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New opinions on the amidoalkylation of hydrophosphorylic compounds

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ABSTRACT

A new and milder version of the procedure for the synthesis of N-protected α-aminoalkylphosphorylic compounds by reaction of alkyl carbamates, aldehydes and hydrophosphorylic compounds in acetic anhydride/acetyl chloride and a new mechanism for this type of reaction are described. The isolation, for the first time, of *N,N′*-benzylidene- and *N,N′*-alkylidenebiscarbamates as intermediates from the reaction medium and studies of the direct reaction of pre-obtained biscarbamates and hydrophosphorylic compounds in acetic anhydride are reported. A new version of the mechanism for this reaction which includes an Arbuzov-type reaction is proposed.

A convenient mimic of a substrate in the transition state of at least two classes of hydrolytic enzymes, for example, Zn-metalloproteases and aspartyl proteases, involves substitution of the peptide bond by a nonhydrolyzable phosphinate moiety (Fig. 1).[1] Construction of the pseudo-peptide fragment (A) is usually accomplished by addition of the pre-obtained N-protected aminoalkylphosphonous component (B) of pseudo-peptide **1** to the corresponding α-substituted acrylates.[2] However, protection of the nitrogen and phosphorus atoms of aminoalkylphosphonous building blocks increases the total number of steps for the process[3,4] and, moreover, attempts to add the aminoalkylphosphonous component to α-R-substituted acrylates were unsuccessful in some cases.[4]

We earlier proposed and now are continuing the development of an alternative synthetic route to pseudo-dipeptides via *reverse construction* of the desired molecules. The route consists of the addition of hypophosphite to α-R-substituted acrylates and creation of the first phosphorus–carbon bond with formation of phosphonous acids **3** followed by generation of the amino acid function and the second phosphorus–carbon bond.[5–7] We are developing this methodology for the synthesis of pseudo-γ-glutamyl peptides,[5] pseudo-γ-aminobutanoyl peptides[6] and pseudo-α,α-dipeptides.[7] Elaboration of methods for the synthesis of phosphinic pseudo-α,α-dipeptides **1** includes the search for a convenient procedure for the step involving the construction of the α-aminophosphorylic function using the phosphonous acid component **3** which contains the isostere of the corresponding amino acid (A). The synthesis of phosphonous acids **3** was described earlier from hypophosphorous acid salts.[7,8]

The procedure for the aminoalkylation of **3** by the addition of phosphonous acids **3** or their silyl esters to the corresponding *N*-protected Schiff bases would involve a series of protection–deprotection steps.[9] An alternative amidoalkylation of trivalent phosphorus compounds could be a more convenient route to pseudo-α,α-dipeptide building blocks **1** (Scheme 1).

The procedure for the Kabachnik–Fields-type reaction with amides as the amino component[10–12] and trivalent phosphorus chlorides, aldehydes or ketones in acetic acid (Oleksyszyn reaction)[11] was modified by Yuan et al.[12] for dialkyl phosphites with carbonyl compounds and amides or carbamates in acetyl chloride.

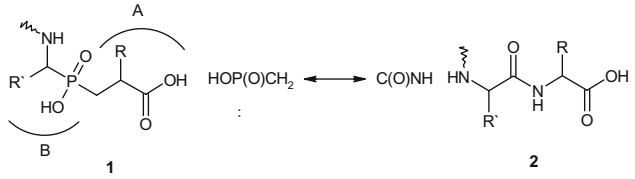
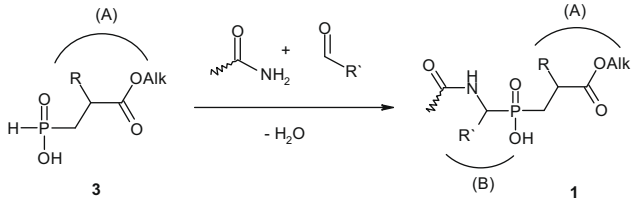


Figure 1. Structures of pseudo-peptide **1** and the peptide fragment **2**.



Scheme 1. Amidoalkylation of phosphonous acids **3** containing the structural isostere of amino acid (A).

