A Simple Method for the Preparation of Diphenylmethyl Esters of *N*-Protected Amino Acids

Lucas LAPATSANIS*, George MILIAS, Spyridon PARASKEWAS

Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, 13A Navarinou Street, Gr-10680 Athens, Greece

The diphenylmethyl (Dpm) esters can serve as an alternative to *t*-butyl esters and can be cleaved either by acid hydrolysis or by hydrogenolysis. The diphenylmethyl esters of *N*-protected amino acids and especially of serine and threonine are useful synthetic derivatives in peptide synthesis, and several methods for their preparation have been described[1-5]. The alkylating properties of diphenyldiazomethane in aprotic solvents are well known[6] and have been used for the preparation of the diphenylmethyl esters of *N*-protected amino acids[1,2]. We have shown earlier that *N*-protected serine and threonine can also be alkylated by diphenyldiazomethane in ethyl acetate without the alcoholic hydroxy group being affected[7]. The disadvantage of this method is the need to prepare diphenyldiazomethane from benzophenone hydrazone either by oxidation with the common oxidant mercury(II) oxide[8] or with peracetic acid in the presence of a base[9]. In addition, diphenylmethyl esters of *N*-protected penicillin *S*-oxides have been prepared by oxidation of benzophenone hydrazone with peracetic acid in the presence of the protected carboxyl component[3]. During this synthesis, it was established that acetic acid, which was present in ~ 39% (w/w) in the commercial peracetic acid used, could not compete effectively with those carboxylic acids.

In our present work, we describe the preparation of diphenylmethyl esters **3** of *N*-protected amino acids **1** in a one-pot reaction by using suitable carboxylic derivatives in the presence of benzophenone hydrazone **(2)** and phenyliodine(III) diacetate as an oxidising agent.

