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Preparation of enantiomerically pure α-hydroxyl phosphinates via hydrophosphorylation of aldehydes with *H*-phosphinate

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ABSTRACT

The hydrophosphorylation of aldehydes with a *P*-stereogenic *H*-phosphinate was realized by heating two compounds in a neat state or catalyzed by a base, to afford *P*-retention α-hydroxyl phosphinates. The (S_P,S_C) and other diastereomers were isolated, and their structures were confirmed by NMR spectroscopy and crystallography.

1. Introduction

α-Hydroxyl phosphonic acid derivatives are an important structural unit in many biologically active substances and are used as important enzyme inhibitors.[1] For example, they are inhibitors of medicinally important enzymes, as renin[2] or HIV protease.[3] They also show anti-virus[4] and anti-cancer activities.[5] Normally, as an optically active substance, only one enantiomer of α-hydroxyl phosphonic acid derivatives shows activity in a racemic mixture. Therefore, methods for the synthesis of enantiomerically pure compounds are highly desirable.

The addition of H-P species to C=O double bonds, known as the Pudovik reaction,[6] is one of the most straightforward and atom-economical pathways to α-hydroxyl phosphonic acid derivatives. Many research groups have dedicated their efforts to develop either highly active catalysts or asymmetric approaches for this reaction. The reported asymmetric Pudovik reaction is mainly used in the synthesis of carbon-stereogenic α-hydroxyl phosphoric derivatives from the addition of non-chiral P-H species to aldehydes, but involves difficult to assemble chiral catalysts or auxiliaries.[7]

Furthermore, the synthesis of α-hydroxyl phosphoric derivatives containing both carbon and phosphorus stereogenic centers is limited. Zhao et al. obtained *P*,*C*-stereogenic α-hydroxyl phosphinates,[8] as a mixture of two diastereomers that have a different configuration on the phosphorus. Montchamp et al. reported the preparation of *P*,*C*-stereogenic α-hydroxyl phosphinates in 94% de by means of a Wittig rearrangement.[9] However, the straightforward synthesis of *P*,*C*-stereogenic α-hydroxyl phosphinates from *P*-stereogenic H-P species has scarcely been reported on.

When *P*-stereogenic H-P species are applied to the Pudovik reaction, up to four possible stereoisomers will be formed due to newly generated carbon and phosphorus stereogenic centers.[10] Tang et al. reported on the Me_3SiCl-promoted addition of diastereomeric mixture of menthyl *H*-phenylphosphinate to aromatic aldehydes. In their procedure, a mixture of four stereoisomers was obtained and no stereoisomer was separated.[10b] Recently, we reported base-catalyzed Pudovik reaction of (R_P)-*O*-(−)-menthyl *H*-phenylphosphinate **1** with ketones, the (S_P,R_C)-stereoisomer of α-hydroxyl phosphinates was formed predominately.[11] However, only tertiary α-hydroxyl phosphinates were obtained from this reaction. For the purpose of obtaining secondary α-hydroxyl phosphinates, a similar reaction of (R_P)-**1** with aldehydes was examined. We found that the reaction proceeded more easily than with the ketone, occurring under catalyst-free conditions at ambient temperature. Although the diastereoselectivities on carbon were unsatisfactory, the same *P*-retention products were obtained, and one or two diastereomers can be isolated. The structures of four possible stereoisomers were confirmed. One pair of diastereomers was converted into each other in the presence of a base, which can be used for the isolation of a single diastereomer.

2. Results and discussions

The hydrophosphorylation of aldehydes was initially examined with a diastereomeric mixture of (R_P)-**1**/(S_P)-**1** (ca. 50:50). When the mixture was heated with *p*-tolualdehyde **2b** at 80 °C in a neat state, four stereoisomers $\mathbf{3b_A}$, $\mathbf{3b_B}$, $\mathbf{3b_C}$, and $\mathbf{3b_D}$ of the α-hydroxyl

