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ARTICLE

Method for the synthesis of *N*-alkyl-*O*-alkyl carbamates

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th ,
Accepted 00th

DOI: 10.1039/x0xx00000x

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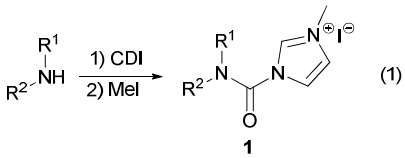
Primary and secondary carbamates were prepared from primary, secondary and *neo*pentyl alcohols, and carbonyl-di-imidazole (CDI), using a new three step method. Non-acidic alcohols reacted with CDI affording carbamoyl-imidazoles with excellent yields (92-97%). The carbamoyl-imidazoles were then converted into the more reactive imidazolium salts, which upon reaction with primary and secondary amines afforded the corresponding carbamates in high isolated yields (66-99%).

Introduction

The synthesis of carbamates plays a key role in different areas of chemistry. For example, carbamates find widespread application in pharmaceutical[1] and agrochemical[2] products. Moreover, carbamates are used as intermediates in organic synthesis,[3] for the protection of amino groups in peptide chemistry,[4] and as linkers in combinatorial chemistry.[5]

Carbamates can be prepared by the reaction of an electrophilic alkoxycarbonyl derivatives with nucleophilic amines. Alternatively, carbamates can also be obtained upon reaction of electrophilic carbamoyl groups with nucleophilic alcohols. Most of these reactions involve the use of toxic phosgene[6] or phosgene equivalents such as isocyanates[7] or di- and triphosgene.[8] Different alternative methods that do not involve the use of toxic reagents have also been reported.[9]

After the seminal works of Salvesen[10] and Rapoport,[11] it was demonstrated by Batey that carbamoylimidazolium salts, which in turn can easily be obtained by a two step procedure from amines and carbonyl dimidazole (CDI, equation 1), can be used for the efficient synthesis of amides[12] and ureas.[12,13]



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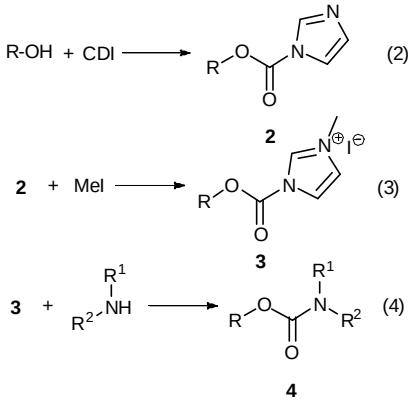
Nucleophilic (and acidic) alcohols, such as phenols,[14] and naphthols, react with carbamoyl imidazolium salts **1** in the presence of triethylamine, affording the corresponding carbamates in good yield. Less nucleophilic aliphatic alcohols react slowly with the carbamoyl imidazolium salts **1**, and good yields of carbamates were only obtained with 2,2,2-trifluoroethanol in large excess, as the reaction solvent. Moreover, allyl and benzyl alcohol required the use of NaH to afford acceptable yields of carbamates.



The reaction of carbamoylimidazolium iodide **1** with the more basic alkoxides of aliphatic alcohols do not afford the required bis-alkyl carbamates, probably due to the acid-base reaction between the nucleophile and the proton at position 2 of the imidazolium salt ring **1**. [10,12b-c, 14]

Taking into account that aliphatic alcohols readily react with CDI affording alkoxycarbonylimidazoles **2** and the increased nucleophilicity of aliphatic amines compared with analogous alcohols, we envisaged that changing the order of the reaction sequence (*i.e.* first the reaction of the aliphatic alcohols with CDI, followed by alkylation and then reaction with the amines),

would be a simple alternative to overcome the limitations of the previously reported methods.

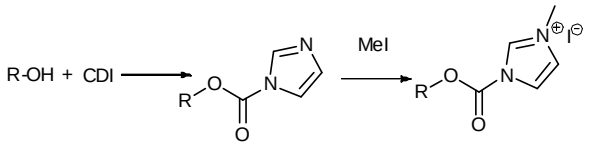
Thus, alkoxycarbonylimidazolium iodides **3** should react with amines to yield carbamates **4** under mild conditions, avoiding the use of strong bases and the use of large excesses of the nucleophiles. Since strong bases are not required in this new reaction sequence, the acid-base reaction of the imidazolium salt **3** and the basic nucleophiles should easily be overcome.

