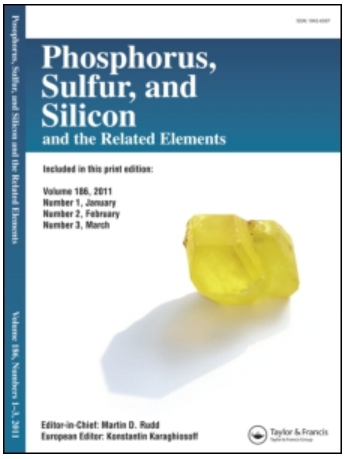

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A NEW AND CONVENIENT SYNTHESIS OF 1-BENZYLOXYAMINOALKYL PHOSPHONIC AND PHOSPHINIC ACIDS FROM OXIMES

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A NEW AND CONVENIENT SYNTHESIS OF 1-BENZYLOXYAMINOALKYL PHOSPHONIC AND PHOSPHINIC ACIDS FROM OXIMES

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A new general method is described for the synthesis of 1-benzyloxyamino-alkyl phosphonic and phosphinic acids by reacting phosphorus trichloride or dichlorophosphines with 0-benzyl oximes.

Key words: 1-Hydroxyaminoalkylphosphonic acid; 2-hydroxyaminoalkylphosphinic acid; phosphorus trichloride; dichlorophosphine; oxime.

INTRODUCTION

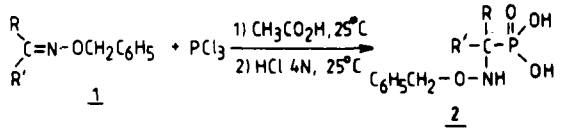
This paper describes a general procedure for the synthesis of 1-benzyloxyaminoalkyl phosphonic and phosphinic acids **2**, **3** and **4** from 0-benzyl ketoximes and aldoximes. These compounds are suitable precursors of peptide analogues in which the normal amide bond is replaced by a *N*-hydroxyphosphonamide or phosphonimide bond.

Until now, only few reports describe the synthesis of alkyl *N*-substituted hydroxyaminoalkylphosphonates.[1–3] Vassella *et al.*[1,2] obtained alkyl *N*-glycosyl *N*-hydroxyaminoalkyl phosphonates in good yields and with diastereoisomeric excess 78–92%, by a nucleophilic addition of lithium or potassium dialkylphosphites to *N*-glycosyl nitrones, which are transformed into enantiomerically pure *N*-hydroxyaminoalkyl phosphonic acid, analogues of alanine, valine and serine.

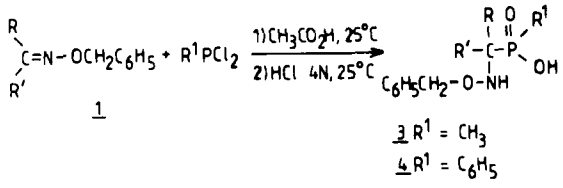
Recently, Yamada *et al.*[3] reported a synthesis of alkyl *N*-substituted 1-alkoxyaminoalkyl phosphonates by a simultaneous addition reaction of an electrophile (alkyl halide) and a nucleophile (trialkyl phosphite) to nitrones (such as 4,5,5-trimethyl-Δ1 pyrroline *N*-oxide, 2,4,4-trimethyl-Δ1 pyrroline *N*-oxide, *N*-benzylidene *N*-methyl amine *N*-oxide). They suggested a push–pull type mechanism.

RESULTS AND DISCUSSION

We now report a new direct method in which the 1-benzyloxyaminoalkyl phosphonic and phosphinic acids **2–4** are easily synthesized from 0-benzyl oximes



SCHEME 1



SCHEME 2

in the presence of phosphorus trichloride or dichlorophosphine. A preliminary study was already carried out in our laboratory.[4] It was known[5,6] that, depending on experimental conditions, a substitution reaction by the oxygen atom, followed by an Arbuzov-type rearrangement, could occur by reacting phosphorus trichloride with three equivalents of ketoxime in the presence of triethylamine.

