Tetrahedron Letters 53 (2012) 5944–5947

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A phosphoryl to spiro-bicyclophosphorane transformation via β-amidic proton elimination in phosphorylated hydrazides

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ARTICLE INFO

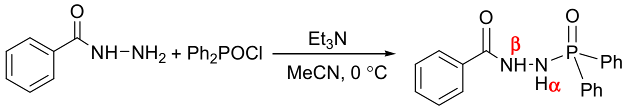
Article history:
Received 25 June 2012
Revised 13 August 2012
Accepted 24 August 2012
Available online 1 September 2012

Keywords:
$^{2}J_{PH}$ Coupling constant
Hydrazide
Phosphoryl
Spiro-bicyclophosphorane

ABSTRACT

The reaction between phosphoryl-containing reagents and hydrazides has been studied. The tetrahedral phosphoryl structure is transformed into a spiro-bicyclophosphorane system with trigonal bipyramidal geometry by the elimination of a β-amidic proton in the reaction between a hydrazide and phosphoryl reagents with at least two leaving groups (Cl) bound to the phosphorus atom, such as $POCl_3$ or $PhPOCl_2$. In the spiro-bicyclophosphorane structure, the C═N imine bond is formed upon β-amidic proton elimination, leading to the conversion of the C═O into a C–O bond and the formation of a P–O bond. All of these structural rearrangements are supported by X-ray crystallography data, and NMR and IR experiments.

The structures of cyclic pentacoordinate phosphoranes have attracted significant interest because they serve as models for biologically active compounds and intermediates.[1–4] Heterocyclic phosphoranes with a P–N–N═C–O unit have been previously prepared via the redox coupling of a trialkyl- or triarylphosphine (PR_3) and a dialkyl azodicarboxylate (ROOCN═NCOOR).[5,6] Such N- and O-cycloadditions also occur in the reaction of a simple hydrazide ($RCONHNH_2$) with phosphorus(III) mono- or triamides to form cyclophosphorane systems.[7,8] Moreover, there are reports on the synthesis and reactivities of phosphorus hydrazides $[P(X)(NRNH_2)_2$, X = O and S],[9–16] although these compounds do not transform into products with the phosphorane structure. To the best of our knowledge, phosphoryl-containing reagents have never been used for the formation of spiro-bicyclophosphoranes. Here, we present the synthesis of such compounds based on the reaction of simple hydrazides (benzhydrazide and 4-pyridinecarboxylic acid hydrazide) with phosphoryl-containing reagents ($POCl_3$, $PhPOCl_2$ and Ph_2POCl). The molecular geometry of the products depends on the number of appropriate leaving groups (Cl) bound to the phosphoryl functional group in the reactant. A simple acid-base reaction between benzhydrazide and a phosphoryl-containing reactant with only one chlorine atom (Ph_2POCl) produces a product with tetrahedral structure at the phosphorus atom. On the other hand, products with a trigonal bipyramidal structure (spiro-bicyclophosphorane) are formed, when phosphoryl reagents with at least two chlorine atoms ($PhPOCl_2$ or $POCl_3$) are used.



Scheme 1. Synthesis of **1**.

Compound **1** was prepared by the reaction between a mixture of benzhydrazide, Ph_2POCl, and triethylamine in acetonitrile[17] (Scheme 1). Figure 1 shows the X-ray crystal structure of **1**. The P═O (1.489(2) Å), P1–N2 (1.659(2) Å), and C═O (1.235(2) Å) distances are similar to those in other well-known phosphoramides[18] and carbacylamidophosphates[19] with tetrahedral configurations at the phosphorus atom. The chemical shift of the β-amidic proton in the ^{1}H NMR spectrum of **1** appeared at 10.17 ppm (Table 1), implying its high acidity and ability to undergo elimination in basic media. The chemical shifts of 21.80 and 166.93 ppm in the ^{31}P and ^{13}C NMR spectra, respectively, and the bands at 1198 (P═O) and 1655 (C═O) cm^{-1} in the IR spectrum confirm the presence of P═O and C═O functional groups in **1**. We have recently shown that the $^{2}J_{PNH}$ coupling constant increases when the P–N distance is shortened.[20] Here, the $^{2}J_{PNH}$ value (21.9 Hz) in **1** is relatively high in magnitude compared with other phosphoramide compounds previously reported,[18,20] although the P1–N2 distance is not too short.

