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Organophosphorus Chemistry: Synthesis of New Phosphonic Acid Derivatives Bearing a Triazole Moiety †

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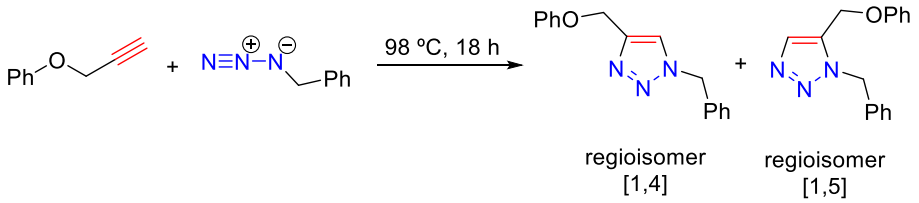
Abstract: a series of new 1,2,3-triazolylphosphonate were synthesized through the multicomponent alkyne-azide 1,3-dipolar cycloaddition catalyzed by copper nanoparticles on activated carbon. The reactions were carried out in water and at a very low copper loading as green conditions, leading to the triazolylphosphonate products in moderate to good yields. Studies about their activity as butyrylcholinesterase inhibitors are underway.

Keywords: phosphonates; triazole; copper nanoparticles

1. Introduction

Nitrogen-based heterocycles and their analogs are well stablished as valuable sources of therapeutic agents in medicinal chemistry [1]. Among them, the 1,2,3-triazole ring is a privileged building block due to the extensive biological activities shown by 1,2,3-triazole hybrids [2]. The reaction between an azide and alkyne to afford 1,2,3-triazole, known as Huisgen's 1,3-cycloaddition, is considered as a revolutionary work in the field of azole chemistry (Scheme 1) [3]. This methodology was improved years later by Sharpless, who have been recently awarded with his second Nobel Prize for introducing the term "Click Chemistry" to describe and develop reactions that are high yielding, wide in scope, create byproducts that can be easily removed without using chromatography, are stereospecific, simple to perform, and can be conducted in easily removable or benign solvents [4].



Scheme 1. First thermal 1,3-dipolar cycloaddition reaction reported by Huisgen.

On the other hand, phosphorus-containing molecules are of extensive interest in synthetic organic chemistry, due to the remarkable biological activities of many of these compounds. More precisely, phosphonic acids and esters are widely known as extremely important structural analogues to the corresponding carboxylic acids and esters [5]. In view of its pyramidal geometry, the phosphonic acid group can provide unique binding interactions with a biologic target, making use of its di- or trivalent chelating properties and potential dual function as a hydrogen acceptor and donor at physiological pH. In particular, phosphonates are well known as non-hydrolyzable analogs of biological phosphates [6].

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Organophosphorus compounds are also relevant as intermediates to access a variety of molecular targets, therefore, new synthetic methodologies for phosphorus derivatives are of huge interest. In continuation of our previous work, we present herein the synthesis of new 1,2,3-triazolylphosphonates, combining simple and efficient methodologies involving the use of supported metal nanoparticles catalysts developed in our research group [7].

2. Materials and Methods

2.1. Synthetic Procedures

Reagents employed were analytical grade. DCM (dichloromethane) was freshly distilled over CaH_2 and DMF (dimethylformamide) was distilled and stored under N_2 in presence of molecular sieves. Moisture-sensitive reactions were conducted under inert atmosphere of dry nitrogen using oven dried glassware. Reactions were monitored by analytical thin layer chromatography (TLC) performed on Merck silica gel 60 F254 plates and visualized under ultraviolet (UV) light. Purification of crude materials was performed by flash column chromatography on silica gel (200–400 mesh, Merck) using a mixture of hexane/EtOAc as eluent.