For this reason, we used 0-benzyl oximes; the benzyl group was chosen on

TABLE 1

Products	R	R′	Yield %	mp °C
2a	Me	H	56	178
2b	Et	H	45	150
2c	iPro	H	40	118
2d	C_6H_5	H	80	165
2e	Me	Me	30	180
3a	Me	Me	25	93
3b	C_6H_5	H	78	134
3c	Me	Me	65	150
4a	Me	H	60	143
4b	C_6H_5	H	65	150
4c	Me	Me	30	164

account of its easy removal under neutral and mild conditions, suitable in the presence of P—N bonds of phosphonopeptides which are now under study.

The reaction proceeded, at room temperature, by the dropwise addition of an equimolar amount of phosphorus trichloride or dichlorophosphine to the 0-benzyl oximes in glacial acetic acid with stirring. After completion of the reaction (TLC), acid hydrolysis, without isolation of the intermediates, followed by the usual work-up, led to the final products in moderate to good yields.

Replacement of aldoximes with ketoximes resulted in decreased yields. Addition of catalytic amounts of boron trifluoride etherate or anhydrous zinc chloride was also tried as a means of activation of the C=N— group, but no positive effects were observed. The results are summarized in Table 1.

EXPERIMENTAL

All melting points are uncorrected. ^{31}P-N.M.R. spectra were recorded on a Bruker WP 80 Spectrometer with H_3PO_4 as external standard. ^{1}H-N.M.R. spectra were recorded on a Varian T60 instrument with TMS as internal standard; abbreviations used are s (singulet), d (doublet), t (triplet), q (quartet), m (multiplet). FAB mass spectra were obtained on a Jeol DX 300 Mass Spectrometer (matrix: glycerol). The microanalyses showed the following maximum deviations from the calculated values: N, +0.30%; P, +0.45%. (For phosphinic acids **3** and **4**, values are in agreement with MW + H_2O, with the exception of **3a** which is unstable.

0-Benzyl oximes were prepared either by reacting the aldehyde or the ketone with 0-benzylhydroxylamine or by alkylation of the oxime sodium salt with benzyl bromide.

Preparation of N-benzyloxyalkyl phosphonic and phosphinic acids

General procedure. A solution of 14.2 mmole of PCl_3 or R^1PCl_2 in 4 ml of glacial acetic acid was added dropwise, with stirring, over a period of 45 minutes at room temperature to 14.2 mmole of the 0-benzyl oxime. After 2 h, 14 ml of 4N hydrochloric acid was added at room temperature and the mixture was stirred overnight. After distillation of the solvent under reduced pressure, 25 ml of methanol was added to the residue and evaporated in vacuo. This operation was repeated 3 or 4 times until complete elimination of water and acetic acid. Solid products were obtained by addition of ether/acetone to the oily crude residue. (**3a** was isolated by addition of hexane). **2a**, **2b** and **4a** were recrystallized from methanol/H_2O, **3b**, **4b** from ethanol and **2c**, **2d**, **2e**, **3c** and **4c** were dissolved in 5% aqueous sodium hydroxide solution, precipitated with 5% hydrochloric acid, and washed with hot ethanol.

NMR and MASS Data

2a. ^{1}H NMR (DMSO d_6) δ = 1.26 (dd, 3 H, J = 6 Hz, J = 16 Hz); 3.30 (m, 1 H); 4.70 (s, 2 H); 7.36 (s, 5 H). ^{31}P NMR (DMSO d_6) δ = 20.05. MS FAB (m/z) $(M + H)^+$: 232.

2b. ^{1}H NMR (DMSO d_6) δ = 1.00 (t, 3 H, J = 7 Hz); 1.73 (m, 2 H); 3.10 (m, 1 H); 4.73 (s, 2 H); 7.43 (s, 5 H). ^{31}P NMR (DMSO d_6) δ = 20.40. MS FAB (m/z) $(M + H)^+$: 246.

2c. ^{1}H NMR (DMSO d_6) δ = 0.91 and 1.11 (2 d, 6 H, J = 6 Hz); 1.90 (m, 1 H); 3.27 (m, 1 H); 5.10 (s, 2 H); 7.55 (s, 5 H). ^{31}P NMR (DMSO d_6) δ = 18.17. MS FAB (m/z) $(M + H)^+$: 260.

