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Modified tert-Butyloxycarbonyl(BOC) Derivatives as New Aminoprotecting Groups

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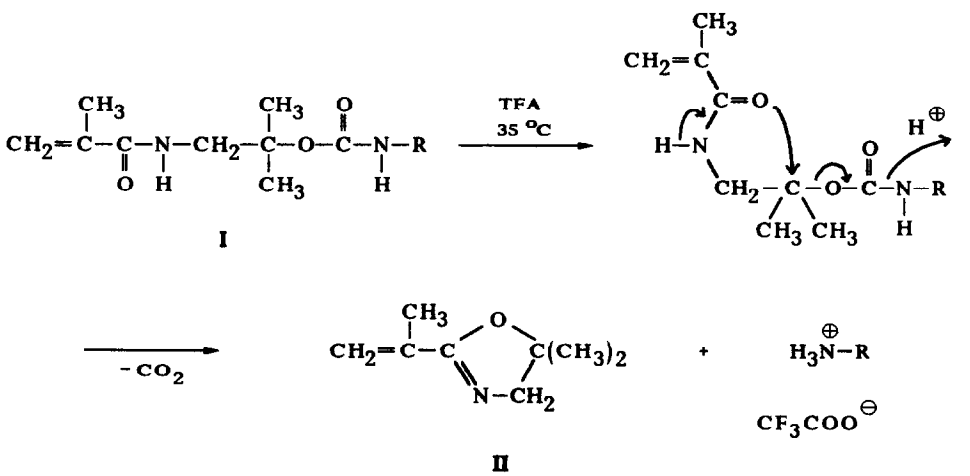
Abstract: Some novel low-molecular weight and polymerizable N-acylamino-modified BOC-type aminoprotecting groups are described. Deprotection with trifluoroacetic acid (TFA) and with HBr in acetic acid, which was followed by NMR spectroscopy, leads to the formation of 4,5-dihydro-oxazole derivatives. Reactivities and solubilities of the new compounds are controlled significantly by the N-acyl moiety.

Since its discovery the BOC-protecting group[1] has been established as one of the most important acid-labile amino protecting groups for liquid-phase and solid-phase peptide synthesis.[2,3] The classical BOC group is removed, e.g. in trifluoroacetic acid or with HBr in acetic acid, which leads to the formation of isobutene or t-butyl bromide and carbon dioxide.[4,5]

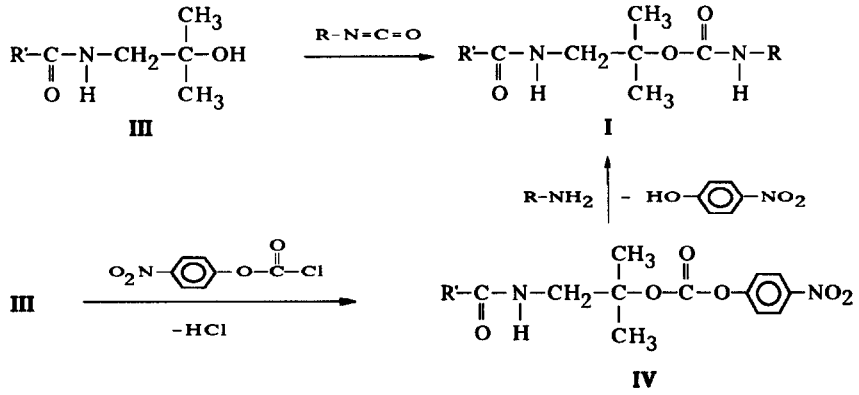
Recently, we synthesized a polymerizable N-methacrylamino-modified BOC-type protecting group **I**, which leads to a 4,5-dihydro-oxazole derivative **II** under acidic conditions.[6,7] (Scheme 1)



I **II**

Scheme 1

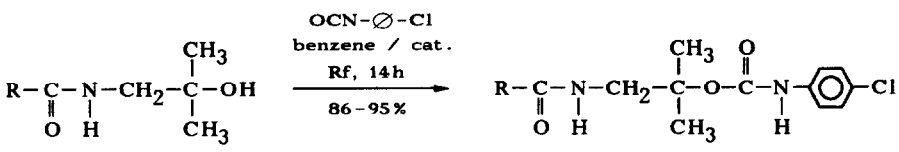
The synthesis of substrate **I** can be performed by addition of isocyanate to N-acylated 1-amino-2-methyl-2-propanol (**III**) or by aminolysis of an activated carbonate (**IV**).[8] (Scheme 2)



Scheme 2

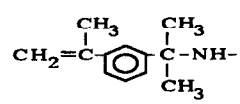
According to the mechanism of the cleavage, typical side reactions of the isobutene, e.g. t-butylation of the indole moiety of tryptophan or the thioether group of methionine, are not expected in the case of the new derivatives.[9,10,11] Moreover, the 4,5-dihydro-oxazole ring may remain on a polymeric support, which can be achieved by polymerization of methacrylic derivatives.

In the present investigation the N-acyl-modified amino tert-butanols **1a-9a** were treated with 4-chlorophenyl isocyanate as model compound under the formation of the urethanes **1b-9b** (Scheme 3). Furthermore, the unsaturated compounds **4b** and **7b** were copolymerized with methylmethacrylate by radical initiation yielding the macromolecular derivatives **4c** and **7c** (Scheme 4).

