molbank

MDPI

Short Note

3-(4-Bromophenyl)-1-carbamothioyl-5-(2-carbamothioylhydrazinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic Acid

Anastasia A. Andreeva, Maksim V. Dmitriev and Andrey N. Maslivets *

Department of Chemistry, Perm State University, ul. Bukireva, 15, 614990 Perm, Russia; aandreeva234@gmail.com (A.A.A.); maxperm@yandex.ru (M.V.D.)
* Correspondence: koh2@psu.ru

Abstract: The reaction of 4-(4-bromophenyl)-2,4-dioxobutanoic acid with thiosemicarbazide, in a ratio of 1:2, when boiled in ethanol gives 3-(4-bromophenyl)-1-carbamothioyl-5-(2-carbamothioylhydrazinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid with a good yield. This compound was fully characterized.

Keywords: thiosemicarbazide; hydrazine; heterocyclization; antibacterial activity; pyrazole; pyrazoline

1. Introduction

Compounds whose structures are based on a pyrazoline fragment are of particular interest to the pharmaceutical industry as substances with anticancer [1–3], antimicrobial and antifungal [1,4] activity and to agriculture as herbicide detoxifiers [5] (Figure 1).

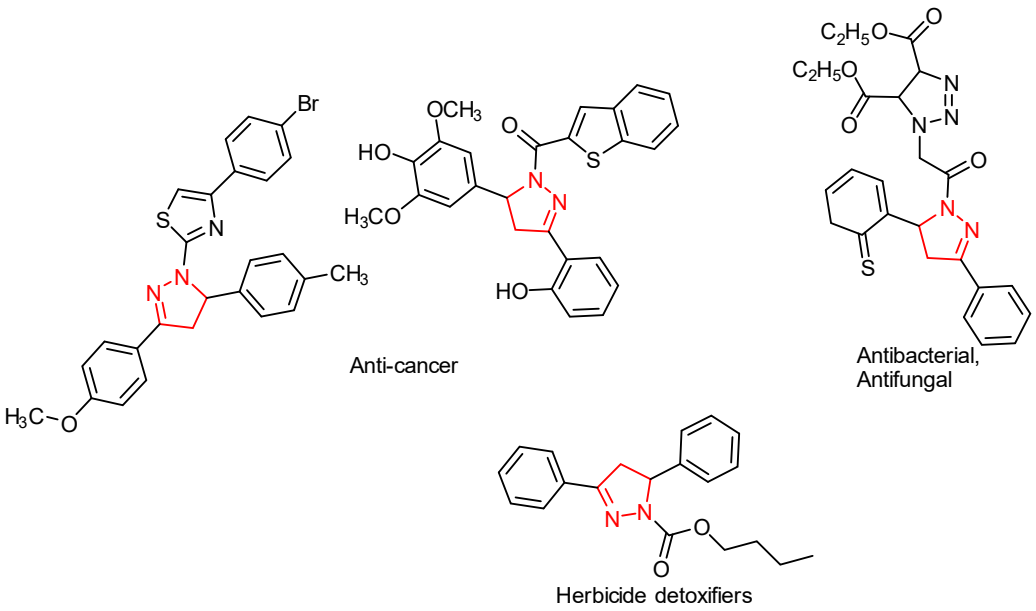


Figure 1. Potential pharmaceutical substances bearing a pyrazoline core.

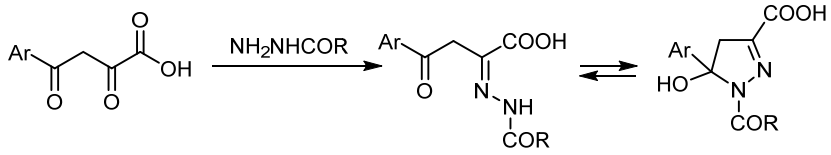
As a continuation of the development of methods for the synthesis of pyrazolines containing potentially functionalizable acyl groups at various positions of the pyrazoline cycle through the reaction of polycarbonyl compounds and substituted hydrazines (Scheme 1) [6,7], we synthesized a new representative of functionally substituted 1-carbamothioyl-3-carboxy-1*H*-pyrazoline **1** via a reaction of aroylpyruvic acid and thiosemicarbazide.