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Usually *N*-acylated α-aminoalkylphosphorylic compounds, without isolation, are subjected to acidic hydrolysis followed by isolation of the α-aminoalkylphosphonic acids.[11] The amidoalkylation of dialkyl phosphites in acetyl chloride can be accompanied by partial dealkylation of the alkoxyphosphorylic fragment. The latter version of the procedure of Yuan et al.[12] in acetyl chloride was extended by Yiotakis[13] using previously dealkylated phosphonous carboxylic acids and Fmoc carbamates for the synthesis of phosphinic pseudo-peptides in an acetyl chloride/acetic acid mixture.

A milder procedure reported by Oleksyszyn[14] consists of the addition of an aldehyde to a pre-heated solution of the phosphorous acid and amide in acetic anhydride, however, the yields were usually low, except for aromatic aldehydes.[14] Nevertheless, this procedure can be of interest for the synthesis of pseudo-peptide blocks with retention of alkoxycarboxylic and alkoxyphosphorylic fragments.

Previously, bisamides **4** and 1-(acylamino)alkyl acetates **5** were postulated as probable reaction intermediates of the amidoalkylation of P^{III} compounds (Scheme 2).[14,15]

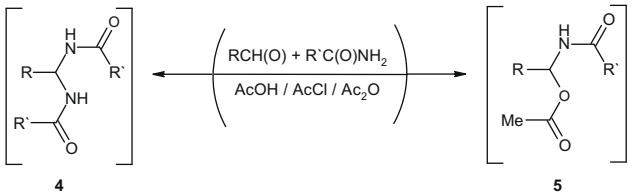
N,N′-Arylidene- or *N,N′*-alkylidenebisamides **4** were proposed as probable intermediates in the direct amidoalkylation of P^{III} compounds by Oleksyszyn,[14] because they react satisfactorily with P^{III} nucleophiles[11] and are easily formed from carbonyl compounds and amides.[16] However, these compounds were not isolated from the reaction medium.[11,12,14]

Soroka[15] ruled out bisamides **4** as the main reaction intermediates and proposed 1-(acylamino)alkyl acetates **5** as possible intermediates but again these compounds were not isolated from the reaction medium (Scheme 2). In this connection, we report the results of our investigations on a milder procedure for the amidoalkylation of P–H compounds.

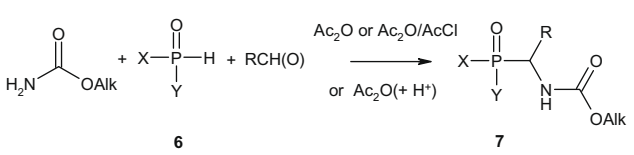
In this Letter, we report new data on the amidoalkylation of hydrophosphorylic compounds **6** in acetic anhydride.

We found that milder conditions for the three-component condensation reaction of dialkyl phosphites, diethylphosphinous acid, different alkylphosphonous acids, methyl and ethyl carbamates and aldehydes in acetic anhydride at room temperature allow *N*-alkoxycarbonyl-α-aminoalkylphosphorylic compounds **7** to be obtained (Scheme 3, Table 1). A mixture of acetyl chloride and acetic anhydride (1:4) proved to be a good medium for the amidoalkylation of hydrophosphorylic compounds, but the search for an optimum mixture was not carried out.

Also, we found that the milder condensation procedure made it possible to isolate *N,N′*-benzylidene- and *N,N′*-alkylidenebiscarbamates (**4**, R′ = OAlk) as intermediates from the reaction. Often



Scheme 2. Proposed intermediates **4** and **5** in the amidoalkylation of trivalent phosphorus compounds.



Scheme 3. Synthesis of N-protected α-aminoalkylphosphorylic compounds **7**.

