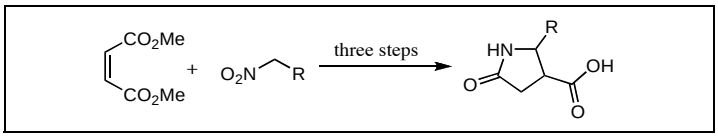
Convenient Preparations of 2-Alkyl-5-oxopyrrolidine-3-carboxylic Acids

Anna D. Photiadou, Christos I. Stathakis and John K. Gallos*

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki GR 541 24, Greece.
E-mail: igallos@chem.auth.gr

Received January 10, 2008

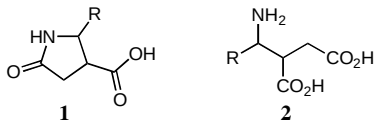


Reduction of the Michael addition products of anions of nitro compounds to dimethyl maleate led to the spontaneous formation of the respective 2-alkyl-5-oxopyrrolidine-3-carboxylic acid methyl esters. Conventional hydrolysis of the later gave the desired compounds.

J. Heterocyclic Chem., **45**, 1251 (2008).

INTRODUCTION

In connection with our recent work on the synthesis of non-natural amino acids [1], we were interested for the synthesis of 2-alkyl-5-oxopyrrolidine-3-carboxylic acids (**1**), which are the equivalents of the respective open chain branched aminodicarboxylic acids (**2**) (Figure I). Such β- and γ-amino acid derivatives have attracted an increasing attention by the synthetic chemists because of their biological properties and also as useful components of modified peptides and in the chemical engineering of proteins [2].



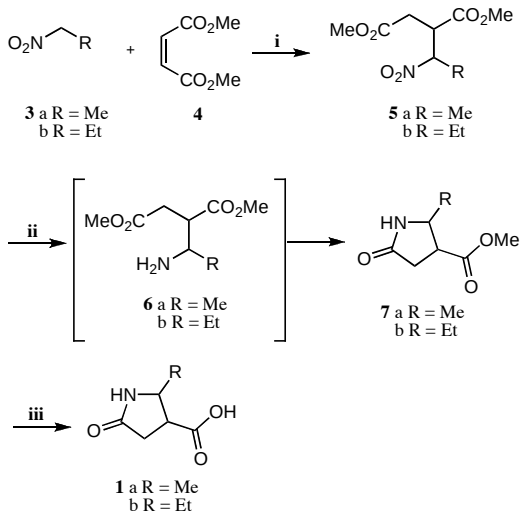
1 **2**

Figure I

RESULTS AND DISCUSSION

A plethora of synthetic methods towards pyrrolidinones exists in the literature [3]. According to our retrosynthetic plan, the preparation of these model compounds could be achieved by reduction of the nitro compounds **5**, which in turn are the Michael addition products of the anion of **3** to a conjugated ester like **4**. We choose dimethyl maleate **4** and nitro compounds **3a,b** (Scheme I) as starting materials in order to demonstrate the feasibility of our method. Thus, treatment [4] of a mixture of these compounds in THF with TBAF.3H_2O led to the isolation of the corresponding adducts **5a** and **5b** in 84% and 87% yields, respectively. In both reactions, the product was a *ca*. 1:1 mixture of diastereoisomers and it was further used as it was. In the case of **5b**, small amounts of the two diastereoisomers were obtained in pure form, by careful chromatographic separation of a small quantity of the diastereoisomeric mixture with hexane-ethyl acetate as the solvent and the respective ^{1}H-NMR spectra were obtained. It is interesting to note that although the parent nitromethane reacts similarly with dimethyl maleate **4**, adduct is not stable and decomposes [5].

Scheme I



Conditions: i. TBAF.3H_2O, THF, r.t., 24 h; ii. Zn, 1.25 M HCl in MeOH, reflux, 24 h; iii. LiOH, THF/H_2O, 20 °C, 45 min

For the reduction of the nitro group, in the next step, we tried a number of reagents (Pd/C and ammonium formate or NH_4Cl, Ni and ammonium formate or H_2) in different solvents (methanol, ethanol, DMF, acetic acid). They either gave low yields or did not react at all or we met serious problems during the work-up. The most convenient procedure we found was the reduction of **5a,b** by refluxing these compounds with Zn in methanolic 1.25 *M* HCl. In this case, the intermediately formed amines **6a,b** are not isolated, but immediately cyclised to lactames **7a** and **7b** in 62% and 65% yields, respectively, as a *ca*. 1:1 mixture of diastereoisomers.