2.2. General Procedure for the Synthesis of β-Azidophosphonates

The synthesis of the β-azidophosphonates begins with the preparation of the corresponding β-ketophosphonates. The alkyne or alkene (1.0 mmol, 1 equiv) and the corresponding dialkylphosphite (1.3 mmol, 1.3 equiv) were added to a suspension of the CuNPs/ZnO catalyst (40 mg, 1.7 mol% Cu) in MeCN (2 mL) under air atmosphere. The reaction mixture was warmed to 70 °C and monitored by TLC until total conversion of the starting material. Water (5 mL) was added to the reaction mixture followed by extraction with EtOAc (3 × 10 mL). The collected organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give the corresponding β-ketophosphonate which were used without further purification in the subsequent reduction of the carbonyl group. For this, the β-ketophosphonate was dissolved in 5 mL of methanol, cooled to 0 °C and stirred overnight with an excess of $NaBH_4$ (3 equiv). The reaction mixture was evaporated in vacuo and water was added (5 mL), followed by extraction with EtOAc (3 × 10 mL). The organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give quantitatively the corresponding β-hydroxyphosphonate. Finally, the β-hydroxyphosphonate was placed in a dry round bottom flask under N_2 atmosphere and filled with 2 mL of dry DCM. The mixture was cooled in an ice bath at 0 °C and Et_3N (1.5 equiv) and mesyl chloride (2 equiv) were added. After 4 h of reaction time, the mixture was diluted with DCM (5 mL) and extracted with water (3 × 5 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give quantitatively the corresponding mesylate derivative. Lastly, NaN_3 (2 equiv) was added to the crude mixture dissolved in dry DMF (2 mL), and the reaction mixture is stirred overnight at room temperature. Once the reaction was completed (TLC), the mixture was poured into ice, and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to afford the corresponding β-azidophosphonate, that was used without further purification.

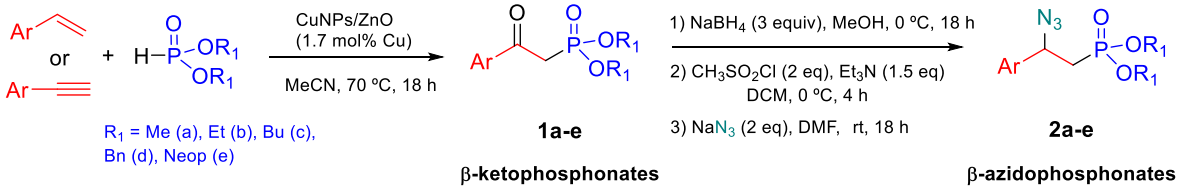
2.3. General Procedure for 1,3-Cycloaddition of β-Azidophosphonates with Alkynes Catalyzed by Copper Nanoparticles Supported on Activate Carbon (CuNPs/C) in Water*

The β-azidophosphonate (1 equiv), the alkyne (1.2 equiv) and CuNPs/C* catalyst (20 mg, 0.5 mol% Cu) were added to a round bottom flask and filled with 2 mL of H_2O. The reaction was heated to reflux overnight. Then, the mixture was extracted with EtOAc (2 × 10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered over celite to remove the catalyst, and the product purified by flash column chromatography.

3. Results and Discussion

3.1. Synthesis of β-Azidophosphonates

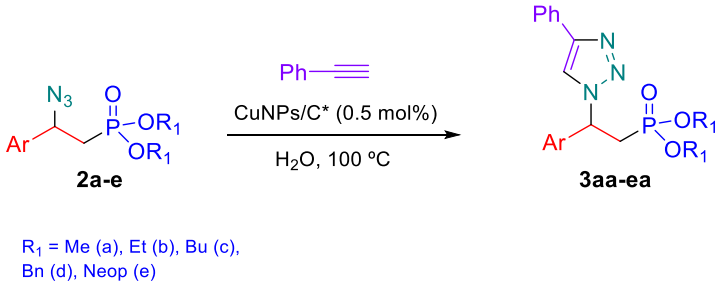
As described above in the Materials and Methods section, the corresponding β-azidophosphonates for their use in the 1,3-dipolar cycloaddition reactions, were synthesized by a multi-step methodology based on the use of β-ketophosphonates as starting materials, developed by our research group [7a]. Is worth mentioning that this methodology requires no purification of the intermediates, nor the final azide products (Scheme 2).



Scheme 2. Synthesis of β-azidophosphonates.

3.2. Synthesis of 1,2,3-Triazolylphophonates

With the β-azidophosphonates in hand, we found that CuNPs/C* efficiently promoted the 1,3-dipolar cycloaddition reaction between the corresponding azides and different terminal alkynes, using water as solvent, and heating to reflux overnight (Scheme 3).



