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# Copper catalyzed one-pot synthesis of $\beta$ -ketophosphine oxides from ketones and H-phosphine oxides

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#### ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online A facile and efficient copper catalyzed one-pot method has been developed for the formation of  $\beta$ -ketophosphine oxides from ketones and H-phosphine oxides under air at room temperature, in which vinylhydrazinedicarboxylate was formed as the key intermediate. Preliminary mechanistic studies indicated that the reaction might involve a radical process and carbonyl oxygen atom of  $\beta$ -ketophosphine oxides came from molecular oxygen.

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Keywords: Copper-catalysis One-pot procedure β-Ketophosphine oxides Ketones Vinylhydrazinedicarboxylates

 $\beta$ -Ketophosphine oxides are extremely valuable organic compounds, which not only serve as versatile building blocks for the construction of various important chemicals in the synthetic chemistry,<sup>1</sup> but also are employed as potential ligands and liquidliquid metal-extracting agents owing to their outstanding metalcomplexing ability.<sup>2</sup> During the past several decades, considerable efforts have been dedicated in the construction of βketophosphine oxides and many useful synthetic methods have been successfully developed. Generally, β-ketophosphine oxides are synthesized by the acylation of alkylphosphine oxides by using of stoichiometric organometallic reagents.<sup>3</sup> Alternative methods include the hydrolysis of enamine phosphine oxides,<sup>4</sup> the reaction of chloroacetophenone with hydrophosphoryl compounds under basic conditions<sup>5</sup> and palladium catalyzed hydration of alkynylphosphine oxides.<sup>6</sup> However, most of the methods suffered from drawbacks such as relatively harsh reaction conditions, uneasily obtained starting materials, or toxic wastes. Recently, the catalytic oxyphosphorylations of alkenes,<sup>7</sup> acids,<sup>10</sup> alkynes,8 cinnamic acids,9 alkynylcarboxylic cinnamyl/alkynylcarboxylates<sup>11</sup> and  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>12</sup> have been developed for the synthesis of  $\beta$ ketophosphine oxides, which have elicited great interest of chemists due to their high efficiency in the cascade formation of C-P and C=O Bonds. Gracefully successive as these oxyphosphorylation reactions could be, there is still a great demand for the development of new, mild, convenient and

efficient methods to access  $\beta$ -ketophosphine oxides from simple and easily accessible starting materials.

In 2015, Lei and co-workers reported a new oxidative coupling of the preformed aryl ketone *O*-acetyloximes with H-phosphine oxides leading to  $\beta$ -ketophosphine oxides using CuCl as catalyst under N<sub>2</sub> at 130°C.<sup>13</sup> With our continuous efforts in the synthesis of phosphorus-containing compounds,<sup>7a, 8d,14</sup> herein, we present a facile and one-pot copper-catalyzed procedure for the synthesis of  $\beta$ -ketophosphine oxides from various ketones and P(O)-H compounds promoted by DIAD (diisopropyl azodicarboxylate) at room temperature, in which vinylhydrazinedicarboxylate was formed as key intermediate (Scheme 1).



Scheme 1. Synthetic route to  $\beta$ -ketophosphine oxides from ketones.

Initially, based on our previous studies on the oxyphosphorylation of alkenes, we hypothesized that  $\beta$ -ketophosphine oxides production might also be feasible through the oxyphosphorylation of vinylhydrazinedicarboxylates, which are easily generated from ketones and DIAD. To test our hypothesis, we started our research by examining the model

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of stable vinylhydrazinedicarboxylate 1a' and reaction diphenylphosphine oxide 2a to determine the optimized reaction conditions (Table 1). No desired product was detected when the model reaction was conducted in CH2Cl2 under metal-free condition (Table 1, entry 1). Further optimization of transitionmetal catalysts (5 mol%) found that the desired product 3a was obtained in moderate to good yields when silver or copper catalysts were used (Table 1, entries 2-8). Among various copper salts examined, CuBr<sub>2</sub> was found to be the best choice, affording the desired product 3a in 95% yield (Table 1, entry 8). The reaction did not proceed in the absence of base (Table 1, entry 9). Subsequent screening on a series of bases revealed that triethylamine was the superior for the formation of product 3a (Table 1, entries 8, 10, 11). The investigations of various solvents indicated that CH<sub>2</sub>Cl<sub>2</sub> still brought about the best result (Table 1, entries 8, 12-15). Notably, the yield of **3a** slightly declined when the model reaction was performed under pure dioxygen (Table 1, entry 16).

