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Acylation of acetals and related geminal systems. The use of this reaction in the synthesis of phospholipids

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Abstract. The practical significance of acylation of acetals, orthoesters, and their aza-analogues (oxazolines) in fine organic synthesis is considered. Attention is mainly focused on the application of this reaction to the design of glycerophosphatides and other types of phospholipids. The use of acylation of these geminal alkoxides and oxazolines makes it possible to optimise the strategy of the synthesis of polyfunctional ester systems. The bibliography includes 76 references.

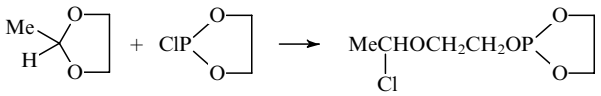
I. Introduction

Acetals,† orthoesters, and other geminal alkoxides are of special interest as stable derivatives of the corresponding carbonyl compounds, which are formed at certain stages of synthetic schemes.[1–3] In addition, they are used as effective donors of α-substituted carbocations in the formation of carbon–carbon[1,4,5] or carbon–hydrogen[6,7] bonds in the design of complex polyfunctional systems. In all these cases, the alkoxide fragment of the above-mentioned compounds as synthetic material is partly or completely lost.

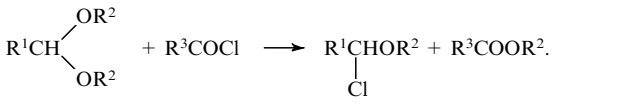
At the same time, geminal alkoxides can also function as synthetically useful derivatives of polyhydric alcohols. This possibility was established as early as the last century, but has been introduced into routine preparative practice only in recent years. The main attention was focused on the conversion of cyclic acetals of polyhydric alcohols into complex lipids. The main results of these investigations are discussed in the present review.

II. Acetals as nucleophiles

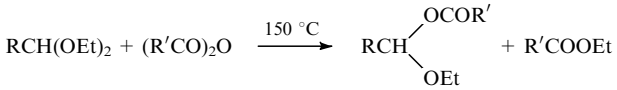
The simplest and functionalised acetals can react with phosphorus and sulfur halides as well as with phosgene to give the corresponding α-haloethers.[1,8,9] The mechanism of these reactions has not been studied in detail. However, it presumably involves an electrophilic attack of the acetal oxygen by phosphorus, sulfur, or carbon to give oxonium compounds, which are transformed into α-haloethers, either directly or via several stages. Simultaneously, the eliminated alkoxyl group is converted either into halophosphite (phosphate), -sulfite (sulfate), or -carbonate or into the corresponding alkyl halides. This rationalisation of the chemical nature of this process has been substantiated by studies of the interaction of acetaldehyde ethylene acetal with ethylene chlorophosphite.[10]



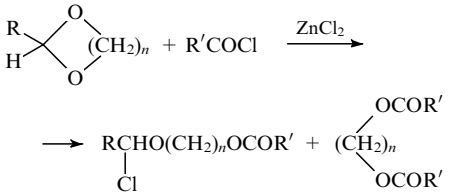
The interaction of acyclic acetals with the simplest carboxylic acid halides in the presence of Lewis acids, which also results in α-haloethers, has been reported.[11–16]



Similarly, C–O bond cleavage occurs when acetals react with anhydrides (as had been shown long ago by Claisen[17]).[18]



The above reactions have also been studied in relation to cyclic acetals, 1,3-dioxolanes and 1,3-dioxanes. It has been established that acylation of cyclic compounds is a complex process, which normally gives a mixture of products.[19–26]



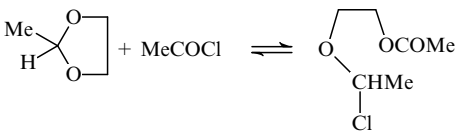
n = 2, 3.

† We use the term 'acetals' to denote geminal alkoxide derivatives of aldehydes and ketones.

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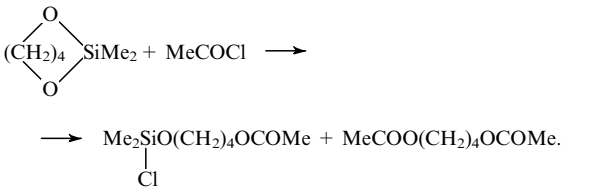
In some experiments it has been shown that ω-acyloxyalkyl chloroalkyl ethers tend to cyclise, which leads to establishment of an equilibrium, for example:[23]



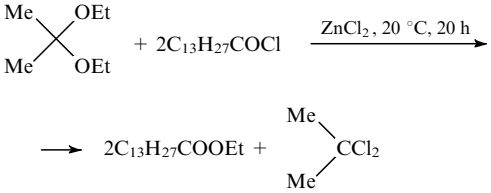
In addition, dehydrochlorination of these α-chloroethers has been observed.[10]

Acylation of ethylidene derivatives of monosaccharides with acetic anhydride in the presence of trifluoroacetic acid with subsequent hydrolysis of the acylal-acetal formed initially has been proposed by Kochetkov et al.[27] as a method for removing acetal protection.

