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Phosphorylation with Pyrophosphoric Acid

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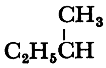
Synopsis. Dihydrogenphosphates of primary and secondary aliphatic alcohols as well as phenol were prepared by a very simple procedure with pyrophosphoric acid. *t*-Butyl and benzyl dihydrogenphosphates could be obtained by a slight modification of the reaction conditions. For the purpose of phosphorylation pyrophosphoric acid was more reactive than orthophosphoric acid.

Organic phosphoric acid esters play a very important role in many fields of organic and biological chemistry, and they are attractive objectives in synthetic organic chemistry. Various synthetic methods and reagents for phosphorylation have been used.[1] Pyrophosphoric acid (abbreviated below as PPA) as well as polyphosphoric acid has been used as a phosphorylating agent by many workers. To elucidate and utilize the presumed remarkable phosphorylating ability of PPA,[2] we also studied its reaction with various alcohols and phenol. Mere by mixing and warming with equimolar PPA, primary and secondary aliphatic alcohols as well as phenol afforded the dihydrogenphosphates, which were isolated as Ba salts and identified as anilinium salts (Table 1). The effect of temperature on the yield of phosphate was studied with reference to EtOH, and the highest yield was obtained at *ca.* 90 °C. Bisethylation became apparent above the temperature and the yield of diethyl ester gradually increased from 1.4% (80 °C) to 7.8% (140 °C). Orthophosphoric acid (100%) gave $EtOPO_3H_2$ in only 2.3% yield at 90 °C.[3] This result clearly indicated the higher reactivity of PPA than H_3PO_4. With regards to secondary alcohols, considerable dehydration occured at higher temperature to decrease the yield of $ROPO_3H_2$.[4] *t*-Butyl and benzyl alcohols did not give the desired phosphates by the simple procedure. But in the presence of CCl_3CN and 2 molar Et_3N, phosphorylation proceeded successfully to yield dihydrogenpyrophosphates, which were isolated as cyclohexylammonium salts and converted to anilinium hydrogenphosphates by ion exchange and concomitant hydrolysis (Table 1). The active phosphorylating agent was probably the imidoylpyrophosphate, which was formed from the PPA dianion and CCl_3CN and reacted with alcohols to give pyrophosphates and trichloroacetamide.[1b,6]

Experimental

Apparatus and Measurements. The melting points were

Table 1. Physical properties of the anilinium hydrogenphosphate $ROPO_3H_2 \cdot C_6H_5NH_2$

R	Mp/°C	^{1}H-NMR, δ from DSS (in D_2O)	IR (cm^{-1})		
			ν (P=O)	ν(C–O–P)	δ (N–H) ν (N–H)
CH_3	166—167 (167—168)[a)]	3.58(3H, d, J_{HP}=10 Hz, CH_3), 7.53 (5H, s, aromatic)	1240	1025 1055	2900 1505
CH_3CH_2	164—165 (164—166)[a)]	1.26 (3H, t, J=7 Hz, CH_3), 3.93 (2H, ap. quin, J=7 Hz, J_{HP}=8 Hz, CH_2), 7.50 (5H, s, aromatic)	1220	1020 1045	2880 1495
$CH_3CH_2CH_2$	150—152 (137—139)[a)]	0.90 (3H, t, J=7 Hz, CH_3), 1.62 (2H, ap. sex, J=7 Hz, CH_2), 3.83 (2H, ap quar, J=7 Hz, J_{HP}=8 Hz, CH_2–O), 7.50 (5H, s, aromatic)	1222	1030 1070	2870 1500
$CH_3(CH_2)_2CH_2$	144—148 (138—140)[a)]	0.92 (3H, br, t, CH_3), 1.13—1.93 (4 H, m, CH_2), 3.85 (2H, ap. quar, J_{HP}=7 Hz, CH_2O)	1230	1030 1060	2890 1500
$HOCH_2CH_2$	127—128	3.53—4.20(4H, m, CH_2), 7.50 (5H, s, aromatic)	1245	1030 1090	2900 1500
$(CH_3)_2CH$	171 (160—162)[a)]	1.25 (6H, d, J=6 Hz, CH_3), 4.20—4.53 (1H, m, J_{HP}=8 Hz, methine) 7.23—7.72 (5H, m, aromatic)	1230	1035	2960 1500
 $C_2H_5\overset{CH_3}{\overset{\vert}{C}}H$	158—159	0.90(3H, t, J=7 Hz, CH_3), 1.23 (3H, d, J=6 Hz, CH_3), 1.40—1.86 (2H m, CH_2), 3.93—4.72 (1H, m, methine), 7.16—7.77(5H, m, aromatic)	1235	1015	2870 1500
Cyclohexyl	166—168 (168—169)[a)]	0.80—2.20 (10H, m, CH_2), 3.56—4.31 (1H, m, methine), 7,06—8.03 (5H, m, aromatic)	1215	1025 1060	2910 1500
Phenyl	169—170 (171—175)	6.92—7.45 (5H, m, aromatic) 7.47—7.92 (5H, m, aromatic)	1230	1040	2860 1495
$(CH_3)_3C$	139—143 dec	1.41 (9H, s, CH_3) 7.01—7.83 (5H, m, aromatic)	1250	1015 1075	2900 1505
Benzyl	151—154 dec[a,b)]	4.93 (2H, d, J_{HP}=7.4 Hz, CH_2), 7.27—7.70 (10H, m, aromatic)	1225	1050	2860 1500

