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Unexpected double α,β-addition of secondary phosphine chalcogenides to 3-phenyl-2-propynenitrile

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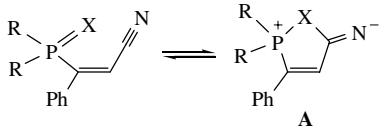
Bis(2-phenylethyl)phosphine oxide and sulfide react with 3-phenyl-2-propynenitrile in the presence of KOH under mild conditions to form unexpectedly α,β-diadducts, 2,3-bis[bis(2-phenylethyl)phosphoryl]- and 2,3-bis[bis(2-phenylethyl)phosphorothioyl]-3-phenylpropionitriles.

Among organophosphorus compounds, diphosphine chalcogenides with asymmetric centres are of special interest as intermediates for the preparation of optically active diphosphine chalcogenides. Reduction of the above compounds affords corresponding optically active diphosphines, which are widely used in catalytic enantioselective synthesis.[1] Moreover, phosphine oxides and phosphine sulfides are unique polydentate ligands for transition metal catalysts[2] (for example, triphenylphosphine sulfide is a more effective ligand for palladium-catalysed bis(alkoxy)carbonylation of olefins than triphenylphosphine).[3] At the same time, synthetic routes to such diphosphine chalcogenides with chiral centres are usually labour-intensive and time-consuming.

Here we describe the synthesis of functional diphosphine oxides and diphosphine sulfides with two chiral centres and an acrylonitrile substituent, which can be easily transformed to the amide or acid function. The approach is exemplified by the nucleophilic addition of bis(2-phenylethyl)phosphine oxide **1a** and bis(2-phenylethyl)phosphine sulfide **1b** (readily available from elemental phosphorus and styrene)[4] to 3-phenyl-2-propynenitrile.[5]

3-Phenyl-2-propynenitrile is known[6] to add easily N-, O-, P- and S-nucleophiles to form in most cases *Z*-isomers of 3-substituted acrylonitriles. However, to our knowledge, the double addition of nucleophiles to both α- and β-acetylenic atoms is unknown not only for 3-phenyl-2-propynenitrile but also for all other disubstituted acetylenes bearing an electron-withdrawing substituent. In this work, using bis(2-phenylethyl)phosphine oxide and sulfide as an example, we found the unexpected double nucleophilic α,β-addition of secondary phosphine chalcogenides **1a**,**b** to 3-phenyl-2-propynenitrile (2:1 ratio) in a KOH–THF suspension to give 2,3-bis[bis(2-phenylethyl)phosphoryl]- and 2,3-bis[(bis(2-phenylethyl)phosphorothioyl]-3-phenylpropionitriles **2a**,**b** (Scheme 1).† Bis(2-phenylethyl)phosphine sulfide **1b** is more reactive in this process: its addition to 3-phenyl-2-propynenitrile occurred at room temperature (1 h) to give product **2b** in 52% yield, while diphosphine oxide **2a** was obtained in 40% yield by heating the reaction mixture at 60–62 °C for 6 h. This fact can be explained by a higher acidity of phosphine sulfides[7] and hence a higher concentration of thiophosphinite anions formed in the presence of KOH, as compared to that of phosphinite anions.

Bis(2-phenylethyl)phosphine chalcogenides **1a**,**b** react with 3-phenyl-2-propynenitrile in the presence of KOH (Scheme 1) chemoselectively: only trace amounts of monoadducts are formed in the reaction even at an equimolar ratio between the reactants. The interaction is regioselective since β,β-adducts were not identified in the reaction mixtures. Unusual is the second stage of the process: the addition of phosphine chalcogenides to the α-position of intermediate acrylonitrile system. Apparently, this is due to the competing electron-withdrawing effect of the added phosphoryl group, which changes the polarization of the double bond contributing zwitterion **A** (Scheme 2).

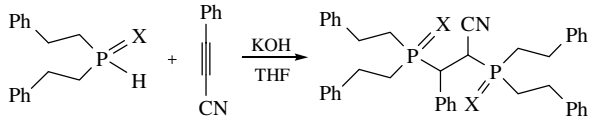


A

Scheme 2

This pathway may be the only one because the alternate addition to the β-carbon is sterically hindered. In addition, the ability to redirect the regioselectivity of nucleophilic addition from the classical β-addition mode to the α-addition mode was previously found in the phosphine-induced addition of nucleophiles to conjugated alkynoates.[8]

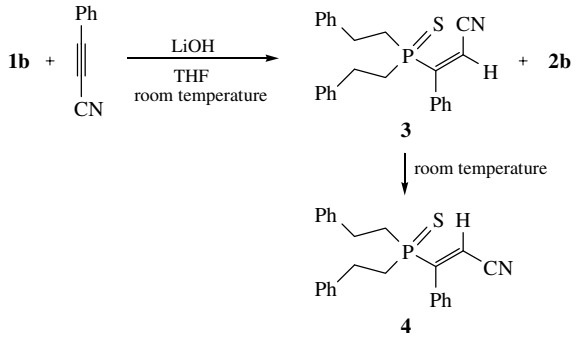
The absence of diadduct **2a**,**b** signal splitting in the ^{31}P and ^{1}H NMR spectra of reaction mixtures may indicate that



1a,**b** **2a**,**b**

a X = O
b X = S

Scheme 1



Scheme 3

only one diastereomer is formed (unless nuclei of diastereomers are magnetically equivalent) and that the reaction is diastereoselective.