The respective diethyl esters of **7a,b** have been previously prepared by an analogous way in generally lower yields and by using different reagents and methods [6]. The given ^{1}H-NMR spectra, although rough and without good resolution, fit well with those recorded for compounds **7a,b**. In both compounds **7a,b**, we were able to obtain some small quantities of each pure diastereoisomer of **7a** and **7b** by careful chromatographic separation of small amounts of the mixtures. This fact allowed us to assign the faster moving product as the *trans*-isomer and the slower moving one as the *cis*-isomer from their ^{1}H-NMR spectra.

There exists a significant difference in the chemical shifts of 4-H: in the faster moving isomer this proton has δ 2.85 (in both **7a** and **7b**) whereas in the slower moving isomer δ 3.42 and 3.45 (in **7a** and **7b**, respectively). It is evident that the proton with the smaller δ value (2.85) is in *cis*-disposition with the neighboring 5-Me or 5-Et group, being shielded by the magnetic anisotropy of the C-Me or C-Et bond. This assignment was further confirmed, since *cis*-**7b** and the ethyl ester of *cis*-**7a**, are known compounds, prepared by hydrogenation of the respective 4-alkoxy-carbonyl-4-pyrrolin-2-ones [7] and their spectra are in very good agreement with ours.

In the final step, the ester hydrolysis was achieved by treating compounds **7a** and **7b** with LiOH in THF/H_2O at 20 °C for 45 min to give the respective acids in 75% and 60% yields, respectively [6]. Interestingly, the diastereoisomeric ratio in these products was found to be ~5:1. This is rather due to the enrichment of the mixture to the thermodynamically more stable *trans*-isomer by the action of the base.

Despite the low diastereoselectivity, the present method towards 2-alkyl-5-oxopyrrolidine-3-carboxylic acids is short and facile, applying simple and convenient procedures and utilizing cheap and easily available materials. Efforts are now focusing to increase the diastereoselectivity of the Michael addition and also to prepare chiral such compounds.

EXPERIMENTAL

All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. Reactions progress was checked by thin layer chromatography (TLC) on Merck silica gel 60F_{254} glass plates (0.25 mm). The spots were visualised by heat staining with anisaldehyde in ethanol/ sulfuric acid. Column chromatography was performed with Merck silica gel 60 (0.063-0.200 mm). The ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard. Microanalyses were performed on a Perkin-Elmer 2400-II Element analyser and High-resolution mass spectra (HRMS) were obtained on a 7 T APEX II mass spectrometer.

Addition of nitroalkanes 3a,b to dimethyl maleate (4). TBAF·3H_2O (1,2 g, 4 mmol) was added to a solution of dimethyl maleate (6.5 g, 45 mmol) and nitroethane (20 mL) or nitropropane (30 mL) in THF 980 mL) and the mixture was allowed to stir at room temperature for 24 h. Saturated NH_4Cl (10 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were dried over Na_2SO_4, the solvent was then taken off in a rotoevaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 4:1 as the eluent to give adducts **5a** (8.273 g, 84%) or **5b** (9.150 g, 87%) as light orange oils.

Dimethyl 2-(1-nitroethyl)succinate (5a). ^{1}H-nmr ($CDCl_3$): δ 1.48 (d, *J* = 7.0 Hz) and 1.50 (d, *J* = 7.0 Hz) [3H, Me], 2.42 (dd, *J* = 17.1, 4.4 Hz), 2.56 (dd, *J* = 17.1, 4.8 Hz) [1H, 2-H_a], 2.75 (m, 1H, 2-H_b), 3.38 and 3.52 (two m, 1H, 3-H), 3.61 and 3.64 and 3.66 (three s, 6H, two MeO), 4.86 (m, 1H, 4-H); ^{13}C-nmr ($CDCl_3$): δ 16.0 (C-5), 31.5/31.7 (C-2), 44.2/44.8 (C-3), 51.9/52.4 (two MeO), 81.8/82.1 (C-4), 170.5/170.6/170.8/171.0 (C=O); HRMS: 242.0641 (M+Na^+) (calculated for $C_8H_{13}NO_6Na$: 242.0635). *Anal.* Calcd. for $C_8H_{13}NO_6$ (219.19): C, 43.84; H, 5.98; N, 6.39. Found: C, 43.69; H, 5.74; N, 6.07.

