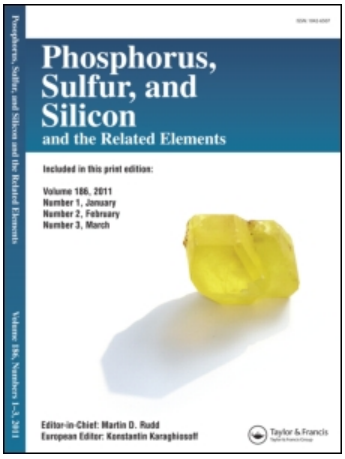

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N-BENZYLOXYAMINO PHOSPHINYL PEPTIDES

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N-BENZYLOXYAMINO PHOSPHINYL PEPTIDES

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The synthesis of N-acetyl N-benzyloxyamino alkyl phosphinyl peptides was achieved via coupling reaction between methyl or phenyl N-acetyl 1-benzyloxyamino benzyl phosphinic acids with glycine and alanine methyl esters.

Key words: Pseudo peptides; N-hydroxy phosphinyl peptides; 1-benzyloxyamino alkyl phosphinic acids; glycine; alanine; DCC; DPPA; BOP; DMAP; HOBT.

In previous works,[1-3] we had suggested a general method for the unambiguous synthesis of 1-benzyloxyamino alkyl phosphinic acids and their corresponding esters. The present paper describes the preparation of N-benzyloxyamino phosphorus analogs of peptides. This series of new compounds differs from common peptides by introducing a phosphinylamide bond in place of an amide link.

These compounds were obtained by coupling reactions between methyl or phenyl N-acetyl N-benzyloxyamino benzyl phosphinic acid with methyl glycine and alanine esters.

Formation of the P—N link gave rise to some difficulties which will be discussed: Protecting groups, activation of the phosphinic acid and coupling reaction to form a phosphinylamide link.

PROTECTING GROUPS

a) Aminoacids are used as their methyl esters, and b) the NH protection of alkyl 1-benzyloxyamino benzyl phosphinic acids **1** or **1'** could not be carried out with the Boc group inappropriate for phosphono peptides due to the acidolabile P—N link.[4] The N—Z derivates were obtained with low yields and the benzyl group cleavage by catalytic hydrogenation would lead to amino phosphinyl peptide by reduction of N—OH into NH_2[5]. The acetyl group, commonly employed with N-hydroxyaminoacids,[6] was chosen, because it can be easily cleaved in basic medium. Moreover, the high solubility of these N-acetylated compounds allowed to effect the coupling reaction within a wide range of organic solvents. The trifluoroacetyl group could also be used.

Activation of the Phosphinic Acid

The activation of phosphonic or phosphinic acids were generally realized through phosphono or phosphino chloridates.[7-11] These compounds were obtained by action

of phosphorus pentachloride with N-protected dialkyl amino phosphonates[4,9-11] or of thionyl chloride with N-protected amino phosphonic hemi-ester or amino phosphinic ester.[7,8] Other methods were also employed in the literature using the Vilsmeier reagent ($SOCl_2$/DMF)[12] or 2,4,6-triisopropylbenzenesulfonyl chloride and 1-(mesitylsulfonyl)-3-nitro-1,2,4-triazole.[13] The (2-Z-aminoethyl) phosphonic monoester [Z-Aep(OR)(OH)] was coupled with various aminoethyl ester hydrochlorides, using diphenylphosphonylazide (DPPA) in DMF or THF, which gives yields ranging from 40 to 60%.[4b,14] In despite of some works mentioning the failure of the P—N link formation in the presence of dicyclohexylcarbodiimide (DCC),[4b,9a] Natchev[15] effected successfully the synthesis of "Bialaphos and plumbemycine A," using this coupling reagent for the introduction of the phosphonamide link.

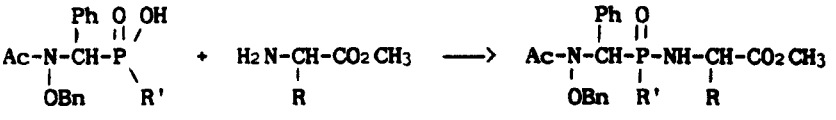
SYNTHESIS OF PSEUDOPEPTIDES

Several attempts for the transformation of the phosphinic acid group into phosphinochloridate have been made without success (PCl_5, $PCl_5/POCl_3$, $SOCl_2$, $SOCl_2$/DMF). Also, a systematic study of the coupling reaction was carried out with methyl N-acetyl 1-benzyloxyamino benzyl phosphinic acid and glycine or alanine methyl esters (Scheme I), using various activating reagents like: benzotriazol-1-yl-tris(dimethylamino)phosphonium hexafluorophosphonate (BOP), diphenylphosphoryl azide (DPPA), DCC or DCC with additives: 4-dimethylaminopyridine (DMAP), 1-hydroxy benzotriazole (HOBT).

