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A three-component reaction involving isocyanide, phosphine and ketenimine functionalities†

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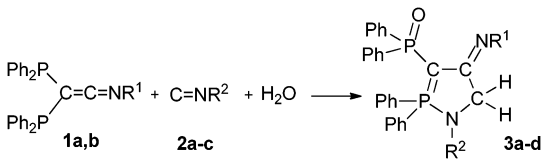
A three-component reaction involving diphosphinoketenimines, isocyanides and water or ethanol leading to the formation of new five-membered azaphosphaheterocycles is described.

Some years ago we reported the synthesis of ketenimine-functionalized diphosphines of formula $(PPh_2)_2C{=}C{=}NR$,[1] and their reactivity with alkynes and heterocumulenes to obtain unique phosphorus heterocycles.[2] We also proved that, upon coordination to a metal center, the ketenimine group in these diphosphines become activated toward nucleophilic addition of organolithium and organomagnesium reagents[3] and amines,[4] allowing the formation of a variety of highly functionalized diphosphines. Even weak nucleophiles such as isocyanides were able to react with coordinated *N*-aryl diphosphinoketenimines yielding indole-functionalized diphosphines.[1] Being aware of the wide range of applications of the isocyanide functionality in synthesis, we have now studied the reactivity of free diphosphinoketenimines themselves with isocyanides. Notably we have found that both molecules can be coupled in a formal [3 + 2] cycloaddition reaction involving ketenimine, phosphine and isocyanide functional groups, but only under special circumstances, that is in the presence of water or ethanol, which were also included in the final reaction product. This reaction can be considered as an unprecedented type of isocyanide-based multicomponent reaction (IMCR), whose relevance in synthesis is nowadays widely recognized.[5]

Diphosphinoketenimines $(PPh_2)_2C{=}C{=}NR^1$ (**1a**: R^1 = Ph, **1b**: R^1 = Xylyl) react at room temperature with isocyanides CNR^2 (**2a**: R^2 = *t*Bu, **2b**: R^2 = Bz, **2c**: R^2 = Xylyl) in the presence of water, in THF as solvent, to afford 1,2-λ^5-azaphospholene derivatives **3a–d** (Scheme 1). The structure of compounds **3a–d** was unambiguously established by spectroscopic methods‡ and, in the case of **3a**, by a single-crystal X-ray diffraction study.§ Two doublets were present in the $^{31}P\{^1H\}$ NMR spectra, the higher-field one (around 28 ppm) corresponding to the phosphine oxide group, whereas the endocyclic phosphorus atom appeared near to 60 ppm. The newly formed endocyclic methylene group was clearly observed both in the ^1H and $^{13}C\{^1H\}$ NMR spectra. The X-ray crystal structure of **3a** (Fig. 1) confirmed the cyclic nature of the new compound, containing an almost planar azaphospholene skeleton. The coordination geometry around the endocyclic nitrogen atom N1 is also planar, allowing electronic delocalization of its lone pair through the phosphorus atom P2, as proved by the short N1–P2 bond distance (1.659(2) Å).



Scheme 1

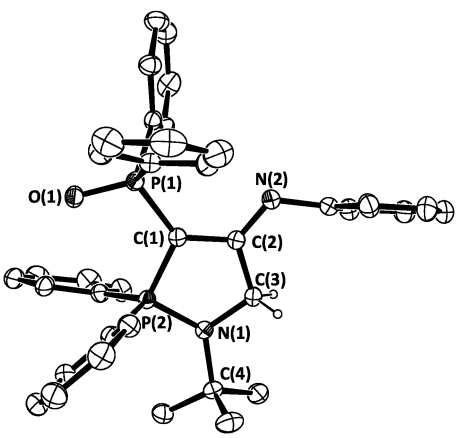


Fig. 1 Crystal structure of **3a** (ORTEP, thermal ellipsoids at 20% probability). Hydrogen atoms, except those of C(3), are omitted for clarity. Selected bond distances [Å] and angles [°]: O(1)–P(1) 1.487(1), P(1)–C(1) 1.749(2), P(2)–N(1) 1.659(2), P(2)–C(1) 1.721(2), C(1)–C(2) 1.421(3), N(1)–C(3) 1.462(3), N(1)–C(4) 1.509(3), N(2)–C(2) 1.294(3), C(2)–C(3) 1.514(3); N(1)–P(2)–C(1) 96.72(9), C(3)–N(1)–C(4) 117.0(2), C(3)–N(1)–P(2) 111.5(1), C(4)–N(1)–P(2) 127.7(1), N(1)–C(3)–C(2) 109.4(2), C(1)–C(2)–C(3) 111.6(2), C(2)–C(1)–P(2) 110.3(1).

