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A Novel Method for the Separation of Bis(α-hydroxyalkyl)phosphinic Acid Diastereoisomers via Formation of Novel Cyclic Phosphinic Acids

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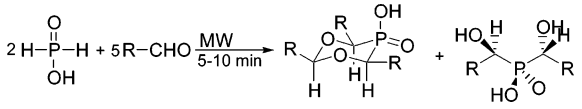

The reaction of aromatic and aliphatic aldehydes with hypophosphorus acid under microwave irradiation was examined. The reaction gave a mixture of a racemic pair of bis(α-hydroxyalkyl)phosphinic acids and acetal derivatives from the corresponding bis(α-hydroxyalkyl)phosphinic acids of *meso*-stereochemistry in good yield. The difference in solubility in organic solvents due to polarity allowed us to readily separate these compounds. This method constitutes an easy, rapid, and good-yielding preparation and separation of bis(α-hydroxyalkyl) phosphinic acid diastereoisomers from simple starting materials using microwave irradiation.

In the past decade, α-functionalized phosphinic acid derivatives have attracted a great deal of attention due to their usefulness both in medicinal and in material chemistry.[1−8] Among α-functionalized phosphinic acids, α-hydroxyphosphinic acids are an important class of compounds that exhibit a variety of interesting and useful properties.[9−16] Some α-hydroxyphosphinic acids are useful intermediates for α-hydroxyphosphinyl peptides, showing good inhibitory activity against renin.[17] Symmetric or pseudo-symmetric bis(α-hydroxyalkyl)phosphinic acid derivatives have also drawn attention in the designs of HIV protease inhibitors.[18,19] Moreover, α-hydroxyphosphinic acid derivatives are useful intermediates in the synthesis of other phosphorus compounds of material interest that are used as organophosphorus polymers possessing flame-resistant, corrosion-resistant, ion-exchange properties and as extractants for the recovery or separation of some metal ions.[20−26] As a part of our effort to explore the utility of microwave-assisted reactions for the synthesis of organophosphorus compounds,[27] we recently described

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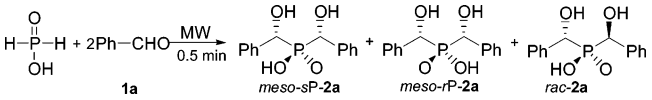
SCHEME 1



a new method for the synthesis and separation of bis(α-hydroxyalkyl)phosphinic acids from the reactions of hypophosphorous acid with aldehydes using microwave irradiation.[28,29] Herein, we report on new aspects of the microwave-assisted reaction of hypophosphorus acid with aldehydes, which are applicable for the separation of bis(α-hydroxyalkyl)phosphinic acid diastereoisomers via formation of novel cyclic phosphinic acids under microwave irradiation. We first carried out the reaction of benzaldehyde **1a** with hypophosphorus acid under microwave irradiation as a model reaction. When the reaction was conducted under microwave irradiation for 0.5 min, a diastereomeric mixture of bis(α-hydroxyphenylmethyl)phosphinic acid (**2a**) was obtained in 82% yield (in a 56:45 ratio of diastereoisomers, Scheme 1). The ^{31}P NMR spectrum of this mixture exhibited two peaks at δ 38.55 and 36.38 ppm due to the diastereoisomers. The ^{1}H NMR spectrum exhibited two doublets at δ 5.09 and 4.80 ppm indicative of H−P coupling (J_{HP} = 7.4 Hz). Because of the presence of two stereogenic carbons bonded to the phosphorus atom, and the phosphorus atom itself having a pseudoasymmetric center, these compounds theoretically exist as three diastereomeric forms: two meso-compounds (*meso-r*P-**2a** and *meso-s*P-**2a**) and one racemic pair (*rac*-**2a**), as shown in Scheme 1. However, the ^{31}P and ^{1}H NMR spectra suggest that *meso-r*P-**2a** and *meso-s*P-**2a** are rapidly interchanged under solution conditions due to the prototopic transfer of the acidic proton between the phosphoryl (P═O) and acidic (P−OH) sites. Thus, only two signals corresponding to the racemic form and the interchangeable *meso* form (*meso*-**2a**)[30] were observed in the NMR spectra. When the reaction mixture was subjected to washing with successively nonpolar and polar solvents, only *rac*-**2a** was extracted with methanol of high-polarity. The stereochemistry of *rac*-**2a** was confirmed after conversion to the corresponding methyl ester using trimethyl orthoformate under microwave irradiation for 10 min.[29]

