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Catalytic Condensation

The Oxorhenium(VII)-Catalyzed Direct Condensation of Phosphoric Acid with an Alcohol**

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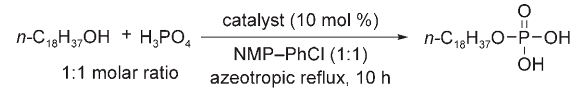
Phosphoric acid monoesters are among the most important substances in materials and medicinal chemistry as well as in many other fields. Many phosphoric acid monoesters are currently synthesized on an industrial scale and are used in everyday life.[1–4] From the perspective of green chemistry, the direct catalytic condensation of equimolar amounts of phosphoric acid and alcohols is attractive for the synthesis of phosphoric acid monoesters, especially for industrial-scale syntheses, since the reaction produces only water as a by-product.[5] Although various methods for the direct catalytic condensation of carboxylic acids with equimolar amounts of alcohols have been reported,[6,7] there is no successful method for the synthesis of phosphoric acid monoesters by the direct catalytic condensation of phosphoric acid and an equimolar amount of alcohols.[8,9] The esterification of phosphoric acid is much more difficult than that of carboxylic acids due to its stronger acidity.[10] We describe here the use of oxorhenium(VII) complexes[11,12] as extremely active catalysts for the direct condensation of phosphoric acid with nearly equimolar amounts of alcohols to give the corresponding phosphoric acid monoesters. Since the present reaction could be easily applicable on a large scale and rhenium salts are believed to exhibit low toxicity,[13] it should be a useful method for the environmentally and industrially important synthesis of phosphoric acid monoesters. To the best of our knowledge, this is the first direct catalytic condensation of a nearly equimolar mixture of phosphoric acid and alcohols for the selective synthesis of phosphoric acid monoesters.

Various metal oxides have been shown to be versatile green catalysts for dehydration reactions.[14,15] We first investigated the catalytic activity of various metal oxides in the dehydrative condensation of phosphoric acid with an equimolar amount of stearyl alcohol in *N*-methyl-2-pyrrolidone (NMP)/chlorobenzene (1:1) at azeotropic reflux with the removal of water (Table 1). A 65–70 wt % aqueous solution of perrhenic acid ((HO)ReO$_3$), trimethylsilyl perrhenate ((TMSO)ReO$_3$), and rhenium(VII) oxide (Re$_2$O$_7$) exhibited remarkable catalytic activities to selectively give the phosphoric acid monoester (97–81 %; Table 1, entries 1–3). When alcohols are treated with more reactive phosphorylating reagents such as phosphoryl chloride and phosphorus pentoxide, excess amounts of the phosphorylating reagents are required to avoid the generation of phosphoric acid di- and triesters as by-products. In contrast, the present condensation gives the phosphoric acid monoesters selectively. Phosphoric acid monoesters of long-chain alkyl alcohols are excellent detergents, while phosphoric acid diesters of long-chain alkyl alcohols exhibit foam-inhibiting properties and are therefore useless as highly foaming detergents.[3] The contamination of phosphoric acid or phosphoric acid diesters in the crude products makes purification of the phosphoric acid monoesters very difficult, therefore this selective synthesis of phosphoric acid monoesters from an equimolar mixture of phosphoric acid and alcohols is very valuable. ReO$_3$ showed lower catalytic activity (35 %; Table 1, entry 5) than the above-mentioned rhenium compounds, and methyltrioxorhenium (MTO, CH$_3$ReO$_3$) and ReO$_2$ were almost inert (Table 1, entries 4 and 6, respectively). Other metal oxides such as MoO$_3$, WO$_3$, and V$_2$O$_5$ were also almost inert (Table 1, entries 7–9).

Table 1: Catalytic activities of metal oxides for the direct condensation of phosphoric acid with an equimolar amount of stearyl alcohol.[a]



Entry	Catalyst	Yield [%][b]	Entry	Catalyst	Yield [%][b]
1	aq. (HO)ReO$_3$	97	6	ReO$_2$	8
2	(TMSO)ReO$_3$	94	7	MoO$_3$	8
3	Re$_2$O$_7$	81	8	WO$_3$	12
4	CH$_3$ReO$_3$	12	9	V$_2$O$_5$	17
5	ReO$_3$	35	10	none	7

[a] Condensation of phosphoric acid (2 mmol) with stearyl alcohol (2 mmol) in NMP/chlorobenzene (1:1, 10 mL). The amount of catalyst was calculated based on the metal. [b] Determined by ^{1}H NMR spectroscopy.

