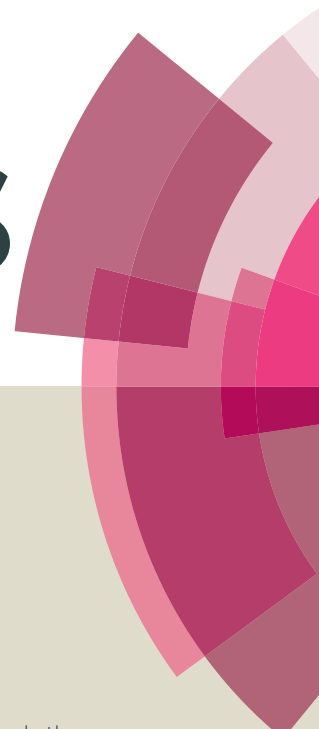


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ARTICLE

Direct synthesis of β -ketophosphonates and vinyl phosphonates from alkenes or alkynes catalyzed by CuNPs/ZnO.

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Copper nanoparticles (CuNPs) supported on ZnO have been shown to effectively catalyze the direct synthesis of β -ketophosphonates from alkenes or alkynes, and that of vinyl phosphonates from alkynes and diethylphosphite, under air and in the absence of any additive or ligand. When using alkynes as starting materials, the selectivity proved to be dependent on the alkyne nature. Thus, alkynes conjugated with an aromatic ring or a carbon-carbon double bond gave β -ketophosphonates as the main reaction products, whereas aliphatic alkynes or alkynes conjugated with a carbonyl group led to the formation of the corresponding vinyl phosphonates.

Introduction

Phosphorus containing organic compounds are of widespread interest in synthetic organic chemistry. This is due to the remarkable biological activities of many phosphorus derivatives which make them of potential interest and application in diverse fields, ranging from medicinal chemistry to the agrochemical industry. Phosphonic acids and esters are widely known as extremely important structural analogues to the corresponding carboxylic acids and esters.¹ Among this family of organophosphorus compounds, β -ketophosphonates have received considerable attention in recent years, not only due to their varied biological activities² and metal-complexing abilities,³ but also because they are valuable precursors for the construction of α,β -unsaturated compounds (Horner-Wadsworth-Emmons reaction)⁴ and for the synthesis of chiral β -amino-⁵ and β -hydroxy⁶ phosphonic acids.

Several methods for the synthesis of β -ketophosphonates can be found in the scientific literature.⁷ The most common approaches are based in the condensation between carboxylic acid derivatives and alkyl phosphonates,⁸ and in the hydration of alkynyl phosphonates,⁹ both protocols having some important drawbacks; while condensation reactions often need for the use of strong bases and/or cryogenic conditions, many of the hydration-based methods require the use of toxic

mercury salts in combination with acids or bases. Although recently published procedures based on the use of Pd¹⁰ or Au¹¹ catalysts for the hydration of alkynylphosphonates circumvent the use of toxic reagents, there is still a need for the development of direct synthetic methodologies to access β -ketophosphonates from simple and readily available starting materials. In this regard, the transition metal-catalysed oxyphosphorylation of alkynes with H-phosphonates has very recently been tackled by two independent research groups. In one of these works, Zaho *et al.*¹² reported a one-pot strategy for the synthesis of β -ketophosphonates using AgNO₃/CuSO₄·5H₂O as catalyst and K₂S₂O₈ as oxidant additive. The reactions are conducted under air and in CH₂Cl₂-H₂O as solvent. In a more recent paper, Song *et al.*,¹³ have communicated the oxyphosphorylation of alkynes or alkynyl carboxylic acids with H-phosphonates, catalysed by CuOTf/FeCl₃ in DMSO, under O₂ atmosphere, in the presence of Et₃N as base.

On the other hand the copper/iron co-catalyzed oxyphosphorylation of alkenes with dioxygen and H-phosphonates published by Wei and Ji,¹⁴ is, to the best of our knowledge, the only transition metal-catalyzed direct synthesis of β -ketophosphonates from alkenes that has been published so far.

Even though the above mentioned transition metal-catalysed methodologies are useful and attractive, in most cases long reaction times (24 h), oxygen atmosphere and/or the use of different additives is required.

Vinyl phosphonates represent another prominent member of the family of phosphorous derivatives, they are well known as important synthetic intermediates¹⁵ and have diverse applications as monomers and co-monomers in polymeric materials.¹⁶ Most of the existing methods for P-C(vinyl) bond formation are based on palladium-catalyzed reactions,^{1,17} which usually require the use of phosphine ligands.

