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ARTICLE

Metal-free site selective cross-coupling of pyridines with secondary phosphine chalcogenides using acylacetylenes as oxidants

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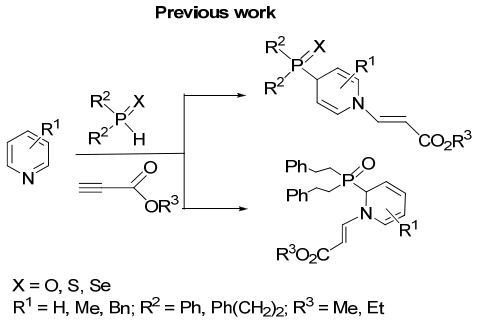
Pyridines undergo site selective cross-coupling with secondary phosphine chalcogenides (oxides, sulfides, and selenides) in the presence of acylphenylacetylenes under metal-free mild conditions (70–75 °C, MeCN) to afford 4-chalcogenophosphoryl pyridines in up to 71% yield. In this S_NHAr new type reaction acylacetylenes act as oxidants, being stereoselectively reduced to the corresponding olefins of *E*-configuration.

Chalcogenophosphoryl pyridines and their precursors, phosphinopyridines, represent in-demand ligands forming a number of biologically active complexes with a variety of metals.[1,2]

However, assortment of available pyridines bearing phosphoryl or phosphine moieties is limited mainly to diphenylphosphinopyridines.[1-3] This is mostly due to certain difficulties with syntheses of other chalcogenophosphoryl and phosphinopyridines requiring hazardous and hardly accessible (in case of other than phenyl substituents) secondary phosphine halides, which are then involved into the BuLi-assisted reactions with bromopyridines.[3] For this purpose, the cross-coupling of halopyridines with secondary phosphine chalcogenides in the presence of Ni and Pd complex was also employed.[4] To follow the trend in organic chemistry with emphasis on safe ecology and pot, atom, and step economy (PASE paradigm[5]), it would be desirable to develop a synthesis of chalcogenophosphoryl pyridines, which does not require transition metals and halopyridines and having a larger substrate scope.

In this communication, we report on the oxidative cross-coupling reaction between pyridines **1a**,**b** and secondary phosphine chalcogenides **2a-j** in the presence of acylphenylacetylenes **3a-d** as the oxidants, MeCN being used as a solvent. We have encountered with this S_NHAr reaction of new type during our on-going investigation of reductive vinylation/phosphorylation of pyridines by alkyl propiolate/secondary phosphine chalcogenide pairs to yield 1-alkoxycarbonylethenyl dihydropyridines (Scheme 1).[6]



Scheme 1 Vinylation/phosphorylation of pyridines by alkyl propiolate/secondary phosphine chalcogenide pairs.

When we replaced alkyl propiolates by acylphenylacetylenes, this reaction took absolutely unexpected direction: instead of the above reductive vinylation/phosphorylation of the pyridine nucleus (Scheme 1), the oxidative cross-coupling between pyridine and secondary phosphine chalcogenides along with reduction of acetylene to the corresponding *E*-ethene was observed (Table 1). This reaction can be referred to oxidative metal-free nucleophilic substitution of hydrogen in (hetero)arenes S_NHAr, which now draws a growing attention.[7]

Table 1 illustrates influence of the acetylene structures on the reaction time and yields of the cross-coupling products. The reaction was monitored by ^{31}P NMR to follow disappearance of signals in the region 17.2 ppm belonging to the starting phosphine oxides and appearance of signals of the target products in the region 27.6 ppm. As seen from Table 1, acetylenes **3c,d** with phenyl and furyl substituents (Ph, 2-Fu) at the carbonyl group appear to be better oxidizers than those with the alkyl groups **3a,b** (entries 3, 4 cf 1, 2), evidently owing to a lower electrophilicity of the triple bond in the latter. The synthesis was carried out up to the complete conversion of phosphine oxide.