a) See Ref. 5. b) Corresponding dianilinium salt was reported, but we could not obtain it.

measured on a Yanagimoto MP-J3 apparatus and corrected. The IR spectra (KBr) were obtained on a JASCO IR-S spectrometer. The ^{1}H-NMR spectra were recorded on a JEOL PMX-60 spectrometer in D_2O using DSS as an internal standard, unless otherwise stated, and given in δ units.

Procedures and Results. Pyrophosphoric acid was prepared from 86% H_3PO_4 (199 g) and P_2O_5 (188 g) as colorless crystals (360.8 g, 97.3%).[7] The spectral data and melting points for all the anilinium hydrogenphosphates were summarized in Table 1. All the compounds described in this paper gave satisfactory elementary analyses. The equivalent weights of Ba salts determined by acid titration (Methyl Orange) were in good agreement with the calculated values. Dihydrogenphosphates of primary and secondary aliphatic alcohols and phenol were prepared by essentially the same procedure described below for the typical ethyl alcohol case.

Ethyl Dihydrogenphosphate: Ethanol (5.0 g, 108.5 mmol) was added dropwise to PPA (18.36 g, 103.2 mmol) with stirring. The mixture was warmed up to 90 °C and kept for 60 min. After cooling down and dilution with water (80 ml), the reaction mixture was neutralized with saturated aqueous $Ba(OH)_2$ (phenolphthalein) and the precipitated $Ba_3(PO_4)_2$ was filtered. Carbon dioxide was bubbled into the filtrate until the red color of indicator disappeared. Then the mixture was again filtered to remove $BaCO_3$ and concentrated under reduced pressure. The residue was triturated with EtOH to obtain $EtOPO_3Ba$ as colorless crystals (21.8 g, 76.9%). The Ba salt (3 g) was dissolved in water (200 ml) and treated with Na_2CO_3 (1.22 g). After removal of $BaCO_3$, the filtrate was subjected to ion exchange (Amberlite CG 120 H^+ form) to yield the free dihydrogenphosphate. The eluent was mixed with a slight excess aniline and concentrated under reduced pressure. The crude crystals (1.76 g) of anilinium ethyl hydrogenphosphate were washed and recrystallized with acetone. As an alternative and simple procedure, the salt could be prepared by treatment of $EtOPO_3Ba$ with equimolar anilinium sulfate in water. Anilinium diethyl phosphate; mp 72—75 °C; IR: 2860 (νNH_3), 1500 (δNH_3), 1200 ($\nu P{=}O$), 1050 (νP-O-C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS): 1.21 (t, $J=$ 7 Hz, 6H, CH_3), 3.92 (ap. quin, $J=7$ Hz, $J_{HP}=8$ Hz, 4H, CH_2), 7.03—7.50 (m, 5H, aromatic), 9.36—9.83 (m, 3H, NH).