The phosphoryl structure is transformed into a spiro-bicyclophosphorane system by a dehydration–cyclization rearrangement, when at least two Cl leaving groups are bound to the P═O functional group in the starting material. The reaction between benzhydrazide and $POCl_3$ (2:1), in acetonitrile under reflux conditions,

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http://dx.doi.org/10.1016/j.tetlet.2012.08.105

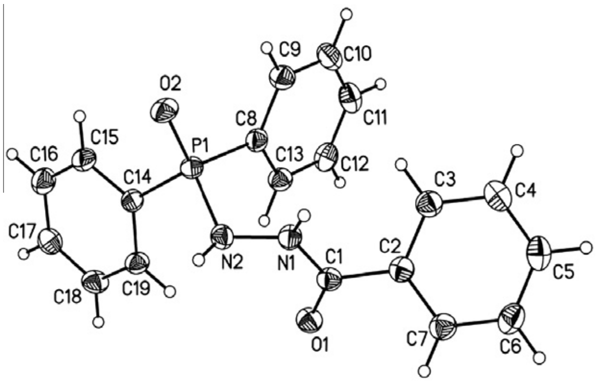
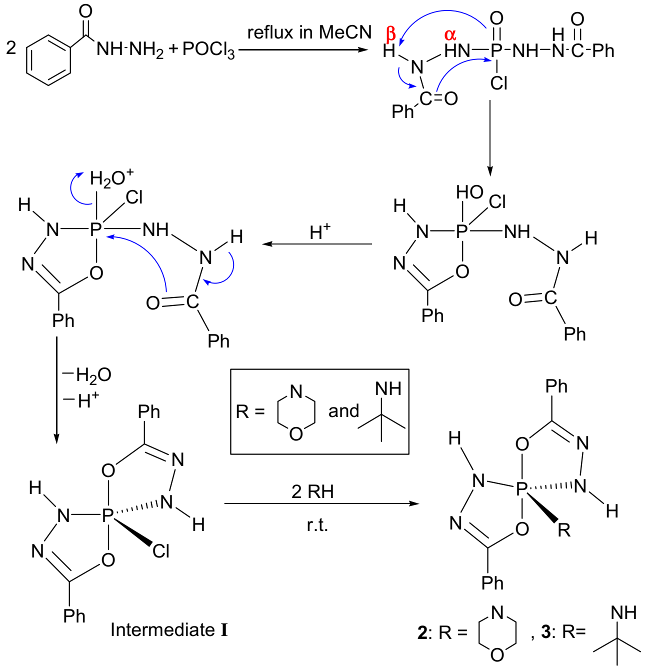


Figure 1. ORTEP representation of compound **1**. Selected bond lengths (Å) and bond angles (°): P1–N2, 1.6587(15); P1–O2, 1.4886(12); P1–C8, 1.7981(18); P1–C14, 1.7941(17); N1–N2, 1.4048(19); C1–N1, 1.346(2); C1–O1, 1.235(2); O1–P1–O2, 170.12(8); O2–P1–N2, 118.55(7); O2–P1–C14, 110.93(7); O2–P1–C8, 111.42(8); C8–P1–C14, 108.41(8); N2–P1–C14, 103.67(7); N2–P1–C8, 103.10(8).

leads to intermediate **I**. Compounds **2** and **3** were prepared by treatment of the appropriate amines (morpholine and *tert*-butylamine) with intermediate **I** (2:1),[21] Scheme 2. The proposed synthetic pathway for products **2** and **3** (Scheme 2) indicates that cyclization of the initial phosphorylated hydrazide is started by elimination of the β-amidic proton followed by dehydration. Compound **2** was recrystallized from a mixture of methanol and acetonitrile (4:1) at room temperature to obtain crystals suitable for X-ray analysis.



