SIMPLE AND VERSATILE SYNTHESIS OF 2-ALKOXYALKYLAMINES

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Abstract

Facile synthesis of 2-methoxyalkylnitriles and 2-ethoxyalkylnitriles and their reduction to amines for potential usage as isocyanide synthesis starting compounds is presented. Alkoxyalkylnitriles (methoxy and ethoxy) were prepared by reaction of corresponding dialkyl ketals and trimethylsilyl cyanide. This reaction was optimized for the highest yield and its usability was confirmed on series of dialkyl ketals. Following standard hydride reduction of appropriate methoxy or ethoxy nitriles gave corresponding methoxy or ethoxyamines. Identity and purity of all newly prepared compounds was confirmed by means of NMR spectroscopy.

Introduction

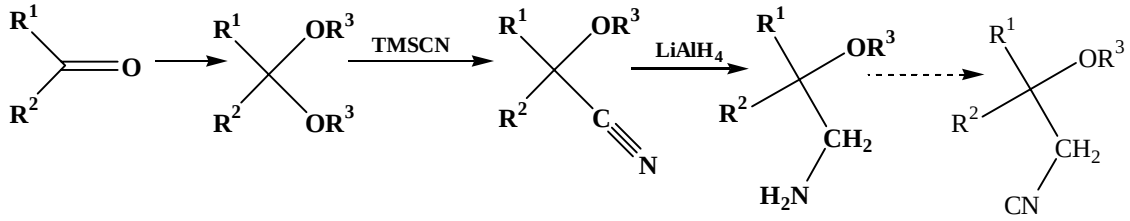
Complexes of ^{99m}Tc with aliphatic alkoxyalkylisocyanides are used as a very powerful radiodiagnostics of heart disease.[1-3] Various isocyanide ligands are applied for these purposes (mainly 2-methoxy-2-methylpropyl isocyanide[4]). The presence of an alkoxy group in the ligand molecule is strongly assumed to be essential for the optimal radiopharmaceutical properties of the resulting complex.[3] Isocyanides are compounds with very unpleasant properties due to their limited stability and unpleasant odour.[5] In contrast, salts of alkoxy amines (e.g. hydrochlorides or oxalates) are much more stable compounds. Since the conversion of amine to isocyanide is a simple reaction,[5] it can be involved in the reaction sequence for the ^{99m}Tc isocyanide complex preparation just before diagnostic application.

Various synthetic approaches leading to corresponding amine precursors could be suggested. One of them is based on direct conversion of dialkyl ketals to alkoxyalkylnitrile for example *via* treatment of ketal with *tert*-butyl isocyanide using $TiCl_4$ as a catalyst[6] followed by standard hydride reduction[7] of nitrile to amine.

Modern approach to this method uses reaction of dialkyl ketals (mostly dimethylketals) of ketones with trimethylsilyl cyanide (TMSCN) using Lewis acid as a catalyst, e.g.: ZnI_2, $SnCl_4$, $FeCl_3$, $TiCl_4$[8,9] and $FB_3.Et_2O$.[10-12]

Results and discussion

In this contribution we report the modification of the latter synthetic method and its large-scale application for the preparation of ligand's precursors (2-alkoxyalkylamines).



Scheme 1.

At first, the 1-methoxycyclohexanecarbonitrile was synthesized *via* modification of published procedure[10-12] from 1,1-dimethoxycyclohexane[13] and TMSCN. Reaction was performed without solvent and the boron trifluoride aetherate was used as a catalyst.[10-12] Modifying the reaction conditions, 1-ethoxycy-clohexanecarbonitrile was prepared *per analogiam*. The reaction conditions were optimized for the highest yield by varying of temperature and time (Table 1 and 2) and the wide reliability and applicability of this reaction was confirmed on the following substrates: 1,1-dimethoxycyclohexane, 1,1-diethoxycyclohexane, 1,1-dimethoxycyclopentane, 1,1-dimethoxycycloheptane, 1,1-diethoxycycloheptane, 1,1-dimethoxycyclooctane, 1,1-diethoxycyclooctane, 4,4-dimethoxyheptane, 3,3-dimethoxyheptane, 3,3-dimethoxypentane, 2,2-dimethoxy-3-methylbutane, 2,2-dimethoxy-4-methylpentane, 1,1-dimethoxy-4-methylcyclo-hexane, 1,1-dimethoxy-3-methylcyclohexane. Resulting nitriles were always reduced by standard procedure using $LiAlH_4$ in aether.[7] By this manner, couples of mostly new nitriles and amines were prepared and characterized by NMR. Experimental