Note that the reaction of bis(2-phenylethyl)phosphine sulfide **1b** with an equimolar amount of 3-phenyl-2-propynenitrile under less basic conditions (LiOH–THF system, room temperature) leads to a mixture of monoadduct (*Z*)-3-[bis(2-phenylethyl)-phosphorothioyl]-3-phenyl-2-propenenitrile **3** and diadduct **2b** in 34 and 17% yields, respectively (Scheme 3).‡

When allowed to stay at room temperature, compound **3** was partially converted (~30% conversion after 1 month) into corresponding *E*-isomer **4** (Scheme 3).‡

In summary, double nucleophilic addition of secondary phosphine chalcogenides to 3-phenyl-2-propynenitrile represents a convenient synthesis of diphosphine chalcogenides with two chiral centres. Amphiphilic functional phosphine oxides and sulfides thus obtained containing polar hydrophilic functions and hydrophobic branched counterparts are promising ligands for the design of metal complex catalysts combining the properties of phase-transfer and micellar catalysts.

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† *General procedure for the preparation of compounds* **2**. To a solution of secondary phosphine chalcogenide **1** (1.26 mmol) and 3-phenyl-2-propynenitrile (0.08 g, 0.63 mmol) in 5 ml of THF, KOH·0.5H_2O (15% water) (0.016 g, 0.25 mmol) was introduced. The suspension obtained was stirred at 60–62 °C for 6 h (in the case of **1a**) or at room temperature for 1 h (in the case of **1b**). KOH was filtered off, and the solvent was removed from the filtrate under reduced pressure. The crude honey-like product was washed with Et_2O (8 ml). After drying in a vacuum (1 Torr), diphosphine chalcogenides **2** were obtained as powders.

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

2,3-Bis[bis(2-phenylethyl)phosphoryl]-3-phenylpropionitrile **2a**. Yield 40% (0.16 g). White powder, mp 186–188 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ: 1.29–1.40 (m, 1H, CH_2P), 1.72–1.93 (m, 5H, CH_2P), 2.19–2.26 (m, 2H, CH_2P), 2.49–2.57 (m, 2H, CH_2Ph), 2.63–2.73 (m, 1H, CH_2Ph), 2.75–3.00 (m, 5H, CH_2Ph), 3.88 (ddd, 1H, CHCN, $^3J_{HH}$ 2.0 Hz, J_{HP} 8.3 Hz, J_{HP} 17.6 Hz), 3.96 (ddd, 1H, CHPh, $^3J_{HH}$ 2.0 Hz, J_{HP} 9.6 Hz, J_{HP} 14.1 Hz), 6.82–7.81 (m, 25H, Ph). C,H-correlation experiment (HSQC) was carried out for the assignment of the protons. ^{13}C NMR ($CDCl_3$) δ: 27.37 (d, CH_2Ph, $^2J_{CP}$ 3.4 Hz), 27.56 (d, CH_2Ph, $^2J_{CP}$ 4.2 Hz), 27.84 (d, CH_2Ph, $^2J_{CP}$ 3.8 Hz), 28.12 (d, CH_2Ph, $^2J_{CP}$ 3.4 Hz), 28.94 (d, CH_2P, $^1J_{CP}$ 61.0 Hz), 29.11 (d, CH_2P, $^1J_{CP}$ 62.2 Hz), 29.22 (d, CH_2P, $^1J_{CP}$ 61.8 Hz), 30.40 (dd, CHCN, $^1J_{CP}$ 50.6 Hz, $^2J_{CP}$ 2.6 Hz), 30.54 (d, CH_2P, $^1J_{CP}$ 63.3 Hz), 41.21 (d, CHPh, $^1J_{CP}$ 57.1 Hz), 117.02 (br. s, CN), 126.85, 126.99, 127.19, 128.16, 128.33, 128.44, 128.47, 128.84, 129.00, 129.10, 129.21, 129.67, 129.98, 130.86 (C_o, C_m, C_p, $PhCH_2$, PhCH), 132.68 (br. s, C_{ipso}, PhCH), 139.96 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 12.3 Hz), 140.19 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 14.2 Hz), 140.65 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 13.0 Hz), 140.70 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 13.8 Hz). ^{31}P NMR ($CDCl_3$) δ: 46.93 (d, $^3J_{PP}$ 27.5 Hz), 49.61 (d, $^3J_{PP}$ 27.5 Hz). IR (ν/cm^{-1}): 2230 (C≡N), 1158 (P=O). Found (%): C, 76.21; H, 6.76; N, 2.38; P, 9.57. Calc. for $C_{41}H_{43}NO_2P_2$ (%): C, 76.50; H, 6.73; N, 2.18; P, 9.62.

