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An approach to the synthesis of 1,2λ^5-azaphosphinines

Yurii V. Svyaschenko, Dmitriy M. Volochnyuk, Aleksandr N. Kostyuk *

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya 5, Kiev 94, 02094, Ukraine

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ABSTRACT

A novel approach to 1,2λ^5-azaphosphinines has been elaborated. Aminophosphonium chlorides bearing a β-dialkylaminocrotonic nitrile residue react with *N*,*N*-dimethylformamide dimethylacetal to afford 1,2λ^5-azaphosphinines.

Phosphorus-containing heterocycles are a less numerous and less accessible class of compounds in comparison with nitrogen or sulfur heterocycles.[1] However, interest in this class of compounds, especially those with an endocyclic P–C bond, has increased due to their applications in a wide variety of areas, such as model compounds in fundamental research,[2] as ligands for new catalysts,[3] for modifying the properties of materials,[4] as important building blocks for drug discovery,[5] etc.

In continuation of our studies directed toward the synthesis of phosphaheterocycles[6] we have discovered a very simple method for the synthesis of 1,2λ^5-azaphosphinines starting from linear phosphorylated enamines.

The heterocyclic 1,2λ^5-azaphosphinine system has been mentioned in the literature in only a few papers. Methods for the synthesis of this heterocycle are depicted in Figure 1. 1,2λ^5-Azaphosphinines were synthesized initially by Khusainova et al. in 1982 starting from allene **II** and phosphorylated amidines **III** (Route 1).[7] Later, Nitta and coworkers reported the Diels–Alder reaction of vinylimidophosphates **V** with acetylenes **IV** to afford the desired compounds (Route 2).[8] Foucaud and coworkers obtained 1,2λ^5-azaphosphinines starting from $PhPCl_2$ and aliphatic imines **VI** via 1,2-dihydro-1,2-azaphosphinines **VII** (Route 3).[9]

Recently, we have found a convenient approach to λ^5-phosphinines based on the reaction of a phosphonium salt (derivative of phosphorylated β-pyrrolidinylcrotonitrile), as a 1,5-bisnucleophile, with the 1,1-biselectrophile, *N*,*N*-dimethylformamide dimethylacetal (DMFDMA).[6a] In this work we apply this approach to the synthesis of 1,2λ^5-azaphosphinines starting from the corresponding aminophosphonium chlorides **VIII** (Route 4). For the synthesis of the aminophosphonium chlorides **VIII** we used phosphonites **3** as the starting materials (Scheme 1). Compounds **3** were synthesized in two-steps via phosphorylation of enaminonitrile **1** using earlier developed procedure (yields: **3a**: 57%, **3b**: 73%).[10] It should be noted that compounds **3** could be used in the subsequent steps without isolation, but isolation of **3** increases yields of the subsequent transformations. Oxidation of phosphonites **3** into aminophosphonium chlorides **5** was performed in two-steps via oxidation into chlorophosphonium chlorides **4** using C_2Cl_6 followed by treatment with gaseous ammonia.[6c,11] The yields of the crude aminophosphonium chlorides **5** were nearly quantitative and these compounds were used in the next step without additional purification. Heating aminophosphonium chlorides **5** in DMFDMA led to the desired 1,2λ^5-azaphosphinines **6** (Scheme 1).[12] It should be noted that azaphosphinines **6** were stable in air over long periods of time (more than one year), unlike the azaphosphinines described earlier by Foucaud.

The structures of the obtained 1,2λ^5-azaphosphinines were confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, mass spectrometry, and elemental analyses. Characteristic features of the 1,2λ^5-azaphosphinine ring in the ^{1}H NMR spectra are spin–spin coupling interactions between the phosphorus atom and the protons of the ring, and in ^{13}C NMR spectra, the signals of the carbon atoms with characteristic C–P coupling constants (Fig. 2).

* Corresponding author. Tel.: +380 44 5373218; fax: +380 44 5373253.
E-mail address: a.kostyuk@enamine.net (A.N. Kostyuk).

