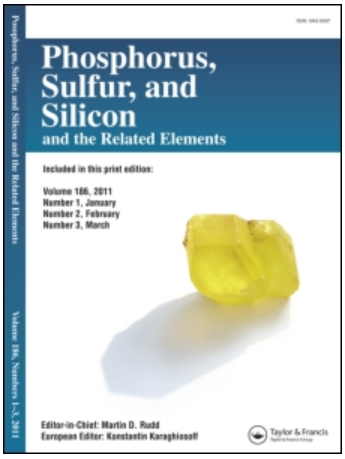

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Synthesis of Peptides and Amides with Alkylphosphonic-and Dialkylphosphinic Anhydrides

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SYNTHESIS OF PEPTIDES AND AMIDES WITH ALKYLPHOSPHONIC- AND DIALKYLPHOSPHINIC ANHYDRIDES

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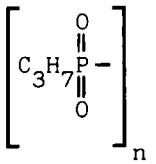
Abstract The application of two new reagents in peptide synthesis is discussed.

Several phosphorus compounds have been used already in peptide synthesis [1 - 4].

For making peptide- and amide bonds:

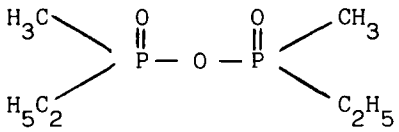
Two new reagents in this field of organic synthesis are gaining increasing importance:

propylphosphonic anhydride (PAA)



and

ethylmethylphosphinic acid anhydride (EMPA)



Both reagents are manufactured by Hoechst.

They have some advantages over the so far mainly used dicyclohexylcarbodiimide in combination with additives such as N-hydroxysuccinimide, N-hydroxybenzotriazole and N-hydroxy-oxobenzotriazine.

Propylphosphonic anhydride is sold and applied as a stable 50 % solution in methylene chloride. Ethylmethylphosphinic anhydride is also stable, and it is distillable. Both reagents do not give rise to insoluble by-products during synthesis, such as dicyclohexylcarbodiimide-mediated synthesis, an advantage which is especially important operating in a technical scale and in the synthesis of large, sparingly soluble peptide derivatives as for instance the Synthesis of the dodekapeptide sequence:

H-Tyr-Gln-Asp-Asn-Ser-Gly-Asp-Val-Gln-Glu-Ile-Leu-NH_2

from the C-terminal region of adenovirus 82 K-Protein and the modified ACTH-partialsequence 7-17:

H-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Lys-NH-$(CH_2)_4$-NH-Boc

Similar Syntheses have been performed with ethylmethylphosphinic acid anhydrides. Phosphonic- and phosphinic acid, respectively, which result from the synthesis are soluble in the organic solvents applied as well as in water. They can be removed easily by extraction with aqueous alkaline buffers.

The new methods are already applied to the technical synthesis of Peptides and peptide-like Pharmaceuticals such as converting-enzyme inhibitors, LHRH-Derivatives and ACTH-17-Derivatives.
The technical application of the described reagents required toxicological studies. They showed, that propylphosphonic anhydride is, besides its etching character as an acid anhydride, relatively nontoxic (no symptoms of intoxication at more than 2000 mg/kg mouse, orally administered). While ethylmethylphosphinic anhydride ehibits a LD_{50} of 7 mg/kg mouse, and an acute dermal toxicity of 519 mg/kg at the rat.

The two reagents have different features concerning their reactivity and their reaction conditions: Propylphosphonicanhydride

(PAA) is the reagent of choice for peptide synthesis in polar, aprotic solvents such as dimethylformamide, dimethylacetamide methylene chloride, acetic acid esters, dioxane and tetrahydrofuran. It shows a relatively fast reaction even with sterically hindered reaction partners.[5]

Ethylmethylphosphinic anhydride (EMPA) shows a significantly reduced reaction rate with sterically hindered reaction partners, but due to its greater stability towards hydrolysis it allows peptide synthesis in aqueous and mixed aqueous solvents:
Such systems are advantageous, when compounds are condensed, which are predominantly or exclusively water-soluble, as for example Proteins. Bovine serumalbumin derivatives from tri- and tetrajodothyronine-alkylesters and p-hydroxyphenylacetylderivative of salmine were synthesized with this reagent.

Conducting the synthesis with EMPA in aqueous systems provides the possibility of direct titrimetric reaction control by plotting the ml versus reaction- time curve of the reaction run under PH-static conditions. The curve shows an asymptotic part towards the end of the reaction. As titrants were used aqueous alkalihydroxyde solutions, the PH-values chosen were between 5,6 and 9.

Racemization was determined by separting esters of the diastereomeric peptides after the condensation reaction by HPLC as described by Wissmann, König, Teetz and Geiger in the case of propylphosphonic anhydride[6]. The results showed racemisations comparable with other low racemising methods, for example the methods using dicyclohexylcarbodiimide/N-hydroxysuccinimide and dicyclohexylcarbodiimide/N-hydroxybenzotriazole. These results could also be confirmed using ethylmethylphosphinic anhydride as the condensing reagent.

The dialkylphosphinic acids obtained from the dialkylphosphinic anhydrides in the course of the synthesis may be recovered after separating the peptide from the reaction mixture. For this purpose the remaining aqueous phase after the synthesis is

acidified and extracted with solvents such as chloroform and butanol, followed by destillative work up. The recovered dialkylphosphinic acids may be converted easily into the anhydrides by a procedure patented for Hoechst (DE-P 2,225 545).

I thank Dr. Kleiner from our Hauptlaboratorium, who kindly provided the reagents and who arranged the scaling up of their production to a technical scale, I thank my colleagues from the peptide synthesis group at Hoechst AG, Prof. Geiger, Dr. König and Dr. Teetz, for helpful discussions on the scope of the synthesis and for investigations concerning the racemization.

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