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Preparation, Structure, and Reactivity of a New Heterocyclic System-1-Thio-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane

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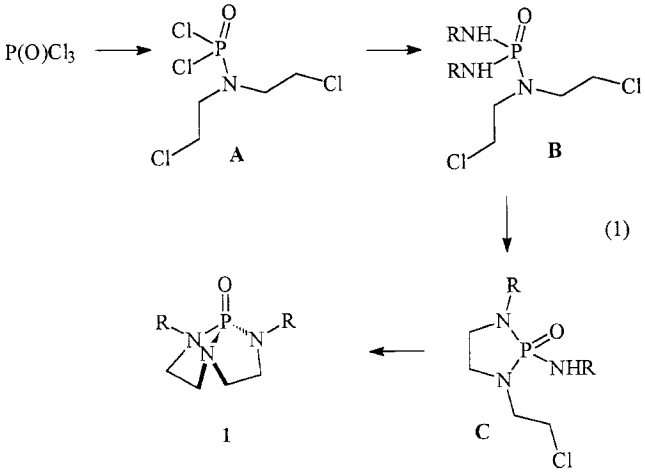
ABSTRACT: *A new heterocyclic system, 1-thio-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane, has been prepared, and its structure was confirmed by single-crystal X-ray diffraction. Preliminary reactivity studies demonstrated a complex mechanism for the acid-catalyzed methanolysis. Gas chromatography–mass spectrometry analysis indicates a reversible substitution leading to the monocyclic, eight-membered product, followed by two rearrangement reactions: isomerization to the 1,3,2-diazaphosphorinane derivative, and to the SMe thioester via the oxygen → sulfur migration of the methyl group.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:327–332, 2001

INTRODUCTION

In a recent series of publications [1], we have reported the preparation, structure, and chemical transformations of a new, bicyclic phosphotriamidate system **1** (Scheme 1). Since the reactions of **1** led to the formation of new and interesting heterocyclic systems, an obvious extension of the project was to prepare the thiophosphoryl analogues of **1** (compounds **2**) and to study their reactivity. The synthesis of **2** proved much more difficult, and we now report the first successful preparation of **2a** (**2**, R = Ph), its crystal structure, and some preliminary results on its reactions.



SCHEME 1

RESULTS AND DISCUSSION

In the first attempt of the synthesis, we tried to apply the sequence shown in Scheme 1 using $P(S)Cl_3$ as the starting material. The first step gave the expected intermediate (the thio-analogue of **A**) with a satisfactory yield and with the melting point in good agreement with the value reported in the literature [2]. Condensation of that product with aniline,

Dedicated to Prof. Naoki Inamoto on the occasion of his 72nd birthday.

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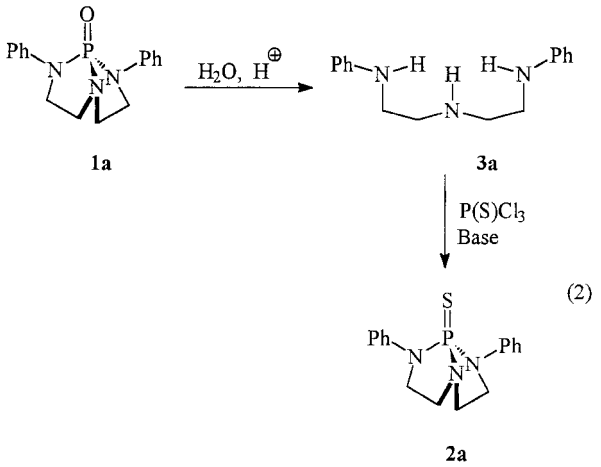
which was expected to yield the thio-analogue of the noncyclic triamidate **B**, failed to give satisfactory results. Under mild conditions (four mol equivalents of $PhNH_2$, CH_2Cl_2, $-40°C$–room temperature) no significant reaction progress was observed. Change of the reagents and conditions (CH_2Cl_2/reflux, two mol equivalents of Et_3N/THF, aq NaOH/CCl_4, BuLi/THF/$-78°C$) resulted in some reactions, but the crude product always consisted of a complex mixture of phosphorus-containing compounds (^{31}P NMR). The attempt to substitute oxygen for sulfur by treating **1a** (**1**, R = Ph) with $P(S)Cl_3$/DMF [3] resulted also in a mixture of products from which **2a** could not be isolated. A solution to the problem was derived from our most recent results [4], according to which the previously difficult to prepare bis(2-arylaminoethyl)amines (**3**) were obtained by exhaustive hydrolysis of triamidates **1**. The triamine **3a** (**3**, R = Ph), obtained in that way, when treated with $P(S)Cl_3$ in the presence of base, was successfully converted to the desired bicyclic product **2a**. The conversion **1a** → **2a** is presented in Scheme 2. Pure **2a** was obtained as a colorless, highly crystalline material, suitable for X-ray analysis; the structure of **2a** is shown in Figure 1. Since the X-ray structure of **1a** had been determined before [1], it was now possible to compare the molecular parameters of those two, closely related bicyclic structures. Selected bond distances and angles for both compounds are listed in Table 1. It is clear that all parameters that describe the geometry of the 2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane system are in both cases approximately the same. The bonding of the thioamidate function does not show any unusual features, with the average P–N bond distance of 1.674 Å, a typical value reported [5] for the amides of phosphoric acid. The length of the thiophosphoryl bond (P=S, 1.926 Å) is also very typical; according to the Cambridge Structural Data Base [6], the average value of the P=S bond distance in 74 listed compounds of the (N,N′,N″)P=S type is 1.929 Å. Compounds **1a** and **2a** represent therefore similar geometry, and any differences in chemical reactivity should therefore reflect the difference between the phosphoryl and thiophosphoryl center, and not the different geometries of the bicyclic skeleton.

The first reaction studied for **2a** was the acid-catalyzed solvolysis of the amide bond. For **1a**, the reaction with ROH/H^+ (R = Me, Et) led to a selective cleavage of the P–N (bridgehead) bond giving the eight-membered cyclic diamidoester **4a** as the kinetic product, which underwent spontaneous rearrangement to the isomeric 1,3,2-diazaphospholidine **5a** (thermodynamic product) [7]. The same sequence of reactions was therefore expected to occur for **2a** (Scheme 3). The results obtained for **2a** as a substrate were, however, very different for those reported earlier for **1a** [7], and, until now, we were not able to prepare either of the corresponding thio derivatives **4b** or **5b**. The conversion of **2a** was complete (^{31}P NMR), and a single phosphorus-containing product ($\delta_P = 76$, as opposed to $\delta_P = 81$ for **2a**) was formed. The attempts to isolate the product and to assign its structure were unsuccessful since it decomposed into a mixture of phosphorus-containing compounds. Gas chromatography–mass spectrometry (GC-MS) analysis of the crude reaction product gave, however, interesting results, worth reporting. Chromatographic separation yielded two components in an approximately 1:1 ratio. The second fraction (retention time 48.5 minutes) was unambigously identified as the phospholidine derivative **5b**, presumably formed via the solvolysis of **2a** followed by a rearrangement. The MS of that fraction gave the expected peak of $m/z = 347$ (M^+, 51%), together with



SCHEME 2

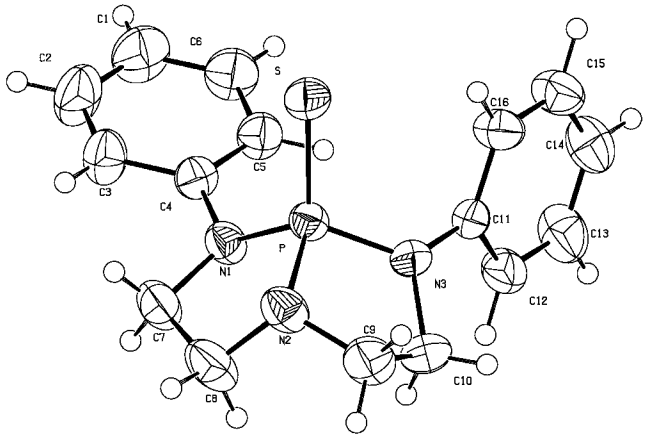
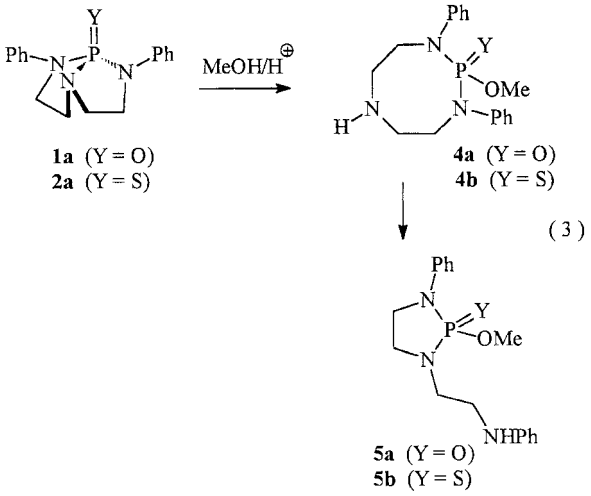


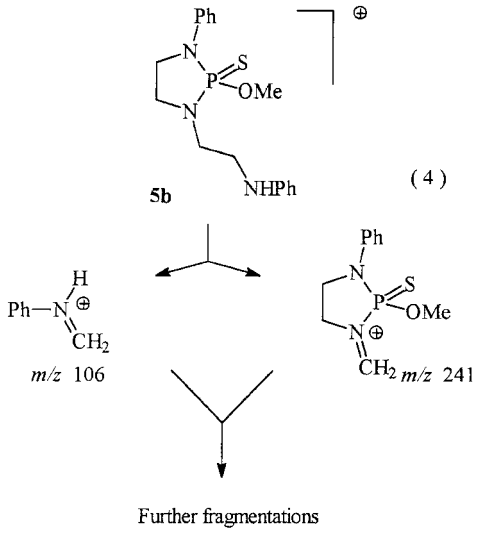
FIGURE 1 ORTEP drawing of **2a**.

TABLE 1 Selected Bond Lengths and Angles for **2a** and **1a**

		Bond Lengths (Å)			
	2a	**1a**		**2a**	**1a**
P=Y	1.926(2)	1.437(2)	N(2)–C(8)	1.470(2)	1.451(3)
P–N(1)	1.682(2)	1.676(3)	N(2)–C(9)	1.476(2)	1.475(2)
P–N(2)	1.674(3)	1.661(2)	N(3)–C(11)	1.426(2)	1.420(3)
P–N(3)	1.665(3)	1.653(3)	N(3)–C(10)	1.476(2)	1.473(2)
N(1)–C(4)	1.422(2)	1.407(3)	C(7)–C(8)	1.498(3)	1.497(3)
N(1)–C(7)	1.467(2)	1.470(2)	C(9)–C(10)	1.516(3)	1.504(2)
		Bond Angles (deg)			
Y=P–N(1)	113.3(1)	114.4(2)	C(8)–N(2)–P	110.5(1)	109.2(2)
Y=P–N(2)	121.1(1)	121.3(1)	C(9)–N(2)–P	108.2(1)	110.9(1)
Y=P–N(3)	114.2(1)	112.7(1)	C(11)–N(3)–C(10)	119.3(1)	121.2(2)
N(1)–P–N(2)	95.4(1)	96.3(2)	C(11)–N(3)–P	127.6(1)	126.0(1)
N(1)–P–N(3)	114.9(1)	114.4(2)	C(10)–N(3)–P	111.3(1)	111.1(1)
N(2)–P–N(3)	95.8(1)	95.7(1)	N(1)–C(7)–C(8)	106.0(1)	104.5(1)
C(4)–N(1)–C(7)	119.1(1)	120.6(1)	N(2)–C(8)–C(7)	107.3(1)	107.1(1)
C(4)–N(1)–P	122.8(1)	127.4(2)	N(2)–C(9)–C(10)	106.9(1)	109.0(1)
C(7)–N(1)–P	109.6(1)	110.3(1)	N(3)–C(10)–C(9)	103.2(1)	106.3(2)
C(8)–N(2)–C(9)	114.2(1)	115.9(1)			



SCHEME 3



SCHEME 4

two major peaks of m/z = 241 (14%), and m/z = 106 (100%); both resulting from the α-bond cleavage, expected for the 1,2-di(heteroatom)-substituted ethylene derivative [8] (Scheme 4). Almost all significant peaks in the spectrum were derived from further fragmentations of the primary ions shown in Scheme 4.

The mass spectrum of the first fraction (retention time 43.8 minutes) contained surprising information. Carefully repeated GC experiments indicated that the fraction consisted in fact of two, almost inseparable, components. The mass spectrum demonstrated unambigously the fraction to be an approximately equimolar mixture of the starting material **2a** (in spite of its full conversion in the methanolysis reaction), and its oxygen analogue **1a** (which was never introduced to the reaction mixture). Since the MS data of pure **1a** and **2a** were available, it could be easily seen that the spectrum of the second fraction represented a perfect overlap of the fragmentations of the individual components, **1a** and **2a**. We explain this unexpected result as follows. Methanolysis of **2a** leads to product **4b**, which undergoes rearrangement to the phospholidine derivative **5b**. Under conditions of the GC-MS experiment, however, the eight-membered cyclic diamidoester **4b** undergoes two additional reactions. The first is the reversal of the methanolysis (elimination of MeOH), yielding the starting material **2a**. Similar

reversal of the ring-opening reactions of the bicyclic system **1** was observed before for **1a** when more acidic compounds (HCl, CF_3SO_3H, phenols) were used as reagents. The origin of the molecule of **1a** in the second fraction is more complex. We postulate that in the first step the thionoester **4b** undergoes thermally induced O → S methyl group migration yielding the isomeric thioloester **4c**. Thermal thiono → thiolo rearrangement of the esters of thiophosphoric acid is a well known reaction and has some synthetic application in the organophosphorus synthesis [9]. The reversal of the ring-opening reaction, leading back to the bicyclic triamidate skeleton, involves now the elimination of thiomethanol rather than MeOH, yielding finally the oxygen analogue of the substrate, that is, compound **1a**. The whole sequence of reactions initiated by the methanolysis step and accounting for all products identified in the GC-MS analysis is presented in Scheme 5. The mechanism needs to be supported by independent experiments, possibly involving the postulated intermediate species. Such experiments are being currently carried out in our laboratory.

EXPERIMENTAL

Solvents and commercially available substrates were purified by conventional methods immediately before use. For column chromatography, Merck Kieselgel 60 (0.063–0.200 mm) was used. NMR spectra were recorded on a Bruker AMX 500 spectrometer. Chemical shifts are given in parts per million relative to $SiMe_4$ (^1H, ^{13}C) as an internal standard and 85% H_3PO_4 (^{31}P) as an external standard.

