Budapesti Műszaki és Gazdaságtudományi Egyetem

Fragmentation properties of bridged P-heterocycles;

7-Phosphanorbornenes, phosphabicyclooctenes and 1,2-oxaphosphabicyclooctenes

Thesis of the PhD dissertation

János Kovács

Supervisor: Prof. György Keglevich

Department of Organic Chemical Technology
Budapest University of Technology and Economics
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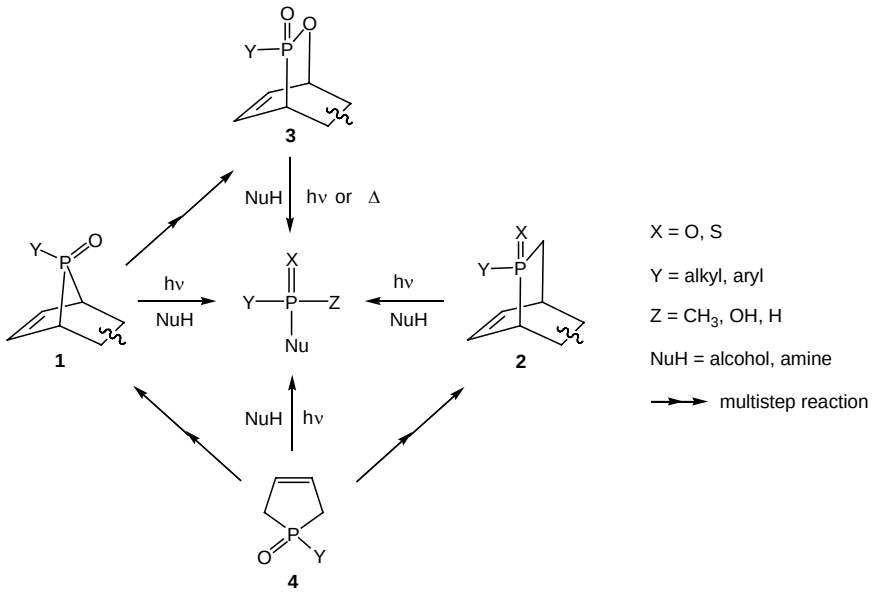
1. Introduction

According to their significant role in life processes, heterocyclic compounds are in the focus of the 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 biological 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 → cAMP transformation metaphosphate units 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. Some phosphonic derivatives can also be found in nature, like 2-aminoethylphosphonic acid and a suprisingly good antibiotic commercialized as Fosfomycin.

All of the products mentioned earlier are 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 and Economics 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 (7-phosphanorbornenes (**1**), phosohabicyclo[2.2.2]octenes (**2**), 1,2-oxaphosphabicyclo[2.2.2]octenes (**3**) and dihydro-1*H*-phosphole oxides (**4**)) and examine their UV light and thermoinduced fragmentations.



3. Publications

[1] Keglevich, Gy., Szelke, H., Kovács, J., *Curr. Org. Synth.*, **2004**, 1, 377.

[2] Kovács, J., Balázsdi, Sz.N., Nagy, Z., Ludányi, K., Keglevich, Gy., *Heteroatom Chem*., **2005**, *in press*.

[3] Kovács, J., Keglevich, Gy., Kerényi, A., Imre, T., Ludányi, K., Tőke, L., *Heterocyclic Commun*., **2004** 10, 238.

[4] Keglevich, Gy., Forintos, H., Szelke, H., Tamás, A., Vaskó, Á.Gy., Kovács, J., Körtvélyesi, T., Kollár, L., Tőke, L., *Phosphorus Sulfur*, **2002**, 177, 1681.

[5] Keglevich, Gy., Kovács, J., Ludányi, K., Tőke, L., *Heterocyclic Commun*., **2002**, 8, 31.

[6] Keglevich, Gy., Kovács, J., Körtvélyesi, T., Parlagh, Gy., Imre, T., Ludányi, K., Hegedűs, L., Hanusz, M., Simon, K., Márton, A., Marosi, Gy., Tőke, L., *Heteroatom Chem.*, **2004**, 15, 97.

