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ACTIVATION OF CARBOXYLIC ACIDS AS DIPHENYLPHOSPHINIC MIXED ANHYDRIDES: APPLICATION TO PEPTIDE CHEMISTRY

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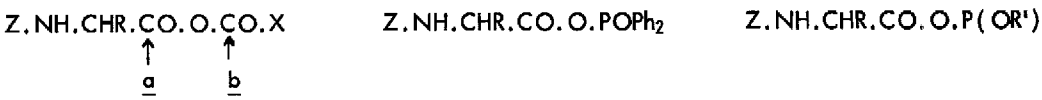
Mixed anhydrides of the type (1) are widely used[1] in peptide chemistry to form an amide bond, but suffer from a tendency towards disproportionation[2] to symmetrical anhydrides. This problem is generally overcome by using low temperatures in the reaction, however another problem is the regiospecificity of nucleophilic attack which may occur by path a (desired) or b (source of impurities and decrease in yield).



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We sought, therefore, to devise a class of mixed anhydrides which would be stable towards disproportionation, react with nucleophiles specifically by path a and also, if possible, be isolable crystalline compounds. Our initial studies have used $Ph_2PO.Cl$ as a readily available[3] reagent for preparation of the mixed anhydride (2). Analogous anhydrides (3) derived from O,O-dialkyl and O,O-diarylphosphoric acids have previously been employed for this purpose[1,4] but have not received general application. The recently introduced[5] reagent $(PhO)_2PO.N_3$ may be considered to proceed via 3, R = Ph) to the acid azide.

Carboxylic-phosphinic anhydrides have not received much study, however some information concerning the cyclic system (4) is available.[6] There is an important change in regiospecificity depending on the nature of the nucleophile in that aminolysis follows path a whereas alcoholysis occurs by attack at P.

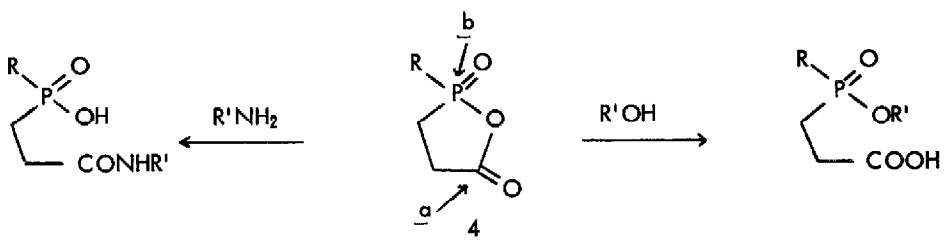

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Table 1

Peptide (↑ indicates point of coupling)	m.p.	$[\alpha]_D^{25}$	Yield %
Z-Orn(Adoc)-Gly-OPh	109-110°	-12.1°	60
Z-Val-Orn(Adoc)-Gly-OPh	138-139°	- 9.1°	64
Z-Tyr(Bu^t)-Orn(Adoc)-Gly-OPh	101°	-11.8°	81
Z-Ser(Bu^t)-Leu-Gly-OPh	99°	-12.6°	73
Z-Tyr(Bu^t)-Ser(Bu^t)-Leu-Gly-OPh	194-197°	-13.2°	55
Bpoc-Leu-Ala-Gly-OPh	92-95°	-29.1°	63
Z-Ser(Bu^t)-Ala-OPh	115-116°	-28.9°	75
Z-Val-Ser(Bu^t)-Ala-OPh	164-165°	-23.1°	72
Bpoc-Pro-Trp-Leu-OPh	83-85°	-42.5°	88
Z-Asn-Gly-OPh	172-174°	- 6.8°	21

These results give general support to our thesis concerning anhydrides (2) with respect to regiospecificity. Further indication of some degree of thermal stability was obtained from the properties of $CH_3CO.O.POPh_2$ (prepared from $Ph_2PO.OH/Ac_2O$ at 60^0C).[7] As a test of the relative merits of pivalic and diphenylphosphinic (Dpp) mixed anhydrides, it was decided to form (5) which would give a measure of tendency towards nucleophilic attack by path b. In the event (5) m.p. 131-133° was prepared[8] ($Ph_2POONa/Bu^tCO.Cl/THF$, 2 hr) and found to react with β-phenethylamine to give (6), m.p. 84-5° exclusively.

$Bu^t.CO.O.POPh_2$ (5)

$Bu^t.CO.NH.CH_2.CH_2.Ph$ (6)

In an attempt to assess the relative reactivity of anhydrides (1) and (2) the Izumiya test sequence[9] (Z-Gly-Ala-OH + H-Leu-OBzl) was applied using pivalic and Dpp mixed anhydrides. Since this test is a measure of racemisation derived from an oxazolone intermediate it gives a measure of the electron density of the terminal peptide carbonyl group. The degrees of racemisation found for Dpp (5.7%) and pivalic (2.6%) mixed anhydrides indicate a greater activation in (2) compared with (1).

Table 1 illustrates the use of Dpp-mixed anhydrides in stepwise peptide synthesis. Initial formation of the mixed anhydride is effected at -20° in CH_2Cl_2 or EtOAc using N-methylmorpholine as base. After 20 min the amino component is added and the reaction mixture allowed to reach room temperature. The yields of crystalline products and ease of purification were generally superior to parallel reactions using anhydrides (1) except in the case of Z-Asn-OH where the pivalic mixed anhydride method is the method of choice. There is an added advantage in large scale reactions in that the $Ph_2PO.OH$ by-product may be isolated, allowing subsequent recycling to the reagent $Ph_2PO.Cl$.

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