Results and discussion

To evaluate our proposed strategy for the synthesis of carbamates, alkoxycarbonyl imidazole **2a** was prepared in high yield from *neo*-pentyl alcohol under mild reaction conditions (95%, entry 1, Table 1). The reaction of carbonyl imidazole **2a** with 4-piperidone was sluggish and only 11% GC yield of carbamate **4a** was obtained after 16 h at room temperature, which is in accordance with the anticipated low reactivity of alkoxycarbonyl imidazoles. Compound **2a** was converted into the more reactive alkoxycarbamoylimidazolum salt **3a** (99%, entry 5, Table 1) by reaction with MeI at room temperature in acetonitrile. Imidazolium salts **3** are unstable compounds and hence they were used and characterized without purification. The activated imidazolium salt **3a** reacted with 4-piperidone in otherwise identical conditions as used for **2a**, affording carbamate **4a** in excellent yield (97 %, entry 1, Table 2).

To test the scope of the method for the synthesis of carbamate derivatives, imidazolium salt **3a** was treated with representative primary and secondary aliphatic amines. Thus, the reaction of carbamoylimidazolium salt **3a** with morpholine, pyrrolidine, *n*-octylamine and benzylamine afforded the desired carbamates **4b-e** with excellent yields (96-99 %, entries 2-5 in Table 2). Only a slight excess of the amines were required to obtain the carbamates in excellent yields, under extremely mild reaction conditions.

Table 1. Synthesis of alkoxycarbonyl imidazoles 3a-d and alkoxycarbonyl-imidazolium iodide 4a-d.



2a-d **3a-d**

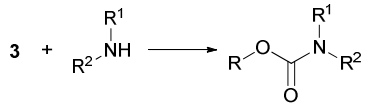
entry	R-OH	Yield[b] (%)	entry	Yield[b] (%)[b]
1[a]	*neo*-pentyl alcohol	95 (**2a**)	5[c]	99(84) (**3a**)
2[a]	*n*-octanol	97 (**2b**)	6[c]	99(86) (**3b**)
3[a]	methoxyethanol	92 (**2c**)	7[c]	93(70) (**3c**)
4[a]	cyclohexanol	97 (**2d**)	8[c]	97(90) (**3d**)

a) 1 eq. of alcohol, 1.2 eq. of CDI, THF, room temperature, 24h. b) isolated yield. c) 1 eq. of alkoxycarbonyl imidazole **3**, 3.5 eq. of MeI, acetonitrile, room temperature, 24h. b) NMR yields are given in parentheses.

Primary aliphatic alcohols are also well-suited for the reaction. *n*-Octyl alcohol reacted with CDI, giving alkoxycarbonylimidazole **2b** in excellent yield (entry 2, Table 1). Upon reaction of **2b** with MeI, alkoxycarbonylimidazolium iodide **3b** was obtained in almost quantitative yield (entry 6, Table 1). In an analogous fashion as **3a**, **3b** reacted with primary and secondary amines yielding the corresponding carbamates, as shown for the reaction of **3b** with piperidone, morpholine, pyrrolidine, *n*-octylamine and benzylamine (carbamates **4f-j**, 78-91 %, entries 6-10, Table 2).

Another primary alcohol, namely 2-methoxyethanol, also proved to be a suitable starting material, as demonstrated by its conversion to the imidazolium iodide **3c** (entries 3 and 7, Table 1), which subsequently afforded the corresponding carbamates **4k-o** with high yields (73-81%, entries 11-15, Table 2) upon reaction with the corresponding amines.

Table 2. Synthesis of carbamates 2a-t by reaction of alkoxycarbonyl-imidazolium iodide 4a-d with primary and secondary aliphatic amines.



entry	salt	amine	Yield[b] (%)
1	**3a**	4-piperidone	97 (**4a**)
2	**3a**	morpholine	96 (**4b**)
3	**3a**	pyrrolidine	99 (**4c**)
4	**3a**	*n*-octylamine	94 (**4d**)
5	**3a**	benzylamine	99 (**4e**)
6	**3b**	4-piperidone	78 (**4f**)
7	**3b**	morpholine	81 (**4g**)
8	**3b**	pyrrolidine	98 (**4h**)
9	**3b**	*n*-octylamine	81 (**4i**)
10	**3b**	benzylamine	91 (**4j**)
11	**3c**	4-piperidone	81 (**4k**)
12	**3c**	morpholine	80 (**4l**)
13	**3c**	pyrrolidine	86 (**4m**)
14	**3c**	*n*-octylamine	79 (**4n**)
15	**3c**	benzylamine	70 (**4o**)
16	**3d**	4-piperidone	91 (**4p**)
17	**3d**	Morpholine	96 (**4q**)
18	**3d**	Pyrrolidine	80 (**4r**)
19	**3d**	*n*-octylamine	66 (**4s**)
20	**3d**	benzylamine	81 (**4t**)

