Preparation of Diphenylmethyl Esters and Ethers of Unprotected Amino Acids and β-Hydroxy-α-amino Acids

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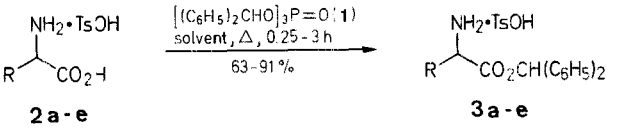
Diphenylmethyl (benzhydryl, Dpm) esters and ethers of amino acids and β-hydroxy-α-amino acids are prepared directly from *N*-unprotected L-α-amino acids using tris(diphenylmethyl) phosphate as alkylating agent. The novel H-Ser(Dpm)-ODpm and H-Thr(Dpm)-ODpm can be hydrolysed to the corresponding ethers H-Ser(Dpm)-OH and H-Thr(Dpm)-OH.

The diphenylmethyl (benzhydryl, Dpm or Dpm) moiety can be cleaved from its ether or ester derivatives by relatively mild hydrogenolytic or acidolytic procedures and consequently has found use, although limited, in the protection of hydroxy and carboxy functions, especially in the field of peptide synthesis.[1,2] The well known alkylating properties of alkyl phosphates have been employed for the preparation of Dpm esters and ethers of hydroxy acids[2] and of *N*-protected α-aminoacids using tris-diphenylmethyl phosphate[2] and diphenyl diphenylmethyl phosphate,[3] while the synthetically more versatile *N*-unprotected Dpm esters have been directly prepared using diphenyldiazomethane.[4]

We have now found that the phosphoric ester tris(diphenylmethyl) phosphate (**1**) can be successfully employed for the *O*-diphenylmethylation of *N*-unprotected amino acids in the form of their tosylate (*p*-toluenesulfonate) salts. Thus, when various amino acids (**2a–e**) were submitted to the reaction with the phosphoric ester **1** in boiling toluene or toluene/chloroform or toluene/tetrachloromethane the esterified amino acid salts (**3a–e**) were easily obtained in good yield.

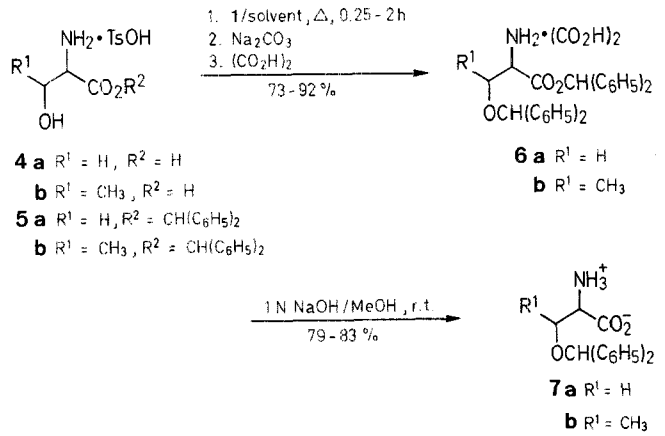


2a–e **3a–e**

2, 3	L-aminoacid	2, 3	L-aminoacid
a	Leucine	**d**	Phenylalanine
b	Valine	**e**	Proline
c	Isoleucine		

3e was isolated and characterized as the hemioxalate salt.

When the tosylate salts of the β-hydroxy-α-amino acids L-serine (**4a**) and L-threonine (**4b**) were similarly treated with reagent **1** simultaneous diphenylmethylation of both hydroxy and carboxy groups occurred and the product in each case was the corresponding ether-ester (**6a, b**) which was conveniently isolated as the hemioxalate salt.



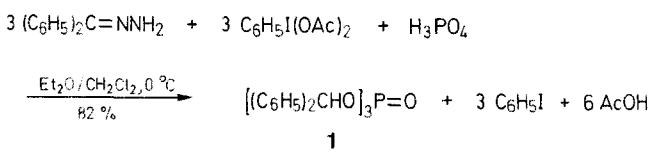
The same products **6a** and **6b** were obtained from the corresponding Dpm esters of the salts[4] **5a** and **5b** by reaction with **1**.

