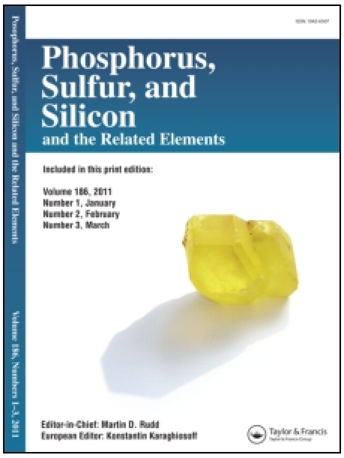

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CONVENIENT SYNTHETIC ROUTE TO MONO- OR DIALKYL PHOSPHATE FROM INORGANIC PHOSPHORUS ACIDS

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Mono- or dialkyl phosphate was synthesized in a favorable yield by oxidation of phosphonic or phosphinic acid in alcohol with oxygen at the presence of a catalytic amount of copper (II) chloride. The reaction may proceed via the formation of corresponding phosphorochloridate or phosphorochloridite.

Key words: Monoalkyl phosphate; dialkyl phosphate; phosphonic acid; phosphinic acid; phosphorylation; copper (I) chloride; copper (II) chloride.

INTRODUCTION

Numerous methods are available for the phosphorylation of alcohols,[1] but few of these are well-suited to the preparation of monoalkyl phosphates (**1**). Most produce mixtures, and separation of **1** from higher esters, or ortho- or polyphosphates, often presents difficulty. The problem can be avoided by use of protecting groups, but this requires the preparation of special reagents and extra reactions to remove the groups concerned. There are a few methods of phosphorylation of alcohol without protecting groups; one of the most simple and effective methods available is that of Kirby in which the direct iodine oxidation of phosphonic acid (**2**) in alcohol in the presence of tertiary amine gives the corresponding **1** in excellent yields.[2] Mukaiyama and Obata also reported the synthesis of **1** by oxidation of **2** in alcohol with mercury (II) acetate in the presence of tertiary amines.[3] However, these oxidative methods require an equimolar amount of expensive and poisonous reagents. Moreover a voluminous amount of tertiary ammonium salt was the by-product.

We have reported the synthesis of mixed trialkyl phosphates by oxidation of dialkyl phosphonate in alcohol with atmospheric oxygen by coupling with the oxidation reduction cycle of copper (I) and (II) chloride.[4]

In the present paper, we report a convenient procedure for preparation of **1** and dialkyl phosphate (**3**) by the oxidation of **2** and phosphinic acid (**4**), in alcohol with oxygen in the presence of catalytic amount of copper (II) chloride.

This procedure possesses several advantages over the reported methods: (1) an expensive reagent is unnecessary and (2) handling potentially hazardous substances can be avoided and water is the sole by-product.

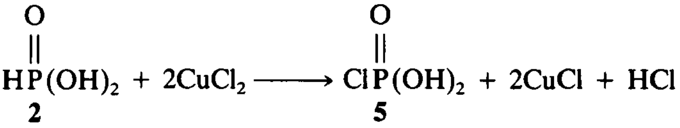
RESULTS AND DISCUSSION

Preparation of monoalkyl phosphate (1)

By bubbling oxygen in the presence of a catalytic amount of copper (II) chloride, alcohol is oxidative phosphorylated with **2** to give the corresponding **1**. The results obtained on the reaction of **2** with ethanol under several temperature conditions are shown in Table I. The product analysis was carried out with isotachophoretic analysis. The proceeding of the reaction was greatly affected by the temperature. At low temperature (below 30°C), the oxidation of **2** was retarded, and ethyl phosphate (**1a**) was hardly obtained. At 70°C, the acid **2** was consumed completely within 5 h, and then **1a** was given in an almost quantitative yield (Table 1).

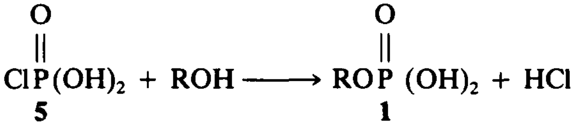
Figure 1 shows the yield of **1a** and the conversion of **2** at the temperature of 50°C as a function of the reaction time. Within 10 h the consumption of **2** reached 90% and **1a** was obtained in a 70% yield.

The difference between the conversion of **2** and the yield of **1a** increased by lowering temperature (Table 1). The difference may be caused by the accumulation of a reaction intermediate. The intermediate may presumably be phosphorochloridate (**5**) which could not be confirmed. The chloride **5** may be produced by the chlorination of **2** with copper (II) chloride (Equation 1).[4]



$$\underset{\mathbf{2}}{H\overset{\overset{O}{\|}}{P}(OH)_2} + 2CuCl_2 \longrightarrow \underset{\mathbf{5}}{Cl\overset{\overset{O}{\|}}{P}(OH)_2} + 2CuCl + HCl \qquad (1)$$

Consequently, it was suggested that the reaction of **5** with alcohol is more affected by reaction temperature (Equation 2), while the chlorination of **2** with copper (II) chloride is not so affected, and therefore, the difference increased by lowering temperature.



$$\underset{\mathbf{5}}{Cl\overset{\overset{O}{\|}}{P}(OH)_2} + ROH \longrightarrow \underset{\mathbf{1}}{RO\overset{\overset{O}{\|}}{P}\,(OH)_2} + HCl \qquad (2)$$

TABLE I

Temperature effect on oxidative phosphorylation of ethanol with **2**

Temp. °C	Conv./%	Yield of 1/%
17	1	0
30	12	4
50	63	53
60	95	92
70	98	98

Reaction conditions; ethanol 1 mol, **2** 0.05 mol, $CuCl_2$ 5 mmol, oxygen flow rate 50 ml min^{-1}, 5 h.

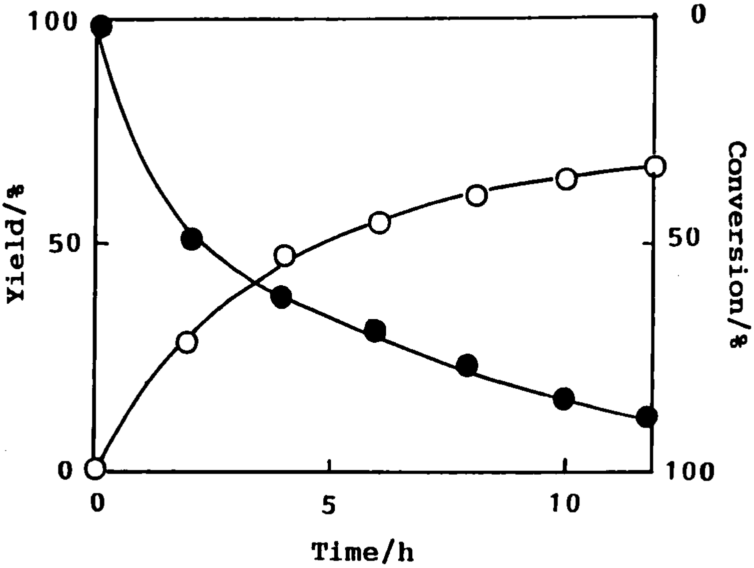


FIGURE 1 Yield of **1a** and conversion of **2** as a function of reaction time (h). Reactions conditions; ethanol 1 mol, **2** 0.05 mol, $CuCl_2$ 5 mmol, oxygen flow rate 50 ml min^{-1}, 50°C. **1a** —○—, **2** —●—.

Among some catalysts examined, only copper (II) chloride was effective, although other copper (II) salts, bromide, sulfate, and acetate were ineffective. From these results, it is also supported that **2** is chlorinated first by copper (II) chloride to afford **5**.

The results of the phosphorylation for some alcohols are shown in Table II. For the synthesis of methyl phosphate (**1a**), this method is effective, but for the higher alcohol, it is not.

On the case of 1-butanol, the corresponding ester could not be obtained. One of the reasons may be poor mutual solubilities of **2** and alcohol, or copper (II) chloride and alcohol.

TABLE II

Oxidative phosphorylation of some alcohols with **2**

ROH R	Conv./%	Yield of 1/%
Me	100	100
Et	63	53
Pr	50	35
Bu	2	0
i-Pr	20	13
s-Bu	13	10

Reaction conditions; ethanol 1 mol, **2** 0.05 mol, $CuCl_2$ 5 mmol, oxygen flow rate 50 ml min^{-1}, 6 h, 50°C.

TABLE III

Temperature effect on oxidative phosphorylation of ethanol with **4**

		Yield/%	
Temp. °C	Conv./%	**6a**	**3a**
17	86	73	0
30	95	71	11
50	100	22	64
70	99	4	89

Reaction conditions; ethanol 1 mol, **4** 0.05 mol, $CuCl_2$ 5 mmol, oxygen flow rate 50 ml min^{-1}, 6 h.

Preparation of Dialkyl Phosphate (3)

The similar oxidation of phosphinic acid (**4**) in ethanol gave **3a**. The temperature effect on the phosphorylation of ethanol with **4** is shown in Table III.

Even at 17°C, the conversion of **4** reached 86% and ethyl phosphonate (**6a**) was obtained in a yield of 73%, although **3a** was not obtained at all. At 30°C, an 11% yield of **3a** was given.

The proceedings of phosphorylation of ethanol with **4** is shown in Figure 2: at first, **4** was consumed rapidly and the resulting primary product **6a** formed, and then, its yield reached a maximum value (65%) after 3 h. Further oxidation resulted in the gradual decrease of **6a** and the formation of **3a**. After 12 h, the yield of **3a** reached a maximum value.

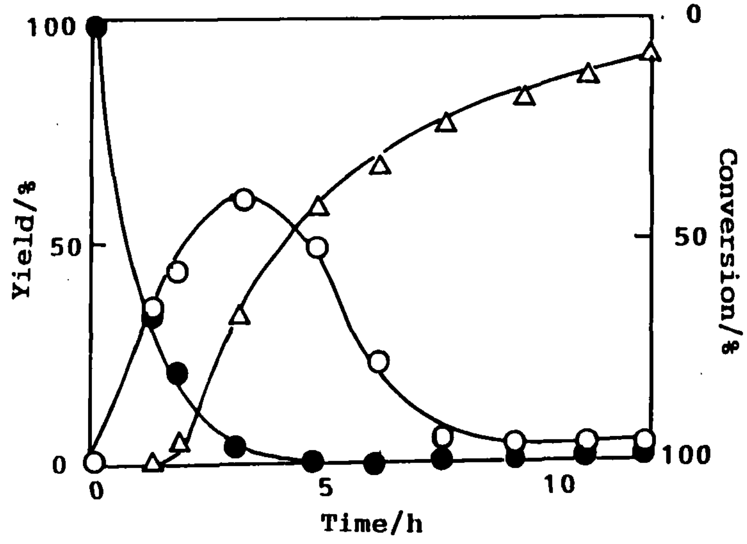
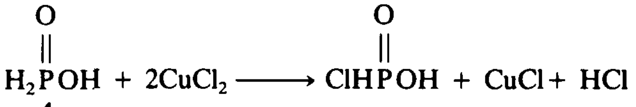
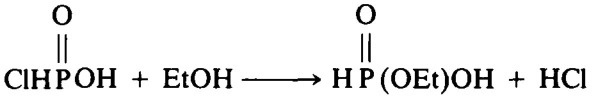


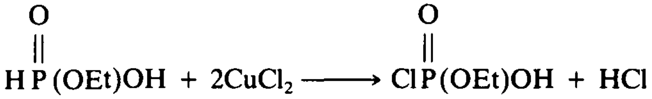
FIGURE 2 Yields of **6a**, **3a**, and conversion of **4** as a function of reaction time (h). Reaction conditions; ethanol 1 mol, **2** 0.05 mol, $CuCl_2$ 5 mmol, oxygen flow rate 50 ml min^{-1}, 50°C. **6a** —○—, **3a** —△—, **4** —●—.



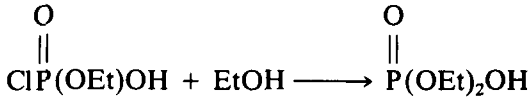
$$\underset{\mathbf{4}}{H_2\overset{\overset{O}{\|}}{P}OH} + 2CuCl_2 \longrightarrow ClH\overset{\overset{O}{\|}}{P}OH + CuCl + HCl \qquad (3)$$



$$ClH\overset{\overset{O}{\|}}{P}OH + EtOH \longrightarrow \underset{\mathbf{6a}}{H\overset{\overset{O}{\|}}{P}(OEt)OH} + HCl \qquad (4)$$



$$\underset{\mathbf{6a}}{H\overset{\overset{O}{\|}}{P}(OEt)OH} + 2CuCl_2 \longrightarrow Cl\overset{\overset{O}{\|}}{P}(OEt)OH + HCl \qquad (5)$$



$$Cl\overset{\overset{O}{\|}}{P}(OEt)OH + EtOH \longrightarrow \overset{\overset{O}{\|}}{P}(OEt)_2OH \qquad (6)$$

The results of the phosphorylation of some alcohols are shown in Table IV.

In all cases, the conversion of **4** is much higher than that of **2**, which may be due to its high reactivity. The conversion of alkyl phosphonate (**6**) to **3** is strongly influenced by the chain-length of the alcohols. The yields of **3** for the higher alcohols were also lower because of poor solubility of **4** in alcohol or copper (II) chloride in alcohol.

The overall reaction process is illustrated in Scheme 1.

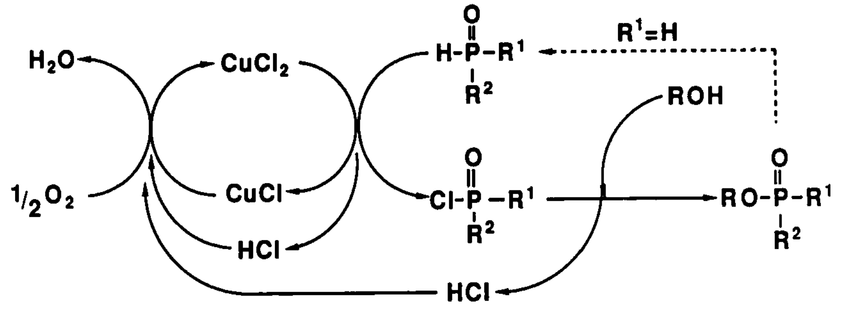
Novel phosphorylation of alcohol by oxidation of lower oxo acid of phosphorus with atmospheric oxygen by coupling with the oxidation reduction cycle of copper (I) and (II) chloride can be interpreted by this Scheme.

TABLE IV

Oxidative phosphorylation of alcohols with **4**

ROH R	Conv./%	Yield/% **6a**	Yield/% **3a**
Me	100	0	86
Et	100	22	64
Pr	100	17	55
Bu	98	48	4
i-Pr	84	50	9
s-Bu	95	20	36

Reaction conditions; ethanol 1 mol, **4** 0.05 mol, $CuCl_2$ 5 mmol, oxygen flow rate 50 ml min^{-1}, 50°C, 6 h.



Scheme 1

(2) $R^1=R^2=OH$
(4) $R^1=H$, $R^2=OH$
(1) $R^1=R^2=OH$
(3) $R^1=OR$, $R^2=OH$

EXPERIMENTAL

Materials. Phosphonic acid (**2**) used was commercially available. Phosphinic acid (**4**) was prepared by decomposition of calcium phosphinate with oxalic acid.[5]

Preparation of Monoalkyl Phosphate (**1**). Typical procedure: Phosphonic acid (**2**, 4.1 g, 0.05 mol), ethyl alcohol (46.0 g, 1.0 mol), and copper (II) chloride (1.3 g, 0.01 mol) were placed in a round flask fitted with a gas-inlet tube and a refluxing condenser. The mixture was vigorously stirred at 50°C, and oxygen gas was bubbled into the reaction mixture at the flow rate of 50 ml min^{-1}. The proceeding of the reaction was monitored by analysis of the products with a Shimadzu Capillary-Type Isotachophoretic Analyzer Model IP-3A, which has a two-stage migration tube system [Leading electrolyte; L-histidine (0.01 mol dm^{-3}), Triton X-100 (0.1%), pH 4–5. Terminal electrolyte; sodium hexanate, 0.01 mol dm^{-3}, pH 7–8].[6] L-Tartaric acid was used as an internal reference. Analytical data were determined by comparison with that obtained on analysis of authentic samples.[7] After the amount of **2** was consumed (12 h), cyclohexylamine was added, and the resulting precipitate was filtered off. The cyclohexylammonium salt of **1a** was recrystallized from ethanol. dp 200–205°C, (yield 74%).

Synthesis of Dialkyl Phosphate. Typical procedure: Into a mixture of **4** (3.3 g, 0.05 mol), ethyl alcohol (46.0 g, 1.0 mol), and copper (II) chloride (1.3 g, 0.01 mol) oxygen gas was bubbled in the similar manner as described above. The reaction products were analyzed in the similar manner as described above. The proceeding of the reaction was monitored by the similar method as described above. After the reaction was completed (10 h), the cyclohexylamine was added, and resulting cyclohexylammonium salt of **3a** was recrystallized from ethanol. mp 78–80°C, (yield 42%).

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