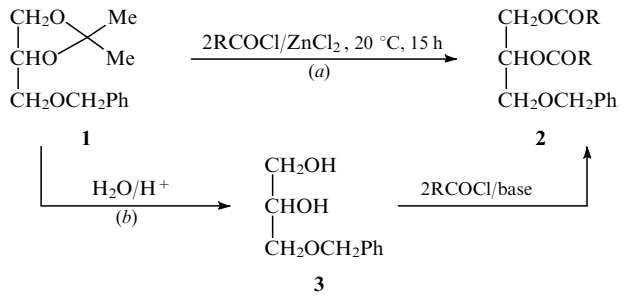
This reaction was further extended to acylation of silicon analogues of cyclic acetals, 1,3,2-dioxasilacyclanes. These compounds react with acid halides to give mono- and di-acylation products.[28]



It can be concluded that in the studies on acylation of acetals with chlorides and anhydrides of simplest carboxylic acids, interesting chemical phenomena have been observed but no new preparative methods for organic synthesis have been developed. These methods were elaborated later in studies of the reactions of acetals with chlorides of higher fatty acids in the presence of zinc chloride or other Lewis acids, for example, of the reaction of acetone diethyl acetal with myristoyl chloride.[29]



A version of this reaction that consists in acylation of cyclic acetals is of great preparative importance. This method was used, in particular, to obtain 1,2-di-*O*-acyl-3-*O*-benzylglycerols **2**, which are important intermediates in the chemistry of lipids, based on accessible 1,2-*O*-isopropylidene-3-*O*-benzylglycerol **1** (pathway *a*).[29, 30] The acetal **1** has been traditionally employed in lipid syntheses: it was hydrolysed to the diol **3**; the latter was isolatied and purified and then acylated to give the final esters **2** (pathway *b*). This synthesis required large amounts of solvents and additional reagents. The yield of the ester **2** was as low as 40% – 45% with respect to the initial acetal **1**.[31]

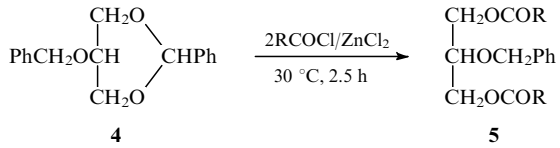


R = $C_{15}H_{31}$, $C_{17}H_{35}$.

A new synthetic method consisting in direct acylation of the acetal **1** is much more simple and efficient, and the yields of the esters **2** obtained in this way reach 65%. This reaction is usually carried out in a small amount of ether or chloroform or without solvents.

An increase in the acylation temperature to 60 °C decreases the yields of the glycerides **2** due to partial debenzylation. It is significant that the glycerides **2** are formed not only when two moles of acid chloride per mole of the acetal **1** are used, but also at an equimolar ratio of the reagents. However, in the latter case, about half of the initial acetal does not react.[29, 30] ‡

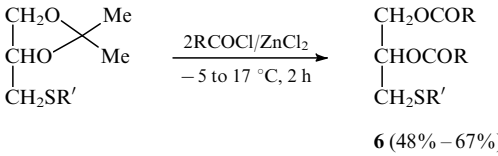
Complete acylation of acetals can also be used for the conversion of 1,3-dioxanes, *e.g.* 1,3-*O*-benzylidene-2-*O*-benzylglycerol **4**, into the corresponding esters **5**.[30, 32]



R = $C_{15}H_{31}$, $C_{17}H_{35}$.

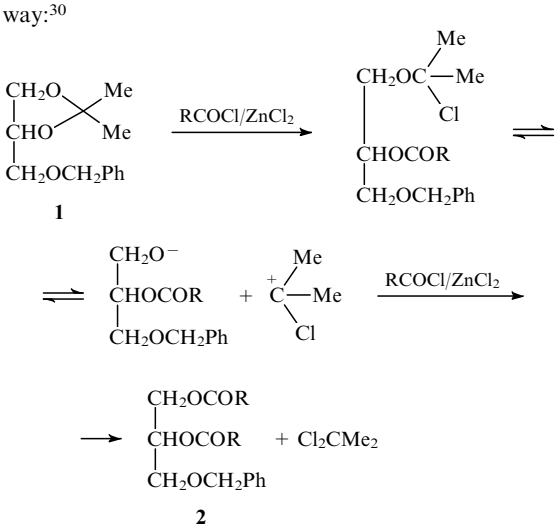
The isomeric glycerides **2** and **5** were investigated by high-resolution NMR spectroscopy. It was noted that no acyl migration along the glycerol system occurred during the synthesis.[32] Thus, the practical utility of this method for target-directed syntheses of more complex lipids was demonstrated.

This method was also used in the synthesis of other natural systems such as diacyl derivatives of *S*-alkylthioglycerol **6**.[33]



R = $C_{15}H_{31}$, $C_{17}H_{35}$; R′ = $C_{16}H_{33}$, $C_{18}H_{37}$.

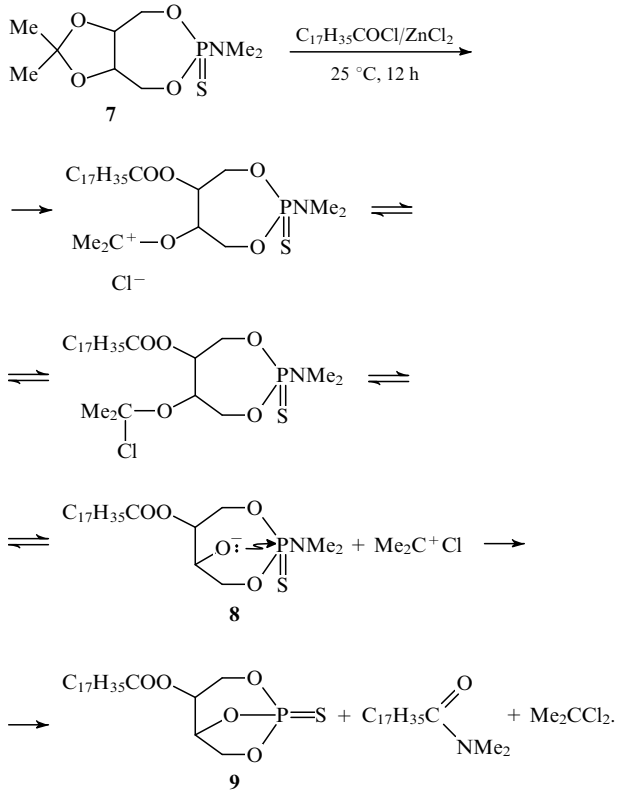
Complete acylation of the cyclic acetal **1** appears to be a two-stage process, which can be schematically presented in the following way:[30]



