,4-oxadiazole, hydrazone, phân tử lai.

Tóm tắt

Để tiếp tục nghiên cứu các hoạt tính sinh học đầy tiềm năng của các dẫn xuất benzofuran và 1,3,4-oxadiazole, quá trình tổng hợp các dẫn xuất 1,3,4-oxadiazole chứa nhóm benzofuran đã được thực hiện. Một phương pháp tổng hợp đơn giản và hiệu quả gồm bốn bước đã được áp dụng, sử dụng các nguyên liệu ban đầu dễ kiếm nhằm tạo ra các dẫn xuất 1,3,4-oxadiazole mới với chức năng hóa học đa dạng. Kết quả đã tổng hợp được hai dẫn xuất 1,3,4-oxadiazole với hiệu suất trung bình. Cấu trúc của các hợp chất được xác định bằng các phương pháp phổ.

1. Introduction

Benzofuran heterocycles are key structural components in many natural compounds and has attracted significant interest from researchers due to its diverse biological activities, including antifungal, antibacterial, antiviral, anticancer, and anti-HIV properties. Moreover, compounds incorporating 1,3,4-oxadiazole, and their derivatives are significant due to their wide range of biological activities, particularly in medicine and pharmacology (e.g., antibacterial, antifungal, anti-inflammatory, analgesic, anticancer, antidiabetic, cardiotonic, anti-HIV, antitubercular activities) and their extensive applications in various sectors of life and industry. Therefore, the aim of this study is to synthesize novel hybrid molecules of 1,3,4-oxadiazole derivatives incorporating a benzofuran scaffold.

2. Bibliographic research

Compounds containing benzofuran rings often exhibit strong biological activities, such as antifungal, antibacterial, antiviral, anticancer, and anti-HIV properties (Ji et al., 2017; Karatas, Koca, Kara, & Servi, 2006; Kirilmis et al., 2008).

Derivatives of 1,3,4-oxadiazole have garnered significant attention due to their notable chemical and biological properties. These compounds exhibit a wide range of biological activities, including antimicrobial (de Oliveira et al., 2012), anticonvulsant (Rajak et al., 2010), analgesic (Husain, Ahmad, Alam, Ajmal, & Ahuja, 2009), antitumor (Puthiyapurayil, Poojary, Chikkanna, & Buridipad, 2012; Savariz et al., 2010) making them valuable scaffolds for the development of new pharmaceuticals. In recent years, various methods for synthesizing 1,3,4-oxadiazole derivatives have been developed, with the use of carbohydrazide as a precursor being one of the most established approaches. This synthetic strategy has been employed to prepare several compounds, such as naphtha[2,1-*b*]furan-2-carboxylic acid (Abdel-Aal, El-Sayed, & El-Ashry el, 2006), 4-pyrrol-1-yl benzoic acid (Joshi, Vagdevi, Vaidya, & Gadaginamath, 2008), …

Given its structural versatility and potential for generating numerous derivatives or combinations with other frameworks, the exploration of synthesizing 1,3,4-oxadiazole derivatives remains a promising and expanding field (Shaveta, Mishra, & Singh, 2016). Accordingly, the objective of this research is to synthesize novel hybrid molecules of 1,3,4-oxadiazole derivatives incorporating the benzofuran moiety. In this study, a four-step synthetic route starting from salicylaldehyde was successfully developed.

3. Materials and methods

3.1. General

All chemicals were purchased from Acros and Sigma-Aldrich while organic solvents were purchased from the commercial source and were used without any further purification. The NMR spectra were acquired using the Bruker Avance III spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are expressed in parts per million (ppm) and reported relative to the residual solvent signal as an internal reference. High resolution mass spectra (HRMS) were recorded using a Bruker MicroOTOF-Q II mass spectrometer in electrospray ionization (ESI) mode. The melting points were determined using a Gallenkamp digital Melting point apparatus 5A-6797 with a rate of heating of 2°C/min. Reactions were monitored using thin layer chromatography (TLC) on silica gel plates (silica gel 60 F_{254}, Merck), visualized under ultraviolet light (254 nm). Column chromatography was performed on silica gel Merck 60 (230–400 mesh) purchased from HiMedia Laboratories Pvt. Ltd. (India).

