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Synthesis of 1,2-azaphosphetidine 2-oxides/sulfides (microreview)

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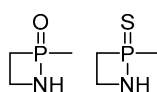
All reported approaches toward synthesis of 1,2-azaphosphetidine 2-oxide/sulfide derivatives are summarized. Synthetic methods for 1,2-azaphosphetidine 2-oxides/sulfides are gathered in four categories: ring expansion of aziridines, cyclizations, carbene insertions, and cycloadditions.

Introduction

1,2-Azaphosphetidine 2-oxides (β-phospholactams) and 2-sulfides (β-thiophospholactams) are important phosphorus analogs of β-lactams (azetidin-2-ones) and β-sultams (1,2-thiazetidine 1,1-dioxides). They can be considered as transition state analogs of β-lactamase inhibitors.[1] Unlike widely investigated β-lactams and β-sultams,[2,3] less attention has been paid to β-phospholactams and β-thiophospholactams, though they show some biological importance.[1]

Ring expansion of aziridines

1-Substituted aziridines react with PCl_3 or $(EtO)_2PCl$ to give aziridine salts, which decompose to $RN(PCl_2)CH_2CH_2Cl$ or $RN[P(OEt)_2]CH_2CH_2Cl$, respectively, and then on heating generate substituted 1,2-azaphosphetidine 2-oxides through intramolecular Arbuzov reaction.[4] The reaction of *N*-phosphorylated 1,2-azaphosphetidine 2-oxides with proton-containing nucleophiles (H_2O, EtOH, or PhOH) leads to the ring cleavage across the P–N bond giving rise to 2-aminoethylphosphonic acid derivatives.[5]
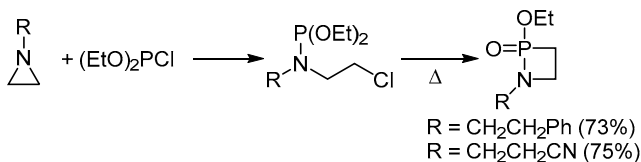
Cyclizations

Treatment of $Br(CH_2)_2NH_2 \cdot HBr$ with $(RO)_2PCl$ and Et_3N under mild conditions gave *N*-phosphorylated 1,2-aza-phosphetidine 2-oxides *via* the formation of $[(RO)_2P]_2NCH_2CH_2Br$ and subsequent Arbuzov reaction. Reaction of *N*-phosphorylated 1,2-azaphosphetidine 2-oxide (R = Et) with tosyl azide afforded its imino derivative.[6]
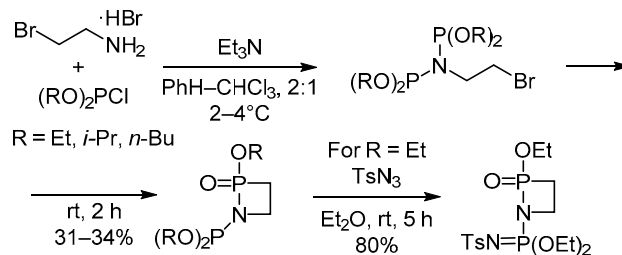
Jiaxi Xu was born in 1963 in Jilin, China. He received his PhD in 1992 from Department of Chemistry at Peking University in China. After a post-doctoral stay at the School of Pharmaceutical Sciences at Beijing Medical University (Health Center of Peking University now), he was appointed as an associate professor at College of Chemistry and Molecular Engineering at Peking University. He also worked as a visiting scholar in the Department of Chemistry at the Chinese University of Hong Kong (1995–1996), Department of Chemistry at Colorado State University (2000–2001), and Medical School at Vanderbilt University (2001–2002). He was promoted a full professor in 2004. At the end of 2007 he started working at the Faculty of Science (College of Chemistry now) at Beijing University of Chemical Technology. His research interests include synthetic methodologies and related mechanisms, asymmetric synthesis and catalysis, synthesis of heterocyclic compounds, unnaturally occurring amino acids and peptides.