BOP, used in peptidic synthesis,[16] could be envisaged for the formation of the phosphinylamid link. A stoichiometric mixture of methyl N-acetyl 1-benzyloxyamino benzyl phosphinic acid **1** and L-alanine methyl ester hydrochloride, treated with BOP, led to the pseudodipeptide **3a** (yield 10%) after column chromatographic purification.

The coupling reaction of **1** with alanine methyl ester **2a**, in presence of 20% excess of DPPA, led to **3a** with a yield of 5%. This method was discarded.

Despite the reported contradictory results,[4b,9b,14] we undertook the coupling reaction with DCC. According to the technic of Natchev,[15] **1** and **2a** were treated with DCC in dichloromethane, during 36 hours; the reaction yield was 20% while the isolated DCU quantity was about 90% of the theorical amount. This yield was



1 R' = CH_3 **1'** R' = Ph

2a R = CH_3 **2b** R = H

3a R' = CH_3, R = CH_3; **3b** R' = CH_3, R = H; **3'b** R' = Ph, R = H

SCHEME I

not improved by longer reaction times. By-products formation, probably N-acyl-ureas, and unreacted starting product like phosphinic acid, easily destroyed by basic treatment, could explain this low yield. The isolated dipeptide **3a** is a mixture of diastereoisomers, as shown by its NMR spectrum. The dipeptide **3b** is obtained from methyl glycinate with a 30% yield. The same coupling reaction between phenyl N-acetyl 1-benzyloxyamino benzyl phosphinic acid **1'** and **2b** gave the dipeptide **3'b** with a 25% yield.

In order to improve the yields, as in classic peptide synthesis, additives (DMAP or HOBT) were used, changing the preactivated acidic form to an activated ester.

The efficiency of DMAP addition to DCC in coupling reaction of hindered aminoacids (cycloleucine, isoleucine, valine) is well documented.[17,18] But, the same conditions applied to **1** and **2a** or **1** and **2b** gave a decrease in yield of 10 and 5% respectively. Traces of the pseudodipeptide **3a** are obtained with a stoichiometric addition of HOBT to DCC as shown by CCM.

Experimental results are summarized in Table I.

TABLE I
Coupling Conditions

Products N°	Starting material	Coupling reagents	Reaction* time (h)	Yield** (%)
3a	1 + 2a	BOP (Et_3N)	72	10
3a	1 + 2a	DPPA (Et_3N)	120	5
3a	1 + 2a	DCC	36	20
3a	1 + 2a	DCC/DMAP(10%)	48	10
3a	1 + 2a	DCC/HOBT(1/1)	60	(trace)
3b	1 + 2b	DCC	36	30
3b	1 + 2b	DCC/DMAP(10%)	48	25
3'b	1'+ 2b	DCC	72	25

* All reactions are effected in dichloromethane as solvent and at room temperature

** The yields (average of several experimental results) are based on 1 or 1' respectively.

These experiments brought out the difference of reactivity between carboxylic and phosphinic acids and proved that DCC could be a possible activation reagent for coupling phosphinic acid functions with aminoacids.

Conditions of deprotection leading to the free peptides are under investigation.

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Varian T60 instrument with TMS as internal standard; abbreviations used are s(singulet), d(doublet), t(triplet), m(multiplet). Mass spectra were obtained on a Jeol JMX DX 300 Mass Spectrometer (matrix: glycerol or NOBA).

Methyl or benzyl N-acetyl 1-benzyloxyamino benzyl phosphinic acids **1** or **1'** were prepared according to procedures previously described.[3]

Methyl N-acetyl 1-benzyloxyamino benzyl phosphinyl)-Ala OMe, **3a**.

1°) Coupling by BOP: To a solution of methyl N-acetyl 1-benzyloxyamino benzyl phosphinic acid **1** (2 mmol), and L-alanine methyl ester hydrochloride (2.4 mmol) in anhydrous dichloromethane (25 ml) was added BOP (2.4 mmole) and triethylamine (4.8 mmol). The mixture was stirred at room temperature for 72 h, the reaction course being monitored by TLC (silica gel, CH_2Cl_2/MeOH: 96/4). The solvent was removed in vacuo, the residue diluted with ethyl acetate, washed successively with 5% sodium hydrogen carbonate and water and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give an oil. The product was purified by silica gel column chromatography with CH_2Cl_2/MeOH (96/4) as eluant. The ^{1}H-RMN spectrum showed the presence of diastereoisomers.
Rf = 0.42. Yield = 10%.
^{1}H NMR ($CDCl_3$) δ: 1.16 and 1.33 (d, 3H, J = 8 Hz); 1.52 and 1.57 (d, 3H, J = 15 Hz); 2.23 and 2.26 (s, 3H); 3.65 (s, 3H); 3.66 (m, 1H); 3.70 (m, 1H); 3.77 (s, 3H); 4.94, 5.12 and 5.18, 5.15 (AB systems, 2H, J = 10 Hz); 5.55 and 5.60 (d, 1H, J = 18 Hz); 7.50 and 7.53 (s, 5H); 7.63 (m, 5H).

