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Acid/Base-Catalyzed Cyclization of *O*-Alkynylphenylphosphonic Acid Monoesters and (*O*-Hydroxyphenyl)ethynylphosphinates

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ABSTRACT: *In this work, we found that acids (i.e., HCl and $NaHSO_3$) rather than bases could catalyze the cyclization of o-alkynylphenylphosphonic acid monoesters at slow rates and give phosphaisocoumarins in low to medium yields, whereas the cyclization of (o-hydroxyphenyl)ethynylphosphinates proceeded very smoothly under basic conditions rather than acidic conditions, and a series of phosphachromones could be prepared in excellent yields at room temperature using K_2CO_3 as catalyst. This is the first example of the synthesis of phosphorus heterocycles via acid/base-catalyzed intramolecular cyclization of alkynes. Possible mechanisms were discussed.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:649–652, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20728

INTRODUCTION

The intramolecular cyclization of alkynes is one of the most efficient methods to construct various heterocycles in current organic synthesis, in which an electrophile or a transition-metal catalyst is usually used to activate the triple bond [1]. In recent years, we have successfully applied this strategy to the synthesis of a series of novel phosphorus heterocycles, including phosphaisocoumarins [2], 2*H*-1, 2-oxaphosphorin 2-oxides [3], phosphaisoquinolin-1-ones [4], and phosphachromones [5] via Pd(II), Ag(I), and Cu(I)-catalyzed cyclization or halocyclization reactions. In the present study, we decided to investigate whether cheap and easily available acid/base alone could catalyze the formation of the phosphorus heterocycles mentioned above.

In recent years, acid- or base-catalyzed intramolecular cyclization of *o*-substituted alkynes has attracted much attention as an ecofriendly, metal-free, and practical procedure to synthesize various heterocycles. Terada and Kanazaw [6] and Uchiyama et al. [7] have reported that acid/base catalysts can control the regioselectivity of the cyclization of *o*-alkynylbenzoic acid, selectively giving six-member-ring isocoumarins or five-member-ring phthalides. Alami and co-workers [8] have successfully prepared a series of isocoumarins, benzofurans, and benzothiophenes via *p*-toluenesulfonic acid (PTSA)-catalyzed cyclization of the corresponding alkynes under microwave irradiation conditions. Bihel et al. [9] found that trifluoroacetic acid (TFA) could mediate the 6-*endo*-dig cyclization of *o*-alkynylbenzoates giving isocoumarins in high

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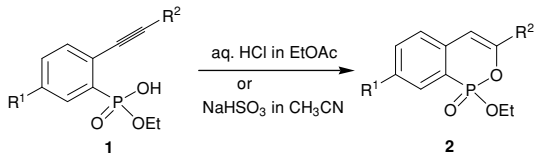
yields. Chromones have also been prepared efficiently via the cyclization of *o*-hydroxy arylalkynones in the presence of acids [10] such as PTSA, or base [11] such as Et_2NH and K_2CO_3. However, to the best of our knowledge, such transition metal-free process has not been applied to the synthesis of phosphorus heterocycles. On the other hand, $NaHSO_3$ has ever been used as an efficient and inexpensive catalyst for the synthesis of imidazoles [12], reducing reagent [13], and dehalogenation reagent for polyfluoroalkyl halides [14], but its use as a catalyst in the intramolecular cyclization reactions has never been reported prior to this work.

RESULTS AND DISCUSSION

We first examined the cyclization of 5-chloro-2-(1-hexynyl)phenylphosphonic acid monoethyl ester (**1a**) under acid/base-catalyzed conditions. The reaction of **1a** with 1 equiv of Et_3N or pyridine in MeCN at 80°C for 12 h did not give any cyclization product. However, the analogues of **1a**, *o*-ethynylbenzoic acid derivatives, could cyclize under weak basic conditions to give phthalides in good yields [6,7]. One possible explanation for such phenomenon is that the carbonyl group of isocoumarins or phthalides is in a big conjugate system, whereas the phosphonyl group of phosphoisocoumrins is not conjugated with the linked arene [2d], which may largely reduce the driving force of the cyclization of **1**. In addition, under weak basic conditions, the hinder P(O)(OH)(OEt) might show lower nucleophilicity, which would make it difficult to attack the inactivated C—C triple bond. Under acid-catalyzed conditions, the reaction of **1a** with PTSA in EtOH, or with neat TFA, or with 37% aq. HCl in dimethylsulfoxide (DMSO), dimethylformamide (DMF), cyclohexane, CH_2Cl_2, or toluene, also gave only trace amounts of the desired phosphaisocoumarin **2a**. Fortunately, when **1a** was treated with 37% aq. HCl in EtOAc and MeCN at room temperature for 60 h, **2a** was isolated in 56% and 35% yield, respectively (entry 1, Table 1); heating could speed up the cyclization process to some extent, but had no apparent effect on the yield of **2a**. To our surprise, further studies showed that sodium bisulfite ($NaHSO_3$), a weak solid acid,was even more effective. The treatment of **1a** with $NaHSO_3$ in MeCN at 80°C for 60 h led to **2a** in 60% yield (entry 1, Table 1). It has been found by thin-layer chromatography (TLC) monitoring that when $NaHSO_3$ is used as catalyst, heating and 1.0 equiv of the catalyst were necessary, and MeCN was the best solvent.