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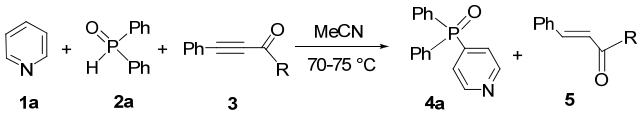
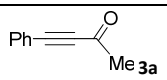
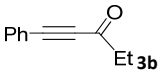
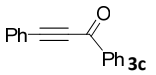
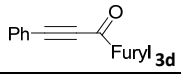
Table 1 Cross-coupling of pyridine **1a** with diphenylphosphine oxide **2a** in the presence of acylacetylenes **3**[a]



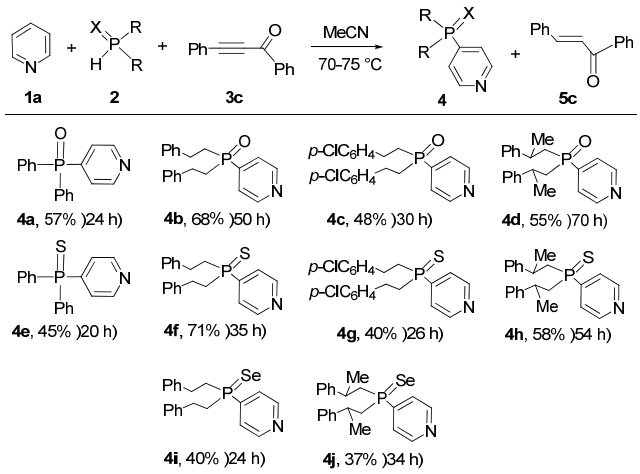
1a 2a 3 4a 5

Entry	Acylacetylene **3a-d**	Time (h)	Isolated yield **4a** (%)
1	 **3a**	28	50
2	 **3b**	35	36
3	 **3c**	24	57
4	 **3d**	26	53

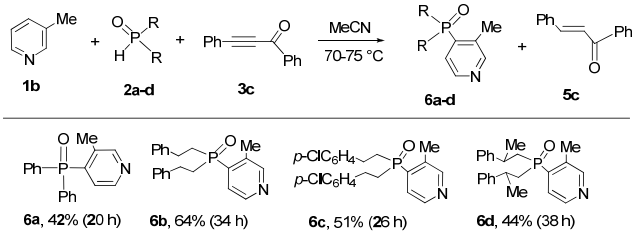
[a]Conditions: **1a** (1.1 mmol), **2a** (1 mmol), **3a-d** (1.1 mmol), MeCN (3 ml), 70–75 °C.

Further, we have studied the scope of phosphine chalcogenides suitable for this synthesis (Scheme 2). As follows from Scheme 2, the reaction tolerates a quite representative number of structurally diverse secondary phosphine chalcogenides (oxides, sulfides and selenides) having both aromatic and alkylaromatic substituents.

As for substituted pyridines, 3-methylpyridine **1b** was found to be also able of cross-coupling with secondary phosphine oxides **2a-d** to give the corresponding phosphorylated pyridines **6a-d** in 42–64% yield (Scheme 3). At the same time, we failed to find the reaction conditions, appropriate for the cross-coupling of pyridine **1b** with any other phosphine chalcogenides studied.



Scheme 2 Scope of secondary phosphine chalcogenides **2a-j**.



Scheme 3 Cross-coupling of 3-methylpyridine **1b** with secondary phosphine oxides **2a-d** in the presence of benzoylphenylacetylene **3c**.

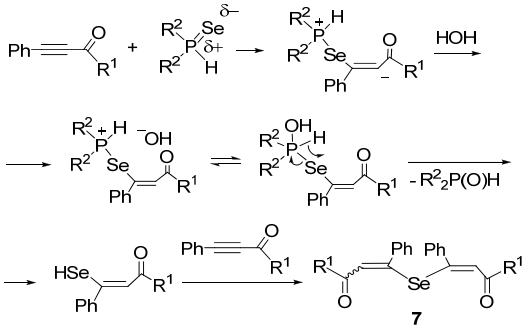
The reaction of perdeuteropyridine (pyridine-d_5) with phosphine sulfide **2f** and acetylene **3c** afforded the corresponding isotopically labelled cross-coupling product, 4-bis(2-phenylethyl)thiophosphorylpyridine-d_4, in 42% yield (for 50 h).

