

Proceeding Paper

Innovative Approaches in Acyl Sonogashira Coupling: Impact of Supported CuNPs and Cu-PdNPs Nanocatalysts [†]

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Abstract: In this work, we present our findings on the acyl Sonogashira coupling catalyzed by copper nanoparticles (CuNPs) or bimetallic copper–palladium (4:1 molar ratio) nanoparticles (Cu-PdNPs) immobilized in various inorganic materials. Both catalysts allowed the synthesis of ynones in good to excellent yields. Cu-PdNPs supported on Celite exhibit high activity, allowing reactions to proceed at room temperature, whereas the monometallic CuNPs catalysts required reactions to be carried out at 80 °C. In addition, Cu-PdNPs/Celite can be also used in Sonogashira coupling reactions with iodoarenes. Both types of catalysts can be reused without any pre-treatment after separation from the reaction medium and subsequent washing.

Keywords: acyl Sonogashira coupling; nanocatalyst; nanoparticles; copper; palladium

1. Introduction

Conjugated ynones, in particular α,β -acetylenic ketones, are of great interest due to their wide range of applications in natural products and in organic synthesis. They are versatile intermediates for the preparation of heterocyclic derivatives such as pyrroles, furans, pyrazoles, isoxazoles and others [1].

There are several methodologies for obtaining ynones (Scheme 1). Carbonilative Sonogashira coupling generally requires high CO pressure and is often performed in the absence of CuI [2]. Since the development of the carbonylative Heck reaction, several catalysts and methods have been developed for this reaction [3]. Recently, the catalytic coupling of acyl chlorides and terminal alkynes to give ynones, known as the acyl Sonogashira reaction, has received considerable attention. Typically, this transformation is conducted under conventional conditions for the Sonogashira coupling involving Pd(PPh₃)₂Cl₂, CuI, and TEA [4,5]. Nevertheless, heterogeneous palladium or copper catalysts have also demonstrated to be efficient in this coupling reaction [2]. In particular, and from a green perspective, there has been a great interest in using metallic nanoparticles as catalysts due to their high activity and selectivity, and the possibility to recover and reuse the catalyst. In this sense, our research group possesses extensive experience in the preparation of metallic nanocatalysts and their application in various chemical transformations, including cycloaddition reactions, C-C and C-Het. bond forming reactions, reduction and oxidation of different functionalities, among others [6,7].

Here we present our findings on the acyl Sonogashira coupling catalyzed by CuNPs or bimetallic Cu-PdNPs (4:1 molar ratio) immobilized in various inorganic materials.



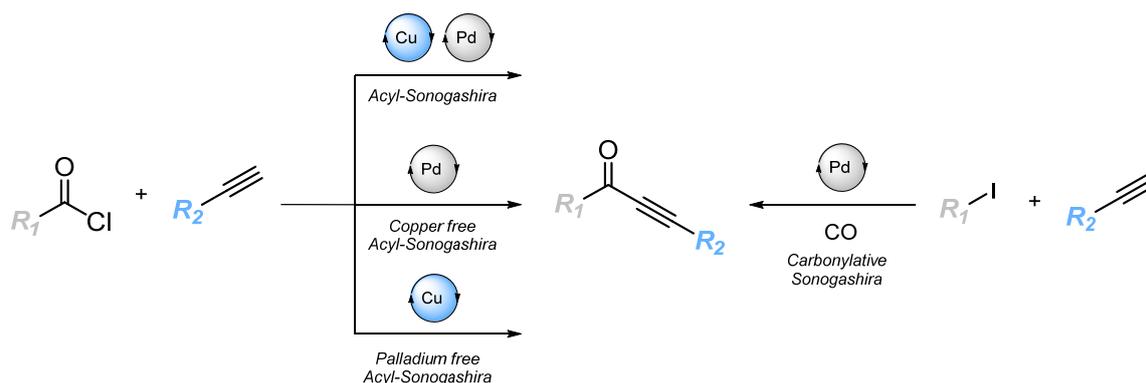
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Scheme 1. Methods of obtention of ynones through modified Sonogashira reactions.

