Pyrrolidine and 1,3-oxazolidine formation from azomethine ylides influenced by change from classical conditions to microwave irradiation

Martin Trávníček and Milan Potáček

Department of Organic Chemistry, Faculty of Sciences, Masaryk University of Brno, Kotlářská 2, CZ-611 37 Brno, Czech Republic
E-mail: potacek@chemi.muni.cz

Dedicated to Professor Miha Tišler on the occasion of his 75th birthday

(received 12 Sep 01; accepted 20 Feb 02; published on the web 28 Feb 02)

Abstract

The reactions of ethyl *N*-alkylaminoacetates **1** in the presence of formaldehyde and dipolarophiles fumaronitrile and dimethylfumarate **3** were investigated. They were followed and the results compared of reactions under classical heating and heating by MW either in solvent or without solvent or with solid supports. It has been found out that application of specific reaction conditions for the preparation of desired trisubstituted pyrrolidines **4a-4c** and **5a-5c** is dependent on the nature of the dipolarophile used. In the case of fumaronitrile the direct solventless reaction under microwave irradiation seems to be the most convenient method; in the case of dimethyl fumarate mineral support (predominantly basic activated Al_2O_3) must be employed. In the absence of olefinic dipolarophile double bond C=O in a formaldehyde molecule serves as dipolarophile[9] to form 1,3-oxazolidines **6a-6c**. These are also by-products when toluene is used as a solvent.[1] Yet in the case of addition of basic Al_2O_3 we do not observe oxazolidine formation and GC-MS analysis shows just a complex set of peaks.

Keywords: 1,3-Dipolar cycloaddition, azomethine ylides, pyrrolidines, 1,3-oxazolidines, microwave initiation, mineral support, solvent free conditions

Introduction

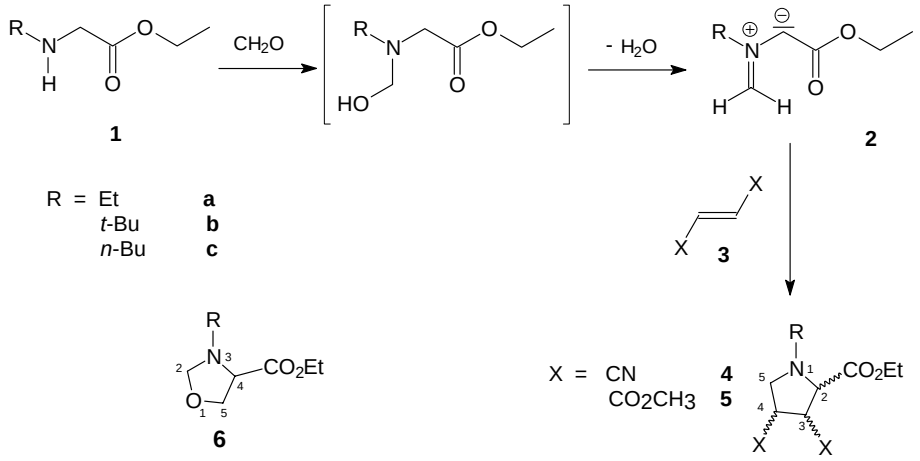
Reaction between ethyl *N*-substituted aminoacetates and formaldehyde affords according to the literature[1-4] *in situ* azomethine ylides. Such a reaction intermediate[1-7] (sometimes prepared also by different reactions) can undergo cycloaddition reactions with dipolarophiles in various solvents under classical heating yielding pyrrolidines as final products. Some of the pyrrolidine derivatives are known for their biological activity.[8] Several solvents have been studied and described[1] giving by-products in addition to the desired pyrrolidines. We aimed by following one

of the most convenient published procedures[1] to prepare further derivatives of pyrrolidine. Nevertheless, having applied the above mentioned commonplace methodology under microwave irradiation we obtained some interesting results indicating the influence of external conditions upon the reaction outcome.

Results and Discussion

N-Substituted aminoacetates **1** with formaldehyde afforded azomethine ylides **2** as a 1,3-dipoles and they were used to react with dipolarophiles **3** (Scheme 1). Since the reactions had been so far carried out in presence of solvent only we also wanted to perform cycloadditions without any solvent under the assistance of microwave irradiation.

First of all we worked with simply mixed components in an appropriate ratio and with irradiation by microwaves. In this case we succeeded in obtaining desired products **4** only when fumaronitrile was used as dipolarophile. Reaction is complete within 15 minutes (compared with hour in toluene), so indicating substantial shortening of the reaction time; other by-products were not detected.