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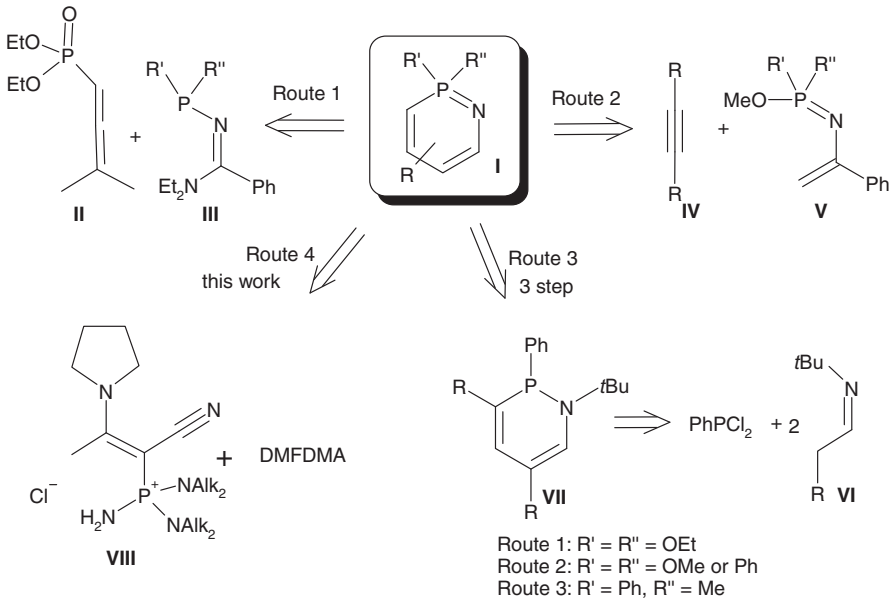
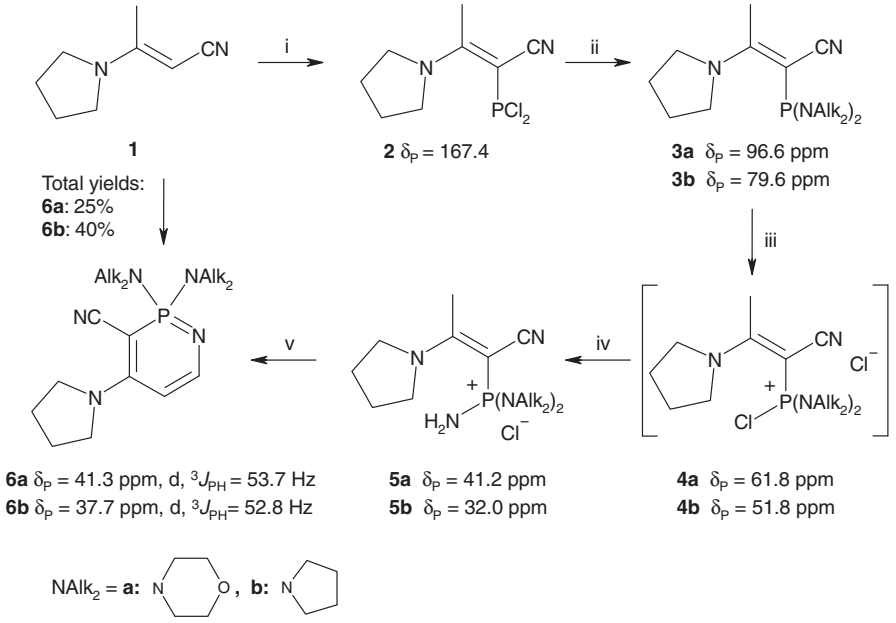


Figure 1. Methods for the synthesis of 1,2λ^5-azaphosphinines.



Scheme 1. Reagents and conditions: (i) PCl_3, Et_3N, C_6H_6, rt, 1 d; (ii) for **3a**: $HN(CH_2CH_2)_2O$, for **3b**: $HN(CH_2CH_2)_2$, Et_3N, C_6H_6; (iii) C_2Cl_6, C_6H_6; (iv) NH_3, CH_2Cl_2; (v) DMFDMA, 110 °C.

To rationalize the reaction we can consider two possible reaction pathways. Thus, the aminophosphonium chlorides bear two active functions, namely P–NH_2 and the Me group that are capable of reacting with DMFDMA.[6a] In both cases, after DMFDMA reaction followed by deprotonation, a phosphazahexatriene system could be generated (Scheme 2). In this case DMFDMA also acts as a base generating MeO^- and Me_2N^- on heating.[13] Electrocyclization of either of these systems with subsequent elimination of dimethylamine would lead to the final 1,2λ^5-azaphosphinines. The exact pathway of the cyclization reaction is still under discussion and needs additional investigation. However, route A involving DMFDMA insertion into the methyl group of the enamine fragment seems more feasible due to the absence of literature data on the reaction of aminophosphonium salts with DMFDMA with participation of the amino function.

