Novel Method for the Synthesis of α-Amino-α′-hydroxyalkylphosphinic Acids and Bis(α-aminoalkyl)phosphinic Acids: Nuclephilic Addition of α-Hydroxy-*H*-phosphinic Acids to Diimines

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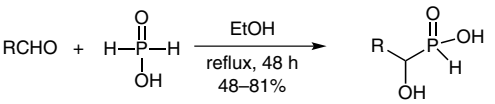
Abstract: We report here a novel and simple method for the synthesis of α-amino-α′-hydroxyalkylphosphinic acids in good yields in two simple steps without any protection–deprotection steps. We have developed an efficient method for the synthesis of α-amino-α′-hydroxyalkylphosphinic acids via the reaction of easily available α-hydroxyalkylphosphinic acids with diimines. Treatment of α-hydroxyalkylphosphinic acids with diimines in the presence of trimethylsilyl chloride (TMSCl) gives α-amino-α′-hydroxyalkylphosphinic acids in good yields. The reaction gave a mixture of two diastereomeric forms of α-amino-α′-hydroxyalkylphosphinic acids. The difference in solubility in organic solvents allowed us to readily separate the diastereoisomers.

Key words: phosphinic acids, hydroxyalkylphosphinic acid, amino-α′-hydroxyalkylphosphinic acid, diimines, bis(α-aminoalkyl)phosphinic acid

Phosphorus–carbon bond formation is an active and important research area for the preparation of organophosphorus compounds such as phosphinates.[1] Phosphinic peptides and pseudopepides are an important class of compounds that exhibit a variety of interesting and useful properties in biological activities.[2] The structure of the phosphinic functional group mimics the transition state of peptide hydrolysis, and the symmetric nature of phosphinic acid derivatives is expected to benefit in their binding to the homodimer of HIV-protease having C_2-axis symmetry.[3] α-Functionalized phosphinic acid derivatives have attracted a great deal of attention due to their usefulness both in medicinal and material chemistry.[4] Among the α-functional phosphinic acids, α-hydroxyphosphinic acids, and α-aminophosphinic are interesting classes of compounds possessing broad biological activities.[5] Some α-hydroxyphosphinic acids are useful intermediates for preparing α-hydroxyphosphinyl peptides showing good inhibitory activity against renin.[6] α-Aminoalkylphosphinic derivatives have potential biological properties such as antibacterial, herbicidal, and fungicidal activity.[7] Furthermore, the conjunction of two functionalities in the same molecule such as α-amino-α′-hydroxyphosphinates or α,α′-diaminophophinates affords powerful inhibitors of HIV-1 protease and human aminopeptidase N (CD13).[8] In contrast to the widely studied synthesis of 1-amino or 1-hydroxy phosphinic acid derivatives, relatively few papers have reported on the chemistry of α-amino-α′-hydroxyphosphinates or α,α′-diaminophophinates.[9] There is currently only one available method, described by Drag and Oleksyzyn in 2005,[10] for the synthesis of α-amino-α′-hydroxyphosphinates starting from α-aminoalkylphosphinic acids. However, this method involves a several-step process, requiring drastic reaction conditions, anaerobic and anhydrous conditions for some steps, long reaction times, several protection–deprotection steps, and gives low overall yields and side products.

Diimines are good precursors for the synthesis of numerous organic compounds, especially heterocyclic compounds.[11] These readily accessible precursors can be produced by the reaction of aromatic aldehydes with aqueous ammonia.[12] Recently, we have reported the reaction of diimines with hypophosphorus acid for the preparation of *N*,*N*-bis(phosphinomethyl)amines, as a new class of 1-aminophosphinic acids.[13] As part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds,[14] herein we report a new and simple method for the synthesis of α-amino-α′-hydroxyphosphinic acids. We have found that the reaction of aromatic aldehydes with ammonia solution followed by reaction with α-hydroxyphosphinic acids, prepared according to well-established procedures, in the presence of TMSCl gives α-amino-α′-hydroxyphosphinates in good yields.

