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Stereoselective synthesis of 4-substituted *cis*-3-(α-hydroxyethyl)-pyrrolidine-2-ones †

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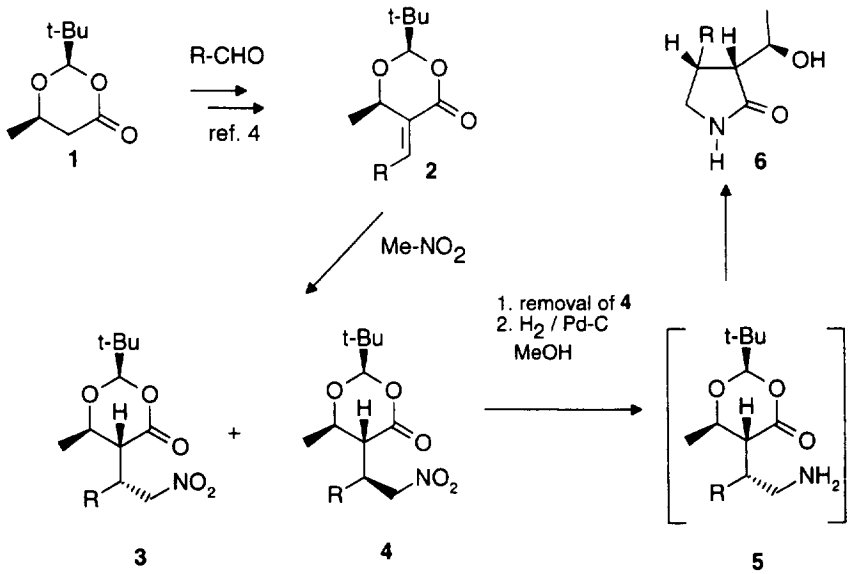
Abstract: Michael-addition of nitromethane anion to 5-ylidene-1,3-dioxane-4-ones **2** gives high yields of 5-(β-nitroalkyl)-1,3-dioxane-4-ones **3** and **4** with a preponderance of **3** (*re*-attack). Hydrogenation of the products in the presence of Raney-Ni affords optically active 4-substituted *cis*-3-(α-hydroxyethyl)-pyrrolidine-2-ones **6**. © 1997 Elsevier Science Ltd

Introduction

Substituted pyrrolidinones are analogues of γ-aminobutyric acid (GABA) and some of them exhibit biological activity.[1] Seebach *et al.*[2] synthesized 4-substituted 3-(α-hydroxyethyl)-pyrrolidine-2-ones **6** as 1:1 mixtures of *cis* and *trans*-isomers by Michael-addition of β-hydroxybutyrates and nitroalkenes followed by hydrogenation of the resulting γ-nitroesters. Intermediate γ-aminoesters cyclized by intramolecular attack of the amino group at the carbonyl carbon atom. The crucial step in this synthesis was the Michael-addition, which was not at all stereoselective. 6-Trifluoromethyl-analogues of the dioxanones **1** undergo Michael-additions to nitrostyrene with 67:33 stereoselectivity. After reduction of the nitro group, the corresponding 4-substituted 3-(2,2,2-trifluoro-1-hydroxyethyl)-pyrrolidine-2-ones were obtained with a *trans* preference.[3]



† Dedicated to Prof. Dr. Waldemar Adam on the occasion of his 60th birthday.

