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SELECTIVE HYDROGENOLYSIS OF BENZYL-PROTECTED 1-HYDROXY-3-HYDROXYIMINO-2-PYRROLIDINONES

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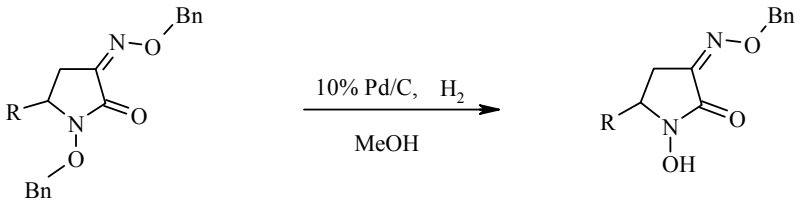
On hydrogenolysis of 1-benzyloxy-3-benzyloxyimino-2-pyrrolidinones in the presence of 10% Pd/C selective removal occurs of the O-benzyl (Bn) protection of the hydroxamic acid, with retention of the double bond and benzyl protection of the oxime group. The yields of reaction products were 66-98%.

Keywords: α-oxyiminohydroxamic acids, 2-pyrrolidinone derivatives, hydrogenolysis.

Acylation of O-benzylhydroxylamine enables protected hydroxamic acids to be obtained. The Bn protection enables subsequent reactions to be carried out with other functional groups of the compound and facilitates the isolation of the desired products. Other functional groups are also frequently reduced on hydrogenolysis of Bn group in the presence of Pd catalysts of various types. On removing benzyl protection from hydroxamic acids in the presence of Pd/C an olefinic bond is also hydrogenated [1], and with $Pd/BaSO_4$ [2] a benzyl ether is split. Hydrogenolysis of the Bn protection of a hydroxamate group in the presence of $Pd(OH)_2/C$ occurs with simultaneous removal of a benzyl ester [3, 4] or with retention of the latter [5]. The oxime bond is not hydrogenated on using 5% Pd/C [6], and the use of $Pd/BaSO_4$ retains a nitro group [7].

Since the presence of a free hydroxamic acid determines the biological activity of compounds, we investigated the hydrogenolysis of derivatives of 1-benzyloxy-3-benzyloxyimino-2-pyrrolidinones [8]. It was established that the hydrogenolysis of 2-pyrrolidinone derivatives **1a-e** in the temperature range 0-20°C in the presence of 10% Pd/C in a current of hydrogen proceeds selectively with removal of the O-benzyl protection and retention of the double bond and Bn protection of the oxime group.



1a–e **2a–e**

1, **2 a** R = Ph, **b** R = 2-thienyl, **c** R = 2-furyl, **d** R = 3,4-$(MeO)_2C_6H_3$, **1e** R = 4-$O_2NC_6H_4$, **2e** R = 4-$H_2NC_6H_4$

The yields of 3-benzyloxyimino-1-hydroxy-2-pyrrolidinones **2** were 66-98%, with the exception of the thienyl derivative of 2-pyrrolidinone **1b**, for which, in spite of prolonged hydrogenation, with fresh catalyst added periodically, a low yield of the desired product was obtained, possibly due to poisoning of the catalyst by

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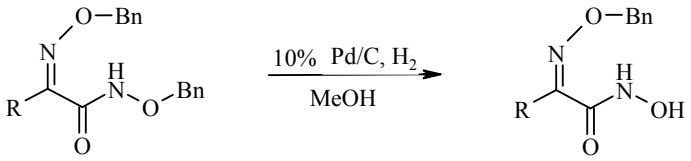
sulfur-containing compounds. In the reaction with nitrophenyl derivative **1e** under these conditions simultaneous reduction of the nitro group occurs.

This method is also applicable to the selective hydrogenolysis of linear benzyl-substituted α-oxyiminohydroxamic acids, such as 2-benzyloxyiminopropano-O-benzylhydroxamate **3a** and 2-benzyloxyimino-4-phenylbutano-O-benzylhydroxamate **3b**. The yields of products **4a** and **4b** were 70 and 59% respectively.