α-Hydroxy-*H*-phosphinic acids **1** were obtained in multigram quantities (48–81% isolated yield, Scheme 1) from the reaction of aldehydes and hypophosphorus acid in refluxing ethanol for 48 hours, according to a literature procedure.[15]



1a R = Ph 52%
1b R = *o*-ClC$_6$H$_4$ 63%
1c R = *p*-ClC$_6$H$_4$ 48%
1d R = α-naphthyl 81%
1e R = C$_6$H$_{13}$ 66%

Scheme 1

Diimines **2** were obtained in quantitative yield from the reaction of aromatic aldehydes with ammonium hydrox-

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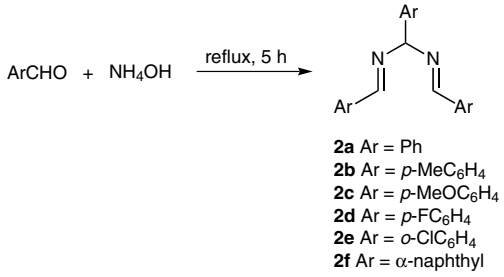
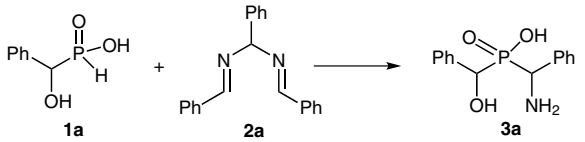
ide solution at reflux for five hours, according to a literature procedure (Scheme 2).[16]



Scheme 2

Initially, the reaction of [α-hydroxy(phenyl)methyl]phosphinic acid (**1a**) with 1-phenyl *N*,*N*′-bis[(1*E*)-phenylmethylidene]methanediamine (**2a**) was chosen as the model reaction, and the experimental data for the screening conditions are listed in Table 1.

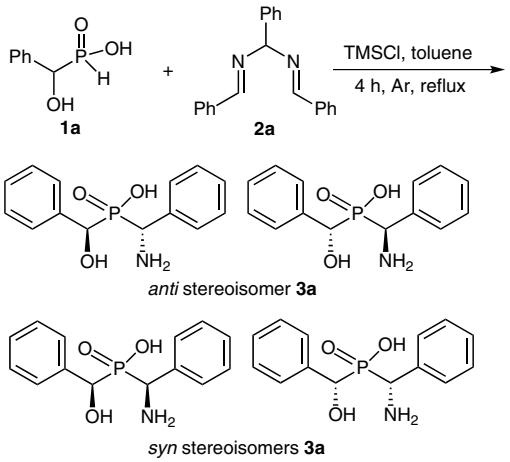
Table 1 Synthesis of **3a** from the Reaction of **1a** with **2a** under Various Conditions



Entry	Reagent	solvent	T (°C)	Time (h)	Yield (%)[a]
1	–	EtOH	r.t.	24	–
2	–	EtOH	reflux	24	–
3	HMDS	toluene	r.t.	24	–
4	HMDS	toluene	reflux	24	–[b]
5	TMSCl–Et_3N	toluene	r.t.	24	–[b]
6	TMSCl–Et_3N	toluene	reflux	12	–[b]
7	TMSCl	toluene	r.t.	24	21
8	TMSCl	toluene	reflux	3	83

[a] Isolated yield of product **3a**.
[b] Unknown mixture.

Treatment of **1a** with **2a** in ethanol at room temperature or reflux failed after 24 hours to form **3a** (Table 1, entries 1 and 2). When the reaction was carried out in the presence of HMDS[17] in dry toluene for 24 hours at reflux, a mixture of unknown products resulted (Table 1, entry 4). Treatment of **1a** with **2a** in toluene in the presence of HMDS at room temperature failed after 24 hours to form **3a** (Table 1, entry 3). When the reaction was carried out in the presence of a mixture of TMSCl and Et_3N in dry toluene for 12 hours at reflux or for 24 hours at room temperature,[18] it gave a mixture of unknown products (Table 1, entries 5 and 6). Treatment of **1a** with **2a** in the presence of TMSCl without any additives in toluene for 24 hours at room temperature gave **3a** in 21% isolated yield (Table 1, entry 7). However, the yield increased to 83% when the reaction was carried out for four hours at reflux (Table 1, entry 8). Therefore, when the reaction was carried out for four hours at reflux in the presence of TMSCl, a diastereomeric mixture of α-amino(phenyl)methy[α′-hydroxy(phenyl)methyl]phosphinic acid (**3a**) was obtained in 83% yield (in a 63:37 ratio of diastereoisomers, Scheme 3).