Scheme 1

Compounds **4** are formed as a mixture of two stereoisomers differing in relative configuration at C-2 and C-3. This can be unambiguously assigned from coupling constants ^{3}J(2,3) ranging from 7-8 Hz for *cis*- to 3-5 Hz for *trans*-configuration. Products contain 50% *trans*-isomer and 50% *cis* isomer, as determined by ^{1}H-NMR spectroscopy and GC-MS analysis. Contrary to *tert*- or *n*-butyl derivatives that were separated on silica in ether:petrolether 1:1, the ethyl esters **4** could not be separated by column chromatography, so isomers could be assigned by C-2 signals only. As signals on the pyrrolidine ring exhibit complex multiplets of higher orders H-2 could be assigned just by correlation spectroscopy, namely H,H-COSY and HMBC experiments. Thus, one can observe interactions of the C=O group carbon atom with H-2, H-3 and OCH_2 and interactions of H-3 and H-4 with the carbon atoms of the cyano groups and this way the nitrile groups can be differentiated. The main fragmentation pathway in the MS is loss

of the CO_2Et group. Molecular ions of **4** were always detectable. The parent peaks are for R = Et 148, for R = *t*-Bu 57 and for R = *n*-Bu 176. The optimal molar ratio of starting compounds ethyl *N*-alkylaminoacetate : paraformaldehyde : fumaronitrile is 1:2:0.8. When carrying out the reaction under MW irradiation in toluene for 20 min, we obtained a mixture of pyrrolidines **4** with configuration on C2, C3 in ratio 40% *trans* and 60% *cis* but with formation of oxazolidine **6**. For R = Et the mixture contained 3% oxazolidine, for R = *t*-Bu or *n*-Bu only traces were detected (according to GC-MS analysis).

Comparable results were obtained when the reaction components were mixed in the same molar ratio in toluene with azeotropic removal of water under conventional heating. The desired cycloadducts 4 were prepared in yields comparable to those in the solventless preparation but the reaction was completed within 1 hour.

When dimethyl fumarate was used the results were somewhat stranger. In the case of direct microwave irradiation of the neat three component mixture in molar ratio 1:2:0.8 we observed transformation, yet the product analysis revealed that another compound was formed. Here we isolated oxazolidine derivatives **6a-6c** as the product of the 1,3-dipolar addition to formaldehyde instead of dimethyl fumarate. Besides the compounds **6a-6c** we recovered unchanged dimethyl fumarate. Oxazolidines **6a-6c** exhibit in the ^{1}H-NMR spectrum both a typical pair of doublets of H-2 and H-2$^{/}$ at 4.4 or 4.7 ppm with coupling constants about 6 Hz and a coupling system for H-4, H-5 and H-5'. To prepare pure oxazolidines in the absence of dimethyl fumarate ethyl *N*-alkylaminoacetates **1a-1c** (1 eq) and paraformaldehyde (6 eq) were mixed in a quartz microwave tube and irradiated for 20 minutes at 150°C. The yields after vacuum distillation reached over 60%.

Under conventional heating of mixture **1**, paraformaldehyde and dimethyl fumarate (molar ratio 1:2:0.8) in toluene with azeotropic removal of water we obtained cycloadducts **5a-5c** together with increased amounts of the appropriate oxazolidines **6a-6c**, namely 7% for R = *t*-Bu and 8% for R = Et or R = *n*-Bu, respectively (GC-MS).

Comparable results were obtained when irradiating the mixture by microwave in toluene within 30 minutes.

In order to get rid of undesired oxazolidines in the reaction with dimethyl fumarate it is necessary to irradiate the reaction material adsorbed on mineral supports. This powder is irradiated by microwaves under stirring until the temperature reaches the constant value; products are obtained after extraction with acetone or chloroform. The extract is evaporated in vacuum, filtered through a short column of silica and directly analyzed by GC-MS and ^{1}H-NMR. Among several adsorbents we studied (silica, basic Al_2O_3, calcinated Al_2O_3, montmorillonites KSF or K10) the best results were obtained on basic Al_2O_3 for which a 4 fold excess of the total mass of reactants has to be used. Reaction time is 20 minutes for R = Et or 40 minutes for R = *t*-Bu and *n*-Bu. The final temperature was 140°C. On basic Al_2O_3 no by-products were observed; pyrrolidines **5** were formed in relative ratio 45% *trans*- and 55% *cis*-isomer, respectively (from ^{1}H-NMR and GC-MS). For R = Et we succeeded in separation of stereoisomers of **5a** formed in relative ratio 45% *trans* or 55% *cis* on silica in CH_2Cl_2:AcOEt 40:1. Therefore, the structures of those could be confirmed by means of H,H-COSY or HMBC experiments. For R = *t*-Bu we were just able to characterise both isomers by doublets on C-2 (coupling constants $^3J_{2,3}$ = 7.9 Hz for

cis- or $^3J_{2,3}$ = 7.0 Hz for *trans*-isomer, for R=*n*-Bu by coupling constant $^3J_{2,3}$ = 7.6 Hz for *cis*- or $^3J_{2,3}$ = 4.7 Hz for *trans*-isomer).

