Budapesti Műszaki és Gazdaságtudományi Egyetem

Synthesis and utilisation of bridged P-heterocycles in fragmentation-related phosphorylations

Thesis of the PhD dissertation

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2004

1. Introduction

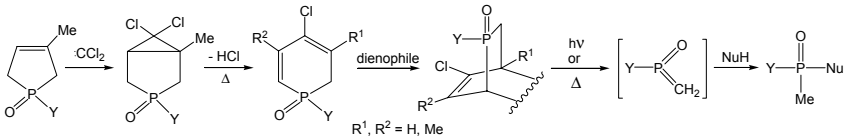
Heterocyclic compounds play an important part in our lives since they have significant role in biochemistry. That is why they are also in the focus of chemical research. Numerous heterocycles containing oxigen, sulfur and nitrogen atoms have been described, but recently the number of cyclic compounds containing other heteroatoms such as phosphorus, boron, selene and tellur is growing as well. In nature, phosphorus can be found in the form of inorganic phosphates is rocks, bones and teeth. Finally, we need to mention some organophosphoric derivatives essential for the proper function of biologycal systems, such as phospholipides and adenosine triphosphate. The latter one is responsible for the storage of energy needed for the life processes. During the ATP → ADP transformation a metaphosphate unit and energy are released. Phosphoric acid moieties connect the sugar units together in vital macromolecules, such as DNA and RNA responsible for the reproduction of genetic information. All these natural products are formed by phosphorylations. There exist also some phosphonic derivatives, like 2-aminoethylphosphonic acid and a suprisingly good antibiotic commercialized as Fosfomycin.

All of the products mentioned earlierare synthesized by the introduction of a –P(O)< moiety to a variety of O-, S-, N- or C-nucleophiles. Further on these reactions will be referred as phosphorylations instead of phosphonylations and phosphinylations.

I have been working at the Department of Organic Chemical Technology of the Budapest University of Technology under the supervision

of *Prof. György Keglevich* for three years, where I had previously completed my thesis for the diploma of chemical engineering.

Our research group has been dealing with phosphorylation reactions utilizing reactive intermediates, generated by the fragmentation of bridged P-heterocycles. Joining this team, our aim was to synthesize novel precursors and examine their UV light and thermoinduced fragmentations. Phosphonic and phosphinic derivatives with three different substituent at the phosphorous atom can be gained selectively by his new method.



Some of our bridged P-heterocycles are being tested for utilisation as a herbicide.

2. New scientific results

2.1 Synthesis of new 1,2-dihydrophosphinine oxides

Our first step was to prepare the dihydrophosphinine oxides, the starting materials of the desired precursors. The five-membered ring of the corresponding phosphole oxides was expanded by addition of dichlorocarbene to the double-bond of the starting material, followed by the thermal ring opening of the phosphabicyclo[3.1.0]hexane 3-oxide (**2d** and **2e**) so formed to give the desired 1,2-dihydrophosphinine oxides (**3d** and **3e**) as a ca 3:1 mixture of double-bond isomers (**A** and **B**).

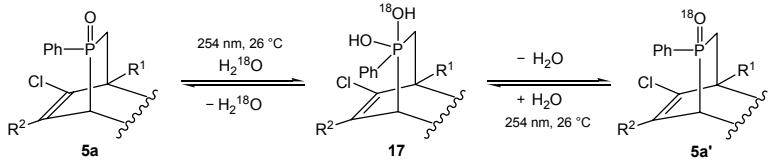
3. Publications

1. Keglevich, Gy., Szelke, H., Nagy, Z., Dobó, A., Novák, T., Tőke, L., *J. Chem. Res.,* **1999**, *35*, 580.
2. Jankowski, S., Rudzinski, J., Szelke, H., Keglevich, Gy., *J. Organomet. Chem.,* **2000**, *595*, 109.
3. Keglevich, Gy., Szelke, H., Tőke, L., *Heterocyclic Comm.,* **2001**, *7*, 365.
4. Keglevich, Gy., Szelke, H., Dobó, A., Nagy, Z., Tőke, L., *Synth. Commun.,* **2001**, *31*, 1737.
5. Keglevich, Gy, Szelke, H., Tamás, A., Harmat, V., Ludányi, K., Vaskó Á. Gy., Tőke, L., *Heteroatom Chem.,* **2002**, *13*, 626.
6. Keglevich, Gy., Forintos, H., Szelke, H., Tamás, A., Vaskó Á. Gy., Kovács, J., Körtvélyesi, T., Kollár, L., Tőke, L., *Phosphorus Sulfur,* **2002**, *177*, 1681.
7. Keglevich, Gy., Szelke, H., Bálint, Á., Imre, T., Ludányi, K., Nagy, Z., Hanusz, M., Simon, K., Harmat V., Tőke, L., *Heteroatom Chem.,* **2003**, *14*, 443.
8. Keglevich Gy., Forintos H., Szelke H., Kovács J., Körtvélyesi T., *Magyar Kémiai Folyóirat*, **2004**, in press.
9. Keglevich, Gy, Szelke, H., Kovács J., *Current Org. Synth.*, **2004,** in press.

