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THE FACILE SYNTHESIS OF DIALKYL 1-AMINOALKYL-PHOSPHONATES

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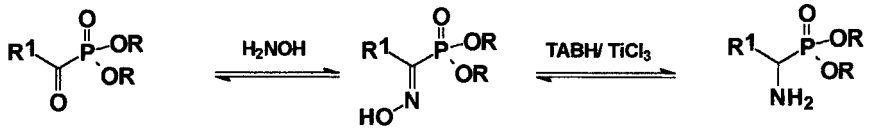
During past several years we have been engaged in the synthesis of phosphono peptides, peptide analogues with phosphonic acid replacing C-terminal carboxylate moiety. They became increasingly important since they appeared useful as carriers of toxic aminoalkylphosphonic acids through bacterial cell wall [1-4] or into plant tissues.[1,5] The most succesful method for the synthesis of these peptides is the condensation of N-blocked amino acids with dialkyl [6,7] or diphenyl [8,9] esters of aminoalkylphosphonic acids followed by removal of protecting groups.

The esters commonly used in phosphono peptide synthesis are obtained by a limited number of specific synthetic methods. Among them the most popular is the reduction of dialkyl 1-hydroxyiminoalkylphosphonates. This may be achieved by: catalytic hydrogenation over Raney nickel in ethanol; [10,11] reduction over aluminium amalgam in ethanol or

anhydrous ether; [11,12] reduction over zinc dust in formic acid [13,14] or zinc-copper couple in warm aqueous ethanol;[15] and using lithium borohydride/trimethylsilyl chloride mixture in dry THF.[16]

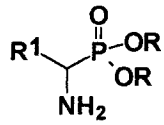
Herein we report that the facile synthesis of diethyl and dimethyl 1-aminoalkylphosphonates may be conveniently achieved in good yield by reduction of dialkyl 1-hydroxyiminoalkylphosphonates with sodium triacetoxyborohydride (TABH)/titanium trichloride system in the methanolic solutions of acetate buffer (pH 4).



Combination of low-valent titanium and borohydrides was used previously as efficient catalyst for the reduction of oximes.[17,18] The availability of 1-oxoalkylphosphonates, and consequently, of 1-hydroxyiminoalkyl-phosphonates should make this a useful route for the preparation of a number of aminophosphonate esters. As seen from Table 1 and Experimental Part, these esters are indeed readily prepared with good yields and their purification is extremely easy. The only exceptions are methyl esters of 1-aminoethylphosphonic and 1-aminopropylphosphnic acids which are readily solouble in water and thus difficult to recover from water phase by extraction.

We have also use tartarate buffer in hope that it allows a formation of an asymmetric complex and perhaps introduce asymmetry in the product. Similarily as reported earlier [18] only racemic mixtures of products were obtained while the yields of reactions were slightly lower than in the case of acetate buffer (Table 1).

Table 1. Dialkyl 1-aminoalyklphosphonates.



R^1	R	Yield (%)	^{1}H-N.M.R. ($CDCl_3$, TMS) δ (ppm)
CH_3	CH_3	5[a]	1.45 (dd, J_{PH}=10.5 Hz, J=7.1 Hz, 3H, $CHCH_3$); 3.20 (s, 2H, NH_2); 3.74 (d, J_{PH}=10.2Hz, $POCH_3$); 4.0-4.25 (m, 1H, CHP)
CH_3	CH_2CH_3	60[a]	1.34 (t, J_{PH}=7.15Hz, 6H, OCH_2CH_3); 1.54 (d, J=7.1Hz, 3H, $CHCH_3$): 3.9-4.35 (m, 7H, 2x$POCH_2$, CHP, NH_2)
CH_3CH_2	CH_3	25[a]	1.07 (t, J=7.1Hz, 3H, CH_3); 1.6-2.05 (m, 2H, CH_2); 3.6-3.8 (m, 3H, CHP, NH_2); 3.82 (d, J_{PH}=10.5Hz, 6H, $POCH_3$)
CH_3CH_2	CH_2CH_3	60[a] 50[b]	1.11 (t, J=7.1Hz,3H, CH_3); 1.37 (t, J=7.1Hz, 6H, $POCH_2CH_3$); 1.5-1.9 (m, 2H,CH_2); 3.02 (s, 2H,NH_2); 3.80 tt, J=5Hz, J_{PH}=10.5Hz,1H, CHP); 4.20 (qq, J=J_{PH}=7.3Hz, 2x$POCH_2$)
$(CH_3)CHCH_2$	CH_3	60[a] 35[b]	0.94 (d, J=6.5Hz, 6H, $CHCH_3$); 1.35-2.2 (m, 3H,$CHCH_2$); 3.2-3.4 (m, 1H, CHP); 3.81 (d, J_{PH}=10.5Hz, 6H, $POCH_3$); 4.01 (s, 2H,NH_2)
$C_6H_5CH_2$	CH_3	55[a] 50[b]	3.0-3.3(m, 4H, CH_2,NH_2); 3.79 (d, J_{PH}=10.3Hz, 6H, $POCH_3$); 4.0-4.2 (m, 1H,CHP); 7.29 (2, 5H,C_6H_5)
$C_6H_5CH_2CH_2$	CH_3	40[a]	1.25 (s, 2H,NH_2); 2.00 (q, J=7.2Hz, 2H, CH_2CHP); 2.60 (t, J=7.6Hz, $C_6H_5CH_2$); 3.76 (t, J_{PH}=10.5Hz, 6H, $POCH_3$); 7.21 (s, 5H, C_6H_5)

