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LETTERS TO THE EDITOR

Synthesis of New *N*-Phosphorylated Vinylhydropyridines

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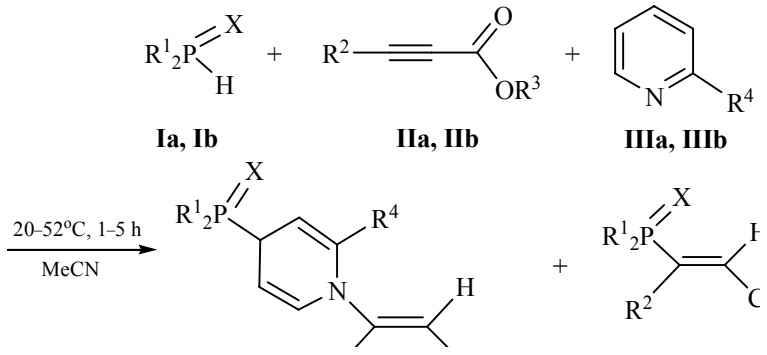
It is known that secondary phosphine halides react with electron-deficient acetylenes in the presence of bases [1–4], radical initiators [1, 5, 6], metal complex catalysts [7, 8], under microwave irradiation [9], and (rarely) in bulk without any catalyst [10] to form tertiary alkenylphosphine halides and the products of bis-addition.

In this work, we performed a three-component reaction of diphenylphosphine sulfide **Ia** and bis(2-phenylethyl)phosphine selenide **Ib** with acetylenecarboxylates **IIa**, **IIb** and pyridines **IIIa**, **IIIb**. The reaction occurred under mild conditions (20–52°C, 1–5 h, MeCN) and led to the regio- and stereoselective formation of (*E*)-*N*-ethenyl-1,4-dihydropyridines **IVa** and **IVb** with yield of 47 and 17%, respectively. In addition, compounds **Va** and **Vb** were obtained (up to 63%) as a result of nucleophilic addition of PH-compounds at the triple bond of alkynes **II** (Scheme 1).

Furthermore, formation of the bis-adduct $Ph_2P(=S)CH_2CH(CO_2Me)(S=P)Ph_2$ **IVa** was detected in the reaction of phosphine **Ia** with propiolate **IIa** in the presence of 2-methylpyridine **IIIa**.

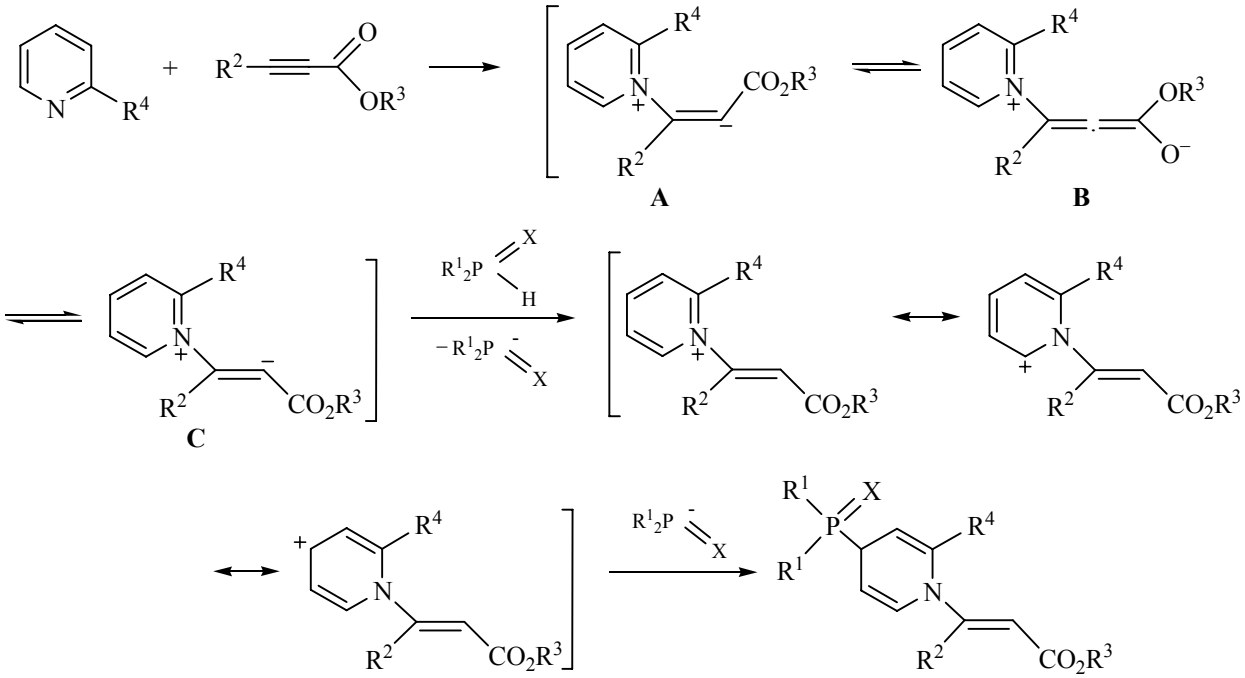
Probably, the reaction pathway included nucleophilic addition of pyridine at the triple bond of electrophilic acetylene, leading to zwitter ion **A** with carbanionic site *trans*-positioned with respect to the nitrogen atom. Zwitterion **A** was in equilibrium with the zwitterion **C** (carbanionic center is *cis* position

