Synthesis of vinyl phosphonates from aliphatic alkynes catalyzed by CuNPs/ZnO. A DFT study of the reaction mechanism, effect of the catalyst and solvent.

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Abstract

Copper nanoparticles (CuNPs) supported on ZnO have shown to effectively catalyze the direct synthesis of vinyl phosphonates from aliphatic alkynes and diethylphosphite in MeCN as solvent, under air and in the absence of any additive or ligand. A copper-catalyzed anti-Markovnikov hydrophosphorylation process, that implies an active role of CuNPs/ZnO and acetonitrile at different stages of the reaction, is proposed as a plausible reaction mechanism based on the experimental and DFT studies.

Keywords: DFT methods, phosphorus nucleophiles, vinyl phosphonates, CuNPs/ZnO

Introduction

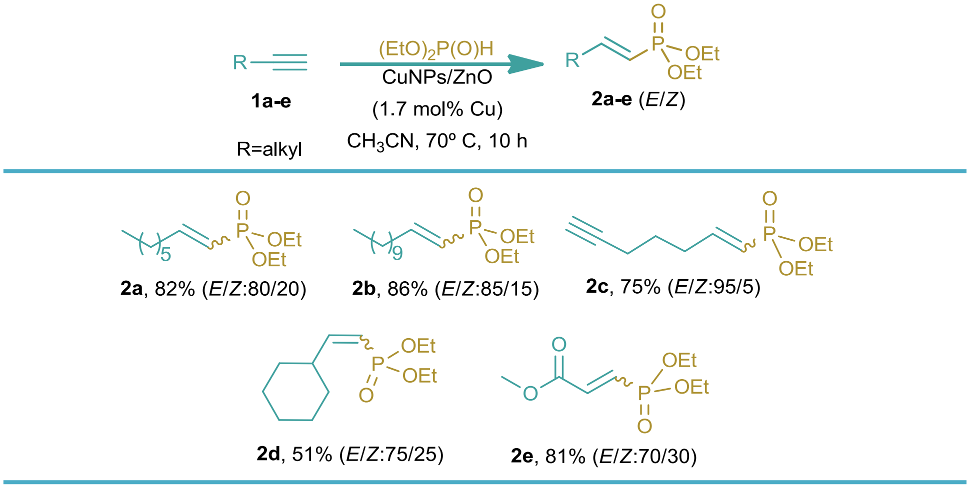
Vinyl phosphonates are well-known constituents of the family of phosphorus containing organic compounds. They are of extensive importance in synthetic organic chemistry both as intermediates and as final products,[1] and have different applications as monomers and co-monomers in polymeric materials.[2] At present, main methods for the synthesis of vinyl phosphonates are based on expensive and/or toxic Pd,[3] Cu[4] or Ni[5] catalysts, most of them requiring the use of phosphine ligands and/or severe reaction conditions. 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.[6] In a recent publication,[7] we informed the direct synthesis of vinyl phosphonates catalyzed by CuNPs supported on ZnO starting from aliphatic alkynes and commercial diethyl phosphite. The reactions were carried out in acetonitrile as solvent, under air, in the absence of any additive or ligand, and under mild reaction conditions. Notably, the use of ZnO as support and MeCN as solvent was mandatory for the reaction to take place. On the other hand, there are few papers in the scientific literature about DFT computational studies of the mechanism of the hydrophosphorylation of alkynes. In this regard, Beletskaya *et al.*[8a] have investigated the Markovnikov-type regioselective hydrophosphorylation of terminal alkynes employing a nickel catalyst and phosphine ligands in THF. More recently, Zhao and coworkers[8b] reported a very interesting study about the reaction mechanism of copper-catalyzed (CuI) phosphorylation of terminal alkynes in the presence of a base (NEt_3) and in DMSO as the solvent.

Prompted by our continuing interest in the use of computational methods for the exploration of organic reaction mechanisms,[9] we carried out a series of experiments and conducted a theoretical study with DFT methods in order to get information about the mechanism involved in the CuNPs/ZnO-catalyzed hydrophosphorylation of alkynes .

