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An efficient one-pot synthesis of bis(α-aminoalkyl)phosphinic acids, phosphorus-isosteric analogues of HIV protease inhibitors

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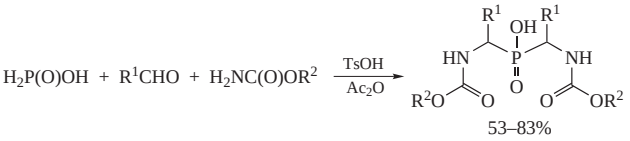
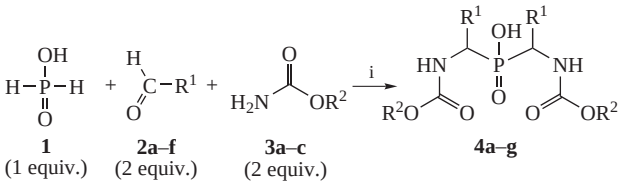
An acid-catalyzed three-component reaction between hypophosphorous acid, aldehydes and alkyl carbamates under mild conditions afforded bis(α-aminoalkyl)phosphinic acids. The proposed facile single-stage protocol is prospective for expansion of a range of phosphinic analogues of HIV protease inhibitors.



The scientific group of Peyman prepared a number of symmetric bis(α-aminoalkyl)phosphinic acids, inhibitors of HIV protease and their analogues,[1–4] by difficult multistage procedures comprising re-alkylation of bis(aminomethyl)phosphinic acids[4] whose synthesis was also complicated.[5] In the current study, we propose a new efficient and simple synthesis of bis(α-aminoalkyl)phosphinic acids based on our previous experience on amidoalkylation of hydrophosphorylic compounds.[6–8]

A three-component single-stage amidoalkylation reaction between hypophosphorous acid (HPA) **1** as the hydrophosphorylic component, aldehydes **2a–f** as the carbonyl component and alkyl carbamates **3a–c** as the amide one afforded symmetric bis(α-aminoalkyl)phosphinic acids **4a–g** in good yields (Scheme 1).†



2a R^1 = Me
2b R^1 = Et
2c R^1 = Pr^i
2d R^1 = Bu^s
2e R^1 = Bu^i
2f R^1 = Ph

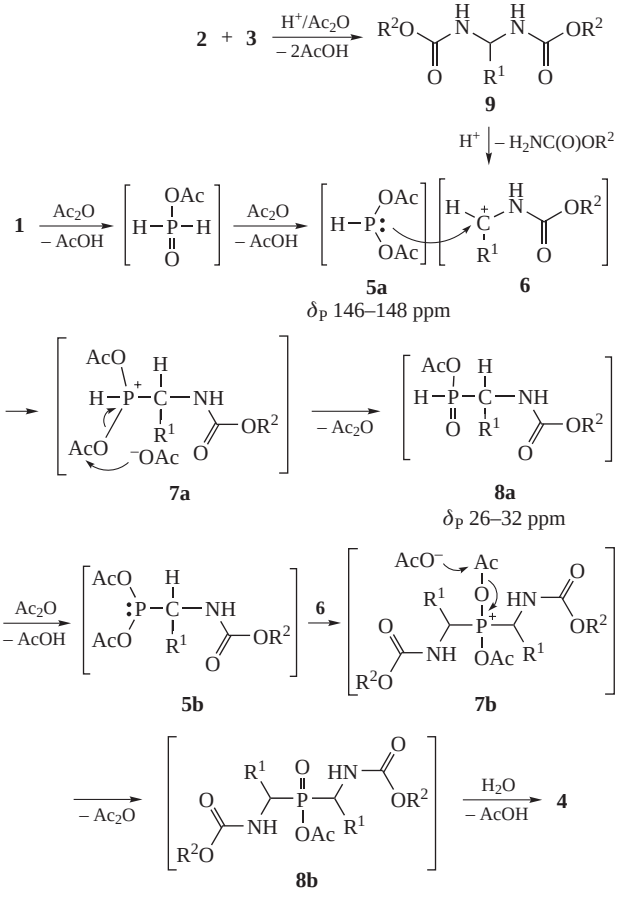
3a R^2 = Me
3b R^2 = Et
3c R^2 = Bn

4a R^1 = Ph, R^2 = Et, 73%
4b R^1 = Pr^i, R^2 = Et, 83%
4c R^1 = Bu^i, R^2 = Et, 68%
4d R^1 = R^2 = Et, 72%
4e R^1 = Bu^s, R^2 = Et, 65%
4f R^1 = Ph, R^2 = Me, 70%
4g R^1 = Me, R^2 = Bn, 73%

Scheme 1 *Reagents and conditions*: i, **1**, **3** and Ac_2O, 0–15 °C, then **2** and TsOH (cat.), then room temperature, 10–24 h.

† Dehydrated hypophosphorous acid **1** (5 mmol) and alkyl carbamate **3** (10 mmol) were added to stirred acetic anhydride (5–8 ml) at 0–15 °C. Aldehyde **2** (10 mmol) and *p*-toluenesulfonic acid (0.15–0.50 mmol) were then slowly added, and the mixture was stirred at 0–15 °C for 15 min. The stirring was continued at room temperature for 10–24 h, and the reaction progress was monitored by ^{31}P NMR. When the reaction was complete, the mixture was poured into ice water (25–40 ml) and the slurry was concentrated *in vacuo*. The oily residue was partitioned between chloroform (20–25 ml) and water (10 ml). The organic layer was dried (Na_2SO_4 or $MgSO_4$) and evaporated *in vacuo*. The residue was purified by crystallization. For details, see Online Supplementary Materials.

In the course of the reaction, synchronous construction of two phosphorus–carbon bonds and two nitrogen–carbon ones occurs (see Scheme 1) leading to a symmetric structure **4** with retaining protective group on nitrogen atoms. The reaction proceeds in acetic anhydride in the presence of TsOH as an acid catalyst. The commonly used acetyl chloride was found unsuitable as the catalyst in our case, probably, due to susceptibility of



Scheme 2

hypophosphorous acid to undergo disproportionation or oxidation in the Ac_2O–AcCl mixture. Our studies show that moderate cooling (5–15 °C) and using TsOH as the acid catalyst make the side reactions negligible.

The assumed reaction mechanism (Scheme 2) is based on our previous data.[8] At the first step the intermediates **5a** and **5b** are formed as the result of acylation of HPA **1** and phosphinate **8a**, respectively. Afterwards they undergo the Arbuzov reactions when their P^{III} atoms act as nucleophiles towards *in situ* generated carbiminium ion **6**. The resulting phosphonium cations **7a**,**b** subsequently transform into phosphinates **8a**,**b** and finally into the reaction products **4**.

Formation of diacetyl hypophosphite **5a** is in a good agreement with the ^{31}P NMR data. In the first minutes of the reaction, signals of trivalent phosphorus can be clearly observed at 146–148 ppm. Carbiminium ion **6** is generated under these conditions from alkylidenebis(carbamate) **9**. Treatment of the reaction mixture with cold water gives N-protected symmetric bis(α-aminoalkyl)-phosphinic acids **4** (see Schemes 1 and 2). The isolated reaction products actually represent mixtures of conformers and diastereomers, which was previously confirmed by NMR and X-ray analysis data.[9]

In summary, we have developed a new one-pot method for obtaining N-protected symmetric bis(α-aminoalkyl)phosphinic acids based on three-component reaction between hypophosphorous acid, aldehydes and carbamates. The results obtained improve synthetic availability of the variety of phosphinic analogues within the range of HIV protease inhibitors.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.022.

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