a) 1 eq. **4**, 1.1 eq. of amine, acetonitrile, room temperature, 24 h. b) isolated yield. c) the product was obtained in three steps without purification of intermediate products.

As expected, cyclohexanol, a secondary aliphatic alcohol, also worked well in the reaction sequence. The reaction of cyclohexanol with CDI afforded alkoxycarbonyl imidazole **2d** with 97% yield, which was further converted in imidazolium

iodide (**3d**) under the standard conditions (97%, entries 4 and 8, Table 1). The reactions of **3d** with the selected amines in all cases afforded the corresponding carbamates **4p-t** in good to excellent yield (66-96%, entries 16-20, Table 2).

Conclusions

In summary, herein we have reported a new three-step method that affords *N*-alkyl-*O*-alkyl carbamates in excellent yields employing readily-available and safe reagents under mild conditions. This method takes advantage of the increased reactivity of amines compared with the related aliphatic alcohols in the second step of nucleophilic acyl substitution, making it suitable for the preparation of *O*-alkyl urethanes using non-acidic alcohols as starting materials. Furthermore, changing the order of the reaction sequence (*i.e.* first the reaction with alcohol, and then the reaction of the corresponding imidazolium salt with the amine) allows the bis-aliphatic carbamates to be obtained, whilst avoiding the use of a large excess of alcohols or basic alkoxides.

Experimental

General Methods

^{1}H NMR and ^{13}C NMR spectra were acquired on a 300 MHz spectrometer (^{1}H NMR, 300.14 MHz; ^{13}C NMR, 75.04 MHz) with $CDCl_3$ as the solvent, unless otherwise indicated. Coupling constants are given in Hz and chemical shifts are reported in ppm. Data are reported as follow: chemical shift, multiplicity (s = singlet, s br = broad singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, ddd = double double doublet, m = multiplet), coupling constants (*J*) and number of protons. Gas Chromatography-Mass Spectrometry analyses were carried out on a GC/MS equipped with a quadrupole detector and an HP-5 column (30 m x 0.25 mm x 0.25 μm). High Resolution Mass Spectra were measured in a MS/MS instrument using pure products. These data were obtained by ESI or APPI modes of ionization and TOF detection. Melting points were measured with an electrical instrument and are uncorrected.

Materials

neo-Pentyl alcohol, *n*-octyl alcohol, cyclohexanol, 2-methoxyethanol, 1,1´-carbonyl-di-imidazole (CDI), triethylamine, morpholine, *n*-octyl amine, benzylamine, 4-piperidone hydrochloride hydrate and pyrrolidine were commercially available and used as received from the supplier. Methyl iodide was obtained following a reported method.[15] THF was distilled over Na/benzophenone and stored over molecular sieves (4 Å). Acetonitrile was distilled and stored over molecular sieves (4 Å).

Representative procedure for the synthesis of alkoxycarbonyl imidazole derivatives 2a-d. In a flame-dried sealed tube equipped with a magnetic stirrer was added 2.0 mL of THF, 1.00 mmol of the alcohol and 1.23 mmol of CDI. The reaction was stirred for 24 h at room temperature. Water (100 mL) was then added and the reaction mixture was extracted with diethyl ether (3 x 30 mL). The organic layer was washed with water and dried over anhydrous calcium chloride, filtered and concentrated *in vacuo*. The product was obtained in high purity and was used without purification in the next step.

neo*-Pentyl 1*H*-imidazole-1-carboxylate 2a:* the pure product was obtained as a white solid (173 mg, 95 %), m.p.: 65-67°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (s, 1H); 7.44 (s, 1H); 7.09 (s, 1H); 4.12 (s, 2H); 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.8; 137.0; 130.7; 117.1; 77.4; 31.7; 26.3. GC-MS (*m/z*): 182 (6, M^+), 95(15), 71(26), 69(17), 68(17), 55(14), 43(100). HRMS (ESI) $[M+ Na]^+$ calcd. for $C_9H_{14}N_2O_2Na$ 205.0953, obtained 205.0950.

