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Armandodoriano Bianco^a; Francesco Bonadies^a; Raffaella Napolitano^b; Giancarlo Ortaggi^b

^a Dipartimento di Chimica, Universita "La Sapienza" Aldo, Roma, ITALY ^b Istituto di Chimica Biomolecolare del CNR Piazzale Aldo, Roma, ITALY

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SYNTHESIS OF URETHANES BY A MODIFIED CURTIUS REACTION WITH ALCOHOLS

Armandodoriano Bianco[†], Francesco Bonadies[†]
Raffaella Napolitano^{*††} and Giancarlo Ortaggi^{††}

[†]*Dipartimento di Chimica, Universita "La Sapienza"*

^{††}*Istituto di Chimica Biomolecolare del CNR Piazzale Aldo Moro 5
00185 Roma, ITALY*

e-mail: <raffaella.napolitano@uniroma1.it>

Urethanes have proven to be useful moieties in several types of compounds, especially those of biomedical interest, owing to the physico-chemical characteristics of this function, which shows suitable biostability and biodegradability. For example, *DC-Chol* (3 β -[N-dimethylaminoethyl]-carbamoylcholesterol (*Fig. 1*)¹ was designed to have a relatively labile carbamoyl linker which, though not as easily hydrolysed as the ester bond, once inside the cell eventually undergoes biodegradation, most likely caused by the cellular esterases. This is apparently one of the reasons for the good pharmaceutical characteristics of *DC-Chol* and analogous lipids, such as GL 67,² BGSC,³ BGTC,³ and Vitamin D based lipids.⁴ In fact, *DC-Chol* and its analogues are cationic lipids which are important for obtaining cationic liposomes for gene therapy.

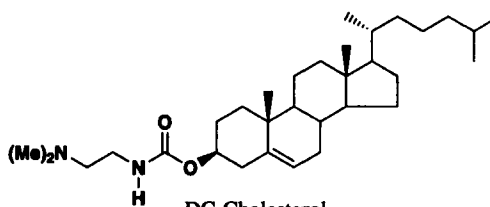


Figure 1

The most common methods for the synthesis of urethanes are the reaction between chloroformates and amines¹⁰ and the Curtius rearrangement of acyl azides,¹¹ followed by reaction of the isocyanates with alcohols. The route involving the reaction of chloroformates with amines has been improved by the use of N-carbalkoxyimidazoles,^{4,12} easily obtained from alcohols and 1,1'-carbonyldiimidazole, which provides high yields of urethanes. Given that isocyanates, especially alkyl isocyanates, are very sensitive to water, the overall yields of the azide method are generally lower than those obtained from the chloroformate procedure. In 1972, Yamada *et al.*¹³ improved the Curtius reaction by introducing diphenylphosphoryl azide (DPPA) as a means for the direct conversion of carboxylic acids into urethanes in 53-74% yields.

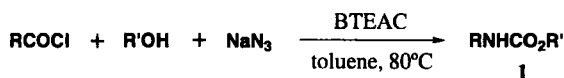
It consists of a one-pot reaction of carboxylic acid, triethylamine, DPPA, and the hydroxy compound under reflux (5-25 hrs). It has been adopted for the preparation of urethanes¹⁴ and for the introduction of urethane bond in natural products.¹⁵ In 1988, Scarpati *et al.*¹⁶ also described a one-pot reaction between acyl chlorides, sodium azide and methanol in the presence of a phase-transfer catalyst, without the isolation of intermediate azides or isocyanates, to give methyl urethanes in 81-99% yields.

Various other, less useful methods have been also described for the preparation of urethanes.⁵⁻⁹ A recent report¹⁷ discussed the possibility of improving the methodology described by Scarpati *et al.* by expanding it to the use of alcohols of various structures, as well as of phenol. The preliminary results showed that, for all of alcohols used, the rearrangement produced very satisfactory yields of the corresponding urethane. In light of the results of this preliminary study, we conducted an extensive investigation of this modified Curtius reaction and the results are reported herein.

The modified Curtius reaction is represented by the following equation, where both R and R' are interchangeably aliphatic and aromatic groups.



