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Synthesis of 2*H*-1,2-Oxaphosphorin 2-Oxides via Ag_2CO_3-Catalyzed Cyclization of (*Z*)-2-Alken-4-ynylphosphonic Monoesters

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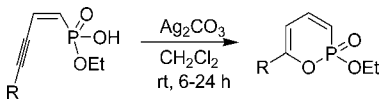
ABSTRACT



Six new 2-ethoxy-2*H*-1,2-oxaphosphorin 2-oxides were synthesized with high regioselectivity in good yields via Ag_2CO_3-catalyzed cyclization of (*Z*)-2-alken-4-ynylphosphonic monoesters in CH_2Cl_2 at room temperature. This cyclization of P-OH to substituted alkynes is reported for the first time. The products are a class of phosphorus heterocycles with potential use and are heretofore prepared with difficulty.

2-Pyrones are important structural subunits in a wide variety of biologically active natural products,[1] as well as useful versatile synthetic intermediates.[2] Recently, the activity of 2-pyrones as potent HIV protease inhibitors[1c] invoked additional interest in the investigation of 2-pyrones and their analogues. Since there is a remarkable similarity in reactivity and bioactivities between the carbon species and their phosphorus counterparts,[3] one would anticipate that phosphorus 2-pyrone analogues might have potential bioactivities similar to those of the 2-pyrones reported herein.

However, so far, only five phosphorus 2-pyrone analogues have been reported in the literature (compounds **1**−**5**, Figure 1). In 1978, Razumov et al. reported the synthesis of **1** and **2** via intermolecular aldol condensation followed by thermal cyclization reactions.[4] In the same year, Sigal et al. prepared **3** by addition of bromine to mesityl-2-butenylphostinate followed by dehydrobromination.[5] In 2002, Cremer et al.[6] prepared a mixture of **4** and **5** through a bromination-dehydrobromination sequence (4 steps) from the corresponding saturated phostone. Unfortunately, the scope of the above methods has not been examined, and they usually suffer from low yields and lengthy procedures. Thus, new and improved methodologies for synthesis of phosphorus 2-pyrone analogues are merited.

Building on methodology that has recently been developed in our group to synthesize phosphaisocoumarins by Cu(I)-catalyzed cyclization of 2-(1-alkynyl)phenylphosphonic mono-

(1) (a) Claydon, N.; Asllan, M.; Hanson, J. R.; Avent, A. G. *Trans. Br. Mycol. Soc.* **1987**, *88*, 503. (b) Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Sanchez, J. F.; Quilez, J. F.; Rojas, F. J.; Reyes, J. F. *Tetrahedron* **1993**, *49*, 141. (c) Vara Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B., Jr.; Fergunson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. A. M.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. *J. Am. Chem. Soc.* **1994**, *116*, 6989. (d) Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71. (e) Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *Z. Naturforsch.* **1998**, *53c*, 89. (f) Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **1998**, *54*, 13013.

(2) (a) Okamura, H.; Shimizu, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2000**, *41*, 4147. (b) Posner, G. H.; Lee, J. K.; White, M. W.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Kensler, T. W. *J. Org. Chem.* **1997**, *62*, 3299. (c) Posner, G. H.; Cho, C.-G.; Anjeh, T. E. N.; Johnson, N.; Horst, R. L.; Kobayashi, T.; Okano, T.; Tsugawa, N. *J. Org. Chem.* **1995**, *60*, 4617.

(3) (a) Dillon, K. B.; Mathey, F.; Nixon FRS, J. F. *Phosphorus: The Carbon Copy*; John Wiley & Sons: Chichester, 1998. (b) Quin, L. D. *A Guide to Organophosphorus Chemistry*; John Wiley & Sons: New York, 2000; Chapter 11.

(4) Razumov, A. I.; Liorber, B. G.; Sokolov, M. P.; Zykova, T. V.; Salakhutdinov, R. A. *Zh. Obshch. Khim.* **1978**, *48*, 51.

(5) Sigal, I.; Loew, L. *J. Am. Chem. Soc.* **1978**, *100*, 6394.

(6) Polozov, A. M.; Cremer, S. E. *J. Organomet. Chem.* **2002**, *646*, 153.

