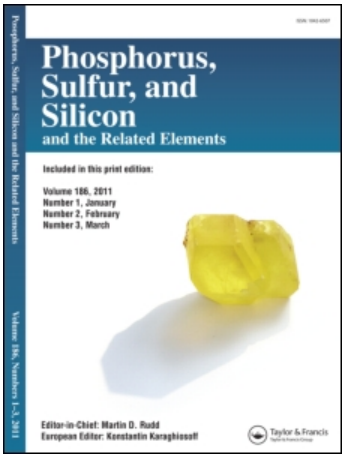

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SOME NEW ASPECTS OF GLYCIDOL PHOSPHORYLATION BY PCl_3

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Glycidol (**1**) reacts with PCl_3 at low temperature in the absence of base forming *(E)*-2-chloro-4-chloromethyl-1,3,2-dioxaphospholane (*(E)*-**2**) in a highly diastereoselective manner. At room temperature (slow) or during the distillation (fast) *(E)*-**2** turns into an equilibrium mixture of isomeric *(E)*- and *(Z)*-**2**. The original configuration on the phosphorus centre may be conserved by low temperature oxidation of *(E)*-**2** to *(E)*-2-oxo-2-chloro-4-chloromethyl-1,3,2-dioxaphospholane (*(E)*-**3**). The phosphorylation of **1** proceeds through the formation of P-H *spiro*-phosphorane (**5**). A new, simple and efficient method of the generation of stable hydrophosphoranes is proposed.

Keywords: Glycidol; phosphorus trichloride; diastereoselective phosphorylation; 1,3,2-dioxaphospholanes; P-chiral compounds; penta-coordinate phosphorus

INTRODUCTION

Parental epoxy alcohol 2,3-epoxypropan-1-ol, glycidol **1** has been the subject of phosphorylation by chlorides of phosphorus acids as long as forty years.[1] It has been stated that the resulting products of this reactions were sometimes the complex mixtures of nonidentified products[2] but more commonly the products were the glycidyl esters of the corresponding phosphorus acid.[1,3–5] Hence **1** in the phosphorylation processes usually appeared as simple hydroxyl containing molecule. On the other hand epoxy function by itself has been the subject of phosphorylation by chlorophosphorus compounds from the early fifties.[6] There are several examples of β-adducts formation when P-Cl functions react with an oxirane moiety,[6–9] but no glycidols have been investigated in this procedures.

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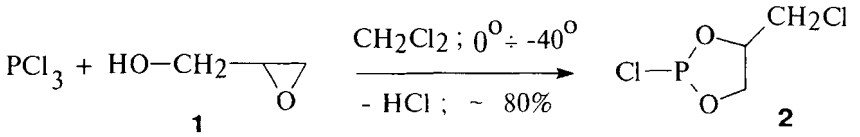


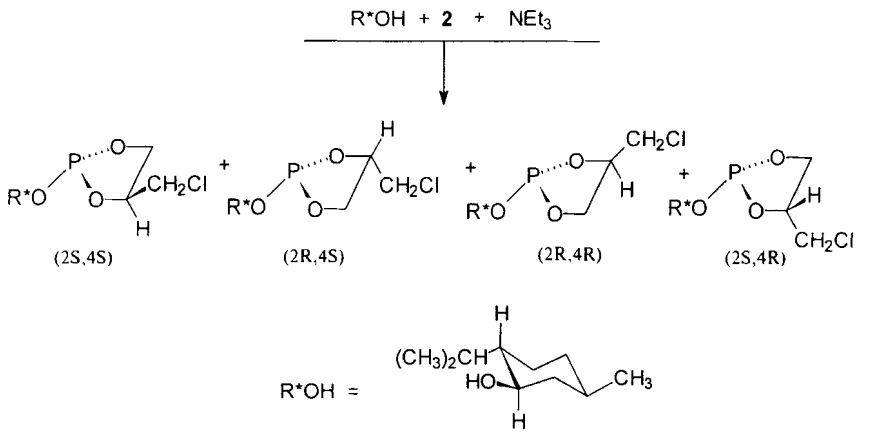
Recently we have found that glycidol readily reacts with PCl_3 in the absence of base in organic solvents forming 2-chloro-4-chloromethyl-1,3,2-dioxaphospholane.[10] To our knowledge there are no other examples of phosphorylation involving both glycidol functionalities. Here we present and discuss some details of this new reaction.