In the first part of the study, we used various aliphatic, aromatic and alicyclic acid chlorides. One ω -haloacyl chloride was also tested with the goal of using this reaction to prepare cationic lipids such as DC-Chol, characterized by the presence of the urethane bond. However, the bromine group of 5-bromovaleryl chloride, was apparently unreactive under the reaction conditions, thus allowing the facile introduction of the ammonium function. We decided to test a secondary alicyclic alcohol, a cyclic alcohol, a tertiary alcohol and phenol. The general procedure of the reaction is as follows. The acyl chloride was kept at 60°C in toluene with sodium azide and benzyltriethylammonium chloride as the transfer-phase catalyst, for 1 hr; then the temperature was raised to 80°C and the alcohol was added and the reaction mixture was stirred overnight at room temperature. After chromatographic purification, the yields ranged between 65% and 98%.



- a) R = C₁₇H₃₃, R' = *i*-Pr; b) R = C₁₇H₃₃, R' = *t*-Bu; c) R = C₁₇H₃₃, R' = *c*-C₅H₉; d) R = C₁₇H₃₃, R' = *c*-C₆H₁₁; e) R = C₁₇H₃₃, R' = *c*-C₆H₅OH; f) R = Ph, R' = *i*-Pr; g) R = Ph, R' = *t*-Bu; h) R = Ph, R' = *c*-C₅H₉; i) R = Ph, R' = *c*-C₆H₁₁; l) R = Ph, R' = *c*-C₆H₅OH; m) R = *c*-C₆H₁₁, R' = *i*-Pr; n) R = *c*-C₆H₁₁, R' = *t*-Bu; o) R = *c*-C₆H₁₁, R' = *c*-C₅H₉; p) R = *c*-C₆H₁₁, R' = *c*-C₆H₁₁; q) R = *c*-C₆H₁₁, R' = *c*-C₆H₅OH; r) R = Br(CH₂)₄, R' = *i*-Pr; s) R = Br(CH₂)₄, R' = *t*-Bu; t) R = Br(CH₂)₄, R' = *c*-C₅H₉; u) R = Br(CH₂)₄, R' = *c*-C₆H₁₁; v) R = Br(CH₂)₄, R' = *c*-C₆H₅OH

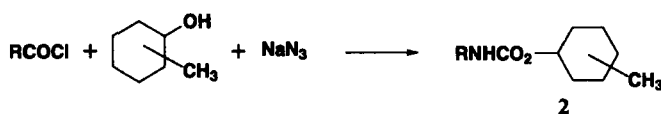
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Table 1. Yields, mps and Elemental Analyses of Urethanes

Cmpd	Yield (%)	Elemental Analysis (Found)			mp (°C)
		C	H	N	
1a	85	74.28 (74.12)	12.17 (12.21)	4.12 (4.01)	<i>a</i>
1b	80	74.73 (74.62)	12.26 (12.33)	3.96 (3.88)	<i>a</i>
1c	89	75.56 (75.46)	11.86 (11.93)	3.83 (3.77)	<i>a</i>
1d	82	75.93 (75.87)	11.95 (11.01)	3.69 (3.58)	<i>a</i>
1e	70	77.16 (77.06)	10.52 (10.42)	3.75 (3.54)	<i>a</i>
1f	90	66.82(67.02)	7.44(7.31)	7.77(7.82)	85-86 ¹⁸
1g	83	68.37 (68.17)	7.82 (7.98)	7.25 (7.12)	133-136 ¹⁹
1h	70	70.22 (70.10)	7.37 (7.42)	6.71 (6.82)	132 ²⁰
1i	73	71.21 (71.02)	7.81 (7.94)	6.39 (6.29)	81 ²¹
1l	76	73.23 (73.12)	5.29 (5.20)	6.57 (6.44)	128-129 ²²
1m	70	64.83 (64.77)	10.34 (10.46)	7.56 (7.36)	66.5-67 ²³
1n	65	66.29 (66.13)	10.70(10.72)	6.93(7.03)	78.5-79 ²⁴
1o	71	68.21 (68.03)	10.02 (10.12)	6.63 (6.53)	<i>a</i>
1p	65	69.29 (69.10)	10.29 (10.33)	6.22 (6.12)	76-77 ²⁵
1q	98	71.21 (71.09)	7.81 (7.91)	6.39 (6.24)	128-130 ²⁶
1r	90	40.35 (40.25)	6.77 (6.81)	5.88 (5.64)	<i>a</i>
1s	75	42.87 (42.75)	7.20 (7.25)	5.55 (5.36)	<i>a</i>
1t	82	45.47 (45.33)	5.30 (5.12)	5.03 (4.82)	<i>a</i>
1u	70	47.49 (47.33)	7.32 (7.58)	5.03 (4.82)	<i>a</i>
1v	71	48.55 (48.43)	5.19 (5.24)	5.15 (5.00)	<i>a</i>

a) Isolated as a viscous oil.