Yield given in relation to strarting acyl chloride if reaction was carried out:

[a] in acetate buffer; [b] in tartarate buffer

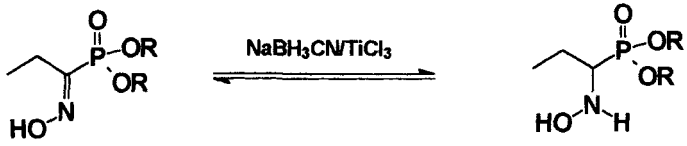
Table 2. The ifluence of the borohydride used on the reduction of diethyl 1-hydroxyiminopropylphosphonate.

Borohydride	Product	Yield (%)	Conversion of the substrate (%)
None	Aminophosphonate	23[a]	60[a]
TABH	Aminophosphonate	60[a] 41[b]	100[a] 50[b]
$NaBH_4$	Aminophosphonate	65[a] 51[b]	85[a] 75[b]
$NaBH_3N$	N-Hydroxyiminophosphonate	75[a] 65[b]	100[a] 100[b]

Yield given in the relation to 1-hydroxyiminopropylphosphonate if: [a] acetate buffer or [b] tartarate buffer were used

The exact mechanism of the reaction is unknown and both components, borohydride and titanium chloride act as reducing agents. Thus we have studied the reduction of diethyl 1-hyroxyimino-propylphosphonate in some detail varying the composition of the reducing mixture. Exclusion of titanium chloride from the reaction medium resulted in complete lack of reduction and substrate was recovered nearly quantitatively despite if sodium triacetoxybotohydride or sodium cyanoborohydride were used. Also a reaction of sodium cyanoborohydride in methanol did not produce the desired aminophosphonate. Titanium chloride if applied alone gave the diethyl 1-aminopropylphosphonate with moderate yield (Table 2). As shown in Table 2 the best results were obtained if the mixtures of titanium trichloride with TABH or sodium borohydride in acetate buffer were used. Application of sodium cyanoborohydride/titanium chloride system yielded corresponding N-

hydroxyaminophosphonate in good yield indicating that this reagent might be useful for the preparation of 1-N-hydroxyaminoalkylphosphonates:



Experimental

General comments

All the reagents were of analytical purity and were used without additional purification. ^{1}H-N.M.R. spectra were taken on Tesla BS 497 spectrometer at 100 MHz.

General procedure for the preparation of dialkyl 1-hydroxyimioalkyl-phosphonates

To the acyl chloride (0.28 mole) dialkylphosphite (0.25 mole) was added dropwise maintaining the temperature at -5^0 C. The mixture was then left overnight at room temperature and the volatile components of the reaction mixture were removed under reduced pressure. The crude products were of satisfactory purity.

Hydroxylamine hydrochloride (6.95 g; 0.1 mole) was dissolved in 50 ml of anhydrous methanol and equimolar amount of pyridine was added (8 ml). After 15 minutes crude dialkyl 1-oxoalkylphosphonate was added and the mixture was stirred overnight. Solvent and other volatile components of the reaction mixture were then removed by evaporation and oily residue was treated with cold 5% solution of hydrochloric acid (50 ml). Product was extracted into chloroform (4x 50 ml) and combined chloroformic extracts were washed with water (7 x 50 ml). The organic layer was then

dried over anhydrous sodium sulfate. Removal of drying agent and solvent yielded dialkyl 1-hydroxyiminoalkylphosphonates with good yields and of satisfactory purity.

Reduction of dialkyl 1-hydroxyalkylphosphonates

To the solution of dialkyl 1-hydroxyiminoalkylphosphonate (4 mmole) in methanol (15 ml) 4M acetate buffer (pH 4; 15 ml) was added followed by addition of 0.9M aqueous titanium chloride. Addition of titanium chloride resulted in characteristic dark green color. After 5 min solid TABH (2.54 g; 12 mmole) was added and slow decolorization of the reaction mixture was observed. The pH of the final white mixture was adjusted to 9 with saturated aqueous dipotassium hydrogen phosphate and finally sodium hydroxide solution and aqueous phase was extracted with chloroform (3 x 50 ml). Chemically pure dialkyl 1-aminoalkylphosphonates were obtained in this manner. They could be additionally purified by conversion into oxalates as described by Kowalik et al. [13]

Tartarate buffer was obtained by dissolving 0.5 mole of tartaric acid and 0.8 mole of sodium hydroxide in 500 ml of distilled water. Replacement of acetate by tartarate buffer (30 ml) yielded the desired 1-aminoalkyl-phosphopnates with good yields and of satisfactory purity.

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