Chemistry of Heterocyclic Compounds, Vol. 45, No. 2, 2009

SYNTHESIS OF SUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

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Monosubstituted oxadiazoles were synthesized by the reaction of hydrazides with triethyl orthoformate. Their reactions with benzoyl chloride gave benzoylcarbohydrazides, which under the action of thionyl chloride were cyclized to the respective 2,5-disubstituted oxadiazoles. 1-Aryl-4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-pyrrolidin-2-ones were synthesized from acid hydrazides using carbon disulfide under basic conditions.

Keywords: acid hydrazides, benzoyl chloride, 2-pyrrolidinone, substituted oxadiazoles, thionyl chloride, 5-thioxo-1,3,4-oxadiazoles.

1,3,4-Oxadiazoles are important for both chemical and biological purposes. A number of these compounds have demonstrated antibacterial [1], antimicrobial [2], herbicidal [3], and anti-inflammatory [4–6] activities.

The present work aims to investigate the synthesis of substituted 1,3,4-oxadiazoles from 1-aryl-5-oxopyrrolidine-3-carbohydrazides and to establish the structure of the products by chemical and spectral methods.

Monosubstituted derivatives of oxadiazole can be obtained directly from acid hydrazides and triethoxymethane. 1,3,4-Oxadiazoles **3** were synthesized by refluxing hydrazides **1a**,**b** in an excess of triethyl orthoformate (Scheme). The target compounds crystallized from the reaction mixture after cooling. In their ^{1}H NMR spectra the signals characteristic for the $NHNH_2$ fragment of the initial hydrazines are absent, while the proton signal of the CH=N fragment in the oxadiazole moiety is observed in lower field (9.23 ppm).

2,5-Disubstituted oxadiazoles **5** were obtained when the respective benzoyl hydrazydes were dehydrated with thionyl chloride. The products were separated from the reaction mixture by column chromatography.

Acyl derivatives of the respective hydrazides **4** were synthesized by stirring acid hydrazides **1a**,**c–e** with benzoyl chloride in pyridine. Hydrazinocarbonyl compounds undergo reaction with carbon disulfide in the presence of potassium hydroxide quite easily. 1-Aryl-4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrrolidin-2-ones **6c–e** were synthesized from acid hydrazides **1c–e** according to the method described in the literature [7]. In their ^{1}H NMR spectra, besides the characteristic proton signals of aromatic and pyrrolidinone ring moieties, singlets of the NH group proton at 14.52, 14.52, and 14.49, are observed.

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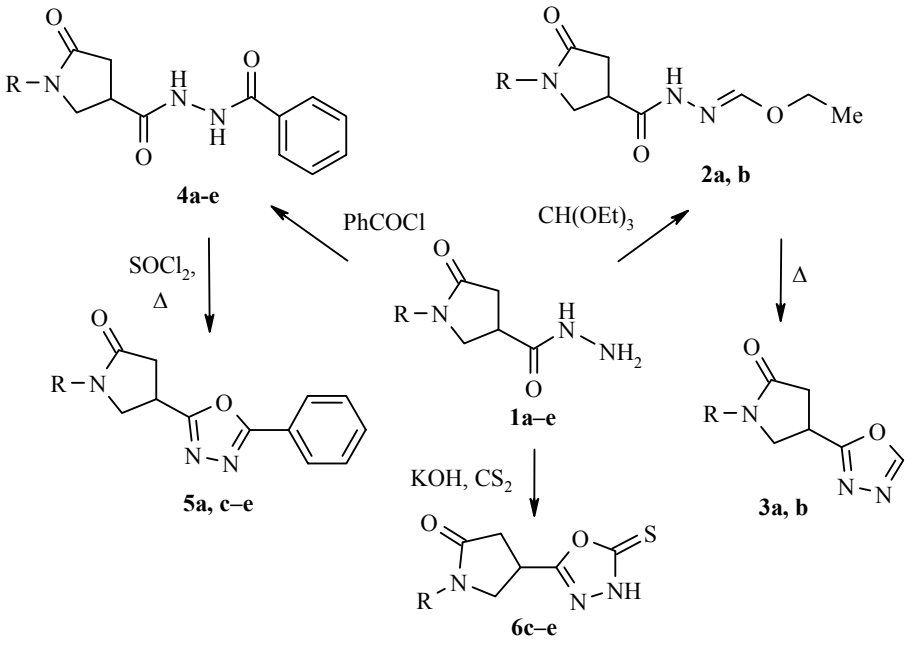
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 269-272, February, 2009. Original article submitted April 7, 2008.



