

Phosphorylated allenes - suitable precursors in organic syntheses

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ABSTRACT

This article deals with the methods of synthesis of phosphorylated allenes, and their application in organic syntheses.

KEYWORDS: 1,2-Alkadienephosphonates, 1,2-alkatrienephosphonates, electrophilic addition reactions, nucleophilic addition reactions, cycloaddition reactions, cycloisomerization reactions

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1. Introduction

It is a very curious and not so popular fact that, right after the prediction of the correct core structure of allenes [1], the first attempt for their synthesis was used to prove the “nonexistence” of this class of organic compounds [2, 3]. However, a closer survey shows that in the period elapsed since 1984, an average of 400 publications on allenes appear annually. Among them the most striking ones are the series of books on the subject such as Muller’s Houben-Weyl issue of allenes, Patai’s issue on allenes, Brandsma’s laboratory manual, Landor’s “Chemistry of Allenes”, Schuster/Coppola “Allenes in Organic Synthesis” and Krause/Haschmi “Modern Allene Chemistry”.

On the basis of the scientific achievements especially in the area of the development of fruitful methods of synthesis of allenes, during the last 10-15 years a rapid development of the chemistry of these compounds took place, which has proven to be very powerful in modern synthetic organic chemistry [4-6].

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Last but not least nowadays about 150 natural products comprising an allenic or cumulenic structure are known (For review see Beilstein database BS0302PR). This number clearly proves that allenes cannot be simply considered as curiosities, but are representatives of important structural elements for a wide variety of different classes of compounds. Almost all allenic natural products reported up to date are chiral and were isolated in non-racemic form, albeit not necessarily as enantiomeric pure compounds. A substantial number of these allenes show interesting biological activities and, in recent years, many attempts have been made to “tune” further the biological and pharmacological properties of certain pharmacologically active compounds simply by introducing allenic moiety into the existing backbone of the molecule.

It is a well-known fact that organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical [7-12], agricultural [13], and chemical agents [14-20]. Recently phosphorus heterocycles [21, 22] have provoked considerable interest because of their unique biological activities as hydrolytic enzyme inhibitors [23] and their anticancer effects [24-26], as well as because of their wide-ranging utilities as synthetic intermediates in organic syntheses. Consequently, much attention has been focused on the synthesis of these compounds [27-34]. Among them, particular interest was paid to the oxaphosphole derivatives. Numerous methods

and synthetic protocols for synthesis of these compounds have been described.

The unique combination of double bonds in the molecules of those compounds, each with different reactivity along with the easy preparation, makes phosphorylated allenes useful substrates for the synthesis of different cyclic and noncyclic organophosphorus compounds. Recent investigations increase the scope of application of phosphorylated allenes as precursors in organic syntheses. Most of them are accompanied by the formation of five- or six-membered phosphorus heterocycles, which in many cases demonstrate certain biological activity.

The subject matter of the present review summarizes the most useful methods for the preparative synthesis of the titled compounds, and also submits some recent data on their application in organic chemistry.

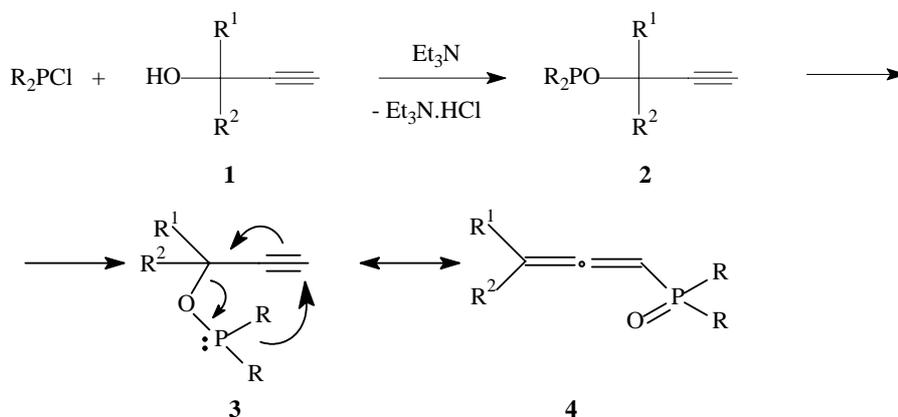
2. Methods for synthesis of phosphorylated allenes

2.1. Historical overview

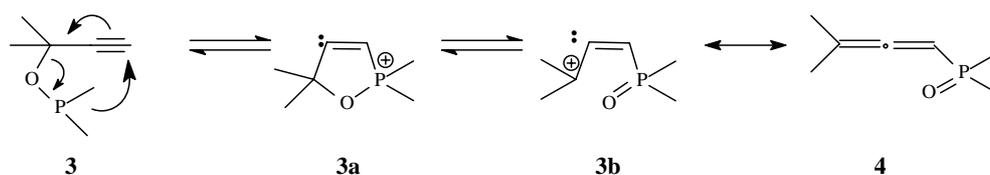
In 1962, Mark reported the obtaining of phosphorylated allenes via 2,3-sigmatropic rearrangement of propargyl phosphites (Scheme 1) [35].

This first report increased the investigations of this reaction [36].

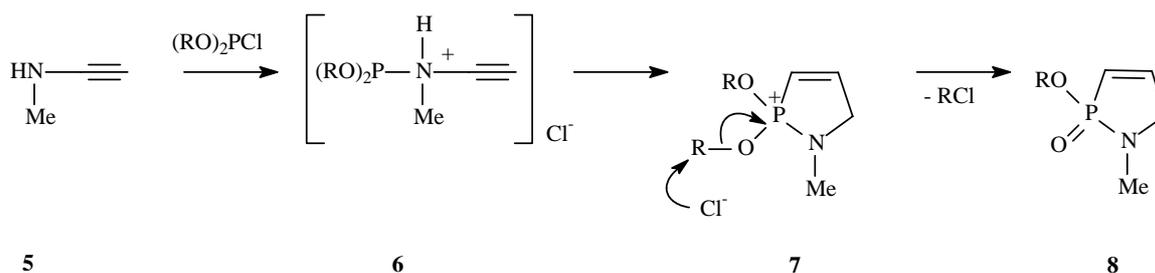
A plausible mechanism of the reaction proposed by authors involved a formation of intermediate with quasi-phosphonium structure (Scheme 2).



