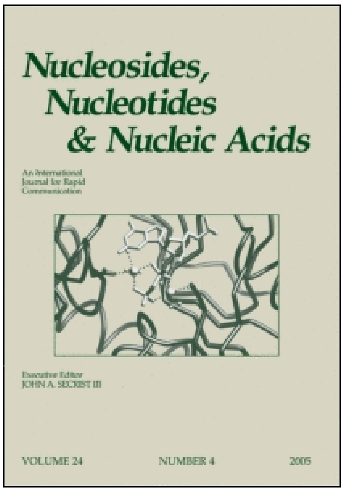

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Phosphite Oxidation and the Preparation of Five-Membered Cyclic Phosphorylating Reagents Via the Phosphites

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PHOSPHITE OXIDATION AND THE PREPARATION OF FIVE-MEMBERED CYCLIC PHOSPHORYLATING REAGENTS VIA THE PHOSPHITES

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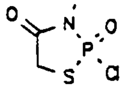
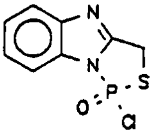
Abstract: The oxaziridines oxidize smoothly phosphites and other P(III) compounds; with chiral oxaziridines the oxidation is enantioselective. Some cyclic phosphorylating reagents are synthetized via the phosphites.

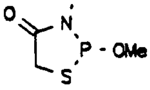
The five-membered cyclic phosphorylating reagents 1 show some promise for the development of automated solid phase syntheses of DNA segments by direct phosphorylation[1]. With O,N,S as P-connected ring atoms and at least one sp^2- carbon as a ring member, the computer program IGOR[1,2] generated 278 constitutional formulas **1.** Since certain thiol phosphates have favorable cleavage properties[3], **1a** and **1b** are particularly interesting candidates to be synthetized[4] and to be tested as five-membered cyclic phosphorylating reagents for oligonucleotide syntheses.



1a



1b



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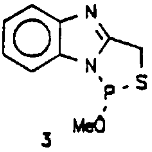

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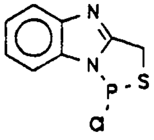

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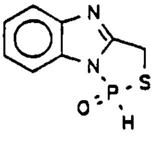

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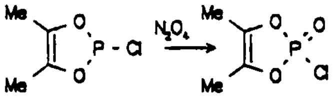
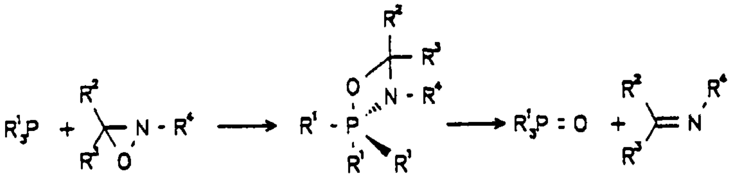


6 1c

The synthesis of **1a**,[1,4] is accomplished via **2** by treatment with chlorinating reagents, e.g. PCl_5. Due to lacking stability of **3**, the reagent **1b** is prepared by chlorination of **5** that is obtained from **4**,[1,4] by hydrolysis with a stoichiometric amount of water in the presence of TMEDA. An excess of water destroys **5**.

Our attempts to synthetize **1b** by oxidation of **4** have not been successful, although **1c** is best prepared by oxidation of **6**[5]. A kinetic study of the deoxygenation of 1-alkyl-3-aryl oxaziridines[6] by tri-n-butylphosphin was described in 1972[7]. Since then the oxidation of P(III) compounds by oxaziridines seems to have been neglected, despite the intense investigation of the oxaziridines as oxidants for thioethers[8,9] and olefins[10].

We have found that P(III) compounds **7** are smoothly oxidized by oxaziridines **8** with electron with-drawing groups R^3,R^4 (a-d: R^2=H; a:R^3=Ph,R^4=iPr; b:R^3=pNO_2Ph, R^4=iPr; c:R^3=Ph,R^4=Tos; d:R^3=pNO_2Ph,R^4=Tos).

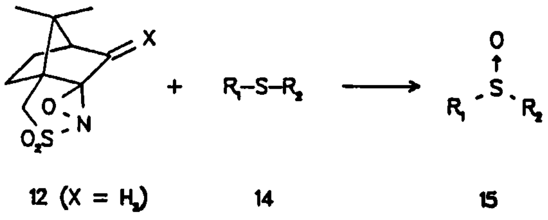


7 **8** **9** **10** **11**

In order to assess the reactivity of the oxaziridines towards P(III), we determined the relative rate constants $k_{rel}=K_x:k_{8a}$ of the oxidation of triethylphosphite (**7a**,R^1 =OEt) and triphenylphosphine (**7b**,R^1=Ph) in $CDCl_3$ at 25° C in competition experiments. The reaction mixtures were analysed by the ^1H-NMR signals of the imine CH protons of **8** and **11**. The experiments were evaluated in analogy to ref.[11]. Within the accuracy of the method, the relative rates $k_{8a}=1$, $k_{8b}=8$, $k_{8c}=10$ and $k_{8d} \geq 10$ are the same for **7a** and **7b**.

The appearance of a ^{31}P-NMR signal at 19.52 ppm H_3PO_4 during the oxidation of **7a** by **8a**, supports the assumtion of phosphorane derivatives **9** as intermediates.

Davis et al.[12] introduced the camphor derivative **12** as a reagent for the enantioselective oxidative conversion of thioethers **4** ($R_1 \neq R_2$) into chiral sulfoxides **15**. These oxidations proceed with a moderate degree of enantioselectivity.



12 (X = H$_2$)

13 (X = O)

In the enantioselective oxidation of thioethers **14** -> **15** the oxaziridine derivative **13** of Herrmann and Glahsl[9] reacts with a substantially higher degree of selectivity than **12**.

In model experiments we have found that chiral phosphites can be obtained by stereoselective[13] destruction of racemic phosphites by **13**. The oxidation of diverse racemic phosphites by 60 - 80 % of the stoichiometrically required amount of **13** was studied in CCl_4 at -78° C by high field ^{31}P-NMR. As was found, the studies destructively selective oxidations, e.g. of the diastereomers of methyl-O'-(1R.3R.4S)-menthyl phoshite N,N-diisopropyl amidate, (δ=146.86, 148.07 ppm, H_3PO_4) are sufficiently selective ($\varkappa \geq 5$)[13] to be of synthetic value. The application of this method to the preparation of stereochemically uniform dinucleotide TCB-phosphites[14] is under study.

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4. The detailed experimental procedures for the preparation of 1a and b and some related reactions will be described by the present authors in Heterocycles (in preparation).

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