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Technical Notes

Reconsideration of the Base-Free Batch-Wise Esterification of Phosphorus Trichloride with Alcohols

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Abstract:

Batch-wise esterification of phosphorus trichloride with different alcohols in the absence of base and cleavage of the reaction products by the HCl released in course of the reaction were reinvestigated. The role of the kind of alcohol, mixing order of reagents, temperature, time of reaction, and excursion of gaseous HCl in the proportional composition of the reaction products were studied. Considering the mechanism of esterification and cleavage of the products, the optimized conditions to retain the cleavage process and high-yield production of dialkyl hydrogen phosphonates were determined.

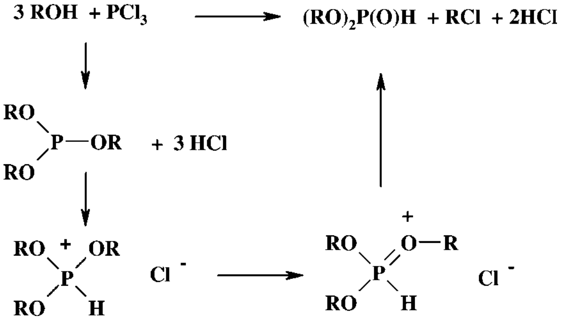
Introduction

Dialkyl hydrogen phosphonates (DAHP) are considered as the essential intermediates to prepare key functionalized phosphonic acid derivatives, i.e., herbicides, fungicides, insecticides, and antibiotics.[1] Dimethyl hydrogen phosphonate is used as a fungicide[2] and an intermediate in the production of trichlorfon (insecticide Dipterex).[3,4]

The reaction of the appropriate alcohol with phosphorus trichloride (known as the McCombie process[5]) is the most common method to prepare DAHP. This reaction can be performed in batch[4−8] or continuous process.[9−12]

The reaction yield in batch process, reported as 35-40% for MeOH, was increased to 80−90% for more bulky alcohols (such as EtOH and *i*-PrOH).[4,7] The reaction yield for MeOH was increased to 70−80% in continuous process.[9,10]

Scheme 1. **Mechanism pathway proposed for the esterification of PCl_3 and formation of DAHP**



Dimethyl and diethyl hydrogen phosphonates were prepared by this method. Diisopropyl hydrogen phosphonate and the higher homologues could also be prepared by another method in which one mole of phosphorus trichloride was reacted with two moles of alcohols and one mole of water to avoid conversion of one mole of alcohol to alkyl halide.[13]

It is said that usually the trialkyl ester is first formed and then cleaved by the hydrogen chloride to give an alkyl chloride and a diester (DAHP).[14] This reaction proceeded by way of quasi-phosphonium ion as an intermediate which upon alkylation, decomposes to a DAHP and an alkyl halide (Scheme 1).[15]

However, this hypothetical mechanism has been questioned. The over-all reaction consists of two steps: (1) the replacement of chlorine by an alkoxy group (esterification), through which hydrogen chloride is liberated and (2) the reaction of hydrogen chloride with the product (HCl cleavage) and a Michaelis−Arbusov rearrangement which results in elimination of an alkyl chloride. This causes the conversion of triple-connected to quadruple-connected phosphorus. A number of different mechanisms may be postulated that differ only with respect to the extent in which step 1 precedes or follows step 2 (Scheme 2).

The formed hydrogen chloride can cause cleavage of DAHP and reduction of product yield in high extent if the

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Scheme 2. **Mechanism pathway for the esterification of PCl_3 and cleavage of the products by HCl**