Scheme 1. Synthesis of phosphorylated allenes via 2,3-sigmatropic rearrangement of propargyl phosphates.



Scheme 2. A plausible mechanism of the alkyne-allene rearrangement of propargyl phosphates.



R=Me, Et, Pr, ⁱPr, ^tBu

Scheme 3. Synthesis of 1-methyl-2-alkoxy-2,5-dihydro-1,2-azaphosphole-2-oxide derivatives.

Some authors [37] define this reaction as Michelis-Arbuzov type reaction. The higher stereospecificity of the reaction was confirmed too [38].

Angelov and Enchev reported the same reaction, but with the N-analog of propargyl alcohol i.e., N-methyl-N-propargyl amine. This substrate reacts with dialkylchlorophosphites with formation of salts **6**. Heating of **6** up to boiling of the solvent leads to 1-methyl-2-alkoxy-2,5-dihydro-1,2-azaphosphole-2-oxide derivatives **8** (Scheme 3) [39].

The rearrangement of **6** to **8** is connected with the intermolecular proton exchange between N and C-atoms, followed by addition of the phosphorus to the triple bond and formation of the intermediates **7**, which undergo dealkylation to formation of **8**.

The isolation of the intermediate of the discussed reaction is a direct evidence for Mark's mechanism.

2.2. Synthesis of phosphorylated allenes via substitution reactions

The discussed 2,3-sigmatropic rearrangement of propargyl phosphites was used for the synthesis of the dichlorides of 1,2-alkadienephosphonic acids. These compounds possess very reactive chlorine

atoms attached to phosphorus atom, which could be substituted with other atoms or functional groups (Scheme 4) [37].

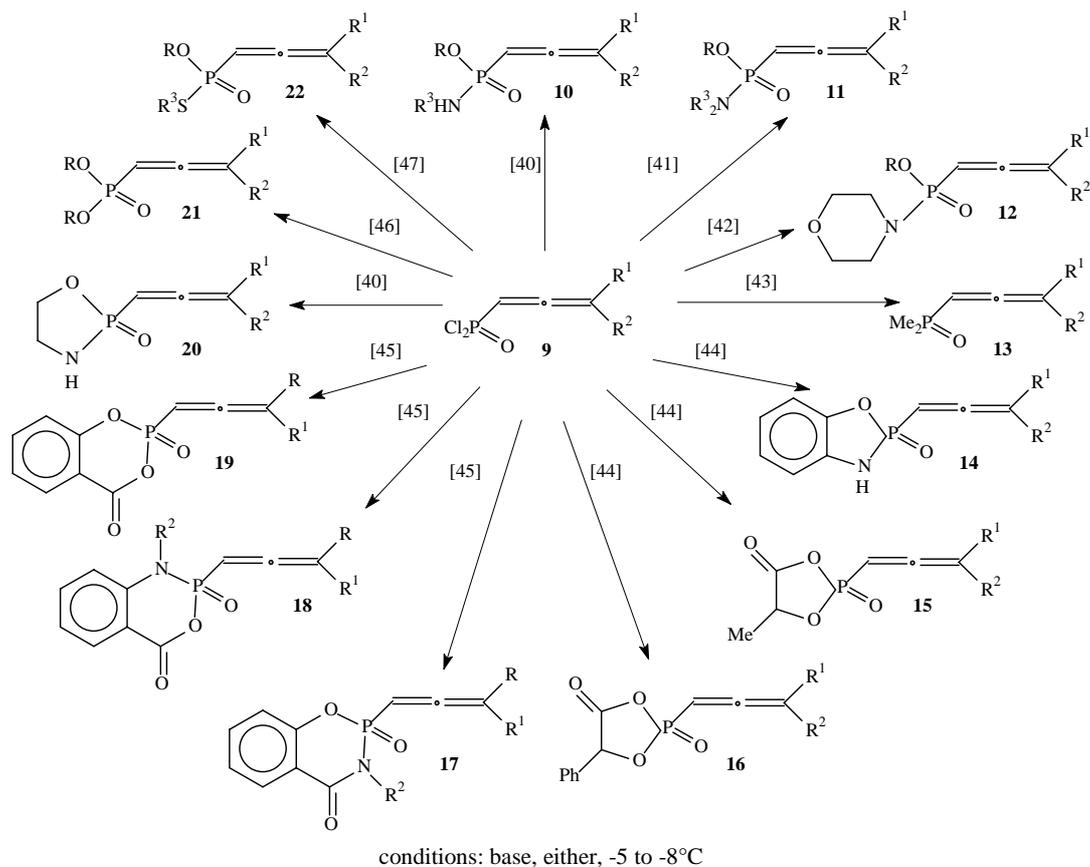
2.3. Synthesis of phosphorylated allenes via 2,3-sigmatropic rearrangement of activated alkynes

An approach involving the exchange of the hydroxyl-group with trimethylsilyl-group in the molecules of some alkyndiols was reported [48]. The reaction of the activated alkyndiols with some electrophilic reagents serves 1-substituted-1,2-alkadienephosphonates (Scheme 5).

