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HETEROCYCLES
IN FOCUS

Phosphinine – synthesis of a heavy sibling of pyridine (microreview)

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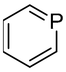


The microreview covers three, most powerful, strategies of the synthesis of phosphinine (systematically called phosphabenzene) starting from pyrylium salts, five-membered heterocycles, and reagents with C≡P bond.

Introduction and brief comparison to pyridine

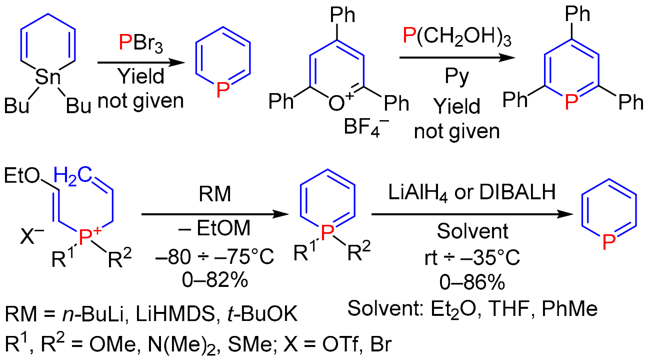
While pyridine constitutes a well-known heterocyclic compound for every chemistry student, its heavier analog, phosphinine (phosphabenzene, phosphorine), is often omitted during lectures and might remain a somehow mysterious molecule. Facing this myth we decided to provide a microreview to shed light on the methods of synthesis of this interesting compound.

For the first time, the unsubstituted phosphinine (along with arsenine) was synthesized by Ashe[1] in 1971 by treating 1,1-dibutyl-1,4-dihydrostannabenzene with phosphorus tribromide. However, five years earlier, the 2,4,6-triphenylphosphinine was obtained by Märkl.[2] The procedure involved treatment of pyrylium salt with tris(hydroxymethyl)phosphine.

Recently, a novel protocol of synthesis of the parent heterocycle *via* intermolecular cyclization of phosphonium salts followed by reduction of the pentacoordinated phosphinine has been published.[3]

Just like pyridine, phosphinine, having 6 π-electrons in a molecule, is an aromatic compound. Depending on the aromaticity index applied it can be shown that the aromaticity of the phosphabenzene is 80–97% of that of benzene.[4]

In terms of reactivity phosphinine differs significantly from both benzene and pyridine. Phosphinine is much weaker base than pyridine (pK_a of conjugated base equals to –16.1). This is easily explained by the fact that the phosphorus atom in phosphinine has about 64% of 3s-orbital character – much higher than 29% for nitrogen in pyridine.[5]



There are only few works devoted to direct transformations of the parent heterocycle. A good example is a coupling of 2-bromophosphinines with organotin or organozinc compounds.[6] The reaction is analogous to the reactions of 2-bromopyridines.[7] The electrophilic substitutions on carbon atoms remain difficult since in typical cases the electrophilic attack occurs at the phosphorus atom.[8] Also nucleophilic attack is more preferred at the phosphorus atom, especially in the case of metal complexes.

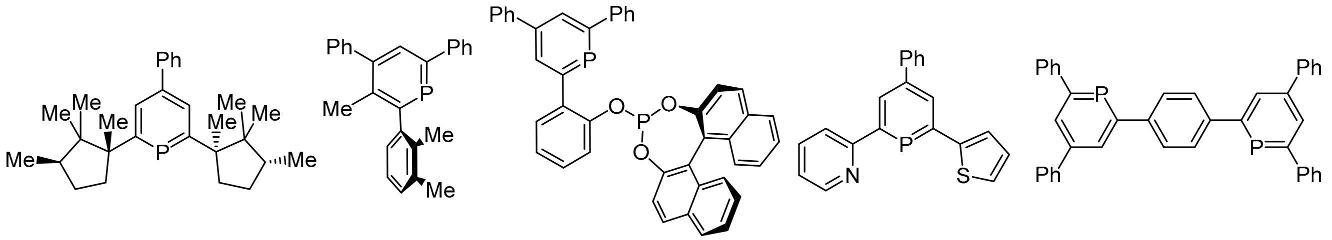
Due to the difficulty in functionalization of the phosphabenzene ring the typical approach to obtain particular derivatives is a synthesis of a ring with the required substituent already present. Recently, the comparison of the reactivity of pyridine and phosphinine has been provided in several reviews.[9]

Paweł Tokarz was born in 1986 in Zduńska Wola, Poland. In 2015, he received his PhD in chemistry at the University of Łódź under the supervision of Prof. Jarosław Lewkowski. At present he is a director of a National Science Centre grant focused on a chemistry of organophosphorus and organofluorine compounds.