Octyl 1*H*-imidazole-1-carboxylate 2b: the pure product was obtained as a white solid (217.4 mg, 97 %), m.p.: 36-37°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (bs, 1H); 7.44 (bs, 1H); 7.08 (bs, 1H); 4.42 (t, *J*=6.8, 2H); 1.81 (m, 2H); 1.50-1.24 (m, 10 H); 0.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.9; 137.1; 130.6; 68.5; 31.7; 29.1; 28.5; 25.7; 22.6; 14.1. GC-MS (*m/z*): 224 (1, M^+), 71(32), 69(44), 68(27), 57(71), 55(22), 43(100), 42(17), 41(74). HRMS (ESI) $[M+ H]^+$ calcd. for $C_{12}H_{20}N_2O_2H$ 225.1603, obtained 225.1598.

2-Methoxyethyl 1*H*-imidazole-1-carboxylate 2c*:* the pure product was obtained as a colorless oil (157 mg, 97 %).[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (bs, 1H); 7.46 (bs, 1H); 7.08 (bs, 1H); 4.58-4.55 (m, 2H); 3.75-3.71 (m, 2H); 3.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.8; 137.2; 130.7; 117.2; 69.9; 67.1; 59.1. GC-MS (*m/z*): 170(14, M^+), 103(14), 68(24), 59(100), 58(25).

Cyclohexyl 1*H*-imidazole-1-carboxylate 2d*:* the pure product was obtained as a white solid (188.4 mg, 97 %), m.p.: 42-44°C (44-46°C lit.).[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (bs, 1H); 7.40 (bs, 1H); 7.03 (bs, 1H); 4.97-4.95 (m, 1H); 2.06-1.16 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.6; 137.6; 131.0; 117.5; 78.1; 31.5; 24.9; 23.9. GC-MS (m/z): 194 (3, M^+); 83(53), 69(22), 68(21), 67(26), 55(100), 54(19), 41(67).

Representative procedure for the synthesis of alkoxycarbonyl imidazolium iodides derivatives 3a-e.

In a flame-dried sealed tube equipped with a magnetic stirrer was added 2.0 mL of CH_3CN, 1.00 mmol of the alkoxycarbonyl imidazole derivative and 3.50 mmol of MeI. The reaction was stirred for 24 h at room temperature. The solvent and volatile compounds were removed *in vacuo*. The products were used in the next step without further purification.

3-Methyl-1-((neo-pentyloxy)carbonyl)-1H-imidazol-3-ium iodide 3a*:* this compound was obtained with a purity of 85 % (determined by ^{1}H-NMR) as yellow solid (321 mg, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.56 (s, 1H); 7.78 (s, 1H); 7.56 (s, 1H); 4.37 (s, 3H); 4.32 (s, 2H); 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ: 146.4; 138.9; 125.2; 120.4; 79.2; 37.1; 31.9; 26.4. HRMS (ESI) $[M-I]^+$ calcd. for $C_{10}H_{17}N_2O_2$ 197.1285, obtained 197.1285.

3-Methyl-1-((octyloxy)carbonyl)-1H-imidazol-3-ium iodide 3b*:* this compound was obtained with a purity of 87 % (determined by ^{1}H-NMR) as yellow solid (362.6 mg, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.43 (bs, 1H); 7.76 (bs, 2H); 4.59 (t, *J*= 7, 2H); 4.35 (bs, 3H); 1.92-1.87 (m, 2H); 1.45-1.29 (m, 10 H); 0.91-0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.3; 138.2; 125.4; 119.3; 72.1; 38.7; 31.7; 29.1; 29.0; 28.3;

25.5; 22.6; 14.1. HRMS (ESI) $[M-I]^+$ calcd. for 236.1754 obtained: 239.1754.

3-Methyl-1-(2-methoxyethyloxy)carbonyl)-1H-imidazol-3-ium iodide 3c: this compound was obtained with a purity of 75 % (determined by ^{1}H-NMR) as a dark orange oil (290.2 mg, 93 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.53 (bs, 1H); 7.81 (t, *J*= 1.8, 1H); 7.66 (t, *J*= 1.8, 1H); 4.76-4.73 (m, 2H); 4.31 (bs, 3H); 3.86-3.83 (m, 2H); 3.43 (bs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.5; 59.2; 69.3; 70.2; 119.6; 125.0; 138.5; 145.3. HRMS (ESI) $[M-I]^+$ calcd. for $C_8H_{13}N_2O_3$ 185.0921 obtained 185.0926.

