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Synthesis and Reactions of Some New Annulated Azaphospholes

Dr. Chandra Bhushan Jain

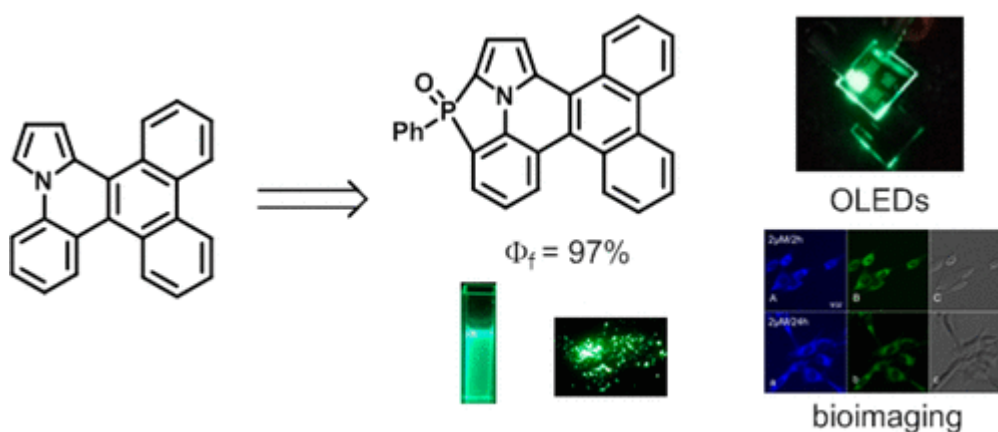
Professor, Dept. Of Chemistry, Government College, Tonk, Rajasthan, India

ABSTRACT: Azaphospholes are 6 π aromatic heterocycles incorporating at least one σ^2 , λ^3 -phosphorus atom and one σ^3 , λ^3 - nitrogen atom. This review covers the synthesis, structural characterization, reactions and theoretical calculations of azaphospholes annellated to a six - or five-membered heterocyclic ring, reported during the last 10-12 years. Three synthetic methods, namely [4+1] cyclocondensation, [3+2] cyclocondensation and 1,5-electrocyclization make a variety of these phosphorus heterocycles available. The aromatic character of these compounds has been confirmed by carrying out density functional theory (DFT) calculations. Mainly ^1H , ^{13}C and ^{31}P NMR studies have been employed for the structural characterization. Almost all the functionalities present in the azaphosphole ring have been investigated and electrophilic substitution reactions of the 1-unsubstituted compounds and Diels-Alder reactions as well as 1,2-addition reactions to the $>\text{C}=\text{P}$ - moiety have been accomplished successfully. The stereo- and regioselectivities observed in the Diels-Alder reactions have been explained on the basis of DFT calculations. Chelotropic cycloadducts formed from [4+1] cycloaddition of *o*-quinones on the σ^2 , λ^3 -P atom have been obtained. A variety of coordination compounds formed by σ -coordination of the σ^2 , λ^3 -P atom have been prepared.

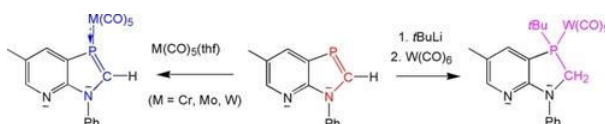
KEYWORDS- Azaphospholes, Heterocycles, Synthesis, Reactions, Annulated

I. INTRODUCTION

A facile synthesis of 1,3-azaphospholes with a pyrrolo[1,2-*a*]quinoline skeleton has been described. These new annulated 1,3-azaphospholes exhibit good photoelectric performance and can be used as the emitting dopant in organic light-emitting diodes (OLEDs) and dye for bioimaging.