RESULTS AND DISCUSSION

When racemic glycidol is added to a slight excess of a cold solution of PCl_3 in CH_2Cl_2 2-chloro-4-chloromethyl-1,3,2-dioxaphospholane **2** is formed as the principal product. Two signals with δ = 170.0 and 171.5 ppm are present in the ^{31}P NMR spectra of distilled samples of **2**. The signals were attributed to different diastereomeric pairs, *(E)*- and *(Z)*-**2** respectively, and the usual *(E)*/*(Z)* ratio lies in the range from 1:0.3 to 1:0.5. The spectral assignments are based on the known facts that in the family of isomeric 1,3,2-diheterophospholanes the downfield ^{31}P NMR signal belongs to the more sterically restricted *(Z)*-diastereomer.[11]

Yet only one of two signals, δ = 170.0, is present in the crude mixture just after the reaction completion. The second signal makes its appearance after about one hour standing at room temperature, and after three days the isomeric composition of the crude mixture becomes identical with that of a distilled product. This behaviour makes it clear that only one of the two diastereomers, namely, *(E)*-**2** is formed in the immediate course of the reaction. The other diastereomer formation is related with the pyramidal inversion of the phosphorus centre or different secondary processes.

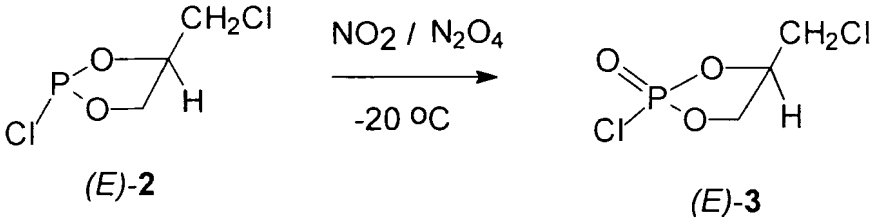
The prolonged existence of the P-chiral chlorophosphite in the form of a single diastereomer is worthy of notice. It is an established fact that similar compounds are configurationally very unstable in the presence of nucleophiles and/or acids.[12] The reasonably close quantities of diastereomeric dioxaphospholanes in the equilibrium mixture are in agreement with our estimations of their energies by quantum chemical PM3 method. After complete geometry optimisation the most stable conformers of *(E)*- and *(Z)*-**2** differ in energy only by 0.3 kcal/mole, *(Z)*-**2** is more stable.



When the final mixture of **2** from racemic **1** is treated with *l*-menthol in the presence of 1 eq of NEt_3, the resulting phosphites are characterized by two pairs of peaks in ^{31}P-{^1H} NMR spectra, δ = 140.5, 140.8 and 144.5, 144.6 ppm.

All four isomeric **2** with different configurations on P-2 and C-4 atoms manifest themselves in the proximity of the enantiopure chiral menthol fragment. We have synthesized the sample of nonracemic (S)-glycidol (*ee* = 91.5%) by the Sharpless asymmetric epoxydation (SAE) method[13] and carried out the reaction between (S)-**1** and PCl_3 in analogous conditions. After the treatment with *l*-menthol the resulting phosphites reveal only two ^{31}P-{^1H} NMR signals, δ = 140.7 and 144.6 ppm. By this is meant that the oxirane ring opening is as expected the stereoselective process, and the final 1,3,2-dioxaphospholanes have the same (or completely opposite, but this is unlikely) 4S configuration on the carbon chiral centre as in the parent glycidol.

