Tetrahedron Letters,Vol.25,No.35,pp 3909-3912,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

O-DIPHENYLMETHYLATION OF ALCOHOLS AND CARBOXYLIC ACIDS USING DIPHENYLMETHYL DIPHENYL PHOSPHATE AS ALKYLATING AGENT

Miltiadis Kolovos and Cleanthis Froussios

Department of Chemistry, University of Athens
13A Navarinou St, 10680 Athens, Greece

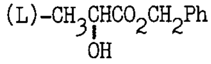
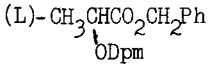
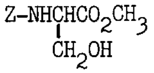
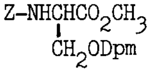
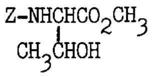
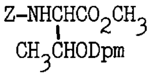
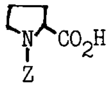
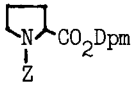
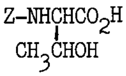
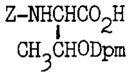
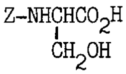
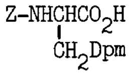
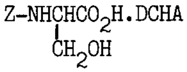
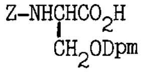
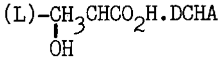
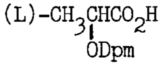
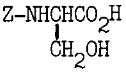
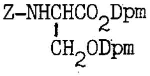
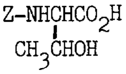
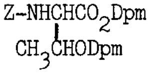
Summary : Diphenylmethyl diphenyl phosphate reacts quickly under mild conditions with various alcohols and carboxylic acids towards diphenylmethyl ethers and esters respectively while hydroxyacids can be selectively alkylated at the alcohol site.

The diphenylmethyl ethers and esters of many alcohols and acids respectively are useful synthetic derivatives due to the easy removal (acidolytic or hydrogenolytic) of the diphenylmethyl moiety and several methods for their preparation have been described in the literature[1]. The alkylating properties of alkyl phosphates at elevated temperature and/or under strong acid catalysis are well known[2] and they have been made use of for the preparation of O-diphenylmethyl derivatives[3].

In our search for an effective yet mild diphenylmethylating reagent we prepared and examined the properties of diphenylmethyl diphenyl phosphate $Ph_2CHOPO(OPh)_2$.

Reaction of diphenylchloromethane with a dichloromethane suspension of silver diphenyl phosphate in the dark affords, after filtration and evaporation of the solvent, the expected phosphoric triester as a white crystalline mass, in very good yield and sufficiently pure to be used as such. This reactive[4] phosphate can be recrystallized from n-C_6H_{14} as fine needles m.p. 74-75°C. It can also be prepared very conveniently by dropwise addition

Table. Diphenylmethylethers and esters prepared from alcohols, acids and hydroxyacids by the action of diphenylmethyl diphenyl phosphate in dichloromethane or acetonitrile solution.