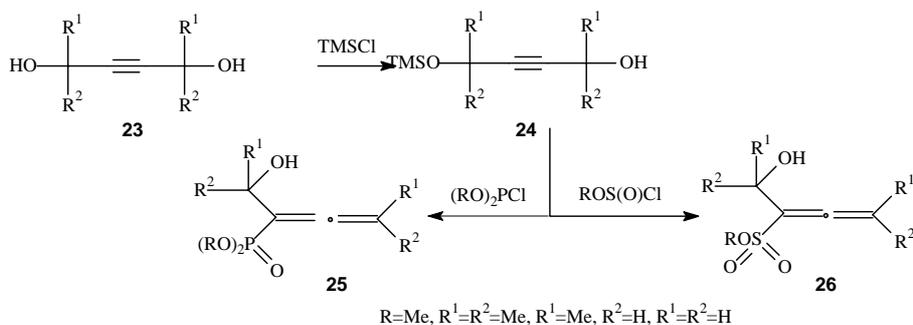
2.4. Synthesis of phosphorylated allenes via 2,3-sigmatropic rearrangement of modified alkynes

2.4.1. Sonogashira reaction

The synthetic potential of the Sonogashira reaction was used for obtaining a number of modified alkynes which react smoothly with dialkylchlorophosphites, following the known mechanism of 2,3-sigmatropic rearrangement. As a result, number of 1-aryl-substituted-1,2-alkadienephosphonates were obtained (Scheme 6) [49].



Scheme 4. Synthesis of phosphorylated allenes via substitution reactions.



Scheme 5. Synthesis of phosphorylated allenes via 2,3-sigmatropic rearrangement of activated alkynols.

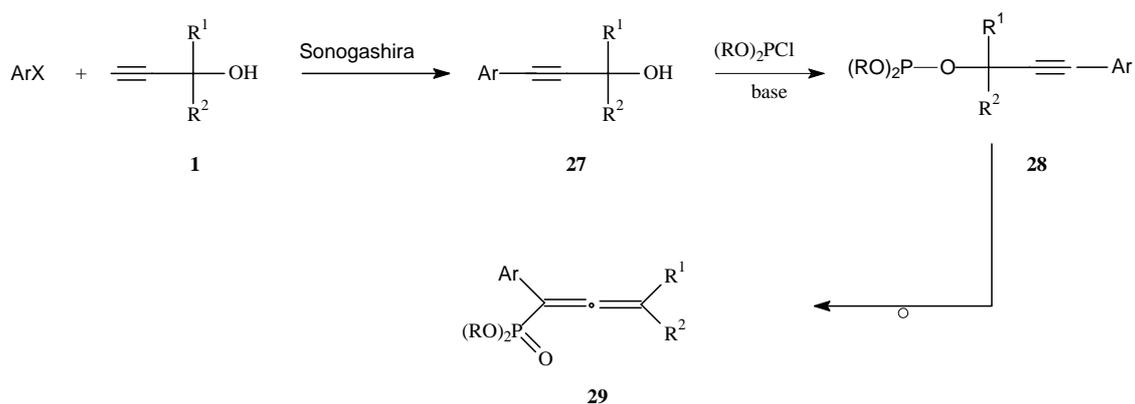
2.4.2. Correy-Fuchs-Barbier type condensation

By treatment of alkynylcarboxylic acid methyl ester with butyllithium and acetone, a reactive intermediate **32** was detected. The subsequent reaction of this intermediate with trimethylchlorosilane leads to the corresponding silyl derivative **33**. Treatment of **33** with certain electrophilic

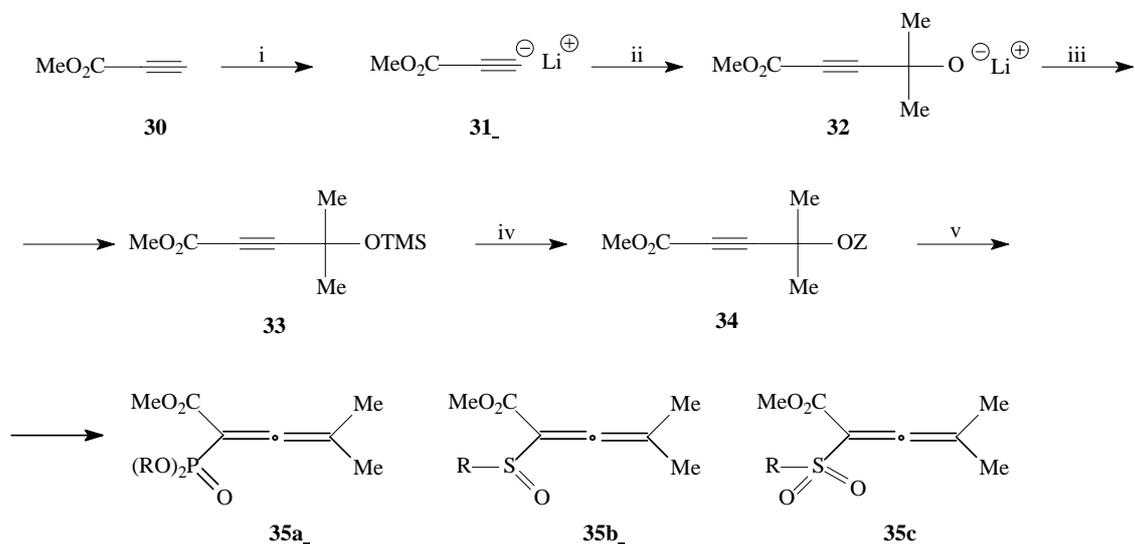
reagents leads to the corresponding 1,2-alkadienes (Scheme 7) [50].