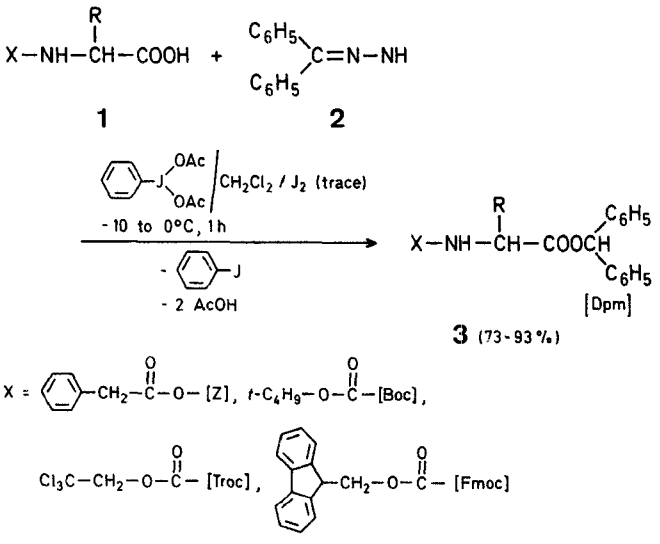


Table. Diphenylmethyl [Dpm] Esters **3a–p** prepared

Diphenylmethyl Ester[a]		Yield [%] found	Yield [%] reported	Reaction Time reported	m.p.[b] [°C]	$[\alpha]^{24D}$ (c 2, $CHCl_3$)[c]	Molecular Formula[d] or Lit. Data
3 a	Z–L–Pro–ODpm	83	61[2]	21 h[2]	96–96.5°	−54.2°	m.p. 96–97°[2]; $[\alpha]_D^{20}$: −54.9° (c 4, $CHCl_3$)[2]
			72[2]	4.5 h[2]			m.p. 93–94°[2]
			87[4]	4.0 h[4]			m.p. 96°[4]; $[\alpha]_D^{28}$: −53.6° (c 2, $CHCl_3$)[4]
			86[e]	1.5 h[e]			m.p. 95–96°[e]; $[\alpha]_D^{24}$: −54.5° (c 2, $CHCl_3$)[e]
3 b	Boc–L–Pro–ODpm	85	83[4]	3.5 h[4]	81–82°	−47.3°	m.p. 81.5–82°[4] $[\alpha]_D^{29}$: −46.7° (c 2, $CHCl_3$)[4]
			87[e]	1.0 h[e]			m.p. 80–81°[e]; $[\alpha]_D^{24}$: −47.7° (c 2, $CHCl_3$)[e]
3 c	Boc–L–Ser–ODpm	84	86[f]	5.0 h[f]	115–117°	− 6.2°	m.p. 115–117°[7]; $[\alpha]_D^{28}$: −6.5° (c 2, $CHCl_3$)[7]
3 d	Troc–D(−)–α–C_6H_5–Gly–ODpm	93	91[3]	1.0 h[3]	176–177°	−61.5°	$C_{24}H_{20}Cl_3NO_4$ (492.8); m.p. 175–177°[3]; $[\alpha]_D^{20}$: −37.0° (c 0.8, $CHCl_3$)[3]
3 e	Dpm–L–Lac–ODpm	84	81[4]	5.0 h[4]	oil[g]	–	oil[4]
3 f	Boc–L–Pro–L–Lac–ODpm	88	87[h]	2.0 h[h]	80–81°	−17.9° (c 1, C_2H_5OAc)	m.p. 80–81°[14]; $[\alpha]_D^{26}$: −18.1° (c 1, C_2H_5OAc)
3 g	Z–L–Ser–ODpm	85	88[h]	3.0 h[h]	124–125°	− 2.3°	m.p. 124–125°[7]; $[\alpha]_D^{28}$: −2.4° (c 2, $CHCl_3$)[7]
3 h	Boc–L–Thr–ODpm	79	80[h]	2.0 h[h]	95–96°	−24.1°	m.p. 94.5–96°[7]; $[\alpha]_D^{28}$: −24.5° (c 2, $CHCl_3$)[7]
3 i	Z–L–Thr–ODpm	81	83[h]	2.0 h[h]	86–87.5°	−21.4°	m.p. 86–87°[7]; $[\alpha]_D^{28}$: −21.0° (c 2, $CHCl_3$)[7]
3 j	Boc–L–Ser($OCH_2C_6H_5$)–ODpm	84	–	–	115–116°	− 8.7°	$C_{28}H_{31}NO_5$ (461.5)
3 k	Fmoc–L–Ser($OCH_2C_6H_5$)–ODpm	83	–	–	139–140°	− 1.7°	$C_{38}H_{33}NO_5$ (583.7)
3 l	Troc–L–Ser($OCH_2C_6H_5$)–ODpm	76[i]	–	–	114–115°	− 3.3°	$C_{26}H_{24}Cl_3NO_5$ (536.8)
3 m	Troc–L–Ser–ODpm	92	–	–	128–129°	− 6.3°	$C_{19}H_{18}Cl_3NO_5$ (446.7)
3 n	Troc–L–Thr–ODpm	83	–	–	65–66°	−21.2°	$C_{20}H_{20}Cl_3NO_5$ (460.7)
3 o	Fmoc–L–Ser–ODpm	77	–	–	99.5–101°	− 3.9°	$C_{31}H_{27}NO_5$ (493.5)
3 p	Fmoc–L–Thr–ODpm	73[i]	–	–	156–157°	−21.3°	$C_{32}H_{29}NO_5$ (507.6)

[a] Normal amino acid abbreviations and Lac = lactic acid

[b] Büchi melting point apparatus, not corrected.

[c] Perkin-Elmer Model P-141 instrument.

[d] Satisfactory microanalyses obtained.

[e] Using diphenyl diphenylmethyl phosphate as alkylating agent[5].

[f] Using diphenyldiazomethane in ethyl acetate[7].

[g] Identified by hydrolysis to the starting Dpm-D-lactic acid[18]; m.p. 93–94°C; $[\alpha]_D^{24}$: −117.8° (c 2, C_2H_5OAc); [Ref.[18], m.p. 93–94°C; $[\alpha]_D^{29}$: −118.2° (c 2, C_2H_5OAc)].

