The Preparation of 2,2,2-Trichloroethyl Esters of Some L-Amino Acids

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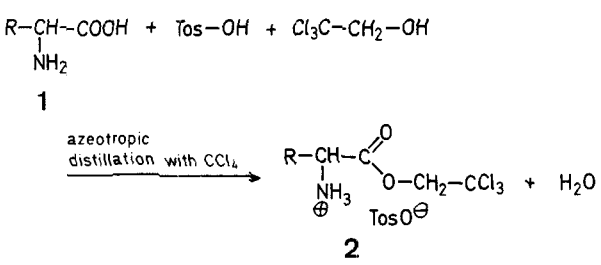
2,2,2-Trichloroethyl esters have been used as carboxy-protecting groups because of their facile removal under mild conditions with zinc dust as a replacement for alkyl esters which are usually removed by base hydrolysis. The D-tartaric acid di-ester has been prepared by azeotropic distillation with toluene and toluenesulfonic acid and also with dicyclohexylcarbodiimide in pyridine[1] as one step in a synthesis of cephalosporin. Marinier et al.[2] have prepared amino acid trichloroethyl esters by conversion of the *N*-benzyloxycarbonyl derivatives to the acid chlorides and reaction of these with trichloroethanol followed by deprotection with hydrogen bromide/acetic acid.

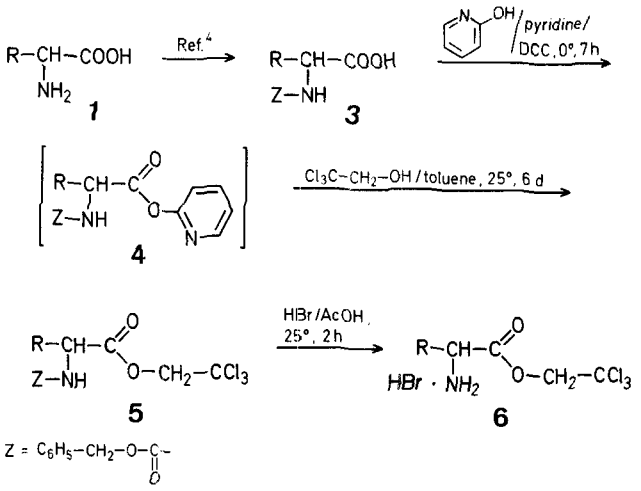
This paper describes alternate procedures for the preparation of amino acid 2,2,2-trichloroethyl esters. A number of amino acid trichloroethyl esters have been obtained as their tosylate salts (**2**) by azeotropic distillation with the amino acid, 2,2,2-trichloroethanol, and *p*-toluenesulfonic acid in carbon tetrachloride as shown in Table 1.



To obtain optimum results, a reflux time of 48 h is required, in general, with a ratio of 8–10 mol of trichloroethanol/mol of amino acid/2–3 mol of *p*-toluenesulfonic acid. Forcing the reaction with refluxing toluene, although satisfactory for glycine, leads to extensive decomposition in the case of methionine and the use of benzene usually gives lower yields with more color formation. The products are readily recrystallized from ethanol or methanol/ether.

The degree of esterification is easily measured by comparison of the integrated proton intensities in the ^{1}H-N.M.R. spectrum in DMSO-d_6. In particular, the $-CH_2-CCl_3$ resonances are well separated from others usually as an AB quartet centered at $\delta \approx 5.0$ ppm (TMS). With glycine (non-asymmetric) and phenylalanine, this absorption appears as a singlet.

In a second procedure, the 2-pyridyl "activated esters"[3] (**4**) are used as intermediates for further reaction with hydroxy compounds. *N*-Benzyloxycarbonylamino acids are reacted with 2-hydroxypyridine to yield the corresponding 2-pyridyl esters which, without isolation, are then reacted with trichloroethanol. The resulting *N*-benzyloxycarbonyl trichloroethyl esters could not be crystallized but were deprotected with hydrogen bromide/acetic acid to yield the crystalline hydrobromides as shown in Table 2. The 2-pyridyl ester method, although tedious and time consuming, may be useful for amino acids which would not survive the long reflux time in the acid-catalyzed esterification.



Several of the amino acid trichloroethyl ester tosylates (**2**) and hydrobromides (**6**) have been condensed with other *N*-protected amino acids, details of which will be described elsewhere.

Specific rotations were measured with a Bendix Automatic Polarimeter, Series 1100 with a cell of 0.2 dm path length. ^{1}H-N.M.R. spectra were measured with a JEOL-PFT-100 spectrometer. 2,2,2-Trichloroethanol and L-amino acids were obtained from Aldrich Chemical Co. Except for *S*-benzylcysteine which was prepared by a well-known method. Melting points are uncorrected capillary melting points.

