Phosphonioethylation of phenylhydrazine and hydroxylamine and selected properties of the resulting derivatives

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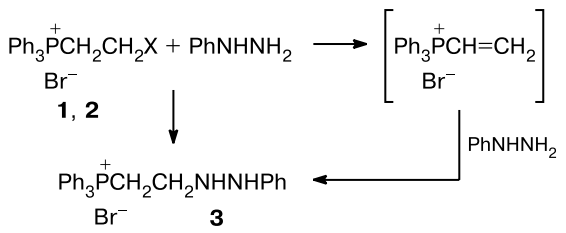
The reactions of phenylhydrazine and hydroxylamine with (β-X-ethyl)triphenylphosphonium salts (X = Ph, $Ph_3P^+Br^-$) (**1**, **2**) afforded the corresponding β-N-ethyl-substituted triphenylphosphonium salts (**3**, **4**). The reaction of triphenyl(2-phenylhydrazinoethyl)phosphonium bromide **3** with an aqueous solution of NaOH in benzene afforded a statistical mixture of the *cis* and *trans* isomers of 2-(diphenylphosphoryl)acetaldehyde phenylhydrazone. (2-Hydroxyaminoethyl)triphenylphosphonium bromide reacted with sodium methoxide to give *O*-phosphobetaine.

Key words: phenylhydrazine, hydroxylamine, 2-(hydroxyaminoethyl)triphenylphosphonium bromide, triphenyl(2-phenylhydrazinoethyl)phosphonium bromide, 2-(diphenylphosphoryl)acetaldehyde phenylhydrazone, triphenylvinylphosphonium bromide.

The nucleophilic addition to triphenylvinylphosphonium salts has been studied extensively.[1] In many reactions, intermediate addition products undergo spontaneous cyclization to give phosphonium salts containing a heterocyclic fragment. The latter salts are not only of theoretical but also of practical interest as potentially biologically active compounds.

In the present study, we examined the possibilities of such heterocyclization reactions involving the P atom for phosphonium salts containing a precursor of the vinyl group.

Scheme 1



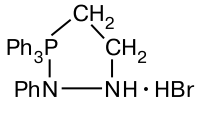
X = OPh (**1**), $[PPh_3]^+Br^-$ (**2**)

Results and Discussion

We carried out the reactions of (2-phenoxyethyl)triphenylphosphonium bromide (**1**) and 1,2-bis(triphenylphosphonium)ethane dibromide (**2**) with phenylhydrazine and hydroxylamine. The reactions of both salts with phenylhydrazine in methanol afforded triphenyl(2-phenylhydrazinoethyl)phosphonium bromide (**3**) in high yields. We believe that compound **3** can be generated both directly from phosphonium salts **1** and **2** through the nucleophilic substitution and from an intermediate salt containing the vinyl group followed by the addition according to Scheme 1.

It should be noted that the reaction of salt **2** with phenylhydrazine was carried out in the presence of triethylamine. The structure of compound **3** was confirmed by ^1H and ^{13}C NMR spectroscopy and single-crystal X-ray diffraction analysis.

The necessity of applying the latter method stemmed from two facts. First, according to the data published in the literature, phenylhydrazine reacts with electrophiles predominantly at the substituted N atom. Second, heterocyclization of salt **3** under the reaction conditions to form a compound with the structure **A** could not be ruled out.



A

The ^1H NMR spectroscopic data did not allow us to unambiguously decide between these possibilities because the spectrum had no signals for the protons of NH groups. The bond lengths and bond angles of compound **3** determined by X-ray diffraction analysis are given in Table 1.

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Table 1. Selected bond lengths (*d*) and bond angles (ω) in molecule **3**

