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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

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To cite this Article Roux, Charlotte Le , Modro, Agnes M. and Modro, Tomasz A.(1994) 'Deactivation of N-Phosphorylated Mustards by the Formation of the 2-Oxo-1,3,2-Oxazaphospholidine Ring', Phosphorus, Sulfur, and Silicon and the Related Elements, 93: 1, 401 – 402

To link to this Article: DOI: 10.1080/10426509408021876

URL: <http://dx.doi.org/10.1080/10426509408021876>

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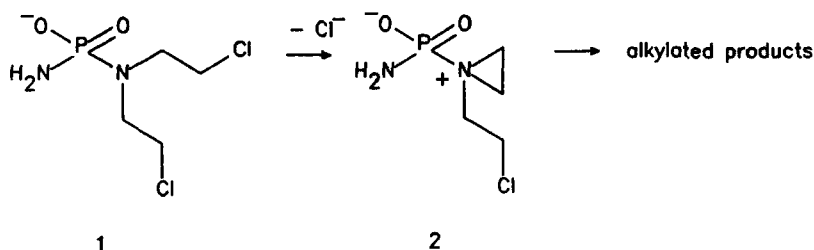
DEACTIVATION OF N-PHOSPHORYLATED MUSTARDS BY THE FORMATION OF THE 2-OXO-1,3,2-OXAZAPHOSPHOLIDINE RING

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Abstract 1,5-Cyclization of the N-phosphorylated mustards leads to 2-oxo-1,3,2-oxazaphospholidine with no further alkylating activity.

INTRODUCTION

Alkylating reactivity of N-phosphorylated Nitrogen Mustards (1), responsible for their application in cancer chemotherapy, is ascribed to the formation of the aziridinium derivative (2), the true alkylating agent, capable of crosslinking nucleophilic centres of cellular DNA (Scheme 1).¹

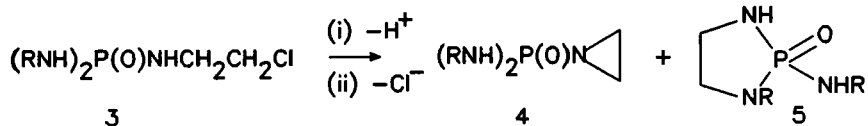


Scheme 1

RESULTS AND DISCUSSION

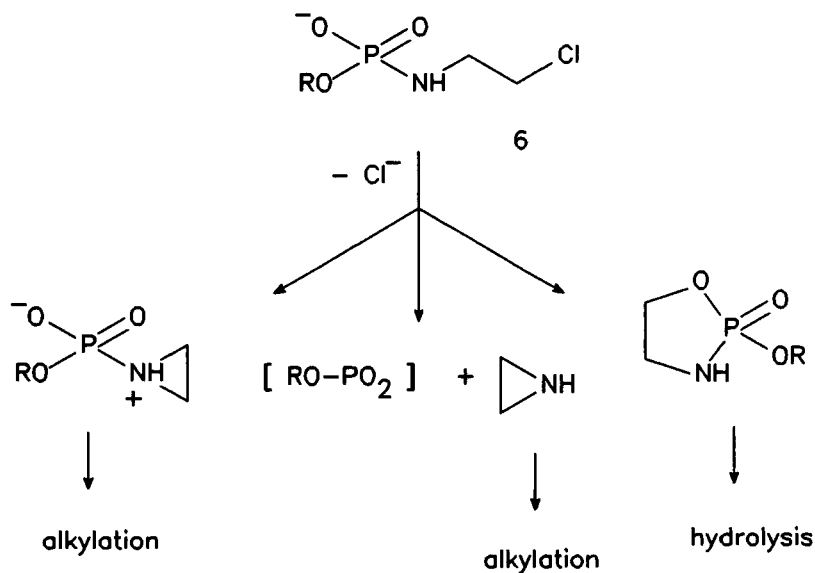
We have found that the N-(2-chloroethyl) substituted phosphorotriamidates (3), when deprotonated, can undergo 1,3-, or 1,5-cyclization, yielding N-phosphorylated aziridines (4) or the 1,3,2-diazaphospholidine derivative (5) (Scheme 2).² The regioselectivity depends on groups R, and

4 and **5** can be converted into each other by bases and nucleophiles.



Scheme 2

Decomposition of an anion (**6**) in water can follow three pathways (Scheme 3). Two of them yield an alkylating intermediate (aziridine derivative), while the last is a deactivating process, as the 1,3,2-oxazaphospholidine hydrolyzes further, depending on the pH, with the P—N, or P—O bond cleavage, yielding the final products with no alkylating activity.



Scheme 3

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2. S. Bauermeister, A. M. Modro, T. A. Modro and A. Zwierzak, *Can. J. Chem.*, **69**, 811 (1991).