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PHOSPHINAMIDES - A NEW CLASS OF AMINO PROTECTING GROUPS IN PEPTIDE CHEMISTRY

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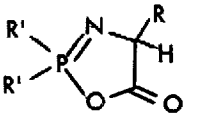
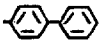
Both classical and solid phase methods of peptide synthesis make extensive use of acid labile urethane protecting groups for amino functions e.g. Boc[1] (1), Bpoc[2] (2), which generate relatively stable carbonium ions on acidolytic cleavage. These highly reactive species may modify the side chain functionaility of tryptophan, tyrosine, methionine and cysteine, thus necessitating the presence of *scavengers, e.g. anisole, thiols, during deprotection.* The concluding stage in the synthesis of a small protein could involve the fission of ca. 50 such protecting groups. It would, therefore, be useful to develop another series of protecting groups having similar selectivity to those exploited so effectively in the synthesis of insulin[3] by the CIBA-GEIGY group, but which would not require the trapping of highly reactive intermediates.

$R'.CMe_2.O.CO.NH.CHR.COOH$ $R'_2PO.NH.CHR.COOH$



1 R' = -Me 3 R' = Ph

2 R' =  4 R' = Ph

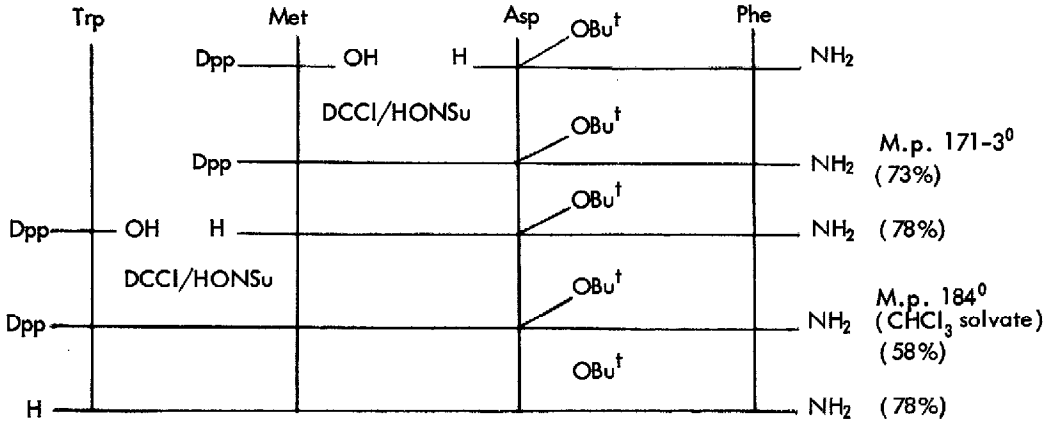
Our approach to this problem has been to utilise the remarkable acid lability of phosphinamides e.g., $Ph_2PO.NH_2$, which is considered[4,5] to involve initial N-protonation followed by solvent attack via an A1 or A2 mechanism, depending on the nature of the substrates. X-ray studies of $Ph_2PO.NMe_2$ [6] and $Ph_2PO.NMe.CH_2.CH_2.Ph$ [7] show the nitrogen geometry to be a flattened tetrahedron in which the lone pair on N is almost in the N-P-O plane, whereas in the amide bond the lone pair of electrons on the trigonal N is orthogonal to the N-C-O plane. This stereoelectronic difference must be reflected in the relative rates of acid hydrolysis of phosphinamides and amides.

$Ph_2PO.Cl$ is readily available[4] and was selected as the reagent for initial studies of the synthesis and properties of Dpp amino acid derivative (3). The 2,4,5-trichlorophenyl ester, $Ph_2PO.OTcp$ m.p. 115-

