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HETEROCYCLES IN FOCUS

Synthesis and stability of thermally labile 1,2-oxaphosphetane 2-oxides and 1,2-thiaphosphetane 2-sulfides (microreview)

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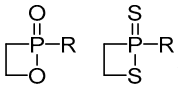


Synthesis and thermal stability of 1,2-oxaphosphetane 2-oxide and 1,2-thiaphosphetane 2-sulfide derivatives are discussed. This microreview covers the available synthetic methods of thermally labile 1,2-oxaphosphetane 2-oxides and 1,2-thiaphosphetane 2-sulfides and their fragmentation. The synthetic approaches may be classified in four distinct categories: cycloaddition, cyclization, fragmentation, and annulation.

Introduction

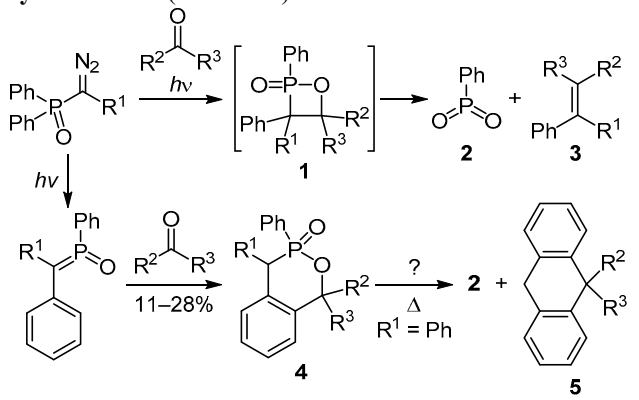
Phosphalactones are important biologically active compounds. Some phosphalactones have been discovered in natural products and have been demonstrated to act as enzyme inhibitors such as inhibitors of acetylcholinesterase, protein tyrosine phosphatases, and pancreatic cholesterol esterase.[1] Recently, we developed an efficient method for the synthesis of δ-phosphalactones.[2] 1,2-Oxaphosphetane 2-oxides (β-phosphalactones) and 1,2-thiaphosphetane 2-sulfides (β-dithiophosphalactones) are important phosphorus-containing analogs of oxetan-2-ones (β-lactones) and 1,2-oxathietane 2,2-dioxides (β-sultones). They are also valuable oxygen or sulfur surrogates of 1,2-azaphosphetidine 2-oxides and 2-sulfides, respectively.[3] Although they can be considered as a class of transition state analogs and inhibitors of β-lactamases, they are thermally labile.[4] Recently, our research group has been focusing on the chemistry of four-membered heterocycles,[5] and β-lactams[6] as well as β-sultams[7] have been widely investigated. Compared with the synthesis of β-phosphalactams and β-thiophosphalactams,[3] β-phosphalactones and β-dithiophosphalactones have been paid less attention. Moreover, preparation of their analogs – 1,2-oxaphosphetane 2-sulfides and 1,2-thiaphosphetane 2-oxides have not been documented to date. This microreview introduces to the synthesis and stability of thermally labile derivatives of 1,2-oxaphosphetane 2-oxide and 1,2-thiaphosphetane 2-sulfide.

Cycloaddition

The first documented synthesis of 1,2-oxaphosphetane 2-oxides **1** is the cycloaddition of aromatic aldehydes, cinnamaldehydes, and ketones to phosphenes, including diphenyl(phenyl)phosphene (diphenylmethylideneoxophenylphosphorane) and benzoyl(phenyl)(phenyl)phosphene (1-benzoylbenzylideneoxophenylphosphorane), generated *in situ* from (diphenylphosphoryl)diazophenylmethane and (diphenylphosphoryl)diazoacetophenone, respectively, *via* Wolff rearrangement under photoirradiation.[8] The structures of 1,2-oxaphosphetane 2-oxides **1** were first assigned according to mass spectral analysis on the basis of the fragmentation products phenylphosphine dioxide (**2**) and the respective olefins **3**. However, further investigation using 2D NMR (^{13}C–^{1}H and ^{1}H–^{1}H COSY) spectroscopy revealed that the obtained compounds are actually 1,1,4-trisubstituted 3,4-dihydro-3-phenyl-1*H*-benzo[2,3]oxaphosphorin 3-oxides **4**. The corresponding fragmentation products were rationalized as phenylphosphine dioxide (**1**) and 9,9-disubstituted 9,10-dihydroanthracenes **5**, which were generated from 3,4-dihydro-3,4-diphenyl-1*H*-benzo[2,3]oxaphosphorin 3-oxides **4** (R^1 = Ph) through retro-Diels–Alder reaction by loss of phenylphosphine dioxide (**2**), 6π-electrocyclic reaction, and subsequent aromatization.[9]