Scheme 3. Synthesis of 1,2,3-triazolylphosphonates by 1,3-dipolar cycloaddition reaction.

Initially, as shown in Figure 1, alkyl (methyl, ethyl, butyl, benzyl and neopentylenyl) β-azidophosphonates and phenyl acetylene were used in the 1,3-dipolar cycloaddition reaction to afford the corresponding 1,2,3-triazolylphosphonates (**3aa**-**3ea**) in moderate to good yields.

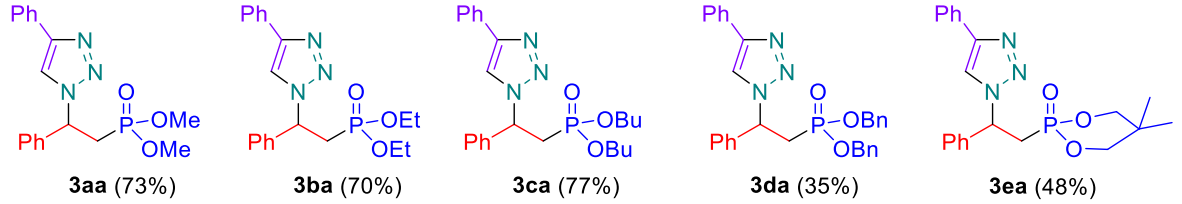


Figure 1. Synthesis of 1,2,3-triazolylphosphonates starting from different alkyl β-ketophosphonates and phenyl acetylene. Isolated yields after column chromatography in parenthesis.

Then, we studied the scope of the method by using different terminal alkynes but maintaining the dibutyl phosphonate moiety, since we observed that dibutyl phosphonyl derivatives were the most active as butyrylcholinesterase inhibitor among all of the 1,2,3-triazolylphosphonates, which is consistent with previous results observed by our group [8] (Figure 2).