3-Methyl-1-((cyclohexyloxy)carbonyl)-1H-imidazol-3-ium iodide 3d: this compound was obtained with a purity of 93 % (determined by ^{1}H-NMR) as orange oil (326 mg, 97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.42 (bs); 7.97 (bs, 1H); 7.80 (bs, 1H); 5.10-5.20 (m, 1H); 4.38 (bs, 3H); 1.23-1.90 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.5; 137.8; 125.4; 119.1; 82.3; 38.4; 30.9; 24.5; 23.3. HRMS (ESI) $[M-I]^+$ calcd. for $C_{11}H_{17}N_2O_2$ 209.1280 obtained 209.1280.

Representative procedure for the synthesis of carbamate derivatives 4a-t.

In a flame-dried sealed tube equipped with a magnetic stirrer was added 4 mL of CH_3CN, 1.00 mmol of the alkoxycarbonyl imidazolium iodide derivative and 1.10 mmol of the corresponding amine. When 4-piperidone hydrochloride hydrate was used, 3.30 mmol of Et_3N were added. The reaction was stirred for 24 h at room temperature. Water (100 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with water, separated and dried over anhydrous calcium chloride, filtered and concentrated *in vacuo*. The pure product was obtained by column chromatography on silica gel.

***neo*-Pentyl 4-oxopiperidine-1-carboxylate 4a:** the pure product was obtained by column chromatography on silica gel, eluting with hexane:acetone (70:30→0:100) as colourless oil (206.7 mg, 97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84-3.78 (m, 6H); 2.48 (t, 4H, *J*= 5.8); 0.97 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4; 155.5; 75.3; 43.1; 41.1; 31.6; 26.5. GC-MS (*m/z*): 213(3, M^+), 142(26), 126(21), 98(21), 71(20), 57(22), 56(25), 55(24), 43(100). HRMS (ESI) $[M+H]^+$ calcd. for $C_{11}H_{19}NO_3H$ 214.1443, obtained 214.1438.

***neo*-Pentyl morpholine-4-carboxylate 4b:** the pure product was obtained by column chromatography on silica gel, eluting with hexane:acetone (50:50→0:100) as colourless oil (193.2 mg, 96 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (s, 2H); 3.67 (t, *J*= 4.5, 4H); 3.48 (t, *J*= 4.6, 4H); 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.7; 74.9; 66.6; 44.0; 31.6; 26.5. GC-MS (*m/z*): 201(2, M^+), 130(8), 114(14), 88(6), 71(17), 57(13), 43(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{10}H_{19}NO_3Na$ 224.1263, obtained: 224.1257.

neo*-Pentyl pyrrolidine-1-carboxylate 4c:* the pure product was obtained after work-up without purification as orange oil (183.5 mg, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.76 (s, 2H); 3.38 (t, *J*= 6.5, 4H); 1.91-1.83 (m, 4H); 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.4; 74.4; 46.1; 45.6; 31.5; 26.5; 25.8; 25.02. GC-MS (*m/z*): 185(2, M^+), 146(35), 114(32), 98(53), 71(36), 56(20), 55(40), 43(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{10}H_{19}NO_2Na$ 208.1313, obtained 208.1308.

***neo*-Pentyl octylcarbamate 4d**: the pure product was obtained by column chromatography on silica gel, eluting with hexane:CH_2Cl_2 (50:50→0:100) as colourless oil (228.4 mg, 94 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.67 (bs, 1H); 3.76 (bs, 2H); 3.18-3.16 (m, 2H); 1.50 (bs, 2H); 1.28 (bs, 10H); 0.92-0.88 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.0; 74.1; 41.0; 31.8; 31.5; 30.1; 29.3; 29.2; 26.8; 26.4; 22.7; 14.1. GC-MS (*m/z*): 243(1, M^+), 144(3), 117(3), 99(3), 71(34), 57(30), 56(13), 55(21), 44(14), 43(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{14}H_{29}NO_2Na$ 266.2091, obtained 266.2098.