Scheme 2. Synthesis of compounds **2** and **3** and the proposed reaction mechanism.

Figure 2 shows the molecular structure of compound **2**. The phosphorus atom adopts a distorted trigonal bipyramidal geometry in spiro-bicyclophosphorane **2** with the oxygen atoms in axial and nitrogen atoms in equatorial positions. The C1–N2 distance (1.282(3) Å) in **2** is considerably shorter than a typical C–N single bond, while the C1–O1 distance (1.351(2) Å) in **2** is longer than the C=O bond in **1**. This is in good agreement with the β-amidic proton elimination and the changes in the C1–N2 and C1–O1 bond lengths upon cyclization. In the ^{31}P NMR spectrum of **2**, a triplet of triplets appeared at −37.72 ppm. This splitting pattern arises from the spin couplings between the phosphorus nucleus and two NH_α ($^2J_{PNH}$ = 40.4 Hz) and two axial N-C$H_{\text{morpholine}}$ ($^3J_{PNCH}$ = 8.9 Hz) protons. The spin couplings between the phosphorus nucleus and two NH_α protons ($^2J_{PNH}$ = 45.2 Hz) and one N$H_{tert\text{-butylamine}}$ ($^2J_{PNH}$ = 12.1 Hz) proton lead to a doublet of triplets for the ^{31}P NMR signal in compound **3**. The $^2J_{PNH}$ coupling constants in compounds **2** and **3** are larger than the corresponding values in **1**. The decrease in δ (^{13}C) values, from 166.93 ppm in **1** to 152.54 and 151.68 ppm, respectively, in compounds **2** and **3** (Table 1), confirms the formation of a CO–P connection between the carbonyl oxygen atom and the phosphorus atom upon cyclization. The CO–P bond leads to spin couplings for the phosphorus and carbon nuclei with $^2J_{POC}$ values in the range of 14.1–14.6 Hz. The sharp bands at ~1330 cm^{-1} in the IR spectra of compounds **2** and **3** confirm the decrease in the bond order from C=O to C–O on cyclization and that the oxygen atom is bound to the phosphorus atom.

Compounds **4–6** were synthesized by the reaction of a mixture of triethylamine and benzhydrazide or 4-pyridinecarboxylic acid

Table 1
Selected spectroscopic data of products **1–8**

Product	δ^a (^{31}P) in ppm	^{1}H: $\delta^{b,c}$ (ppm)/$^2J_{PNH}$ (Hz)	^{13}C: $\delta^{b,c}$ (ppm)/$^2J_{POC}$ (Hz)	ν(C=O) in cm^{-1}
1	21.80	H^α:7.76/21.9 H^β:10.17/–	166.93/–	1655
		^{1}H: $\delta^{b,c}$/$^2J_{PNH}$ (Hz)	^{13}C: $\delta^{b,c}$/$^2J_{POC}$ (Hz)	ν (C=O/C–O) in cm^{-1}
2	−37.72	8.57/40.4	152.54/14.1	–/1330
3	−43.31	3.69/12.1 8.17/45.2	151.68/14.6	–/1328
4	−36.19	8.85/36.9	154.20/10.9	–/1324
5	−47.40	7.15/13.4 8.58/39.9	152.52/15.1	–/1324
6	−46.92	7.32/13.3 8.99/40.9	150.71/15.4	–/1326
7	−45.23	6.75/36.6 8.48/39.6 9.88/–	152.06/14.6 166.39/–	1669/1329
8	−45.31	7.12/37.3 8.98/41.1 10.38/–	150.41/15.4 164.91/–	1686/1323

[a] The ^{31}P NMR spectra were recorded for DMSO-d_6 solutions at 202.45 MHz.
[b] The ^{31}H and ^{13}C NMR spectra were recorded for DMSO-d_6 solutions at 500.13 and 125.77 MHz, respectively.
[c] The chemical shifts for the amidic protons and carbonyl (or imine) carbon atoms are provided.