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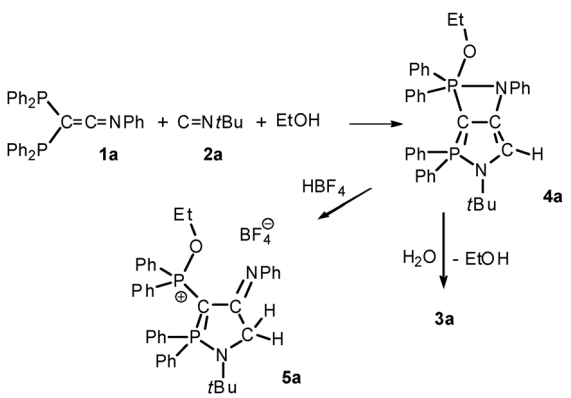
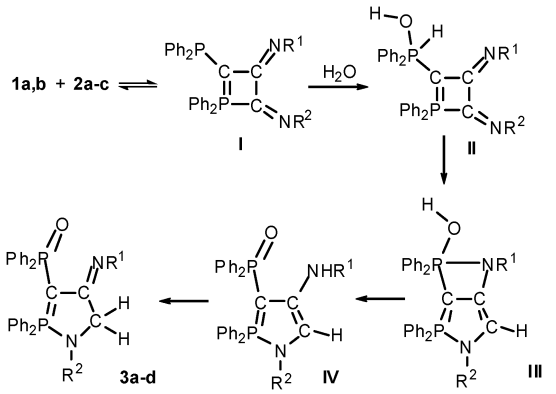
In the absence of water (a rigorous drying of isocyanide over molecular sieves is needed), no reaction occurred between **1a,b** and isocyanide **2**. We have also checked that diphosphinoketenimines **1a,b** do not react with water, showing that the presence of the three compounds is needed for the reaction to take place. Additionally, to ascertain that both the oxygen atom of the diphenylphosphinyl group and the methylene hydrogen atoms arise from water and not from other sources such as traces of molecular oxygen or solvent, two independent isotopic labeling experiments were carried out. Thus, a mixture of **1a** and **2a** was treated first with D_2O and then with $H_2{}^{17}O$. In both cases, the $^{31}P\{^1H\}$ NMR spectra of the resulting compound showed formation of the azaphospholene derivative **3a** similarly as when using H_2O, but, in the first experiment, the signal of the methylene protons was absent in the ^1H NMR spectrum, whereas in the second experiment, the $^{17}O\{^1H\}$ NMR spectrum showed clearly a signal at 60.1 ppm, which is typical for a phosphine oxide.[6]

It should be emphasized that, as far as we know, this is the first time that a phosphine–isocyanide coupling has been observed. Furthermore, to our knowledge, the 1,2-λ^5-azaphosphol-2-ene ring generated has no precedents in the literature.[7]

To extend the IMCR above to hydroxyl-containing molecules different from water, we carried out the reaction of a mixture of **1a** and **2a** with EtOH, affording compound **4a**, for which we propose the bicyclic structure depicted in Scheme 2 containing two fused λ^5-azaphosphole and λ^5-azaphosphetidine heterocycles. The presence of the ethoxy group as a substituent on the phosphorus atom in the four-membered heterocycle shows that in this case only the O–H bond of ethanol has been activated whereas the O–Et bond is maintained. In the $^{31}P\{^1H\}$ NMR spectrum of **4a** the signal due to the P-phosphole atom appears at 57.8 ppm, this means an almost identical chemical shift to that found for the P-phospholene atom in **3a**. The remaining phosphorus atom appears in the high-field region (−14.5 ppm), which, together with the high value of the $^2J_{PP}$ coupling constant (181 Hz), is consistent with the phosphorane nature of this phosphorus atom.[8] Signals corresponding to the ethoxy group are clearly identified in the ^1H and $^{13}C\{^1H\}$ NMR spectra, where the coupling constants of both methylene and methyl groups with the P-phosphorane atom are resolved.‡ The nature of compound **4a** was additionally supported by derivatization reactions.[9] Thus simple hydrolysis with water readily produces compound **3a**, whereas treatment with HBF_4 yields the



Scheme 2



Scheme 3 Proposed mechanism for the formation of 1,2-λ^5-azaphospholene compounds **3a–d**.

phosphonium salt **5a** (Scheme 2). The $^{31}P\{^1H\}$ NMR spectrum of **5a** shows the disappearance of the high-field phosphorane signal and the presence of two doublets with chemical shifts and coupling constant similar to those found for **3a**.