2.5. Synthesis of phosphorylated allenes via Pd-catalyzed cross-coupling reactions

Chakravarty and Swamy reported a copper and amine free Pd-catalyzed cross-coupling



Scheme 6. Synthesis of phosphorylated allenes via Sonogashira reaction.



i= BuLi, THF, -78°C, argon
 ii= Me₂CO, THF, -78°C
 iii=TMSCl, THF, -78°C - room, argon
 iv_a ZCl= (RO)₂PCl, THF, -8 - -5°C, argon
 iv_b ZCl=RS(=O)Cl, THF, -8 - -5°C, argon
 iv_c ZCl=RS(O)Cl, THF, -8 - -5°C, argon
 v=isomerization

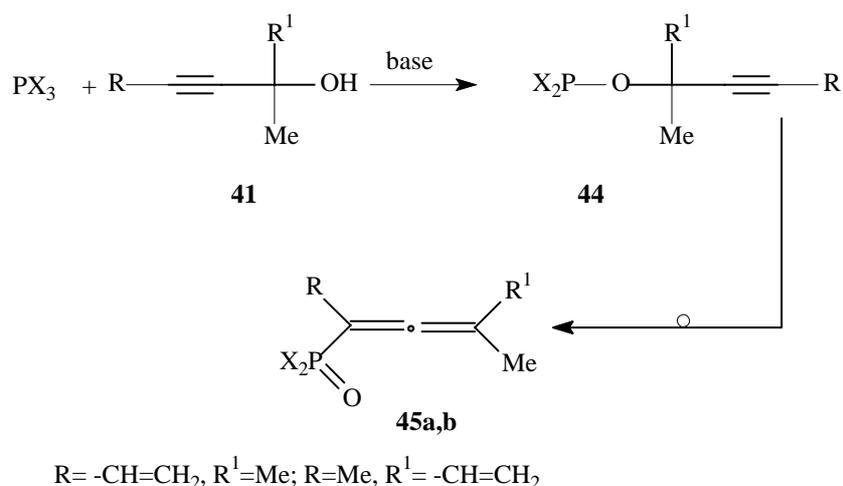
Scheme 7. Synthesis of phosphorylated allenes via Correy-Fuchs- Barbier type condensation.

reaction protocol in their investigation of the reactivity of 5,5-dimethyl-2-(1,2-alkadienyl)-[1,3,2] dioxaphosphinan-2-oxide [51].

The same procedure was applied for the obtaining of 1,2-alkadienephosphonates **37** (Scheme 8) [50].

2.6. Synthesis of phosphorylated allenes via allenyl anions

The deuterioexchange of the olefinic proton at C1 atom of the 1,2-alkadienephosphonates is well documented [52]. The synthetic protocol reported involves the obtaining of the reactive intermediate



Scheme 11. Synthesis of 1- and 3-vinyl-substituted allenephosphonic dichlorides.

3. Electrophilic addition reactions of phosphorylated allenes

After the discovery of electrophile-induced heterocyclization of alkadienephosphonic dialkyl esters [54] this reaction was investigated in details.

On the basis of prior reports [55] we have demonstrated that electron-deficient allenes, such as 1,2-alkadiene- and alkatrienephosphonates and phosphine oxides smoothly undergo electrophilic addition reactions which afforded 2,5-dihydro-1,2-oxaphosphole 2-oxide derivatives with anomeric phosphorus atom.

Recently it was proven that the latest compounds could be applied as heterocyclic building blocks in organic chemistry (Scheme 12) [56a,b,c].

4. Nucleophilic addition reactions of phosphorylated allenes

1,2-Propadienylphosphine oxides and phosphonates are good Michael acceptors and react smoothly with organometallic reagents (Scheme 13) [57].

The nucleophilic addition of NaN_3 to phosphorylated allenes leads to 2-azido-2-alkenylphosphonates, which react with PPh_3 to phosphineimines (Scheme 14) [58].

The reaction of monoacylhydrazide with 1,2-alkadienephosphine oxide, leads to the formation of β -iminylphosphine oxide. By this reaction, the unaffected double carbon-carbon bond

tautomerized to double carbon-nitrogen bond (Scheme 15) [59].

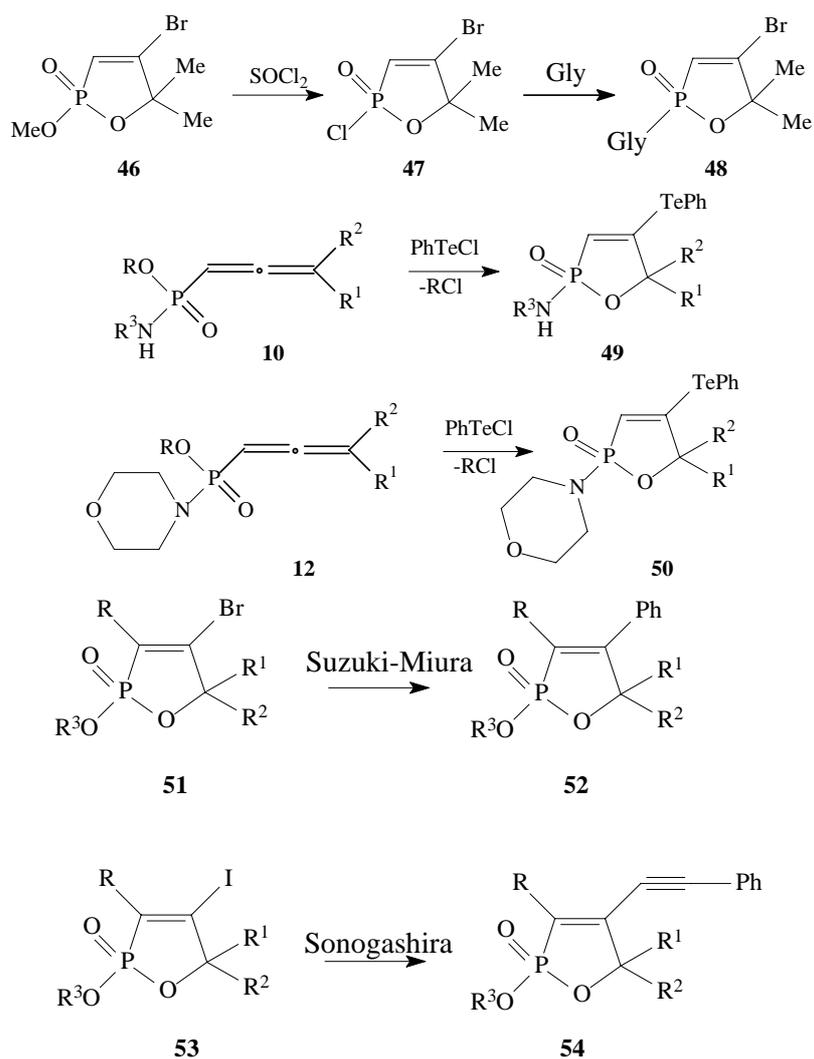
A similar reaction takes place between the same reagent and 1,2-allylphosphonamide affording a cyclic product (Scheme 16) [60].

