# Efficient "One-Pot" Synthesis of *N*-Trityl Amino Acids[1]

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A sequential procedure has been developed whereby neutral amino acids **1** were tritylated via their corresponding trimethylsilyl esters **2** to afford, after mild hydrolysis, *N*-trityl amino acids **3** in high yields and purity. Hydroxy amino acids **4** were preferentially tritylated at the amino function by using either $Me_3SiCl$ or $Me_2SiCl_2$ (or $Ph_2SiCl_2$) for temporary protection of the hydroxy and carboxyl groups. Finally, $N^{im}$-tritylhistidine (**9c**) was prepared in 97% yield with the aid of the $Me_2SiCl_2$, whereas the use of $Me_3SiCl$ produced, after tritylation, $N^{\alpha}$-tritylhistidine (**9b**) and **9c** in almost equimolar amounts.

It is well-known that the trityl moiety as an $\alpha$-amino protecting group in peptide synthesis can be selectively removed, under extremely mild acidic conditions[2], in the presence of other acid-sensitive protecting group.[3] In addition, racemization during the coupling step using *N*-trityl amino acids is expected to be lower in comparison to otherwise N-protected amino acids.

However, the application of the trityl function in peptide synthesis is limited because of the low yields in the preparation[2,4] of *N*-trityl amino acids and their failure, with a few exceptions,[2] to couple with other amino acids in acceptable yields.[2]

While the latter obstacle has been overcome, when dicyclohexylcarbodiimide, mediated with 1-hydroxybenzotriazole, was used as the coupling agent,[5] the facile preparation of *N*-trityl amino acids remains to be a serious problem.

The present synthesis readily provides *N*-trityl amino acids in high yields by an experimentally simple "one-pot" procedure involving tritylation of silylated esters of amino acids followed by mild cleavage of the susceptible oxygen–silicon bond.

## Results and Discussion

Tritylation of amino acids in aqueous systems[4] gives *N*-tritylamino acids in low yields due to partial hydrolysis of the Trt-Cl. Better results can be obtained by using amino acid alkyl esters in aprotic solvents.[2] The *N*-trityl amino acid alkyl esters can be saponified under strong alkaline conditions, which cause racemization, or by tedious and carefully controlled hydrogenolysis in the case of the corresponding benzyl esters.[4]

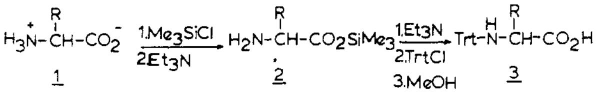
In order to overcome the above difficulties the silyl esters[6] **2**, known to be hydrolyzed under extremely mild conditions,[7] were employed instead. Indeed, a series of compounds **2**, without isolation, were treated with $Et_3N$ and Trt-Cl at room temperature and hydrolyzed with methanol to afford the expected derivatives **3** in high yields and purity (Table I), according to Scheme I. For better characterization compounds **3** were converted into the corresponding crystalline diethylammonium salts (Table I).

Table I. Yields and Physical Data

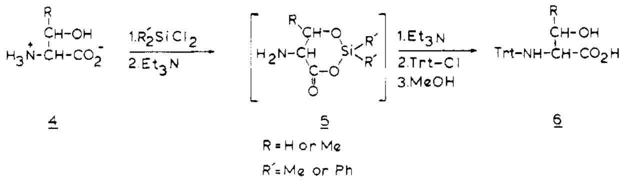
| *N*-trityl amino acid | yield,[a] % | yield,[b] % | mp,[c,d] °C | $[\alpha]^{25}{}_D$,[c-e] deg |
|---|---|---|---|---|
| Gly | 92 | 83 | 132 | |
| Ala | 96 | 81 | 156-157 | −19.0 |
| Val | 94 | 78 | 160 | +6.8 |
| Leu | 93 | 83 | 152-154 | +3.5 |
| Ile | 100 | 88 | 152 | +13.0 |
| Phe | 99 | 92 | 150 | +12.7 |
| Met[f] | 97 | 90 | 153 | +22.0 |
| Pro | 80 | 65 | 164 | −57.8 |
| Asn[g] | 75 | | 172-174[h] | −6.2[h] |

