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Solvent-free synthesis of 4-chalcogenophosphorylpyridines *via* $\mathrm{S_N^HAr}$ reaction of pyridines with secondary phosphine chalcogenides

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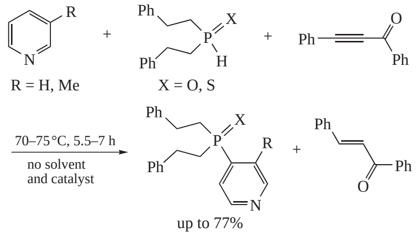
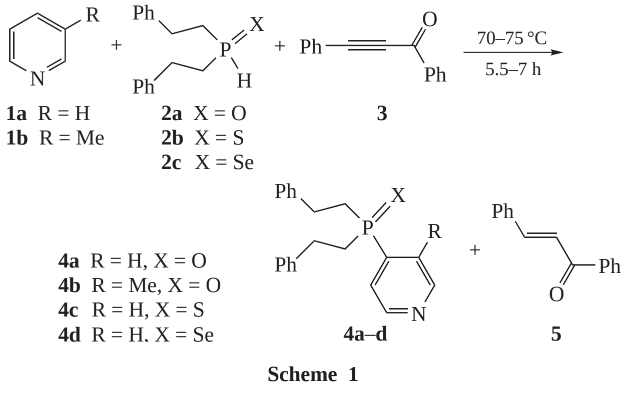
Solvent- and catalyst-free synthesis of 4-chalcogenophosphorylpyridines by oxidative regioselective cross-coupling of pyridines with secondary phosphine chalcogenides using 1,3-diphenylprop-2-yn-1-one as a trigger and oxidant under mild conditions (70–75 °C, 5.5–7 h) is reported.



Solvent-free organic synthesis now attracts a special attention as one of the most promising approaches toward waste prevention and environmental protection.[1–8] During the last years, the solvent-free green methodology has been successfully used in the organophosphorus chemistry for the C–P bond formation.[8–14] Of particular note is a crucial role of the concentration effect in the solvent-free version of alkenes,[9–11,13,14] alkynes[8,13] and aldehydes[12] phosphorylation with H-phosphines and their chalcogenides.

Recently, we have reported[15] the nucleophilic substitution ($\mathrm{S_N^HAr}$ reaction) of the hydrogen atom in pyridines under the action of secondary phosphine chalcogenides, phosphorus-centered nucleophiles, in the presence of ynones as initiators (triggers) and oxidants. The reaction proceeded in organic solvent (acetonitrile) at a prolonged heating (70–75 °C, 20–70 h) and led to 4-chalcogenophosphorylpyridines in 36–71% yield, wherein the ynones were reduced to the corresponding *E*-enones. The secondary phosphine chalcogenides could be easily prepared from styrene and red phosphorus.[16]

Here we report the improved procedure of such a reaction under solvent-free conditions. In fact, pyridines **1a**,**b** easily react with bis(2-phenylethyl)phosphine oxide **2a** or bis(2-phenylethyl)phosphine sulfide **2b** in the presence of 1,3-diphenylprop-2-yn-1-one **3** under mild conditions (70–75 °C, 5.5–7 h) to afford the corresponding 4-[bis(2-phenylethyl)chalcogenophosphoryl]pyridines **4a–c** in 62–77% yield (Scheme 1).† The secondary product in this process was the expected chalcone **5**. This solvent-free procedure not only makes this process environmentally benign, but also significantly (by 5–8 times) shortens the reaction time and in some cases increases the products yield (Table 1).



Scheme 1

Under studied conditions, bis(2-phenylethyl)phosphine selenide **2c** did not react properly with pyridine, although the expected 4-[bis(2-phenylethyl)phosphoroselenoyl]pyridine **4d** was formed when the reaction was carried out in MeCN[15] (see Table 1, entry 4).