In conclusion, a convenient approach to 1,2λ^5-azaphosphinines was developed starting from readily available compounds. The total yields of the products starting from β-dialkylaminocrotonic nitrile are 25–40%. The approach is attractive for future investigation of this class of compounds.

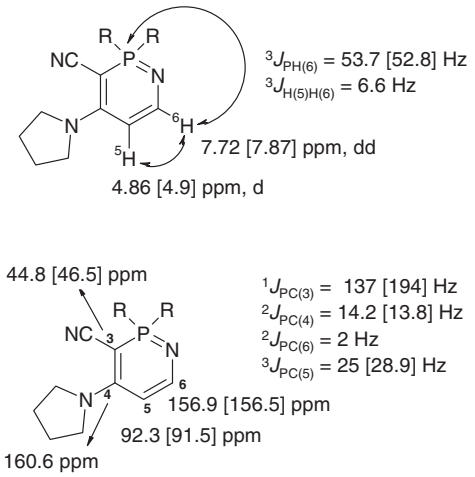
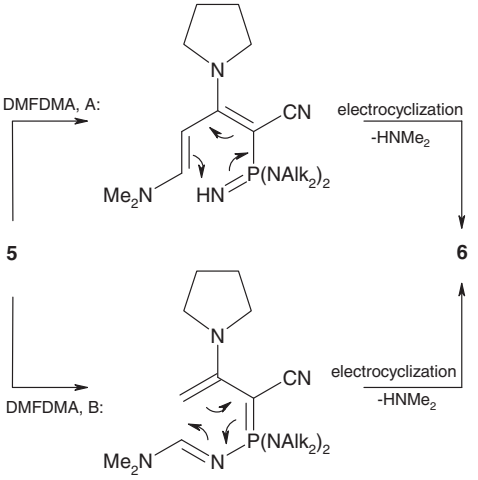


Figure 2. Diagnostic ^{1}H and ^{13}C NMR data of 1,2λ^5-phosphinines **6a** and [**6b**].



Scheme 2.