Results and discussion

The reaction between aliphatic alkynes and $(EtO)_2P(O)H$ was tested in the presence of CuNPs supported on a variety of organic and inorganic materials (ZnO, CeO_2, PVP, cellulose, Celite, MWNT, MCM-41) using acetonitrile as the solvent, under N_2 atmosphere and in the absence of any additive or ligand. All these CuNPs-based catalysts were prepared according to the methodology previously reported by us,[6] the CuNPs (3–6 nm in size) being synthesized by fast reduction of anhydrous $CuCl_2$ with an excess of lithium sand and a catalytic amount of DTBB (4,4'-di-tert-butylbiphenyl) as electron carrier. The best results were obtained by working at 70°C and using ZnO as support. The lower conversions obtained when using any of the other supports tested, could suggest the necessity for the presence of Lewis acid (Zn^{2+}) and/or Lewis basic (O^{2-}) sites on the support for the reaction to take place at a reasonable rate. The optimal amount of catalyst was found to be 40 mg giving a copper loading of 1.7 mol% referred to the starting alkyne. 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 alkyne to the desired product. Then, the effect of the solvent and added bases 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, tetrahydrofuran and water gave almost no conversion of the starting material. The addition of a base (Cs_2CO_3, Na_2CO_3, TMDA or triethylamine) proved counterproductive for the reaction, giving no conversion of the starting alkyne. 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.

Table 1. Synthesis of vinyl phosphonates from aliphatic alkynes[a,b]



[a]Isolated product yield after chromatographic purification. [b]*E*/*Z* isomeric ratio determined by GC/MS.

As shown in Table 1, under the optimized reaction conditions, the anti-Markovnikov vinyl phosphonates **2a–e** 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 **1e**, which is not aliphatic but conjugated with a C=O, gave the corresponding vinyl phosphonate **2e** as the main reaction product, whereas, 1-ethynylcyclohex-1-ene, which is conjugated with a C=C bond gave the corresponding β-ketophosphonate product (82%). This selectivity dependent on the alkyne nature has not been observed in previously reported copper-catalysed phosphorylation of alkynes, and represents a very important feature of this CuNPs/ZnO catalyst. On the other hand, when internal alkynes were tested, low conversions to a complex mixture of products were obtained.

We conducted a series of additional experiments in order to get some information about the mechanism involved. 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 did not inhibit the transformation of 1-octyne into the corresponding vinyl phosphonate **2a**. Therefore, the reaction should take place through a non-radical process under the optimized conditions. On the other hand, the reaction of 1-octyne with diethylphosphite carried out under N_2 atmosphere, gave the vinyl phosphonate product **2a** with almost the same conversion and in a similar reaction time to that of the same reaction conducted under air. When the reaction was conducted under O_2 atmosphere, after 8 h of reaction time, a very low conversion to octanoic acid as the only organic product was observed, together with a large amount of diethylphosphate, produced by oxidation of diethylphosphite. Additionally, the reaction carried out by using 1-deuterio-oct-1-yne as starting alkyne, led to the corresponding deuterated-vinyl phosphonate product, thus suggesting that copper acetylide species would not be formed under the reaction conditions. Although the exact mechanism involved in the transformation studied is not clear enough at this stage, based on our experimental observations and previous reports by other authors, we suppose that the reaction is more likely to occur via a copper-catalyzed *anti*-Markovnikov hydrophosphorylation process (Figure 1), leading to the corresponding vinyl phosphonates through the addition of the $(EtO)_2(HO)P$: nucleophile **(I)** to the carbon-carbon triple bond. As it was mentioned above, we assume that ZnO could be playing a non-innocent role in the catalytic system, probably through the P-H bond activation. Finally, the protonated ZnO species would be responsible for the proton transfer to give the final product and the Cu/ZnO catalyst to restart the catalytic cycle.

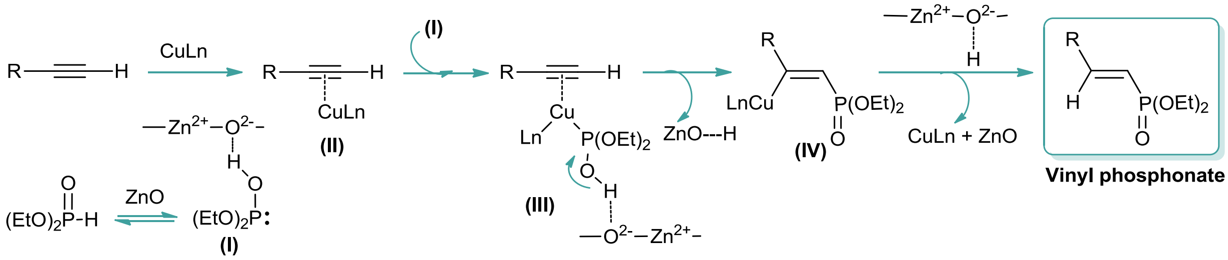


Figure 1. Proposed mechanistic pathway for the synthesis of vinyl phosphonates from aliphatic alkynes catalysed by CuNPs/ZnO.

