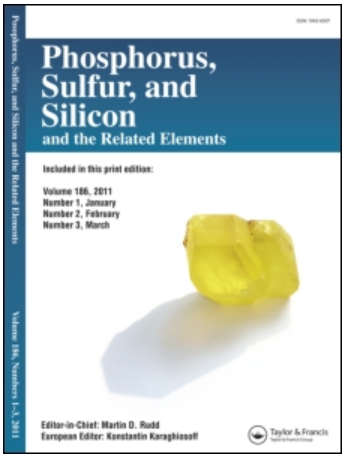

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A CONVENIENT SYNTHESIS OF ALKYL AND DIALKYL 1-BENZYLOXYAMINO ALKYL PHOSPHONATES AND PHOSPHINATES

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A CONVENIENT SYNTHESIS OF ALKYL AND DIALKYL 1-BENZYLOXYAMINO ALKYL PHOSPHONATES AND PHOSPHINATES

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The synthesis of diethyl 1-benzyloxyamino alkyl phosphonates was achieved via reduction of diethyl 1-benzyloxyimino alkyl phosphonates by amino-borane. However, the best result was obtained by esterification of 1-benzyloxyamino alkyl phosphonic and phosphinic acids with O-alkylisoureas.

Key words: Dialkyl and monoalkyl 1-benzyloxyamino phosphonates; alkyl 1-benzyloxyamino phosphinates; borane-amine; O-substituted isoureas.

As a part of our study related to the synthesis of pseudopeptides, we wish to report practical routes for the preparation of alkyl and dialkyl 1-benzyloxyamino alkyl phosphonates and phosphinates.

Two methods were developed:

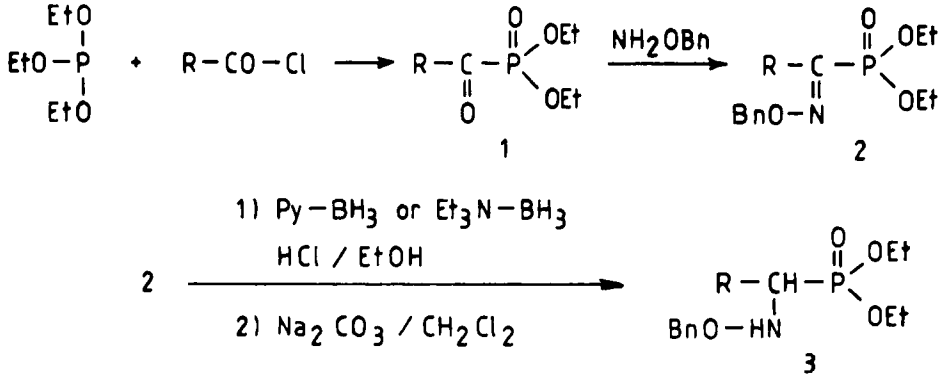
1. Reduction of diethyl 1-benzyloxyimino alkyl phosphonates
2. Esterification of 1-benzyloxyamino alkyl phosphonic and phosphinic acids, previously described.[1]

1. REDUCTION OF DIETHYL 1-BENZYLOXYIMINO ALKYL PHOSPHONATES

The reduction of 1-oximino carboxylic acids or esters by boron complexes is an attractive and simple route for the synthesis of the corresponding hydroxyamino compounds.[2] Cyanoboronhydrides are required for the reduction of 1-oximino carboxylic acids[2a–2c] while the use of borane-amine complex is described for the reduction of α-benzyloximino acids esters[2d–2g]. We have applied this method for the selective reduction of 1-diethyl 1-benzyloximino alkyl phosphonates **2** to the corresponding diethyl 1-benzyloxyamino alkyl phosphonates **3**.