3a,**b** **4a**,**b**

3, **4 a** R = Me, **b** R = $PhCH_2CH_2$

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Mercury 200 (200 MHz) spectrometer in DMSO-d_6, internal standard was TMS. Column chromatography was carried out on Acros silica gel (0.035-0.070 mm), eluent was petroleum ether–AcOEt–2-PrOH, 1:1:0.4. All the synthesized compounds **2a-e** gave a characteristic lilac coloration with $FeCl_3$ solution. The progress of reactions was checked by TLC, using Merck silica gel (F_{254}) plates and the above mentioned eluent. Hydrogenation was carried out in a stream of hydrogen at a temperature from -18 to 20°C in methanol (Acros) in the presence of 10% Pd/C (Acros).

3-Benzyloxyimino-1-hydroxy-2-oxo-5-phenylpyrrolidine (2a) (General Procedure). 10% Pd/C (15 mg) (2.4 mg Pd per mmol of initial compound) was added to a 0.03 M solution of compound **1a** (0.24 g) in MeOH (25 ml). The mixture was hydrogenated in a stream of hydrogen at 20°C for 25 min. The reaction mixture was filtered through Celite, washed with methanol, and the filtrate evaporated. The residue was chromatographed. The 1-hydroxypyrrolidine **2a** (0.12 g, 66%) was obtained as colorless crystals; mp 139-141°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.17-7.45 (10H, m, $2C_6H_5$); 5.30 (2H, s, $OC\underline{H}_2Ph$); 4.97 (1H, dd, J_1 = 8.2, J_2 = 3.4, $C\underline{H}Ph$); 3.35 (1H, dd, J_1 = 19.2, J_2 = 8.2, CH_2); 2.77 (1H, dd, J_1 = 19.2, J_2 = 3.4, CH_2). Found, %: C 68.80; H 5.45; N 9.46. $C_{17}H_{16}N_2O_3$. Calculated, %: C 68.91; H 5.44; N 9.45.

3-Benzyloxyimino-1-hydroxy-2-oxo-5-(2-thienyl)pyrrolidine (2b). A solution of compound **1b** (0.5 g, 1.27 mmol) in MeOH (40 ml) was hydrogenated analogously in the presence of 10% Pd/C at 20°C for 72 h. After chromatography the 1-hydroxy-pyrrolidine **2b** (0.1 g, 26%) was obtained as colorless crystals of mp 156-158°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.27-7.42 (6H, m, C_6H_5, α-Th); 7.07-7.11 (1H, m, β-Th); 6.99 (1H, dd, J_1 = 5.0, J_2 = 3.6, β-Th); 5.31 (2H, s, $OC\underline{H}_2Ph$); 5.21 (1H, dd, J_1 = 8.1, J_2 = 3.8, $C\underline{H}Ph$); 3.40 (1H, dd, J_1 = 19.1, J_2 = 8.1, CH_2); 2.95 (1H, dd, J_1 = 19.1, J_2 = 3.8, CH_2). Found, %: C 9.67; H 4.64; N 9.19; S 10.57. $C_{15}H_{14}N_2O_3S$. Calculated, %: C 59.59; H 4.67; N 9.26; S 10.60.

3-Benzyloxyimino-5-(2-furyl)-1-hydroxy-2-oxopyrrolidine (2c). Compound **1c** (0.5 g, 1.33 mmol) in MeOH (40 ml) was hydrogenated analogously over Pd/C at 0°C for 1 h. The 1-hydroxypyrrolidine **2c** was isolated by crystallization from ethyl acetate as colorless crystals. Yield 0.3 g (78%); mp 129-130°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.35-7.41 (6H, m, C_6H_5, α-Fur); 6.45 (1H, d, *J* = 3.2, β-Fur); 6.37 (1H, dd, J_1 = 3.2, J_2 = 1.9, β-Fur); 5.32 (2H, s, $OC\underline{H}_2Ph$); 5.00 (1H, dd, J_1 = 8.0, J_2 = 4.0, $C\underline{H}Ph$); 3.24 (1H, dd, J_1 = 19.0, J_2 = 8.0, CH_2); 3.06 (1H, dd, J_1 = 19.0, J_2 = 4.0, CH_2). Found, %: C 62.53; H 4.93; N 9.76. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.78.

