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AMIDOALKYLATION OF PHOSPHOROUS ACID

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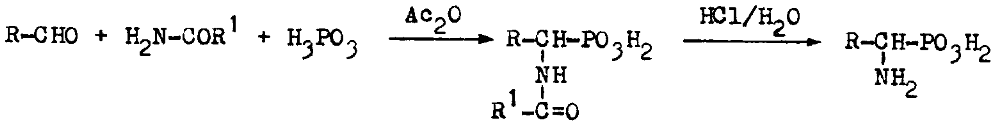
Abstract: Amidoalkylation of phosphorous acid by the reaction of mixture of phosphorous acid and amide with carbonyl compounds in acetic anhydride, followed by hydrolysis to give 1-aminoalkanephosphonic acids, is described.

Whereas the aminoalkylation of phosphorous acid by the Mannich-type reaction[1] or by its addition to imines[2] is known, the corresponding amidoalkylation of this compound has not been reported yet.

Basing on our previous investigations on the amidoalkylation of trivalent phosphorus chlorides[3,4], we have found that phosphorous acid can undergo an analogous reaction.

The addition of carbonyl compounds to a solution of phosphorous acid and amide in acetic anhydride (according to Scheme 1) is accompanied by a strong exothermic effect to give N-acylated 1-aminoalkanephosphonic acids.



$$R{-}CHO + H_2N{-}COR^1 + H_3PO_3 \xrightarrow{Ac_2O} R{-}\underset{\substack{|\\ NH\\ |\\ R^1{-}C{=}O}}{CH}{-}PO_3H_2 \xrightarrow{HCl/H_2O} R{-}\underset{\substack{|\\ NH_2}}{CH}{-}PO_3H_2$$

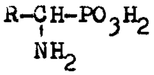
Scheme 1

Hydrolysis of the latter crude product gives the corresponding 1-aminoalkanephosphonic acid (Table).

A typical experimental procedure for amidoalkylation of phosphorous acid is as follows:

To a well stirred mixture of amide (0.1 mol) and phosphorous acid (0.1 mol) in Ac_2O (20 ml) preheated to 45°C, (0.15 mol) of carbonyl compound is slowly added over a period of ca. 15 min. A strong exothermic effect is always observed and the temperature of the reaction mixture rises to 80-120°C. A temperature of 70-80°C is maintained during next 3 hrs. After that time, volatile materials are removed <u>in vacuo</u>. To the residue, 50 ml of conc. hydrochloric acid is added and the resulting solution is refluxed for 4 hrs. The cooled solution is then washed with toluene and the aqueous solution evaporated to dryness <u>in vacuo</u>. The resulting crude hydrochloride of the 1-aminoalkanephosphonic acid is dissolved in methanol and treated gradually with pyridine until pH 4 is reached. The precipitate is filtered off and recrystallized from aqueous ethanol.

1-Aminoalkanephosphonic acids obtained by amidoalkylation of phosphorous acid

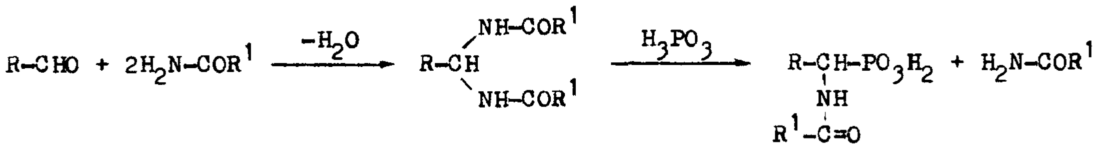


$R-CH(NH_2)-PO_3H_2$

	Amide	Yields a/	m.p.	Lit. m.p.
CH_3	benzyl carbamate	10	272-4°	272-4° 6)
CH_3	benzamide	27	273-5°	
i-Pr	benzyl carbamate	34	272-4°	274° 7)
C_6H_5	acetamide	75	282-4°	280-2° 6)
$3-O_2N-C_6H_4$	benzamide	59	271-3°	272-4° 8)
$4-Cl-C_6H_4$	acetamide	67	279-81°	291,3 - 2,5° 7)
$4-CH_3-C_6H_4$	benzamide	37	274-5°	272-3° 9)

a/ yields based on phosphorous acid

This reaction seems to involve initial formation of N,N'-alkylidene or - arylidenebisamide followed by its electrophilic attack on phosphorous acid (Scheme 2)



$$\text{R-CHO} + 2\text{H}_2\text{N-COR}^1 \xrightarrow{-\text{H}_2\text{O}} \text{R-CH}(\text{NH-COR}^1)_2 \xrightarrow{\text{H}_3\text{PO}_3} \text{R-CH(NH-C(=O)-R}^1\text{)-PO}_3\text{H}_2 + \text{H}_2\text{N-COR}^1$$

Scheme 2

Thus, we have examined bisamides as amidoalkylating agents phosphorous acid. For example, heating a mixture of equimolar amounts of benzylidenebisacetamide and phosphorous acid in acetic acid solution produces N-acetyl 1-aminobenzylophosphonic acid and acetamide in nearly quantitative yields. The procedure via bisamides is not recommended because it requires their prior synthesis.

Previous papers[1,2] suggest that strong acidity of the reaction mixture is required in the aminoalkylation reaction because only neutral phosphorous acid is sufficiently nucleophilic to add to an imine. We have found that changes of solvent from acetic anhydride to acetic chloride[5] or addition of a strong acid (e.g., p-toluenesulphonic acid) to the reaction mixture do not increase the yield. This fact suggests that the electrophilicity of bisamides is more important than the nucleophilicity of phosphorous agent (see Table). The reaction described above seems to be general for all P(III) acids[4] and further investigations on this topic are in progress, especially from the point of view of the reaction mechanism.

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