The isolation of 2,2-dichloropropane is evidence in favour of this mechanism. In addition, to confirm the above mechanism, a model acetal was specially 'designed'; its structure was to ensure

‡ The benzylacetal **1** can also be converted into the ester **2** by treatment with carboxylic acids in the presence of *p*-toluenesulfonic acid. However, in a preparative sense, this procedure is more complex because it requires heating to 110 °C and removal of the H_2O and acetone formed in the process.[30]

that the negatively charged oxygen atom (if it was generated at the first stage of acylation) comes close to the electrophile. The electrophile should 'trap' the alkoxy-anionic centre thus preventing diacylation. For this purpose, 2-dimethylamido-5,6-isopropylidenedioxy-2-thiono-1,3,2-dioxaphosphepane **7** was used as the model compound. At the first step of acylation, this compound generates alkoxy anion **8**, which, due to the proximity to the dimethylamidothiophosphoryl group, effectively interacts with it by a nucleophilic substitution mechanism. As a result, no second acylation takes place and the phosphorus framework compound **9** is formed instead of the diacylate:[34, 35]

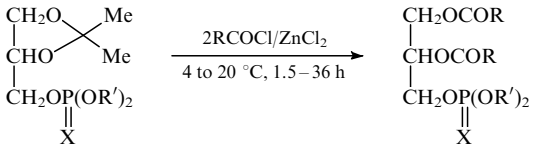


Orthoesters and other geminal alkoxides are also nucleophilic and susceptible to acylation. In the studies of these compounds, some interesting chemical features have been found. Therefore, their acylation will be considered separately in the foregoing sections.

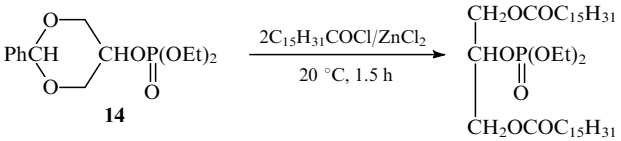
III. Synthesis of phospholipids based on glycerol acetals

Complete acylation of acetals has been investigated most extensively and thoroughly in connection with the synthesis of glycerophospholipids and their analogues. 1,2-*O*-Isopropylidene- or 1,3-*O*-benzylideneglycerols were used in these studies as the initial compounds; they were consecutively introduced into phosphorylation, direct acylation, and subsequent auxiliary transformations of the polar fragments of the molecules. It was found that acylation of phosphorylated acetals, occuring under mild conditions corresponding to the acylation of the simplest cyclic acetals, is effective, and has a broad range of synthetic applications. It is noteworthy that acylation of glycerol acetals was studied in parallel with the development of new methods for the design of a lipid–phosphorus unit.[36, 37] These two lines of research successfully complemented each other and greatly contributed to progress in the synthetic chemistry of phosphoglycerides.

Let us consider acylation of glycerol acetals aimed at the synthesis of phosphatidic acids and their thio- and seleno-analogues. This task can be solved using accessible compounds, such as acetal phosphates **10a, b**, **14** and thionophosphates **11a** as initial substances.[29, 30, 32, 38]



10a,b; 11 **12a,b; 13** (51%–65%)



14 **15** (56%)

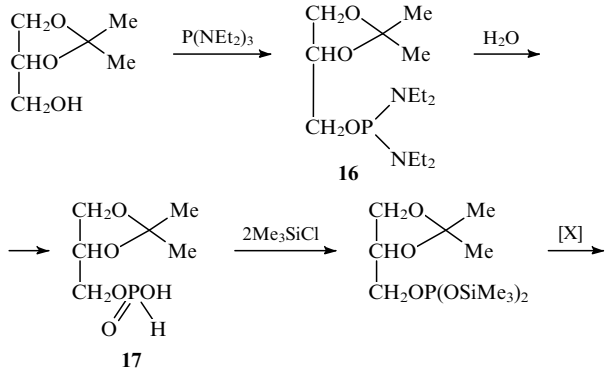
R′ = Et (**10a**, **11**, **12a**, **13**), Ph (**10b**, **12b**); X = O (**10**, **12**), S (**11**, **13**).

An increase in the molar amount of the acid chloride (more than 2 moles per mole of the acetal **10a**) has no substantial influence on the yield of the phosphates **12a**. An increase in the reaction temperature (> 50–60 °C) results in the formation of various side products. For example, in the case of the acetal **10a**, considerable amounts of ethyl carboxylates are formed, while the acetal **10b** gives 1,2-di-*O*-acyl-3-chloro-3-deoxyglycerols.[30]

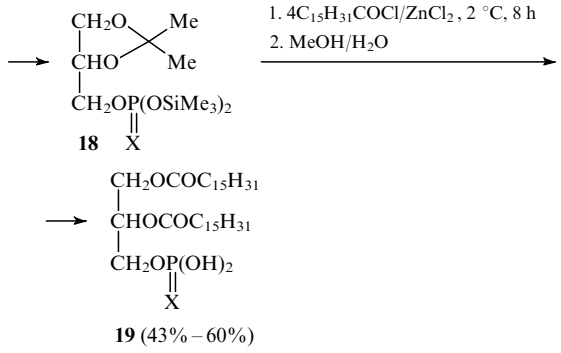
In order to elucidate whether migration is possible during the acylation, the chromatographic mobility and ^{1}H, ^{13}C, and ^{31}P NMR spectra of ethyl esters of α-phosphatidic acid **12a** and of its β-isomer **15** have been analysed. From chromatographic and spectral data it was concluded that acyl migration did not occur during the synthesis.[32]