TABLE 1

Dpp derivative (crystallisation solvent)		M.p.	$[\alpha]_D^{25}$
Dpp-Gly-OMe	EtOH/H_2O	118°	
Dpp-Gly-OH	EtOAc/cyclohexane	132°	
Dpp-Ala-OMe	EtOAc/cyclohexane	114-5°	+12.2°
Dpp-Ala-OH	EtOAc/cyclohexane	152-3°	-21.4°
Dpp-Val-OMe	EtOAc/cyclohexane	119-124°	-32.7°
Dpp-Val-OH	Et_2O	103°	-15.2°
Dpp-Leu-OBzl	Et_2O/petrol (40-60)	102°	-27.8°
Dpp-Leu-OH	EtOAc/hexane	131-4°	-20.0°
Dpp-Ile-OBzl	EtOAc/cyclohexane	105-8°	-30.7°
Dpp-Ile-OH	EtOAc/hexane	113-4°	- 7.2°
$(Dpp)_2$Lys-OMe	EtOAc/Et_2O	152-3°	+ 5.8°
Dpp-Lys(Z)-OH	(DCHA salt)	153-4°	+13.3°
Dpp-Met-OMe	Et_2O	93-4°	-35.8°
Dpp-Met-OH	EtOAc/petrol (40-60)	141-2°	-14.0°
Dpp-Trp-OMe	EtOAc	147-9°	-48.5°
Dpp-Trp-OH	EtOAc/petrol (40-60)	165-9°	-60.5°
Dpp-Pro-OBzl	Et_2O/hexane	81-2°	-43.3°
Dpp-Pro-OH	MeOH/Et_2O	170-3°	-16.2°
Dpp-Phe-OBzl	EtOAc/petrol (40-60)	158°	-46.1°
Dpp-Phe-OH	MeOH/EtOAc/petrol (40-60)	133°	-40.1°

SCHEME 1



117° proved to be less useful. Although it has not proved feasible to prepare (3) directly, these compounds[8] (Table 1) may be prepared from the corresponding methyl or benzyl esters using $Ph_2PO.Cl$/N-methylmorpholine (NMM) followed by mild alkaline hydrolysis or hydrogenolysis, respectively. The diphenylphosphinamide (Dpp) group is also stable during hydrazinolysis of esters.

Investigation of cleavage conditions (room temperature) for $Ph_2PO.NH.CH_2CH_2Ph$, m.p. 140-142°, showed incomplete cleavage in 80% HOAc (3 days) whereas HOAc/HCOOH/H_2O (7/1/2) gave complete cleavage (24 hr) indicating that Dpp is slightly more acid labile than Boc.[2] 80% TFA, 0.4M HCl in 90% trifluoroethanol, 2 eq. p-toluenesulphonic acid in H_2O/MeOH all proved to be satisfactory deprotection conditions for peptide derivatives; the choice depending on ease of separation of the product from Ph_2POOH or $Ph_2PO.OR$. Dpp-Gly-Gly-OBu^t, m.p. 88-90°, was synthesised (DCCI) and found to undergo selective cleavage of the Dpp group in 15% TFA/$CDCl_3$ using NMR as the probe. Dpp-Lys(Z)-Gly-OMe, m.p. 112-113°, was prepared (pivalic mixed anhydride) and deprotection [2N HCl in dioxan/H_2O (2/1) for 2.5 hr] was found to be selective for Dpp in the presence of ε-Z protection.[9]

Dpp-Ile-Gly-OBu^t, m.p. 92-94°, was synthesised (DCCI) and was shown to contain no allo-Ile by amino acid analysis suggesting that the Dpp group was comparable to urethane protection in preserving the chirality of the derivative during activation. As a further test, Dpp-Leu-Ala-OBzl was prepared by the following methods: (i) pivalic mixed anhydride, (ii) DCCI, (iii) DCCI/HONSu (NMM as base) and the Leu-Ala produced after deprotection was analysed according to Manning and Moore.[10] Less than 1% racemisation was found for Dpp-Leu-OH and Z-Leu-OH in parallel experiments. Thus Dpp amino acid derivatives (3) do not have the disadvantage of the analogous benzoyl derivatives, PhCO.NH.CHR.COOH, which suffer racemisation during activation due to formation of an oxazolone intermediate. From the stereoelectronic considerations mentioned earlier the enolic form of the P-analogue of an oxazolone (4) would not be expected to enjoy stabilisation through π-delocalisation.

In order to test the compatability of Dpp cleavage with Trp and Met residues, in the absence of scavengers, it was decided to synthesis the partially protected C-terminal tetrapeptide of gastrin (Scheme 1). Dpp-Met-Asp(OBu^t)-Phe.OPh, m.p. 168-9°, and Dpp-Trp-Met-Asp(OBu^t)-Phe-OPh, m.p. 188-190° were also synthesised successfully by the same route whereas difficulty had been encountered previously in analogues having Bpoc or Nps-N$_{in}$ protection. Cleavage of N$_{in}$-Dpp protection in the presence of

-Asp(OBu^t)- requires careful experimentation and work is now in progress to develop a range of phosphinamide protecting groups of varying degrees of acid lability.

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