Efficient Synthesis of *N*-Triphenylmethyl α-Amino Acids

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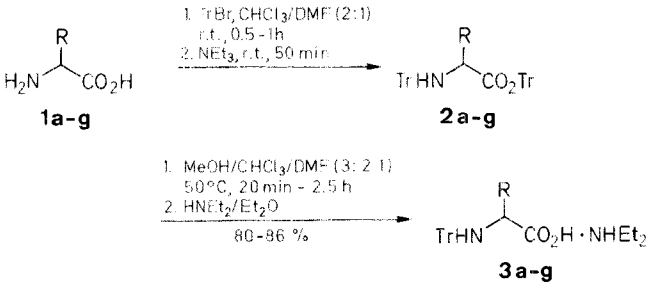
A new one-pot synthesis of *N*-triphenylmethyl(trityl) α-amino acids **3** via their trityl ester **2** has been developed.

Present peptide synthesis experiences a growing need for orthogonal protection techniques.[1-2] The trityl function represents a convenient temporary amino protecting group in combination with the commonly used *tert*-butoxycarbonyl (Boc) and the 9-fluorenylmethoxycarbonyl (Fmoc) groups.[3] Several syntheses of *N*-trityl α-amino acids have been described so far.[4] However, yields are generally low, and the procedures are not free of by-products. For example, the synthesis via silyl ester intermediates described by Barlos et al. results in the formation of trityl



1–3	R	1–3	R
a	H	**e**	$CH(CH_3)CH_2CH_3$
b	CH_3	**f**	CH_2Ph
c	*i*-Pr	**g**	$(CH_2)_4NHBoc$
d	$CH_2CH(CH_3)CH_3$	**h**	$(CH_2)_4NHFmoc$

ester **2** as a by-product.[5] We describe here a new synthesis of **3** in which the *N*-tritylamino acid trityl ester **2** represents a key intermediate.

The free amino acid **1** is suspended in a solution of triphenylmethyl bromide (trityl bromide, TrBr) in dry chloroform and dimethylformamide (2:1). After vigorously stirring for about one hour a homogeneous reaction mixture is obtained. A clear solution is mandatory for obtaining high yields of reaction. Also, the use of trityl bromide proves to be superior to the commonly used trityl chloride due to its higher reactivity and its reduced hygroscopic character.[6] Addition of an excess of triethylamine starts the reaction to give the *N*-tritylamino acid trityl ester **2**, which is selectively cleaved *in situ* to **3** by methanolysis at 50 °C (Table 1). Slight excess of the base prevents a cleavage of the amine trityl group of **2**. After evaporation of the solvents at reduced pressure the product is taken up in ether and washed with 5% citric acid and water. The pure crystalline *N*-tritylamino acid diethylamine salt **3** is precipitated directly from the ether solution by adding an equivalent of diethylamine (for **3g**, dicyclohexylamine). The yields range from 80 to 86% (Table 1).

The improved synthesis is also applicable to side-chain protected trifunctional amino acids without splitting off the protecting group during tritylation: this has been established for **3g** and **3h** where the ε-*tert*-butoxycarbonyl (Boc) and the ε-9-fluorenylmethoxycarbonyl (Fmoc) protected lysine derivatives are used. Unsatisfying yields are obtained only for proline, possibly due to the poor selectivity in the methanolysis reaction of the intermediate trityl ester.

Table 1. *N*-Trityl Amino Acid Diethylamine Salts **3** Prepared

Product **3**	Methanolysis Time (h)	Yield (%)	Molecular Formula[a]	$[\alpha]_D$ (c = 5%, MeOH)[b]	MS (Xe, 8 kV)[c] m/z (%)
a	0.3	82	$C_{25}H_{30}N_2O_2$ (390.5)		391 (M^+, 5); 243 (100); 165 (30); 74 (82)
b	1.5	86	$C_{26}H_{32}N_2O_2$ (404.6)	−21.3	405 (M^+, 3); 254 (13); 243 (100); 74 (37)
c	1.5	86	$C_{28}H_{36}N_2O_2$ (432.6)	+ 5.0	433 (M^+, 3); 282 (21); 243 (100); 165 (32); 74 (54)
d	2.0	85	$C_{29}H_{38}N_2O_2$ (446.6)	+ 2.2	447 (M^+, 4); 296 (21); 243 (100); 165 (30); 74 (79)
e	2.5	85	$C_{29}H_{38}N_2O_2$ (446.6)	+12.6	447 (M^+, 2); 296 (17); 243 (100); 165 (31); 74 (37)
f	1.0	86	$C_{32}H_{36}N_2O_2$ (480.7)	+13.2	481 (M^+, 2); 330 (6); 243 (100); 165 (23); 74 (73)
g	1.5	82	$C_{42}H_{59}N_3O_4$[d] (669.9)	+ 5.3	670 (M^+, 3); 489 (3); 243 (100); 182 (100)
h	1.5	80	$C_{44}H_{49}N_3O_4$ (683.9)	+10.2	684 (M^+, <1); 611 (3); 243 (100); 179 (25); 165 (22)