[h] Using diphenyldiazomethane in dichloromethane at room temperature.

[i] After removal of dichloromethane, the solid residue is washed with petroleum ether (40–60°C) and recrystallised either from acetone or ethyl acetate/petroleum ether (40–60°C).

The present method has been tested with benzyloxycarbonyl-, *t*-butyloxycarbonyl-, 2,2,2-trichloroethoxycarbonyl-, and 9-fluorenylmethoxycarbonyl-amino acids without additional oxidisable functional groups (Table).

We would like to point out that in our method, the diphenyldiazomethane may not be the only alkylating agent responsible for the esterification, there are also other intermediates which arise from the oxidation of benzophenone hydrazone. This conclusion has been reached from our efforts to prepare diphenyldiazomethane from benzophenone hydrazone by oxidation with phenyliodine(III) diacetate in the presence of a base (i.e. 1,1,3,3-tetramethylguanidine) at 0 °C following an analogous procedure[9]. In this experiment, only a 16% yield of diphenyldiazomethane was calculated (without isolation) by its absorbance at 523 nm[10].

The use of phenyliodine(III) diacetate instead of peracetic acid in our method has the following advantages. This reagent is a very efficient oxidising agent[11,12], easily prepared[13], commercially available and stable crystalline compound which is also easy to handle. Its use therefore in this method makes the esterification easier in comparison to others which we have reported previously in which tris[diphenylmethyl] phosphate[4] and diphenylmethyl diphenyl phosphate[5] have been used as alkylating agents. These phosphates are sensitive compounds and need to be prepared in advance.

N-Protected Amino Acids 1:

The *N*-protected amino acids were prepared by known procedures: Z-[15], Boc-[16], Troc-[17], Fmoc-[17].

Troc-D(−)-α-aminophenylacetic acid [**1d**, Troc-D(−)-α-phenylglycine] is prepared similarly; yield: 76%; m.p. 143–145 °C; $[\alpha]_D^{24}$: −61.0 °C (*c* 2, $CHCl_3$).

$C_{11}H_{10}Cl_3NO_4$	calc.	C 40.45	H 3.06	N 4.28
(326.6)	found	40.50	3.10	4.22

Diphenylmethyl Esters 3a–p; General Procedure:

The protected amino acid **1** (3 mmol) and benzophenone hydrazone (**2**; 4.5 mmol) are dissolved or suspended in dichloromethane (10 ml, purified over a column containing basic aluminum oxide activity 1 according to Brockmann). After addition of 1% (w/v) iodine in purified dichloromethane (0.4 ml), the solution or suspension is cooled at −10 °C and under continued stirring crystalline phenyliodine(III) diacetate (4.5 mmol) is added during 30–40 min. The solution is stirred for another 20 min while the temperature rises to 0 °C. Dichloromethane is evaporated under reduced pressure at 25–30 °C. The residue, which also contains acetic acid and iodobenzene is dissolved in ethyl acetate (100 ml), washed with water (1 × 10 ml), 5% aqueous sodium hydrogen carbonate solution (3 × 10 ml), water until pH about 6, dried with sodium sulphate, and evaporated to a small volume under reduced pressure. On addition of petroleum ether (40–60 °C) a crystalline product is obtained. All products are homogeneous on T.L.C. [siliga gel, 2:3 ethyl acetate/petroleum ether (60–80 °C) or 9:1 chloroform/methanol].

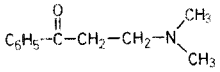
We thank Dr. Mantzos of the Analytical Laboratory of the National Research Foundation for microanalyses.