Table. Diphenylmethyl (Dpm) Esters and Ethers **3a–d** and **6a, b** Prepared

Product	Reaction Conditions Time (h), Refluxing Medium	Yield (%)	m.p. (°C)[a] (solvent)	$[\alpha]_D^{18}$[b]	Molecular Formula[c] or m.p. (°C) from Lit.
3a	0.75, toluene	63	204–206 (2-PrOH)	−14.4° (*c* = 2, MeOH)	197–198 °C (CH_3CN)[4]
3b	1, toluene	91	170–172 (2-PrOH)	−20.6° (*c* = 2, MeOH)	170–171 °C (CH_3CN)[4]
3c	0.75, toluene/CCl_4 (6 : 4)	74	167–169	−21.1° (*c* = 2, MeOH)	$C_{26}H_{31}NO_5S$ (419.6)
3d	0.5, toluene	90	203–205 (CH_3CN)	−12.5° (*c* = 2, MeOH)	195–197 °C[4]
6a (from **4a**)	2, toluene/$CHCl_3$[d] (3 : 1)	87	175 (dec)	−4.4° (*c* = 2, DMF)	$C_{31}H_{29}NO_7$ (527.6)
(from **5a**)	0.25, toluene	92	175 (dec)	−4.4° (*c* = 2, DMF)	
6b (from **4b**)	3, toluene/$CHCl_3$[d] (3 : 1)	73	180 (dec)	−4.6° (*c* = 2, DMF)	$C_{32}H_{31}NO_7$ (541.6)
(from **5b**)	0.25, toluene	84	180 (dec)	−4.6° (*c* = 2, DMF)	

[a] Büchi melting point apparatus, not corrected.
[b] Perkin-Elmer Model P-141 polarimeter.
[c] Satisfactory microanalyses obtained: C ±0.49, H ±.14, N ±0.15.
[d] Chloroform used in the alkylation reaction was passed through a column of aluminum oxide (activity I) prior to use.

Phosphate **1** has been prepared from silver phosphate and chlorodiphenylmethane;[5] it is a relatively stable crystalline compound although it gradually deteriorates on storage. We have thus developed two alternative procedures for the convenient and fast preparation of the reagent just prior to use by direct esterification of phosphoric acid either with diphenyldiazomethane or with the stable commercial reagents diacetoxy(phenyl)iodine and benzophenone hydrazone according to the following Scheme:



$$3\,(C_6H_5)_2C{=}NNH_2 + 3\,C_6H_5I(OAc)_2 + H_3PO_4 \xrightarrow[82\,\%]{Et_2O/CH_2Cl_2,\,0\,^\circ C} [(C_6H_5)_2CHO]_3P{=}O + 3\,C_6H_5I + 6\,AcOH$$

1

It is worthy of note that ordinary concentrated phosphoric acid (85%) can be successfully substituted for the anhydrous acid in the above reaction although this results in a somewhat lower yield of **1**.

Our present method has the advantage of affording directly the previously inaccessible derivatives H-Ser(Dpm)-ODpm (**6a**) and H-Thr(Dpm)-ODpm (**6b**) with an unprotected amino group available for coupling with a suitable carboxy component. Thus, compound **6a** prepared by the present method was reacted with Z-Phe-ONp and the completely protected dipeptide Z-Phe-Ser(Dpm)-ODpm (**8**) was obtained in good yield.

Although we were not able to convert the above dipeptide to the desired Z-Phe-Ser(Dpm)-OH by treatment with trifluoroacetic acid/dichloromethane 1:1 at room temperature for 4 h (conditions proposed[2] for the selective carboxy deprotection of Z-Ser(Dpm)-ODpm) we did achieve complete removal of the Dpm protection with 10% trifluoroacetic acid in dichloromethane at room temperature (1 h) in the presence of anisol as scavenger and obtained the *N*-protected dipeptide Z-Phe-Ser-OH (**9**).

The free bases of **6a** and **6b** can be further converted by alkaline hydrolysis of their ester groups into the corresponding hydroxy-protected amino acid zwitterions H-Ser(Dpm)-OH (**7a**) and H-Thr(Dpm)-OH (**7b**) which might serve as hydrogenolysable alternatives to H-Ser(*t*Bu)-OH and H-Thr(*t*Bu)-OH.

The amino acid *p*-toluenesulfonic acid salts **2a–d** and **4a, b** were prepared by known procedures.[4] Compound **2e** was obtained by the same procedure as a glassy solid; $[\alpha]_D^{22} -9.2^\circ$ ($c = 1$, $CHCl_3$).