Bond	*d*/Å	Angle	ω/deg
P—C(23)	1.793(4)	C(23)—P—C(11)	108.6(2)
P—C(1)	1.794(4)	C(11)—P—C(1)	110.0(2)
C(1)—C(2)	1.538(6)	C(11)—P—C(17)	110.1(2)
N(3)—N(4)	1.396(6)	C(2)—C(1)—P	114.1(3)
C(5)—C(6)	1.381(6)	N(4)—N(3)—C(2)	114.4(4)
C(6)—C(7)	1.390(7)	C(6)—C(5)—C(10)	119.3(4)
C(8)—C(9)	1.369(8)	C(10)—C(5)—N(4)	125.5(4)
C(11)—C(12)	1.382(7)	C(8)—C(7)—C(6)	120.5(5)
C(12)—C(13)	1.382(8)	C(8)—C(9)—C(10)	120.7(5)
C(14)—C(15)	1.867(9)	C(12)—C(11)—C(16)	190.0(4)
C(17)—C(18)	1.383(7)	C(16)—C(11)—P	119.9(3)
C(18)—C(19)	1.415(9)	C(14)—C(13)—C(12)	120.6(6)
C(20)—C(21)	1.336(10)	C(14)—C(15)—C(16)	121.3(6)
C(23)—C(28)	1.379(6)	C(18)—C(17)—C(22)	120.2(5)
C(24)—C(25)	1.374(7)	C(22)—C(17)—P	121.7(4)
C(26)—C(27)	1.370(9)	C(20)—C(19)—C(18)	119.7(6)
P—C(11)	1.793(40)	C(20)—C(21)—C(22)	120.2(7)
P—C(17)	1.794(4)	C(28)—C(23)—C(24)	119.5(4)
C(2)—N(3)	1.452(6)	C(24)—C(23)—P	119.6(3)
N(4)—C(5)	1.394(5)	C(26)—C(25)—C(24)	120.1(5)
C(5)—C(10)	1.388(7)	C(26)—C(27)—C(28)	119.5(6)
C(7)—C(8)	1.353(8)	C(23)—P—C(1)	109.5(2)
C(9)—C(10)	1.382(7)	C(23)—P—C(17)	111.3(2)
C(11)—C(16)	1.387(6)	C(1)—P—C(17)	107.3(2)
C(13)—C(14)	1.339(10)	N(3)—C(2)—C(1)	113.1(4)
C(15)—C(16)	1.368(7)	C(5)—N(4)—N(3)	117.9(4)
C(17)—C(22)	1.392(7)	C(6)—C(5)—N(4)	118.1(4)
C(19)—C(20)	1.367(10)	C(5)—C(6)—C(7)	119.9(5)
C(21)—C(22)	1.397(8)	C(7)—C(8)—C(9)	120.1(5)
C(23)—C(24)	1.384(6)	C(9)—C(10)—C(5)	119.5(5)
C(25)—C(26)	1.359(8)	C(12)—C(11)—P	121.0(4)
C(27)—C(28)	1.382(7)	C(11)—C(12)—C(13)	119.9(6)
		C(13)—C(14)—C(15)	119.9(6)
		C(15)—C(16)—C(11)	119.2(5)
		C(18)—C(17)—P	118.0(4)
		C(17)—C(18)—C(19)	118.6(6)
		C(21)—C(20)—C(19)	121.8(6)
		C(17)—C(22)—C(21)	119.4(6)
		C(28)—C(23)—P	120.6(3)
		C(25)—C(24)—C(23)	120.0(5)
		C(25)—C(26)—C(27)	120.9(5)
		C(23)—C(28)—C(27)	120.0(5)

The overall view of molecule **3** is shown in Fig. 1. The complete data from X-ray diffraction analysis for compound **3**, including the atomic coordinates and isotropic thermal parameters for nonhydrogen atoms, were deposited with the Cambridge Structural Database.

Salt **3** would be expected to undergo heterocyclization under the action of an aqueous alkaline solution. However, the reaction afforded a mixture of the *cis* and *trans* isomers of 2-(diphenylphosphoryl)acetaldehyde phenylhydrazone (**4**). We believe that compound **4** was generated according to Scheme 2 through the intermediate

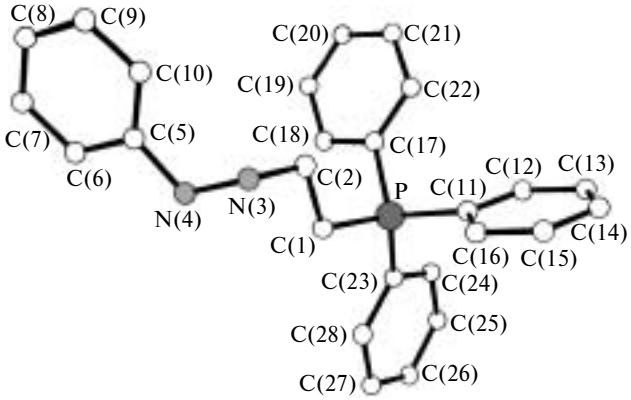
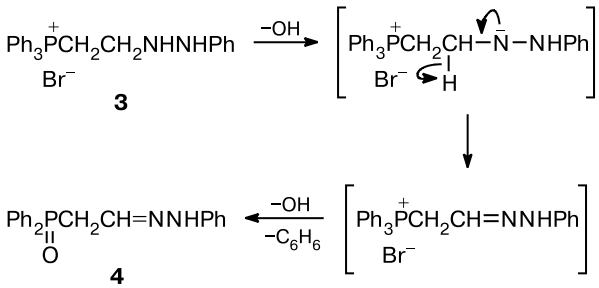