Table 1 Solvent-free cross-coupling of pyridines **1a**,**b** with secondary phosphine chalcogenides **2a–c** in the presence of ynone **3** and the known data for the similar syntheses in MeCN.[a]

Entry	Pyridine **1**	Phosphine chalcogenide **2**	Reaction time/h	Product **4**	Isolated yield (%)
1	**1a**	**2a**	6.0[b] (50[c])	**4a**	77[b] (68[c])
2	**1b**	**2a**	7.0[b] (35[c])	**4b**	62[b] (64[c])
3	**1a**	**2b**	5.5[b] (34[c])	**4c**	75[b] (71[c])
4[d]	**1a**	**2c**	5.0[b] (24[c])	**4d**	traces[b] (40[c])

[a] Conditions: 70–75 °C, **1** (1.1 mmol), **2** (1.0 mmol), **3** (1.1 mmol). [b] Reaction time and product yield for solvent-free process. [c] Reported data[15] for the reaction in MeCN. [d] Bis(3-oxo-1,3-diphenylprop-2-en-1-yl) selenide, formed from bis(2-phenylethyl)phosphine selenide **2c** and ynone **3**,[17] was detected (^{77}Se NMR) in the reaction mixture (conversion of **2c** was ~100%).

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† The ^{1}H, ^{13}C, ^{15}N, ^{31}P NMR spectra were recorded on Bruker DPX 400 and Bruker AV 400 spectrometers (400.13, 100.62, 40.56 and 161.98 MHz, respectively) in $CDCl_3$ solutions and referenced to HMDS (^{1}H, ^{13}C), $MeNO_2$ (^{15}N) and H_3PO_4 (^{31}P). The C, H, N microanalyses were performed on a Flash EA 1112 Series elemental analyzer. The P, S content was determined by the combustion method.

4-Chalcogenophosphorylpyridines **4a–c** (*general procedure).* Pyridine **1a**,**b** (1.1 mmol), secondary phosphine chalcogenide **2a**,**b** (1.0 mmol) and ynone **3** (1.1 mmol) were stirred under argon at 70–75 °C for 5.5–7 h (Table 1). After completion of the reaction (^{31}P NMR monitoring), the resulted mixture was purified by column chromatography on SiO_2 (eluent for **4a**,**b**: ethylacetate; for **4c**: toluene–Et_2O, 1 : 2) to yield the individual 4-chalcogenophosphorylpyridine **4a–c** as well as crude enone **5**. The latter was additionally purified by recrystallization from hexane.

^{1}H, ^{13}C, ^{15}N and ^{31}P NMR data for compounds **4a–c** and **5** are in accordance with the known data.[15]

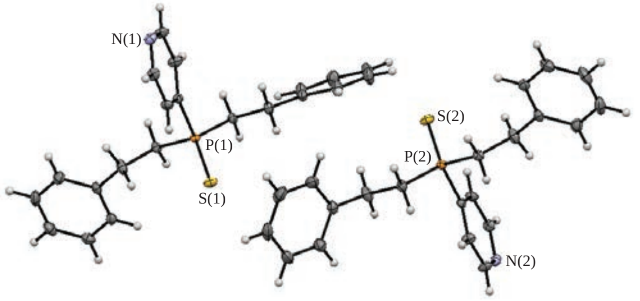

Figure 1 Compound **4c** in thermal vibration ellipsoids at 50% probability.