Material and methods

Gas chromatograph Varian 3400 (30 m DB-5 J α W Scientific column) with mass spectrometer the Incos 50 Finnigan MAT (temperature of ion source was 150°C and energy of ionizating electrons was 75 eV) was used for GC-MS measurement. ^{1}H NMR spectra were recorded on Varian ^{UNITY}*INOVA* 400 (400 MHz, FT mode). Chemical shifts are presented in δ (ppm). In $CDCl_3$, the scale (δ, ppm) was referenced to tetramethylsilane, in D_6-DMSO to DMSO signal (δ=2.50) and in D_2O to HDO (δ=4.70) signal or to internal standard, 2-methyl-2-propanole (δ=1.25). ^{13}C NMR spectra were recorded on the same instrument, Varian ^{UNITY}*INOVA* 400 (100 MHz). The scale was referenced to the solvent signal ($CDCl_3$, δ=77.00), (D_6-DMSO, δ=39.50) and in D_2O to 2-methyl-2-propanol (δ=31.60).

Gas chromatography was performed on Varian Vista 6500 with 30 m capillary column DB-5 J α W Scientific and FID detector. Inlets were done splitless with *n*-decane as an external standard. For column preparative chromatography Kieselgel 60 Merck and for thin layer preparative chromatography Kieselgel 60 G were used.

All ketones (Lachema) used as starting compounds for synthesis were distilled before use. Solvents (Lachema) were distilled, dried and purified by standard laboratory methods. All dialkyl ketals from ketones were synthesized *via* standard treatment of trimethyl orthoformate or triethyl orthoformate using *p*-toluensulfonic acid as an acidic catalyst.[14] Samples for melting points were dried in oil pump vacuum for 72 h at 40ºC (this long time is necessary, because there were problems with crystalline water). Melting points are not corrected. Elemental analyses were performed on Perkin Elmer 240 C elemental analyser.

General procedure

To 1 g of 1,1-dimethoxycyclohexane (6.94 mmol) in a round bottomed flask equipped with a septum and a magnetic stirring bar 1.85 ml of TMSCN (13.88 mmol) was added in one portion. Mixture was cooled to 0°C and boron trifluoride aetherate (5 mol % with respect to dialkyl ketal) was added with microsyringe and the mixture was stirred for 1 hour at 0°C under nitrogen atmosphere. Then, 10 ml of water was added to the mixture (HCN (g) evolved from the reaction mixture.) After 12 h of stirring at room

temperature, the rest of dissolved HCN was washed out with nitrogen. Aqueous phase was then extracted with 3 x 5 ml of dichloromethane. Combined organic layers were dried over $MgSO_4$. After removing solvent in vacuum, the residual colourless oil was distilled at reduced pressure. Yield of isolated 1-methoxy-1-cyclohexanecarbonitrile was 0.79 g (82%). All other methoxy-alkylnitriles were prepared by the same manner. For preparation of all ethoxyalkylnitriles the reaction procedure was modified: reaction time was prolonged to 24 h and reaction temperature was enhanced to 25ºC.

