molbank

MDPI

Short Note

4,5-Dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one

Kirill A. Gomonov [1], Vasilii V. Pelipko [1], Igor A. Litvinov [2], Ruslan I. Baichurin [1] and Sergey V. Makarenko [1,*]

[1] Laboratory of Nitrocompounds, Department of Organic Chemistry, Faculty of Chemistry, Herzen State Pedagogical University of Russia, 48 Moika Embankment, 191186 St. Petersburg, Russia
[2] A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russia; litvinov@iopc.ru
* Correspondence: makarenkosv@herzen.spb.ru

Abstract: The synthesis of previously unknown 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one has been proposed and structurally characterized via a single-crystal X-ray diffraction analysis, ^{1}H, ^{13}C–{^{1}H}, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC NMR spectroscopy, and IR spectroscopy.

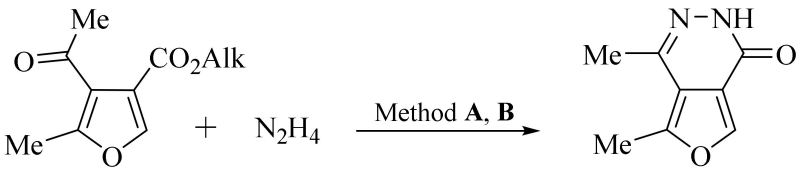
Keywords: furo[3,4-*d*]pyridazin; furans; pyridazinones; cyclocondensation; crystal structure; X-ray diffraction analysis

1. Introduction

The furan ring is a component of many medications with a wide spectrum of action [1–4]. The development of methods for obtaining new furan derivatives is one of the most dynamic areas of modern organic and medicinal chemistry [5,6]. Of particular interest in this case are condensed biheterocyclic systems containing a furan and another heterocycle [7–11]. Thus, based on tetrasubstituted furans containing ester and acetyl groups in positions 3 and 4, the corresponding furo[3,4-*d*]piridazines were obtained in a reaction with hydrazine (1,2-binucleophile) [11,12]. In this article, we will focus on the synthesis of a new fused biheterocycle—4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one—and the characterization of its fine structure using NMR (nuclear magnetic resonance), FTIR (Fourier-transform infrared spectroscopy), and an X-ray diffraction analysis. This study will contribute to our understanding of the properties of furo-containing biheterocycles and may have important implications for the development of new biologically active substances.

2. Results and Discussion

We have proposed a method for the synthesis of an original biheterocycle, 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one **2**, based on the reaction of acetyl-containing furan-3-carboxylates **1a**, **b** [13] with hydrazine hydrate. It turned out that boiling furancarboxylates **1a**, **b** with an excess of hydrazine hydrate in acetic acid (method **A**) leads to the preparation of the target 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one **2** with yields up to 32%. Changing the synthesis conditions, namely, the reaction of furan-3-carboxylate **1b** with an excess of hydrazine hydrate in ethanol solution in the presence of catalytic amounts of trifluoroacetic acid at room temperature (method **B**), led to the formation of biheterocycle **2** with a yield of 44% (Scheme 1).



1a, b **2**

A: Alk = Me (**1a**), Et (**1b**), Δ, AcOH, 1h; **B**: Alk = Et (**1b**), cat. TFA, 20°C, EtOH, 2h

Scheme 1. Synthesis of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one **2**.

check for updates

Citation: Gomonov, K.A.; Pelipko, V.V.; Litvinov, I.A.; Baichurin, R.I.; Makarenko, S.V. 4,5-Dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one. *Molbank* **2024**, *2024*, M1776. https://doi.org/10.3390/M1776

Academic Editor: René T. Boeré

Received: 11 January 2024
Revised: 31 January 2024
Accepted: 4 February 2024
Published: 20 February 2024

The synthesized 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one **2** can exist in the form of lactim or lactam tautomeric (Figure 1). Studying the structure of biheterocycle **2** using IR and ^{1}H, ^{13}C–{^{1}H} NMR spectroscopy, as well as an X-ray structural analysis, unambiguously confirmed that its molecule exists in the lactam form in solution and in the solid phase.