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Table 1. 5-(β-Nitroalkyl-1,3-dioxane-4-ones **3** and (3*S*, 4*S*, α*R*)-3-(α-hydroxyethyl)-pyrrolidine-2-ones **6**

R	**3**	yield (%)	d. r. (**3**:**4**)	**6**	yield (%)
Me	**a**	87	76:24 [a]	**a**	76
Et	**b**	88	77:23	**b**	88
i-Pr	**c**	50	82:18		
Ph	**d**	89	86:14	**d**	59

[a] 4% of a third diastereomer

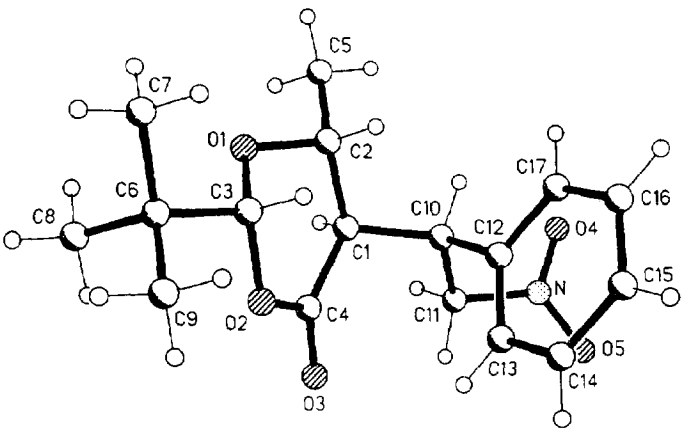

Figure 1. X-Ray crystal analysis of compound **3d**.

Results and discussion

We now report an alternative and stereoselective access to 4-substituted 3-(α-hydroxyethyl)-2-pyrrolidinones, allowing the synthesis of enantiomerically pure *cis* isomers **6**. Again the dioxanone **1**, a 3-hydroxybutyric acid derivative, was used as starting material. It was transformed to ylidene-dioxanones **2** by aldol reaction with aldehydes.[4] Michael-addition of nitromethane in the presence of DBU gave high yields of γ-nitroesters **3** (major isomer) and **4** (minor isomer) with reasonable stereoselectivities (see Table 1). Alternatively, catalytic amounts of tetrabutylammonium fluoride in THF (−30 to 20°C, 15 h) can be used.

Sometimes traces of a third stereoisomer were found in the crude reaction products (see Table 1, footnote a). The stereochemical mode of the Michael-addition (*re*-attack) was the same as previously observed in cuprate additions to 5-ylidene-1,3-dioxane-4-ones **3**.[5] The major diastereomer **3** could be obtained pure by recrystallization or column chromatography in the cases of **3b** and **3d**. Otherwise mixtures of diastereomers **3** and **4** were used for further transformations.

Hydrogenation of the nitro group of the nitroesters **3** in methanol in the presence of Raney-Ni directly gave the corresponding 4-substituted *cis*-3-hydroxyethyl-2-pyrrolidinones **6** in optically active form presumably via non-isolated 5-aminoalkyl-1,3-dioxane-4-ones **5**. The structure elucidation is based on X-ray crystal analysis of the γ-nitroester **3d** (see Figure 1) proving the Michael-addition of nitromethane to **2** as *re*-attack. All compounds **3** gave similar NMR spectra. Coupling constants appeared >7 Hz for the *trans* H-atoms at positions 5 and 6. Similar coupling constants, and thus *trans*-configurations, were found in the minor isomers **4**, demonstrating the same stereochemical mode of protonation in the course of the competing Michael-addition of nitromethane to **2** from the *si*-face.

The aforementioned results demonstrate that the synthesis of 4-substituted 3-(α-hydroxyethyl)-

pyrrolidine-2-ones **6** out of dioxanone **1** is advantageous if the total transformation starts with aldol reaction followed by Michael-addition (i.e. **1**→**2**→**3**) rather than going the reversed sequence.[2]

Experimental part

The ^{1}H NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer, the ^{13}C NMR spectra on a Bruker AC-300 (75 MHz) spectrometer. The samples were dissolved in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad singlet. Elemental analyses were performed in a Leco CHNS-932 apparatus. Optical rotations were measured on a Perkin Elmer 241 polarimeter using a 2 ml cell.