Table 1. Optimization of reaction conditions<sup>a</sup>



<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), catalyst (5 mol% base (0.5 mmol), solvent (2.0 mL), air (balloon), rt, 3 h.

<sup>b</sup> Isolated yields based on 1a'.

DIPEA = Ethyldiisopropylamine; DBU = 1,8-Diazabicyclo[5.4.0]undec-7ene.

<sup>c</sup> Under O<sub>2</sub>

Subsequently, we explored the domino one-pot procedure by combining acetophenone **1a**, DIAD and Bu<sub>3</sub>P in CH<sub>2</sub>Cl<sub>2</sub> at room temperature.<sup>15a</sup> Once the reaction reached completion, the above optimized conditions were applied to the reaction mixture under air. To our delight, the desired product **3a** was still obtained in 71% yield (Table 2, entry 1). Further optimization showed that the reaction efficiency was improved (78% yield) when the loading of **2a** was increased to 3 equiv (Table 2, entry 2). Based on the results, we decided to use the two-step, one-pot procedure given in Table 2, entry 2 as our standard reaction conditions.

Table 2. Optimization of conditions for one-pot reaction<sup>a</sup>



<sup>a</sup> Reaction conditions: 1) **1a** (0.5 mmol), DIAD (0.75 mmol), Bu<sub>3</sub>P (0.75 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL), rt, 4 h; 2) **2a** (1.25 or 1.5 mmol), CuBr<sub>2</sub> (5 mol%), Et<sub>3</sub>N (0.5 mmol), rt, 12 h.

<sup>b</sup> Isolated yields based on **1a** 

With the optimized conditions in hand, the substrate scopes and limitations of this one-pot strategy were investigated (Table 3).

**Table 3.** Screening of substrate scope in one-pot strategy <sup>a, b</sup>



<sup>a</sup> Reaction conditions: 1) **1** (0.5 mmol), DIAD (0.75 mmol), Bu<sub>3</sub>P (0.75 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL), rt, 4 h; 2) **2** (1.5 mmol), CuBr<sub>2</sub> (5 mol%), Et<sub>3</sub>N (0.5 mmol), air (balloon), rt, 12 h.

<sup>b</sup> Isolated yields based on **1**.

° THF as solvent.

In general, both electron-donating and electron-withdrawing groups substituted acetophenones were all suitable for this reaction to afford β-ketophosphine oxides in moderate to good yields (3a-3i). Notably, the present transformation was not significantly affected by the steric effect, and ortho-, meta- or para- methyl substituted substrates were also compatible with this process to deliver the corresponding products in good yields (3b-3d). In addition, various function groups such as ester (3f), chloro (3g), fluoro (3h), and cyano (3i) were all well tolerated in this reaction, which could be used for further structural manipulation. 1-(Naphthalen-2-yl)ethanone was also demonstrated to be compatible with the standard conditions to give the desired product 3j in 80% yield. In addition, heteroaryl ketones such as 1-(pyridin-3-yl)ethanone and 1-(furan-2yl)ethanone could also transformed smoothly into the corresponding products (3k and 3l) in 55% and 63% yields, respectively. Notably,  $\alpha$ -position single substituted ketones were tolerated in this process leading to desired products (3m and 3n) in moderate yields. It should be noted that aliphatic ketones such as acetone and 2-pentanone were also compatible with this reaction, but leading to the desired products (30 and 3p) in relatively low yields. Moreover, the scopes of phosphine oxides were also examined. In addition to diphenylphosphine oxide 2a, methyl or fluoro substituted diphenylphosphine oxides and ethyl phenylphosphinate were also suitable for this reaction, affording the corresponding products (3q-3s) in moderate yields.

Furthermore, the synthetic applicability of this one-pot procedure was investigated on a gram scale by using the model reaction between **1a** and **2a**. As shown in Scheme 2, the reaction could afford 2.54g of **3a** in 79% yield without any loss of efficiency, suggesting that this reaction could serve as a practical protocol to construct  $\beta$ -ketophosphine oxides.



#### Scheme 2. Gram scale experiment

Considering that the mechanism of transformation from ketones to vinylhydrazinedicarboxylates had been reported in previous literatures,<sup>15a, 16</sup> we focused our attentions on the pathway from vinylhydrazinedicarboxylates to  $\beta$ -ketophosphine oxides in the present reaction system. Several control experiments were performed to gain some insights into the mechanism. None of the desired product was obtained when the reaction was conducted under N<sub>2</sub> (Scheme 3, Eq (1)), indicating that dioxygen is essential for the reaction. To elucidate the origination of the carbonyl oxygen atom of  $\beta$ -ketophosphine oxide, an isotope-labeling experiment was carried out. When the reaction of **1a'** and **2a** was performed under <sup>18</sup>O<sub>2</sub>, the <sup>18</sup>O isotope-labeled product was obtained in 80% yield, suggesting the carbonyl oxygen atom of the  $\beta$ -ketophosphine oxide originated from dioxygen (Scheme 3, Eq (2)).



Subsequently, the addition of the radical scavenger TEMPO (2, 2, 6, 6-tetramethylpiperidine-1-oxyl) to model reaction completely inhibited the reactivity, which indicated the present reaction might involve a radical pathway (Scheme 3, Eq (3)).

Based on the above results and previous reports, 7a, 8a-8d, 15, 16 a tentative reaction pathway was illustrated in Scheme 4. Initially, acetophenone (1a) reacted with the Huisgen zwitterions 4a that was formed from tributylphosphine and DIAD, producing by vinylhydrazinedicarboxylate (1a') eliminating tributylphosphine oxide. Then, a single electron transferred from diphenylphosphine oxide 2a to a  $Cu^{II}$  species leading to diphenylphosphine oxide cation radical 5a in the presence of molecular oxygen. Then, the abstraction of the H<sup>+</sup> by Et<sub>3</sub>N from the diphenylphosphine oxide cation radical gave Cu<sup>II</sup>-(•OOH) (hydroperoxide) species and the P-radical 6a. Subsequently, the resulting phosphonyl radical 6a selectively added to 1a' giving alkyl radical **7a**, which interacted with Cu<sup>II</sup>-(•OOH) (hydroperoxide) species leading to intermediate 8a. Vinylperoxyl intermediate 10a was formed via the elimilation of diisopropyl hydrazine-1, 2-dicarboxylate (9a) from intermediate 8a. Finally, the reduction of hydroperoxide 10a by another diphenylphosphine oxide 2a gave enolate 12a, which quickly underwent tautomerization leading to the desired product 3a. To our delight, the proposed intermediates 6a, 7a, 10a, and byproduct 11a were all detected by LC-MS analysis (See supporting information for detailed description).





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In conclusion, a new copper-catalyzed one-pot procedure has been developed for the synthesis of  $\beta$ -ketophosphine oxides from various ketones and H-phosphine oxides under air at room temperature. The present protocol provides an efficient and attractive route to various  $\beta$ -ketophosphine oxides in moderate to good yields with good functional group tolerance. Preliminary mechanistic studies revealed that the reaction might involve a radical process and the carbonyl oxygen atom was derived from molecular oxygen. Further studies to clearly understand the reaction mechanism and the potential synthetic applications are ongoing in our laboratory.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.\*\*\*\*

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  - The present oxyphosphorylation reaction can be performed under air at room temperature