Articels in an other field

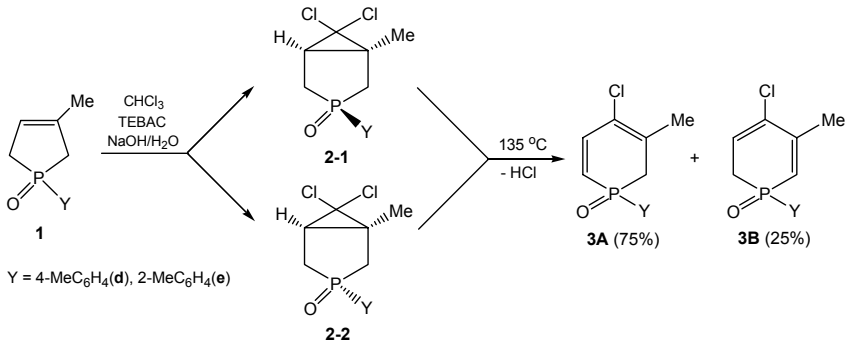
10. Denis, J-M., Forintos, H., Szelke, H., Keglevich, Gy., *Tetrahedron Lett.,* **2002***, 43,* 5569.
11. Denis, J-M., Forintos, H., Szelke, H., Toupet, L., Pham, T-N., Madec, P-J.,Gaumont, A-C., *Chem Commun.,* **2003***,* 54.

We performed the photolysis of phosphabicyclooctene **5a** in the presence of $H_2{}^{18}O$. As the reaction proceeded, via intermediate **17,** incorporation of ^{18}O in **5a** could be detected by FAB-MS. This way we were able to prove that the transient adduct (**17**) was formed in a reversible manner. For the sample which was kept in darkness, the pairs of isotopic ratios were the same and corresponded to the natural abundance. This means that the isotopic exchange occurs only on irradiation.



In conclusion, new phosphabicyclo[2.2.2]oct-5-enes and phosphabicyclo-[2.2.2]octa-5,7-dienes were synthesized and utilised in photo- and thermoinduced phosphinylation of alcohols, hydroquinone and primary amines. Mechanistic studies on the UV-light mediated phosphorylation of phosphabicyclooctenes in the presence of equimolar mixtures of different nucleofiles supports the suggestion of the novel addition-elimination reaction path. Isotope exchange experiments proved that the pentacoordinate intermediate is formed in a reversible way.

The *para*-methylphenyl phosphabicyclohexane (**2d**) was formed as a single isomer **2-1**, while the *ortho*-methylphenyl counterpart (**2e**) as a 80–20% mixture of isomers **2-1** and **2-2**. The assignment that **2-1** is the diastereomer containing the aryl group *cis* to the dichlorocyclopropane ring, while the other one (**2-2**) is the species with *anti* geometry is in full agreement with earlier cases according to which the dichlorocarbene addition reaction of the phenylphospholene oxide only the *cis* isomer was formed, while during the cyclopropanation of model compounds with sterically demanding substituents, such as the 2,4,6-trimethylphenyl- and the 2,4,6-triisopropylphenyl, the resulting phosphabicyclohexane consisted of two isomers with minor *cis* component.

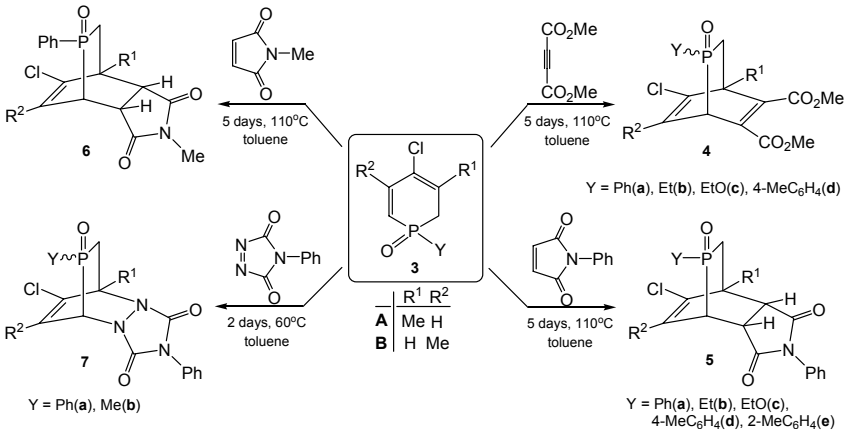


2.2 The synthesis of new bridged P-heterocycles

In the next stage of our work, the dihydrophosphinine oxides (**3**) were utilised in the synthesis of bridged P-heterocycles (**5-7**). The Diels-Alder reaction of the 3:1 isomeric mixture of **3** dihydrophosphinine oxides with dimethyl acetilenedicarboxilate in boiling toluene furnished

