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Facile Synthesis and Properties of 2- λ^5 -Phosphaquinolines and 2- λ^5 -Phosphaquinolin-2-ones**

Chris L. Vonnegut[†],

Department of Chemistry & Biochemistry and Materials Science Institute, University of Oregon,
Eugene, OR 97403-1253 (USA)

Airlia M. Shonkwiler[†],

Department of Chemistry & Biochemistry and Materials Science Institute, University of Oregon,
Eugene, OR 97403-1253 (USA)

Muhammad M. Khalifa,

Department of Chemistry & Biochemistry and Materials Science Institute, University of Oregon,
Eugene, OR 97403-1253 (USA)

Dr. Lev N. Zakharov,

CAMCOR—Center for Advanced Materials Characterization in Oregon, University of Oregon,
Eugene, OR 97403-1443 (USA)

Prof. Darren W. Johnson^{*}, and

Department of Chemistry & Biochemistry and Materials Science Institute, University of Oregon,
Eugene, OR 97403-1253 (USA)

Prof. Michael M. Haley^{*}

Department of Chemistry & Biochemistry and Materials Science Institute, University of Oregon,
Eugene, OR 97403-1253 (USA)

Abstract

Treatment of 2-ethynylanilines with P(OPh)_3 gives either 2,2-diphenoxy-2- λ^5 -phosphaquinolines or 2-phenoxy-2- λ^5 -phosphaquinolin-2-ones under transition metal-free conditions. This reaction offers unparalleled access to an underexplored heterocycle, which opens study of the fundamental nature of the $\text{N}=\text{P}^{\text{V}}$ double bond and its potential for delocalization within a cyclic π -electron system. This heterocycle can inherently serve as a carbostyryl mimic, with application as a bioisostere for pharmaceuticals based on the 2-quinolone scaffold. Additionally, the molecule holds promise as a new fluorophore, as initial screening reveals quantum yields upwards of ~40%, Stokes shifts of 50–150 nm, and emission wavelengths of 380–540 nm. The phosphaquinolin-2-ones possess one of the strongest solution-state dimerization constants for a D-A system (130 M^{-1}) due to the close proximity of a strong acceptor, $\text{P}=\text{O}$, and a strong donor, the

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^{*}dwj@uoregon.edu; haley@uoregon.edu.

[†]These authors contributed equally.

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phosphoramidate N–H, suggesting this class of compounds might hold promise as new hydrogen bonding hosts for optoelectronic sensing of anions and/or small molecules.

Keywords

Phosphorus heterocycles; fluorescent probes; dimerization; phosphazenes; alkynes

The azaphosphinine scaffold has been explored as an analogue of hydrocarbon-based molecules for nearly half a century. The simplest six-membered ring systems, analogous to benzene, are comprised of three structural isomers—1,4- λ^3 -azaphosphinine (**1**) was first made in 1972,^[1] followed by the 1,3- (**2**) and 1,2- λ^3 -azaphosphinine (**3**) congeners in 1987.^[2] Until recently, nearly all azaphosphinines have featured phosphorus atoms formally in the +3 oxidation state,^[3] except for one notable example, compound **4**, with phosphorus in the +5 oxidation state, prepared in 1991.^[4] The pioneering studies of Dewar and Campbell on 1,2-azaphosphinines in the early 1960s, however, met with varying degrees of success.^[5] While Dewar was able to prepare the HI salt of **5**, attempts by both groups to isolate the corresponding λ^3 -derivatives yielded unstable systems that required isolation as λ^5 -phosphoramidates such as **6**. While there have since been a handful of other investigations of 1,2-azaphosphinine structure and reactivity, the difficulty of their synthesis has precluded rigorous investigations.^[6] On the other hand, examination of the fully inorganic variants has proceeded extensively, with cyclotriphosphazenes such as **7** being one of the most studied inorganic heterocycles.^[7] For example, the first cyclotriphosphazene was described in 1834 by Liebig, though the exact structure remained contested until the 1860s.^[8]

The choice of substituents on the phosphorous atom can significantly affect the stability and reactivity of the 1,2- λ^5 -azaphosphinine scaffold. P-C_{alkyl} and P-C_{aryl} derivatives such as **4** and **5** are very sensitive to oxygen and water and decompose readily upon atmospheric exposure.^[4–6] On the other hand, 1,2- λ^5 -azaphosphinines with alkoxy and phenoxy groups tend to hydrolyze from their phosphonimide form (e.g., **4**, **5**) to the considerably more stable phosphoramidate form (e.g., **6**, **8**).

Phosphonates and analogues have seen extensive use as ester- and amide-hydrolysis transition-state mimics. For instance, compound **8** has been explored recently as a bioisostere of isocarboxtyril^[9] and shows promise in pharmacological applications.^[10] In addition to the ability of phosphonates/phosphoramidates to act as ester and amide bioisosteres, these compounds have relevance for a number of other health-related uses.^[11] As a result, new, efficient, metal-free reactions to make phosphonate derivatives of common heterocyclic scaffolds, such as the quinolinone substructure, are highly desirable.^[12] Herein we describe a simple synthesis to assemble the 2- λ^5 -phosphaquinoline framework in a single step from easily attainable starting materials.

Reaction of P(OPh)₃ with 2-ethynylanilines **9a–j**, accessible via Sonogashira cross-coupling of known alkynes with 2-iodoaniline, furnished phosphaquinolines **10** (i.e., imide form, Scheme 1) along with varying amounts of phosphaquinolinones **11** (i.e., amide form), the latter of which arise from the partial hydrolysis of **10** by adventitious water during work-up and purification. The yields in Table 1 thus reflect our best efforts to rigorously exclude (i.e.,

10) or include (i.e., **11**) water as part of the overall sequence; nonetheless, **10a,d,i** were too labile to isolate purely as the phosphaquinoxaline. This cyclization is tolerant to a variety of electron-rich and electron-poor arenes, as well as alkyl functionality attached at the ethynyl group (entry i); however, the reaction did not tolerate silyl-protected or terminal alkynes, nor were ketones stable to the cyclization conditions due to competing Kabachnik-Fields condensation,^[13] all of which resulted in intractable polymers. Interestingly, ethyl ester derivative **10c** does not undergo a “traceless” Staudinger ligation.^[14] This and the general stability of the phosphonimide toward hydrolysis at room temperature once purified lend credence to increased stability from electron delocalization within the heterocycle.

Single crystal x-ray diffraction provided the solid-state structures of **10j** (Figure 2) and **11j** (Figure 3a), which allowed us to directly compare the imide and amidate forms, respectively (Table S1).^[15] The P–N bond length in **10j** (1.565 Å) is much shorter than the amidate P–N bond in **11j** (1.635 Å) yet is similar to the analogous bond in hexaphenoxycyclo-triphosphazene (1.575 Å).^[16] The imide structure indicates some π -electron delocalization within the heterocycle, with the C(1)–C(2) double bond length (1.367 Å) intermediate between benzene and an isolated double bond, whereas the same bond in **11j** (1.341 Å) is nearly identical to the corresponding bond length in carbostyryl (1.343 Å).^[17] The azaphosphinine ring in **10j** shows only small deviations from planarity (RMSD 0.014 Å). Analysis of crystal structure and computational models (see Supporting Information) indicate that the enhanced stability of **10j** to hydrolysis is likely due to coplanarity of pyridine and the azaphosphinine ring, held by a weak hydrogen bond between the hydrogen atom on C(2) and the pyridine nitrogen atom. This conformation limits water addition at phosphorus, as attack would likely occur 180° from the P=N bond. Phosphates hydrolyze via an associative mechanism, making a dissociative pathway unlikely.^[18] Moreover, the S_N2-type displacement that is commonly found for alkyl phosphonates is impossible to occur with the phenyl substituents within **10**.