Alkoxynitriles were then reduced to amines using $LiAlH_4$ in aether.[7] All amines were isolated as oxalates and were crystallized from MeOH. After amine releasing with aqueous solution of NaOH (10 %) followed by extraction with diethyl aether, chromatography on silica gel ($CHCl_3$: MeOH: NH_4OH (aq. 25 %) / 6: 4: 0.1) was used in the case when further purification was necessary.

Results

Optimisation of yield for reaction of dimethyl and diethyl ketal and TMSCN was performed by using GC. Starting ketone, dialkyl ketal, and ketone cyanhydrine was present in reaction mixture. We found that amount of impurities is mostly temperature and time dependent. The yields of main products in different temperatures are presented in the following tables.

Table 1. Optimisation of reaction conditions for 1-methoxycyclohexanecarbonitrile (GC-yields in %)

Temp. (ºC)/time	15 min	1 h	3 h	6 h	12 h	24 h	48 h
0	82	92	92	91	90	88	81
25	34	37	42	40	38	32	26

Table 2. Optimisation of reaction conditions for 1-ethoxycyclohexanecarbonitrile (GC-yields in %)

Temp. (°C)/time	15 min	1 h	3 h	6 h	12 h	24 h	48 h
0	2	4	10	15	22	31	34
25	6	10	18	36	48	57	66
50	12	22	26	40	38	32	18

Table 3. Nitriles and their spectral data

Compound	Yield %	Spectral data
1-Ethoxycyclohexane-carbonitrile	83	Colourless oil – boiling point: 74 - 78°C (2 kPa), *Anal.*: Calculated for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; O, 10.44. Found: C, 70.95; H, 10.01; N, 9.03. **^{1}H NMR** ($CDCl_3$): 1.25 (t, 3H, J=6.9, CH_3); 1.50 – 1.80 (m, 6H); 2.08 (m, 4H), (5 x CH_2); 3.66 (q, 2H, J=6.9, OCH_2). **^{13}C NMR** ($CDCl_3$): 15.20 (CH_3); 22.34 ($C_{3,5}$); 24.63 (C_4); 37.63 ($C_{2,6}$); 60.43 (OCH_2); 69.35 (C_1); 121.92 (CN).
1-Methoxycyclopentane-carbonitrile[15]	82	Colourless oil – boiling point: 58-62°C (2 kPa), *Anal.*: Calculated for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19; O, 12.78. Found: C, 68.01; H, 8.52; N, 12.04. **^{1}H NMR** ($CDCl_3$): 1.68 (m, 4H, 2 x CH_2); 1.97 (m, 4H, 2 x CH_2); 3.29 s, 3H, (OCH_3). **^{13}C NMR** ($CDCl_3$): 22.67 ($C_{3,4}$); 37.14 ($C_{2,5}$); 53.20 (OCH_3); 79.93 (C_1); CN (119.83).
1-Methoxycycloheptane-carbonitrile	85	Colourless oil – boiling point: 95-97°C (2 kPa), *Anal.*: Calculated for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; O, 10.44. Found: 70.02; H, 9.64; N, 9.89. **^{1}H NMR** ($CDCl_3$): 1.50 (m, 8H; 1.82 m, 2H; 1.96 m, 2H, 6 x CH_2); 3.27 s, 3H, (OCH_3). **^{13}C NMR** ($CDCl_3$): 21.07 ($C_{3,6}$); 27.81 ($C_{4,5}$); 37.38 ($C_{2,7}$); 52.62 (OCH_3), 78.11 (C_1), CN (120.51).

Table 3 Continued.