Piotr M. Zagórski was born in 1982 in Zgierz, Poland. In 2015, he received his PhD in chemistry at the University of Łódź under the supervision of Prof. Andrzej Jóźwiak. Presently, he works at his Alma Mater. His research is focused on the chemistry of heterocyclic compounds.

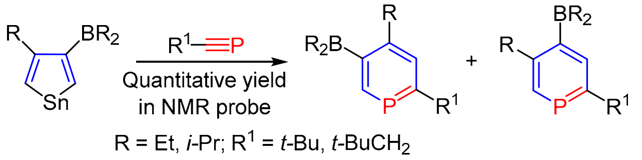
Starting from pyrylium salts

Since the initial discovery and further improvement[10] the Märkl phosphinine synthesis (see previous section) has been extensively used. As notable examples, chiral derivatives containing asymmetric carbon atom[11] or possessing atropoisomeric chirality[12] should be mentioned. Similarly, chiral bidentate[13] and polydentate[14] ligands, as well as bisphosphinines with tethered aromatic system[15] have recently been prepared.

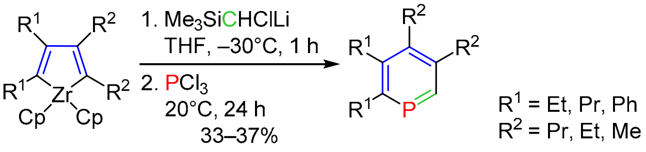


Starting from five-membered heterocycles

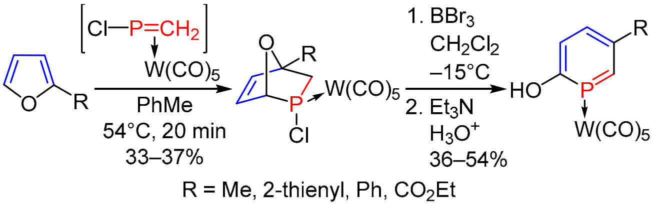
A commonly used strategy to build the phosphabenzene moiety is to expand a heterocyclic five-membered ring. The historically first examples[16] were (4+2) cycloadditions of stannoles and phosphaalkynes yielding mixtures of isomeric phosphinines.



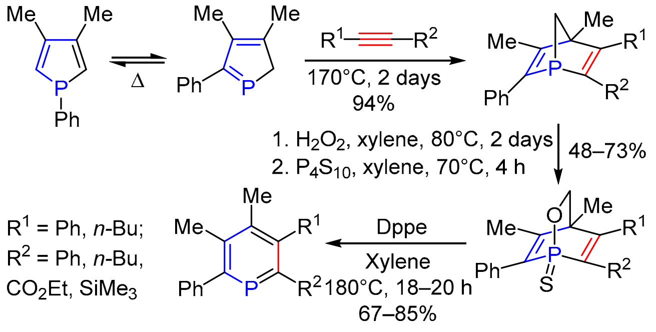
Other class of metalloles that have been exploited belong to a zirconocene family. Ring expansion, caused by insertion of a carbon atom into a Zr–C bond, followed by a substitution of zirconium by phosphorus, and subsequent elimination of silyl chloride provided an access to the 1,2,3,4-substituted phosphinines.[17]