The structures of the synthesized compounds **4a–c** have been proved by multinuclear (^{1}H, ^{13}C, ^{15}N and ^{31}P) NMR spectroscopy, elemental analysis, and X-ray diffraction analysis {for 4-[bis(2-phenylethyl)phosphorothioyl]pyridine **4c**, Figure 1}.[‡]

Compound **4c** crystallizes in colourless prisms of the monoclinic system, $P2_1/c$ centrosymmetric space group. The independent part of the elementary crystal cell contains two molecules, differing in spatial arrangement of the phenyl and pyridine rings. According to X-ray analysis data (see Figure 1), P atom has a pyramidal coordination, the length of the P–S bond is 1.9591(5) Å, and those of the P–C bonds are 1.816(1)–1.824(1) Å. The valence angles S–P–C [112.22(5)–114.10(5)°] and C–P–C [103.96(7)–106.28(7)°] differ from the ideal tetrahedral angle (109.5°). The lengths of the C–C alkyl bonds are 1.532(2)–1.539(2) Å, those of the C–C bonds in the phenyl rings are 1.376(3)–1.395(2) Å. In the pyridine ring, the lengths of the C–C bonds are 1.385(2)–1.395(2) Å and those of the C–N bonds are 1.336(2)–1.341(2) Å.

A plausible mechanism of the transformation is, apparently, the same as we reported for the solvent protocol.[15]

In conclusion, an environmentally acceptable method for the synthesis of 4-chalcogenophosphorylpyridines, promising ligands[19,20] and drug precursors,[21,22] has been developed. The depriving of an organic solvent from the procedure allows one not only to increase its environmental friendliness, but also to significantly reduce the heating time. In this S_N^HAr reaction of pyridines with secondary phosphine chalcogenides in the presence of 1,3-diphenylprop-2-yn-1-one as a trigger and oxidant, the corresponding chalcone is also formed. This enone is a valuable building block for organic synthesis[23] and biologically active substances.[24]

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4-[Bis(2-phenylethyl)phosphoryl]pyridine **4a**. Yield 258 mg (77%), yellow powder, mp 80–81 °C (lit.,[15] mp 81–82 °C). ^{31}P NMR, δ: 37.5. Found (%): C, 75.39; H, 6.58; N, 4.09; P, 9.08. Calc. for $C_{21}H_{22}NOP$ (%): C, 75.21; H, 6.61; N, 4.18; P, 9.24.

4-[Bis(2-phenylethyl)phosphoryl]-3-methylpyridine **4b**. Yield 217 mg (62%), waxy product. ^{31}P NMR, δ: 39.6. Found (%): C, 75.58; H, 6.79; N, 4.11; P, 8.73. Calc. for $C_{22}H_{24}NOP$ (%): C, 75.62; H, 6.92; N, 4.01; P, 8.86.

4-[Bis(2-phenylethyl)phosphorothioyl]pyridine **4c**. Yield 264 mg (75%), crystalline compound (from hexane), mp 84–85 °C (lit.,[15] mp 83–84 °C). ^{31}P NMR, δ: 45.7. Found (%): C, 71.63; H, 6.37; N, 3.92; P, 8.67; S, 8.89. Calc. for $C_{21}H_{22}NPS$ (%): C, 71.77; H, 6.31; N, 3.99; P, 8.81; S, 9.12.

[‡] *Crystal data for* **4c**. Data were collected on a Bruker D8 Venture PHOTON 100 CMOS diffractometer with MoKα radiation (λ = 0.71073 Å) using the φ- and ω-scan techniques. The structures were solved and refined by direct methods using SHELX.[18] Data were corrected for absorption effects using the multi-scan method (SADABS). All non-hydrogen atoms were refined anisotropically using SHELX.[18] The coordinates of the hydrogen atoms were calculated from geometrical positions. The crystal of $C_{21}H_{22}NPS$ is monoclinic, space group $P2_1/c$, a = 38.2260(18), b = 9.0661(4) and c = 10.8855(5) Å, β = 97.3460(10)°, V = 3741.5(3) Å^3, Z = 8, reflections collected 91206, of which 9010 unique reflections (R_{int} = 0.0400) were used in all calculations. The final parameters are R_1 = 0.0383, wR_2 = 0.0951 [$I > 2\sigma(I)$] and R_1 = 0.0456, wR_2 = 0.0992 (all data). GOOF = 1.076. Completeness 99.8%.

CCDC 1837673 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.