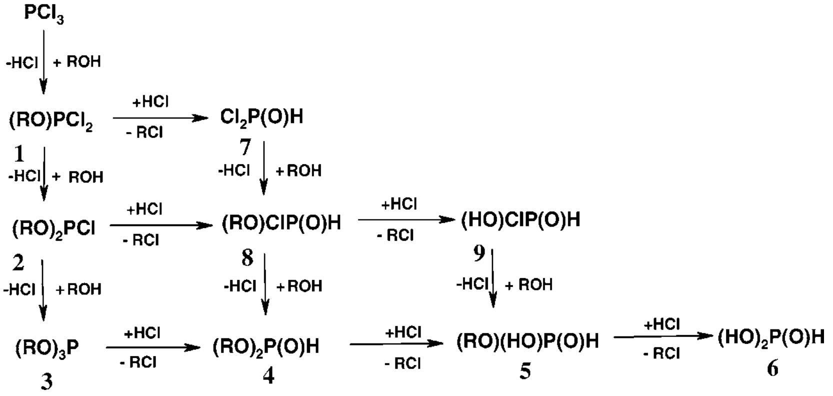

Table 1. **Proportional composition (%)[a] of the phosphonic acid derivatives after the esterification of PCl_3 with appropriate alcohol[b]**

expt[b]	PCl_3 (mol, mL)	ROH (mol, mL)	solvent (mL)	time (h)	temp (°C)	$(RO)_2P(O)H$ **4** (%)	(RO)(HO)P(O)H **5** (%)	$(HO)_2P(O)H$ **6** (%)	(RO)ClP(O)H **8** (%)
1	0.05, 4.4	MeOH (0.15, 6)	–	1	25	73	26	1	–
2	0.05, 4.4	MeOH (0.15, 6)	$CHCl_3$ (8)	0.5	25	58	36	6	–
3	0.05, 4.4	MeOH (0.15, 6)	$CHCl_3$ (8)	0.5	25	83	14	–	3
4	0.05, 4.4	MeOH (0.15, 6)	$CHCl_3$ (8)	0.5	0	84	–	–	16
5[c]	0.05, 4.4	MeOH (0.15, 6)	CH_2Cl_2 (8)	1	0	91	9	–	–
6	0.5, 44	*i*-PrOH (1.5, 115)	CH_2Cl_2 (48)	0.5	0	97	3	–	–
7	0.1, 8.8	*n*-BuOH (0.3, 27.5)	$CH_2 Cl_2$ (16)	0.5	0	98	2	–	–
8	0.5, 44	*i*-BuOH (1.5, 138.5)	CH_2Cl_2 (48)	0.5	0	98	2	–	–

[a] Based on ^{31}P NMR spectroscopy. [b] Addition order of the reagents in experiments 1 and 2 (dropwise addition of PCl_3 to alcohol) was reversed in experiments 3−8. [c] Vacuum stripping of HCl was performed in experiments 5−8.

reaction conditions are not controlled. The hydrogen chloride can be eliminated by saturating the reaction mixture with dry ammonia and filtering the resulting solid ammonium chloride prior to fractional vacuum distillation of the alkyl halide and DAHP.

Another method for obviating such a side reaction is to react the alcohol and phosphorus trichloride in a continuous system under conditions in which the hydrogen chloride is lost at once as a gas and the reaction heat is removed by the reaction products. Here, the presence of a low-boiling temperature solvent reduces the amount of heat in reaction medium as well.[9−12]

Attempts have been made to ameliorate the yield of the above reaction in batch process, but some parameters of the reaction influencing the yield have not been deeply considered yet. High-yield production of DAHP (**4**), depends on the relative rate of esterification and HCl cleavage reactions and on the reagent mixing order. The intensive and high exothermic reaction of phosphorus trichloride with alcohol prohibits mixing equal amounts of the two reagents together, and one should be added dropwise to the other. Thus, the order of each reagent in the mixing procedure can influence the relative amount of esterification and HCl cleavage products. This fact has not been properly investigated, and in most cases, phosphorus trichloride was added dropwise to alcohol.

In this contribution, batch process esterification of phosphorus trichloride by different alcohols have been reconsidered. Special attention has been paid to the parameters such as mixing order of reagents (precedent of alcohol or phosphorus trichloride), temperature, time of reaction, and immediate removal of the formed hydrogen chloride.

Result and Discussion

The esterifications of phosphorus trichloride by the appropriate alcohol (ROH; R = Me, *i*-Pr, *n*-Bu, *i*-Bu) have been performed under different conditions, and the product compositions of reaction mixture were characterized by ^{31}P NMR spectroscopy (Table 1). The esterification of phosphorus trichloride by MeOH was done in 0.05 M scale, and after obtaining the optimized conditions, the same reactions were performed in higher molar scale (0.5−1 M) to prepare diisopropyl, di-*n*-butyl, and diisobutyl hydrogen phosphonates.