MS FAB (Matrix: glycerol) 419 $(M+H)^+$; 837 $(2M+H)^+$;

316 $(M-102)^+$ $\longleftrightarrow$ $CH_3CO-N(BnO)-CH(Ph)-P^+(O)(CH_3)$; 212 $(M-206)^+$ $\longleftrightarrow$ Ph—CH=NH—OBn

91 Ph—CH_2^+.

2°) Coupling by DPPA: To a solution of **1** (2 mmol) and L-alanine methyl ester hydrochloride (2.4 mmol) in anhydrous dichloromethane (25 ml) was added DPPA (2.4 mmol) and triethylamine (4.8 mmol). The mixture was stirred at room temperature for 5 days. Triethyl ammonium hydrochloride was filtered off, the solvent was removed under vacuum (the temperature of water bath kept below 50°C. The oily residue, dilute in ethylacetate (25 ml), was treated as above. Yield 5%.

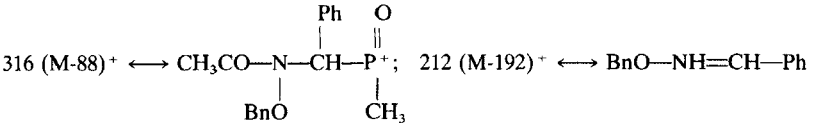
3°) Coupling by DCC: a) To a stirred solution of **1** (2 mmol) and L-alanine methyl ester hydrochloride (2.2 mmol) in anhydrous dichloromethane (15 ml), was added DCC (2.2 mmol) at 0°C. The mixture was stirred for 1h at 0°C and 36h at room temperature. The course of reaction was monitored by TLC (silica gel, CH_2Cl_2/CH_3OH 96/4). After filtration of the DCU precipitate and removal of the solvent, the oily residue was diluted with ethyl acetate and treated as above. Yield 20%.

b) DCC/DMAP. A similar procedure was employed, adding DMAP (0.22 mmol) to the reaction mixture. Reaction time: 48h. Yield: 10%.

c)DCC/HOBT. A similar procedure, used above, was employed, adding HOBT (2 mmol) to the reaction mixture. Reaction time: 60h. Traces of **3a** were detected in the crude product of reaction by ^{1}H NMR and TLC.

(Methyl N-acetyl 1-benzyloxyamino benzyl phosphinyl)-Gly Ome, **3b**. a) The coupling reaction was realized by DCC with a similar procedure to the one used (3°a) for the preparation of **3a** with 2.2 mmol of glycine methyl ester hydrochloride.
Rf ($CHCl_3$/CH_3OH: 92/8) = 0.75. Yield: 30%.
^{1}H NMR ($CDCl_3$) δ: 1.55 (d, 3H, J = 15 Hz); 2.25 (s, 3H); 3.63 (m, 2H); 3.76 (s, 3H); 3.83 (m, 1H); 4.98 and 5.19 (AB system, 2H, J = 10 Hz); 5.57 (d, 1H, J = 20 Hz); 7.45 (s, 5H); 7.60 (m, 5H).

MS FAB (matrix: glycerol) 405 $(M+H)^+$;



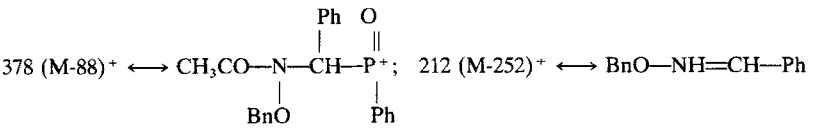
316 $(M\text{-}88)^+$ ⟷ $CH_3CO—N(BnO)—CH(Ph)—P^+(CH_3)$; 212 $(M\text{-}192)^+$ ⟷ BnO—NH=CH—Ph

91 Ph—CH_2^+.

b) The coupling reaction was realized by DCC/DMAP with experimental conditions used (3°b) for the preparation of **3a** with 2.2 mmol of glycine methyl ester.
Yield: 25%.

Phenyl (N-acetyl 1-benzyloxyamino benzyl phosphinyl)-Gly OMe, **3'b**. A similar procedure to the one used for the preparation of **3a** with DCC was employed (3°a): 2.2 mmol of phenyl (N-acetyl 1-benzyloxyamino benzyl phosphinic acid **1'** and 2.2 mmol of glycine methyl ester hydrochloride **2b**.
Rf (CH_3Cl/CH_3OH: 96/4) = 0.39. Yield: 25%.
^1H NMR ($CDCl_3$) δ: 1.97 (s, 3H); 3.60 (m, 2H); 3.66 (s, 3H); 3.86 (m, 1H); 4.80 and 5.25 (AB system, 2H, J = 10 Hz); 6.07 (d, 1H, J = 16 Hz); 7.45 (s, 5H); 7.60 (m, 10H).

MS FAB (matrix: NOBA) 467 $(M+H)^+$;



378 $(M\text{-}88)^+$ ⟷ $CH_3CO—N(BnO)—CH(Ph)—P^+$; 212 $(M\text{-}252)^+$ ⟷ BnO—NH=CH—Ph

91 Ph—CH_2^+.

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