Acknowledgment

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References and notes

1. (a) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus Systems Based on the Phosphorus–Carbon Bond*; Wiley: New York, 1981; (b) Mathey, F. J. *Top. Phosphorus Chem.* **1980**, *10*, 1–128; (c) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281; (d)Dillon, K. B., Mathey, F., Nixon, J. F., Eds.Phosphorus: The Carbon Copy; Wiley: Chichester, 1998. Chapters 8 and 9.
2. (a) Madsen, G. K. H.; Krebs, F. C.; Lebech, B.; Larsen, F. K. *Chem. Eur. J.* **2000**, *6*, 1797; (b) Toshimitsu, A.; Saeki, T.; Tamao, K. *J. Am. Chem. Soc.* **2001**, *123*, 9210; (c) Edwards, P. G.; Paisey, S. J.; Tooze, R. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3122; (d) Heinicke, J.; Gupta, N.; Surana, A.; Peulecke, N.; Witt, B.; Steinhauser, K.; Bansal, R. K.; Jones, P. G. *Tetrahedron* **2001**, *57*, 9963–9972.
3. (a) Applications of phosphorus heterocycles in homogeneous catalysis. In *Phosphorus–Carbon Heterocyclic Chemistry*; Mathey, F., Ed.; Pergamon Press: Oxford, 2001; pp 753–772; (b) Le Floch, P. *Coord. Chem. Rev.* **2006**, *250*, 627–681; (c) Müller, C.; Vogt, D. *Dalton Trans.* **2007**, 5505–5523; (d) Kollar, L.; Keglevich, G. *Chem. Rev.* **2010**, *110*, 4257–4302; (e) Herwig, J.; Bohnen, H.; Skutta, P.; Sturm, S.; van Leeuwen, P. W. N. M.; Bronger, R. WO 02,68,434, 2002; *Chem. Abstr.* **2002**, *137*, 201440.; (f) Karacar, A.; Freytag, M.; Jones, P. G.; Bartsch, R.; Schmutzler, R. *Z. Anorg. Allg. Chem.* **2001**, *627*, 1571; (g) Kenten, J. H.; Von Borstel, R.; Casadei, J. M.; Kamireddy, B.; Martin, M. T.; Massey, R. J.; Napper, A. D.; Simpson, D. M.; Smith, R. G.; Titmas, R. C.; Williams, R. O. U.S. 740,501, 1993; *Chem. Abstr.* **1993**, *119*, 210716.
4. (a) Hirai, Y.; Suzuki, H.; Takeda, Y. JP 200,30,49,051, 2003; *Chem. Abstr.* **2003**, *138*, 154807.; (b) Chikamasa, N. JP 200,30,41,473, 2003; *Chem. Abstr.* **2003**, *138*, 138749.; (c) Krebs, F. C.; Larsen, P. S.; Larsen, J.; Jacobsen, C. S.; Boutton, C.; Thorup, N. *J. Am. Chem. Soc.* **1997**, *119*, 1208; (d) Mizukura, N.; Kita, H. JP 040,29,237, 1992; *Chem. Abstr.* **1992**, *117*, 17188.; (e) Müller, 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*, 4548–4559.
5. (a) Martinek, T.; Forro, E.; Günther, G.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2000**, *65*, 316–321; (b) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119–2123; (c) Hoffmann, M. G.; Bauer, K.; Bieringer, H.; Rosinger, C.; Lindell, S. D. DE 195,42,305, 1997; *Chem. Abstr.* **1997**, *127*, 5196.
6. (a) Kostyuk, A. N.; Svyaschenko, Y. V.; Volochnyuk, D. M. *Tetrahedron* **2005**, *61*, 9263–9272; (b) Svyaschenko, Y. V.; Kostyuk, A. N.; Barnych, B. B.; Volochnyuk, D. M. *Tetrahedron* **2007**, *63*, 5656–5664; (c) Volochnyuk, D. M.; Kovaleva, S. A.; Chernega, A. N.; Chubaruk, N. G.; Kostyuk, A. N.; Pinchuk, A. M.; Tolmachev, A. A.; Schmutzler, R. *Synthesis* **2006**, 1613–1624.
7. (a) Khusainova, N. G.; Bredikhina, Z. A.; Sinitsa, A. D.; Kal'chenko, V. I.; Pudovik, A. N. *Russ. J. Gen. Chem.* **1982**, *52*, 684–689; (b) Bredikhina, Z. A.; Khusainova, N. G.; Efremov, Yu. Ya.; Korshunov, R. L.; Pudovik, A. N. *Russ. J. Gen. Chem.* **1985**, *55*, 1519–1525.
8. (a) Kobayashi, T.; Nitta, M. *Chem. Lett.* **1985**, *14*, 1459–1462; (b) Yamamoto, H.; Kobayashi, T.; Nitta, M. *Heterocycles* **1998**, *48*, 1903–1916.
9. (a) Bedel, C.; Foucaud, A. *Tetrahedron Lett.* **1991**, *32*, 2619–2620; (b) Wai Tan, W. H. L.; Bourdieu, C.; Foucaud, A. *Tetrahedron* **1990**, *46*, 6715–6730.