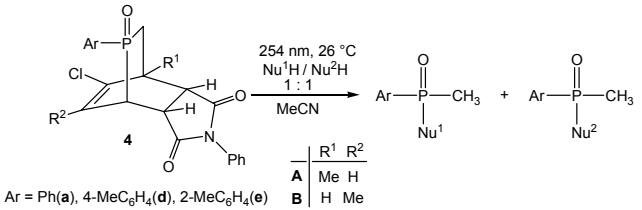
phosphabicyclooctadienes **4** as an isomeric mixture of **A** and **B** consisting of configurational isomers. The dihydrophosphinine oxides (**3**) were also converted to the corresponding phosphabicyclooctenes (**5A** and **5B**) using N-phenylmaleimide. In this case, the double-bond isomers (**5A** and **5B**) did not consist of configurational isomers.

The Diels-Alder reaction of the double-bond isomers (**A** and **B**) of dihydrophosphinine oxide **3a** with N-methyl maleimide gave a similar isomeric mixture of phosphabicyclooctenes **6A** and **6B**. It seemed to be interesting to explore the effect of the introduction of heteroatoms, such as nitrogen atoms, into the phosphabicyclooctene skeleton. The cycloadditions of dihydrophosphinine oxides **3a** and **3b** with 4-phenyl-1,2,4-triazoline-3,5-dione afforded the diazaphosphabicyclooctenes **7a** and **7b**, respectively, consisting of the four possible isomers.

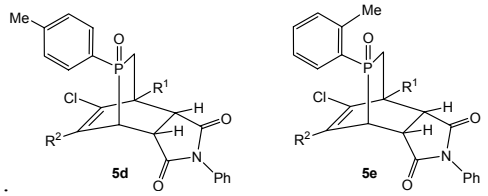


2.9 Mechanistic studies on the photochemical reaction

The new precursors were applied in mechanistic investigations. In a kind of competitive experiment, the aryl-phosphabicyclooctenes (**5a,d** and **5e**) were irradiated in the presence of an equimolar mixture of different nucleophiles. As we expected, there was a significant selection between the nucleophiles. Precursors **5a,d** and **5e** reacted faster with the more nucleophilic or the sterically less demanding reactant which seems to support the involvement of the AE mechanism with the intermediate of type **16** present.

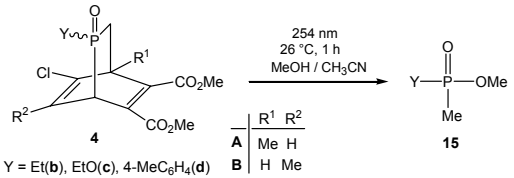


We wondered if the *para*-methylphenyl- and the *ortho*-metylphenyl substituted phosphabicyclooctenes (**5d** and **5e**) show a similar or a somewhat different reactivity during the phosphinylations. According to our observations the *ortho*-methylphenyl cycloadduct (**5e**) reacted somewhat slower than the *para*-methylphenyl counterpart (**5d**) as a consequence of the more relevant steric hindrance due to the *ortho*-methyl substituent.



2.7 Photoinduced phosphorylations using phosphabicyclooctaidenes

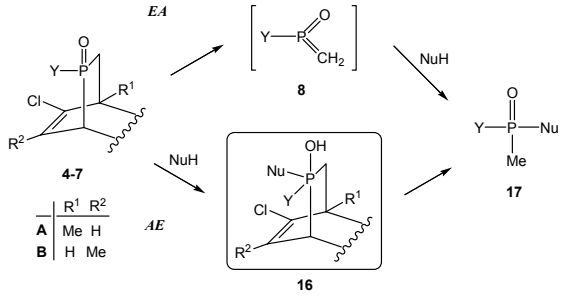
Because of the abscence of reactivity of ethyl- and ethoxy-phosphabicyclooctenes (**5b** and **5c**) during the photochemical fragmentation, **15b** phosphinate and **15c** phosphonate were synthesized using phosphabicyclooctadienes **4b** and **4c**. Compound **15d** could, however, be prepared not only by the photolysis of **5d**, but also by using phosphabicyclooctadiene **4d.**



4 Y = Et(**b**), EtO(**c**), 4-MeC$_6$H$_4$(**d**) 15

2.8 Mechanism of the photochemical reaction

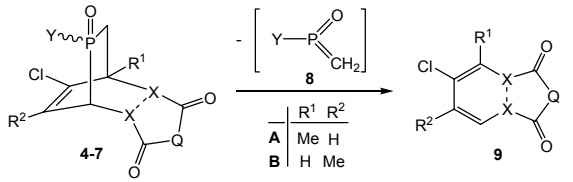
While the thermoinduced phosphinylations obviously take place through an elimination–addition (EA) mechanism involving methylenephosphine oxide (**8**) as the intermediate, the photochemically initiated phosphinylations may also involve a novel addition–elimination (AE) route via an intermediate with a pentavalent pentacoordinated phosphorus atom (**16**).