With the aim to explain these experimental results and find a close understanding of the reaction mechanism, we performed a computational analysis with the Gaussian09[10] software package. For this purpose, we simplified the reactive system and theoretically studied the process by using the alkyne **1d** and the dimethoxy analog of $(EtO)_2P(O)H$ as model compounds. The density functional theory (DFT)[11] calculations were performed with the B3LYP[12] functional, which is known to be an appropriate methodology for the mechanistic studies on Cu-catalyzed reactions,[8b] and the 6-31+G* basis set. The energies in solution were obtained with the Tomasi's polarized continuum model (PCM)[13] as implemented in Gaussian09.

As we assume that the reaction could start when the alkyne is activated by the copper catalyst, it was necessary to establish which were the ligands and how these ligands were attached to the metal surface in order to act as stabilizers. The computational modelling showed that ZnO may occurs as a dimer with an exothermicity of 93.9 kcal/mol and that copper would be attached to this ZnO dimer through the oxygen atoms, giving rise to the initial Cu-ZnO complex (-36.0 kcal/mol). As shown in Figure 2, this Cu-ZnO complex, in the presence of the acetonitrile solvent acting as ligand, would render the active copper catalyst. Our results indicate that the formation of the $CuZnO(MeCN)_2$ catalyst takes place exothermically (-51.4 kcal/mol). When the catalyst was modelled using DMSO as ligand, the process showed to be highly endothermic (40.5 kcal/mol). This theoretical result is in agreement with the experimental results, since no conversion of the starting alkyne was observed when DMSO was used as the reaction solvent.

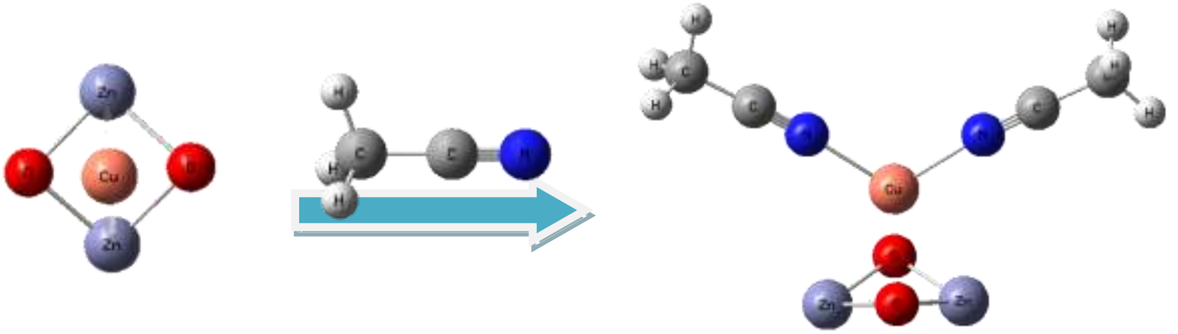


Figure 2. Proposed structures of the support (ZnO-ZnO) and the active copper catalyst $[CuZnO(MeCN)_2]$

In the first stage, the reaction mechanism would involve the formation of alkynyl copper complex **II** (Figure 3) with an exothermicity of 49.1 kcal/mol, through a π-coordination between the alkyne and the copper catalyst.

It is known that H-phosphonate species may exist in two tautomeric forms being the P=O form more stable (6 kcal/mol) than the P-OH one. Despite this, as shown in Figure 3, phosphorus compound **(I)**, would be the active phosphorylating agent, which through a nucleophilic attack over **II**, would led to the intermediate **III** (-14.0 kcal/mol), the driving force for the tautomerization process being the formation of P-Cu bond (2.3 Å).