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Electronic Supplementary Information (ESI) available: Detailed experimental procedures, characterization data, and copies of ¹H, ¹³C and ³¹P NMR spectra of all phosphonate products. Full characterization of catalyst is also included. See DOI: 10.1039/x0xx00000x

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Alternatively, the use of Cu(I)¹⁸ or Ni(II)¹⁹ catalysts have also been reported but both methodologies need for harsh reaction conditions or phosphine ligands to give the desired vinyl phosphonates in reasonable yields.

In the last years we have actively been working in the development of new and mild methodologies based on the use of bare or supported copper nanoparticles (CuNPs) for their application in the construction of C-C and C-heteroatom bonds.²⁰ During the course of our investigations about CuNPs-catalysed C-P coupling reactions, we have found that the reaction between aryl acetylenes or terminal alkenes with commercial diethyl phosphite, catalysed by CuNPs supported on ZnO, led to the direct formation of β -ketophosphonates. Notably, when aliphatic alkynes were reacted under the same reaction conditions, the corresponding vinyl phosphonates were obtained instead as the major products. We want to present herein our results on the development of a new and simple methodology that allow the direct synthesis of β -ketophosphonates and vinyl phosphonates from alkenes or alkynes as simple and readily available starting materials, under air atmosphere and mild reaction conditions, catalysed by CuNPs/ZnO.

Results and Discussion

We started our study by choosing phenylacetylene (**1a**) as model substrate to optimize the reaction conditions. The reactions were performed under air atmosphere and in the absence of any other additive or ligand. Initially, the reaction of **1a** with (EtO)₂P(O)H was tested in the presence of CuNPs supported on a variety of organic and inorganic materials using acetonitrile as the solvent (Table 1). All the CuNPs based catalysts were prepared according to the methodology previously reported by us,²⁰ the CuNPs (3-6 nm in size) being synthesized by fast reduction of anhydrous CuCl₂ with an excess of lithium sand and a catalytic amount of DTBB (4,4'-di-tert-butylbiphenyl) as electron carrier. Figure 1 shows a TEM image and size distribution graphic for CuNPs/ZnO catalyst (see Supporting Information for experimental details and characterization of the catalyst). As can be seen, well dispersed spherical copper nanoparticles with an average particle size of 6.0 \pm 0.5 nm are obtained.

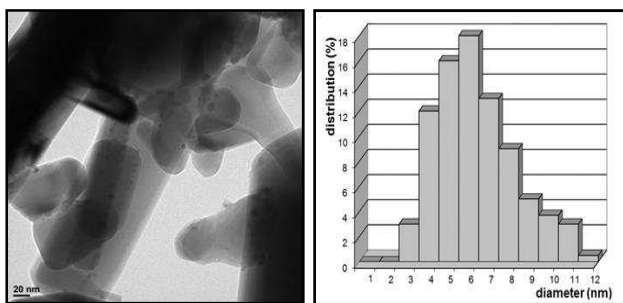


Figure 1. TEM image and size distribution graphic of CuNPs in CuNPs/ZnO catalyst.

As shown in Table 1, the best results were obtained by working at 70 °C and using ZnO as support for the CuNPs (Table 1, entry

1). The lower conversions obtained when using any of the other supports listed in Table 1, could suggest the necessity for the presence of Lewis acid (Zn²⁺) and/or Lewis basic (O²⁻) sites on the support for the reaction to take place at a reasonable rate.

Table 1. Screening of different CuNPs-based catalysts^a

Entry	Catalyst	Conversion (%) ^b
1	CuNPs/ZnO	86
		83 ^c
		69 ^d
2	CuNPs/CeO ₂	52
3	CuNPs/PVP	42
4	CuNPs/cellulose	28
5	CuNPs/Celite®	14
6	CuNPs/MWNT	40
7	CuNPs/MCM-41	38
8	CuCl ₂ /ZnO	83 ^e
9	CuCl/ZnO	39 ^e

^aReaction conditions: phenylacetylene (1 mmol), diethyl phosphite (2 mmol), catalyst (40 mg, 1.7 mol % Cu), in acetonitrile (2 mL) at 70 °C under air atmosphere, 6 h. ^bDetermined by GC using an internal standard. ^cReaction performed using 60 mg of catalyst. ^dReaction performed using 20 mg of catalyst. ^eConversion obtained at 24 h of reaction time.

The optimal amount of catalyst was found to be 40 mg (see Table 1, footnotes c and d), giving a copper loading of 1.7 mol% referred to the starting alkyne. Interestingly, we found that when using CuCl₂ as copper source, a similar conversion to the β -ketophosphonate product was obtained, although in a significantly longer reaction time (Table 1, entry 8). On the contrary, the use of CuCl/ZnO as catalyst demonstrated to be less effective (Table 1, entry 9).