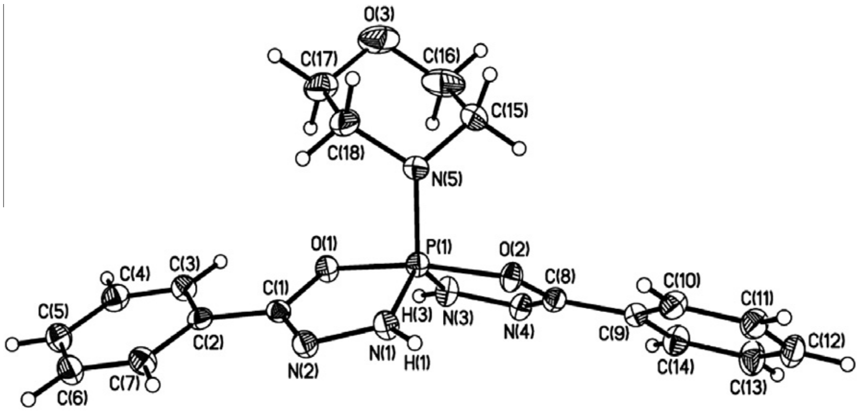
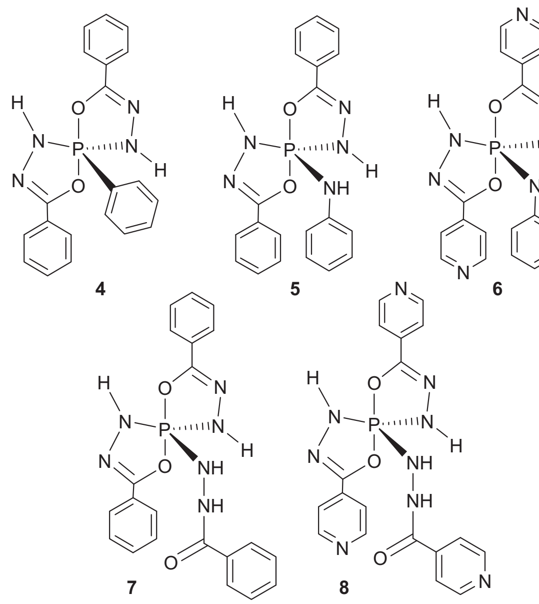


Figure 2. ORTEP representation of compound **2**. Selected bond lengths (Å) and bond angles (°): P1–N1, 1.6588(18); P1–N3, 1.6562(18); P1–N5, 1.662(2); P1–O1, 1.7296(15); P1–O2, 1.7150(14); C1–N2, 1.282(3); C8–N4, 1.285(3); C1–O1, 1.351(2); C8–O2, 1.357(2); O1–P1–O2, 170.12(8); O1–P1–N1, 86.08(8); O1–P1–N3, 88.61(8); O1–P1–N5, 95.73(9); O2–P1–N1, 90.22(8); O2–P1–N3, 86.23(8); O2–P1–N5, 94.13(9); N1–P1–N3, 126.46(10); N3–P1–N5, 118.39(10); N1–P1–N5, 115.14(10).



Scheme 3. Structures of compounds **4**–**8**.

hydrazide with $PhPOCl_2$ and $PhNHPOCl_2$ (Scheme 3). The formation of the CO–P bond was again confirmed by the values observed for δ (^{13}C) in the range of 150.71–154.20 ppm with $^{2}J_{POC}$ couplings of about 10–15 Hz. The ^{31}P NMR signal of compounds **4** appeared as a triplet of triplets at −36.19 ppm, as a result of spin coupling of the phosphorus nucleus with two $NH_{hydrazide}$ and two *ortho*-phenyl protons. A doublet of triplets splitting pattern was observed for the ^{31}P NMR signal in compounds **7** and **2**, due to spin coupling between the phosphorus and the $NH_{aniline}$ and $NH_{hydrazide}$ protons. In the ^{1}H NMR spectrum of compound **5**, two signals at 7.15 and 8.58 ppm correspond to the $NH_{aniline}$ and $NH_{hydrazide}$ amide protons with $^{2}J_{PNH}$ coupling constant values of 13.4 and 39.9 Hz, respectively. Similarly, the chemical shifts of 7.32 and 8.99 ppm were assigned to the $NH_{aniline}$ and $NH_{hydrazide}$ protons, respectively, with $^{2}J_{PNH}$ values of 13.3 and 40.9 Hz in compound **6**.