Contrary to the above results, when the same reaction was carried out under prolonged irradiation (5 min) in the presence of an excess of benzaldehyde, a mixture of two products was obtained in an 80% yield. The ^{31}P NMR spectrum of the mixture exhibited two peaks at δ 38.63 and 16.80 ppm because of the phosphorus atom of the two products. Although one of the peaks was consistent with that of *rac*-**2a**, surprisingly we found that the peak due to *meso*-**2a** disappeared and another new peak appeared in the ^{31}P NMR spectrum. This new peak was found to correspond with the compound shown in structure **3a**, which was readily separated by column chromatography on silica gel (Scheme 2). The ^{1}H NMR spectrum of **3a** exhibited two doublets

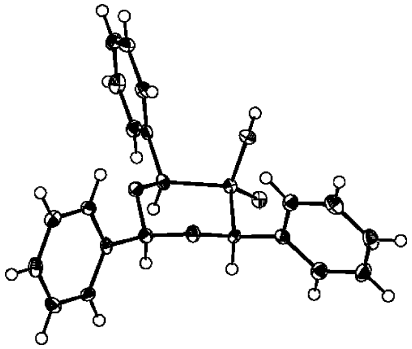
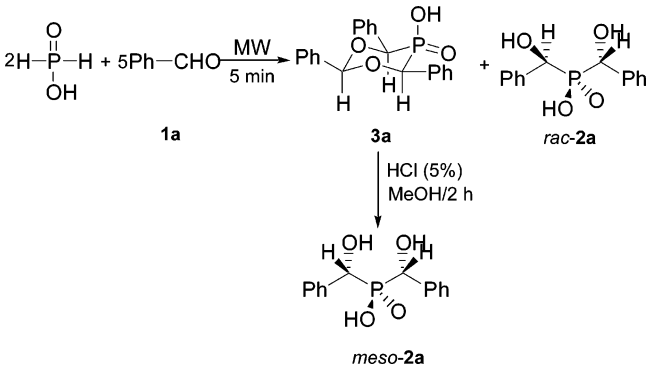


FIGURE 1. ORTEP drawing of **3a**.

SCHEME 2



at δ 5.65 and 6.28 ppm indicative of H−P coupling ($^{2}J_{HP}$ = 3.7 and $^{4}J_{HP}$ = 2.0 Hz). On the other hand, the ^{13}C NMR spectrum of **3a** exhibited one doublet peak at 81.1 ppm (α-carbon to phosphorus atom) and a single peak at 102.9 ppm corresponding to the acetal carbon atom. The structure and stereochemistry of **3a** were unambiguously determined by X-ray crystallographic analysis. The ORTEP drawing of **3a** and its crystal packing in the unit cell are shown in Figures 1 and 2, respectively. While all phenyl groups of **3a** were in the equatorial position as expected, the acidic site (P−OH) of the phosphinate function took an axial position rather than an equatorial position in the ORTEP. It is worthy to note that **3a** has a hydrogen bond with other molecules **3a** in the unit cell of the crystal with a stereochemistry such that P═O exists in an equatorial position as shown in Figures 1 and 2. It should be noted that, like acetal formation, a diol (*meso*-**2a**) was treated with benzaldehyde (**1a**) to give a cyclic acetal (**3a**). Hydrolysis of **3a** using 5% HCl in methanol gave the *meso* diastereoisomer (*meso*-**2a**)[27]of bis(α-hydroxyphenylmethyl)phosphinic acid (Scheme 2). The diastereoisomers (*rac*-**2a** and *meso*-**2a**) do not interconvert under the reaction conditions.