Since these results were quite encouraging, it was decided to test the stereoselectivity of this reaction, in order to determine whether the last step of the reaction (*i. e.*, the addition of alcohol to the intermediate isocyanate) could be influenced by the structure of the alcohol. 2-, 3- and 4- Methylcyclohexanols were selected as alcohols because the proton geminal to the OH group, resonates at significantly different fields in the NMR spectra, depending on the relative (*cis/trans*) relation with the methyl group. A 1:1 *cis/trans* mixture of two stereoisomers was used. The ratio between *cis*- and *trans*-urethane isomers was calculated on the basis of the ratio between the signal intensity of the corresponding proton geminal and oxygen in NMR spectra. The reaction with 4-methyl- and 3-methyl-cyclohexanols (*Table 2*), showed significant stereoselectivity, with the *trans* urethane diastereoisomer predominating in these cases.



- a) R = C₁₇H₃₃, 2-methylcyclohexanol; b) R = C₁₇H₃₃, 3-methylcyclohexanol; c) R = C₁₇H₃₃, 4-methylcyclohexanol; d) R = Ph, 2-methylcyclohexanol; e) R = Ph, 3-methylcyclohexanol; f) R = Ph, 4-methylcyclohexanol; g) R = *c*-C₆H₁₁, 2-methylcyclohexanol; h) R = *c*-C₆H₁₁, 3-methylcyclohexanol; i) R = *c*-C₆H₁₁, 4-methylcyclohexanol; l) R = Br(CH₂)₄, 2-methylcyclohexanol; m) R = Br(CH₂)₄, 3-methylcyclohexanol; n) R = Br(CH₂)₄, 4-methylcyclohexanol

Table 2. Yields, mps and Stereoisomeric Ratio of Urethanes from *cis/trans* Methylcyclohexanols

Cmpd	Yield (%)	Ratio <i>cis/trans</i>	Elemental Analysis (Found)			mp (°C)
			C	H	N	
2a	66	1:1	76.28 (76.15)	12.03 (12.23)	3.56 (3.42)	<i>a</i>
2b	87	1:9	76.28 (76.13)	12.03 (12.13)	3.56 (3.48)	<i>a</i>
2c	89	1:9	76.28 (76.12)	12.03 (12.13)	3.56 (3.44)	<i>a</i>
2d	62	1:3	76.12 (76.28)	12.03 (12.13)	3.56 (3.46)	105-106.5 ²⁷
2e	65	1:5	76.28 (76.18)	12.03 (12.24)	3.56 (3.46)	96 ²⁸
2f	65	1:5	76.28 (76.25)	12.03 (12.10)	3.44 (3.56)	125 ²⁸
2g	62	1:2	70.25 (70.13)	10.53 (10.62)	5.85 (5.77)	<i>a</i>
2h	66	1:6	70.25 (70.11)	10.53 (10.63)	5.85 (5.76)	<i>a</i>
2i	68	1:6	70.25 (70.12)	10.53 (10.66)	5.85 (5.74)	<i>a</i>
2l	60	1:2	49.32 (49.15)	7.59 (7.66)	4.79 (4.64)	<i>a</i>
2m	66	1:5	49.32 (49.18)	7.59 (7.62)	4.79 (4.66)	<i>a</i>

a) Isolated as a viscous oil.

In the case of the 2-methylcyclohexanol, the prevalence of the *trans* urethane is less pronounced, although this result is probably due to the steric effect of the methyl group, which is adjacent to the reaction center. All compounds were colorless and the confirmation of the structures was achieved by ¹H- and ¹³C-NMR (Table 3).

