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Bicyclic Organophosphorus Amides. Nucleophilic Cleavage of 1-Oxo-2,3-benzo-10-phenyl-4,7,10-triaza-1λ^5-phosphabicyclo-[5.3.0]decane and its *p*-Anisyl Analogues†

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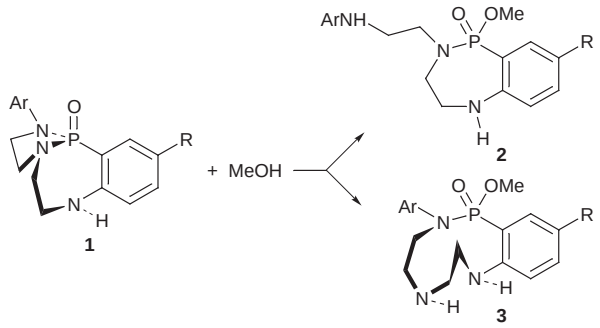
Methanolysis of the title substrates leads to different products depending on the conditions: in the presence of HCl both P–N bonds are broken yielding a non-cyclic phosphonic diester while the MeO^- ion reacts selectively breaking the P–N(Ar) bond and yielding a cyclic, seven-membered phosphonic amidoester.

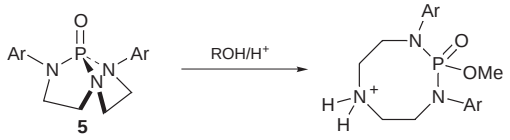
Recently we reported the preparation of a new type of bicyclic phosphonic diamide **1** *via* the lithiation-induced N→C migration of phosphorus in a bicyclic phosphoric triamide.[1] Now we report the nucleophilic cleavage of the P–N bond(s) in **1** by methanol leading to new cyclic and non-cyclic phosphonic derivatives. Methanolysis of one of the two P–N bonds in **1** can lead to a seven-membered **2**, or a ten-membered **3** cyclic phosphonic amidoester (Scheme 1).



Scheme 1

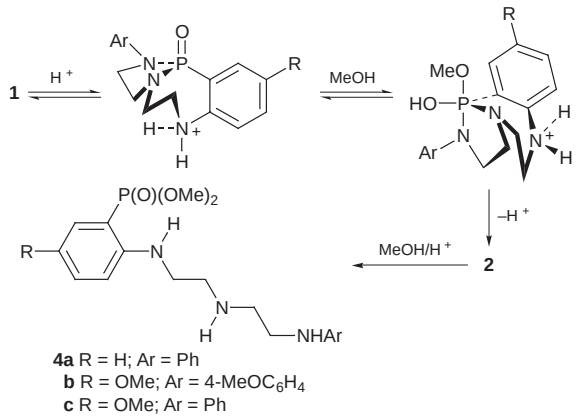
Acid-catalysed alcoholysis of a similar bicyclic phosphotriamidate proceeds with a selective cleavage of the P–N (bridgehead) bond yielding a monocyclic eight-membered phosphoric diamidoester.[2] In the case of **1** we have found that the solvolysis is non-selective and leads to the cleavage of both P–N bonds, *i.e.* to the opening of both heterocyclic rings.

Although both amide bonds are broken under those conditions, we think that the P–N(10) bond is cleaved first yielding **2**, which then undergoes subsequent solvolysis to **4**; both steps occurring with comparable rates. In one case (**1a**) we were able to isolate small quantities of the intermediate product **2a**, identical to that prepared from **1a** under basic conditions (*vide infra*). The product, when subjected to the methanolysis under the same conditions as for **1a**, yielded **4a** at approximately the same rate as for the direct formation of **4a**. The first cleavage of the P–N(Ar), and not the P–N (bridgehead) bond in **1** is in contrast with the acid-catalysed solvolysis of its precursor **5**, where the P–N (bridgehead) bond was cleaved selectively, giving the eight-membered monocyclic product (Scheme 2).[2] In the latter case the selectivity was explained in terms of the greater basicity of the bridgehead nitrogen.[2] In the case



Scheme 2

of **1**, the situation is different. The most basic atom in the molecule is the *amine* nitrogen N(4), protonation of which does not catalyse the P–N (*amide*) bond cleavage. We believe that the reaction involves an associative step of addition of the MeOH molecule to the conjugate acid of **1**, followed by the proton transfer-assisted cleavage of the P–N(10) bond in the P^V intermediate. The amidoester **2** formed in the first reaction would be expected to be activated towards substitution relative to **1** (exchange of one of the nitrogen substituents at P for the OMe group), and thus would undergo further methanolysis to the diester **4**. The observed selectivity in the first product-determining step (formation of **2**, but not of **3**) can be explained in terms of the stereoelectronic effects. The P^V intermediate with the N(10) atom occupying the apical position [required for the first cleavage of the P–N (Ar) bond] is much less strained relative to the conformer with the equatorial location of the N(10) atom because in the latter case the seven-membered ring has to accommodate the 90° apical–equatorial (as opposed to the 120° equatorial–equatorial) bond angle in the tbp structure of the intermediate. The proposed mechanism for the acid-catalysed methanolysis of **1** *via* the first cleavage of the five-membered ring is shown in Scheme 3.



Scheme 3

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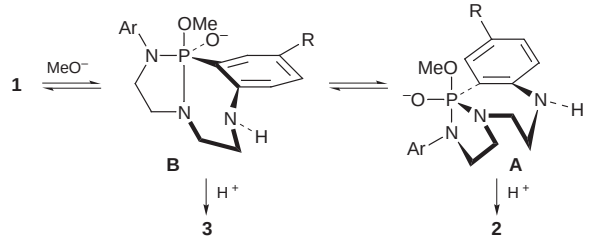
† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Unlike the acidic methanolysis, reaction of **1** with sodium methoxide in methanol proved to be fully regioselective and yielded the monocyclic seven-membered phosphonic amidoesters **2** (**2a**, R = H; Ar = Ph; **2b**, R = OMe; Ar = 4-$MeOC_6H_4$; **2c**, R = OMe; Ar = Ph) as the exclusive products. Again, we propose that the observed regioselectivity is a consequence of the generally accepted mechanism of the nucleophilic substitution at phosphorus in cyclic organophosphorus amides and of the relative stability of the corresponding intermediates. Extensive work by Hudson and co-workers[3] and Hall and Inch[4] on the base hydrolysis of cyclic organophosphorus amidoesters demonstrated that the rates and products of the reaction can be explained in terms of an addition–elimination mechanism in which a P^V intermediate can undergo pseudorotation before the bond breaking product-determining step. As discussed above for the acidic methanolysis, application of the mechanism to the reaction of **1** with MeO^- ion can lead to two isomeric P^V intermediates (**A** and **B**) as the direct precursors of products **2** and **3** (Scheme 4). The $C_{arom}-P-N_{bridgehead}$ bond angle in **1**, as shown in the X-ray crystal structure, is 107.7°.[1] Location of the bridgehead nitrogen in the apical position (intermediate **B**) involves contraction of that angle by 17.7°, while the equatorial location of the same atom (intermediate **A**) results in expanding the angle by 12.39°. It seems that the seven-membered ring in the substrate molecule accommodates the latter angular change in preference to the possible contraction, particularly in view of the restrictions existing already due to the 2,3-benzo substituent.

Under the basic conditions of the methanolysis, the products **2** are stable and do not undergo further reaction. This behaviour is in agreement with the known resistance of the tertiary, non-strained phosphoramidates to undergo base-catalysed cleavage.[5]



Scheme 4

Experimental

NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ and δ values are relative to $SiMe_4$ (^1H, ^{13}C) or 85% H_3PO_4 (^{31}P). ^{13}C NMR spectra were proton-decoupled, but the proton-coupled spectra gave the expected patterns of signals. Proton and ^{13}C NMR spectra were in full agreement with the indicated structures for all the prepared compounds. For column chromatography Merck Kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. Elemental analyses (C, H, N) were performed at the Chemistry Department, University of Cape Town. Solvents and commercially available reagents were purified by conventional methods immediately before use. Bicyclic substrates **1** were prepared from the corresponding bicyclic triamidates **5**.[1]

General Procedure for the Preparation of **1**.—A solution of BuLi (10.0 mmol, 1.6 M solution in hexane) was added by means of a syringe to a stirred and cooled to −78 °C solution of **5** (0.2 mmol) in anhydrous THF (100 ml) under an atmosphere of dry nitrogen. The solution was stirred at −78 °C for 1 h, warmed to room temperature and stirred for an additional 5 h. Methanol (1–2 ml) was added, followed by $CHCl_3$ (100 ml), the solution was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$–acetone, 1 : 1). **1a**, white solid (0.51 g, 85%); mp 236.4–237.7 °C (from THF); δ_P 23.7 (Found: C, 64.61; H, 6.17; N, 14.08. $C_{16}H_{18}N_3OP$ requires C, 64.21; H, 6.06; N, 14.04%). **1b**, white solid (0.45 g, 63%); mp 201.8–203 °C (from $CHCl_3$ acetone, 1:1); δp 23.3 (Found: C, 59.16; H, 6.15; N, 11.50. $C_{18}H_{22}N_3O_3P$ requires C, 60.16; H, 6.17; N, 11.69%). **1c**, white solid (0.39 g, 59%); mp 208.4–209.0 °C (from $CHCl_3$ acetone, 1 : 1), δ_P 24.0 (Found: C, 61.80; H, 6.19; N, 12.83. $C_{17}H_{20}N_3O_2P$ requires C, 62.00; H, 6.12; N, 12.76%).