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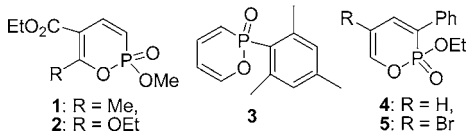
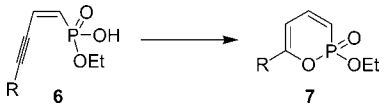
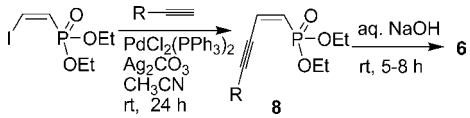


Figure 1. Known phosphorus 2-pyrone analogues.

Scheme 1. Approach To Synthesize **7**



Scheme 2. Synthesis of Monoesters **6**

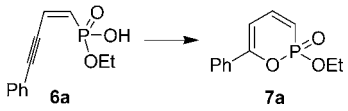


esters,[7] we envisaged that 2*H*-1,2-oxaphosphorin 2-oxides **7** will be accessible starting from (*Z*)-2-alken-4-ynylphosphonic monoesters **6** (Scheme 1). 2-Pyrones,[8] alkylidene lactones,[9] and other oxygenated heterocycles[10] have been prepared by cyclization of the corresponding substituted alkynes, but such methodology has never been used to synthesize 2*H*-1,2-oxaphosphorin 2-oxides. In this communication, we wish to report a new and efficient procedure to synthesize 2*H*-1,2-oxaphosphorin 2-oxides by transition-metal-catalyzed cyclization of (*Z*)-2-alken-4-ynylphosphonic monoesters.

The key starting materials **6** were readily prepared from basic hydrolysis of compounds **8**, which were synthesized by the Pd-catalyzed cross-coupling reaction of (*Z*)-2-iodovinylphosphonates with terminal alkynes[11] (Scheme 2).

We first examined the cyclization of (*Z*)-2-alken-4-phenylethynylphosphonic monoester **6a** (Table 1). Although 2-(1-alkynyl)phenylphosphonic monoesters were converted to phosphaisocoumarins in good yields in the presence of CuI, AgI, or $AgNO_3$ in DMF, or in toluene by addition of a general base, no cyclization product **7a** was observed under similar conditions even at 100 °C and adding Et_3N (Table 1, entries 1−5). We found that this reaction was very sensitive to the solvent and the catalyst. When using CH_2Cl_2 as the solvent, $AgNO_3$ or Ag_2CO_3 could catalyze the reaction at room temperature to give **7a** in 52% and 56% yields, respectively (Table 1, entries 6, 7), whereas CuI and AgI were still ineffective for this reaction (Table 1, entries 8, 9).

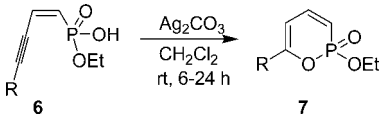
Table 1. Transition-Metal-Catalyzed Cyclization of (*Z*)-2-Alken-4-phenylethynyl-phosphonic Monoesters **6a**[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1	CuI	DMF	20−100	8	0
2	AgI	DMF	20−100	8	0
3	$AgNO_3$	DMF	20−100	8	0
4	Ag_2CO_3	DMF	20−100	8	0
5	CuI + Et_3N	DMF	20−100	8	0
6	$AgNO_3$	CH_2Cl_2	20	24	52
7	Ag_2CO_3	CH_2Cl_2	20	24	56
8	CuI	CH_2Cl_2	20	24	0
9	AgI	CH_2Cl_2	20	24	0

[a] Reaction conditions: **6a** (0.05 mmol), catalyst (0.005 mmol), anhydrous solvent (0.50 mL). [b] Isolated yield.

Table 2. Ag_2CO_3-Catalyzed Cyclization of (*Z*)-2-Alken-4-ynyl-phosphonic Monoesters **6**[a]



entry	R	time (h)	product	yield (%)[b]
1	Ph	24	**7a**	56
2	*p*-EtC_6H_4	24	**7b**	50
3	*n*-Bu	6	**7c**	84
4	*n*-C_6H_{13}	6	**7d**	92
5	cyclopropyl	6	**7e**	77
6	CH_2OCH_3	12	**7f**	54

[a] General reaction conditions: **6** (0.20 mmol), catalyst (0.02 mmol), anhydrous CH_2Cl_2 (2.0 mL). [b] Isolated yield.

