Budapesti Műszaki és Gazdaságtudományi Egyetem

Thesis of the PhD dissertation

REACTION OF HETEROCYCLIC TRIALKYLPHENYLPHOSPHINE OXIDES AND DIMETHYL ACETYLENEDICARBOXYLATE

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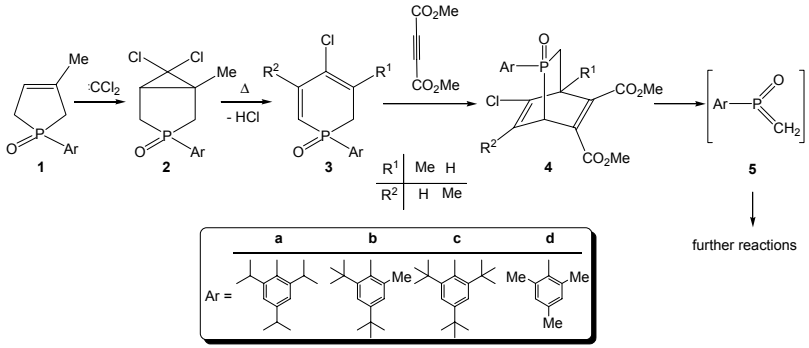
2003

1. Aims of the work

Heterocycles play an important role in the chemistry and they appear also in the nature. The big part of them has explicit physiological, pharmacology effects and a biochemical importance. 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 for example is growing up as well. The most important ones of these are probably the phosphorus heterocycles. Beside the theoretical importance they also have practical significance. In the preparative chemistry they are used as reactants, for example as *Wittig* reactant in the synthesis of olefines, as the *Lawesson* reactant for addition of sulfur, or as different phosphines as reducing agents. Among them, one can find potencialy biological active molecules used as drugs or insecticides. In the last few years, the *P*-heterocycles are more often used as precursors of phosphorylating reagents, as well as ligands in transition metal mediated catalysts.

I have been working in the Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology of the Budapest University of Technology and Economics (Head of the Research Group: ***Prof. L. Tőke***, Supervisor: ***Prof. Gy. Keglevich***), where I previously completed my thesis for the diploma of chemical engineering. In the laboratory phosphorus-heterocycles such 5-, 6- and 7-membered as well as briged P-heterocycles were discovered in the last two decades. The work till now has synthetic importance, but we plan further studies concerning the biological activity of this new molecules.

The 1,2-dihydophosphinine 1-oxides with phenyl-, alkyl- or alkoxy substituents on the phosphorus atom proved to be suitable starting materials for the synthesis of phosphabicyclo[2.2.2]octadienes, which are precursors of low-coordinated fragments, methylenephosphine oxides useful in the phosphorylation of nucleophiles. In our work we wished to synthetise 5- and 6-membered (**1-3**) as well as bridged (**4**) P-heterocycles with sterically demanding substituents (**a-d**) on the phosphorus atom. The phosphabicyclooctadienes of type **4** seemed to be promising compounds for the generation of sterically hindered and hence relatively stable methylenephosphine oxides (**5**).



2. New scientific results

2.1 The synthesis of dihydrophosphinine oxides with sterically demanding substituent on the phosphorus atom

Dichlorocyclopropanation of the dihydrophosphole oxides (**1a-d**) by $CHCl_3$–$NaOH/H_2O$ under phase transfer catalysis (PTC) gave adduct **2B** in a selectivity of 80%.

4. Articles

[1] Keglevich Gy., Keserű Gy. M., **Forintos H.**, Szöllősy Á., Ludányi K., Tőke L., *J. Chem. Soc., Perkin Trans. 1*., **1999**, 1801; *Magyar Kémiai Folyóirat*, 107, **2001**, 12, 544.

[2] Keglevich Gy., **Forintos H.**, Szöllősy Á., Tőke L., *Chem. Commun*., **1999**, 1423.

[3] Kollár L., Berente Z., **Forintos H.**, Keglevich Gy., *Tetrahedron Asym*., **2000**, 11, 4433.

[4] Keglevich Gy., **Forintos H.**, Keserű Gy. M., Hegedűs L., Tőke L., *Tetrahedron*, **2000**, 56, 4823.

[5] Keglevich Gy., **Forintos H.**, Sipos M., Dobó A., Ludányi K., Vékey K., Tungler A., Tőke L., *Heteroatom Chem.*, **2001**, 12, 6, 528.

