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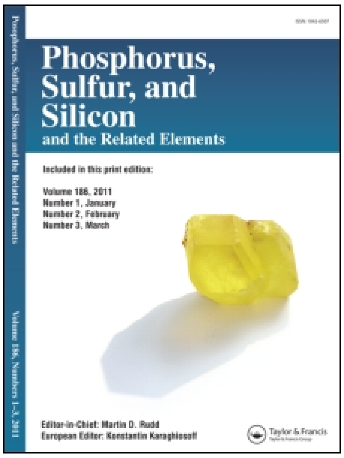

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SYNTHESIS OF FUNCTIONALIZED HETEROCYCLES BEARING PHOSPHONATE MOIETY VIA PHOSPHORYLNITRILE OXIDES. STEREOCHEMISTRY AND UNUSUAL CYCLOADDITIONS.

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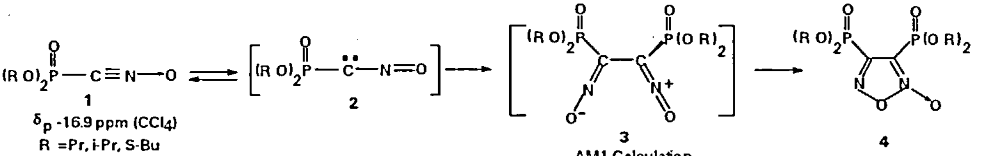
Abstract. C-(Dialkoxyphosphoryl)nitrile oxides, due to their availability and high reactivity, make it possible to conduct reactions of indirect phosphorylation of heterocyclic systems and to use them as a convenient "instrument" in studying the stereochemistry of cycloaddition and chemical transformations of labile compounds.

The interest to 1,3-dipolar cycloaddition reactions going with participation of oxides of nitrile is explained by the fact, that the application of "nitrile oxide strategy" of synthesis with the involvement of a wide range of dipolarophiles into cycloaddition reactions is often the only possible way to obtain various heterocyclic systems containing different functional groups, including phosphorus-containing moiety.

The information on nitrile oxides containing phosphoryl unit came to view recently [1]. We for the first time obtained (dialkoxyphosphoryl)nitrile oxides **1** by treatment of (dialkoxyphosphoryl)formylhalogenide oximes with bases [2]. The obtained dipole **1** quickly produces dimers and polymers at ambient temperature. Lowering of temperature below 0 °C slows the process down and makes it possible to obtain and keep for quite a long time a pure solution of **1**. Maintenance of a low concentration of **1** in the solution at room temperature promotes the formation of bis(dialkoxyphosphoryl)furoxan **4** despite quite a strong steric hindrance of nitrile oxide **1**[3]. AM1 Calculations testify that dimerisation is a stepwise process[4]. At the first stage, interaction of two molecules of nitrile oxide in nitroso-carbenic form **2** takes place. Transition state at the first stage of dimerisation is *gosh*-conformation of dimeric structure **3** forming *cis*-isomer of dinitrosoethylene.



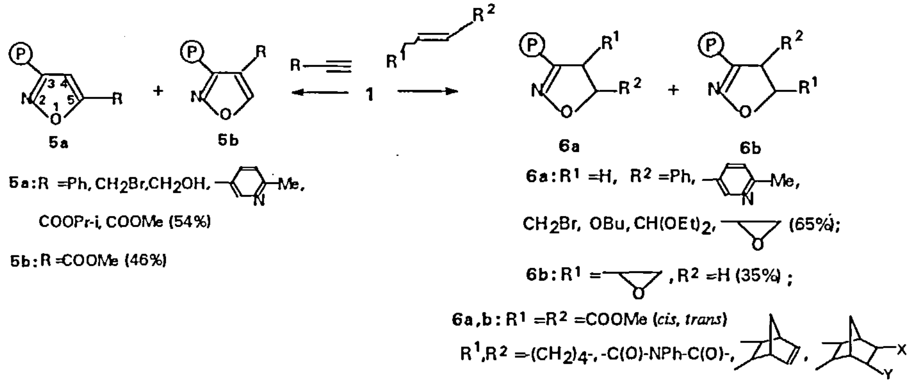
δ_P -16.9 ppm (CCl$_4$)
R =Pr, i-Pr, S-Bu