Jiaxi Xu was born in 1963 in Jilin, China. He received his PhD in 1992 from Department of Chemistry at the Peking University in China. After a post-doctoral stay in the School of Pharmaceutical Sciences at the Beijing Medical University (Health Center of Peking University now), he was appointed as an associate professor at the College of Chemistry and Molecular Engineering at the Peking University. He also worked as a visiting scholar in Department of Chemistry at the Chinese University of Hong Kong (1995–1996), Department of Chemistry at the Colorado State University (2000–2001), and Medical School at the Vanderbilt University (2001–2002). He promoted a full professor in 2004. At the end of 2007, he started working at the Faculty of Science (College of Chemistry now) at the Beijing University of Chemical Technology. His research interests include synthetic methodologies and the related mechanisms, asymmetric synthesis and catalysis, synthesis of heterocyclic compounds, naturally not occurring amino acids and peptides.

Cycloaddition (continued)

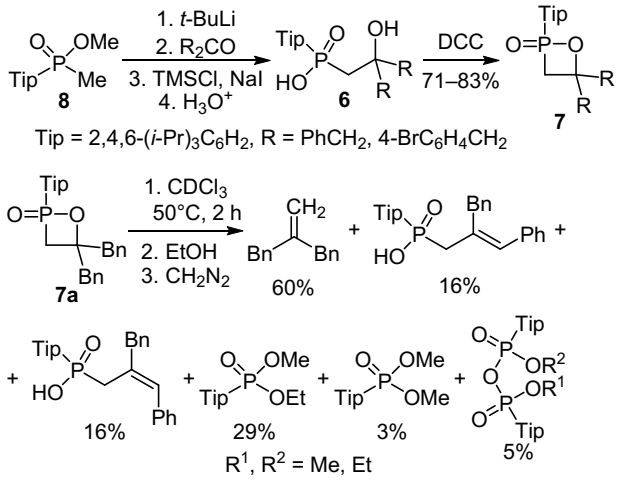


R^1 = Ph, C(O)Ph; R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-Naphth, R^3 = H; R^2 = PhCH=CH, 4-$MeOC_6H_4$CH=CH, R^3 = H; R^2 = PhCH=CH, 4-MeC_6H_4CH=CH, 4-$MeOC_6H_4$CH=CH, R^3 = Ph; R^2 = PhCH=CHCH=CH, R^3 = 4-MeC_6H_4

Recently, this cycloaddition was carefully reinvestigated. The results indicated that the reaction generates 3,4-dihydro-3-phenyl-1*H*-benzo[2,3]oxaphosphorin 3-oxide **4**, olefin **3**, and phenylphosphine dioxide (**2**). Actually, the cycloaddition first provides both 3,4-dihydro-3-phenyl-1*H*-benzo[2,3]oxaphosphorin 3-oxide **4** and 1,2-oxaphosphetane 2-oxide **1**. However, the obtained 1,2-oxaphosphetane 2-oxides **1** are thermally labile and undergo thermal fragmentation leading to the formation of the respective olefin **3** and phenylphosphine dioxide (**2**) because structure of 1,2-oxaphosphetane 2-oxides **1** is similar to the structure of the intermediates produced in Wittig–Horner (Horner–Wadsworth–Emmons) reaction.[10] Thus, the first documented photo-assisted cycloaddition of aldehydes and ketones to diphenyl(phenyl)phosphenes is not an efficient method for the synthesis of 1,2-oxaphosphetane 2-oxides **1** due to the competitive (2+2) and (2+4) cycloaddition reactions.