The above described migration and tautomerization of the unaffected carbon-carbon double bond could be observed also in reactions with hydroxylamine [60, 61], hydrazine [62, 63] and primary amines [64] as nucleophiles. The β -iminylphosphineoxides, which are the products of these reactions, could be used as Wittig reagents (Scheme 17).

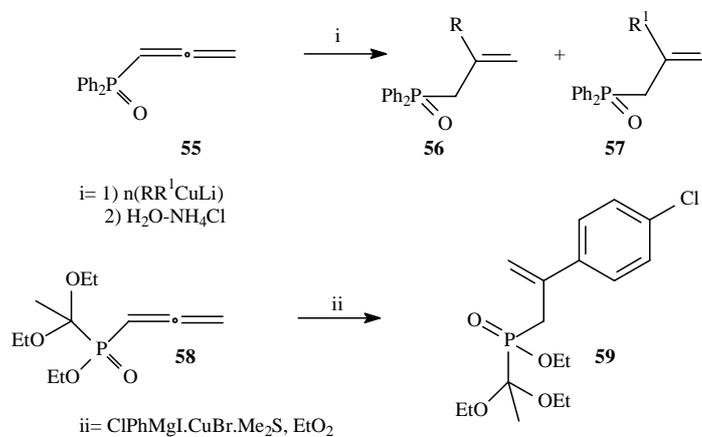
When dialkylamines were used as nucleophile, no migration of the unaffected carbon-carbon double bond was possible and 2-amino-2-alkenylphosphonate derivatives were isolated (Scheme 18) [65].

The nucleophilic addition of EtOH to phosphorylated allenes, followed by hydrolysis lead to the corresponding β -ketophosphonates [65]. The intramolecular addition of hydroxyl group to phosphorylated allenes gave 2,3-dihydrofuran derivatives [65].

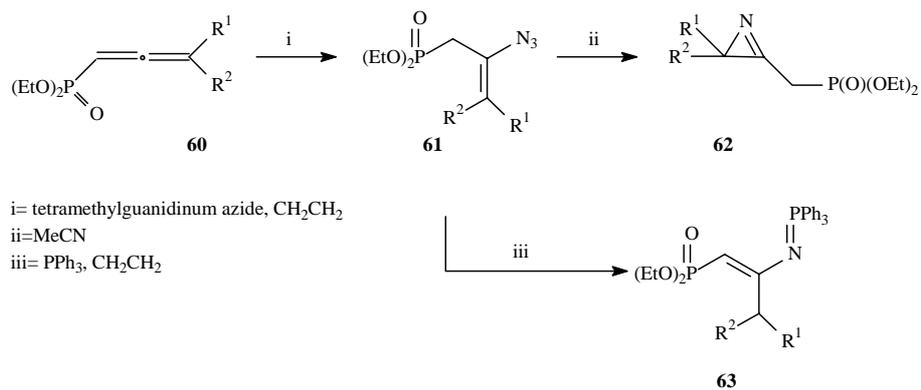
The corresponding reaction of diethyl-[1,2-propadienyl]-phosphonates, sulphones and sulfoxides with N-phenylhydroxylamine lead to formation of β -anionic- N-phenylvinylamine, which by [3,3]-sigmatropic rearrangement leads to anionic- 2-(2'-oxoalkyl)phenylamine. The described cyclization was an effective synthetic protocol for indole derivatives (Scheme 19) [66].



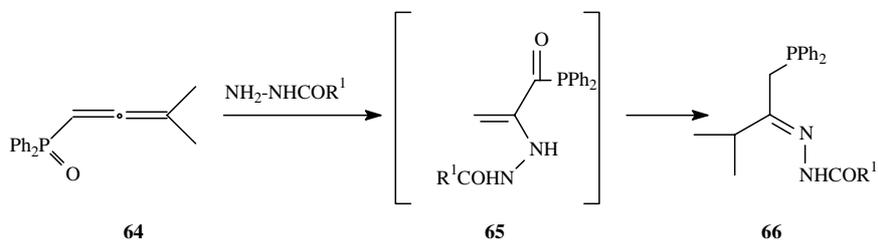
Scheme 12. 2,5-dihydro-1,2-oxaphosphole building blocks.



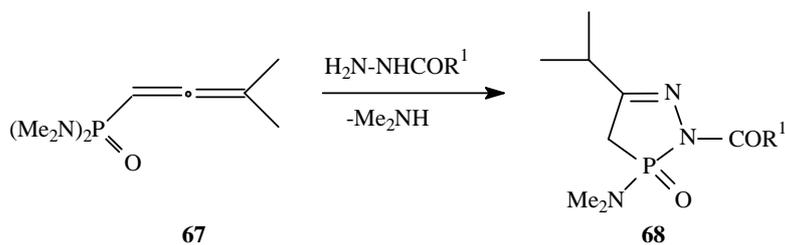
Scheme 13. Nucleophilic addition of organometallic reagents to phosphorylated allenes.