L-Methionine Trichloroethyl Ester Tosylate; Typical Procedure: A mixture of L-methionine (15 g, 0.101 mol), trichloroethanol (120 g, 0.80 mol), *p*-toluenesulfonic acid monohydrate (38 g, 0.20 mol), and tetrachloromethane (500 ml) is refluxed in a device with a Dean-Stark trap for 48 h. After 4, 8, 24, and 32 h, refluxing is interrupted for removal of water. The reaction solution is then concentrated in vacuo to ~ 150 ml. The product is precipitated by the addition of ether (350 ml) and after refrigeration overnight, the ester is isolated by suction and washed with ether (4 × 75 ml); yield: 42 g with a 70% ester content by N.M.R. analysis. Recrystallization from ethanol (320 ml; overnight at 25°) gives pure L-methionine 2,2,2-trichloroethyl ester tosylate as fibrous needles; yield: 27.3 g (60%); m.p. 176–177°; $[\alpha]_D^{25}$: +1.3° (DMF).

The other esters, except the phenylalanine derivative, may be purified and freed from unreacted amino acid tosylate salt by recrystallization from ethanol. The phenylalanine derivative tends to gel in ethanol, but is satisfactorily recrystallized from methanol/ether. The proline derivative could not be crystallized. Yields are in some cases very sensitive to the proportions of trichloroethanol and acid catalyst. The yield of the alanine derivative decreased from 56 to 35% when the trichloroethanol was decreased from 9 to 5 mol and the toluenesulfonic acid decreased from 3 to 2 mol. Similar behavior was observed with valine.

L-Valine 2,2,2-Trichloroethyl Ester Hydrobromide; Typical Procedure:

L-Valine (11.72 g, 0.100 mol) is converted to the *N*-benzyloxycarbonyl derivative by the procedure of Schwartz et al.[4] in 97% yield. In the following steps, solid reagents are dried in vacuo over phosphorus pentoxide and solvents are dried with molecular sieves.

N-Benzyloxycarbonyl-L-valine obtained from the previous step is combined with 2-hydroxypyridine (10.9 g, 0.114 mol) in pyridine (220 ml). The solution is cooled to 0°, dicyclohexylcarbodiimide (25.4 g, 0.123 mol) is added, and the thick suspension is stirred at 0° for 7 h and stored overnight at 0° under anhydrous conditions. The suspension is then concentrated in vacuo to a solid. Because of the reported instability[3] of *N*-benzyloxycarbonyl 2-pyridyl esters, this material is used directly in the next step. A suspension of the solid in toluene (150 ml) + trichloroethanol (40 ml) is stirred

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Table 1. Amino Acid 2,2,2-Trichloroethyl Ester Tosylates (**2**)

Amino Acid **1**	Yield of **2** [%]	m.p.	$[\alpha]_D^{25}$ (DMF)[a]	Molecular formula[b]	^{1}H-N.M.R. (DMSO-d_6/TMS) δ [ppm]
Glycine[c]	95	149–149.5°		$C_{11}H_{14}Cl_3NO_5S$ (378.7)	2.31 (s, 3H, CH_3); 4.04 (s, 2H, CH_2); 5.02 (s, 2H, $-CH_2-CCl_3$)
L-Alanine	56	160–161°	− 5.7°	$C_{12}H_{16}Cl_3NO_5S$ (392.7)	1.50 (d, 3H, CH_3); 2.30 (s, 3H, CH_3); 4.33 (q, 1H, CH); 5.04 (q, 2H, CH_2); 8.50 (s, 3H, $NH_3^{\oplus}$)
L-Valine	45	199–200°	+ 8.5°	$C_{14}H_{20}Cl_3NO_5S$ (420.7)	1.06 [q, 6H, $CH(CH_3)_2$]; 2.22 (s, 4H, CH + Ar—CH_3); 4.13 (d, 1H, CH—$NH_3^{\oplus}$); 5.04 (q, 2H, $-CH_2-CCl_3$); 8.46 (s, 3H, $NH_3^{\oplus}$)
L-Leucine	51	216–218°	+ 1.9°	$C_{15}H_{22}Cl_3NO_5S$ (434.8)	0.9 [d, 6H, $CH(CH_3)_2$]; 1.70 (m, 3H, CH_2 + CH); 2.30 (s, 3H, CH_3); 4.12 (t, 1H, CH); 5.00 (q, 2H, $-CH_2-CCl_3$); 8.42 (s, 3H, $NH_3^{\oplus}$)
L-Phenylalanine	64	181.5–182°	+ 7.2°	$C_{18}H_{20}Cl_3NO_5S$ (468.8)	2.15 (s, 3H, CH_3); 3.17 (d, 2H, $-CH_2$—Ar); 4.52 (t, 1H, CH); 4.95 (s, 2H, $-CH_2-CCl_3$); 7.00–7.60 (m, 9 H_{arom})
L-Methionine	60	176–177°	+ 1.3°	$C_{14}H_{20}Cl_3NO_5S_2$ (452.8)	2.06 (s, 3H, S—CH_3); 2.30 (s, 3H, Ar—CH_3); 4.36 (t, 1H, CH); 5.07 (q, 2H, $-CH_2-CCl_3$); 8.0–9.0 (3H, $NH_3^{\oplus}$)
S-Methyl-L-cysteine	37	148–149°	− 6.0°	$C_{13}H_{18}Cl_3NO_5S_2$ (438.8)	2.14 (s, 3H, Ar—CH_3); 2.31 (s, 3H, S—CH_3); 3.06 (d, 2H, CH_2); 4.51 (t, 1H, CH); 5.03 (q, 2H, $-CH_2-CCl_3$); 7.14 (d, 2 H_{arom}); 7.55 (d, 2 H_{arom})
S-Benzyl-L-cysteine	54	156–156.5°	−64.7°	$C_{19}H_{22}Cl_3NO_5S_2$ (514.9)	2.32 (s, 3H, Ar—CH_3); 2.95 (d, 2H, S—CH_2); 2.87 (s, 2H, $-CH_2$—Ar); 4.55 (t, 1H, N—CH—CO—); 5.03 (q, 2H, $-CH_2-CCl_3$); 7.00–7.60 (m, 9 H_{arom}); 8.70 (s, 3H, $NH_3^{\oplus}$)