Experimental Section

General Procedures. IR spectra were recorded on a FTIR ATI MATTSON spectrophotometer in NaCl kyvettes, unless given otherwise. Microwave irradiation was carried out in PROLABO 402 Synthewave oven (power 300W, frequency 2450 MHz). NMR spectra were recorded on Avance 300 Varian apparatus with working frequency 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$ with TMS as an internal standard. Chemical shifts are given in ppm, coupling constants J in Hz. Mass spectra were recorded on a FISONS INSTRUMENTS TRIO 1000 spectrometer in positive mode with EI (70 eV). Gas chromatography was carried out onto SPIRA KI 8 column (30 m, 5% diphenyldimethylsiloxane) with FISONS INSTRUMENTS TRIO 1000 spectrometer as a detector. Column chromatography was carried out on Merck silica 63-100 μm.

General method[10-12] for preparation of ethyl *N*-alkylaminoacetates 1

To a solution of appropriate alkylamine (240 mmol) in acetonitrile (100 ml) cooled to 5 °C ethyl bromoacetate (60 mmol, 10.1 g) was dropwise added under stirring and cooling. The temperature should be maintained below 10°C during this operation. After the exothermic reaction has ceased, the stirring continued for another 1 hour at lowered temperature and finally the reaction mixture was chilled to ambient temperature. Solvent was evaporated under reduced pressure, 1 M solution NaOH and CH_2Cl_2 (50 ml) were added and the layers were separated. The extraction was repeated twice. The combined organic phases were separated, dried over Na_2SO_4 and solvent evaporated. The remainder was distilled under reduced pressure.

Ethyl *N*-ethyl aminoacetate (1a). Yield 68% of colourless liquid, b.p.: 42-45°C / 2 mm Hg. For $C_6H_{13}NO_2$ calculated 131.17 g.mol^{-1}. EI-MS (m/z, %): 132 (M^++1, 2), 131 (M^+, 6), 60 (2), 58 (100), 56 (9), 42 (15). IR: 3301 s (NH), 2971 m, 2934 w, 2874 w, 1739 s (C=O), 1658 m, 1539 w, 1452 w, 1377 w, 1262 w, 1203 s (C-O), 1137 m, 1032 w cm^{-1}. ^{1}H-NMR: δ 1.04 (t, J = 7.15 Hz, 3H, CH_3CH_2N, 1.2 (t, J = 7.2 Hz, 3H, CH_3CH_2O), 2.58 (q, J = 7.15, 2H, CH_3CH_2N), 1.74 (s, 1H, NH), 3.32 (s, 2H, CH_2C=O), 4.11 (q, J = 7.15 Hz, 2H, CH_3CH_2N). ^{13}C-NMR: δ 14.02 (CH_3CH_2N), 14.90 (CH_3CH_2O), 43.57 (CH_3CH_2N), 50.57 (NCH_2C=O), 60.48 (CH_3CH_2O), 172.27 (C=O).

Ethyl *N*-(*tert*-butyl) aminoacetate (1b). Yield 80% of colourless liquid, b.p.: 50-53°C / 2 mm Hg. For $C_8H_{17}NO_2$ calculated 159.22 g.mol^{-1}. EI-MS (m/z, %): 160 (M^++1, 3), 159 (M^+, 2), 145 (10), 144 (100), 116 (22), 86 (83), 71 (11), 70 (92), 57 (49), 56 (13), 41 (30). IR: 3329 s (NH), 2966 s, 2875 s, 1741 s (C=O), 1471 s, 1369 s, 1190 s (C-O), 1136 m, 1027 s, 852 m cm^{-1}. ^{1}H-NMR: δ 1.12 (s, 9H, 3xCH_3), 1.29 (t, J = 7.1 Hz, 3H, CH_3CH_2O), 1.66 (s, 1H, NH), 3.40 (s, 2H, CH_2C=O), 4.19 (q, 2H, J = 7.1 Hz, CH_3CH_2O). ^{13}C-NMR: δ 13.77 (CH_3CH_2O), 28.48 (3xCH_3), 44.64 (CH_2C=O), 49.98 (C_q), 60.49 (CH_3CH_2O), 172.72 (C=O).

