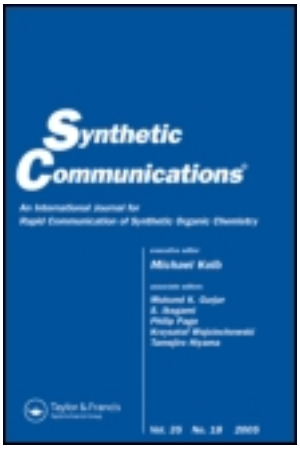

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A Practical Synthesis of ω-Aminoalkanoic Acid Derivatives from Cycloalkanones

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A PRACTICAL SYNTHESIS OF ω-AMINOALKANOIC ACID DERIVATIVES FROM CYCLOALKANONES

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Abstract. A practical synthetic route to *N*-Boc protected or Boc-amino acid coupled ω-aminoalkanoic acids is reported and exemplified by the preparation of 8-(*t*-butoxycarbonylamino)caprylic acid **2** and (*N*-*t*-butoxycarbonylphenylalanyl)-8-aminocaprylic acid **3**. The sequence does not involve column chromatography, hydrogenation, azide or bromine related rearrangements, and therefore is amenable to scale-up. Homologues of the ω-aminoalkanoic acid derivatives may also be prepared by using different cycloalkanones.

ω-Aminoalkanoic acids **1** have been extensively used as spacer molecules in solid phase peptide synthesis (SPPS).[1] These spacer molecules serve to distance the growing peptide chains from the solid resin support allowing the supported biopolymers to be more accessible for subsequent chemical reactions. Incorporation of such spacers becomes important in the preparation of combinatorial libraries wherein large enzymes or antibodies are frequently used to assess the *in-vitro* activities of the pendant peptides. Minimization of restrictions

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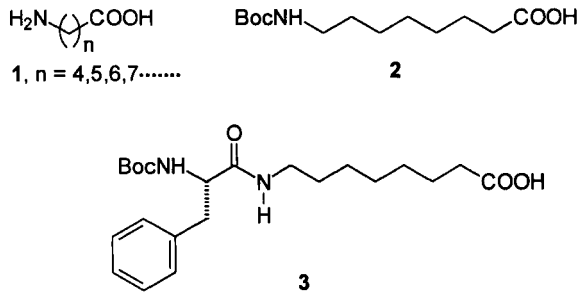
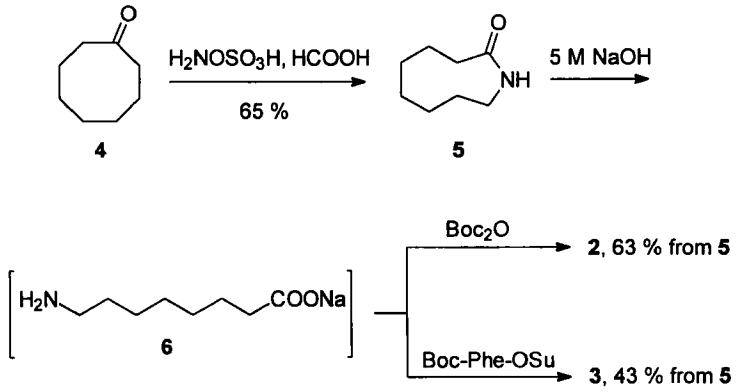
exerted by the resin allows a more effective interaction between the protein and peptide.[2] Furthermore, substituted ω-aminoalkanoic acid has been used to induce and maintain conformational rigidity in peptide fragments. When a Ala-Gly dipeptide was cyclized with the stereoisomers of 6-amino-3,5-dimethylhexanoic acid, the resulting cyclic compounds show type I and type II β-turn conformations.[3]



A number of methods for the preparations of ω-aminoalkanoic acids have been reported. Generally, the amine group is introduced by the conversion of a ketone to an oxime[4] or a carboxylate to a nitrile[5] followed by reduction, by azide opening of an anhydride followed by Schmidt rearrangement,[6] or by Hofmann rearrangement of an amide with aqueous base and bromine.[7] In this paper, a convenient synthetic route to *N*-Boc protected or Boc-amino acid coupled ω-aminoalkanoic acids is reported and exemplified by the preparation of 8-(*t*-butoxycarbonylamino)caprylic acid **2** and (*N*-*t*-butoxycarbonylphenylalanyl)-8-aminocaprylic acid **3**.

SCHEME



Sodium 8-aminocaprylate **6** was prepared from cyclooctanone **4** by hydroxyamine-*O*-sulfonic acid mediated Beckmann rearrangement,[8] followed by hydrolytic cleavage of the resulting 2-azacyclononanone **5** (Scheme). Refluxing lactam **5** in ethanolic base (15% KOH in ethanol, 30 h) resulted in incomplete hydrolysis with about 19% recovery of the starting material. Complete hydrolysis was achieved using aqueous acid (5M H_2SO_4) or aqueous base (5M, NaOH). This latter procedure has the advantage that it avoids neutralization of the acid amine salt before the subsequent coupling step. Attempts to isolate the 8-aminocaprylic acid by adjusting the pH of the reaction mixture, followed by repeated extraction with an organic solvent gave a low yield. For synthetic purposes, the sodium 8-aminocaprylate solution was used directly as an aqueous solution with no isolation necessary.