check for updates

Citation: Andreeva, A.A.; Dmitriev, M.V.; Maslivets, A.N. 3-(4-Bromophenyl)-1-carbamothioyl-5-(2-carbamothioylhydrazinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic Acid. *Molbank* **2024**, *2024*, M1757. https://doi.org/10.3390/M1757

Academic Editor: Fawaz Aldabbagh

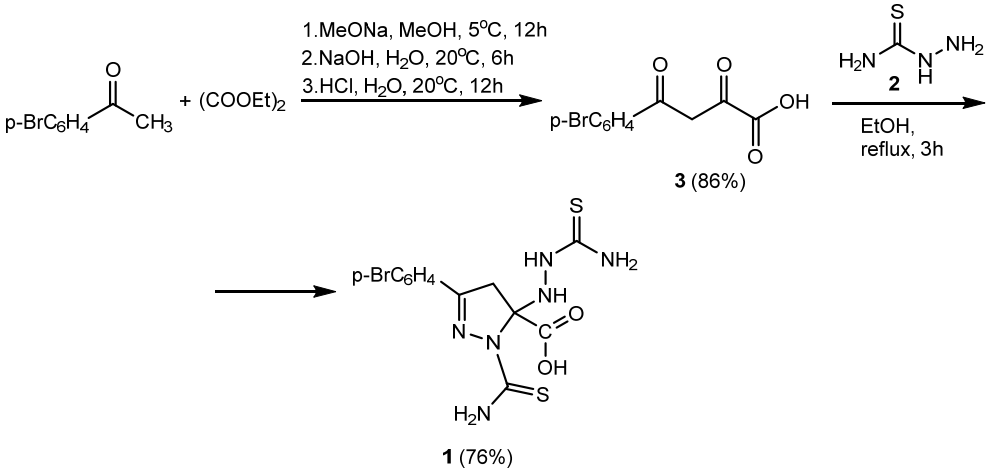
Received: 29 November 2023
Revised: 18 December 2023
Accepted: 19 December 2023
Published: 2 January 2024



Scheme 1. Synthesis of pyrazolines via a reaction of acylpyruvic acids and substituted hydrazines.

2. Results and Discussion

The title compound **1** was synthesized in several stages (Scheme 2). Initially, 4-(4-bromophenyl)-2,4-dioxobutanoic acid **3** was obtained via the Claisen condensation of 4-bromoacetophenone and diethyl oxalate. Then, as a result of the reaction of compound **3** and thiosemicarbazide **2**, 3-(4-bromophenyl)-1-carbamothioyl-5-(2-carbamothioylhydrazinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid **1**, the target compound, was obtained for the first time.



Scheme 2. Synthesis of 3-(4-bromophenyl)-1-carbamothioyl-5-(2-carbamothioylhydrazinyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid **1**.

The structure of compound **1** was unambiguously confirmed by X-ray diffraction analysis of a single crystal (CCDC 2310650) (Figure 2). Compound 1 crystallizes as a racemate in the centrosymmetric space group P21/c.

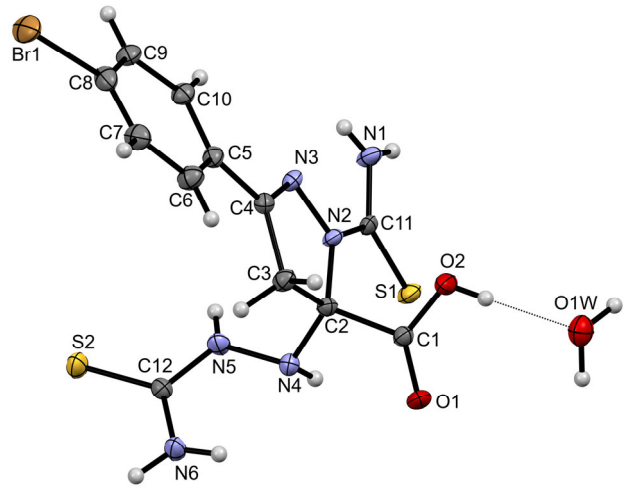


Figure 2. Structure of compound **1**, obtained by X-ray diffraction analysis.

