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4-Halogeno-3-Oxides and Sulfides of the 3,4-Dihydro-2H-1,2,3-Diazaphosphole System

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ABSTRACT

4-Bromodiazaphosphole-3-oxides or sulfides can be obtained by reaction of the corresponding unsubstituted derivative with appropriate reagents. PTAB was demonstrated to be very regio- and stereoselective, allowing bromination exclusively at the 4-position of the ring with prevalent or exclusive formation of one of the two possible isomers. However, when regioselectivity is not required, cheaper and more available bromine or NBS can be used conveniently. 4-Chlorodiazaphosphole-3-oxides can be obtained by reaction of the corresponding unsubstituted derivative with NCS. 4-Bromodiazaphosphole-3-oxides undergo stereoselective methanolysis as well as parent unsubstituted oxides.

INTRODUCTION

2H-1,2,3-Diazaphosphole derivatives have been intensively studied by different research groups [1]. In addition, we recently discovered the importance of the 3,4-dihydro-2H-1,2,3-diazaphosphole system as an intermediate in mild procedures for the preparation of indoles [2], pyrroles [3], and pyrazolones [4]. Then, major efforts were devoted to the synthesis of new diazaphosphole derivatives. Recently, two different methods have been reported: one utilizing the reaction of azoalkenes with dichlorophosphines [5], and the other the reaction of phosphinoallenes with hydrazines [6].

Our previous studies on the reactivity of this system included reports of the formation of transition metal complexes [7], of stable pentacoordinate derivatives [8], and of the highly stereoselective formation of only one isomer of the corresponding β-phenylhydrazone methylphosphinate by simple methanolysis [9].

In this article, a further expansion of studies on the reactivity of diazaphosphole oxides is reported.

RESULTS AND DISCUSSION

Synthesis of Diazaphosphole Sulfides

The reaction of 2,3,4,5-tetraphenyl-3,4-dihydro-2H-1,2,3-diazaphosphole-3-oxide (**1a**) with phosphorus pentasulfide (P_4S_{10}) leads to the formation of the corresponding 3-sulfide in 70% overall yield, but in a nonstereospecific manner (Scheme 1). In fact, starting from both pure racemic *cis*-(**1a**) and racemic *trans*-(**1a**) [10], a mixture of both racemates of the phosphine sulfide **1c** were obtained in about a 1:1 ratio. It has been reported [11] that, in several cases, P_4S_{10} was able to convert stereospecifically phosphoryl into thiophosphoryl groups. Although the mechanism of this reaction is unknown, very likely the observed isomerization can be explained in terms of the formation of fluxional pentacoordinate phosphorus intermediates stabilized by the presence of the diazaphosphole ring. This behavior is in agreement with previous findings both in open chain phosphine oxides [11] and in our system [5]. Correct configurational assignments of the two racemates were made on the basis of ^{1}H-NMR chemical shifts and H–P coupling constants according to our previous findings on diazaphosphole derivatives [5].

Functionalization of the 4-Position

Very little attention has been devoted to the synthesis of compounds carrying a substituent different from hydrogen in the 4 position. Attempts to pre-

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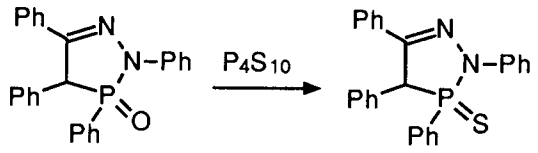


SCHEME 1

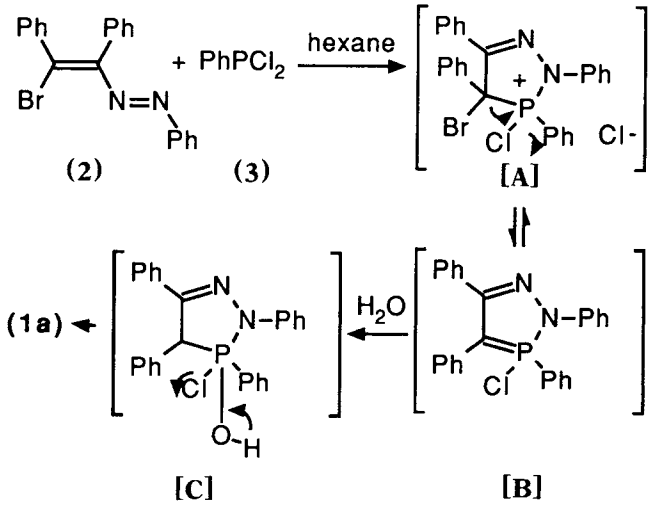
pare 4-trimethylsilyl-substituted diazaphospholes from acylsilane hydrazones and phosphorus trichloride failed, because a β-desililative elimination to nitriles occurred [12]. Furthermore, 4-bromodiazaphospholes cannot be obtained directly by reaction of bromoazoalkenes with dichlorophosphines. In fact, from this reaction oxides **1** were prevalently recovered. The reaction very likely proceeds through elimination of BrCl from the first adduct [**A**], with subsequent hydrolysis of the hypothetical intermediate [**B**], leading to the oxides **1** (Scheme 2).

On the other hand, 4-bromo derivatives could be obtained from oxides **1** by treatment with a brominating agent. Among these, phenyltrimethylammonium perbromide (PTAB) is reported to be an efficient and regioselective reagent to brominate the most substituted α-position of ketones, cyclic ketals [13], and hydrazones [14]. In fact, the reaction of the 5-R-2,3,4-triphenyl-3,4-dihydro-2H-1,2,3-diazaphosphole-3-oxides (**1a-c**) with phenyltrimethylammonium perbromide (PTAB) afforded the 4-bromo derivatives **4a-c** in good yields (Scheme 3).

It should be noted the highly regioselective bromination of **1b** is almost exclusively the result of apparent hydrogen-bromine exchange at the ring position. More classical and available reagents, bromine and NBS, lead to mixtures of brominated products when two different α positions with respect to the C=N double bond are present, such as in **1b**. However these reagents can be employed conveniently in the reactions of **1a, c.**

In addition, the same cis:trans ratio of **4b** isomers was obtained starting from both pure *cis* and *trans*-**1b**, supporting the concept that reaction occurs through the tautomer [**D**], in which no chiral carbon is present at the 4 position. The configuration of the **4b** isomers is assigned on the basis of the C4-P coupling constants. In fact, we have found that the trans derivatives show lower coupling constants than the cis ones (Table 1).

It is noteworthy that starting from both pure cis and trans isomers of compounds **1a, c** the same bromo derivatives were almost exclusively obtained. Very likely, owing to a different steric hindrance effect exerted by the phenyl group in the



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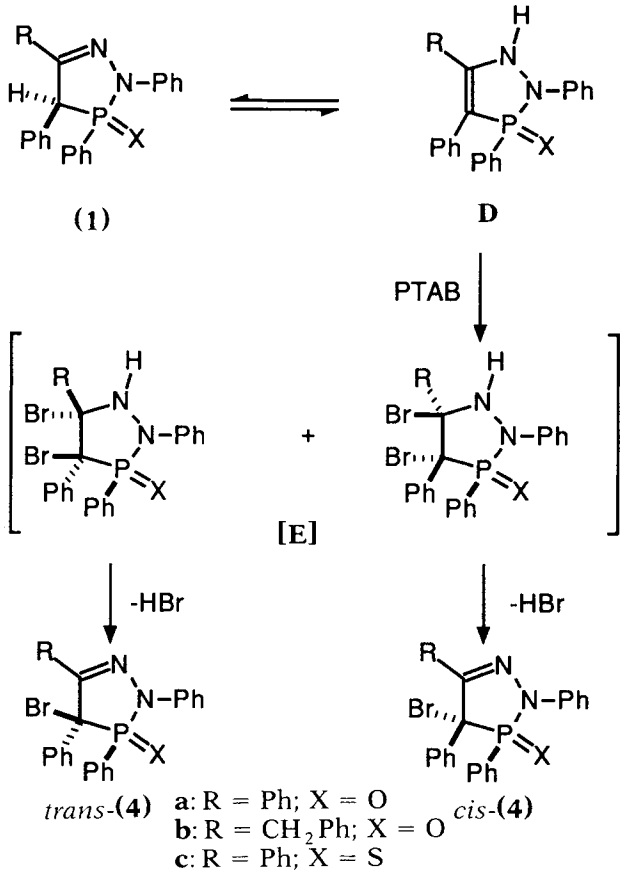


SCHEME 3

5-position with respect to a benzyl framework, bromine is ultimately preferentially utilized to form only one of the possible isomers of [**E**] and, as a consequence, only one **4a, c** racemate. The exact configuration of these compounds cannot be assigned on the basis of either ^{13}C and ^{1}H-NMR

TABLE 1 C4-P Coupling Constants of some Diazaphosphole Derivatives

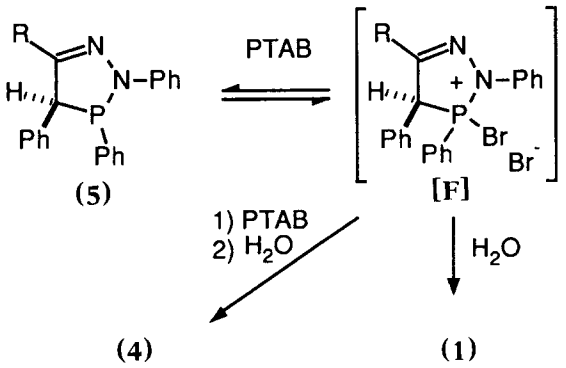
Compound	*J (Hz)*
cis-**5a**	17
trans-**5a**	13
cis-**1a**	90
trans-**1a**	86
cis-**1b**	91
trans-**1b**	88
cis-**4b**	96
trans-**4b**	92

chemical shifts C4-P coupling constants, because unequivocal assignment can be made only in the presence of both isomers. Moreover, no suitable crystals for X-ray analysis were obtained. The reaction of **1a** with *N*-chlorosuccinimide (NCS) gave the corresponding 4-chloro derivative **4d** (Scheme 4) with the same stereochemical behavior.

In contrast to the behavior of the oxides **1**, the corresponding phosphines **5** do not react with brominating agents to give 4-bromo-substituted phosphines. Actually, the reaction of each **5** with an equimolecular amount of PTAB gives almost exclusive formation of the corresponding oxide **1**, very likely through formation of a phosphonium salt [**F**] followed by hydrolysis. Moreover, use of a twofold excess of brominating agent affords the corresponding bromooxide **4** (Scheme 5).

Bromo derivatives **4** seem to show the same reactivity behavior as their unsubstituted homologues. In fact, methanolysis of **4a** in absolute methanol leads to only one of the possible open chain methyl phosphinates (**6a**) according to our previous finding [9]. Apparently, the 4-bromo substituent has no influence on the relative stabilities of pentacoordinate intermediates involved in this reaction.

In conclusion, 4-bromodiazaphosphole-3-oxides or sulfides **4** can be obtained from reaction of the corresponding 4-unsubstituted derivatives **1** with brominating agents. In particular, PTAB was demonstrated to be very regioselective, allowing bromination to occur exclusively at the 4-position of the ring. However, when such high regioselectivity is not required, the cheaper and more available bromine can be conveniently used. Furthermore, a

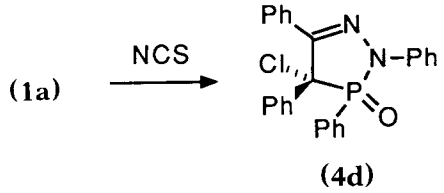


SCHEME 5

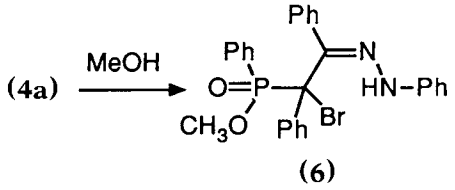
much higher degree of stereoselectivity is observed with the 5-phenyl derivative **1a, c** than with the 5-benzyl derivative **1b**. In addition, it should be noted that these halogenations represent the first examples of reactions not involving the phosphorus atom carried out on the 3,4-dihydro-2H-1,2,3-diazaphosphole system. The 4-halogeno derivatives obtained could be versatile starting materials for the synthesis of diazaphospholenoxides arising from azoalkenes that are not readily available.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a Varian EM360L instrument. Chemical shifts are given from Me_4Si (internal standard) in $CDCl_3$ solutions. ^{31}P and ^{13}C-NMR spectra were recorded with a Varian FT 80A instrument. Positive ^{31}P chemical shifts are downfield of external phosphoric acid (85%). Mass spectra were recorded with a VG 7070 spectrometer. Melting points are uncorrected and were determined with a Büchi apparatus. Hexane, THF and benzene, and CCl_4 were dried by double distillation over sodium wire. Diazaphospholes **5**, oxides **1** [4], and PTAB [13] were synthesized as previously reported. 1-bromo-2-(phenylazo)stilbene (mp 84–85°C) was prepared by reaction at room temperature of equimolecular amounts of phenylazostilbene and PTAB dissolved in THF and purified by chromatography (cyclohexane/benzene 7:3 as eluent).



SCHEME 4



SCHEME 6

Synthesis of Diazaphosphole Sulfides

To 2,3,4,5-tetraphenyl-3,4-dihydro-2H-1,2,3-diazaphosphole-3-oxide (**1a**) (2 mmol) dissolved in 10 cm^3 of anhydrous benzene, phosphorus pentasulfide (2 mmol) was added at room temperature with stirring. The mixture was refluxed for 3 h, then the solution was cooled and evaporated, and the crude mixture of isomers **1c** was submitted to chromatographic separation (hexane: ethyl ether: benzene 6/2/1 as eluant).

cis-**1c**: 35%, mp 139–141°C; NMR ($CDCl_3$) δ_H 4.98 (d, 1H J_{PCH} = 8 Hz); δ_P 77.6. *m/z* 424.116299 ($M^+C_{26}H_{21}N_2PS$ required 424.116300, base); 391 (78).

trans-**1c**: 35%, mp 170–172°C; NMR ($CDCl_3$) δ_H 5.32 (d, 1H J_{PCH} = 20 Hz); δ_P 80.2. *m/z* 424.116297 ($M^+C_{26}H_{21}N_2PS$ required 424.116300, base); 391 (78).

Reaction of 1-Bromo-2-(phenylazo)stilbene with Dichlorophosphine

The reaction was carried out as previously described [5]. After chromatography of the mixture, the following products were recovered: mixture of cis and trans oxides **1a** in 60% yield. Recognized by comparison with authentic samples; mixture of two β-phenylhydrazonebromophosphinates **7** isomers [15] 20%; ^{1}H-NMR ($CDCl_3$) δ 4.67 (d, 1H J_{PCH} = 22 Hz first isomer); 6.00 (d, 1H J_{PCH} = 15 Hz second isomer); 11.9 (s, 1H, NH). IR (KBr) 3340 (NH) 1260–80 (P=O) cm^{-1}. *m/z* 490–488.065350 ($M^+C_{26}H_{22}N_2POBr$ required 488.065356), 411–409 (base).

Synthesis of 4-Halo-3,4-dihydro-2H-1,2,3-diazaphospholes-3-oxides (**4a, b, d**) *and 4-Bromo-3,4-dihydro-2H-1,2,3-diazaphospholes-3-sulfide* (**4c**)

PTAB Procedure. To each diazaphosphole-3-oxide (**1a-c**) (2 mmol) dissolved in 10 cm^3 of anhydrous THF, PTAB (2 mmol in 20 cm^3 of THF) was added at room temperature with stirring. After 50 min, the mixture was filtered, and the filtrate was washed with 5% sodium carbonate, dried, and evaporated. The crude product was crystallized from hexane:

4a: 70%. mp 177–9°C, NMR ($CDCl_3$) δ_C 60.6 (d, C4, J_{PC4} = 94 Hz); δ_P 42.7 IR (KBr) 1440 (P–N) 1240–60 (P=O) cm^{-1}. *m/z* 488–486.049710 (M^+ $C_{26}H_{20}N_2POBr$ required 486.049706), 409–407 (base).

cis-**4b** and *trans*-**4b**: 60% total yield. Isomer ratio 2:3. *cis*-**4b** [16] NMR ($CDCl_3$) δ_H 3.88–4.40 (AB, 2H, CH_2Ph); δ_C 61.5 (d, C4, J_{PC4} = 96 Hz). *m/z* 502–500. (M^+), 423–421 (base). *trans*-**4b** mp 150–2°C, ^{1}H-NMR ($CDCl_3$) δ 3.64–3.96 (AB, 2H, CH_2Ph). ^{13}C-NMR ($CDCl_3$) δ 64.4 (d, C4, J_{PC4} = 92 Hz). *m/z* 502–500.065350 ($M^+C_{27}H_{22}N_2POBr$ required 500.065356), 423–421 (base).

4c: 62%; mp 174–76°C; NMR ($CDCl_3$) δ_C 73.2 (d, C4, J_{PC4} = 35 Hz) δ_P 85.6. *m/z*: 504–502.0268645 (M^+, $C_{26}H_{20}N_2PSBr$ required 502.0268651) 269 (base).

Bromine Procedure. To 2,3,4,5-tetraphenyl-3,4-dihydro-2H-1,2,3-diazaphosphole-3-oxide (**1a**) (2 mmol) dissolved in 10 cm^3 of anhydrous carbon tetrachloride, bromine (2 mmol in 20 cm^3 of CCl_4) was added at room temperature with stirring. After 40 min, the solution was evaporated and the crude product (**4a**) was crystallized from hexane: 68%.

The same procedure applied to **1b** afforded an intractable reaction mixture.

NBS Procedure. To 2,3,4,5-tetraphenyl-3,4-dihydro-2H-1,2,3-diazaphosphole-3-oxide (**1a**) (2 mmol) dissolved in 10 cm^3 of anhydrous carbon tetrachloride, NBS (2 mmol in 20 cm^3 of CCl_4) and 5 mg of benzoyl peroxide were added at room temperature with stirring. The reaction mixture was refluxed for 3 h, cooled, filtered and the filtrate evaporated. The crude product (**4a**) that resulted was crystallized from hexane: 67%.

The same procedure applied to **1b** afforded an intractable reaction mixture.

NCS Procedure. To 2,3,4,5-tetraphenyl-3,4-dihydro-2H-1,2,3-diazaphosphole-3-oxide (**1a**) (2 mmol) dissolved in 10 cm^3 of anhydrous carbon tetrachloride, NCS (2 mmol in 20 cm^3 of CCl_4) and 5 mg of benzoyl peroxide were added at room temperature with stirring. The reaction mixture was refluxed for 48 h, cooled, and filtered, and the filtrate was evaporated. The crude product (**4d**) that resulted was crystallized from hexane: 49%; mp 112–4°C; NMR ($CDCl_3$) δ_C 70.6 (d, C4, J_{PC4} = 95 Hz); δ_P 41.5. *m/z*: 444–442.100169 (M^+, $C_{26}H_{20}N_2POCl$ required 442.100170) 409–7 (base).

Methanolysis of Bromo Derivative **4a**. The methanolysis was performed under the same experimental conditions previously described [9]. β-Phenylhydrazone methyl phosphinate **6** was recovered in 64% yield; mp 168–70°C; NMR ($CDCl_3$) δ_H 3.60 (d, 3H, Me, J_{PMe} = 11 Hz); δ_P 30.3. *m/z* 520–518.075922 (M^+ $C_{27}H_{24}N_2PO_2Br$ required 518.075919), 440–438 (base).

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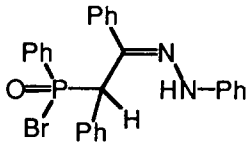

[15] **(7)**

[16] The cis-**4b** fraction was always contaminated by its trans isomer. Therefore, it was impossible to determine a melting point. However, the sample showed a satisfactory elemental analysis for the formula $C_{27}H_{22}N_2POBr$.