THE SYNTHESIS OF 2-CHLORO-2-OXO-4.5-DIMETHYL-1.3.2. λ^5 -DIOXA-PHOSPHOLENE (CEP CHLORIDE)

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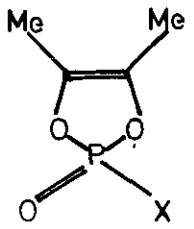
Abstract - An efficient synthesis of CEP chloride has been developed. The cyclic diethylaminophosphite ester of 2-butene-2.3-diol is converted into the clorophosphite by treatment with HCl; subsequent oxidation with N_2O_4 leads to CEP chloride.

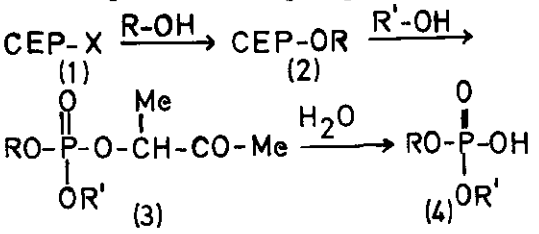
The cyclophosphates of 2-butene-2.3-diol (1)



(1)
(CEP-X; X = Et_2N, MeO, EtO, MeS)

and other cyclic phosphates with a five-membered ring which contain as ring members sp^2 hybridized carbon atoms are extremely reactive towards apicophilic reagents.[1-5]

Compounds of type (1) with a leaving group X (halogen or azole) are particularly well - suited as phosphorylating reagents in the synthesis of "unsymmetrical" phosphate esters (4)[2,4-6].



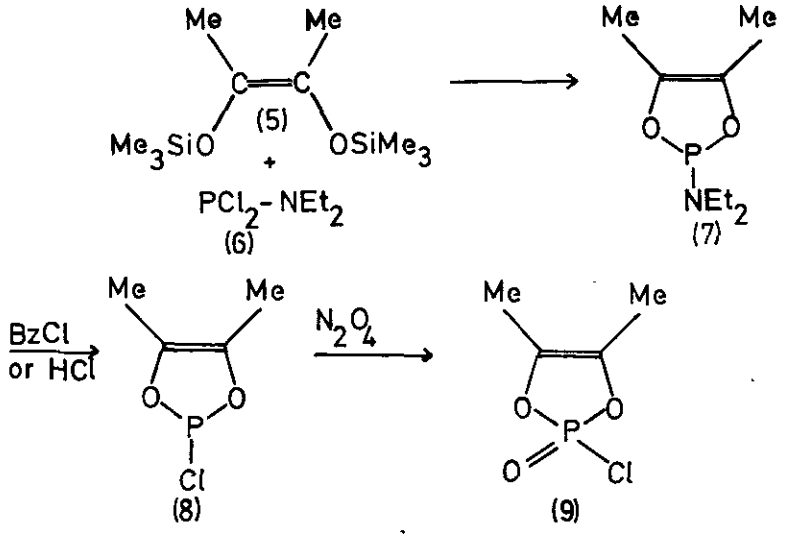
As phosphorylating reagents the CEP derivatives have the advantage that the 2-oxo-3-butyl groups can be cleaved from (3) by very mild alkaline hydrolysis[1]. Despite their clear advantages the CEP derivatives have not yet become very popular as phosphorylating reagents, presumably because there is no convenient method available for their preparation.

Until recently [6,7], the CEP derivatives and related compounds could be prepared only by degradation of corresponding oxyphosphorane derivatives[8], a somewhat cumbersome procedure.

Gozman et al[9,10] were the first to prepare CEP derivatives with a reactive leaving group. Gozman[10] observed that CEP-OEt can be reacted with PCl_5 to form 42% of CEP-Cl (see also ref.[6]).

Schwarz and Ugi[7] found (1981) that the O-trimethylsilylated enediols, e.g. (6) and related compounds react smoothly with the alkyldichlorophosphates to yield corresponding cyclic phosphates. A similar synthesis of CEP-Cl with $POCl_3$ does, however, not seem to be possible.

Kudriavtseva et al.[11] reported recently the preparation of (7) and analogs by reacting (5) with (6). These authors observed also that (7) cannot be oxidized to CEP - NEt_2 by any of the customary reagents. When Kudriavtseva et al.[11] reacted (7) with benzyl chloride, they obtained (8). We have prepared (8) by treating (7) with HCl.
Oxidation of (8) succeeds with N_2O_4[12] to yield CEP-Cl (1,X=Cl).



With CEP-Cl for the first time a cyclic phosphorylating reagent with a reactive leaving group has become relatively readily available. It will probably assume an important role in the introduction of such reagents to oligonucleotide synthesis. Very high relative rates of phosphorylation and the easy, selective

cleavage of tertiary acetoin phosphates belong to the particular advantages of CEP-Cl and its analogs, which make them potentially good reagents for solid-phase syntheses of oligonucleotides. The CEP derivatives should afford syntheses that have in common with the now popular phosphite methods[13,14] short reaction times. A CEP based method would not have any of the disadvantages of the phosphite methods, namely the necessity to oxidize, and the lability of phosphite esters, as well as the difficulties of removing the customary phosphate protecting groups, e.g. O-methyl.

The present synthesis of CEP-Cl is open to future improvements, but for the near future it will probably remain the most efficient way to prepare a CEP derivative (1) with a good leaving group. It is conceivable that CEP-F will be found superior to CEP-Cl. It can be made from(7)by reaction with HF and subsequent oxidation, or by decomposition of a suitable phosphorane derivative[15]. In the long, however there is a good chance that some cyclic phosphorylating derivative of an α-hydroxyacid[7] will be favored over any CEP derivative.

EXPERIMENTAL

2-Chloro-4.5-dimethyl-1.3.2 λ^5-dioxaphospholene (8).

At 0° 100 ml of 1 M HCl in dry diethyl ether are added to a stirred solution of 18.9 g (1oommol) (7)[11] in 100ml dry ether. the colorless precipitate that forms is removed by filtration. The solution is evaporated in vacuo, leaving 14.4g (90%) of a colorless oil (see also ref.[11]). Bp:42-43°/12Torr.

^{31}P-NMR (C_6D_6, 85% aqueous H_3PO_4 as external standard, proton-decoupled):
δ = 169,0 ppm
^{1}H-NMR ($CDCl_3$, TMS) =1.95 ppm (singlett)
^{13}C-NMR ($CDCl_3$, TMS as standard, proton-decoupled)
δ = 10,9 ppm (saturated C, singlett),
132,7 ppm (unsaturated C, dublett, J_{COP} = 7.5 Hz)
I.R. (Film) 1728 cm^{-1} weak C=C
Anal calcd. for $C_4H_6ClO_2P$:C,31.49;H,3.96 found: C,31.71;H,4.19.

2-Chloro-2-oxo-4.5-dimethyl-1.3.2. λ^5-dioxaphospholene (1,X=Cl).

At -20°C 2.00g (21mmol) N_2O_4 (dried over P_4O_{10}) are condensed into a stirred solution of 1.37 g (9.0 mmol) of (8) in 15ml dry ether. ether. The now green reaction mixture is allowed to reach 20°C. After 12h it is evaporated. Vacuum distillation (82-83°C/5 Torr) yields 0.84g (56%) CEP-Cl[6a,10].
^{31}P-NMR (C_6D_6) δ =22,8 ppm ^{1}H-NMR (C_6D_6, TMS) δ = 1,8ppm (singlett).

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