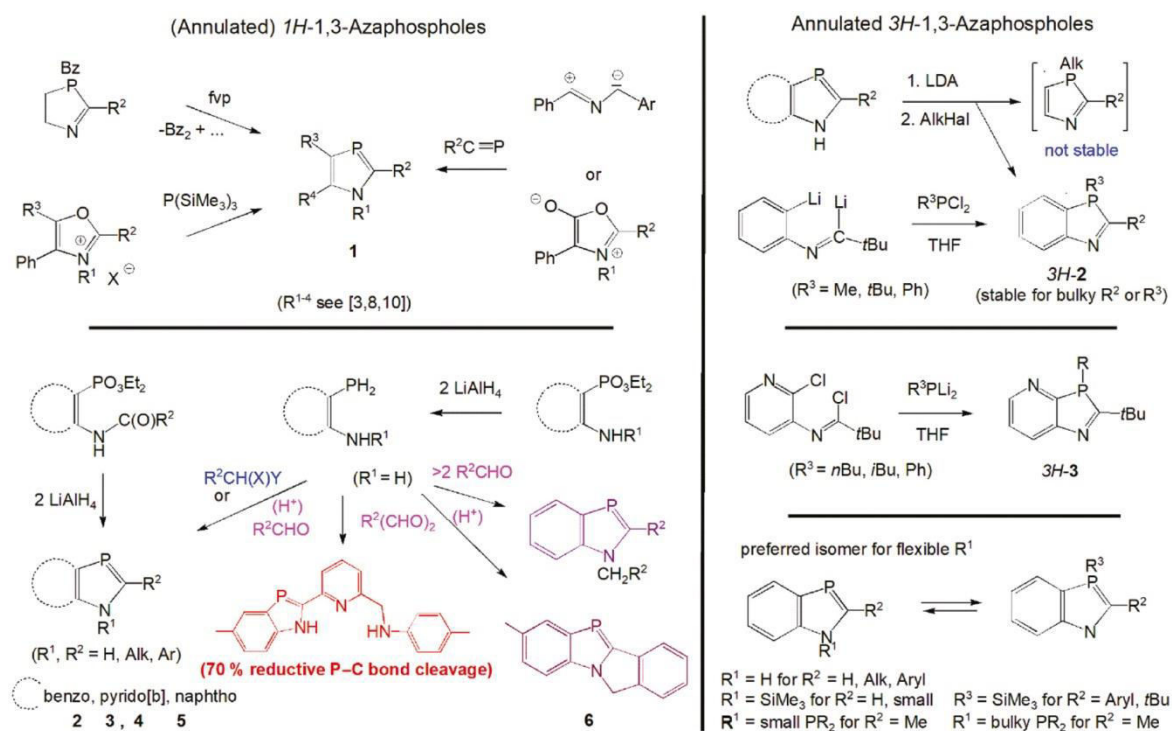


Pyrido-annulated 1,3-azaphospholes were synthesized by reduction of 2-aminopyridine-3-phosphonates and cyclocondensation with dimethylformamide or dimethylacetamide dimethyl acetal. [1,2,3] The $\text{P}=\text{C}$ bond is resistant to diluted aqueous acids and bases but adds $t\text{BuLi}$. $\text{M}(\text{CO})_5(\text{thf})$ form preferably η^1 -P-coordinated (azaphospholo[5,4-*b*]pyridine) $\text{M}(\text{CO})_5$ complexes ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) and exhibits π -acceptor properties.



Pyrido-annulated σ^2 -phosphorus heterocycles, 1,3-azaphospholo[5,4-b]pyridines 4 and 5, were synthesized by reduction of diethyl 2-aminopyridine-3-phosphonates 1 with LiAlH_4 and cyclocondensation of the resulting 2-amino-3-phosphanylpyridines 2 with dimethylformamide and dimethylacetamide dimethyl acetal, respectively, via intermediate phosphalkenes 3. [4,5,6] The P=C–N heterocycles are stable in the presence of OH and NH compounds but add $t\text{BuLi}$ at the P=C bond. Reaction with one equivalent of $\text{M}(\text{CO})_5(\text{thf})$ leads to η^1 -P-coordinated (azaphospholo[5,4-b]pyridine) $\text{M}(\text{CO})_5$ complexes (M = Cr, Mo, W). Spectroscopic data are in accordance with the dominance of π -acceptor properties. X-ray crystal structure analyses reveal “base-pairing” of 2-amino-3-phosphanylpyridine (2a) and NH-functional azaphospholopyridine 5a by N–H \cdots N hydrogen bonds, and the competing formation of 1,3-diphosphetane 6c from the phosphalkene intermediate. [7,8,9]

