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A convenient one-pot synthesis of phosphino-dipeptide analogs

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Abstract—A general one-pot synthesis is described for the preparation, in good overall yields, of phosphinopeptides as building blocks for peptide synthesis in the field of new enzyme inhibitors. This method, consisting of the addition of alkyl hypophosphites to imines and then in the Michael-addition of the resulting alkyl α-aminophosphonites on acrylates, affords the possibility of variations for the substituents in α and β position to the phosphorus atom and in α position to the nitrogen atom.

1-Aminoalkylphosphonic acids and the corresponding peptides (phosphonopeptides) are analogous to α-aminocarboxylic acids and their derived peptides. They could interfere in biological mechanisms: the phosphonodipeptides **1**, through their hydroxyphosphonyl design [-P(O)OH-], approximating a presumed enzymatic reactive tetrahedral intermediate, can induce enzyme inhibitor properties.[1] But owing to some sensitivity of the (O)P–N phosphonamidate bond to hydrolysis, their P–C analogs **2** are better candidates for the elaboration of more stable biologically active compounds. The construction of such phosphinopeptides requires the synthesis of the phosphinodipeptides analogs of type **2** as building blocks (Fig. 1).

Compounds **2** are generally prepared in a multistep synthesis from the corresponding adequately protected 1-aminoalkylphosphonous acids: (i) by Michael additions using a basic activation;[2] (ii) by Michael additions or Arbuzov reactions using silyl derivatives, and[2b–d,3] (iii) by nucleophilic substitution under basic conditions.[2g,4]

The 1-aminoalkylphosphonous acids themselves can be synthesized in several ways: (a) by Kabachnik–Fields type reactions involving addition of hypophosphorous acid or its derivatives to a C=N double bond;[5–7] (b) by the oxime procedure;[8] (c) by a Michaelis–Arbuzov reaction with the bis(trimethylsilyl) phosphonite;[5f,9] (d) by alkylation of a suitably protected 1-aminomethylphosphinic acid according to the procedure of Schöllkopf;[10] (e) by a Mitsunobu reaction on 1-hydroxyalkylphosphinates;[11] (f) by amination of chloromethylphosphinic acid,[12] or (g) by a Michael reaction of ethyl diethoxymethyl phosphonite with ethyl acetamidomethylenemalonate.[13]

Generally, the syntheses of compounds **2** are performed stepwise with purification of the various intermediates. In order to develop a convenient preparation of phosphinodipeptides of type **2**, we have thoroughly investigated the three steps of a general synthetic method so that by reaching high yields for each step, we could avoid the intermediate purifications and perform the synthesis of compounds **2** in a one-pot procedure. The synthetic method, which affords the possibility of variation of R^1 and R^2 groups, is illustrated here in the case

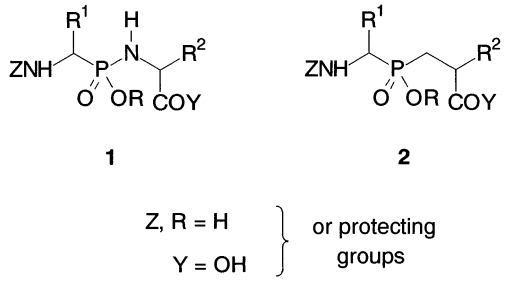

Figure 1. Phosphonodipeptides **1** and their analogous phosphinodipeptides **2**.

Keywords: alkyl hypophosphite; aminoalkylphosphinic acids; Kabachnik–Fields reaction; Michael addition.