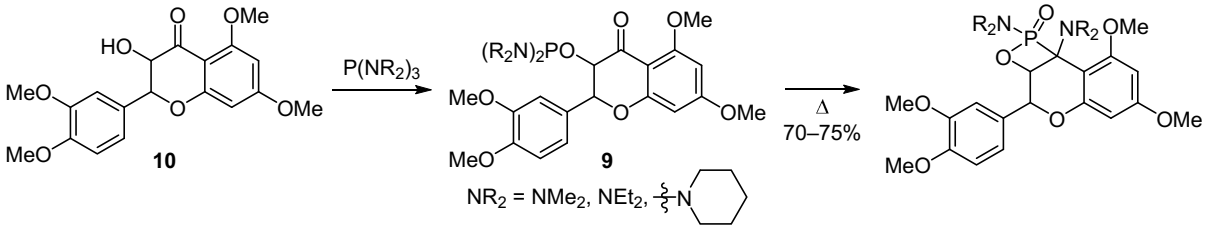
Cyclization

Esterification of β-hydroxyalkylphosphinic acids **6** is an efficient method to prepare 1,2-oxaphosphetane 2-oxides **7**. Methyl methyl(2,4,6-triisopropylphenyl)phosphinate (**8**) was converted into β-hydroxyalkylphosphinic acids **6** in four steps. Intramolecular dehydration of β-hydroxyalkylphosphinic acids **6** using *N*,*N*'-dicyclohexylcarbodiimine (DCC) afforded 2-(2,4,6-triisopropylphenyl)-1,2-oxaphosphetane 2-oxides **7**, which were stable in air at room temperature due to the presence of bulky 2,4,6-triisopropylphenyl group at the phosphorus atom. However, 4,4-dibenzyl-2-(2,4,6-triisopropylphenyl)-1,2-oxaphosphetane 2-oxide (**7a**) fragmented into a series of products after heating and treatment with EtOH and CH_2N_2.[4]



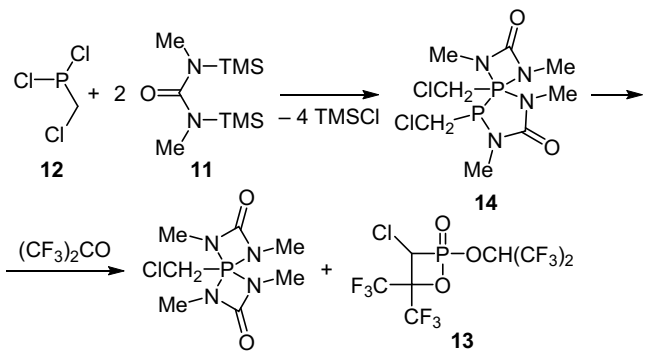
Tip = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R = PhCH$_2$, 4-BrC$_6$H$_4$CH$_2$

As another cyclization strategy, thermal cyclization of 3',4',5,7-tetramethyldihydroquercetin amidophosphites **9**, which were prepared from 3',4',5,7-tetramethyldihydroquercetin (**10**) and phosphorus triamides, was demonstrated. The cyclization is assumed to proceed as a rearrangement process. However, detailed mechanism of this reaction is unclear to date.[11]