Acid-catalysed Methanolysis of **1**. *General Procedure*.—A solution of **1** (1.0 mmol) in methanol (30 ml) containing anhydrous HCl (2.2 mmol) was kept at room temperature and the reaction progress was monitored by recording the ^{31}P NMR spectrum of the solution. When the signal derived from **1** had almost disappeared the solution was evaporated under reduced pressure. Chloroform (50 ml) was added, followed by finely powdered K_2CO_3 (1.6 g). After filtration (or centrifugation), the chloroform solution was washed with water (3 × 5 ml), dried [Na_2SO_4) and evaporated under reduced pressure. Column chromatography ($CHCl_3$—ethyl acetate, 1 : 1, followed by $CHCl_3$–MeOH, 20 : 1) yielded the following products. From **1a** (reaction time 35 days, 50% conversion after approx. 5 days): unreacted **1a** (5%), **2a** (0.02 g, 6%); viscous oil solidifying on standing, NMR spectra identical to those of **2a** obtained in base-catalysed methanolysis (*vide supra*), and **4a** (0.22 g, 61%); viscous oil; δ_P 25.7 (Found: C, 59.10; H, 7.30; N, 11.25. $C_{18}H_{26}N_3O_3P$ requires C, 59.49; H, 7.21; N, 11.56%). From **1b** (reaction time 44 days, 50% conversion after approx. 10 days): unreacted **1b** (15%) and **4b** (0.28 g, 67%); viscous oil; δ_P 24.9 (Found: C, 56.52; H, 7.20; N, 9.58. $C_{20}H_{30}N_3O_5P$ requires C, 56.73; H, 7.14; N, 9.92%). From **1c** (reaction time 43 days, 50% conversion after approx. 7 days): unreacted **1c** (7%) and **4c** (0.25 g, 64%); viscous oil; δ_P 24.8 (Found: C, 57.59; H, 7.20; N, 10.55. $C_{19}H_{28}N_3O_4P$ requires C, 58.00; H, 7.17; N, 10.68%).

Base-catalysed Methanolysis of **1**. *General Procedure*.—A solution of **1** (1.0 mmol) in methanol (15 ml) containing sodium methoxide (3.0 mmol) was kept at 50–55 °C and the progress of the reaction was monitored by ^{31}P NMR spectroscopy. The reaction was stopped at 60–80% conversion, since further incubation led to the formation of some unidentified, phosphorus-containing products. Finely powdered NH_4Cl (6.0 mmol) was added to the solution, the solvent was evaporated under reduced pressure, chloroform (50 ml) was added and the solution was washed with water and dried (Na_2SO_4). After evaporation of the solvent the crude product was purified by column chromatography ($CHCl_3$–AcOEt, 1 : 1). The following products were obtained. From **1a** (reaction time 42 days, 50% conversion after approx. 36 days): unreacted **1a** (38%) and **2a** (0.11 g, 34%); colourless needles, mp 125.4–126.8 °C (from THF–hexane, 1 : 2); δ_P 27.9 (Found: C, 61.52; H, 6.85; N, 12.48. $C_{17}H_{22}N_3O_2P$ requires C, 61.62; H, 6.69; N, 12.68%). From **1b** (reaction time 35 days, 50% conversion after approx. 27 days): unreacted **1b** (22%) and **2b** (0.08 g, 21%); viscous oil; δ_P 27.7 (Found: C, 58.01; H, 6.95; N,10.66. $C_{19}H_{26}N_3O_4P$ requires C, 58.30; H, 6.70; N, 10.74%). From **1c** (reaction time 35 days, 50% conversion after approx. 25 days): unreacted **1c** (23%) and **2c** (0.15 g, 42%); viscous oil; δ_P 27.8 (Found: C, 59.58; H, 7.01; N, 11.50. $C_{18}H_{24}N_3O_3P$ requires C, 59.82; H, 6.69; N, 11.63%).

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