[7] Keglevich, Gy., Forintos, H., Szelke, H., Kovács, J., Körtvélyesi, T., *Magyar Kémiai Folyóirat*, **2004**, 109-110, 1, 37.

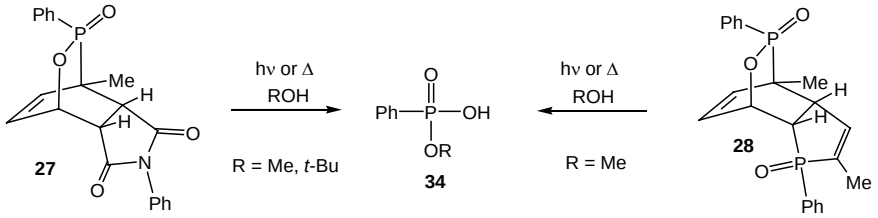
[8] Keglevich, Gy., Kovács, J., Szöllősy, Á., Kovács, A., Szabó, A., Ludányi, K., Kádas, I., Tőke, L., *Heteroatom Chem*., **2003**, 14, 29.

[9] Kovács, J., Imre, T., Ludányi, K., Tőke, L., Keglevich, Gy., *Synth. Commun.*, **2004**, 34, 1033.

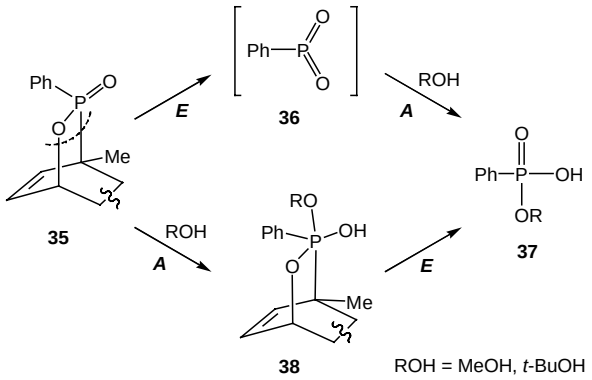
Articles in an other field

[10] Pete, B., Varga, F., Kovács, J., *J. Het. Chem*., **2005**, *in press.*

2.6.5. Oxaphosphabicyclooctene derivatives **27** and **28** proved to be suitable precursors in the photochemical and also in thermo-induced phosphorylation of alcohols. These bridged P-heterocycles (**27** and **28**) could also be used in the phosphorylation of the less reactive *tert*-buthylalcohol.



Phosphorylation reaction, carried out in the presence of a 1:2 mixture of methanol and *tert*-buthylalcohol gave the two phosphonates in nearly equal amount, which seems to support the concurrent involvement of the addition-elimination mechanism, beside the known elimination-addition reaction path. This elimination-addition mechanism – in case of the thermally induced fragmentation reaction of oxaphosphabicyclooctenes – was first observed by us.

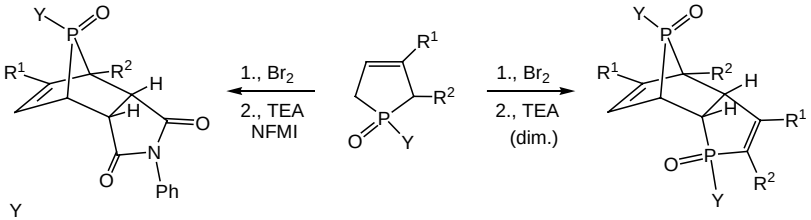


2. New scientific results

2.1. The synthesis of novel 7-phosphanorbornene derivatives

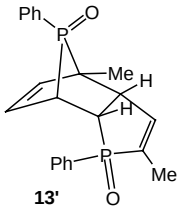
2.1.1. To study the effect of the P-substituent on the UV-light mediated fragmentation related phosphorylation of methanol using 7-phosphanorbornenes we synthesized four P-alkyl-phosphanorbornene derivatives (**5**, **6**, **11**, **12**) [2].

2.1.2. We also prepared 7-phosphanorbornene derivetives **7** and **13**, bearing the methyl group in the bridge-head position, to examine the effect of the position of the skeletal methyl group on its fragmentation and oxigen insertion reaction.[2].



