Reagents and Synthetic Methods; 19. Synthesis of *N*-(*N*-Aryl- or *N*-Alkylaminocarbonyl)-amino Acids by Addition of *N,O*-Bis[trimethylsilyl]amino Acids to Isocyanates

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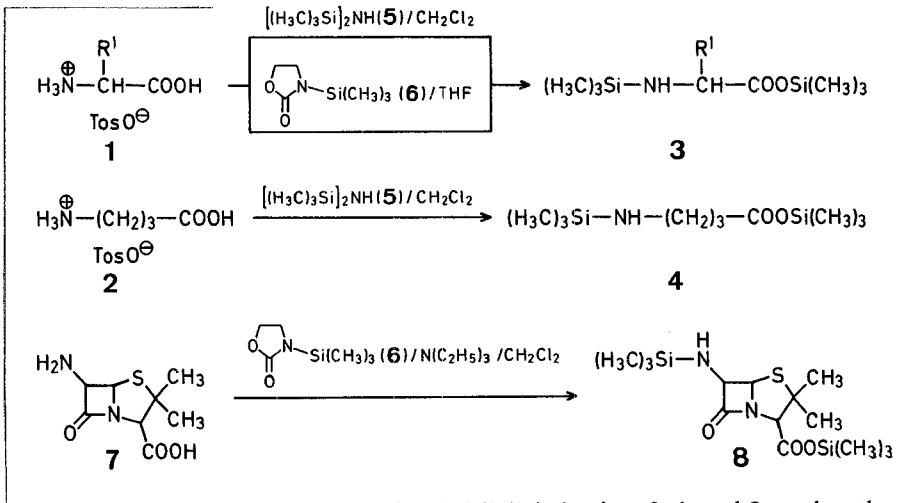
N-(Aminocarbonyl)-amino acids are important starting materials for the synthesis of some potential antitumor compounds[1] and are commonly prepared by treatment of amino acids with potassium cyanate[2] or alkyl (aryl) isocyanates[3]. The reaction of the amino acids with isocyanates is generally carried out in aqueous alkaline solution, from which the resulting aminocarbonyl derivate is usually precipitated by addition of mineral acid. However, this method has some drawbacks:

- The alkyl or aryl isocyanate reacts with water to afford a symmetrical *N,N'*-disubstituted urea that causes a decrease in the yield of the reaction and makes the isolation of the products difficult.
- In certain cases, a hydantoin, or a cyclic anhydride of the *N*-(aminocarbonyl)-amino acid, is obtained on acidification of the alkaline reaction mixture[1,3].
- Under the basic conditions used, racemization of the amino acids can take place[4], and in the case of penicillanic acid, epimerization at C-6 and opening of the β-lactam ring is also to be expected.

In order to overcome these drawbacks, we have developed a convenient method to prepare the *N*-(aminocarbonyl)-amino acids **9a–e** and **10**. The starting materials for our synthesis, *N,O*-bis[trimethylsilyl]amino acids[5–11] **3** and **4** are obtained from the reaction of the amino acid tosylate salts **1** and **2** with hexamethyldisilazane **(5)** or with 2-oxo-3-trimethylsilyltetrahydro-1,3-oxazole[11,12] **(6)** in dichloromethane or tetrahydrofuran, respectively, at room temperature. The tosylate salts **1** and **2** are readily prepared from the amino acid (1 equiv) and *p*-toluenesulfonic acid (1.5 equiv) in a suitable solvent (Table 1). We have also prepared the disilyl derivative **(8)** of the 6-aminopenicillanic acid **(7)** by silylation with **6** in the presence of a catalytic amount of triethylamine.



The *N,O*-bis[trimethylsilyl] derivatives **3, 4,** and **8** need not be isolated but can be converted *in situ* to the corresponding *N*-(aminocarbonyl)-amino acids **9, 10,** and **11** by treatment with an alkyl or aryl isocyanate **12** at room temperature (Table 2).