1-Ethoxycycloheptane-carbonitrile	80	Colourless oil – boiling point: 122-124ºC (2 kPa), *Anal.*: Calculated for $C_{10}H_{17}NO$: C, 71.81; H. 10.25; N, 8.37; O, 9.57. Found: C, 72.11; H, 10.19; N, 8.42. **^{1}H NMR** ($CDCl_3$): 1.23 (t, 3H, J = 7.0, CH_3); 1.64 (m, 8H, 4 x CH_2); 1.96 (m, 2H, CH_2); 2.10 (m, 2H, CH_2); 3.62 (q, 2H, J=7.0, OCH_2). **^{13}C NMR** ($CDCl_3$): 15.31 (CH_3); 21.31 ($C_{3,6}$); 28.01 ($C_{4,5}$); 38.10 ($C_{2,7}$); 60.94 (OCH_2), 77.64 (C_1); 121.25 (CN).
1-Methoxycyclooktane-carbonitrile	88	Colourless oil – boiling point: 120-124ºC (2 kPa), *Anal.*: Calculated for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37; O, 9.57. Found: C, 72.03; H, 10.03; N, 8.41. **^{1}H NMR** ($CDCl_3$): 1.59 (m, 10H); 2.04 (m, 4H), (7 x CH_2); 3.41 (s, 3H, OCH_3). **^{13}C NMR** ($CDCl_3$): 20.64 ($C_{3,7}$); 24.12 (C_5); 27.48 ($C_{4,6}$); 32.33 ($C_{2,8}$); 52.67 (OCH_3); 78.22 (C_1); 120.45 (CN).
1-Ethoxycyclooctane-carbonitrile	88	Colourless oil – boiling point: 162-166ºC (2 kPa), *Anal.*: Calculated for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73; O, 8.83. Found: C, 73.01; H, 10.32; N, 7.62. **^{1}H NMR** ($CDCl_3$): 1.23 (t, 3H, J = 7.0, CH_3); 1.57 (m, 8H); 1.70 (m, 2H); 2.03 (m, 4H), (7 x CH_2); 3.61 (q, 2H, J=7.0, OCH_2); **^{13}C NMR** ($CDCl_3$): 15.31 (CH_3); 20.76 ($C_{3,7}$); 24.19 (C_5); 27.59 ($C_{4,6}$); 32.92 ($C_{2,8}$); 60.83 (CH_2); 77.61 (C_1); 121.05 (CN).
2-Methoxy-2-propylpentanenitrile	82	Colourless oil – boiling point: 84-86ºC (2 kPa), *Anal.*: Calculated for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; O, 10.31. Found: C, 70.01; H, 11.05; N, 9.12. **^{1}H NMR** ($CDCl_3$): 0.97 (t, 6H, J=6.8, 2 x CH_3); 1.47 (m, 4H); 1.74 (m, 4H), (4 x CH_2); 3.41 (s, 3H, OCH_3). **^{13}C NMR** ($CDCl_3$): 13.94 ($C_{5,3'}$); 16.82 ($C_{4,2'}$); 38.17 ($C_{3,1'}$); 52.90 (OCH_3); 78.12 (C_2); 119.61 (CN).
2-Ethyl-2-methoxyhexanenitrile	84	Colourless oil – boiling point: 89-91ºC (2 kPa), *Anal.*: Calculated for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; O, 10.31. Found: C, 69.52, H, 11.12; N, 9.52. **^{1}H NMR** ($CDCl_3$): 0.94 (t, 3 H, J=7.2, CH_3); 1.01 (t, 3H, J=7.3, CH_3); 1.39 (m, 4H, 2 x CH_2); 1.75 (m, 2H, CH_2); 1.82 (q, 2H, J=7.5, CH_2); 3.41 (s, 3H, OCH_3). **^{13}C NMR** ($CDCl_3$): 7.70 ($C_{2'}$); 13.85 (C_6); 22.59 (C_5); 25.44 (C_4); 28.95 ($C_{1'}$); 35.22 (C_3); 52.91 (OCH_3); 78.68 (C_2); 119.56 (CN).

Table 3 Continued.