R^1	R^2	Y			
Me	H	Et	**5**	**8**	**11**
Me	H	Cy	**6**	**9**	**12**
H	Me	Ph	**7**	**10**	**13**

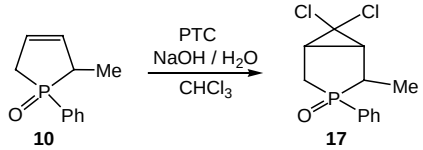
2.1.3. According to the literature, the dimerisation of phosphole oxides is regio- and stereoselective. In spite of this observation we have found that the dimerisation reaction of 2-methyl-1-phenyl-phosphole oxide afforded the product as a 4:1 mixture of two diastereomers, **13** and **13'**, respectively. [2].



13'

2.2. Experiments on the ring expansion of 1-phenyl-2-methyl-2,5-dihydro-1*H*-phosphole oxide

We wished to explore, how the 2-methyl-1-phenyl-dihydro-1*H*-phosphole oxide (**10**) can be utilised through ring expansion in the synthesis of novel dihydrophosphinine oxides [3].

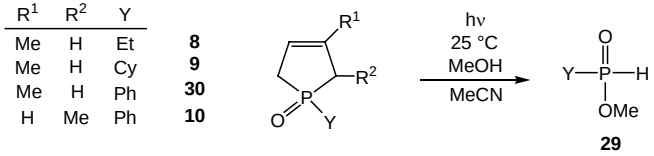


10 **17**

The dichlorocarbene addition on the double bond of dihydro-1*H*-phosphole oxide (**10**) took place only with low efficiency. The reactivity of the double bond towards dichlorocarbene could not be increased even by the exchange of the electron withdrawing P=O group to P-BH_3 function [3].

2.3. The synthesis of novel phosphabicyclo[2.2.2]octene derivatives

The double bond isomers (**A** and **B**) of dihydrophosphinine oxides **16** entered into a [4+2] cycloaddition to furnish novel phosphabicyclo[2.2.2]octene **18** [3,6].



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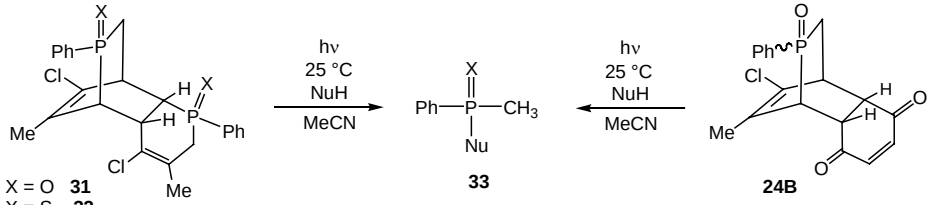
Our results suggested that the ring strain of the P-heterocycles **5-13,** and **30** has a determining role in the formation of the H-phosphinates (**29**).

2.6.3. To realise the selective synthesis of methylphosphonic acid derivatives, bearing three different substituents on the phosphorus atom, phosphabicyclo[2.2.2]octenes **31, 32** and **24B** were irradiated by a 254 nm UV-light in the presence of nucleophiles. The corresponding methylphosphonic acid derivatives (**33**, X = O) were prepared under mild conditions, in good yields [6].



X = O **31**
X = S **32**

NuH = MeOH, EtOH, *n*-PrOH, *i*-PrOH, *i*-$PrNH_2$

33

X = O, S

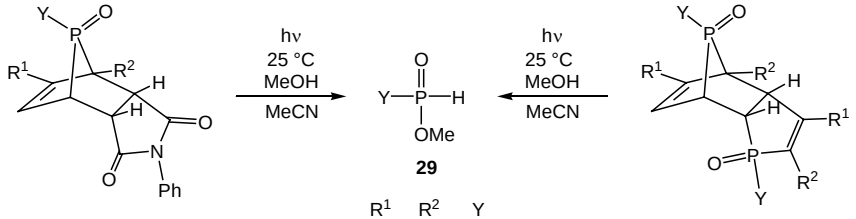
24B

NuH = MeOH, EtOH, *n*-PrOH

2.6.4. Any modification of the phosphabicyclooctene **31**, X = O (ring saturation, P=O→P=S exchange) resulted in the decrease of the reaction rate [6]. Our experimental results suggested that beside the previously proved elimination-addition mechanism, an other, additional-eliminational route might also be involved.