Based on the solubility and reactivity of phosphoric acid, aprotic polar solvents such as amides and ureas are suitable for the dehydrative condensation of phosphoric acid with alcohols. The investigation of solvents for the present dehydrative condensation indicated that NMP should be suitable. However, the boiling point of NMP is very high (202 °C), which makes it difficult to remove the generated water by azeotropic reflux. Therefore, mixtures of NMP with lower boiling solvents such as chlorobenzene (132 °C) and *o*-xylene (144 °C) were used for the dehydration under azeo-

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tropic reflux. Thus, phosphoric acid was dissolved in a 1:1 mixture of NMP and chlorobenzene, and dehydrative condensation with an equimolar amount of stearyl alcohol proceeded smoothly in the presence of a catalytic amount of perrhenic acid.[16]

Under the reaction conditions described above, oxorhenium(VII) complexes gradually decomposed to dark insoluble, catalytically inactive species (probably oligomeric low-valent rhenium oxides).[14] Furthermore, when the reaction was conducted in the presence of only 1 mol% of perrhenic acid at azeotropic reflux in NMP/*o*-xylene (1:1) for 12 h, stearyl phosphate was obtained in very low yield (16%, Figure 1, red circles). A similar yield resulted even in the absence of perrhenic acid (black squares). We therefore examined additives under the present reaction conditions, and found that several organic amines (10–20 mol%) can stabilize perrhenic acid efficiently and allow it to promote the condensation. Sterically less hindered secondary and tertiary amines, such as dibutylamine (Bu_2NH) and dimethyloctylamine, gave particularly good results. For example, the reaction catalyzed by 1 mol% of perrhenic acid in the presence of 20 mol% of Bu_2NH gave stearyl phosphate in excellent yield (98%, Figure 1, green circles). The reaction mixture was a clear, dark brown solution when the reaction was conducted in the presence of Bu_2NH. When the reaction was conducted with Bu_2NH (20 mol%) in the absence of perrhenic acid, stearyl phosphate was obtained in only 39% yield (Figure 1, blue squares), which clearly indicates that Bu_2NH contributes significantly to the stabilization of perrhenic acid. It is interesting to note that a mixture of perrhenic acid (1 mol%) and Bu_2NH (20 mol%) showed good catalytic activity even though Lewis acidic metal oxides are generally deactivated by bases.

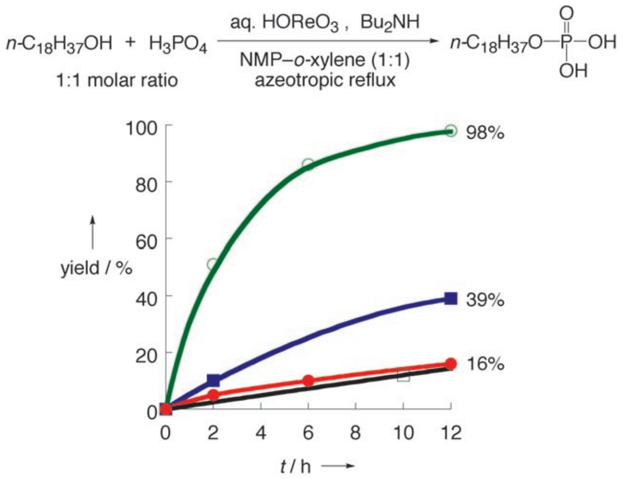
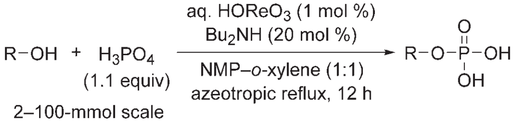
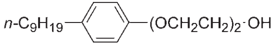
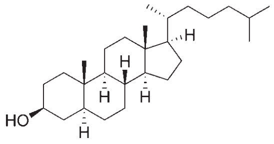


Figure 1. Plot of conversion versus time for the dehydrative condensation of phosphoric acid with an equimolar amount of stearyl alcohol catalyzed by perrhenic acid. Green: $(HO)ReO_3$ (1 mol%) and Bu_2NH (20 mol%); blue: Bu_2NH (20 mol%); red: $(HO)ReO_3$ (1 mol%); black: no $(HO)ReO_3$ or Bu_2NH.

To explore the scope of the dehydrative condensation catalyzed by perrhenic acid, the reaction of phosphoric acid (1.1 equiv) with various alcohols was examined (Table 2). The phosphoric acid monoesters were isolated after purification on ion-exchange resins. Unsaturated primary alcohols such as (*E*)- and (*Z*)-oleyl alcohol could be easily converted into the corresponding phosphoric acid monoesters in excellent yields (100%; Table 2, entries 2 and 4). The configurations of the C=C double bonds in oleyl alcohol were maintained during the reaction. The present protocol could be easily applied to a large-scale process. The condensation of phosphoric acid (1.1 equiv) with oleyl alcohol catalyzed by $(HO)ReO_3$ (0.5 mol%) gave oleyl phosphate in 96% yield at a 100-mmol scale (Table 2, entry 3). Diethylene glycol dodecyl ether and diethylene glycol *p*-nonylphenyl ether (Igepal CO-210)[17] also showed high reactivities (100%; Table 2, entries 5 and 6). The phosphoric acid monoesters of diethylene glycol dodecyl ether and diethylene glycol *p*-nonylphenyl ether are surfactants that are commonly used in detergents. A secondary alcohol such as β-cholestanol was also converted into the corresponding phosphoric acid monoester in 95% yield (Table 2, entry 7). The product decomposed completely when the reaction was conducted in the absence of Bu_2NH because of the high acidity of the reaction medium. Bu_2NH therefore contributes to the stabilization of acid-sensitive substrates as well as perrhenic acid.[18]