Interestingly, the amidate-type structures tend to crystallize as dimers between the two enantiomers, forming a complementary association between the N–H and P=O groups (Figure 3a), with correspondingly short intermolecular distances (N...O 2.837–2.840 Å in **11j**) and nearly linear N–H...O angles (164–174°). Dimer formation is mirrored in solution, as compound **11b** possesses a dimerization constant (K_{dim}) of $130 \pm 4 \text{ M}^{-1}$ in CDCl₃. This corresponds to an energy of ca. 1.5 kcal mol^{−1} per H-bond, large compared to cis-amides such as pyrrolidone or caprolactam, which show dimerization constants ranging 1–5 M^{−1} in CHCl₃.^[19] Along with phosphonamides possessing both a stronger hydrogen bond acceptor (P=O vs. C=O) and a stronger hydrogen bond donor (P(O)N–H vs. C(O)N–H) than amides, the non-coplanar arrangement of donor/acceptor and lower directional preference of P=O donors allow the pseudo 6-membered ring to adopt a chair conformation and minimize repulsive secondary interactions (Figure 3b–c).^[20] As a result, this dimer deviates from trends noted by Schneider and Sartorius, where each attractive interaction gives −1.88 kcal mol^{−1} of energy to G, and each repulsive secondary interaction gives +0.74 kcal mol^{−1}.^[21] Following the same schema, two repulsive secondary interactions in our dimer yield only +0.76 kcal mol^{−1} of destabilization, roughly half of what is expected.

The 2-phosphaquinolinone scaffold demonstrates a wide range of fluorescent emission wavelengths (383–554 nm), dependent on substitution and protonation state (Figure 4 and Table 2). The fluorescence behavior is similar to that of carbostyryl, though somewhat red-shifted (3-phenylcarbostyryl ex: 345 nm, em: 410 nm; **11e** ex: 354 nm, em: 427 nm).^[22] Significant differences between the azaphosphinine and carbostyryl include: (1) a more dramatic solvatofluorescent effect in azaphosphinines (**11b** CHCl₃ em: 430 nm, MeCN em: 450 nm, see Supporting Information), and (2) an easily deprotonated amidate N-H yielding a red-shifted fluorescent response, with the anion possessing a surprisingly large Stokes shift of 102–151 nm, dependent upon substitution. Fluorophores possessing such a large Stokes shift are very useful due to their lack of overlap between excitation and emission, lending promise for their use in imaging/sensing applications.^[23] In addition, though the more promising red-shifted derivatives of **11** possess only modest quantum yields (~4–5%) the anions of those fluorophores show quantum yields in the range of 30–40%, demonstrating potential for their use as fluorescent tags, especially if design principles for carbostyryl fluorophore development were to be followed to further red-shift emission and increase the quantum yield.^[24]

