Synthesis of N-Trityl-L-homoserine

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Homoserine, Silylation, Triylation, Methionine Degradation

L-Homoserine was tritylated via its silylated product with Me₂SiCl₂ or Ph₂SiCl₂ in 65-68\% yield. Also N-Trt-L-methionine upon treatment with Mel and degradation of the resulting sulfonium salt with KOH yielded N-Trt-L-homoserine in 75\% yield. Both routes provided N-Trityl-L-homoserine with identical physical data. In contrast to N-alkyloxycarbonyl-L-homoserine derivatives, N-Trt-L-homoserine shows no tendency to spontaneous lactonization.

During the past ten years the chemistry of homoserine [1, 2] and its derivatives became of considerable importance for structure activity studies in pharmacology [3-5] biology [6] plant physiology [7] and peptide synthesis [8-10]. Indeed the conversion of optically active homoserine (1) or methionine (2) into amino-protected derivatives 3 has been the target of several laboratories. Derivatives 3 constitute the key intermediates to further synthetic goals. To date mainly two synthetic approaches have yielded 3. One route utilizes conventional methods of peptide chemistry for the preparation of 3 [8, 11, 12], the other involves replacement of the SCH₃ group of 2 by the hydroxy function [3, 13, 14].

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\begin{align*}
    &\text{CH}_2\text{CH}_2\text{OH} & \text{CH}_2\text{CH}_2\text{SCH}_3 \\
    &\text{H}_2\text{N}-\text{CH}-\text{CO}_2\text{H} & \text{H}_2\text{N}-\text{CH}-\text{CO}_2\text{H} \\
    &\text{1} & \text{2} \\
    &\text{a: L} & \text{b: D,L} \\
    &\text{CH}_2\text{CH}_2\text{OH} & \text{X-NH-CH-\text{CO}_2\text{H}} \\
    &\text{3} & \text{X=\text{Et}, \text{DMC,} Z, \text{Ts}} \\
\end{align*}
\]

It is well experienced that the alkyloxy carbonyl derivatives 3 or the tosyl derivative have a strong tendency for lactonization [2, 12] which is almost spontaneous and autocatalysed by their acidity.

We now wish to report a high yield synthesis of N-Trt-L-homoserine (4a) either by "one pot" triylation of 1a or by transformation of N-Trt-L-methionine (5) into the optically active 4a. The first strategy [15] involves treatment of 1 with the bifunctional protecting agent Me₂SiCl₂ in the presence of Et₃N. Tritylation and desilylation under extremely mild conditions gave 4a as a foam in 65-68\% yield (1). Attempts to crystallize 4a were not successful; the D.L-isomer (4b) however, could be easily crystallized from acetone-petroleum ether. Most important, 1a and its D.L-isomer (4b) can be stored in the dark at room temperature for several months with no sign of lactonization. In contrast, the N-alkyloxycarbonyl derivatives 3 have to be isolated quickly in form of an appropriate salt [9]. Moreover, the preparation of 3 in pure form was not always successful in our hands. Naturally, compound 4 can be converted smoothly to the corresponding diethylamine salt 6 in crystalline form and high yield.

Already we have reported that 5 can be easily prepared in high yield [15]. Treatment of 5 with excess Mel under reflux in ethyl acetate produced the quaternary salt 7 in 75\% yield. Treatment of 7 with two equivalents of KOH in H₂O-THF followed by controlled acidification and addition of diethylamine gave finally the diethylammonium salt 6 in 74\% yield [2].

On the other hand, addition of one equivalent of KOH in H₂O-THF solution of 7 at room temperature provided N-Trt-L-homoserine lactone (8a) in 89\% yield. The same lactone was also prepared from 4a upon treatment with DCC in 81\% yield. Both routes provided 8a with identical melting points and [\alpha]_D values.

Experimental Section

Melting points are uncorrected. IR spectra (Nujol mulls) were determined with a Perkin-Elmer 457 grating spectrometer. ¹H NMR spectra were recorded on a Varian spectrometer (A-60); chemical shifts are reported relative to Me₄Si in CDCl₃.
Elemental analyses were carried out by the Analytical Laboratory of the Hellenic Research Foundation. Thin-layer chromatography (TLC) was performed on Riedel–de Haën silica Si F₂₅₄ gel films (0.20 mm layer thickness) precoated on aluminium foils. The following solvent systems were used:

A, n-BuOH/Pyridine/H₂O (20:10:11);
B, n-BuOH/AcOH/H₂O (4:1:5);
C, CHCl₃/CH₃OH (8:2).

Tritylation and methylation of methionine was run under nitrogen atmosphere. All solvents used were dried immediately before use and were acid free.

**N-Trityl-L-homoserine (4a) from L-Homoserine**

A mixture of L-homoserine (1.19 g, 10 mmol), (1.21 ml, 10 mmol) Me₂SiCl₂ or (2.11 ml, 10 mmol) Ph₂SiCl₂ and (2.8 ml, 20 mmol) Et₃N in 15 ml of CH₂Cl₂ was refluxed for 30 min. After cooling to room temperature a portion of trityl chloride (2.75 g, 10 mmol) and (1.4 ml, 10 mmol) of Et₃N were added and the resulting mixture was stirred for 3 h. Then 5 ml of methanol were added and the reaction mixture was evaporated to dryness in vacuo. To the residue 75 ml of NaOH were added and the slurry was stirred for 30 min and extracted twice with Et₂O. The water layer, after being cooled, was adjusted to pH 6.5–7 by dropwise addition of acetic acid. The resulting precipitate was extracted with Et₂O and the organic layer was washed three times with water, dried (MgSO₄) and concentrated in vacuo to yield 2.35 g (63%) using Me₂SiCl₂ and 2.46 g (68%) using Ph₂SiCl₂. This product was crystallized out as light yellow rhombes.