This process was successfully applied to other aldehydes (**1**) as summarized in Table 1. As shown in Scheme 3 and Table 1, the reaction of hypophosphorus acid with aromatic aldehydes (**1a**−**1k**), under microwave irradiation, afforded a readily separable mixture of acetals (**3a**−**3k**) and *rac*-**2a**−**k** in good yield.

Aliphatic aldehyde (**1l**) also reacted with hypophosphorus acid under the same conditions. However, in this reaction, acetal formation of the *meso*-diastereomer did not proceed and an inseparable mixture (1:1) of *meso*-**2l** and *rac*-**2l** was obtained in 67% yield (Scheme 4).

The reaction of heterocyclic aromatic aldehydes and *p*-nitrobenzaldehyde with hypophosphorus acid under microwave irradiation gave unknown mixed products.

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(30) A product number *meso*-**2a** is designated for the interchangeable *meso-s*P-**2a** and *meso-r*P-**2a**. In Scheme 2, the structure of *meso-s*P-**2a** is drawn as *meso*-**2a** for the purpose of convenience.

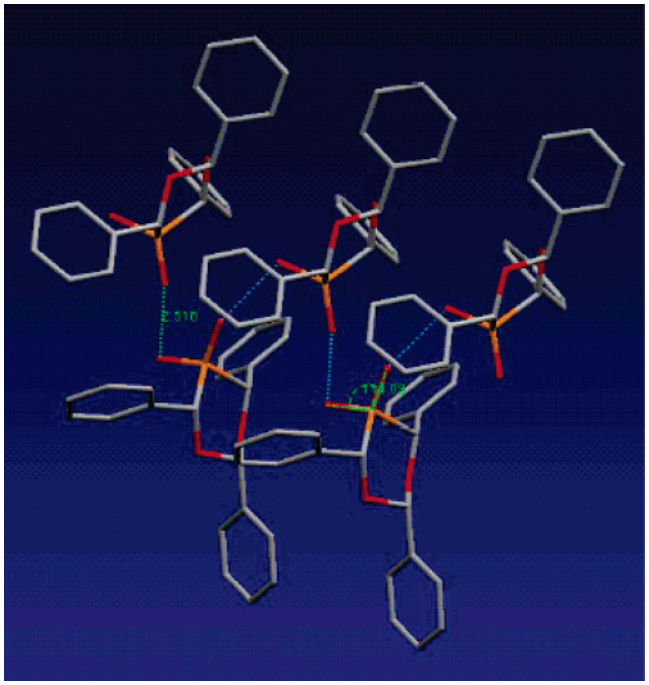


FIGURE 2. Crystal packing of **3a** in the unit cell.

TABLE 1. Reaction of Hypophosphorus Acid with Aldehydes under Microwave Irradiation

entry	R **1**	time[a] (min)	yields (**3**)[b] (%)	yields (**2**)[a] (%)
a	C_6H_5	5	44	36
b	*p*-ClC_6H_4	5	34	40
c	*p*-BrC_6H_4	5	37	35
d	*p*-FC_6H_4	6	36	35
e	*m*-BrC_6H_4	10	35	35
f	*m*-FC_6H_4	10	35	41
g	*m*-ClC_6H_4	10	41	41
h	*m*-$CH_3OC_6H_4$	7	42	34
i	*m*-$CH_3C_6H_4$	10	29	39
j	*o*-FC_6H_4	10	32	33
k	*o*-$CH_3C_6H_4$	10	30	32

[a] Reaction temperature is 90−95 °C in all experiments. [b] Yields refer to the isolated pure products after column chromatography.

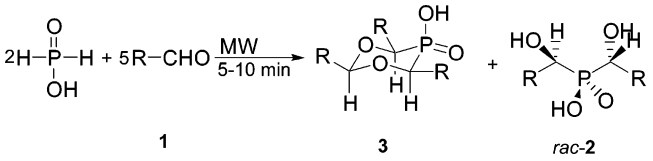
The reaction of **1a** with hyphophosphorus acid was successfully carried out under thermal heating at 90 °C for 3 h, to give **3a** and *rac*-**2a** in 30% and 26% yields, respectively.