The phosphates **12a** and **15** and thionophosphates **13** obtained were transformed into phosphatidic acids **19** and their thiono-analogues; first, they were made to react with Me_3SiX and then the silyl derivatives thus formed were hydrolysed.[29, 30, 32, 38]

An alternative method for preparing the phosphatidic acids **19** is acylation of the glycerophosphate silyl ester acetal **18**. In this case, the synthetic scheme involves preparation of amidophosphites of 1,2-*O*-isopropylideneglycerol **16**, their hydrolysis to primary phosphites **17**,§ and silylation of the latter. This is followed by oxidation or addition of sulfur (selenium), acylation, and desilylation.[39, 40]



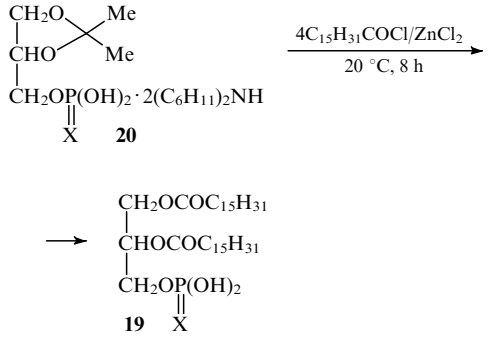
§ These compounds are often called *H*-phosphonates, which is not, in our opinion, a very adequate term.



X = O, S, Se.

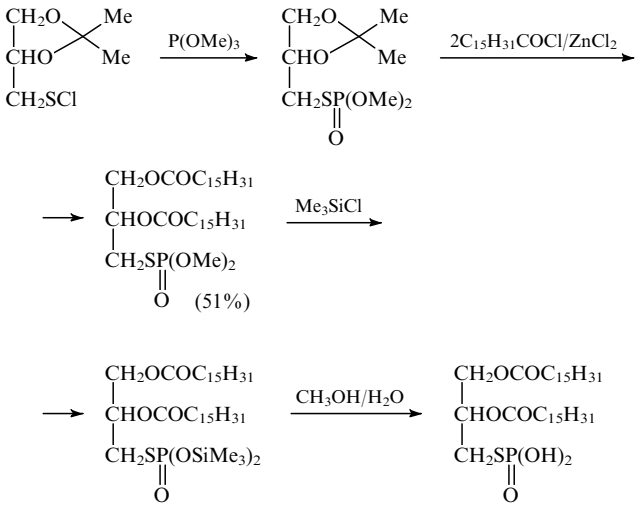
In this case, as in those described above, the efficiency of acylation was found to be higher for thione derivatives than for selenone derivatives. Using the latter synthetic scheme, an optically active phosphatidic acid, 1,2-di-*O*-palmitoyl-*sn*-glycero-3-phosphate, was obtained. The synthesis was not accompanied by changes in the chirality of the glycerol system.[39]

If required, phosphatidic acids and their thione analogues **19** can be obtained by acylation of salts of 1,2-*O*-isopropylideneglycero-3-phosphates **20**.[39,40]



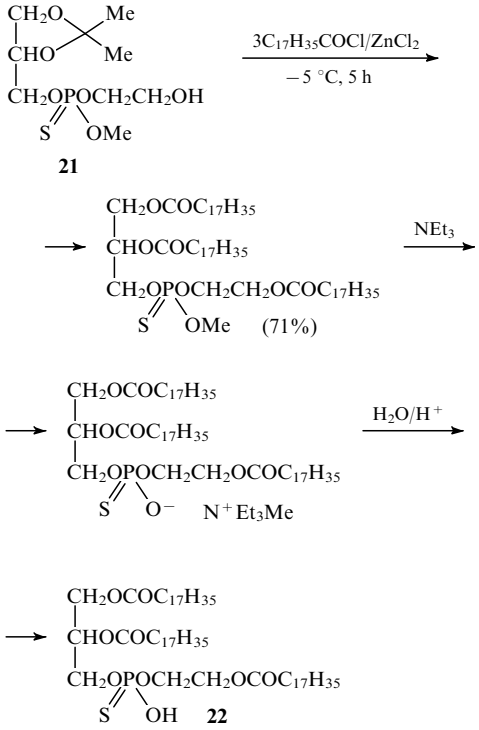
X = O, S.

In recent years, enzymological demands have stimulated studies of thiol analogues of natural phosphate systems. Derivatives of this kind of the series of phosphatidic acids were obtained by an elegant procedure.[41]



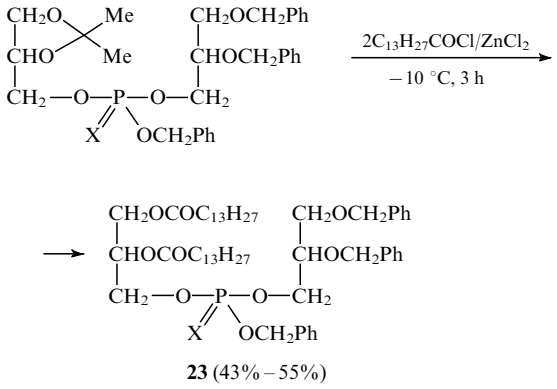
Another trend in phospholipid synthesis involving acylation of acetals is the design of natural esters of phosphatidic acids and their S-analogues. For this purpose, a preparative scheme has been developed, which includes the initial formation of glycerol acetals with protected phosphate groups. These phosphorylated acetals are first acylated and then deprotected. Methyl, ethyl, and benzyl groups are used most frequently as protective groups in these syntheses.