[a] Satisfactory microanalyses obtained (for **3a**, **3b** as dicyclohexylamine salt): C ±0.31, H ±0.32, N ±0.31.
[b] Measured on a Perkin-Elmer 141 polarimeter.
[c] Recorded on a VG 70-250.
[d] Dicyclohexylamine salt.

Table 2. Spectral Data of Compounds **3**

Compound	IR (KBr)[a] ν(cm^{-1})	^{1}H-NMR (CD_3OD/TMS)[b] δ, J(Hz)	^{13}C-NMR (CD_3OD/TMS)[c] δ
3a	3350, 3320, 3300, 1715, 1635, 1600	1.26 (t, 6H, J = 7.3); 2.94 (s, 2H); 2.99 (q, 4H, J = 7.3); 7.16–7.42 (m, 15H)	11.67 (q); 43.46 (t); 72.39 (s); 127.54 (d); 128.83 (d); 130.06 (d); 147.36 (s); 178.98 (s)[d]
3b	3335, 3315, 3065, 3030, 2985, 1635, 1570	0.91 (d, 3H, J = 6.9); 1.25 (t, 6H, J = 7.3); 2.96 (q, 4H, J = 7.3); 3.17 (q, 1H, J = 6.9); 7.13–7.53 (m, 15H)	11.72 (q); 22.36 (q); 43.39 (t); 55.74 (d); 72.96 (s); 127.32 (d); 128.69 (d); 130.22 (d); 148.16 (s); 183.52 (s)
3c	3338, 3310, 3095, 3065, 2970, 2880, 1630, 1600	0.83 (d, 3H, J = 7.0); 0.87 (d, 3H, J = 6.8); 1.24 (t, 6H, J = 7.3); 1.51–1.55 (m, 1H); 2.94 (q, 4H, J = 7.3); 3.08 (d, 1H, J = 4.2); 7.11–7.49 (m, 15H)	11.87 (q); 18.65 (q); 20.75 (q); 34.76 (d); 43.39 (t); 64.67 (d); 72.74 (s); 127.17 (d); 128.52 (d); 130.47 (d); 148.58 (s); 180.96 (s)
3d	3320, 3300, 3070, 3040, 2970, 2955, 1635, 1630, 1600	0.69 (d, 3H, J = 6.5); 0.73 (d, 3H, J = 6.6); 0.95–1.00 (m, 1H); 1.25 (t, 6H, J = 7.3); 1.26–1.30 (m, 1H); 1.61–1.65 (m, 1H); 2.95 (q, 4H, J = 7.3); 3.10–3.14 (m, 1H); 7.11–7.51 (m, 15H)	11.80 (q); 22.81 (q); 24.49 (q); 26.02 (d); 43.38 (t); 46.87 (t); 59.04 (s); 72.82 (s); 127.15 (d); 128.58 (d); 130.34 (d); 148.48 (s); 183.41 (s)
3e	3350, 3095, 3065, 3040, 2965, 2880, 1640, 1550	0.67 (t, 3H, J = 7.1); 0.84 (d, 3H, J = 6.5); 1.11–1.14 (m, 2H); 1.24 (t, 6H, J = 7.3); 1.30–1.40 (m, 1H); 2.94 (q, 6H, J = 7.3); 3.16 (d, 1H, J = 3.4); 7.11–7.49 (m, 15H)	11.87 (q); 12.95 (q); 15.24 (q); 28.30 (t); 42.11 (d); 43.38 (t); 63.66 (d); 72.92 (s); 127.17 (d); 128.54 (d); 130.45 (d); 148.56 (s); 180.78 (s)
3f	3335, 3315, 3100, 3080, 3050, 1635, 1500	1.22 (t, 6H, J = 7.3); 2.50–2.63 (m, 2H); 2.90 (q, 4H, J = 7.3); 3.38 (t, 1H, J = 6.0); 7.08–7.43 (m, 20H)	11.77 (q); 43.02 (t); 43.33 (t); 61.92 (d); 72.57 (s); 126.86 (d); 127.11 (d); 128.56 (d); 128.78 (d); 130.37 (d); 131.37 (d); 140.96 (s); 148.38 (s); 182.02 (s)
3g	3340, 3085, 3060, 2930, 2855, 1715, 1625	1.10–1.38 (m, 16H); 1.41 (s, 9H); 1.68–1.72 (m, 2H); 1.83–1.87 (m, 4H); 2.02–2.04 (m, 4H); 2.88–2.92 (m, 2H); 3.10–3.14 (m, 3H); 7.12–7.50 (m, 15H)	23.70 (t); 25.56 (t); 26.23 (t); 28.85 (q); 30.71 (t); 31.11 (t); 36.15 (t); 41.36 (t); 54.36 (d); 59.73 (d); 72.84 (s); 79.67 (s); 127.18 (d); 128.60 (d); 130.30 (d); 148.49 (s); 158.43 (s); 182.46 (s)
3h	3650, 3445, 3300, 3075, 3040, 2960, 2880, 1740, 1725, 1640	1.11–1.43 (m, 6H); 1.24 (t, 6H, J = 7.3); 2.91–3.00 (m, 2H); 2.94 (q, 4H, J = 7.3); 3.15–3.17 (m, 1H); 4.17 (t, 1H, J = 6.9); 4.30 (d, 2H, J = 6.9); 7.10–7.78 (m, 23H)	11.77 (q); 23.70 (t); 31.05 (t); 36.16 (t); 41.77 (t); 43.38 (t); 48.60 (d); 59.76 (s); 67.60 (t); 72.84 (s); 120.91 (d); 126.22 (d); 127.21 (d); 128.18 (d); 128.62 (d); 128.77 (d); 130.30 (d); 142.61 (s); 145.39 (s); 148.46 (s); 158.81 (s); 182.66 (s)