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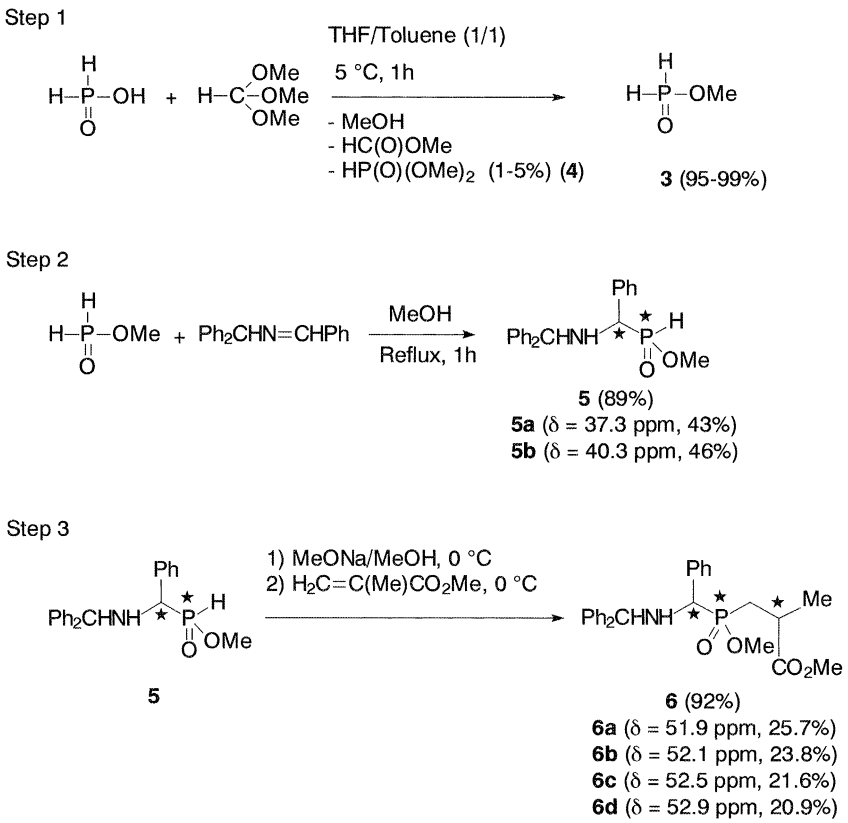
of compound **6** (R^1 = Ph, R^2 = Me) obtained in an 81% overall yield (Scheme 1).

The intermediate 1-aminoalkylphosphonous acid **5** was prepared by modifying the method proposed by Baylis et al.:[5b] we used the addition of an alkyl hypophosphite, instead of hypophosphorous acid, to a *N*-diphenylmethylimine. Indeed, even if alkyl hypophosphites are known to be rather unstable,[14] they are more reactive than hypophosphorous acid. Moreover, we preferred to use an alkyl hypophosphite rather than bis(trimethysilyl) phosphonite, which is highly pyrophoric.[15] Finally, this protected hypophosphorous acid derivative as a starting compound avoids a supplementary protection step of the phosphinic function, which is necessary if a subsequent Michael addition to an acrylate is carried out under basic conditions.

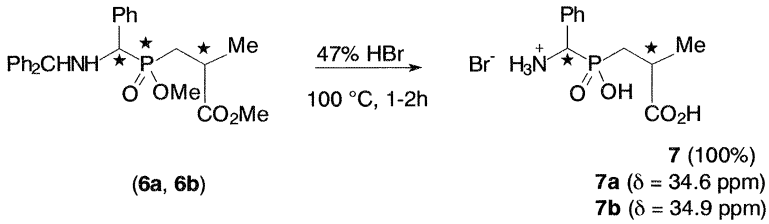
The *N*-diphenylmethyl group used in this synthesis has the major advantage of being cleaved under a variety of conditions (under acidic treatment[5b] or by hydrogenolysis[10]), which offers versatility in the handling of functionalities.

After an exhaustive study of the esterification reaction of hypophosphorous acid by alkyl orthoformates,[16,17] we chose to use the in situ generated methyl hypophosphite **3**, which was formed in good yield (95–99%), together with small amounts of dimethyl phosphonate **4** (step 1, Scheme 1). The addition of methyl hypophosphite **3** to the imine derived from diphenylmethylamine and benzaldehyde (91% yield) in refluxing anhydrous methanol afforded the methyl phosphinate **5** as a mixture of two diastereomers **5a** and **5b** in a 89% yield (step 2, Scheme 1). The product **5** was directly used without purification in the third step, the Michael addition to an acrylate, performed according to the method developed by Parsons et al.[2a] using an alcoholate activation. So, treatment of **5** with sodium methoxide in methanol and then with methyl methacrylate afforded the phosphinodipeptide analog **6** in a 92% average yield as a mixture of four diastereomers **6a**, **6b**, **6c** and **6d** (step 3, Scheme 1).[18]

The separation of two pairs of diastereomers (**6a**, **6b**) and (**6c**, **6d**) was achieved by chromatography on silica gel. Compounds **6a** and **6b** were isolated as a white



Scheme 1. One-pot synthetic method for the preparation of phosphinodipeptides of type **2**.