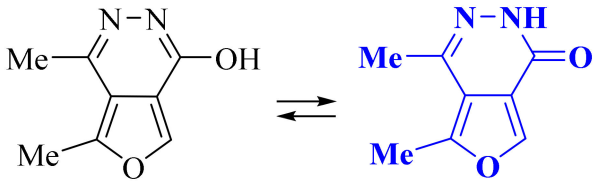


Figure 1. Tautomeric forms of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one **2**.

Indeed, the IR spectrum of biheterocycle **2** contains an intense band at 1668 cm^{-1} (C=O), which belongs to the valence vibrations of the amide carbonyl group, as well as a broadened band of the amino group of the amide fragment at 3167 cm^{-1} (NH).

The ^{13}C–{^{1}H} NMR spectrum of biheterocycle **2** contains a carbon atom signal at 157.92 ppm (C=O), characteristic of the carbonyl group of the amide fragment. In addition, the cross peak 11.44 (NH)/140.51 (C^{4}) in the ^{1}H–^{13}C HMBC experiment spectrum also confirms the existence of the synthesized bicycle **2** in solution in the lactam form.

The assignment of signals of protons and carbon atoms in the ^{1}H and ^{13}C NMR spectra was carried out using heteronuclear (^{1}H–^{13}C HMQC, ^{1}H–^{13}C HMBC) experiments. The key cross peaks used for interpretation in the ^{1}H–^{13}C HMBC spectra are as follows: 2.34 (C^{4}C<u>H</u>$_3$)/115.26 (C^{4a})/140.51 (C^{4}); 2.61 (C^{5}C<u>H</u>$_3$)/115.26 (C^{4a})/150.92 (C^{5}); 8.43 (C^{7}H)/115.26 (C^{4a})/117.71 (C^{7a})/150.92 (C^{5}); and 11.44 (NH)/117.71 (C^{7a})/140.51 (C^{4}) (Figure 2).

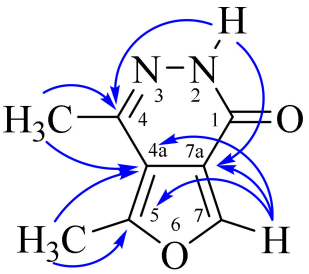


Figure 2. Key correlations in ^{1}H–^{13}C HMBC spectra.

The lactam molecular and crystal structures of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one (**2**) have been determined via an X-ray analysis. Light-brown crystals were grown from a saturated ethanol solution by slow solvent evaporation.

The title compound (**2**) crystallizes in the monoclinic space group $P2_1/c$. Figure 3 represents the molecular structures of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one.

The molecule has a planar conformation, and the deviation of atoms from the least-square plane is lower than 0.039(3) Å. The pyridazinone fragment exists in the lactam form.

The distribution of bond lengths in a molecule indicates the presence of a conjugation in it, which ensures the planar conformation of the entire molecule (see Supplementary Materials Table S2).

The crystal structure of compound **2** is primarily determined by intermolecular hydrogen bonds (N2-H2. . ..O12′ (−x,−1/2 + y,1/2 − z)) and stacking interactions between planar conjugated molecules. The hydrogen bond parameters are as follows: N2-H2 0.87(3), N2. . ..O12′ 2.787(4), H2. . ..O12′ 1.97(3) Å, and angle N2-H2. . ..O12′ 156(3)°. Due to these H-bonds, ribbons are formed along the b axis of the crystal (Figure 4).

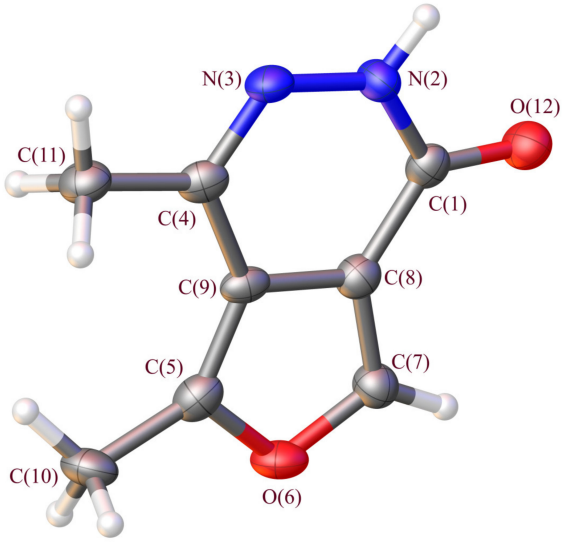


Figure 3. Geometry of molecule **2** in the crystal. Ellipsoids of anisotropic displacements are shown with 50% probability.

