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Synthesis and properties of new derivatives of 4h-1,2,4-oxadiazin-5(6H)-one

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Abstract: This paper presents an improved method for the synthesis of new derivatives of 4H-1,2,4-oxadiazine-5(6H)-one, which are an important class of heterocyclic compounds with wide potential for use in medical and pharmaceutical chemistry. The synthesis was carried out based on the interaction of (Z)-N'-hydroxy-4-methylbenzimide and (Z)-N'-hydroxy-5-methylthiophene-2-carboxymidide with a number of methyl and ethyl-halogen derivatives of carboxylic acids. The study found that the use of sodium tert-butylate in dimethyl sulfoxide at room temperature provides effective cyclization with the formation of target products with yields of up to 76%. It was revealed that the effect of substituents in the aromatic or heterocyclic fragment of the original amidoximes does not have a significant effect on reactivity, which confirms the universality of the proposed approach. All synthesized compounds were characterized by modern analysis methods, including NMR (1H, 13C) and high-resolution mass spectrometry (HRMS), which fully confirmed their structure and purity. The developed method is characterized by mild conditions, ease of execution, and environmental friendliness, as it does not require the use of toxic reagents or metal catalysts.

Keywords: *4H-1,2,4-oxadiazin-5(6H)-one, Amidoximes; Cyclization, Heterocyclic compounds, Reaction optimization, Spectroscopic characterization.*

1. Introduction

An important direction in the chemistry of 1,2,4-oxadiazines and oxadiazoles is associated with the development of effective synthesis methods.

In Presnukhina et al. [1], an unusual way of nucleus formation of 1,2,4-oxadiazine was proposed by the interaction of amidoximes with maleic and fumaric esters. This result turned out to be non-trivial and opened up prospects for the search for new synthetic routes.

In a study, Jiang et al. [2], an electrochemical method for the synthesis of 1,2,4-oxadiazoles from amidoximes was developed. The use of electrochemical conditions made it possible to carry out dehydrogenative cyclization under mild conditions, which makes this approach environmentally friendly and promising for scaling.

Works Baykov et al. [3]; Baykov et al. [4], and Tarasenko et al. [5] demonstrate the importance of synthesis under mild conditions. Thus, the article by Baykov et al. [3] describes a method for obtaining biologically active 1,2,4-oxadiazoles at room temperature, which provides good yields of products. The paper by Baykov et al. [4] is the first to show a one-step synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acid esters without heating, which greatly simplifies the process of pharmaceutically significant carboxylic acids [6] containing an oxadiazole ring [5].

In addition, Phakhodee et al. [7] proposed a convenient one-step method for obtaining N-substituted amidoximes, which were further used for the synthesis of oxadiazole-5-ones. This method was distinguished by its versatility and a wide range of available derivatives.

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Thus, modern approaches to the synthesis of oxadiazines are characterized by the desire to simplify processes, reduce energy costs, and use "green" technologies.

A significant contribution to the understanding of the structure and properties of derivatives was made by a study Kara and Diran [8], where the authors studied the effect of various substituents on chemical shifts in the ^{13}C NMR spectra of new 1,2,4-oxadiazines. This approach made it possible to identify structure-property patterns, which are important for further targeted modification of compounds [9-12].

The paper by Basak et al. [13] describes the synthesis of 1,2,4-oxadiazoles using graphene oxide (GO) as a metal-independent catalyst. Here, special attention was paid to the double catalytic activity of GO, which simultaneously acted as an oxygen donor and an electron acceptor. This approach opens new opportunities for the functionalization of oxadiazines and the production of derivatives with unique properties.

Thus, research in this direction allows for a deeper understanding of the effect of substituents on the electronic characteristics of the molecule and expands the possibilities for the targeted synthesis of new derivatives.

Significant interest in oxadiazines and oxadiazoles is due to their pharmacological potential [14, 15]. These compounds can be considered as promising structures for drug development. The review Dhameliya, et al. [16] summarizes information on synthetic approaches to 1,2,4-oxadiazoles and emphasizes their anti-infective potential. Thus, the literature data indicate that derivatives of 1,2,4-oxadiazines and related structures are not only of interest for organic synthesis but also have significant pharmacological potential. This explains the active development of research in this area in recent years.