Diethyl α-ketophosphonates **1**, obtained by reaction of acid chlorides with triethylphosphite at room temperature,[3] were converted to the corresponding oximes **2** by treatment with O-benzylhydroxylamine hydrochloride in pyridine/ethanol. Compounds **2** were reduced with pyridine-borane or triethylamine-borane, under strongly acidic conditions (hydrochloric acid/ethanol under argon atmosphere). The borane-amine complex, treated by solid sodium carbonate released diethyl 1-benzyloxyamino alkyl phosphonates **3**. Decomposition of the complex with 1N NaOH is not suitable, due to partial hydrolysis of the phosphonic ester group.

_ Scheme 1 _



a : R = CH_3 b : R = $CH_2-C_6H_5$

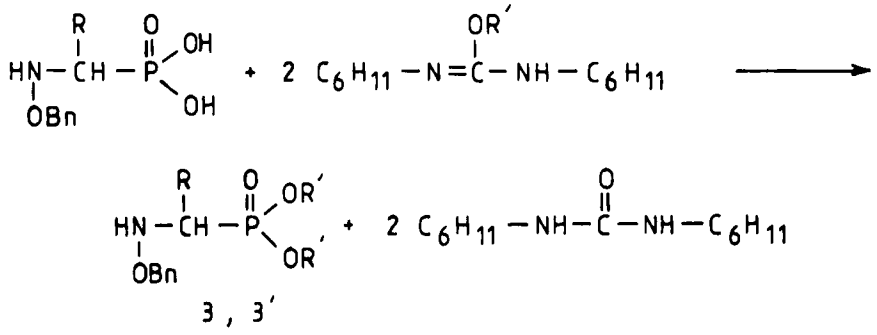
However, it is difficult to obtain compounds 3 in a pure state and a second method was investigated.

2. ESTERIFICATION OF 1-BENZYLOXYAMINO ALKYL PHOSPHONIC AND PHOSPHINIC ACIDS

Several methods have been developed for the synthesis of mono and diesters of amino alkyl phosphonic acids by treatment of the corresponding acid with alcohols in the presence of dicyclohexylcarbodiimide (DCC),[4] trichloroacetonitrile[5] or thionyl chloride in dimethylformamide.[6]

This last procedure was not successful and unchanged 1-benzyloxyamino alkyl phosphonic acids were recovered. Ethyl and propyl 1-benzyloxyamino benzyl phosphonate **4c** and **4"c** were obtained by GILMORE and BRIDE's technique[4a] with a low yield.

_ Scheme 2 _



3c : R' = C_2H_5 , R = C_6H_5

3'a : R' = Bn , R = CH_3 ; 3'c : R' = Bn , R = C_6H_5 ; 3'd : R' = Bn , R = C_2H_5

Other methods have been developed for the synthesis of dialkyl 1-amino alkyl phosphonates. For instance, the reaction of diazoalkanes with N-Boc 1-amino alkyl phosphonic acids or monoesters led to diesters.[7] A possible pathway proceeded via treatment of 1-amino alkyl phosphonic acid[8] or its N-protected derivatives[9] with triethyl orthoformiate. But, 1-benzyloxyamino benzyl phosphonic acid led to inseparable complex mixtures.

Another procedure involved simultaneous addition of phosphorus pentachloride and triethylamine to a mixture of 1-amino alkyl phosphonic acid and alcohol;[10] but the reaction starting with 1-benzyloxyamino benzyl phosphonic acid failed and unchanged acid was isolated with or without triethylamine.

We report here an easy and general way for the synthesis of 1-benzyloxyamino alkyl phosphonic or phosphinic acid mono and diesters, using O-alkyl or O-aryl isoureas.[11] Thus, 2 moles of O-substituted isoureas reacted with 1 mole of 1-benzyloxyamino alkyl phosphonic acid, affording only the dialkyl 1-benzyloxyamino alkyl phosphonates in about 70% yields. (Scheme 2—Table I). N-Benzyl O-benzyloxyaminophosphonates were also isolated in 25% yield.

