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Direct synthesis of α-hydroxyketone phosphates from terminal alkynes and *H*-phosphine oxides in the presence of $PhI(OAc)_2$ and H_2O

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ABSTRACT

A simple and highly efficient one-pot method for the construction of α-hydroxyketone phosphates from terminal alkynes and *H*-phosphine oxides has been developed in the presence of $PhI(OAc)_2$ and H_2O. The present protocol provides an attractive approach to α-hydroxyketone phosphates in good to high yields, with the advantages of operation simplicity, the use of commercially available materials, broad substrate scope, high atom efficiency and good tolerance to scale-up synthesis.

1. Introduction

Organophosphates have attracted increasingly synthetic pursuit of chemists because of their widely applications in many major physiological processes [1], drug discovery [2], organic synthesis [3] and agrochemicals [4]. Particularly, α-hydroxy-ketone phosphates can be used as sugar analogues [5] and important intermediates for the construction of phospholipid and oligonucleotide through the selective hydrolytic removal of the ketoxide motif [6]. As such, the development of general and efficient methods to access α-hydroxyketone phosphates is of great interest. Traditionally, α-hydroxyketone phosphates are synthesized by the α-phosphoryloxylation of ketones with the [hydroxy(phosphoryloxy)iodo]arenes [7], the reaction of 2,2,2-trialkoxy-1,3,2-dioxaphospholen with hydrogen chloride [5], and the oxyphosphorylation of silyl enol ethers with phosphoric acid and *p*-(difluoroiodo) toluene [8]. An alternative method for the construction of α-hydroxyketone phosphates has also been developed *via* the addition of terminal alkynes with unstable hypervalent iodine compound intermediate, which was preformed from the reaction of phosphonic acid with iodosobenzene (Scheme 1, Eq. (1)) [9]. However, all these methods suffer from limitations such as unreadily available starting materials, tedious work-up procedures, relatively harsh reaction conditions, toxic chemical wastes, the poor substrate scope, or low yields. Therefore, it is still highly desirable to develop a simple, convenient and efficient approach to α-hydroxyketone phosphates.

In 2012, Yan [10] and co-workers reported iodobenzene/*m*-chloroperbenzoic acid (*m*-CPBA) mediated the α-phosphoryloxylation of ketones with $(RO)_2PO_2H$ (Scheme 1, Eq. (2)). Very recently, Wang *et al.* [11] reported a new method for the construction of α-hydroxyketone phosphates through I_2O_5/DBU mediated direct α-phosphoryloxylation of ketones with H-phosphonates (Scheme 1, Eq. (3)). Nevertheless, stoichiometric amount of potentially dangerous peroxide oxidant or base are still required in the two well developed reactions. Here, we wish to report a simple, convenient and highly efficient $PhI(OAc)_2$ mediated procedure for the construction of α-hydroxyketone phosphates from alkynes and *H*-phosphine oxides in the presence of water under mild conditions (Scheme 1, Eq. (4)). The present protocol provides an alternative and highly attractive route to various α-hydroxyketone phosphates from the commercially available starting materials, and especially it avoids the use of

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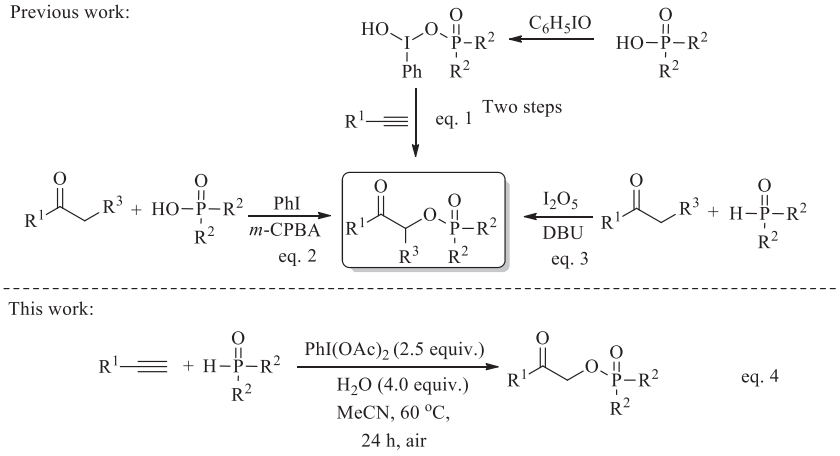

Scheme 1. Methods for the synthesis of α-hydroxyketone phosphates.

unstable reagents, and stoichiometric amounts of bases, toxic or potentially dangerous oxidants.

