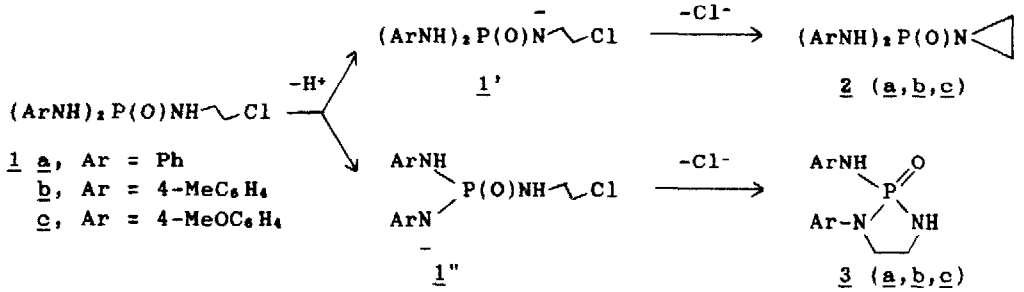
Tetrahedron Letters,Vol.30,No.16,pp 2141-2144,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

PHOSPHORIC AMIDES. PART 10. BASE - PROMOTED CYCLIZATION OF PHOSPHOROTRIAMIDATES BEARING THE N-(2-CHLOROETHYL) SUBSTITUENT, AND THE INTERCONVERSION OF CYCLIC PRODUCTS

S. Bauermeister, A. M. Modro, and T. A. Modro*
Department of Chemistry, University of Pretoria, Pretoria 0002, S. Africa

Summary: *N,N'-Diaryl-N"-(2-chloroethyl)phosphorotriamidates undergo base-promoted 1,3 and 1,5 cyclizations, yielding the N-phosphorylated aziridines and 1,3,2-diazaphospholidines, respectively. The former products are stable towards bases, while the latter undergo base-promoted ring contraction, resulting in the isomeric aziridine derivatives.*

Intramolecular 1,5 displacement of chloride ion in the NPNCCCl system, yielding the 1,3,2-diazaphospholidine derivative, has been postulated[1] as the first step in the nonenzymatic hydrolysis of cyclophosphamide. The existence of such intermediate was later supported[2] by its preparation from this substrate upon treatment with NaH. For an N-(2-chloroethyl)substituted phosphorodi- (or tri-) amidate of the type $RNH\text{-}P(O)(X)NHCH_2CH_2Cl$ (1) base-promoted displacement of chloride ion can, in principle, lead to the 1,3 and 1,5 cyclization with the endo- or exo-cyclic location of phosphorus in the reaction product. The proportion of these two products should be governed by the relative acidity of the two NH hydrogen atoms, and by the relative rates of the subsequent 1,3 *vs.* 1,5 ring closure. We have tested the base-promoted reactivity of (1) using N,N'-diaryl-N"-(2-chloroethyl) phosphorotriamidates (1a, b, c) as substrates.[3] The two cyclization routes available for these substrates are presented below.



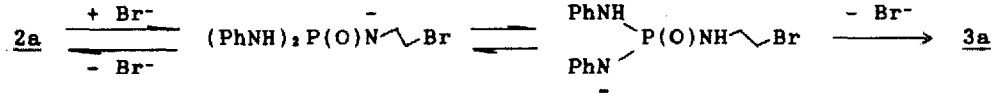
It is difficult to predict the regioselectivity of the cyclization in 1, as the structural effects on the deprotonation and the ring closure steps operate in opposite directions. Although it is known[4] that the stereoelectronic factors favour the formation of three membered rings over larger structures, the relative acidity of the hydrogen atoms in 1 should favour[5] the conjugate base 1", necessary as a precursor of 3. We have found that when substrates 1a - c are treated with bases in the presence of the PTC catalyst,[7] both cyclic products, 2a - c, and 3a - c are formed in comparable quantities. For each substrate the corresponding products 2 and 3 were separated by column chromatography and characterized by ^1H (300 MHz) and ^{31}P n.m.r. spectroscopy, and elemental analyses.[8] The typical results of cyclization of substrates 1 under variable conditions are given in the Table.