It is especially noteworthy that this reaction is connected with the exclusive

TABLE I

Ester	Yield	m.p.[°C] or Rf	MS FAB[a]	^{1}H NMR ($CDCl_3$)
3c	30	Rf = 0,54[b]	M + $\overline{H}^+$:350 + $C_5H_6CH{=}NOBn$:212 | H	1,10(t, 3H, *J = 7Hz*); 1,20(t, 3H, *J = 7Hz*); 4,03(q, 4H, *J = 8Hz*); 4,53(d, 1H, *J = 18Hz*); 4,73(s, 2H); 7,38(s, 5H); 7,56(m, 5H)
3'a	45	Rf = 0,31[c]	M + $\overline{H}^+$:412 + $CH_3CH{=}NOBn$:150 | H	1,37(dd, 3H, *J = 7Hz*, *J = 17Hz*); 3,47(m, 1H); 4,73(s, 2H); 5,06(d, 4H, *J = 7Hz*); 5,23(broad s, 1H); 7,20(s, 15H)
3'c	70	m.p. = 86[d]	M + $\overline{H}^+$:474 + $C_5H_6CH{=}NOBn$:212 | H	4,56(d, 1H, *J = 18Hz*); 4,70(s, 2H); 5,03(d, 4H, *J = 7Hz*); 7,31(s, 15H); 7,46(m, 5H)
3'd	40	Rf = 0,4[c]	M + $\overline{H}^+$:426 + $C_2H_5CH{=}NOBn$:164 | H	1,00(t, 3H, *J = 7Hz*); 1,80(m, 2H); 3,17(m, 1H); 4,72(s. 2H); 5,03(d, 2H, *J = 7Hz*); 5,06(d, 2H, *J = 7Hz*); 5,33(broad s, 1H); 7,33(s, 15H)

[a] (Matrix:Glycérol)
[b] (EtOH/EtOAc 1/9)
[c] (EtOAc/CH_2Cl_2 1/9)
[d] (EtOAc)