Entry	Compound used	Time	Yield[c]	Product	m.p. °C, $[\alpha]_D^t$	
		min	%		found	(reported)
1.	PhCH_2OH	20[a]	82	PhCH_2ODpm	49-50	(50)[12]
2.	Ph_2CHOH	40[a]	95	Ph_2CHODpm	105-107	(107)[12]
3.	 $\text{(L)-CH}_3\underset{\text{OH}}{\text{CH}}\text{CO}_2\text{CH}_2\text{Ph}$	40[b]	81	 $\text{(L)-CH}_3\underset{\text{ODpm}}{\text{CH}}\text{CO}_2\text{CH}_2\text{Ph}$	oil[13]	
4.	 $\text{Z-NH}\underset{\text{CH}_2\text{OH}}{\text{CH}}\text{CO}_2\text{CH}_3$	30[a]	88	 $\text{Z-NH}\underset{\text{CH}_2\text{ODpm}}{\text{CH}}\text{CO}_2\text{CH}_3$	86-87 $[\alpha]_D^{23}$ +2.05° C2 AcOEt	(86-87)[3c] ($[\alpha]_D^{28}$ +2.1° C2 AcOEt)
5.	 $\text{Z-NH}\underset{\text{CH}_3\text{CHOH}}{\text{CH}}\text{CO}_2\text{CH}_3$	40[a]	80	 $\text{Z-NH}\underset{\text{CH}_3\text{CHODpm}}{\text{CH}}\text{CO}_2\text{CH}_3$	75-76 $[\alpha]_D^{23}$ -36.1° C1 AcOEt	(75-76)[3c] ($[\alpha]_D^{28}$ -35° C1 AcOEt)
6.	PhCO_2H	40[a]	86	PhCO_2Dpm	85-86	(87-88)[14]
7.	$\text{CF}_3\text{CO}_2\text{H}$	1[a]	76	$\text{CF}_3\text{CO}_2\text{Dpm}$	oil[15]	
8.	$\text{PhCONHCH}_2\text{CO}_2\text{H}$	180[a]	92	$\text{PhCONHCH}_2\text{CO}_2\text{Dpm}$	121-123	(122-123)[1c]
9.		90[b]	90		95-96 $[\alpha]_D^{23}$ -55.6° C2 CHCl$_3$	(96-97)[1a] ($[\alpha]_D^{20}$ -54.9° C2 CHCl$_3$)
10.	 $\text{Z-NH}\underset{\text{CH}_3\text{CHOH}}{\text{CH}}\text{CO}_2\text{H}$	30[b]	62	 $\text{Z-NH}\underset{\text{CH}_3\text{CHODpm}}{\text{CH}}\text{CO}_2\text{H}$	CHA salt[e]: 182-183 $[\alpha]_D^{23}$+5.07° C2 CH$_3$OH	
11.	 $\text{Z-NH}\underset{\text{CH}_2\text{OH}}{\text{CH}}\text{CO}_2\text{H}$	30[b]	67	 $\text{Z-NH}\underset{\text{CH}_2\text{Dpm}}{\text{CH}}\text{CO}_2\text{H}$	DCHA salt: 158-159 $[\alpha]_D^{23}$+19.3° C2 CH$_3$OH	(158-160)[3c]
12.	 $\text{Z-NH}\underset{\text{CH}_2\text{OH}}{\text{CH}}\text{CO}_2\text{H.DCHA}$	360[b]	56	 $\text{Z-NH}\underset{\text{CH}_2\text{ODpm}}{\text{CH}}\text{CO}_2\text{H}$	DCHA salt: 159-160 $[\alpha]_D^{23}$+19.25° C2 CH$_3$OH)	(158-160)[3c]
13.	 $\text{(L)-}\underset{\text{OH}}{\text{CH}_3}\text{CHCO}_2\text{H.DCHA}$	360[b]	51	 $\text{(L)-CH}_3\underset{\text{ODpm}}{\text{CH}}\text{CO}_2\text{H}$	94 $[\alpha]_D^{25}$ -119.1° C2 AcOEt	(93-94)[3a] ($[\alpha]_D^{29}$ -118.2° C2 AcOEt)
14.	 $\text{Z-NH}\underset{\text{CH}_2\text{OH}}{\text{CH}}\text{CO}_2\text{H}$	10[d]	90	 $\text{Z-NH}\underset{\text{CH}_2\text{ODpm}}{\text{CH}}\text{CO}_2\text{Dpm}$	117-118 $[\alpha]_D^{25}$ -5.35° C2 CHCl$_3$	(117-118)[3c] ($[\alpha]_D^{28}$ -5.38° C2 CHCl$_3$)
15.	 $\text{Z-NH}\underset{\text{CH}_3\text{CHOH}}{\text{CH}}\text{CO}_2\text{H}$	10[d]	88	 $\text{Z-NH}\underset{\text{CH}_3\text{CHODpm}}{\text{CH}}\text{CO}_2\text{Dpm}$	86-87 $[\alpha]_D^{25}$ -9.1° C1 CHCl$_3$	(87-88)[3c] ($[\alpha]_D^{28}$ -8.9° C1 CHCl$_3$)

a: in dichloromethane; b: in acetonitrile; c: yields refer to isolated products;
d: a small amount of trifluoroacetic acid was added to the reaction mixture (approximately 1 µl/ml); e: satisfactory analysis was obtained for entry 10 product.

of a petroleum ether 40 -60° solution of diphenyldiazomethane[5] in a dichloromethane solution of anhydrous diphenylphosphoric acid (m.p. 51 -52°C) until the colour of the diazo compound persists, followed by evaporation of solvents and decantation of the crystalline residue from petroleum ether. The ^1H NMR spectrum ($CDCl_3$) shows the aromatic proton signals as an unresolved multiplet and a 1H doublet[6] $J_{p-H} = 7$ Hz at δ 6.15 for $>C\underline{H}-O-P$.

We have found that this phosphoric ester quickly[7] reacts in equivalent amounts with various alcohols (Table, entries 1-5) and carboxylic acids (Table, entries 6-9), in an inert organic solvent[8] at room temperature, in the absence of any added[3] strong acid as catalyst, producing the corresponding O-alkylated products (Figure 1).

Under those conditions alcohols seemed to react faster than carboxylic acids (see Table) and subsequently some α- and β-hydroxyacids could be selectively alkylated at the alcohol hydroxyl and the corresponding diphenylmethyl ethers[9,10] isolated in reasonable yields thus allowing for their convenient one-step synthesis (Table, entries 10-11). Employed on the DCHA salts of hydroxyacids (Table, entries 12-13) the reaction still affords the ether-acids, although at a considerably slower rate.