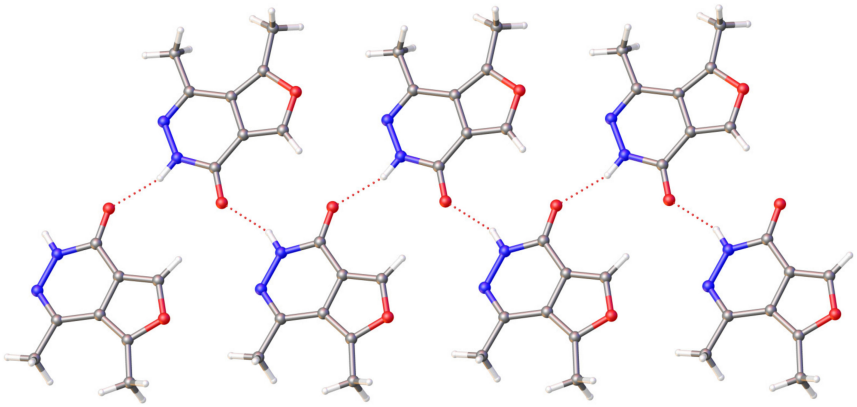


Figure 4. Hydrogen bonding in the crystal of molecule **2**. H-bonds are shown by dotted lines.

Figure 5 shows a fragment of the packaging of crystal **2**, which demonstrates interplanar interactions, due to which the formation of double layers is observed. The interplanar distances are 3.19(1) Å, and the angle between the planes of molecules is 0.16(12)°.

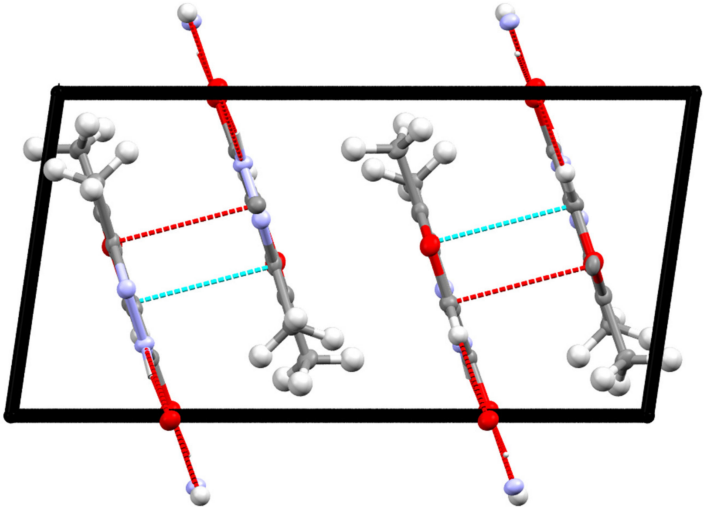


Figure 5. Stacking interaction in crystal **2**. Short contacts are shown by dotted lines. Projection along the b axis.

3. Materials and Methods

Alkyl 4-acetyl-5-methylfuran-3-carboxylates (**1a**, **b**) [13] were prepared according to published methods. All reagents were of commercial grade and used without purification.

Method A: To a solution of 0.2 g (1.09 mmol) of methyl 4-acetyl-5-methylfuran-3-carboxylate **1a** [13] in 5 mL of glacial acetic acid, 0.275 g (5.5 mmol) of hydrazine hydrate was added. The reaction mixture was refluxed for 1 h. Then the solvent was evaporated and the residue was crystallized from ethanol. Yield 0.017 g (10%), light-brown crystals, mp. 273–275 °C (EtOH).

IR: 1345, 1546, 1617, 1668 (C=O), 3167 (NH).