Ethyl *N*-(*n*-butyl) aminoacetate (1c). Yield 60% of colourless liquid, b.p.: 65-69°C / 2 mmHg. For $C_8H_{17}NO_2$ calculated 159.22 g.mol^{-1}. EI-MS (m/z, %): 161 (M^++2, 8), 160 (M^++1, 70), 159

(M^+, 35), 117 (6), 116 (65), 86 (100), 72 (17), 60 (12), 57 (38), 56 (20), 44 (80), 42 (68). IR: 3338 m (NH), 2959 s, 2931 m, 2870 s, 1741 s (C=O), 1465 m, 1374 m, 1341 w, 1192 s (C-O), 1159 m, 1026 m, 928 w, 857 w, 807 w, 759 w cm^{-1}. ^{1}H-NMR: δ 0.86 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2CH_2N$), 1.22 (t, J = 7.2 Hz, 3H, CH_3CH_2O), 1.30 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 1.59 (s, 1H, NH), 2.54 (m, 2H, CH_2); 3.33 (s, 2H, CH_2C=O), 4.13 (q, 2H, J = 7.2 Hz, CH_3CH_2O). ^{13}C-NMR: δ 13.71 ($CH_3CH_2CH_2CH_2N$), 14.02 (CH_3CH_2O), 20.14 (CH_2), 31.98 (CH_2), 49.12 (CH_2C=O), 50.87 (CH_2), 60.44 (CH_3CH_2O), 172.39 (C=O).

General method for preparation of 4

Mixture of 1 (3.14 mmol), finely powdered paraformaldehyde (7.3 mmol, 0.22 g) and fumaronitrile (3.14 mmol, 0.29g for R=*t*-Bu, *n*-Bu or 0.26g for R=Et) was under stirring irradiated for15 minutes. The final temperature reached 140 °C. On cooling product was extracted twice by chloroform, filtered with an addition of silica, filtrate was evaporated and chromatographed on silica column.

Ethyl 1-ethyl-3,4-dicyanopyrrolidine-2-carboxylate (4a). Yield (50%) of both isomers. Yellowish oil. Eluent: diethylether. For $C_{11}H_{15}N_3O_2$ calculated 221.25 $g.mol^{-1}$. EI-MS: 221 (M^+, 8), 148 (100), 120 (22), 93 (12), 79 (7), 66 (7), 56 (7). IR: 2977 s, 2941 m, 2248 m (CN), 1734 s (C=O), 1460 m, 1382 m, 1295 m, 1195 s (C-O-), 1071 m, 1021 m, 850 w cm^{-1}. ^{1}H NMR: δ 3.81 (d, $J_{2,3}$ = 4.9 Hz, 1H, H-2 *trans*-isomer), 3.98 (d, $J_{2,3}$ = 7.6 Hz, 1H, H-2, *cis*-isomer).

Ethyl 1-(*tert*-butyl)-3,4-dicyanopyrrolidine-2-carboxylate (4b). Yield 0.52 g (78 %) of both isomers. Separation on silica in diethyl ether:petrol ether 1:1.

2,3-c*is*: Yield 0.25 g. Yellowish oil. For $C_{13}H_{19}N_3O_2$ calculated 249.31 $g.mol^{-1}$. EI-MS (m/z, %): 249 (M^+, 3), 234 (28), 206 (13), 176 (22), 120 (41), 93 (8), 57 (100), 41 (19). IR: 2975 s, 2876 s, 2249 m (CN), 1734 s (C=O), 1472 m, 1395 m, 1370 s, 1262 m, 1224 s, 1196 s, 1098 w, 1027 m, 845 w cm^{-1}. ^{1}H-NMR: δ 1.08 (s, 9H, 3xCH_3), 1.27 (t, J = 7.15 Hz, 3H, CH_3CH_2O), 3.08 (dd, J = 8.8 Hz, 1H, H-5), 3.21 (dd, $J_{3,4}$ = 11.0 Hz, $J_{2,3}$ = 8.1 Hz, 1H, H-3), 3.52 (dd, J = 8.8 Hz, 1H, H-5'), 3.69 (m, 1H, H-4), 3.99 (d, $J_{2,3}$ = 8.1 Hz, 1H, H-2), 4.21 (m, 2H, CH_3CH_2O). ^{13}C-NMR: δ 13.86 (CH_3CH_2O), 26.40 (3xCH_3), 31.40 (C-4), 36.17 (C-3), 49.14 (C-5), 53.83 (C_q), 61.02 (C-2), 61.74 (CH_3CH_2O), 115.12 (CN), 117.44 (CN), 171.41 (C=O).