10. Kostyuk, A. N.; Svyaschenko, Y. V.; Barnych, B. B.; Sibgatulin, D. A.; Rusanov, E. B.; Volochnyuk, D. M. *Heteroat. Chem.* **2009**, *20*, 194–201.
11. General procedure for aminophosphonium chlorides **5**: To a solution of **3** (5.9 mmol) in CH_2Cl_2 (30 mL) was added C_2Cl_6 (1.4 g, 5.9 mmol) in one portion. After 10 min **4a** had formed (monitored by ^{31}P NMR) and gaseous ammonia was bubbled through the reaction mixture for 10 min. The precipitated solid was filtered off and the filtrate evaporated in vacuo affording **5** as yellow-brown amorphous solids. The crude salts were used in following transformations without additional purification. According to NMR data the purity of the salts ca. 85–90%. Compound **5a**: ^{31}P NMR ($CDCl_3$, 121 MHz) δ, ppm: 41.2. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.84–1.95 (4*H*, m, CH_2), 2.42 (3*H*, s, CH_3), 3.19–3.35 (8*H*, m, $PNCH_2$), 3.51–3.62 (2*H*, m, NCH_2), 3.66–3.81 (8*H*, m, OCH_2), 3.83–3.93 (2*H*, m, NCH_2), 6.54 (2*H*, br s, PNH_2). Compound **5b**: ^{31}P NMR ($CDCl_3$, 121 MHz) δ, ppm: 32.0. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.73–1.94 (12*H*, m, CH_2), 2.37 (3*H*, s, CH_3), 3.15–3.36 (8*H*, m, $PNCH_2$), 3.53–3.62 (2*H*, m, NCH_2), 3.80–3.92 (2*H*, m, NCH_2), 5.96 (2*H*, br s, PNH_2).
12. General procedure for 1,2λ^5-azaphosphinines **6**: A stirred suspension of **5** (all the quantity obtained in the previous step) in DMFDMA (20 mL) was heated at 110 °C for 4 h. After cooling, the mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo. Finally, the residue was kept at 80 °C, in vacuo (0.03 Torr) till complete removal of DMFDMA. Compound **6a**: Yield 43% (for the two-step transformation), as a yellow-brown oil which crystallized on standing, mp 120–125 °C. ^{31}P NMR (C_6D_6, 121 MHz) δ, ppm: 41.3 (d, $^3J_{PH}$ = 53.7 Hz). ^{1}H NMR (C_6D_6, 300 MHz), δ, ppm: 1.13–1.19 (4*H*, m, CH_2), 3.03–3.17 (8*H*, m, $PNCH_2$), 3.25–3.33 (4*H*, m, NCH_2), 3.47–3.53 (8*H*, m, OCH_2), 4.86 (1*H*, d, $^3J_{HH}$ = 6.6 Hz, C(5)H), 7.72 (1*H*, dd, $^3J_{HH}$ = 6.6 Hz, $^3J_{PH}$ = 53.7 Hz C(6)H). ^{13}C NMR (C_6D_6, 75 MHz), δ, ppm: 25.2 (CH_2), 44.8 ($^1J_{PC}$ = 137 Hz, C(3)), 45.0 ($PNCH_2$), 50.1 (NCH_2), 67.1 ($^3J_{PC}$ = 5.5 Hz, OCH_2), 92.3 ($^3J_{PC}$ = 25.5 Hz, C(5)), 121.6 ($^2J_{PC}$ = 3 Hz, CN), 156.9 ($^2J_{PC}$ = 2 Hz, C(6)), 160.6 ($^3J_{PC}$ = 14.2 Hz, C(4)). APSI MS: M$^+$+1 = 364. Calculated for $C_{17}H_{26}N_5O_2P$: C 56.19, H 7.21, N 19.27, P 8.52. Found: C 56.11, H 7.22, N 19.32, P 8.49. Compound **6b**: 55% as a yellow-brown oil which crystallized on standing. ^{31}P NMR (C_6D_6, 121 MHz) δ, ppm: 37.7 (d, $^3J_{PH}$ = 52.8 Hz). ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 1.13–1.19 (4*H*, m, CH_2), 1.47–1.58 (8*H*, m, CH_2), 3.23–3.39 (12*H*, m, $PNCH_2$, NCH_2), 4.90 (1*H*, d, $^3J_{HH}$ = 6.6 Hz, C(5)H), 7.87 (1*H*, dd, $^3J_{HH}$ = 6.6 Hz, $^3J_{PH}$ = 52.8 Hz C(6)H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ, ppm: 25.0 (CH_2), 26.3 ($^3J_{PC}$ = 7.5 Hz, CH_2), 46.5 ($^1J_{PC}$ = 194 Hz, C(3)), 46.5 ($^2J_{PC}$ = 3.8 Hz, $PNCH_2$), 49.8 (NCH_2), 91.5 ($^3J_{PC}$ = 28.9 Hz, C(5)), 121.1 (CN), 156.5 ($^2J_{PC}$ = 2 Hz, C(6)), 160.6 ($^3J_{PC}$ = 13.8 Hz, C(4)). APSI MS: M$^+$+1 = 332. Calculated for $C_{17}H_{26}N_5P$: C 61.61, H 7.91, N 21.13, P 9.35. Found: C 61.60, H 7.93, N 21.17, P 9.31.
13. (a) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675–1735; (b) Simchen, G.; Hoffmann, H.; Bredereck, G. *Chem. Ber.* **1968**, *101*, 51.