Scheme 1.



R^1 = Ph (**Ia, IVa, Va**), R^2 = H, R^3 = Me (**IIa, IVa, Va**), R^4 = Me (**IIIa, IVa**), X = S (**Ia, IVa, Va**); R^1 = $PhCH_2CH_2$ (**Ib, IVb, Vb**), R^2 = EtO_2C, R^3 = Et (**IIb, IVb, Vb**), R^4 = H (**IIIb, IVb**), X = Se (**Ib, IVb, Vb**).

Scheme 2.



relative to the nitrogen atom). The allene intermediate **B** was involved in that equilibrium as well. The carbanion center of zwitterion **C** was further neutralized with the proton of the secondary phosphine halide, and the formed phosphorus-centered anion attacked position 4 in the pyridinium cation to yield (*E*)-*N*-ethenyl-1,4-dihydropyridine (Scheme 2).

Hence, we proposed suitable atom-economic approach towards synthesis of phosphorylated *N*-vinyl-1,4-dihydropyridines with a rare combination of functional groups (phosphoryl and acrylate), which can serve as promising pharmacologically active compounds and convenient building blocks for further organic and organometallic synthesis. Dihydropyridine fragments are part of antihypertensive drugs such as nifedipine, amlodipine, felodipine, and compounds showing cytotoxic [11], anticoagulant [12] and antibiotic [13] activity.

Three-component reaction of diphenylphosphine sulfide Ia with propiolate IIa and 2-methylpyridine IIIa. A mixture of 218 mg (1 mmol) of phosphine **Ia**, 84 mg (1.1 mmol) of methyl propiolate **IIa**, and 93 mg (1.1 mmol) of pyridine **IIIa** in 3 mL of acetonitrile was stirred at 50–52°C during 5 h. According to ^{31}P NMR spectral data, the reaction mixture contained (*E*)-*N*-ethenyl-1,4-dihydropyridine **IVa** (57%), monoadduct **Va** [9] (21%, *E* : Z = 2.5 : 1), and methyl-2,3-bis-(diphenylthiophosphoryl)propenoate **VIa** (14%). The solvent was removed under reduced pressure, and the residue was purified via column chromatography (Al_2O_3, hexane : chloroform : acetone = 14 : 2 : 1) to give methyl-(*E*)-3-[4-(diphenylthiophosphoryl)-2-methyl-1-(4*H*)-pyridinyl]-2-propenoate **IVa** and a mixture of mono- and bis-adducts **Va** and **VIa** (46 mg, **Va** : **VIa** = 1 : 1, ^{31}P NMR).