2,3-*trans*: Yield 0.27 g. Yellowish oil. For $C_{13}H_{19}N_3O_2$ calculated 249.31 $g.mol^{-1}$. EI-MS (m/z, %): 249 (M^+, 3); 234 (22), 206 (18), 176 (24), 120 (36), 93 (8), 57 (100), 41 (19). IR: 2975 s, 2876 s, 2249 m (CN), 1734 s (C=O), 1472 m, 1395 m, 1370 s, 1262 m, 1224 s, 1196 s, 1098 w, 1027 m, 845 w cm^{-1}. ^{1}H-NMR: δ 1.04 (s, 9H, 3xCH_3), 1.27 (t, J = 7.15 Hz, 3H, CH_3CH_2O), 3.31 (m, 1H, H-5), 3.38 (m, 1H, H-4), 3.47 (1H, m, 1H, H-5'), 3.51 (m, 1H, H-3), 4.03 (d, $J_{2,3}$ = 3.6 Hz, 1H, H-2), 4.42 (q, 2H, J = 7.15 Hz, J = 3.3 Hz CH_3CH_2O). ^{13}C-NMR: δ 13.74 (CH_3CH_2O), 26.28 (3xCH_3), 32.31 (C-4), 36.88 (C-3), 49.34 (C-5), 53.75 (C_q), 63.51 (C-2), 61.86 (CH_3CH_2O), 117.53 (CN), 117.82 (CN), 171.34 C=O.

Ethyl 1-(*n*-butyl)-3,4-dicyanopyrrolidine-2-carboxylate (4c). Yield 0.50 g (78 %) of both isomers. Separation on silica in diethyl ether:petrol ether 1:1.

2,3-*trans*: Yield 0.25 g. Colourless needles from ether:petrolether. m. p. 47-49 °C. For $C_{13}H_{19}N_3O_2$ calculated 249.31 $g.mol^{-1}$. EI-MS (m/z, %): 249 (M^+, 55), 222 (11), 206 (18), 176 (100), 134 (27), 120 (30), 93 (8), 57 (54), 41 (33). IR (KBr): 2955 m, 2869 w, 2827 w, 2250 m

(CN), 1744 s (C=O), 1469 w, 1377 w, 1253 w, 1208 m, 1153 w, 1082 w, 1026 w, 839 w cm^{-1}. ^{1}H-NMR: δ 0.91 (t, J =7 Hz, 3H, **C**$H_3CH_2CH_2CH_2N$), 1.30 (t, J = 7 Hz, 3H, **C**H_3CH_2O), 1.31 (m, 2H, CH_2), 1.46 (m, 2H, CH_2), 2.56 (m, 2H, CH_2); 2.78 (m, 2H, CH_2N), 3.13 (m, 1H, H-5), 3.28 (t, J = 9 Hz, 1H, H-5‘), 3.50 (m, 1H, H-3), 3.62 (dd, J = 9 Hz, J = 6 Hz, 1H, H-4), 3.89 (d, $J_{2,3}$ = 5 Hz, 1H, H-2), 4.27 (m, 2H, CH_3CH_2O). ^{13}C-NMR: δ 13.91 (**C**$H_3CH_2CH_2CH_2N$), 14.31 (**C**H_3CH_2O), 20.28 ($CH_3CH_2CH_2CH_2N$), 30.10 (CH_3CH_2**C**H_2CH_2N), 31.98 (C-4), 35.99 (C-3), 52.11 ($CH_3CH_2CH_2$**C**H_2N), 54.90 (C-5), 62.29 (CH_3**C**H_2O), 68.16 (C-2), 118.16 (CN), 118.21 (CN), 168.92 (C=O).

2,3-c*is*: Yield 0.25 g. Colourless oil. For $C_{13}H_{19}N_3O_2$ calculated 249.31 $g.mol^{-1}$. EI-MS (m/z, %): 249 (M^+, 55), 222 (10), 206 (13), 176 (100), 134 (29), 120 (41), 93 (12), 57 (62), 41 (29). IR (neat): 2960 s, 2869 s, 2871 s, 2249 m (CN), 1733 s (C=O), 1466 w, 1376 m, 1299 m, 1262 m, 1194 s, 1098 m, 1021 m, 952 w, 849 w cm^{-1}. ^{1}H-NMR: δ 0.91 (t, J = 7 Hz, 3H, C**H$_3$**$CH_2CH_2CH_2N$), 1.33 (t, J = 7 Hz, 3H, C**H$_3$**CH_2O), 1.34 (m, 2H, CH_3C**H$_2$**CH_2CH_2N), 1.46 (m, 2H, CH_3CH_2C**H$_2$**CH_2N), 2.60 (m, 2H, $CH_3CH_2CH_2CH_2N$), 3.12 (dd, J = 9 Hz, J = 6 Hz, 1H, H-5), 3.43 (t, J = 9 Hz, 1H,H-4), 3.50 (m, 1H, H-3), 3.62 (dd, J = 9 Hz, J = 6 Hz, 1H, H-5‘), 3.89 (d, $J_{2,3}$ = 7.3 Hz, 1H, H-2), 4.27 (m, 2H, CH_3CH_2O). ^{13}C-NMR: δ 13.94 (**C**H_3CH_2**C**H_2CH_2N), 14.22 (**C**H_3CH_2O), 20.36 ($CH_3CH_2CH_2CH_2N$), 30.23 (CH_3CH_2**C**H_2CH_2N), 31.40 (C-4), 35.80 (C-3), 51.74 ($CH_3CH_2CH_2$**C**H_2N), 54.48 (C-5), 62.05 (CH_3**C**H_2O), 66.12 (C-2), 115.99 (CN), 118.61 (CN), 168.85 C=O.