^{1}H NMR: 2.34 (3H, s, C^{4}C$\underline{H}_3$), 2.61 (3H, s, C^{5}C$\underline{H}_3$), 8.43 (1H, s, C^{7}H), 11.44 (1H, s, NH). (Atom labeling shown in Figure 2).

^{13}C{^{1}H} NMR: 13.87 [C$^{5}\underline{C}H_3$], 19.92 [C$^{4}\underline{C}H_3$], 115.26 (C^{4a}), 117.71 (C^{7a}), 140.51 (C^{4}), 150.92 (C^{5}), 157.92 (C=O).

Found, %: C 58.53; H 4.91, N 17.06. $C_8H_8N_2O_2$. Calculated, %: C 58.23; H 4.84, N 16.94.

To a solution of 0.2 g (1.02 mmol) of ethyl 4-acetyl-5-methylfuran-3-carboxylate **1b** [13] in 5 mL of glacial acetic acid, 0.255 g (5.1 mmol) of hydrazine hydrate was added. The reaction mixture was refluxed for 1 h. Then the solvent was evaporated and the residue was crystallized from ethanol. Yield 0.054 g (32%), light-brown crystals, mp. 273–275 °C (EtOH).

Method B: To a solution of 0.15 g (0.077 mmol) of ethyl 4-acetyl-5-methylfuran-3-carboxylate 1b [13] in 5 mL of ethanol, 0.077 g (1.53 mmol) of hydrazine hydrate and catalytic amount of trifluoroacetic acid were added. The reaction mixture was kept for 2 h at room temperature. Then the solvent was evaporated and the residue was crystallized from ethanol. Yield 0.055 g (44%), light-brown crystals, mp. 273–275 °C (EtOH).

A mixing test with a sample obtained by methods **A** and **B** did not result in a depression in the melting point.

Elemental analysis was performed with a Euro Vector EA 3000 analyzer (CHN Dual). Melting points were determined on a PTP-M melting point apparatus.

IR spectra (Figure S1) were registered on Shimadzu IR Prestige-21 spectrometers with samples in KBr pellets. ^{1}H, ^{13}C–{^{1}H} NMR spectra (Figures S2 and S3), ^{1}H–^{13}C HMQC (Figure S4), and ^{1}H–^{13}C HMBC (Figure S5) experiments were performed using a Jeol ECX400A spectrometer (400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei) in DMSO-d_6. The residual signals of the solvent (DMSO-d_6: 2.50 ppm for ^{1}H nuclei and 39.6 ppm for ^{13}C nuclei) were used as internal standard.

X-ray diffraction analysis was performed at 108 K on a Bruker D8 QUEST automatic three-circle diffractometer (graphite monochromator, λMoK$_\alpha$ = 0.71073 Å, ω- and φ-scan with a step of 0.5°) at the Distributed Spectral-Analytical Center of Shared Facilities for Study of Structure, Composition and Properties of Substances and Materials of FRC Kazan Scientific Center of RAS.

An X-ray diffraction analysis of **2** was performed on a Bruker D8 QUEST automatic three-circle diffractometer with a PHOTON III two-dimensional detector and an I_S DIAMOND microfocus X-ray tube (Mo K$_\alpha$ radiation, λ = 0.71073 Å) at cooling conditions. Data collection and the processing of diffraction data were performed using APEX3 software package. Structure **2** was solved by the direct method using the SHELXT program [14]. It was refined by the full-matrix least-squares method over F^2 using the SHELXL program [15]. Crystal **2** was found to be two-component twin and twin rot matrix (−0.694 0 −0.424)/(0 −1 0)/(−1.223 0 0.694), with the estimated BASF line = 0.46. Final model was refined using a combined diffraction data set (HKLF 5), with parameter BASF refined to 0.33285. All calculations were performed in the WinGX software package [16]. The calculations of the geometry of molecules and intermolecular interactions in crystals were carried out using the PLATON program [17]. The drawings of molecule were performed using the MERCURY [18] programs. Non-hydrogen atoms were refined using the anisotropic approximation. The position of the hydrogen atom H(N2) was determined using difference Fourier map. The remaining hydrogen atoms were placed in geometrically

calculated positions, and all hydrogen atoms were included in the refinement in the "riding" model.