The lower yield and longer reaction time compared to those for non-deuterated pyridine (71%, 35h, Scheme 2) are expected to be due to deuterium kinetic isotope effect. Notably, 3-fluoropyridine appeared unable to undergo the above cross-coupling, obviously because of its lower basicity/nucleophilicity (electron-acceptor effect of fluorine atom).

In accordance with S_NH nature of the reaction, the second products of the cross-coupling were reduced starting acylphenylacetylenes, ethenes **5**, which were formed in approximately equivalent quantities as phosphorylated pyridines (according to ^{1}H NMR spectra of the reaction mixture). Usually, the samples of *E*-ethenes were contaminated by small admixtures of the starting acetylenes. If necessary, *E*-ethenes **5** can be isolated in isomerically pure state. For instance, in the cases of benzoyl and 2-furoylacetylenes **3c**,**d** (R^3 = Ph and 2-Furyl), the corresponding *E*-ethenes were purified chromatographically (SiO_2 column), the yields being 35 and 45%, respectively.

The low yields of the cross-coupling products with phosphine selenides **2i,j** (Scheme 2) are resulted from the side selenylation of the starting acetylenes to furnish the corresponding divinyl selenides **7** (Scheme 4).[9] The selenium transfer involves trace water from the solvent (MeCN).

The structures of the synthesized compounds were proved by spectral data (^{1}H, ^{13}C, ^{15}N, ^{31}P, ^{77}Se NMR, IR-spectroscopy and elemental analysis, see supporting).



Scheme 4 Selenylation of the acylphenylacetylenes by secondary phosphine selenides.

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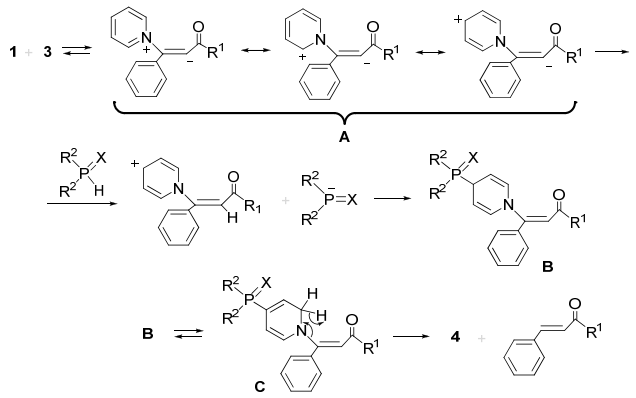
The mechanism of the cross-coupling likely includes the reversible formation of 1,3-dipole (intermediate **A**) resulted from nucleophilic addition of the pyridine to acetylenes **3** (Scheme 5).



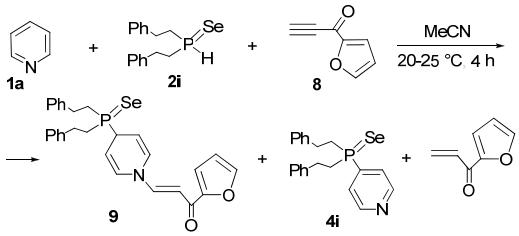
Scheme 5 A plausible reaction pathway.