Table 1
N-Alkoxycarbonyl-α-aminoalkylphosphorylic compounds (**7a–k**)

Entry	Compound	X	Y	R	Alk	Yield (%)
1	**7a**	MeO	MeO	Ph	Et	70[a]; 67[c]; 63[d]
2	**7b**	BuO	BuO	Ph	Et	71[c]; 53[d]
3	**7c**	Me	OH	Ph	Et	77[c]; 73[b]; 59[a]; 52[d]
4	**7d**	Me	OH	Ph	Me	79[a]; 61[d]
5	**7e**	Me	OH	*i*-Bu	Et	48[c]; 38[b]; 33[a]; 28[d]
6	**7f**	Me	OH	*i*-Pr	Me	31[a]
7	**7g**	Me	OH	*i*-Bu	Me	51[c]; 32[a]
8	**7h**	$HOCH_2$	OH	Ph	Et	54[a]
9	**7i**	$EtOC(O)CH_2CH_2$	OH	Ph	Et	71[c]; 65[b]; 57[a]
10	**7j**	$EtOC(O)CH_2CH_2$	OH	*i*-Bu	Me	32[a]
11	**7k**	Et	Et	Ph	Et	54[a]

[a] TFA (10 mol %) or [b] TSA (2 mol %) as catalysts.
[c] ($AcCl/Ac_2O$ = 1:4).
[d] Ac_2O.

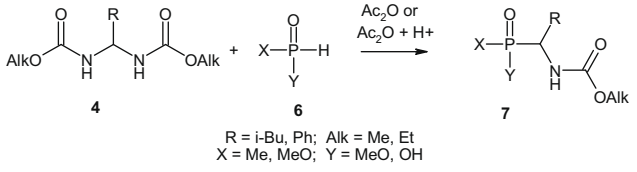
the initial formation of insoluble *N,N′*-alkylidene- or *N,N′*-benzylidenebiscarbamates **4** and simultaneous disappearance of the crystalline intermediate on their reaction with the hydrophosphorylic component **6** were observed. We obtained a mixture of biscarbamates (**4**, R′ = OAlk) and N-protected α-aminophosphorylic compounds **7** in different ratios, when the three-component reaction was stopped early. Silica gel chromatography allowed the separation of the intermediate biscarbamates **4** and the desired compounds **7**.

These results were unexpected, as 1-(acylamino)alkyl acetates **5** would appear to be more preferable intermediates, if we accept the reaction mechanism including nucleophilic attack of the phosphorus atom of the P–H component on the electrophilic carbon atom of 1-(acylamino)alkyl acetate **5** containing MeC(O)O as a good leaving group.

These data formed a good basis for the studies on the direct reaction of hydrophosphorylic compounds **6** and pre-obtained *N,N′*-alkylidenebiscarbamates **4** in acetic anhydride (Scheme 4).

We found that biscarbamates **4** and dimethyl phosphite (**6**, X = Y = MeO) or methylphosphonous acid (**6**, X = Me, Y = OH) in acetic anhydride at room temperature reacted to give dimethyl *N*-alkyloxycarbonyl-α-aminoalkyl phosphonates or *N*-alkyloxycarbonyl-α-aminoalkyl methylphosphinic acids **7** in 45–72% yields. Moreover, we found that *N,N′*-benzylidenebiscarbamates (**4**, R = Ph) reacted with hydrophosphorylic compounds **6** to give α-aminoalkylphosphorylic compounds **7** in higher yields than *N,N′*-isoamylidenebiscarbamates (**4**, R = *i*-Bu). Therefore, *N,N′*-benzylidenebiscarbamates (**4**, R = Ph) are more reactive than *N,N′*-isoamylidenebiscarbamates (**4**, R = *i*-Bu). These results confirm the electrophilic character of the biscarbamates. Note that P–H compounds with different structures, namely, dialkyl phosphites, diethylphosphinous acid and alkylphosphonous acids, were studied in the three-component version of the condensation in acetic anhydride. However, the hydrophosphorylic compounds showed no apparent nucleophilic nature.

These data confirm the multistep character of the reaction mechanism, and that the nucleophilic attack of the phosphorus atom of the hydrophosphorylic compound at the electrophilic



Scheme 4. Synthesis of N-protected α-aminoalkylphosphorylic compounds **7** via reaction of biscarbamates **4** and hydrophosphorylic compounds **6**.

carbon atom of the biscarbamate does not determine the general reaction rate of the amidoalkylation process.