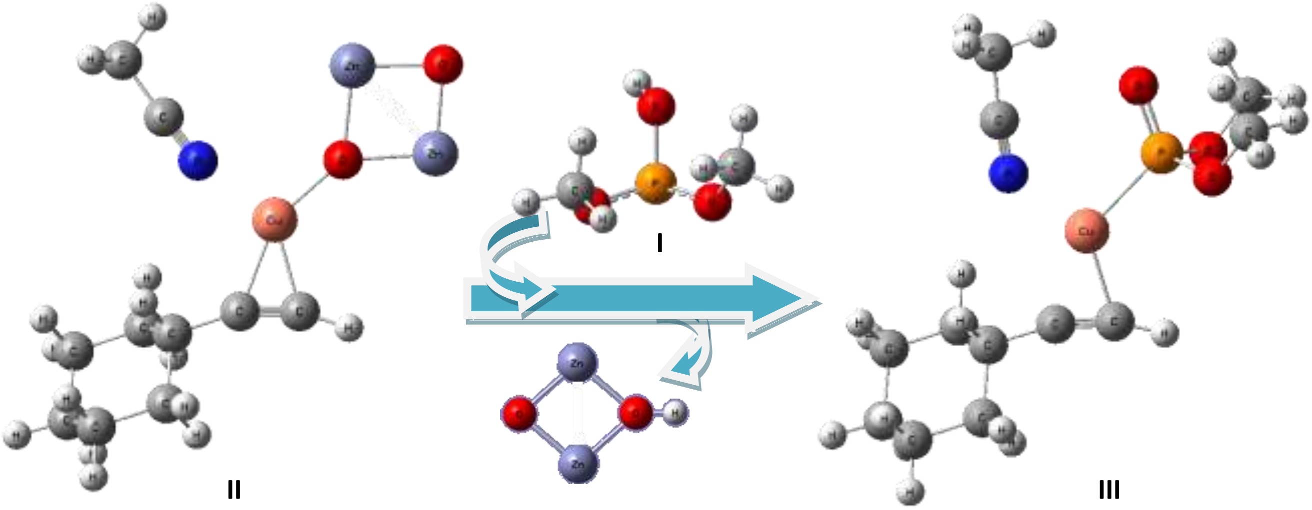


Figure 3. Nucleophilic attack from the active phosphorylating agent **I**

In a subsequent step, the P-C bond is formed leading to the five members cyclic intermediate **IV** (-20.3 kcal/mol), which shows a strong coordination between copper and the oxygen atom of P=O group, with a O-Cu distance of 2.5 Å (showed as a red dotted line in Figure 4). The next step involves the proton transfer from the protonated ZnO, through a strong interaction between zinc and the oxygen atom of the P=O group, originating the intermediate **V** with an exothermicity of 37.6 kcal/mol.

