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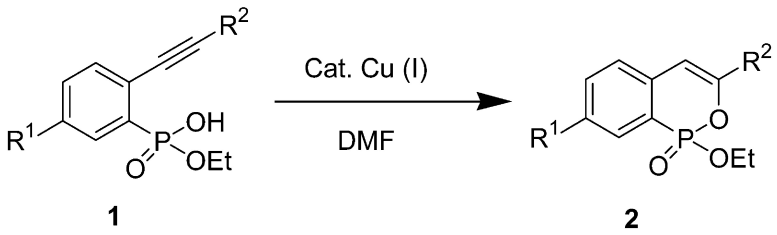

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The Synthesis of Phosphaisocoumarins by Cu(I)-Catalyzed Intramolecular Cyclization of *o*-Ethynylphenylphosphonic Acid Monoesters

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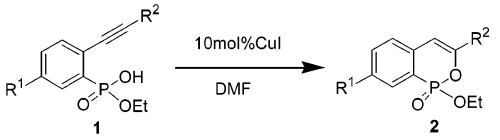
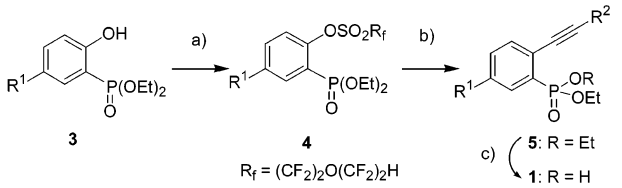
Isocoumarins have gained considerable synthetic and pharmacological interest for a long time because of their diverse biological activities, such as inhibition of serine proteases,[1] antifungal,[2] antibacterial,[3] antiangiogenic,[4] cytoxic,[5] immunomodulatory,[6] and differentiation inducing activity against leukemic cells.[7] Because phosphonates are an important bioactive compound and phosphonic acid analogues of naturally occurring carboxylic acids might inhibit similar biochemical work of the carboxylic acids,[8] one can anticipate that the phosphonic acid analogues of isocoumarins (i.e., phosphaisocoumarins) would have potential bioactivities similar to those of isocoumarins. However, phosphaisocoumarins are a new type of phosphorus heterocycles that have never been synthesized thus far.[8c,9] To enrich the phosphorus chemistry and find new bioactive compounds, we decided to study the syntheses and bioactivities of them.

The transition-metal-catalyzed cyclization of alkynes possessing a nucleophile in proximity to the triple bond is one of the most important processes in organic synthesis, which can construct various heterocycles in an efficient and atom economic way. Over the past few years, the intramolecular annulations of carboxylic acids,[10] alcohols,[11] amines,[12] amides,[13] and imines[14] to a triple bond have been extensively investigated using Pd, Cu, Ag, Zn, Hg, W, Ru, or Rh reagents as effective catalysts. However, to the best of our knowledge, analogue intramolecular cyclization of P−OH to alkynes has never been reported thus far, and there were only a few examples of the intermolecular addition of P−OH to alkynes.[15] In this study, we first report a mild and efficient copper-catalyzed intramolecular cyclization of *o*-ethynylphenylphosphonic acid monoethyl esters **1**, leading to the formation of the phosphaisocoumarins **2** (Scheme 1).

Scheme 1



Scheme 2 [a]



[a] (a) R_fSO_2F, Et_3N, room temperature; (b) $R^2C{\equiv}CH$, 5 mol % $PdCl_2(PPh_3)_2$, Et_3N, DMF, 90 °C; (c) NaOH, H_2O, reflux 2−3 h, then HCl.

Table 1. CuI-Catalyzed Cyclization of the *o*-Ethynylphenylphosphonic Acid Monoethyl Esters **1**[a]

entry	**1**	R^1	R^2	**2**	isolated yield of **2** (%)
1	**1a**	H	C_6H_5	**2a**	80
2	**1b**	H	*n*-Bu	**2b**	79
3	**1c**	Cl	*n*-Bu	**2c**	75
4	**1d**	Cl	C_6H_5	**2d**	83
5	**1e**	Cl	*p*-$CH_3CH_2C_6H_4$	**2e**	92
6	**1f**	Cl	*p*-$NO_2C_6H_4$	**2f**	63
7	**1g**	Cl	CH_2OH	**2g**	62
8	**1h**	Cl	CH_2OCH_3	**2h**	74
9	**1i**	Cl	H	**2i**	55
10	**1j**	Cl	cyclopropyl	**2j**	71
11	**1k**	OMe	C_6H_5	**2k**	88
12	**1l**	NO_2	*p*-$CH_3CH_2C_6H_4$	**2l**	60

[a] The reaction of **1** was carried out in the presence of 10 mol % CuI at 90 °C in DMF for 4 h.