Dimethyl 2-(1-nitropropyl)succinate (5b). ^{1}H-nmr ($CDCl_3$): δ 1.00 (t, 3H, *J* = 7.2 Hz, Me), 1.80 (m, 1H, 5-H_a), 2.10 (m, 1H, 5-H_b), 2.52 (dd, *J* = 17.1, 3.5 Hz, 2-H_a), 2.85 (dd, *J* = 17.1, 10.1 Hz, 2-H_b), 3.39 (m, 1H, 3-H), 3.70 (s, 3H, MeO), 3.77 (s, 3H, MeO), 4.73 (m, 1H, 4-H) for the faster moving diastereoisomer and 0.99 (t, 3H, *J* = 7.2 Hz, Me), 1.90 (m, 1H, 5-H_a), 2.05 (m, 1H, 5-H_b), 2.72 (dd, *J* = 17.1, 5.3 Hz, 2-H_a), 2.80 (dd, *J* = 17.1, 8.3 Hz, 2-H_b), 3.55 (m, 1H, 3-H), 3.71 (s, 3H, MeO), 3.74 (s, 3H, MeO), 4.80 (m, 1H, 4-H) for the slower moving diastereoisomer; ^{13}C-nmr ($CDCl_3$) (for the diastereoisomeric mixture): δ 10.0/10.2 (C-6), 23.9/24.7 (C-5), 31.9/32.1 (C-2), 43.5/44.2 (C-3), 52.1/52.6 (MeO), 88.6/89.3 (C-4), 170.7/170.9/171.0/171.1 (C=O); HRMS (for the diastereoisomeric mixture): 256.0797 (M+Na^+) (calculated for $C_9H_{15}NO_6Na$: 256.0792). *Anal.* Calcd. for $C_9H_{15}NO_6$ (233.22): C, 46.35; H, 6.48; N, 6.01. Found: C, 46.83; H, 6.33; N, 5.84.

Methyl 2-alkyl-5-oxopyrrolidine-3-carboxylates (7a,b). A 1.25 *M* solution of HCl in CH_3OH (50 mL) was dropwise added to a flask containing 1.0 g of compound **5a** (4.63 mmol) or **5b** (4.34 mmol) under stirring followed by careful addition of Zn (3.0 g). The mixture was refluxed for 24 h, the solids were then filtered off and the solution was neutralized with saturated Na_2CO_3 to pH=8-9 before being extracted with ethyl acetate (5x50 mL). The organic layer was dried over Na_2SO_4, the solvent was taken off in a rotoevaporator to give 445 mg of **7a** or 527 mg of **7b** in 62% and 65% yields, respectively, in satisfactory purity. The two diastereoisomers of a small amount of each compound were separated with a preparative plate chromatography, using ethyl acetate as the solvent.

Methyl 2-methyl-5-oxopyrrolidine-3-carboxylate (7a). ^{1}H-nmr ($CDCl_3$): δ 1.33 (d, 3H, *J* = 6.5 Hz, 5-Me), 2.59 (dd, 1H, *J* = 17.1, 9.7 Hz, 3-H_a), 2.71(dd, 1H, *J* = 17.1, 8.6 Hz, 3-H_b), 2.85 (m, 1H, 4-H), 3.74 (s, 3H, MeO), 3.91 (quint., 1H, *J* = 6.5 Hz, 5-H), 7.28 (br s, 1H, N-H) for the faster moving diastereoisomer (trans) and 1.13 (d, 3H, *J* = 6.7 Hz, 5-Me), 2.40 (dd, 1H, *J* = 17.1, 8.8 Hz, 3-H_a), 2.80 (dd, 1H, *J* = 17.1, 8.4 Hz, 3-H_b), 3.42 (m, 1H, 4-H), 3.73 (s, 3H, MeO), 4.04 (quint., 1H, *J* = 6.7 Hz, 5-H), 7.29 (br s, 1H, N-H) for the slower moving diastereoisomer (cis); ^{13}C-nmr ($CDCl_3$): δ 21.5 (5-Me), 29.7 (C-3), 34.1 (C-4), 46.5 (C-5), 54.0 (MeO), 172.1 (C-2), 177.6 (C=O) for the faster moving diastereoisomer; HRMS (for the diastereoisomeric mixture): 180.0637 (M+Na^+) (calculated for $C_7H_{11}NO_3Na$:

180.0631). *Anal.* Calcd. for $C_7H_{11}NO_3$ (157.17): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.24; H, 6.76; N, 8.95.