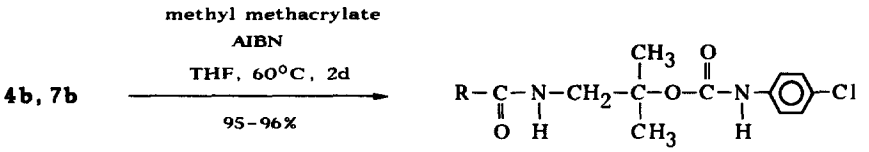


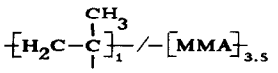
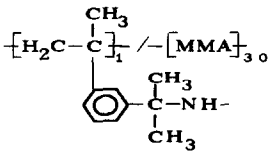
1a - 9a **1b - 9b**

number	R
1	$(CH_3)_3C-$
2	$(CH_3)_2CH-$
3	$CH_3-(CH_2)_{16}-$
4	$CH_2=C(CH_3)-$
5	

number	R
6	$CH_3-(CH_2)_2-N(H)-$
7	
8	CH_3-CH_2-O-
9	$(CH_3)_2CH-CH_2-O-$

Scheme 3



number	R
4c	
7c	

Scheme 4

The kinetic studies of the deprotections were performed by ^{1}H-NMR spectroscopy. The urethanes **1b - 9b**, **4c** and **7c** were dissolved in TFA resp. in HBr / HOAc and the time-depend release of the 4-chloroaniline was measured by integration of the aromatic signals at 7.25 ppm vs. the signals of the released aniline at 7.49 ppm. In the case of TFA as solvent, it is also possible to follow the intensity of the singlet of the dimethyl-group resonance at 1.44 ppm of the original BOC-type structure in comparison with the methyl signals of the 4,5-dihydro-oxazole moiety at 1.72 ppm. With both methodes the same results were obtained.

The recorded half-time values of deprotection are summarized in Tab 1. The influence of $CaCl_2$, which exhibits an accelerating effect, is also illustrated in Tab.1. It has to be noticed that the classical BOC system is more reactive in TFA than the described modified derivatives while in HBr/HOAc a similar reactivity has been observed.

Table 1:

Half-times ($t_{1/2}$) of deprotection and salt effect of the N-acylated BOC-type derivatives at 35°C [error ± 5%]

number of compound	**1b**	**2b**	**3b**	**4b**	**4c**	**5b**	**6b**	**7c**	**8b**	**9b**
$t_{1/2}$ in TFA [min]	100	165	225	60	200	205	295	>450	40	65
$t_{1/2}$ in TFA/$CaCl_2$ [min]	30	70	100	15	30	95	120	180	10	15
$t_{1/2}$ in HBr/HOAc [min]	<5	<10	10	<5	<5	10	10	15	<5	<5

The monomer **7b** became unsoluble in TFA and HBr/HOAc because of spontaneous polymerization. Kinetic measurements could not be carried out in this case.

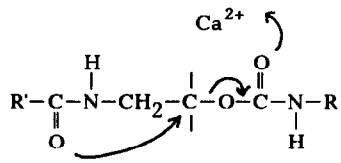
The different reactivities of the amide derivatives **1b - 3b** are based on electronic effects. The electronic density of the carbonyl-oxygen of the amide function which reacts as a nucleophile to form the oxazole ring is controlled by the inductive effect of the alkyl groups. An increased electron donor effect, corresponds with a more rapid deprotection. The relatively high release rate of compound **4b** is based on the enhanced nucleophilie of the methacryl carbonyl-oxygene because of the vinyl conjugation.

In the case of the urea derivatives **5b** and **6b**, strong interactions between the carbonyl group and TFA as a protic solvent, may be the main reason for the observed lower reactivity.

The urethane compounds **8b** and **9b** contain more nucleophilic carbonyl groups than the corresponding amide compounds. Thus, the release of the amine and the ring formation is much faster

In the case of the copolymers **4c** and **7c**, neighbouring group effects,[6,11] lower the reactivity in comparison to the monomers.

In all cases, the calcium ions reduce the kinetic half-time values. It is assumed that this effect is due to a complexing property of Ca^{2+}-ions which may activate the urethane group.[6,12] (scheme 5)



Scheme 5

As mentioned above the cleavage of **1b - 9b, 4c** and **7c** in HBr/HOAc as solvent is generally much faster with violent CO_2 evolution compared with a TFA solvent.

As expected, the solubilities of the compounds are controlled by the N-acyl component. For example, only the fatty acid containing structure **3b** shows a good solubility in hexane.

According to the obtained results, it can be concluded that the new, acid labile N-acylamino-modified BOC-type protecting groups, in contrast to the classical BOC-group, are cleaved via a peculiar cleavage mechanism which includes a self-trapping of the tert-butyl cation intermediate. Polymerizability, reactivities and solubilities can be controlled by the modification of the acylamido portion. Therefore, some practical applications are now opened especially in the area of solid phase and liquid peptide chemistry

EXPERIMENTAL

The syntheses of **N-(2-hydroxy-2-methyl-propyl)-2-methyl-acrylamide (4a)**, **1,1-dimethyl-2-(2-methyl-acrylamido)-ethyl-N-4-chlorophenyl-carbamate (4b)** and the copolymer **4c** are described in ref.[6]

The applied reagents are commercial available (FLUKA CHEMIE AG, Buchs) if not noted otherwise. All solvents were purified by standard methods and dried if necessary.

Melting points were determined on a Büchi Melting Point Determinator 510, and are not corrected. The NMR spectra were recorded on Varian EM 390 (90 MHz) with TMS as internal standard and Bruker AC 250 (^{1}H: 250.00 MHz; ^{13}C: 62.98 MHz) with TMS as external standard. The ^{13}C NMR spectra were measured proton-decoupled. IR spectra were obtained using Perkin-Elmer spectrometer 397 and 1420. The elemental analyses were carried out with a Perkin-Elmer Elemental Analyser 204 B.