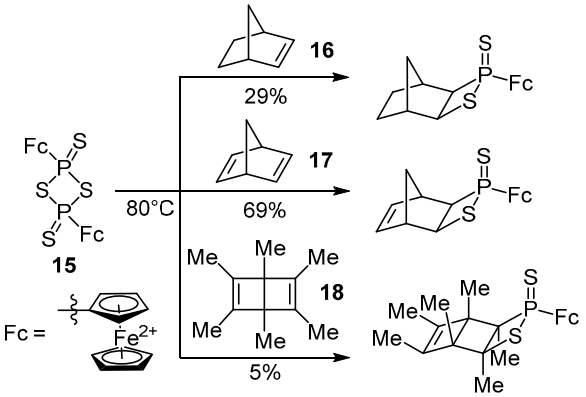
Fragmentation

When Schmutzler and coworkers prepared spirophosphoranes by the reaction of *N*,*N*'-dimethyl-*N*,*N*'-bis(trimethylsilyl)urea (**11**) and dichloro(chloromethyl)phosphine (**12**) followed by treatment with $(CF_3)_2CO$, 3-chloro-2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-4,4-bis(trifluoromethyl)-1,2-oxaphosphetane 2-oxide (**13**) was obtained as a yellow byproduct. 1,2-Oxaphosphetane 2-oxide **13** was assumed to be produced *via* the reaction of $(CF_3)_2CO$ and spirophosphorane **14** generated in the first step of the reaction. Unfortunately, detailed description on this transformation was not provided.[12]

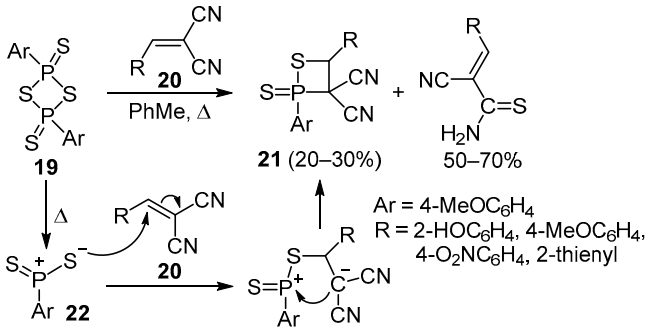


Annulation

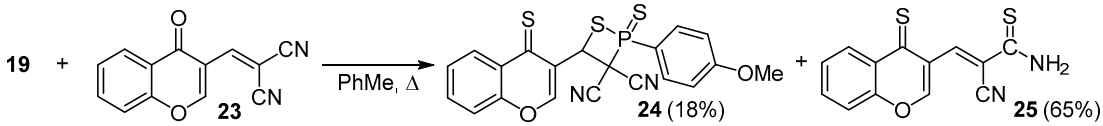
(2+2) Annulation of arylphosphine disulfides and olefins is a general method for the synthesis of 1,2-thiaphosphetane 2-sulfides. Under heating, 2,4-bisferrocenyl-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**15**) can work as a source of ferrocenylphosphine disulfide, which reacts with tenfold excess of electron-rich olefins – norbornene (**16**), norbornadiene (**17**), or hexamethyldewarbenzene (**18**) at 80°C to afford the corresponding fused 1,2-thiaphosphetane 2-sulfides. Only norbornadiene (**17**) produces the desired adduct in a satisfactory yield (69%).[13]



The reaction of Lawesson's reagent (**19**) and electron-deficient olefins – arylmethylidenemalononitriles **20** provides the corresponding 1,2-thiaphosphetane 2-sulfides **21** in 20–30% yields. The Lawesson's reagent (**19**) first dissociates into its monomeric form **22**, which undergoes nucleophilic addition to arylmethylidenemalononitriles **20** followed by a nucleophilic cyclization to afford 1,2-thiaphosphetane 2-sulfides **21** in low yields.[14]



Similarly, the reaction of Lawesson's reagent (**19**) and (4-oxo-4*H*-chromen-3-yl)methylidenemalononitrile (**23**) generates the corresponding 1,2-thiaphosphetane 2-sulfide – 2-(4-methoxyphenyl)-4-(4-thioxo-4*H*-chromen-3-yl)-1,2-thiaphosphetane-3,3-dicarbonitrile 2-sulfide (**24**) in 18% yield and (*E*)-2-cyano-3-(4-thioxo-4*H*-chromen-3-yl)prop-2-enethioamide (**25**) as the major product in 65% yield.[15]



Conclusion

In summary, 1,2-oxaphosphetane 2-oxides and 1,2-thiaphosphetane 2-sulfides are important phosphorus-containing four-membered heterocycles. However, synthetic methods for the preparation of these compounds are limited and some chemical transformations of the reported methods are not clear to date. Development of new synthetic approaches toward 1,2-oxaphosphetane 2-oxides and 1,2-thiaphosphetane 2-sulfides is in high demand.

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