A series of 2-(1-alkynyl)phenylphosphonic acid monoesters **1** with a variety of substituents were then allowed to react with 37% aq. HCl in EtOAc at room temperature and with $NaHSO_3$ in MeCN at 80°C, respectively. As shown in Table 1, all substrates examined could be cyclized in 6-*endo* model [15] to phosphaisocoumrins **2** exclusively, and $NaHSO_3$ was more effective than HCl for most of the cases. However, compared with our previous Cu(I)-catalyzed cyclization reactions of these substrates, the present acid-catalyzed reactions were generally slow and the yields were relatively low, indicating that H^+ (proton acid) is not so effective as transition metal in catalyzing the present cyclization reactions. In addition, whether under HCl- or $NaHSO_3$-catalyzed conditions, the yields of **2** were all much more dependent on the nature of R^2 rather than R^1. In cases where R^2 is an aryl group, the reactions proceeded very slowly and gave the products in low yields after 5 days (120 h), and some of the starting materials were still recovered unchanged.

TABLE 1 Acid-Catalyzed Cyclization of **1**



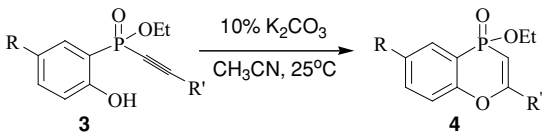
1 **2**

Entry	R^1	R^2	*Time (h)*	*Product*	*Yield (%)*[a]	*Yield (%)*[b]
1	Cl	*n*-Bu	60	**2a**	56	60
2	Cl	*c*-C_3H_5	60	**2b**	21	56
3	Cl	Ph	120	**2c**	19	26
4	OMe	*c*-C_3H_5	60	**2d**	10	50
5	OMe	Ph	120	**2e**	25	33
6	H	*n*-Bu	60	**2f**	30	25
7	H	Ph	120	**2g**	18	20

[a]Isolated yield under HCl-catalyzed conditions.
[b]Isolated yield under $NaHSO_3$-catalyzed conditions.

We then turned our attention to examine whether acid/base could catalyze the cyclization of (*o*-hydroxyphenyl)ethynylphosphinates **3**. When ethyl 5-chloro-2-hydroxyphenyl(1-hexynyl)phosphinate (**3a**) was treated with the addition of a catalytic amount of PTSA in CH_2Cl_2 or with $BF_3{\cdot}Et_2O$ in toluene under refluxed conditions, no cyclization product was observed even if increasing the amount of the acid and extending the reaction time. To our delight, in the presence of 10 mol% of K_2CO_3, **3a** was converted completely to the desired phosphachromone **4a** within 2 h at room temperature in MeCN and DMF. When a nonpolar solvent such as CH_2Cl_2 or toluene was used, the reaction was slower but could be accelerated by the addition of quantitative amount of K_2CO_3 or

TABLE 2 Base-Catalyzed Cyclization of **3**



3 **4**

Entry	*R*	*R*	*Time (h)*	*Product*	*Isolated Yield (%)*
1	Cl	*n*-Bu	2	**4a**	94
2	Cl	Ph	6	**4b**	90
3	Cl	4-EtC_6H_4	6	**4c**	88
4	Ph	*n*-Bu	2	**4d**	86
5	Ph	Ph	2	**4e**	84

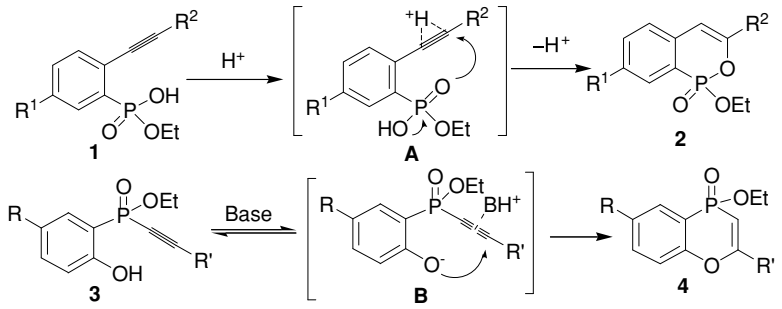
by heating. $NaHCO_3$, a weak inorganic base, was less effective since the completion of the reaction required longer time while using it as a catalyst. In addition, Et_3N could also catalyze the cyclization reaction efficiently, whereas other weak organic bases such as pyridine and imidazole proved ineffective. However, when 5 mol% of $PdCl_2$ was added to the above reaction in pyridine or imidazole, the yield of **4a** was increased apparently as found by TLC monitoring.