N-(2-Hydroxy-2-methyl-propyl)-2,2-dimethyl-propionamide (1a)

To a stirred solution of 1-amino-2-methyl-2-propanol[13] (1.78g, 20mmol) and triethylamine (2.8mL, 20mmol) in THF (25mL) trimethylacetyl chloride (2.41g, 20mmol) were added slowly at -15°C while NEt_3*HCl precipitated. The suspension was stirred at room temperature for 24h, filtered and evaporated. The resulting oil was diluted with $CHCl_3$ (25mL) and the organic phase was washed with sat. aq $NaHCO_3$ (2*10mL) and water (10mL) and then dried ($MgSO_4$). The solvent was reduced by evaporating until 10mL and the precipitation was induced by covering ether/petroleumether (1:1, 50mL). The crystallization was completed at -10°C yielding colorless crystals; yield: 2.97g (89%); m.p 115-117°C; Analysis calcd. for $C_9H_{19}O_2N$ (173.2) C, 62.39; H, 11.05; N, 8.08. Found: C, 62.59; H, 11.12, N, 7.94; IR(KBr) 3100-3500 (NH,OH), 1630 (amide I), 1540 (amide II) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (s, 9H, $C(C\underline{H}_3)_3$), 1.22 (s, 6H, $C(C\underline{H}_3)_2$), 2.83 (s, 1H, OH), 3 24 (d, J = 5.9Hz, 2H, NH-$C\underline{H}_2$), 6.15 (b, 1H, NH); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 27.15 (2C, $C(\underline{C}H_3)_2$), 27.49 (3C, $C(\underline{C}H_3)_3$), 38.65 (1C, $\underline{C}(CH_3)_3$), 50.18 (1C, NH-$\underline{C}H_2$), 70.82 (1C, $\underline{C}(CH_3)_2$), 179.54 (1C, $\underline{C}$=O).

N-(2-Hydroxy-2-methyl-propyl)-2-methyl-propyl-amide (2a)

Analogously the same procedure as above, now it was used isobutyryl chloride (2.13g, 20mmol) Colorless crystals were obtained; yield: (1.97g, 62%); m.p. 56-58°C; Analysis calcd. for $C_8H_{17}O_2N$ (159.2) C, 60.34; H, 10.76; N, 8.79. Found: C, 60.13; H, 10.82; N, 8.70; IR(KBr) 3100-3500 (NH,OH), 1645 (amide I), 1535 (amide II) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, J = 6.2 Hz, 6H, $C(C\underline{H}_3)_2$), 1.24 (s, 6H, $C(C\underline{H}_3)_2$), 2.43 (sept, J = 6.2 Hz, 1H, $C\underline{H}(CH_3)_2$), 2.90 (s, 1H, OH), 3.24 (d, J = 5.9Hz, 2H, NH-$C\underline{H}_2$), 6.20 (b, 1H, NH); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 19.53 (2C, $CH(\underline{C}H_3)_2$), 27.08 (2C, $C(\underline{C}H_3)_2$), 35.52 (1C, $\underline{C}H(CH_3)_2$), 50.07 (1C, NH-$\underline{C}H_2$), 70.74 (1C, $\underline{C}(CH_3)_2$), 178.67 (1C, $\underline{C}$=O).

Octadecanoic acid-2-hydroxy-2-methyl-propyl-amide (3a)

A stirred solution of octadecanoic acid (5 68g, 20mmol) and NEt_3 (2.8mL, 20mmol) in THF (50mL) was precooled. Ethyl chloroformate (1.9mL, 20mmol) was added slowly at -15°C. After 2h at room temperature 1-amino-2-methyl-2-propanol (1.78g, 20mmol) in THF (10mL) was added. The solution was filtered after 2 days and evaporated. The residue was diluted in $CHCl_3$ (50mL), extracted twice with sat. aq $NaHCO_3$ (20mL) and water (20mL) and dried ($MgSO_4$).

The solvent was evaporated and the residue treated with ether (30mL), resulting in a colorless crystalline product; yield: 5.12g (72%); mp 170-171°C. Analysis calcd. for $C_{22}H_{45}O_2N$ (355.6) C, 74.40; H, 12.67; N, 3.90 Found: C, 74.22; H, 12.54; N, 3.77: IR(KBr) 3200-3550 (NH,OH), 1630 (amide I), 1540 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, J = 6.8 Hz, 3H, $C\underline{H}_3$), 1.22 (s, 6H, $(C\underline{H}_3)_2$), 1.24-1.34 (m, 28H, $-C\underline{H}_2-$), 1.63 (m, 2H, $OC-CH_2-C\underline{H}_2-$), 2.43 (t, J = 7.3 Hz, 2H, $OC-C\underline{H}_2-$), 2.90 (s, 1H, OH), 3.25 (d, J = 6.0 Hz, 2H, $NH-C\underline{H}_2-$), 6.03 (b, 1H, NH); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 13.99 (1C, $\underline{C}H_3-CH_2-$), 22.56 (1C, $CH_3-\underline{C}H_2-$), 25.72 (1C, $-\underline{C}H_2-$), 27.14 (2C, $C(\underline{C}H_3)_2$), 29.20-29.57 (12C, $-(\underline{C}H_2)-$), 31.79 (1C, $CH_3-CH_2-\underline{C}H_2-$), 36.67 (1C, $OC-C\underline{H}_2-$), 50.21 (1C, $NH-\underline{C}H_2-$), 70.75 (1C, $\underline{C}(CH_3)_2$), 174.28 (1C, $\underline{C}$=O).