GC-MS Analysis

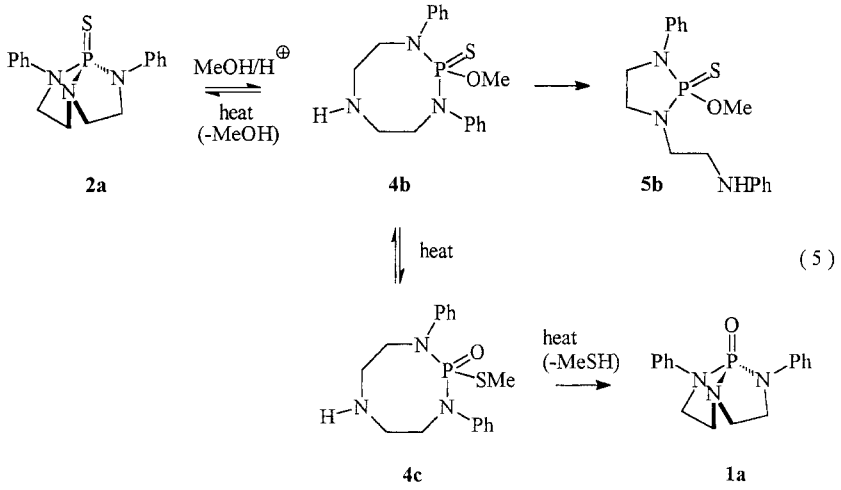
A 1 μL aliquot of the sample was injected into the injection port of a Hewlett-Packard 5890 series II "plus" gas chromatograph, using a HP 7683 autoinjector. Data collection and instrument control was performed with a HP 59970 MS ChemStation. The injector port temperature was set to 250°C, and splitless injection was performed. Separation was achieved with a DB-1 capillary column, J & W Scientific (30 m × 0.25 mm and 0.1 μm film thickness) at a helium flow rate of 1.0 mL/min. An initial oven temperature of 100°C was held for 3 minutes and subsequently raised at a rate of 5°C/minutes, up to 250°C, and then held for 40 minutes at that temperature. The column outlet was inserted directly into the ion source of a HP 5973 Mass Selective Detector (Hewlett Packard). The mass spectrometer was operated with a filament current of 300 μA and electron energy of 70 eV in the electron ionization (EI) mode. The mass range scanned was 50–800 atomic mass units (amu). The transfer line was set at 280°C, and the quadrupole and source temperatures were 150°C and 230°C, respectively.

*Bis(2-phenylaminoethyl)amine (***3a***)*

Compound **3a** was prepared as described previously [4].

Preparation of N,N-Bis(2-chloroethyl)thiophosphodichloridate (Thio-analogue of **A***)*

Rigorously dry bis(2-chloroethyl)ammonium chloride was dissolved in four mol equivalents of freshly distilled $P(S)Cl_3$, and the solution was heated under



(5)

SCHEME 5

TABLE 2 Crystal Data and Structure Refinement for **2a**

Empirical formula	$C_{16}H_{18}N_3PS$
CCDC deposit no.	152961
Formula weight	315.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	a = 8.2311(14)Å a = 115.417(11)° b = 10.4883(18)Å b = 91.825(10)° c = 10.6538(9)Å g = 105.479(14)°
Volume	789.2(2) Å^3
Z	2
Density (calculated)	1.327 Mg/m^3
Absorption coefficient	0.303 mm^{-1}
F(000)	332
Crystal size	0.55 × 0.42 × 0.26 mm
θ range for data collection	2.15–29.96°
Index ranges	$-11 \leftarrow h \leftarrow 11$; $-14 \leftarrow k \leftarrow 14$; $-14 \leftarrow l \leftarrow 14$
Reflections collected	9131
Independent reflections	4580 [*R*(int) = 0.0242]
Reflections observed (>2s)	3558
Absorption correction	Numerical
Max. and min. transmission	0.9253 and 0.8510
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4580/0/204
Goodness-of-fit on F^2	1.049
Final *R* indices [$I > 2s(1)$]	R_1 = 0.0397 wR_2 = 0.1093
R indices (all data)	R_1 = 0.0557 wR_2 = 0.1177
Largest diff. peak and hole	0.390 and −0.276 e.A^{-3}

TABLE 3 Atomic Coordinates (× 10^{-4}) and Equivalent Isotropic Displacement Parameters (Å^2 × 10^{-3}) for **2a**

Atom	*x*	*Y*	*z*	**U***(eq)*[a]
P	8741(1)	7652(1)	685(1)	36(1)
S	10949(1)	8411(1)	1849(1)	49(1)
N(3)	7750(2)	8920(1)	972(1)	40(1)
N(1)	7516(2)	6042(1)	600(1)	42(1)
N(2)	8551(2)	7040(1)	−1061(1)	48(1)
C(11)	7320(2)	9837(1)	2270(1)	38(1)
C(4)	7502(2)	5726(2)	1772(2)	41(1)
C(16)	8556(2)	10752(2)	3464(2)	50(1)
C(10)	6913(3)	8744(2)	−363(2)	57(1)
C(12)	5642(2)	9841(2)	2349(2)	53(1)
C(5)	7222(2)	6734(2)	3046(2)	49(1)
C(14)	6439(3)	11625(2)	4781(2)	61(1)
C(7)	7330(3)	4834(2)	−820(2)	58(1)
C(3)	7712(3)	4418(2)	1662(2)	57(1)
C(15)	8101(2)	11628(2)	4712(2)	58(1)
C(8)	7375(3)	5514(2)	−1805(2)	67(1)
C(9)	8044(3)	8117(2)	−1405(2)	60(1)
C(1)	7355(3)	5118(3)	4067(2)	74(1)
C(6)	7157(3)	6425(2)	4185(2)	62(1)
C(2)	7637(3)	4125(2)	2816(2)	73(1)
C(13)	5217(3)	10731(2)	3594(2)	68(1)

[a]U(eq) is defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

reflux for 16 hours. The excess of $P(S)Cl_3$ was distilled off, and the product was purified by bulb-to-bulb distillation (20°C/1 mmHg); m.p. 32–34°C (Ref. [2], 33–34°C), 71%. ^{31}P NMR ($CDCl_3$): δ 62.6; ^{1}H NMR: δ 3.87–4.04 (overlapping t and dt, 4 × CH_2).

*1-Thio-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane, (***2a***)*

Bis(2-phenylaminoethyl)amine **3a** ([4], 0.450 g, 1.8 mmol) and triethylamine (0.725 g, 7.2 mmol) were dissolved in rigorously anhydrous ether (50 mL). The solution was cooled to −10°C, and freshly distilled $P(S)Cl_3$ (0.430 g, 2.5 mmol), dissolved in ether (10 mL), was added dropwise with stirring and cooling in the atmosphere of dry argon. The temperature of the mixture was kept between −20 and −10°C and was then allowed to warm to room temperature. The precipitated triethylammonium chloride was filtered off, the filtrate was evaporated under reduced pressure, and the crude product (72%) was purified by column chromatography (CH_2Cl_2). The product (0.228 g, 41%) was obtained as colorless, crystalline material; m.p. 153°C. ^{31}P NMR ($CDCl_3$): δ 81.5; ^{1}H NMR: δ 3.21–3.31 (m, 2H), 3.62–3.78 (m, 4H), 3.83–3.92 (m, 2H), 7.01–7.06 (t, J = 7.0 Hz, 2H), 7.16–7.25 (m, 8H); ^{13}C NMR: δ 47.8 (s), 49.6 (d, J = 16.2 Hz), 121.7 (s), 123.5 (s), 128.9 (s). Anal. Calcd for $C_{16}H_{18}N_3PS$: C, 60.93; H, 5.75; N, 13.32; S, 10.17. Found: C, 60.70; H, 5.85; N, 13.28; S, 9.98.

X-Ray Structure Analysis of **2a**

The data were collected on an Enraf-Nonius CAD4 diffractometer using Mo K_α radiation and an ω-2Θ scan. The structure was solved by direct methods using SHELX97-2 [10] in conjunction with WinGX [11]. Hydrogen atoms were introduced in calculated positions using the SHELX instruction HFIX 44 for the aromatic hydrogens and HFIX 24 for the hydrogens on the secondary carbon atoms. Crystal data and structure refinement parameters are given in Table 2. Atomic coordinates and equivalent isotropic displacement parameters are given in Table 3.

ACKNOWLEDGMENTS

We thank Dr. J. B. Laurens for his help in the GC-MS analysis.

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