Table 3. ¹H NMR and ¹³C NMR Spectra of Compounds 1 and 2

Cmpds	¹ H-NMR (δ)	¹³ C-NMR (δ)
1a [(<i>Z</i>)-heptadec-8-enyl]-carbamic acid isopropyl ester	3.20 (2H, bq, CH ₂ NH), 4.62 (1H, bs, NH), 4.91 (1H, m, (CH ₃) ₂ CH), 5.36 (2H, t, CH = CH)	14.1, 22.2, 22.7, 26.8, 27.2, 27.3, 29.3(x2), 29.4(x2), 29.6(x2), 29.7, 29.8, 30.1, 32.0, 40.9, 67.9, 129.8, 130.1, 157.2
1b [(<i>Z</i>)-heptadec-8-enyl]-carbamic acid <i>t</i> -butyl ester	3.20 (1H, q, CHNH), 3.60 (1H, t, CHNH), 5.36 (2H, t, CH = CH)	14.2, 22.7, 27.0, 27.3(x2), 29.4(x2), 29.6(x2), 29.8(x2), 29.8(x2), 30.4(x2), 32.0, 40.6, 129.8, 130.1, 158.7

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Table 3. Continued...

Cmpds	¹ H-NMR (δ)	¹³ C-NMR (δ)
1c [(Z)-heptadec-8-enyl]- carbamic acid cyclopentyl ester	3.20 (1H, q, CHHNH), 4.60 (1H, bs, NH), 5.06 (1H, bt, NH), 5.36 (2H, t, CH = CH)	14.1, 22.7, 23.8(x2), 25.1, 27.2, 27.3, 29.2(x2), 29.2, 29.4, 29.6, 29.8, 29.8, 32.0, 32.7(x2), 34.7, 77.7, 129.8, 130.1, 173.7
1d [(Z)-heptadec-8-enyl]- carbamic acid cyclohexyl ester	3.20 (1H, q, CHHNH), 4.65 (1H, bs, NH), 5.06 (1H, bt, NH), 5.36 (2H, t, CH = CH)	14.2, 22.7, 23.9, 25.5, 26.7, 27.2, 27.3, 29.2(x2), 29.4(x2), 29.6(x2), 29.7(x2), 29.8(x2), 32.0, 41.2, 73.6, 129.7, 130.1, 156.4
1e [(Z)-heptadec-8-enyl]- carbamic acid phenyl ester	3.20 (1H, q, CHHNH), 5.06 (1H, bt, NH), 5.36 (2H, t, CH = CH), 7.30 (5H, m, C ₆ H ₅)	14.2, 14.8, 21.9, 22.7, 26.8, 27.3, 29.3(x2), 29.4(x2), 29.6(x2), 29.8(x2), 32.0, 41.4, 115.4, 121.7, 125.3, 129.3(x2), 129.5, 129.8, 130.1, 156.2