[a] Yield of chromatographically (TLC) pure free acid. [b] Yield of diethylammonium salt. [c] Melting point and $[\alpha]_D$ values refered to the diethylammonium salt. [d] Literature[4] data almost identical. [e] $c$ 5% in MeOH; for the proline analogue $CHCl_3$ was used. [f] Tritylation was run under a nitrogen atmosphere. [g] Silylation of asparagine *monohydrate* was effected with a twofold excess of $Me_3SiCl$ and $Et_3N$. [h] Data for the free acid.

Scheme I



Scheme II



It is worth mentioning that in all examined cases the formation of a small quantity of a nonpolar byproduct was monitored by TLC. This was identified as the trityl ester of the corresponding **3** by comparison with authentic sample.[8] It is plausible to attribute its formation to an electrophilic siloxane splitting of the O–Si bond by Trt-Cl.

The N-tritylation of **4** presents a special problem. Thus, in order to achieve selective N-tritylation in nonaqueous media, we had to protect the carboxyl and the hydroxy

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[1] All optically active amino acids are of the L configuration. Abbreviations follow the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature as found in: *Biochemistry* **1975**, *14*, 449; *Biochem. J.* **1972**, *126*, 773.

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Scheme III

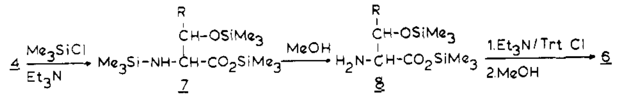


Table II. Yields and Physical Data

| diethylammonium salts of *N*-trityl-hydroxy amino acids | yield, % | mp, °C | $[\alpha]^{25}{}_D$, deg |
|---|---|---|---|
| Ser | 33,[a] 35,[b] 80[c] | 137-139[d] | −33.0[d,e] |
| Thr[f] | 58,[a] 92,[b] 83[c] | 165 | −6.7[g] |
| Hyp[h] | 40,[a] 55,[b] 70[c] | 154-156 | −4.2[e] |

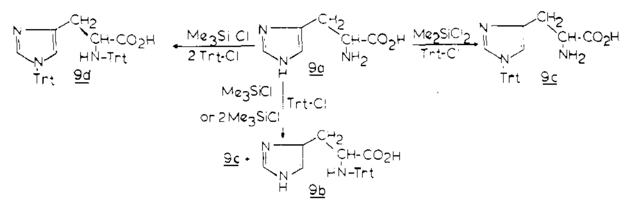
[a] Yield by procedure A. [b] Yield by procedure B. [c] Yield by procedure C. [d] Lit.[14] mp 137-138 °C; $[\alpha]^{25}{}_D$ −29.0 (*c* 1, MeOH). [e] *c* 1%, MeOH. [f] Recrystallized from acetone–petroleum ether. [g] *c* 2%, MeOH. [h] Recrystallized from $CHCl_3$–*n*-hexane: IR 3330, 2800–2200, 1650–1550, 750, 700 cm$^{-1}$. Analytical data were within ±0.3% of the theoretical values.

functions simultaneously. Indeed, we were able to protect both functions either directly by using the bifunctional $Me_2SiCl_2$ or $Ph_2SiCl_2$ reagents or indirectly with the use of an excess of $Me_3SiCl$. In the first case equimolar amounts of **4** and $Me_2SiCl_2$ or $Ph_2SiCl_2$ were refluxed in dichloromethane, and the resulting reaction mixture was treated with $Et_3N$ and Trt-Cl at room temperature. Subsequent hydrolysis with methanol afforded **6** (Scheme II) as the main product. It is assumed that during the silylation reaction the intermediate **5** is formed and is sequentially tritylated and hydrolyzed to afford **6**, according to Scheme II. However, the existence of dimeric or even polymeric silylation intermediates cannot be excluded, the net result being the temporary protection both of the hydroxy and the carboxyl functions at the same time. In the second case the nonisolated pertrimethylsilylated hydroxy amino acid **7**, prepared similarly to reported procedure,[9] was treated with the calculated amount of anhydrous methanol to deprotect selectively the amino function. Subsequent treatment of the resulting intermediate product **8** with $Et_3N$ and Trt-Cl at room temperature, followed by hydrolysis with methanol, gave the expected **6** in good yields (Scheme II), according to Scheme III. The thus prepared compounds **6** were also converted to their corresponding diethylammonium salts (Table II).