2-Methoxy-2,3-dimethylbutanenitrile	89	Colourless oil – boiling point 79-81 ºC (2 kPa), *Anal.*: Calculated for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01; O, 12.58. Found: C, 66.71; H, 11.00; N, 11.02. **^{1}H NMR** ($CDCl_3$): 1.02 (d, 3H, J=6.8, $\underline{CH_3}$-CH); 1.07 (d, 3H J=6.8, $\underline{CH_3}$-CH); 1.45 (s, 3H, CH_3); 2.02 (septet, 1H, J=6.8, CH); 3.43 (s, 3H, OCH_3). **^{13}C NMR** ($CDCl_3$): 16.51, 17.23 (CH($\underline{C}H_3)_2$); 19.67 (C_2-$\underline{C}H_3$); 35.98 (C3); 52.98 (OCH_3); 78.74 (C_2); 119.50 (CN).
2-Methoxy-2,4-dimethylpentanenitrile	81	Colourless oil – boiling point 62-65ºC (2 kPa), *Anal.*: Calculated for $C_8H_{15}NO$: C, 68.04; H, 10.71; N. 9.92; O, 11.33. Found: C, 68.56; H, 10.82; N, 10.02. **^{1}H NMR** ($CDCl_3$): 1.01 (d, 3H, J=6.4, $\underline{CH_3}$-CH); 1.02 (d, 3H, J=6.4, $\underline{CH_3}$-CH); 1.53 (s, 3H, CH_3); 1.66 (dd, 1H, J_1=14.4, J_2=6.3) and 1.72 (dd, 1H, J_1=14.4, J_2=6.3), (CH_2); 1.94 (septet, 1H, J=6.6, CH). **^{13}C NMR** ($CDCl_3$): 23.60, 23.67 (CH($\underline{C}H_3)_2$); 24.15 (C_2-CH_3); 24.57 (C_4); 47.99 (C_3); 52.85 (OCH_3); 74.29 (C_2); 120.12 (CN).
1-Methoxy-4-methyl-cyclohexancarbonitrile	88	Colourless oil – boiling point: 78-82ºC (2 kPa), *Anal*: Calculated for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; O, 10.44. Found: C, 70.72; H, 10.06; N, 9.29.**^{1}H NMR** ($CDCl_3$): 0.95 (d, 3H, J=6.4, CH_3); 1.28 (m, 2H); 1.47 (m, 2H); 1.79 (m, 2H), (3 x CH_2); 2.21 (m, 3H, CH_2 + CH); 3.44 (s, 3H, OCH_3).**^{13}C NMR** ($CDCl_3$): 21.22 (CH_3); 31.12 ($C_{3,5}$); 33.01 (C_4); 34.82 ($C_{2,6}$), 52.29 (OCH_3); 76.23 (C_1), 119.28 (CN).
1-Methoxy-3-methyl-cyclohexancarbonitrile	95	Colourless oil – boiling point: 95-100ºC (2 kPa), *Anal*: Calculated for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; O, 10.44. Found: C, 71.00; H, 9.91; N, 9.14. **^{1}H NMR** ($CDCl_3$) : 0.98 (d, 3H, J=6.2, CH_3); 1.50 – 1.90 (m, 6 H); 2.20 (m, 3H); 3.44 (s, 3H, OCH_3). **^{13}C NMR** ($CDCl_3$): 21.53 (C_5); 22.47 (CH_3); 29.70 (C_4); 33.32 (C_6); 33.38 (C_3); 34.72 (C_2); 52.12 (OCH_3); 76.43 (C_1); 119.41 (CN).

Table 4. Amine hydrogen oxalates and their spectral data.

