

Copper- and Amine-free Sonogashira Cross-Coupling in the Presence of Ligandless Pd-containing Catalyst

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In this work, the effect of reaction conditions (temperature and composition of the reaction mixture) on the Cu-free Sonogashira cross-coupling of 4-iodoanisole (IAN) and phenylacetylene using nanoparticulate ligandless palladium catalyst based on hyper-cross-linked aromatic polymer (HAP) was studied. Main idea of the study is the ability of HAP to stabilize small Pd nanoparticles that allows developing effective catalysts. It was shown that > 99 % conversion of IAN can be achieved in the presence of Pd/HAP for 1 h at 90 °C at the absence of amines and copper while using DMSO as a medium. DMSO allowed high solubility of all the reaction components and likely played a role of ligand in the Sonogashira reaction cycle. After the reaction, the cross-coupling product (1-methoxy-4-(phenylethynyl)benzene) was purified, its structure was confirmed by NMR.

1. Introduction

The reaction of Sonogashira C-C cross-coupling has been widely used in fine organic synthesis for its relative simplicity and flexibility (Mohajer et al., 2021). The most significant drawback of the conventional Pd-catalyzed Sonogashira reaction is the use of CuI (Khazaei et al., 2013). The addition of copper allows increasing the catalyst reactivity. At the same time, the addition of copper(I) has some shortcomings such as the necessity of avoiding the presence of oxygen in order to block the undesirable formation of alkyne homocoupling (Chinchilla and Nájera, 2011). The addition of amines has also promoting effect due to the formation of the cationic complex in the reactions involving electron-rich alkynes. Amines may also reduce Pd(II) to Pd(0) through formation of iminium cations, which results to acceleration of the oxidative addition. Besides, amines can substitute one ligand in the complex formed after the oxidative addition (Chinchilla and Nájera, 2011). Thus, two routes of Sonogashira cross-coupling are possible: (i) Cu-mediated of alkyne activation; (ii) Cu-free reaction cycle with alkyne playing the role of one of possible ligands (see Figure 1). It is noteworthy that in both cases the addition of amines is necessary for successful reaction proceeding.

Both homogeneous palladium complexes (Schilz and Plenio, 2012) and ligandless catalysts (Blaser et al., 2001) containing palladium nanoparticles (NPs) as a source of catalytically active forms are used as catalysts for the Sonogashira reaction. Homogeneous palladium catalysts cannot be separated completely from the products, which strongly hinders their large-scale application (Sun et al., 2012). There are numerous ligandless catalysts, for the synthesis of which different organic and inorganic supports can be used in order to prevent agglomeration of Pd NPs, as well as to facilitate the procedure of catalyst separation, its subsequent regeneration and reuse. Highly porous inorganic supports can provide high reaction rates. However, such supports reveal relatively low stability in alkaline media, while the procedure of functionalization with organic groups for preparation of heterogeneous catalysts with high activity and excellent recyclability is complex (Sun et al., 2012). Polymer materials are promising carriers for the synthesis of metal NPs (in particular, Pd) and their stabilization for use in cross-coupling reactions. Alonso et al. (2018) have distinguished two types of palladium catalysts (independently of the support): (i) Pd NPs immobilized on the support and (ii) Pd complexes linked to the support. It was found that the Sonogashira cross-coupling with the supported catalysts is usually carried out under copper-free conditions (Alonso et al., 2018).

