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Nucleophilic addition of secondary phosphine chalcogenides to α,β-acetylenic γ-hydroxy acid nitriles and a rearrangement of the adducts

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Bis(2-phenylethyl)phosphine oxide and sulfide and bis[2-(2-pyridyl)ethyl]phosphine sulfide add easily (LiOH–THF, 28–30 °C) to 4-hydroxy-4-methyl-2-pentynenitrile to give regio- and stereoselectively 3-substituted (*Z*)-4-hydroxy-4-methyl-2-pentenenitriles in 82–91% yield; the latter, upon heating (58–60 °C) in the presence of LiOH in THF, rearrange cleanly to the corresponding 3-cyano-2-propen-1-yl phosphinates and phosphinothioates (isolated yields of 82–86%).

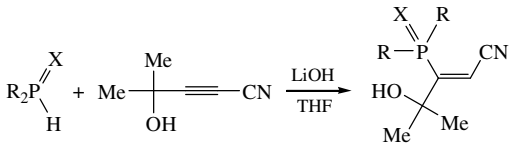
The addition of secondary phosphine oxides or sulfides to substituted acetylenes is an attractive route[1] to promising ligands for usable metallocomplexes[2] and rewarding building blocks[1(*d*)] for organic synthesis. In addition, these reactions contribute to the basic chemistry of both organophosphorus and acetylenic compounds.[3]

However, the above addition reactions for the nitriles of α,β-acetylenic γ-hydroxy acids have not been reported, though they would lead to new highly functionalised tertiary phosphine oxides and sulfides and provide additional information on the reactivity of P–H and C≡C bonds.

For this reason, we studied the addition of bis(2-phenylethyl)phosphine oxide **1a** and sulfide **1b** and bis[2-(2-pyridyl)ethyl]phosphine sulfide **1c** to the nitriles of α,β-acetylenic γ-hydroxy acids using 4-hydroxy-4-methyl-2-pentynenitrile as a typical representative. These experiments showed that while the uncatalysed reaction did not occur at 35–40 °C (20 h, THF) the base-catalysed addition (LiOH–THF) proceeded readily at 28–30 °C to afford selectively adducts **2a**–**c** in almost quantitative yields (82–91%) (Scheme 1).†

Sulfides **1b**,**c** were found much more reactive than phosphine oxide **1a** (the reaction time of 2.5–3 h against 22 h) owing to their higher nucleophilicity.

The structure of adducts **2a**–**c** follows from their ^{31}P NMR chemical shifts (~46–49 ppm), the observed P–C$_{ethenyl}$ coupling ($^1J_{P–C}$ ~47–49 Hz) in their ^{13}C NMR spectra and the stretching vibrations of the OH group (3300–3350 cm^{-1}) in their IR spectra. These data provide unequivocal evidence for the presence of the X=P–C=C–C–OH fragment (X = O, S) and hence the molecular structures of **2a**–**c**. The *Z*-configurations of phosphine



1a–c **2a–c**

a R = $PhCH_2CH_2$, X = O
b R = $PhCH_2CH_2$, X = S
c R = 2-$PyCH_2CH_2$, X = S

Scheme 1

† *General procedure for the preparation of compounds* **2**. To a mixture of secondary phosphine chalcogenide **1** (1.00 mmol) and LiOH (0.02 g, 0.84 mmol) in 4 ml of THF, a solution of 4-hydroxy-4-methyl-2-pentynenitrile (0.11 g, 1.00 mmol) in 4 ml of THF was added dropwise for 10 min. The reaction mixture was stirred at 28–30 °C for 22 (**1a**) or 2.5–3 h (**1b**,**c**), passed through a layer of Al_2O_3 (0.5 cm), then THF was removed under reduced pressure; the residue was dried in a vacuum.

The ^{1}H, ^{13}C and ^{31}P NMR spectra were measured on a Bruker DPX 400 spectrometer (400.13, 101.61 and 161.98 MHz, respectively). The IR spectra were recorded on a Bruker IFS-25 spectrometer in films.