In a similar manner, aspartic and glutamic acids were N-tritylated in satisfactory yields (see Experimental Section).

The usefulness of the method which is both simple and practical was demonstrated by the selective synthesis of $N^{im}$-tritylhistidine (**9c**). To our knowledge no other convenient method leading selectively to $N^{im}$ derivatives is known, except the benzylation of the $N^{im}$ moiety of histidine (**9a**) in liquid ammonia.[10] When silylation of **9a** with $Me_3SiCl$ was effected in a 1:1 or 1:2 molar ratio and Trt-Cl was used in an equimolar amount to that of **9a**, both derivatives **9b** and **9c** were isolated almost in equimolar amounts (Scheme IV). In contrast, the silylation of **9a** with $Me_2SiCl_2$ in a 1:1 molar ratio gave, after tritylation with 1 equiv of Trt-Cl and hydrolysis, compound **9c** in 97% yield (Scheme IV). It should be noted that $N^{\alpha}$,$N^{im}$-ditritylhistidine (**9d**) can also be prepared in high yield by tritylation of the trimethylsilyl ester of **9a** with 2 molar equiv of Trt-Cl (Scheme IV).

Scheme IV



Difficulties were met with the basic amino acids lysine and arginine for the selective preparation of trityl derivatives. Experimental work along this line is still in progress.

The reported methodology has been applied in the protection of certain amino acids with the *N*-trifluoroacetyl- or *N*-[(*o*-nitrophenyl)sulfenyl] groups[11] and the preparation of $N^{\alpha}$,$N^{G}$,$N^{G}$-tris(benzyloxycarbonyl)-L-arginine.[12]

## Experimental Section

Capillary melting points were taken on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were determined with a Carl Zeiss precision polarimeter (0.005°). IR spectra were recorded as Nujol mulls on a Perkin-Elmer 457 grating spectrophotometer. Elemental analyses were performed by the Laboratory of Microanalysis of the National Hellenic Research Foundation, Athens, Greece. Amino acids were purchased from the Protein Research Foundation. Histidine was used as the free base. All solvents and chemicals used were dried and purified according to standard procedures.[13] Analytical thin-layer chromatography (TLC) was performed on Riedel-de Haën silica SI $F_{254}$ gel films (0.20-mm layer thickness) precoated on aluminum foils. The solvent systems used were the following: A, 1-butanol–acetic acid–water (4:1:5, organic phase); B, 1-butanol–pyridine–water (20:10:11); C, 1-butanol–acetic acid–pyridine–water (30:6:20:24); D, methanol–chloroform (8:2). Spots were visualized with UV light at 254 nm, with ninhydrin and chlorine-tolidine reagent. Experiments were carried out under anhydrous conditions.

All compounds listed in Tables I and II were synthesized and isolated by using procedures identical with those detailed for the specific examples presented below, unless otherwise stated.

***N*-Tritylleucine.** To a magnetically stirred suspension of leucine (1.31 g, 10 mmol) in 18 mL of $CHCl_3$–MeCN (5:1) was added $Me_3SiCl$ (1.27 mL, 10 mmol) at room temperature. The reaction mixture was heated under reflux for 2 h and then allowed to attain room temperature. Addition of $Et_3N$ (2.79 mL, 20 mmol) at a rate sufficient to maintain gentle reflux was followed by a portion of Trt-Cl (2.79 g, 10 mmol) dissolved in 10 mL of $CHCl_3$. The resulting mixture was stirred for 1 h at room temperature, and then excess of MeOH (50 mmol) was added. Evaporation under reduced pressure left a residue, which was partitioned between $Et_2O$ (50 mL) and a 5% precooled solution of citric acid (50 mL). The organic phase was collected and washed with 1 N NaOH (2 × 20 mL) and water (2 × 10 mL). The combined aqueous layers were washed with 20 mL of $Et_2O$, cooled to 0 °C, and neutralized with glacial AcOH. The precipitated product was extracted with $Et_2O$ (2 × 30 mL), and the combined organic layers were washed twice with water and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave 3.47 g of the desired product as a light yellow foam, which upon dissolution in 20 mL of $Et_2O$ and addition of $Et_2NH$ (1 mL, 10 mmol) afforded the corresponding crystalline diethylammonium salt. Yield, melting point, and $[\alpha]^{25}{}_D$ are presented in Table I.

