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Short Note

4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazol-3-amine

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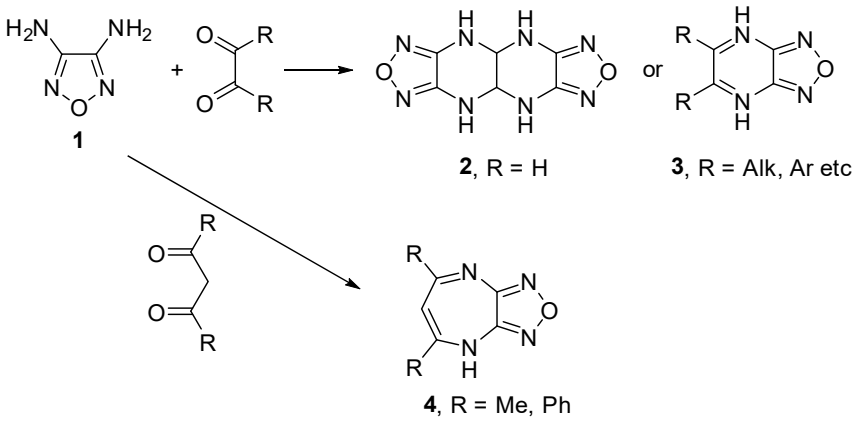
Abstract: 1,2,5-Oxadiazol-3-amines with a heterocyclic substituent in the 4-position are being intensively investigated as compounds with valuable pharmacological activity. In this communication, the reaction of 1,2,5-oxadiazole-3,4-diamine with 2,5-hexanedione was shown to selectively give 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazol-3-amine as a product of the Paal–Knorr reaction. The structure of the synthesized compound was established by elemental analysis, high-resolution mass spectrometry, ^{1}H and ^{13}C NMR, and IR spectroscopy.

Keywords: 1,2,5-oxadiazoles; 1,2,5-oxadiazole-3,4-diamine; Paal–Knorr reaction; 2,5-hexanedione

1. Introduction

1,2,5-Oxadiazoles (furazans) are an important class of heterocyclic compounds that exhibit various forms of biological activity [1]. Of greatest interest among these heterocycles are 3-aminofurazans and especially the commercially available 1,2,5-oxadiazole-3,4-diamine **1** (CAS 17220-38-1), which is the starting material for the synthesis of compounds with biological activity [2] and components of powerful energy compositions [3]. One of the most studied reactions for *ortho*-substituted aromatic and heterocyclic amines is the reaction with diketo derivatives, which leads to various polycyclic compounds. Treatment of 1,2,5-oxadiazole-3,4-diamine **1** with α-diketones gave 4a,5,9a,10-tetrahydro-4*H*,9*H*-[1,2,5]oxadiazolo[3′,4′:5,6]pyrazino[2,3-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine **2** (R = H) [4] or [1,2,5]oxadiazolo[3,4-*b*]pyrazines **3** (R = Alk, Ar) [5,6], and with β-diketones led to 4*H*-[1,2,5]oxadiazolo[3,4-*b*][1,4]diazepines **4** [7] (Scheme 1). Other diketo derivatives in the reaction with 1,2,5-oxadiazole-3,4-diamine have not been previously studied. Meanwhile, it is difficult to predict the course of reaction for various diketo derivatives, and the reaction products may be of interest as biologically active compounds. Herein, we report the study of the reaction between 1,2,5-oxadiazole-3,4-diamine **1** and 2,5-hexanedione and the synthesis of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazol-3-amine **5**.



Scheme 1. Reaction of 1,2,5-oxadiazole-3,4-diamine **1** with α-diketones.

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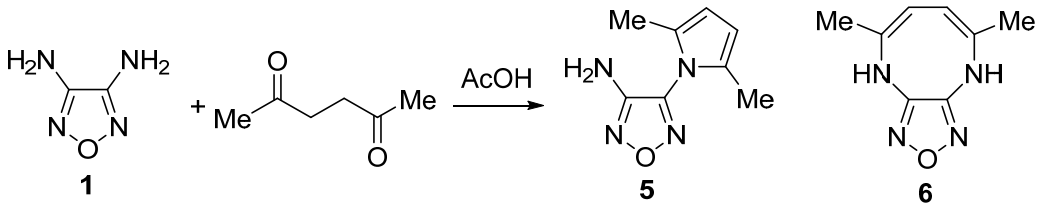
2. Results and Discussion