With these optimized conditions in hand, the reactions of **3a**–**3e** with 10 mol% of K_2CO_3 were carried out in MeCN at room temperature and the results are summarized in Table 2. As the results show, all substrates tested could be converted to the corresponding phosphachomones in high yields. The nature of the substituents seems not to influence the yields but affect the reaction rate. In cases where R is chloro and R′ is an aryl group, the disappearance of the substrates needed about 6 h, whereas for those cases where R is a phenyl group and R′ is an alkyl group, the reactions could complete within 2 h.

Based on the above results and related literatures, plausible mechanisms are proposed in Scheme 1. In the presence of an acid catalyst, the triple bond of **1** is activated by the coordination of H^+ [16], which is then attacked by the adjacent phosphonyl oxygen leading to the formation of **2**. In this course, as H^+ exhibits weaker affinity to the triple bond than the transition-metal catalyst, the acid, whether HCl or $NaHSO_3$, is not as effective as CuI in catalyzing the cyclization. H^+ showed especially worse catalytic activity for the cases where R^2 is an aryl group, probably because H^+ is difficult to coordinate with the triple bond in a larger conjugate system. Thus, the present acid-catalyzed process is not a very practical way to synthesize phosphaisocoumarins. For the substrates **3**, the cyclization reaction can occur under base-catalyzed conditions since the base can deprotonate or partially deprotonate the hydroxyl so as to enhance the nucleophilicity of the oxygen, and the triple bond may be activated by the conjugate acid of the base. The intramolecular Michael addition of ArO^- onto the activated C—C triple bond followed by proton transfer leads to the desired products **4** [6,7,11c].

CONCLUSIONS

In summary, we have shown that the cyclization of *o*-alkynylphenylphosphonic acid monoesters **1** can be catalyzed by acid (HCl or $NaHSO_3$), and the cyclization of (*o*-hydroxyphenyl)ethynylphosphinates **3** can be catalyzed by base (K_2CO_3). The results demonstrated that the acid is mainly used to activate the triple bond, whereas the base is usually used to increase the nucleophilicity of the nucleophile. Although the acid-catalyzed cyclization is not very effective for the synthesis of phosphaisocoumrins, the present work has shown that $NaHSO_3$ has the potential to catalyze the cyclization reactions and provides an ecofriendly, economical, and practical access to phosphachromones via K_2CO_3-catalyzed cyclization of **3** under mild conditions.



SCHEME 1 Plausible mechanisms of the acid-catalyzed cyclization of **1** and base-catalyzed cyclization of **3**.

EXPERIMENTAL

NMR spectra were all recorded on a Varian Mercury300 spectrometer (Varian, Inc., Palo Alto, CA) using $CDCl_3$ as the solvent unless stated otherwise. The ^1H NMRspectra and^{13}C NMR spectra used $CDCl_3$ (with tetramethylsilane) as the internal reference at 7.27 and 77.0 ppm, respectively. ^{31}P NMR spectra used 85% H_3PO_4 as the external reference. All reagents and solvents were used as received. The starting materials **1** [2e] and **3** [5a] were prepared according to our previous procedures. The products **2** [2e] and **4** [5a] were confirmed by the results of the NMR spectra data compared with the literature values.

General Procedure for HCl-Catalyzed Synthesis of 2

To a stirred solution of **1** (0.5 mmol) in EtOAc (15 mL), 37% aq. HCl (1.5 mL) was added dropwise. After stirring at room temperature for an appropriate period of time as shown in Table 1, the reaction mixture was diluted with EtOAc and washed with 5% (w/v) K_2CO_3, brine, and water, and then dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (4:1–2:1) as eluent to give the corresponding product **2**.

General Procedure for $NaHSO_3$-Catalyzed Synthesis of 2

The mixture of **1** (0.5 mmol) and $NaHSO_3$ (0.5 mmol) in CH_3CN (10 mL) was stirred at 80°C for an appropriate period of time as shown in Table 1. The reaction mixture was then filtered and evaporated. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (4:1–2:1) as eluent to give the corresponding product **2**.

General Procedure for K_2CO_3-Catalyzed Synthesis of 4

The mixture of **3** (0.5 mmol) and K_2CO_3 (0.05 mmol) in CH_3CN (5 mL) was stirred at room temperature for an appropriate period of time as shown in Table 2. The reaction mixture was then filtered and evaporated. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (2:1–1:1) as eluent to give the corresponding product **4**.

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