2d. ^{1}H NMR (DMSO d_6) δ = 4.33 (d, 1 H, J = 20 Hz); 4.56 (s, 2 H); 7.27 (s, 5 H); 7.42 (m, 5 H). ^{31}P NMR (DMSO d_6) δ = 14.85. MS FAB (m/z) $(M + H)^+$: 294.

2e. ^{1}H NMR (DMSO d_6) δ = 1.23 (d, 6 H, J = 16 Hz); 4.73 (s, 2 H); 7.43 (s, 5 H). ^{31}P NMR (DMSO d_6) δ = 18.17. MS FAB (m/z) $(M + H)^+$: 246.

3a. ^{1}H NMR (DMSO d_6) δ = 1.30 (d, 3 H, J = 22 Hz); 1.40 (dd, 3 H, J = 6 Hz, J = 14 Hz); 3.30 (m, 1 H); 4.70 (s, 2 H); 7.46 (s, 5 H). ^{31}P NMR (DMSO d_6) δ = 40.62. MS FAB (m/z) $(M + H)^+$: 230.

3b. ^{1}H NMR (DMSO d_6) $\delta = 1.26$ (d, 3 H, $J = 15$ Hz); 4.43 (d, 1 H, $J = 18$ Hz); 4.56 (s, 2 H); 7.43 (s, 5 H); 7.53 (m, 5 H). ^{31}P NMR (DMSO d_6) $\delta = 39.65$. MS FAB (m/z) $(M + H)^+$: 292.

3c. ^{1}H NMR (DMSO d_6) $\delta = 1.35$ (d, 6 H, $J = 13$ Hz); 1.42 (d, 3 H, $J = 15$ Hz); 5.05 (s, 2 H); 7.50 (s, 5 H). ^{31}P NMR (DMSO d_6) $\delta = 46.62$. MS FAB (m/z) $(M + H)^+$: 244.

4a. ^{1}H NMR (DMSO d_6) $\delta = 1.16$ (dd, 3 H, $J = 16$ Hz); 3.23 (m, 1 H); 4.53 (s, 2 H); 7.30 (s, 5 H); 7.60 (m, 5 H). ^{31}P NMR (DMSO d_6) $\delta = 32.91$. MS FAB (m/z) $(M + H)^+$: 292.

4b. ^{1}H NMR (DMSO d_6) $\delta = 4.66$ (d, 1 H, $J = 14$ Hz); 4.55 (s, 2 H); 7.26 (s, 5 H); 7.33 (m, 5 H); 7.46 (m, 5 H). ^{31}P NMR (DMSO d_6) $\delta = 28.05$. MS FAB (m/z) $(M + H)^+$: 354.

4c. ^{1}H NMR (DMSO d_6) $\delta = 1.15$ (d, 6 H, $J = 14$ Hz); 4.56 (s, 2 H); 7.33 (s, 5 H); 7.60 (m, 5 H). ^{31}P NMR (DMSO d_6) $\delta = 37.14$. MS FAB (m/z) $(M + H)^+$: 306.

REFERENCES

1. A. Vassella and R. Voeffray, *Helv. Chim. Acta*, **65**, 1953 (1982).
2. R. Huber, A. Knierzinger, J. P. Obrecht and A. Vassella, *Helv. Chim. Acta*, **68**, 1730 (1985).
3. Y. Yamada and K. Mukai, *Tetrahedron Lett.*, **29**, 663 (1988).
4. M. El Goul, These Montpellier, 1986.
5. Y. Kruglyak, G. Leibovskaya, I. Sretenskaya, V. Sheluchenko and I. Martynov, *Zhur Obsh. Khim.*, **38**, 943, (1968); [*J. Gen. Chem. (USSR), Engl. Transl.*, **38**, 908 (1968)].
6. C. Brown, R. Hudson, A. Maron and K. Record, *J. Chem. Soc., Chem. Comm.*, 663 (1976).