Treatment of 1,2,5-oxadiazole-3,4-diamine **1** with 1.1 equivalents of 2,5-hexanedione in AcOH gave a new product **5** (Scheme 2). When the reaction was carried out at room temperature, the starting compound **1** did not disappear within 10 h. Heating the mixture to 40–45 °C accelerated the reaction, which was completed within two hours with the formation of compound **5**. According to the HRMS, elemental analysis, and ^{1}H and ^{13}C NMR data (Supplementary Materials), compound **5** is formally the product of the addition of 2,5-hexanedione and elimination of two H_2O molecules. The ^{1}H spectra of compound **5** showed the presence of two methyl groups (2.13 ppm), two identical C-H groups (5.98 ppm), and a broad signal (4.17 ppm) that can be attributed to the amino group. The IR spectrum had characteristic bands for the NH_2 group (3409, 3328, 3255 and 3211 cm^{-1}). The presence of five signals in the ^{13}C NMR spectrum of compound **5** makes it possible to reject the symmetrical structure of (5*Z*,7*Z*)-5,8-dimethyl-4,9-dihydro-[1,2,5]oxadiazolo[3,4-*b*][1,4]diazocine **6**, which should contain four signals in the ^{13}C NMR spectrum. Thus, the spectral data unambiguously confirm the structure of compound **5** as a Paal–Knorr reaction product of 1,2,5-oxadiazole-3,4-diamine **1** at one amino group. When a mixture of one equiv. of compound **1** was refluxed in AcOH with four equiv. of 2,5-hexanedione, compound **5** was formed, and then gradually decomposed with the formation of a mixture of products, from which we were unable to isolate individual compounds including 3,4-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazole. It is known that the reaction of *ortho*-phenylenediamine with 2,5-hexanedione leads to mono- and bis-pyrrole products of the Paal–Knorr reaction [8,9].



Scheme 2. Synthesis of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazol-3-amine **5**.

In conclusion, the selective synthesis of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazol-3-amine **5** was developed in the reaction of 1,2,5-oxadiazole-3,4-diamine **1** with 2,5-hexanedione in AcOH. 1,2,5-Oxadiazoles containing a pyrrole group at position 3 are known to exhibit antiproliferative activity in the sea urchin embryo model and in cultured human cancer cell lines [10,11]. In addition, many 1,2,5-oxadiazole-3-amines with a heterocyclic substituent at position 4 are known to have valuable pharmacological activity, see, for example, references [12–16]. Therefore, compound **5** may also have useful pharmacological properties.

3. Materials and Methods

The solvents and reagents were purchased from commercial sources and used as received. Elemental analysis was performed on a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and is uncorrected. ^{1}H and ^{13}C NMR spectra were taken with a Bruker AM-300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) at frequencies of 300 and 75 MHz, correspondingly. The high-resolution MS spectrum was measured using a Bruker micrOTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) with electrospray ionization (ESI). The IR spectrum was measured with a Bruker "Alpha-T" instrument in KBr pellet.

Synthesis of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,2,5-oxadiazol-3-amine **5** (Supplementary Materials).

2,5-Hexanedione (0.51 mL, 4.4 mmol) was added to a solution of 1,2,5-oxadiazole-3,4-diamine (400 mg, 4 mmol) in AcOH (5 mL). The reaction mixture was stirred for 2 h at 40–45 °C, and then cooled to room temperature. Water (40 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over

$MgSO_4$, and the solvent was evaporated under reduced pressure. The solvent was removed and the residue was purified by column chromatography on silica gel (Silica gel Merck 60, eluent hexane/EtOAc, 10:1, *v*/*v*). Yield 510 mg (72%), colorless solid. Mp = 93–94 °C. IR spectrum (KBr), ν, cm^{-1}: 3409, 3328, 3255, and 3211 (NH_2), 2952, 2927 (C-H), 1646 (C=N), 1557, 1428, 1382, 1067, 989, 851, 778, 583. ^{1}H NMR ($CDCl_3$, ppm): δ 5.98 (2H, s, CH), 4.17 (2H, br s, NH_2), 2.13 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 153.1 (C-N), 144.5 (C-N), 129.5 (C-CH_3), 108.8 (CH), 12.1 (CH_3). HRMS (ESI-TOF), *m*/*z*: calcd for $C_8H_{11}N_4O$ $[M + H]^+$ 179.0927. Found, 179.0930. Anal. calcd for $C_8H_{10}N_4O$: C, 53.91; H, 5.66; N, 31.45. Found: C, 53.87; H, 5.61; N, 31.39%.

Supplementary Materials: The following are available online: copies of ^{1}H, ^{13}C NMR, IR, and HR mass-spectra for the compound **5**.

Author Contributions: Conceptualization, N.V.O.; methodology, O.A.R.; software, N.V.O.; validation, O.A.R.; formal analysis, investigation, N.V.O.; resources, O.A.R.; data curation, O.A.R.; writing—original draft preparation, O.A.R.; writing—review and editing, O.A.R.; visualization, O.A.R.; supervision, O.A.R.; project administration, O.A.R.; funding acquisition, O.A.R. All authors have read and agreed to the published version of the manuscript.

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Sample Availability: Samples of compound **5** are available from the authors.