2. Experimental Procedures

2.1. General Methods

All starting materials were sourced from the highest quality grade from Sigma-Aldrich (St. Louis, MO, USA), Merck (Darmstadt, Germany), Alfa Aesar (Haverhill, MA, USA), and were utilized without additional purification. Reactions sensitive to moisture were conducted under a nitrogen atmosphere. THF was freshly distilled from sodium benzophenone ketyl. Anhydrous copper(II) chloride was prepared from the corresponding dihydrate by heating in an oven (150 °C, 45 min) before being employed in the synthesis of the CuNPs. Reactions were monitored by thin-layer chromatography (TLC) carried on TLC aluminum sheets with silica gel 60 F254 (Merck, Darmstadt, Germany) and visualized under UV light and/or staining with phosphomolybdic acid, vanillin, or ferric trichloride solutions. Column chromatography was performed using silica gel 60 (0.040–0.063 μm , 240–400 mesh, Merck) and hexane/ethyl acetate (EtOAc) mixtures as eluents. Mass spectra (EI) were acquired at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with an HP-5972 selective mass detector, or on an Agilent Model 1100 Series High-Performance Liquid Chromatograph simultaneously coupled to a UV-visible variable wavelength detector and an ion trap analyzer mass spectrometer (Agilent Model 1100 Series LC/MSD Trap SL).

2.2. Preparation of Catalysts

2.2.1. Preparation of CuNPs Catalysts

4,4'-di-tert-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) was added to a suspension of lithium (21 mg, 3 mmol) in anhydrous THF (2 mL). Upon the formation of the radical-anion-reducing agent, evidenced by the appearance of a dark-green color, anhydrous copper chloride (135 mg, 1 mmol) was added. The suspension rapidly turned black, indicating the formation of copper nanoparticles. Subsequently, THF (8 mL) and the support (0.8 g) were added and the resulting mixture was stirred at room temperature for 4 h. Finally, the catalyst was filtered, washed with water (20 mL), ethanol (20 mL), and diethyl ether (20 mL), and then dried under vacuum.

2.2.2. Preparation of Cu-Pd Catalysts

4,4'-di-tert-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) was added to a suspension of lithium (28 mg, 4 mmol) in anhydrous THF (2 mL). Upon the formation of the radical-anion-reducing agent, indicated by the appearance of a dark-green color, anhydrous copper chloride (162 mg, 1.2 mmol) and palladium(II) chloride (177 mg, 0.3 mmol) were added. The suspension rapidly turned black, indicating the formation of bimetallic nanoparticles. Subsequently, THF (15 mL) and the support, Celite (HyFloSuper Cel[®], 1 g), were added and the resulting mixture was stirred at room temperature for 4 h. Finally, the catalyst was filtered, washed with water (20 mL), ethanol (20 mL), and diethyl ether (20 mL), and then dried under vacuum.

2.3. General Procedure for Acyl Sonogashira Reactions

Over a suspension of benzoyl chloride (1.5 eq.) and the catalyst, the corresponding alkyne (1 eq.) and triethylamine (3 eq.) were added and the reaction mixture was stirred at the specified temperature in a sealed tube purged with nitrogen. Upon completion, the reaction mixture was diluted with EtOAc (5 mL), and an aliquot was filtered and analyzed by GC-MS, using dodecane as internal standard.

For reactions involving other acyl chlorides, the corresponding carboxylic acid was treated with thionyl chloride at reflux for 1 h. The mixture was then concentrated under vacuum and subjected to the acyl Sonogashira reaction.

For studies on catalyst reuse, the crude reaction was centrifuged, and the catalyst was washed with H₂O, EtOAc, followed by drying under vacuum prior to reuse. In the case of CuNPs/MagSiO₂, the catalyst was retained in the reaction vessel using an external magnet.

2.4. General Procedure for Sonogashira Reactions

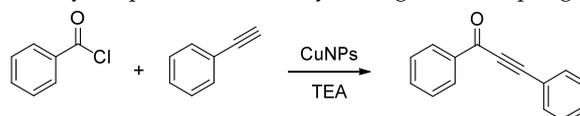
Over a suspension of iodobenzene (1 eq.) and the catalyst, the corresponding alkyne (1 or 1.2 eq.) and triethylamine (3 eq.) were added and the reaction mixture was stirred at 80 °C in a sealed tube purged with nitrogen. Upon completion, the reaction mixture was diluted with EtOAc (5 mL), and an aliquot was filtered and analyzed by GC-MS, using dodecane as internal standard.