4-7 8 16 17

2.3 Thermal examination of the precursors

Thermal examinations (TG and DTG) of the precursors **4-7** revealed that the bridging moiety (**8**) was ejected in the range of 190–440 °C and a phtalate (**9**) remained as a side-product. Because of their more strained framework, phosphabicyclooctadienes **4** are less stable thermally than **5** phosphabicyclooctenes. Since **6** N-methylphosphabicyclooctene was fragmented in the range of 335–410 °C, like the N-phenyl analogue, it is noted that the change of the phenyl group to a methyl substituent on the nitrogen atom does not have a significant impact on the thermostability. Cycloadduct **7a** underwent fragmentation in the range of 228–315 °C, suggesting its lower thermostability compared to that of the carbocyclic analogue (**5a,** 350–440 °C)



4-7 9

Y = Ph (**a**), Et (**b**), EtO (**c**), 4-MeC$_6$H$_4$ (**d**)

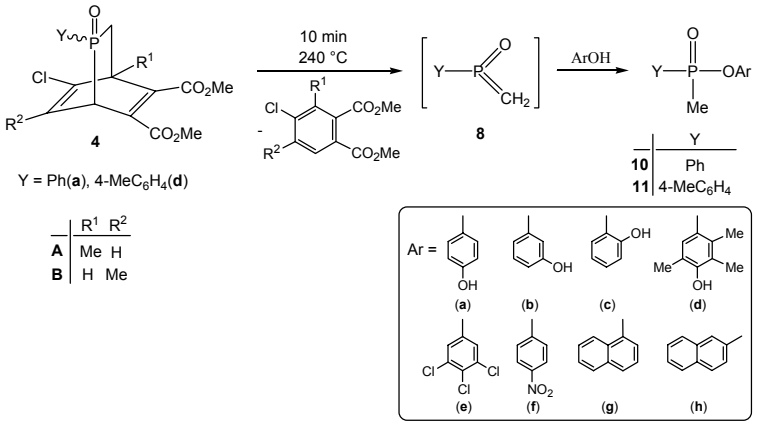
X---X = HC—CH, C═C, N—N

Q = (OMe)$_2$, N—Ph

2.4 Thermoinduced phosphorylations using phosphabicyclooctadienes

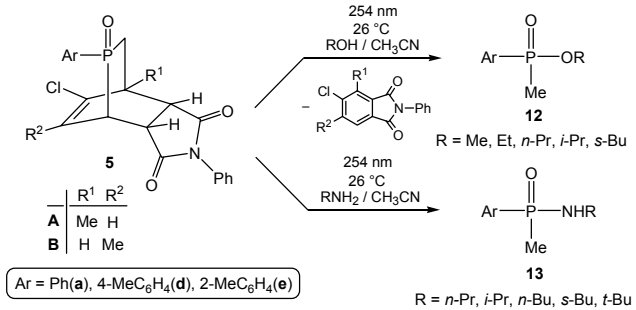
The thermolysis of phosphabicyclooctadienes (**4a,d**), having a more strained skeleton as compared to the phosphabicyclooctenes, seemed to be a good choice for the generation of methylenephosphine oxides (**8**) to phosphorylate phenol derivatives. To ensure fast fragmentation, a temperature

of 240 °C had to be applied, so this process can only be utilized in the phosphorylation of non volatile aromatic hydroxy compounds.



2.5 UV-light mediated phosphorylations using arylphosphabicyclooctenes as precursors

The P-aryl precursors (**5a,d,e**) were utilised in fragmentation-related phosphinylations. The acetonitrile solutions of the corresponding phosphabicyclooctenes (**5a,d,e**) were irradiated (254 nm) at 26 °C in the presence of alcohols or primary amines to give phosphinic esters (**12**) or amides (**13**). The above mentioned method is an elegant way to synthesize methylphosphinic derivatives in a selective and clean reaction.



2.6 Dechlorination reaction of ethyl- and ethoxy-phosphabicyclooctenes

Phosphabicyclooctenes containing an ethyl or an ethoxy group on the phosphorus (**5b** and **5c**) could not be used in UV-light mediated phosphorylations. However, the dechlorinated derivatives (**14b** and **14c**) of the precursors (**5b** and **5c**) were observed to have been formed under the conditions of the photochemical reaction. It seems that the P-substituent has a significant role in the absorption of energy.