4-AMINOSUBSTITUTED 1,2,4-OXADIAZOLIDIN-3,5-DIONES

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Abstract: 4-Aminosubstituted 1,2,4-oxadiazolidin-3,5-diones (7) are prepared by cyclic carbonylation of 1,1-disubstituted 4-hydroxysemicarbazides (5) with methyl chloroformate.

INTRODUCTION

Since their discovery in 1959 by Zinner [1], 1,2,4-oxadiazolidin-3,5-diones **1** have found wide application in medicinal chemistry [2] and agrochemistry [3]. Although numerous derivatives originated from the parent heterocycle [4] over the past decades, the corresponding 4-aminosubstituted 1,2,4-oxadiazolidin-3,5-diones **7** remained unknown until hitherto. Herein we wish to report on a synthetic route to the title molecules which can be regarded as bioisosters of the antifungal 3-amino-2,4-oxazolidindiones **2** [6].

Scheme 1

RESULTS AND DISCUSSION

According to the known cyclic carbonylation of hydroxyureas to give **1** [1] we envisioned 4-hydroxy-semicarbazides (**5**) as suitable starting materials for the target molecules **7**. By reacting equimolar amounts of 1,1'-carbonyldiimidazole with 1,1-disubstituted hydrazines (**3**) and subsequent hydroxylaminolysis of the intermediate **4** we obtained **5a-f** in 65-70 % yields as crystalline compounds, characterized by a blue or purple color reaction with ferric chloride in ethanol.

When **5** was treated with methyl chloroformate in the presence of triethylamine cyclization took place via the open-chained **6**, the (C=O)-absorptions of which (1790, 1690 cm⁻¹) gradually disappeared in favour of the two ring carbonyls of **7** at 1837-1814 and 1738-1755 cm⁻¹. After simple work-up of the reaction mixture **7a-f** could be obtained in satisfactory yields of 45-73% as crystalline and stable compounds, the structure of which follows unambiguously from the analytical data (s. Experimental).

Scheme 2

Conclusion

4-Amino-1,2,4-oxadiazolidin-3,5-diones (7) have been successfully prepared by cyclic carbonylation of 1,1-disubstituted 4-hydroxysemicarbazides (5). Application of this synthetic method to 1-monosubstituted 4-hydroxy-semicarbazides as well as studies directed towards the reactivity and biological activity of 7 are in progress.

Experimental

Melting points were determined on a Mettler FP 62 and are uncorrected. The IR spectra were scanned on a Perkin Elmer 1600 FTIR spectrophotometer. The ¹H-NMR- (400 MHz) and ¹³C-NMR-spectra (100,6 MHz) were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d₆ as solvent. Elemental analysis were performed on a Heraeus CHN-O-Rapid. For all compounds satisfactory microanalyses were obtained (C, H, N : ± 0.4%). Column chromatography was performed on silica gel (ICN Silica 100-200, active).

General procedure for the synthesis of 5a-f

To a stirred, ice-cooled mixture of 1,1'-carbonyldiimidazole (10 mmol) in CH₂Cl₂ (30 ml) was added slowly a solution of the appropriate hydrazine (10 mmol) in CH₂Cl₂ (10 ml). After stirring at ambient temperature for 30 min the corresponding N-substituted hydroxylamine (10 mmol) in CH₂Cl₂ (10 ml) was added. The reaction was followed by running IR-spectra from the mixture until disappearance of the absorption at 1730 cm⁻¹. The solvent was evaporated and the residue chromatographed (THF/diethyl ether, 3:1). Fractions which were devoid of eluted imidazole (IR control) and gave a blue or purple color reaction with FeCl₃ were combined, evaporated and the residue recrystallized from THF/diethyl ether (8:1).

4-Hydroxy-1,4-dimethyl-1-phenylsemicarbazide (5a)

Yield 65 %; mp 151°C; IR (KBr): 3353 (OH), 1637 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 2.99 (s, 3H, NCH₃),

3.07 (s, 3H, NCH₃), 6.70 (m, 3 ArH), 7.15 (m, 2 ArH), 9.15 (s, NH), 9.54 (s, OH); ¹³C-NMR (DMSO-d₆): δ (ppm) 38.3 (CH₃), 40.2 (CH₃), 11.9, 117.3, 128.5, 150.4 (ArC), 159.8 (C=O).