3.2. Synthesis of ethyl benzofuran-2-carboxylate (1)

A solution of salicylaldehyde (24.4 g, 0.2 mol) and K_2CO_3 (82.2 g, 0.6 mol) in DMF (200 mL) was stirred at room temperature for 30 minutes. Then, ethyl chloroacetate (24.5 g, 0.2 mol) was slowly dropped into that solution while the mixture was stirred during two hours at 80‒90 °C. The color of the solution was changed from yellow to green, dark green, brown and finally black. Consequently, that solution was poured into crushed ice and was extracted with ethyl acetate (100 mL × 3). Then, the combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford ethyl benzofuran-2-carboxylate **(1)** (30.8 g, 81%).

Dark yellow liquid; ^{1}H–NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.75 (*dd*, *J* = 8.0 Hz, 1.2, 1H), 7.67 (*dd*, *J* = 8.4, 1.2 Hz, 1H), 7.65 (*s*, 1H), 7.47 (*ddd*, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.31(*ddd*, *J* = 8.0, 7.3, 1.2 Hz, 1H), 4.32 (*q*, *J* = 7.1 Hz, 2H), 1.30 (*t*, *J* = 7.1 Hz, 3H); ^{13}C–NMR (125 MHz, DMSO-d_6) δ_C (ppm): 158.6, 155.1, 145.1, 127.7, 126.6, 123.8, 123.0, 113.8, 111.9, 61.1. These data are consistent with that reported in the literature. (Parekh et al., 2011).

3.3. Synthesis of benzofuran-2-carbohydrazide (2)

A solution of ethyl benzofuran-2-carboxylate **(1)** (9.5 g, 50 mmol) in absolute ethanol (30 mL) was slowly continuously added by hydrazine hydrate 50% (15.0 g, 150 mmol) under reflux for four hours. Upon completion, the reaction mixture was kept at 2−4 °C overnight to solidify the product. Consequently, the separated solid was filtered, washed with cold ethanol and then recrystallized in absolute ethanol to give benzofuran-2-carbohydrazide **(2)** (6.7 g, 76%).

White crystals, melting point 190−194 °C (lit. (Parekh et al., 2011) 190−194 °C); ^{1}H–NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.01 (*s*, 1H), 7.76 (*dd*, *J* = 8.0, 0.9 Hz, 1H), 7.63 (*dd*, *J* = 8.4, 0.9 Hz, 1H), 7.51 (*s*, 1H), 7.44 (*ddd*, *J* = 8.4, 7.3, 0.9 Hz, 1H), 7.32 (*ddd*, *J* = 8.0, 7.3, 0.9 Hz, 1H), 4.58 (*br*, 2H); ^{13}C–NMR (125 MHz, DMSO-d_6) δ_C (ppm): 157.8, 154.2, 148.4, 127.0, 126.6, 123.6, 122.6, 111.7, 108.7. These data are consistent with that reported in the literature.(Parekh et al., 2011)

3.4. General procedure for the synthesis of benzylidenebenzofuran-2-carbohydrazide derivatives (3)

Compound **2** (1.76 g, 10 mmol) and benzaldehyde derivatives (10 mmol) were dissolved in a suitable amount of absolute ethanol with some drops of glacial acetic acid. This solution was refluxed for 2 hours. The reaction mixture was monitored by TLC. Consequently, it was cooled to room temperature and the resulted solid was collected by filtration and recrystallized in ethanol to give corresponding products **3a**–**b**.

N'-(4-chlorobenzylidene)benzofuran-2-carbohydrazide (**3a**): 2.51 g, yield: 84%, white needle crystals; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H (ppm): 12.26 (s, 1H), 8.52 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.74 – 7.79 (m, 3H), 7.72 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H) 7.46 – 7.54 (m, 1H), 7.38 (dd, J = 8.0, 7.7 Hz, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C (ppm): 155.2, 154.9, 148.3, 147.8, 135.2, 133.6, 129.5, 129.3, 127.8, 127.4, 124.4, 123.4, 112.4, 111.5.

N'-(4-hydroxybenzylidene)benzofuran-2-carbohydrazide (**3b**): 2.52 g, yield: 90%, white crystals; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H (ppm): 11.97 (s, 1H), 9.97 (s, 1H), 8.42 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.69 – 7.71 (m, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.50 (dd, J = 7.8, 7.4 Hz, 1H), 7.36 (dd, J = 7.7, 7.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C (ppm): 159.6, 154.4, 154.3, 149.0, 148.2, 129.0, 127.1, 127.0, 125.1, 123.8, 122.8, 115.7, 111.9, 110.5.

3.5. General procedure for the synthesis of 1-(5-(benzofuran-2-yl)-2-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one derivatives (4)

Compound **3** (5 mmol) was liquefied in acetic anhydride and this mixture was refluxed for 4 hours. At the completion of reaction, the reaction mixture was poured into cold water and the separated solid was collected and recrystallized from the mixture of DMF and ethanol to give corresponding products **4a–b**.