1,3,2-Dioxaphospholanes represent one of the most popular classes of organic P(III) derivatives. The usual mode of their preparation is the reaction of $RPHal_2$ (R = Hal, OR^1, etc.,) with 1,2-diols with or without base and organic solvent. The examples of other routes to this valuable compounds are few in number. As for now, enantiopure glycidols with required configuration are more accessible by means of straightforward SAE procedure than enantiopure 1,2-diols. The situation may change however after the Sharpless asymmetric dihydroxylation[14] will become common in organic practice. Nontheless, we have known no examples of stereoselective 1,3,2-dioxaphospholanes formation directly from 1,2-diols. Thus we believe, the high diastereoselectivity, coupled with the retention of enantiomeric purity of the carbon part of the molecule, makes this newly found reaction a promising subject for further synthetic developments. The main problem is to contain the single configuration on the phosphorus centre. This is

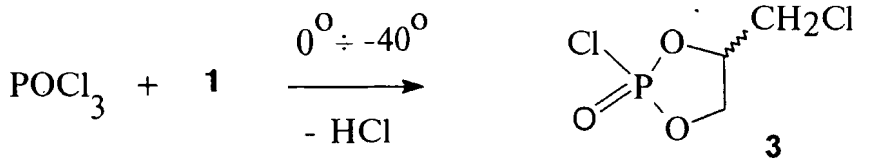


(E)-**2** *(E)*-**3**

a difficult task within the limits of P(III) compounds, and a more reliable line of efforts is to convert P(III) to P(IV) derivatives.

Our attempts to add elemental sulphur to chlorophosphites **2** in the temperature range of $-20\ ^{\circ}C \div 0^{\circ}C$ were unsuccessful, and the heating of the reaction mixture with S_8 would be absolutely undesirable. More fortunate were the attempts to oxidize *(E)*-2-chloro-4-chloromethyl-1,3,2-dioxaphospholane by gaseous NO_2/N_2O_4 with appropriate precautions against overheating and moisture. Only one main signal with $\delta = 19.9$ ppm is present in the crude reaction mixture and we believe that this is the signal of *(E)*-2-oxo-2-chloro-4-chloromethyl-1,3,2-dioxaphospholane (*(E)*-**3**). We have observed previously that compound **3** is obtained as a diastereomeric mixture by the reaction of $POCl_3$ with glycidol:[15] Two signals of **3** with $\delta = 19.9$ and 20.0 ppm are present in ^{31}P NMR spectra of the crude reaction mixture as well as in distilled samples. Consequently the single peak of *(E)*-**3** in the described experiment means that the above objective to fix the phosphorus configuration has been achieved in a certain sense.

We must note at least two weak points of the above described procedure of P-centre configuration conservation by direct oxidation. First, we never were able yet to reproduce our procedure on a multigram scale. Under the conditions given above both *(E)*- and *(Z)*-**3** always have been obtained. And second, chlorophosphates **3** are not the most convenient substances for further developments. It is known from the literature[16] and from our experience[15] that **3** are not sufficiently stable during storage and can not be purified by distillation without substantial losses.



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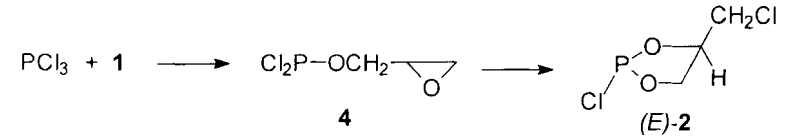
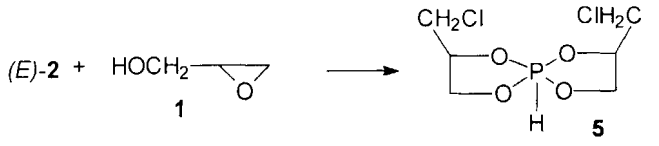


(1)



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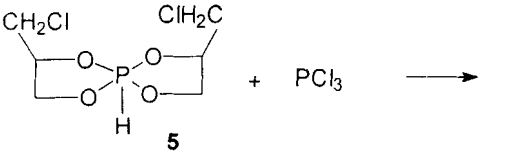
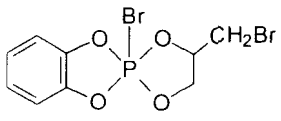


