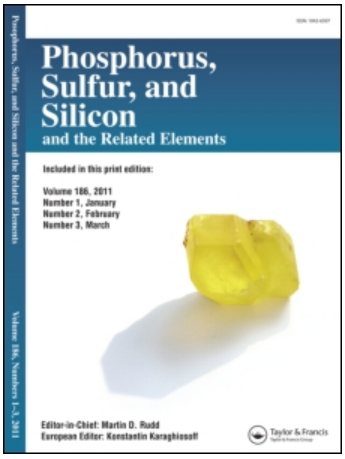

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A Convenient One-Pot Synthesis of Phosphino-Dipeptide Analogs

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A CONVENIENT ONE-POT SYNTHESIS OF PHOSPHINO-DIPEPTIDE ANALOGS

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*A general "one-pot" synthetic method is described for the preparation of phosphinodipeptides of type **1**, in 60–80% overall yield, allowing the variation of the substituents in α and/or β position to the phosphorus atom and also in α position to the nitrogen atom.*

Keywords: Alkyl hypophosphite; aminoalkylphosphinic acids; Kabachnik–Fields reaction; Michael addition; phosphinopeptides

Analogous to α-amino-carboxylic acids and their derived peptides, 1-aminoalkylphosphonic acids, and the corresponding peptides (phosphonopeptides) interfere with biological mechanisms through their hydroxyphosphonyl function.[1] The phosphinopeptides **1**, P–C analogs of phosphonopeptides, are better candidates for the elaboration of more stable biologically active compounds. Construction of such compounds requires the synthesis of the phosphinodipeptides analogs of type **1** as building blocks.

Compounds **1** are generally prepared in a multistep synthesis from the corresponding adequately protected 1-aminoalkylphosphonous acids.[2]

We developed a general "one-pot" three-step synthesis for the preparation of phosphinodipeptides of type **1** affording the possibility of variation of R^1 and R^2 groups (Figure 1). Each step of this reaction was improved separately until the yield was more than 90%; then all the steps were carried out without purification, for combinatorial or parallel synthesis.

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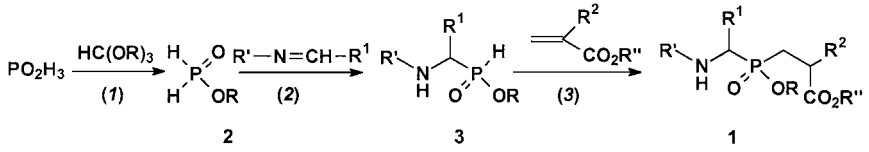

FIGURE 1 Synthesis of phosphino-dipeptide analogs.

RESULTS AND DISCUSSION

Synthesis of Alkyl Hypophosphites 2

Alkyl hypophosphites, unstable but more reactive than the hypophosphorous acid, were preferred to the bis(trimethysilyl) phosphonite, which is highly pyrophoric (Step 1, Figure 2).

In spite of many changes in the reaction conditions, the poor yield obtained in pure ethyl hypophosphite **2a** does not permit one to proceed with the synthesis using ethyl hypophosphite as starting material. However, methyl hypophosphite **2b** could be generated in situ[3] in very good yield and at good purity (95 to 99%). Therefore we decided to use methyl hypophosphite **2b** for the next step.

Synthesis of Methyl Phosphinate 3

Improving on the Baylis method,[4] the intermediate 1-aminoalkylphosphonous acids **3** were prepared by a dropwise addition of an excess (1.6 equivalents) of several imines (or triazine), to methyl hypophosphite **2b**, in refluxing dry methanol (Figure 3). Thus, the methyl phosphinates **3** were obtained in good yield (79–89%), and the purity could be increased up to 85–95% by simple precipitating out of by-products.

Products **3b** were then used directly, without additional purification, in Step 3 of the synthesis.

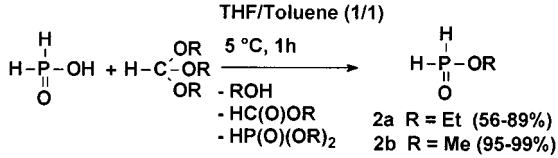

FIGURE 2 Preparation of alkyl hypophosphite **2** (Step 1).

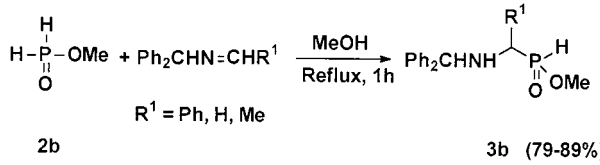

FIGURE 3 Preparation of methyl phosphinates **3** (Step 2).

Synthesis of Phosphinodipeptide Analogs 1

The last step of the synthesis (Step 3), a Michael addition of the phosphinates **3b** to various α-substituted acrylates was performed according to the method developed by Parsons et al., but by using *t*-BuOK in tetrahydrofuran (THF), an overcrowded base in catalytic amount, instead of MeONa in MeOH, as basic activating agent in order to reduce the demethylation of the phosphinate as side reaction. Compounds **1b**, from differently substituted acrylates, are obtained in 78–87% yields (Figure 4) as a mixture of diastereoisomers that can be partially separated by chromatography.

Selective and Total Deprotection of Phosphinodipeptide Analogs 1

In order to show the value of phosphinodipeptide analogs **1** as building blocks, examples of selective deprotection of the various functional groups were performed, by acid (47% HBr) or basic hydrolysis (NaOH), by hydrogenolysis (H_2/Pd·C), or by methanolysis ($BrSiMe_3$; MeOH) in almost quantitative yields.

CONCLUSION

A general three-step synthesis has been developed for the "one-pot" preparation of phosphinodipeptides **1**, as a mixture of diastereoisomers,

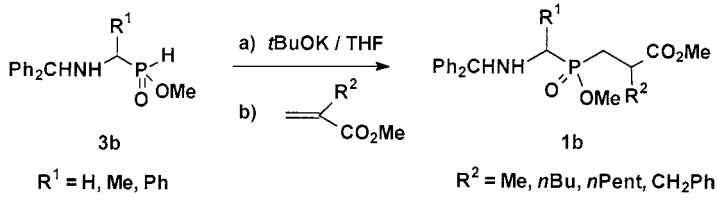

FIGURE 4 Preparation of phosphinopeptides analogs **1** (Step 3).

in 60–80% overall yield, which allows variation of the substituents on the carbon in positions α and/or β to the phosphorus.

Selective or complete cleavages of the various protective groups were performed, in usual ways, in almost quantitative yields.

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