All possible reactions relating to esteification (vertical reactions) and HCl cleavage of the products (horizontal reactions) are outlined in Scheme 2.

Dropwise addition of phosphorus trichloride to MeOH at 25 °C during 1 h in dry and solvent-less conditions, afforded a mixture of **4**, **5**, and **6** (R = Me) with proportional composition of 73, 26, and 1% respectively (Table 1, experiment 1; Figure 1a). Allowing this mixture to stand at current conditions for 3 h, modified the proportional composition of **4**, **5**, and **6** to 40, 50, and 10%, respectively (Figure 1b). It can be deduced that some part of **4** was cleaved by the HCl present in the reaction medium to form **5** and **6**.

^{31}P NMR spectra of the reaction mixture displayed a concentration-dependent upfield chemical shift of phosphorus in **5** (0.3 ppm) and **6** (1.3 ppm). This should be attributed to

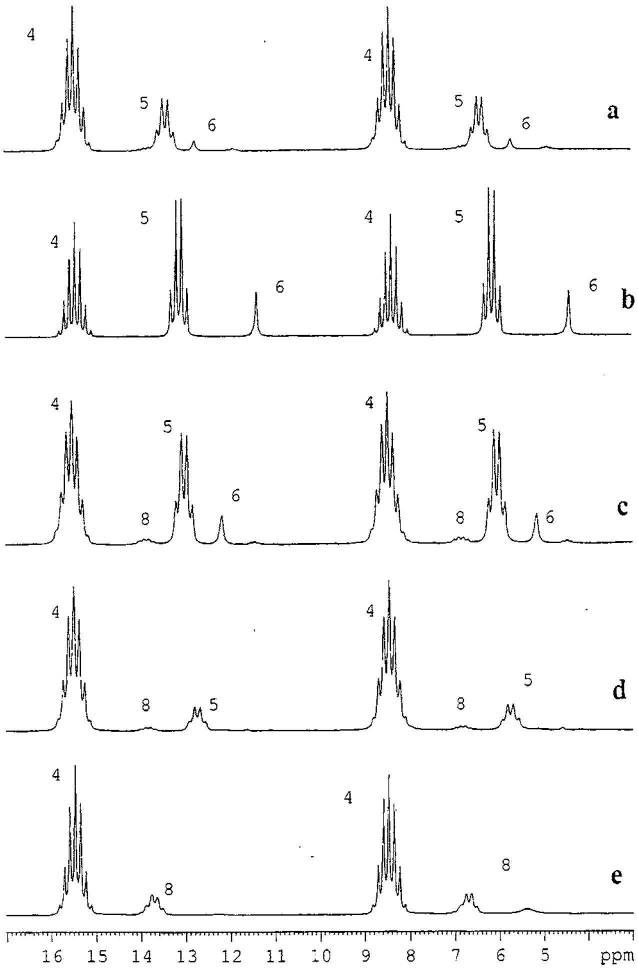

Figure 1. **^{31}P NMR spectrum (in $CDCl_3$) of the reaction mixture (a) after dropwise solvent-less addition of PCl_3 to MeOH at 25 °C (experiment 1, Table 1), (b) after stirring the precedent mixture during 3 h at 25 °C, (c) after dropwise addition of PCl_3 to MeOH at 25 °C (experiment 2, Table 1); (d) after dropwise addition of MeOH to PCl_3 at 25 °C (experiment 3, Table 1); (e) after dropwise addition of MeOH to PCl_3 at 0 °C (experiment 4, Table 1) (experiments 2−4 were performed using $CHCl_3$ as solvent).**

the possibility of hydrogen bonding in concentrated solutions of **5** and **6**.

Performing the same experiment with $CHCl_3$ as solvent afforded a mixture in which the cleavage of the intended principal product (**4**) and formation of **5** and **6** have been increased (Table 1, experiment 2; Figure 1c). This could be assigned to the augmentation of reaction medium volume (because of the solvent presence) and dissolution of HCl therein.