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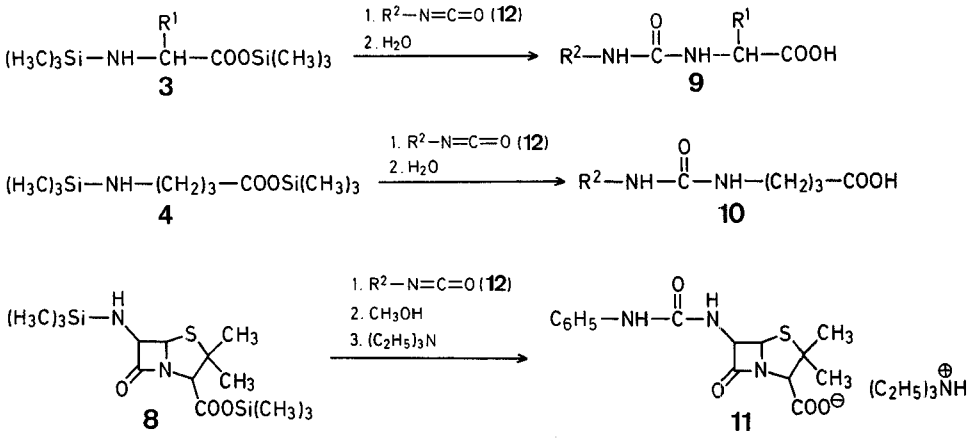

Similar results can be obtained from the free amino acids by silylation with chlorotrimethylsilane/triethylamine in dichloromethane and *in situ* reaction with the isocyanate **12** but the yields are somewhat lower. Direct reaction of the free amino acid with the isocyanate **12** in the presence of sodium carbonate in water at 0 °C also results in the desired products but in low yields (22–57%).

The described method has the following advantages: mild and easy synthesis of *N,O*-bis[trimethyl]silyl esters **3a–d, 4,** and **8** acids; high yields and purity in the corresponding *N*-aminocarbonyl derivatives **9a–d, 10,** and **11** in contrast to the conventional method; and essentially neutral reaction conditions are maintained through the whole sequence and cyclization has not been observed.

D-(−)-α-Phenylglycine *p*-Toluenesulfonate Salt (1d); Typical Procedure:

D-(−)-α-Phenylglycine (6.04 g, 0.04 mol) is added portionwise to a stirred solution of *p*-toluenesulfonic acid (11.6 g, 0.06 mol) in 1,2-dimethoxyethane (20 ml) and dichloromethane (20 ml) during 15 min at 40 °C. The resulting mixture is stirred at the same temperature for 30 min. The precipitate is filtered off to give D-(−)-α-phenylglycine *p*-toluenesulfonate salt (**1d**); yield: 12.27 g (95%); m.p. 208–209 °C (from THF/CH_3OH); $[\alpha]_D^{20}$: −63.75° (*c* 2, H_2O).

$C_{15}H_{17}NO_5S$	calc.	C 55.72	H 5.30	N 4.33	S 9.92
(323.3)	found	55.32	5.10	4.53	10.52

I.R. (KBr): ν = 3430–3200 ($-\overset{\oplus}{N}H_3$); 3500–2500 (OH); 1730 (C=O); 1630–1600 (C=C); 1500 (N—H); 1420–1150 (SO_2—O); 1060–1010 cm^{-1} (S=O).

***N*-(*N*-Methylaminocarbonyl)-D-(−)-α-phenylglycine (9; $R^1 = C_6H_5$, $R^2 = CH_3$); Typical Procedure using Hexamethyldisilazane (5):**

A suspension of D-(−)-α-phenylglycine *p*-toluenesulfonate salt (**1d**; 3.23 g, 10 mmol) and hexamethyldisilazane (**5**; 2 ml, 10 mmol) in dichloromethane (10 ml) is stirred at room temperature for 30 min. Methyl isocyanate (**12**, $R^2 = CH_3$; 0.6 ml, 10 mmol) is added and stirring is continued for 60 min. Water (5 ml) is added and the precipitated product is isolated by suction and washed with water and then with *n*-hexane to give the product; yield: 2 g (96%); m.p. 182–183 °C, 184–186 °C (from water); $[\alpha]_D^{20}$: −138.61° (*c* 0.6, DMSO).

$C_{10}H_{12}N_2O_3$	calc.	C 57.68	H 5.81	N 13.45
(208.2)	found	57.38	5.71	13.65

I.R. (KBr): ν = 3500 (NH); 3400–2500; 1710 (C=O); 1650 (C=O); 1600 cm^{-1} (C=C).

