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"One-Pot" Preparation of *N*-(Carbonylamino)amino Acids and Half-Acid/Half-Ester Urea Dipeptides Directly from α-Amino Acids

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Abstract: *N*-(Carbonylamino)amino acids and half-acid/half ester urea dipeptides can be prepared in a "one-pot" sequence directly from α-amino acids by employing TMS as a "transient" protecting group. The 4-step sequence: selective *O*-silylation of the α-amino acid, transformation of the amino group to the isocyanate, reaction of the isocyanate with an amine or amino acid ester, and mild deprotection using MeOH affords the *N*-(carbonylamino)amino acids or half-acid/half ester urea dipeptides in overall yields ranging from 45-85%. Comparison of chiral HPLC assays of an enantiomeric pair of products prepared from their respective L- and D-amino acids using this methodology indicates that no racemization occurs during the sequence.

N-(Carbonylamino)amino acids and half-acid/half ester urea dipeptides are starting materials or structural components for a variety of pharmacologically active compounds of recent importance, including, HIV-protease inhibitors,[1] renin inhibitors,[2] selective antagonists for the endothelin receptors,[3] and cysteine protease inhibitors,[4] to name just a few.

N-(Carbonylamino)amino acids are often prepared in step-wise fashion by transforming α-amino acid esters to either imidazole carbonates using 1,1-carbonyldiimidazole,[1,3b,5] or to α-isocyanato esters using triphosgene,[6] diphosgene,[2,3c] or phosgene,[7] followed by reaction with amines, and then de-esterification. Half-acid/half-ester urea dipeptides can be prepared similarly; for example, by coupling amino acid esters via imidazole carbonates followed by selective manipulation of an ester substituent.[1]

The capability to prepare the title compounds directly from α-amino acids[8] as a one-pot procedure via the isocyanate was desired. To do so, the carboxylic acid functionality would have to be blocked momentarily so as not to interfere with isocyanate formation. The ideal *O*-protecting group, in the context of this desired one-pot procedure, is one that can be installed selectively in the presence of an amine, and is sufficiently labile to be removed during work up.

It previously has been demonstrated that trimethylsilyl chloride (TMSCl) can be employed to selectively *O*-silylate amino acids.[9] The TMS group has been used for transient *O*-protection of amino acids,[10] e.g., in the preparation of *N*-9-phenylfluoren-9-yl,[11] *N*-trityl,[10,12] and *N*-sulfonyl[13] amino acids.

We report here that the transient TMS-protecting technology can be coupled with *in situ* isocyanate formation to prepare *N*-(carbonylamino)amino acids and half-acid/half ester urea dipeptides directly from α-amino acids in a "one-pot"[14] sequence as outlined in Scheme 1.

Thus, treatment of amino acid **1** with 1.0-1.1 eq of Me_3SiCl in CH_2Cl_2 or 1:5 acetonitrile/$CHCl_3$ or CH_2Cl_2 by heating for several hours or stirring overnight at room temperature, gives a solution of the selectively *O*-protected amino acid hydrogen chloride **2**, which is added, in the presence of base, to a solution of triphosgene[15] in chloroform or DCM. The resulting solution is treated with 1.0-1.2 eq of amine **4** or amino acid ester **6** and additional DIEA, and following mild deprotection using MeOH, the

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N-(carbonylamino)amino acid **5** or half-acid/half ester urea dipeptide **7**, respectively, is obtained. Isocyanate **3**[16,17] is an *in situ*-generated intermediate in the sequence.

