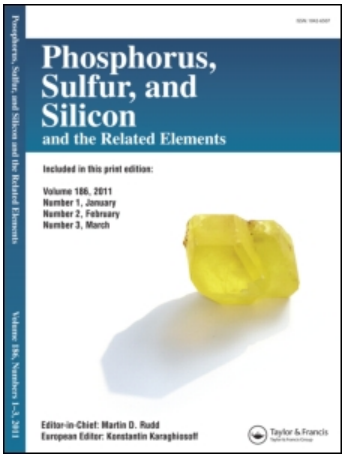

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1-HYDROXYAMINO ALKYL PHOSPHONIC AND PHOSPHINIC ACIDS

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1-HYDROXYAMINO ALKYL PHOSPHONIC AND PHOSPHINIC ACIDS

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The removal of the benzyl protecting group of 1-benzyloxyamino alkyl phosphonic and phosphinic acids and their N-acetylated derivates was effected by boron tris(trifluoroacetate) (BFTA) or by catalytic transfer hydrogenation (CTH) with ammonium formate and 10% Pd/C. The corresponding 1-hydroxyamino acids were obtained with yields ranging 60–80%.

Key words: 1-Benzyloxyamino alkyl phosphonic or phosphinic acids; 1-hydroxyamino alkyl phosphonic or phosphinic acids; debenzylation; BTFA; CTH; ammonium formate.

As part of our program directed to the synthesis of phosphonic analogs of peptides, we studied various and suitable benzyl group cleavage methods which are applicable for the synthesis of benzyloxyamino-1 alkyl phosphonic or phosphinic acids[1] and their N-acetylated derivatives. These methods will be subsequently used with N-benzyloxyamino phosphono peptides.

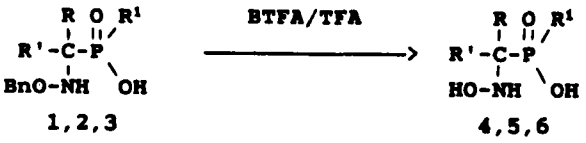
In this paper, we report our results obtained with: 1) Boron tris(trifluoroacetate): BTFA; 2) Catalytic transfert hydrogenation (CTH) with ammonium formate and Pd/C 10%.

I. BORON TRIS (TRIFLUOROACETATE) (BTFA)

Boron halogenated compounds such as BBr_3 and BI_3 are well known to effect quantitative removal of benzyloxycarbonyl or other acid labile groups. BTFA is easily obtained as a solid in the reaction of BBr_3 with trifluoroacetic acid (TFA) in dichloromethane at 0°C and can be handled with no special cautionary measures or apparatus.[2]

The cleavage of a benzyl group from 1-benzyloxyamino alkyl phosphonic and phosphinic acids is undertaken with BTFA in TFA at 0°C, followed by stirring at room temperature during about 12 hours to ensure the completion of the reaction. Yields of unprotected products are not improved by longer reaction times. 1-Hydroxyamino alkyl phosphonic and phosphinic acids are obtained as solids with good yields (60–80%).

Although BTFA can be applied for the removal of benzyl groups in phosphono peptides with terminal phosphonate or phosphinate moieties, it cannot be used with compounds having a phosphonamido or phosphinamido link, because of their lability in acidic medium.[3]



1a, 4a	R = H	R' = CH_3	R^1 = OH
1b, 4b	R = H	R' = C_6H_5	R^1 = OH
2b, 5b	R = H	R' = C_6H_5	R^1 = CH_3
3b, 6b	R = H	R' = C_6H_5	R^1 = C_6H_5
3c, 6c	R = CH_3	R' = CH_3	R^1 = C_6H_5

Scheme 1

II. CATALYTIC TRANSFERT HYDROGENATION (CTH) WITH AMMONIUM FORMATE AND 10%Pd/C

The use of CTH is postulated in the literature as a very selective method for the cleavage of O-Bn and N-Bn links.[4] The most employed hydrogen donors are: cycloxene,[5-8] cyclohexadiene-1,3 or 1,4,[9] formic acid and sodium or ammonium formates.[10-15]

It is necessary to protect the amine function to avoid the reduction of the HN-OBn moiety into NH_2 group as reported in the case of unprotected NH-OH compounds.[16,17]