1-(2-Hydroxy-2-methyl-propyl)-3-phenyl-urea (5a)

Phenyl isocyanate (2.17mL, 20mmol) in EtOAc (20mL) was dropped at 0°C to 1-amino-2-methyl-2-propanol (1.78ml, 20mmol) in EtOAc (20mL). While the urea precipitated, it was stirred for 1d at room temperature. The product was filtered, washed with a small amount of EtOAc and dried in a desiccator to result in colorless crystals; yield: 3.99g (96%); m.p. 167-169°C; Analysis calcd. for $C_{11}H_{16}O_2N_2$ (208.26) C, 63.44; H, 7.74; N, 13.45. Found: C, 63.70; H, 7.75; N, 13.71; IR(KBr) 3100-3450 (NH,OH), 1685 (urea), 1540 (amide II) cm^{-1}; ^1H NMR (250 MHz, d_6-DMSO) δ 1.09 (s, 6H, $C(C\underline{H}_3)_2$), 3.04 (d, J = 5.8Hz, 2H, $NH-C\underline{H}_2$), 4.53 (s, 1H, OH), 6.14 (t, J = 5.5Hz, 1H, $N\underline{H}-CH_2$), 6.87-7.39 (AA'BB'X, 5H, $C_6\underline{H}_5$), 8.60 (b, 1H, N$\underline{H}$); ^{13}C NMR (62.98 MHz, d_6-DMSO) δ 27.17 (2C, $C(\underline{C}H_3)_2$), 50.05 (1C, $NH-\underline{C}H_2$), 69.19 (1C, $\underline{C}(CH_3)_2$), 117 43 (2C, C-2), 120.87 (1C, C-4), 128.65 (2C, C-3), 140.66 (1C, C-1), 155.50 (1C, $\underline{C}$=O).

1-(2-Hydroxy-2-methyl-propyl)-3-propyl-urea (6a)

Propyl isocyanate (1.89mL, 20mmol) and 1-amino-2-methyl-2-propanol (1.78g, 20mmol) were dissolved in EtOAC (30mL) The clear solution was heated 5h under reflux. While the solvent was evaporated under reduced pressure, colorless crystals precipitated. The precipitation was completed by covering with ether; yield: 3.30g (95%); m.p. 79-81°C; Analysis calcd. for $C_8H_{18}O_2N_2$ (174.24) C, 55.15; H, 10.41; N, 16.08. Found: C, 55.43; H, 10.46; N, 15.97; IR(KBr) 3100-3550 (NH,OH), 1665 (C=O,urea), 1580 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J=7.3 Hz, 3H, $C\underline{H}_3$), 1.18 (s, 6H, $C(C\underline{H}_3)_2$), 1.49 (sext, J=7.3 Hz, 2H, $CH_3-C\underline{H}_2-CH_2-$), 3.07-3.13 (m, 4H, $NH-C\underline{H}_2-$, $C\underline{H}_2-NH-$), 5.35, 5.53 (b, 2H, 2NH), ^{13}C NMR (62.98 MHz, $CDCl_3$) 11.23 (1C, $\underline{C}H_3-CH_2-$), 23.27 (1C, $CH_3-\underline{C}H_2-$), 26.91 (2C, $C(\underline{C}H_3)_2$), 42.11 (1C, $CH_3-CH_2-\underline{C}H_2-$), 51.39 (1C, $NH-\underline{C}H_2-$), 71.12 (1C, $\underline{C}(CH_3)_2$), 159.94 (1C, $\underline{C}$=O).

1-(2-Hydroxy-2-methyl-propyl)-3-[1-(3-isopropenyl-phenyl)-1-methyl-ethyl]-urea (7a)

In the same procedure as **5a** α,α-dimethyl-3-isopropenyl-benzyl isocyanate (1.84mL, 10mmol, ALDRICH GmbH, Steinheim, Germany) were used, yielding colorless crystals (2.76g, 95%); m.p. 90-92°C; Analysis calcd. for $C_{17}H_{26}O_2N_2$ (290.14) C, 70.31; H, 9.02; N, 9.64. Found C, 70.45; H, 8.91; N, 9.53; IR(KBr) 3150-3600 (NH,OH), 1650 (C=O, urea), 1630 (C=C-alkyl), 1540 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (s, 6H, $C(C\underline{H}_3)_2$), 1.61 (s, 6H, $NH-C(C\underline{H}_3)_2$), 2.13 (s, 3H, $C-C\underline{H}_3$), 2.98 (d, J = 5.9 Hz, 2H, $NH-C\underline{H}_2-$), 3.21 (s, 1H, O$\underline{H}$), 4.94 (b, 1H, N$\underline{H}$), 5.08, 5.34 (AB, 2H, $\underline{H}_2C$=), 5.51 (b, 1H, N$\underline{H}$), 7.26-7.54 (ABCX, 4H, $C_6\underline{H}_4$), ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 21.69 (1C, $=C-\underline{C}H_3$),

26.69 (2C, CH_2-C($\underline{C}H_3)_2$), 30.15 (2C, N-C($\underline{C}H_3)_2$), 50.92 (1C, NH-$\underline{C}H_2$-), 54.63 (1C, N-$\underline{C}(CH_3)_2$), 70.77 (1C, CH_2-$\underline{C}(CH_3)_2$), 112.60 (1C, $H_2\underline{C}$=), 122.18 (1C, C-4), 124.02 (1C, C-6), 124.10 (1C, C-2), 128.34 (1C, C-5), 141.47 (1C, C-1), 143.07 (1C, =$\underline{C}(CH_3)$), 146.56 (1C, C-3), 158.51 (1C, $\underline{C}$=O).