Fig. 1. Molecular structure of compound **3**.

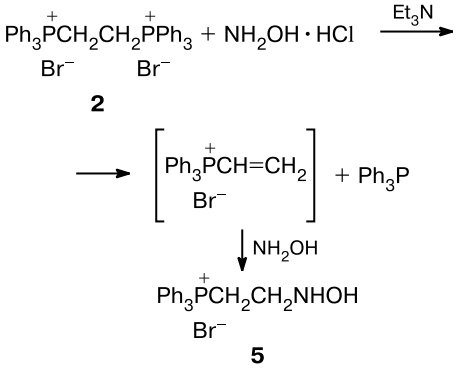
formation of *N*,*P*-betaine followed by elimination of the hydride ion.

Scheme 2



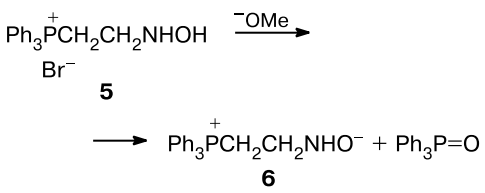
The reaction of 1,2-bis(triphenylphosphonium)ethane dibromide **2** with hydroxylamine hydrochloride in the presence of an excess of Et_3N gave rise to (2-hydroxyaminoethyl)triphenylphosphonium bromide (**5**) and triphenylphosphine in 62 and 72% yields, respectively (Scheme 3). Apparently, salt **5** was generated through an intermediate vinyl salt, which added the hydroxylamine molecule under the reaction conditions.

Scheme 3



The reaction of salt **5** with a methanolic solution of sodium methoxide afforded triphenylphosphine oxide and *O*,*P*-betaine **6** (Scheme 4).

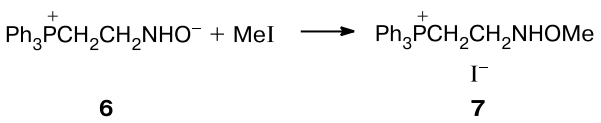
Scheme 4



The formation of betaine structure **6** is supported both by the fact that the ^{31}P NMR spectrum has a signal in the region (δ +33.5) characteristic of triphenylphosphonium salts as well as by the upfield shifts of the signals for the methylene protons in the ^{1}H NMR spectrum of compound **6** compared to those observed in the spectrum of the starting salt **5**.

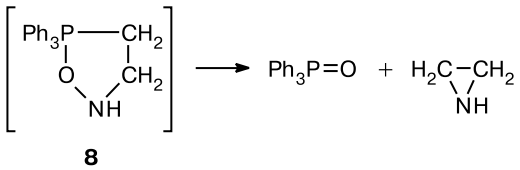
Phosphobetaine **6** readily reacted with iodomethane to give the corresponding phosphonium salt **7** (Scheme 5) whose ^{1}H NMR spectrum has a signal at δ 3.4 characteristic of the methoxy group.

Scheme 5



Apparently, triphenylphosphine oxide in this reaction was produced according to a scheme involving synchronous cyclization—cleavage of intermediate phosphorane **8** (Scheme 6).

Scheme 6



Experimental

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Mercury-300 Varian spectrometer (300 MHz) in $CDCl_3$. Crystals of compound **3** suitable for X-ray diffraction analysis were prepared by slow evaporation of a solution of **3** in an ethyl acetate—ethanol mixture. The starting salts **1** and **2** were synthesized according to known procedures.[2,3] Their physicochemical parameters are consistent with the data published in the literature.