AM1 Calculation

Angles	NCC	PCC	PCCP	NCCN	NCCP
Degrees	114.2	105.1	95.3	88.7	-89.7

δ_P -3.32, -4.69 ppm
$^3J_{PP}$ 3.1 Hz (CDCl$_3$)

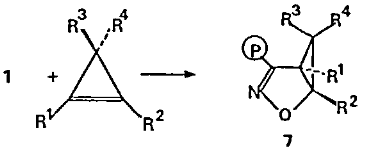
The presence of phosphoryl substituent in nitrile oxides **1** makes these synthons to the indispensable agents of indirect phosphorylation and allows to plan the synthesis of heterocycles bearing phosphonate moiety. Phosphorylnitrile oxides **1** easily enter the cycloaddition reactions with unsaturated compounds. 3-C-Phosphoryl-5-R-isoxazoles **5a** have been obtained with alkynes[3]. Interaction with terminal olefins leads to the corresponding 3-dialkoxyphosphoryl-5-R-isoxazolines **6a**[3]. Cycloaddition goes in regiocontrolled manuer. Here, the main role is played by steric factor, caused by capacious dialkoxyphosphoryl group of nitrile oxide. Regiospecificity of the process is broken only in the case of small-volume electron-acceptor substituents in dipolarophile. Then electronic factors compete with steric factors leading to two regioisomers.



Cycloaddition (at -60 °C) of dimethylfumarate gives a pure *trans*-diastereomeric product, but dimethylmaleate adds not stereospecifically leading to the mixture of *cis*-(27%) and *trans*-(73%) stereoisomeric isoxazolines[3]. Non-stereospecific occurence of the reaction with dimethylmaleate is probably explained by the balance between cycloadducts caused by tautomeric transition. Here, the decrease of the energetic barrier is supported by the presence of a phosphoryl group that easies formal migration of proton and promotes the formation of *trans*-diastereomeric cycloadduct. The cyclic alkenes have been also involved into cycloaddition with 1[3]. Interaction with norbornene dipolarophiles yields with high stereoselectivity cycloadducts with *exo*-orientated isoxazoline cycle.

Thus, dialkoxyphosphorylnitrile oxides, being element substituted nitrile oxides, are comparable with alkyl - and arylnitrile oxides by the type of chemical behaviour. Evaluation of the reactivity of phosphorylnitrile oxides in approximation of MO perturbation theory with taking into account the contributions of orbital interactions into the energy of stabilization of *dipole-dipolarophile* reaction pairs have showed that (dialkoxyphosphoryl)nitrile oxides, despite the lowering energy of HOMO as compared with benzonitrile oxide by approximately 1.7 eV, should be classified with electron-donating agents in which interactions with participation of LUMO can influence regioselectivity of cycloaddition. In doing so, phosphorylnitrile oxides are close to trifluoroacetonitrile oxide as for the type of orbital interactions[5].The electron-donating property of dialkoxyphosphorylnitrile oxides is the consequence of the inertness of phosphoryl moiety rather, than its influence. This follows from the fact that the separation of phosphoryl group and nitrile oxide fragment by methylene link in dialkoxyphosphorylacetonitrile oxide has a little influence on changing the character of FMO's and chemical properties of nitrile oxides.

The reactions with participation of strained cycloalkenes such as cyclopropenes go ambiguously. The cycloaddition of 1 to some substituted cyclopropenes occurs as a typical dipolar addition to the π-bond of alkene, to give bicyclic adducts 7 with three-carbon ring being unchanged[6]. The stereochemistry of addition is controlled by a competitive influence of steric and electronic effects (ratio of stereo- and regio-isomers).