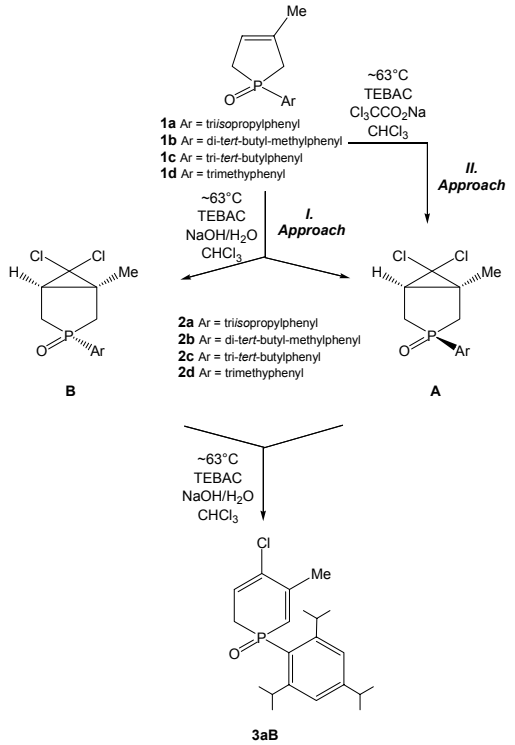
[6] Keglevich Gy., Körtvélyesi T., **Forintos H.**, Tamás A., Ludányi K., Izvekov V., Tőke L., *Tetrahedron Letters*, **2001**, 42, 4417.

[7] Keglevich Gy., **Forintos H.**, Körtvélyesi T., Tőke L., *J. Chem. Soc. Perkin Trans. 1*., **2002**, 26.

[8] Keglevich Gy., Körtvélyesi T., **Forintos H.**, Lovas S., *J. Chem. Soc. Perkin Trans. 2*., **2002**, 1645.

[9] Keglevich Gy., **Forintos H**., Szelke H., Tamás A., Vaskó Á. Gy., Kovács J., *Phosphorus, Sulfur and Silicon*, **2002**

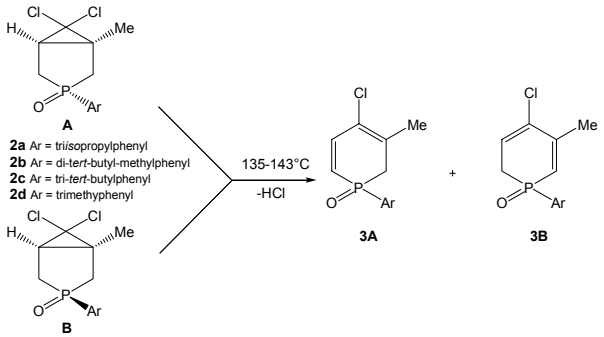
[10] Keglevich Gy., Körtvélyesi T., **Forintos H.**, Vaskó Á. Gy., Vladiszlav I., Tőke L., *Tetrahedron*, **2002**, 58, 3721.



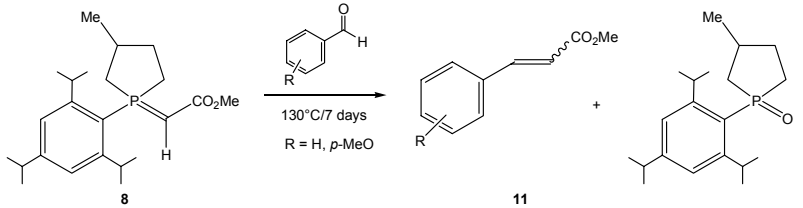
The isomeric composition of the phosphabicyclohexane (**2**) may be explained by the steric hindrance due to the space demanding *P*-aryl substituent: the diastereomer where the dichlorocyclopropane ring and the *P*-aryl group are in the *trans* disposition (**2B**) may be more easily formed than the other one with *cis* geometry (**2A**). Interestingly, the reaction of dihydrophosphole **1** with dichlorocarbene generated from sodium trichloroacetate under PTC conditions, gave isomer **2A** exclusively (**Approach II.**). We observed that during the dichlorocyclopropanation of dihydrophosphole **1a** according to the "**Approach I.**" a considerable proportion (*ca.* 48%) of dihydrophosphinine oxide **3aB** was also formed beside the phosphabicyclohexanes **(2aA** and **2aB**). Dihydrophosphinine **3aB**

was probably formed from the isomers of adduct **2a** by base-induced opening of the dichlorocyclopropane ring. This seems to be confirmed by the observation that the **3a**:**2a** proportion increased with the increase in the quantity of the sodium hydroxide used. In the course of the preparation of the phosphabicyclohexanes, we have never been able to observe the base-induced opening of the cyclopropane ring. It is also noteworthy that the dihydrophosphinine oxide (**3a**) was formed as a single isomer (**B**) in a selective manner; in earlier syntheses, the dihydrophosphinines were always formed as the mixture of two double-bond isomers.

