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A CONVENIENT SYNTHESIS OF PHOSPHOENOLPYRUVATE VIA SILYL-ESTER INTERMEDIATE¹

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Summary: Phosphoenolpyruvate was synthesized in high yield by a simple procedure starting from pyruvic acid and dimethyl trimethylsilyl phosphite through trimethylsilylation, bromination, and the Perkow reaction.

The concept of "high energy phosphate bond" was originally proposed by Lipman in 1941.²⁾ Several types of high energy phosphates such as phosphoenolpyruvate (PEP), phosphocreatine, and acetyl phosphate were listed. They make a role of phosphate-transfer reaction involving ATP synthesis in biological systems Cramer³⁾ has studied 'Zur Chemie der energiereichen Phosphate' and proposed several types of compounds as phosphorylating agents. One of the interesting high energy phosphates is PEP since it has the highest free energy difference of hydrolysis (ΔG° =-14.8 Kcal/mole). While several synthetic routes to the esters of PEP have been developed,⁴⁾ the synthesis of naturally occuring unesterified PEP has not yet been achieved in satisfactory yields (< 50%).^{4,5)}

This paper describes a convenient synthesis of PEP by the Perkow reaction using silyl phosphites which are versatile agents in the synthesis of orgnophosphorus compounds.¹⁾ The most important subject of the synthesis of PEP by the Perkow reaction is the selection of the starting materials, both α -halopyruvic acid derivatives and phosphites, since the reaction is known to afford generally an enol-phosphate (the Perkow reaction product) and/or a phosphonate (the Arbuzov reaction product). Tris(trimethylsilyl) phosphite seems to be useful but it can not be employed in this reaction because it affords not only the desired PEP silyl esters but also 1,2-carbonyl addition products as described previously.⁶⁾ After several screanings, it was found that pyruvic acid and dimethyl trimethylsilyl phosphite were the most suitable starting materials for this purpose.

When pyruvic acid was allowed to react with trimethylsilyl chloride (TMSCl) (2.2 equiv.) and triethylamine (2.2 equiv.) in the presence of a catalytic amount (0.017 equiv.) of 4-dimethylaminopyridine⁷⁾ in dry benzene under reflux for 2 h, trimethylsilyl 2-trimethylsilyloxy-2-propenoate (1) (bp. 88-92°) was obtained and purified by distillation in 91% yield. Compound 1 was treated with one equiv. of bromine in methylene chloride at -78°.

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The reaction mixture was successively treated with dimethyl trimethylsilyl phosphite⁸⁾ (0.9 equiv) at 0°C overnight. After removal of the solvent, tris(trimethylsilyl) ester of PEP (4) (bp. 112-116°/2.2 mmHg) was obtained in 90% yield. The structure of 4 was confirmed by its TR and ^{1}H -NMR spectra. It was treated with 3 equiv. of sodium ethoxide in dry ether. The preciptate of trisodium salt of PEP (5) was collected and dried over P_4O_{10} . The yield was almost quantitative based on 4. It was homogeneous on tlc and characterized by its IR and ¹H-NMR spectra and also by elemental analysis.

The one-flask reaction seems to proceed efficiently without addition of trimethylsilyl bromide (TMSBr) as follows: A mixture of trimethylsilyl a-bromopyruvate (2) and TMSBr is formed by bromination of 1. Intermediate 2 reacts further with dimethyl trimethylsilyl phosphite to afford trimethylsilyl ester of dimethyl phosphoenolpyruvate (3) and TMSBr. It is noteworthy that two equiv. of TMSBr formed from the reaction sequence is very efficiently used for the transformation of the dimethyl ester (3) to the bis(trimethylsilyl) ester (4) according to the Voronkov reaction.9)

-OSiMe₃ $CH_2 = C - C - OSiMe_3$ Me₃SiOP(OMe)₂ CH2=C-C-ONa 2 TMSBr 3 NaOEt δő 0=P(OMe)2 -TMSBr $0=\dot{P}(0SiMe_3)_2$ 0=P-0Na ONa (5) (4)

By this method, the silylated PEP (4) was obtained by the one-flask reaction starting from 1 and the yield of the pure sodium salt of PEP available for biochemical studies is very high (around 90%) based on 1.

References

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