The synthesis of thionophosphatidyl acyl glycols of type **22** can serve as an example.[42]



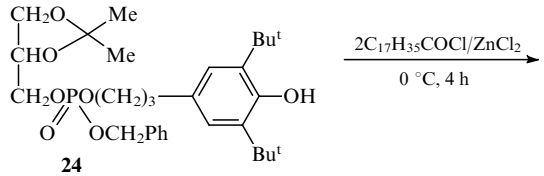
Acylation of the phosphatoacetal **21** was carried out with a threefold molar excess of palmitoyl chloride; therefore, both the acetal group and the alcohol hydroxyl underwent acylation.

The synthesis of phosphatidyl ethylene glycol systems **22** was supplemented by the synthesis of phosphatidyl glycerol derivatives **23**. A simple method that proved to be effective was used for this purpose.[43]

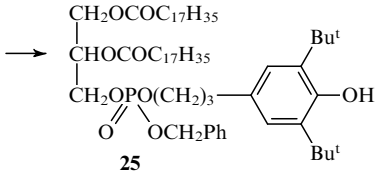


X = O, S.

Glycerophosphates with a protected phosphate group were also used to produce membrane-directed antioxidants by chemical combination of phosphatidic acids and sterically hindered phenols. In fact, phosphatidyl ionols **25** containing 4-γ-oxypropyl-2,6-di(*tert*-butyl)phenol as the protective moiety were obtained by acylation of the acetal **24** with stearoyl chloride.[44]



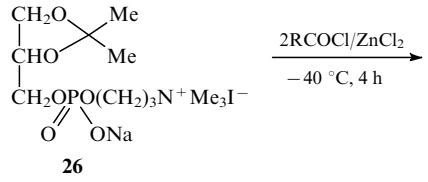
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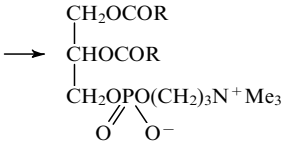
25

It should be noted that the acylation does not affect the sterically hindered phenolic hydroxyl.

Synthesis of lipid phosphodiesters by acylation of glycerol acetals can also be performed without protection of the free phosphate hydroxyl. For example, the phosphatidyl homocholines **27** have been effectively prepared by acylation of the sodium salt of the glycerol homocholine phosphate **26**.[45]



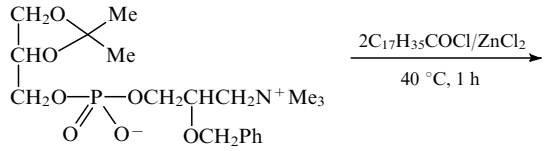
26



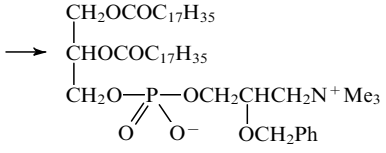
27 (58% – 64%)

R = $C_{15}H_{31}$, $C_{17}H_{35}$.

More complex lecithin derivatives **29** containing a hydroxyhomocholine residue were also synthesised by acylation of the phosphoacetals of type **28**.[46]

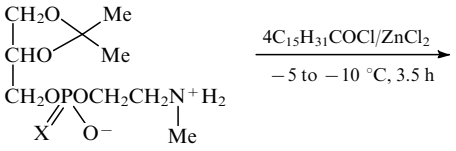


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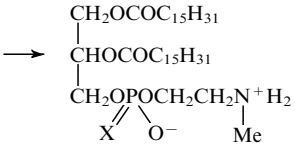


29 (56%)

Acylation was also used in the synthesis of phosphatidyl-*N*-methylethanolamines and their thione analogues **31**.[47] For this purpose, *N*-methylaminoethyl phosphate **30** was treated with an excess of palmitoyl chloride. It is noteworthy that this reaction does not involve *N*-acylation.



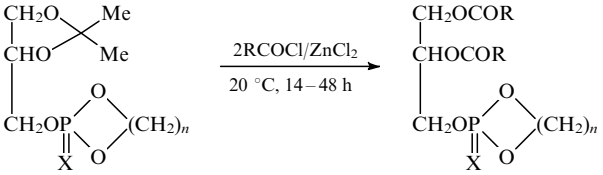
30



31 (40% – 52%)

X = O, S.

Acylation of compounds containing phospha-rings (these compounds play a significant role in the synthetic chemistry of phospholipids) constitutes a special line of research.[37] For example, acylation of acetals containing six- and seven-membered rings with phosphoryl, thiophosphoryl, and selenophosphoryl groups has been carried out.[48 – 51]

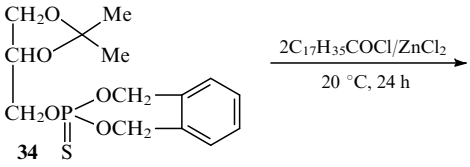


32 **33**

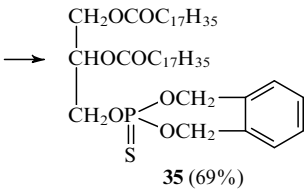
X = O, S, Se; n = 3, 4; R = $C_{15}H_{31}$, $C_{17}H_{35}$.

It should be emphasised that acylation was not accompanied by opening of the phospha-rings. The yields of the target products **33** depended on the ring size; for phosphorinanes they reached 68%, whereas for simplest phosphepanes, they were only 25% – 58%.

Fused phosphepanes appeared to be more convenient starting compounds than their monocyclic analogues **32**. For example, phosphepane **34** is readily and effectively converted into the lipid system **35**.[52]

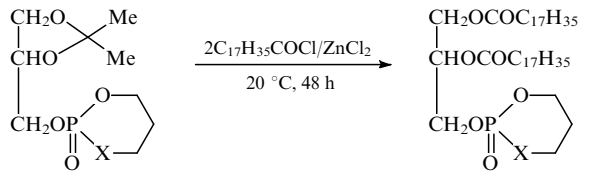


34



35 (69%)

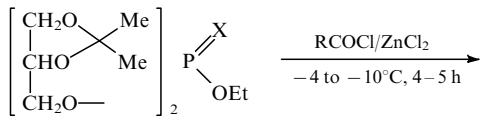
Acylation of systems **36** the rings of which contain sulfur or selenium atoms, in addition to phosphorus and oxygen atoms, has also been studied.[49] The yields of the target products **37** in this reaction were relatively low (45% – 47%), which may be due to the partial acylation of the sulfide or selenide centres in the initial phosphates **36**.