A number of works are devoted to X-ray diffraction analysis of oxadiazines and oxadiazinone derivatives. In the study, Ţînţaş et al. [17] structural characteristics of new 2-aryl-5-phenyl-1,3,4-oxadiazine-6-ones and their precursors were carried out.

In Squire et al. [18], a derivative of oxadiazinon from D-camphor was obtained, which was characterized using X-ray diffraction analysis. It was established that the presence of a rigid camphor system imposes restrictions on the stereochemical use of oxadiazinons as chiral auxiliary groups.

Classical studies Steglich et al. [19] have also contributed to the understanding of the geometry of oxadiazines: they contain a series of crystallographic data for 2,5-diphenyl-6-oxo-1,3,4-oxadiazines, making it possible to trace the relationship between structure and reactivity.

Spectroscopic methods traditionally play a key role in confirming the structure of heterocycles. In Sert et al. [20], a comprehensive experimental analysis (FT-IR, laser-Raman, and NMR) for thiophenyl-substituted oxadiazole-thione was carried out, and a comparison with quantum-chemical calculations was performed.

A similar approach was implemented in the study [21], where spectroscopic and theoretical analysis were carried out for 5-(thiophen-2-yl)-2,3-dihydro-1,3,4-oxadiazole-2-thione. This made it possible to identify the characteristic absorption bands and clarify the electronic structure of the compound.

In Shekarbeygi et al. [22], the effect of the solvent on the IR and NMR spectra of 1,2,4-oxadiazole-5(4H)-one derivatives was considered. The authors demonstrated that the polarity of the medium significantly influences chemical shifts and the intensity of the bands, which should be taken into account when interpreting the spectra.

Along with experimental methods, combined approaches are actively used [23-26]. In Kelleghan et al. [27], the authors described the synthesis of 2,5-diaryloxadiazinons and demonstrated the potential applications of these compounds in further structural studies.

In the study, Sarma et al. [28] solid-phase synthesis of oxadiazinon and oxadiazolone libraries was implemented, after which spectroscopic and structural studies were carried out to confirm the identity of the constructed skeletons.

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In the review, Salassa and Terenzi [29] consider metal complexes with oxadiazole ligands are considered. The authors systematized data on coordination, spectroscopy, and electron effects, which is valuable for understanding the influence of substituents and the environment on physicochemical properties.

Finally, in Anthony et al. [30], the emphasis is placed on the mechanistic aspects of the formation of oxadiazinons from unstable intermediates. The article presents the results of spectroscopic and theoretical characterization of transition states, which allows for a deeper understanding of the reactivity of these compounds.

Antibacterial activity: the development of new antibacterial agents based on the oxadiazole nucleus remains an urgent task [31-33]. The review by Atmaram and Roopan [34] contains information on the antibacterial activity of oxadiazole and thiadiazole derivatives, including against resistant strains. In the study, Buommino et al. [35] compounds containing the 1,2,4-oxadiazole moiety have been shown to enhance the anti-MRSA antibiotic effect, providing pronounced synergy. Such an effect opens up opportunities for combined therapy of infections. The work Barbachyn [36] describes a novel 1,2,4-oxadiazole with high specific activity against *Clostridioides difficile*, which is especially important for the treatment of severe intestinal infections. Finally, the article Pitcher et al. [37] discusses strategies for the structural modification of oxadiazoles to improve their antimicrobial properties, including permeability and metabolic stability.

Some oxadiazole derivatives show promising activity against enzymes involved in neurodegenerative processes. Ayoup et al. [38] synthesized new compounds that showed inhibitory activity against key enzymes associated with Alzheimer's disease. Molecular docking confirmed the ability of these structures to bind to active enzyme sites. Study Sahu, et al. [39] is devoted to oxadiazole-piperazine hybrids that have demonstrated monoamine oxidase (MAO) inhibition. Such compounds can be considered as candidates for the creation of new antidepressants and neuroprotectors.

The search for new drugs against parasitic diseases remains an important direction. In Barbosa et al. [40], it was shown that derivatives of 1,2,4-oxadiazole have activity against *Leishmania infantum*. It was experimentally established that a number of compounds exhibited a significant antiparasitic effect, which opens opportunities for the development of drugs against leishmaniasis.