The reaction most likely involves nucleophilic attack of a hydroxyl or carboxyl group on the diphenylmethyl cation generated from the phosphate under proton catalysis[11] (Figure 1), and optically active compounds are converted to optically pure O-alkylated derivatives.

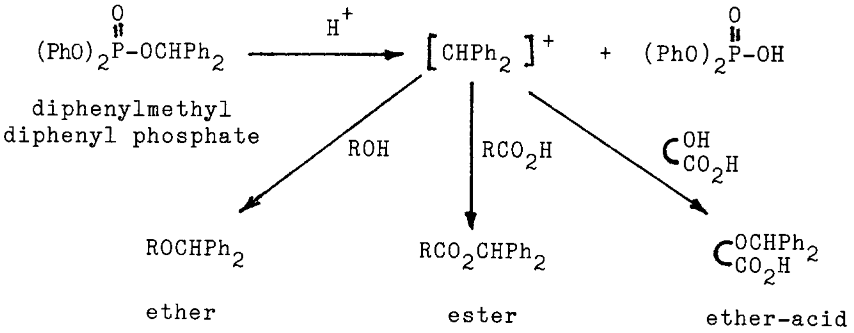


Figure 1

We found that small quantities of strong acids (like p-toluenesulfonic or trifluoroacetic) greatly enhance the rate of the reaction with both alcohols and acids, while with hydroxyacids selective etherification is no longer observed and the etherified-esterified product is obtained instead (Table, entries 14-15).

REFERENCES AND NOTES

Abbreviations : DCHA = Dicyclohexylamine, CHA = Cyclohexylamine, Z = Benzyloxycarbonyl, Dpm = Diphenylmethyl.

1. a- G.C. Stelakatos, A. Paganou and L. Zervas, J. Chem. Soc. (c), 1191 (1966).
   b- A. Aboderin, R. Delpierre and S. Fruton, J. Amer. Chem. Soc., 87, 5470 (1965).
   c- R.G. Hiskey and J.B. Adams, Jr, J. Amer. Chem. Soc., 87, 3969 (1965).
2. a- G.O. Dudek and F.H. Westheimer, J. Amer. Chem. Soc., 81, 2641 (1959).
   b- G.N. Kenner and J. Mather, J. Chem. Soc., 3524 (1956).
   c- L. Zervas, A. Cosmatos and P. Diamantis, Experientia, 21, 5 (1965).
3. L. Lapatsanis, a- This Journal, 3943-3944 (1978), b- This Journal, 4697-4698 (1978), c- Proceedings of the 15th European Peptide Symposium, Gdańsk, Poland, 1978, Ed. by I.Z. Siemion and G. Kupryszewski, p. 105.
4. The recrystallized product protected from atmospheric humidity is stable at room temperature for several hours. Exposed to water it is rapidly converted to a mixture of diphenylphosphoric acid, diphenylmethanol and bis-diphenylmethyl ether.
5. J.B. Miller, J. Org. Chem., 24, 560 (1959).
6. The ^{1}H NMR ($CDCl_3$) spectrum of tri-diphenylmethyl phosphate^{2c} shows the >CH-O-P at δ 6.17, doublet, J_{P-H} = 7 Hz.
7. The progress of the reactions was followed by silica gel TLC.
8. Dry dichloromethane or dry acetonitrile were used as solvents.
9. Small amounts of esterified and etherified-esterified product were observed on TLC and identified by comparison with authentic materials.
10. 100% molar excess of the phosphoric ester and reaction time of 6 hours did not increase appreciably the quantity of ether-ester.
11. The phosphoric ester is itself converted during the reaction to diphenylphosphoric acid, a moderately strong acid which can further act as a proton donor.
12. E.F. Pratt and J.D. Draper, J. Amer. Chem. Soc., 71, 2846 (1949).
13. The benzyl ester was identified by hydrolysis to the free acid: m.p. 93-94°C, $[\alpha]^{25}_{D}$ -119.5° C2 AcOEt (m.p. 93-94°C, $[\alpha]^{29}_{D}$ -118.2 C2 AcOEt)^{3a}.
14. H. Staudinger, Eug. Anthes and F. Phenninger, Ber., 49, 1932 (1916).
15. The labile ester was identified by conversion to trifluoroacetamide with anhydrous ammonia gas in benzene solution: Leaflets m.p. 74-75°C from $CHCl_3$ (75.5°C)^{16}.
16. H. Gilman and R.G. Jones, J. Amer. Chem. Soc., 65, 1459 (1943).

(Received in UK 7 June 1984)