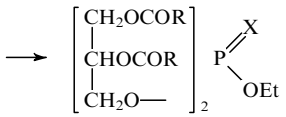
36 **37**

X = S, Se.

Acylation of diacetals, which are represented by diglycerophosphate systems **38**, is of considerable interest. Their acylation by myristoyl and stearoyl chlorides gives esters of bisphosphatidic acids and their thiono analogues **39**.[43]



38

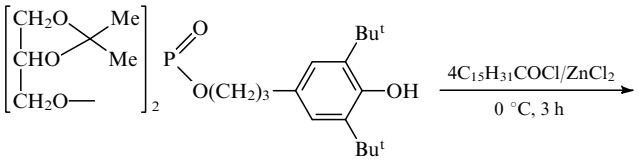


39 (45% – 60%)

X = O, S; R = $C_{13}H_{27}$, $C_{17}H_{35}$.

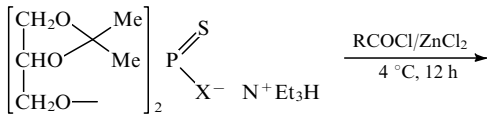
Synthetic operations with diacetal systems require that acylation conditions be carefully selected. It has been found that if acylation of the phosphatoacetals **38** by stearoyl chloride is carried out at room temperature rather than at −10 °C (yield 50% – 60%), the yield significantly decreases (to 5% – 10%). At the same time, in the case of myristoyl chloride, when the temperature increases from −4 °C (45% – 50%) to room temperature, the yield decreases to a lesser degre (to 20% – 25%).

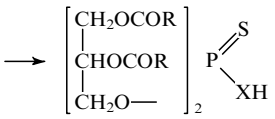
Acylation of bisacetal derivatives has also been used in the synthesis of diglycerophosphate lipid antioxidants **40**.[44]



40

The synthesis of thio- and dithio-bisphosphatidic acids **41** has been performed without recourse to phosphate protection.[43]





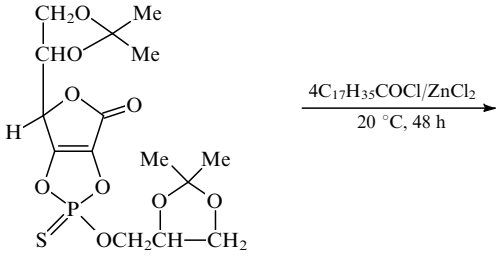
41 (45% – 49%)

X = O, S; R = $C_{13}H_{27}$, $C_{15}H_{31}$.

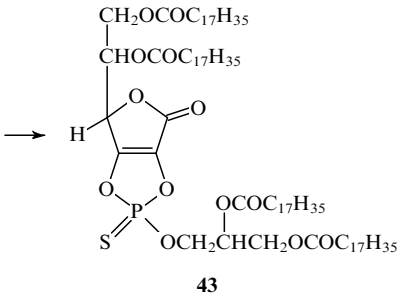
It can thus be concluded that acylation of glycerophosphate acetals is a convenient and promising method for the synthesis of many types of phosphatides.

IV. Synthesis of lipid systems based on phosphatide and 5,6-di-*O*-acylascorbic acids

Derivatives of phosphatidic acids, in which the phosphate function is linked to the hydrophobic residue of 5,6-di-*O*-acylascorbic acid **43**, can be of interest in the solution of some bioregulatory problems. It has been proposed to prepare these derivatives using the synthetic methods described above. 5,6-*O*-Isopropylidene-L-ascorbic acid and 1,2-*O*-isopropylideneglycerol served as the main starting compounds. They were coupled to give a diacetal thionophospholene system **42**. The final stage of this synthesis involves total acylation of this system.[53, 54]

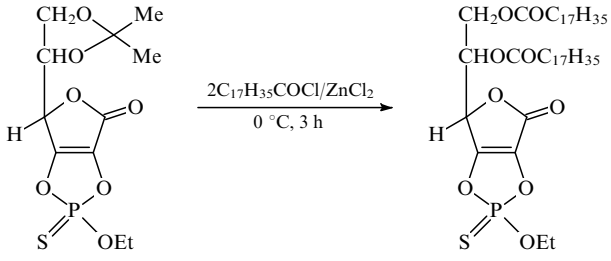


42



43

It is necessary to emphasise that the acetal fragments of the monosaccharide and glycerol in the compound **42** possess different nucleophilicities. The former can be acylated even at 0 °C, as has been demonstrated in relation to model system **44**.[54]