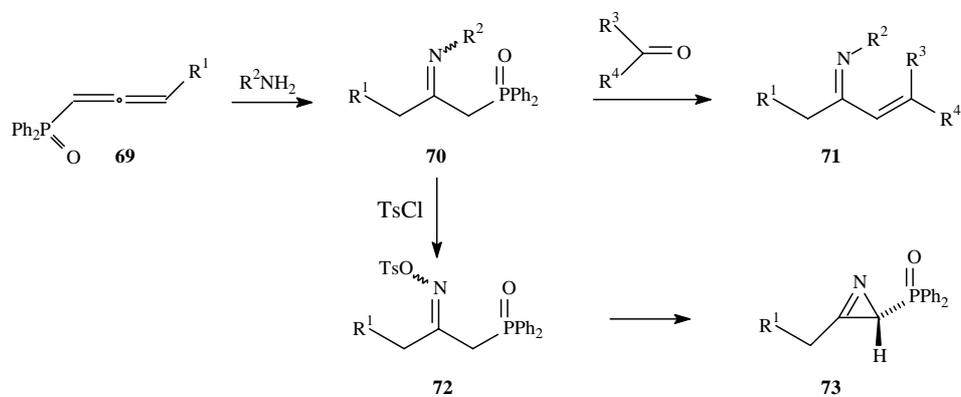
Scheme 14. Nucleophilic addition of NaN₃ to phosphorylated allenes.



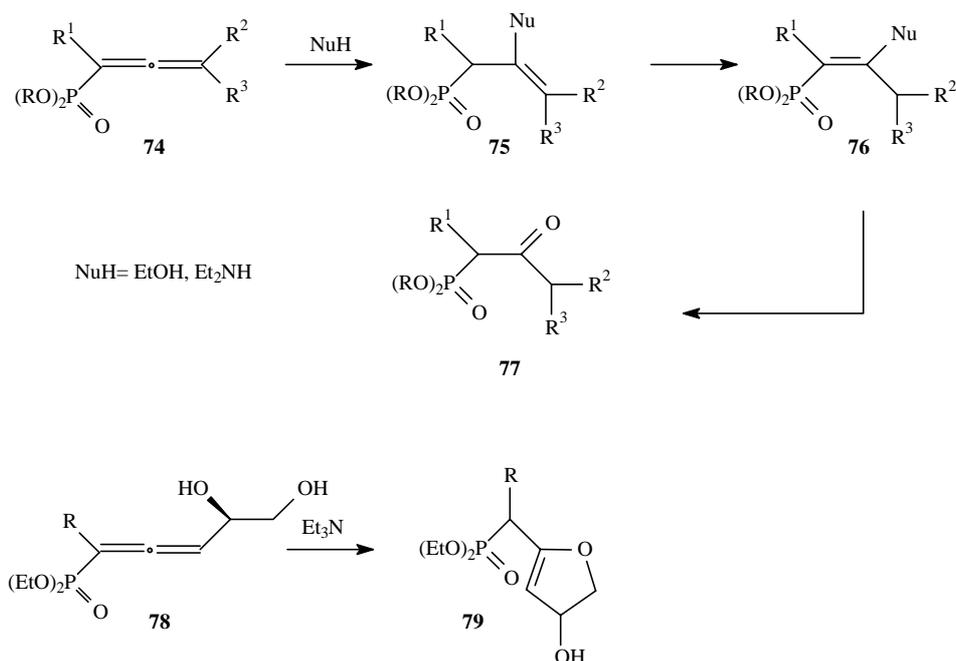
Scheme 15. Nucleophilic addition of monoacylhydrazide to 1,2-alkadienephosphine oxide.



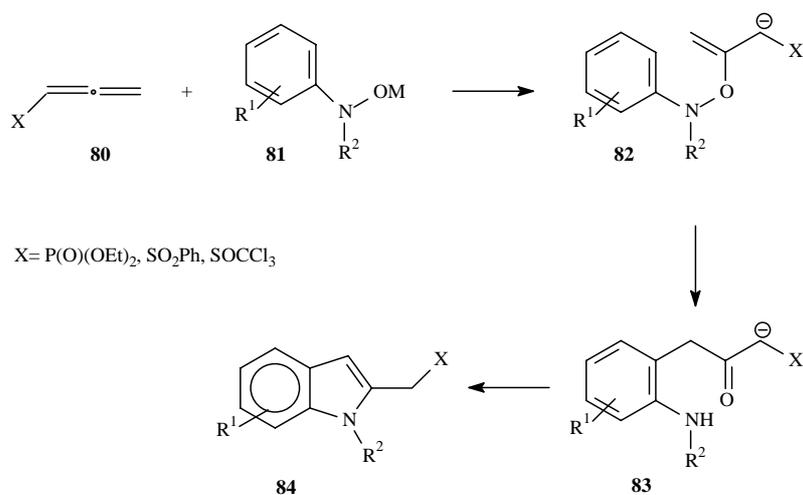
Scheme 16. Nucleophilic addition of monoacylhydrazide to 1,2-allylphosphonamide.



Scheme 17. Phosphorylated allenes as precursors for Wittig reagents.



Scheme 18. Nucleophilic addition of diethylamine and ethanol to phosphorylated allenes.