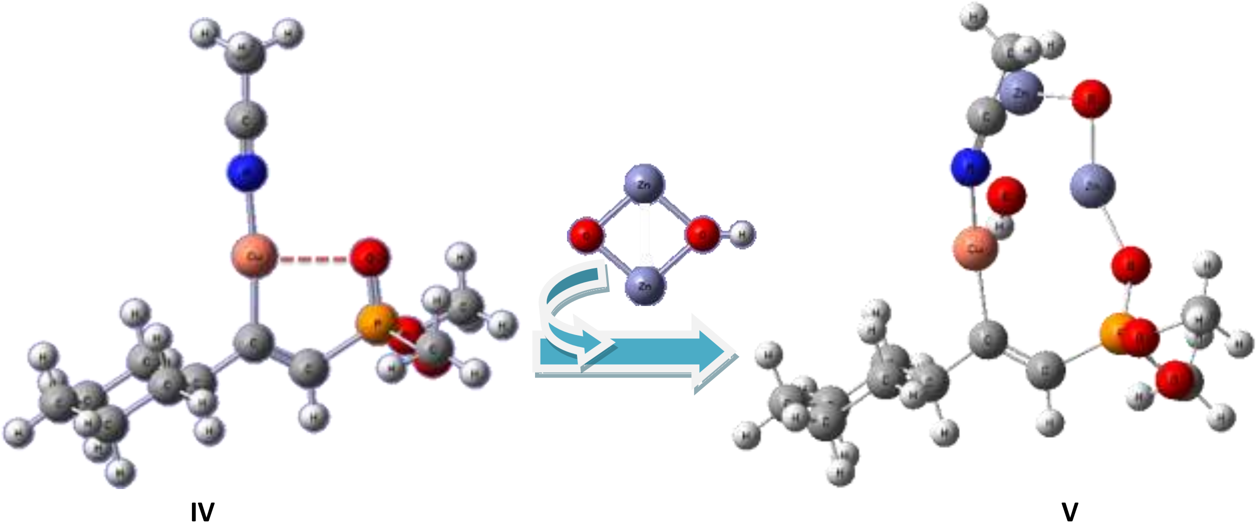
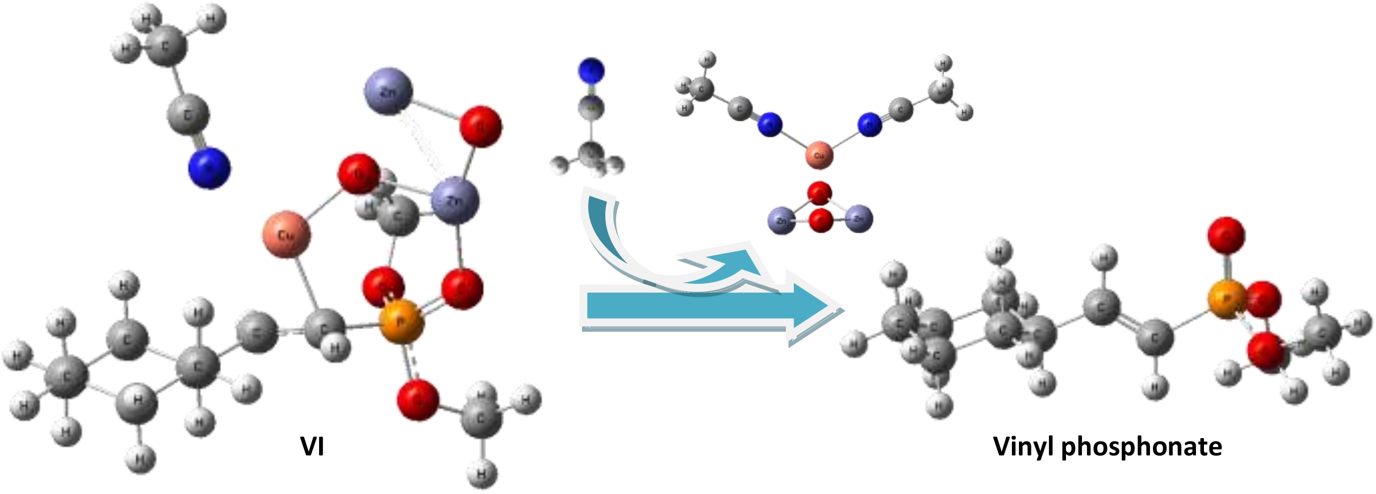


Figure 4. Proton transfer from protonated ZnO

The formation of intermediate **VI** (Figure 5) requires 9.0 kcal/mol, being the most energy-demanding reaction step. Finally, a ligand exchange process would led to the vinyl phosphonate product regenerating the active copper catalyst.



VI

Vinyl phosphonate

Figure 5. Ligand exchange to give the vinyl phosphonate product and regenerate the copper catalyst

Conclusions

In conclusion, we have developed a new mild, simple and economical methodology for the direct synthesis of vinyl phosphonates from commercial or readily available starting materials, catalyzed by CuNPs/ZnO. The catalyst showed to be very efficient working under air atmosphere and in the absence of any additive or ligand. Although the exact mechanistic pathway is difficult to ascertain, based on the experimental data and the results of our DFT studies, we have proposed a plausible reaction mechanism that implies a crucial role of both acetonitrile (as ligand) and ZnO (activating the P-H bond and acting as a proton transfer agent in different steps of the reaction). DFT results showed a strong coordination between both metals (Cu and Zn) and the oxygen atom of P=O group, thus suggesting that the participation of stable cyclic structures as intermediates would be very likely to occur in the CuNPs/ZnO-catalyzed hydrophosphorylation of aliphatic alkynes. Further mechanistic details are now under study.

Computational procedure

The calculations were performed with Gaussian09. The initial conformational analysis of compounds was performed with the semiempirical PM6 method. The geometry of the most stable conformers thus obtained was used as starting point for the B3LYP studies with the 6-31+G* basis set. The characterization of all stationary points was done by Hessian matrix calculations of geometries obtained with full optimization for a minimum. The zero point energy corrections were made for the thermodynamic quantities. The energies in solution were obtained with full geometry optimization within the Tomasi's polarized continuum model (PCM) as implemented in Gaussian09. The figures were built with the GaussView program.

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