The antitumor properties of oxadiazole derivatives have been actively studied in recent years. In Habib et al. [41], conjugates of 1,2,4-oxadiazole with sulfonamide were synthesized, which showed pronounced cytotoxic activity against tumor cells. In the study, Gelain et al. [42] anti-profiling screening of a library of 1,2,5-oxadiazole derivatives was carried out; compounds with high antitumor activity were identified, and key patterns within the framework of structure-activity analysis (SAR). The review Khasawneh et al. [43] summarizes the data on the anticancer potential of oxadiazoles for 2019–2023, emphasizing strategic approaches to the design of molecules and prospects for their use in antitumor therapy. Antibacterial to antitumor.

2. Materials and Research Methods

Reagents and solvents were obtained from Merck and used without additional purification. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on Macherey–Nagel Silufol UV–254 plates (Macherey–Nagel GmbH & Co. KG, Düren, Germany) under UV light.

NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer (Bruker Optics GmbH & Co. KG, Ettlingen, Germany) operating at 400 MHz for ^{1}H and 101 MHz for ^{13}C, using DMSO-d_6 or $CDCl_3$ as solvents. Chemical shifts (δ) are expressed in parts per million (ppm) with solvent signals as internal references: 2.50 ppm (^{1}H) and 39.50 ppm (^{13}C) in DMSO-d_6, 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C) in $CDCl_3$. Signal multiplicities are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (J) are given in Hertz (Hz). Melting points were

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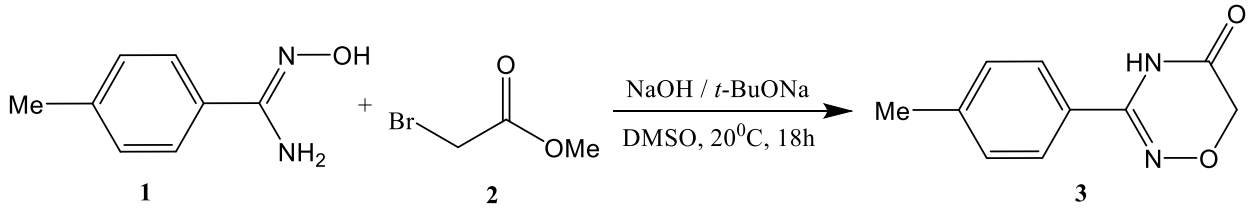
measured using open capillary tubes on an Electrothermal IA 9300 digital melting point apparatus (Electrothermal Engineering Ltd, Rochford, UK). High-resolution mass spectra (HRMS) were obtained on a Bruker Maxis-qTOF instrument (Bruker Daltonics GmbH & Co. KG, Bremen, Germany) in electrospray ionization (ESI) negative mode.

3. Results and Discussion

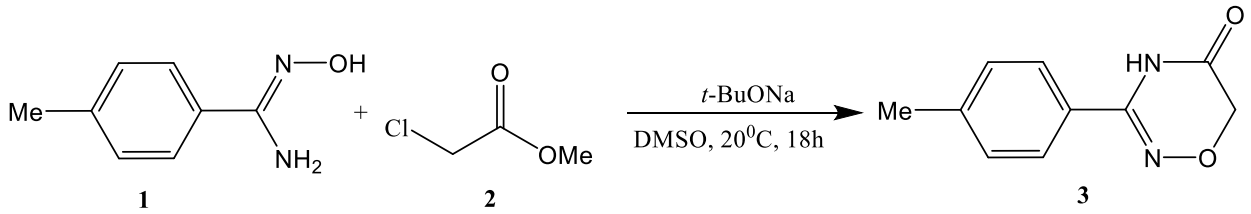
In this study, the primary objective was to optimize the conditions for the condensation of (*Z*)-*N*'-hydroxy-4-methylbenzimide **1** with methyl 2-haloacetates 2a,b. The reaction between (*Z*)-*N*'-hydroxy-4-methylbenzimide **1** and methyl 2-bromoacetamide **2a** was conducted at room temperature in dimethyl sulfoxide in the presence of sodium hydroxide for 18 hours (Scheme 1). The yield of the product was 29.5%. Subsequently, sodium tert-butylate was used instead of sodium hydroxide. This substitution allowed an increase in the proportion of the cyclization product 3-(p-tolyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one **3**, which was isolated with a yield of 43%.

Scheme 1



3-(*p*-tolyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one **3** was obtained by reacting (Z)-*N*'-hydroxy-4-methylbenzimide **1** with methyl 2-chloroacetate **2** at room temperature in dimethyl sulfoxide in the presence of sodium *tert*-butylate, with a yield of 51% (Scheme 2). Extending the reaction time to 48 hours also did not lead to an increase in product yield (remained at 46%).