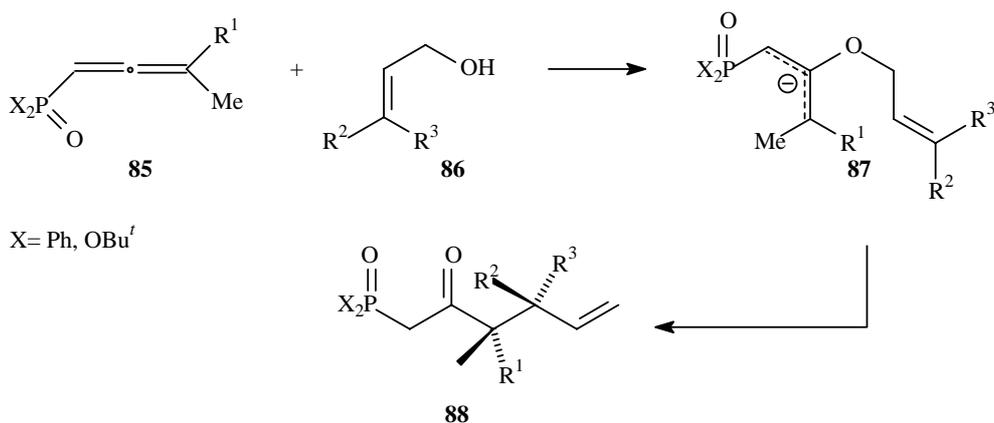
Scheme 19. Phosphorylated allenes as precursors for synthesis of indol derivatives.

The Claisen rearrangement of the intermediate **87** leads to 2-oxo-5-alkenylphosphonate or phosphine oxide (Scheme 20) [67].

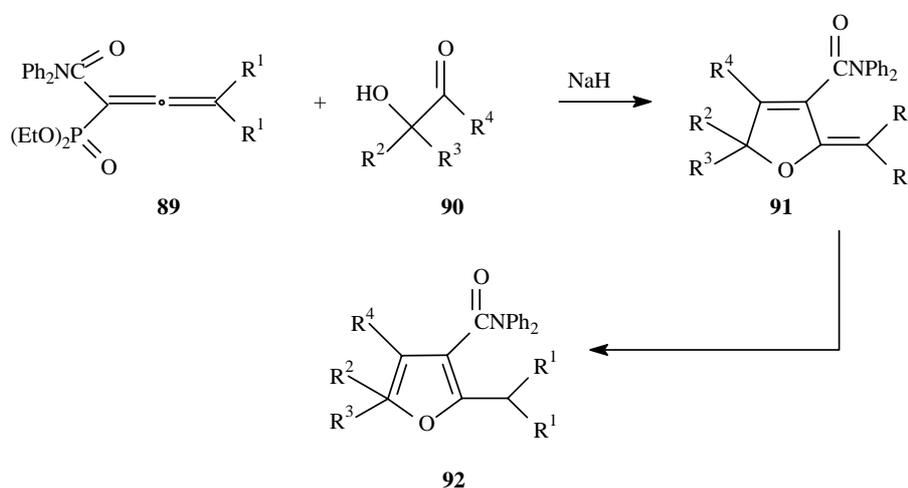
1-Amido-1,2-allenephosphonates react with α -hydroxyketones affording 2-alkylidene-2,5-dihydrofuran via secondary conjugated nucleophilic addition and subsequent Wittig-Horner reaction (Scheme 21) [68].

The reaction of 1,2-propadienyldiphenylphosphine oxide and MX (M = Na, Li; X = Cl, Br, I) leads to 2-halo-2-propenyldiphenylphosphine oxide (Scheme 22) [69].

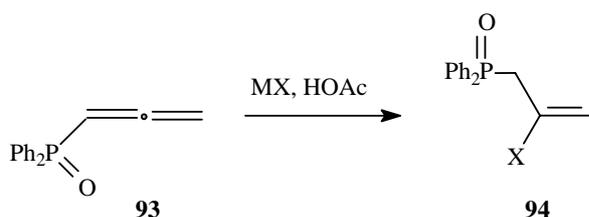
The amidoesters of 1,2-alkadienephosphonic acids react with secondary amines affording the corresponding β -ketophosphonates (Scheme 23) [41, 42].



Scheme 20. Phosphorylated allenes as precursors for alkenylphosphonates and alkenylphosphine oxides.



Scheme 21. Phosphorylated allenes as precursors for synthesis of furan derivatives.



Scheme 22. Phosphorylated allenes as precursors for 2-halo-alkenylphosphines.

5. Cycloaddition reaction of 1- and 3-vinyl-substituted phosphorylated allenes

The 1,4-cycloaddition of SO_2 to 1- and 3-vinyl-substituted phosphorylated allenes leads to

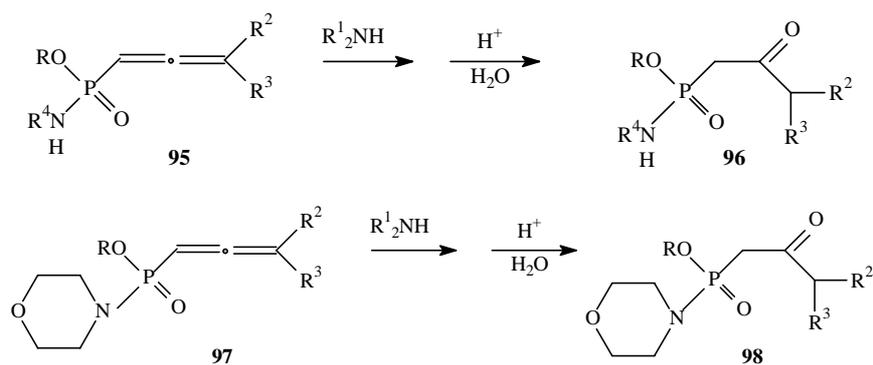
the corresponding cyclic sulphonophosphonates (Scheme 24) [70].

The same substrates react with trivalent phosphorus compounds. (Scheme 25) [71].