Compound	Yield %	Spectral data
(1-Methoxycyclohexyl)-methanamine	86	White crystalline solid – melting point: 157-162ºC (recryst. methanol), *Anal.*: Calculated for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00; O, 34.29. Found: C, 52.11; H, 8.44; N, 5.89. **^{1}H NMR** (D_6-DMSO): 1.20 – 1.80 (m, 10H, 5 x CH_2); 2.68 (s, 2H, CH_2N); 3.17 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 21.65 ($C_{3',5'}$); 25.92 ($C_{4'}$); 31.72 ($C_{2',6'}$); 45.69 (CH_2N); 48.11 (OCH_3); 75.01 ($C_{1'}$); 164.79 (oxalate).
(1-Ethoxycyclohexyl)-methanamine	79	White crystalline solid – melting point: 138-142ºC (recryst. methanol), *Anal.*: Calculated for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66; O, 32.35. Found C, 53.82; H, 8.62; N, 5.78. **^{1}H NMR** (D_6-DMSO): 1.12 (t, 3H, J=6.9, CH_3); 1.20 – 1.72 (m, 10 H, 5 x CH_2), 2.85 (s, 2H, CH_2N); 3.29 (q, 2H, J=6.9, OCH_2). **^{13}C NMR** (D_6-DMSO): 15.54 (CH_3); 21.20 ($C_{3',5'}$); 25.20 ($C_{4'}$); 34.54 ($C_{2',6'}$); 42.69 (CH_2N); 55.20 (OCH_2); 72.63 ($C_{1'}$); 164.67 (oxalate).
(1-Methoxycyclopentyl)-methanamine	79	White crystalline solid – melting point: 160-164ºC (recryst. methanol), *Anal.*: Calculated for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39; O, 36.49. Found: C, 49.92; H, 7.72; N, 6.48. **^{1}H NMR** (D_6-DMSO): 1.56 (m, 6H, 3 x CH_2); 1.77 (m, 2H, CH_2); 2.97 (s, 2H, CH_2N); 3.08 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 23.27 ($C_{3',4'}$); 33.04 ($C_{2',5'}$); 42.56 (CH_2N); 49.36 (OCH_3); 84.02 ($C_{1'}$); 168.24 (oxalate).
(1-Methoxycycloheptyl)-methanamine	79	White crystalline solid – melting point: 142-144ºC (recryst. methanol), *Anal.*: Calculated for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66; O 32.35. Found: C, 53.92; H, 8.66; N, 5.72. **^{1}H NMR** (D_6-DMSO): 1.43 (m, 10H); 1.74 (m, 2H), (6 x CH_2); 2.86 (s, 2H, CH_2N); 3.09 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 21.38 ($C_{3',6'}$); 29.13 ($C_{4',5'}$); 33.92 ($C_{2',7'}$); 43.18 (CH_2N); 48.62 (OCH_3); 76.83 ($C_{1'}$); 163.92 (oxalate).

Table 4 Continued.