Crystal **2** monoclinic at 108(2) K a = 7.024(4), b = 7.659(4), c = 13.714(7) Å, β = 98.312(17)°, V = 730.1(6) Å^3, Z = 4 ρ_{calc} 1.493 g/cm^3, and μ 0.110 mm^{-1}. Reflections collected: 19508, independent reflections: 1464, and observed reflections: I $\geq$ 2σ(I) 831. Final R-factors were as follows: *R* factors [I >= 2σ (I)] R_1 = 0.0802, wR_2 = 0.1895, *R* factors (all reflections) R_1 = 0.1442, wR_2 = 0.2182, and GOOF on F^2 1.003

Crystallographic data, experimental parameters, and refinement of the condensed biheterocyclic structure were deposited at the Cambridge Crystallographic Data Center; registration numbers and the most important characteristics are provided in Tables S1–S3 (see Supplementary Materials).

4. Conclusions

A method has been proposed for the synthesis under mild conditions of a previously unknown representative of biheterocyclic compounds—4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one—with a free α-position of the furan ring based on the reaction of acetyl-containing furan-3-carboxylates with excess hydrazine hydrate. Its fine structure is characterized via NMR and IR spectroscopy, as well as an X-ray diffraction analysis. The existence of its molecule in lactam form in solution and in the solid phase has been established.

Supplementary Materials: Figure S1: IR spectrum of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one in KBr; Figure S2: ^{1}H NMR spectrum of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one in DMSO-d_6; Figure S3: ^{13}C–{^{1}H} NMR spectrum of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one in DMSO-d_6; Figure S4: ^{1}H–^{13}C HMQC spectrum of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one in DMSO-d_6; Figure S5: ^{1}H–^{13}C HMBC spectrum of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one in DMSO-d_6; Figure S6: Geometry of the 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one in the crystal; Figure S7: Hydrogen bonding in the crystal 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one; Figure S8: Stacking interaction in the crystal 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one; Table S1: Crystallographic data, experimental parameters, and refinement of the 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one; Table S2: Bond lengths (*d*) in the molecule of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one; Table S3: Angles (τ) in the molecule of 4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one. CCDC 2321540 (accessed on 13 December 2023) contains the supplementary crystallographic data for this paper.

Author Contributions: Conceptualization, S.V.M. and V.V.P., synthesis, K.A.G., methodology, V.V.P.; investigation, R.I.B. and I.A.L.; writing—original draft preparation, S.V.M., V.V.P. and R.I.B.; writing—review and editing, S.V.M. All authors have read and agreed to the published version of the manuscript.

Funding: The research was supported by an internal grant of the Herzen State Pedagogical University of Russia (project № 3VG). The X-ray diffraction study was financially supported within the framework of the state assignment for the 'Kazan Scientific Center of the Russian Academy of Sciences' Federal Research Center.

Data Availability Statement: The data presented in this study are available in this article (and Supplementary Material).