3. Results and Discussion

3.1. CuNPs Catalyzed Acyl Sonogashira Coupling

Considering our special interest in developing palladium-free methodologies for the acyl Sonogashira reaction, we first evaluated a catalyst consisting of CuNPs supported on montmorillonite K-10 in the coupling between benzoyl chloride and phenylacetylene [8]. The optimization results are presented in Table 1.

Table 1. CuNPs/MK-10 catalyzed palladium-free acyl Sonogashira coupling ^a.



| Entry | CuNPs/MK-10 (mg) | T (°C) | T (h) | Yield% ^{b,c} |
|-------|------------------|--------|-------|-----------------------|
| 1 | 5 | 60 | 20 | 59 |
| 2 | 10 | 60 | 20 | 88 (100) |
| 3 | 20 | 60 | 20 | 71 |
| 4 | 10 | 20 | 20 | 42 (45) |
| 5 | 10 | 40 | 20 | 71 (82) |
| 6 | 10 | 60 | 4 | (81) |
| 7 | 10 | 60 | 8 | (92) |
| 8 | 10 | 80 | 4 | (100) |
| 9 | 10 ^d | 80 | 4 | (99) |

^a Reaction conditions: benzoyl chloride (1.5 eq.), alkyne (1 eq.), TEA (3 eq.) and the CuNPs/MK-10 catalyst (1.7 mol% Cu) were heated in a sealed tube. ^b n-dodecane was used as internal standard for the determination of reaction yields by GC-MS. ^c In parentheses, the reaction yields when performed under nitrogen atmosphere. ^d CuNPs/MagSilica was used as the catalyst (2.2 mol% Cu).

As can be seen from Table 1, a temperature of 80 °C is required for the reaction to occur in a short period of time, and a nitrogen atmosphere is also needed to achieve complete conversion of phenylacetylene. Considering the advantages of having a magnetically recoverable catalyst [9,10], we decided to apply the optimum conditions to the reaction catalyzed with CuNPs/MagSilica, and we observed that this catalyst is also suitable for efficiently carrying out this transformation. In addition, the catalyst can be retained in the reaction vessel employing an external magnet. After washing, it can be reused for several

cycles without any apparent loss of activity. In order to assess the scope of the method, various ynones were synthesized as shown in Figure 1.

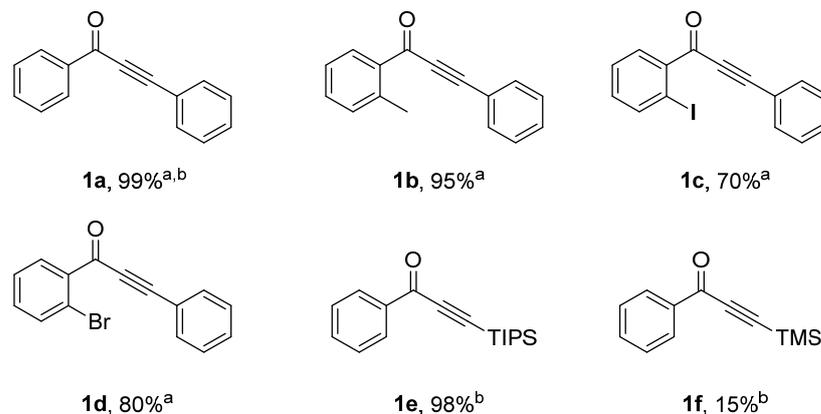


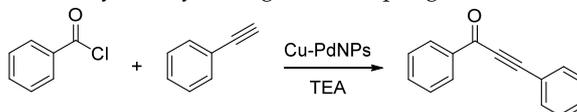
Figure 1. Ynones obtained through Pd-free acyl Sonogashira reaction catalyzed by CuNPs. ^a CuNPs/MK-10 was employed. ^b CuNPs/Magsilica was used.

The reaction showed yields ranging from very good to excellent. Also, this palladium-free methodology allows working with halogenated starting materials (**1c–1d**) without undergoing classical Sonogashira coupling. Ynone **1f** was obtained in low yield, presumably due to the partial loss of the low boiling point starting alkyne. The interest in obtaining silylated ynones lies in the possibility of developing multicatalytic processes involving acyl Sonogashira coupling followed by desilylation and click reaction promoted by the same copper catalyst. Processes involving desilylation and in situ cycloaddition of TMS-protected alkynes promoted by homogeneous copper catalysts has been already described in the literature [11].