Received: September 27, 1984
(Revised form: November 15, 1984)

[1] Hiskey, R.G., Adams, Jr., J.B. *J. Am. Chem. Soc.* **1965**, *87*, 3969.
[2] Stelakatos, G.C., Paganou, A., Zervas, L. *J. Chem. Soc.* [C] **1966**, 1191.
[3] Bywood, R., Gallagher, G., Sharma, F.K., Walker, D. *J. Chem. Soc. Perkin Trans. 1* **1975**, 2019.
[4] Lapatsanis, L. *Tetrahedron Let.* **1978**, 4697.
[5] (a) Lapatsanis, L. *Habilitation*, University of Athens, Greece, 1983.
(b) Lapatsanis, L., Milias, G., Cosmatos, A., in *Peptides 1984*, Ragnarsson, V., Ed., Almquist & Wiksell International, Stockholm, 1984, pp. 85–87.
[6] Eistert, B., Regitz, M., Heck, G., Schwall, H. in Houben-Weyl. *Methoden der organischen Chemie*, 4th Edn., Müller, E., Ed., Vol. X/4, Georg Thieme Verlag, Stuttgart, 1968, p. 665.
[7] Lapatsanis, L., in *Peptides 1978*, Siemion, I.Z., Kupryszweski, G., Eds., Wroclaw University Press, Wroclaw, 1979, pp. 105–108.
[8] Miller, J.B. *J. Org. Chem.* **1959**, *24*, 560.
[9] Adamson, J.R., Bywood, R., Eastlick, D.T., Gallagher, G., Walker, D., Wilson, E.M. *J. Chem. Soc. Perkin Trans. 1* **1975**, 2030.
[10] Roberts, J.D., Watanabe, W. *J. Am. Chem. Soc.* **1950**, *72*, 4869.
[11] Review: Varvoglis, A. *Synthesis* **1984**, 709.
[12] α-Hydroxy acids are dehydrogenated by this reagent: Vaidyanathan, K., Venkatasubramani, N. *Indian J. Chem.* **1973**, *11*, 1146.
[13] Pausacker, K.H. *J. Chem. Soc.* **1953**, 107.
[14] Lapatsanis, L., Profilis, Chr., Catsoulacos, P. *J. Chem. Eng. Data* **1980**, *25*, 287.
[15] Bergmann, M., Zervas, L. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1192.
[16] Moroder, L., Hallett, A., Wünsch, E., Keller, O., Wersin, G. *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, *357*, 1651.
[17] Lapatsanis, L., Milias, G., Froussios, K., Kolovos, M. *Synthesis* **1983**, 671.
[18] Lapatsanis, L. *Tetrahedron Lett.* **1978**, 3943.

Errata and Addenda 1985

K. Matsumoto, A. Sera, T. Uchida, *Synthesis* **1985** (1), 1–26:
The structure of the second product in Table 16 (p. 18) should be:

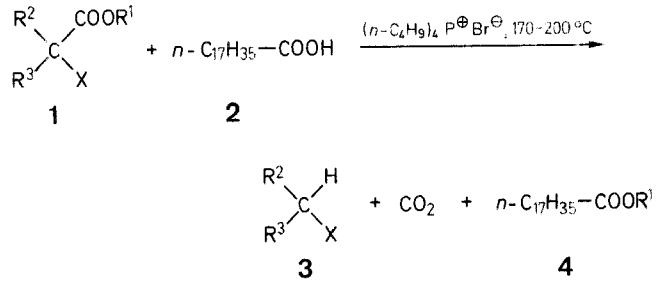


Y. Vo Quang, D. Carniato, L. Vo Quang, F. Le Goffic, *Synthesis* **1985** (1), 62–64:
The substituents R^1 for the compounds **2–4b** and **c** (p. 63) should be $C_6H_5—CH_2—O—CO—$ and $C_2H_5—O—CO—$, respectively.

K. N. Mehrotra, I. S. Singh, J. Roy, *Synthesis* **1985** (1), 81–83:
In the Table (p. 82), the I. R. assignment (C=O) should read (C=C) for all products.

J. M. Aizpurua, C. Palomo, *Synthesis* **1985** (2), 206–207:
The following paragraph should be added:
The procedure described is a specific adaption of Roesky's method [H. W. Roesky, H. H. Gieve, *Z. Naturforsch. [b]* **25**, 773 (1970)].
The authors regret the omission of this acknowledgement in the above communication.

