September, 1988] NOTES *Bull. Chem. Soc. Jpn.*, *61*, *3359—3361 (1988)*

Synthesis of Mixed Trialkyl Phosphates: Oxidative Phosphorylation of Alcohols with Dialkyl Phosphonates in the Presence of Copper(II) Chloride

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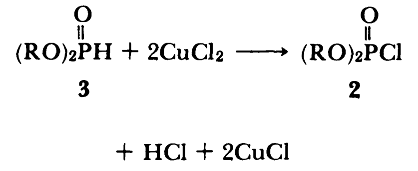
(Received January 13, 1988)

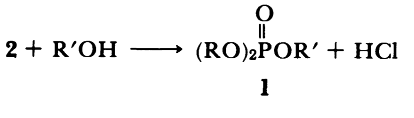
Synopsis. Mixed trialkyl phosphates were synthesized by oxidative phosphorylation of alcohols with dialkyl phosphonates and oxygen in the presence of copper(II) chloride in fairly good yields.

Various methods for the phosphorylation of alcohol have been reported.[1] The most frequently used method to prepare mixed trialkyl phosphate (**1**) involves the phosphorylation of alcohol with dialkyl phosphorochloridate (**2**), which is generally prepared by the chlorination of dialkyl phosphonate (**3**) with chlorine. Some modifications have been designed so as to avoid handling potentially hazardous chlorine gas. One is the reaction of alcohol with **3** in carbon tetrachloride and tertiary amine.[2] The other is an anodic phosphorylation of alcohol with **3** in the presence of lithium chloride.[3] In these reactions, **2** is presumed to be involved as an intermediate.

In the present paper, we report a more convenient procedure for preparation of **1** by the oxidation of **3** with oxygen by coupling with oxidation–reduction cycle of Cu(II) and Cu(I) chlorides in alcohol. This procedure possesses several advantages over the known methods: (1) handling potentially hazardous substances can be avoided, (2) water is the sole by-product, and (3) expensive reagents and special apparatus are unnecessary. Therefore, this method could be satisfactorily employed for the technical production of **1**. This procedure probably consists of three unit processes: (1) the chlorination of **3** with copper(II) chloride to give **2** and hydrogen chloride,[4] (2) the phosphorylation of alcohol with **2** to afford **1** and hydrogen chloride, and (3) the oxidation of hydrogen chloride and copper(I) chloride with oxygen to reproduce copper(II) chloride.[5] Consequently, in the presence of a catalytic amount of copper(II) chloride and by bubbling oxygen, alcohol is phosphorylated with **3** to give the corresponding **1**.



$$\underset{\mathbf{3}}{(RO)_2\overset{\overset{O}{\|}}{P}H} + 2CuCl_2 \longrightarrow \underset{\mathbf{2}}{(RO)_2\overset{\overset{O}{\|}}{P}Cl} + HCl + 2CuCl \qquad (1)$$



$$\mathbf{2} + R'OH \longrightarrow \underset{\mathbf{1}}{(RO)_2\overset{\overset{O}{\|}}{P}OR'} + HCl \qquad (2)$$

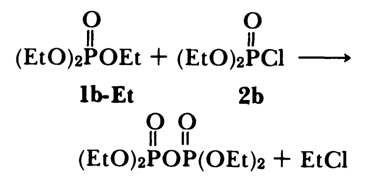
$$4CuCl + 4HCl + O_2 \longrightarrow 4CuCl_2 + 2H_2O \qquad (3)$$

Table 1. Results of Oxidative Phosphorylation of Ethanol with **3b**[a)]

EtOH/**3b**	$CuCl_2$[b)]	Temp	Conv.[c)]	Yield[c)]
mole ratio	mol%	°C	%	%
1.2	10	5	84	19
1.2	10	17	86	44
1.2	10	50	98	97
1.2	10	70	95	34
3.0	10	50	98	95
10.0	10	50	98	78
1.2	2	50	33	32
1.2	3	50	90	88
1.2	5	50	98	97
1.2	7	50	98	82

a) Conditions; 10 ml of mixture EtOH/**3b** was charged in a reaction tube (ϕ=10 mm) and oxygen was bubbled through it at flow rate 30 ml min^{-1} for 5 h. b) Based on **3b** used. c) Conversion and yield based on **3b** were determined by GLC using biphenyl as an internal standard.