(3)

In the course of our work we have investigated the glycidol phosphorylation by the low temperature ^{31}P NMR method. When the approximately equimolar quantities of racemic **1** and PCl_3 have been consecutively placed and frozen in the NMR sample tube and the mixture was allowed to thaw until $\approx -70°C$ the spectra consisted of two principal signals of about equal intensity with $\delta = -25.9$ and 217.2 ppm. The remarkable feature of the high field signal is the great value of $^1J_{PH} = 845$ Hz. The general view of the spectra under this temperatures is constant and reproducible and may be interpreted as evidence that only one half of the involved PCl_3 (217 ppm) has been consumed whereas all available glycidol was used up in the first step of the process. After raising the temperature to $\approx -20°C$ a fast exothermic process begins in the course of which both existing signals are diminishing and the signal of *(E)*-**2** ($\delta = 170.0$ ppm) appearing until the latter remains the only signal in the ^{31}P NMR spectrum.

We believe that all the spectral changes are consistent with the following scheme of chemical transformations.

After displacement of one of the homotopic chlorine atoms by the chiral glycidol molecule PCl_3 transforms into monoglycidyl phosphite **4**. The oxygen atom of the oxirane ring substitutes intramoleculary one of the chlorine atoms (now diastereotopic) of the short living reactive intermediate **4** to produce the cycle **2** in a diastereoselective fashion (eq. 1). Monochlorophosphite **2** can further react (eq. 2) with remaining **1** forming *spiro*-hydrophosphorane **5** (the signal in the region of -25 ppm). With the temperature rise hydrophosphorane **5** interacts with remaining PCl_3 (eq. 3) stereoselectively regenerating *(E)*-**2**. All the depicted processes (and the isomerization of *(E)*-**2** as well) run simul-



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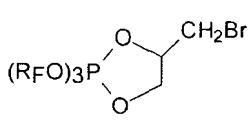

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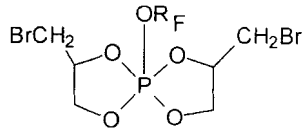

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taneously with rather different rates as the participants arise and/or remain. Hence final results of phosphorylation of glycidol by PCl_3 are very dependent on the reactant ratio and reaction conditions.

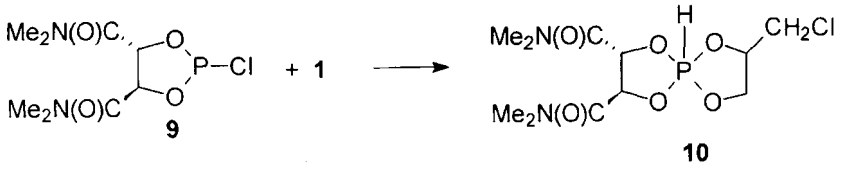
The scheme does not represent all real reaction intermediates. With the knowledge of the abilities of penta-coordinated phosphorus to come into equilibrium processes[17] and the role of HCl in the chemistry of three-coordinated phosphorus[18] it is easy to suppose the presence of many other short living neutral and charged particles in the reaction mixture and to draw formulas for a number of them. On the contrary the products in the terminal parts of the equations are isolable and relatively stable compounds. So we were able to confirm our interpretation by a series of direct independent experiments.

Thus when a double excess of racemic glycidol is added to a solution of PCl_3 in CH_2Cl_2 without base at $\approx -70°C$ the phosphorane **5** becames the principal product. The same results, i.e. the formation of **5**, have been observed when distilled samples of **2** were involved in the reaction with equimolar quantities of glycidol. Finally when a purified sample of **5** was allowed to react with equimolar quantities of PCl_3 the chlorophosphites **2** were obtained as a mixture of diastereomers with high yield.