N-(2-Hydroxy-2-methyl-propyl)-ethyl-carbamate (8a)

To a solution of 1-amino-2-methyl-2-propanol (1.78g, 20mmol) and triethylamine (2.8mL, 20mmol) in THF (50mL), ethyl chloroformate (1.9mL, 20mmol) was added at -10°C for over 1h. After stirring 12h at room temperature the suspension was filtered, evaporated, the resulting oil diluted with $CHCl_3$ (30mL), washed with sat. aq $NaHCO_3$ (2*20mL) and water (20mL) and finally dried ($MgSO_4$). Evaporation of the solvent led to a colorless, sticky oil; yield: 2.09g (65%); Analysis calcd. for $C_7H_{15}O_3N$ (161.20) C, 52.16; H, 9.37; N, 8.68. Found: C, 52.39; H, 9.39; N, 8.45; IR (film) 3200-3550 (NH,OH), 1700 (C=O, urethane), 1530 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (s, 6H, C($C\underline{H}_3)_2$), 1.20 (t, J = 7.1 Hz, 3H, $C\underline{H}_3$-CH_2-O), 2.96 (s, 1H, O$\underline{H}$), 3.12 (d, J = 5.9 Hz, 2H, NH-$C\underline{H}_2$-), 4.08 (q, J = 7.1 Hz, 2H, CH_3-$C\underline{H}_2$-O), 5.31 (b, 1H, NH); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 14.40 (1C, $\underline{C}H_3$-CH_2-), 26.76 (2C, C($\underline{C}H_3)_2$), 51.41(1C, NH-$\underline{C}H_2$-), 60 80 (1C, CH_3-$\underline{C}H_2$-), 70.66 (1C, $\underline{C}(CH_3)_2$), 158.63 (1C, $\underline{C}$=O).

N-(2-Hydroxy-2-methyl-propyl)-2-methyl-propyl-carbamate (9a)

Isobutyl chloroformate (2.59mL, 20mmol) were added to a solution of 1-amino-2-methyl-2-propanol (1.78g, 20mmol) and triethylamine (2.8mL, 20mmol) in THF (50mL) at -10°C. After stirring 3h at -10°C the suspension was filtered, evaporated and dissolved in CH_2Cl_2 (30mL). Washing with sat. aq $NaHCO_3$ (2*15ml) and water (10mL), drying ($NaSO_4$) and removal of the solvent under reduced pressure a colorless residue was obtained. The residue was washed with a little bit of cold ether yielding colorless crystals after drying in the desiccator; yield: 2.61g (69%); m.p. 30-32°C; Analysis calcd. for $C_9H_{19}O_3N$ (189.25) C, 57.12; H, 10.12; N, 7.40. Found: C, 56.90; H, 10.05; N, 7.24; IR(KBr) 3200-3600 (NH, OH), 1700 (C=O,urethane), 1530 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.7 Hz, 6H, CH($C\underline{H}_3)_2$), 1.17 (s, 6H, C($C\underline{H}_3)_2$), 1.86 (m, J = 6.7 Hz, 1H, -$C\underline{H}(CH_3)_2$), 2.97 (s, 1H, OH), 3.12 (d, J = 6.2 Hz, 2H, NH-$C\underline{H}_2$), 3.80 (d, J = 6.6 Hz, 2H, $C\underline{H}_2$-CH-), 5.36 (b, 1H, NH); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 18.79 (2C, CH($\underline{C}H_3)_2$), 26.72 (2C, C($\underline{C}H_3)_2$), 27.77 (1C, $\underline{C}H(CH_3)_2$), 51.37 (1C, NH-$\underline{C}H_2$), 70.67 (1C, $\underline{C}(CH_3)_2$), 70.98 (1C, CH-$\underline{C}H_2$-), 157.61 (1C, $\underline{C}$=O).

All syntheses to form the p-chlorophenyl carbamates **1b-9b** took place analogously. As an example the synthesis of **1b** is described:

1,1-Dimethyl-2-(2,2-dimethyl-propionyl-amino)-ethyl-N-4-chlorophenyl-carbamate (1b)

Compound **1a** (0.69g, 4mmol) were dissolved together with 4-chlorophenyl isocyanate (0.61g, 4mmol) and dibutyltin dilaurate (0.02mL) as catalyst in benzene (15mL) and heated under reflux for 14h. After evaporating the benzene the resulting oily residue was diluted with $CHCl_3$ (10mL) and washed twice with water (5mL). The organic phase was dried ($MgSO_4$), the solvent evaporated and the resulting oil was covered with ether to induce crystallisation at -5°C. The colorless crystals were subsequently dried in a desiccator; yield: 1.20g (92%); m.p. 146-147°C;

Analysis calcd. for $C_{16}H_{23}O_3N_2Cl$ (326.82) C, 58.80; H, 7.09; N, 8.57. Found C, 58.40; H, 7.12; N, 8.27; IR (KBr) 3200-3450 (NH), 1710 (C=O, urethane), 1645 (amide I), 1535, 1515 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (s, 9H, $C(C\underline{H}_3)_3$), 1.44 (s, 6H, $C(C\underline{H}_3)_2$), 3.56 (d, J = 5.9Hz, 2H, NH-$C\underline{H}_2$), 6.91 (b, 1H, NH), 7.23-7.34 (AA'XX', 4H, $C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 24.50 (2C, $C(\underline{C}H_3)_2$), 27.48 (3C, $C(\underline{C}H_3)_3$), 38.75 (1C, $\underline{C}(CH_3)_3$), 47.88 (1C, NH-$\underline{C}H_2$), 82.66 (1C, $\underline{C}(CH_3)_2$), 119.93 (2C, C-2), 128.88 (3C, C-3,C-4), 136.42 (1C, C-1), 152.90 (1C, $\underline{C}$=O, urethane), 178.57 (1C, $\underline{C}$=O, amide).

