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Ag(I)-catalyzed cyclization reaction of ethyl *o*-hydroxyphenylethynylphosphinates to phosphachromones

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Abstract

An Ag(I)-catalyzed intramolecular cyclization of ethyl *o*-hydroxyphenylethynylphosphinate to phosphachromones has been developed with high regioselectivity and good yields. The present reaction represents the first example of intramolecular addition of phenol to 1-alkynylphosphonates, which provides an approach to synthesize new phosphorus heterocycles. The resulting phosphachromones could have potential bioactivities.

The chromones have gained considerable synthetic and pharmacological interest for a long time because of their diverse biological activities, such as lipid-altering capabilities,[1] antiinflammatory activity,[2] cytotoxic activity,[3] and mediating DNA strand cleavage.[4–6]

Organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems,[7] and their potential to serve as novel pharmaceuticals.[8]

Recent studies have indicated that a lot of natural heterocycle analog containing phosphorus show the expected bioactivity. For example, phosphacoumarins showed good inhibitory activity against SHP-1,[9] and phosphaisocoumarins served as inhibitors of protein tyrosine phosphatase 1B (PTP1B).[10a] Phosphaisoquinolin-1-ones have an inhibitory activity against the A-549 lung cell growth.[10b] The synthesis of more natural heterocycle analog containing phosphorus and the assessment of their biological properties are very attractive. Because there is a remarkable similarity in reactivity and bioactivities between the carbon species and their phosphorus counterparts,[11] one can anticipate that the phosphachromone analog of chromone would have potential bioactivities similar to those of chromones (Fig. 1). To the best of our knowledge, phosphachromones are a new type of phosphorus heterocycles that have never been synthesized thus far. This Letter reports the synthesis and results of bioactivity screen of phosphachromones.

The transition-metal-catalyzed cyclization of alkynes possessing a nucleophile in proximity to the triple bond is an important process in organic synthesis, which can construct various heterocycles in an efficient and atom-economic way. Over the past few years, the intramolecular annulations of amines,[12] amides,[13] imines,[14] carboxylic acids,[15] alcohols,[16] and phosphonic acid monoesters[10] to a triple bond have been extensively investigated using transition-metal reagents as effective catalysts, such as Pd, Cu, Ag, Zn, Hg, W, Ru, or Rh reagents. However, analogous intramolecular cyclization of OH to 1-alkynylphosphonates has never been reported thus far. In this Letter, we wish to report a mild and efficient Ag(I)-catalyzed intramolecular cyclization of *o*-hydroxyphenylethynylphosphinates, leading to the formation of the phosphachromones (Scheme 1).

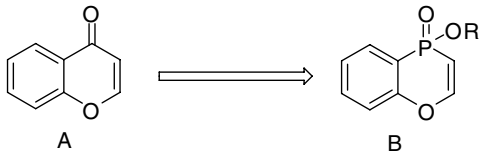

Fig. 1.

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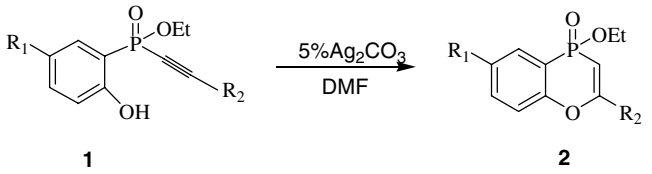


Scheme 1.

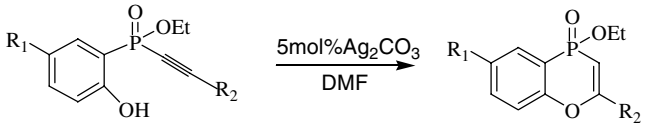
The intramolecular cyclization of ethyl *o*-hydroxyphenyl-1-hexynylphosphinate (**1a**) was first examined. Through control experiments, we found that the use of 0.2 equiv $Hg(OAc)_2/BF_3{\cdot}Et_2O$ as a catalyst in toluene at 80 °C for 5 h gave product **2a** in 80% yield, and in acetonitrile only 40%; the result of $HgCl_2$ is poorer. Although Pd(II) was an excellent catalyst for the addition of OH to alkynyl,[10] but it was less effective for the intramolecular cyclization of ethyl *o*-hydroxyphenyl-1-hexynylphosphinate (**1a**). Palladium(II) catalysts (e.g., $PdCl_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(CH_3CN)_2$, and $Pd(OAc)_2$) gave only unchanged starting materials. $Pd(PPh_3)_4$ can catalyze the cyclization of **1b** in DMF at 70 °C with low yield. Next, copper salts (CuI, $CuCl_2$) were tested, CuI was effective for the cyclization of **1a**, but less active to $R_2 = Ar$. Silver salts (Ag_2CO_3, $AgNO_3$, Ag_2O, or AgOAc) were excellent catalysts for all substrates. In the presence of Ag_2CO_3 (5 mol %), the reaction of **1** was performed at 30 °C for 2 h in DMF to give good yield. DMF is best among the researched solution, similar to the cyclization of 2-(2-phenylethynyl)phenylphosphonic acid monoethyl esters.[15b,17] Whereas AgI did not promote the reaction and with $AgBF_4$ as catalyst the reaction required heating. All facts showed that the silver catalyst was crucial for this reaction.