_ Scheme 3 _

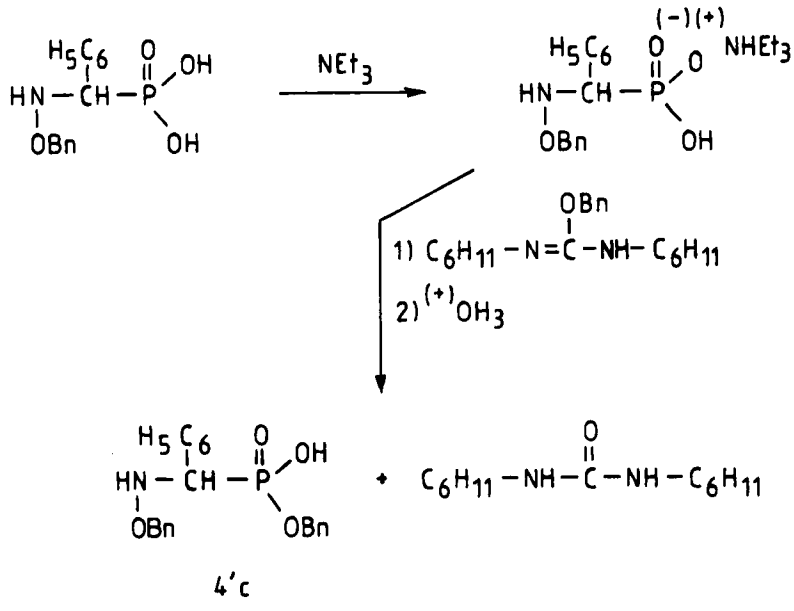


TABLE II

Ester	Method* Yield %	m.p.[°C] or Rf	MS FAB[a]	^{1}H NMR ($CDCl_3$)
4'c	*A:20 *C:60	m.p. = 146[b]	M + $\overline{H}^+$:384 + $C_5H_6CH{=}NOBn$:212 | H	4,66(d, 1H, *J = 22Hz*); 4,73(s, 2H); 5,00(d, 2H, *J = 7Hz*); 7,43(s, 10H); 7,63(m, 5H)
4c	*C:15	m.p. = 115[c]	M + $\overline{H}^+$:322 + $C_6H_5CH{=}NOBn$:212 | H	1,20(t, 3H, *J = 7Hz*); 3,56(m, 2H); 4,50(d, 1H, *J = 18Hz*); 4,66(s, 2H); 7,33(s, 5H); 7,53(m, 5H)
4"c	*C:15	m.p. = 121[c]	M + $\overline{H}^+$:336 + $C_6H_5CH{=}NOBn$:212 | H	0,90(t, 3H, *J = 7Hz*); 1,50(m, 2H); 3,66(m, 2H); 4,66(d, 1H, *J = 18Hz*); 4,93(s, 2H); 7,26(s, 5H); 7,40(m, 7H)

[a] Matrix:Glycerol
[b] EtOAc/EtOH
[c] EtOH

preparation of diesters. When the reaction is carried out with various concentrations of isoureas, monoesters or mixtures of mono and diesters have never been found. The best yields were obtained when stoichiometric amounts of reagents were employed.

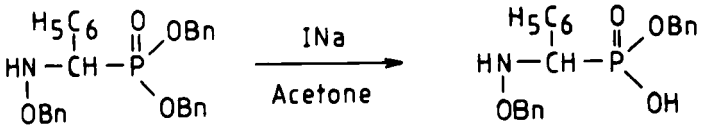
Also noteworthy is the fact that monoesters can be prepared by a modification of the reaction. One acidic function was first neutralised by triethylamine. Addition of O-substituted isoureas to this salt led to alkyl hydrogen 1-benzyloxyamino alkyl phosphonate after hydrolysis by hydrochloric acid (Scheme 3—Table II).

However, the yield of hemiester **4** in this reaction did not exceed a range of 10–20% after purification; the crude product contained phosphonic acid and some diester. Hemiesters **4** could be obtained from diesters, using a procedure described for dialkyl amino alkylphosphonates.[12] They were synthesized by monodealkylation of the corresponding dialkyl 1-benzyloxyamino alkyl phosphonates by means of sodium iodide in acetone, with a yield of 50%. (Scheme 4—Table II).

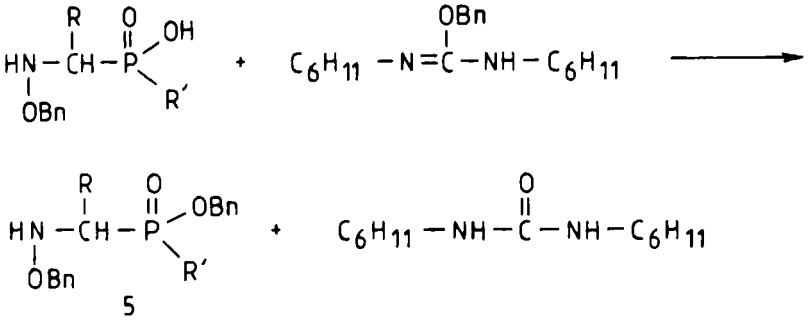
The reaction of O-alkyl or O-aryl isoureas can be generalized to 1-benzyloxyamino alkyl phosphinic acids and allows the synthesis of the corresponding phosphinates as a mixture of diastereoisomers, detected by NMR and only separated in the case of **5'c** by fractional cristallization (Scheme 5—Table III).

Benzylic esters can be used for the unambigous synthesis of N-hydroxy phosphonopeptides.