**N-Trityl-D,L-homoserine (4b) from D,L-Homoserine**

To a solution of 4a (361 mg, 1 mmol) in 15 ml of CH₂Cl₂–Et₂O (2:1), (400 mg, 1.94 mmol) of DCC was added with stirring at room temperature. After 1 h 0.2 ml of H₂O and two drops of AcOH were added and the reaction mixture, after being cooled, was filtered from the precipitated N,N′-dicyclohexylurea. The solvent was evaporated in vacuo and the remaining residue was dissolved in 5 ml of Et₂O–CHCl₃ (4:1). This solution was dried (MgSO₄) for several hours and filtered. Petroleum ether was added with caution until the solution remained clear. After cooling for two days the product 8a crystallized out as light yellow rhombes.

**N-Trityl-L-homoserine Lactone (8a), from 4a and DCC**

To a solution of 4a (301 mg, 1 mmol) in 15 ml of CH₂Cl₂–Et₂O (2:1), (400 mg, 1.94 mmol) of DCC were added with stirring at room temperature. After 1 h 0.2 ml of H₂O and two drops of AcOH were added and the reaction mixture, after being cooled, was filtered from the precipitated N,N′-dicyclohexylurea. To the residue 75 ml of NaOH were added and the slurry was stirred for 30 min and extracted twice with Et₂O. The water layer, after being cooled, was adjusted to pH 6.5–7 by dropwise addition of acetic acid. The resulting precipitate was extracted with Et₂O and the organic layer was washed three times with water, dried (MgSO₄) and concentrated in vacuo to yield 2.35 g (63%) using Me₂SiCl₂ and 2.46 g (68%) using Ph₂SiCl₂. This product was crystallized out as light yellow rhombes.

**N-Trityl-D,L-homoserine (4b) from D,L-Homoserine**

In a manner exactly analogous to the preceding procedure for the preparation of 4a, D,L-homoserine (1.19 g, 10 mmol) yielded 2.4 g (66%) N-Trt-D,L-homoserine as foam. This product was crystallized out from acetone–petroleum ether, m.p. 145 °C; Rf values in solvent systems A, B and C were found to be identical to those of 4a.

Analysis for C₂₃H₂₁NO₃
Calcd C 76.43 H 6.41 N 3.87.  
Found C 76.28 H 6.47 N 3.76.

**N-Trityl-L-homoserine diethylammonium salt (6)**

(See below)
Conversion of 4a to N-Trityl-D,L-homoserine Lactone (8b)

In an identical manner used for 8a compound 4b was converted to lactone 8b in 83% yield; m.p. 161 °C; $R_f$ values identical to those of 8a.

N-Trityl-S-methyl-methionine sulfoxonium iodide (7)

To a solution of N-Trt-L-methionine [15] (150 g, 383 mmol) in 100 ml ethyl acetate 100 ml (1.605 mol) of MeI were added and the mixture was refluxed for 4 h. The thus produced solid material was filtered off and washed well with ethyl acetate, Et$_2$O and petroleum ether. The obtained light yellow powder was dried in vacuo (KOH and P$_2$O$_5$). Yield 153.9 g (75%) of 7; m.p. 160–164 °C. IR indicated some decomposition to 8a (1775 cm$^{-1}$).

Analysis for C$_{25}$H$_{28}$INO$_2$S

Calcd C 56.28 H 5.29 N 2.62,

Found C 56.87 H 5.13 N 2.71.

N-Trityl-L-homoserine lactone (8a) from 7

A suspension of 7 (2.4 g, 4.5 mmol) in 5 ml of THF was treated with 0.25 g (4.5 mmol) KOH dissolved in 1 ml of water. After stirring for 1 h at room temperature the resulting solution was concentrated to dryness in vacuo. The remaining residue was partitioned between 10% citric acid and ethyl acetate. The organic phase was then washed three times with water and concentrated in vacuo.

THF was treated with 0.25 g (4.5 mmol) KOH and the solution became colorless and clear. Addition of 200 ml water precipitated out 4a which was dissolved by addition of 200 ml NaOH and stirring. This solution was then extracted with 2 x 150 ml Et$_2$O and the water layer, after being cooled, was neutralized with 30% acetic acid. The precipitated 4a was extracted with 500 ml Et$_2$O. The organic layer was dried (MgSO$_4$) and concentrated in vacuo to yield 41.4 g (76%) 4a as light yellow foam, with $R_f$ values identical to those found from tritylation of L-homoserine. This product was converted into the corresponding diethylammonium salt by treating 4a in 240 ml mixture acetone-ether (3:7) with 14.6 g (200 mmol) Et$_2$NH. After addition of petroleum ether, standing for 12 h at room temperature and cooling for 6 h at 4 °C crystalline 7 was collected by filtration and recrystallized from acetone-petroleum ether to yield 48 g (96%) of 7, m.p. 141–142 °C; $[a]_D^{29}$ = 16.5 (c 2, CH$_3$OH); $R_f$ 0.37; IR 3530, 1635, 1567, 785, 739, 690 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.05–1.63 (8H, multiplet, C-CH$_3$ and C$_2$-H). 2.86 (4H, quartet, $J$ = 7.1 Hz, and C$_3$-H). 7.13–7.68 (15H, multiplet).

Analysis for C$_{25}$H$_{28}$N$_2$O$_3$

Calcd C 76.42 H 7.88 N 6.44,

Found C 76.53 H 7.75 N 6.52.

References: