

Reactivity of Iminophosphoranes. Formation of the Piperazine Ring

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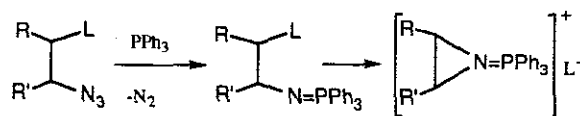
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Reaction of 3-azidopropyl methanesulfonate with triphenylphosphine produced the 1,4-bis(triphenylphosphino)piperazine **5** by intermolecular cyclization, instead of formation azidine derivatives by an intramolecular pathway. Structural formulation of **5** was achieved by both spectral and X-ray crystal analysis. Hydrolysis of **5** under basic condition gives piperazine, whereas reaction of lithium diphenylphosphide with **5** produced 1,2-bis(diphenylphosphino)ethane (dppe) exclusively.

INTRODUCTION

Since discovery of the Staudinger reaction, iminophosphorane is an important synthetic intermediate leading to nitrogen-containing compounds.¹⁻⁶ β -Substituted halides or alcohols of iminophosphoranes undergo the intramolecular cyclization to form aziridine derivatives (Scheme I).^{2,5,6} Such nucleophilic substitution is common for formation of three-membered ring systems and even for four-membered rings, and few examples exist involving iminophosphoranes of this kind in intermolecular reactions.⁷ Here we report intermolecular cyclization of $\text{CH}_3\text{SO}_3\text{CH}_2\text{CH}_2\text{N}=\text{PPh}_3$ to yield a six-membered ring product, which provides another way to prepare piperazine.

Scheme I

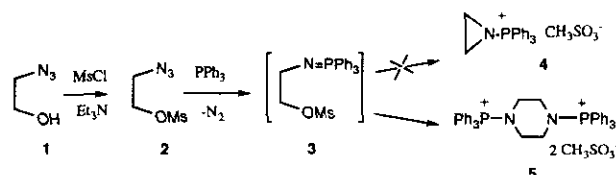


RESULTS AND DISCUSSION

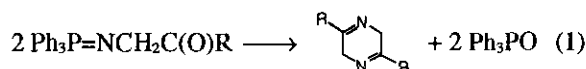
According to the method in the literature,⁸ azido compound **1** was prepared on nucleophilic substitution of $\text{ClCH}_2\text{CH}_2\text{OH}$ with sodium azide in dimethylformamide solution. The alcoholic function was converted into methanesulfonate **2** by a standard procedure in high yield. Treatment of **2** with triphenylphosphine in equimolar proportions in benzene at room temperature provided piperazine salt **5** in high yield. This formation is rationalized by intervention of iminophosphorane-mesylate **3** via a Staudinger reaction of the azido group with triphenylphosphine and subsequent intermolecular cyclization. Even under dilute conditions (ca

0.01 M), cyclized product **5** was the major product without formation of **4**. Alternation of solvent from benzene to dichloromethane did not affect the outcome.

Scheme II



It appears that mesylate **3** does not undergo intramolecular cyclization to form aziridine **4**, instead it proceeds via an intermolecular fashion, which is the first example, to our knowledge, of the saturated carbon frame backbone proceeding such way of cyclization. For comparison, a related intramolecular cyclization of iminophosphorane system **6** (equation 1) was reported by Zbiral and Stroh due to the ring strain.⁷



Compound **5** was characterized by not only spectral methods but also X-ray single crystal analysis. A suitable crystal was obtained by slow evaporation of a solution of **5** in chloroform/ether. An ORTEP plot of cationic **5** appears in Figs. 1 and 2 and selected bond distances and bond angles are summarized in Table 1. All bonds and angles are in normal ranges. As shown in Fig. 2, piperazine adopts a chair conformation with two triphenylphosphine substituents situated at equatorial orientations.

As an electron pair of nitrogen is adjacent to the positively charged phosphorus atom, compound **5** becomes inert toward any electrophile, but it readily underwent hydrolysis

under basic conditions to give piperazine and triphenylphosphine oxide as a typical reaction of phosphonium salts.⁹ It also reacted with diphenylphosphide to give dppe exclusively, indicating that the nucleophile attacked at the same ethylene unit of the piperazine ring.

Table 1. Selected Bond Distances Å and Bond Angles deg

P-N	1.631(6)	P-N-C(1)	123.4(4)
N-C(1)	1.462(9)	P-N-C(2)	122.0(4)
N-C(2)	1.486(9)	C(1)-N-C(2)	111.0(5)
C(1)-C(2)A	1.51(1)	N-C(1)-C(2)A	109.3(6)
P-C(11)	1.785(8)	N-C(2)-C(1)A	108.4(5)
P-C(21)	1.798(7)	N-P-C(11)	113.5(3)
P-C(31)	1.801(8)	N-P-C(21)	106.0(3)
		N-P-C(31)	106.7(3)

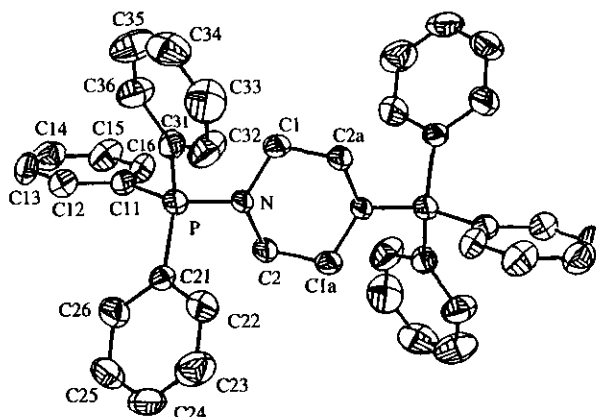


Fig. 1. ORTEP Plot of Cationic 5.

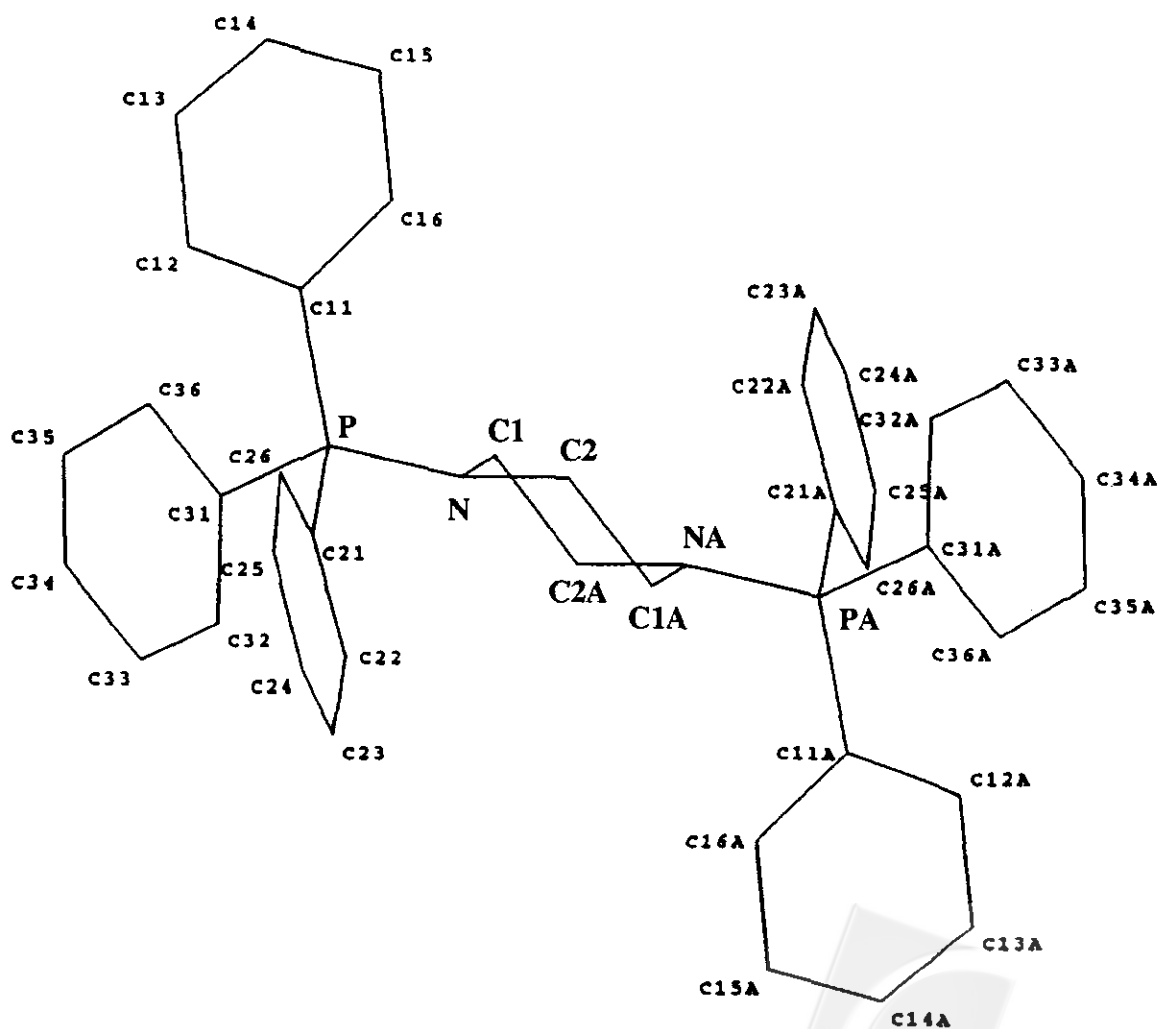
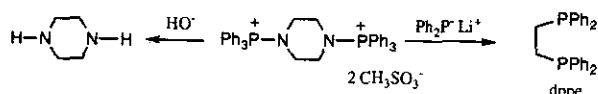


Fig. 2. Another view of Cationic 5.

Scheme III



EXPERIMENTAL SECTION

General Information

Nuclear magnetic resonance spectra were recorded on either a Bruker AC-E 200 or a AM-300 spectrometer. For ^{31}P NMR spectra, the chemical shifts are given in parts per million (δ) relative to 85% H_3PO_4 . Infrared spectra were measured on a Biorad FT-30 instrument. All of the reaction, manipulation and purification steps involving phosphines were performed under a dry nitrogen atmosphere. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl. Benzene was distilled from sodium under nitrogen. Other chemicals and solvents were used from commercial sources without further purification. 1-Azidoethanol (1) was prepared according to the literature method.⁸

2-Azidoethyl Methanesulfonate (2)

To a solution of 1 (1.0 g, 11.5 mmol) in dichloromethane (40 mL) and triethylamine (2.4 mL, 17.3 mmol) was added methanesulfonyl chloride (1.1 mL, 13.8 mmol) at ice temperature. The reaction mixture was stirred for 1 h and quenched with NaOH solution (0.1 M). The organic layer was separated and washed with HCl solution (10%), saturated NaHCO_3 and brine. The organic portion was concentrated and the residue chromatographed on silica gel with dichloromethane as eluent. The eluate was concentrated to give 2 as a clear liquid (1.80 g, 95 %): IR(neat) 2114 cm^{-1} ($-\text{N}_3$); ^1H NMR δ 4.26 (t, $J = 10\text{ Hz}$, 2 H), 3.52 (t, $J = 10\text{ Hz}$, 2 H), 3.00 (s, 3 H); ^{13}C NMR δ 67.7, 49.6, 37.3; Anal. calcd for $\text{C}_3\text{H}_7\text{N}_3\text{O}_3\text{S}$: C, 21.82; H, 4.27; N, 25.44. Found C, 21.72; H, 4.26; N, 25.29.

Compound 5

A solution of triphenylphosphine (1.6 g, 6.12 mmol) in benzene (50 mL) was added to a solution of 2 (1.01 g, 6.12 mmol) in benzene (50 mL) with stirring. During stirring for 3 h, white solids precipitated. The solid was collected and crystallized from chloroform and diethyl ether to give 5 as a colorless, crystalline solid: mp $365-368^\circ\text{C}$ (dec); ^1H NMR δ 8.20-8.14 (m, 18H), 7.8 (d, $J = 6.8\text{ Hz}$, 12H), 3.52 (s, 6H), 2.90 (s, 4 H); ^{31}P NMR δ 46.3; Anal. calcd for $\text{C}_{42}\text{H}_{44}\text{P}_2\text{N}_2\text{S}_2\text{O}_6$: C, 63.15; H, 5.55; N, 3.51. Found C,

Table 2. Atomic Coordinates and B_{iso} of 5

	x	y	z	Beq
P	0.32414(20)	0.18469(15)	0.46017(11)	2.82(9)
N	0.4174(5)	0.0868(4)	0.4873(3)	2.8(3)
C1	0.3586(7)	-0.0056(6)	0.5110(4)	3.1(4)
C2	0.5678(7)	0.0945(5)	0.5155(4)	3.0(4)
C11	0.2785(7)	0.2591(6)	0.5308(4)	2.9(4)
C12	0.2036(8)	0.3489(6)	0.5184(4)	3.8(4)
C13	0.1726(8)	0.4040(6)	0.5750(6)	4.2(5)
C14	0.2150(9)	0.3717(7)	0.6425(5)	4.8(5)
C15	0.2873(9)	0.2840(7)	0.6556(5)	4.7(5)
C16	0.3188(8)	0.2283(6)	0.5994(4)	3.5(4)
C21	0.4273(7)	0.2573(6)	0.4084(4)	2.9(4)
C22	0.4834(9)	0.2106(6)	0.3550(5)	4.4(4)
C23	0.5670(10)	0.2633(9)	0.3157(5)	5.8(6)
C24	0.5949(9)	0.3618(9)	0.3299(6)	5.1(5)
C25	0.5385(10)	0.4084(7)	0.3816(6)	5.1(5)
C26	0.4544(8)	0.3582(7)	0.4215(4)	4.0(4)
C31	0.1670(8)	0.1389(6)	0.4081(4)	3.1(4)
C32	0.1714(8)	0.0837(7)	0.3479(5)	5.2(5)
C33	0.0502(11)	0.0466(7)	0.3102(5)	6.1(6)
C34	-0.0728(10)	0.0630(8)	0.3310(6)	5.6(5)
C35	-0.0795(9)	0.1182(8)	0.3901(6)	6.3(6)
C36	0.0404(8)	0.1561(7)	0.4303(4)	4.7(5)
S	-0.0066(3)	0.54726(19)	0.74604(17)	5.52(15)
O1	0.4453(8)	0.0417(6)	0.2165(5)	11.4(6)
O2	0.5294(10)	0.0441(7)	0.6785(5)	11.4(6)
O3	0.3689(7)	0.0718(6)	0.7527(4)	9.4(5)
C4	0.1087(15)	0.3561(12)	0.2826(8)	14.0(10)
C5	0.8200(9)	0.3205(7)	0.6051(5)	5.8(5)
CL1	0.6528(3)	0.3279(3)	0.62755(20)	10.62(23)
CL2	0.1136(3)	-0.20027(22)	0.37995(17)	8.77(18)
CL3	0.8098(3)	0.3465(3)	0.51541(17)	9.70(20)