Methyl-(*E*)-3-[4-(diphenylthiophosphoryl)-2-methyl-1-(4*H*)-pyridinyl]-2-propenoate (IVa). Yield 185 mg (47%), pale yellow powder, mp 138–139°C (hexane). IR (KBr), ν, cm^{-1}: 1726 pl, 1699, 1691 s (C=O), 1601 br.s (C=C), 613 m (P=S). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.86 d (3H, MeC^2, $^4J_{PH}$ 4.0 Hz), 3.66 s (3H, OMe), 4.35 d.t (1H, H^4, $^2J_{PH}$ 16.1, $^3J_{4–5}$ = $^3J_{4–3}$ 4.4 Hz), 4.74 m (1H, H^3), 7.32 d (1H, >NCH=, $^3J_{trans}$ 13.5 Hz), 5.10 m (1H, H^5), 6.33 d.d (1H, H^6, $^3J_{6–5}$ 8.0, $^4J_{PH}$ 5.1 Hz), 4.94 d (1H, =CHCO$_2$Me, $^3J_{trans}$ 13.5 Hz), 7.45 m (6H, H^m, H^p), 7.81 m (4H, H^o). ^{13}C NMR spectrum, δ_C, ppm: 18.9 (MeC^2), 42.5 d (C^4, $^1J_{PC}$ 51.3 Hz), 51.1 (OMe), 91.8 (>NCH=), 99.7 d (C^3, $^2J_{CP}$ 5.6 Hz), 104.1 d (C^5, $^2J_{PC}$ 6.0 Hz), 127.3 d (C^6, $^3J_{PC}$ 8.6 Hz), 128.4 d and 128.5 d (C^m, $^3J_{PC}$ 12.1 Hz), 130.3 d and 130.7 d (C^{ipso}, $^1J_{CP}$ 75.0 Hz), 131.7 d and 131.8 d (C^p, $^4J_{PC}$ 3.0 Hz), 132.1 d and 132.3 d (C^o, $^2J_{PC}$ 8.8 Hz), 137.1 d (C^2, $^3J_{PC}$ 8.6 Hz), 139.6 (=CHCO$_2$Me), 168.7 (CO$_2$Me). ^{31}P

NMR spectrum: δ_P 43.8 ppm. ^{15}N NMR spectrum: δ_N –245.7 ppm. Found, %: C 66.69; H 5.68; N 3.47; P 7.71; S 8.03. $C_{22}H_{22}NO_2PS$. Calculated, %: C 66.82; H 5.61; N 3.54; P 7.83; S 8.11.

Methyl-3-(diphenylthiophosphoryl)-2-propenoate (Va). *Z*-Isomer (minor product). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.31 s (3H, OMe), 6.64 d.d (1H, =CHC, $^3J_{HH}$ 13.3, $^3J_{HP}$ 38.3 Hz), 6.85 d.d (1H, =CHP, $^3J_{HH}$ 13.3, $^2J_{HP}$ 17.2 Hz), 7.38 m (2H, H^p), 7.51 m (4H, H^m), 7.84 (4H, H^o). ^{31}P NMR spectrum: δ_P 33.2 ppm. *E*-Isomer (major product). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 3.77 s (3H, OMe), 6.76 d.d (1H, =CHP, $^3J_{HH}$ 16.4, $^2J_{HP}$ 20.1 Hz), 7.65 d.d (1H, =CHC, $^3J_{HH}$ 16.4, $^3J_{HP}$ 19.9 Hz), 7.45 m (6H, H^m, H^p), 7.73 (4H, H^o). ^{31}P NMR spectrum: δ_P 34.4 ppm.

Methyl-2,3-bis(diphenylthiophosphoryl)propanoate (VIa). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.63 d.t (1H, CH_AH, $^3J_{HH} \approx {}^2J_{HP}$ 14.8, $^2J_{HH}$ 13.8 Hz), 3.35 s (3H, Me), 3.49 m (1H, CH_BH), 4.54 d.t (1H, CHP, $^3J_{HH} \approx {}^2J_{HP}$ 11.8, $^3J_{HH}$ 14.8 Hz), 7.33–8.05 m (10H, Ph). ^{31}P NMR spectrum, δ_P, ppm: 43.12 d ($^3J_{PP}$ 49.9 Hz), 49.68 d ($^3J_{PP}$ 49.9 Hz).

Three-component reaction of bis(2-phenylethyl) phosphine selenide Ib with diethylacetylenedicarboxylate IIb and pyridine IIIb. A mixture of 321 mg (1 mmol) of phosphine selenide **Ib**, 170 mg (1 mmol) of acetylenedicarboxylate **IIb**, and 79 mg (1 mmol) of pyridine **IIIb** in 4 mL of acetonitrile was stirred at 20–22°C during 1 h. According to ^{31}P NMR spectral data, the reaction mixture contained two organophosphorus products: (*E*)-*N*-ethenyl-1,4-dihydropyridine **IVb** (25%) and monoadduct **Vb** (75%). The reaction mixture was evaporated under reduced pressure. The products **IVb** and **Vb** were isolated via column chromatography (silica gel, hexane : benzene = 2 : 1).