Scheme 2



Thus, optimal reaction conditions (e.g., base selection, reactant amount, solvent, and time) were determined under which the use of methyl 2-chloroacetate as a substrate yields the target 3-(*p*-tolyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one **3** with a yield of 51%.

Using optimized conditions, we reacted with (Z)-*N*'-hydroxy-5-methylthiophene-2-carboxymidamide **4** with carbonyl compounds **2,6,8**. The compound 3-(5-methylthiophene-2-yl)-4*H*-1,2,4-oxadiazine-5(6*H*)-one **5** was obtained by reacting (Z)-*N*'-hydroxy-5-methylthiophene-2-carboxymidamide **4** with methyl-2-chloroacetate **2** at room temperature in dimethyl sulfoxide in the presence of *tert*-sodium butylate with a yield of 76%, a reaction duration of 18 hours (Scheme 3).

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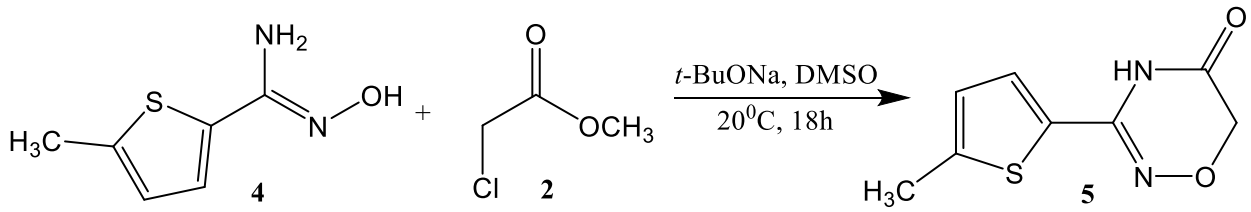
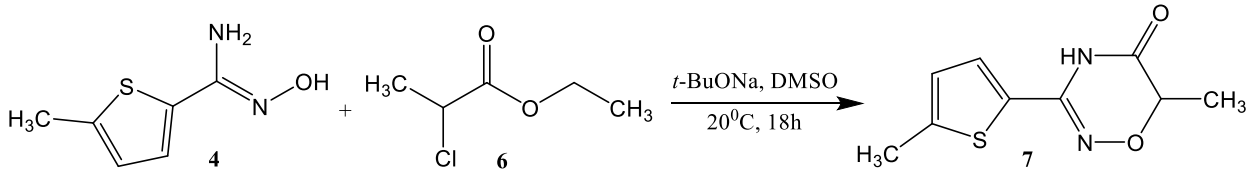
Scheme 3



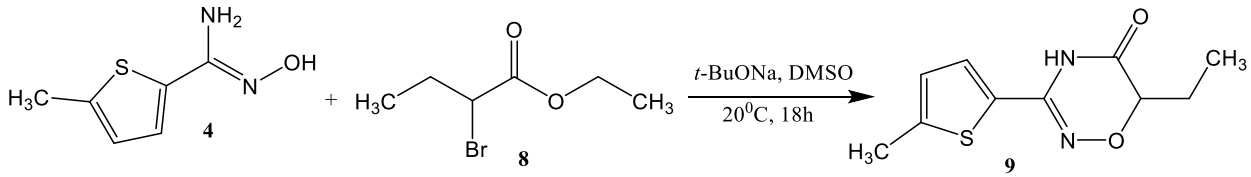
When (Z)-*N*'-hydroxy-5-methylthiophene-2-carboximidamide **4** reacts with ethyl-2-chloropropanoate, **6**, 6-methyl-3-(5-methylthiophene-2-yl)-4*H*-1,2,4-oxadiazine-5(6*H*)-one **7** is formed with a yield of 75% (Scheme 4).

Scheme 4



In the reaction of (Z)-*N*'-hydroxy-5-methylthiophene-2-carboximidamide **4** with ethyl-2-bromobutanoate **8**, 6-ethyl-3-(5-methylthiophene-2-yl)-4*H*-1,2,4-oxadiazine-5(6*H*)-one **9** was obtained. The yield of the product is 75% (Scheme 5).