***N*-Tritylthreonine. Procedure A.** A mixture of threonine (3.57 g, 30 mmol) and $Me_2SiCl_2$ (3.62 mL, 30 mmol) in 40 mL of $CH_2Cl_2$ was refluxed for 2 h with stirring and then allowed to reach

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[14] Sheehan, J. C.; Hasspacher, K.; Yeh, Y. L. *J. Am. Chem. Soc.* **1959**, *81*, 6086.

room temperature. Then $Et_3N$ (12.55 mL, 90 mmol) was added dropwise followed by a solution of Trt-Cl (8.36 g, 30 mmol) in 20 mL of $CH_2Cl_2$, and the resulting suspension was stirred for 5 h at room temperature. Subsequently, excess of MeOH and $Et_3N$ (4.18 mL, 30 mmol) were added, and volatile components were removed by rotary evaporation. The "workup" was done in a similar manner to that described for *N*-tritylleucine with the exception that $Et_2O$ was replaced by EtOAc as the solvent for the final extraction of the product and its conversion to diethylammonium salt. Yield, melting point, and $[\alpha]^{25}{}_D$ values are presented in Table II: IR 3340, 2800–2200, 1640–1550, 750, 700 $cm^{-1}$. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.77; H, 7.80; N, 6.68.

**Procedure B.** A mixture of threonine (3.57 g, 30 mmol) and $Ph_2SiCl_2$ (6.23 mL, 30 mmol) in 40 mL of $CH_2Cl_2$ was refluxed for 2 h and tritylated exactly as in procedure A to afford *N*-tritylthreonine diethylammonium salt (Table II).

**Procedure C.** To a stirred suspension of threonine (4.76 g, 40 mmol) in 70 mL of $CH_2Cl_2$ was added $Me_3SiCl$ (17.75 mL, 140 mmol), and the mixture was refluxed for 20 min. It was then allowed to reach room temperature, treated with a solution of $Et_3N$ (19.51 mL, 140 mmol) in 40 mL of $CH_2Cl_2$, and refluxed for 45 min. The reaction mixture, at 0 °C, was treated dropwise with anhydrous methanol (2.43 mL, 60 mmol) in 10 mL of $CH_2Cl_2$ and allowed to attain room temperature. Then $Et_3N$ (5.58 mL, 40 mmol) was added followed by the addition of Trt-Cl (11.25 g, 40 mmol) in two portions over a 15-min period. Stirring for 5 h and a workup as in procedure A afforded the desired diethylammonium salt (Table II).

***N*-Tritylaspartic Acid Bis(diethylammonium) Salt.** Procedure C was used to convert 2.66 g (20 mmol) of aspartic acid to *N*-tritylaspartic acid bis(diethylammonium) salt. The workup was done as for the leucine analogue, with one modification. Thus, the water solution, at 0 °C, was set to pH 6 with glacial AcOH and extracted with $Et_2O$ (2 × 50 mL). The combined organic layers were washed twice with water and dried ($MgSO_4$). After filtration the solution was treated with $Et_2NH$ (2.07 mL, 20 mmol) and evaporated to dryness. The remaining oily residue was crystallized from $CHCl_3$–petroleum ether to yield 7 g (67%) of product: mp 163 °C; $[\alpha]^{25}{}_D$ −16.7° (*c* 2, MeOH); IR 2800–2100, 1650–1530, 750, 700 $cm^{-1}$. Anal. Calcd for $C_{31}H_{43}N_3O_4$: C, 71.37; H, 8.31; N, 8.05. Found: C, 71.43; H, 8.20; N, 8.25.