To explore the scope of this reaction, the variation of substituent R was investigated in the presence of catalytic amounts of Ag_2CO_3 in CH_2Cl_2 (see Table 2). For those cases where R is aryl, the presence of Ag_2CO_3 is essential and the yields of **7** are only moderate (Table 2, entries 1 and 2). However, in cases where R is *n*-Hex, *n*-Bu, and cyclopropyl, Ag_2CO_3 is very effective (Table 2, entries 3−5); these substrates were found to proceed in the desired cyclization reaction at slow rates even in the absence of a silver salt. When R is an electron-withdrawing methoxymethyl group, the reaction gave the desired product **7f** in only 54% yield (Table 2, entry 6). Thus, the nature of R groups has much effect on this reaction.

Unlike the cyclization of (*Z*)-2-en-4-ynoic acids, which often leads to five- and six-membered ring products,[8,9] this

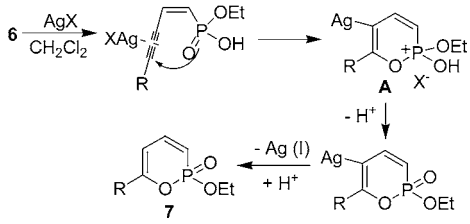
(7) Peng, A.-Y.; Ding, Y.-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006.
(8) (a) Anastasia, L.; Xu, C.; Negishi, E.-i. *Tetrahedron Lett.* **2002**, *43*, 5673. (b) Biagetti, M.; Bellina, F.; Carpita, A.; Viel, S.; Mannina, L.; Rossi, R. *Eur. J. Org. Chem.* **2002**, 1063. (c) Ogawa, Y.; Marun, M.; Wakamatsu, T. *Heterocycles* **1995**, *42*, 2587. (d) Wiley, R. H.; Jarboe, C. H.; Hayes, F. N. *J. Am. Chem. Soc.* **1957**, *79*, 2602. (e) Jacobs, T. L.; Dankner, D.; Dankner, A. R. *J. Am. Chem. Soc.* **1958**, *80*, 864.
(9) (a) Dalla, V.; Pale, P. *New J. Chem.* **1999**, *23*, 803. (b) Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281. (c) Belil, C.; Pascual, J.; Serratosa, F. *Tetrahedron* **1964**, *20*, 2701.
(10) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019.
(11) Huang, X.; Zhang, C.; Lu, X. *Synthesis* **1995**, 769.

reaction shows high 6-*endo-dig*[12] regioselectivity for six-membered ring products, and no five-membered ring products were detected by TLC monitoring in each case. The structure of **7** was confirmed by spectroscopic methods (especially by ^{1}H NMR spectral analysis; see Supporting Information). For example, the vinylic proton at the C5 position of **7c** resonates at 5.48 ppm as a double doublet with coupling constants of $^3J_{H,H} = 6.3$ Hz and $^4J_{H,P} = 1.5$ Hz, which was similar to that of **4** in the literature[6] and consistent with the proposed structure.

All of the obtained products (**7a**−**f**) were stable upon chromatography with silica gel and amenable to full characterization. However, if left at room temperature for extended periods, they began to decompose to strongly polar compounds, which have not been fully characterized; **7c**−**f** were relatively more stable than the aryl-substituted **7a** and **7b**. The decomposition processes were much slower when they were stored in a refrigerator in sealed anhydrous flasks and accelerated under basic conditions. This might account for the result that cyclization of **6a** did not give **7a** under basic conditions (in DMF or addition of Et_3N). Compared to **7**, phosphaisocoumarins exhibit greater stability and are not prone to decomposition even under thermal and basic conditions.[7]

On the basis of the above results and the related literature,[9,10] a plausible mechanism is proposed in Scheme 3. The coordination of the alkynyl moiety of **6** with Ag_2CO_3 or $AgNO_3$ activates the triple bond. Regioselective nucleophilic attack of the triple bond by the phosphonyl oxygen in the *endo* mode would give the vinyl silver species **A**, which subsequently undergoes proton transfer with regeneration of the silver catalyst to produce **7**.

Scheme 3. Plausible Mechanism that Leads to Formation of **7**



In conclusion, we have developed a novel and effective Ag_2CO_3-catalyzed cyclization of (*Z*)-2-alken-4-ynylphosphonic monoesters to 2-ethoxy-2*H*-1,2-oxaphosphorin 2-oxides under mild conditions. This cyclization of P-OH to substituted alkynes is reported for the first time and is of synthetic interest because the products are a class of phosphorus heterocycles with potential use and are heretofore prepared with difficulty. Further investigations of this process are underway.

Supporting Information Available: Typical experimental procedures and spectral data for **6**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.