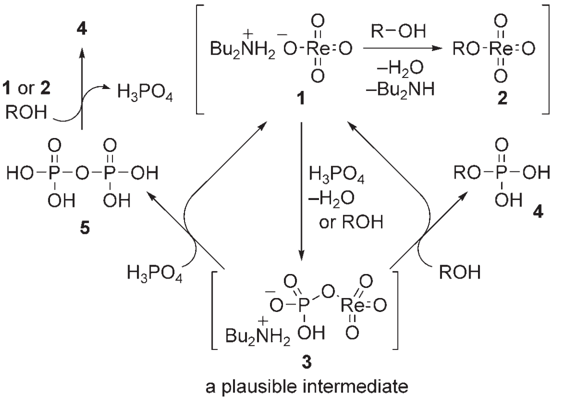
Table 2: The direct condensation of phosphoric acid with alcohols catalyzed by perrhenic acid and dibutylamine.[a]



Entry	Substrate	Yield [%][b]
1	$n\text{-}C_{18}H_{37}OH$	98
2	$(Z)\text{-}n\text{-}C_8H_{17}CH{=}CH(CH_2)_8OH$	100
3[c]	$(Z)\text{-}n\text{-}C_8H_{17}CH{=}CH(CH_2)_8OH$	96[d]
4	$(E)\text{-}n\text{-}C_8H_{17}CH{=}CH(CH_2)_8OH$	100
5	$n\text{-}C_{12}H_{25}(OCH_2CH_2)_2OH$	100
6		100
7		95[e]/(0)[d,f]

[a] Condensation of phosphoric acid (2.2 mmol) with an alcohol (2 mmol) in NMP/*o*-xylene (1:1, 10 mL). [b] Yield of isolated product. [c] Reaction of phosphoric acid (110 mmol) and alcohol (100 mmol) in the presence of aq. $(HO)ReO_3$ (0.5 mol%) and Bu_2NH (20 mol%). [d] Determined by ^1H NMR spectroscopy. [e] Reaction time 10 h. [f] In the presence of aq. $(HO)ReO_3$ (10 mol%) without Bu_2NH.

A possible reaction mechanism for the catalytic dehydrative condensation of phosphoric acid with alcohols is shown in Scheme 1. Perrhenic acid salt **1** might be converted into an alkyl perrhenate **2** under the azeotropic reflux conditions.[19] Phosphoric acid would react with compound **1** or **2** to give an intermediate such as the mixed anhydride **3**.[20] Since the acidity of perrhenic acid ($pK_a = -1.25$) is higher than that of



Scheme 1. Proposed mechanism for the dehydrative condensation of phosphoric acid with alcohols catalyzed by perrhenic acid.

phosphoric acid (pK_{a1} = 2.1),[21] nucleophilic substitution of **3** by alcohols occurs preferentially at the phosphorus atom to produce the phosphoric acid monoester **4**. Phosphoric acid mono- and diesters are stronger acids than phosphoric acid itself. For example, the pK_a values of MeOPO(OH)$_2$ and (MeO)$_2$PO(OH) are 1.54 and 1.29, respectively. Therefore, the nucleophilic substitution of **1** or **2** with phosphoric acid monoester **4** should be slower than with phosphoric acid. Thus, phosphoric acid monoesters are selectively produced by the present condensation. Alternatively, the active species **3** might react with phosphoric acid to produce pyrophosphoric acid (**5**), which could easily react with alcohols to give **4**.[22]

In conclusion, we have achieved the direct catalytic condensation of phosphoric acid with an equimolar amount of an alcohol and have synthesized several useful phosphoric acid monoesters. This catalytic condensation can be readily applied to large-scale processes with high efficiency. The present method should be useful for the environmentally and industrially important synthesis of phosphoric acid monoesters. Studies on the recyclability of the catalyst using oxorhenium(VII) complexes immobilized on secondary amine resins are in progress.

Experimental Section

In a typical procedure (Table 2), a 30-mL single-necked round-bottomed flask containing a Teflon-coated magnetic stirring bar and equipped with a 5-mL pressure-equalized addition funnel containing a cotton plug and about 2 g of 4 Å molecular sieves (pellets) and a reflux condenser was charged with phosphoric acid (2.2 mmol), the alcohol (2.0 mmol), dibutylamine (0.4 mmol), and a 65–75 wt% aqueous solution of perrhenic acid (3.5 μL, ca. 1 mol%) in NMP/*o*-xylene (1:1, 10 mL). The mixture was heated for 12 h under azeotropic reflux with the removal of water. After the reaction mixture had cooled to ambient temperature the solvents were removed under vacuum. The resulting crude product was purified on an ion-exchange resin (DOWEX 50WX2-200) to give the corresponding phosphoric acid monoester. The small excess of phosphoric acid could be removed by ion-exchange purification.

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[17] Igepal CO-210 (purchased from Aldrich) is a mixture of isomers. A representative structure of Igepal CO-210 is shown in Table 2.

[18] Acid-sensitive alcohols might be converted into the corresponding phosphoric acid monoesters in the presence of one or more equivalents of dibutylamine.

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