4-Benzyl-4-hydroxy-1-methyl-1-phenylsemicarbazide (5b)

Yield 65%; mp 164 °C; IR (KBr): 3350 (OH), 1635 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 3.10 (s, 3H, NCH₃), 4.57 (s, 2H, CH₂Ph), 6.70 (m, 3ArH), 7.18 (m, 2ArH), 7.32 (m, 5 ArH), 9.21 (s, NH), 9.53 (s, OH); ¹³C-NMR (DMSO-d₆): δ (ppm) 39.7 (CH₃), 53.9 (CH₂), 111.7, 117.5, 126.2, 128.0, 128.5, 138.1, 150.3 (ArC), 158.7 (C=O).

1-(Ethylenoxyethylcn)-4-hydroxy-4-methylsemicarbazide (5c)

Yield 65%; mp 120 °C; IR (KBr): 3224 (OH), 1639 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 2.91 (s, 3H, NCH₃), 2.72 (t, J = 4.6 Hz, 4H, NCH₂), 3.57 (t, J = 4.6 Hz, 4H, OCH₂), 7.96 (s, NH), 9.31 (s, OH); ¹³C-NMR (DMSO-d₆): δ (ppm) 38.5 (CH₃), 54.7 (CH₂), 66.0 (CH₂), 159.2 (C=O).

4-Benzyl-1-(ethylenoxyethylen)-4-hydroxy-semicarbazide (5d)

Yield 75%; mp 150 °C; IR (KBr): 3229 (OH), 1639 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 2.87 (t, J = 4.6 Hz, 4H, NCH₂), 3.61 (t, J = 4.7 Hz, 4H, OCH₂), 4.50 (s, 2H, CH₂Ph), 7.28 (m, 5ArH), 8.08 (s, NH), 9.35 (s, OH); ¹³C-NMR (DMSO-d₆): δ (ppm) 53.8 (CH₂Ph), 54.8 (NCH₂), 66.0 (OCH₂), 126.8, 127.9, 128.0, 137.8 (ArC), 158.7 (C=O).

4-Hydroxy-4-methyl-1-(pentamethylen)semicarbazide (5e)

Yield 70%; mp 142 °C; IR (KBr): 3225 (OH), 1654 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 1.35 (m, 2H, CH₂), 1.57 (m, 4H, CH₂), 2.72 (t, 4H, NCH₂), 2.98 (s, 3H, NCH₃), 7.59 (s, NH), 9.21 (s, OH); ¹³C-NMR (DMSO-d₆): δ (ppm) 22.9 (CH₂), 25.3 (CH₂), 38.6 (NCH₃), 55.7 (NCH₂), 159.2 (C=O).

4-Benzyl-4-hydroxy-1-(pentamethylen)semicarbazide (5f)

Yield 76%; mp 128 °C; IR (KBr): 3211 (OH), 1639 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 1.31 (m, 2H, CH₂), 1.54 (m, 4H, CH₂), 2.70 (t, J = 5.1 Hz, 4H, NCH₂), 4.48 (s, 2H, CH₂Ph), 7.29 (m, 5ArH), 7.80 (s, NH), 9.30 (s, OH); ¹³C-NMR (DMSO-d₆): δ (ppm) 23.4, 25.8 (CH₂), 54.3 (CH₂Ph), 56.2 (NCH₂), 127.2, 128.3, 128.9, 138.3 (ArC), 159.1 (C=O).

General procedure for the synthesis of 7a-f

An ice-cooled solution of **5** (5 mmol) and triethylamine (5 mmol) in CH₂Cl₂ (20 ml) was treated dropwise with methyl chloroformate (5.5 mmol) in CH₂Cl₂ (7 ml). The reaction was followed by IR. After disappearance of the absorptions at 1790 and 1690 cm⁻¹ in favour of (C=O)-bands at 1820 and 1750 cm⁻¹, the reaction mixture was washed with cold brine, the organic layer dried over anhydrous MgSO₄, the solvent evaporated and the residue recrystallized from diethyl ether.

