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Synthesis of 1-Phosphono-2-aza-1,3-dienes and their Conversion into 1-Vinyl-2-phosphonoaziridines.

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Abstract

1-Phosphono-2-aza-1,3-dienes were formed by 1,4-dehydrochlorination of the corresponding N-(phosphonomethyl)-α-chloroimines, and reacted smoothly with diazomethane to give 1-vinyl-2-phosphonoaziridines. © 1999 Elsevier Science Ltd. All rights reserved.

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Organophosphates have played a significant role in agrochemistry during the past decades but have mostly been abandoned because of their acute toxicity. Recently, a lot of effort has been devoted to the synthesis of organophosphonates. More specifically, α-aminophosphonates have been an important research topic because of their analogy to α-amino acids resulting in enzyme inhibitor activity [1]. Heterocyclic analogues of α-amino phosphonates have not been studied in detail and, therefore, we have been engaged in developing straightforward methodologies for the synthesis of azaheterocyclic organophosphonates in order to investigate their physiological properties. Recently, we reported on the synthesis of phosphonylated 2-bromomethylaziridines [2].

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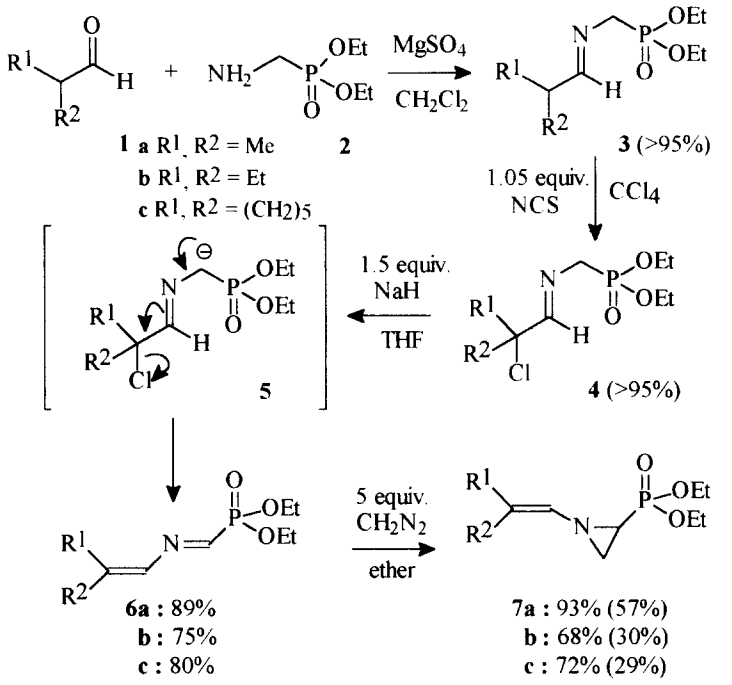
To our knowledge, the first synthesis of 1-phosphono-2-aza-1,3-dienes is described in this paper and their conversion into 1-vinyl-2-phosphonoaziridines upon treatment with diazomethane is unravelled.

2-Aza-1,3-dienes are known to be accessible from α-chloroimines upon treatment with potassium *t*-butoxide [3, 4]. The synthesis of 2-aza-1,3-dienes with electron-donating substituents [5] or neutral 2-aza-1,3-dienes [6] have been studied in detail because of their importance for the construction of a wide range of cycloadducts by Diels-Alder methodology. Electron-deficient 2-aza-1,3-dienes have been investigated less (except for heterocyclic azadienes [7]) because only selected examples are known to react in Diels-Alder reactions [8].

In order to develop an entry towards 1-phosphono-2-aza-1,3-dienes, aminomethylphosphonate **2** was synthesized from bromomethyl phthalimide using the method described by Seyferth [9] and distilled before use. Condensing the amine **2** and an aldehyde (**1**) in the presence of magnesium sulfate led to imine **3**, which was then α-chlorinated with *N*-chlorosuccinimide (1.05 equiv.) in carbon tetrachloride in quantitative yield. The amine **2** can also be condensed with the corresponding α-chloroaldehyde but the latter route is problematic for large-scale experiments.

The α-chloro N-(phosphonomethyl)imines **4** were then treated with 1.5 equivalents of sodium hydride in tetrahydrofuran at room temperature overnight, followed by refluxing the solution until the production of hydrogen gas ceased (mostly after approximately two hours). The time during which the reaction mixture was refluxing seemed to be very important to prevent decomposition of the azadiene. Several bases (sodium methoxide, sodium ethoxide, potassium *t*-butoxide, butyllithium, LDA, ...) were evaluated for the 1,4-dehydrohalogenation of the α-chloroimines **4**, but sodium hydride was the only base which could be used to obtain pure 1-phosphono-2-aza-1,3-dienes **6**. These compounds are not very stable and are preferably stored at –18°C to prevent decomposition and tar formation. The azadienes were not purified by chromatographic methods, but used as such in the following reaction (purity > 90%).

1-Phosphono-2-aza-1,3-dienes **6** are new compounds which seemed to be promising substrates as starting materials for the synthesis of azaheterocyclic phosphonates because of their multiple reactive centers.



The yield between brackets are the yields after flash chromatography

An initial reactivity study revealed that the azadienes are not as flexible substrates as thought. Reaction with nucleophiles (cyanide, methoxide, azide, phosphite, Grignard reagents,...) did not lead to the expected adducts, but resulted in complex reaction mixtures. Reaction with some electrophilic reagents (bromine, acetone cyanohydrin, cyanogen bromide, ...) resulted also in very complex reaction mixtures.

Reaction of the azadienes **6a-c** with an excess of diazomethane (approximately 5 equivalents, generated from *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide and potassium hydroxide) in ether, however, led to the clean generation of 1-vinyl-2-phosphonoaziridines **7a-c** in good yield. The phosphonoaziridines are the only products formed during the reaction and are sufficiently pure (> 95%) for use in further reactions. However, pure compounds can be obtained after flash chromatography, although a considerable loss of material was noted during the chromatography.

The addition of carbenoid species to the C=N bond has only been described in the case of activated or aromatic imino bonds, e.g. addition of diazomethane to iminium salts [10] or phenyldiazomethane to aromatic imines [11], metal catalyzed reactions of aromatic imines with

ethyl diazoacetate [12,13], and addition of dimethylsulfonium methylide to azirines [14] or aromatic imines [15, 16].

The addition of diazomethane to non-aromatic imines has not been reported. Even though carbenes are electrophilic species, resulting in a decrease in reactivity in the reaction with electron deficient olefins [17], diazomethane reacted smoothly with the phosphonyl substituted imine at room temperature.

On the other hand, carbenes are known to react with different kinds of olefins, but no formation of the corresponding cyclopropanes could be detected during the reaction with 2-phosphono-1,3-azadienes. Because the reaction occurs smoothly at room temperature and no evidence could be obtained of intermediate triazoline derivatives, the mechanism of the reaction is believed to proceed by the addition of a carbene to the imino bond.

The synthetic potential of N-vinyl-2-phosphonoaziridines as a building block for the synthesis of more elaborate azaheterocyclic phosphonates is currently under investigation and will be reported in due course.

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