In another attempt to prepare dimethyl hydrogen phosphonate, the amount of reactants were tripled, but the quantity of solvent remained constant as in experiment 5 (Table 1). As a result, the yield of product (weighted) was raised to about 98%, confirming the influence of the reaction medium volume on the HCl cleavage of the product.

Inversion of the reagent mixing order (addition of MeOH to phosphorus trichloride) caused the augmentation of the proportional amount of **4** and formation of a minor quantity of **8** (3%) (Table 1, experiment 3; Figure 1d).

Performing the same reaction in 0 °C inhibited the formation of **5** and **6** (the first and second cleavage products) and led to some extent of **8** (16%) (Table 1, experiment 4 and Figure 1e). Lowering the reaction temperature (from 25 to 0 °C), seemed to influence the esterification rate of phosphorus trichloride (Table 1, experiments 3 and 4). However, it had little effect on the HCl cleavage of the principal intended product (**4**) in the time required for completion of the esterification procedure (Table 1, experiments 3 and 5).

Vacuum stripping of the HCl released in course of the reaction during 1 h afforded the best yield of dimethyl hydrogen phosphonate (91% based on ^{31}P NMR and 84% based on the product weighted after evaporation of solvent) (Table 1, experiment 5). In this experiment—performed in CH_2Cl_2 as solvent during 1 h—despite vacuum stripping, some amount of cleavage product (**5**) was present in the reaction mixture (9%), but the esterification procedure was completed, and **8** was absent in the reaction mixture. CH_2-Cl_2 has been used as solvent regarding industrial consideration and also for maintaining the reaction temperature, not exceeding 40 °C in an uncontrolled situation.

The alcohols such as *i*-PrOH, *n*-BuOH, and *i*-BuOH have been successfully applied to the phosphorus trichloride esterification beyond the optimized conditions of MeOH (Table 1, experiments 6, 7, and 8).

In our experimental conditions, we never observed **1** and **2** or **7** and **9**. Observation of **8** in certain conditions indicated the formation of **2** before HCl cleavage. The esterification of phosphorus trichloride proceeding by three successive steps, mono-, di-, and triesterification and the influence of mixing order of the reagents in the inhibition of HCl cleavage of the product seemed to indicate the order of esterification rate as $PCl_3 > Cl_2P(OR) > ClP(OR)_2$. Effectively, if this was not the case, the mixing order should not have affected the mixture composition, and at once trialkyl hydrogen phosphonate would have been formed and cleaved by HCl.

Esterification of **7**, **8**, and **9** seemed to be more difficult than that of **1** and **2** (such as for their homologues in which H is substituted by an alkyl group) and in our experimental conditions should not occur. Thus, HCl cleavage of **3** occurred more readily than that of **1** and **2** and increased with the degree of esterification. However, the minor amount of production of **4**, via esterification of **8**, could not be excluded.

It is worthy to note that freshly distilled dimethyl hydrogen phosphonate was unstable and strongly hydrolyzed when exposed to air moisture; therefore, it should be used immediately after preparation. The others—more bulky dialkyl hydrogen phosphonates—are more stable and were not readily hydrolyzed. Stirring the reaction mixture after the esterification of phosphorus trichloride by *i*-PrOH during 2 h at 25 °C did not alter the composition of the reaction mixture. The reverse effect is observed concerning the correspondents trialkyl phosphite. Indeed, trimethyl phosphite is more resistant to the hydrolysis reaction than other trialkyl phosphites with more bulky alkyl groups (R = *i*-Pr, *n*-Bu, and *i*-Bu).