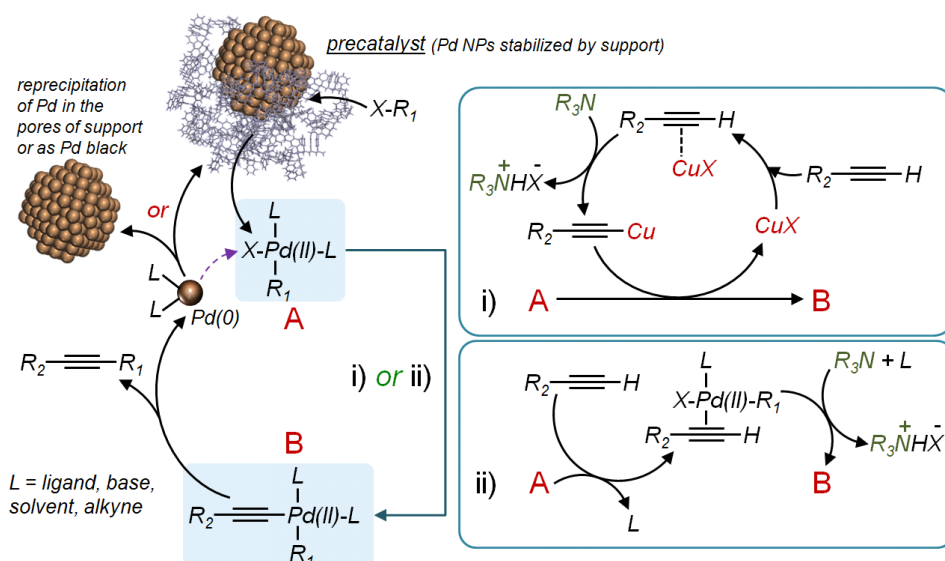


Figure 1: Copper-cocatalyzed (i) and copper-free (ii) mechanisms of Sonogashira cross-coupling (adopted from Chinchilla and Nájera, 2007)

Reaction conditions, such as temperature, nature of base and solvent, have strong effect on Sonogashira reaction (Rosa et al., 2015). Many different solvents are available for cross-coupling reactions (Chinchilla and Nájera, 2011): N,N-dimethylacetamide (DMA), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,4-dioxane, toluene, 1,2-dimethoxyethane (DME), methanol, ethanol, water, etc. It was emphasized that the solvent has significant influence on the reaction rate, selectivity with respect to cross-coupling product and equilibrium (Sherwood et al., 2019). Moreover, the catalyst stability can be affected by coordinating solvents competing with ligands (see Figure 1). In Cu-free Sonogashira reaction the role of the solvent (i.e. coordinating to Pd and defining the active form of the catalyst) can be undertaken by the base (Sherwood et al., 2019).

During our previous study (Nikoshvili et al., 2019) it was shown that non-functionalized hyper-cross-linked polystyrene (HPS) is promising support for the synthesis of Pd-containing catalysts of Suzuki cross-coupling in EtOH-water mixture in the absence of phase-transfer agents. The choice of solvent and base was shown to play an important role in the Suzuki reaction while using HPS-based catalysts (Nemygina et al., 2016).

In this paper the behavior of Pd/HPS catalyst in copper-free Sonogashira cross-coupling of phenylacetylene (PhAc) and 4-iodoanisole (IAN) is discussed for the first time.

2. Experimental

2.1 Materials

HPS Macronet MN270 (Purolite Int., UK) was washed with distilled water and acetone and dried under vacuum as described elsewhere (Sulman et al., 2012). Diphenylamine (DPA, 99 %), 4-iodoanisole (IAN, 98 %), phenylacetylene (PhAc, 99 %), tetrahydrofuran (THF, $\geq 99.9\%$), isopropanol (*i*-PrOH, 99.5 %), ethanol (EtOH, $\geq 99.8\%$), toluene (99.8 %), hexane ($\geq 99\%$), N,N-dimethylformamide (DMF, 99.8 %), dimethyl sulfoxide (DMSO, $\geq 99.9\%$), triethylamine (Et₃N, $\geq 99\%$), sodium acetate (Na₂OAc, $\geq 99\%$) and palladium(II) acetate (Pd(CH₃COO)₂, $> 99\%$), were obtained from Sigma-Aldrich. All chemicals were used as received. Distilled water was purified with an Elsi-Aqua water purification system.

2.2 Catalyst synthesis and characterization

Pd-containing HPS-based catalyst was synthesized via wet-impregnation method. In a typical experiment, 1 g of pretreated, dried and crushed ($< 63\ \mu\text{m}$) granules of MN270 were impregnated with 2.8 mL of the THF solution of precursor (Pd(CH₃COO)₂) of a certain concentration. The Pd-containing polymer was dried at 70 °C until the constant weight was achieved. Thus the catalyst 2.5 %-Pd/HPS was synthesized (palladium content was confirmed by the XFA). Before the Sonogashira reaction, preliminarily reduction of 2.5 %-Pd/HPS in hydrogen flow (100 mL/min) at 300 °C for 3 h was carried out. After the reduction, the catalyst contained Pd NPs with mean diameter $8.2 \pm 2.4\ \text{nm}$.

2.3 Procedure of Sonogashira cross-coupling

Testing of HPS-based catalyst in Sonogashira cross-coupling between PhAc and IAn (Figure 2) was carried out in 50 mL three-necked round-bottom flask in inert atmosphere at stirring rate 900 rpm. The total volume of liquid phase was 30 mL. The following parameters were varied: temperature (60-100 °C), solvent nature (water, EtOH, EtOH/water (volumetric ratio 5 : 1), DMF, toluene, DMSO) and the ratio of all the reaction components. In each experiment the quantity of IAn was equal to 1 mmol. Catalyst loading in each experiment was 10 mg, which corresponds to 0.235 mol.% with respect to IAn.