3.2. Cu-PdNPs-Catalyzed Acyl Sonogashira Coupling

With the aim of conducting the acyl Sonogashira coupling under milder reaction conditions, we evaluated the performance of a bimetallic nanocatalyst composed of Pd-Cu nanoparticles supported on Celite. In previous studies, we observed that Celite is an excellent support material because nanoparticles are confined in its mesopores [7]. The palladium–copper ratio (4:1 molar ratio) is adjusted to ensure the formation of nanoparticles homogeneous in size while maintaining a low palladium loading, thus generating an efficient and cost-effective catalyst. The optimization of reaction conditions for the acyl Sonogashira coupling using this catalyst is shown in Table 2.

Table 2. Cu-PdNPs/Celite-catalyzed acyl Sonogashira coupling ^a.



| Entry | Cu-PdNPs/Celite (mg) | T (°C) | T (h) | Yield% ^b |
|-------|----------------------|--------|-------|---------------------|
| 1 | 5 | r.t | 2 | 40 |
| 2 | 10 | r.t | 2 | 70 |
| 3 | 5 | r.t | 4 | 99 |
| 4 | 5 | r.t | 4 | 83 ^c |
| 5 | 10 | r.t | 4 | 85 ^c |

^a Reaction conditions: benzoyl chloride (1.5 eq.), alkyne (1 eq.), TEA (3 eq.) and the catalyst (0.8 mol% Cu and 0.2 mol% Pd) were heated in a sealed tube under nitrogen atmosphere. ^b Yields were determined by GC-MS using dodecane as internal standard. ^c Reactions were conducted with 1.05 eq. of PhCOCl.

The main advantage associated with this method is the ability to carry out the coupling at room temperature within short reaction times (Table 2, entry 3). It is also important

to note that an excess of benzoyl chloride is required to ensure complete conversion of phenylacetylene. Ynones synthesized through this method are shown in Figure 2.

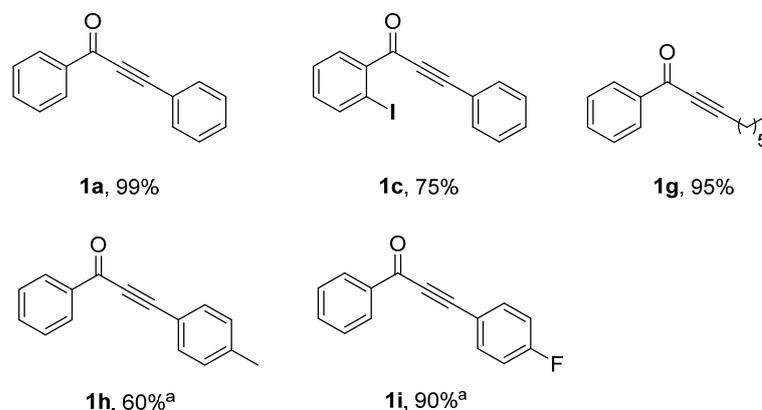
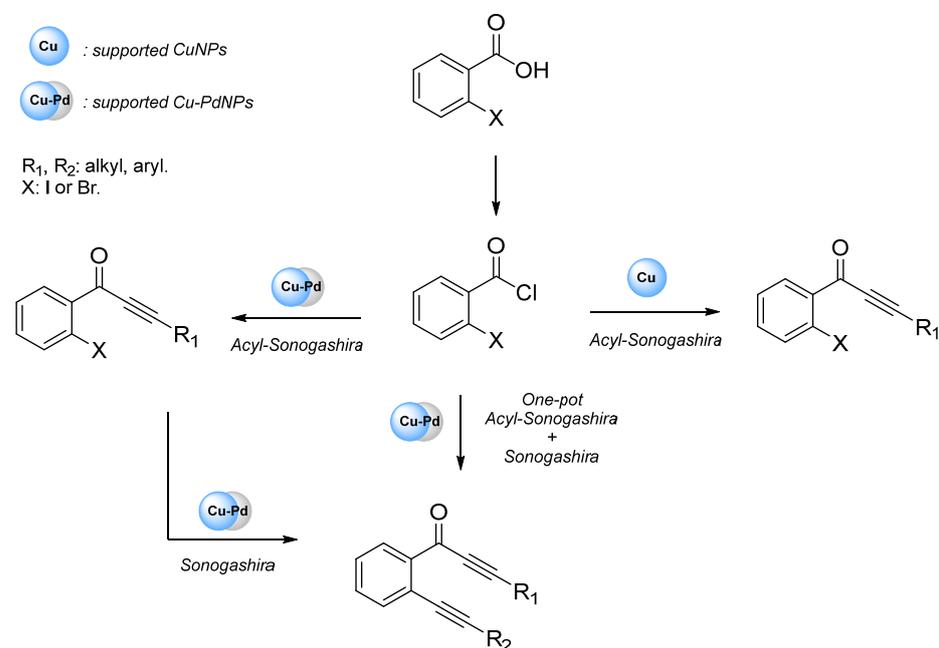