Products **7** and **8** were obtained by the reaction between $POCl_3$ and a mixture of triethylamine and benzhydrazide (**7**) or 4-pyridinecarboxylic acid hydrazide (**8**). A quartet splitting pattern was observed for the ^{31}P NMR signal in compounds **7** and **8**, due to spin coupling between the phosphorus nucleus and three NH_{α} (endocyclic and exocyclic) protons. The ^{1}H NMR spectrum of **7** showed two doublets at 6.75 and 7.48 ppm confirming the presence of two types of α-amidic protons with $^{2}J_{PNH}$ values of 39.6 Hz (for the endocyclic NH_{α} proton) and 36.6 Hz (for the exocyclic NH_{α} proton), respectively. Two signals at 152.06 and 166.39 ppm in the ^{13}C NMR spectrum of **7** corresponded to the carbon atom in the ring (C–O) and the free carbonyl group (C═O), respectively. Two bands at 1329 and 1669 cm^{-1} in the IR spectrum of **7** were assigned to the C–OP and C═O bonds. Similar spectroscopic features were observed for compound **8**.

In summary, the products of the reactions between hydrazides and different phosphoryl-containing reagents have been compared. The phosphoryl to spiro-phosphorane transformation was observed when using phosphoryl reactants with at least two chlorine atoms. The synthesis, characterization, structural determination, and quantum mechanical calculations are now being performed in our laboratory for a number of additional phosphorylated hydrazides in order to investigate the question of why the $^{2}J_{PNH}$ values in these compounds are surprisingly high in magnitude.

Acknowledgements

Financial support of this work by the Tarbiat Modares University research council is gratefully acknowledged.

Supplementary data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 817641 (**1**) and 786389 (**2**). Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data (the experimental procedures and characterization data for compounds **4**–**8**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.105.