$R^1 = R^2 = H$: $R^3 = Me$, $R^4 = Ph$ (80 %)
$R^3 = Ph$, $R4 = Me$ (20 %)
$R^3 = Me$, $R^4 = CN$ (100 %)
$R^3 = R^4 = Me, R^1 = H$: $R^2 = H, Me, SiMe_3$, COOMe (81%), COOEt (86%)
$R^3 = R^4 = Me, R^1 = COOMe$: $R^2 = H$ (19 %), Me (100%)
$R^3 = R^4 = Me, R^1 = COOEt$: $R^2 = H$ (14 %), Me (100%)
$R^3 = R^4 = Me$: $R^1 = Me$, $R^2 = SiMe_3$ (82%); $R^1 = SiMe_3$, $R^2 = Me$ (18%)

The reaction of 1,2-dichloro-3,3-dimethylcyclopropene 8a with 1 leads to 3-phosphoryl-1,2-oxazines 13[7]. This reaction is quite different from the above addition to simple cyclopropenes. It is known that some cyclopropenes (such as 8a) ring-open at ambient temperature to produce vinylcarbenes 11 or undergo rearrangement into alkynes[8]. In the given example the reaction went at T °C -60 in the presence of methyl lithium and lithium salts. This was the catalysing factor promoting cyclopropene ring-opening at such a low temperature.

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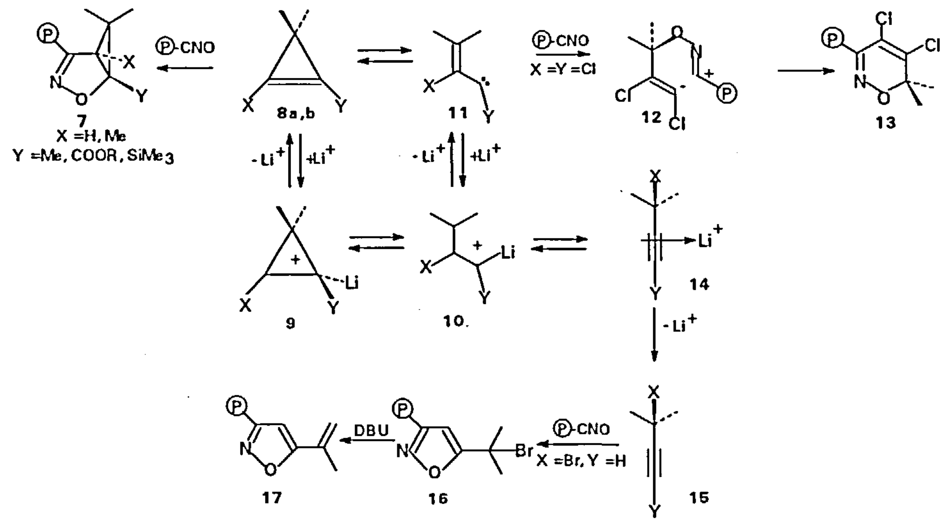
Destruction of lithium-vinylcarbene complexes 10 during the reaction causes reverse cyclisation of vinylcarbenes 11 to mother cyclopropenes 8 which interacting with 1 give cycloadducts 7.

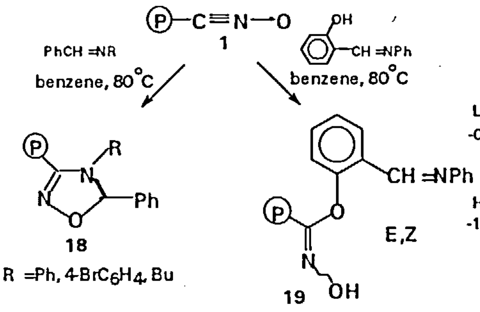
The formation of 1,2-oxazine could formally occur by 3-centre plus 3-centre cycloaddition of the intermediate singlet vinylcarbene 11 to the nitrile oxide 1. Although it is not clear as yet whether this process occurs in a stepwise or concerted manner.