General method for preparation of 5

To a mixture of 1 (0.5 g, 3.81 mmol for R=Et or 3.14 mmol for R=*t*-Bu and *n*-Bu) and dimethyl fumarate (3.05 mmol, 0.44 g for R=Et or 0.36 g for R=*t*-Bu and *n*-Bu) in 15 ml CH_2Cl_2 finely powdered mixture of paraformaldehyde (7.3 mmol, 0.22 g) and basic Al_2O_3 (4.0g) was added and solvent was left to evaporate under reduced pressure. The so formed powder was irradiated for 20 minutes for R=Et and 40 minutes for R=*t*- and *n*-Bu, respectively, until the temperature reached the constant value (130 °C). On cooling products were three times extracted with acetone, the fitrate was evaporated in vacuum and the remainder chromatographed on silica.

2-Ethyl-3,4-dimethyl 1-ethylpyrrolidine-2,3,4-tricarboxylate (5a). Total yield 0.38 g (35%). Separation on silica in CH_2Cl_2:AcOEt 40:1.

2,3-*cis*: Yield 0.16g. Yellowish oil. For $C_{13}H_{21}NO_6$ calculated 287.31 $g.mol^{-1}$. EI-MS (m/z, %): 287(M^+, 21), 228 (30), 214 (82), 182 (100), 154 (96), 122 (38), 96 (44), 58 (29). IR: 2976 m, 2963 m, 2888 w, 1742 s (C=O), 1441 m, 1369 m, 1187 s, 1106 m, 1023 m, 945 w, 859 w cm^{-1}. ^{1}H-NMR: δ 1.06 (t, J = 7.3 Hz, 3H, CH_3CH_2N), 1.22 (t, J = 7.0 Hz, 3H, CH_3CH_2O), 2.55 (m, 2H, CH_3CH_2N), 2.87 (m, 1H, H-4), 3.25 (m, 1H, H-5), 3.63 (s, 3H, OCH_3), 3.65 (m, 1H, H-3), 3.67 (m, 1H, H-5’), 3.69 (s, 3H, OCH_3), 3.84 (d, 1H, J = 7.9 Hz, H-2), 4.11 (q, 2H, J = 7.0 Hz, CH_3CH_2O). ^{13}C-NMR: δ 13.36 (CH_3CH_2N), 14.35 (CH_3CH_2O), 44.26 (C-4), 46.94 (CH_3CH_2N), 49.04 (C-3), 52.19 (OCH_3), 52.36 (OCH_3), 54.52 (C-5), 60.75 (CH_3CH_2O), 66.64 (C-2), 170.83 (C=O), 171.27 (C=O), 173.89 (C=O).

2,3-*trans*: Yield 0.16g. Yellowish oil. For $C_{13}H_{21}NO_6$ calculated 287.31 $g.mol^{-1}$. EI-MS (m/z, %): 287(M^+, 21), 228 (30), 214 (82), 182 (100), 154 (96), 122 (38), 96 (44), 58 (29). IR: 2976 m, 2963 m, 2888 w, 1742 s (C=O), 1441 m, 1369 m, 1187 s, 1106 m, 1023 m, 945 w, 859 w cm^{-1}.

^{1}H-NMR: δ 1.05 (t, J = 7.3 Hz, 3H, CH_3CH_2N), 1.25 (t, J = 7.0 Hz, 3H, CH_3CH_2O), 2.41 (m, 2H, H-4), 2.74 (m, 1H, H-5), 2.84 (m, 1H, H-5‘), 3.39 (q, J = 7.3 Hz, 2H, CH_3CH_2N), 3.46 (d, $J_{2,3}$ = 9.95 Hz, 1H, H-2), 3.64 (s, 3H, OCH_3), 3.67 (m, 1H, H-3), 3.71 (s, 3H, OCH_3), 4.19 (m, 2H, CH_3CH_2O). ^{13}C-NMR: δ 13.28 (CH_3CH_2N), 14.34 (CH_3CH_2O), 45.29 (C-4), 47.14 (CH_3CH_2N), 50.08 (C-3), 52.20 (OCH_3), 52.33 (OCH_3), 54.52 (C-5), 61.91 (CH_3CH_2O), 69.73 (C-2), 170.83 (C=O), 171.82 (C=O), 173.02 (C=O).

