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# A mechanistic insight into the chemoselectivity of the reaction between 3-phenyl-2-propynenitrile, secondary phosphine oxides and pyridinoids

**Pavel A. Volkov,[a] Nina K. Gusarova,[a] Kseniya O. Khrapova,[a] Anton A. Telezhkin,[a] Alexander I. Albanov,[a] Sergey F. Vasilevskiy[b] and Boris A. Trofimov*[a]**

[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 41 9346; e-mail: boris_trofimov@irioch.irk.ru*

[b] *V. V. Voevodsky Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation*

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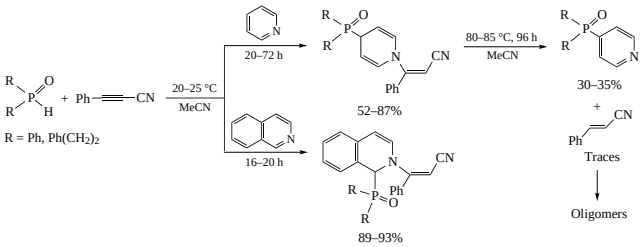
**Reactions between 3-phenyl-2-propynenitrile, secondary phosphine oxides and pyridinoids have been implemented and studied. Pyridine and isoquinoline react with propynenitrile and phosphine oxides at room temperature according to the *N*-vinylation/*C*-phosphorylation scheme to afford (*Z*)-*N*-(2-cyano-1-phenyl)ethenylphosphoryl-1,4-dihydropyridines or -1,2-dihydroisoquinolines. In the case of pyridine on heating (80–85 °C), the reaction gives 4-phosphorylpyridines ($S_N^H$Ar reaction) and 3-phenylacrylonitrile oligomers.**

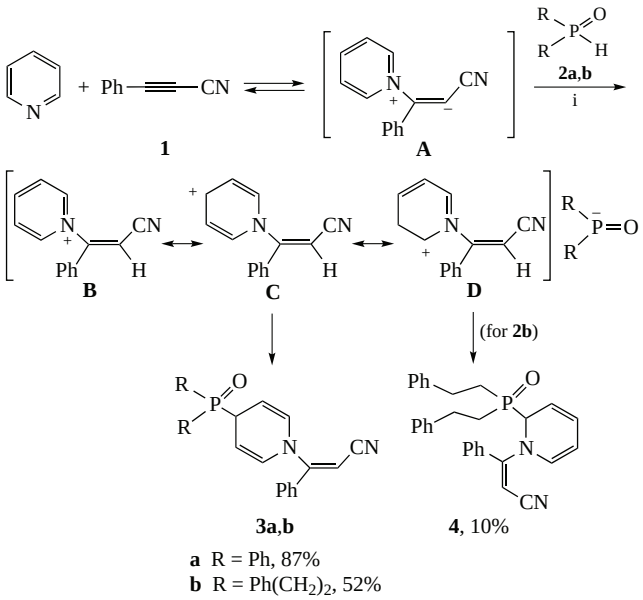



*Keywords*: 3-phenyl-2-propynenitrile, secondary phosphine oxides, pyridinoids, isoquinoline, $S_N^H$Ar reaction, *N*-vinylation/*C*-phosphorylation.

A typical internal electron-deficient acetylene, 3-phenyl-2-propynenitrile **1**, is known to react with bis(2-phenylethyl)-phosphine oxide in the presence of bases (alkali metal hydroxides) forming α,β-diadduct, 2,3-bis[bis(2-phenylethyl)phosphoryl]-3-phenylpropanenitrile.[1] A new type of nucleophilic substitution of hydrogen ($S_N^H$Ar reaction) in pyridines under the action of secondary phosphine oxides in the presence of an internal acetylene, benzoylphenylacetylene, (no catalyst, 70–75 °C, MeCN) to furnish 4-chalcogenophosphorylpyridines and phenyl vinyl ketone (*E*-chalcone) was also reported.[2] At the same time, under similar conditions isoquinoline reacted with benzoylphenylacetylene and bis(2-phenylethyl)phosphine oxide according to the *N*-vinylation/*C*-phosphorylation scheme to afford functionalized 1,2-dihydroisoquinoline, 3-[1-[bis(2-phenylethyl)-phosphoryl]isoquinolin-2(1*H*)-yl]-1,3-diphenylprop-2-en-1-one.[3]

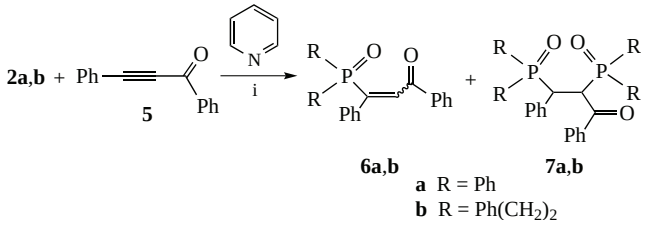
Here, in order to gain the clearer insight into chemoselectivity and nature of the interaction between internal electron-deficient acetylenes, secondary phosphine chalcogenides, and pyridinoids, we have studied the reaction of 3-phenyl-2-propynenitrile with phosphine oxides and pyridine or isoquinoline.