Methyl 2-ethyl-5-oxopyrrolidine-3-carboxylate (7b). ^{1}H-nmr ($CDCl_3$): δ 0.99 (t, 3H, *J* = 7.4 Hz, Me), 1.59 (m, 1H, C*H*HMe), 1.70 (m, 1H, CH*H*Me), 2.59 (dd, 1H, *J* = 17.1, 9.7 Hz, 3-H_a), 2.71(dd, 1H, *J* = 17.1, 7.5 Hz, 3-H_b), 2.85 (m, 1H, 4-H), 3.74 (s, 3H, MeO), 3.77 (m, 1H, 5-H), 7.16 (br s, 1H, N-H) for the faster moving diastereoisomer (*trans*) and 0.98 (t, 3H, *J* = 7.4 Hz, Me), 1.58 (m, 1H, C*H*HMe), 1.70 m, 1H, CH*H*Me), 2.43 (dd, 1H, *J* = 17.1, 8.6 Hz, 3-H_a), 2.80 (dd, 1H, *J* = 17.1, 8.6 Hz, 3-H_b), 3.45 (q, 1H, *J* = 8.6 Hz, 4-H), 3.73 (s, 3H, MeO), 3.80 (m, 1H, 5-H), 7.32 (br s, 1H, N-H) for the slower moving diastereoisomer (*cis*); ^{13}C-nmr ($CDCl_3$) (for the diastereoisomeric mixture): δ 9.8/10.5 (Me) 25.0/29.1 (5-CH_2), 32.4/33.7 (C-3), 43.4/44.6 (C-4), 52.4/53.4 (C-5), 56.9/58.5 (MeO), 171.5/173.1 (C-2), 175.8/176.5 (C=O); HRMS (for the diastereoisomeric mixture): 194.0793 ($M+Na^+$) (calculated for $C_8H_{13}NO_3Na$: 194.0788). *Anal.* Calcd. for $C_8H_{13}NO_3$ (171.19): C, 56.13; H, 7.65; N, 8.18. Found: C, 56.02; H, 7.37; N, 8.31.

2-Alkyl-5-oxopyrrolidine-3-carboxylic acids (1a,b). To a solution of **7a** (470 mg, 2.99 mmol) in a mixture of THF/H_2O (28 mL, 10 mmol/mL) or to a solution of **7b** (370 mg, 2.16 mmol) in a mixture of THF/H_2O (20 mL, 10 mmol/mL) was added LiOH (289 mg or 216 mg respectively) and the mixture was stirred at 20 °C for 45 min, then neutralized with aqueous 1 *M* HCl to pH=4-5 before extracted with ethyl acetate (5x50 mL). The organic layer was dried over Na_2SO_4, the solvent was taken off in a rotoevaporator to give 321 mg of **1a** or 185 mg of **1b** in 75% and 60% yields, respectively, as white microcrystals [8], which in the case of **1b** were further purified by recryctalisation from ethyl acetate.

2-Methyl-5-oxopyrrolidine-3-carboxylic acid (1a). ^{1}H-nmr ($CD_3OD/CDCl_3$ 1:1): δ 1.37 (d, 3H, *J* = 6.4 Hz, 5-Me), 2.61 (dd,1H, *J* = 17.1, 9.0 Hz, 3-H_a), 2.72 (dd,1H, *J* = 17.1, 7.9 Hz, 3-H_b), 2.82 (m, 1H, 4-H), 3.96 (quint., 1H, *J* = 6.4 Hz, 5-H), 7.43 (br s, 1H, N-H) for the major diastereoisomer and 1.23 (d, 3H, *J* = 6.5 Hz, 5-Me), 2.42 (dd,1H, *J* = 17.1, 8.9 Hz, 3-H_a), 2.82 (dd hidden,1H, 3-H_b), 3.30 (m, 1H, 4-H), 4.10 (quint., 1H, *J* = 6.5 Hz, 5-H), 7.48 (br s, 1H, N-H) for the minor diastereoisomer; ^{13}C-nmr ($CD_3OD/CDCl_3$ 1:1): δ 21.1, 33.7, 47.0, 53.2, 175.0, 176.4 for the major diastereoisomer and 16.8, 32.2, 43.7, 50.8, 173.8, 177.1 for the minor diastereoisomer; HRMS (for the diastereoisomeric mixture): 166.0480 ($M+Na^+$) (calculated for $C_6H_9NO_3Na$: 166.0475). *Anal.* Calcd. for $C_6H_9NO_3$ (143.14): C, 50.35; H, 6.34; N, 9.79. Found: C, 50.42; H, 6.09; N, 10.01.