Some further comments should be made on the subject. We believe that the reaction of glycidol (and substituted glycidols as well) with P-Hal containing compounds is a general route to dioxyphosphoranes. Previously we reported about the phosphoranes **6–8** formation in the glycidol **1** reactions with catecholhalophosphites[19] and tris(fluoroalkoxy)bromo quasiphosphonium bromides.[20]

The reaction of easily accessible substituted 2-chloro-1,3,2-dioxaphospholanes with **1** is assumed to be a convenient method for the preparative synthesis of *spiro*-hydrophosphoranes. We have obtained hydrophosphorane **5** by this procedure in multigram scale. The compound has been almost pure just after removal of volatile impurities by evacuation and has exhibited sufficient stability to be distilled *in vacuo* in a short path apparatus.

When we refer to substance **5** we constantly bear in mind that the structural formula does represent the family of diastereo- as well as permutational isomers. The substantially singlet character of the NMR spectrum of **5** may be the result



of a small anisochrony of ^{31}P nuclei in the isomers and/or fast exchange processes. In relation to this topic we can remark that three distinct peaks with δ_P −24.4, −24.0, and −23.8 ppm (average $^1J_{PH}$ = 846 Hz) have been observed by us in the spectrum of phosphorane **10**, the product of the reaction of racemic **1** and enantiopure (4R,5R)-(N,N-dimethyl-amido)-2-chloro-1,3,2-dioxaphospholane **9**.

The investigation of the *spiro*-hydrophosphoranes **5**, static and dynamic stereochemistry, was beyond the aims of the present paper. But it cannot be doubted that this topic is of utmost importance for understanding of the nature of diastereoselectivity of dioxaphospholanes formation. One can suppose that at least half of the formation of (E)-2 has its origin in the stereoselective phosphorylation of **5**.

EXPERIMENTAL

All solvents were distilled and dried before use. All reactions were carried out under argon atmosphere. The IR spectra were recorded on a UR-20 spectrophotometer. The NMR spectra were recorded on a Bruker WM-250 (^1H, 250.132 MHz) and Bruker MSL-400 (^{13}C, 100.624 MHz; ^{31}P, 161.92 MHz) spectrometers, in $CDCl_3$ (^1H, ^{13}C) or CH_2Cl_2 (^{31}P) as a solvent and TMS (^1H, ^{13}C) as an internal or H_3PO_4 (^{31}P) as an external standard.

(E)- and (Z)-2-Chloro-4-Chloromethyl-1,3,2-Dioxaphospholane (*(E)*-2 and *(Z)*-2)

A solution of racemic glycidol (5.5 g, 74 mmol) in 20 ml of CH_2Cl_2 was dropped into a stirred solution of phosphorus trichloride (13.7 g, 0.1 mol) in 20 ml of the same solvent at −30°C during 30 min. The mixture was allowed to attain room temperature slowly and the solvent was evacuated. The crude product was distilled under reduced pressure to give pure **2** as a mixture of (E)- and (Z)-diastereomers in the ratio 1:0.4.

Yield: 10.2 g (79%), b.p.: 73–74°C/10 mm, $n_D^{[20]}$ 1.5115

The IR spectrum is coincident with the published one.[21]

^{1}H-NMR: δ = 3.62 (d, $^3J_{HH}$ = 4.6 Hz, CH_2Cl), 4.13–4.25 and 4.47–4.62 (m, OCH_2), 4.87–4.96 (m, OCH).

(E)-**2**.

^{13}C-NMR: δ = 46.52 (t, $^1J_{CH}$ = 152.1 Hz, CH_2Cl), 70.21 (dt, $^2J_{PC}$ = 7.8 Hz, $^1J_{CH}$ = 154.4 Hz, OCH_2), 78.83 (dd, $^2J_{PC}$ = 8.7 Hz, $^1J_{CH}$ = 153.0, OCH);

^{31}P-NMR: δ = 170.0.

(Z)-**2**.

^{13}C-NMR: δ = 46.49 (t, $^1J_{CH}$ = 153.3 Hz, CH_2Cl), 71.80 (dt, $^2J_{PC}$ = 8.6 Hz, $^1J_{CH}$ = 153.5 Hz, OCH_2), 80.99 (dd, $^2J_{PC}$ = 9.2 Hz, $^1J_{CH}$ = 158.7 Hz, OCH);

^{31}P-NMR: δ = 171.5.