For compounds **3a**, **3c**, and **6a** the NMR data of the major diastereomer are given. Ylidenedioxanones **2** were synthesized according to literature procedures.[4]

5-(β-Nitroalkyl)-1,3-dioxane-4-ones **3** *(general procedure)*

Nitromethane (1 ml) was added dropwise to a solution of 5-ylidene-1,3-dioxanone **2** (0.7 mmol) and DBU (0.77 mmol, 0.12 ml) in dry dichloromethane (20 ml) at −30°C. The mixture was stirred at this temperature for 4 h and was allowed to warm up to room temperature overnight. The mixture was combined with ether (50 ml) and was washed with 2 M HCl (2×20 ml) and with saturated brine (30 ml). After drying with sodium sulfate the combined organic layers were concentrated under vacuum at room temperature and were purified by recrystallization or by column chromatography over silica gel (eluent: hexanes/ether 6:1). In the latter cases no total separation of diastereomers was possible.

*2(*R*),6(*R*),1′(*R*)-2-*tert*-Butyl-6-methyl-5-(1-methyl-2-nitroethyl)-1,3-dioxane-4-one* **3a**

Colorless oil, 77:23 mixture of diastereomers **3a** and **4a**; R_f=0.5; ^{1}H NMR (δ/ppm, J/Hz): 0.89 [s, 9H, $(CH_3)_3C$], 1.01 (d, 3H, 6.9, 1′-CH_3,), 1.34 (d, 3H, 6.2, 6-CH_3), 2.32–2.49 (m, 2H, 5-H, 1′-H); 3.81 (qd, 1H, 6.1/10.2, 6-H); 4.30 and 4.52 (ABX, 2H, 12.7/8.3/6.5, CH_2-N), 4.84 (s, 1H, 2-H); ^{13}C NMR (δ/ppm): 13.1 (1′-CH_3), 19.6 (6-CH_3), 23.7 (CH_3)$_3$C, 31.1 (CH-1′), 35.1 [$C(CH_3)_3$], 49.7 (CH-5), 73.3 (CH-6), 79.9 (CH_2), 108.4 (CH-2), 169.0 (C=O); Anal. Calcd. for $C_{12}H_{21}O_5N$ (259.30): C: 55.56%, H: 8.16%, N: 5.40%, Found: C: 55.68%, H: 8.42%, N: 5.40%.

*2(*R*),6(*R*),1′(*R*)-2-*tert*-Butyl-6-methyl-5-(1-nitromethyl-propyl)-1,3-dioxane-4-one* **3b**

Colorless crystals, mp 80–82°C (ether); R_f=0.5; $[\alpha]_{546}^{20}$=+18.9 (c=0.2; $CHCl_3$) ^{1}H NMR (δ/ppm, J/Hz): 0.89 [s, 9H, $(CH_3)_3C$], 0.94 (t, 3H, 7.4, CH_3CH_2), 1,30 (d, 3H, 6.0, 6-CH_3), 1.55–1.80 (m, 2H, CH_2CH_3), 2.31 (m, 1H, 1′-H), 2.43 (dd, 1H, 1.9/10.5, 5-H), 3.68 (qd, 1H, 6.0/10.5, 6-H), 4.37 and 4.48 (ABX, 2H, 12.6/6.6/7.5, CH_2-N), 4.85 (s, 1H, 2-H); ^{13}C NMR ((δ/ppm): 11.5 CH_3-Et, 20.0 6-CH_3, 23.7 (CH_3)$_3$C, 25.5 CH_2-Et, 35.0 $C(CH_3)_3$, 38.6 CH-1′, 48.8 CH-5, 73.2 CH-6, 77.1 CH_2-N, 108.0 CH-2, 168.8 C=O; Anal. Calcd. for $C_{13}H_{23}O_5N$ (273.33): C: 57.13%, H: 8.48%, N: 5.12%, Found: C: 57.23%, H: 8.40%, N: 5.15%.