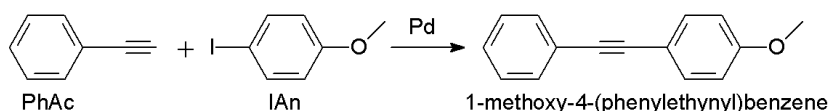


Figure 2: Simplified scheme of Sonogashira cross-coupling

In most of experiments Na_2OAc was used (its quantity was varied from 1.5 mmol up to 2 mmol) as a stabilizer of homogeneous palladium species, which form *in situ* in the reaction course from Pd NPs serving as reservoirs of catalytically active phase (Kashin and Ananikov, 2013). Moreover, in spite of the fact that such solvents as DMSO can successfully dissolve all the reagents, TBAB (10 mol.% with respect to IAn) was added. In order to avoid formation of PhAc homocoupling products, Cu-free reaction was carried out.

Samples of reaction mixture were periodically taken and analyzed via GC-MS (Shimadzu GCMS-QP2010S) equipped with a capillary column HP-1 (100 m \times 0.25 mm i.d., 0.50 μm film thickness). Helium was used as a carrier gas at pressure of 233.2 kPa and linear velocity of 20.6 cm/s. Oven temperature was programmed: 120 °C (6 min) \rightarrow 15 °C/min (260 °C) \rightarrow 260 °C (10 min) \rightarrow 15 °C/min (300 °C) \rightarrow 300 °C (2 min). Duration of analysis was 30 min. Temperature of injector, interface and ion source was 260 °C, range from 10 up to 500 m/z. The concentrations of the reaction mixture components were calculated using the internal standard calibration method (DPA dissolved in *i*-PrOH was used as an internal standard).

3. Results and discussion

The influence of temperature in the range of 60-100 °C on the rate of IAn conversion in Sonogashira cross-coupling was studied while using DMSO as a solvent at the following reaction conditions: inert atmosphere (N_2), 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc, 1.5 mmol of Na_2OAc , 3 mmol of Et_3N , 10 mol.% of TBAB (all the components with the exception of PhAc were added simultaneously. PhAc was introduced in the reactor after 30 min of stirring). It was shown that at 100 °C, after five minutes of reaction, the conversion of IAn reached 76 %. Further decrease in temperature obviously caused the decrease in the reaction rate. While reaching 60 °C the Sonogashira reaction proceeded very slowly (the conversion of IAn was only 21 % in 180 minutes of the reaction). The optimal temperature was chosen to be equal to 90 °C, the use of which allowed achieving high conversion of IAn (99.2 %) in 180 minutes and at the same time analyzing the initial part of kinetic curves of the dependence of IAn conversion on time.

At the selected temperature (90 °C) in DMSO medium, the effect of the addition of some reagents on the reaction was investigated (Figure 3).

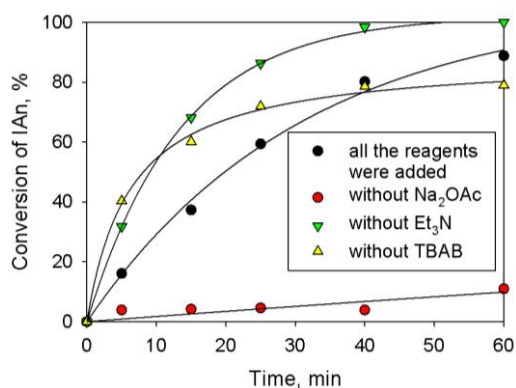


Figure 3: Effect of the composition of reaction mixture on the dependence of IAn conversion on time (DMSO, 90 °C, N_2 , 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc)

First Et_3N was excluded from the reaction, which resulted in noticeable increase of the reaction rate: the conversion of IAn reached 100 % after 60 min. It is noteworthy that while excluding one of the reagents, all other components were remained at concentrations used for the study of temperature effect (see above). Then the Na_2OAc was excluded and it was found that the conversion of IAn decreased to about 16.7 % in 180 min. This observation is likely due to the fact that sodium acetate can stabilize homogeneous palladium species formed *in situ* and having catalytic activity in the Sonogashira reaction. However, the increase of the quantity of Na_2OAc up to 2 mmol the conversion of IAn slightly decreased from 100 % to 84.5 % in 60 min. Finally, the effect of TBAB was studied, and it was found that the addition of TBAB, which usually serves as a phase-transfer agent, also beneficial for the Sonogashira reaction. Thus all the further experiments were conducted at the absence of Et_3N .