Tris(diphenylmethyl) Phosphate (1):

Method A: Anhydrous H_3PO_4 (0.20 g, 2 mmol) is dissolved in Et_2O (2 mL), the solution is cooled in an ice bath, and diphenyldiazomethane[6] (an ~ 2 molar solution in CH_2Cl_2) is added dropwise with stirring until evolution of N_2 ceases and the pink color of diphenyldiazomethane persists. The solution is then allowed to warm to room temperature and as the color slowly fades, more diphenyldiazomethane is added to restore the color. The mixture is then evaporated under reduced pressure. The oily residue is treated with Et_2O (5 mL) and the crystalline product is isolated by suction, washed with Et_2O (2 mL) and with petroleum ether (b.p. 40–60 °C; 2 × 5 mL), and dried briefly under vacuum at room temperature; yield: 1.12 g (93%); m.p. 125–127 °C.

This material is satisfactory for the uses described in the present work. Crystallization from dry EtOAc affords the pure product **1**; m.p. 127–128 °C (Lit.[5] m.p. 128–129 °C). When 85% phosphoric acid was used in the above procedure instead of the anhydrous material, reagent **1** was obtained in a yield of 0.92 g (90%); m.p. 124–126 °C.

Method B: To a solution of 85% phosphoric acid (0.47 g, 4 mmol) in Et_2O (12 mL) + CH_2Cl_2 (28 mL), benzophenone hydrazone (3.2 g, 16.4 mmol) and diacetoxy(phenyl)iodine (5.2 g, 16 mmol) are added simultaneously in small portions, with stirring at room temperature, at such rate that the evolution of N_2 is kept under control. After the end of addition, the reddish solution is quickly evaporated under vacuum. The oily residue is treated with petroleum ether (b.p. 40–60 °C; 40 mL). The crystalline product is isolated by suction, washed with petroleum ether (b.p. 40–60 °C; 2 × 20 mL) and Et_2O (2 × 5 mL), dried briefly, and redissolved in CH_2Cl_2 (3 mL). Upon addition of Et_2O (15 mL) and cooling in ice, compound **1** crystallizes out. It is isolated by suction, washed with petroleum ether (b.p. 40–60 °C; 10 mL), and dried briefly under vacuum at room temperature; yield: 1.63 g (68%); m.p. 124–126 °C.

Amino Acid Diphenylmethyl Esters, *p*-Toluenesulfonic Acid Salts (3a–d); General Procedure:

The amino acid *p*-toluenesulfonic acid salt (**2a–d**; 2 mmol) and tris-(diphenylmethyl) phosphate (**1**; 0.6 g, 1 mmol) are suspended in the appropriate solvent system (8 mL) and refluxed with stirring. At the end of reaction time (Table), the homogeneous solution is evaporated under vacuum (**3d** may crystallize at this stage), the oily residue is treated with Et_2O (10 mL), and the precipitated ester (**3a–d**) is isolated by suction, dried in the air, and recrystallized from the appropriate solvent.

Hemioxalate salts of (*O*-Diphenylmethyl)-L-serine Diphenylmethyl Ester (6a) and (*O*-Diphenylmethyl)-L-threonine Diphenylmethyl Ester (6b); General Procedure:

The amino acid *p*-toluenesulfonic acid salt (**4a, b, 5a, b**; 2 mmol) and tris(diphenylmethyl) phosphate (**1**; 1.2 g, 2 mmol) are suspended in the appropriate solvent system and refluxed with stirring for the time indicated (Table). The solution is then poured into 10% aqueous Na_2CO_3 (20 mL) and the resultant mixture is extracted with Et_2O (2 × 15 mL). The combined extracts are washed with H_2O (10 mL), dried (Na_2SO_4), and added to a stirred solution of oxalic acid (0.2 g, 2.2 mmol) in MeOH (2 mL) + Et_2O (10 mL). The precipitated hemioxalate **6a, b** is isolated by suction, washed with Et_2O (2 × 5 mL), and dried.

L-Proline Diphenylmethyl Ester, Hemioxalate Salt (3e):

A solution of L-proline *p*-toluenesulfonic acid salt (**2e**; 0.57 g, 2 mmol) and tris(diphenylmethyl) phosphate (**1**; 0.6 g, 1 mmol) in toluene (8 mL) is heated to boiling for 2 h. The cooled solution is diluted with Et_2O (20 mL), and extracted with 10% aqueous Na_2CO_3 (2 × 5 mL) and with H_2O (5 mL). The organic phase is dried (Na_2SO_4) and added to a stirred solution of oxalic acid (0.2 g, 2.2 mmol) in MeOH (2 mL) + Et_2O (10 mL). The precipitated product **3e** is isolated by suction, washed with Et_2O (5 mL), and recrystallised from MeOH; yield: 0.60 g (81%); m.p. 174 °C dec; $[\alpha]_D^{18} -28.9$ ($c = 1$, DMF).