*2(*R*),6(*R*),1′(*R*)-2-*tert*-Butyl-6-methyl-5-(2-methyl-1-nitromethyl-propyl)-1,3-dioxane-4-one* **3c**

Colorless oil, 82:18 mixture of diastereomers **3c** and **4c**; R_f=0.5; ^{1}H NMR (δ/ppm, J/Hz): 0.91 [s, 9H, $(CH_3)_3C$], 0.92 [m, 6H, $(CH_3)_2C$], 1.16 [m, 4H, $CH(CH_3)_2$, 6-CH_3], 2.03 (m, 1H, 1′-H), 2.48 (dd, 1H, 1.4/106, 5-H), 3.69 (qd, 1H, 6.0/10.5, 6-H), 4.43 and 4.58 (ABX, 2H, 13.5/6.5/8.0, CH_2-N), 4.86 (s, 1H, 2-H); ^{13}C NMR (δ/ppm): 19.7 6-CH_3, 21.0 and 21.4 (CH_3)$_2$C, 23.9 (CH_3)$_3$C, 27.9 $CH(CH_3)_2$, 35.0 $C(CH_3)_3$, 42.1 CH-1′, 48.5 CH-5, 74.1 CH-6, 75.8 CH_2, 108.1 CH-2, 169.3 C=O.

*2(*R*),6(*R*),1′(*R*)-2-*tert*-Butyl-6-methyl-5-(2-nitro-1-phenyl-ethyl)-1,3-dioxane-4-one* **3d**

Colorless crystals, mp 220°C (ether); R_f=0.6; $[\alpha]_{546}^{20}$=−123.5 (c=0,2; $CHCl_3$); ^{1}H NMR (δ/ppm, J/Hz): 0.80 [s, 9H, $(CH_3)_3C$], 1.42 (d, 3H, 6.1, 6-CH_3), 2.72 (dd, 1H, 3.6/9.9, 5-H), 3.55 (m, 1H, 1′-H), 3.60 (qd, 1H, 6.1/9.9, 6-H), 4.22 (s, 1H, 2-H), 5.08–5.24 (ABX, 2H, 14.0/6.7/8.1, CH_2-N),

7.12–7.25 (m, 5H, C_6H_5); ^{13}C NMR (δ/ppm): 19.5 CH_3, 23.7 (CH_3)$_3C$, 35.0 $C(CH_3)_3$, 42.8 CH-1′, 50.3 CH-5, 73.1 CH-6, 78.8 CH_2-N, 108.0 CH-2, 128.7 *C*H (Ph), 129.4 *C*H (Ph), 135.5 *C* (Ph), 169.0 C=O; Anal. Calcd. for $C_{17}H_{23}O_5N$ (321.37): C: 63.54%, H: 7.21%, N: 4.36%, Found: C: 63.47%, H: 7.06%, N: 4.36%.

Crystal structure analysis of ***3d***

Crystal data: monoclinic, space group $P2_1$, a=1080.0(2), b=646.51(12), c=1291.3(2) pm, β=113.335(10)°, V=0.8279 nm^3, Z=2, μ(Mo $K\alpha$)=0.095 mm^{-1}, F(000)=344, D_x=1.289 Mg m^{-3}, T=−100°C. *Data collection*: colourless lath, 0.85×0.3×0.15 mm, Siemens P4 diffractometer, $2\theta_{max}$ 55°, 2044 independent reflections. *Structure refinement*: on F^2 (program SHELXL-93); 212 parameters, $wR(F^2)$=0.124 (all refl.), conventional $R(F)$ 0.045, S 1.08, max. Δ/σ <0.001, max. $\Delta\rho$ 320 e nm^{-3}. Full details have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, 76344 Eggenstein-Leopoldshafen; this material be obtained on quoting a full literature citation and the deposition number CSD 406533.

3-(1-Hydroxyethyl)-pyrrolidine-2-ones ***6*** *by hydrogenation of nitroalkyldioxanones* ***3*** *(general procedure)*

A mixture of freshly prepared Raney-Ni (about 100 mg), nitroalkyldioxanone **3** (0.4 mmol) and dry methanol (20 ml) was hydrogenated at 1 atm at room temperature for 20 h. After Celite filtration, methanol was removed by a rotary evaporator and the residue was submitted to column chromatography on silica gel (eluent: trichloromethane/methanol 5:1).