3-Benzyloxyimino-5-(3,4-dimethoxyphenyl)-1-hydroxy-2-oxopyrrolidine (2d). Compound **1d** (0.13 g, 0.29 mmol) in MeOH (10 ml) was hydrogenated analogously with 10% Pd/C at 0°C for 3 h. The 1-hydroxypyrrolidine **2d** (0.076 g, 73%) was isolated by crystallization from ethanol and diethyl ether as colorless crystals; mp 140-141°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.32-7.36 (5H, m, C_6H_5); 6.86 (1H, d, *J* = 8.2, CH_{arom}); 6.80 (1H, dd, J_1 = 8.2, J_2 = 1.7, CH_{arom}); 6.74 (1H, d, *J* = 1.7, CH_{arom}); 5.28 (2H, s, $OC\underline{H}_2Ph$); 4.91 (1H, dd, J_1 = 8.1, J_2 = 3.6, $C\underline{H}$–$(CH_3O)_2C_6H_3$); 3.87 (6H, s, $2CH_3O$); 3.35 (1H, dd, J_1 = 19.3, J_2 = 8.1, CH_2); 3.73 (1H, dd, J_1 = 19.3, J_2 = 3.6, CH_2). Found, %: C 63.72; H 5.62; N 7.73. $C_{19}H_{20}N_2O_5$. Calculated, %: C 64.04; H 5.66; N 7.86.

5-(4-Aminophenyl)-3-benzyloxyimino-1-hydroxy-2-oxopyrrolidine (2e). Compound **1e** (0.07 g, 0.16 mol) in MeOH (10 ml) was hydrogenated with 10% Pd/C analogously to the general procedure at 0°C for 2 h. After chromatography the 1-hydroxypyrrolidine **2e** (0.050 g: 98%) was obtained as colorless crystals; mp 175-176°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.1 (1H, br. s, OH); 7.27-7.40 (5H, m, C_6H_5); 6.80-6.91 (2H, m, CH_{arom}); 6.46-6.56 (2H, m, CH_{arom}); 5.20 (2H, s, $OC\underline{H}_2Ph$); 5.10 (2H, br. s, NH_2); 4.61 (1H, dd, J_1 = 7.8, J_2 = 3.4, CH_2); 3.28 (1H, dd, J_1 = 18.5, J_2 = 7.8, CH_2); 2.49 (1H, dd, J_1 = 18.5, J_2 = 3.4, CH_2). Found, %: C 64.66; H 5.45; N 13.26. $C_{17}H_{17}N_3O_3 \cdot 0.2H_2O$. Calculated, %: C 64.83; H 5.67; N 13.34.

2-Benzyloxyiminopropanohydroxamic Acid (4a). Compound **3a** (0.076 g, 0.25 mmol) was hydrogenated analogously using 10% Pd/C in MeOH (7 ml) at -18°C for 2 h 45 min. The hydroxamic acid **4a** (0.037 g, 70%) was isolated by crystallization from ethanol and petroleum ether as colorless crystals; mp 76-78°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.8 (1H, br. s, OH); 9.0 (1H, br. s, NH); 7.27-7.43 (5H, m, C_6H_5); 5.14 (2H, s, $OC\underline{H}_2Ph$); 1.90 (3H, s, CH_3). Found, %: C 57.71; H 5.74; N 13.24. $C_{10}H_{12}N_2O_3$. Calculated, %: C 57.69; H 5.81; N 13.45.

2-Benzyloxyimino-4-phenylbutanohydroxamic Acid (4b). Compound **3b** (0.158 g, 0.41 mmol) was hydrogenated analogously using 10% Pd/C in MeOH (15 ml) at 5°C for 2 h. Compound **4b** (0.072 g: 59%) was obtained as colorless crystals; mp 80°C (ethyl acetate–petroleum ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.93 (1H, br. s, OH); 8.04 (1H, br. s, NH); 7.11-7.42 (10H, m, C_6H_5); 5.12 (2H, s, $OC\underline{H}_2Ph$); 2.72-2.96 (4H, m, CH_2–CH_2). Found, %: C 68.31; H 6.05; N 9.42. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44; H 6.08; N 9.39.

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