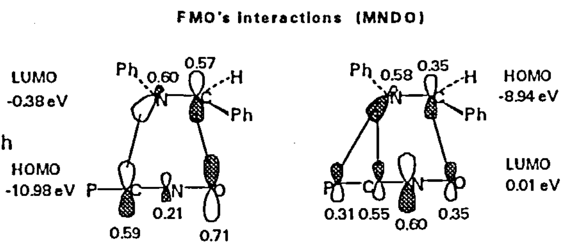


Under the same conditions catalytic isomerisation of 1-bromo-3,3-dimethylcyclopropene 8b does not stop at the corresponding lithium-vinylcarbene complex 10, but yields thermodynamically beneficial bromobutyne 15 which interacts with nitrile oxide 1 to produce isoxazole 16.

Thus phosphorylnitrile oxide 1 possessing the property to easily enter cycloaddition reactions with dipolarophiles has been used as a convenient and universal trap for both cyclopropenes and intermediates and products of their isomerisation.

Reactions of dipolar cycloaddition of phosphorylnitrile oxides were extended on dipolarophiles with carbon-heteroatom multiple bonds. 1,2,4-Oxadiazolines 18 have been synthesized with Schiff bases[9]. The reaction occurs in a highly regiocontrolled manner. This is explained by dissimilarity of the constitution of LUMO of dipole and HOMO of dipolarophile at reaction centres. Nucleophilic activity of oxygen in hydroxyl in 2-hydroxybenzylidene-aniline is higher than dipolarophilic activity of azomethin-bond. The result is 1,3-nucleophilic addition with formation 19.





Bond $C\equiv N$ is a much poorer dipolarophile than C=C and C=N. The attempt to conduct the cycloaddition with excess of acetonitrile with reflux did not give positive result. However, the crystalline bisadduct 20 containing two oxadiazole rings was isolated in the reaction

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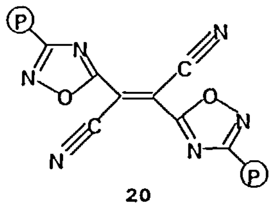
with tetracyanethylene. Here, C=C bond did not react because of the secondary orbital interactions occurring at initial orientation of the addends.



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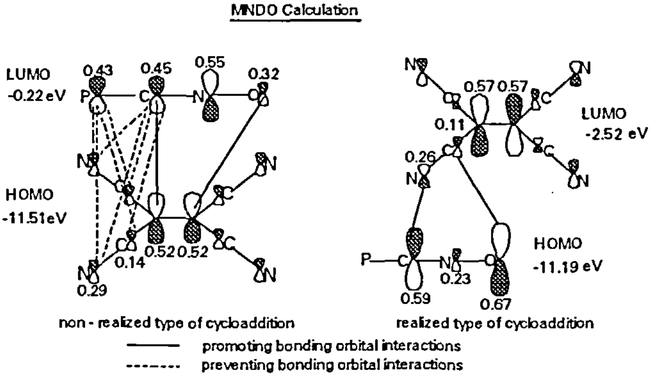
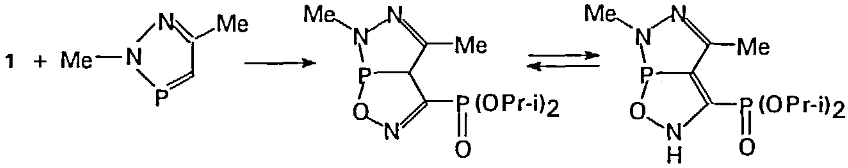


Unlike arylnitrile oxides[10], diisopropoxyphosphorylnitrile oxide adds to the P=C bond of 1,2,3-diazaphosphole with the phosphorus becoming bonded to the oxygen and not to the nitrile carbone. It happens probably because a new σ -bond of P with O is more energetically beneficial. Besides, stereochemistry of cycloaddition can be determined by stereoelectronic control of the reaction. The forming bicyclic adduct 21 exists probably in tautomeric form 22 (NMR).



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