Scheme 1

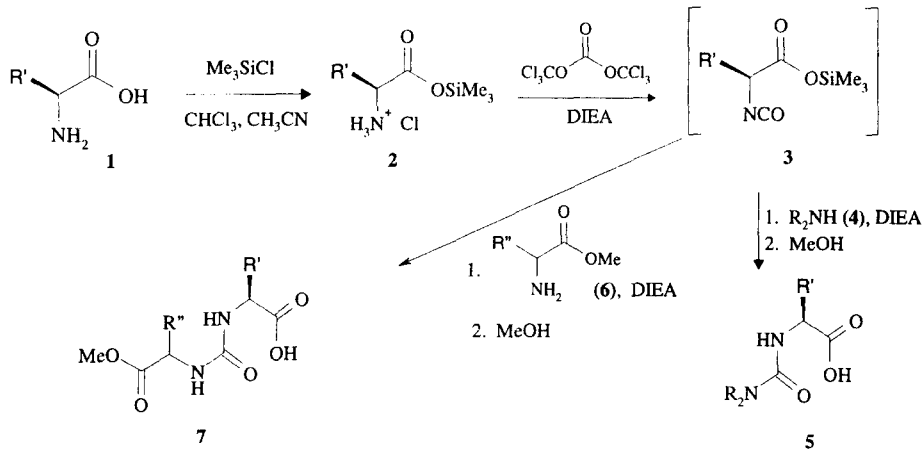
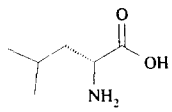
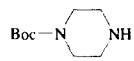
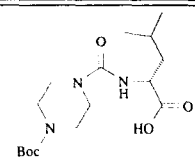
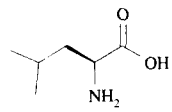
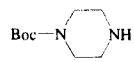
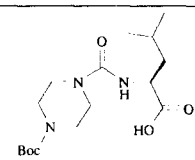
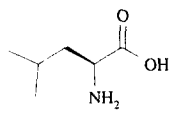
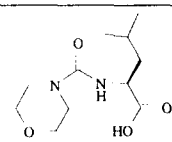
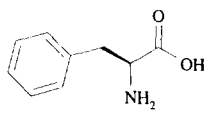
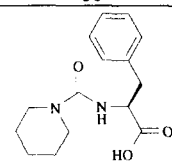
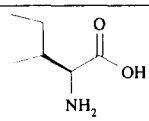
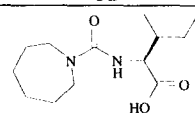
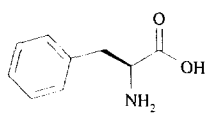
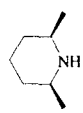
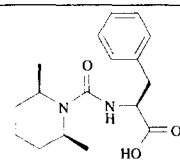
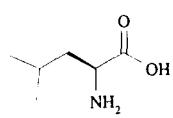
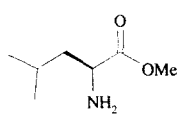
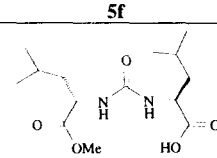
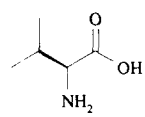
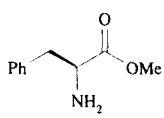
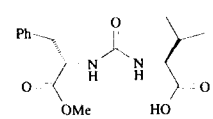


Table 1 lists the amines and amino acids that have been employed in this process. The sequence has been performed on a multi-gram scale. Overall yields of **5** or **7** from **1** are fair to good.[18] Moreover, the acid functionality of the products conveniently provides the opportunity during acid/base extractive work up to remove any unreacted amine and amino acid with an acid wash of the organic extracts, and any neutral by-products with an organic wash of the basic aqueous phase. Thus, the isolated products are typically obtained as pure, white solids, that are generally homogeneous by TLC[19] and for most purposes do not need recrystallization or purification by column chromatography.

The retention of optical purity is of utmost importance. Comparison of the chiral hplc assays[20] of enantiomers **5a** and **5b**, prepared using this methodology from D-Leu (**1a**) and L-Leu (**1b**), respectively, shows that racemization does not occur. This observation is consistent with previous reports.[6,7,21,22]

Typical procedure for N-(carbonylamino)amino acids:[23] A dry, 500 mL, 3-necked, round-bottomed flask equipped with a thermocouple probe, static nitrogen supply, condenser and a mechanical stirrer was charged with 7.04 g (53.7 mmol) of finely divided (mortar and pestle) D-Leu (**1**), 200 mL of $CHCl_3$, 40 mL of CH_3CN and 1.0 – 1.1 eq of Me_3SiCl. The suspension was heated at 55-63 °C for several hours with vigorous stirring. After cooling to 10-20 °C, 20.6 mL (118.1 mmol) of diisopropylethyl amine (DIEA) was added. The solution (or thin suspension) was then added using an addition funnel (syringe pump in the case of suspensions) over a period of 1 h at 15-22 °C to a solution of 5.89 g (0.37 eq) of triphosgene (**caution**: handle in a well-ventilated hood) in 75 mL of $CHCl_3$. After stirring for ca. 20 min, a solution made from 10.3 g (10.0 g corrected for 97% purity, 53.67 mmol) of *N*-Boc-piperazine, 14 mL of DIEA and 60 mL of $CHCl_3$ was added in one portion. After stirring for 30 min, 10.8 mL (268 mmol) of MeOH was added. The solution was concentrated to an oil which was partitioned with EtOAc and 0.5 N NaOH. The aqueous phase was washed with EtOAc, then acidified with 10% $KHSO_4$. Product was extracted into methylene chloride, washed with aq NaCl, water, then dried (Na_2SO_4), filtered, and concentrated, to give 13.33 g of a white solid. A 12.15 g portion of this material was dried (90 – 100 °C/in vacuo) to give 11.75 g (71.8% yield from **1a**, adjusted for sampling) of **5a**: mp 153-154 °C (dec.); IR (KBr) 3380, 2960, 2930, 2870, 1700, 1615, 1550, 1420, 1370, 1260, 1235, 1170, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.6-8.1 (1H, br s, exchanges with D_2O), 5.42 (NH, d, J = 7.7 Hz), 4.41 (NH, dt, J = 8.8 and 4.1 Hz), 3.40 (8 H, m), 1.8-1.5 (3 H, complex overlapping m), 1.46 (9 H, s), 0.95 (3 H, d, J = 6.0 Hz), 0.94 (3 H, d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 176.54, 157.83, 154.68, 80.36, 52.49, 43.60, 40.89, 28.32, 24.86, 22.85, 21.81 ppm; CI/MS, *m/z* (relative intensity) 344