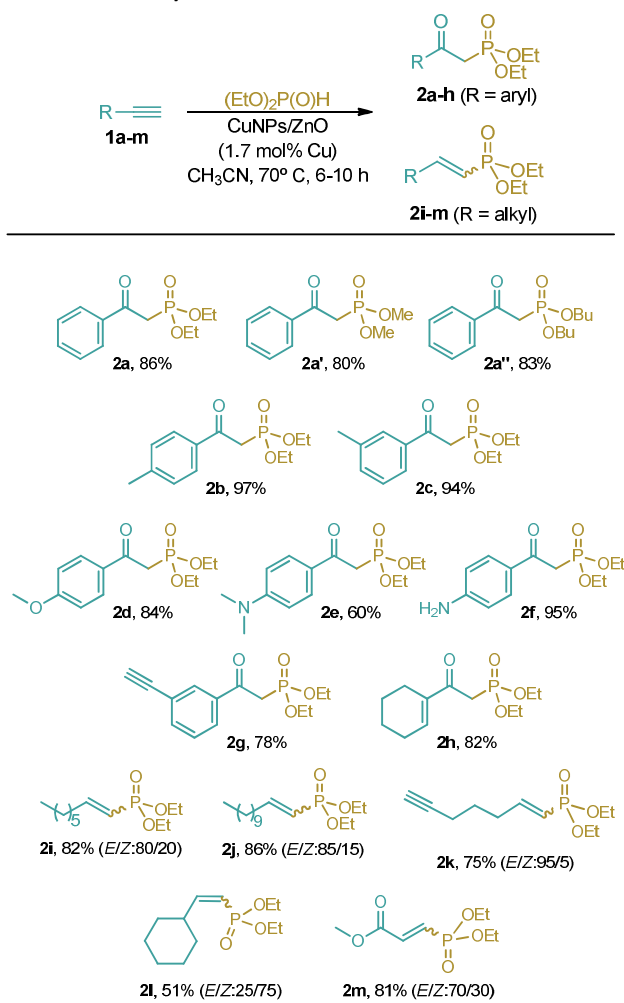
Control experiments carried out, both in the absence of the CuNPs/ZnO catalyst or in the presence of the support or the CuNPs alone, gave no conversion of the starting phenylacetylene to the desired product.

Then, the effect of the solvent, added bases and reaction atmosphere was studied. Among the different solvents tested acetonitrile demonstrated to be the solvent of choice. Other solvents such as methanol, dimethyl sulfoxide, dichloromethane, toluene, acetone and tetrahydrofuran gave almost no conversion of the starting material, whereas a 15% conversion to the alkyne homocoupling product was observed when water was used as the reaction medium. The reaction carried out under N₂ atmosphere gave low conversion to the desired product **2a** (near 15%). The addition of a base (Cs₂CO₃, Na₂CO₃, TMEDA or triethylamine) proved counterproductive for the reaction, giving no conversion of the starting alkyne after 24 h of reaction time.

Another interesting observation was that the suspension of the catalyst in the solvent was kept for those cases in which no conversion was measured. On the contrary, for those reactions which progressed to the desired products, the catalyst was completely dissolved in the reaction media, forming a single clear phase.

Under the optimized conditions, a series of aromatic and aliphatic terminal alkynes were then tested. As can be seen in Table 2, terminal aryl acetylenes gave the corresponding β -ketophosphonates **2a-h** as the major reaction products in good to excellent yields. Other dialkyl phosphites such as dimethyl- or dibutyl phosphite, were also suitable phosphorylating agents (Table 2, compounds **2a'** and **2a''**). Interestingly, 1-ethynylcyclohex-1-ene gave the corresponding β -ketophosphonate in good yield (Table 2, compound **2h**), thus suggesting that the presence of a conjugated C=C in the starting alkyne is mandatory for the formation of the β -ketophosphonate products.

Table 2. Synthesis of β -ketophosphonates and vinyl phosphonates from terminal alkynes^{a,b}



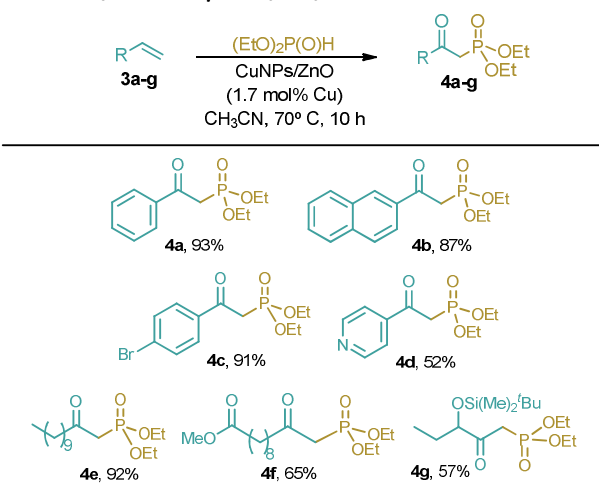
^aIsolated yield after chromatographic purification (Hexane/AcOEt).