Scheme 4



Schema 5



5a : R = CH_3 R' = C_6H_5 ; 5c : R = R' = C_6H_5 ; 5'c : R = C_6H_5, R' = CH_3

TABLE III

Ester	Yield	m.p. [°C] or Rf	MS FAB[a]	^{1}H NMR ($CDCl_3$)
5a	65	Rf = 0,61[b]	M + $\overline{H}^+$:382 + $CH_3CH{=}NOBn$:150 | H	1,30 and 1,32(dd, 3H, *J = 7Hz, J = 17Hz*); 3,56(m. 1H); 4,60 and 4,65(s, 2H); 4,96 and 5,10(d, 2H, *J = 8Hz*); 7,30 and 7,38(s, 10H); 7,70(m, 5H)
5c	75	m.p. = 100[b]	M + $\overline{H}^+$:444 + $C_6H_5CH{=}NOBn$:212 | H	4,56 and 4,66(s, 2H); 4,68 and 4,92(d, 1H, *J = 16Hz*); 4,90 and 5,16(d, 2H, *J = 7Hz*); 7,33 and 7,43(s, 10H); 7,66(m, 10H)
5'c	70	m.p. = 91*	M + $\overline{H}^+$:382 + $C_6H_5CH{=}NOBn$:212 | H	5'c_1: 1,28(d, 3H, *J = 14Hz*); 4,46(d, 1H, *J = 16Hz*); 4,75(s, 2H); 4,90(d, 2H, *J = 7Hz*); 7,40(s, 10H); 7,56(m, 10H) 5'c_2: 1,45(d, 3H, *J = 14Hz*); 4,40(d, 1H, *J = 16Hz*); 4,75(s, 2H); 5,13(d, 2H, *J = 7Hz*); 7,46(s, 10H); 7,56(m, 5H)

* 2 Diastereoisomers (50/50) were isolated by recristallisation in EtOAc: 5'c_1 m.p. = 126°C and 5'c_2 m.p. = 98°C.

[a] Matrix:glycerol

[b] EtOAc

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), q(quartet), m(multiplet). Mass spectra were obtained on a Jeol DX 300 Mass Spectrometer.

Diethyl 1-Benzyloxyamino Alkyl Phosphonates **3**

Diethyl 1-oxoalkyl phosphonates **1a**, **1b** and the corresponding oximes **2a**, **2b** were synthetised according to the procedure of Asano, Kitahara, Ogawa and Matsui.[3]

Method A: Reduction with pyridine-BH_3 complex. A stirred solution of 25 mmol of **2** and 125 mmol of pyridine-BH_3 complex in 50 ml of dry ethanol was treated with 37.5 ml of normal ethanolic HCl, the temperature of the mixture being kept below 40°C, under nitrogen. Stirring was continued at room temperature for 3 h. The solvent was evaporated under vacuo. Then, 25 ml of CH_2Cl_2 were added together with 12.5 g of Na_2CO_3. After 3 h stirring, the precipitate was filtered and the solvent evaporated; the product was purified through a silica gel column chromatography using a mixture of chloroform and ethylacetate (1/1 for **3a** and 1/2 for **3b**) as solvent.

Method B: Reduction with triethylamine-BH_3 complex. A normal ethanolic hydrochloric acid solution (37.5 ml) was added in one portion to a stirred mixture of 5 mmol of **2** and 5 mmol of triethylamine-BH_3 complex at room temperature. Stirring was continued for 16 h and the solvent evaporated. The residue was worked-up as described for method A.

Diethyl 1-benzyloxyamino ethyl phosphonate **3a** *from diethyl 1-benzyloximino ethyl phosphonate* **2a**. Method A: Yield = 35%. Method B: Yield = 40%. ^{1}H NMR ($CDCl_3$) = 1.23 (t, 6H, *J* = 7 Hz); 1.36 (m, 3H); 3.36 (q, 1H, *J* = 7 Hz); 4.13 (m, 4H); 5.15 (m, 1H); 4.10 (s, 2H); 7.25 (s, 5H). MS (E.I.) M^+: 287

Diethyl 1-benzyloxyamino 2-phenylethyl phosphonate **3a** *from diethyl 1-benzyloximino ethyl posphonate* **2b**. Method A: Yield = 55%. Method B: Yield = 30%. ^{1}H NMR ($CDCl_3$) = 1.10 (t, 6H, J = 7 Hz); 3.03 (d, 2H, J = 11 Hz); 3.4 (m, 1H); 3.93 (m, 4H); 4.51 (s, 2H); 5.81 (dd, 1H, J = 6 Hz, J = 18 Hz); 7.10 (s, 5H); 7.15 (s, 5H). MS (E.I.) M^+: 363.