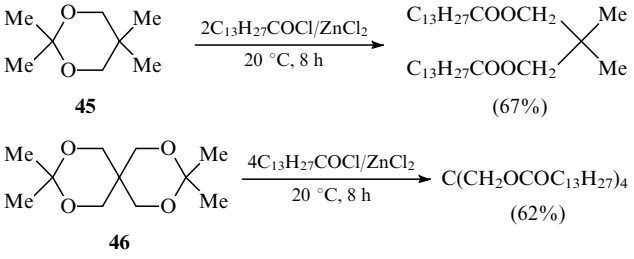


44

V. Synthesis of phospholipids based on acetals of tri- and tetramethylolalkanes

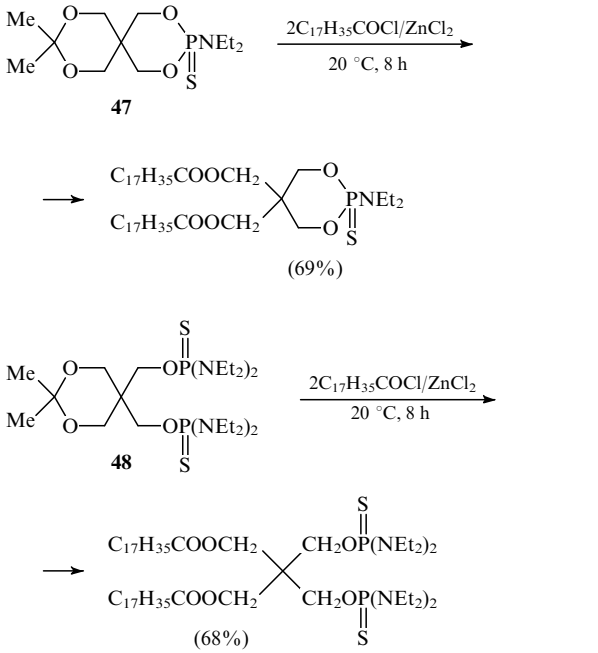
In modern lipidology, a new trend has appeared, devoted to the study of systems derived from unusual polyhydric alcohols. Acylphosphopentaerythritols and related compounds belong to this group. Acylation of mono- and diacetals of oligomethylolalkanes has been widely used in the synthesis of these lipids.

The design of new phospholipids was preceded by studies on acylation of model systems **45** and **46** based on 2,2-dimethyl-1,3-dioxane. It was shown that the mono- and diacetals **45** and **46** are smoothly and effectively acylated, according to the method described above.[55, 56]



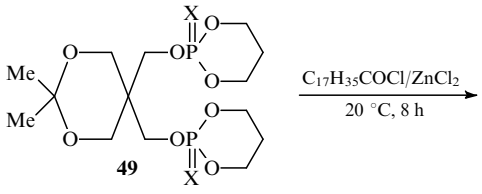
45 **46**

It was then demonstrated that mono- **47** and dithiophosphamide **48** acetals of pentaerythritol are acylated with an equal efficiency.[55, 56]

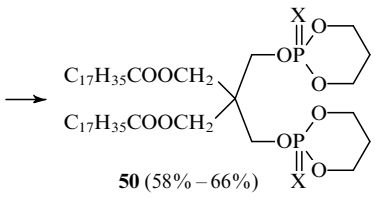


47 **48**

To obtain bis(dioxaphosphorinane) derivatives of diacylpentaerythritol **50**, the corresponding acetals **49** were introduced into the reaction with stearoyl chloride under standard conditions.[55, 56]



49

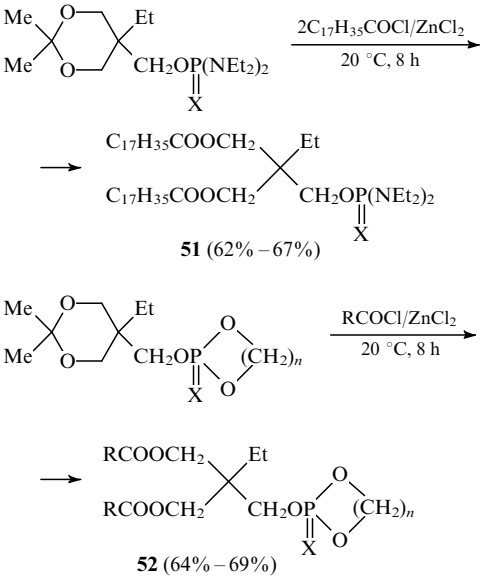


50 (58% – 66%)

X = O, S.

The distearoyl bisphosphates **50** possess an important structural feature: they contain two phosphopropylene rings. This permits these compounds to be used in the synthesis of phospholipids containing two hydrophilic residues in their molecules.[55, 56] In recent years, lipids of this type with enriched hydrophilic fragments have attracted attention of investigators due to their peculiar behaviour in some enzymic reactions [57] and in membrane modification [58–60] and also due to the prospects for their clinical application.[61]

The acylation reactions considered above have also been extended to the synthesis of erythritol phospholipids of the amidophosphite **51** and phosphate types **52**.[62]



51 (62% – 67%)

52 (64% – 69%)

X = O, S, Se; n = 2, 3; R = $C_{15}H_{31}$, $C_{17}H_{35}$.

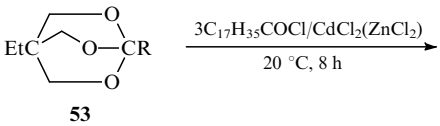
It is noteworthy that the efficiency of acylation in the case of phosphoryl, thionophosphoryl, and selenophosphoryl derivatives of erythritol is virtually identical. In this respect, trimethylol phospholipids differ from glycerophospholipids.

VI. Synthesis of phospholipids based on orthoesters

Orthoesters are classical reagents for fine organic synthesis, which are widely used in preparative practice, especially in the synthesis of heterocyclic compounds. As a rule, their transformations are associated with the formation of stabilised carbocations that are attacked by nucleophiles.[2, 3, 5] The reactions of orthoesters with electrophiles have received much less attention.

The interaction of orthoesters with phosphorus and sulfur halides resulting in esters of the corresponding mineral acids has been reported.[63–65] Reactions of orthoesters with carboxylic acids, their anhydrides, acyl chlorides, and acyl cyanides have also been described.[66–70] These reactions give mixtures of esters and other products. For example, mixing of ethyl orthoformate and acetyl chloride at 20 °C results in ethyl formate, ethyl acetate, and ethyl chloride.[63] The use of chlorides of higher fatty acids in acylation has led to similar results.[71]

The interaction of acid chlorides with bicyclic orthoesters **53** proceeds in a different way; In this case, complete acylation occurs to give triesters **54**.[71]

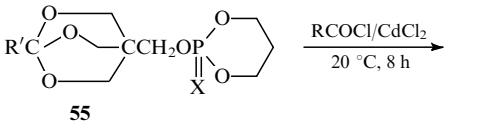


53

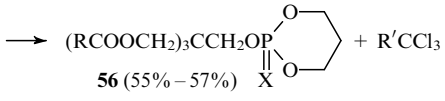
54 (60% – 62%)

R = H, Me.