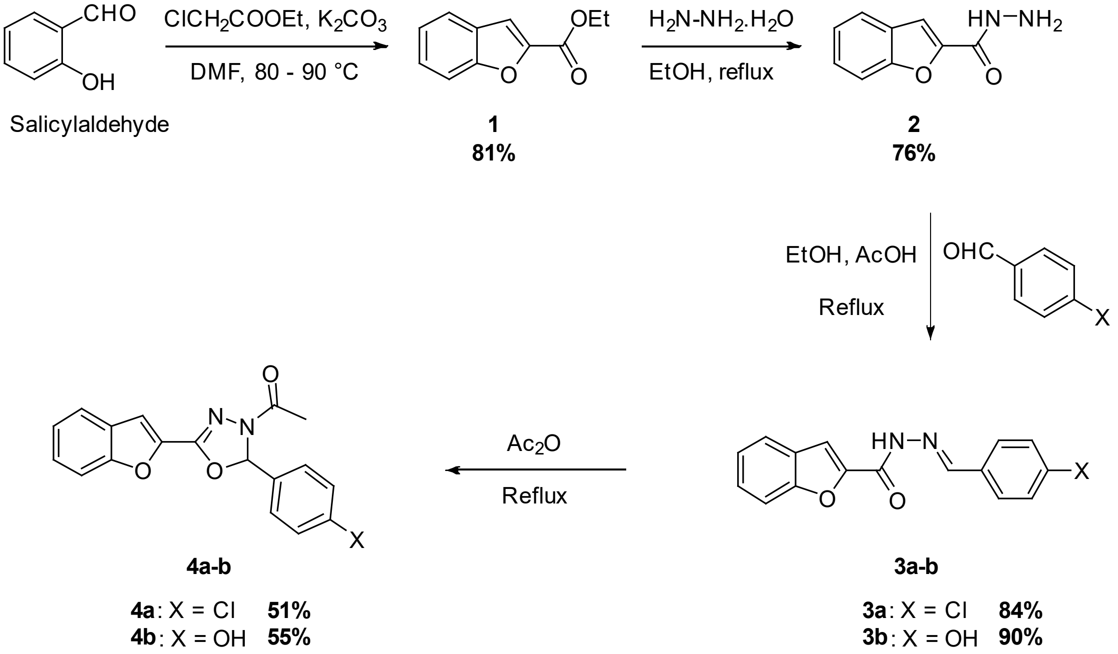
1-(5-(benzofuran-2-yl)-2-(4-chlorophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one (**4a**): 870 mg, yield: 51%, white crystals; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.76 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.40 – 7.58 (m, 4H), 7.48 – 7.52 (m, 1H), 7.37 (dd, J = 7.8, 7.4 Hz, 1H), 7.26 (s, 1H), 2.28 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C (ppm): 167.0, 155.1, 147.9, 140.5, 135.1, 134.7, 128.9, 128.7, 127.3, 126.8, 124.2, 122.6, 111.8, 111.3, 91.5, 21.3; HR-MS (ESI) calcd. for $C_{18}H_{14}N_2O_3{}^{35}Cl$ $[M+H]^+$: 341.0643, found: 341.0645.

4-(3-acetyl-5-(benzofuran-2-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate (**4b**): 1000 mg, yield: 55%, white needle crystals; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.76 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.50 (dd, J = 7.8, 7.8 Hz, 1H), 7.37 (dd, J = 7.9, 7.5 Hz, 1H), 7.26 (s, 1H), 7.22 (d, J = 8.6 Hz, 2H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.1, 167.0, 155.1, 151.6, 147.9, 140.6, 133.7, 128.1, 127.3, 126.8, 124.1, 122.5, 122.4, 111.8, 111.3, 91.8, 21.3, 20.8; HR-MS (ESI) calcd. for $C_{20}H_{17}N_2O_5$ $[M+H]^+$: 365.1137, found: 365.1107.

4. Results and discussion

The synthesis of 1,3,4-oxadiazole derivatives (**4a-b**) was carried out as outlined in ***Scheme 1***. The key intermediate, benzofuran-2-carbohydrazide (**2**), was obtained through a two-step process. In the initial step, ethyl benzofuran-2-carboxylate (**1**) was synthesized from salicylaldehyde and ethyl chloroacetate in dimethylformamide (DMF) as the solvent. The reaction mixture was heated at 80-90 °C for 6 hours, resulting in the formation of compound **1** with a yield of 83%. Subsequently, compound **1** was converted into benzofuran-2-carbohydrazide (**2**) by reacting it with hydrazine hydrate, achieving a yield of 75%.