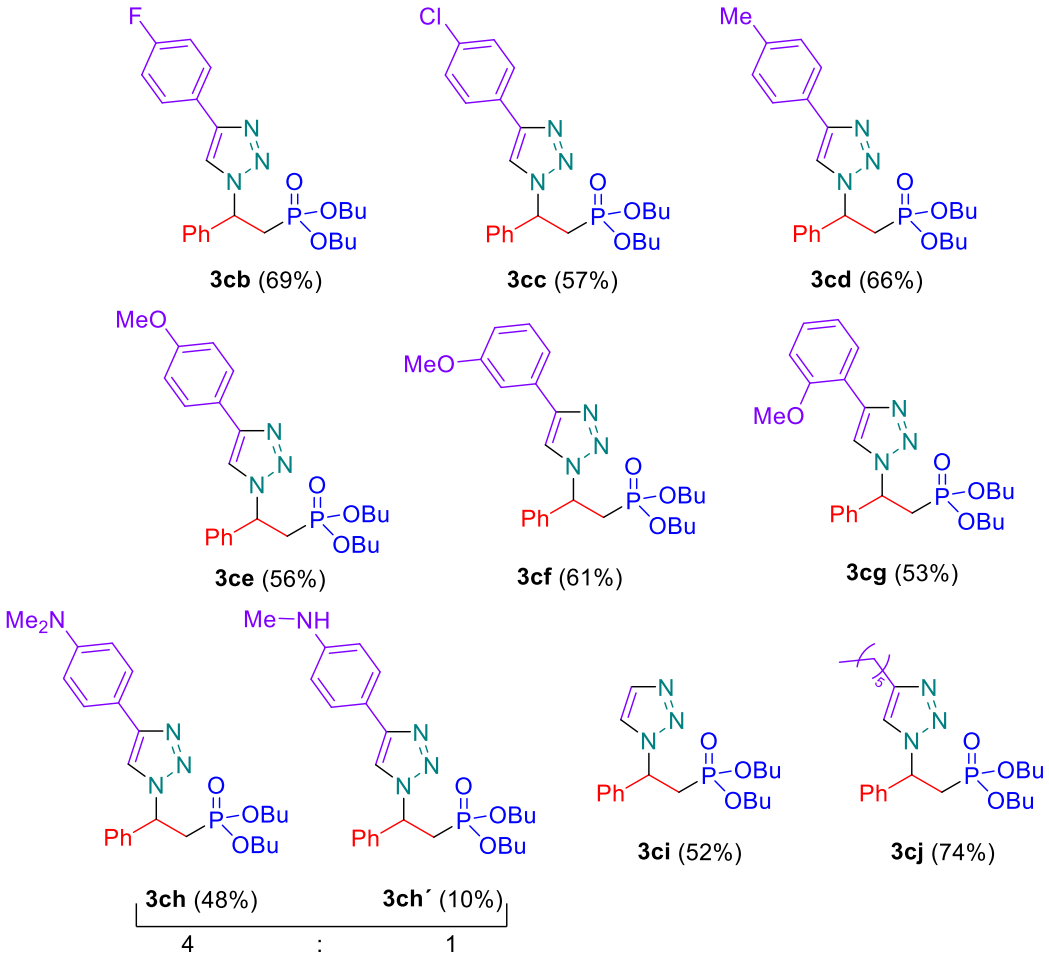


Figure 2. Scope of the cycloaddition reaction with dibutyl (2-azido-2-phenylethyl)phosphonate. Isolated yields after column chromatography in parenthesis.

As can be seen from the results in Figure 2, all the aromatic terminal alkynes used in the 1,3-dipolar cycloaddition with dibutyl (2-azido-2-phenylethyl)phosphonate, afforded the final products in good yields, irrespective of the electronic nature of the substituent attached to the aromatic ring. The use of electron-poor terminal alkynes such as (4-fluorophenyl)acetylene and (4-chlorophenyl)acetylene, led to the corresponding 1,2,3-triazolylphosphonates **3cb** and **3cc** in 69 and 57% isolated yield, respectively. The reaction of dibutyl β-azidophosphonate **2c** with the electron-rich terminal alkyne (4-methylphenyl)acetylene, afforded the dibutyl (2-phenyl-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)ethyl)phosphonate **3cd** in a 66% isolated yield. On the other hand, the success of the 1,3-dipolar cycloaddition was barely affected by the position of the substituent at the aromatic ring of the arylacetylene, as (4-methoxyphenyl)acetylene, (3-methoxyphenyl)acetylene and (2-methoxyphenyl)acetylene afforded the corresponding 1,2,3-triazolylphosphonates **3ce**, **3cf** and, **3cg** in 56, 61, and 53% isolated yield, respectively. It is worth noting that when 4-ethynyl-N,N-dimethylaniline was used as starting alkyne in the reaction with dibutyl β-azidophosphonate **2c**, the corresponding dibutyl (2-(4-(4-(dimethylamino)phenyl)-1H-1,2,3-triazol-1-yl)-2-phenylethyl)phosphonate **3ch** was obtained (48% isolated yield), along with the N-demethylated product (**3ch'**, 10% isolated yield), which is consistent with a similar oxidative demethylation process reported by us in a previous work regarding the N-acylation of N,N-dimethylamines catalyzed by copper nanoparticles [9]. The scope was also extended to non-aromatic terminal alkynes such as ethynyltrimethylsilane and 1-octyne, in both cases affording the corresponding 1,2,3-triazolylphosphonates **3ci** and **3cj** in 52 and 74% isolated yield,

respectively. Is worth mentioning that phosphonate **3ci** was obtained as the only reaction product after complete desilylation of the trimethylsilyl group under the reaction conditions.

In future work, the scope is planned to be extended to different dibutyl β-azidophosphonates, obtained from a variety of starting aryl acetylenes and/or styrenes, in the 1,3-dipolar cycloaddition reaction with phenylacetylene. These compounds will be evaluated as butyrylcholinesterase inhibitors and structure activity relationship (SAR) will be studied and considered for further structural modifications.

4. Conclusions

We have successfully synthesized a new series of potentially bioactive 1,2,3-triazolylphosphonate derivatives through simple and straightforward methodologies developed in our group, involving the use of copper nanoparticles as catalysts. The 1,3-dipolar cycloaddition reaction between different β-azidophosphonates and terminal alkynes was carried out in the presence of copper nanoparticles supported on activated carbon (CuNPs/C*) with good isolated yields. Further studies regarding their bioactivity as butyrylcholinesterase inhibitors are underway.

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Conflicts of Interest: The authors declare no conflict of interest.

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