a R = Ph; **b** R = 4-$MeOC_6H_4$; **c** R = 4-$EtOC_6H_4$; **d** R = 4-$PhOC_6H_4$; **e** R = 4-ClC_6H_4

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were obtained on a Varian Unity Inova spectrometer (300 and 75 MHz respectively) in DMSO-d_6 with TMS as internal standart. The IR spectra were recorded on a Perkin-Elmer Spectrum Bx FT IR instrument in tablets with potassium bromide. The mass spectra were determined on a Waters ZQ 2000 spectrometer with electrospray ionization (ESI, 20 V). Silica gel plates Alugram Sil G/UV-254 were used for monitoring the reaction and the purity of the products. Elemental analysis was carried out on the C,H,N Analyzer CE 440, and the melting point was determined on the auto probe analyzer APA 1.

1-Aryl-4-(1,3,4-oxadiazol-2-yl)pyrrolidin-2-ones 3a,b (General Method). A mixture of the respective hydrazide **1a**,**b** (10 mmol) and triethyl orthoformate (13.3 ml, 80 mmol) was heated under reflux for 8 h and cooled. The crystals that separated after the mixture was cooled were filtered off, washed with ether, and dried.

4-(1,3,4-Oxadiazol-2-yl)-1-phenylpyrrolidin-2-one (**3a**). Yield 89%; mp 135-136°C (2-propanol). IR spectrum, ν, cm^{-1}: 1693 (C=O). ^1H NMR spectrum, δ, ppm: 2.9-3.2 (2H, m, H-3); 4.0-4.2 (2H, m, H-5); 4.2-4.3 (1H, m, H-4); 7.1–7.7 (5H, m, ArH); 9.23 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 27.29 (C-4); 35.62 (C-3); 50.25 (C-5); 119.29, 123.95, 128.36, 138.57 (C arom); 154.56 (C-4'); 166.09 (C-1'); 170.78 (C=O). Mass spectrum, *m/z* (*I*, %): 230 $[M+H]^+$ (100). Found, %: C 62.52; H 4.79; N 18.40. $C_{12}H_{11}N_3O_2$. Calculated, %: C 62.87; H 4.84; N 18.33.

1-(4-Methoxyphenyl)-4-(1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**3b**). Yield 82%; mp 133-134°C (2-propanol). IR spectrum, ν, cm^{-1}: 1694 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.8-3.1 (2H, m, H-3); 3.74 (3H, s, OCH_3); 4.0-4.2 (2H, m, H-5); 4.2–4.3 (1H, m, H-4); 6.9–7.6 (4H, 2d, *J* = 9, ArH); 9.23 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 27.58 (C-4); 35.67 (C-3); 50.87 (C-5); 55.15 (CH_3); 113.78, 121.48, 131.98, 155.987 (C arom); 154.82 (C-4′); 166.42 (C-1'); 170.54 (C=O). Mass spectrum, *m/z* (*I*, %): 260 $[M+H]^+$ (100). Found, %: C 60.16; H 5.01; N 16.30. $C_{13}H_{13}N_3O_3$. Calculated, %: C 60.23; H 5.05; N 16.21.

N'-Benzoyl-5-oxo-1-phenylpyrrolidine-3-carbohydrazides 4a–e (General Method). A solution of the respective hydrazide **1a–e** (10 mmol) in 10 ml of pyridine was stirred and over 10 min benzoyl chloride (1.74 ml, 15 mmol) was added dropwise. A mixture was additionally stirred for 6 h and then diluted with 40 ml of ~5% hydrochloric acid. The formed solid was filtered off, washed with water, and dried.

N'-Benzoyl-5-oxo-1-phenylpyrrolidine-3-carbohydrazide (**4a**). Yield 74%; mp 213-214°C (ethanol). IR spectrum, ν, cm^{-1}: 3196, 3030 (NH); 1677, 1594, 1577 (C=O). ^1H NMR spectrum, δ, ppm: 2.6-2.9 (2H, m, H-3); 3.6-3.8 (2H, m, H-5); 3.9–4.3 (1H, m, H-4); 7.2-8.1 (10H, m, ArH); 10.19 (1H, s, NH); 10.41 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 324 $[M+H]^+$ (100). Found, %: C 66.94; H 5.15; N 13.11. $C_{18}H_{17}N_3O_3$. Calculated, %: C 66.86; H 5.30; N 13.00.