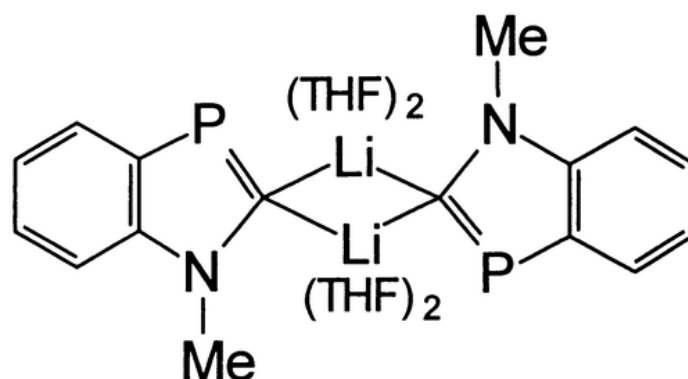
Syntheses, properties, structure aspects and reactivity of non- and aromatically carbo- and heterocyclic annulated 1H- and 3H-1,3-azaphospholes are compared to illuminate the impact of annulation, substituent effects, aromatic stabilization and π -excess at phosphorus of the 1H-isomers, to demonstrate the current knowledge and open questions in this field of research. The principal synthetic strategies for 1,3-azaphospholes differ for non-annulated 1H-isomers 1 (3H-isomers still unknown), C–C bridgehead annulated 1H- and 3H-1,3-azaphospholes 2–5 and 3H-2, 3H-3 (Scheme 1a–c) and for a larger variety of N-heterocyclic C–N bridgehead annulated 1,3-azaphospholes [4], [11]. The latter have been reviewed recently in much detail by Bansal et al. [20], [21], [22], [23] and are not included in this contribution. Non- or 2-monosubstituted compounds of type 1 were prepared by flash-vacuum pyrolysis of C=N unsaturated 1,3-azaphospholines, multiple substituted derivatives by O \rightarrow P replacement of oxazolium salts with $\text{P}(\text{SiMe}_3)_3$ or cycloadditions of phosphalkynes with suitable azadiene precursors [3], [8], [10]. Benzo- and pyrido[b]-annulated 3H-1,3-azaphospholes 3H-2 and 3H-3 were synthesized by organometallic routes whereas the 1H-isomers 2–4 [10], [18] as well as naphtho- and tetracyclic systems 5–7 [24], [25], [26], including the skeleton of 2, were synthesized by cyclocondensation of o-aminoarylphosphanes with suitable carboxylic acid derivatives or aldehydes. NH-Derivatives of 2 are also directly accessible by reductive cyclization of N-secondary o-phosphonoanilides of alkyl- or arylcarboxylic acids. [10,11,12] This circumvents the preparation of highly air-sensitive primary o-anilinophosphanes by reduction of the respective o-anilinophosphonates or -phosphonites but is applicable only for N-secondary amides that were reduced slower by LiAlH_4 than the PO_3Et_2 group [18] The above mentioned cyclocondensation with RCHO leads primarily to 2,3-dihydro compounds, which on heating in the presence of p-toluene sulfonic acid undergo aromaticity-driven redox processes leading in part to reductive P–C bond cleavage, RCH_2OH and, for primary o-anilinophosphanes with excess RCHO, to N- CH_2R -substituted 1H-1,3-benzazaphospholes. For o-diformylarenes this opens a high-yield route to 6 and related systems with extended planar π -system, confirmed by crystal structure analysis and spectroscopic data [13,14,15]



1,2-Azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines are prominent phosphorus heterocycles and are of interest due to their potent pharmacological activities. In this review, we provide the available literature data on the synthesis of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines.[16]