The results obtained on the reaction of ethanol with diethyl phosphonate (**3b**) under several conditions are shown in Table 1. At a lower temperature (5 °C), the yield of triethyl phosphate (**1b-Et**) was low, despite the large conversion of **3b**. The intermediate, diethyl phosphorochloridate (**2b**), remained almost unreacted. The yield of **1b-Et** increased remarkably upon raising the temperature, and reached a maximum at 50 °C. At a higher temperature (70 °C), the yield was again reduced due to the formation of tetraethyl pyrophosphate (**4**), which may have been formed by a reaction between **1b-Et** and **2b** (Eq. 4).



$$\underset{\mathbf{1b\text{-}Et}}{(EtO)_2\overset{\overset{O}{\|}}{P}OEt} + \underset{\mathbf{2b}}{(EtO)_2\overset{\overset{O}{\|}}{P}Cl} \longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}O\overset{\overset{O}{\|}}{P}(OEt)_2 + EtCl \qquad (4)$$

It has been reported that Eq. 4 may be catalyzed with a small amount of copper.[6] Figure 1 shows the conversion of **3b** and the yield of **1b-Et** under optimum conditions as the function of the reaction time. The consumption of **3b** was completed within 5 h, and the yield of **1b-Et** became quantitative. Table 2 shows the obtained results regarding reactions of the other **3** with alcohols. With an increasing number of carbons of the alkyl group, the conversion of **3** decreased slightly; however, the yield of **1** decreased to a great extent. This result suggests that an increase in the bulkiness of alkyl groups affected the phosphorylation rate of **2** (Eq. 2) more than the chlorination rate of **3** (Eq. 1). When isopropyl or *t*-butyl alcohol was used, the yield of **1** became reduced and **4** was yielded in substantial quantity. The phosphates (**1**) of these alcohols may particularly tend to dimerize while easily liberating the corresponding alkyl chlorides, according to the reaction similar to Eq. 4. The phosphorylation of phenol with **3b** gave only a 3% yield of diethyl phenyl phosphate. In this case, the reaction mixture became turbid and a white precipitate was observed. Since phenol is more acidic than aliphatic alcohol, this precipitate may be the copper salt of phenol. The formation of the salt impaired the catalytc activity of copper. However, diphenyl phosphonate (**3e**) reacted with ethyl alcohol to give a similar result as in the cases of dipropyl phosphonate (**3c**) or dibutyl phosphonate (**3d**). Reactions using other copper(II) salts, such as bromide, acetate, and sulfate, failed. This suggests that chloride is necessary in order to propagate the reaction. The reaction (Eq. 1) can be explained by using the following radical mechanism:

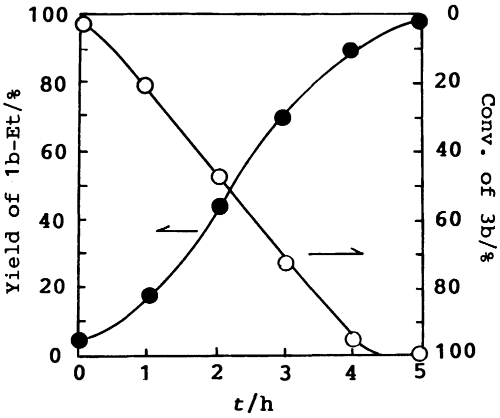
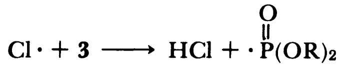
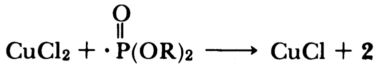


Fig. 1. Yield of **1b-Et** and conversion of **3b** as a function of reaction time.
Conditions: Ten ml of reaction mixture (EtOH/**3b** mole ratio=1.2 and CuCl₂ 10% based on **3b**) was bubbled with oxygen gas (flow rate 50 ml min⁻¹) at 50 °C. ●; Yield of **1b-Et**, ○; conversion of **3b**.

$$\mathrm{CuCl_2} \longrightarrow \mathrm{CuCl} + \mathrm{Cl}\cdot \tag{5}$$

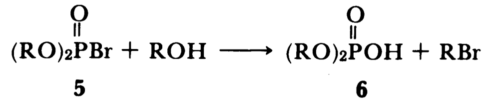


$$\mathrm{Cl}\cdot + \mathbf{3} \longrightarrow \mathrm{HCl} + \cdot\overset{\overset{\displaystyle O}{\|}}{\mathrm{P}}\mathrm{(OR)_2} \tag{6}$$



$$\mathrm{CuCl_2} + \cdot\overset{\overset{\displaystyle O}{\|}}{\mathrm{P}}\mathrm{(OR)_2} \longrightarrow \mathrm{CuCl} + \mathbf{2} \tag{7}$$