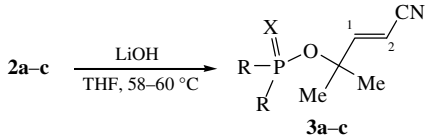
(Z)-3-[Bis(2-phenylethyl)phosphoryl]-4-hydroxy-4-methyl-2-pentenenitrile **2a**: yield 82% (0.30 g); white powder, mp 100–101 °C (Et_2O) (lit.,[7] 100–102 °C). ^{1}H NMR ($CDCl_3$) δ: 1.55 (s, 6H, Me), 2.30–2.45, 2.52–2.65 (m, 4H, CH_2P), 2.85–2.98, 3.00–3.10 (m, 4H, CH_2Ph), 5.25 (s, 1H, OH), 6.02 (d, 1H, =CH, $^3J_{PH}$ 32.2 Hz), 7.18–7.31 (m, 10H, Ph), non-equivalence of protons in the CH_2P and CH_2Ph moieties resulted from their diastereotopy. ^{31}P NMR ($CDCl_3$) δ: 46.93. IR (ν/cm^{-1}): 3300 (OH), 2210 (C≡N), 1160 (P=O). Found (%): C, 71.62; H, 7.39; N, 3.60; P, 8.69. Calc. for $C_{22}H_{26}NO_2P$ (%): C, 71.92; H, 7.13; N, 3.81; P, 8.43.

(Z)-3-[Bis(2-phenylethyl)phosphorothioyl]-4-hydroxy-4-methyl-2-pentenenitrile **2b**: yield 91% (0.35 g); yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.66 (s, 6H, Me), 2.44–2.54 (m, 2H, CH_2P), 2.89–2.99 (m, 4H, CH_2P, CH_2Ph), 3.05–3.17 (m, 2H, CH_2Ph), 5.25 (s, 1H, OH), 6.20 (d, 1H, =CH, $^3J_{PH}$ 32.3 Hz), 7.22–7.34 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ: 29.30 (CH_2Ph), 31.41 (Me), 36.11 (d, CH_2P, $^1J_{PC}$ 49.1 Hz), 77.15 (d, *C*Me$_2$, $^2J_{PC}$ 5.2 Hz), 105.54 (=CH), 116.50 (d, C≡N, $^3J_{PC}$ 9.2 Hz), 127.73 (C$_p$), 129.39 (C$_o$), 129.78 (C$_m$), 140.90 (d, C$_i$, $^3J_{PC}$ 16.3 Hz), 165.90 (d, =CP, $^1J_{PC}$ 47.4 Hz). ^{31}P NMR ($CDCl_3$) δ: 46.30. IR (ν/cm^{-1}): 3350 (OH), 3100 (=CH), 2210 (C≡N), 1660 (C=C), 680 (P=S). Found (%): C, 68.73; H, 6.67; N, 3.89; P, 8.20; S 8.15. Calc. for $C_{22}H_{26}NOPS$ (%): C, 68.90; H, 6.83; N, 3.65; P, 8.08; S 8.36.

(Z)-3-{Bis[2-(2-pyridyl)ethyl]phosphorothioyl}-4-hydroxy-4-methyl-2-pentenenitrile **2c**: purified by precipitation from chloroform to hexane; yield 88% (0.34 g); yellow powder, mp 60–62 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.59 (s, 6H, Me), 2.67–2.77 (m, 2H, CH_2P), 3.07–3.18 (m, 4H, CH_2P, CH_2Py), 3.25–3.35 (m, 2H, CH_2Py), 5.40 (s, 1H, OH), 6.15 (d, 1H, =CH, $^3J_{PH}$ 32.1 Hz), 7.12 (m, 2H, H^5, Py), 7.20 (d, 2H, H^3, Py, $^3J_{3–4}$ 7.7 Hz), 7.59 (m, 2H, H^4, Py), 8.51 (d, 2H, H^6, Py, $^3J_{5–6}$ 4.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 30.51 (Me), 30.58 (CH_2Py), 32.49 (d, CH_2P, $^1J_{PC}$ 50.9 Hz), 76.05 (d, *C*Me$_2$, $^2J_{PC}$ 4.2 Hz), 105.30 (=CH), 115.36 (d, C≡N, $^3J_{PC}$ 9.2 Hz), 121.80 (C^5, Py), 123.15 (C^3, Py), 136.65 (C^4, Py), 149.48 (C^6, Py), 159.33 (d, C^2, Py, $^3J_{PC}$ 16.2 Hz), 164.29 (d, =CP, $^1J_{PC}$ 48.7 Hz). ^{31}P NMR ($CDCl_3$) δ: 48.65. IR (ν/cm^{-1}): 3350 (OH), 2210 (C≡N), 640 (P=S). Found (%): C, 62.49; H, 6.48; N, 10.65; P, 7.85; S, 8.26. Calc. for $C_{20}H_{24}N_3OPS$ (%): C, 62.32; H, 6.28; N, 10.90; P, 8.04; S, 8.32.

chalcogenides **2a–c** were confirmed by the cross peaks of the ethenyl and methyl protons in the ^{1}H–^{1}H NOESY spectra, indicating their *cis* disposition relative to the double bond.

Upon heating (58–60 °C, 7–10 h) in the presence of equimolar amounts of LiOH in THF, adducts **2a–c** cleanly and quantitatively (^{31}P NMR) rearranged to (2*E*)-3-cyano-1,1-dimethyl-2-propen-1-yl bis(2-phenylethyl)phosphinate **3a**, *O*-[(2*E*)-3-cyano-1,1-dimethyl-2-propen-1-yl] bis(2-phenylethyl)phosphinothioate **3b** and *O*-[(2*E*)-3-cyano-1,1-dimethyl-2-propen-1-yl] bis[2-(2-pyridyl)ethyl]phosphinothioate **3c** (Scheme 2) with isolated yields of 82–86% after purifying on Al_2O_3.‡

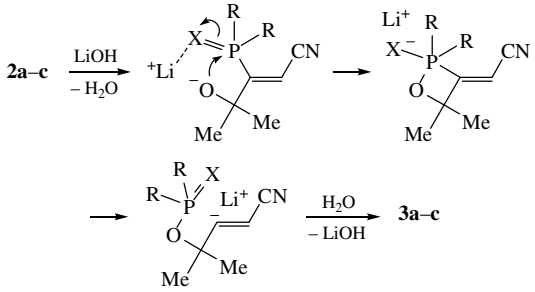


a R = $PhCH_2CH_2$, X = O
b R = $PhCH_2CH_2$, X = S
c R = 2-$PyCH_2CH_2$, X = S

Scheme 2

In the absence of LiOH this process did not occur. The mechanism of the rearrangement observed can be rationalised as intramolecular nucleophilic substitution at the four-coordinated phosphorus atom by the alkoxide anion. It seems likely that the process is Li^+-assisted (Scheme 3).

The mechanism shown in Scheme 3 is in accordance with the *E*-configuration of rearrangement products **3a–c**. The presence of the X=P–O–C–CH=CH fragment (X = O, S) in products



Scheme 3

3a–c is supported by the ^{31}P NMR chemical shifts (54.92 ppm for **3a** and 96–97 ppm for **3b**,**c**), the availability of signals for two ethenyl protons in the ^{1}H NMR spectra, the absence of a $^1J_{P–C_{ethenyl}}$ coupling in the ^{13}C NMR spectra and the absence of the stretching vibrations of the OH group in the IR spectra.

To the best of our knowledge, a rearrangement of this type for β-hydroxyalkylphosphine chalcogenides is unknown, although α-hydroxy analogues are reported to isomerise with oxygen atom insertion into the neighbouring P–C bond, most often in the presence of bases.[4]

Thus, the synthesis of two families of functionalised unsaturated organophosphorus compounds from available secondary phosphine chalcogenides[5] and the nitriles of α,β-acetylenic γ-hydroxy acids[6] has been developed, and a new intramolecular rearrangement of the initial adducts involving oxygen atom insertion into the P–C bond has been observed.

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‡ *General procedure for the preparation of compounds* **3**. A mixture of pentenenitrile **2** (0.60 mmol) and LiOH (0.014 g, 0.60 mmol) in 5 ml of THF was stirred at 58–60 °C for 7 (**2a**) or 10 h (**2b**,**c**), cooled and passed through a layer of Al_2O_3 (0.5 cm). Then, THF was removed under reduced pressure; the residue was dried in a vacuum.

*(2*E*)-3-Cyano-1,1-dimethyl-2-propen-1-yl bis(2-phenylethyl)phosphinate* **3a**: yield 86% (0.19 g); brown oil. ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 6H, Me), 1.97–2.02 (m, 4H, CH_2P), 2.80–2.87 (m, 4H, CH_2Ph), 5.38 (d, 1H, H^2, $^3J_{HH}$ 16.4 Hz), 6.66 (dd, 1H, H^1, $^3J_{HH}$ 16.4 Hz, $^4J_{PH}$ 1.5 Hz), 7.10–7.27 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ: 28.30 (Me, CH_2Ph), 32.17 (d, CH_2P, $^1J_{PC}$ 88.0 Hz), 80.81 (d, *C*Me$_2$, $^2J_{PC}$ 8.1 Hz), 98.22 (C^2), 116.76 (C≡N), 126.65 (C$_p$), 128.10 (C$_o$), 128.80 (C$_m$), 140.49 (d, C$_i$, $^3J_{PC}$ 14.6 Hz), 157.93 (d, C^1, $^3J_{PC}$ 6.13 Hz). ^{31}P NMR ($CDCl_3$) δ: 54.92. IR (ν/cm^{-1}): 3100 (=CH), 2210 (C≡N), 1640 (C=C), 1160 (P=O), 1145 (C–OP), 980 (P–O). Found (%): C, 71.65; H, 7.36; N, 3.64; P, 8.55. Calc. for $C_{22}H_{26}NO_2P$ (%): C, 71.92; H, 7.13; N, 3.81; P, 8.43.