1,1-Dimethyl-2-(2-methyl-propionyl-amino)-ethyl-N-4-chlorophenyl-carbamate (2b)

Colorless crystals; yield: 1.18g (95%); m.p. 140-142°C; Analysis calcd. for $C_{15}H_{21}O_3N_2Cl$ (312.79) C, 57.60; H, 6.76; N, 8.95. Found: C, 57.42; H, 6.68; N, 9.03; IR(KBr) 3300 (NH), 1730 (C=O, urethane), 1640 (amide I), 1535 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (d, J = 6.8 Hz, 6H, $C(C\underline{H}_3)_2$), 1.46 (s, 6H, $C(C\underline{H}_3)_2$), 2.42 (sept, J = 6.9 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.58 (d, J = 6.1Hz, 2H, NH-$C\underline{H}_2$), 6.53, 6.71 (b, 2H, 2NH), 7.24-7.33 (AA'XX', 4H, $C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 19.56 (2C, $CH(\underline{C}H_3)_2$), 24.41 (2C, $C(\underline{C}H_3)_2$), 35.74 (1C, $\underline{C}H(CH_3)_2$), 47.66 (1C, NH-$\underline{C}H_2$), 82.66 (1C, $\underline{C}(CH_3)_2$), 119.89 (2C, C-2), 128.95 (3C, C-3,C-4), 136.30 (1C, C-1), 152.72 (1C, $\underline{C}$=O, urethane), 177.13 (1C, $\underline{C}$=O, amide).

1,1-Dimethyl-2-(octadecanoyl-amino)-ethyl-N-4-chlorophenyl-carbamate (3b)

Colorless crystals, yield: 1.79g (88%); m.p. 89-91°C; Analysis calcd. for $C_{29}H_{49}O_3N_2Cl$ (509.17) C, 68.41; H, 9.70; N, 5.50. Found: C, 68.25; H, 9.52; N, 5.30; IR(KBr) 3340 (NH), 1690 (C=O, urethane), 1640 (amide I), 1530 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, J = 6.2 Hz, 3H, $C\underline{H}_3$), 1.24-1.30 (m, 28H, -$C\underline{H}_2$-), 1.47 (s, 6H, $C(C\underline{H}_3)_2$), 1.63 (m, 2H, OC-CH_2-$C\underline{H}_2$-), 2.22 (t, J = 7.3 Hz, 2H, OC-$C\underline{H}_2$-), 3.58 (d, J = 6.1 Hz, 2H, NH-$C\underline{H}_2$-), 6.44, 6.81 (b, 2H, 2NH), 7.23-7.33 (AA'XX', 4H, $C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 14.00 (1C, $\underline{C}H_3$-CH_2-), 22.56 (1C, CH_3-$\underline{C}H_2$-), 24.38 (1C, -$\underline{C}H_2$-), 29.20-29.57 (12C, -$(\underline{C}H_2)$-), 31.79 (1C, CH_3-CH_2-$\underline{C}H_2$-), 36.67 (1C, OC-$C\underline{H}_2$-), 47.79 (1C, NH-$\underline{C}H_2$-), 82.66 (2C, $C(\underline{C}H_3)_2$), 119.90 (2C, C-2), 128.32 (1C, C-4), 128.91 (1C, C-3), 136.33 (1C, C-1), 152.83 (1C, $\underline{C}$=O, urethane), 173.33 (1C, $\underline{C}$=O, amide)

1,1-Dimethyl-2-(phenyl-ureido)-ethyl-N-4-chlorophenyl-carbamate (5b)

Cream colored crystals; yield: 0.98g (68%), m.p. 75-77°C, Analysis calcd. for $C_{18}H_{20}O_3N_2Cl$ (361.83) C, 59.75; H, 5.57; N, 11.61. Found: C, 59.83; H, 5.82, N, 11.74; IR(KBr) 3200-3450 (NH), 1710 (C=O, urethane), 1650 (C=O, urea), 1550, 1520 (2* amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 6H, $C(C\underline{H}_3)_2$), 3.52 (d, J = 6.1Hz, 2H, NH-$C\underline{H}_2$), 5.99 (t, J = 5.6 Hz, 1H, N$\underline{H}$-CH_2), 7.00-7.48 (AA'BB'X, AA'XX', b, 11H, $C_6\underline{H}_5$-, $C_6\underline{H}_4$-, 2*N$\underline{H}$); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 24.11 (2C, $C(\underline{C}H_3)_2$), 48.77 (1C, NH-$\underline{C}H_2$), 82.36 (1C, $\underline{C}(CH_3)_2$), 119.83 (2C, C-2'), 120.33 (2C, C-2), 120.48 (1C, C-4'), 128.80 (2C, C-3), 128.82 (2C, C-3'), 129.02 (1C, C-4), 136.43 (1C, C-1), 138.49 (1C, C-1'), 152.68 (1C, $\underline{C}$=O, urethane), 156.21 (1C, $\underline{C}$=O, urea).

1,1-Dimethyl-2-(propyl-ureido)-ethyl-N-4-chlorophenyl-carbamate (6b)

Colorless crystals; yield: 0.49g (72%); m.p. 102-104°C; Analysis calcd. for $C_{15}H_{22}O_3N_3Cl$ (327.81) C, 54.96, H, 6.76; N, 12.82 Found: C, 54.89, H, 6.78; N, 12.69; IR (KBr) 3100-3400 (NH), 1690

(C=O, urethane), 1630 (C=O, urea), 1540 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H, $C\underline{H}_3$), 1.45 (s, 6H, $C(C\underline{H}_3)_2$), 1.47 (sext, J = 7.5 Hz, 2H, CH_3-$C\underline{H}_2$-CH_2-), 3.10 (t, J = 6.7 Hz, 2H, $CH_3CH_2C\underline{H}_2$-), 3.44 (d, 2H, J = 5.5 Hz, NH-$C\underline{H}_2$-), 5.03, 5.72 (b, 2H, 2 NH), 7.19-7.32 (AA'XX', 4H, $C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 11.18 (1C, $\underline{C}H_3$-CH_2-), 23.29 (1C, CH_3-$\underline{C}H_2$-), 24.01 (2C, $C(\underline{C}H_3)_2$), 42.12 (1C, CH_3-CH_2-$\underline{C}H_2$-), 49.14 (1C, NH-$\underline{C}H_2$-), 82.36 (1C, $\underline{C}(CH_3)_2$), 119.72 (2C, C-2), 128.04 (1C, C-4), 128.78 (1C, C-3), 136.65 (1C, C-1), 152.77 (1C, $\underline{C}$=O, urethane), 158.80 (1C, $\underline{C}$=O, urea).