2-Ethyl 3,4-dimethyl 1-(*tert*-butyl)pyrrolidine-2,3,4-tricarboxylate (5b). Total yield 0.34 g (%) of both isomers. Yellowish oil. Elution with diethyl ether. For $C_{15}H_{25}NO_6$ calculated 315.36 g.mol^{-1}. EI-MS (m/z, %): 315 (M^+, 3), 300 (36), 242 (78), 210 (43), 154 (100), 126 (71), 58 (48), 57 (48), 41 (28). IR: 2975 s, 2957 s, 2846 m, 2823 m, 1739 s (C=O), 1439 m, 1376 m, 1193 s, 1106 m, 1029 m, 944 m, 857 w cm^{-1}. ^{1}H-NMR: δ 3.80 (d, 1H, $J_{2,3}$ = 5.8 Hz, H-2, 2,3-*trans*-isomer), 3.96 (d, 1H, $J_{2,3}$ = 9.0 Hz, H-2, 2,3-*cis*-isomer).

2-Ethyl 3,4-dimethyl 1-(*n*-butyl)pyrrolidine-2,3,4-tricarboxylate (5c). Total yield 0.34 g (%) of both isomers. Yellowish oil. Elution with diethyl ether. For $C_{15}H_{25}NO_6$ calculated 315.36 g.mol^{-1}. EI-MS (m/z, %): 315 (M^+, 3), 256 (28), 242 (80), 210 (98), 182 (100), 150 (29), 124 (29), 82 (15), 68 (22), 41 (14). IR: 2956 m, 2936 w, 2863 w, 1739 s (C=O), 1459 w, 1438 m, 1374 w, 1196 s, 1096 w, 1026 m, 944 m, 857 w cm^{-1}. ^{1}H-NMR: δ 3.69 (d, $J_{2,3}$ = 4.7 Hz, 1H, H-2, 2,3-*trans*-isomer), 3.87 (d, $J_{2,3}$ = 7.6 Hz, 1H, H-2, 2,3-*cis*-isomer).

General method for preparation of 6

Mixture of **1** (5.0 g, 3.81 mmol for R = Et or 3.14 mmol for R = *t*-Bu and *n*-Bu) and finely powdered paraformaldehyde (22.86 mmol, 1.32 g) was under stirring irradiated for 15 minutes. The final temperature reached 130 °C. On cooling product was extracted twice by chloroform (15 ml), filtered with an addition of silica, evaporated and the remainder was distilled under reduced pressure.

Ethyl 3-ethyl-1,3-oxazolidine-4-carboxylate (6a). Yield 3.8 g (58%) of colourless liquid. b.p.: 100-103°C / 2 mm Hg. For $C_8H_{15}NO_2$ calculated 173.21 g.mol^{-1}. EI-MS (m/z, %): 173 (M^+, 8), 143 (10), 114 (31), 100 (100), 72 (90), 56 (23), 55 (12), 44 (27), 42 (32). IR: 2975 s, 2938 m, 2878 m, 1737 s(C=O), 1468 m, 1378 m, 1353 w, 1184 s, 1098 w, 1064 m, 1027 m, 906 w cm^{-1}. ^{1}H-NMR: δ 1.05 (t, J = 7.3 Hz, 3H, CH_3CH_2N), 1.20 (t, J = 7.15 Hz, 3H, CH_3CH_2O), 2.64 (m, 2H, CH_3CH_2N), 3.52 (dd, J = 7.8 Hz, J = 5.6 Hz, 1H, H-5), 3.75 (dd, J = 8.3 Hz, J = 5.6 Hz, 1H, H-5), 4.04 (m, 1H, H-4), 4.12 (q, J = 7.15 Hz, 2H, CH_3CH_2O), 4.30 (d, J = 5.1 Hz, 1H, H-2), 4.39 (d, 1H, J = 5.1 Hz, H-2’). ^{13}C-NMR: δ 13.82 (CH_3CH_2N), 13.94 (CH_3CH_2O), 48.81 (CH_3CH_2N), 60.91 (CH_3CH_2O), 64.42 (C-4), 67.20 (C-5), 86.76 (C-2), 171.93 (C=O).