This reaction has been used in the total synthesis of pentaerythritol homocholine phospholipids. To this end, phosphorylated bicyclic orthoesters **55** were converted into triacylphosphates **56** by direct acylation with palmitoyl and stearoyl chlorides.[71]



55

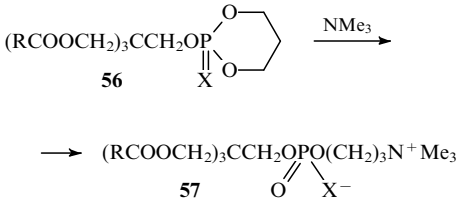


56 (55% – 57%)

R′ = H, Me; X = O, S; R = $C_{15}H_{31}$, $C_{17}H_{35}$.

It has been expedient to include this reaction in the scheme of the synthesis of phospholipids, because, in this case there is no need to protect three alcoholic hydroxyls prior to phosphorylation of pentaerythritol and to remove protective groups after phosphorylation.

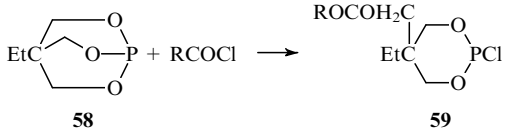
This reaction has a wide range of synthetic applications, since both phosphate and thiophosphate compounds successfully enter into it. Its practical utility becomes even more evident from the fact that the cyclic phosphates **56** formed proved to be effective alkylating agents. Owing to this property, they were used for obtaining previously unknown pentaerythritol homocholines **57**.[71]



56 **57**

X = O, S; R = $C_{15}H_{31}$, $C_{17}H_{35}$.

Like bicyclic orthoesters of carboxylic acids, the corresponding orthoesters of phosphorous acid (bicyclic phosphites) **58** also undergo acylation. Here the electrophilic reagent attacks the oxygen atoms rather than the phosphorus atom as could be expected for an Arbuzov reaction.[72]



58 **59**

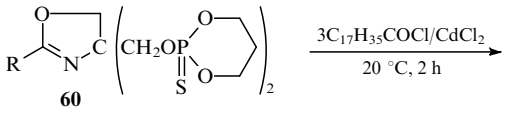
R = CH_3, $C_{15}H_{31}$, $C_{17}H_{35}$.

A specific feature of the bicyclic phosphites **58** is their relative inertness in acylation in which only one acyl group is introduced into their molecules.

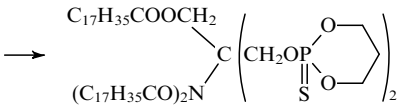
The resulting cyclic chlorophosphites **59** were used in the syntheses of various lipid-like compounds and other products.[72]

VII. Synthesis of phospholipids based on oxazolines

Further extension of studies on the acylation of geminal systems has led to the involvement in this process of oxazolines, which had been barely regarded as nucleophiles before.[3,63] Recently, it has been shown that these accessible and convenient compounds interact specifically with higher carboxylic acid chlorides to yield new types of nitrogenous phospholipids. For example, the reaction of cyclic bis(thiophosphates) of the oxazoline series **60** with stearoyl chloride gave the product of extensive acylation **61**.[73]



60



61 (45% – 47%)

R = H, Me.

In this case, as well as the oxygen atoms of the oxazolines, the nitrogen atoms were also attacked by the electrophilic acylating agent. This reaction is also unique, because it occurs as double *N*-acylation.

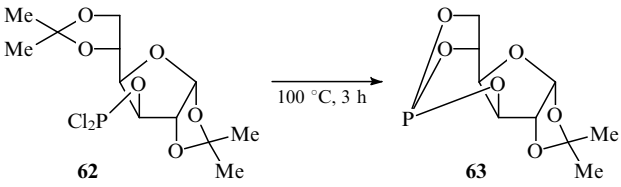
It should be noted that in early syntheses of *N*-monoacyl analogues of glycerophosphocholines based on D- and L-serines with the use of oxazoline protection, the introduction of fatty acid residues into lipid molecules has been carried out in two stages: deprotection in a strongly acidic medium and acylation of the amino alcohols formed with acid chlorides, anhydrides, or esters.[74,75] The new reaction of direct acylation of oxazolines has broadened considerably the potentialities of phospholipid synthesis.

VIII. Conclusion

The main conclusion of the present review is that a new method of *O*- and *N*-acylation has been added to the arsenal of fine organic synthesis; this method can be applied to the design of lipids and other complex polyfunctional systems. The method is facile and is therefore promising. At the same time, it has a number of specific features as regards the design of synthetic schemes; in particular, it may exclude the stage of obtaining intermediate polyhydroxylic structures.

Studies of the acylation of acetals have been mostly carried out in relation to the synthesis of carboxylic acid esters. Meanwhile, this reaction is also promising for the synthesis of phosphorous acid esters and, obviously, of other types of esters. We have already mentioned the interaction of 1,3-dioxolanes with ethylene chlorophosphite, which occurs as *O*-phosphorylation of the cyclic acetal.[10] Recent studies have demonstrated the possibility of conducting related phosphorylation. It is the intramolecular cyclisation of acetals **62**, the molecules of which contain a dichlorophosphite group.[76]

This simple reaction is a convenient method for the synthesis of framework bicyclophosphites of carbohydrates **63**.



62 **63**

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