The N-protection of the amino group can be effected by different ways:

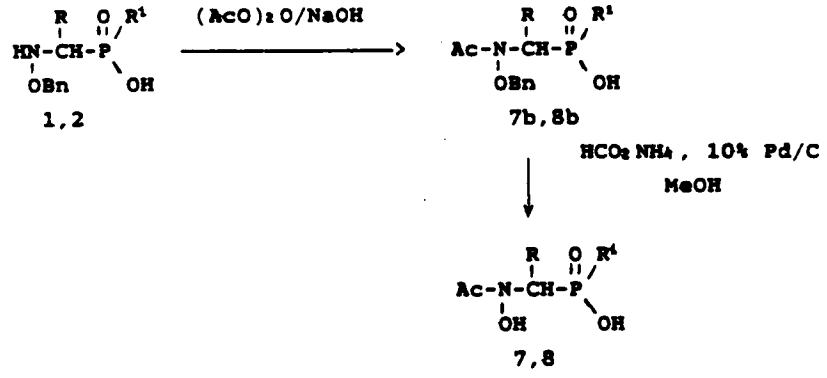
—N-Boc derivative, usually employed in the synthesis of N-hydroxy peptides[18] is not appropriate for phophono peptide due to the acido-labile P—N link.

—N—Z compounds, obtained under GILMORE's reaction conditions[19] are also not suitable: catalytic hydrogenolysis removes simultaneously the benzyl group of N-OBn and peptide benzylic esters groups [—C(O)(OBn)]; [—P(O)$(OBn)_2$]. The best protecting N-substitution for these compounds are: acetyl and trifluoracetyl, which are cleavable in basic medium.

Our experiments were realized with ammonium formate and 10% Pd/C on N-acetylated compounds obtained by acetylation of benzyloxyamino-1 alkyl phosphonic or phosphinic acids without solvent or in refluxing dioxane.[20] N-acetylated derivates 2′ et 3′ treated by ammonium formate and 10% Pd/C in methanol, at ambiant temperature, led to N-acetyl hydroxyamino-1 alkyl phosphonic and phosphinic acids with good yields.

It is interesting to note that these cleavage reactions with 1-benzyloxyamino alkyl phosphonic or phosphinic acids do not occur in methanol at room temperature, initial products being recovered. Only decomposition products are obtained if the reaction is conducted under solvent reflux.

These cleavage methods will be subsequently applied to the synthesis of fully unprotected N-hydroxy phosphono peptides which are now under study.



1b, 7b, 7 R = C_6H_5 R^1 = OH

2b, 8b, 8 R = C_6H_5 R^1 = CH_3

Scheme 2

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). FAB mass spectra were obtained on a Jeol DX 300 Mass Spectrometer.

1-Hydroxyamino Alkyl Phosphonic and Phosphinic Acids **4, 5, 6.**

BTFA was synthesized according to the procedure of Pless and Bauer.[2]

1-Benzyloxyamino alkyl phosphonic and phosphinic acids were obtained according to Reference 1.

General procedure

1-Benzyloxyamino alkyl phosphonic acids **1** or phosphinic acids **2, 3** (2 mmol) were added to a solution of 10 mmol of BTFA in 5 ml of TFA at 0°C. The mixture was stirred at room temperature for 12 hours, diluted with methanol and filtered. The filtrate was evaporated to dryness under reduced pressure. This operation was repeated several times for complete removal of boron compounds and impurities.

After distillation of the solvent under vacuum, the solid was washed with hot ethanol for purification.

1-Hydroxyamino ethyl phosphonic acid **4a** from 1-benzyloxyamino ethyl phosphonic acid **1a**. Yield = 65%. mp = 173°C. ^{1}H NMR (TFA) δ = 1.83 (dd, 3H, J = 7 Hz, J = 14 Hz); 4.26 (m, 1H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 142.

1-Hydroxyamino benzyl phosphonic acid **4b** from 1-benzyloxyamino benzyl phosphonic acid **1b**. Yield = 80%. mp = 188°C. ^{1}H NMR (TFA) δ = 5.43 (d, 1H, J = 18 Hz); 7.73 (s, 5H). MS: unattainable (**4b** was not soluble for recording MS spectrum).