[a] KBr, recorded on a Perkin-Elmer 781 Infrared spectrophotometer.
[b,c] Recorded on a VXR 400 Varian spectrometer.
[d] C-2 signal between solvent peaks (48.40–49.68).

To establish the stereochemical integrity of the amino acids we performed gas chromatographic enantiomeric separations. No detectable racemization has been found.

DMF was dried over molecular sieves (4 Å) and $CHCl_3$ distilled over P_2O_5. NEt_3, $HNEt_2$, dicyclohexylamine, and TrBr (97%) were purchased from Fluka A.G. TrBr was recrystallized from hot hexane/$CHCl_3$. Amino acids were products of Merck and Fluka; *prior* to use they were finely powdered and dried *in vacuo* over P_2O_5.

N-Trityl α-Amino Acids 3; General Procedure:
The finely powdered α-L-amino acid (**1**; 10 mmol) is suspended in a solution of TrBr (7.11 g, 22 mmol) in $CHCl_3$/DMF (50 mL, 2:1) in a dry flask and vigorously stirred at r.t. until a clear solution is obtained (30 min up to one hour). Then, NEt_3 (5.6 mL, 40 mmol) in $CHCl_3$/DMF (10 mL, 2:1) is dropped to the reaction mixture over a period of 20 min, and stirring is continued for another 30 min. After addition of MeOH (50 mL) the reaction mixture is heated to 50 °C for 20 min to 2.5 h (see Table 1). The solvent is evaporated at reduced pressure, the residue is taken up in Et_2O (100 mL), and the organic phase is extracted with 10% citric acid (3 × 50 mL) and H_2O (3 × 50 mL). The organic phase is dried (Na_2SO_4), and $HNEt_2$ (1.0 mL, 10 mmol) [for **3g** dicyclohexylamine (2.0 mL, 10 mmol)] in Et_2O (10 mL) is dropped to the solution. The precipitating product **3** is filtered off and washed several times with cold Et_2O. The crystalline product is dried *in vacuo*; it proves to be homogeneous according to TLC, ^1H-, and ^{13}C-NMR. Yield: 80–86%.

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