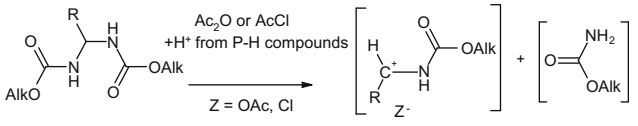
It is known that both the formation of amidoalkylation reagents from aldehydes and amides and α-amidoalkylation of carbon compounds require acid catalysis.[16] In this connection, we report that biscarbamates **4** and hydrophosphorylic compounds **6** react to afford *N*-alkyloxycarbonyl-α-aminoalkylphosphorylic compounds **7** in yields usually lower than those obtained by the addition of catalytic quantities of trifluoroacetic (TFA) or *p*-toluenesulfonic (TSA) acids in contrast to the data of Oleksyszyn.[14] These authors earlier reported that the addition of TSA to the reaction mixture containing an aldehyde, an amide and phosphorous acid did not increase the yield of the desired α-aminoalkylphosphonic acids.[14] However, Yuan[12c] showed the positive influence of acidification on the three-component condensation of 2-haloalkaneamides, benzaldehydes and dialkyl phosphites. Moreover, we found that the positive catalysis by TSA is more powerful than that by TFA. Also we observed the positive influence of the addition of acetyl chloride on the interaction of pre-obtained biscarbamate **4** and methylphosphonous acid in acetic anhydride.

Our data suggest that the protonation of the oxygen (C=O) or nitrogen atom of intermediate biscarbamates **4** followed by the formation of the *N*-alkoxycarbonylimine cation (and salt) **8** and alkyl carbamate is the key step and is the rate-determining step of the reaction (Scheme 5). Interestingly, compound **8** (Z = OAc) represents an ionic analogue of intermediates **5**, which were proposed earlier by Soroka.[15]

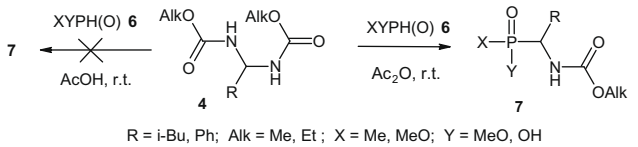
We propose that all the following steps are very fast and exert no effect on the general rate of the reaction. Our data is in agreement with the formation of proposed bisamides **4**(R′=Alk) (Scheme 2) followed by the formation of the *N*-acylimine cation (analogue of *N*-alkoxycarbonylimine cation **8**) (Scheme 5).[11e]

Surprisingly, the reaction of hydrophosphorylic compounds **6** and biscarbamates **4** does not occur at room temperature in acetic acid. However, biscarbamates **4** and dimethyl phosphite or methylphosphonous acid **6** react to give the corresponding *N*-alkoxycarbonyl-α-aminoalkylphosphorylic compounds **7** in acetic anhydride at room temperature (Scheme 6). In the latter case, acetic acid formed during the reaction was the acidic catalyst.

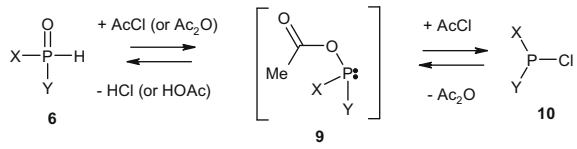
These data suggest the formation of a more reactive intermediate (towards the alkoxycarbonylimine cation **8**) than the starting hydrophosphorylic compounds **6**. In this connection, we propose P–OAc derivatives **9** of trivalent phosphorus compounds as possible intermediates (Scheme 7) in the discussed three-component reaction of alkyl carbamates, aldehydes and hydrophosphorylic compounds **6** in acetic anhydride.



Scheme 5. Formation of alkoxycarbonylimine salt **8** as a possible intermediate from biscarbamate **4**.



Scheme 6. Reactions of biscarbamates **4** and P–H compounds **6** in Ac_2O.



Scheme 7. Proposed reactive P–OAc intermediates **9** formed from P–H compounds **6** in Ac_2O/AcCl.