1f Benzylcarbamic acid isopropyl ester	1.23(d, 6H, CH(CH ₃) ₂); 4.85(m, 1H, C(CH ₃) ₃), 5.66(m, 1H, NH); 7.26-7.45 (m, 5H, C ₆ H ₅)	22.1(x2), 30.8, 128.7, 129.0, 129.5(x2), 130.4, 138.3, 153.8
1g Benzylcarbamic acid <i>t</i> -butyl ester	δ: 1.50(s, 9H, C(CH ₃) ₃); 5.40(m, 1H, NH); 7.27-7.44(m, 5H, C ₆ H ₅)	22.0(x3), 22.2, 118.7(x2), 123.3(x2), 137.1, 153.5
1h Benzylcarbamic acid cyclopentyl ester	5.23(m, 1H, CHOH); 6.94(m, 1H, NH); 7.26-7.45(m, 5H, C ₆ H ₅)	23.8(x2), 37.9(x2), 78.1, 118.7, 123.3, 129.1(x2), 138.3, 153.7
1i Benzylcarbamic acid cyclohexyl ester	4.79(m, 1H, CHOH); 6.73(m, 1H, NH); 7.28-7.56(m, 5H, C ₆ H ₅)	23.9, 25.5, 32.0, 32.9, 73.8, 120.8, 123.3, 124.7, 129.1(x2), 137.3, 153.6
1l Benzylcarbamic acid phenyl ester		119.1, 121.9, 124.0, 125.9, 125.8(x2), 128.8(x2), 129.2, 129.5, 137.6, 150.8, 152.0
1m Cyclohexylcarbamic acid isopropyl ester	1.23(d, 6H, J = 6.8 MHz, CH(CH ₃) ₂); 3.46(m, 1H, CHNH); 4.35(bs, 1H, CHOH), 4.90 (m, 1H, CH(CH ₃) ₂); 5.66(m, 1H, NH)	24.7, 25.0(x2), 49.8, 67.7, 155.6
1n Cyclohexylcarbamic acid <i>t</i> -butyl ester	1.40(s, 9H, C(CH ₃) ₃); 3.43(m, 1H, CHNH); 4.31(bs, 1H, CHOH), 5.68(m, 1H, NH)	25.0(x3), 25.7, 26.6, 28.5, 32.8, 34.0, 49.1, 53.0, 155.5
1o Cyclohexylcarbamic acid cyclopentyl ester	3.44(bq, 1H, CHNH), 4.31(bs, 1H, CHOH), 5.40(s, 1H, NH)	24.9(x2), 25.5(x2), 32.8(x3), 33.5, 49.7, 77.9, 155.8
1p Cyclohexylcarbamic acid cyclohexyl ester	3.38(bq, 1H, CHNH), 4.55(bs, 1H, CHOH), 5.80(s, 1H, NH)	24.0, 24.9(x2), 25.5(x2), 30.3, 32.1, 33.0, 33.2, 33.6, 49.8, 70.3, 156.5
1q Cyclohexylcarbamic acid phenyl ester	3.58(bq, 1H, CHNH), 5.40(s, 1H, NH), 7.13-7.40(m, 5H, C ₆ H ₅)	21.8, 31.8, 32.0, 33.1, 60.4, 123.1, 128.7, 129.0(x2), 129.5, 130.7, 134.4, 172.5