Acknowledgments: NMR and IR spectral studies were performed at the Center for Collective Use «Physico-chemical methods for the study of nitro compounds, coordination compounds, biologically active substances, and nanostructured materials» of the Interdisciplinary Resource Center for Collective Use «Modern physico-chemical methods of formation and research of materials for the needs of industry, science, and education» of the Herzen State Pedagogical University of Russia. The structural studies were carried out using the equipment of the A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Patel, P.; Shakya, R.; Asati, V.; Kurmi, B.D.; Verma, S.K.; Gupta, G.D.; Rajak, H. Harish Rajak Furan and benzofuran derivatives as privileged scaffolds as anticancer agents: SAR and docking studies (2010 to till date). *J. Mol. Struct.* **2024**, *1299*, 137098. [CrossRef]
2. Iroegbu, A.O.; Sadiku, E.R.; Ray, S.S.; Hamam, Y. Sustainable Chemicals: A Brief Survey of the Furans. *Chem. Afr.* **2020**, *3*, 481. [CrossRef]
3. Loğoğlu, E.; Yilmaz, M.; Katircioğlu, H.; Yakut, M.; Mercan, S. Synthesis and biological activity studies of furan derivatives. *Med. Chem. Res.* **2010**, *19*, 490. [CrossRef]
4. Lukevits, É.; Demicheva, L. Biological activity of furan derivatives (review). *Chem. Heterocycl. Compd.* **1993**, *29*, 243. [CrossRef]
5. Deepthi, A.; Babu, B.P.; Balachandran, A.L. Synthesis of Furans–Recent Advances. *Org. Prep. Proc. Inter.* **2019**, *51*, 409. [CrossRef]
6. Duc, D.X. Recent Progress in the Synthesis of Furan. *Mini-Rev. Org. Chem.* **2019**, *16*, 422. [CrossRef]
7. Manna, S.K.; Giri, S.; Mondal, S.; Sana, R.N.; Samal, A.K.; Mandal, A. A Detailed Review on C-Fused Furan/3,4-Fused Furan Analog and its Potential Applications. *ChemistrySelect* **2023**, *8*, e202203150. [CrossRef]
8. Gould, K.J.; Hacker, N.P.; McOmie, J.F.W.; Perry, D.H. Benzocyclobutenes. Part 4. Synthesis of benzocyclobutene-1,2-diones by pyrolytic methods. *J. Chem. Soc. Perkin Trans.* **1980**, *1*, 1834. [CrossRef]
9. Oleinik, A.F.; Adamskaya, E.V.; Okinshevich, O.V.; Pershin, G.N. Synthesis and antimicrobial activity of derivatives of 2-aryl-3,4-bis(carboxy)furans. *Pharm. Chem. J.* **1983**, *17*, 408. [CrossRef]
10. Du, Q.; Neudörfl, J.-M.; Schmalz, H.-G. Chiral Phosphine–Phosphite Ligands in Asymmetric Gold Catalysis: Highly Enantioselective Synthesis of Furo[3,4-*d*]-Tetrahydropyridazine Derivatives through [3 + 3]-Cycloaddition. *Chem. Eur. J.* **2018**, *24*, 2379. [CrossRef] [PubMed]
11. Hu, J.; Wei, Y.; Tong, X. Phosphine-Catalyzed [3 + 2] Annulations of γ-Functionalized Butynoates and 1*C*, 3*O*-Bisnucleophiles: Highly Selective Reagent-Controlled Pathways to Polysubstituted Furans. *Org. Lett.* **2011**, *13*, 3068. [CrossRef]
12. Bakavoli, M.; Feizyzadeh, B.; Rahimizadeh, M. Investigation of hydrazine addition to functionalized furans: Synthesis of new functionalized 4,4′-bipyrazole derivatives. *Tetrahedron. Lett.* **2006**, *47*, 8965. [CrossRef]
13. Gomonov, K.A.; Pelipko, V.V.; Litvinov, I.A.; Baichurin, R.I.; Makarenko, S.V. Synthesis of substituted furan-3-carboxylates from alkyl 3-bromo-3-nitroacrylates. *Mend. Comm.* **2023**, *33*, 11. [CrossRef]
14. Sheldrick, G.M. SHELXT—Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr. A Found. Adv.* **2015**, *71*, 3–8. [CrossRef] [PubMed]
15. Sheldrick, G.M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr. C Struct. Chem.* **2015**, *71*, 3–8. [CrossRef] [PubMed]
16. Farrugia, L.J. WinGX and ORTEP for Windows: An update. *Appl. Crystallogr.* **2012**, *45*, 849–854. [CrossRef]
17. Spek, A.L. Structure validation in chemical crystallography. *Acta Crystallogr. Sect. D* **2009**, *65*, 148–155. [CrossRef] [PubMed]
18. Macrae, C.F.; Sovago, I.; Cottrell, S.J.; Galek, P.T.A.; McCabe, P.; Pidcock, E.; Platings, M.; Shield, G.P.; Stevens, J.S.; Towler, M.; et al. Mercury 4.0: From visualization to analysis, design and prediction. *J. Appl. Crystallogr.* **2020**, *53*, 226. [CrossRef] [PubMed]