The thermolysis of phosphabicyclohexanes (**2**) is a useful approach for the preparation of dihydrophosphinine oxides (**3**). Thermolysis of adduct **2aA** at 143°C resulted in the dihydrophosphinine oxide (**3a**) as a single isomer (**A**). No traces of the other isomer (**3aB**) could be detected. It was not then surprising that the thermolysis of isomer **2aB** also gave dihydrophosphinine **3aA** selectively. The 1,2-dihydrophosphinine oxides (**3b-d**) so formed were obtained as a mixture of two double-bond isomers. Surprisingly, the *tert*-butyl group in the para position of the aryl ring was also split during the termolysis of tri-*tert*-butyl derivative (**2c**).



Phosphorane/ylide **8** underwent, however, the Wittig reactions with benzaldehyde (or with anisaldehyde) to furnish a mixture of isomers of the corresponding cinnamic acid ester **11** and phosphine oxide.

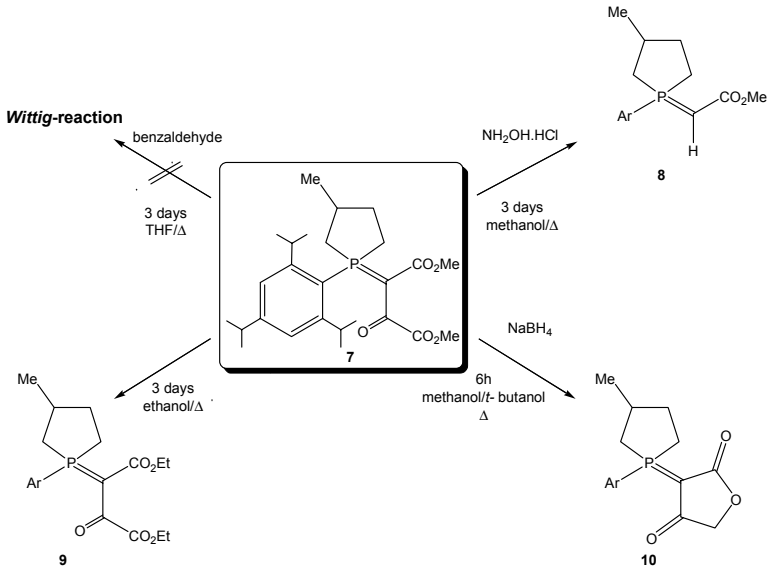


3. Conclusion

To summarise our results, by a novel reaction we synthetised several heterocyclic phosphonium ylides, and we examined the reactivity of this molecules. Stability and geometry of the products and intermediates were evaluated by quantum chemical calculations, and finally we examined the mechanism of the reaction.

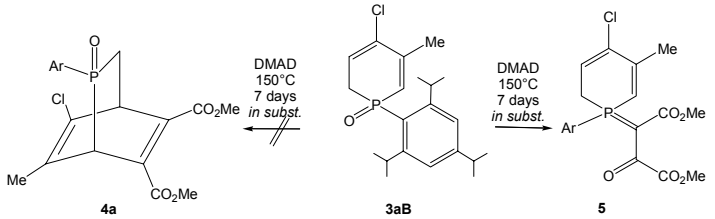
2.5 Reactivity of phosphonium ylides

The strong delocalisation has an effect on the reactivity of the stabilised phosphonium ylides **7** in Witttig reaction, **7** would not enter into reaction with benzaldehyde. Aiming at the synthesis of the corresponding oxime, **7** was reacted with hydroxylamine hydrochloride. The result of the reaction was, however, an other phosphorane/ylide (**8**). The reaction may have been the consequence of the attack of hydroxylamine on the β-keto group, or took place on the effect of hydrochloric acid.



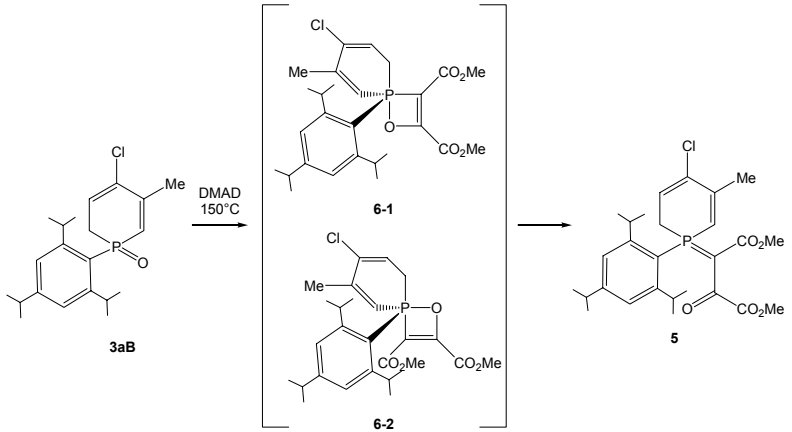
2.2 The reactivity of dihydrophophinine oxides