***N*-Tritylglutamic Acid Bis(diethylammonium) Salt.** This was prepared as described above. A portion of glutamic acid (1.47 g, 10 mmol) yielded after recrystallization from $CHCl_3$–petroleum ether 2.14 g (40%) of product: mp 141–143 °C; $[\alpha]^{25}{}_D$ + 4.65° (*c* 2, MeOH); IR 2800–2100, 1650–1500, 750, 700 $cm^{-1}$. Anal. Calcd for $C_{32}H_{45}N_3O_4$: C, 71.74; H, 8.47; N, 7.84. Found: C, 71.80; H, 8.50; N, 7.92.

**$N^{im}$-Tritylhistidine (9c).** To a stirred suspension of histidine (1.55 g, 10 mmol) in 15 mL of $CH_2Cl_2$ was added $Me_2SiCl_2$ (1.21 mL, 10 mmol), and the mixture was refluxed for 4 h. Then $Et_3N$ (2.79 mL, 20 mmol) was added, and reflux was continued for additional 15 min. Subsequently, $Et_3N$ (1.39 mL, 10 mmol) followed by a solution of Trt-Cl (2.79 g, 10 mmol) in 10 mL of $CH_2Cl_2$ was added with stirring at room temperature. After 2 h, an excess of MeOH was added and the solvent evaporated in vacuo. Water was added to the residue, and the pH was adjusted to 8–8.5 by dropwise addition of $Et_3N$. The resulting slurry was shaken well with $CHCl_3$, and the insoluble material was filtered off with suction. Further washing with water and $Et_2O$ provided 3.85 g (97%) of **9c** (negative Pauly test); mp 218–220 °C. An analytical sample was prepared by recrystallization from THF–water (1:1): mp 220–222 °C; $[\alpha]^{25}{}_D$ −2.1° [*c* 1, THF–$H_2O$ (1:1)]; TLC $R_{f_A}$ 0.41; $R_{f_B}$ 0.55; $R_{f_D}$ 0.145; IR 3550–2200, 1650–1560, 750, 700 $cm^{-1}$. Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.80; H, 5.70; N, 10.34.

**$N^{\alpha}$,$N^{im}$-Ditritylhistidine (9d).** A stirred suspension of histidine (0.77 g, 5 mmol) and $Me_3SiCl$ (0.63 mL, 5 mmol) in 15 mL of $CH_2Cl_2$ was refluxed for 2 h and cooled, $Et_3N$ (0.65 mL, 5 mmol) was added, and the mixture was again refluxed for 5 min. To the resulting mixture, after it attained room temperature, were added $Et_3N$ (1.39 mL, 10 mmol) and a portion of Trt-Cl (2.79 g, 10 mmol) in 15 mL of $CH_2Cl_2$. After the mixture was stirred for 3 h at room temperature, excess of MeOH was added, and the reaction mixture was concentrated in vacuo. The resulting oily residue was partitioned between $CHCl_3$ and 5% citric acid solution. The chloroform layer was washed with brine and dried ($MgSO_4$). Evaporation of the solvent to a small volume, addition of *n*-hexane, and standing for 4 days at room temperature yielded 2.75 g (86%) of crystalline **9d**: mp 198 °C (lit.[4] mp 198–200 °C); $[\alpha]^{25}{}_D$ + 3.6° (*c* 5, pyridine) [lit.[4] $[\alpha]^{20}{}_D$ + 3.7° (*c* 5, pyridine)].