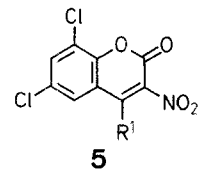
E. V. Dehmlow, E. Kunesch, *Synthesis* **1985** (3), 320–321:
The first formula scheme (p. 320) should be:



X = $COOC_2H_5$, $COOCH_3$, $CO—CH_3$, —CN

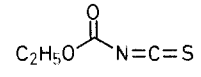
R. J. K. Taylor, *Synthesis* **1985** (4), 364–392:
The heading for the experimental procedure on p. 379 should be:
2-Benzyl-3-*n*-butylcyclopentanone (23)[90]:

A. Cașcaval, *Synthesis* **1985** (4), 428–429:
The structure of product **5** (p. 428) should be:



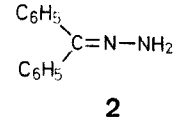
5

Y. Sanemitsu, *Synthesis* **1985** (4), 429–430:
The structure of compound **2** (p. 429) should be:



2

L. Lapatsanis, G. Milias, S. Paraskewas, *Synthesis* **1985** (5), 513–515:
The structure of compound **2** should be:

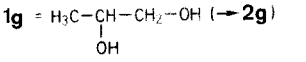


2

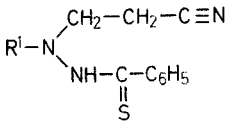
T. Eicher, R. Rohde, *Synthesis* **1985** (6/7), 619–625:
The heading for the last experimental procedure on p. 621 should be:
***endo*/*exo*-6a-Dimethylamino-6-oxo-4,5-diphenyl-2a,6,6a,7-tetrahydro-7*H*-cyclobuta[b]pyrrolizin (*endo*/*exo*-3d):**
The heading for the 3rd experimental procedure on p. 624 (left-hand column) should be:

11a-Dimethylamino-1,2-diphenyl-3-oxo-5,6,11,11a-tetrahydro-3*H*-pyrrolo[2,1-b][3]benzazepin (17):

Xue-Ping Gu, I. Ikeda, M. Okahara, *Synthesis* 1985 (6/7), 649–651:
The structure of product **1g** (p. 650) should be:



I. Yamamoto, K. Fukui, S. Yamamoto, K. Ohta, K. Matsuzaki, *Synthesis* **1985** (6/7), 686–688:
The structure of compounds **3e, f** should be:

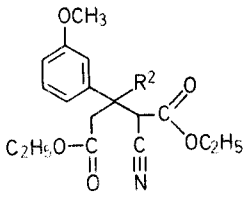


3e,f

I. Monkovic, H. Wong, C. Bachand, *Synthesis* **1985** (8), 770–773:
Reference 9 (p. 772) should be:
[9]Scherer, C. A., Dorschel, C. A., Cook, J. M., Le Quesne, P. W. *J. Org. Chem.* **1972**, *37*, 1083.

A. Cornelis, P. Laszlo, *Synthesis* **1985** (10), 909–918:
Footnotes a and b of Table 10 (p. 916) should be:
[a] 5-Methyl-2-nitro product.
[b] 3-Hydroxy-4-nitro product.

Abstract 7192, *Synthesis* **1985** (11), 1079:
The structure of product **3** should be:



3

D. Moderhack, *Synthesis* **1985** (12), 1083–1096:
The abbreviated name of compound **23** (p. 1087) should read 3-amino-4-imino-2-azetine.

S. M. Fahmy, R. M. Mohareb, *Synthesis* **1985** (12), 1135–1137:
The heading for the last experimental procedure on p. 1136 should be:
3-Amino-N^5-(2-aminophenyl)-2-cyano-2-pentenediamide (15):

F. Fülöp, G. Bernáth, *Synthesis* **1985** (12), 1148–1149:
The heading for the first experimental procedure on p. 1148 should be:
2-Substituted-1,2,3,4,5,6,7,8-octahydroquinazolines (3); General Procedure: