Tetrahedron Letters Vol.21, pp2705-2708 0040-4039/80/0708-2705$02.00/0
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REACTION OF CARBOXYLATE SALTS WITH CYCLIC PHOSPHORAMIDATES : AMIDE BOND FORMATION BY PRIOR AMINE CAPTURE

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Abstract : Tri- or tetraalkyl-ammonium carboxylates react with 2-alkylamino-2-oxo-1,3,2-benzodioxaphospholes at 25°C to give amides or peptides, probably by a nucleophilic attack on phosphorous followed by a cascade of intramolecular acyl transfer reaction.

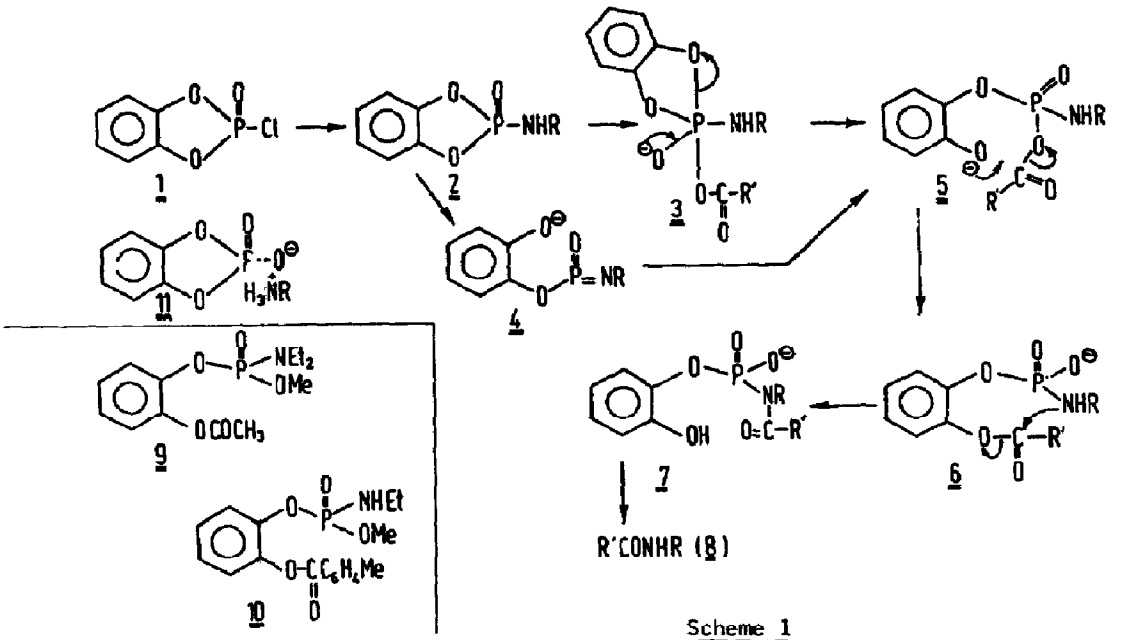
One of the strategies for minimizing racemization is to create the peptide bond by an intramolecular couplig between acyl and amine captive components (1) : aminoacyl insertion (2), prior amine capture (3) ...

The following considerations led us to check the possibilities of the cascade of reactions shown on scheme 1 :

- strained five membered cyclic phosphates are highly reactive (4). In the most probable pentacoordinated intermediate 3 (4a) formed by apical nucleophilic attack on phosphorus (5) pseudorotation is unnecessary, the phenol leaving group being already in a good apical position for departure (7) ;
- 7-membered ring acyl transfer reactions are known to occur (3a) ;
- some acylations of phosphoramidates are known (9) ;
- hydrolysis (10) and alcoholysis (11) of the $\overset{\delta}{P}\text{-}\overset{\delta}{N}\text{-}C$ bond are easy ;
- 2-chloro-2-oxo-1,3,2 benzodioxaphosphole 1 (12,13) is commercially available and some reactions with amines have been described in a patent (15).

As a model of the first steps of scheme 1, 2b (R = H = Et ; 0.001 mole) was allowed to react with an equimolar quantity of tetrabutylammonium acetate in 5 cm^3 of dry CH_2Cl_2 at 25°C. A carbonyl absorption at 1765 cm^{-1} appeared and after 3 hours, acidification with 0.5 cm^3 of 54 % HBF_4 in ether (16), addition of an excess of diazomethane and purification by thin layer chromatography (SiO_2 : AcOEt) led to 9 as an oil (20 % yield), $C_{13}H_{20}O_5P$ (C,H analysis).
δ ($CDCl_3$) 7.3 (broad m, 4H, ArH), 3.75 (d, 3H, $-PO\underline{CH_3}$, J = 11), 3.13 (dq, 4H, $\underline{CH_2}-CH_3$), 2.3 (s, 3H, $-CO\underline{CH_3}$), 1.1 (t, 6H, $-CH_2-\underline{CH_3}$, J = 7).