Ethyl 3-(*tert*-butyl)-1,3-oxazolidine-4-carboxylate (6b). Yield 4.0 g (64%) of colourless liquid. b.p.: 80-85°C / 2 mm Hg. For $C_{10}H_{19}NO_2$ calculated 201.26 g.mol^{-1}. EI-MS (m/z, %): 201 (M^+, 5), 186 (22), 158 (12), 144 (7), 128 (91), 115 (33), 86 (11), 72 (100), 70 (11), 69 (13), 68 (48), 57 (80), 44 (33), 41 (44). IR: 2971 s, 2875 s, 1740 s (C=O), 1472 m, 1369 m, 1186 s, 1101 w, 1031 m, 919 m, 843 w cm^{-1}. ^{1}H-NMR: δ 1.11 (s, 9H, 3xCH_3), 1.27 (t, J = 7.05 Hz, 3H, CH_3CH_2O), 3.78 (dd, J = 8.0 Hz, J = 5.6 Hz, 1H, H-5), 3.86 (dd, J = 8.0 Hz, J = 5.6 Hz, 1H, H-5), 4.05 (t, J = 8.0 Hz, 1H, H-4), 4.19 (q, J = 7.05 Hz, 2H, CH_3CH_2O), 4.40 (d, J = 5.7 Hz, 1H, H-2), 4.71 (d, J

= 5.71 Hz, 1H, H-2). ^{13}C-NMR: δ 13.98 (CH_3CH_2O), 27.44 ($3xCH_3$), 51.98 (C_q), 59.41 (CH_3CH_2O), 60.77 (C-4), 68.76 (C-5), 82.32 (C-2), 173.52 (C=O).

Ethyl 3-(*n*-butyl)-1,3-oxazolidine-4-carboxylate (6c). Yield 3.3 g (53%) of colourless liquid. b.p.: 98-101°C / 2 mmHg. For $C_{10}H_{19}NO_2$ calculated 201.26 g.mol^{-1}. EI-MS (m/z, %): 201 (M^+, 4), 158 (10), 144 (2), 129 (13), 128 (100), 100 (28), 98 (28), 86 (13), 72 (11), 70 (7), 57 (18), 44 (22). IR: 2959 s, 2934 s, 2871 s, 1739 s (C=O), 1465 m, 1374 m, 1278 w, 1185 s, 1085 m, 1029 m, 926 w, 879 w cm^{-1}. ^{1}H-NMR: δ 0.88 (t, J = 7.3, 3H, C**H$_3$**$CH_2CH_2CH_2N$), 1.26 (t, J = 7.1 Hz, 3H, C**H$_3$**CH_2O), 1.32 (m, 2H, CH_3C**H$_2$**CH_2CH_2N), 1.44 (m, 2H, CH_3CH_2C**H$_2$**CH_2N), 2.62 (m, 2H, $CH_3CH_2CH_2$C**H$_2$**N), 3.54 (dd, J = 8.0 Hz, J = 5.6 Hz, 1H, H-5), 3.79 (dd, J = 8.0 Hz, J = 5.6 Hz, 1H, H-5'), 4.07 (m, 1H, H-4), 4.16 (q, J = 7.1 Hz, 2H, CH_3CH_2O), 4.32 (d, J = 5.0 Hz, 1H, H-2), 4.42 (d, J = 5.0 Hz, 1H, H-2'). ^{13}C-NMR: δ 13.69 (CH_3CH_2N), 13.99 (CH_3CH_2O), 20.12 ($CH_3CH_2CH_2CH_2N$), 31.07 ($CH_3CH_2CH_2CH_2N$), 54.76 ($CH_3CH_2CH_2CH_2N$), 60.89 (CH_3CH_2O), 64.82 (C-4), 67.18 (C-5), 87.25 (C-2), 171.98 C=O.

Acknowledgements

Authors are obliged to thank for the support to Ministry of Education within EU project COST OC D 10.20.

References

1. Lubineau, A.; Bouchain, G.; Queneau, *J. Chem. Soc., Perkin Trans.* 1 **1995**, 2433.
2. Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron Asymmetry* **1991**, *2*, 1189.
3. Orsini, F.; Pellizoni, F.; Forte, M.; Sisti, M.; Merati, F.; Gariboldi, P. *J. Heterocycl. Chem*. **1988**, *25*, 1665.
4. Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D.; Wong, L. F. *Tetrahedron Asymmetry* **1991**, *2*, 1343.
5. Imai, N.; Nemoto, M.; Terao, Y.; Achiwa, K.; Kekiya, M. *Chem. Pharm. Bull*. **1986**, *34*, 1080.
6. Imai, N.; Terao, Y.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1984**, *25*, 1579.
7. Imai, N.; Terao, Y.; Achiwa, K. *Heterocycles* **1985**, *23*, 1107.
8. Burns, B.; Coates, B.; Neeson, S.; Stevenson, P. J. *Tetrahedron Let.* **1990**, *31*, 4351.
9. Joucla, M.; Mortier, J. *Tetrahedron Lett.* **1987**, *28*, 2973.
10. Saha, U. K.; Roy, R. *J. Chem. Soc. Chem. Commun.* **1995**, *24*, 2571.
11. Saha, U. K.; Roy, R. *Tetrahedron Lett.* **1995**, *36*, 3635.
12. Tran, P. L.; Brienne, M. J.; Malthete, J.; Lacombe, L. *Tetrahedron Lett*. **1986**, *27*, 2371.