The experiments have shown that 3-phenyl-2-propynenitrile **1**, phosphine oxides **2a**,**b** and pyridine enter into a three-component interaction at room temperature (20–72 h, MeCN) to stereoselectively deliver (*Z*)-*N*-(2-cyano-1-phenyl)ethenyl-4-phosphoryl-1,4-dihydropyridines **3a**,**b** in 87 and 52% yields, respectively (Scheme 1). In the case of phosphine oxide **2b**, minor amounts of the corresponding 1,2-dihydropyridine **4** are also formed.† The (*Z*)-configuration of the ethenyl substituents of phosphoryldihydropyridines **3a**,**b** and **4** is predetermined by




**Scheme 1** *Reagents and conditions*: i, MeCN, 20–25 °C, 20 h (for **2a**) or 72 h (for **2b**).

† *Reaction of secondary phosphine oxides* **2a**,**b** *with pyridine and 3-phenyl-2-propynenitrile* **1**. To a solution of secondary phosphine oxide **2a**,**b** (1.0 mmol) in MeCN (3 ml), pyridine (79 mg, 1.0 mmol) and 3-phenyl-2-propynenitrile **1** (127 mg, 1.0 mmol) were added, and the mixture was stirred under argon at 20–25 °C for 20 h (in the case of **2a**) or 72 h (in the case of **2b**). After the reaction completion ($^{31}$P NMR monitoring), the solvent was removed under reduced pressure. In the case of diphenylphosphine oxide **2a**, the residue was reprecipitated from $CHCl_3$ into hexane to give 1,4-dihydropyridine **3a**. For bis(2-phenylethyl)-phosphine oxide **2b**, the residue was purified by column chromatography on $SiO_2$ (ethyl acetate was used as an eluent) to give the corresponding phosphorylated 1,2- and 1,4-dihydropyridines **4** and **3b**.




**Scheme 2** *Reagents and conditions*: i, MeCN, 20–25 °C, 48 h.

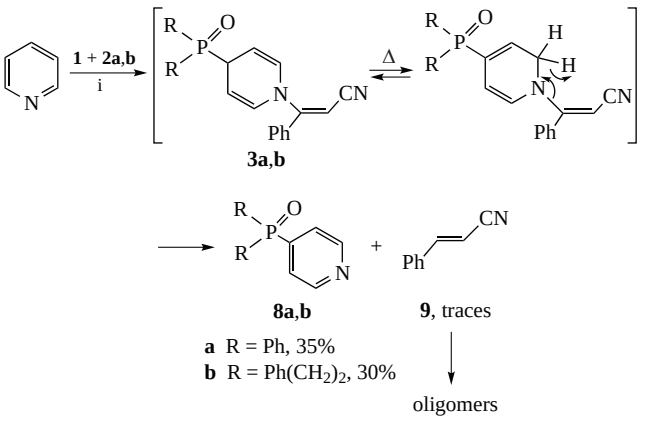
the known *trans*-mode of concerted nucleophilic addition to substituted acetylenes.[4] 1,2-Dihydropyridine **4** was found to be stable and it did not undergo the expected[5] 2 → 4-migration of the phosphoryl group even upon heating (70–75 °C, 3 h).

This three-component reaction probably proceeds according to Scheme 1 involving the sequential formation of the intermediate zwitterions **A**, cations **B**–**D** and phosphorus-centered anions.[2,6] The latter would attack the more accessible pyridinium 4-position of intermediate **C**. However, in the case of less sterically hindered[7] phosphine oxide **2b** both 4 (mesomer **C**) and 2 (mesomer **D**) pyridinium positions are attacked. As a result, final products **3a**,**b** and **4** are formed (see Scheme 1).