Table 1. Synthesis of *N*-(Carbonylamino)amino acids and half-acid/half ester urea dipeptides

1	4 or 6	5 or 7	yield
 **1a**	 **4a**	 **5a**	72%
 **1b**	 **4a**	 **5b**	77%
 **1b**	 **4b**	 **5c**	49%
 **1c**	 **4c**	 **5d**	64%
 **1d**	 **4d**	 **5e**	85%
 **1c**	 **4e**	 **5f**	63%
 **1b**	 **6a**	 **7a**	49%
 **1e**	 **6b**	 **7b**	45%

(M^+ + H, 20), 328 (19), 316 (38), 289 (18) 288 (100), 270 (5), 242 (5), 158 (9), 130 (15), 87 (5); $[\alpha]_d^{22}$ = +28.21° (*c* = 1.00, MeOH).[24] Anal. Calcd. for $C_{16}H_{28}N_3O_5$: C, 55.96%; H, 8.51%; N, 12.24%. Found: 55.62%; H, 8.76%; N, 12.18%. *Typical procedure for half-acid/half ester urea dipeptides:* A solution prepared from 1.2 eq of **6b** (as the HCl salt), 2.5 eq of DIEA and 40 mL of $CHCl_3$ was added to a $CHCl_3$ solution containing 26.83 mmol of isocyanate prepared from **1e** and 1.1 eq Me_3SiCl in a manner as described above. After quenching with MeOH, and adding 75 mL of water, the pH was adjusted to 1 with 10% HCl. The organic phase was washed[25] twice with 0.5 N HCl and water, then extracted with 2 x 100 mL of 5% $NaHCO_3$. The basic extracts were washed with $CHCl_3$, acidified to pH 1.9 with 10% HCl, then extracted with 2 x 60 mL $CHCl_3$. The organic extracts were combined, dried (Na_2SO_4), filtered, concentrated and dried to afford 3.92 g (45.3%) of **7b** as a white, slightly hygroscopic foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.0-8.1 (1 H, br s, exchanges with D_2O), 7.25-7.12 (3 H, m), 7.06-7.03 (2 H, m), 6.07 (NH, d, *J* = 9.1 Hz), 5.86 (NH, d, *J* = 8.2 Hz), 4.82 (1 H, dt, *J* = 8.0 and 6.3 Hz), 4.40 (1 H, dd, *J* = 8.8 and 4.9 Hz), 3.59 (3 H, s), 3.08 (1 H, dd, *J* = 13.7 and 5.2 Hz), 3.00 (1 H, dd, *J* = 13.7 and 6.6 Hz), 2.12 (1 H, m), 0.93 (3 H, d, *J* = 6.6 Hz), 0.84 (3 H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 176.32, 173.86, 157.95, 136.00, 129.35, 128.49, 127.03, 58.14, 54.22, 52.23, 38.76, 30.89, 18.89, 17.52 ppm; $[\alpha]_d^{22}$ = +35.4 ° (*c* = 1.00, MeOH).

Acknowledgement: Brian Regg is thanked for developing and performing the chiral hplc assays.

[1] Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L.; Peña, M. *J. Org. Chem.* **1997**, *62*, 6420-6423.

[2] Yamada, Y. et al. *Chem. Pharm. Bull.* **1997**, *45*, 1631-1641.

[3] See, for example, (a) von Geldern, T. W. et al. *J. Med. Chem.* **1996**, *39*, 957-967. (b) Fukami, T. et al. *J. Med. Chem.* **1996**, *39*, 2313-2330, and references cited therein. (c) He, J. X.; Cody, W. L.; Doherty, A. M. *J. Org. Chem.* **1995**, *60*, 8262-8266.