We propose that P–OAc derivatives **9** of trivalent phosphorus compounds are intermediate structures in equilibrium between P–H compounds **6** and chlorides **10** in AcOH/Ac_2O/AcCl medium (Scheme 7). Two signals due to trivalent phosphorus compounds were observed in the ^{31}P NMR spectrum of methylphosphonous acid in acetyl chloride or methyldichlorophosphine in acetic anhydride. One signal at about δ 198 corresponds to $MePCl_2$. We propose that another signal at about δ 185 corresponds to the P–OAc derivative of methylphosphonous acid **9** (Supplementary data, part 3).

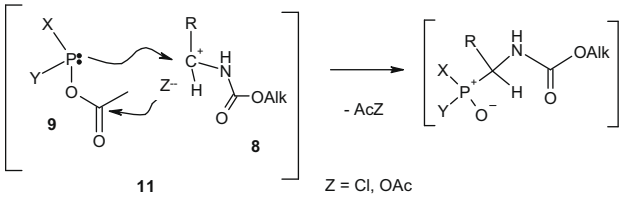
The proposed intermediate **9** contains both a nucleophilic phosphorus atom and an electrophilic carbon atom (acetyl fragment). Therefore, compound **9** can readily participate in the Arbuzov-type reaction.[17] The formation of intermediate P–OAc derivatives **9** can explain the unique role of acetic anhydride in this reaction. We propose that nucleophilic attack of the phosphorus atom of the intermediate P–OAc compound **9** on the positively charged carbon atom of the *N*-alkoxycarbonylimine cation **8** occurs followed by the formation of the phosphorus–carbon bond and simultaneous attack of anion Z on the electrophilic carbon atom of the acylic fragment of the P–OAc derivative with subsequent isolation of AcZ according to the Arbuzov-type reaction (Scheme 8).

Additional studies are required for a more comprehensive understanding of the role for proposed P–OAc intermediates **9** in the mechanism for this reaction.

It is thought that complex **11** is a possible intermediate structure for the formation of the desired *N*-alkyloxycarbonyl-α-aminoalkylphosphorylic compounds **7**. Thus, we propose that the three-component Oleksyszyn reaction with hydrophosphorylic compounds, aldehydes and alkyl carbamates includes an Arbuzov-type reaction step (Scheme 8).

Also, we suggest a milder version of the undeservedly forgotten procedure of Oleksyszyn[14] with some minor modifications as an improved method for the amidoalkylation of various hydrophosphorylic compounds in acetic anhydride/acetyl chloride. This milder procedure may be of interest for the synthesis of N-protected α-aminophosphorylic compounds **7**, which are promising as substrates in combinatorial peptide synthesis.

In conclusion, we have presented a new, milder version of the procedure for the synthesis of N-protected α-aminoalkylphosphorylic compounds **7** by reaction of ethyl and methyl carbamates, aldehydes and hydrophosphorylic compounds in acetic anhydride/acetyl chloride, and new data on the mechanism of this



Scheme 8. Proposed scheme for the Arbuzov-type reaction of acyl derivatives of P^{III} compounds **9** and alkoxycarbonylimine salt **8**.

reaction. We also isolated for the first time, *N,N′*-benzylidene- and *N,N′*-alkylidenebiscarbamates (**4**, R′ = OAlk) as intermediates from the reaction medium and have proposed a new version of the mechanism for this reaction involving an Arbuzov-type reaction step.

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Supplementary data

Detailed experimental procedures for the three-component reaction of alkyl carbamates, hydrophosphorylic compounds and aldehydes in acetic anhydride, isolation of intermediate biscarbamates from the reaction medium, synthesis of *N,N′*-alkylidenebiscarbamates in acetic anhydride, and investigation of the reaction of pre-obtained *N,N′*-alkylidene- and *N,N′*-benzylidenebiscarbamates **4** and hydrophosphorylic compounds **6** in acetic anhydride with addition of an acidic catalyst, as well as spectral and analytical data, copies of ^{1}H, ^{13}C and ^{31}P NMR and MS spectra for intermediate biscarbamates **4a–c** and amidoalkylphosphorylic compounds **7a–k** are available as Supplementary data, Parts I, II and III. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.020.

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