***N*-(*N*-Phenylaminocarbonyl)-DL-alanine (9; $R^1 = CH_3$, $R^2 = C_6H_5$); Typical Procedure using 2-Oxo-3-trimethylsilyltetrahydro-1,3-oxazole (6):**

A suspension of DL-alanine *p*-toluenesulfonate salt (**1b**; 1.30 g, 5 mmol) and 2-oxo-3-trimethylsilyltetrahydro-1,3-oxazole (**6**; 2.35 ml, 15 mmol) in tetrahydrofuran (10 ml) is stirred at room temperature for 30 min. Phenyl isocyanate (**12**, $R^2 = C_6H_5$; 0.57 ml, 5 mmol) is added to the resulting solution and stirring is continued for 60 min. Triethylamine (0.7 ml, 5 mmol), methanol (3 ml), and water (0.3 ml) are then added. Evaporation of the solvent gives an oil which is treated with water (10 ml), the resulting precipitate is filtered off and washed with water to give the product; yield: 1.0 g (96%); m.p. 172–173° (from water) (Ref.[13], m.p. 168 °C).

Triethylammonium *N*-(*N*-Phenylaminocarbonyl)-penicillate (11):

2-Oxo-3-trimethylsilyltetrahydro-1,3-oxazole (**6**; 1.55 ml, 10 mmol) is added to a suspension of 6-aminopenicillanic acid (**7**; 1.08 g, 5 mmol) and triethylamine (0.14 ml, 1 mmol) in dichloromethane (10 ml) and

Table 1. *p*-Toluenesulfonate Salts of Amino Acids prepared

Product No.	R^1	Reaction Conditions (solvent/temp./time)	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (D_2O) δ [ppm]
1a	H	CH_3CN/45 °C/90 min	70	180–183° (CH_3OH)	$C_9H_{13}NO_5S$ (247.3)	1750	2.40 (s, 3H); 3.85 (s, 2H); 7.5 (m, 5H_{arom})
1b	CH_3	CH_3CN/40 °C/90 min	94	192–193° (CH_3OH/DME)	$C_{10}H_{11}NO_5S$ (261.3)	1750	1.52 (d, 3H); 2.35 (s, 3H); 4.1 (m, 1H); 7.5 (m, 4H_{arom})
1c	i-C_3H_7	DME/40 °C/90 min	94	163–165° (THF/*n*-hexane)	$C_{12}H_{19}NO_5S$ (289.4)	1735	1.07 (d, 6H); 2.35 (s, 3H); 2.3 (m, 1H); 3.90 (d, 1H); 7.5 (m, 4H_{arom})
D-(−)-**1d**	C_6H_5	DME/CH_2Cl_2/40 °C/120 min	95	208–209° (THF/CH_3OH)	$C_{15}H_{17}NO_5S$ (323.3)	1730	2.33 (s, 3H); 5.10 (s, 1H); 7.5 (m, 9H_{arom})
L-(+)-**1d**	C_6H_5	DME/CH_2Cl_2/40 °C/120 min	95	207–208° (THF/CH_3OH)	$C_{15}H_{17}NO_5S$ (323.3)	1730	2.33 (s, 3H); 5.10 (s, 1H); 7.5 (m, 9H_{arom})
2	—	THF/25 °C/150 min	98	126–129° (THF)	$C_{11}H_{17}NO_5S$ (275.3)	1730	1.85 (m, 2H); 2.35 (s, 3H); 2.40 (t, 2H); 2.95 (t, 2H); 7.45 (m, 4H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.2, N ±0.2, S ±0.6.