Cyclizations (continued)

Reaction of diethyl phosphorisocyanatidite with muco-chloric acid led to a bicyclic 1,2-azaphosphetidine 1-oxide derivative.[7] The highly reactive isocyanate fragment at the P atom permits one to effect cyclization after the 1st stage of the Arbuzov reaction, thus extending the synthetic potential of mucochloric acid derivative phosphorylation.
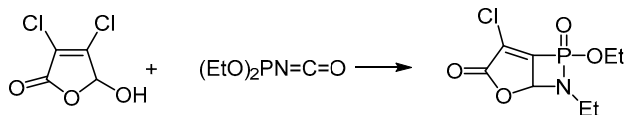
In an effort to test whether a transition state analog is an inhibitor of the metallo-β-lactamases, a phospholactam analog of carbapenem was synthesized from hexanedioic acid.[1] It was first converted into β-aminoalkylphosphonic

monomethyl ester, which was transformed to the designed fused bicyclic 1,2-azaphosphetidine 2-oxide derivative, phosphacarbapenem, by treatment with SOCl₂ in CHCl₃ and, then, NaH in the presence of 15-crown-5 in MeCN. The phospholactam proved to be a weak, time-dependent inhibitor at a 100 μM concentration. Docking study was carried out to explain binding and to offer suggestions for modifications of the phospholactam scaffold to improve binding affinities.
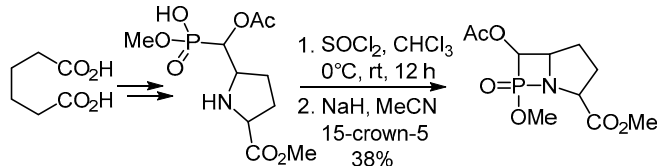

Carbene insertions

[Bis(diisopropylamino)phosphanyl](trimethylsilyl)diazo-methane (*i*-Pr₂N)₂PC(=N₂)SiMe₃ reacted with *p*-toluene-sulfinyl chloride or *p*-toluenesulfonyl chloride, affording the same product – 1,2-azaphosphetidine 2-oxide in 85 or 80% yield, respectively.[8] These results were rationalized by the transient formation of the carbene (*i*-Pr₂N)₂PC(:)S(=O)*p*-Tol, which rearranged into carbene (*i*-Pr₂N)₂P(=O)C(:)S*p*-Tol *via* an intramolecular Wittig-type reaction involving the multiple bond character of phosphanylcarbenes. [Bis(diiso-propylamino)thiophosphoranyl](trimethylsilyl)diazomethane reacted with *p*-TolSCl giving 1,2-azaphosphetidine 2-sulfide in 86% yield. The same derivative was also obtained by photolysis of the *C*-thiophosphoranyl *C*-sulfanyl phosphorus ylide Ph₃P=C(S*p*-Tol)P(=S)(N*i*-Pr₂)₂.

Refluxing of bis[bis(diisopropylamino)phosphinyl]diazo-methane in PhH for 48 h quantitatively led to the corresponding azaphosphetane as the only one diastereoisomer. This result was explained in terms of carbene insertion into the methine C–H bond of an isopropyl substituent. Treatment with S₈ afforded the corresponding 1,2-aza-phosphetidine 2-sulfide.[9]

UV irradiation of thiophosphoranyl-substituted (triphenyl-phosphoranylidene)methanes yielded Ph₃P and 1,2-aza-phosphetidine 2-sulfides.[10] The formation of these heterocycles was explained by invoking insertion of the intermediate carbenes into the methine C–H bond of one of the isopropyl groups.