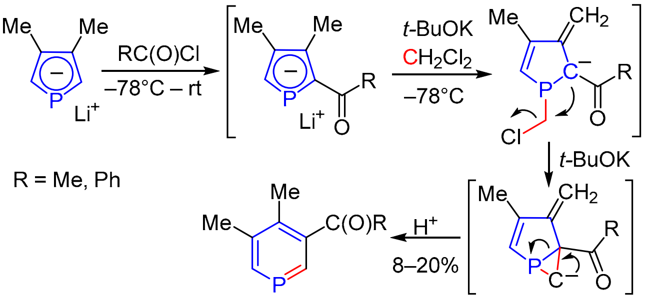
While stannoles and zirconocenes might be useful, they appear to be relatively exotic starting materials. In opposite, it has been shown that phosphinines could be successfully synthesized by (4+3) cycloaddition of furans and methylenechlorophosphane tungsten complex. The synthetic path goes *via* bicyclic intermediate, which upon bromination and acidic workup yields 2-hydroxyphosphinines as tungsten complexes.[18]



Instead of the incorporation of phosphorus atom into a five-membered heterocycle one can start with phosphole and then expand the system *via* (4+2) cycloaddition into a bicyclic moiety containing six-membered ring. After oxidation with H_2O_2 and subsequent P-thiation with P_4S_{10} another bicyclic compound is obtained which undergoes extrusion and aromatization, leading to pentasubstituted phosphinine either as a free molecule or a tungsten complex.[19]

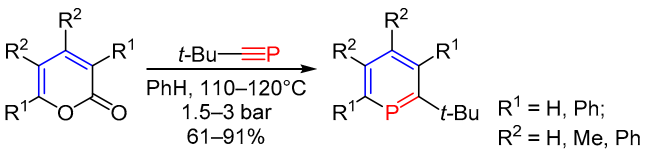


Transformation of five-membered phosphorus heterocycles to phosphinines does not necessarily require a cycloaddition in order to expand the ring. For example, ketone or aldehyde treated with strong base and dichloromethane forms a bicyclic intermediate. Further deprotonation and intramolecular nucleophilic attack after an acidic workup yields the phosphinine.[20]

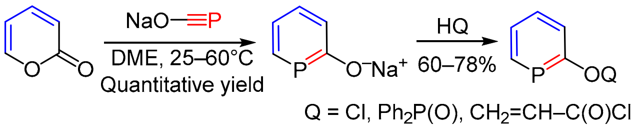


Starting from reagents with C≡P bond

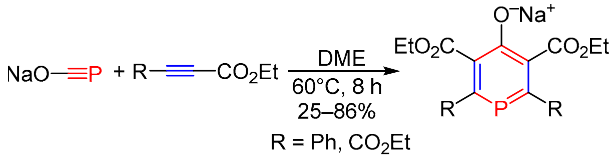
Beside the aforementioned reactions with stannoles, phosphaalkynes can lead to substituted phosphinines when reacted with much more accessible 2-pyrones. The reaction goes *via* (4+2) cycloaddition leading to the bicyclic lactone, which after elimination of carbon(IV) oxide yields 2,6-disubstituted phosphinines.[21]



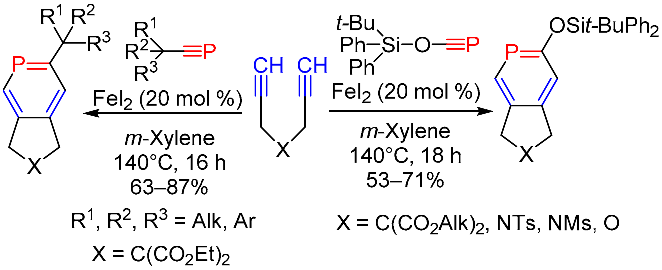
Similarly, unsubstituted 2-pyrone treated with sodium phosphaethynolate forms a sodium salt of 2-phosphaphenol, which is surprisingly stable, even in water solution. The salt can be further O-functionalized like regular phenol.[22]



Sodium phosphaethynolate can also lead to 4-phosphaphenolanes when reacted with two molecules of ethynylcarboxylate. The reaction goes *via* two subsequent (2+2) cycloadditions with formation of four-membered antiaromatic intermediate.