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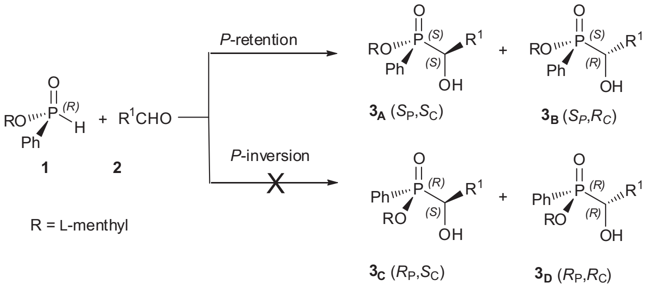
phosphinate were formed, which had the corresponding peaks on ^{31}P NMR spectra at δ 36.9, 36.5, 35.7, and 34.7 ppm. The multiple peaks were located around δ 4.9–5.1 ppm on proton NMR spectra, and which were assigned as protons linked to α-carbons. When enantiomerically pure (R_P)-**1** was used, the above four stereoisomers might be formed depending on a *P*-retention or inversion mechanism (Scheme 1). However, the observation of two peaks at 36.5 and 34.7 ppm indicated that only two stereoisomers were formed. We believed the stereoisomers were derived from the (*R*)- and (*S*)-configuration on the α-carbon, assigned as **3b**$_{\mathbf{A}}$ (S_P,S_C) and **3b**$_{\mathbf{B}}$ (S_P,R_C), and *P*-retention reaction occurred (vide infra).[10–12] When (R_P)-**1**/(S_P)-**1** was used, (S_P)-**1** afforded **3b**$_{\mathbf{C}}$ and **3b**$_{\mathbf{D}}$ simultaneously, via the same *P*-retention mechanism.



Scheme 1. Proposed formation of four stereoisomers **3**$_{\mathbf{A}}$–**3**$_{\mathbf{D}}$.

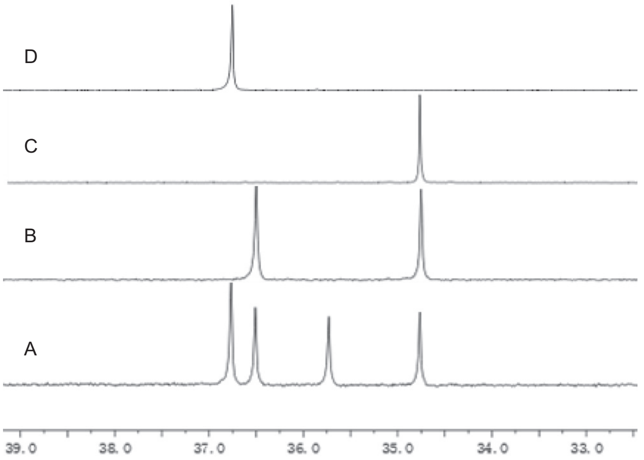


Figure 1. Display of peaks in the ^{31}P NMR spectra for four stereoisomers **3b**$_{\mathbf{A}}$ to **3b**$_{\mathbf{D}}$. (A) **3b**$_{\mathbf{A}}$ to **3b**$_{\mathbf{D}}$; (B) **3b**$_{\mathbf{A}}$ and **3b**$_{\mathbf{B}}$; (C) Isolated **3b**$_{\mathbf{A}}$; (D) Isolated **3b**$_{\mathbf{C}}$.

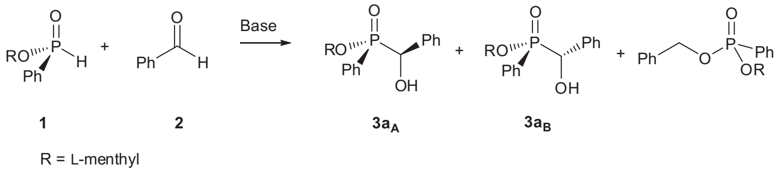
The ^{31}P NMR spectra for the hydrophosphorylation of **2b** with (R_P)-**1** or (R_P)-**1**/(S_P)-**1** are shown in Figure 1. When (R_P)-**1** was used, the peak at 34.7 ppm belonged to **3b**$_{\mathbf{A}}$, whose S_PS_C structure was confirmed by X-ray diffraction. The peak at 36.5 ppm was assigned to its associated diastereomer **3b**$_{\mathbf{B}}$ (S_PR_C) (part B and C). The isolated **3b**$_{\mathbf{C}}$ has a peak at 36.9 ppm (part D), which confirms its (R_P,S_C)-structure was confirmed. Therefore, the remaining peak at 35.7 ppm was assigned as **3b**$_{\mathbf{D}}$. The four peaks in part A were confirmed as **3b**$_{\mathbf{C}}$ (R_P,S_C), **3b**$_{\mathbf{B}}$ (S_P,R_C), **3b**$_{\mathbf{D}}$ (R_P,R_C), and **3b**$_{\mathbf{A}}$ (S_P,S_C), going from downfield to upfield. Similar peaks for the reaction of **2a** with (R_P)-**1**/(S_P)-**1** were also confirmed based on the structures and chemical shifts of **3a**$_{\mathbf{A}}$ and **3a**$_{\mathbf{D}}$.