BOC protected 8-aminocaprylic acid **2** was prepared by dilution of the basic solution followed by the addition of di-*t*-butyl-dicarbonate. A 63% yield of

8-(*t*-butoxycarbonylamino)caprylic acid **2** was isolated from the lactam **5**. However, attempts to acylate the free amine of **6** with an -OSu (succinimidoxy) ester of a Boc-amino acid failed. The major product was the parent Boc-amino acid resulting from hydrolysis of the -OSu ester. Apparently, the rate of hydrolysis of the -OSu ester is faster than the amide bond formation under these conditions. To overcome this problem, the pH of the solution was adjusted to 8.2 before the addition of the Boc-Phe-OSu. This reduced the amount of hydrolysis of the ester and produced a 43% yield (over two steps) of the desired (*N-t*-butoxycarbonylphenylalanyl)-8-aminocaprylic acid **3**.

Boc protected and *N*-acylated ω-aminoalkanoic acids can also be obtained by hydrolysis of the *N*-Boc and *N*-acylated lactams, respectively. However, chromatographic purification of the *N*-alkoxycarbonyl or *N*-acyl lactams is usually required.[9] Aubé and coworkers recently reported the syntheses of cyclic peptide analogs from dipeptide fragments linked to stereoisomers of 6-amino-3,5-dimethylhexanoic acid. The procedure involves protection of the carboxyl terminus of the 6-amino-3,5-dimethylhexanoic acid as a methyl ester before coupling and subsequent deprotection by basic hydrolysis.[3] Since our syntheses of 8-aminocaprylic acid analogs **2** and **3** described in the Scheme do not require chromatographic purification nor protection of the carboxyl function, these useful compounds can be prepared with less handling. In addition, by avoiding hydrogenation, azide or bromine related rearrangements, the subject syntheses are very readily amenable to scale-up. We have prepared **6** in 100 g amounts for

further reaction in our own laboratory while up to 1 kg amounts of this material have been prepared in a kilo lab.[10] Consequently, analogs **2** and **3** are suitable for solution or solid phase peptide synthesis using BOC chemistry, and homologues with variable chain length may be prepared by using different cycloalkanones.

Experimental. Melting points were uncorrected. NMR spectra were measured using a Bruker AM300 (300 MHz) spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). ^{1}H and ^{13}C chemical shifts are reported in δ ppm relative to DMSO as internal standard (2.49 ppm and 39.5 ppm, respectively). The carbon multiplicities are assigned via DEPT sequence experiments. Thin-layer chromatography was performed on Whatman MK6F plates and visualized by UV, I_2 or ninhydrin stain. Microanalytical data was obtained from Robertson Microlit Laboratory, Inc. (Madison, NJ). Starting materials were purchased from commercial sources and used without further purification.

2-Azacyclononanone (5). Hydroxylamine-*O*-sulfonic acid (196.7 g, 1.74 moles, 1.1 equiv) and formic acid (1 L) were charged to a 5 L three-neck round bottom flask and stirred to form a white slurry. A solution of cyclooctanone (200.0 g 1.58 moles, 1.0 equiv) in formic acid (600 mL) was charged to an addition funnel and added dropwise. After the addition was complete, the funnel was replaced by a reflux condenser. The reaction was heated to reflux (internal temperature *ca.* 105 °C) under argon for 1 h to give a brown solution. After the solution was cooled to room temperature, it was poured into a mixture of saturated ammonium

chloride (1.5 L) and water (1.5 L). The aqueous mixture was extracted with chloroform (3 x 1.2 L). The combined chloroform layers were transferred to a beaker and saturated sodium bicarbonate (2 L) was added slowly *(caution: gas was evolved during the neutralization process. This should be performed in an open system such as a beaker. A separatory funnel should be avoided).* The chloroform layer was separated, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford a brown oil. The oil was placed in a 500 mL round bottom flask with a magnetic stirrer. The round bottom flask was placed in a silicon oil bath and fitted with a short path vacuum distillation head equipped with a thermometer and a three arm Cow-type receiver. 2-Azacyclononanone (145 g, 65 %) was obtained by vacuum distillation (fraction with head temperature range from 80 to 120 °C at pressure between 3.0 to 3.4 mmHg). mp 64 -69 °C (no depression of mp was observed when mixed with authentic sample obtained from Aldrich Chemical, Milwaukee, WI).[8a]

Sodium 8-aminocaprylate (6). A suspension of 2-azacyclononanone (83 g, 0.59 moles, 1.0 equiv) in 5 M aqueous sodium hydroxide (650 mL, 3.23 moles, 5.5 equiv) was charged to a 5 L three-neck round bottom flask equipped with an overhead mechanical stirrer and a condenser. The mixture was heated to reflux (internal temperature ca 110 °C) for 4 h to afford a clear yellow solution. The solution was diluted with water (650 mL) to afford the sodium 8-aminocaprylate solution (*ca* 0.45 mmol mL^{-1}).