For the comparison, we have shown that the reaction of benzoylphenylacetylene **5** with secondary phosphine oxides **2a**,**b** and pyridine does not practically take place at room temperature as the *N*-vinylation/*C*-phosphorylation process (Scheme 2). Under these conditions, adducts **6a**,**b** and **7a**,**b** lacking pyridine moiety were formed (~64–67% according to $^{31}$P NMR) as a result of base-catalyzed (pyridine) nucleophilic addition of phosphine oxides **2a**,**b** to the triple bond of acetylene **5**, similarly to that we observed previously.[8]

Carrying out the reaction between propynenitrile **1**, phosphine oxides **2a**,**b** and pyridine on prolonged heating (80–85 °C, 96 h) does not give adducts **3** and **4** (Scheme 3). In this case, a nucleophilic substitution of hydrogen in pyridine occurs to furnish 4-phosphorylpyridines **8a**,**b** in 30–35% yields. This reaction is accompanied by the release of 3-phenylacrylonitrile **9** oligomers.‡ This $S_N^H$Ar cross-coupling process proceeds as oxidative elimination of 3-phenylacrylonitrile **9** from *N*-ethenyl-4-phosphoryldihydropyridines **3a**,**b**.[2]

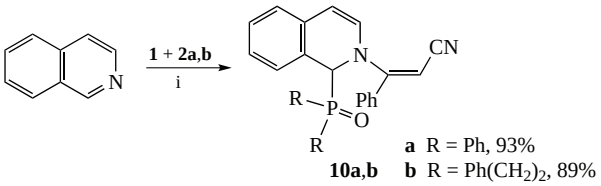
Noteworthy that possible adducts of secondary phosphine oxides **2** to acetylene **1** are not formed in the studied reactions




**Scheme 3** *Reagents and conditions*: i, MeCN, 80–85 °C, 96 h.

(see Schemes 1 and 3) that implies domination of zwitterions **A** generation over the nucleophilic addition of PH-compound **2a**,**b** to the triple bond of acetylene **1**.

Isoquinoline has also been introduced into the reaction with propynenitrile **1** and phosphine oxides **2a**,**b**, which proceeded at room temperature (16–20 h, MeCN) according to the *N*-vinylation/*C*[1]-phosphorylation combined process to stereoselectively give (*Z*)-*N*-(2-cyano-1-phenyl)ethenyl-1-phosphoryl-1,2-dihydroisoquinolines **10a**,**b** in 89–93% yields (Scheme 4).§




**Scheme 4** *Reagents and conditions*: i, MeCN, 20–25 °C, 16 h (for **2a**) or 20 h (for **2b**).

In summary, the preliminary results on the interaction of 3-phenyl-2-propynenitrile with secondary phosphine oxides and pyridinoids have been obtained. The reaction proceeds, depending on the substrate structure or temperature, either *via* three-component *N*-vinylation/*C*-phosphorylation to form functionalized 1,4-dihydropyridines **3** or 1,2-dihydroisoquinolines **10**, or as nucleophilic substitution of hydrogen in the pyridine ring ($S_N^H$Ar reaction) by the phosphoryl group to afford 4-phosphorylpyridines **8**. As a result, a simple route to new pharmaceutically relevant functionalized dihydropyridinoids with phenylacrylonitrile and phosphoryl groups is sketched. Dihydropyridine, dihydroquinoline and dihydroisoquinoline motifs are key fragments of antihypertensive and antibacterial drugs such as amlodipine,[9] felodipine,[10] nifedipine,[11] ciprofloxacin,[12] levofloxacin,[13] moxifloxacin[14] and gemifloxacin.[15] Additionally, some dihydropyridinoid derivatives exhibit antitumor,[16] anticonvulsant,[17] anticoagulant[18] and antitubercular[19] activities. In turn, on the basis of 3-phenylacrylonitrile (cinnamonitrile, a natural compound) derivatives drugs (rilpivirine, fosdevirine, entacapone) and medicines for the treatment of HIV-1 and Parkinson's disease have been created.[20] A combination of these two pharmacophore fragments (pyridinoids and acrylonitrile) in one molecule can give a significant synergistic effect.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.026.

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‡ *Synthesis of 4-phosphorylpyridines* **8a**,**b**. A solution of pyridine (79 mg, 1.0 mmol), secondary phosphine oxide **2a**,**b** (1.0 mmol) and 3-phenyl-2-propynenitrile **1** (127 mg, 1.0 mmol) in MeCN (3 ml) was stirred under argon at 80–85 °C for 96 h. After the reaction completion ($^{31}$P NMR monitoring), the solvent was removed under the reduced pressure. The obtained residue was purified by column chromatography on $SiO_2$ (ethyl acetate as an eluent) to yield 4-phosphorylpyridines **8a**,**b**.

§ *Reaction of secondary phosphine oxides* **2a**,**b** *with isoquinoline and 3-phenyl-2-propynenitrile* **1**. To a solution of secondary phosphine oxide **2a**,**b** (1.0 mmol) in MeCN (3 ml), isoquinoline (129 mg, 1.0 mmol) and 3-phenyl-2-propynenitrile **1** (127 mg, 1.0 mmol) were added, and the mixture was stirred under argon atmosphere at 20–25 °C for 16–20 h. After the reaction completion ($^{31}$P NMR monitoring), the solvent was removed under reduced pressure, and the residue was reprecipitated from $CHCl_3$ into hexane to give 1,2-dihydroisoquinolines **10a**,**b**.

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