3(R),*4*(R),*1′*(R)*-3-(1-Hydroxyethyl)-4-methyl-pyrrolidine-2-one* ***6a***

Yellow oil, 76:24 mixture of diastereomers; R_f=0.75; ^1H NMR (δ/ppm, J/Hz): 1.13 (d, 3H, 6.6, 4-CH_3), 1.20 (d, 3H, 6.4, 1′-CH_3), 1.88 (pseudo t, 1H, 8.8, 3-H), 2.25 (m, 1H, 4-H), 2.85 (dd, 1H, 8.2/9.6, 5-H), 3.81 (dd, 1H, 6.3/8.6, 5-H), 4.03 (m, 1H, 1′-H), 6.67 (b, 1H, NH); ^{13}C NMR (δ/ppm): 14.6 4-CH_3, 21.0 1′-CH_3, 32.3 CH-4, 48.2 CH_2, 54.0 CH-3, 69.2 CH-1′, 180.7 C=O.

3(R),*4*(R),*1′*(R)*-4-Ethyl-3-(1-hydroxyethyl)-pyrrolidine-2-one* ***6b***

Colorless oil; R_f=0.65; $[\alpha]_{546}^{20}$=−61.2 (c=1.5; $CHCl_3$); ^1H NMR (δ/ppm; J/Hz): 0.86 (t, 3H, 7.4, CH_3CH_2), 1.18 (d, 3H, 6.2, 1′-CH_3), 1.37 (m, 1H, CH_2CH_3), 1.67 (m, 1H, CH_2CH_3), 1.91–2.05 (m, 2H, 3-H, 4-H), 2.91 (dd, 1H, 7.0/9.7, 5-H), 3.41 (pseudo-t, 1H, 9.0, 5-H), 3.81 (qd, 1H, 6.3/7.9, 1′-H), 4.71 (b, 1H, OH), 7.24 (s, 1H, NH); ^{13}C NMR (δ/ppm): 11.3 CH_3CH_2, 20.9 1′-CH_3, 27.5 CH_2CH_3, 38.6 CH-4, 46.4 CH_2-N, 52.3 CH-3, 69.1 CH-1′, 180.6 C=O; Anal. Calcd. for: $C_8H_{15}O_2N$ (157.21): C: 61.12%, H: 9.62%, N: 8.91%, Found: C: 61.23%, H: 9.65%, N: 9,21%.

3(R),*4*(R),*1′*(R)*-3-(1-Hydroxyethyl)-4-phenyl-pyrrolidine-2-one* ***6d***

Light yellow oil, R_f=0.85; ^1H NMR (δ/ppm, J/Hz): 0.96 (d, 3H, 6.1, CH_3), 2.55 (pseudo-t, 1H, 8.8, 3-H,), 3.34 (pseudo-d, 1H, 9.9, 5-H), 3.50 (pseudo-t, 1H, 7.9, 4-H), 3.63 (qd, 1H, 6.1/9.3, 1′-H), 3.72 (dd, 1H, 6.7/9.9, 5-H), 4.94 (b, 1H, NH), 7.12–7.25 (m, 5H, C_6H_5); ^{13}C NMR (δ/ppm): 20.9 CH_3, 42.9 CH-4, 48.7 CH_2, 51.3 CH-3, 65.8 CH-1′, 127.5 CH (Ph), 127.6 CH (Ph), 128.8 CH (Ph), 140.3 C (Ph), 180.5 C=O; Anal. Calcd. for: $C_{12}H_{15}O_2N$ (205.26): C: 70.22%, H: 7.37%, N: 6.82%, Found: C: 70.56%, H: 7.23%, N: 6.51%.

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