In summary, fast reaction rates, mild reaction conditions, good yields, a simple workup, relatively clean reactions with no tar formation, and simple separation of diastereoisomers make this method an attractive and a useful contribution to the existing methodologies. Further investigations on this reaction are now in progress.

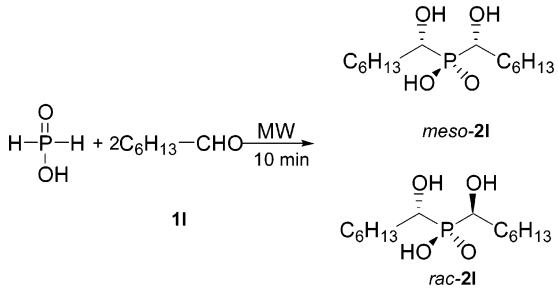
Experimental Section

General Procedure for the Preparation of Cyclic Phosphinic Acids (3) and Bis(α-hydroxyalkyl)phosphinic Acids (*rac*-2). A 50% aqueous solution of hypophosphorus acid (20 mmol) was added to 50 mmol of aldehyde, and the mixture was irradiated with microwaves for 5−10 min (step by step) at 180 W (a kitchen-type microwave was used in all experiments). After irradiation, 10 mL of ethyl acetate was added to the reaction mixture and stirred for 5 min. *n*-Hexane (30 mL) was added to this mixture, and a white powder precipitated. The precipitates were filtered, and column chromatography was performed on the silica gel with chloroform−methanol (99:1). Evaporation of the solvent under reduced pressure gave cyclic phosphinic acids **3** in a pure state as white crystals. Successive elution with methanol (300 mL) gave bis(α-hydroxyalkyl)phosphinic acid (*rac*-**2**) as white crystals, after evaporation of the solvent. All products gave satisfactory spectral data in accordance with the assigned structures.

SCHEME 3



SCHEME 4



(4*R,6*S**)-2,4,6-Triphenyl-1,3,5-dioxaphosphinan-5-ol 5-oxide (3a).** mp 210−212 °C (methanol). ^{1}H NMR (CD_3SOCD_3/TMS-250 MHz): 3.0−4.25 (1H, br, OH), 5.65 (2H, d, J = 3.75 Hz), 6.28 (1H, d, J = 2 Hz), 7.2−7.65 (15H, m). ^{31}P NMR (CD_3SOCD_3/H_3PO_4): 16.8. ^{13}C NMR (CD_3SOCD_3/TMS-62.9 MHz): 81.4 (d, J_{PC} = 94.0 Hz), 101.8 (d, J_{PC} = 3.6 Hz), 126.7, 127.5 (d, J_{PC} = 4.2 Hz), 128.2, 128.5, 128.6, 129.3, 133.8 (d, J_{PC} = 7.3 Hz), 138.2. Anal. Calcd for $C_{21}H_{19}O_4P$: C, 68.85; H, 5.19. Found: C, 68.78; H, 5.41.

(*R)-Hydroxy(phenyl)methyl[(*S**)-hydroxy(phenyl)methyl]-phosphinic Acid (*rac*-2a).** mp 196−198 °C (methanol). ^{1}H NMR (CD_3SOCD_3/TMS-250 MHz): 5.01 (2H, d, J = 7.4 Hz), 7.2−7.45 (10H, m). ^{31}P NMR (CD_3SOCD_3/H_3PO_4): 38.68. ^{13}C NMR (CD_3SOCD_3/TMS-62.9 MHz): 69.5 (d, J_{PC} = 106.7 Hz), 127.2, 127.9, 128.0, 139.2 (d, J_{PC} = 2.5 Hz). Anal. Calcd for $C_{14}H_{15}O_4P$: C, 60.43; H, 5.40. Found: C, 60.40; H, 5.41.

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Supporting Information Available: Experimental procedures and spectroscopic characterization for compounds **3b**−**3k**, and **2a**−**2l**, copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for *rac*-**2a**, *meso*-**2a**, and **3a**, ORTEP of **3a**, and X-ray data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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