2-Hydroxyethyl Dihydrogenphosphate: Crude Ba salt (4.74 g), obtained as a mixture of mono-, bis-, and cyclic phosphates by the reaction (1 h) of $HOCH_2CH_2OH$ (2.23 g, 35.5 mmol) and PPA (6.24 g, 34.7 mmol) at 100 °C, was mixed with $Ba(OH)_2$ (3.43 g, 20 mmol) in water (150 ml) and heated to reflux for 30 min. After cooling down, the mixture was neutralized (phenolphthalein) with CO_2 and filtered to remove $BaCO_3$. The filtrate was concentrated under reduced pressure and the residue was triturated with methanol to crystallize the desired salt, $HOCH_2CH_2OPO_3Ba$ (4.92 g, 51.1%); cyclohexylammonium salt; mp 165—167 °C.[1c]

The Yields of Other Ba Salts were Shown Below with the Reaction Temperatures of Synthses: Methyl, 65 °C, 80.6%; propyl, 90 °C, 84.3%; butyl, 90 °C, 70.6%; isopropyl, 90 °C, 60.9%; *s*-butyl, 50 °C, 30.7% (60 °C, 10.5%; 90 °C, 0%); cyclohexyl, 80 °C, 49.5%; phenyl, 70 °C, 22.3%.

t-Butyl Dihydrogenphosphate: To the mixture of PPA (5.08 g, 28.5 mmol) and CCl_3CN, Et_3N (5.77 g, 57.1 mmol) was added. *t*-Butyl alcohol (8.44 g, 114.1 mmol) was added dropwise to this mixture and warmed at 35 °C for 60 min with stirring. The reaction mixture was poured into cyclohexylamine (20 g, 200 mmol) in acetone (200 ml) and stored in a freezer overnight. Light yellow precipitates obtained were washed with chilled acetone and recrystallized from EtOH (100 ml) containing cyclohexylamine (10 ml). By a usual ion exchange followed by neutralization with aniline, the salt was converted to the anilinium salt, which was recrystallized from acetone (0.78 g, 11.1%.) The crystals were identical with the authentic specimen synthesized.[6b]

Benzyl Dihydrogenphosphate: The mixture of PPA (5.15 g, 28.9 mmol), CCl_3CN (25.2 g, 175 mmol) and Et_3N (5.84 g, 57.8 mmol) was stirred for 60 min at room temperature. Benzyl alcohol (12.50 g, 115.7 mmol) was added to the mixture and heated to 75 °C for 2 h with stirring . The reaction mixture was poured into water and extracted with ether. The aqueous layer was mixed with cyclohexylamine (20 g, 200 mmol) and concentrated *in vacuo*. The residue was recrystallized from water (60 ml) to yield the bis(cyclohexylammonium) dibenzyl pyrophosphate. Vacuum concentration of the mother liquor afforded the cyclohexylammonium dibenzyl phosphate, which was recrystallized from acetone–H_2O (2 : 3 v/v). Both of the crystals were converted to the free acids by ion exchange and neutralized with aniline to yield dianilinium dibenzyl pyrophosphate (1.39 g, 8.8%, mp 151—153 °C; ^{1}H-NMR: 4.83—5.10 (m, 4H, CH_2), 7.20—7.68 (m, 20H, aromatic)) and anilinium dibenzyl phosphate (1.00 g, 9.3%, mp 115—117 °C; ^{1}H-NMR ($CDCl_3$, TMS): 5.78 (d, $J_{HP}=7$ Hz, 4H, CH_2), 6.93—7.42 (m, 15H, aromatic), 8.03—8.45 (m, 3H, NH_3)) respectively. The aqueous solution (160 ml) of free dibenzyl pyrophosphate (2.24 mmol) was refluxed for 2 h to obtain the benzyl dihydrogenphosphate, which was identified as anilinium salt (1.6 mmol).[5,6a]

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