3. Materials and Methods

3.1. General Information

^{1}H and ^{13}C NMR spectra (Supplementary Materials) were obtained on a Bruker Avance III 400 HD spectrometer (Fällanden, Switzerland) (at 400 and 100 MHz, respectively) in DMSO-d_6 using the solvent residual signal (in ^{1}H NMR, 2.50 for DMSO-d_6; in ^{13}C NMR, 39.51 for DMSO-d_6) as an internal standard. IR spectrum was recorded on a Perkin Elmer Spectrum Two Spectrometer (Shelton, CT, USA) as mulls in mineral oil. The melting point was measured on the device of the Khimlabpribor PTP (USSR). Elemental analysis was carried out on a Vario MICRO Cube analyzer (Langenselbold, Germany). The single crystal X-ray analysis of compound 1 was performed on an Xcalibur Ruby diffractometer (Agilent Technologies, Wroclaw, Poland). An empirical absorption correction was introduced via the multi-scan method using the SCALE3 ABSPACK algorithm [8]. Using OLEX2 [9], the structure was solved with the SHELXT [10] program and refined by a full-matrix least-squares minimization in the anisotropic approximation of all non-hydrogen atoms with the SHELXL [11] program. Hydrogen atoms bound to carbon were positioned geometrically and refined using a riding model. Hydrogen atoms of OH, NH and NH_2 groups were refined independently with isotropic displacement parameters. Thin-layer chromatography (TLC) was performed on Macherey-Nagel Alugram Sil G/UV$_{254}$ (Düren, Germany) plates using EtOAc/MeOH, 3:1 *v*/*v*, as eluents and was manifested with iodine vapor. The starting compound 3 was obtained according to the reported procedures [12] from commercially available reagents. All procedures with compound 3 were performed in oven-dried glassware. All other solvents and reagents were purchased from commercial vendors and used as received.

3.2. 3-(4-Bromophenyl)-1-carbamothioyl-5-(2-carbamothioylhydrazinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic Acid **1**

A suspension of 2 g (7.4 mmol) 4-(4-bromophenyl)-2,4-dioxobutanoic acid 3 and 1.345 g (14.8 mmol) thiosemicarbazide 2 in 30 mL EtOH was refluxed for 2 h. Next, the reaction mixture was cooled to room temperature. The formed precipitate was filtered off and recrystallized from ethanol to yield the title compound 1. Yield: 1,84 г (76%); yellow solid; mp 253–255 °C (decomp.). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.50 d, 3.64 d (2H), 6.33 (s, 1H), 7.60–7.97 (m, 2H), 7.68 (d, 2H), 7.79 (d, 2H), 8.15 (d, 2H), 8.39 (s, 1H), 13.47 (br.s, 1H). ^{13}**C** NMR (DMSO-d_6, 100 MHz): δ = 41.9, 83.5, 124.0, 128.8, 129.5, 131.6, 150.2, 169.1, 175.7, 183.3. IR (mineral oil): 3439, 3309, 3176, 1766, 1660 cm^{-1}. Anal.Calcd (%) for $C_{12}H_{13}BrN_6O_2S_2$: C 34.54; H 3.14; N 20.14. Found: C 34.79; H 3.08; N 20.06.

Crystal Data of **1**. $C_{12}H_{13}BrN_6O_2S_2 \cdot H_2O$, M = 435.33, monoclinic, space group $P2_1/c$, a = 9.2792(15) Å, b = 17.129(4) Å, c = 10.939(2) Å, β = 92.809(15)°, V = 1736.6(6) Å^3, T = 295(2) K, Z = 4, μ(Mo Kα) = 2.632 mm^{-1}. The final refinement parameters: R_1 = 0.0479 (for observed 3031 reflections with $I > 2\sigma(I)$); wR_2 = 0.1232 (for all independent 4020 reflections, R_{int} = 0.0446), S = 1.034. Largest diff. peak and hole were 0.451 and –0.907 ēÅ^{-3}. Crystal structure of compound **1** was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2310650.