neo*-Pentyl benzylcarbamate 4e:* the pure product was obtained by column chromatography on silica gel, eluting with hexane:CH_2Cl_2 (50:50→0:100) as white solid, mp: 65-67°C (219.1 mg, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.27 (m, 5H); 5.06 (bs, 1H); 4.37 (d, *J*= 5.9, 2H); 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.0; 138.7; 128.7; 127.6; 74.4; 45.1; 31.5; 26.4. GC-MS (*m/z*): 221(3, M^+), 151(49), 150(74), 133(20), 106(31), 105(21), 92(10), 91(100), 79(13), 71(10), 65(19), 57(44), 56(14), 55(29), 51(18), 44(10), 43 (77), 41(60). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{13}H_{19}NO_2Na$ 244.1313, obtained 244.1308.

Octyl 4-oxopiperidine-1-carboxylate 4f*:* the pure product was obtained by column chromatography on silica gel, eluting with hexane: CH_2Cl_2 (50:50→0:100) as colourless oil (199.0 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.13 (t, *J*= 6.7, 2H); 3.77 (t, *J*= 6.1, 4H); 2.46 (t, *J*= 6.1, 4H); 1.71-1.64 (m, 2H); 1.33-1.28 (m, 10H); 0.90-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.2; 155.1; 65.8; 42.7; 40.8; 31.5; 28.9; 28.8; 28.6; 25.6; 22.3; 13.8. GC-MS (*m/z*): 142(12, $[M-C_8H_{17}]^+$), 126(6), 100(13), 99(24), 98(18), 70(17), 57(48), 56(49), 55(34), 43(100), 42(67), 41(91). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{14}H_{25}NO_3Na$ 278.1727, obtained 278.1735.

Octyl morpholine-4-carboxylate 4g*:* the pure product was obtained by column chromatography on silica gel, eluting with pentane:CH_2Cl_2 (50:50→0:100) as colourless oil (197.0 mg, 81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.09 (t, *J*= 6.7, 2H); 3.67-3.64 (m, 4H); 3.48-3.45 (m, 4H); 1.65-1.61 (m, 2H); 1.31-1.27 (m, 10H); 0.90-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.6; 66.6; 65.7; 43.9; 31.7; 29.2; 29.1; 28.9; 25.9; 22.6; 14.1. GC-MS (*m/z*): 243(1, M^+), 131(16), 116(32), 88(27), 87(24), 86(12), 74(11), 57(60), 56(43), 55(29), 44(21), 43(100), 42(60). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{13}H_{25}NO_3Na$ 266.1727, obtained 266.1735.

Octyl pyrrolidine-1-carboxylate 4h*:* the pure product was obtained by column chromatography on silica gel, eluting with hexane:CH_2Cl_2 (50:50→0:100) as colourless oil (222.0 mg, 98%).^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.06 (t, *J*= 6.6, 2H); 3.41-3.31 (m, 10H); 1.87-1.85 (m, 4H); 1.65-1.60 (m, 2H); 1.30-1.26 (m, 10H); 0.90-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1; 22.7; 25.0; 25.8; 26.0; 29.1; 29.2; 29.3; 31.8; 45.7; 46.1; 65.1; 155.4. GC-MS (*m/z*): 227(1, M^+), 113(11), 83(15), 71(58), 57(82), 41(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{13}H_{25}NO_2Na$ 250.1778, obtained 250.1789.

Octyl octylcarbamate 4i: the pure product was obtained by column chromatography on alumina, eluting with hexane:diethyl ether (80:20) as white solid, m.p.: 36-38ºC (231.0 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.59 (bs, 1H); 4.02 (t, *J*= 6.6, 2H); 3.15 (q, *J*= 6.5, 2H); 1.66-1.54 (m, 4H); 1.49-1.45 (m, 2H); 1.39-1.21 (m, 20H); 0.89-0.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.8; 69.8; 64.9; 54.9; 41.0; 31.8; 30.0; 29.4; 29.3; 29.2; 29.1; 26.8; 28.9; 22.7. GC-MS (*m/z*): 285(1, M^+), 186(5), 174(29), 112(10), 99(3), 84(21), 69(41), 62(21), 55(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{17}H_{35}NO_2Na$ 308.2560, obtained 308.2574.