**Formation of a Mixture of 9b and 9c.** A stirred mixture of histidine (1.55 g, 10 mmol) and $Me_3SiCl$ (1.27 mL, 10 mmol) in 15 mL of $CH_2Cl_2$ was refluxed for 2 h and cooled, and $Et_3N$ (1.39 mL, 10 mmol) was added. After additional reflux for 10 min, the mixture was allowed to attain room temperature and treated with $Et_3N$ (1.39 mL, 10 mmol) and Trt-Cl (2.79 g, 10 mmol) in 15 mL of $CH_2Cl_2$. The resulting mixture was stirred over a period of 3 h at room temperature, and then an excess of MeOH was added. After evaporation to dryness, the oily residue was stirred well in a mixture of 80 mL of $CHCl_3$–water (1:1). The solidified material was filtered off to yield 1.27 g (32%) of **9c**. The collected water phase, after being washed with $Et_2O$, was adjusted to pH 6 by dropwise addition of glacial AcOH. After standing at room temperature for 2 h, the resulting precipitate was collected and recrystallized from ethanol to give 1.07 g (27%) of **9b**: mp 199 °C (lit.[4] mp 202 °C); $[\alpha]^{25}{}_D$ +23° (*c* 3.3, pyridine) [lit.[4] $[\alpha]^{25}{}_D$ +23.7 (*c* 3.3, pyridine)].

In a similar manner to that above, histidine (1.55 g, 10 mmol) was treated sequentially with $Me_3SiCl$ (2.54 mL, 20 mmol), $Et_3N$ (4.18 mL, 30 mmol), and Trt-Cl (2.79 g, 10 mmol) to yield 1.32 g (33%) of **9c** and 1.18 g (30%) of **9b**.

**Registry No.** **1** (R = H), 56-40-6; **1** (R = $CH_3$), 56-41-7; **1** (R = $CH(CH_3)_2$), 72-18-4; **1** (R = $CH_2CH(CH_3)_2$), 61-90-5; **1** (R = $CH(CH_3)CH_2CH_3$), 73-32-5; **1** (R = $CH_2Ph$), 63-91-2; **1** (R = $CH_2CH_2SCH_3$), 63-68-3; **1** (R = $CH_2CONH_2$), 70-47-3; **1** (R = $CH_2CO_2H$), 56-84-8; **1** (R = $CH_2CH_2CO_2H$), 56-86-0; **3** (R = H), 5893-05-0; **3**·EtNHEt (R = H), 3226-93-5; **3** (R = $CH_3$), 80514-64-3; **3**·EtNHEt (R = $CH_3$), 80514-65-4; **3** (R = $CH(CH_3)_2$), 47522-06-5; **3**·EtNHEt (R = $CH(CH_3)_2$), 3485-55-0; **3** (R = $CH_2CH(CH_3)_2$), 32225-38-0; **3**·EtNHEt (R = $CH_2CH(CH_3)_2$), 3226-94-6; **3** (R = $CH(CH_3)CH_2CH_3$), 80514-66-5; **3**·EtNHEt (R = $CH(CH_3)CH_2CH_3$), 80514-67-6; **3** (R = $CH_2Ph$), 47672-25-3; **3**·EtNHEt (R = $CH_2Ph$), 3226-92-4; **3** (R = $CH_2CH_2SCH_3$), 80514-68-7; **3**·EtNHEt (R = $CH_2CH_2SCH_3$), 80514-69-8; **3** (R = $CH_2CONH_2$), 57618-17-4; **3**·EtNHEt (R = $CH_2CONH_2$), 80514-70-1; **3**·2EtNHEt (R = $CH_2CO_2H$), 80514-72-3; **3**·2EtNHEt (R = $CH_2CH_2CO_2H$), 80514-74-5; **4** (R = H), 56-45-1; **4** (R = $CH_3$), 72-19-5; **6** (R = H), 4465-45-6; **6**·EtNHEt (R = H), 80514-75-6; **6** (R = $CH_3$), 80514-76-7; **6**·EtNHEt (R = $CH_3$), 80514-77-8; **9a**, 71-00-1; **9b**, 58995-29-2; **9c**, 35146-32-8; **9d**, 74853-62-6; H-Pro-OH, 147-85-3; $Ph_3C$-Pro-OH, 1911-74-6; $Ph_3C$-Pro-OH·EtNHEt, 80514-78-9; H-Hyp-OH, 51-35-4; $Ph_3C$-Hyp-OH, 80514-79-0; $Ph_3C$-Hyp-OH·EtNHEt, 80514-80-3.