Photolytic or Rh-catalyzed decomposition of α-diazo-β-ketophosphonamidates and subsequent intramolecular C–H insertion of the resulting carbene intermediates gave mono and bicyclic 1,2-azaphosphetidine 2-oxides.[11]
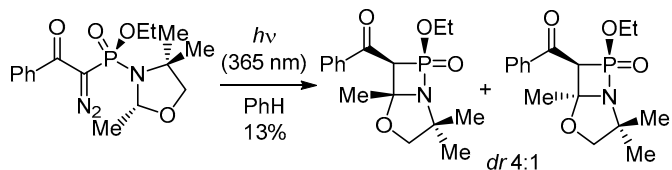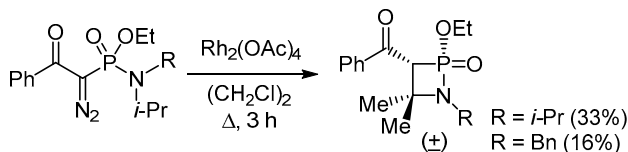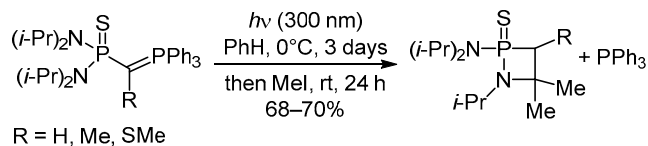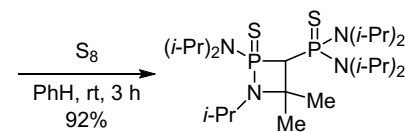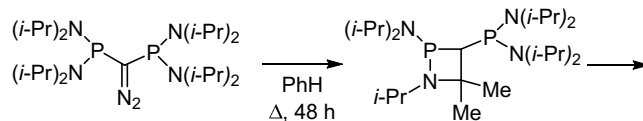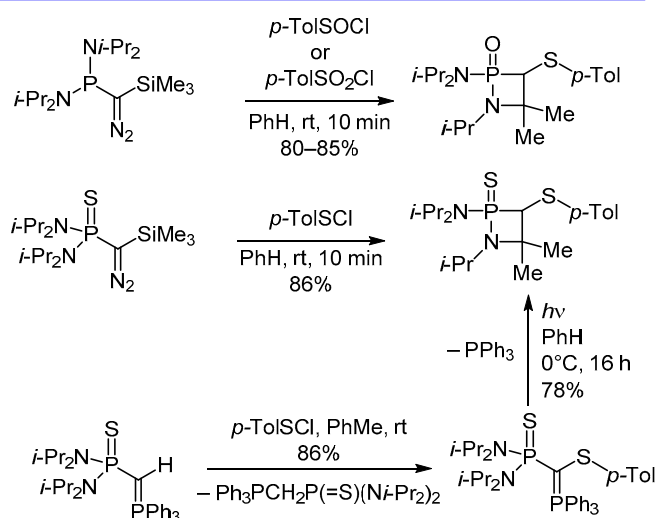
Cycloadditions

Vacuum thermolysis of $Me_3SiP=C(OSiMe_3)C_6H_2Me_3$-2,4,6 provided 3,5-dimesityl-1,2,4-oxadiphosphole, which reacted with tri-*tert*-butylazete to furnish fused polycyclic 1,2-azaphosphetidine 2-oxide derivative in 41% yield.[12] The reaction started with hetero-Diels–Alder cycloaddition followed by rearrangement, phospha-ane reaction, 4-electron electrocyclic ring opening, 6-electron electrocyclic ring opening, [1,5]-H sigmatropic shift, and [2+2] cycloaddition sequence.

1-Alkyl-1,2-diphospholes reacted with *N*-R-α-phenyl-nitrones to give, depending on the temperature, either dimers of 1-alkyl-1-oxo-1,2-diphospholes or 1-alkyl-1,7-dioxo-6-azo-1,7-diphosphabicyclo[3.2.0]hept-2-enes, phosphorus analogs of β-lactams.[13] Mixing of 1-alkyl-1,2-diphospholes with nitrones at room temperature led to oxidation products, i.e., 1-alkyl-1-oxo-1,2-diphospholes, and, then, the corresponding dimers. At elevated temperatures, the latter underwent retro-Diels–Alder reaction and subsequent [2+2] cycloaddition with imines generated in the first step, resulting in the formation of fused bicyclic 1,2-azaphosphetidine 2-oxides.
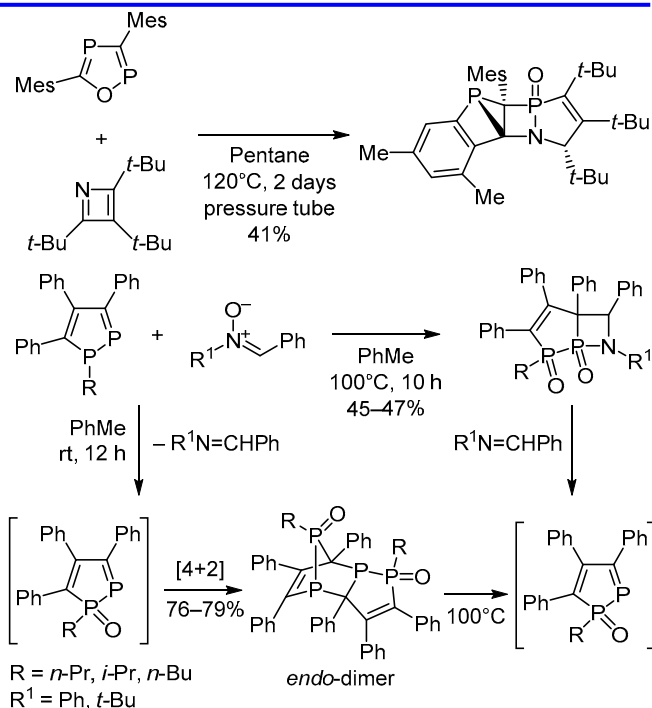
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