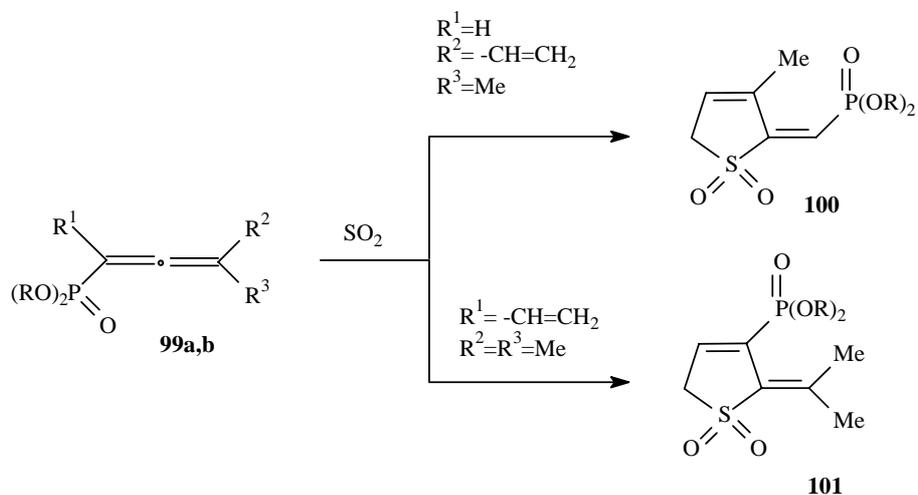
6. Transition metal induced cycloisomerization of phosphorylated allenes

The phenylphosphonic acid reacts with $AgClO_4$ with formation of the corresponding cyclic derivatives (Scheme 26) [72, 73].

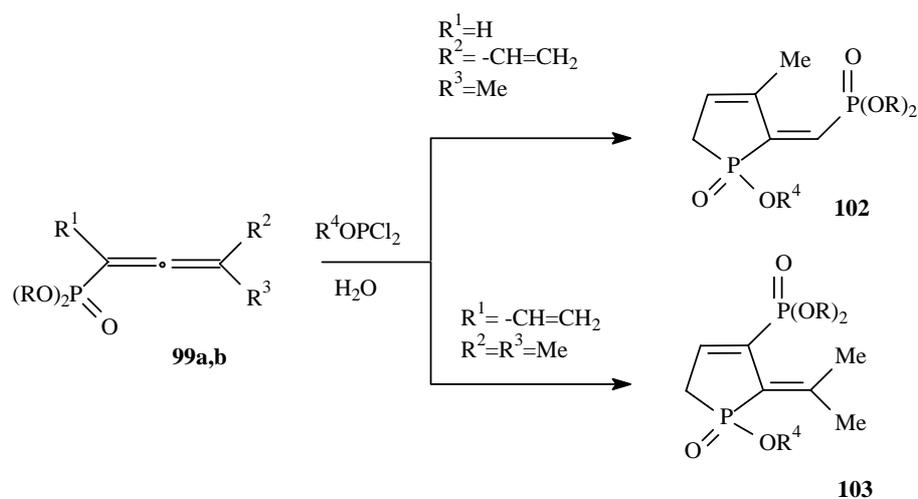
We investigate the reactivity of 1,2-alkadienephosphonic acids in this reaction and show that oxaphosphole derivatives were obtained. When amidoesters of 1,2-alkadienephosphonic



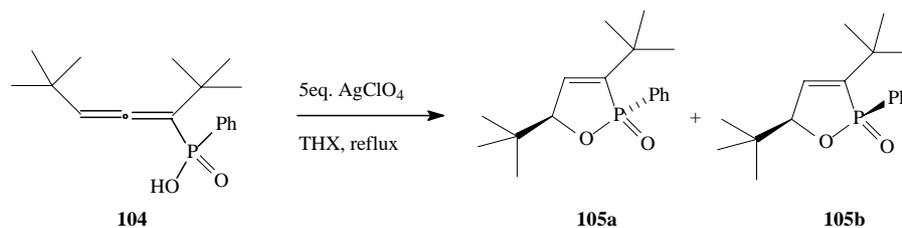
Scheme 23. Phosphorylated allenes as precursors for β -ketophosphonates.



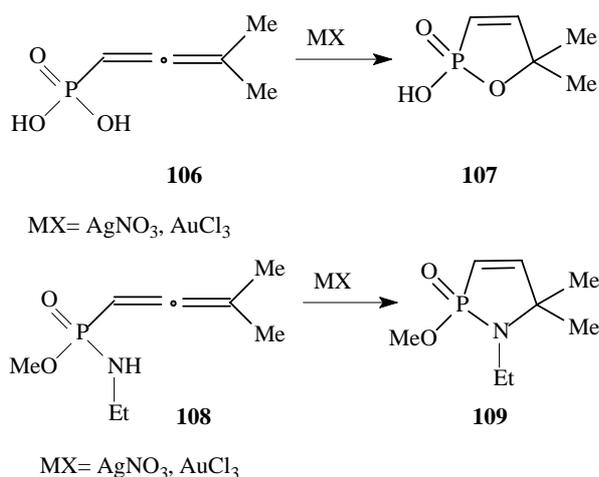
Scheme 24. Phosphorylated allenes as precursors for cyclic sulphonephosphonates.



Scheme 25. Phosphorylated allenes as precursors for McCormack reaction.



Scheme 26. Transition metals induced cycloisomerization of phosphorylated allenes.



Scheme 27. Cycloisomerization of phosphorylated allenes to oxaphosphole and azaphosphole derivatives.

acids were used as substrates, the azaphosphole derivatives were isolated (Scheme 27) [74].

7. Conclusions

The described methods represent phosphorylated allenes as suitable substrates for electrophilic and nucleophilic addition reactions, cycloisomerization reactions, as well as cycloaddition reactions.

All discussed aspects in this paper show that allenephosphonates, being minorities in the big family of allenic hydrocarbons, are actually very important precursors in organic synthesis.

It is important to underline that:

1. All the described methods for preparation of the phosphorylated allenes are environment-friendly;
2. All the reactions proceed with almost total atom economy;
3. All of the described compounds are biologically active substances.

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