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A NEW METHOD FOR THE PREPARATION OF DIPHENYLMETHYL ESTERS BY USING TRI-DIPHENYLMETHYL PHOSPHATE AS ALKYLATING AGENT

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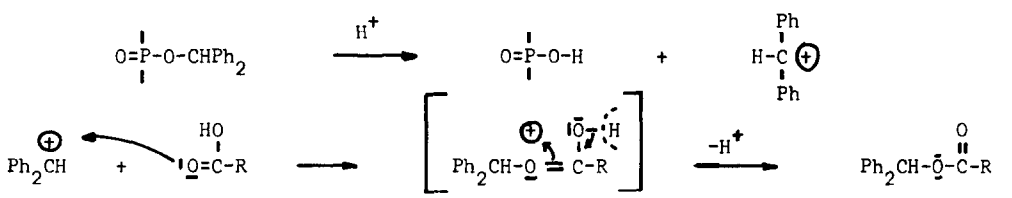
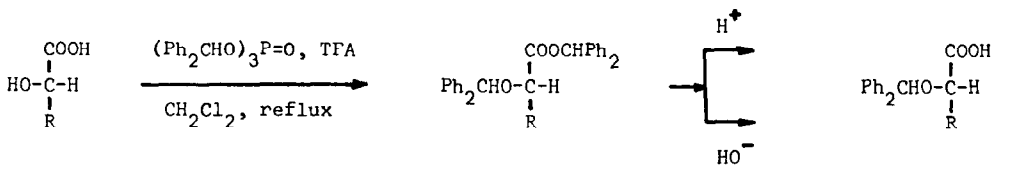
Summary. The diphenylmethyl group is introduced for the protection of the hydroxyl group of α-hydroxy acids.

The diphenylmethyl group has been used for the protection of phosphoric acid[1] and for the protection of the carboxyl group of α-amino acids[2]. The diphenylmethyl esters of N-protected amino acids have been synthesized either by reaction of their carboxyl group with diphenylmethyldiazomethane or by treatment of their silver salts with diphenylchloromethane.
In the present work these esters were found to be easily prepared by refluxing a dichloromethane solution of N-protected amino acids and tri-diphenylmethyl phosphate under the catalytic effect of trifluoroacetic acid. The possible mechanism of this esterification seems to be similar to that recently reported[3] for the etherification of alcohols using the same procedure. There[3] has taken place a nucleophilic attack of the alcoholic hydroxyl group on the diphenylmethyl cation, whereas in this work, we have an attack of the carboxyl group.



When this method is applied to hydroxy acids, an etherification of the hydroxyl group also takes place simultaneously with the esterification of the carboxyl group. Removal of the carboxyl protecting diphenylmethyl group by acidic or alkaline hydrolysis results the O-Diphenylmethyl protected acids in optically pure state.



Some characteristic diphenylmethyl esters prepared according to this procedure are given in the following table.

Table. Diphenylmethyl Esters Prepared from Tri-Diphenylmethyl Phosphate and Organic Acids, α-Protected Amino Acids, O-Alkylated α-Hydroxy Acids and α-Hydroxy Acids[4] Using Trifluoroacetic Acid as Catalyst and Dichloromethane as Solvent[5].

Acid used	Time hours	Diphenylmethyl Esters Yield %	m.p., °C Found	m.p., °C Reported	Yield %	Time hours
1. Benzoic	2	82	87- 87.5	Lit.[6] 87.5- 88	77	6
2. Hippuric	3.5	46	122-123(ace/peth)	" 123 -124	83	24
3. Z-L-Proline	4	87	96(EtoAc/peth)	Lit.[7] 96 - 97	61	21
"			($[\alpha]_D^{28}$=-53.6, c=2,	" $[\alpha]_D^{20}$=-54.9, c=4,chloroform)		
4. Boc-L-Proline	3.5	83	81.5-82, ($[\alpha]_D^{29}$=-46.7, c=2, $CHCl_3$). Lit. no report.			
5. O-DPM-L-Lactic[3]	5	81(oil, tlc not pure, was hydrolyzed to the free acid;m.p.94-95.5				
"		$[\alpha]_D^{30}$=-116.5,c=2,EtoAc, rep.[3] $[\alpha]_D^{29}$=-118.2,c=2 and m.p. 93-94)				
6. L-Lactic	2	71(oil, identified as mentioned above[3]). Lit. no report.				
7. L-Hiv[9]	1.5	74	62- 62.5, ($[\alpha]_{546}^{28}$=-166.5, c=2,EtoAc). Lit. no report[8].			

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References and Notes

Abbreviations: DPM=diphenylmethyl, Z=benzyloxycarbonyl, Boc=t-butyloxycarbonyl, Hiv=α-hydroxy-isovaleric acid, ace=acetone, EtoAc=ethylacetate, peth=petroleum ether.

1. L.Zervas, A.Cosmatos and P.Diamantis, Experientia, 21, 5 (1965).

2. Houben-Weyl, Methoden der Organischen Chemie, Vol.XV, 4th ed., Synthese von Peptiden, E. Wünsch, Ed., Part I, p. 385.

3. L. Lapatsanis, accepted for publication in Tetrahedron Letters.

4. The DPM-esters of the O-DPM-hydroxy acids are obtained. I have found that the DPM-esters can be directly prepared by the action of diphenyldiazomethane on the α-hydroxy acids according to reference 6. As example is given the L-Hiv-ODPM; m.p. 78-79, $[\alpha]_D^{30}$=-30, c=2, EtoAc. The etherification of this ester by tri-DPM-phosphate gave the DPM-L-Hiv-ODPM in a 88% yield.

5. For ester 2 was used a mixture of dichloromethane with ethylacetate and acetone. Equivalent moles of the reactants were used, except with acids 6 and 7, where 1.2 equivalents of the phosphoric ester were used.

6. R.G.Hiskey and J.B.Adams,Jr., J. Amer. Chem. Soc. 87, 3969 (1965).

7. G.C.Stelakatos, A.Paganou and L.Zervas, J. Chem. Soc. (C), 1191 (1966).

8. The ^{1}H-NMR of the DPM-L-Hiv-ODPM was run on a Varian Anaspect (60MHz) in $CDCl_3$ and gave the following results: δ 7.25 unresolved complex multiplet (21H: 1H, $Ph_2\underline{CH}$-O-CO-; 20H, aromatic); δ 5.35 singlet (1H, $Ph_2\underline{CH}$-O-C-); δ 3.8 doublet (1H, Ph_2CHO-$\underline{CH}$-); δ 2.13 septet (1H, $(CH_3)_2\underline{CH}$-); δ 0.9 triplet (6H, $\underline{CH_3}$-C-$\underline{CH_3}$). The acidolysis of this ester gave the DPM-L-Hiv-OH, which was isolated as dicyclohexylamine salt: m.p. 166-166.5, $[\alpha]_D^{30}$=-14, c=2 in methyl alcohol. L-Hydroxy-isovaleric acid was obtained by the catalytic hydrogenation of the O-DPM-L-Hiv-ODPM.

9. G.Losse and G.Bachmann, Chem. Ber., 97, 2671 (1964).

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