1,1-Dimethyl-2-[1-(3-isopropenyl-phenyl)-1-methyl-ethyl]-urea-N-4-chlorophenyl-carbamate (7b)

Colorless crystals; yield: 1.20g (68%); m.p. 86-88°C; Analysis calcd. for $C_{24}H_{30}O_3N_3Cl$ (443.97) C, 64.93; H, 6.81; N, 9.46. Found: C, 64.26; H, 7.10; N, 8.99; IR(KBr) 3410, 3250 (NH), 1740 (C=O, urethane), 1700 (C=O, urea), 1650 (C=C-alkyl), 1560, 1530 (2*amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (s, 6H, $C(C\underline{H}_3)_2$), 1.62 (s, 6H, NH-$C(C\underline{H}_3)_2$), 2.12 (s, 3H, C-$C\underline{H}_3$), 3.33 (d, J = 5.9 Hz, 2H, NH-$C\underline{H}_2$-), 5.04, 5.33 (AB, 2H, $\underline{H}_2C$=), 5.59 (b, 1H, N$\underline{H}$), 6.73 (b, 1H, N$\underline{H}$), 7.23-7.57 (AA'XX' and ABCX, 8H, 2*$C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 21.61 (1C, =C-$\underline{C}H_3$), 23.66 (2C, CH_2-$C(\underline{C}H_3)_2$), 30.17 (2C, N-$C(\underline{C}H_3)_2$), 48.91 (1C, NH-$\underline{C}H_2$-), 54.80 (1C, N-$\underline{C}(CH_3)_2$), 81.91 (1C, CH_2-$\underline{C}(CH_3)_2$), 112.84 (1C, $H_2\underline{C}$=), 119.57 (2C, C-2), 122.34 (1C, C-4'), 124.21 (1C, C-6'), 124.24 (1C, C-2'), 127.93 (1C, C-4), 128.43 (1C, C-5'), 128.73 (2C, C-3), 136.53 (1C, C-1), 141.62 (1C, C-1'), 142.92 (1C, =$\underline{C}$-CH_3), 145.91 (1C, C-3'), 152.09 (1C, $\underline{C}$=O, urethane), 157.75 (1C, $\underline{C}$=O, urea).

1,1-Dimethyl-2-(ethyl-carbamate)-ethyl-N-4-chlorophenyl-carbamate (8b)

Colorless crystals; yield: 0.92g (73%); m.p. 50-52°C; Analysis calcd. for $C_{14}H_{19}O_4N_2Cl$ (314.86) C, 53.41; H, 6.08; N, 8.89. Found: C, 53.62; H, 6.07; N, 8.53; IR (KBr) 3370, 3290 (NH), 1700 (2*C=O, urethane), 1540 (2*amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H, $C\underline{H}_3$-CH_2-O), 1.49 (s, 6H, $C(C\underline{H}_3)_2$), 3.47 (d, J = 6.3 Hz, 2H, NH-$C\underline{H}_2$-), 4.12 (q, J = 7.1 Hz, 2H, CH_3-$C\underline{H}_2$-O), 5.31 (b, 1H, NH), 6.75 (s, 1H, NH), 7.16-7.28 (AA'XX', 4H, $C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 14.47 (1C, $\underline{C}H_3$-CH_2-), 23.94 (2C, $C(\underline{C}H_3)_2$), 49.68 (1C, NH-$\underline{C}H_2$-), 60.87 (1C, CH_3-$\underline{C}H_2$-), 82.26 (1C, $\underline{C}(CH_3)_2$), 119.76 (2C, C-2), 128.79 (1C, C-4), 128.87 (1C, C-3), 136.41 (1C, C-1), 152.31 (1C, $\underline{C}$=O, phenylurethane), 156.89 (1C, $\underline{C}$=O, alkylurethane).

1,1-Dimethyl-2-(2-methyl-propyl-carbamate)-ethyl-N-4-chlorophenyl-carbamate (9b)

Colorless crystals; yield: 1.09g (80%); m.p. 113-115°C; Analysis calcd. for $C_{16}H_{23}O_4N_2Cl$ (342.82) C, 56.05; H, 6.76; N, 8.17. Found: C, 56.39; H, 6.52; N, 8.09; IR(KBr) 3380, 3260 (NH), 1720, 1695 (C=O, urethane), 1530 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, J = 6.7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.49 (s, 6H, $C(C\underline{H}_3)_2$), 1.90 (m, J = 6.7 Hz, 1H, -$C\underline{H}(CH_3)_2$), 3.48 (d, J = 6.4 Hz, 2H, NH-$C\underline{H}_2$), 3.86 (d, J = 6.7 Hz, 2H, $C\underline{H}_2$-CH-), 5.29 (b, 1H, NH), 6.70 (s, 1H, NH), 7.22-7.32 (AA'XX', 4H, $C_6\underline{H}_4$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 18.92 (2C, $CH(\underline{C}H_3)_2$), 23.94 (2C, $C(\underline{C}H_3)_2$), 27.91 (1C, $\underline{C}H(CH_3)_2$), 47.70 (1C, NH-$\underline{C}H_2$), 71.10 (1C, CH-$\underline{C}H_2$-), 82.33 (1C, $\underline{C}(CH_3)_2$), 119.78 (2C, C-2), 128.27 (1C, C-4), 128.89 (1C, C-3), 136.40 (1C, C-1), 152.31 (1C, $\underline{C}$=O, phenylurethane), 157.07 (1C, $\underline{C}$=O, alkylurethane).

Poly [1,1-dimethyl-2-[1-(3-isopropenyl-phenyl)-1-methyl-ethyl]-urea-N-4-chlorophenyl-carbamate-co-methyl-methacrylate] (7c)

A mixture of **7b** (0.22g, 0.5mmol), methyl methacrylate (0.27mL, 2.5mmol), α,α'-azoisobutyronitrile (AIBN)(20mg, 0.15mmol, 5mol%) and THF (5mL) was stirred 48h at 60°C under nitrogen. The solution was poured in a mixture of ether/petroleumether (1:5, 200mL). The obtained polymer is colorless; yield: 0.35g (95%); m.p. 110-112°C; Analysis calcd. for $(C_{24}H_{30}O_3N_3Cl)_1$ $(C_5H_8O_2)_{3.0}$ (743.97) C, 62.96; H, 7.31; N, 5.64. Found: C, 62.74; H, 7.52; N, 5.52; IR(KBr) 3400, 3300(NH), 1740 (C=O,urethane), 1730 (C=O,ester), 1690 (C=O,urea), 1530-1560 (2*amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80-2.00 (b, 32H, 2*C-C$\underline{H}_2$-, 2*C-C$\underline{H}_3$, CH-C(C$\underline{H}_3$)$_2$, NH-C(C$\underline{H}_3$)$_2$), 3.40-3.60 (b, 17H, -OC$\underline{H}_3$, NH-C$\underline{H}_2$-), 7.23-7.57 (b,8H, 2*C$_6\underline{H}_4$-).

Evidence of the 4,5-dihydro-oxazole-ring:

For example, **1,1-dimethyl-2-(2-methyl-propionyl-amino)-ethyl-N-4-chlorophenyl-carbamate (2b)** was deprotected by dissolving in TFA. At the end of the reaction, the solvent was cautiously neutralized with NaOH. This solution, which contained **2-isopropyl-5,5-dimethyl-4,5-dihydro-oxazole**, was measured by MS (Finnegan MAT 90), IR and NMR; MS m/e (relative intensity) 141 (M^+,10%); IR (film) 1670 (C=N) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20 (d, J = 7Hz, 6H, CH(C$\underline{H}_3$)$_2$), 1.60 (s, 6H, C(C$\underline{H}_3$)$_2$), 2.45 (sept, J = 7 Hz, 1H, C$\underline{H}$(CH$_3$)$_2$), 3.72 (s, 2H, =N-C$\underline{H}_2$-); ^{13}C NMR (62.98 MHz, $CDCl_3$) δ 20.02 (2C, CH(C$\underline{H}_3$)$_2$), 25.99 (2C, C(C$\underline{H}_3$)$_2$), 36.78 (1C, C$\underline{H}$(CH$_3$)$_2$), 55.28 (1C, =N-C$\underline{H}_2$), 94.99 (1C, C$\underline{(}$CH$_3$)$_2$).

Deprotection of the modified BOC-type groups

The samples were prepared by dissolving each urethane (100mg) in trifluoroacetic acid (400μL) resp. in HBr/HOAc and the chemical shifts were measured at 35°C by recording spectra (^1H NMR, 90MHz) in defined intervals. The addition of $CaCl_2$ leads to the formation of a sediment.

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References

1. Anderson, G.W.; McGregor, A.C *J. Am. Chem. Soc.* **1957**, *79*, 6180-6183.
2. Mutter, M.; Uhmann, R.; Bayer, E. *Liebigs Ann. Chem.* **1975**, 901-915.
3. Barany, G.; Kneib-Cordonier, N.; Mullen, D.G. *Int. J. Peptide Protein Res.* **1987**, *30*, 705-739.
4. Wünsch, E. in *Houben-Weyl* , 4th ed.; Müller, E., Ed.; Thieme: Stuttgart, 1974; Vol.15/1, pp. 46ff., 117ff..
5. Schwyzer, R.; Rittel, W.; Kappeler, H.; Iselin, B. *Angew. Chem.* **1960**, *72*, 915-917.
6. Rehse, H.; Ritter, H. *Makromol. Chem.* **1989**, *190*, 697-706.
7. Gormanns, M.; Ritter, H. *Makromol. Chem.* **1993**, *194*, in press.
8. Gormanns, M.; Rehse, H.; Ritter, H. *Makromol. Chem.* **1991**, *192*, 745-755.
9. Alakhov, Y.B.; Kiryushkin, A.A.; Lipkin, V.M. *J. Chem. Soc. Chem. Commun.* **1970**, 406-407.
10. Sieber, P.; Riniker, B.; Brugger, M.; Kamber, B.; Rittel, W. *Helv. Chim. Acta* **1970**, *53*, 2135-2150.
11. Lundt, B.F.; Johansen, N.L.; Voelund, A.; Markussen, J. *Int. J. Peptide Protein Res.* **1978**, *12*, 258-268.
12. Rehse, H.; Ritter, H. *Polymer Bull.* **1990**, *23*, 1-6.
13. Krassuki, M.K. *C.R Hebd. Seances Acad. Sci.* **1908**, *46*, 236-238.