*O-[(2*E*)-3-Cyano-1,1-dimethyl-2-propen-1-yl] bis(2-phenylethyl)phosphinothioate* **3b**: yield 83% (0.19 g); brown oil. ^{1}H NMR ($CDCl_3$) δ: 1.67 (s, 6H, Me), 2.21–2.29 (m, 4H, CH_2P), 2.87–2.94 (m, 4H, CH_2Ph), 5.37 (d, 1H, H^2, $^3J_{HH}$ 16.3 Hz), 6.78 (dd, 1H, H^1, $^3J_{HH}$ 16.3 Hz, $^4J_{PH}$ 1.4 Hz), 7.14–7.30 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$) δ: 28.92 (d, Me, $^3J_{PC}$ 3.7 Hz), 29.92 (d, CH_2Ph, $^2J_{PC}$ 2.0 Hz), 39.14 (d, CH_2P, $^1J_{PC}$ 67.8 Hz), 81.87 (d, *C*Me$_2$, $^2J_{PC}$ 8.1 Hz), 98.16 (C^2), 116.78 (C≡N), 127.46 (C$_p$), 129.07 (C$_o$), 129.61 (C$_m$), 140.42 (d, C$_i$, $^3J_{PC}$ 14.7 Hz), 158.25 (d, C^1, $^3J_{PC}$ 5.2 Hz). ^{31}P NMR ($CDCl_3$) δ: 96.08. IR (ν/cm^{-1}): 3100 (=CH), 2220 (C≡N), 1653 (C=C), 1132 (C–OP), 984 (P–O), 617 (P=S). Found (%): C, 68.73; H, 6.68; N, 3.94; P, 8.28; S 8.17. Calc. for $C_{22}H_{26}NOPS$ (%): C, 68.90; H, 6.83; N, 3.65; P, 8.08; S 8.36.

*O-[(2*E*)-3-Cyano-1,1-dimethyl-2-propen-1-yl] bis[2-(2-pyridyl)ethyl]-phosphinothioate* **3c**: yield 82% (0.19 g); brown oil. ^{1}H NMR ($CDCl_3$) δ: 1.67 (s, 6H, Me), 2.46–2.53 (m, 4H, CH_2P), 3.09–3.15 (m, 4H, CH_2Py), 5.43 (d, 1H, H^2, $^3J_{HH}$ 16.4 Hz), 6.80 (dd, 1H, H^1, $^3J_{HH}$ 16.4 Hz, $^4J_{PH}$ 1.7 Hz), 7.11 (m, 2H, H^5, Py), 7.16 (m, 2H, H^3, Py), 7.59 (m, 2H, H^4, Py), 8.50 (m, 2H, H^6, Py). ^{13}C NMR ($CDCl_3$) δ: 28.08 (d, Me, $^3J_{PC}$ 2.0 Hz), 31.27 (CH_2Py), 35.81 (d, CH_2P, $^1J_{PC}$ 69.1 Hz), 81.86 (d, *C*Me$_2$, $^2J_{PC}$ 8.8 Hz), 98.22 (C^2), 116.88 (C≡N), 121.71 (C^5, Py), 123.08 (C^3, Py), 136.64 (C^4, Py), 149.51 (C^6, Py), 158.24 (d, C^1, $^3J_{PC}$ 5.4 Hz), 159.79 (d, C^2, Py, $^3J_{PC}$ 15.5 Hz). ^{31}P NMR ($CDCl_3$) δ: 97.01. IR (ν/cm^{-1}): 3100 (=CH), 2210 (C≡N), 1640 (C=C), 1140 (C–OP), 980 (P–O), 620, 605 (P=S). Found (%): C, 62.45; H, 6.48; N, 10.65; P, 7.85; S, 8.09. Calc. for $C_{20}H_{24}N_3OPS$ (%): C, 62.32; H, 6.28; N, 10.90; P, 8.04; S, 8.32.