Table 3. Continued...

Cmpds	¹ H-NMR (δ)	¹³ C-NMR (δ)
1r (5-bromovaleryl)- carbamic acid isopropyl ester	1.21(d, 6H, J = 6.2 Hz CH(CH ₃) ₂); 1.66(bq, 2H, CH ₂ CH ₂ NH); 1.82(bq, 2H, BrCH ₂ CH ₂); 3.19(bq, 2H, CH ₂ NH); 3.37(t, 2H, CH ₂ Br); 4.87m, 1H, CH(CH ₃) ₂ ; 5.66(m, 1H, NH)	22.9, 25.5, 28.1, 30.9, 48.1 68.0, 156.5
1s (5-bromovaleryl)- carbamic acid <i>t</i> -butyl ester	1.46(s, 9H, C(CH ₃) ₃); 1.68(m, 2H, CH ₂ CH ₂ NH); 1.87(m, 2H, BrCH ₂ CH ₂); 3.19(m, 2H, CH ₂ NH); 3.43(t, 2H, J = 7 Hz, CH ₂ Br); 5.40(m, 1H, NH)	25.5, 27.2, 28.4, 33.3, 39.2, 39.0, 40.1, 48.1, 157.3
1t (5-bromovaleryl)- carbamic acid cyclopentyl ester	0.87 (d, 1H, J = 6.6, CH ₃) 3.22(bq, 2H, CH ₂ NH); 3.42(t, 2H, J = 6.8 Hz, CH ₂ Br); 4.80 (m, 1H, CHOH) 5.40(m, 1H, NH)	14.1; 23.6; 29.8; 29.9, 30.8; 32.8; 33.0; 40.1; 60.4; 77.9, 156.6
1u (5-bromovaleryl)- carbamic acid cyclohexyl ester	3.20(bq, 2H, CH ₂ NH); 3.44(t, 2H, J = 6.6Hz, CH ₂ Br); 4.80 (m, 1H, CHOH) 5.20(m, 1H, NH)	22.4; 28.7; 29.9; 30.2; 31.4; 33.3; 34.0; 40.2; 41.0; 74.1; 156.8
1v (5-bromovaleryl)- carbamic acid phenyl ester	1.61(m, 2H, CH ₂ CH ₂ NH); 1.80(m, 2H, BrCH ₂ CH ₂); 3.16(bq, 2H, CH ₂ NH); 3.34(t, 2H, J = 6.6Hz, CH ₂ Br); 5.80(m, 1H, NH); 7.11-7.39(m, 5H, C ₆ H ₅)	28.4, 29.9, 33.6, 40.3, 121.8(x2), 125.4, 129.4(x2), 151.2, 155.2
2a [(<i>Z</i>)-heptadec-8-enyl]- carbamic acid 2-methyl- cyclohexyl ester	3.18 (2H, CH ₂ NH), 4.36 (1H, m, CHOH, <i>trans</i>), 4.60 (1H, bm, CHOH, <i>cis</i>), 5.17 (1H, bt, NH), 5.40 (2H, t, CH = CH)	14.2, 22.4, 22.7, 24.1, 26.8, 27.2, 27.3, 29.3(x2), 29.4(x2), 29.6(x2), 29.7, 29.8, 30.1, 31.4, 32.0, 32.0, 34.1, 41.1, 73.5, 129.8, 130.1, 158.5
2b [(<i>Z</i>)-heptadec-8-enyl]- carbamic acid 3- methylcyclohexyl ester	3.16 (2H, CH ₂ NH), 4.56 (1H, bm, CHOH, <i>trans</i>), 4.94 (1H, bm, CHOH, <i>cis</i>), 5.17 (1H, bt, NH), 5.36 (2H, t, CH = CH)	14.2, 18.5, 22.7, 24.8, 25.5, 26.8, 27.3, 29.3(x2), 29.4(x2), 29.6(x2), 29.7(x2), 29.8, 32.0, 32.3, 33.7, 37.7, 73.5, 129.8, 130.1, 156.4
2c [(<i>Z</i>)-heptadec-8-enyl]- carbamic acid 4-methyl- cyclohexyl ester	3.15 (2H, CH ₂ NH), 4.57 (1H, bm, CHOH, <i>trans</i>), 4.88 (1H, bm, CHOH, <i>cis</i>), 5.17 (1H, bt, NH), 5.36(2H, t, CH = CH)	14.2, 21.9, 22.7, 23.6, 26.8, 27.3, 29.3(x2), 29.43(x2), 29.6(x2), 29.75(x2), 29.8, 31.8, 32.0, 32.2, 33.2, 41.0, 73.7, 74.4, 129.8, 130.1, 156.4
2d Benzylcarbamic acid 2-methylcyclohexyl ester	1.00(d, 3H, J = 6.2 MHz, CH ₃); 4.43(m, 1H, CHOH, <i>trans</i>); 4.99(m, 1H, CHOH, <i>cis</i>); 6.65(bs, 1H, NH); 7.07-7.44(m, 5H, C ₆ H ₅)	18.5, 24.8, 25.4, 29.7, 32.2, 33.6, 79.5, 118.6, 123.3(x2), 129.1, 138.3, 153.6
2e Benzylcarbamic acid 3-methylcyclohexyl ester	0.94(d, 3H, J = 6.2 MHz, CH ₃); 4.78(m, 1H, CHOH, <i>trans</i>); 5.17(m, 1H, CHOH, <i>cis</i>); 6.86(bs, 1H, NH); 7.27-7.44(m, 5H, C ₆ H ₅)	22.4, 24.1, 31.4, 31.9, 34.1, 40.9, 74.3, 118.8, 123.2, 128.8, 129.1, 129.6, 138.4, 153.5