2,3-Bis[bis(2-phenylethyl)phosphorothioyl]-3-phenylpropionitrile **2b**. Yield 52% (0.22 g). White powder, mp 68–70 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ: 1.25–1.49 (m, 1H, CH_2P), 1.70–2.07 (m, 5H, CH_2P), 2.17–2.31 (m, 2H, CH_2P), 2.39–2.54 (m, 3H, CH_2Ph), 2.64–2.76 (m, 1H, CH_2Ph), 2.85–3.09 (m, 4H, CH_2Ph), 4.23 (ddd, 1H, CHCN, $^3J_{HH}$ 2.0 Hz, J_{HP} 11.1 Hz, J_{HP} 15.9 Hz), 4.44 (ddd, 1H, CHPh, $^3J_{HH}$ 2.0 Hz, J_{HP} 13.1 Hz, J_{HP} 15.1 Hz), 6.78–8.11 (m, 25H, Ph). C,H-correlation experiment (HSQC) was carried out for the assignment of the protons. ^{13}C NMR ($CDCl_3$) δ: 27.99 (d, CH_2Ph, $^2J_{CP}$ 2.2 Hz), 28.12 (d, CH_2Ph, $^2J_{CP}$ 3.5 Hz), 28.45 (d, CH_2Ph, $^2J_{CP}$ 3.5 Hz), 28.78 (d, CH_2Ph, $^2J_{CP}$ 2.6 Hz), 30.89 (d, CH_2P, $^1J_{CP}$ 45.7 Hz), 31.12 (d, CH_2P, $^1J_{CP}$ 45.8 Hz), 31.44 (d, CH_2P, $^1J_{CP}$ 47.6 Hz), 32.10 (d, CH_2P, $^1J_{CP}$ 48.8 Hz), 33.21 (d, CHCN, $^1J_{CP}$ 35.6 Hz), 43.18 (d, CHPh, $^1J_{CP}$ 41.8 Hz), 117.03 (d, CN, $^2J_{CP}$ 3.7 Hz), 126.60, 126.64, 126.75, 126.98, 128.04, 128.33, 128.44, 128.59, 128.77, 128.87, 129.00, 129.65, 130.78 (C_o, C_m, C_p, $PhCH_2$, PhCH), 132.15 (d, C_{ipso}, PhCH, $^2J_{CP}$ 3.2 Hz), 139.59 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 14.8 Hz), 139.80 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 14.8 Hz), 140.27 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 14.8 Hz), 140.38 (d, C_{ipso}, $PhCH_2$, $^3J_{CP}$ 14.8 Hz). ^{31}P NMR ($CDCl_3$) δ: 58.18 (d, $^3J_{PP}$ 36.1 Hz), 60.47 (d, $^3J_{PP}$ 36.1 Hz). IR (ν/cm^{-1}): 2229 (C≡N), 607, 614 (P=S). Found (%): C, 72.57; H, 6.43; N, 2.35; P, 8.87; S, 9.39. Calc. for $C_{41}H_{43}NP_2S_2$ (%): C, 72.86; H, 6.41; N, 2.07; P, 9.17; S, 9.49.

‡ To a solution of 3-phenyl-2-propynenitrile (0.20 g, 1.57 mmol) in 5 ml of THF, LiOH (0.02 g, 0.84 mmol) was introduced. To the suspension obtained, phosphine sulfide **1b** (0.38 g, 1.39 mmol) was added dropwise for 30 min. The reaction mixture was stirred at room temperature for 2 h, LiOH was filtered off, the solvent was removed from the filtrate under reduced pressure. According to ^{1}H and ^{31}P NMR spectroscopy, the crude honey-like product contained diadduct **2b** and monoadduct **3** in a 1:4 ratio along with small amounts of unidentified products. The mixture was washed with Et_2O (10 ml), the precipitate thus obtained was filtered off and dried in a vacuum (1 Torr) to give 0.08 g (17%) of diadduct **2b**.

Compound **3** (identified in a mixture with small amounts of unidentified products by ^{1}H and ^{31}P NMR spectroscopy); yield 34% (calculated from the ^{1}H NMR spectrum of the crude product on the basis of the ratio between compounds **2b** and **3**). ^{1}H NMR ($CDCl_3$) δ: 2.38–2.51 (m, 2H, CH_2P), 2.56–2.67 (m, 2H, CH_2P), 2.82–3.05 (m, 4H, CH_2Ph), 6.03 (d, 1H, =CH, $^3J_{HP}$ 29.3 Hz), 7.03–7.46 (m, 15H, Ph). ^{31}P NMR ($CDCl_3$) δ: 46.50. IR (ν/cm^{-1}): 2210 (C≡N).

Compound **4** (identified in a mixture with **3** and small amounts of unidentified products by ^{1}H and ^{31}P NMR spectroscopy). ^{1}H NMR ($CDCl_3$) δ: 2.05–2.30 (m, 4H, CH_2P), 2.82–3.05 (m, 4H, CH_2Ph), 7.03 (d, 1H, =CH, $^3J_{HP}$ 17.6 Hz), 7.03–7.46 (m, 15H, Ph). ^{31}P NMR ($CDCl_3$) δ: 50.98. IR (ν/cm^{-1}): 2210 (C≡N).