2-Ethyl-5-oxopyrrolidine-3-carboxylic acid (1b). ^{1}H-nmr ($CD_3OD/CDCl_3$ 1:1): δ 0.99 (t, 3H, *J* = 7.3 Hz, Me), 1.62 (m, 1H, C*H*HMe), 1.72 (m, 1H, CH*H*Me), 2.62 (dd,1H, *J* = 17.3, 9.6 Hz, 3-H_a), 2.72 (dd,1H, *J* = 17.3, 7.5 Hz, 3-H_b), 2.90 (m, 1H, 4-H), 3.82 (m, 1H, 5-H), 7.77 (br s, 1H, N-H) for the major diastereoisomer and 0.98 (t, 3H, *J* = 7.3 Hz, Me), 1.22 (m, 2H, C*H*$_2$Me), 2.44 (dd,1H, *J* = 17.1, 8.8 Hz, 3-H_a), 2.77 (dd,1H, *J* = 17.1, 8.1 Hz, 3-H_b), 3.41 (m, 1H, 4-H), 3.82 (m, 1H, , 5-H), 7.86 (br s, 1H, N-H) for the minor diastereoisomer; ^{13}C-nmr ($CD_3OD/CDCl_3$ 1:1): δ 9.3, 28.7, 33.4, 44.0, 58.7, 174.8, 176.6 for the major diastereoisomer and 10.0, 24.5, 32.5, 43.2, 56.9, 173.2, 177.4 for the minor diastereoisomer; HRMS (for the diastereoisomeric mixture): 180.0637 ($M+Na^+$) (calculated for $C_7H_{11}NO_3Na$: 180.0641). *Anal.* Calcd. for $C_7H_{11}NO_3$ (157.17): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.36; H, 6.93; N, 8.75.

REFERENCES AND NOTES

[1a] Gallos, J. K.; Sarli, V. C.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N, G. *Tetrahedron Lett.* **2003**, *44*, 3905-3909; [b] Gallos, J. K.; Sarli, V. C.; Massen, Z. S.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N, G. *Tetrahedron* **2005**, *61*, 565-574; [c] Gallos, J. K.; Alexandraki, E. S.; Stathakis, C. I. *Heterocycles* **2007**, *71*, 1127-1134.

[2a] Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117-128; [b] Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181-2204; [c] Ordóñez, M.; Cativiela, C. *Tetrahedron:Asymmetry* **2007**, *18*, 3-99.

[3] Selected publications of related compounds: [a] Meisterhans, C.; Linden, A.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 644-656; [b] Błaszczyk, E.; Krawczyk, H.; Janecki, T. *Synlett* **2004**, 2685-2688; [c] Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621-1625; [d] Béji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Tetrahedron*, **2001**, *57*, 9959-9962; [e] Kuciak, R.; Sas, W. *Tetrahedron Lett.* **1994**, *35*, 8647-8648; [f] Domingos, J. L. O.; Lima, E. C.; Dias, A. G.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2313-2314.

[4a] Gallos, J. K.; Koumbis, A. E.; Xiraphaki, V. P.; Dellios, C. C.; Coutouli-Argyropoulou, E. *Tetrahedron* **1999**, *55*, 15167-15180; [b] Patrocinio, V. L.; Costa, P. R. R.; Correia, C. R. D. *Synthesis* **1994**, 474-476; [c] Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002-4006.

[5] Kloetzet, M. C. *J. Am. Chem. Soc.* **1948**, *70*, 3571-3576.

[6] Klein, K. P.; Reimschuessel, H. K. *J. Polym. Sci. A-1* **1972**, *10*, 1987-1996.

[7] Garcia, E. Z.; Asensi, L. R. D.; Sepulveda-Arques, J.; Carrera, J. E.; Solesio, B. Y. *Anal. Quim.* **1995**, *91*, 594-598.

[8] M.p.s were not clear, since compounds are mixtures of diastereoisomes.