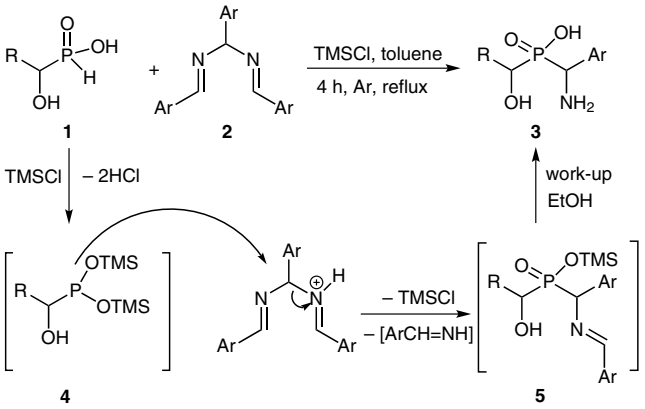
Scheme 3

The ^{31}P NMR spectrum of this mixture exhibited two peaks at δ = 32.90 and 33.37 ppm due to the diastereoisomers. The ^{1}H NMR spectrum exhibited two doublets at δ = 4.02 and 4.08 ppm indicative of N–HC–P coupling. Because of the presence of two stereogenic carbons bonded to the phosphorus atom and due to the prototropic transfer of the acidic proton between the phosphoryl (P=O) and acidic (P–OH) sites, these compounds theoretically exist as four diastereomeric forms: two *syn* compounds and two *anti* compounds as shown in Scheme 4. When the mixture of diastereoisomers **3a** was washing with a solvent mixture of ethanol–water (9:1) and dried in air at room temperature a single diastereoisomer was obtained. As we were unable to obtain an X-ray crystal of the two diastereoisomers of **3a**, their unambiguous stereochemical assignments have not been determined.

This process was successfully applied to other α-hydroxy-*H*-phosphinic acids **1** and dimines **2** as summarized in Table 2. As shown in Table 2, the reaction of α-hydroxy-*H*-phosphinic acids **1a**–**e** with dimines **2a**–**f**, in the presence of TMSCl, afforded a mixture of diastereoisomers of α-amino-α′-hydroxyphosphinates **3a**–**m** in good yields.

A plausible mechanism is outlined in Scheme 4 for the synthesis of α-amino-α′-hydroxyphosphinic acids. On the basis of literature reports for the activation of phosphinic acids[17–19] and the reactions reported for diimines,[20] we believe that the present process proceeds via the activation of α-hydroxy-*H*-phosphinic acid by TMSCl and attack of activated intermediate [21,22]**4** to the protonated diimine giving an α-imino-α′-hydroxyphosphinic acid intermediate **5**

which undergoes subsequent hydrolysis in the workup to the α-amino-α′-hydroxyphosphinic acid compound (Scheme 4).

