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N-Hydroxy-α-Amino Phosphonate Derivatives As Potential Haptens For Eliciting Catalytic Antibodies

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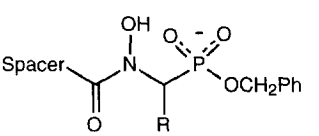
Abstract: *an efficient synthesis of N-hydroxy–α-amino phosphonate derivatives has been developed using a Mitsunobu reaction with N-phenoxycarbonyl-O-tert-butyl-alkoxycarbonyl hydroxylamine and α-hydroxy phosphonates.* Copyright © 1996 Elsevier Science Ltd

Key words: *catalytic antibodies, N-hydroxy-α-amino acids, N-hydroxy-α-amino phosphonates , Mitsunobu reaction*

Enantiomerically pure α-amino acids are of immense interest, particularly as chiral building blocks for the synthesis of more complex molecules, chiral reagents, and catalysts.[1] Although a large number of natural amino acids and their enantiomers are commercially available, the corresponding N-hydroxy-α-amino acids are not. These compounds are important in many metabolic and biological processes and are good synthons for other uncommon amino acids.[2] The synthesis of enantiomerically pure N-hydroxy-α-amino acids is still a challenging problem because in solution, they undergo pH dependent oxidative decarboxylation or dismutation.[3] One of the best asymmetric synthetic route to this class of compound is the electrophilic amination of bornanesultam-derived enolates with 1-chloro-1-nitrosocyclohexane.[4]

We set out to explore the possibility of kinetically resolving N-hydroxy-α-amino ester derivatives using antibodies possessing an *esterase activity.* [5] Like enzymes, antibodies can operate under very mild conditions and this should be compatible with fragile amino acid derivatives. In addition, this strategy offers the possibility to obtain antibodies that are specific for D- or L-aminoesters. These antibodies can be elicited by using the transition-state analogs, N-hydroxy-α-amino phosphonate derivatives I, as it has been previously shown that antibodies raised against haptens containing charged tetrahedral phosphorous can catalyse hydrolytic reactions in a stereospecific manner. [6]

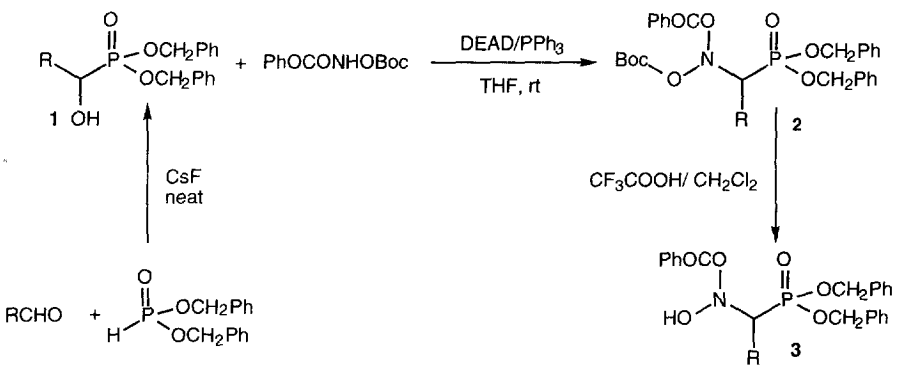


I

Although the chemistry of α-amino phosphonic acids is extensively studied [7], we were surprised to note that to our knowledge, only a few synthesis of racemic or enantiomerically pure N-hydroxy-α-amino phosphonic acids have been reported in the literature.[8] The only asymmetric synthesis of N-hydroxy-α-amino phosphonic acids involved as the key step the addition of tris(trimethylsilyl)phosphite to a chiral N-glycosylnitrone derivative.

This communication reports preliminary results on a new approach for the synthesis of N-hydroxy-α-amino phosphonate derivatives. The key step is a Mitsunobu SN_2-type displacement reaction[9] of the corresponding α-hydroxy phosphonates **1** with N-(phenoxycarbonyl)-O-tert-butyloxycarbonyl hydroxylamine[10] (Scheme 1, Table 1). This reaction has been previously used successfully for the preparation of N-hydroxy-α-amino carboxylic acid derivatives. [11]

Compounds **1** were easily prepared following a known procedure[12] employing a cesium fluoride catalysed addition of dibenzylphosphite to the corresponding aldehydes. The reactions of the α-hydroxy phosphonates **1** with N-(phenoxycarbonyl)-O-tert-butyloxycarbonyl hydroxylamine afforded the corresponding N-(phenoxycarbonyl)-O-tert-butyloxycarbonyl-hydroxyamino phosphonates **2** as homogeneous oils after column chromatography in moderate to good yields (Scheme 1, Table 1). [13,14]



Scheme 1

No side products were observed in the crude mixtures, except for the reaction of dibenzyl α-hydroxy-2-phenylethylphosphonate (Table 1, entry 5). In this particular case, product **2** was isolated in only 36% yield with the major product being $PhCH=CHPO(OCH_2Ph)_2$ formed by a β elimination process.

The corresponding N-(phenoxycarbonyl)-α–N-hydroxylamino phosphonates **3** were readily obtained in satisfactory yields by treating at room temperature compounds **2** with a 20% solution of trifluoroacetic acid in dichloromethane (Scheme 1, Table 1).[13]

Table 1. Preparation of compounds **1**, **2** and **3**.

Entry	R	yield **1** [a] (%)	yield **2** [a] (%)	yield **3** [a] (%)
1	Me	69	53	40
2	Et	62	50	75
3	$CH(CH_3)_2$	73	29	50
4	$CH_2CH(CH_3)_2$	61	64	66
5	CH_2Ph	67	36[b]	57
6	CH_2CH_2Ph	90	96	58

a: isolated yields after column chromatography; b: the major product is $PhCH{=}CHPO(OCH_2Ph)_2$ (62%)

The synthesis of N-hydroxy-α-amino phosphonic acids derivatives using the Mitsunobu reaction of a hydroxylamine derivative with α-hydroxy phosphonates has not been described previously in the literature. The procedure reported herein complements those already reported[8] and has the added advantage of obtaining the desired products by using readily available substrates and cheap reagents.

The extension of this methodology to the synthesis of a large variety of enantiomerically pure N-hydroxy-α-amino phosphonic acid derivatives from the corresponding optically pure α-hydroxy phosphonates [15] is under current investigation in this laboratory.

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(13) Compounds **1**, **2** and **3** are new and have been characterized by ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, IR and mass spectroscopy.

(14) A typical procedure is as follows: to a solution of freshly distilled THF (5ml) containing compound **1** (1eq, 0.66mmol), triphenylphosphine (2eq, 1.32mmol) and hydroxylamine (1.5eq, 0.99mmol), was added dropwise neat DEAD (2eq, 1.32mmol) under argon. The solution was stirred at room temperature until disappearance of the starting material (1-2 hours) and then concentrated in vacuo. The residue was purified by flash column chromatography over silica gel using a mixture of hexane-ethylacetate as eluant.

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