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17. Synthesis and characterization of **1**: 5 mmol (1.183 g) of diphenylphosphinic chloride was added dropwise to a mixture of 5 mmol (0.506 g) of Et_3N and 5 mmol (0.681 g) of benzhydrazide in dry MeCN at 0 °C and the mixture was stirred for 10 h. The resulting white product was filtered off and crystals suitable for X-ray diffraction were obtained from a CH_3OH/CH_3CN (1:2) solution of **1** at room temperature. Yield 74% (1.237 g), m.p. 165–168 °C, Anal. Calcd for $C_{19}H_{17}N_2O_2P$ (336.32): C 67.84, H 5.09, N 8.33; Found C 67.63, H 5.17, N 8.44. ^{31}P NMR (DMSO-d_6): δ 21.80 (m) ppm.^{1}H NMR (DMSO-d_6): δ 7.36 (t, $^3J_{HH} = 7.5$ Hz, 2H, Ar-H), 7.46 (m, 5H, Ar-H), 7.52 (t, $^3J_{HH} = 7.1$ Hz, 2H, Ar-H), 7.63 (d, $^3J_{HH} = 7.9$ Hz, 2H, Ar-H), 7.76 (d, $^2J_{PNH} = 21.9$ Hz, 1H, NH_α), 7.94 (dd, $^3J_{HH} = 7.6$ Hz, $^2J_{PCH} = 11.3$ Hz, 4H, CH$_{ortho}$), 10.17 (s, 1H, NH_β) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6): δ 127.3 (s), 128.2 (s), 128.3 (s), 131.4 (s), 131.5 (s), 131.8 (s), 132.1 (d, $^2J_{PC} = 9.5$ Hz, C$_{ortho}$), 132.5 (d, $^1J_{PC} = 63.4$ Hz, C$_{ipso}$), 166.9 (s) ppm. Selected IR data (KBr, cm^{-1}): 3155 (s), 3005 (m), 2840 (m), 1655 (s), 1544 (m), 1434 (s), 1319 (m), 1198 (s), 1123 (s), 1067 (m), 908 (m), 725 (s), 689 (s), 523 (m).
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20. Gholivand, K.; Mahzouni, H. R.; Esrafili, M. D. *Dalton Trans.* **2012**, *41*, 1597–1608.
21. General procedure for synthesis of compounds **2** and **3**: 10 mmol (1.362 g) of benzhydrazide was added to a cooled solution of 5 mmol (0.766 g) of phosphoryl chloride in CCl_4 at 0 °C and the mixture was stirred for 1 h. The resulting white product was filtered off and treated with a solution of 10 mmol of morpholine (**2**) or *tert*-butylamine (**3**) in 40 ml MeCN at room temperature for 8 h. The resulting suspension was filtered and the solvent evaporated under vacuum to afford an oily residue. The product was washed with H_2O followed by MeCN to give a white powder. (a) Characterization data of **2**: Yield 67% (1.287 g), m.p. 237–240 °C, Anal. Calcd for $C_{18}H_{20}N_5O_3P$ (385.36): C 56.09, H 5.23, N 18.17; Found C 56.23, H 5.44, N 18.33. ^{31}P NMR (DMSO-d_6): δ −37.72 (t of t, $^2J_{PNH\text{-}\alpha} = 40.4$ Hz and $^3J_{PNCH} = 8.9$ Hz) ppm. ^{1}H NMR (DMSO-d_6): δ 2.76 (m, 4H, CH_2), 3.50 (m, 4H, CH_2), 7.42 (m, 6H, Ar-H), 7.70 (d, $^3J_{HH} = 7.1$ Hz, 4H, Ar-H), 8.57 (d, $^2J_{PNH} = 40.4$ Hz, 2H, NH_α) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6): δ 45.9 (s), 66.6 (d, $^2J_{PC} = 6.5$ Hz), 124.6 (s), 128.5 (s), 128.7 (s), 129.4 (s), 152.5 (d, $^2J_{POC} = 14.1$ Hz) ppm. Selected IR data (KBr, cm^{-1}): 3370 (s), 1668 (m), 1444 (m), 1330 (s), 1110 (m), 1066 (s), 956 (s), 707 (s). (b) Characterization data of **3**: Yield 63% (1.166 g), m.p. 244–248 °C, Anal. Calcd for $C_{18}H_{22}N_5O_2P$ (371.36): C 58.21, H 5.97, N 18.86; Found C 58.11, H 5.80, N 18.97%. ^{31}P NMR (DMSO-d_6): δ −43.31 (d of t, $^2J_{PNH\text{-}\alpha} = 45.2$ Hz and $^2J_{PNH\text{-}tert\text{-butylamine}} = 12.1$ Hz) ppm. ^{1}H NMR (DMSO-d_6): δ 1.17 (s, 9H, CH_3), 3.69 (d, $^2J_{PNH} = 12.4$ Hz, 1H, N$H_{tert\text{-butylamine}}$), 7.41 (m, 6H, Ar-H), 7.71 (d, $^3J_{HH} = 7.3$ Hz, 4H, Ar-H), 8.17 (d, $^2J_{PNH} = 45.2$ Hz, 2H, NH_α) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6): δ 31.8 (d, $^2J_{PC} = 5.6$ Hz), 50.6 (s), 124.6 (s), 128.29 (s), 129.0 (s), 129.3 (s), 151.7 (d, $^2J_{POC} = 14.6$ Hz) ppm. Selected IR data (KBr, cm^{-1}): 3435 (s), 1606 (m), 1328 (s), 1224 (m), 1070 (s), 1046 (m), 868 (m), 720 (s), 688 (s).