BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49(4), 1159—1160 (1976)

A Synthesis of Methyl 2-Dimethylphosphoenolpyruvate by Dephosphorylation

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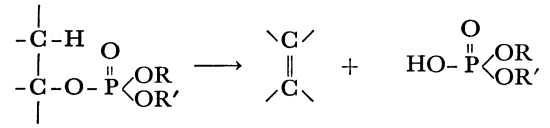
(Received September 25, 1975)

Synopsis. Methyl 2-dimethylphosphoenolpyruvate was obtained by base-catalyzed dephosphorylation of methyl 2,3-bis(dimethylphospho)glycerate.

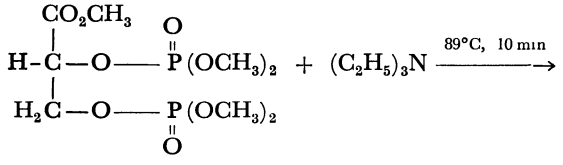
Phosphoenolpyruvate(PEP) has a very large free energy of hydrolysis among the so called "energy-rich" phosphates in biological systems.[1] In glycolysis, it is considered that 3-phosphoglycerate is transformed into 2-phosphoglycerate by phosphoglycerate mutase with the help of 2,3-diphosphoglycerate, and the PEP is formed by dehydration of 2-phosphoglycerate[2]. Organic syntheses of PEP have been performed by various methods.[3]

In the present work, a synthesis of methyl 2-dimethylphosphoenolpyruvate by dephosphorylation was investigated. The term "dephosphorylation" is used here for the reaction in which a phosphoric acid or ester is eliminated from a mono-, di- or tri-ester of phosphoric acid to form an alkene;

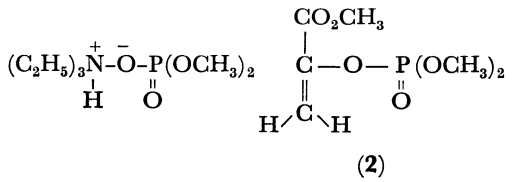


Dephosphorylation of bis-phosphate should lead to the formation of enolphosphate.

No decomposition took place when 1,2-bis(dimethylphospho)propanediol was subjected to pyrolysis at 250 °C. Methyl 2,3-bis(dimethylphospho)glycerate was prepared by the phosphorylation of methyl glycerate, decomposition taking place at 250 °C. The reaction mixture turned dark brown. It was difficult to isolate the products. On the other hand, when the reaction was carried out in the presence of triethylamine, the dephosphorylation occurred at a much lower temperature. The amine acts not only as a catalyst but it is consumed by forming a salt. Pyridine could be also used as a base, but was found less effective.



(1)



(2)

When a mixture of diphosphoglycerate(**1**) and two mole equivalent of triethylamine was kept in a oil-bath of 89 °C for 10 min and the ammonium salt was removed, the methyl ester of phosphoenolpyruvate was obtained in 50% yield by use of a short-path distillation apparatus *in vacuo*. The distillate showed identical H^1-NMR and IR spectra with those of phosphoenolpyruvate methyl ester (**2**) prepared by the Perkow reaction from methyl β-bromopyruvate and trimethyl phosphite.[4] 2,3-Diphosphoglycerate is known to be extremely stable toward hydrolysis among the biologically important phosphoric esters[5]. However, the lability of its esters toward elimination is not known. We are investigating the dephosphorylation of 2,3-diphosphoglycerate and its other esters under various conditions.

Experimental

The IR spectra were taken with a JASCO IRA-2 spectrophotometer, and NMR spectra with a Hitachi-Perkin Elmer R-20 spectrometer. The chemical shifts in NMR measurement were recorded in δ values relative to tetramethylsilane (TMS) as an internal standard.

*Preparation of Methyl 2,3-Bis(dimethylphospho)glycerate(**1**)* Glyceric acid was converted into methyl ester by the usual way,[6] and the methyl glycerate was phosphorylated with dimethylphosphorochloridate in the following way. To an ethereal solution of methyl glycerate(1.2 g, 0.01 mol) and pyridine(1.6 ml, 0.02 mol) was added dimethylphosphorochloridate(3.0 g, 0.02 mol) dropwise under cooling and stirring. The mixture was left to stand overnight at room temperature and the pyridinium salt was removed by decantation and extraction with water from chloroform solution. After removal of the solvent, methyl 2,3-bis(dimethylphospho)-glycerate(**1**) (1.5 g, 45%, bp 80 °C/0.1 mmHg) was obtained by distillation. NMR δ ppm (in $CDCl_3$); 2.92(12H, doublet, $POCH_3$, J=11.3 Hz), 3.00(2H, multiplet, CH_2), 3.17(3H, singlet, $COCH_3$), 3.90(1H, multiplet, CH). IR νcm^{-1} (in $CHCl_3$); 1270(s) νP=O, 1185(m), νC–O–P, 1035(s) νC–O–P.

*Dephosphorylation of Methyl 2,3-Bis(dimethylphospho)glycerate (**1**).* A mixture of methyl 2,3-bis(dimethylphospho)-glycerate (0.42 g, 12 mmol) and triethylamine (0.20 g, 24 mmol) was kept in an oil-bath of 89 °C for 10 min and extracted with CCl_4 at room temperature. The extract was concentrated under reduced pressure and distilled *in vacuo*. Methyl 2-dimethylphosphoenolpyruvate(**2**), 0.13 g (50.0%, bp 60—64 °C/0.02 mmHg), was obtained as a colorless liquid. NMR δ ppm(in CCl_4); 3.79(3H, singlet, CO_2CH_3), 3.80(6H, doublet, P–OCH_3, J=11.3 Hz), 5.56 and 5.86 (2H, two triplets, =CH_2). IR ν cm^{-1} (in CCl_4); 3020(w) νH–C=, 1750(vs) νC=O, 1650(s) νC=C, 1290(vs) νP=O, 1160(vs) νC–O–(C), 1050(vs) νP–O–(C). The IR and NMR spectra of the compound were identical with those of **2** prepared by the Perkow reaction.

*Preparation of Methyl 2-Dimethylphosphoenolpyruvate(**2**) by Perkow Reaction.* Compound **2** was synthesized from α-bromopyruvate (0.83 g., 5 mmol) and trimethyl phosphite (0.57 g, 5 mmol) in benzene according to the procedure of Cramer and Garther[4]. The product was distilled at 65—67 °C/0.03 mmHg, and **2** was obtained in 68.5% yield.

References

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