Table 2. *N*-(*N*-Aryl- or *N*-Alkylaminocarbonyl)-amino Acids prepared

Product No.	R^1	R^2	Reactants	Reaction conditions (solvent/temp./time)	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
9	H	C_6H_5	**1a** + **5**	CH_2Cl_2/r.t./30 min	90	195–196°	195–197°[13]	1760, 1740	3.76 (d, 2H); 6.23 (t, 1H); 7.0 (m, 5 H_{arom} + NH); 8.50 (s, 1H)
9	H	CH_3	**1a** + **5**	CH_2Cl_2/r.t./30 min	92	137–141°	147–148°[1]	1720, 1620	2.85 (s, 3H); 3.80 (s, 2H)[b]
9	CH_3	C_6H_5	**1b** + **6**	THF/r.t./30 min	96	172–173°	168°[13]	1710, 1650	1.35 (d, 3H); 4.2 (m, 1H); 6.50 (d, 1H); 7.3 (m, 5 H_{arom} + NH); 8.65 (s, 1H)
9	*i*-C_3H_7	C_6H_5	**1c** + **6**	THF/r.t./45 min	94	164°	$C_{12}H_{16}N_2O_3$ (236.3)	1740, 1640	0.92 (d, 6H); 2.1 (m, 1H); 4.12 (d, 1H); 6.90 (d, 1H); 7.25 (m, 5 H_{arom} + NH); 8.70 (s, 1H)
9	*i*-C_3H_7	CH_3	**1c** + **5**	CH_2Cl_2/r.t./30 min	~100	145–147° (water)	$C_6H_{13}N_2O_3$ (174.2)	1720, 1640	1.70 (d, 6H); 1.9 (m, 1H); 2.46 (s, 3H); 3.64 (d, 1H)[b]
9	C_6H_5	C_6H_5	D-(−)-**1d** + **5**	CH_2Cl_2/r.t./30 min	~100	171–173° (methanol)	$C_{15}H_{14}N_2O_3$ (270.3)	1720, 1640	5.05 (d, 1H); 6.9 (m, 10 H_{arom} + 2NH); 8.45 (s, 1H)
9	C_6H_5	C_2H_5	D-(−)-**1d** + **5**	CH_2Cl_2/r.t./30 min	~100	160–161° (water)	$C_{11}H_{14}N_2O_3$ (222.2)	1700, 1620	1.00 (t, 3H); 3.00 (q, 2H); 5.2 (m, 1H); 6.00 (t, 1H); 6.32 (d, 1H); 7.25 (s, 5 H_{arom}); 10.10 (s, 1H)
9	C_6H_5	CH_3	D-(−)-**1d** + **5**	CH_2Cl_2/r.t./30 min	96	184–186° (water)	$C_{10}H_{12}N_2O_3$ (208.2)	1700, 1620	2.45 (d, 3H); 5.00 (d, 1H); 5.8 (m, 1H); 6.40 (d, 1H); 7.05 (s, 5 H_{arom} + OH)
10	—	C_6H_5	**2** + **5**	CH_2Cl_2/r.t./30 min	95	120–121° (methanol)	$C_{11}H_{14}N_2O_3$ (222.2)	1760, 1740	1.66 (q, 2H); 2.16 (t, 2H); 3.00 (t, 2H); 6.03 (s, 1H); 7.0 (m, 5 H_{arom} + NH); 8.16 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.1, N ±0.2. [b] D_2O/NaOD solution.

the mixture is stirred at room temperature for 30 min. Phenyl isocyanate (**12**, $R^2 = C_6H_5$; 0.57 ml, 5 mmol) is then added and the stirring is continued for further 30 min. Methanol (1 ml) is added, the solution is stirred at room temperature for 60 min, then triethylamine (0.7 ml, 5 mmol) is added and the resulting precipitate is filtered off to give the product; yield: 1.1 g (50%); m.p. 180–181 °C (Ref.[14], m.p. 180–182 °C).

The organic layer is diluted with ether (2 ml) and the precipitate is filtered off to give a further crop of **11** (0.2 g); total yield: 1.3 g (60%); $[\alpha]_D^{20}$: +189.6° (*c* 0.0818, water).

$C_{21}H_{32}N_3O_4S$	calc.	C 59.69	H 7.63	N 9.94
(422.6)	found	59.69	7.53	9.74

I.R. (KBr): ν = 3600–2500 [$H\overset{\oplus}{N}(C_2H_5)_3$]; 1780 (C=O); 1700 (C=O); 1600 (C=C); 1540 cm^{-1} (C=O).

^{1}H-N.M.R. (D_2O): d = 1.30 (t, 9H); 1.55 (s, 3H); 1.60 (s, 3H); 3.14 (q, 6H); 4.26 (s, 1H); 5.5 (m, 2H); 7.23 ppm (s, 5 H_{arom}).

D-(−)-*N,O*-Bis[trimethylsilyl]-α-phenylglycine (3; $R^1 = C_6H_5$); Typical Procedure for the Isolation of Disilyl Derivatives:

A suspension of D-(−)-α-phenylglycine *p*-toluenesulfonate salt (**1d**; 6.5 g, 0.02 mol), hexamethyldisilazane (**5**; 4 ml, 0.02 mol) in acetonitrile (30 ml) is stirred at room temperature for 20 min. The precipitate is filtered off; evaporation of the solvent gives a crude *N,O*-bis[trimethylsilyl]-α-phenylglycine which is distilled under reduced pressure to give the pure product; yield: 5.6 g (95%); b.p. 90 °C/2 torr.

$C_{14}H_{25}NO_2Si_2$	calc.	C 56.90	H 8.53	N 4.74
(295.5)	found	56.67	8.50	4.84

I.R. (film): ν = 3390 (N—H); 1720 (C=O); 1600 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.00 (s, 9H); 0.10 (s, 9H); 1.78 (s, 1H); 4.31 (s, 1H); 7.05 (s, 5 H_{arom}).

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