Octyl benzylcarbamate 4j*:* the pure product was obtained by column chromatography on silica gel, eluting with hexane:diethyl ether (100:0→50:50) as a white solid, m.p.: 48-50ºC (239.7 mg, 91 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.25 (m, 5H); 4.95 (bs, 1H); 4.37 (d, *J*=5.9, 2H); 4.11-4.06 (m, 2H); 1.69-1.55 (m, 2H); 1.37-1.23 (m, 10H); 0.88 (t, *J*= 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.8; 138.6; 128.7; 127.6; 127.5; 65.2; 45.0; 31.8; 29.2; 29.0; 25.9; 22.7; 14.1. GC-MS (*m/z*): 263(2, M^+), 151(100), 133(23), 106(30), 105(21), 104(16), 91(60), 79(15), 77(18), 56(44), 55(50), 43(72). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{15}H_{23}NO_2Na$ 286.1778, obtained 286.1797.

2-Methoxyethyl 4-oxopiperidine-1-carboxylate 4k: the pure product was obtained by column chromatography on silica gel, eluting with hexane:diethyl ether (100:0→50:50) as a colourless oil (163.0 mg, 81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.31-4.28 (m, 2H); 3.79 (t, *J*= 6.3, 4H); 3.65-3.62 (m, 2H); 3.40 (s, 3H); 2.47 (t, *J*=6.2, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4; 155.2; 70.8; 64.9; 58.9; 43.1; 41.0. GC-MS (*m/z*): 201(1, M^+), 142(6), 126(7), 98(24), 70(15), 58(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_9H_{15}NO_4Na$ 224.0893, obtained 224.0903.

2-Methoxyethyl morpholine-4-carboxylate 4l*:* the pure product was obtained by column chromatography on silica gel, eluting with hexane:diethyl ether (100:0→50:50) as a colourless oil (151.0 mg, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.27-4.24 (m, 2H); 3.66-3.65 (m, 4H); 3.62-3.59 (m, 2H); 3.50-3.47 (m, 4H); 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.3; 70.9; 66.6; 64.2; 58.9; 43.9. GC-MS (*m/z*): 189(2, M^+), 131(20), 116(27), 85(17), 71(46), 58(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_8H_{15}NO_4Na$ 212.0893, obtained 212.0892.

2-Methoxyethyl pyrrolidine-1-carboxylate 4m: the pure product was obtained by column chromatography on silica gel, eluting with hexane:diethyl ether (100:0→50:50) as a colourless oil (149.0 mg, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.26-4.22 (m, 2H); 3.63-3.59 (m, 2H); 3.40-3.36 (m, 7H); 1.87-1.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.4; 71.1; 64.0; 58.9; 46.2; 45.8; 25.7; 24.9. GC-MS (*m/z*): 173(2, M^+), 114(64), 98(51), 87(15), 70(31), 55(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_8H_{15}NO_3Na$ 196.0944, obtained 196.0966.

2-Methoxyethyl octylcarbamate 4n: the pure product was obtained by column chromatography on silica gel, eluting with hexane:diethyl ether (100:0→50:50) as a colourless oil (183.0 mg, 79 %).^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.79 (bs, 1H); 3.59-3.56 (m, 2H); 3.38 (s, 3H); 3.19-3.12 (m, 2H); 1.49-1.45 (m, 2H); 1.31-1.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.4; 71.1; 63.7; 59.0; 41.1; 31.8; 29.9; 29.3; 29.2; 26.8; 14.1. GC-MS (*m/z*): 231(1, M^+), 132(6), 112(7), 99(19), 85(7), 77(6) 71(9), 58(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{12}H_{25}NO_3$ 254.1727, obtained 254.1730.

2-Methoxyethyl benzylcarbamate 4o: the pure product was obtained by column chromatography on silica alumina, eluting with hexane:ethyl ether (50:50) as a colourless oil (147.0 mg, 70 %).[18]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.26 (m, 5H); 5.10 (bs, 1H); 4.37 (d, *J*= 5.9, 2H); 4.28-4.25 (m, 2H); 3.61-3.58 (m, 2H); 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.4; 138.3; 128.7; 127.5; 70.9; 64.1; 59.0; 45.1. GC-MS (*m/z*): 209(3, M^+), 150(73), 132(7), 106(41), 91(100), 77(36).