In the reaction of the monoalkylphosphoramidate 2a (R = Et ; m.p. 95°) with p-toluic acid and Et_3N at 25°C a carbonyl band was observed at 1735 cm^{-1}. Treatment of the reaction mixture with CH_2N_2 led to the isolation of 10 (m.p. 78-80°C).
δ (CD_3CN) : 8.1 and 7.3 (m, 8H, ArH), 3.6 (d, 3H, $PO\underline{CH_3}$, J = 11) ; 2.9 (m, 2H, $PNH\underline{CH_2}$, ^1J = 11, ^2J = 7.5, ^3J = 7) ; 2.5 (s, 3H, $Ar\underline{CH_3}$), 1.0 (t, 3H, $CH_2-\underline{CH_3}$, J = 7).



Scheme 1

The ester band decreases by heating the reaction mixture and p-$CH_3C_6H_4CONHC_2H_5$ may be isolated. The same amide is formed by heating the methylated derivatives 10 in the condition of the reaction.

The reactions of various phosphoramidates 2 with acids and Et_3N (or tetrabutylammonium salts) in CH_2Cl_2 leading directly to amides and peptide esters at 25°C are summarized in tables 1 and 2. The reaction can also be run in acetonitrile or DMF.

Isolation of the end-products can be achieved by chromatography (methods B or C) ; procedure A is easy to perform, the phosphorylated by-product being soluble in aqueous sodium bicarbonate.

Reaction of 2d with Z-Gly-L-Phe is an application of the Anderson test (23). The extent of racemization is about 0.85 % with Et_3N (table 1) and no racemization is observed with the tetrabutylammonium salt (table 2).

The monoalkyl phosphoramidates 2 are very sensitive to moisture with formation of the ammonium salts 11. Therefore, they lead to higher yields when prepared in situ (table 1).

Consequently, we propose the chloride 1 as a coupling reagent in peptide synthesis in a one-pot reaction, the amino component being added first.

TABLE 1 : 2 + R'COOH + Et_3N ⟶ R'CONHR

Phosphoramide		Amide					
n°	m.p. °C	R	R'CO	m.p. °C	m.p. (litt.) °C	Yield %	Method of isolation
2c	138	$PhCH_2$	CH_3CO	61	61 (18)	84	B
2c		$PhCH_2$	PhCO	104-105	105-108 (19)	42.5	B a)
2c		$PhCH_2$	ZGly	118-119	-	63	A
2d	108-111	EtO_2CCH_2	ZGly	80-81	79-80 (20)	65	C
						76 b)	A
2d		EtO_2CCH_2	Z-L-Phe	108-111	(L) 109-111 (DL) 100-102 (21)	31	B
2d		EtO_2CCH_2	Z-L-Pro	oil	oil (22)	52	A
2d		EtO_2CCH_2	ZGly-L-Phe	114-116	(L) 116.5-119.5 (23)	62.5	A c)
2e(17)		nPr	ZGly	100-101	-	80	A

A : Evaporation of the solvent, addition of 5 cm^3 of 5 % $NaHCO_3$ per mmole and cooling.

B : Thick-layer chromatography (SiO_2, AcOEt 100 %).

C : Column chromatography (SiO_2, AcOEt-cyclohexane : 8-2) and recristallization in benzene.

a) 8 h reflux in benzene ; b) one pot reaction (phosphoramidate prepared in situ) ;

c) 0.85 % of DL (m.p. 132-133) are isolated.

TABLE 2 : 2 + $R'COO^- \ ^+NBu_4$ ⟶ R'CONHR

Phosphoramide	Amide					
	R	R'CO	m.p. °C	m.p. (litt.) °C	Yield %	Method of isolation
2c	$PhCH_2$	CH_3CO	61	61 (18)	84	B
2d	EtO_2CCH_2	ZGly	80	70-80 (20)	52 a)	A
2d	EtO_2CCH_2	ZGly-L-Phe	118-119	116.5-119.5 (23)	62.5 b)	A
2e	nPr	ZGly	100-101		80	A

a) in DMF ; b) Anderson test : no D,L are isolated.

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(Received in France 9 May 1980)