Table Base-promoted cyclization of triamidates (1) in benzene

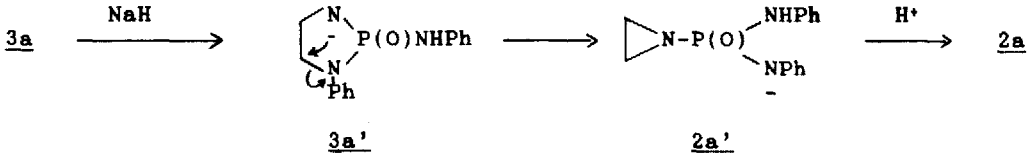
Substrate	Reaction conditions	Conversion (%)	2 (%)[a]	3 (%)[a]
1a	NaH (2 equiv), TBAB[b] (5 mole-%), r.t., 15 min	100	53	47
1a	NaH (1 equiv), TBAB (5 mole-%), reflux, 5 h	88	67	21
1a	NaH (2 equiv), TBAB (5 mole-%), reflux, 8 h	100	100	
1b	NaH (1.5 equiv), TBAB (10 mole-%), reflux, 18 h	91	65	26
1b	$NaOH/K_2CO_3$ (4 equiv), TBAB (10 mole-%), reflux, 19 h	92	92	
1b	t-BuOK (2.5 equiv), TBAB (10 mole-%), reflux, 18 h	93	92	1
1c	NaH (1.1 equiv), TBAB (10 mole-%), reflux, 5 h	85	48	37
1c	t-BuOK (2.5 equiv), TBAB (10 mole-%), reflux, 18 h	100	100	

[a] Determined by ^{31}P n.m.r. spectroscopy.
[b] Tetra-n-butylammonium bromide.

The first, fourth, and seventh entries in the Table indicate that both cyclizations occur with similar rates. The ratio 2/3 increases however with time and temperature, and can vary from *e.g.* 1.1 to ∞ (1st and 3rd entry). These results suggest subsequent interconversion of the primary products under reaction conditions. The possibility of secondary reactions was tested by investigating independently the effect of base (NaH) and of PTC (TBAB) on the reaction products, 2a and 3a. While 3a was unaffected by TBAB in refluxing benzene, 2a was gradually converted under these conditions into 3a, presumably *via* the nucleophilic opening of the aziridine ring,[9] internal proton transfer, and the 1,5 ring closure:



With respect to the base, the situation is reversed: 2a remained unchanged when heated in benzene solution in the presence of NaH, while 3a was quantitatively converted under these conditions into 2a. The absence of the intramolecular opening of the aziridine ring upon deprotonation of 2a illustrates the rule, according to which the "5-Endo-Tet" cyclization process is disfavoured on stereoelectronic grounds.[4] The interconversion of 3a to 2a upon treatment with NaH (or in the presence of the excess of base in the cyclization of 1) can be explained by the following sequence.



3a' 2a'

Although the 3a' ⟶ 2a' interconversion corresponds to the known[10] preference for the formation of a three membered ring, we observe in our case an unusual example of a "3-Exo-Tet" ring closure with the *syn* orientation of the nucleophilic center and the departing group.

Acknowledgement Financial assistance of the University of Pretoria and the Council for Scientific and Industrial Research is gratefully acknowledged.

References and Notes

1. O. M. Friedman, S. Bien, and J. K. Chakrabarti, *J. Am. Chem. Soc.*, 1965, 87, 4978.

2. G. Zon, S. M. Ludeman, and W. Egen, *J. Am. Chem. Soc.*, 1977, 99, 5785.

3. Triamides 1a - c were prepared from $POCl_3$ and the corresponding amines. For all compounds ^{31}P n.m.r. spectra showed the presence of a single peak, and the ^1H n.m.r. spectra and elemental analyses were in full agreement with the expected structure.