(1-Ethoxycycloheptyl)-methanamine	89	White crystalline solid – melting point 128-132ºC (recryst. methanol), *Anal.*: Calculated for $C_{12}H_{23}NO_5$: C, 55.16; H, 8.87; N, 5.36; O, 30.61. Found: C, 55.52; H, 8.67; N, 5.28. **^{1}H NMR** (D_6-DMSO): 1.10 (t, 3H, J=6.8, CH_3); 1.46 (m, 10H, 5 x CH_2); 1.75 (m, 2H, CH_2); 2.85 (s, 2H, CH_2N); 3.31 (q, 2H, J=6.8, OCH_2). **^{13}C NMR** (D_6-DMSO): 15.62 (CH_3); 21.40 ($C_{3',6'}$); 29.06 ($C_{4',5'}$); 34.53 ($C_{2',7'}$); 43.82 (CH_2N); 55.75 (OCH_2); 76.65 ($C_{1'}$); 165.55 (oxalate).
(1-Methoxycyclooctyl)-methanamine	89	White crystalline solid – melting point 142-145ºC (recryst. methanol), *Anal.*: Calculated for $C_{12}H_{23}NO_5$: C, 55.16, H, 8.87; N, 5.36; O, 30.61. Found: C, 55.42; H, 8.62; N, 5.38. **^{1}H NMR** (D_6-DMSO): 1.48 (m, 12H, 6 x CH_2); 1.73 (m, 2H, CH_2); 2.85 (s, 2H, CH_2N); 3.06 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 20.74 ($C_{3',7'}$); 24.21 ($C_{5'}$); 27.58 ($C_{4',6'}$); 29.11 ($C_{2',8'}$); 41.31 (CH_2N); 48.58 (OCH_3); 76.26 ($C_{1'}$), 164.26 (oxalate).
(1-Ethoxycyclooctyl)-methanamine	87	White crystalline solid – melting point 138-142ºC (recryst. methanol), *Anal.*: Calculated for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09; O, 29.05. Found: C, 57.01; H, 9.02; N, 5.00. **^{1}H NMR** (D_6-DMSO): 1.09 (t, 3H, J=7.0, CH_3); 1.48 (m, 12 H); 1.74 (m, 2H), (7 x CH_2); 2.84 (s, 2H, CH_2N); 3.28 (q, 2H, J=7.0, OCH_2). **^{13}C NMR** (D_6-DMSO): 15.52 (CH_3); 20.72 ($C_{3',7'}$); 24.16 ($C_{5'}$); 27.59 ($C_{4',6'}$); 29.52 ($C_{2',8'}$); 42.05 (CH_2N); 55.71 (OCH_2); 76.10 ($C_{1'}$), 164.46 (oxalate).
2-Methoxy-2-propyl-1-pentanamine	62	White crystalline solid – melting point 115-120ºC (recryst. methanol), *Anal.*: Calculated for $C_{11}H_{23}NO_5$: C, 52.99; H, 9.30; N, 5.62; O, 32.09. Found: C, 53.02; H, 9.25; N, 5.72. **^{1}H NMR** (D_6-DMSO): 0.87 (t, 6H, J=7.3, 2 x CH_3); 1.19 (m, 4H); 1.40 (m, 4H), (4 x CH_2); 2.82 (s, 2H, CH_2N); 3.07 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 14.24 ($C_{5,3'}$); 15.83 ($C_{4,2'}$); 33.99 ($C_{3,1'}$); 40.85 (CH_2N); 48.27 (OCH_3); 76.03 (C_2); 164.58 (oxalate).

Table 4 Continued.

2-Ethyl-2-methoxy-1-hexanamine	64	White crystalline solid – melting point 115-119ºC (recryst. methanol), *Anal.*: Calculated for $C_{11}H_{23}NO_5$: C, 52.99; H, 9.30; N, 5.62; O, 32.09. Found: C, 53.12; H, 9.45; N, 5.63. **^{1}H NMR** (D_6-DMSO): 0.77 (t, 3H, J=7.5, CH_3); 0.88 (t, 3H, J=7.3, CH_3); 1.10 – 1.50 (m, 8H, 4 x CH_2); 2.83 (s, 2H, CH_2N); 3.07 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 7.29 ($C_{2'}$); 13.86 (C_6); 22.48 (C_5); 24.22 (C_4); 24.49 ($C_{1'}$); 30.82 (C_3); 40.40 (CH_2N); 48.28 (OCH_3); 76.27 (C_2); 164.35 (oxalate).
2-Ethyl-2-methoxy-1-butanamine	68	White crystalline solid – melting point 107-110ºC (recryst. methanol), *Anal.*: $C_9H_{19}NO_5$: C, 48.86; H, 8.66; N, 6.33, O, 36.16. Found: C, 48.84; H, 8.42; N, 6.42. **^{1}H NMR** (D_6-DMSO): 0.77 (t, 6H, J=7.4, 2 x CH_3); 1.47 (m, 4H, 2 x CH_2); 2.83 (s, 2H, CH_2N); 3.08 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 7.18 ($C_{2',4}$); 23.64 ($C_{1',3}$); 40.00 (CH_2N); 48.28 (OCH_3); 76.50 (C_2), 163.91 (oxalate).
2-Methoxy-2,3-dimethyl-1-butanamine	65	White crystalline solid – melting point 135-139ºC (recryst. methanol), *Anal.*: Calculated for $C_9H_{19}NO_5$: C, 48.86; H, 8.66; N, 6.33; O, 36.16. Found: C, 49.11; H, 8.52; N, 6.21. **^{1}H NMR** (D_6-DMSO): 0.82 (d, 3H, J=6.8); 0.84 (d, 3H, J=6.8); 1.06 (s, 3H), (3 x CH_3); 1.95 (septet, 1H, J = 6.8, CH); 2.87 (s, 2H, CH_2N); 3.10 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 16.25, 16.48, 16.82 (3 x CH_3); 31.15 (C_3); 41.58 (C_1); 48.53 (C_2); 76.37 (OCH_3), 164.15 (oxalate).
2-Methoxy-2,4-dimethyl-1-pentanamine	68	White crystalline solid – melting point 115-119ºC (recryst. methanol), *Anal.*: Calculated for $C_{10}H_{21}NO_5$: C, 51.05; H, 9.00; N, 5.95; O, 34.00. Found: C, 51.03; H, 9.10; N, 6.05. **^{1}H NMR** (D_6-DMSO): 0.91 (d, 3H, J=6.8); 0.92 (d, 3H, J=6.8); 1.15 (s, 3H), (3 x CH_3); 1.40 (m, 2H, CH_2); 1.70 (septet, 1H, J=6.8, CH); 2.85 (s, 1H, CH_2N); 3.09 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 20.32 (C_2-$\underline{C}H_3$); 24.05, 24.14 ($CH(\underline{C}H_3)_2$); 23.06 (C_4); 42.83 (C_3); 44.64 (C_1); 48.80 (OCH_3); 74.49 (C_2); 167.25 (oxalate).