Esterification of 1-Benzyloxyaminoalkyl Phosphonic and Phosphinic Acids

1-Benzyloxyamino alkyl phosphonic and phosphinic acids were prepared according to a procedure previously described.[1]

O-benzyl and O-ethyl N,N'-dicyclohexylisoureas, obtained from N,N'-dicyclohexylcarbodiimide and the corresponding alcohol,[12] were used without further purification and characterized by NMR.

O-Ethyl N,N'-dicyclohexylisourea. ^{1}H NMR ($CDCl_3$) = 1.23 (t, 3H, J = 6 Hz); 1.53 (m, 21H); 2.93 (m, 1H); 3.53 (broad s, 1H); 4.16 (q, 2H, J = 6 Hz).

O-Benzyl N,N'-dicyclohexylisourea. ^{1}H NMR ($CDCl_3$) = 1.56 (m, 21H); 2.90 (m, 1H); 3.60 (broad s, 1H); 5.23 (s, 2H); 7.43 (s, 5H).

Dialkyl 1-Benzyloxyamino Alkyl Phosphonates **3**, **3'**

1-Benzyloxyaminoalkyl phosphonic acid (5 mmol) was added to O-alkyl N,N'-dicyclohexylisourea (10 mmol) in benzene (25 ml). The stirred mixture was refluxed for 4 h. The reaction course was monitored by TLC: silica gel, EtOAc/CH_2Cl_2 1/9. The precipitated DCU was filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in EtOAc. The solution was treated with a 3% aq. $NaHCO_3$ solution (2 × 25 ml), water, dried on $MgSO_4$ and evaporated under reduced pressure. The solid residue was purified by recristallization and the oily residue was purified by a silica gel column chromatography (Table I).

Monoalkyl 1-Benzyloxyamino Benzyl Phosphonates **4**

Method A. To a solution of 1-benzyloxyamino benzyl phosphonic acid (5 mmol) and triethyl amine (5.5 mmol) in benzene (15 ml), was added O-benzyl N,N'-dicyclohexylisourea (5 mmol) in benzene (5 ml). The mixture was refluxed for 5 h with stirring. The reaction course was monitored by TLC (silica gel, EtOAc). The precipitated DCU was filtered, the solvent removed in vacuo and the residue diluted in CH_2Cl_2. The solution was washed with HCl 1N. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure. The addition of ether to the residue yielded a solid purified by recristallisation (Table II).

Method B. The 1-benzyloxyamino benzyl phosphonic acid was treated following the technique of Gilmore and Bride[4a] with DCC/Et_3N and ethanol or propanol, giving **4c** and **4"c** (Table II).

Method C. A mixture of 10 mmol of dibenzyl 1-benzyloxyamino benzyl phosphonate and 10 mmol of NaI in acetone was refluxed with stirring until total disappearance of the starting product (TLC). The solvent was removed; the residue, dissolved in chloroform (100 ml), was treated with HCl 2N. The organic layer was dried with $MgSO_4$ and evaporated. The residue was taken up in ethyl acetate and the product precipitated by freezing (Table II).

Alkyl 1-Benzyloxyamino Alkyl Phosphinate **5**.

A similar procedure to the one used for the preparation of 3 and 3' was employed: 5 mmol of 1-benzyloxyamino alkyl phosphinic acid and 5 mmol O-alkyl N-N'-dicycohexylisourea (Table III).

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