^bE/Z isomeric ratio determined by GC/MS.

When aliphatic alkynes were subjected to the same reaction conditions, the anti-Markovnikov vinyl phosphonates **2i-m** (Table 2) were formed as the main reaction products, together with minor amounts of the corresponding β -ketophosphonates. In all cases, an inseparable mixture of E/Z isomers was obtained. It must be pointed out that alkyne **1m**, which is not aliphatic but conjugated with a C=O, gave the corresponding vinylphosphonate **2m** as the main reaction product, whereas, as above mentioned, alkyne **1h** which is conjugated with a C=C bond gave the corresponding β -ketophosphonate product (**2h**). This selectivity dependent on the alkyne nature has not been observed in previously reported copper-catalysed oxyphosphorylation of alkynes, and represents a very important feature of this CuNPs/ZnO catalyst. On the other hand, when internal alkynes were tested, both diaryl- and dialkyl alkynes, as well as aryl alkyl ones, low conversions to a complex mixture of products were obtained.

Then, we decided to test the reaction of alkenes with diethyl phosphite under the same optimized reaction conditions. We observed that only terminal alkenes were converted to the corresponding β -ketophosphonates (Table 3). It is worthy of note that the CuNPs/ZnO catalyst demonstrated not to be compatible with the presence of hydroxyl or carboxylic acid groups in the starting alkyne or alkene. These functional groups could form strong hydrogen-bonds with the Lewis basic sites at the catalyst support, thus preventing its participation in the reaction pathway. All of the above experimental observations would suggest that the ZnO support could be playing a non-innocent role in the catalytic system, probably through the P-H bond activation.²¹

Table 3. Synthesis of β -ketophosphonates from alkenes



^aIsolated yield after chromatographic purification (Hexane/AcOEt).

We conducted a series of additional experiments in order to get some information about the reaction mechanism involved in each of the transformations studied. Initially, based on our experimental observations and previous reports, we studied the effect of the addition of TEMPO as radical scavenger. Under the optimized conditions, the presence of TEMPO

inhibited the formation of β -ketophosphonates, both starting from phenylacetylene (**1a**) or styrene (**3a**), suggesting a radical pathway for the mechanism of these reactions. On the contrary, the transformation of 1-octyne into the corresponding vinyl phosphonate **2i**, was not affected by the addition of TEMPO to the reaction mixture. On the other hand, the reaction of 1-octyne under the optimized conditions but carried out under N_2 atmosphere, gave the vinyl phosphonate product **2i** with almost the same conversion and in a similar reaction time to that of the same reaction conducted under air. As above mentioned, the synthesis of β -ketophosphonate **2a** from phenylacetylene failed when it was carried out in the absence of air. The use of an O_2 atmosphere, both for the reaction of 1-octyne and phenylacetylene, proved counterproductive.²²

With the aim to get information on the oxidation state of copper in the catalyst, XPS analyses were performed, unfortunately the XPS spectra obtained were not conclusive, mainly due to a low signal-to-noise ratio that could be attributed to the low concentration of copper in the catalyst. Despite this, based on our previous works²⁰ and the results showed in Table 1 (entries 8 and 9), we assume that copper(II) is most likely to be the active species in the catalyst.

Although the exact mechanism involved in the transformations studied is not clear enough at this stage, based on our experimental observations and previous reports by other authors,^{12,13} we suppose that a radical oxyphosphorylation process is more likely to occur in the synthesis of β -ketophosphonates. As shown in Fig. 2, Cu(II) species in combination with ZnO would be promoting the formation of

the phosphorus radical **III** (Figure 2). Addition of this radical intermediate to the $C\equiv C$ or $C=C$ bond, and subsequent reaction with an active-oxygen copper complex, formed by reaction of CuNPs with dioxygen present in air, would lead to reactive hydroperoxide intermediates.^{12,13} Finally, these reactive intermediates would evolve to the corresponding β -ketophosphonate products, through a keto-enol tautomerism in the case of alkynes, and by elimination of water in the case of alkenes.