Triphenyl(2-phenylhydrazinoethyl)phosphonium bromide (3). ***A.*** Phenylhydrazine (2.8 g, 2.6 mmol) was added to a solution of (2-phenoxyethyl)triphenylphosphonium bromide (**1**) (6 g, 13 mmol) in MeOH (40 mL) and the reaction mixture was kept at ~20 °C for 3 days. The solvent was distilled off and the dry residue was thoroughly washed with dry ether. The ethereal extracts were combined and the ether was distilled off. Distillation of the residue afforded the phenol with the b.p. 70 °C (10 Torr) in a yield of 1 g (81%). The residue obtained after washing with ether was dried and recrystallized from an ethyl acetate—ethanol mixture to obtain salt **3** in a yield of 4.8 g (76.9%), m.p. 218 °C. Found (%): Br, 16.10. $C_{26}H_{26}BrN_2P$. Calculated (%): Br, 16.77. ^{1}H NMR, δ: 3.28 (dt, 2 H, NCH_2, $^{3}J_{P,H}$ = 11.1 Hz, $^{3}J_{H,H}$ = 7.0 Hz); 4.04 (dt, 2 H, PCH_2, $^{2}J_{P,H}$ = 12.9 Hz, $^{3}J_{H,H}$ = 7.0 Hz); 6.63 (t, 1 H, *p*-PhN, $^{3}J_{H,H}$ = 7.2 Hz); 6.79 (d, 2 H, *o*-PhN, $^{3}J_{H,H}$ = 8.1 Hz); 7.01 (dd, 2 H, *m*-Ph); 7.56—7.78 (m, 15 H, Ph_3P). ^{13}C NMR, δ: 22.22 (d, PCH_2, ^{1}J = 49.4 Hz); 44.64 (CH_2N); 149.28 (*ipso*-NPh); 128.67 and 113.27 (*o*- and *m*-NPh); 118.37 (*p*-NPh); 118.41 (d, *ipso*-PPh, $^{1}J_{P,C}$ = 86.0 Hz); 130.32, 133.99 (d, *o*- and *m*-PPh, $J_{P,C}$ = 12.8 Hz, $J_{P,C}$ = 9.8 Hz); 134.82 (*p*-PPh).

B. Triethylamine (0.8 g, 8 mmol) was added to a mixture of 1,2-bis(triphenylphosphonium)ethane dibromide (**2**) (6 g, 8 mmol) and phenylhydrazine (1.6 g, 16 mmol) in MeOH (30 mL) and the reaction mixture was kept at ~20 °C for 24 h. The solvent was distilled off and the residue was thoroughly washed with dry ether. After the removal of the ether from the combined ethereal extracts, triphenylphosphine (m.p. 78—82 °C) was isolated in a yield of 1.8 g (85%). A mixture with an authentic sample showed no melting point depression. The residue was washed with ether and dried *in vacuo*. After recrystallization from an ethyl acetate—ethanol mixture, salt **3** was obtained in a yield of 3.4 g (87.5%). Its physicochemical constants were identical with those described above.

Reaction of salt 3 with sodium hydroxide. A 25% aqueous solution of NaOH was added to a solution of salt **3** (2.5 g, 5 mmol) in benzene (0.3 g, 7 mmol). The reaction mixture was kept at ~20 °C for 3 days. The benzene solution was decanted. The residue was twice washed with benzene and dried to obtain unconsumed starting salt **3** in a yield of 1 g (40%). A mixture of the *cis* and *trans* isomers of phenylhydrazone **4** was isolated from the combined benzene solutions in a yield of 0.9 g (54%), m.p. 193—194 °C. Found (%): C, 72.2; H, 6.02. $C_{20}H_{19}N_2OP$. Calculated (%): C, 71.85; H, 5.68. ^{1}H NMR, δ: 3.44 and 3.49 (both t, 1 H each, PCH_2, $^{1}J_{P,C}$ = $^{2}J_{H,H}$ = 6.2 Hz); 6.51 (q, 0.5 H, =CH, $^{3}J_{H,H}$ = $^{3}J_{H,H}$ = 6.2 Hz); 6.79—6.89 and 7.10—7.32 (both m, 5.5 H, NPh, 0.5 H, =CH); 7.54—7.81 (m, 10 H, PPh_2). ^{31}P NMR, δ: 32.75, 30.91.