4. P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, 1983, ch. 5.

5. Athough the relationship between δ value of a proton and its acidity is only an approximate one,[6] the *ca.* 2 ppm down-field shift of the ArNH protons relative to the alkyl-NH hydrogen found for 1a - c, allows to expect the conjugate base 1" to be favoured in the deprotonation step.

6. J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill, 1959, ch. 2.3.

7. A. Zwierzak, *Synthesis*, 1984, 332.

8. Mp (uncorrected): 2a, 183-184°C; 3a, 203.5°C; 2b, oil; 3b, 180-182°C; 2c, 47-51°C; 3c, 200-202°C. ^1H n.m.r. ($CDCl_3$): 2a, δ 2.30 (4H, d, J_{HP} 16.2 Hz, C_2H_4N), 5.48 (2H, d, J_{HP} 8.4 Hz, 2 x NHAr), 6.69 - 7.23 (10H, m, 2 x C_6H_5). 3a, δ 2.87 (1H, d, J_{HP} 10.5 Hz, endo-NH), 3.40 - 3.54 (1H, m) and 3.58 - 3.64 (3H, m) (CH_2CH_2), 5.43 (1H, d, J_{HP} 6.6 Hz, exo-NH), 6.82 - 6.97 (5H, m, C_6H_5), 7.08 - 7.25 (5H, m, C_6H_5). 2b, δ 2.22 (6H, s, 2 x CH_3), 2.25 (4H, d, J_{HP} 11.4 Hz, C_2H_4N), 5.78 (2H, d, J_{HP} 8.7 Hz, 2 x NHAr), 6.95 (4H, d, J_{HH} 8.4 Hz, 2,6,2',6'-H), 6.99 (4H, d, J_{HH} 8.4 Hz, 3,5,3',5'-H). 3b, δ 2.20 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.85 (1H, b.s, endo-NH), 3.34 (1H, m) and 3.65 (3H, m) (CH_2CH_2), 5.37 (1H, d, J_{HP} 6.6 Hz, exo-NH), 6.74 (2H, d, J_{HH} 8.1 Hz, 3,5-H of the endo-NAr), 6.94 (2H, d, J_{HH} 8.1 Hz, 2,6-H of the endo-NAr), 7.02 (2H, d, J_{HH} 8.6 Hz, 3',5'-H of the exo-NAr), 7.08 (2H, d, J_{HH} 8.6 Hz, 2',6'-H of the exo-NAr). 2c, δ 2.22 (4H, d, J_{HP} 15.6 Hz, C_2H_4N), 3.68 (6H, s, 2 x OCH_3), 5.80 (2H, d, J_{HP} 8.7 Hz, 2 x NHAr), 6.69 (4H, d, J_{HH} 8.8 Hz, 2,6,2',6'-H), 7.00 (4H, d, J_{HH} 8.8 Hz, 3,5,3',5'-H). 3c, δ 2.73 (1H, d, J_{HP} 10.1 Hz, endo-NH), 3.36 (1H, m) and 3.56 (3H, m) (CH_2CH_2), 3.71 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.95 (1H, d, J_{HP} 7.5 Hz, exo-NH), 6.69 (2H, d, J_{HH} 8.8 Hz, 2,6-H of the endo-NAr), 6.78 (2H, d, J_{HH} 8.4 Hz, 2',6'-H of the exo-NAr), 6.81 (2H, d, J_{HH} 8.4 Hz, 3',5'-H of the exo-NAr), 7.11 (2H, d, J_{HH} 8.8 Hz, 3,5-H of the endo-NAr). ^{31}P n.m.r. ($CDCl_3$, rel. to trimethyl phosphate): 2a, 12.1. 3a, 13.1. 2b, 12.8. 3b, 13.6. 2c, 13.4. 3c, 14.6.

9. The ^{31}P n.m.r. spectrum of the reaction mixture after quenching revealed the presence of 3a, unreacted 2a, and a small quantity of the product with the δ ^{31}P value almost identical to that of 1a. It was identified therefore as the corresponding N-(2-bromoethyl) derivative, the neccessary intermediate for the 2a ⟶ 3a interconversion.

10. G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, 1974, 96, 5270.

(Received in UK 27 February 1989)