On the other hand, the observed formation of vinyl phosphonates from aliphatic alkynes, which was not inhibited by the presence of TEMPO (and also works in the absence of air), should be occurring through a non-radical process, probably due to the lower stability of the corresponding vinyl radical intermediate. Instead, a copper-catalysed anti-Markovnikov hydrophosphorylation of the aliphatic alkyne leading to the corresponding vinyl phosphonates, could take place. It is noteworthy that most of the reported methods for the metal-catalysed hydrophosphorylation of alkynes are based on the use of expensive and/or toxic palladium, nickel or rhodium catalysts,^{17c-e} whereas copper-based ones have remained almost unexplored to date.²³ With the aim to confirm this hypothesis, we carried out the reaction by using 1-deuterio-oct-1-yne as starting alkyne. As expected, the corresponding deuterated-vinyl phosphonate product was obtained, thus showing that, in the case of aliphatic alkynes, copper acetylides would not be formed under the reaction conditions and the reaction is more likely to occur via a copper-catalysed hydrophosphorylation process.

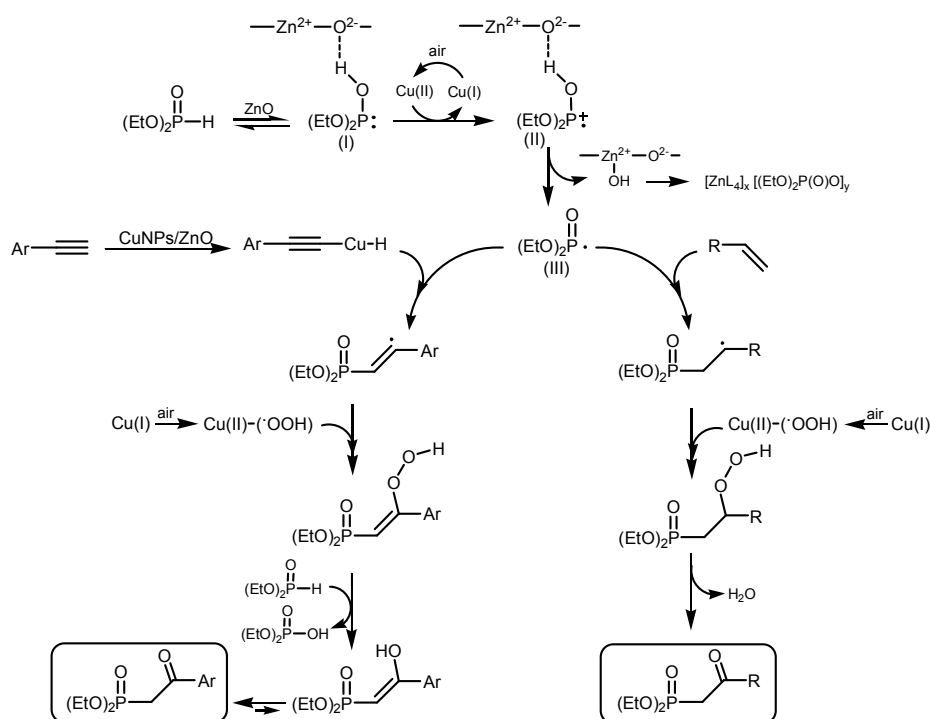


Figure 2. Proposed mechanistic pathway for the synthesis of β -ketophosphonates from aromatic alkynes and alkenes catalysed by CuNPs/ZnO.

Conclusions

In conclusion, we have developed a new mild, simple and economical methodology for the direct synthesis of β -ketophosphonates and vinyl phosphonates from commercial or readily available starting materials, catalysed by CuNPs/ZnO. The catalyst showed to be very efficient working under air atmosphere and in the absence of any additive or ligand. Alternative copper sources such as CuCl₂ in combination with ZnO, can also be utilized, however longer reaction times are needed. Although the exact mechanistic pathway is difficult to ascertain at this stage, based on our experimental observations, we propose that a copper-catalysed radical oxyphosphorylation mechanism would be involved in the formation of β -ketophosphonates, whereas a non-radical copper-catalysed hydrophosphorylation process would be more likely to occur in the formation of vinyl phosphonates. Furthermore, it should not be ruled out a bifunctional mode of action by the CuNPs/ZnO catalyst, where the CuNPs could be activating the C-H and/or the C \equiv C bond of the starting alkyne and the ZnO activating the diethyl phosphite P-H bond. Further mechanistic details and other useful synthetic applications of this catalytic system are now under study. The simplicity and high atom economy of this new methodology will surely be of wide interest among synthetic organic chemists.

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Direct synthesis of β -ketophosphonates and vinyl phosphonates from alkenes or alkynes catalyzed by CuNPs/ZnO.

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