Diethyl-(*E*)-2-[4-(diphenylethylselenophosphoryl)-1(4*H*)-pyridinyl]-2-betenedioate (IVb). Yield 91 mg (17%), viscous oil. IR spectrum (thin layer), ν, cm^{-1}: 1786, 1740, 1684 br.s (C=O), 1624 pl, 1590 br.s (C=C), 488 m (P=Se). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (6H, $OCH_2\underline{Me}$, $^3J_{HH}$ 7.2 Hz), 2.11–2.30 m (4H, CH_2P), 2.94 m (4H, $PhCH_2$), 3.62 d.t (1H, H^4, $^2J_{PH}$ 18.1, $^3J_{4-3(5)}$ 4.7 Hz), 4.11 q (2H, $OC\underline{H}_2Me$, $^3J_{HH}$ 7.2 Hz), 4.36 q (2H, $OC\underline{H}_2Me$, $^3J_{HH}$ 7.2 Hz), 5.13 d.d. d (2H, $H^{3,5}$, $^3J_{3(5)-2(6)}$ 8.0, $^3J_{3(5)-4}$ 4.7, $^3J_{PH}$ 3.6 Hz), 5.21 s (1H, $=C\underline{H}CO_2Et$), 6.33 d.d (2H, $H^{2,6}$, $^3J_{3(5)-2(6)}$ 8.0, $^4J_{PH}$ 4.5 Hz), 7.18 m (6H, H^o, H^p), 7.26 m (4H, H^m). ^{13}C NMR spectrum, δ_C, ppm: 13.4 and 13.9 ($OCH_2\underline{Me}$), 28.3 d (CH_2P, $^1J_{CP}$ 39.2 Hz), 28.8 d ($PhCH_2$, $^2J_{CP}$ 2.3 Hz), 39.3 d (C^4, $^1J_{CP}$ 42.2 Hz), 59.9 and 62.4 ($O\underline{C}H_2Me$), 93.7 (NC=), 103.4 d ($C^{3,5}$, $^2J_{CP}$ 5.6 Hz), 126.2 (C^p), 126.6 d ($C^{2,6}$, $^3J_{CP}$ 7.8 Hz), 127.9 (C^o), 128.3 (C^m), 140.1 d (C^{ipso}, $^3J_{CP}$ 12.9 Hz), 145.8 ($=\underline{C}HCO_2Et$), 163.3 and 165.5 ($\underline{C}O_2Et$). ^{31}P NMR spectrum, δ_P, ppm: 43.5 (+ satellite doublet: $^1J_{PSe}$ 710.2 Hz). ^{77}Se NMR spectrum, δ_{Se}, ppm: –421.9 d ($^1J_{PSe}$ 710.2 Hz). ^{15}N NMR spectrum: δ_N –255.0 ppm. Found, %: C 60.86; H 5.93; N 2.42; P 5.29; Se 13.68. $C_{29}H_{34}NO_4PSe$. Calculated, %: C 61.05; H 6.01; N 2.46; P 5.43; Se 13.84.

Diethyl-(*E*)-2-(diphenylethylselenophosphoryl)-2-butenedioate (Vb). Yield 310 mg (63%), viscous oil. IR spectrum (thin layer), ν, cm^{-1}: 1726 br.s (C=O), 1621, 1603 m (C=C), 472 m (P=Se). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (6H, $OCH_2\underline{Me}$, $^3J_{HH}$ 7.1 Hz), 2.27 and 2.52 m (4H, CH_2P), 2.78–3.01 m (4H, CH_2Ph), 4.23 and 4.31 q (4H, $OC\underline{H}_2Me$, $^3J_{HH}$ 7.1 Hz), 7.20 d (1H, CH=, $^3J_{HP}$ 21.3 Hz), 7.16–7.26 m (10H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 14.0 and 14.1 ($OCH_2\underline{Me}$), 29.0 d (CH_2Ph, $^2J_{CP}$ 1.9 Hz), 32.9 d (PCH_2, $^1J_{CP}$ 44.9 Hz), 61.8, 62.7 ($O\underline{C}H_2Me$), 126.6 (C^p), 128.4, 128.7 (C^o, C^m), 139.1 d (PC=, $^1J_{CP}$ 43.8 Hz), 140.3 d (C^{ipso}, $^3J_{CP}$ 17.0 Hz), 141.8 d (CH=, $^2J_{CP}$ 10.2 Hz), 163.5 d ($O=\underline{C}CH=$, $^3J_{CP}$ 20.6 Hz), 165.6 d [$O=\underline{C}C(P)=$, $^2J_{CP}$ 9.1 Hz]. ^{31}P NMR spectrum, δ_P, ppm: 41.3 (+ satellite doublet: $^1J_{PSe}$ 758.7 Hz). ^{77}Se NMR spectrum, δ_{Se}, ppm: –417.8 d ($^1J_{PSe}$ 758.7 Hz). Found, %: C 58.47; H 5.89; P 6.18; Se 15.92. $C_{24}H_{29}O_4PSe$. Calculated, %: C 58.66; H 5.95; P 6.30; Se 16.07.