Table 2. ^{31}**P and** ^{1}**H NMR spectra of dialkyl hydrogen phosphonate DAHP (alkyl = Me, *i*-Pr, *n*-Bu, *i*-Bu)**

DAHP	^{31}P NMR δ, J (ppm, Hz)	^{1}H NMR δ, J (ppm, Hz)
$(MeO)_2P(O)H$	8.5, 15.5 (dm, 700, 12)	3.5 (d, CH_3, 7.5), 5.1, 7.9 (ds, PH)
$(i\text{-}PrO)_2P(O)H$	1.9, 8.7 (dt, 680, 8)	1.3 (d, CH_3, 7.5), 4.7 (m, CHO), 5.4, 8.2 (ds, PH)
$(i\text{-}BuO)_2P(O)H$	5.1, 12.0 (dq, 690, 8)	0.6 (d, CH_3, 7), 1.5 (m, CH), 3.4 (t, CH_2O, 10), 5, 7.8 (ds, PH)
$(n\text{-}BuO)_2P(O)H$	5.1, 12.0 (dq, 690, 8)	0.95 (t, CH_3, 7.5), 1.4 (m, CH_2), 1.7 (m, CH_2), 4.0 (m, CH_2O), 5.4, 8.1 (ds, PH)

Summary

Determining the mechanism of the esterification and cleavage reaction have permitted us to accomplish the optimized conditions in batch process following which DAHPs (alkyl = Me, *i*-Pr, *n*-Bu, *i*-Bu) were prepared with yield and purity of over 95%. The mixing order of reagents (dropwise addition of ROH to phosphorus trichloride) and the use of a minimum amount of solvent seem to influence considerably the product yield. The esterification of phosphorus trichloride occurring in three steps (mono-, di-, and triesterification) and the influence of mixing order of the reagents on the yield of the products (DAHP) illustrate the order of esterification as $PCl_3 > ROPCl_2 > (RO)_2PCl$. Each of the esterification products ($(RO)PCl_2$, $(RO)_2PCl$, and $(RO)_3P$) can also be subjected to the cleavage process by hydrogen chloride released in the course of the reaction. However, the influence of mixing order of the reagents on product yield showed that the cleavage rate increased with the degree of the phosphorus trichloride esterification and was in the order of $(RO)_3P > (RO)_2PCl > ROPCl_2$. It was observed that dimethyl hydrogen phosphonate was unstable and strongly sensitive toward the cleavage by HCl and hydrolysis by the environmental moisture. Depending on the number of carbons in the alkyl groups, the more bulky DAHPs were more stable toward the above reaction.

Experimental Section

General Methods. NMR spectra were recorded on a Bruker DPX-250 instrument (250 MHz for ^{1}H and 100 MHz for ^{31}P). $CDCl_3$ was used as solvent; chemical shifts were reported in δ (ppm) from TMS (^{1}H) and 85% H_3PO_4 (^{31}P), with downfield shifts positive.

Esterification of Phosphorus Trichloride with ROH (R = Me, *i*-Pr, *n*-Bu, and *i*-Bu). Phosphorus trichloride (11 mL, 0.125 mol) and CH_2Cl_2 (4 mL) were placed in a 100-mL flask immersed in an ice bath and equipped with a magnetic stirrer and a condenser (the head of which was connected to a water vacuum pump). Methanol (12.75 mL, 0.375 mol) diluted with CH_2Cl_2 (4 mL) was dropwise added (0.5 mL/min) to the precedent mixture. The mixture was stirred for another 10 min. Evaporation of CH_2Cl_2 afforded 13.5 g (0.122 mol, 98%) of dimethyl hydrogen phosphonate of 91% purity (^{1}H and ^{31}P NMR characteristics in Table 2).

The above procedure was performed for esterification of phosphorus trichloride by other alcohols, and after evaporation of CH_2Cl_2 and alkyl chloride—formed in the course of reaction—the following results were obtained (^{1}H and ^{31}P NMR characteristics in Table 2).

Esterification of phosphorus trichloride (44 mL, 0.5 mol) by 2-propanol (115 mL, 1.5 mol) yielded 69.6 g (0.419 mol, 84%) of diisopropyl hydrogen phosphonate of 97% purity.

Esterification of phosphorus trichloride (8.8 mL, 0.1 mol) by *n*-butyl alcohol (27.5 mL, 0.3 mol) yielded 18.3 g (0.094 mol, 94%) of di-*n*-butyl hydrogen phosphonate of 98% purity.

Esterification of phosphorus trichloride (44 mL, 0.5 mol) by isobutyl alcohol (138.5 mL, 1.5 mol) yielded 91 g (0.468 mol, 94%) of diisobutyl hydrogen phosphonate of 98% purity.

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