SYNTHESIS OF URETHANES BY A MODIFIED CURTIUS REACTION WITH ALCOHOLS

Table 3. Continued...

Cmpds	¹ H-NMR (δ)	¹³ C-NMR (δ)
2f Benzylcarbamic acid 4-methylcyclohexyl ester	δ : 0.78(d, 3H, J = 6.2 MHz, CH ₃); 4.56(m, 1H, CHOH, <i>trans</i>); 4.95(m, 1H, CHOH, <i>cis</i>); 6.73(bs, 1H, NH); 7.15-7.38(m, 5H, C ₆ H ₅)	21.9, 29.6, 29.8, 31.4, 31.8, 33.1, 74.5, 118.7, 126.3(x2), 128.8, 129.1, 138.3, 153.5
2g Cyclohexylcarbamic acid 2-methylcyclohexyl ester	3.80(bq, 1H, CHNH), 4.40(bs, 1H, CHOH, <i>trans</i>), 4.62(m, 1H, CHOH, <i>cis</i>), 5.20(m, 1H, NH)	18.5, 20.7, 24.7, 24.9, 25.4, 25.6, 28.8, 32.3, 33.0, 33.6, 35.9, 37.87, 71.2, 156.4
2h Cyclohexylcarbamic acid 3-methylcyclohexyl ester	3.80(bq, 1H, CHNH), 4.10(bs, 1H, CHOH, <i>trans</i>), 4.30(m, 1H, CHOH, <i>cis</i>), 5.40(m, 1H, NH)	22.3, 24.0, 24.8, 25.4, 26.6, 30.2, 32.0, 32.9, 33.1, 33.5, 49.7, 73.4, 156.5
2i Cyclohexylcarbamic acid 4-methylcyclohexyl ester	3.82(bq, 1H, CHNH), 4.15(bs, 1H, CHOH, <i>trans</i>), 4.36(m, 1H, CHOH, <i>cis</i>), 5.35(m, 1H, NH)	21.9, 24.9, 25.6(x2), 29.97(x2), 31.8, 32.2, 33.0, 33.2(x2), 33.5, 49.8, 73.6, 155.6
2l (5-bromovaleryl)-carbamic acid 2-methylcyclohexyl ester	0.86(d, 1H, J = 6.6, CH ₃), 3.20(bq, 2H, CH ₂ NH); 3.42(t, 2H, CH ₂ Br); 4.20(m, 1H, CHOH, <i>trans</i>), 4.80(m, 1H, CHOH, <i>cis</i>) 5.20(m, 1H, NH)	18.5, 24.8, 25.4, 28.8, 29.9, 32.2, 33.3, 33.6, 37.7, 40.2, 46.0, 79.0, 157.0
2m (5-bromovaleryl)-carbamic acid 3-methylcyclohexyl ester	0.87 (d, 1H, J = 6.6, CH ₃), 3.15(bq, 2H, CH ₂ NH); 3.39(t, 2H, CH ₂ Br); 4.43 (m, 1H, CHOH, <i>trans</i>), 4.90(m, 1H, CHOH, <i>cis</i>) 5.90(m, 1H, NH)	22.3; 24.0; 28.7; 29.9; 30.2; 31.4; 33.3; 34.0; 40.2; 41.0; 74.1; 156.8
2n (5-bromovaleryl)-carbamic acid 4-methylcyclohexyl ester	0.87(d, 1H, J = 6.6, CH ₃), 3.20(bq, 2H, CH ₂ NH); 3.40(t, 2H, CH ₂ Br); 4.30(m, 1H, CHOH, <i>trans</i>), 4.90(m, 1H, CHOH, <i>cis</i>) 5.90(m, 1H, NH)	28.8, 29.6, 29.9, 31.8, 32.1, 33.1, 33.3, 40.2, 46.0, 74.1, 156.6

This modified Curtius reaction¹⁶ to prepare urethanes appears to be particularly versatile, given that it is not necessary to isolate any intermediate and thus it could be of great use in synthesis, since satisfactory yields are obtained with primary, secondary and tertiary alcohols, as well as with phenol. Moreover, the best yields obtained by Yamada *et al.*¹⁴ are in the range of our lowest yields which could probably be increased further with the use of a Dry Box; our ultimate goal was to test the performance, scope and the ability of the reaction that to be performed in any laboratory.

EXPERIMENTAL SECTION

All reactions were carried out under dry argon using anhydrous solvents from Sigma-Aldrich. Glassware was flame-dried prior to use. Commercial reagents were purchased from Sigma-Aldrich or Fluka and were used without further purification. Reactions were monitored by TLC on Merck silica gel plates (0.25 mm) using UV light or phosphomolibdic reagent for revelation. Flash chromatography was performed on Merck silica gel 60 (particle size 0.040-0.063 mm).

Yields refer to materials after chroma-tographic purification. NMR spectra were recorded in CDCl_3 solution on Varian Gemini 200 spectrometer at room temperature. Chemical shifts are reported in δ relative to the residual solvent peak (CHCl_3 at $\delta_{\text{H}} = 7.26$, CDCl_3 at $\delta_{\text{C}} = 77.0$).

General Procedure.- The acyl chloride (1 mmol) and dry benzytriethyl-amonium chloride (0.1 mmol) were dissolved in dry toluene (2 mL for each mmol of acyl chloride) with stirring for 5 min at 60°C . Dry sodium azide (2.4 mmol) was added in portions (4 x 0.6 mmol) over 1 h at 60°C under stirring; the solution was kept for 15 min at 80°C . Then the alcohol (5 mmol) was added and stirred overnight at room temperature. The solution was diluted with ethyl ether (50 mL), washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product which was purified on silica gel column eluted with 5% ethyl acetate in petroleum ether (compounds from **1a** to **1h**) and methyl alcohol in chloroform (compounds from **1i** to **2n**). Yields are reported in *Tables 1 and 2*. NMR data are reported in *Table 3*.

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