The carbanionic site of the intermediate **A** is quenched by proton of the phosphine chalcogenides **2** and the P-centered anion, thus released, attacks position 4 of the pyridine ring, affording intermediate dihydropyridine **B**. The selective attachment of the anion to position 4, avoiding position 2, is probably due to the steric screening of both alpha-positions of the pyridine ring by the phenyl substituent from one side and by acylethenyl group from the other one. The elimination of *E*-acylphenylethenes **5** from prototropically isomerized intermediate **B** ⇌ **C** affords the cross-coupling products **4**. The elimination process may have a concerted character: cleavage of the C-N-bond in the intermediate **C** is accompanied by simultaneous transfer of the hydride anion from the position 2 of the dihydropyridine ring to emerging carbocation in the four-membered transition state. Although the four-membered transition state is not as favourable as five or six ones, it is quite common for C-H activation.[10] By virtue, this cross-coupling reaction represents regioselective nucleophilic substitution of hydrogen in the pyridine ring by the P-centred anion (this S_N^HAr reaction is now at its height[7]). The driving force of the elimination should be a higher thermodynamic stability of the final products (phosphorylated pyridines and conjugated functionalized ethenes) as compared to intermediate dihydropyridines **B** ⇌ **C**. Kinetically, it might be initiated by the known stability of the benzylic type carbocationic species originated from the C-N-bond cleavage.

The assumed mechanism is supported by the faster reactions of phosphine sulfides (Scheme 2, for examples **4a** and **4e**) in comparison with the corresponding phosphine oxides, since the former are more acidic[11] and, hence, the proton transfer to carbanionic center of intermediate **A** should be more facile.

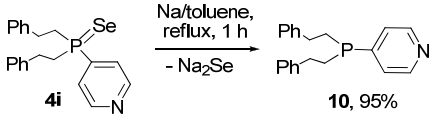
The Scheme 5 is also in keeping with a higher reactivity of 3-methylpyridine **1b** as compared to unsubstituted pyridine **1a**. In fact, 3-methylpyridine **1b**, being more basic than pyridine **1a** (pK_a 5.68 and 5.25, respectively[12]) and likely more nucleophilic, should generate 1,3-dipole intermediate **A** in a higher concentration. In view of the suggested mechanism, it is understandable why 2- and 4-methylpyridines and 3-fluoropyridine do not undergo the above cross-coupling with secondary phosphine chalcogenides: the position 6 is sterically screened by the bulky substituted ethenyl moiety, while the position 2 and 4 are occupied by the methyl group, and fluorine atom as an electron acceptor decreases nucleophilicity of the pyridine ring. Also, the slow-down of the reaction rate and low yield of the target products in the case of pyridine-d_5 are in consistence with the expected deuterium kinetic isotope effect associated with the above hydrogen transfer steps.

Also, in support of Scheme 5, the intermediate dihydropyridine **9** was fixed in a mixture (^{1}H and ^{31}P NMR) with the corresponding pyridine **4i**, when pyridine **1a** reacted (room temperature, MeCN, 4 h) with terminal furoylacetylene **8** (having no phenyl substituent in the position 2) and phosphine selenide **2i** (Scheme 6). This result additionally confirms the importance of 2-phenyl substituents in acetylenes **3a-d** to complete the elimination of substituted ethenes **5a-d** from the intermediate dihydropyridine **C** (Scheme 5).



Scheme 6 Reaction of pyridine, phosphine selenide **2i** and furoylacetylene **8**.

The selenophosphorylpyridine **4i** has been quantitatively reduced to the corresponding phosphine **10** (Scheme 7). This result implies that the cross-coupling might open a simple access to the related phosphines, prospective ligands for new metal complexes for drug design and catalysis.



Scheme 7 Synthesis of 4-pyridyl-bis(2-phenylethyl)phosphine.

In conclusion, pyridines are easily cross-coupled with secondary phosphine chalcogenides in the presence of acylphenylacetylenes under mild conditions (70–75 °C) to afford 4-chalcogenophosphorylpyridines in up to 71% yield. This metal-, halogen-free regioselective cross-coupling represents a new type of nucleophilic substitution of hydrogen in heteroaromatic ring, when electron-deficient acetylene plays a role of an oxidant, being simultaneously stereoselectively reduced to the corresponding functionalized ethenes of the *E*-configuration.

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Conflicts of interest

The authors declare no competing financial interest.

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Notes and references

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