The reaction of (R_P)-**1** to **2a** under various conditions was investigated. As can be seen in Table 1, the reaction did not occur at room temperature in the absence of base, either in a neat state or in solution (entries 1 and 6). When (R_P)-**1** and **2a** were heated at 80 °C, the reaction was completed with entire conversion of (R_P)-**1** (entry 2). In entries 3–5, it can be seen that the addition was obviously accelerated by a base but was not by a free radical initiator AIBN; therefore an ionic rather than free radical[13] mechanism was presumed.[6d,14]

The acceleration of a base can also be observed in DMSO solution. In the presence of potassium carbonate, all of (R_P)-**1** was consumed within one hour at room temperature (entry 8). Prolonged stirring resulted in a side reaction, forming O-phosphorylated product **4** (entries 9 and 10). The side reaction can be avoided when catalyzed by calcium hydroxide (entry 7). Although the chirality on the phosphorus was retained, attempts to improve the dr$_C$ of **3a**$_{\mathbf{A}}$/**3a**$_{\mathbf{B}}$ were unsuccessful when the reaction was carried out in different solvents or at low temperature.

Hydrophosphorylation of various aldehydes with (R_P)-**1** was carried out by heating two starting materials at 80 °C in a neat state. In most cases shown in Table 2, adducts were obtained and no obvious side reaction was detected. Some aliphatic aldehydes also afforded **3**$_{\mathbf{A}}$/**3**$_{\mathbf{B}}$ in high yield. For isobutyraldehyde **2m**, the best dr$_C$ of 70:30 was acquired (entry 15), which might be due to the spatial hindrance of the large substituent of **2m**.[10a] Single diastereomers **3**$_{\mathbf{A}}$ could be isolated from the mixture of **3**$_{\mathbf{A}}$/**3**$_{\mathbf{B}}$ by recrystallization

Table 1
Hydrophosphorylation of **2a** with (R_P)-**1** under various conditions



Entry	Catalyst (mol %)	Solvent	Temp./time	Yield % (dr$_C$)[a]
1	No	No	Rt/24 h	NR
2	No	No	80 °C/9 h	99 (46:54)
3	AIBN (10)	No	80 °C/1 h	24 (57:43)
4	No	No	80 °C/1 h	23 (57:43)
5	LiOH (25)	No	80 °C/1 h	41 (49:51)[b]
6	No	DMSO	Rt/24 h	NR
7	$Ca(OH)_2$ (25)	DMSO	Rt/24 h	99 (49:51)[b]
8	K_2CO_3 (25)	DMSO	Rt/1 h	99 (53:47)
9	K_2CO_3 (25)	DMSO	Rt/24 h	90 (48:52)[c]
10	K_2CO_3 (25)	DMSO	Rt/48 h	81 (41:59)[c]
11	KOH (25)	DMSO	Rt/17 h	84[c]

[a] The yield and dr$_C$ [ratio of (S_P,S_C)-**3a**$_{\mathbf{A}}$/(S_P,R_C)-**3a**$_{\mathbf{B}}$ stereoisomers] were estimated by ^{31}P NMR spectra.
[b] Catalyst was suspended in the reaction mixture.
[c] The yield of O-phosphorylated product **4**.