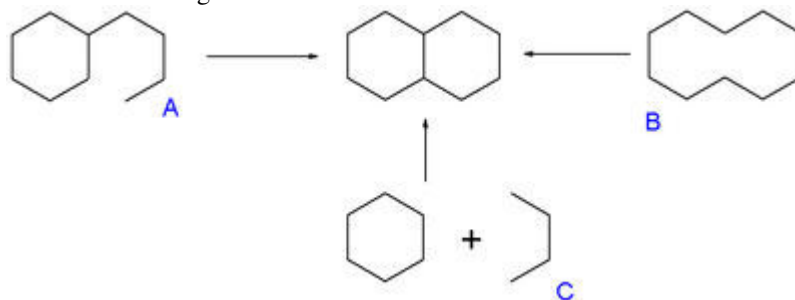
II.DISCUSSION

Organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical, 1–9 agricultural, 10 and chemical agents. 11–15 Recently, phosphorus heterocycles 16,17 have received considerable interest because of their unique biological activities as antimicrobial 18 and their anticancer effects. 19–22 Ifosfamide and cyclophosphamide are two important examples of phosphorus heterocycles that were launched on the market more than 30 years ago and are still used in treatment of cancer. 23,24 Much attention has been directed to the synthesis of phosphorus heterocycles due to their wide-ranging utilities as synthetic intermediates in organic syntheses. 25–31 Among these phosphorus heterocycles, 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines are of interest in several laboratories due to their potent pharmacological activities such as antitumor, 32 complexing agents, 33,34 and inhibitor of mammalian dihydroorotase. 35 The present review is focused on the most methodologies for the construction of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines up to the end of 2019 and to supplement the information available in literature. In addition, there is discussion of mechanisms. The preparation, NMR data, a crystal structure, and the reactivity of isolable 2-lithio-1,3-benzazaphospholes are described. The compounds are or belong to the most stable PCLi species, although they lack steric congestion. Reactions with organoelement or organometal halides W(CO)₆ as well as with CO₂ or benzophenone allow access to various novel functionally substituted 1,3-benzazaphospholes (2-R = SnMe₃, Fe(CO)₂Cp, C[W(CO)₅]OLi(THF)₃, CPh₂OH, PPh₂, P(O)Ph₂). The crystal structure of the tungsten-carbene derivative is described. Attempts to lithiate and functionalize a 1,3-benzazaphosphole P–W(CO)₅ complex failed, but reactions of 1-methyl-2-stannyl- and 1-methyl-2-phosphino-1,3-benzazaphosphole with W(CO)₅(THF) furnished examples for a 2-metalated benzazaphosphole P–W(CO)₅ complex and the preferred complexation of the phosphino substituent, respectively. The considerable upfield shifts of the ³¹P NMR signals after complexation of the low-coordinated phosphorus atom by W(CO)₅ attest that the ligands are stronger acceptors than donors.[17]

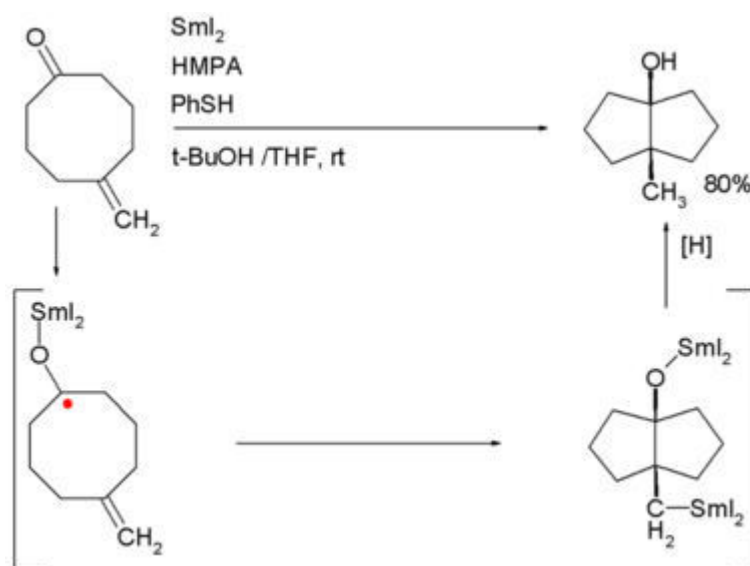


III.RESULTS

In organic chemistry, annulation (from Latin anellus 'little ring'; occasionally annelation) is a chemical reaction in which a new ring is constructed on a molecule.^[1]



Examples are the Robinson annulation, Danheiser annulation and certain cycloadditions. Annular molecules are constructed from side-on condensed cyclic segments, for example helicenes and acenes. In transannulation a bicyclic molecule is created by intramolecular carbon-carbon bond formation in a large monocyclic ring. An example is the samarium(II) iodide induced ketone - alkene cyclization of 5-methylenecyclooctanone which proceeds through a ketyl intermediate[18,19]



IV. CONCLUSION

Syntheses, properties, structure aspects and reactivity of non- and aromatically carbo- and heterocyclic annulated 1H- and 3H-1,3-azaphospholes are compared to illuminate the impact of annulation, substituent effects, aromatic stabilization and π -excess at phosphorus of the 1H-isomers, to demonstrate the current knowledge and open questions in this field of research.[20]

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