Methyl 1-hydroxyamino benzyl phosphinic acid **5b** from methyl 1-benzyloxyamino benzyl phosphinic acid **2b**. Yield = 70%. mp = 146°C. ^{1}H NMR (TFA) δ = 1.87 (d, 3H, J = 16 Hz); 5.36 (d, 1H, J = 12 Hz); 7.76 (s, 6H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 202.

Phenyl 1-hydroxyamino benzyl phosphinic acid **6b** from phenyl 1-benzyloxyamino benzyl phosphinic acid **3b**. Yield = 70%. mp = 153°C. ^{1}H NMR (TFA) δ = 5.37 (d, 1H, J = 12 Hz); 7.60 (s, 5H); 7.66 (m, 5H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 264.

Phenyl 1-hydroxyamino 1,1-dimethyl methyl phosphinic acid **6c** from phenyl 1-benzyloxyamino 1,1-dimethyl methyl phosphinic acid **3c**. Yield = 60%. mp = 169°C. ^{1}H NMR (TFA)(δ = 1.40 (d, 6H, J = 14 Hz); 7.66 (m, 5H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 216.

N-Acetyl 1-Hydroxyamino Alkyl Phosphonic and Phosphinic Acids **7, 8.**

a) N-Acetyl 1-benzyloxyamino alkyl phosphonic and phosphinic acids **7b, 8b**.

To a stirred solution of 10 mmol of **1b** or **2b** in dioxane (15 ml) were added 2N NaOH (10 ml for **1b** and 5 ml for **2b**) and 10 ml of acetic anhydride. After refluxing for 2 h, the solvent was evaporated under vacuum. The residue was diluted with 30 ml of chloroform, acidified with 1N/HCl until pH = 1.5. The organic layer was separated, dried over sodium sulfate, concentrated to dryness. The residue was extracted with ethanol and evaporated many times until complete removal of acetic acid. The product precipitated by addition of cold ethanol.

N-Acetyl 1-benzyloxyamino benzyl phosphonic acid **7b**. **7b** from **1b**: Yield = 75%. mp (ethanol) = 167°C, ^{1}H NMR ($CDCl_3$/$DMSOd_6$) δ = 2.20 (s, 3H); 4.93 and 5.23 (AB system, 2H, J = 10 Hz); 6.00 (d, 1H, J = 25 Hz); 7.50 (s, 5H); 7.66 (m, 5H). MS FAB (Matrix: NOBA) (m/z) $(M + H)^+$: 336.

Methyl N-acetyl 1-benzyloxyamino benzyl phosphinic acid **8b**. **8b** from **2b**: Yield = 80%. mp (acetone/ethanol) = 174°C. ^{1}H NMR ($CDCl_3$) δ = 1.40 (d, 3H, J = 15 Hz); 2.15 (s, 3H); 4.99 and 5.10 (AB system, 2H, J = 10 Hz); 5.60 (d, 1H, J = 21 Hz); 7.43 (s, 5H); 7.60 (m, 5H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 334.

b) N-Acetyl 1-hydroxyamino alkyl phosphonic and phosphinic acids **7, 8.**

To a solution of **7b** or **8b** (2 mmol) in methanol (15 ml) were added ammonium formate (10 mmol) and an equal weight of 10% Pd/C. The mixture was stirred at room temperature for 1.5 h. The black precipitate was filtered on celite. After evaporation of the solvent under vacuum, the solid was purified by crystallization.

N-Acetyl 1-hydroxyamino benzyl phosphonic acid **7**. **7** from **7b**: Yield = 95%. mp (ethanol/methanol) = 173°C. ^{1}H NMR ($DMSOd_6$) δ = 2.02 (s, 3H); 5.72 (d, 1H, J = 21 Hz); 7.52 (m, 5H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 246.

Methyl N-acetyl 1-hydroxyamino benzyl phosphinic acid **8**. **8** from **8b**: Yield = 97%. mp (ethanol) = 190°C. ^{1}H NMR ($DMSOd_6$) δ = 1.00 (d, 3H, J = 13 Hz); 2.03 (s, 3H); 5.53 (d, 1H, J = 15 Hz); 7.43 (m, 5H). MS FAB (Matrix: glycerol) (m/z) $(M + H)^+$: 244.

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