N'-Benzoyl-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carbohydrazide (**4b**). Yield 73%; mp 203-204°C (ethanol). IR spectrum, ν, cm^{-1}: 3198, 3049 (NH); 1668, 1595, 1577 (C=O). ^1H NMR spectrum, δ, ppm: 2.6-2.9 (2H, m, H-3); 3.73 (3H, s, OCH_3); 3.8-4.2 (3H, m, H-4, 5); 6.9-7.9 (9H, m, ArH); 10.21 (1H, s, NH); 10.46 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 354 $[M+H]^+$ (100). Found, %: C 64.51; H 5.38; N 11.95. $C_{19}H_{19}N_3O_4$. Calculated, %: C 64.58; H 5.42; N 11.89.

N'-Benzoyl-1-(4-ethoxyphenyl)-5-oxopyrrolidine-3-carbohydrazide (**4c**). Yield 74%; mp 204-205°C (ethanol). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.3, CH_3); 2.6-2.9 (2H, m, H-3); 3.3-3.5 (2H, m, H-5); 3.8-4.1 (3H, m, H-4, OCH_2); 6.9–7.9 (9H, m, ArH); 10.21 (1H, s, NH); 10.45 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 368 $[M+H]^+$ (100). Found, %: C 65.50; H 5.48; N 11.37. $C_{20}H_{21}N_3O_4$. Calculated, %: C 5.38; H 5.76; N 11.44.

N'-Benzoyl-5-oxo-1-(4-phenoxyphenyl)pyrrolidine-3-carbohydrazide (**4d**). Yield 81%; mp 194-195°C (dioxane). ^1H NMR spectrum, δ, ppm: 2.6-2.9 (2H, m, H-3); 3.3–3.6 (2H, m, H-5); 3.9-4.3 (1H, m, H-4); 6.7-8.0 (9H, m, ArH); 10.22 (1H, s, NH); 10.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 33.86 (C-4); 35.45 (C-3); 50.67 (C-5); 118.08, 119.18, 121.22, 123.18, 127.39, 128.47, 129.99, 131.89, 132.23, 134.89, 152.51, 157.03 (C arom); 165.53 (NH–CO–CH); 171.60 (CH–CO–NH); 172.01 (C=O). Mass spectrum, *m/z* (*I*, %): 416 $[M+H]^+$ (100). Found, %: C 69.01; H 5.49; N 10.13. $C_{24}H_{21}N_3O_4$. Calculated, %: C 69.39; H 5.10; N 10.11.

N'-Benzoyl-1-(4-chlorophenyl)-5-oxopyrrolidine-3-carbohydrazide (**4e**). Yield 84%; mp 226-227°C (dioxane). IR spectrum, ν, cm^{-1}: 3302, 3208 (NH); 1678, 1654, 1648 (C=O). ^1H NMR spectrum, δ, ppm: 2.6-2.9 (2H, m, H-3); 3.3-3.6 (2H, m, H-5); 3.9-4.3 (1H, m, H-4); 7.3-8.0 (9H, m, ArH); 10.18 (1H, s, NH); 10.41 (1H, s, NH). Found, %: C 60.13; H 4.83; N 11.80. $C_{18}H_{16}ClN_3O_3$. Calculated, %: C 60.43; H 4.51; N 11.74.

1-Aryl-4-(5-aryl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-ones 5a,c-e (General Method). A mixture of the respective acylhydrazide **4a–c,e** (0.01 mol) and chloroform (10 ml) was stirred and thionyl chloride (0.72 ml, 10 mmol) was added dropwise. The mixture was heated under reflux for 20 h, and the obtained transparent liquid distilled *in vacuo*. The product formed after the vacuum distillation was purified by the method of column chromatography.

1-Phenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**5a**). Yield 29%; mp 127–128°C; R_f 0.36 (acetone–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1697 (C=O). ^1H NMR spectrum, δ, ppm: 2.8–3.1 (2H, m, H-3); 4.1–4.3 (3H, m, H-5, 4); 7.1–8.2 (10H, m, ArH). Mass spectrum, *m/z* (*I*, %): 306 $[M+H]^+$ (100). Found, %: C 70.41; H 4.71; N 13.83. $C_{18}H_{15}N_3O_2$. Calculated, %: C 70.81; H 4.95; N 13.76.

