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New cholesterol derivatives via acylation of phosphonium salts

Vitalii Lystvan
Zhytomyr Ivan Franko State University, Zhytomyr
https://orcid.org/0000-0002-8366-2813

Abstract. *The interaction between phosphorus ylides and cholesteryl chloroformate has been investigated. The conditions and characteristics of this reaction in single-phase and two-phase systems using different bases have been established. A series of new acylated phosphorus ylides containing a cholesteryl fragment has been obtained. The reaction proceeds under convenient conditions, starting from phosphonium salts, without the need to isolate the corresponding ylides in their individual state.*

Keywords: *ylid, phosphorane, phosphonium salt, cholesterol, acylation.*

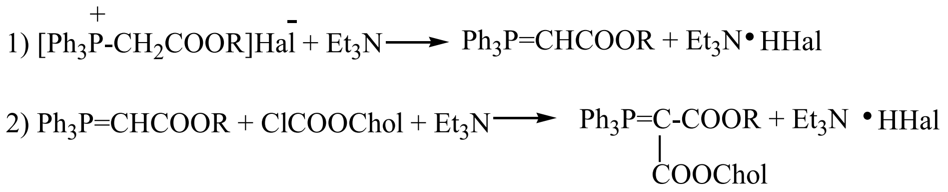
Cholesterol derivatives, particularly esters, are valuable in various fields, primarily due to their liquid-crystalline properties. Compounds of this class also exhibit significant optical activity [1] and a temperature-dependent color change [2]. The practical significance of cholesterol derivatives has prompted the search for new methods of their synthesis.

We propose an efficient approach to the synthesis of new cholesterol derivatives based on the reaction of organic phosphorus compounds – alkylidenephosphoranes – with acylating agents.

While the Wittig reaction (reaction with aldehydes) is the best-known application of phosphorus ylides in synthesis [3], another promising direction involves their interaction with acylating agents [4]. The outcome of such acylation depends on the structure of the phosphorane and the acyl halide, as well as the reaction conditions, and may result in the formation of compounds with triple bonds, cumulated double bonds, enol esters, and others.

We have investigated the reaction of phosphorus ylides with cholesteryl chloroformate as a method for synthesizing alkylidenephosphoranes bearing a cholesteryl moiety. We established the reaction conditions and features both in a single-phase system (chloroform with triethylamine) and a two-phase system (dichloromethane – 50% aqueous NaOH).

Since some alkylidenephosphoranes are not sufficiently stable to allow isolation and purification, we employed a previously described method [5] that enables their use



1) $[Ph_3\overset{+}{P}-CH_2COOR]\overset{-}{Hal} + Et_3N \longrightarrow Ph_3P=CHCOOR + Et_3N\bullet HHal$

2) $Ph_3P=CHCOOR + ClCOOChol + Et_3N \longrightarrow Ph_3P=\underset{\displaystyle COOChol}{\underset{|}{C}}-COOR + Et_3N\bullet HHal$

in situ from phosphonium salts without isolating the free ylides. The reaction scheme in the single-phase system is as follows:

In the two-phase system, the reaction proceeds via a slightly different pathway:

$$[Ph_3\overset{+}{P}\text{-}CH_2COOR]\overset{-}{Hal} + NaOH + ClCOOChol \xrightarrow{CH_2Cl_2} Ph_3P{=}\underset{\displaystyle COOChol}{\underset{|}{C}}\text{-}COOR + 2NaHal$$

In a series of reactions between cholesteryl chloroformate and various phosphorus ylides, we found that acylation with acid chlorides can lead to re-ylidation, with approximately half of the phosphorane converting back into the corresponding phosphonium salt. To prevent this, reactions were performed in the presence of bases – triethylamine or sodium hydroxide – which bind the HCl or HBr formed.

This method offers simplicity and employs readily available reagents, in contrast to procedures using alcoholates or organometallic bases (e.g., PhLi, BuLi), which require anhydrous solvents and an inert atmosphere. We found that simple and readily available metal hydroxides can be used to generate ylides from phosphonium salts, offering a more convenient alternative to moisture-sensitive reagents. In particular, NaOH allows acylation to be performed as a one-pot process, without preliminary isolation of alkylidenephosphoranes.