(2-Hydroxyaminoethyl)triphenylphosphonium bromide (5). Triethylamine (3 g, 0.03 mol) was added to a mixture of 1,2-bis(triphenylphosphonium)ethane dibromide (**2**) (7.1 g, 0.01 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) in $CHCl_3$ (40 mL). The reaction mixture was refluxed for 13 h and then water (10 mL) was added. The organic layer was separated and dried over $MgSO_4$. After the removal of $CHCl_3$, the residue was washed with ether and ethyl acetate. Triphenylphosphine was isolated from the combined extracts in a yield of 1.9 g (72%) (m.p. 78—80 °C). A mixture with an authentic sample showed no melting point depression. The residue was

dried and recrystallized from an ethyl acetate—ethanol mixture to obtain salt **5** in a yield of 3.7 g (92%), m.p. 234 °C. Found (%): Br, 19.1. $C_{20}H_{21}BrNOP$. Calculated (%): Br, 19.9. ^{1}H NMR, δ: 3.33 (dt, 2 H, NCH_2, $^3J_{P,H}$ = 11.4 Hz, $^3J_{H,H}$ = 6.9 Hz); 3.78 (dt, 2 H, PCH_2, $^2J_{P,H}$ = 13.2 Hz, $^3J_{H,H}$ = 6.9 Hz); 7.62—7.86 (m, 15 H, Ph). ^{13}C NMR, δ: 21.75 (d, PCH_2, $^1J_{P,C}$ = 51.3 Hz); 52.67 (NCH_2); 118.40 (d, *ipso*-PhP, $^1J_{P,C}$ = 86.8 Hz); 130.60 and 134.00 (d, *o*- and *m*-PhP, $^1J_{P,C}$ = 12.1 Hz, $^1J_{P,C}$ = 10.6 Hz); 134.86 (*p*-PhP).

Reaction of salt 5 with sodium methoxide. A solution of MeONa in NaOH, which was prepared from sodium (0.04 g, 0.002 g-at.) in MeOH (1 mL), was added dropwise to a solution of salt **5** (1 g, 2 mmol) in MeOH (10 mL). The reaction mixture was heated at 60 °C for 1 h and then the solvent was removed. The residue was twice washed with dry benzene and dried. The unconsumed starting salt **5** was obtained in a yield of 0.1 g (10%). The benzene solutions were combined and the benzene was removed. According to the data from ^{31}P NMR spectroscopy, the residue obtained in a yield of 0.55 g contained a mixture of triphenylphosphine oxide and phosphobetaine **6** (δ_P 29.5 and 33.5, respectively) in a ratio of 7 : 3. Triphenylphosphine oxide was isolated (m.p. 156 °C) by recrystallization of this mixture from EtOH. The compound thus obtained showed no melting point depression with an authentic sample. ^{1}H NMR of compound **6**, δ: 2.6 (dt, 2 H, NCH_2); 2.9 (dt, 2 H, PCH_2); 7.30—7.8 (m, 15 H, Ph).

Iodomethane was added to a solution of the mixture of phosphobetaine **6** and triphenylphosphine oxide (0.3 g) prepared previously in benzene (5 mL). The precipitate that formed was filtered off, thoroughly washed with ether, and dried. Triphenyl(2-(*N*-methoxyamino)ethylphosphonium iodide (**7**) was obtained in a yield of 0.1 g (77.5%). Found (%): I, 27.12. $C_{21}H_{23}INOP$. Calculated (%): I, 27.45. ^{1}H NMR, δ: 3.38 (dt, 2 H, NCH_2); 3.71 (dt, 2 H, PCH_2); 3.42 (s, 3 H, OMe); 7.45—8.00 (m, 15 H, Ph).

X-ray diffraction study of salt **3** was carried out at ~20 °C on a four-circle automated Entraf-Nonius CAD-4 diffractometer (Mo-Kα radiation, ω/2θ scan technique, graphite monochromator, θ_{max} = 28°). The crystals are monoclinic, a = 9.535(2), b = 18.172(4), c = 13.715(3) Å, β = 95.72(3)°, V = 2364.6(9) Å, Z = 4, d_{calc} = 1.341 g cm^{-3}, space group $P2_1/n$. The calculations and refinement were carried out with the use of 2973 independent reflections. The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. The positions of all H atoms were revealed from the difference electron synthesis and refined with fixed isotropic thermal parameters B_{iso} = 7.5 Å. All calculations were carried out using the SHELXL-93 program package. The final reliability factors were as follows: R = 0.0465, wR_2 = 0.1101 ($GOOF$ = 1.074) for 2801 reflections with $I > 2\tau(I)$. The selected bond lengths and bond angles are given in Table 1.

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