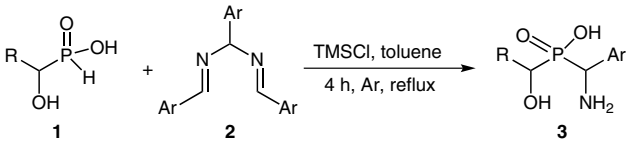


Scheme 4

Surprisingly, we found that when the reaction of [α-hydroxy-(*o*-chlorophenyl)methyl]phosphinic acid (**1b**) with 1-(*p*-methoxyphenyl)-*N*,*N*′-bis[(1*E*)-(*p*-methoxyphenyl)-methylidene]methanediamine (**2d**) was carried out under reflux for 24 hours in the presence of TMSCl, the reaction mixture was very complex and only one product was isolated in pure form after workup. The reaction gave a white solid that was determined to have the molecular formula $C_{16}H_{21}N_2O_4P$ by ESI-HRMS {observed $[M + 2Na]^+$ at $m/z = 381.0961$} and elemental analysis. This molecular formula is consistent with bis[α-amino(*p*-methoxyphenyl)methyl]phosphinic acid. The ^{31}P NMR spectrum of the product exhibited one peak at $\delta = 36.14$ ppm. The ^1H NMR spectrum of the product exhibited a doublet peak at $\delta = 3.08$ ppm indicative of HC–P coupling ($^3J_{HP} = 9.1$ Hz). On the other hand, the ^{13}C NMR of the product exhibited one doublet peak at $\delta = 53.0$ ppm (α-carbon to phosphorus atom). As we were unable to obtain an X-ray crystal of the single diastereoisomer of **6d**, its unambiguous stereochemical assignment has not been determined. It is suggested that the intermediate **7d** may be generated in situ by P–C bond breaking of **3d** and followed by nucleophilic attack of activated intermediate **7d** to the protonated diimine **2d**, affording bis[α-amino(*p*-methoxyphenyl)]phosphinic acid (**6d**, Scheme 5, *o*-chlorobenzaldehyde was detected by TLC). Similar results were obtained when [α-hydroxy-(α-naphthyl)methyl]phosphinic acid (**1d**) was used as a phosphinic acid precursor.

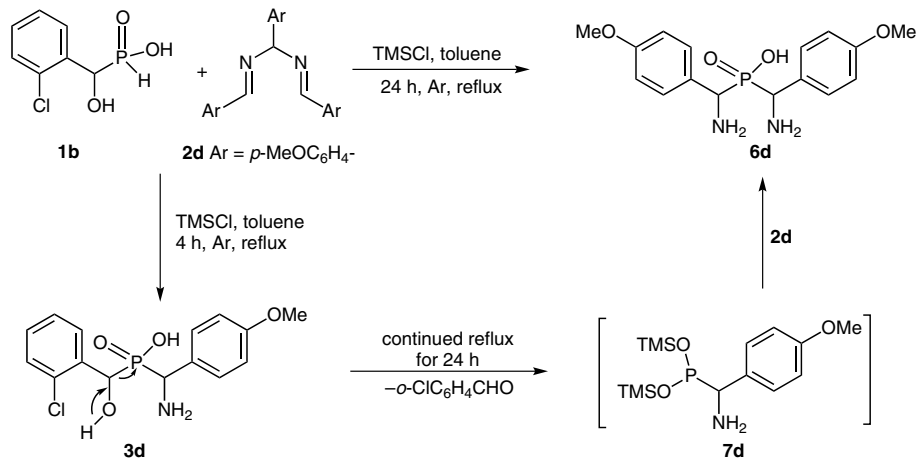
In summary, we report herein a novel and simple method for the synthesis of α-amino-α′-hydroxyalkylphosphinic

Table 2 Reaction of 1-Hydroxyphosphinic Acids **1** with Diimines **2**



Entry	**1** R	**2** Ar	Product **3**	Yield of **3** (%)[a]	dr[b]
1	Ph	Ph	**3a**	83	63:37
2	Ph	*p*-MeC_6H_4	**3b**	80	67:33
3	Ph	*p* -FC_6H_4	**3c**	78	65:35
4	*o*-ClC_6H_4	*p*-$MeOC_6H_4$	**3d**	71	70:30
5	*p*-ClC_6H_4	Ph	**3e**	64	58:42
6	*p*-ClC_6H_4	*o*-ClC_6H_4	**3f**	60	88:12
7	*p*-ClC_6H_4	*p*-MeC_6H_4	**3g**	73	59:41
8	*p*-ClC_6H_4	*p*-FC_6H_4	**3h**	54	75:25
9	*p*-ClC_6H_4	β-naphthyl	**3i**	87	63:37
10	α-naphthyl	Ph	**3j**	54	85:15
11	α-naphthyl	*p*-MeC_6H_4	**3k**	66	76:24
12	α-naphthyl	*p*-FC_6H_4	**3l**	56	70:30
13	*n*-C_6H_{13}	Ph	**3m**	44	88:12

[a] Isolated yields of mixtures of two diastereoisomers.
[b] Diastereomeric ratio was calculated by ^{31}P NMR spectroscopy.