1-(4-Ethoxyphenyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**5c**). Yield 27%; mp 126-127°C; R_f 0.28 (acetone–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1697 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.3, CH_3); 2.9-3.1 (2H, m, H-3); 3.98 and 4.10 (2H, q, *J* =7.3, OCH_2); 4.2-4.6 (3H, m, H-5, 4); 6.9-8.1 (9H, m, ArH). Mass spectrum, *m/z* (*I*, %): 350 $[M+H]^+$ (100). Found, %: C 68.90; H 5.27; N 11.87. $C_{20}H_{19}N_3O_3$. Calculated, %: C 68.75; H 5.48; N 12.03.

1-(4-Phenoxyphenyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**5d**). Yield 35%; mp 137-138°C; R_f 0.30 (acetone–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1691 (C=O). ^1H NMR spectrum, δ, ppm: 2.9-3.1 (2H, m, $CO–CH_2$); 4.1-4.3 (2H, m, NCH_2); 6.9-7.7 (14H, m, ArH). Mass spectrum, *m/z* (*I*, %): 398 $[M+H]^+$ (100). Found, %: C 72.44; H 4.89; N 10.48. $C_{24}H_{19}N_3O_3$. Calculated, %: C 72.53; H 4.82; N 10.57.

1-(4-Chlorophenyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**5e**). Yield 33%; mp 163-164°C; R_f 0. 30 (acetone–hexane, 1:2). ^{1}H NMR spectrum, δ, ppm: 2.8-3.2 (2H, m, H-3); 4.2-4.7 (3H, m, H-5, 4); 6.8-8.0 (9H, m, ArH). Mass spectrum, *m/z* (*I*, %): 340 $[M+H]^+$ (100), 342 $[M+2+H]^+$ (30). Found, %: C 63.51; H 4. 35; N 12.42. $C_{18}H_{14}ClN_3O_2$. Calculated, %: C 63.63; H 4.15; N 12.37.

1-Aryl-4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrrolidin-2-ones 6c-e (General Method). A mixture of the respective hydrazide **1c-e** (10 mmol), potassium hydroxide (0.56 g, 10 mmol), and carbon disulfide (1.52 g, 20 mmol) was heated for 48 h in 2-propanol (40 ml), cooled, and acidified with glacial acetic acid. The formed residue was filtered off, washed with water, and dried.

1-(4-Ethoxyphenyl)-4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**6c**). Yield 62%; mp 176–177°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* =7.2, CH_3); 2.8-3.0 (2H, m, H-3); 3.9-4.1 (5H, m, H-5, H-4, O$\underline{CH_2}CH_3$); 6.95 and 7.52 (4H, 2d, *J* = 8.1, ArH,); 14.49 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 306 $[M+H]^+$ (100). Found, %: C 55.37; H 5.20; N 13.79. $C_{14}H_{15}N_3O_3S$. Calculated, %: C 55.07; H 4.95; N 13.76.

1-(4-Phenoxyphenyl)-4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**6d**). Yield 78%; mp 211-212°C (2-propanol). IR spectrum, ν, cm^{-1}: 1666 (C=O), 693 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.9-3.1 (2H, m, H-3); 3.8-4.2 (3H, m, H-5, 4); 7.0-7.8 (9H, m, ArH); 14.52 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 354 $[M+H]^+$ (100). Found, %: C 61.10; H 4.43; N 12.00. $C_{18}H_{15}N_3O_3S$. Calculated, %: C 61.18; H 4.28; N 11.89.

1-(4-Chlorophenyl)-4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (**6e**). Yield 77%; mp 222-223°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.9-3.1 (2H, m, H-3); 4.0-4.4 (3H, m, H-5, 4); 7.46 and 7.71 (4H, 2d, *J* = 6.9, ArH); 14.52 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 296 $[M+H]^+$ (100), 296 $(M+2+H)^+$ (30). Found, %: C 48.32; H 3.13; N 14.36. $C_{12}H_{10}ClN_3O_2S$. Calculated, %: C 48.74; H 3.41; N 14.21.

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