2.6. UV-light mediated phosphorylations using P-heterocycles

2.6.1. The UV-light mediated phosphorylation reaction of methanol using P-phenyl and P-alkyl (ethyl, cyclohexil) phosphanorbornene derivatives (**5-7**, **11-13**) resulted in the formation of the corresponding H-phosphinates (**29**).



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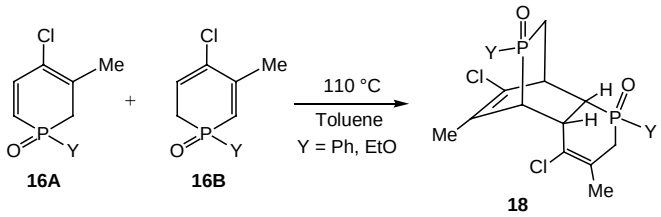
R^1	R^2	Y		
Me	H	Et	**5**	**11**
Me	H	Cy	**6**	**12**
H	Me	Ph	**7**	**13**

Saturation of the phosphanorbornene skeleton of cycloadduct **7** caused a decrease in the reaction rate.

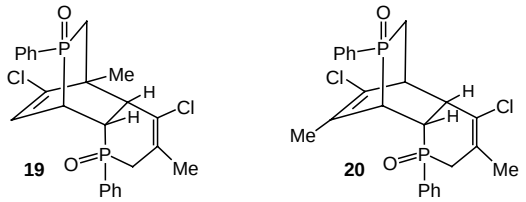
2.6.2. In certain cases phosphanorbornenes could be replaced by the more simple dihydrophosphole oxides (**8-10**, **30**) in the UV-light mediated phosphorylation of methanol, resulting the corresponding H-phosphinates (**29**). According to the UV spectra of the precursors the P-substituent plays a determining role in the efficiency of the phosphorylation of nucleophyles. Phosphorylation of methanol using 1-phenyl-dihydrophosphole oxide (**10, 30**) led to the corresponding H-phosphinate (**29**, Y = Ph). P-alkyl-H-phosphinates (**29**, Y = Et, Cy) could only be synthesized by the UV-irradiation of the appropriate phosphanorbornene derivatives.

The position of the skeletal methyl group does not have an influence on the fragmentation properties of the dihydro-1*H*-phosphole oxides.



16A **16B** **18**

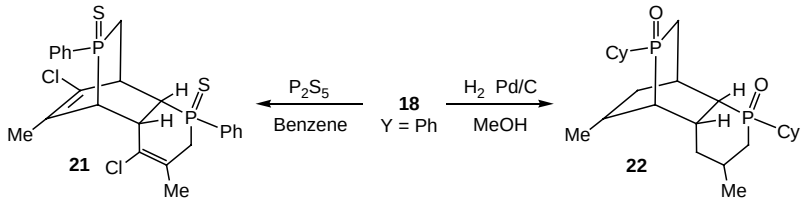
Careful refinement of the reaction mixture of the dimerisation of 1-phenyl-dihydrophosphinine oxide (**16**, Y = Ph) led to two minor components (**19**, **20**) that are new kinds of dimers of dihydrophosphinine oxide **16**, Y = Ph. [6].



19 **20**

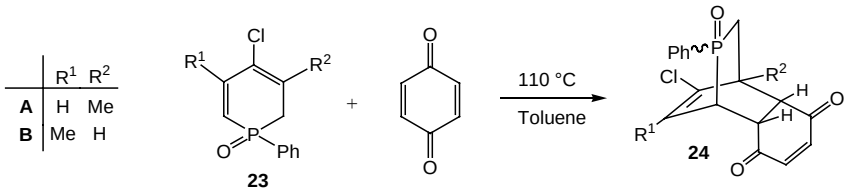
To evaluate the relative stability of the products, values of the heat of formation (ΔH_f^o) were calculated for the possible isomers.