No doubt the mechanism of formation of compounds **3a–d** should be rather complex; nevertheless a tentative reaction pathway is proposed in Scheme 3. Taking into account that, as we have reported previously,[2] diphosphinoketenimines behave as 1,3 dipoles through a phosphorus atom and the C=N carbon atom of the ketenimine group, α-addition of **1a,b** to isocyanide **2** could form the intermediate adduct **I**. [1 + 3] cycloadditions of isocyanides to 1,3 dipoles to afford four-membered rings are well documented in the literature.[10] It is also worth noting that α-addition is a key step in IMCRs such as the Ugi 4CR.[5,11] Adduct **I** would be unstable and readily could revert to **1a,b** and **2**,[12] as no reaction occurred in the absence of water. However, in the presence of H_2O (or ethanol) **I** could undergo oxidative addition at the exocyclic diphenylphosphino group giving **II**.[13,14] In a further step, the transfer of the P–H hydrogen atom to the carbon atom of the former isocyanide accompanied by expansion of the strained λ^5-phosphetene ring would afford **III**, which, upon a proton transfer would give **IV** and finally **3a–d**, by an enamine–imine transformation. Note that intermediate **III** is analogous to compound **4a**, but, unlike **4a**, **III** was not detected even by carrying out the reaction at low temperature. We are currently performing theoretical DFT calculations to gain light on the mechanism of this unique cyclization process.

In summary, we have described herein an unprecedented isocyanide-based multicomponent reaction involving diphosphinoketenimines, isocyanides and water (or ethanol), which leads to the formation of new five-membered azaphosphaheterocycles. It is expected that this reaction can be extended to other molecules containing E–H groups such as a variety of alcohols or thiols, which will be pursued in the near future in our laboratory.

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Notes and references

‡ Selected spectroscopic data: **3a**: ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 1.02 (s, 9H, CH_3), 4.02 (d, ^3J(P,H) = 8 Hz , 2H, CH_2), 6.6–8.1 ppm (25H, Ph); $^{13}C\{^1H\}$ NMR (75.5 MHz, CD_2Cl_2, 25 °C): δ = 29.6 (s, CH_3), 52.0 (t, ^2J(P,C) = ^3J(P,C) = 10 Hz, CH_2), 56.6