An electron transfer from the chloride to copper(II) occurs (Eq. 5), and the hydrogen atom of **3** is abstracted by the chlorine atom (Eq. 6). Since the oxidation potentials of the sulfate and acetate ions are higher than that of the chloride ion (oxidation of these ions are more difficult), consequently, the reactions using copper(II) sulfate and acetate did not occur. When copper(II) bromide is used, the resulting dialkyl phosphorobromidate (**5**) gives dialkyl hydrogenphosphate (**6**) and



$$\underset{\mathbf{5}}{\mathrm{(RO)_2}\overset{\overset{\displaystyle O}{\|}}{\mathrm{P}}\mathrm{Br}} + \mathrm{ROH} \longrightarrow \underset{\mathbf{6}}{\mathrm{(RO)_2}\overset{\overset{\displaystyle O}{\|}}{\mathrm{P}}\mathrm{OH}} + \mathrm{RBr} \tag{8}$$

alkyl bromide in place of **1** and hydrogen bromide (Eq. 8).

Upon the addition of triethylamine, the reaction was interrupted. Since hydrogen chloride may be consumed while binding the triethylamine, the progress of the reaction (Eq. 3) finally stopped. When acetonitrile was used as a solvent, **3** did not react, probably because of the extremely low solubility of

Table 2. Yields of Mixed Trialkyl Phosphates (**1**)[a]

Substrate		Conversion	Product	
$\mathrm{(RO)_2P(O)H}$ (**3**) R	R'OH R'	%	$\mathrm{(RO)_2P(O)OR'}$ (**1**)	Yield %[b]
Me (**3a**)	Et	99	$\mathrm{(MeO)_2P(O)OEt}$	90
Me	*n*-Pr	99	$\mathrm{(MeO)_2P(O)OPr^{\mathit{n}}}$	72
Me	*n*-Bu	98	$\mathrm{(MeO)_2P(O)OBu^{\mathit{n}}}$	62
Et (**3b**)	Et	98	$\mathrm{(EtO)_2P(O)OEt}$ (**1b-Et**)	95(87)
Et	*n*-Pr	99	$\mathrm{(EtO)_2P(O)OPr^{\mathit{n}}}$ (**1b-Pr**)	85(78)
Et	*n*-Bu	86	$\mathrm{(EtO)_2P(O)OBu^{\mathit{n}}}$ (**1b-Bu**)	73(69)
Et	*i*-Pr	83	$\mathrm{(EtO)_2P(O)OPr^{\mathit{i}}}$	31[c]
Et	*t*-Bu	99	$\mathrm{(EtO)_2P(O)OBu^{\mathit{t}}}$	25[d]
Et	Ph	5	$\mathrm{(EtO)_2P(O)OPh}$	3
n-Pr (**3c**)	Et	92	$\mathrm{(Pr^{\mathit{n}}O)_2P(O)OEt}$ (**1c-Et**)	65(52)
n-Bu (**3d**)	Et	95	$\mathrm{(Bu^{\mathit{n}}O)_2P(O)OEt}$	63
Ph (**3e**)	Et	92	$\mathrm{(PhO)_2P(O)OEt}$	61

a) Conditions: R'OH/**3** mole ratio; 1.3, CuCl₂; 10% based on **3**, oxygen flow rate; 30 ml min⁻¹, 50 °C, 5 h. b) Yields and conversion based on **3** were determined by GLC. Yields indicated in parentheses were for isolated product by distillation (**1b-Et**; bp 92—94 °C/12 mmHg, **1b-Bu**; bp 123—124 °C/15 mmHg, **1c-Et**; bp 110—112 °C/23 mmHg). In all cases, the phosphates were identified by comparison with authentic samples.[1] c) Tetraethyl pyrophosphate (**4**, 45%), which was assigned by comparison with an authentic sample[1] by means of GLC, yielded. d) The yield of **4** was 48%.

copper(I) chloride.

Experimental

Typical Procedure: A mixture of diethyl phosphonate (**3b**, 13.8 g, 0.1 mmol), propyl alcohol (7.2 g, 0.12 mmol), and copper(II) chloride (1.3 g, 0.01 mmol) was placed in a cylindrical reaction vessel (ϕ=10 mm). Copper(II) chloride was easily soluble in the mixture; however, after some time, white copper(I) chloride gradually precipitated due to its poor solubility. With bubbling of oxygen (flow rate 30 ml min^{-1}) at 50 °C, the precipitates soon disappeared and the solution became blue. The progress of the reaction was monitored by GLC (a 1-m glass column packed with Silicone OV 17 (2%) on Chromosorb W AW DMCS) at prescribed time intervals. After the conversion of **3 b** was complete, the reaction mixture was distilled in vacuo to afford diethyl propyl phosphate (**1b-Pr**, 78%, 100—101 °C/0.1 mmHg (1 mm Hg=133.322 Pa)).

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