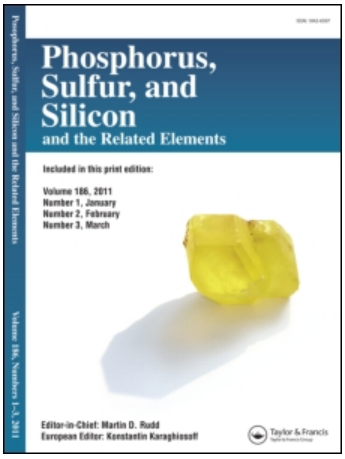

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NEW POTENTIALITIES OF TRIVALENT PHOSPHORUS REAGENTS IN PHOSPHOLIPID SYNTHESES

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The design of phospholipids can be based on various synthetic strategies. We have chosen the strategy, which includes two main stages. The first stage is the phosphorylation with simple reagents, and the second stage is the modification of primary products to form natural lipids and their analogues.

We now direct our attention to the problems of phosphorylation, which is traditionally investigated in many scientific centers. It is very important to note that, for a long time, all scientific centers in the world have used only the reagents of pentavalent phosphorus for the synthesis of phospholipids. The similar strategy was applied to obtain nucleic acids and other phosphorus-containing natural compounds. One can explain this situation by the fact, that the reagents of pentavalent phosphorus were rather available and well-understood and that their applicability for the purposes of fine organic synthesis was evident. Whereas, these reagents had many considerable defects. So, they provided only small rates of phosphorylation and tended to alkylate the electrophiles, present in reaction system, and to participate in other side processes; in addition, the reagents of pentavalent phosphorus have the narrow range of synthetic potentialities.

In connection with the foregoing, in the chemistry of phospholipids there is a tendency to turn to the reagents of trivalent phosphorus, which differ from the reagents of pentavalent phosphorus by their high phosphorylating ability, preparative efficiency and design variability.

We have shown, that the amide method is the most convenient way to phosphorylate glycerols and other oligools:

$$R{-}OH \;+\; R'_2N{-}P\langle \;\longrightarrow\; RO{-}P\langle \;+\; HNR'_2$$

The phosphamides were found to be efficient and soft reagents. Their application furnished the maximum selectivity and efficiency of phosphorylation. The use of phosphamides, in addition to target esters, gives also amides, which can be easily evacuated from the reaction mixture and do not destruct the initial substances and reaction products. It is necessary to point out, that the substituents at the nitrogen atom can strongly affect the activity of phosphamides.

Today the phosphamides find use in the syntheses of various lipid systems. So, it is proposed to apply phosphorous monoamides for the phosphorylation of glycerol acetals and corresponding esters.

Amides of cyclic phosphites and amidophosphites are especially convenient in handling and promising for further transformations. To by the present time, a series of reactions with amides of phospholanes, phosphorinanes, phosphepanes, oxaazaphospholanes and oxaazaphosphorinanes have been investigated.

Phosphorous diamides are yet in more wide use, they are proposed as a base to produce mono- and diphosphoglycerides, par example, in the design of compounds, which includes fragment of spatially hindered phenols.

These and other similar compounds can be built in the biological membranes and protect them from homolytic oxidation.

Phosphorous triamides are also proposed to be used as phosphorylating agents. In this case, mono- or diglyceroamidophosphites can be obtained, depending on the reagents' ratio. We have successfully used phosphorous amides in the syntheses of nonglyceride phospholipids: derivatives of ascorbic acid, 1,1,1-trimethylolalkanes, pentaerythritol, glycols.

Amido- and diamidophosphites of oligools have attracted considerable attention not only by their availability and convenience in work. They are optimum half-products in syntheses of a variety of phospholipids, because they easily phosphorylate nucleophiles, which insert choline, aminoalkyl, carbohydrate, acylglycerol, amino acid, and other important synthons into phospholipid systems.

We also proposed to apply hydrophosphoryl derivatives like diesters and diamides of phosphorous acid for the phosphorylation of glycerols.It may be useful to use hydrophosphoryl compounds for the oxidative phosphorylation of glycerols after Todd-Atherton too.

Alongside with glycerols, we used glycols and amino alcohols in oxidative phosphorylation. In the latter case, the conditions for a selective N-phosphorylation were found. In this way, little-studied amidoalcohol phospholipids can be obtained

Another line of the work was concerned with the transformations of glycerol phosphites and amidophosphites into phospholipids.

It was shown, that one can easily oxidize glycerophosphites and introduce them in the reaction with sulfur. The resulting neutral phosphates, after removal of alkyl protections at the phosphorus atom, readily change to phosphatidic and thiophosphatidic acids.

The second direction in use of glycerol amidophosphates consists in their reactions with proton-containing nucleophiles. We have shown, that a directed monophosphorylation takes place in the reaction of these diamidophosphites with equimolar amounts of amino alcohols, carbohydrates, amino acids, spatially hindered phenols, and other compounds, which are carriers of bioregulator action. The phosphorylation with glycerol monoamidophosphites proceeds in a similar way

In this case, diacylate derivatives and acetals can be used as the glycerol components. In the latter case, the acylation occurs at the last stages of synthetic pattern. The group X, linked to the phosphorus, can be easily changed, for example, to benzyloxy one. Then O-X lipid is intended for the synthesis of natural compounds. These cyclophosphites take part in various modifications of Arbuzov reaction with opening of the ring system. An alkyl radical with a terminal functional group is here formed at the phosphorus atom. The synthesis of phospholipids, which contain an arylene moiety in the side phosphate chane, can be of interest for some problems. We suggest to study these lipids on the basis of glycerol benzophosphepanes.

Focus our attention to glycerol dioxaphosphepanes. Their molecules already contain nearly all structural elements of numerous complex phospholipids. It is even possible to consider these compounds as the synthetic equivalents for the central synthons of glycerol phosphatides

In fact, just a terminal substituent in the ester radical and an anion center at the phosphorus atom are lacking here. Meanwhile, they can be created in one step by the chemical contact of phospholane with a prototype of the β-substituent, for example, with trimethylamine. This and some similar possibilities were successfully realized.

We also lanched the study on the interaction of glycerol phosphites and amidophosphites with the salts of heavy metals. In this case, phosphito-metallocomplexes of lipids are formed, which are apparently of interest for the creation of membrans with physical and chemical peculiarities.

The work is begun on the creation of phosphitolipid complexes. It is shown, that phosphites and amidophosphites easily form stable complexes with the salts of monovalent copper, as well as with monovalent rhodium and divalent platinum.

The structure and behavior of these complexes can be investigated by means of ^{31}P NMR spectroscopy, including the study of the spin-spin coupling of phosphorus atom on the nuclei of rhodium and platinum. It is interesting, that the chemical shifts and, especially, coupling constants appreciably depend on the structure of glycerol unity of molecule, that is, on the fact, whether this unity is acetal or ester.

Unfortunately, these complexes are often not so stable. To have more stable systems, we obtain chelate complexes on the basis of glycerol aldehydes.

Such complexes are considerably more stable than the above compounds. At present, the study of their chemical and physical properties is in progress.

Thus, glycerol derivatives of trivalent phosphorus represent a new large-scale and promising class of lipid compounds.