On the basis of the above optimization efforts, this method was applied to the synthesis of a variety of 2-, 6-substituted phosphachromones, and results are summarized in Table 1. In the presence of catalytic amounts of Ag_2CO_3, *o*-hydroxyphenylethynylphosphinates **1** with a variety of substituents (R^1, R^2) could be cyclized to form phosphachromones **2** in DMF with moderate heating, in good to excellent yields.[18]

The chemical properties of substituents (R^2) on the acetylene terminal did not affect the yields of the phosphachromones. Both aryl-substituted (entries 2, 3, 5, and 8) and alkyl-substituted (entries 1, 4, 7, and 9) alkynes were able to tolerate the reaction conditions. However, the 2-phenylethenylsubstituted ethyne (entry 6) has a significant effect on the yield of the phosphachromone. Reactant **1f** only gave a trace of product **2f** under the typical reaction condition. However, on heating to 60 °C, the reaction could give **2f** in 90% yield. In this instance, a conjugated double bond inhibits the form of species **C** to afford **2f** (see proposed reaction mechanism in Scheme 2).

Functionalities such as chloro and phenyl on the aromatic ring also did not affect the reaction efficiency. In addition, the unsubstituted *o*-hydroxyphenylethynylphosphinates

Table 1
Ag_2CO_3-catalyzed cyclization of *o*-hydroxyphenylethynylphosphinate **1**



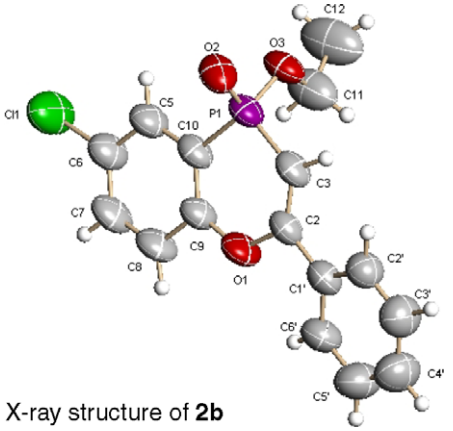
1 **2**

Entry	Substrate[a]	R_1	R_2	Temp (°C)	Product	Yield (%)[b]
1	**1a**	Cl	C_4H_9-*n*	30	**2a**	95
2	**1b**	Cl	Ph	30	**2b**	96
3	**1c**	Cl	PhEt-*p*	30	**2c**	93
4	**1d**	H	C_4H_9-*n*	30	**2d**	88
5	**1e**	H	Ph	30	**2e**	94
6	**1f**	H	CH=CHPh	60	**2f**	92
7	**1g**	Ph	C_4H_9-*n*	30	**2g**	88
8	**1h**	Ph	Ph	30	**2h**	86
9	**1i**	Ph	cyclopropyl	30	**2i**	95

[a] The reaction of **1** was carried out in the presence of 5 mol % of Ag_2CO_3 in DMF for 2 h.
[b] Isolated yield.

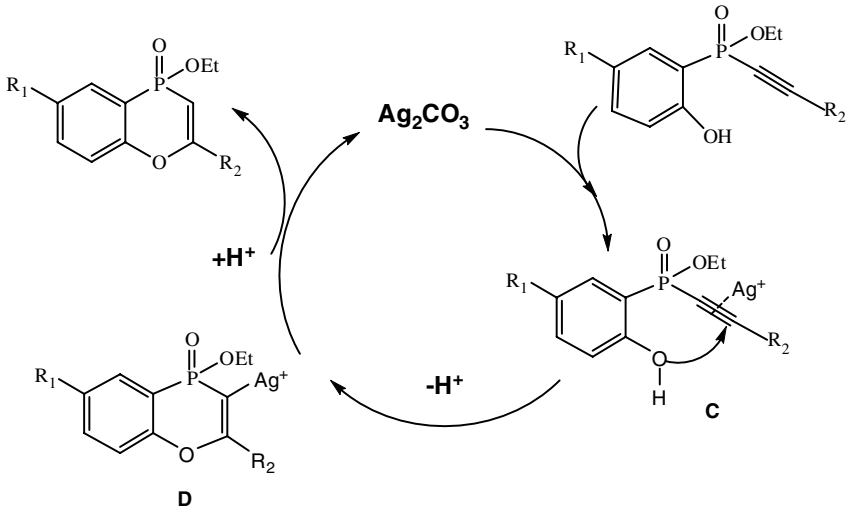
compounds (entries 4–6) can also afford the cyclization products in good yields.