IR spectra were recorded using a Bruker Vertex 70 spectrometer (KBr pellets or thin film). ^1H, ^{13}C, ^{15}N, ^{31}P and ^{77}Se NMR spectra ($CDCl_3$) were obtained with a Bruker DPX-400 instrument (400.13, 100.62, 40.56, 161.98, and 76.31 MHz, respectively) relative to internal HMDS, Me_2Se (^{77}Se NMR) or external 85% H_3PO_4 (^{31}P NMR) references. The assignment of the proton signals was performed taking advantage of 2D homonuclear correlation methods COSY and NOESY. Signals of the carbon atoms were assigned basing on the analysis of 2D heteronuclear correlation spectra HSQC and HMBC.

All the reactions were performed under inert atmosphere (argon). The reaction progress was monitored via ^{31}P NMR spectroscopy.

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REFERENCES

1. Semenzin, D., Etemad-Moghadam, G., Albouy, D., Diallo, O., and Koenig, M., *J. Org. Chem*., 1997, vol. 62, p. 2414. DOI: 10.1021/jo9622441.
2. Arbuzova, S.N., Gusarova, N.K., and Trofimov, B.A., *Arkivoc*, 2006, p. 12. DOI: 10.3998/ark.5550190.0007.503.
3. Glotova, T.E., Dvorko, M.Yu., Gusarova, N.K., Arbuzova, S.N., Ushakov, I.A., Kazantseva, T.I., and Trofimov, B.A., *Phosphorus, Sulfur, Silicon, Relat. Elem*., 2008, vol. 183, p. 1396. DOI: 10.1080/10426500701648069.
4. Dvorko, M.Yu., Glotova, T.E., Ushakov, I.A., and Gusarova, N.K., *Russ. J. Org. Chem*., 2010, vol. 46, no. 4, p. 485. DOI: 10.1134/S1070428010040056.
5. Trofimov, B.A., Gusarova, N.K., Malysheva, S.F., Belogorlova, N.A., Vasilevsky, S.F., Kobychev, V.B., Sukhov, B.G., and Ushakov, I.A., *Mendeleev Commun*., 2007, vol. 17, p. 181. DOI: 10.1016/j.mencom.2007.05.017.
6. Trofimov, B.A., Gusarova, N.K., Arbuzova, S.N., Ivanova, N.I., Artem'ev, A.V., Volkov, P.A., Ushakov, I.A., Malysheva, S.F., and Kuimov, V.A., *J. Organomet. Chem*., 2009, vol. 694, p. 677. DOI: 10.1016/j.jorganchem.2008.11.043.
7. Glueck, D.S., *Top. Organomet. Chem*., 2010, vol. 31, p. 65. DOI: 10.1007/978-3-642-12073-2_4.
8. Tanaka, M., *Top. Organomet. Chem*., 2013, vol. 43, p. 167. DOI: 10.1007/3418_2011_20.
9. Keglevich, G., Bálint, E., Tákacs, J., Drahos, L., Huben, K., and Jankowski, S., *Curr. Org. Synth*., 2014, vol. 11, p. 161. DOI: 10.2174/15701794119991403041427 47.
10. Artem'ev, A.V., Malysheva, S.F., Gusarova, N.K., Belogorlova, N.A., Shagun, V.A., Albanov, A.I., and Trofimov, B.A., *Synthesis*, 2015, vol. 47, p. 263. DOI: 10.1055/s-0034-1379207.
11. Abbas, H.-A.S., El Sayed, W.A., and Fathy, N.M., *Eur. J. Med. Chem*., 2010, vol. 45, p. 973. DOI: 10.1016/j.ejmech.2009. 11.039.
12. Kumar, R.S., Idhayadhulla, A., Nasser, A.J.A., and Selvin, J., *Eur. J. Med. Chem*., 2011, vol. 46, p. 804. DOI: 10.1016/j.ejmech. 2010.12.006.
13. Abu-Melha, H., *Spectrochim. Acta (A)*, 2013, vol. 113, p. 115. DOI: 10.1016/j.saa.2012.12.069.