2.3.2. To examine the structural effects on the fragmentation reaction of dimer **18**, Y = Ph, compounds **21** and **22** were also synthesized by exchanging the oxigen atom of the P=O group to sulfur or by catalytic hydrogenation of dimer **18**, Y = Ph [6].



21 **22**

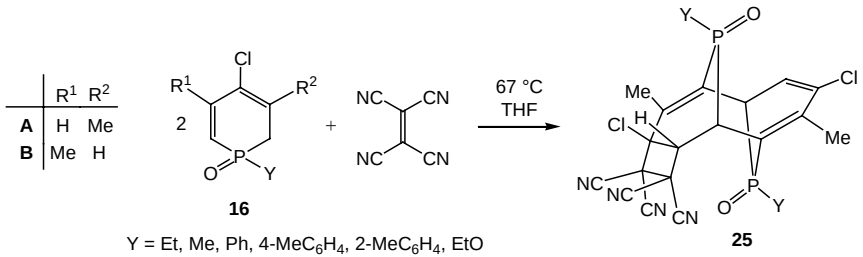
2.3.3. The [4+2] cycloaddition reaction of dihydrophosphinine oxide **16**, Y = Ph (**23**) and *p*-benzoquinone led to four isomers of the corresponding phosphabicyclooctene derivative **24** [6].



Compounds **18-22**, and **24** are the first members of a novel phosphabicyclooctene-family in which the dihydrophosphinine oxide (**16**) is condensed with an other six membred ring [5-7].

2.4. The unexpected reaction of dihydrophosphinine oxides in the presence of tetracianoethylene

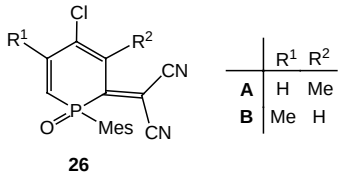
The reaction of dihydrophosphinine oxides (**16**) and tetracyanoethylene followed an unexpected route to afford diphosphatricyclododecatrienes **25**, instead of the corresponding Diels-Alder cycloadducts [8].



Y = Et, Me, Ph, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, EtO

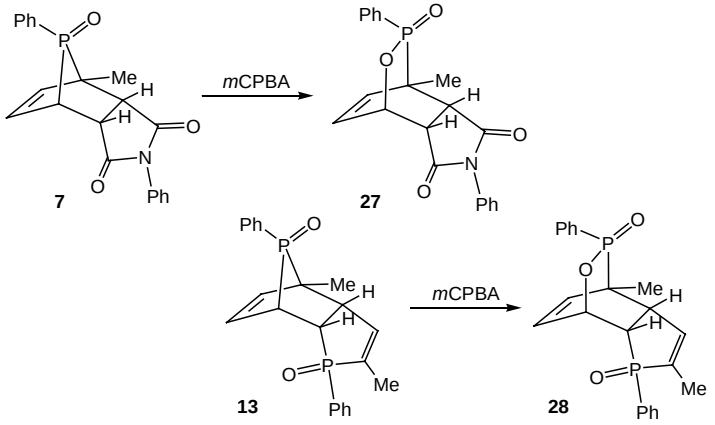
Structures of the products have been elucidated by a joint application of spectroscopy and quantum chemical calculations [8].

The reaction of 1-mesityle-dihydrophosphinine oxide **16** (Y=Mes) with tetracianoethylene led to α-dicianimethylene dihydrophosphinine oxide **26**. This observation could be the key to understand the mechanism of this reaction. [9].



2.5. The synthesis of novel 1,2-oxaphosphabicyclo[2.2.2]octene derivatives

The O-insertion reaction of 7-phosphanorbornenes **7** and **13** resulted in the formation of the corresponding 1,2-oxaphosphabicyclooctene derivatives **27** and **28**, respectively, as a single isomer. In both cases the O-insertion took place opposite the skeletal methyl group.



The mechanism of this reaction was also studied using quantum chemical calculations.