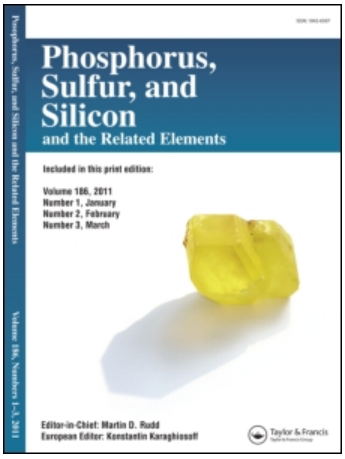

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Robert Jacquier[a]; Clement Petrus[a]
[a] Laboratoire de synthèse et d'études physicochimiques d'aminoacides et de peptides, Montpellier Cédex, France

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SYNTHESIS OF 1-BENZYLOXYAMINOMETHYL PHOSPHONIC AND PHOSPHINIC ACIDS FROM FORMALDOXIME-*O*-BENZYLETHER

ROBERT JACQUIER and CLEMENT PETRUS

Laboratoire de synthèse et d'études physicochimiques d'aminoacides et de peptides, U.A. C.N.R.S. 468. Université Montpellier II, Sciences et Tecniques du Languedoc, 34095 Montpellier Cédex 2, France

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A convenient and original synthesis of 1-benzyloxyaminomethyl phosphonic and phosphinic acids by reacting phosphorus trichloride and dichlorophosphines with formaldoxime-*O*-benzylether is described.

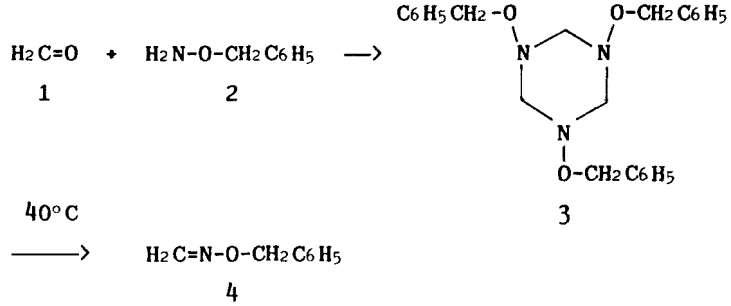
Key words: 1-Benzyloxyaminomethyl phosphonic acid; 1-benzyloxyaminomethyl phosphinic acid; phosphorus trichloride; dichlorophosphines; formaldoxime-*O*-benzylether.

INTRODUCTION

In connection with our studies on the synthesis of *N*-benzyloxyamino phosphinyl peptides,[1] we became interested in developing a method for the synthesis of *O*-benzylaminomethyl phosphonic and phosphinic acids.

N-Monosubstituted hydroxylamines, in particular *N*-alkyl hydroxylamines, condensed in a Mannich-type reaction with formaldehyde and secondary phosphites, led to *N*-alkyl *N*-hydroxyaminomethyl phosphonates, the synthesis of which is well documented.[2]

Contrary to *N*-monosubstituted hydroxylamines and based upon the studies of Hellmann and Tiechmann,[3] *O*-benzylhydroxylamine cannot be converted into a Mannich base, but is assumed to provide Schiff base **4** with formaldehyde. This result was confirmed and proved by means of ^{1}H- and ^{13}C-NMR and also IR by Respondek.[4]



-Scheme 1-

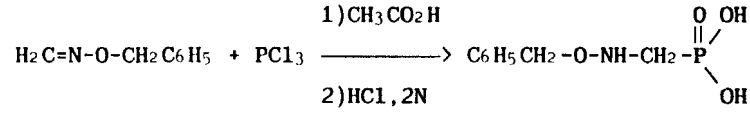
The formaldoxime-*O*-benzylether **4** obtained in this way is used in our synthesis.

RESULTS AND DISCUSSION

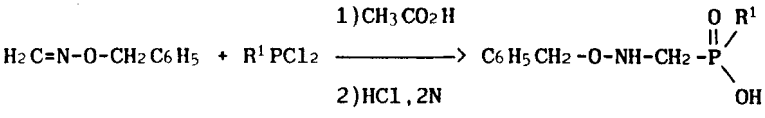
We describe here a simple and original method in which previously unreported 1-benzyloxyaminomethyl phosphonic and phosphinic acids are easily synthesized in the reaction of formaldoxime-*O*-benzylether with phosphorus trichloride or dichlorophosphines.