In summary, we have disclosed a facile synthesis of 2- λ^5 -phosphaquinoline derivatives from 2-ethynylanilines. The ease of preparation and the range of diverse structures that can be readily accessed will permit detailed examination of this rare class of heterocycles, both from the fundamental perspective of the study of the delocalization of P^V=N bonds to applications of the phosphaquinolinones as carbostyryl mimics and as novel switchable fluorophores with high quantum yields and large Stokes shifts in the ON state. In addition, the surprisingly large dimerization constant of **11b**, a system bound by only two hydrogen bonds, hints at the potential of the phosphaquinolinones as new hydrogen-bonding scaffolds in supramolecular chemistry. Our group is currently working to expand upon these varied and exciting applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. Crystallographic data for **10j**: C₂₅H₁₉N₂O₂P, M = 410.39, 0.17 × 0.16 × 0.12 mm, T = 173(2) K, Monoclinic, space group *P*2₁/*c*, *a* = 11.0967(14) Å, *b* = 9.6020(13) Å, *c* = 19.319(2) Å, β = 90.982(4)°, *V* = 2058.2(5) Å³, *Z* = 4, *D*_c = 1.324 Mg/m³, μ = 0.158 mm⁻¹, *F*(000) = 856, 2θ_{max} = 50.0°, 22128 reflections, 3633 independent reflections [*R*_{int} = 0.0525], *R*1 = 0.0428, *wR*2 = 0.0921 and *GOF* = 1.024 for 3633 reflections (347 parameters) with *I* > 2σ(*I*), *R*1 = 0.0763, *wR*2 = 0.1078 and *GOF* = 1.024 for all reflections, max/min residual electron density +0.290/−0.311 eÅ⁻³. Crystallographic Data for **11j**: C₁₉H₁₅N₂O₂P, M = 334.30, 0.12 × 0.09 × 0.04 mm, T = 223(2) K, Triclinic, space group *P*-1, *a* = 8.4050(3) Å, *b* = 10.5908(4) Å, *c* = 20.2049(7) Å, α = 103.100(2)°, β = 94.314(3)°, γ = 109.365(2)°, *V* = 1630.36(11) Å³, *Z* = 4, *Z'* = 2, *D*_c = 1.362 Mg/m³, μ = 1.607 mm⁻¹, *F*(000) = 696, 2θ_{max} = 134.32°, 18307 reflections, 5681 independent reflections [*R*_{int} = 0.0529], *R*1 = 0.0544, *wR*2 = 0.1447 and *GOF* = 1.050 for 5681 reflections (553 parameters) with *I* > 2σ(*I*), *R*1 = 0.0738, *wR*2 = 0.1576 and *GOF* = 1.050 for all reflections, max/min residual electron density +0.742/−0.441 eÅ⁻³. CCDC-1416795 and 1416794 contain the supplementary crystallographic data for these compounds, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Figure 1.

(a) Early examples of azaphosphinines. (b) Carbostyryl and isocarbostyryl and their structural similarity to bioisosteres like phosphonate **8**.

Figure 2.
X-ray crystal structure of **10j**.

Figure 3.

(a) ORTEP of the dimer of **11j**. (b) An angled view, with C atoms removed for clarity, shows the chair conformation of H-bonding ring. (c) A view from above the ring with relevant bond-angles demonstrates their similarity to idealized chair-conformation angles.

Figure 4.

(a) Visual depiction of the fluorescent emission of 2-phosphaquino-lin-2-ones under neutral and basic conditions. (b) Graphical depiction of the differing emissions of 2-phosphaquinolines and 2-phosphaquinolin-2-ones in CHCl_3 and upon the addition of DBU, demonstrating the emission range from UV to yellow.

Scheme 1.

Synthesis of 2-phosphaquinolines and phosphaquinolinones.

Table 1

Synthetic scope and isolated yields of azaphosphinine cyclization.

Entry	R	Yield (10)	Yield (11)
a	3,5-(CF ₃) ₂ Ph	...[a]	39%
b	4-CNPh	54%	79%
c	4-(CO ₂ Et)Ph	54%	74%
d	4-ClPh	...[a]	80%
e	Ph	45%	72%
f	4-MePh	63%	82%
g	4-MeOPh	56%	66%
h	4-(NMe ₂)Ph	68%	...[a]
i	<i>n</i> -Pen	...[a]	73%
j	2-pyridyl	71%	31%

[a] Not isolable.

Table 2Fluorescence properties of compounds **10**, **11**, and deprotonated **11**.^[a]

Entry	10	11	11 + DBU
a	---	434, 85	523, 128
b	483, 83	430, 81, 4%	554, 137, 41%
c	473, 90	432, 81, 5%	553, 151, 31%
d	---	422, 63	499, 126
e	453, 80	418, 76	491, 127
f	450, 81	413, 72	482, 114
g	447, 78	410, 71	473, 107
h	454, 85	---	---
i	---	383, 65	425, 102
j	467, 79	442, 79	514, 102

^[a] Each entry listed with emission maximum, Stokes shift (nm), and photoluminescent quantum yield (if present), in that order.