As the Sonogashira reaction requires second tandem cycle (Figure 1), it was surprising that in the case of Pd/HPS in DMSO medium no copper and no amine addition were required. Recently, it was revealed that transmetalation-centred tandem Pd/Pd catalytic cycle, analogous to the tandem Pd/Cu mechanism, is possible (Gazvoda et al., 2018). At the same time DMSO is known to be an effective solvent and reagent allowing a number of unique organic syntheses (Tashrfi et al., 2020).

It should be mentioned that activity of synthesized 2.5 %-Pd/HPS was comparable with some other reported results. For example, Pd/Nf-G (Pd NPs supported on nafion-graphene), 0.3 mol.% with respect to IAn, allowed 94% of IAn conversion for 8 h at 78 °C while using EtOH as a solvent (Balsane et al., 2015). Urgaonkar and Verkade (2004) used pure $\text{Pd}(\text{CH}_3\text{COO})_2$ (2 mol.%) as a catalyst, which allowed 77% of IAn conversion for 6 h at ambient temperature in DMF medium.

Solvent influence was studied at the temperature either 90 °C (for water, DMF, toluene and DMSO) or 70 °C (for EtOH or its mixture with water) at the following reaction conditions: inert atmosphere (N_2), 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc, 1.5 mmol of Na_2OAc , 10 mol.% of TBAB (all the components with the exception of PhAc were added simultaneously. PhAc was introduced in the reactor after 30 min of stirring). It was shown that in DMF medium the conversion of IAn reached 65 % after 60 min of the Sonogashira reaction. In the case of toluene, the conversion of IAn decreased to about 15 % in 60 min of the reaction. Best results were observed in the case of DMSO: 100 % conversion of IAn was found (Figure 4).

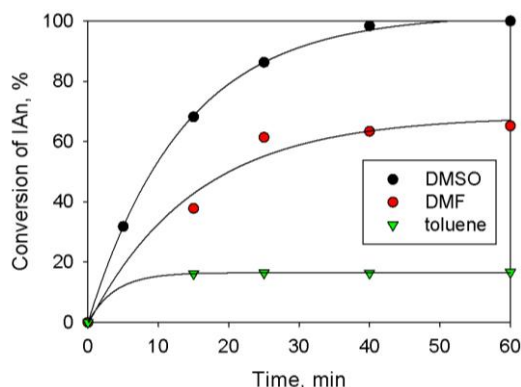


Figure 4: Effect of solvent nature on the dependence of IAn conversion on time (90 °C, N_2 , 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc, 1.5 mmol of Na_2OAc , 10 mol.% of TBAB)

The use of water as a solvent was ineffective, as it resulted to the aggregation of the catalyst due to hydrophobic nature of HPS. In the case of EtOH and its mixture with water, the Sonogashira reaction proceeded slowly: only 23.8 % of IAn conversion was achieved for 60 min at 70 °C. The addition of Et_3N to the reaction mixture did not result in any noticeable changes.

The study of the effect of the sequence of main reagents (IAn and PhAc) introduction was carried out. In first experiment all the components with the exception of PhAc were added simultaneously (i.e. catalyst Pd/HPS, IAn, Na_2OAc and TBAB), while PhAc was introduced in the reactor after 30 min of stirring.

It should be mentioned that coordination of alkynes to Pd slows oxidative addition (Sherwood et al., 2019), so even the strong electron donating solvent cannot fend off a degree of alkyne coordination. In the case of electron rich alkynes the Sonogashira reaction proceeds via a cationic complex, in which the base replaces the halide ligand only after alkyne coordination, and then abstracts the proton from the alkyne (see Figure 1, mechanism (ii)). Thus there is no necessity to introduce PhAc simultaneously with the catalyst. However, it was not clear what was the mechanism, which resulted to the conversion of pre-catalyst (Pd NPs stabilized in HPS) in its active form during the reaction.

The second experiment was carried out, when all the reagents including PhAc were added simultaneously and only the catalyst Pd/HPS was placed in the reactor after 30 min of stirring. As it can be seen from Figure 5, the long induction period can be observed on the kinetic curve of IAn conversion. This fact suggests that Pd NPs in HPS environment are the sources of "hot" catalytically active species, which form in the presence of IAn, Na₂OAc and selected solvent and rapidly start the Sonogashira cross-coupling as soon as PhAc is added.