[4] Palmer, J. T.; Rasnick, D.; Klaus, J. L.; Brömme, D. *J. Med. Chem.* **1995**, *38*, 3193-3196.

[5] Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267-6270.

[6] Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, *59*, 1937-1938.

[7] Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364-7366.

[8] (a) A method for preparing *N*-(carbonylamino)amino acids by reaction of *N,O*-bis(trimethylsilyl)amino acids with isocyanates is suitable for the synthesis of *N,N'*-disubstituted ureas, but it is not applicable for preparing the trisubstituted ureas reported here. See: Arrieta, A.; Palomo, C. *Synthesis* **1982**, 1050-1052. Similarly, *N,N'*-disubstituted ureas can also be prepared from reaction of amino acids with trichloroacetamides. See: Atanassova, I. A.; Petrov, J. S.; Balabanova, A. N.; Mollov, N. M. *Synth. Commun.* **1989**, *19*, 2947-2954. (b) A solid phase, combinatorial approach to preparing half-acid/half-ester urea dipeptides has been described: Nieuwenhuijzem, J. W.; Conti, P. G. M.; Ottenheijm, H. C. J.; Linders, J. T. M. *Tetrahedron Lett.* **1998**, *39*, 7811-7814.

[9] Hils, J.; Rühlmann, K. *Chem. Ber.*, **1967**, *100*, 1638-1345.

[10] (a) Kricheldorf, H. R. *Synthesis* **1970**, 592-593. (b) Kricheldorf, H. R. *Liebings Ann. Chem.* **1972**, *763*, 17-38.

[11] (a) Gmeiner, P. G.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068-3074. (b) Jamison, T. F.; Rapoport, H. *Org. Synth.* **1992**, *71*, 226-235.

[12] (a) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324-1326. (b) Hipskind, P. A. et al. *J. Org. Chem.* **1995**, *60*, 7033-7036.

[13] (a) Kricheldorf, H. R.; Schultze, J. *Synthesis* **1976**, 739-741. (b) Chung, J. Y. L.; Zhao, D.; Hughes, D. L.; Grabowski, E. J. J. *Tetrahedron* **1993**, *49*, 5767-5776.

[14] The sequence is considered "one-pot" in the sense that no intermediates are isolated.

[15] Eckert, H.; Forster, B. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 894-895.

[16] In one example, where **1c** was *O*-silylated in DCM by stirring at ambient temperature overnight, and treated with triphosgene and then **4e**, in a fashion as described in the experimental section, the reaction sequences were followed by collecting real-time *in situ* FT IR spectra. A transient isocyanate band at 2260 cm^{-1} was observed. It appears from this preliminary experiment that the silyl group participates in the formation of isocyanate **3**. Additional *in situ* FT IR studies probing this reaction are on-going, and will be reported in due time.

[17] *O*-Silyl protected α-isocyanato acids **3** have been prepared from amino acids via *N*-(aryloxycarbonyl)amino acids. See: Kricheldorf, H. R. *Synthesis* **1970**, 649-651.

[18] In limited experience, isolated yields were generally lower and more variable for compounds **7** than for compounds **5**.

[19] SiO_2, 90:10:1 EtOAc/MeOH/HOAc, ninhydrin.

[20] Sample preparation: injected 5 μL of solution prepared from ca. 0.5 mg of compound dissolved in 1 mL of the mobile phase; column: 4.6 mm x 25 cm Chirobiotic T (Teicoplanin); mobile phase: 70:30 EtOH (USP)/20 mM ammonium citrate dibasic (pH 4.0); flow: 1 mL/min; detection: uv at 210 nm; retention times: **5a**, 3.75 min, **5b**, 3.15 min. Compounds were enantiomerically homogeneous within the detection limits of the method.

[21] Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Hauling, S.-L. *J. Org. Chem.* **1996**, *61*, 3929-3934.

[22] Further, epimerization during the preparation of dipeptide ureas **7a** and **7b** would generate diastereomeric mixtures of products, which were not detected by ^{1}H NMR spectroscopy.

[23] Techniques such as using finely divided amino acid and vigorous agitation were employed in the heterogeneous silylations. Also, to prevent loss of TMSCl, joints were carefully sealed and an efficient condenser was used.

[24] This compares to an optical rotation of $[\alpha]_d^{22}$ = -27.6° (*c* = 1.00, MeOH) for enantiomer **5b** obtained from L-Leu (**1b**).

[25] If necessary, nuisance emulsions at the interfaces can be broken by using Celite® and filtering through a 40-μ fritted filter.