Under interfacial catalysis conditions, acylation proceeds readily, especially for triphenylphosphoranes substituted with benzyl or arylmethylene groups (semi-stable or “moderate” ylides). These ylides form in the organic phase by treating benzylic phosphonium halides in CH_2Cl_2 with 50% NaOH solution. Hydroxide ions are transferred into the organic phase by phosphonium cations, eliminating the need for an additional catalyst. Upon addition of the acyl halide, the reaction begins immediately.

We also found that under these conditions, aromatic acid chlorides such as benzoyl chloride react efficiently with phosphoranes, yielding good to satisfactory results. However, less reactive aroyl chlorides like *ortho*-bromobenzoyl chloride give poor yields due to steric hindrance. Aliphatic acid chlorides are generally ineffective or provide only trace amounts of product. Carboxylic anhydrides and other less active acylating agents are also unsuitable under these conditions, with steric factors further hindering the process.

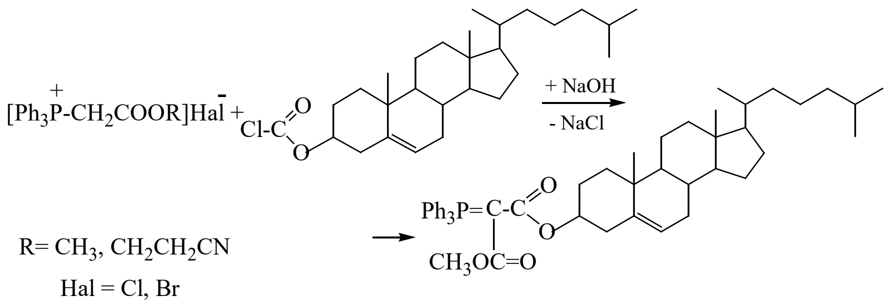
In the single-phase system, phosphonium salt and cholesteryl chloroformate are dissolved in chloroform, triethylamine is added, and the solution is stirred at room temperature for 24 hours. After solvent evaporation, the residue is washed, dried, and purified by recrystallization (e.g., from heptane, methanol, 2-propanol).

In the two-phase system, equimolar amounts of reagents are dissolved in dichloromethane, followed by the addition of aqueous NaOH. The mixture is stirred vigorously for 1–2 hours and left to react at room temperature for 24 hours. Product isolation and purification follow the same procedure as in the single-phase system.

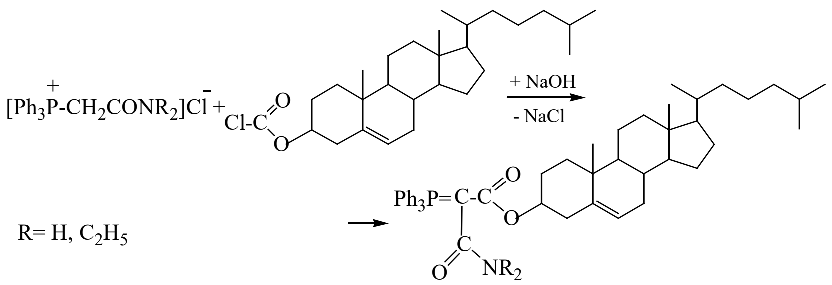
The multistep acylation of phosphonium salts in the presence of triethylamine or NaOH leads to the formation of acylated phosphoranes with a cholesteryl fragment.

The reaction proceeds to completion in 1–2 days at room temperature, using a 1:1:2 molar ratio (salt:cholesteryl chloroformate:base).

The developed methods also enable the efficient acylation of phosphonium salts bearing ester groups in the cation, which are obtained by reacting triphenylphosphine with haloacetic acid esters. Subsequent reaction with cholesteryl chloroformate affords the corresponding phosphoranes:



Phosphonium salts with amide groups also undergo acylation under similar conditions:



Obtained phosphoranes form a mesophase upon melting, indicating liquid-crystalline behavior. Attempts to acylate benzylic-type phosphonium salts in a single-phase system failed, likely due to the insufficient basicity of triethylamine required to generate the ylide.

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