Supplementary Materials: Copies of the NMR spectra for the new compound can be downloaded online.

Author Contributions: Conceptualization, A.N.M.; methodology, A.A.A. and A.N.M.; validation, A.A.A. and A.N.M.; investigation, A.A.A. (synthetic chemistry) and M.V.D. (X-ray analysis); writing—original draft preparation, A.A.A. and A.N.M.; writing—review and editing, A.A.A. and A.N.M.; visualization, A.A.A.; supervision, A.N.M.; project administration, A.N.M.; funding acquisition, A.N.M. All authors have read and agreed to the published version of the manuscript.

Funding: This study was performed with financial support from the Perm Research and Educational Center "Rational subsoil use".

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The presented data are available in this article.

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

References

1. Nehra, B.; Rulhania, S.; Jaswal, S.; Kumar, B.; Singh, G.; Monga, V. Recent advancements in the development of bioactive pyrazoline derivatives. *Eur. J. Med. Chem.* **2020**, *205*, 112666. [CrossRef] [PubMed]
2. Nasab, N.H.; Azimian, F.; Shim, R.S.; Eom, Y.S.; Shah, F.H.; Kim, S.J. Synthesis, anticancer evaluation, and molecular docking studies of thiazolyl-pyrazoline derivatives. *Bioorg. Med. Chem. Lett.* **2023**, *80*, 129105.
3. Anant, A.; Ali, A.; Ali, A.; Gupta, G.; Asati, V. A Computational approach to discover potential quinazoline derivatives against CDK4/6 kinase. *J. Mol. Struct.* **2021**, *1245*, 131079. [CrossRef]
4. Idemudia, O.; Sadimenko, A.; Hosten, E. Metal Complexes of New Bioactive Pyrazolone Phenylhydrazones; Crystal Structure of 4-Acetyl-3-methyl-1-phenyl-2-pyrazoline-5-one phenylhydrazone Ampp-Ph. *Int. J. Mol. Sci.* **2016**, *17*, 687. [CrossRef] [PubMed]
5. Jia, L.; Gao, S.; Zhang, Y.-Y.; Zhao, L.-X.; Fu, Y.; Ye, F. Fragmenlt Recombination Design, Synthesis, and Safener Activity of Novel Ester-Substituted Pyrazole Derivatives. *J. Agric. Food Chem.* **2021**, *69*, 8366–8379. [CrossRef] [PubMed]
6. Igidov, S.N.; Turyshev, A.; Makhmudov, R.R.; Shipilovskikh, D.A.; Igidov, N.M.; Shipilovskikh, S.A. Synthesis, Intramolecular Cyclization, and Analgesic Activity of Substituted 2-[2-(Furancarbonyl)hydrazinylydene]-4-oxobutanoic Acids. *Russ. J. Gen. Chem.* **2022**, *92*, 1629–1636. [CrossRef]
7. Lipin, D.V.; Denisova, E.I.; Devyatkin, I.O.; Okoneshnikova, E.A.; Shipilovskikh, D.A.; Makhmudov, R.R.; Igidov, N.M.; Shipilovskikh, S.A. Recyclization of 3-(Thiophen-2-yl)imino-3H-furan-2-ones under the Action of Cyanoacetic Acid Derivatives. *Russ. J. Gen. Chem.* **2020**, *91*, 809.
8. *CrysAlisPro*, Version 1.171.42.74a; Rigaku Oxford Diffraction: Wroclaw, Poland, 2022. Available online: https://www.rigaku.com/products/crystallography/crysalis (accessed on 1 December 2023).
9. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341. [CrossRef]
10. Sheldrick, G.M. SHELXT–Integrated space-group and crystal-structure determination. *Acta Crystallogr. Sect. A Found. Adv.* **2015**, *71*, 3–8. [CrossRef] [PubMed]
11. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8. [CrossRef] [PubMed]
12. Andreychikov, Y.S. *Guidelines for Student Research Work: Methods of Synthesis of Biologically Active Heterocyclic Compounds*; Perm University: Perm, Russia, 1988; p. 13. (In Russian)