(E)-2-Oxo-2-Chloro-4-Chloromethyl-1,3,2-Dioxaphospholane (*(E)*-3)

A reaction of glycidol (1 g) and phosphorus trichloride (1.9 g) was carried out as described above, but the reagents were mixed at −80°C. The solution was kept another 30 min at ≈ 0°C. Only the signal δ_P 170.0 ppm was registered in the aliquot. Then the mixture was cooled to −20°C and NO_2/N_2O_4 in a stream of dry air was passed in. The gaseous NO_2/N_2O_4 has been obtained by a thermal decomposition of $Pb(NO_3)_2$. The end-point was determined by the appearance of a permanent faint green colour in the previously colourless solution.

^{1}H-NMR: δ = 3.86 (d, $^3J_{HH}$ = 4.2 Hz, CH_2Cl), 4.33–4.70 (m, OCH_2), 4.83–5.00 (m, OCH).

^{31}P-NMR : δ = 19.9 ppm.

Synthesis of *Spiro*-Phosphorane (5)

Method (A): A solution of racemic glycidol (5.2 g, 70 mmol) in 20 ml of CH_2Cl_2 was dropped into a stirred solution of phosphorus trichloride (4.8 g, 35 mmol) in 10 ml of CH_2Cl_2 at −70°C. The mixture was allowed to warm to room temperature then the solvent was evacuated. The residue was maintained under oil-pump vacuum at 30°C to give the almost pure phosphorane **5** as a viscous colourless liquid. The product may be kept for a long time with due precautions against acids and moisture.

Yield: 92%, b.p. 95–100°C/0.05 mm, n_D^{20} [20] 1.5020, d_4^{20} [20] 1.4776.

IR: ν = 2963, 2895, 2419 (P-H), 1475, 1446, 1428, 1380, 1320, 1290, 1262, 1235, 1200, 1180, 1115, 1080, 1060 (PO-C), 1040, 1005, 925, 895, 790, 740.

^{1}H-NMR: δ = 3.31–3.71 (m, OCH and OCH_2), 3.71–3.97 and 3.98–4.26 (m, CH_2Cl), 7.10 (d, $^1J_{PH}$ = 846 Hz, PH).

^{13}C-NMR: δ = 44.54–44.93 (m, $^3J_{PC}$ = 5.6 Hz, $^1J_{CH}$ = 153.0 Hz, CH_2Cl), 62.87–64.32 (m, $^2J_{PC}$ = 2.1 Hz, $^1J_{CH}$ = 151.6 Hz, OCH_2), 70.5–71.42 (m, $^2J_{PC}$ = 1.4 Hz, $^1J_{CH}$ = 152.9 Hz, OCH)

^{31}P-NMR: δ = −25.2 (d, $^1J_{PH}$ = 845 Hz)

Method (B): A solution of racemic glycidol (0.46 g, 8.6 mmol) in 2 ml of CH_2Cl_2 was dropped into a stirred solution of 2-chloro-4-chloromethyl-1,3,2-dioxaphospholane (mixture of diastereomers, 1.5 g, 8.6 mmol) in 2 ml of the same solvent at −70°C. After the room temperature was attained the solvent was distilled in vacuo. The residue was maintained under oil-pump vacuum at 30°C to give the almost pure phosphorane **5**. It's physical constants and spectra were identical with the sample described above.

Synthesis of (2) from (5)

A solution of phosphorus trichloride (1.18 g, 8.6 mmol) in 2 ml of CH_2Cl_2 was dropped into a stirred solution of **5** (2.14 g, 8.6 mmol) in 2 ml of the same solvent at −70°C. The mixture was allowed to attain room temperature and then was distilled under reduced pressure to give 2-chloro-4-chloromethyl-1,3,2-dioxaphospholanes **2** as a mixture of diastereomers. Physical and spectral characteristics of **2** were identical with those given above.

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