Searching for new synthetic methods in *P*-heterocyclic chemistry, we found that the reaction of tri*iso*propylphenyl-dihydrophophinine oxide (**3aB**) and DMAD at 150°C (in a bomb) did not lead to cycloadduct (**4a**), instead product **5** isomeric with **4a** could be isolated. The δ_P value of 24 obtained for product **5** supported the phosphonium salt character. Cycloadduct **4a** could not be detected, not even in traces.



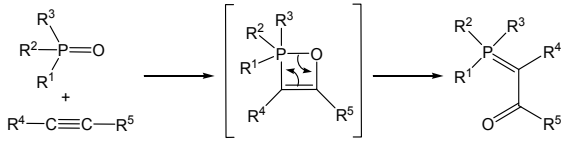
2.3 Explanation of the formation of the phosphonium ylide

We suppose that in the first step, a [2+2] cycloaddition reaction of the P=O group of tri*iso*porpylphenyl-dihydrophophinine oxide **3aB** and the acetylene moiety (-C≡C-) of DMAD affords an oxaphosphetene (**6**). First we thought that this spirocyclic compound (**6**) was our product, later on it turned out to be only an intermediate.



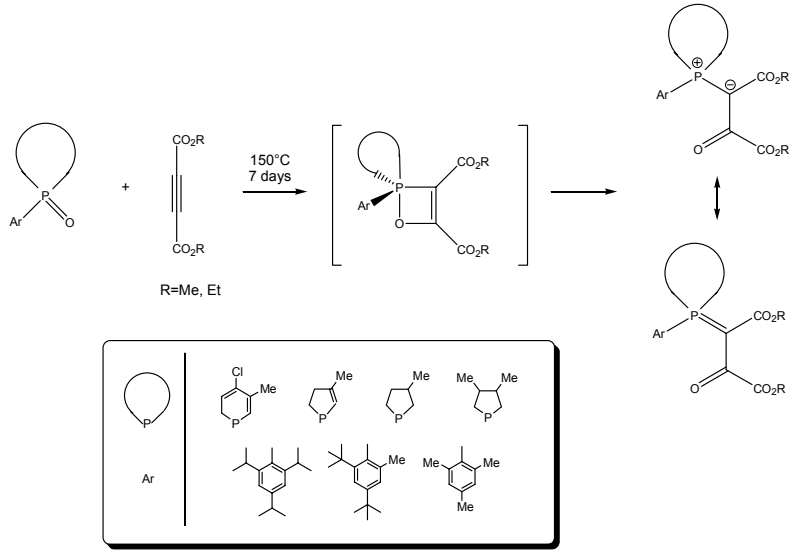
The oxaphosphete ring in **6** is highly strained and the trigonal bipyramidal geometry around the central phosphorus atom is considerably distorted due to the rigid spirocyclic system and due to the bulky *P*-substituent. *Ab initio* calculations showed that the spirocyclic intermediate with an equatorial oxygen atom (**6-2**) is more stable than that with an apical oxygen atom (**6-1**). The highly strained oxaphosphete (**6**) led to the more stable ring-opened product (**5**). For the **6** → **5** transformation, the enthalpy of activation was only 0.88 kJ/mol, while the entalphy gain was 28.0 kJ/mol indicating the intermediacy of **6**.

The ring-opening of the oxaphosphete can be regarded to be an intramolecular inverse Wittig reaction, as it formally involves the rupture of the P-O bond and the formation of a P=C and a C=O double bond. This kind of reaction has never been observed before.



2.4 Extension of the reaction

It was examined if other P-heterocycles with trialkylphenyl substituents on the phosphorus atom can also be involved in the above type of [2+2] cycloaddition.



The [2+2] cycloaddition reaction is of general value and was extended to 5- and 6-membered cyclic phosphine oxides (dihydrophosphol oxides and their saturated derivatives, or dihydrophosphinine oxides) with different trialkyl-phenyl substituents (2,4,6-tri*iso*propylphenyl, 2,4-di-*tert*-butyltolil or 2,4,6-trimetilphenyl) on the phosphorus atom. The only criterion of the novel reaction is that the phosphorus atom should bear an electron-donating trialkylphenyl substituent. In some cases we used diethyl acetylenedicarboxylate as a reactant.