Recently, in two subsequent works[23] the Nishibayashi group presented the usage of diynes as substrates for the synthesis of bicyclic phosphinine systems in a (2+2+2) cycloaddition. As a source of the phosphorus the appropriate phosphaalkynes or silylated phosphaethynolate were used.



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References

1. Ashe, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3293.
2. Märkl, G. *Angew. Chem.* **1966**, *78*, 907.
3. Savateev, A.; Vlasenko, Y.; Shtil, N.; Kostyuk, A. *Eur. J. Inorg. Chem.* **2016**, 628.
4. Nyulaszi, L. *Chem. Rev.* **2001**, *101*, 1229.
5. Weemers, J. J. M. *Phosphinine-Based Ligands: Unique Phosphorus Heterocycles in Homogeneous Catalytic Reactions*; Eindhoven: Technische Universiteit Eindhoven, 2014, DOI: 10.6100/IR762991.
6. Kostenko, N.; Ericsson, C.; Engqvist, E.; Gonzalez, S. V.; Bayer, A. *Eur. J. Org. Chem.* **2013**, 4756.
7. Mastalir, M.; Kirchner, K. *Monatsh. Chem.* **2017**, *148*, 105.
8. Muller, C.; Broeckx, L. E. E.; de Krom, I.; Weemers, J. J. M. *Eur. J. Inorg. Chem.* **2013**, 187.
9. (a) Müller, C.; Broeckx, L. E. E.; de Krom, I.; Weemers, J. J. M. *Eur. J. Inorg. Chem.* **2013**, 187. (b) Corbridge, D. E. C. *Phosphorus: Chemistry, Biochemistry, and Technology*; Taylor & Francis, 2013, 6th ed.
10. Märkl, G. *Angew. Chem., Int. Ed.* **1967**, *6*, 944.
11. Van der Velde, N. A.; Korbitz, H. T.; Garner, C. M. *Tetrahedron Lett.* **2012**, *53*, 5742.
12. Muller, C.; Pidko, E. A.; Staring, A. J. P. M.; Lutz, M.; Spek, A. L.; Van Santen, R. A.; Vogt, D. *Chem.–Eur. J.* **2008**, *14*, 4899.
13. Muller, C.; Lopez, L. G.; Kooijman, H.; Spek, A. L.; Vogt, D. *Tetrahedron Lett.* **2006**, *47*, 2017.
14. Muller, C.; Wasserberg, D.; Weemers, J. J. M.; Pidko, E. A.; Hoffmann, S.; Lutz, M.; Spek, A. L.; Meskers, S. C. J.; Janssen, R. A. J.; Van Santen, R. A.; Vogt, D. *Chem.–Eur. J.* **2007**, *13*, 4548.
15. Nagahora, N.; Ogawa, T.; Honda, M.; Fujii, M.; Tokumaru, H.; Sasamori, T.; Shioji K.; Okuma, K. *Chem. Lett.* **2015**, *44*, 706.
16. Wrackmeyer, B.; Klaus, U. *J. Organomet. Chem.* **1996**, *520*, 211.
17. Hunter, R. A.; Whitby, R. J.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2004**, *45*, 7633.
18. Mao, Y.; Mathey F. *Chem.–Eur. J.* **2011**, *17*, 10745.
19. Wang, H.; Li, C.; Geng, D.; Chen, H.; Duan, Z.; Mathey, F. *Chem.–Eur. J.* **2010**, *16*, 10659.
20. Grundy, J.; Mathey, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1082.
21. (a) Rösch, W.; Regitz, M. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1986**, *41*, 931. (b) Habicht, M. H.; Wossidlo, F.; Weber, M.; Muller, C. *Chem.–Eur. J.* **2016**, *22*, 12877.
22. Chen, X.; Alidori, S.; Puschmann, F. F.; Santiso-Quinones, G.; Benko, Z.; Li, Z.; Becker, G.; Grutzmacher, H.-F.; Grutzmacher, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 1641.
23. (a) Nakajima, K.; Takata, S.; Sakata, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 7597. (b) Nakajima, K.; Liang, W.; Nishibayashi, Y. *Org. Lett.* **2016**, *18*, 5006.