(s, $C(CH_3)_3$), 154.8 (s, C_{ipso} NPh), 163.7 ppm (dd, ^2J(P,C) = 18 Hz, ^2J(P,C) = 4 Hz, *C*=NPh); $^{31}P\{^1H\}$ NMR (121.4 MHz, CD_2Cl_2, 25 °C): δ = 27.4 (d, ^2J(P,P) = 52 Hz, Ph_2P=O), 57.1 ppm (d, ^2J(P,P) = 52 Hz, Ph_2P=C). **3b**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.97 (s, 9H, CH_3 (*t*Bu)), 1.90 (s, 6H, CH_3 (Xylyl)), 3.58 (d, ^3J(P,H) = 8 Hz, 2H, CH_2), 6.7–8.1 ppm (23H, aryl); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 18.8 (s, CH_3 (Xylyl)), 29.5 (s, CH_3 (*t*Bu)), 52.7 (t, ^2J(P,C) = ^3J(P,C) = 10 Hz, CH_2), 56.0 (s, $C(CH_3)_3$), 152.5 (s, C_{ipso} NXylyl), 162.2 ppm (br, *C*=NXylyl); $^{31}P\{^1H\}$ NMR (121.4 MHz, CD_2Cl_2, 25 °C): δ = 29.3 (d, ^2J(P,P) = 52 Hz, Ph_2P=O), 58.5 ppm (d, ^2J(P,P) = 52 Hz, Ph_2P=C). **3c**: ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 3.81 (d, ^3J(P,H) = 8 Hz, 2H, CH_2), 4.09 (d, ^3J(P,H) = 7 Hz, 2H, CH_2), 6.63 (d, ^3J(H,H) = 7 Hz, 2H, H_{ortho} NPh), 6.78 (t, ^3J(H,H) = 7 Hz, 1H, H_{para} NPh), 6.7–8.0 ppm (27H, Ph); $^{31}P\{^1H\}$ NMR (121.4 MHz, CD_2Cl_2, 25 °C): δ = 27.4 (d, ^2J(P,P) = 49 Hz, Ph_2P=O), 62.2 ppm (d, ^2J(P,P) = 49 Hz, Ph_2P=C). **3d**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.71 (s, 6H, CH_3 (Xylyl)), 2.10 (s, 6H, CH_3 (Xylyl)), 3.86 (d, ^3J(P,H) = 7 Hz, 2H, CH_2), 6.7–8.1 ppm (26H, aromatics); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 18.4 (s, CH_3 (Xylyl)), 18.8 (s, CH_3 (Xylyl)), 50.7 (t, ^1J(P,C) = 110 Hz, P_2C), 58.9 (t, ^2J(P,C) = ^3J(P,C) = 11 Hz, CH_2), 151.7 (s, C_{ipso} NXylyl), 163.0 ppm (d, ^2J(P,C) = 13 Hz, *C*=NXylyl); $^{31}P\{^1H\}$ NMR (121.4 MHz, CD_2Cl_2, 25 °C): δ = 26.1 (d, ^2J(P,P) = 46 Hz, Ph_2P=O), 60.4 ppm (d, ^2J(P,P) = 46 Hz, Ph_2P=C). **4a**: ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 0.62 (s, 9H, CH_3 (*t*Bu)), 1.56 (t, ^3J(H,H) = 7 Hz, 3H, OCH_2CH_3), 4.65 (q, ^3J(P,H) = ^3J(H,H) = 7 Hz, 2H, OCH_2CH_3), 6.2–7.9 ppm (26H, Ph and C=CH); $^{13}C\{^1H\}$ NMR (75.5 MHz, CD_2Cl_2, 25 °C): δ = 17.3 (d, ^3J(P,C) = 7 Hz, OCH_2CH_3), 28.9 (s, CH_3 (*t*Bu)), 52.8 (d, ^1J(P,C) = 18 Hz, P_2C), 58.2 (s, $C(CH_3)_3$), 65.7 (d, ^2J(P,C) = 6 Hz, OCH_2CH_3), 152.2 (s, C_{ipso} NPh), 156.6 (d, ^2J(P,C) = 12 Hz, C=CH), 169.2 ppm (dd, ^2J(P,C) = 8 Hz, ^2J(P,C) = 2 Hz, *C*–NPh); $^{31}P\{^1H\}$ NMR (121.4 MHz, CD_2Cl_2, 25 °C): δ = −14.5 (d, ^2J(P,P) = 181 Hz, Ph_2P=O), 57.8 ppm (d, ^2J(P,P) = 181 Hz, Ph_2P=C). **5a**: ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 0.86 (s, 9H, CH_3 (*t*Bu)), 1.56 (t, ^3J(H,H) = 7 Hz, 3H, OCH_2CH_3), 2.87 (s, 2H, CH_2), 4.76 (q, ^3J(P,H) = ^3J(H,H) = 7 Hz, 2H, OCH_2CH_3), 6.0–7.9 ppm (25H, Ph); $^{13}C\{^1H\}$ NMR (75.5 MHz, CD_2Cl_2, 25 °C): δ = 16.6 (d, ^3J(P,C) = 6 Hz, OCH_2CH_3), 28.7 (s, CH_3 (*t*Bu)), 44.2 (d, ^2J(P,C) = 8 Hz, CH_2), 50.6 (s, $C(CH_3)_3$), 65.5 (d, ^2J(P,C) = 6 Hz, OCH_2CH_3), 151.2 (s, C_{ipso} NPh), 172.1 ppm (d, ^2J(P,C) = 8 Hz, *C*=NPh); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$, 25 °C): δ = 21.4 (d, ^2J(P,P) = 54 Hz, Ph_2P=O), 50.6 ppm (d, ^2J(P,P) = 54 Hz, Ph_2P=C).

§ Crystal data for **3a** ($C_{37}H_{36}N_2OP_2{\cdot}CH_2Cl_2$): M = 671.54, crystal size 0.13 × 0.10 × 0.08 mm, a = 11.6478(6) Å, b = 18.985(1) Å, c = 16.179(1) Å, β = 99.847(4)°, V = 3525.0(4) Å^3, ρ_{calcd} = 1.265 g cm^{-3}, μ = 2.76 mm^{-1}, Z = 4, monoclinic, space group $P2_1/n$, λ = 1.54184 Å, T = 293(2) K, θ_{max} = 70, independent reflections = 6543, refined parameters = 546, largest diff. peak and hole 0.31 and −0.41 e Å^{-3}, wR_2 = 0.129, R_1 = 0.048.

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