The reaction proceeds by dropwise addition of an equimolar amount of phosphorus trichloride or dichlorophosphine to a cooled solution of formaldoxime-*O*-benzylether in glacial acetic acid with stirring.

After completion of the reaction (checked by TLC), acidic hydrolysis of the mixture by HCl,2N, followed by the usual work-up, leads to the corresponding acids in good yield.



4 5



4 6 , 7

6 R^1 = CH_3

7 R^1 = C_6H_5

-Scheme 2-

It is interesting to note that the best yields of final products are obtained when: a) the reaction is conducted at low temperature without freezing the reaction mixture; b) phosphorus chloride is added dropwise as slowly as possible; and c) hydrolysis of the reaction mixture is carried out about 20 h after the end of the addition of the phosphorus derivative.

Acids **5, 6, 7** are of interest, being useful starting materials for the synthesis of chiral 1-benzyloxyamino alkyl phosphonic and phosphinic acids.

EXPERIMENTAL

All melting points are uncorrected. ^{31}P-NMR spectra were recorded on a Bruker WP 200 SY spectrometer with H_3PO_4 as external standard. ^{1}H-NMR spectra were recorded on a Bruker WP 80 CW instrument with TMS as internal standard; abbreviations used are s (singulet), and d (doublet). Fab mass spectra were obtained on a Jeol JMS DX 300 Mass Spectrometer (matrix: glycerol).

Formaldoxime-*O*-benzylether (Rf_{EtOAc} = 0.61) was prepared following the procedures of Hellmann and Teichmann[3] and Respondek.[4]

Preparation of 1-benzyloxyaminomethyl phosphonic and phosphinic acids. General procedure. A solution of 20 mmoles of PCl_3 or R^1PCl_2 in 8 ml of glacial acetic acid was slowly added dropwise, with

stirring over a period of one hour to a cooled solution of formaldoxime-*O*-benzylether (20 mmoles) in glacial acetic acid (8 ml). After the end of the addition, the mixture was allowed to warm to room temperature. After 20 h, 20 ml of HCl,2N was added dropwise at room temperature. Stirring was continued for a further 3 h. Solvents were removed in vacuo. This operation was repeated 3 or 4 times until complete elimination of water, HCl and acetic acid. Solid products were obtained by addition of methanol/acetone to the oily crude residue and were recrystallized from methanol.

1-Benzyloxyaminomethyl phosphonic acid **5** from PCl_3.
Yield: 75%—mp (ethanol) = 174–176°C.
^{1}H-NMR (DMSOd_6)δ = 3.26 (d, 2H, J = 14 Hz, CH_2—P); 4.77 (s, 2H, $C\underline{H_2}$—C_6H_5); 7.52 (s, 5H, C_6H_5).
^{31}P-NMR (DMSOd_6)δ = 17.7.
MS FAB (m/z) $(M + H)^+$:218.

1-Benzyloxyaminomethyl methyl phosphinic acid **6** from CH_3PCl_2.
Yield: 80%—mp (ethanol) = 140–142°C.
^{1}H-NMR (DMSOd_6)δ = 1.57 (d, 3H, J = 16 Hz, CH_3—P); 3.63 (d, 2H, J = 12 Hz, CH_2—P); 5.20 (s, 2H, $C\underline{H_2}$—C_6H_5); 7.60 (s, 5H, C_6H_5).
^{31}P-NMR (DMSOd_6)δ = 38.24.
MS FAB (m/z) $(M + H)^+$:216.

1-Benzyloxyaminomethyl phenyl phosphinic acid **7** from $C_6H_5PCl_2$.
Yield: 75%—mp (ethanol) = 138–140°C.
^{1}H-NMR (DMSOd_6)δ = 3.45 (d, 2H, J = 11 Hz, CH_2—P); 4.62 (s, 2H, $C\underline{H_2}$—C_6H_5); 7.40 (s, 5H, C—C_6H_5); 7.55–8.10 (m, 5H, C_6H_5—P).
^{31}P-NMR (DMSOd_6)δ = 29.90.
MS FAB (m/z) $(M + H)^+$:278.

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