[a] Specific rotations measured in 4–5 % solutions.
[b] Satisfactory microanalyses were obtained for all compounds **2**: C, ±0.26%; H, ±0.17%; Cl, ±0.38%; N, ±0.14%.
[c] 28 h reflux in toluene.

Table 2. Amino Acid 2,2,2-Trichloroethyl Ester Hydrobromides (**6**)

Amino Acid **1**	Yield of **6** [%]	m.p.	$[\alpha]_D$ (DMSO)	Molecular formula	^{1}H-N.M.R. (DMSO-d_6/TMS) δ [ppm]
L-Alanine	58	237° (dec.)[a]	−20.5°[a]	$C_5H_9BrCl_3NO_2$ (301.4)	1.54 (d, 3H, CH_3); 4.37 (q, 1H, CH); 5.06 (q, 2H, $-CH_2-CCl_3$); 8.58 (s, 3H, $NH_3^{\oplus}$)
L-Phenylalanine	62	193°[b]	+ 0.9°[b]	$C_{11}H_{13}BrCl_3NO_2$ (377.5)	3.23 (d, 2H, $-CH_2$—Ar); 4.60 (t, 1H, CH); 5.00 (s, 2H, $-CH_2-CCl_3$); 7.35 (s, 5 H_{arom}); 8.64 (s, 3H, $NH_3^{\oplus}$)
L-Valine	66	182.5–183°[c]	+ 3.3°[c]	$C_7H_{13}BrCl_3NO_2$ (329.5)	1.08 [q, 6H, $CH(CH_3)_2$]; 2.10–2.46 [m, 1H, $CH(CH_3)_2$]; 4.15 (d, CH—N); 5.08 (q, 2H, $-CH_2-CCl_3$); 8.60 (s, 3H, $NH_3^{\oplus}$)

[a] Ref. [2], m.p. 240–243°; $[\alpha]_D$: −1.8° (DMF).
[b] Ref. [2], m.p. 194–196°; $[\alpha]_D$: (0.88 in DMF).
[c] Ref. [2], m.p. 182–183°; $[\alpha]_D$: +3.93 (DMF).

under anhydrous conditions for 6 days at 25° whereupon acetic acid (2 ml) is added and the suspension concentrated in vacuo to dryness. The solids are suspended in ethyl acetate (300 ml), dicyclohexylurea is filtered off, and the filtrate is successively extracted with 1 normal hydrochloric acid (5 × 30 ml), 4 % aqueous sodium hydrogen carbonate (5 × 30 ml), and saturated sodium chloride solution (30 ml). The solution is dried with sodium sulfate and evaporated in vacuo to give an oil; yield: 37.2 g [this oil could not be crystallized]. A portion of the oil (13.9 g) is dissolved in 3 normal hydrogen bromide/acetic acid (75 ml) in a flask protected with a drying tube. The solution is stirred for 2 h at room temperature and then concentrated to a thick crystalline slurry. Ether (125 ml) is added at 0°, the crystalline product (10.6 g, 88 %) isolated by suction, and recrystallized from ethanol/ether (1 : 5); yield of L-valine 2,2,2-trichloroethyl ester hydrobromide: 7.9 g (66%); m.p. 182.5–183°; $[\alpha]_D^{25}$: +3.3° (DMSO).

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