Scheme 5

acids via the reaction of easily available α-hydroxyalkylphosphinic acids with diimines. The reaction gave a mixture of two diastereomeric forms of α-amino-α′-hydroxyalkylphosphinic acids. The difference in solubility in organic solvents due to polarity allowed us to readily separate the diastereoisomers. Fast reaction rates, mild reaction conditions, good yields, a simple workup, clean reactions with no protection or deprotection steps, and simple separation of diastereoisomers make this method an attractive and a useful contribution to current methodology. We have also developed an efficient method for the synthesis of bis(α-aminoalkyl)phosphinic acids via treatment of [α-hydroxy-(*o*-chlorophenyl)methyl]phosphinic acid or [α-hydroxy-(α-naphthyl)methyl]phosphinic acid with diimines in the presence of TMSCl at reflux toluene for 24 hours in good yields.[23]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(23) **General Procedure for the Preparation of α-(Aminoalkyl)-α′-(hydroxyalkyl)phosphinic Acid (3)**
Trimethylsilyl chloride (6 mmol, 0.75 mL) was added dropwise to a suspension of 1-hydroxy-*H*-phosphinic acid (2 mmol) in anhyd toluene (10 mL) under argon, and the mixture was stirred at 0 °C for 30 min. A solution of diimine (3 mmol) in toluene (5 mL) was added to the reaction mixture, and the mixture was stirred at reflux for 4 h. EtOH (5 mL) was added to this mixture, and the mixture was stirred at reflux for 1 h, during which time a white solid precipitated. This was collected by filtration, washed with EtOH (2 mL), and air drying to give a mixture of diastereoisomers of α-amino-α′-hydroxyphosphinic acid in 41–83% yield. All products gave satisfactory spectral data in accordance with the assigned structures.
α-Amino(phenyl)methyl[α′-hydroxy(phenyl)methyl]-

phosphinic Acid (3a)

White solid, mixture of two diastereoisomers. ^{1}H NMR (400 MHz, D_2O): δ = 4.02 (d, 1 H, *J* = 12.4 Hz), 4.08 (d, 1 H, *J* = 8.8 Hz), 4.60 (d, 1 H, *J* = 4.8 Hz), 4.85 (d, 1 H, overlap with D_2O signal), 7.19–7.45 (m, 20 H) ppm. ^{13}C NMR (100 MHz, D_2O–TMS): δ = 54.0 (d, J_{PC} = 89.0 Hz), 54.2 (d, J_{PC} = 88.0 Hz), 72.2 (d, J_{PC} = 101.0 Hz), 72.4 (d, J_{PC} = 102.0 Hz), 127.0–127.5 (Ar), 127.6 (d, J_{PC} = 4.0 Hz), 127.7 (d, J_{PC} = 4.0 Hz), 128.1 (d, J_{PC} = 1.0 Hz), 128.3 (d, J_{PC} = 2.0 Hz), 128.4 (d, J_{PC} = 1.0 Hz), 138.6 (d, J_{PC} = 3.0 Hz), 138.8 (d, J_{PC} = 2.0 Hz), 139.1 (d, J_{PC} = 2.0 Hz) ppm. ^{31}P NMR (162 MHz, D_2O–H_3PO_4): δ = 32.90, 33.37 ppm. HRMS: *m/z* calcd for $C_{14}H_{15}NO_3PNa_2$ [M + 2Na$^+$]: 322.0585; found: 322.0581.