Scheme 5



All products were obtained with a good yield. It was found that the presence of electron-acceptor or electron-donor substituents in the phenyl ring of amidoximes does not have a noticeable effect on the yield of the target product.

3.1 General procedure for the synthesis of 4*H*-1,2,4-oxadiazin-5(6*H*)-one derivatives (3,5,7,9).

To a solution of (Z)-*N*'-hydroxy-4-methylbenzimidamide **1** and (Z)-*N*'-hydroxy-5-methylthiophene-2-carboximidamide **4** (2 mmol) in DMSO (3 mL), sodium *tert*-butylate (384 mg, 4 mmol) was rapidly added at room temperature. The reaction mixture was stirred at room temperature for 10 min, and ester **2,6,8** (2.4 mmol) was added. The reaction mixture was stirred at room temperature for another 18 h and was then diluted with HCl (10% solution in water) (30 mL). The resulting precipitate was collected by filtration, washed with cold water (5 mL), and air-dried at 50°C.

3-(4-Methylphenyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**3**). White powder; 51% yield; mp 140–141°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.47 (s,

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2H), 2.43 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 151.0, 142.3, 129.8, 126.0, 125.7, 66.9, 21.5. HRMS (ESI), m/z: [M-H]$^-$ calcd for $C_{10}H_9N_2O_2$. calcd for 189.0669; found 189.0667.

3-(5-Methylthiophen-2-yl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**5**). Pale beige powder; 76% yield; mp 216–218°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.35 (d, J = 3.7 Hz, 1H), 6.80 (d, J = 3.5 Hz, 1H), 4.47 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 148.4, 144.6, 129.7, 128.9, 126.8, 67.5, 15.7. HRMS (ESI), m/z: [M-H]$^-$ calcd for $C_8H_8N_2O_2S^-$ 195.0234; found 195.0235.

6-Methyl-3-(5-methylthiophen-2-yl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**7**). Pale beige powder; 75% yield; mp 167–169°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H), 7.56 (d, J = 3.7 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 4.34 (q, J = 6.7 Hz, 1H), 2.45 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 148.4, 144.5, 129.6, 129.0, 126.7, 72.7, 15.7, 13.8. HRMS (ESI), m/z: [M-H]$^-$ calcd for $C_9H_9N_2O_2S^-$ 209.0390; found 209.0391.

6-Ethyl-3-(5-methylthiophen-2-yl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**9**). Pale beige powder; 75% yield; mp 151–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 7.55 (d, J = 3.7 Hz, 1H), 6.85 (d, J = 3.7 Hz, 1H), 4.19 (dd, J = 7.8, 4.6 Hz, 1H), 2.45 (s, 3H), 1.90–1.81 (m, 1H), 1.73–1.65 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.8, 148.2, 144.5, 129.6, 129.0, 126.7, 77.2, 21.5, 15.7, 10.0. HRMS (ESI), m/z: [M-H]$^-$ calcd for $C_{10}H_{11}N_2O_2S^-$ 223.0547; found 223.0554.

4. Conclusions

As a result of the study, an effective method for the synthesis of new derivatives of 4H-1,2,4-oxadiazine-5(6H)-one based on the reactions of (Z)-N'-hydroxy-4-methylbenzimide and (Z)-N'-hydroxy-5-methylthiophene-2-carboximidide with various alkyl halogen derivatives of carboxylic acids was developed and experimentally confirmed. The optimization of reaction conditions made it possible to establish that the best results are achieved when using sodium tert-butylate in dimethyl sulfoxide at room temperature, which ensures the formation of target products with yields of up to 76%. Extending the reaction time to 48 hours does not have a significant impact on yield, indicating that the process is stable and complete within 18 hours.

It has been shown that the nature of the substituents in the aromatic or heterocyclic fragment of the parent amidoximes does not significantly affect the efficiency of cyclization, making this method versatile and reproducible. All synthesized compounds were characterized by NMR (^{1}H, ^{13}C) and high-resolution mass spectrometry (HRMS), which confirmed their structure and purity.

The developed approach is simple, environmentally friendly, and there is no need to use toxic reagents or metal catalysts, which makes it promising for large-scale laboratory and industrial use. The obtained oxadiazine derivatives are of considerable interest as potential pharmacophores with pronounced biological potential – antibacterial, antitumor, and neuroprotective. The results obtained create the basis for further research in the field of directed synthesis, structural modification, and assessment of the biological activity of new heterocyclic systems.

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Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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