2. Experimental

All chemicals and solvents were purchased from Aldrich, J&K and Alfa Aesar Chemical Company as reagent grade and used without further purification unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were collected in $CDCl_3$ on a Bruker Avance 400 spectrometer with TMS as internal standard at room temperature, ^{31}P NMR spectra were recorded at 162 MHz, and chemical shifts (δ) reported relative to external 85% phosphoric acid (δ = 0.0 ppm), the chemical shifts (δ) were expressed in parts per million (ppm) and *J* values were given in hertz (Hz). HRMS were performed on a Brucker Daltonics Bio-TOF-Q mass spectrometer by the ESI method and LC–MS were obtained on a on a Waters Xevo TQ (Waters, Manchester, UK) equipped with an ESI source. The products were purified by flash column chromatography on silica gel (200–300 mesh).

2.1. General procedure for the synthesis of α-hydroxyketone phosphates **3**

To a solution of diarylphosphine oxides **2** (0.5 mmol) in acetonitrile (3.0 mL) were added $PhI(OAc)_2$ (1.25 mmol), H_2O (2.0 mmol) and alkynes **1** (0.75 mmol). The reaction mixture was then stirred for 24 h at 60 °C in air. After the reaction, the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (1:1) as eluent to give the desired product **3**.

2.2. The procedure of gram-scale reaction for the synthesis of ***3aa***

To a solution of diphenylphosphine oxide **2a** (2.02 g, 10.0 mmol) in acetonitrile (60.0 mL) were added $PhI(OAc)_2$ (8.05 g, 25.0 mmol), H_2O (720.0 μL, 40.0 mmol) and phenylacetylene **1a** (1.53 g, 15.0 mmol). The reaction mixture was then stirred for 24 h at 60 °C in air. After the reaction, the solvents were removed under vacuum. Water (60.0 mL) was added to the reaction mixture, and then the mixture was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (1:1) as eluent to give the desired product **3aa** (2.99 g, 89%).

2.3. The reaction of diphenylphosphine oxide ***2a*** with $PhI(OAc)_2$

To a solution of diphenylphosphine oxide **2a** (1.0 mmol) in acetonitrile (6.0 mL) were added $PhI(OAc)_2$ (1.0 mmol) and H_2O (4.0 mmol). The reaction mixture was then stirred for 24 h at 60 °C in air. After the reaction, the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel using a mixture of dichloromethane and methanol (5:1) with addition of AcOH (1‰) as eluent to give the desired product **6a** (209.0 mg, 96%).

2.4. The reaction of phenylacetylene ***1a*** with diphenylphosphinic acid ***6a***

To a solution of diphenylphosphinic acid **6a** (0.5 mmol) in acetonitrile (3.0 mL) were added $PhI(OAc)_2$ (1.25 mmol), H_2O (2.0 mmol) and phenylacetylene **1a** (0.75 mmol). The reaction mixture was then stirred for 24 h at 60 °C in air. After the reaction, the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (1:1) as eluent to give the desired product **3aa** (153.0 mg, 91%).

3. Results and discussion

At the outset of our investigation, the reaction of phenylacetylene **1a** and diphenylphosphine oxide **2a** was chosen as the model reaction to optimize the reaction conditions. Gratifyingly, the desired product **3aa** was obtained in 26% yield when the model reaction was performed in the presence of $PhI(OAc)_2$ (1.0 equiv.)/H_2O (1.0 equiv.) at 60 °C in air for 24 h (Table 1, entry 1). It was found that the reaction gave a better yield 40% when the loading of H_2O was increased to 4.0 equiv. (Table 1, entry 4). Further optimization suggested that the reaction efficiency was obviously improved with the increasing of $PhI(OAc)_2$ loading, the best yield was obtained when 2.5 equivalent of $PhI(OAc)_2$ was used (Table 1, entry 9). The screening of other oxidants, such as $K_2S_2O_8$, *m*-CPBA, TBHP and H_2O_2 could not improve the reaction efficiency (Table 1, entries 11–14). Subsequent investigation on the effect of solvents showed that the reaction performed in MeCN was found to be superior for the formation of **3aa** (Table 1, entries 15–20). In addition, we found that the reaction temperature also played an important role in this transformation (Table 1, entries 9, 21–23). The desired product **3aa** was isolated in only 36% yield when the model reaction was carried out at room temperature (Table 1, entry 21), and the best yield was obtained when the reaction was

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