Cyclohexyl 4-oxopiperidine-1-carboxylate 4p*:* the pure product was obtained by column chromatography on silica gel, eluting with hexane:Cl_2CH_2 (100:0→20:80), as a colourless oil, (205.0 mg, 91 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.76-4.70 (m, 1H); 3.72 (t, *J*= 6.2, 4H); 2.46 (t, *J*= 6.2, 4H); 1.90-1.87 (m, 2H); 1.73-1.66 (m, 2H); 1.58-1.25 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4; 154.9; 74.0; 43.0; 41.2; 31.9; 25.4; 23.7. GC-MS (*m/z*): 197(1, M^+), 116(71), 114(10), 98(10), 83(25), 70(28), 67(16), 56(22), 55(100), 54 (13). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{12}H_{19}NO_3Na$ 248.1257, obtained 248.1277.

Cyclohexyl morpholine-4-carboxylate 4q: the pure product was obtained by column chromatography on silica gel, eluting with hexane:acetone (100:0→0:100) as a colourless oil, (205.0 mg, 96 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.72-4.67 (m, 1H); 3.66-3.64 (m, 4H); 3.46 (t, 4H, *J*= 4); 1.87-1.25 (m, 10H) . ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.2; 73.5; 66.7; 44.0; 31.9; 25.4; 23.7. GC-MS (*m/z*): 213(2, M^+), 132(15), 116(10), 88(31), 83(37), 70(18), 57(30), 56(25), 55(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{11}H_{19}NO_3Na$ 236.1257, obtained 236.1285.

Cyclohexyl pyrrolidine-1-carboxylate 4r: the pure product was obtained by column chromatography on silica gel, eluting with hexane:Cl_2CH_2 (100:0→20:80), as a colourless oil, (157.7 mg, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.70-4.64 (m, 1H); 3.39-3.30 (m, 4H); 1.85-1.25 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.9; 72.4; 45.9; 45.7; 32.1; 25.7; 25.5; 25.0; 23.7. GC-MS (*m/z*): 197(1, M^+), 116(71), 114(10), 98(10), 83(25), 70(28), 67(16), 56(22), 55(100), 54(13). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{11}H_{19}NO_2Na$ 220.1308, obtained 220.1351.

Cyclohexyl octylcarbamate 4s: the pure product was obtained by column chromatography on silica gel, eluting with hexane:Cl_2CH_2 (100:0→50:50) as an orange oil, (168.5 mg, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.61 (bs, 2H); 3.15 (q, *J*= 6.5, 2H); 1.90-1.86 (m, 2H); 1.75-1.71 (m, 2H); 1.56-1.20 (m, 18H); 0.88 (t, *J*=6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3; 72.8; 40.9; 32.1; 31.8; 30.0; 29.3; 29.2; 26.8; 25.5; 23.9; 23.8; 22.7; 14.1. GC-MS (*m/z*): 174(15, $[M-C_6H_{11}]^+$), 99(10), 83(30), 67(20), 57(26), 56(16), 55(20), 44(31), 43(44), 41(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{15}H_{29}NO_2Na$ 278.2091, obtained 278.2098.

Cyclohexyl benzylcarbamate 4t: the pure product was obtained by column chromatography on silica gel, eluting with hexane: Cl_2CH_2 (100:0→50:50), as a white solid mp: 86-88°C, (188.2 mg (81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.26

(m, 5H); 4.94 (bs, 1H); 4.69-4.66 (m, 1H); 4.36 (d, 2H, J= 5 Hz); 1.88-1.72 (m, 1H); 1.56-1.22 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3; 138.7; 128.7; 127.6; 127.4; 73.3; 45.0; 32.1; 32.0; 25.4; 23.9. GC-MS (*m/z*): 151(17, $[M-C_6H_{11}]^+$), 133(13), 106(23), 105(21), 104(18), 91(41), 82(14), 79(11), 77(17), 74(13), 67(40), 65(16), 55(60), 41(100). HRMS (ESI) $[M+Na]^+$ calcd. for $C_{14}H_{19}NO_2Na$ 256.1308, obtained 256.1337.

Acknowledgments

This work was supported by Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) and by the Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET) from Argentina. VAV and JPP deeply acknowledges CONICET for the fellowships. MG deeply acknowledges the joint fellowship received from CONICET-CARBONFE. The authors thank Dr. Karl Bonney (RWTH Aachen University) for proofreading of the manuscript.

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† This work is dedicated to the memories of Professors R.J.A. Grau and M.I. Cabrera.

Electronic Supplementary Information (ESI) available: copies of ^{1}H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/b000000x/

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