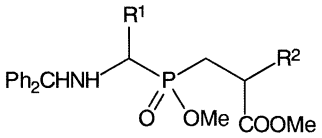
Scheme 2. Deprotection of compound **6**.

solid, whereas **6c** and **6d** afford a viscous oil. Compounds **6** were fully characterized by ^{31}P, ^{1}H, ^{13}C NMR, COSY $^{1}H/^{1}H$, COSY $^{1}H/^{13}C$, mass spectroscopy, IR and elementary analysis.

Compounds **6a** and **6b** were completely deprotected by using an excess of 47% bromhydric acid at 100°C, affording compounds **7** in a quantitative yield as a mixture of two diastereomers (Scheme 2).[19]

In order to show the value of phosphinodipeptide analog **6** as a synthetic intermediate, selective deprotection of the various protective groups is under progress in our laboratory.

Moreover, to check its generality, we will apply this synthetic method to various *N*-diphenyl methylimines and acrylates to obtain a large number of compounds **8**.



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Further, in order to avoid the separation of each diastereoisomer **6a–d** from the mixture, asymmetric inductions will be investigated to obtain stereocontrol in the formation of the various chiral centers,[20,21] affording stereoselectively only the desired diastereomer.

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18. To a solution of anhydrous hypophosphorous acid (0.66 g, 10 mmol) in dry THF (2.4 ml) and toluene (2.4 ml) stirred at 5°C under N_2 was added trimethyl orthoformate (4.4 ml, 40 mmol). After 1 h at 5°C, the mixture was allowed to warm to room temperature and stirred for 2 h to afford 98% of **3**. ^{31}P NMR (THF/toluene) of **3**: δ 16.8 (tq, $^1J_{P\text{-}H}=565.6$ Hz, $^3J_{POCH}=12.7$ Hz). To the reaction mixture dry methanol (20 ml) and benzylidenebenzhydrylamine (2.62 g, 9.67 mmol) were then added. After 1 h reflux, 91% of compounds **5** were obtained as a mixture of two diastereomers **5a** and **5b**. ^{31}P NMR (THF/toluene, MeOH) for **5**: $\delta_{\mathbf{5a}}=37.3$ ppm (43.3%), $\delta_{\mathbf{5b}}=40.3$ ppm (47.7%). To the solution containing **5a** and **5b** was added at 0°C first a solution of sodium methoxide in MeOH (5.2 ml of a 2N solution) dropwise over 20 min, and then methyl methacrylate (1.1 ml, 10.4 mmol) also dropwise over 20 min. The reaction mixture was then stirred for 1 h 10 min at 0°C and at 24°C overnight. This step provided 87% of compounds **6**. ^{31}P NMR (THF/toluene, MeOH) for **6**: $\delta_{\mathbf{6a}}=51.92$ ppm (24.3%), $\delta_{\mathbf{6b}}=52.11$ ppm (22.5%), $\delta_{\mathbf{6c}}=52.51$ ppm (20.5%), $\delta_{\mathbf{6d}}=52.93$ ppm (19.7%). The reaction was quenched with 1N HCl and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product, by chromatography on silica gel (15–40 μm) with hexane/EtOAc (90/10) as the starting eluant, gave two pairs of diastereomers (**6a**, **6b**) as a white solid and (**6c**, **6d**) as a viscous oil.
19. The pair of diastereomers (**6a**, **6b**) (0.6 g, 1.33 mmol) was heated together with an excess of 47% HBr (2 ml) at 100°C for 1–2 h until two distinct phases have separated. The mixture was evaporated to dryness under reduced pressure and the residue taken up in water. The aqueous solution was washed several times with ether to remove diphenylmethyl bromide and then evaporated to dryness. Deprotected compounds were obtained as their hydrobromide salts **7** in a quantitative yield. ^{31}P NMR (D_2O) for **7**: $\delta_{\mathbf{7a}}=34.6$ ppm, $\delta_{\mathbf{7b}}=34.9$ ppm.
20. Concerning the stereochemical control in phosphinodipeptide synthesis, few asymmetric inductions are known. Pure diastereomers can be obtained simply and directly by reaction of hypophosphorous acid salts of (+)- or (−)-α-methylbenzylamine with aldehydes[21] or by using 2-hydroxypinan-3-one, efficient chiral auxiliary, in the alkylation of imine phosphinate.[10]
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