2-Methyl-4-(N-methyl-N-phenyl)amino-1,2,4-oxadiazolidin-3,5-dione (7a)

Yield 58%; mp 87 °C; IR (KBr): 1837, 1744 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 3.32 (s, 3H, NCH₃), 3.40 (s, 3H, NCH₃), 6.90 (m, 2 ArH), 6.98 (m, 1 ArH), 7.30 (m, 2 ArH); ¹³C-NMR (DMSO-d₆): δ (ppm) 36.2 (CH₃), 38.6 (CH₃), 112.7, 120.7, 129.2, 146.7 (ArC), 150.0, 154.7 (C=O).

2-Benzyl-4-(N-methyl-N-phenyl)amino-1,2,4-oxadiazolidin-3,5-dione (7b)

Yield 70%; mp 135 °C; IR (KBr): 1814, 1758 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ (ppm) 3.29 (s, 3H, NCH₃), 4.95 (s, 2H, CH₂Ph), 6.59 (m, 2 ArH), 7.25 (m, 3 ArH), 7.47 (m, 5ArH); ¹³C-NMR (DMSO-d₆): δ (ppm) 39.0 (CH₃), 54.3 (CH₂Ph), 112.8, 121.2, 128.9, 129.2, 133.7, 144.7, 148.2 (ArC), 150.0, 162.3 (C=O).

4-(Ethylenoxyethylen)amino-2-methyl-1,2,4-oxadiazolidin-3,5-dione (7e)

Yield 57%; mp 98 °C; IR (KBr): 1830, 1738 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ (ppm) 3.23 (t, $J = 4.6$ Hz, 4H, NCH_2), 3.28 (s, 3H, CH_3), 3.68 (t, $J = 4.6$ Hz, 4H, OCH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ (ppm) 36.2 (CH_3), 51.2 (NCH_2), 65.9 (OCH_2), 149.9, 155.4 (C=O).

2-Benzyl-4-(ethylenoxyethylen)amino-1,2,4-oxadiazolidin-3,5-dione (7d)

Yield 73%; mp 108 °C; IR (KBr): 1827, 1755 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ (ppm) 3.21 (t, $J = 4.7$ Hz, 4H, NCH_2), 3.67 (t, $J = 4.7$ Hz, 4H, OCH_2), 4.85 (s, 2H, CH_2Ph), 7.38 (m, 5 ArH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ (ppm) 51.7 (NCH_2), 54.9 (CH_2Ph), 66.4 (OCH_2), 128.5, 128.9, 129.6, 150.0 (ArC), 154.9, 160.0 (C=O).

2-Methyl-4-(pentamethylen)amino-1,2,4-oxadiazolidin-3,5-dione (7e)

Yield 45%; mp 60 °C; IR (KBr): 1830, 1750 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ (ppm) 1.38 (m, 2H, CH_2), 1.59 (m, 4H, CH_2), 3.18 (t, $J = 5.1$ Hz, 4H, NCH_2), 3.27 (s, 3H, CH_3); $^{13}\text{C-NMR}$ (DMSO- d_6): δ (ppm) 22.6, 25.3 (CH_2), 36.1 (CH_3), 52.0 (NCH_2), 150.0, 155.6 (C=O).

2-Benzyl-4-(pentamethylen)amino-1,2,4-oxadiazolidin-3,5-dione (7f)

Yield 55%; mp 76 °C; IR (KBr): 1827, 1748 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6): δ (ppm) 1.35 (m, 2H, CH_2), 1.60 (m, 4H, CH_2), 3.12 (t, $J = 5.1$ Hz, 4H, NCH_2), 4.85 (s, 2H, CH_2Ph), 7.35 (m, 5 ArH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ (ppm) 22.5, 25.3 (CH_2), 52.0 (CH_2Ph), 53.3 (NCH_2), 125.8, 128.4, 128.5, 150.2 (ArC), 156.3, 160.2 (C=O).

References and Notes

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