8-(*tert*-Butoxycarbonylamino)caprylic acid (2). To a 250 mL three-neck round

bottom flask equipped with a magnetic stirrer and an addition funnel, was added a solution of sodium 8-aminocaprylate (0.45 mmol mL^{-1}, 22.5 mmol, 50 mL). The solution was cooled in an ice-bath. Di-*tert*-butyl dicarbonate (24.75 mmol, 5.40 g, 1.1 equiv) was dissolved in 1,4-dioxane (50 mL), charged to the addition funnel and added dropwise over 15 min. The mixture was stirred in the ice-bath for 15 min and at ambient temperature for 1 h. The dioxane was evaporated under vacuum, ethyl acetate (30 mL) was added and the heterogeneous solution was cooled in an ice-bath. The solution was acidified with 0.5 M sulfuric acid to pH 2. The ethyl acetate was separated and the aqueous layer was further extracted with 2 x 30 mL ethyl acetate. The combined organic layers were washed with water (2 x 30 mL), dried and evaporated. The residue was suspended in hot hexanes (30 mL), followed by dropwise addition of ethyl acetate until a homogenous solution was obtained. The solution was cooled at -5 °C for 4 h. A white solid formed and was collected by filtration to afford 8-(*tert*-butoxycarbonylamino)caprylic acid **(2)** (3.67 g, 63 %). mp 54-55 °C; IR(KBr): 3362, 2947, 1690, 1520, 1321, 940 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 11.93 (br s, 1H), 8.72 (br s, 1H), 2.87 (q, J = 6.54, 12.86 Hz, 2H), 2.19 (t, J = 7.33 Hz, 2H), 1.47 (m, 2H), 1.36 (br s, 11H), 1.23 (br s, 6H); ^{13}C NMR (DMSO-d_6) δ: 174.2 (C), 155.4 (C), 77.1 (C), 39.6 (CH_2), 33.5 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 28.1 (CH/CH_3), 26.0 (CH_2), 24.3 (CH_2). Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.30; H, 9.66; N, 5.33.

(*N*-*tert*-Butoxycarbonylphenylalanyl)-8-aminocaprylic acid (3). To a 250 mL

round bottom flask equipped with an addition funnel was added a solution of sodium 8-aminocaprylate **(6)** (14.61 mmol, 32.5 mL, 1.2 equiv). The pH of the solution was adjusted to 8.2 by addition of concd HCl. The solution was then cooled in an ice-bath. Boc-Phe-OSu (12.42 mmol, 4.50 g, 1.0 equiv) was dissolved in 1,4-dioxane (20 mL) and added dropwise. The mixture was stirred in the ice-bath for 30 min and at ambient temperature for 12 h. The solution was acidified with 1 M sulfuric acid (80 mL) and extracted with ether (100 + 50 mL). The combined organic layers were washed with water (40 mL), dried and evaporated to give a pale yellow oil. The oil was trituated with hexanes (3 x 50 mL) to afford (*N-tert*-butoxycarbonylphenylalanyl)-8-aminocaprylic acid **(3)** (2.17 g, 43 %) as a colorless solid. mp 96-100 °C; IR (KBr): 3296, 2980, 1705, 1677, 1631, 1558, 1407 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 12.00 (br s, 1H), 7.82 (t, J = 5.34 Hz, 1H), 7.18 (m, 5H), 6.86 (d, J = 8.58 Hz, 1H), 4.09 (m, 1H), 3.00 (m, 2H), 2.88 (dd, J = 5.09, 13.64 Hz, 1H), 2.72 (dd, J = 9.72, 13.51 Hz, 1H), 2.17 (t, J = 7.31 Hz, 2H), 1.47 (m, 2H), 1.29 (2 overlapped br s, 19H). ^{13}C NMR (DMSO-d_6) δ: 174.2 (C), 171.0 (C), 137.9 (CH/CH_3), 129.0 (CH/CH_3), 127.8 (CH/CH_3), 125.9 (CH/CH_3), 77.8 (C), 55.54 (CH/CH_3), 38.3 (CH_2), 37.7 (CH_2), 33.5 (CH_2), 28.8 (CH_2), 28.3 (2 x CH_2), 27.9 (CH/CH_3), 26.0 (CH_2), 24.3 (CH_2). MS (FAB, thioglycerol): 407 (13, M^{+1} + 1), 351 (13), 307 (100), 289 (5), 261 (11). HRMS (EI) calcd for $C_{22}H_{35}N_2O_5$ (M^{+1} + 1) 407.2546, found 407.2562; calcd for $C_{22}H_{34}N_2O_5$ (M^{+1}) 406.2468, found 406.2476. Anal. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.43; H, 8.24; N, 6.73.

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