Table 4 Continued.

(1-Methoxy-4-methyl-cyclohexyl)methanamine	72	White crystalline solid – melting point 142-145ºC (recryst. methanol), *Anal.*: Calculated for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66; O, 32.35. Found: C, 53.98; H, 8.32; N, 5.44. **^{1}H NMR** (D_6-DMSO): 0.82 (d, 3H, J=6.3, CH_3); 1.50 (m, 9H); 2.31 (s, 2 H, CH_2N); 3.12 (s, 3 H, OCH_3). **^{13}C NMR** (D_6-DMSO): 22.13 (CH_3); 29.45 ($C_{3',5'}$); 32.84 ($C_{2',6'}$); 37.28 ($C_{4'}$); 47.25 (CH_2N); 51.27 (OCH_3); 74.23 ($C_{1'}$), 166.28 (oxalate).
(1-Methoxy-3-methyl-cyclohexyl)methanamine	69	White crystalline solid – melting point 104-109ºC (recryst. methanol), *Anal.*: Calculated for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66; O, 32.35. Found: C, 52.99; H, 8.50; N, 5.70. **^{1}H NMR** (D_6-DMSO) : 0.86 (d, 3H, J=6.3, CH_3); 1.50 (m, 9H); 2.98 (s, 2H, CH_2N); 3.12 (s, 3H, OCH_3). **^{13}C NMR** (D_6-DMSO): 21.95 ($C_{5'}$); 22.30 (CH_3); 28.69 ($C_{4'}$); 30.80 ($C_{3'}$); 33.71 ($C_{6'}$); 39.62 ($C_{2'}$); 40.13 (CH_2N); 47.20 (OCH_3), 74.20 ($C_{1'}$) 165.29 (oxalate).

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Povzetek

Opisana je enostavna sinteza 2-metoksialkilnitrilov in 2-etoksialkilnitrilov, njihova redukcija do aminov ter potencialna uporaba le-teh v sintezi izocianidov. Sinteza je potekla iz ustreznih dialkilketalov in trimetilsilil cianida. Reakcijski pogoji so bili optimizirani za dosego največjega izkoristka. S standardno redukcijo s hidridi so bili pripravljeni metoksi oziroma etoksiamini. Strukture novih spojin so bile potrjene z NMR spektroskopijo.