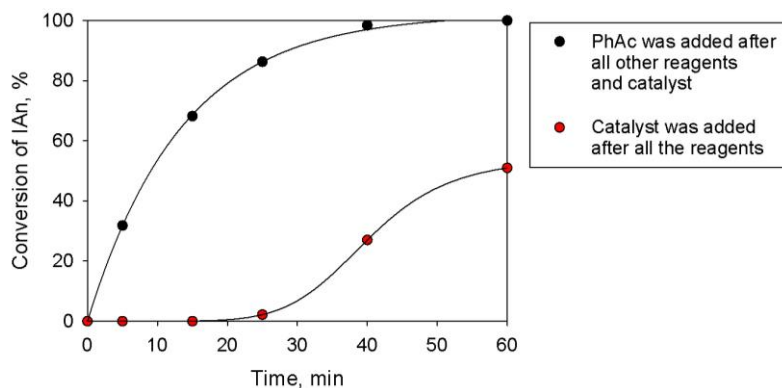


Figure 5: Effect of the sequence of IAn and PhAc introduction in the reaction mixture (DMSO, 90 °C, N₂, 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc, 1.5 mmol of Na₂OAc, 10 mol.% of TBAB)

The influence of gas phase was studied at 90 °C in DMSO medium using 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc, 1.5 mmol of Na₂OAc and 10 mol.% of TBAB. It was found that the conversion of IAn is about twice lower (49 % in 60 min) under air in comparison with N₂ (Figure 6). The most effective was the use of Ar since it can better displace oxygen in comparison with N₂. It is noteworthy that the Sonogashira reaction protocol in aerobic conditions is rarely found in literature even for Cu-free cross-coupling (Suzuka et al., 2015).

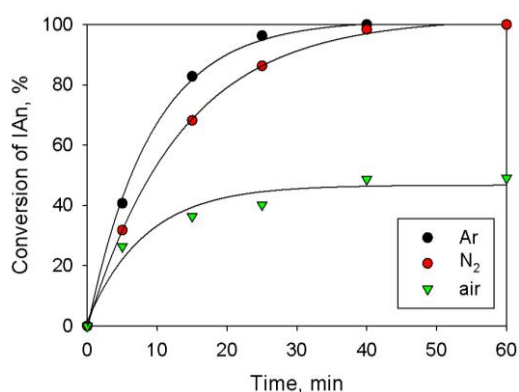


Figure 6: Influence of solvent nature on the dependence of IAn conversion on time (DMSO, 90 °C, 0.235 mol.% of Pd, 1 mmol of IAn, 1.5 mmol of PhAc, 1.5 mmol of Na₂OAc, 10 mol.% of TBAB)

Thus at chosen reaction conditions the Sonogashira cross-coupling was carried out and the reaction product (1-methoxy-4-(phenylethynyl)benzene) was extracted from DMSO to hexane and purified via column chromatography using silica as a stationary phase. After evaporation of hexane under vacuum at ambient temperature, solid residue was analyzed via NMR. ¹H-NMR (250 MHz, CDCl₃) δ: 3.76 (s, 3H, CH₃), 6.79 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.21-7.25 (m, 3H, Ar-H), 7.37-7.44 (m, 4H, Ar-H) ppm. ¹³C-NMR (62.9 MHz, CDCl₃) δ: 55.2, 88.0, 89.4, 114.0, 115.3, 123.6, 127.9, 128.3, 131.4, 133.0, 159.6 ppm; MS (m/e) = 208 [M⁺].

4. Conclusions

Pd/HPS catalyst was shown to be active in Sonogashira cross-coupling between IAn and PhAc at the absence of copper and amine. The effect of temperature on the rate of IAn conversion was studied and 90 °C was chosen to be the optimal temperature. Influence of solvent nature allowed concluding that DMSO is optimal solvent and it can likely play a role of ligand in cross-coupling mechanism. Thus at chosen conditions (90 °C,

argon atmosphere, 0.235 mol.% of Pd and the addition of Na₂OAc and TBAB) 100 % conversion of IAn in 40 min was achieved. Moreover, the study of the effect of the sequence of main reagents (IAn and PhAc) introduction was carried out, which revealed that in order to escape the induction period, PhAc was added after all other reaction components (including the catalyst). Thus it was proven that Pd NPs in HPS are the sources of catalytically active species, which form in the presence of IAn, Na₂OAc and solvent (DMSO).

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