References

1. Makhova, N.N.; Fershtat, L.L. 1,2,5-Oxadiazoles. In *Comprehensive Heterocyclic Chemistry IV*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 190–251. [CrossRef]
2. Sheremetev, A.B.; Makhova, N.N.; Friedrichsen, W. Monocyclic furazans and furoxans. *Adv. Heterocycl. Chem.* **2001**, *78*, 65–188. [CrossRef]
3. Fershtat, L.L.; Makhova, N.N. 1,2,5-Oxadiazole-Based High-Energy-Density Materials: Synthesis and Performance. *Chempluschem* **2020**, *85*, 13–42. [CrossRef]
4. Willer, R.L.; Moore, D.W. Synthesis and chemistry of some furazano- and furoxano[3,4-b]piperazines. *J. Org. Chem.* **1985**, *50*, 5123–5127. [CrossRef]
5. Gasco, A.; Ruà, G.; Menziani, E.; Nano, G.M.; Tappi, G. Studies in the chemistry of 1,2,5-oxadiazole. I. Synthesis of some furazanopyrazines from 3,4-diamino-1,2,5-oxadiazole. *J. Heterocycl. Chem.* **1969**, *6*, 769–770. [CrossRef]
6. Ignat'Ev, N.V.; Schulte, M.; Koppe, K.; Barthen, P.; Zlotin, S.G.; Makhova, N.N.; Sheremetev, A.B.; Valente, A.A. Ionic Liquids—Advanced Reaction Media for Organic Synthesis. *Phosphorus Sulfur Silicon Relat. Elem.* **2011**, *186*, 1205–1216. [CrossRef]
7. Gasco, A.; Ruá, G.; Menziani, E.; Nano, G.M.; Tappi, G. Studies in the chemistry of 1,2,5-oxadiazole (II). Synthesis and properties of furazanodiazepines. *J. Heterocycl. Chem.* **1970**, *7*, 131–133. [CrossRef]
8. Guo, L.; Zhou, M.; Guo, H.; Xu, W.; Li, Z. Dilithium complex incorporating phenyl bridged neutral pyrrolyl-arylamide ligand: Synthesis, characterization, reaction, and catalytic activity. *Inorg. Chem. Commun.* **2020**, *119*, 108036. [CrossRef]
9. Akbaşlar, D.; Demirkol, O.; Giray, S. Paal–Knorr Pyrrole Synthesis in Water. *Synth. Commun.* **2014**, *44*, 1323–1332. [CrossRef]
10. Stepanov, A.I.; Astrat'Ev, A.A.; Sheremetev, A.B.; Lagutina, N.K.; Palysaeva, N.V.; Tyurin, A.Y.; Aleksandrova, N.S.; Sadchikova, N.P.; Suponitsky, K.Y.; Atamanenko, O.P.; et al. A facile synthesis and microtubule-destabilizing properties of 4-(1H-benzo[d]imidazol-2-yl)-furazan-3-amines. *Eur. J. Med. Chem.* **2015**, *94*, 237–251. [CrossRef] [PubMed]
11. Kulikov, A.S.; Epishina, M.A.; Batog, L.V.; Rozhkov, V.Y.; Makhova, N.N.; Konyushkin, L.D.; Semenova, M.N.; Semenov, V.V. Synthesis and antineoplastic properties of (1H-1,2,3-triazol-1-yl)furazans. *Russ. Chem. Bull.* **2013**, *62*, 836–843. [CrossRef] [PubMed]
12. Li, Q.; Chen, Y.; Xing, S.; Liao, Q.; Xiong, B.; Wang, Y.; Lu, W.; He, S.; Feng, F.; Liu, W.; et al. Highly Potent and Selective Butyrylcholinesterase Inhibitors for Cognitive Improvement and Neuroprotection. *J. Med. Chem.* **2021**, *64*, 6856–6876. [CrossRef]
13. Wlodarchak, N.; Teachout, N.; Beczkiewicz, J.; Procknow, R.; Schaenzer, A.J.; Satyshur, K.; Pavelka, M.; Zuercher, W.; Drewry, D.; Sauer, J.-D.; et al. In Silico Screen and Structural Analysis Identifies Bacterial Kinase Inhibitors which Act with β-Lactams to Inhibit Mycobacterial Growth. *Mol. Pharm.* **2018**, *15*, 5410–5426. [CrossRef]

14. Schaenzer, A.J.; Wlodarchak, N.; Drewry, D.H.; Zuercher, W.J.; Rose, W.E.; Striker, R.; Sauer, J.-D. A screen for kinase inhibitors identifies antimicrobial imidazopyridine aminofurazans as specific inhibitors of the Listeria monocytogenes PASTA kinase PrkA. *J. Biol. Chem.* **2017**, *292*, 17037–17045. [CrossRef] [PubMed]
15. Pyrkov, T.V.; Sevostyanova, I.A.; Schmalhausen, E.V.; Shkoporov, A.N.; Vinnik, A.A.; Muronetz, V.I.; Severin, F.F.; Fedichev, P.O. Structure-Based Design of Small-Molecule Ligands of Phosphofructokinase-2 Activating or Inhibiting Glycolysis. *ChemMedChem* **2013**, *8*, 1322–1329. [CrossRef] [PubMed]
16. Bandarage, U.; Hare, B.; Parsons, J.; Pham, L.; Marhefka, C.; Bemis, G.; Tang, Q.; Moody, C.S.; Rodems, S.; Shah, S.; et al. 4-(Benzimidazol-2-yl)-1,2,5-oxadiazol-3-ylamine derivatives: Potent and selective p70S6 kinase inhibitors. *Bioorganic Med. Chem. Lett.* **2009**, *19*, 5191–5194. [CrossRef] [PubMed]