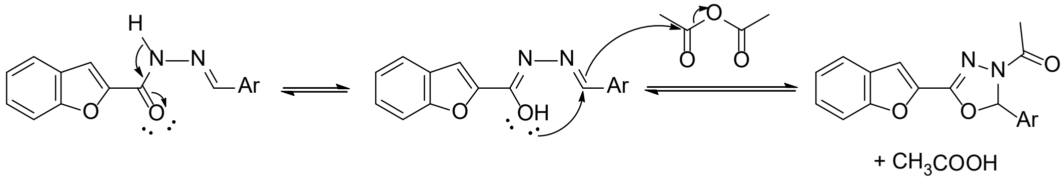
The condensation reactions of compound carbohydrazide **2** with various benzaldehyde derivatives resulted in the formation of the corresponding hydrazone derivatives **3a–b** with yields ranging from good to excellent. The important step of this synthetic pathway is cyclization between hydrazone derivatives (**3**) and acetic anhydride. We obtained 1,3,4-oxadiazole derivatives **4a–b** with moderate yields.



Scheme 1: The synthetic pathway for preparation of 1-(5-benzofuran-2-yl)-2-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethan-1-one derivatives (4a−b)

The chemical structures of these products were elucidated using the ^{1}H and ^{13}C NMR spectra. The ^{1}H-NMR spectrum of each 1,3,4-oxadiazole derivative **4a–b** showed *singlet* signal of proton –C**H**– of the oxadiazole ring at about 7.26 ppm and *singlet* signal of protons of the acetyl group in the range of 2.2−2.3 ppm. Furthermore, each ^{13}C-NMR spectrum also showed signals of carbon –**C**H– of the oxadiazole ring at about 91 ppm and carbons of the acetyl group (–**C**O–**C**H_3) at about 167 and 21 ppm, respectively. The analysis of ^{1}H and ^{13}C-NMR of each derivative allowed us to confirm the successful cyclization. Furthermore, the HSQC and HMBC spectra were further supportive of this structure. Additionally, all these chemical structures were further confirmed by HR-MS.

The formation of 1,3,4-oxadiazole derivatives **4a–b** was proposed to occur through a two-step mechanism,{Hamdi, 2011 #22} as shown in ***Scheme 2***. Initially, benzofuran-2-carbohydrazide undergoes a rearrangement, generating a nucleophilic oxygen species. This nucleophilic center subsequently attacks the electrophilic carbon of the imine group, resulting in the transfer of electrons from the double bond towards the carbonyl group of acetic anhydride. This reaction proceeds with the elimination of acetic acid, yielding the 1,3,4-oxadiazole derivatives **4a–b**.



Scheme 2: Proposed reaction mechanism of the formation of 1,3,4-oxadiazole derivatives.

It was observed that, during the reaction, the hydroxyl group in compound **3b** (X = OH) was also esterified by acetic anhydride. As a result, the ^{1}H and ^{13}C-NMR spectra of compound **4b** present an additional *singlet* signal at δ_H 2.28 ppm and δ_C 169 ppm, respectively.

5. Conclusions

A straightforward and efficient synthetic approach for the synthesis of novel 1,3,4-oxadiazole derivatives incorporating a benzofuran moiety from readily accessible starting materials has been developed. Beginning with salicylaldehyde, two 1,3,4-oxadiazole derivatives, **4a** and **4b**, were synthesized over four reaction steps. The chemical structures of the synthesized compounds were confirmed through NMR and HR-MS spectral analysis. These synthesized derivatives serve as foundational compounds for subsequent bioactivity evaluation, indicating potential applications in drug development.

ABBREVIATIONS

^{1}H–NMR: Proton Nuclear Magnetic Resonance

^{13}C–NMR: Carbon-13 Nuclear Magnetic Resonance

HR–MS: High resolution - Mass spectrometry

ESI- Electrospray ionization

TLC: thin layer chromatography

s: singlet

d: doublet

dd: doublet of doublets

m: multiplet

J: coupling constant (Hz)

DECLARATION OF COMPETING INTERESTS

The author(s) declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Tan-Tai Nguyen designed the research, performed the experiments and interpreted the NMR and MS data, wrote the first draft, reviewed and edited the manuscript and managed the investigation.

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