$C_{20}H_{21}NO_6$	calc.	C 64.68	H 5.70	N 3.77
(371.4)	found	64.29	5.68	3.71

***O*-Diphenylmethyl-L-serine (7a):**

O-Diphenylmethyl-L-serine diphenylmethyl ester hemioxalate salt (**6a**; 0.53 g, 1 mmol) is added to a stirred mixture of methanol (4 mL) and 1 normal aqueous NaOH (4 mL) at room temperature. Stirring is continued for 2 h and the mixture then concentrated under vacuum. The residue is diluted with H_2O (5 mL), washed with Et_2O (2 × 5 mL), and added to 1 normal AcOH (10 mL). The precipitated product **7a** is isolated by suction, washed with H_2O (2 mL), acetone (2 mL), and Et_2O (10 mL), and dried; yield: 0.21 g (79%); m.p. 216 °C (dec); $[\alpha]_D^{22}$ + 2.6° ($c = 0.5$, MeOH).

$C_{16}H_{17}NO_3$	calc.	C 70.83	H 6.31	N 5.15
(271.3)	found	70.54	6.31	5.11

***O*-Diphenylmethyl-L-threonine (7b):**

O-Diphenylmethyl-L-threonine diphenylmethyl ester hemioxalate salt (**6b**; 0.54 g, 1 mmol) is treated as above; yield of **7b**: 0.24 g (83%); m.p. 208 °C (dec); $[\alpha]_D^{22} -24.6^\circ$ ($c = 1$, MeOH).

$C_{17}H_{19}NO_3$	calc.	C 71.55	H 6.71	N 4.90
(285.3)	found	71.17	6.69	4.75

***N*-Benzyloxycarbonyl-L-phenylalanyl-L-(*O*-diphenylmethyl)-L-serine Diphenylmethyl Ester (Z-Phe-Ser(Dpm)-ODpm; 8):**

(O-Diphenylmethyl)-L-serine diphenylmethyl ester hemioxalate salt (**6a**; 1.00 g, 1.9 mmol) is suspended in 10% Na_2CO_3 solution (10 mL). This suspension is extracted with Et_2O (2 × 10 mL) and the combined extracts are dried (Na_2SO_4) and evaporated under vacuum. The oily residue is dissolved in dry THF (10 mL), *N*-benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester[7] (0.80 g, 1.9 mmol) is added, and the solution is allowed to stand overnight. After an additional heating at 50 °C for 1 h, the solution is evaporated under vacuum and the residue is dissolved in EtOAc (30 mL). This solution is washed free of 4-nitrophenol with 10% Na_2CO_3 solution; it is then washed with 1

normal citric acid (10 mL), dried (Na_2SO_4), and evaporated under vacuum. The residue is crystallized once from 95% EtOH and once from EtOAc/petroleum ether (b.p. 40–60°C) to afford the dipeptide **8**: yield: 0.99 g (72%); m.p. 141–143°C; $[\alpha]_D^{20}$ + 9.3° (*c* = 2, $CHCl_3$).

$C_{46}H_{42}N_2O_6$	calc.	C 76.86	H 5.88	N 3.89
(718.8)	found	76.53	5.84	3.87

N-Benzyloxycarbonyl-L-phenylalanyl-L-serine (Z-Phe-Ser-OH; 9):
To a solution of compound **8** (100 mg 0.14 mmol) in CH_2Cl_2 (0.9 mL) is added trifluoroacetic acid (0.1 mL) and two drops of anisole. After 1 h at room temperature, the solution is evaporated under vacuum, the semisolid residue triturated with petroleum ether 40–60°C (3 mL). The residue is isolated by suction, washed with Et_2O (1 mL)), and recrystallized from EtOAc/Et_2O to afford the dipeptide **9**; yield: 35 mg (65%); m.p. 150–152°C; $[\alpha]_D^{20}$ + 1.9° (*c* = 1, DMF); $[\alpha]_D^{20}$ + 9.3° (*c* = 1, acetone) [Lit.[8] m.p. 155–156°C (154 sint); $[\alpha]_D^{21}$ – 2.6° (*c* = 1, DMF)].

For comparison, dipeptide **9** was prepared by alkaline hydrolysis of the known[9,10] Z-Phe-Ser-OCH_3; m.p. 150–152°C (EtOAc/Et_2O); $[\alpha]_D^{20}$ + 2.0° (*c* = 1, DMF); $[\alpha]_D^{20}$ + 10.2° (*c* = 1, acetone).

Received: 28 January 1987; revised: 19 May 1987

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