The key starting materials **1** were readily prepared from the basic hydrolysis of compounds **5**, which were synthesized by the Pd-catalyzed cross-coupling reaction[16] of the corresponding phenyl perfluoroalkanesulfonates **4**[17] with alkynes (Scheme 2, see Supporting Information).

Cyclization of the 2-(phenylethynyl)phenylphosphonic acid monoethyl ester (**1a**) was first examined. In the presence of 10 mol % CuI, the reaction of **1a** proceeded smoothly at 90 °C in DMF to give **2a** in 80% isolated yield (entry 1, Table 1). Both the metal catalyst and thermal conditions were necessary for this reaction. When the reaction of **1a** was performed in the absence of CuI or at room temperature, the reactant **1a** was recovered completely. Through control experiments, we found that silver salts (e.g., AgI, $AgNO_3$) did not promote the reaction, and palladium complexes (e.g., $PdCl_2(PPh_3)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$) were less effective to this reaction. Moreover, just like the cyclization of alkynoic acids,[10] this reaction also needs a solvent with Lewis basicity or a general base. For example, the use of DMF or DMSO as the solvent could lead to the formation of **2a** in good yield, whereas very little desired product was detected by TLC in toluene, 1,4-dioxane, and CH_3CN without a base. When 2 equiv of Et_3N was added to the above reaction in toluene, the isolated yield of **2a** increased to 78%. It is also worth noting that this reaction does not need anhydrous and oxygen-free conditions.

The application of this methodology to the synthesis of a variety of 3- and 7-substituted phosphaisocoumarins is summarized in Table 1. In the presence of catalytic amounts of CuI, *o*-ethynylphenylphosphonic acid monoethyl esters **1** with a variety of substituted R^1 and R^2 groups can be cyclized to form phosphaisocoumarins **2** in DMF with moderate heating in good to excellent yields. The current reaction is extremely versatile and provides a convenient method for the synthesis of various phosphaisocoumarins. For example, alkyne can bear alkyl, aryl, and free hydroxyl (entry 7); chloro, methoxy, and nitro substituents on the benzene ring are tolerated.

This reaction shows very high regioselectivity. In each case, only the six-membered endocyclic phosphaisocoumarins from 6-*endo*-*dig*[18] cyclization were obtained, and no five-membered exocyclic

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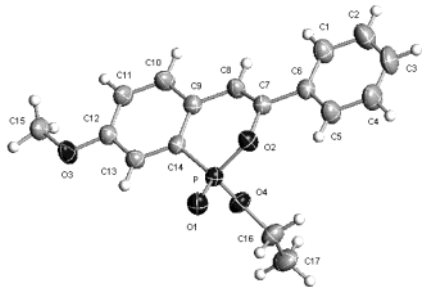

Figure 1. X-ray structure of **2k**.

Scheme 3. Plausible Mechanism that Leads to the Formation of **2**

products were detected by TLC monitoring. Our observations are in contrast to those of the cyclization of the alkynoic acids, which proceeded 5-*exo-dig* cyclization predominantly in the presence of AgI or CuI.[10] Factors affecting the above regioselectivity are not yet very clear. A possible explanation is that the longer C−P and P−O bond lengths would make less geometric constraint for an *endo* ring closure[19] and lower the stability of the exocyclic products. The structures of **2** were assigned on the basis of ^{1}H NMR and ^{13}C NMR spectra and X-ray crystallographic analysis (see Supporting Information). The structure of **2k** was shown as in Figure 1.

On the basis of the above observations and the nucleophilicity to strong electrophiles of phosphonyl,[20] a plausible mechanism may be proposed in Scheme 3. It presumably involves the formation of the π-complex **A**. In this step, a general base can deprotonate P−OH of compound **1**, and DMF, a Lewis base, can form a P−O−H$\cdots$O═C hydrogen bond, both of which can enhance the nucleophilicity of phosphonyl. The coordination of the alkynyl moiety of **1** to Cu(I) activates the triple bond. Regioselective nucleophilic attack of the triple bond by phosphonyl in the endo mode would give the vinylcopper species **B**, which subsequently undergoes in situ protonation with regeneration of the Cu(I) catalyst to produce the product **2**.

In summary, we have developed a novel CuI-catalyzed cyclization reaction of *o*-ethynylphenylphosphonic acid monoesters to phosphaisocoumarins with high regioselectivity and good yields. The present reaction represents the first example of intramolecular addition of P−OH to alkynes, which provides a new approach to synthesize phosphorus heterocycles. Phosphaisocoumarins may have potential bioactivities, and we have tested them preliminarily as inhibitors of Protein Tyrosine Phoshatase 1B (PTP1B). At a concentration of 50 μM, the PTP1B inhibition ratios of **2d**, **2k**, **2l** are 41%, 52.8%, 45.8%, respectively. The further biochemical evaluation of them and the extension of this reaction are underway.

Supporting Information Available: Typical experimental procedures and spectra data for previously undisclosed compounds and crystallographic data of **2k** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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