Figure 2. Ynones obtained through Cu-PdNPs/Celite-catalyzed acyl Sonogashira coupling. ^a Reactions carried out at 40 °C.

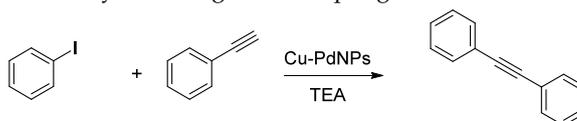
It can be seen that this method is applicable to aliphatic alkynes and various substituted phenylacetylenes, although in some cases the reaction needs to be carried out at 40 °C. It is also noteworthy that iodinated derivatives can be used without simultaneous classical Sonogashira coupling (ynone **1c**). This is particularly relevant taking into account that when homogeneous Pd catalysts are used with such substrates, no chemoselectivity is observed and both types of couplings occur at room temperature [5]. Thus, the chemoselectivity observed for the Cu-PdNPs/Celite in catalyzing either acyl Sonogashira or classic Sonogashira coupling would allow for the bis-functionalization of halogenated acid chlorides with different alkynes, as shown in Scheme 2.



Scheme 2. Strategies for the bis-functionalization of halogenated acyl halides using Cu-PdNPs/Celite.

3.3. Cu-PdNPs-Catalyzed Sonogashira Coupling of Aryl Iodides and Terminal Alkynes

With regard to the possibilities of bis-functionalization of halogenated acyl halides mentioned in the previous section, it became necessary to evaluate the performance of Cu-PdNPs as the catalyst for the Sonogashira coupling. The optimization results using iodobenzene and phenylacetylene are shown in Table 3.

Table 3. Cu-PdNPs/Celite-catalyzed Sonogashira coupling ^a.

| Entry | Cu-PdNPs/Celite (mg) | T (°C) | T (h) | Yield% ^b |
|-------|----------------------|--------|-------|---------------------|
| 1 | 5 | 80 | 4 | 65 |
| 2 | 10 | 80 | 4 | 76 |
| 3 | 5 | 80 | 6 | 82 |
| 4 | 5 | 80 | 6 | 84 ^c |
| 5 | 10 | 80 | 6 | 88 ^c |

^a Reaction conditions: iodobenzene (1 eq.), alkyne (1 eq.), TEA (3 eq.) and the catalyst (1.6 mol% Cu and 0.4 mol% Pd) were heated in a sealed tube under nitrogen atmosphere. ^b Yields were determined by GC-MS using dodecane as internal standard. ^c Reactions were conducted with 1.2 eq. of phenylacetylene.

Fortunately, Cu-PdNPs are also capable of promoting solvent-free Sonogashira coupling. With a slight excess of phenylacetylene, very good yields of the coupling product can be obtained. It is noteworthy that higher temperatures are required compared to those used for acyl Sonogashira coupling. In addition, the catalyst can be recovered from the reaction mixture by filtration and, after washing and drying, it can be reused for several cycles without any apparent loss of activity.

4. Conclusions

In this study, different heterogeneous catalytic methodologies for Sonogashira and acyl Sonogashira couplings were presented. In the palladium-free version, the use of the magnetically recoverable catalyst CuNPs/MagSilica allows the synthesis of ynones with good to excellent yields. On the other hand, the bimetallic catalyst Cu-PdNPs/Celite shows great versatility, catalyzing one or both types of couplings depending on the reaction temperature. These interesting results introduce the opportunity for developing multicatalytic systems for the bis-functionalization of halogenated acyl chlorides to produce useful building blocks in organic synthesis.

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