63.00; H, 5.45; N, 3.50.

Formation of Piperazine from 5

A suspension of compound 5 (5 g) in NaOH solution (10%) was heated at 60°C for 1 h. By GC analysis, the formation of piperazine is confirmed and the yield is quantitative. Distillation of the reaction mixture give piperazine in 57 % yield.

Formation of 1,2-Bis(diphenylphosphino)ethane from 5

Diphenylphosphide anion was prepared by treating diphenylphosphine (1.47 g, 7.9 mmol) in THF (60 mL) with a 1.6 M hexane solution of *n*-BuLi (5.4 mL, 8.69 mmol). The anion solution was added to a solution of 5 (6 g, 7.52 mmol) in THF (20 mL) with stirring at 30°C overnight. The reaction mixture was concentrated; the residue was extracted with benzene (50 mL \times 2). On removal of insoluble materials, the red solution was added to acetonitrile (100 mL). Upon standing at -5°C for 5 h, white solids precipi-

tated and were collected (1.5 g, 50%). The white solid was identified as 1,2-bis(diphenylphosphino)ethane (dppe) by spectral methods: ^{31}P NMR -13.0 (lit. -13.0).¹⁰

X-ray Crystallography

Single crystals suitable for X-ray analysis of 5·2 CHCl_3 were obtained by slow evaporation of a solution of chloroform and diethyl ether. Cell dimensions were measured and intensity data were collected on a CAD-4 diffractometer at 298 K. Empirical formula: $\text{C}_{22}\text{H}_{23}\text{Cl}_3\text{NO}_3\text{PS}$, $F_w = 519.01$. Crystal size $0.45 \times 0.40 \times 0.40 \text{ mm}^3$. Space group: monoclinic $\text{P}2_1/\text{n}$. Cell parameters: $a = 9.744(4)$, $b = 13.365(5)$, $c = 19.083(8) \text{ \AA}$, $\beta = 98.81(4)^\circ$, $V = 2456(2) \text{ \AA}^3$, $Z = 4$, $D_x = 1.403 \text{ g cm}^{-3}$, $F(000) = 1072$, $\mu = 2.06 \text{ cm}^{-1}$, $\lambda = 0.7107$. The intensity were collected in the θ - 2θ scan mode with scan width $2(0.90 + 0.35 \tan\theta)$. $2\theta_{\text{max}} = 45.0^\circ - 10 < h < 10$, $0 < k < 14$, $0 < l < 20$. A total of 3220 unique reflections were measured, of which 2112 were observed [$I > 2.0 \sigma(I)$]. Transmission factors were 0.85-1.00.

The structure was solved according to the heavy atom method. The least-squares method was applied for calculation with 54 atoms and 280 parameters. Refinements were as follows, in which F_o and F_c are observed and calculated structure factor amplitudes respectively; the function minimized was $\sum w(F_o - F_c)^2$, with $w = 1/\sigma^2(F_o)$, $R_t = \sum |F_o - F_c| / \sum (F_o)$, $R_w = [\sum (w(F_o - F_c)^2) / \sum w(F_o)^2]^{1/2}$, $S = [\sum (w(F_o - F_c)^2) / (\text{No. of reflns} - \text{No. of params.})]^{1/2}$. For significant reflections, $R_t = 0.074$, $R_w = 0.074$, $S = 4.08$. Atomic scattering factors were taken from "International Tables for X-ray Crystallography".¹¹ The NRCC SDP VAX program package was used for calculation.¹² Atomic coordinates and B_{iso} are listed in Table 2. Tables of anisotropic thermal parameters and complete bond distances and angles of **5** are available from the authors.

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Key Words

Piperazine; Phosphinimine; Iminophosphorane.

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