The current reaction shows very high regioselectivity to give the 6-*endo*-dig[19] cyclization products. In each case, only the six-membered endocyclic phosphachromones were obtained, and the reaction monitored by TLC and ^1H NMR spectra indicated that no other regioisomers had been observed during the reaction progress. Factors affecting the above regioselectivity are not yet very clear. A possible explanation is that the longer C–P would be less favorable for the transition state leading to five-membered ring products than that leading to six-membered ring products. The structure of **2b** was assigned on the basis of ^1H NMR and X-ray crystallographic analyses.[20]



X-ray structure of **2b**

On the basis of the above results and the related literatures,[21] a plausible reaction mechanism is shown in Scheme 2. It presumably involves (i) the formation of complex **C** through the coordination of the alkynyl moiety of **1** with Ag_2CO_3; (ii) regioselective nucleophilic attack of the activation triple bond by oxygen in the endo mode to give the vinylsilver species **D** (iii) which subsequently undergoes



Scheme 2.

in situ protonation with the regeneration of the Ag(I) catalyst to product **2**.

To probe whether the synthesized phosphachromones possessed biological activities, their in vitro antitumor properties were evaluated in a human breast cancer cell line MDA-MB-468 by the SRB assay. At a concentration of 10^{-4} mol/L for 72 h, the MDA-MB-468 cell growth inhibition ratios of **2a**–**i** are 51.0, 69.6, 98.7, 18.8, 35.9, 45.2, 58.5, 98.2, 98.1, and 83.6, respectively, but their biological activities drop obviously with the decrease of concentration. So, further studies are needed to confirm this possibility.

In summary, we have developed a novel Ag_2CO_3-catalyzed cyclization reaction of *o*-hydroxyphenylethynylphosphinates to phosphachromones with high regioselectivity and good yields. The present reaction represents the first example of intramolecular addition of OH to phosphonylethynes, which provides an effective approach to synthesize the new kind of phosphorus heterocycles. Their further biochemical evaluation and the extension of this reaction are underway.

Acknowledgements

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18. *Typical procedure*: To a solution of 2-butyl-6-chloro-phosphachromone (0.2 mmol) and DMF (1 mL) was added Ag_2CO_3 (0.01 mmol), and the mixture was heated at 30 °C for 2 h. The reaction mixture was diluted with water and extracted with EtOAc, dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography using hexane/EtOAc as eluent to give the corresponding **2**. 2-Butyl-6-chloro-phosphachromone (**2a**) yield: 95%, oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.803 (dd, 1H, 5-ArH, $J = 2.6$ Hz, 13.2 Hz), 7.497 (dd, 1H, 7-ArH, $J = 2.6$ Hz, 8.6 Hz), 7.179 (dd, 1H, 8-ArH, $J = 9.0$ Hz, 7.3 Hz), 5.365 (s, 1H, =CH), 4.015 (dq, 2H, OCH_2, $J = 7.2$ Hz, 8.7 Hz), 2.477 (t, 2H, $=CCH_2$, $J = 8.2$ Hz), 1.600–1.700 (m, 2H, CH_2CH_2), 1.374–1.474 (m, 2H, CH_2CH_2), 1.319 (t, 3H, OCH_2CH_3, $J = 7.1$ Hz), 0.955 (t, 3H, CH_2CH_3, $J = 7.4$Hz) MS (EI): m/z: 300 (M^+, 14), 260 (22), 258 (74), 256 (14), 232 (32), 230 (100), 214 (24), 165 (25), 190 (34); IR (KBr, cm^{-1}): 2959, 2930, 1625, 1466, 1390, 1331, 1226, 1131, 1110, 1033, 951; Anal. Calcd for $C_{14}H_{18}ClO_3P$: C, 55.92; H, 6.03. Found: C, 55.84; H, 6.07.
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