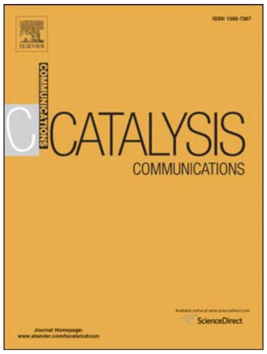

Gallic acid-derived palladium(0) nanoparticles as *in situ*-formed catalyst for Sonogashira cross-coupling reaction in ethanol under open air

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Gallic acid-derived palladium(0) nanoparticles as *in situ*-formed catalyst for Sonogashira cross-coupling reaction in ethanol under open air

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Abstract

A simple and eco-friendly protocol using gallic acid-derived palladium(0) nanoparticles as *in situ*-formed catalyst for Sonogashira reactions in ethanol under optimum thermal conditions have been developed. Excellent yields were obtained with the addition of a small amount of gallic acid (1 mol %) to the reaction mixture. The formation of the PdNPs was confirmed by using UV/Vis spectroscopy, and their size and morphology were determined by TEM and XRD analysis. Both aliphatic and aromatic terminal alkynes displayed efficient reactivity with the catalytic system. Moreover, the reaction condition is highly compatible with less reactive aryl bromides at moderate temperature, further can be reused repeatedly up to four recycles. Since gallic acid is a non-toxic naturally abundant phytochemical, the present method provides an efficient alternative route for Sonogashira reaction with natural feedstock as additive.

Keywords: Sonogashira coupling, palladium nanoparticle, gallic acid, ligandfree, ethanol, air,

1. Introduction

The C-C triple bond of alkynes occurs in various molecules of biochemistry and material sciences and is one of the most ideal functional group for the synthesis of significant and versatile organic molecules [1,2]. The Pd/Cu-catalyzed C_{sp2}-C_{sp} Sonogashira coupling of aryl halides with terminal acetylene is one of the most powerful tool to prepare these functionalized alkyne derivatives [3,4]. Since its discovery, most of the catalyst systems for these transformation are composed of Pd(0) or Pd(II) derivatives associated with various ligands such as phosphanes [5], amines [6], NHC [7], salen [8], hydrazone [9], pyrimidine [10], ligand-free [11] and also with salt additives [12] in organic medium or solvent-less [5], using excess amount of base [13]. These developments have significantly reduced the use of toxic and volatile solvents and stoichiometric amount of reagent. However, the prime drawback still associated with Sonogashira reaction is the formation of side-products due to homo-coupling of terminal alkynes in the presence of copper salts or at high temperature [14] or in air (Glaser coupling [15] or Hay coupling [16]). This hampers isolation and purification processes of the desired products due to similar chromatographic mobility [17]. Thus, the designs of ideal synthetic protocol to remove these drawbacks are prime necessity of present development.

Literature reports reveals that copper acetylide undergoes homo-coupling in air or O_2 [16, 18], or in some cases inhibits the cross-coupling reaction [19]. By careful selection, Ho et al. have found that the Sonogashira reaction proceeds more efficiently in an atmosphere of hydrogen gas diluted with nitrogen or argon [20]. Under this condition the side product due to terminal acetylene (homo-coupling) can be reduced to nearly 2%. Although, the exact role of hydrogen was not known, it was assumed that it may reduces O_2 in the presence of nascent Pd(0) [21] to form water and decreases its concentration during the reaction. Thus, a reducing atmosphere which controls the excessive paramagnetic oxygen may lower the acetylene homodimers to enhance cross-coupling [22]. Therefore, a high level of efficiency could be achieved by using preformed Pd(0) catalyst, or more precisely a Pd(0) nanoparticle (PdNPs) as catalyst [23]. However in majority of cases, synthesis of PdNPs requires high temperature, sonication and additional stabilizer, thereby making the process tedious and lengthy [24]. The development of process to prepare PdNPs in minimum step with reducing agent from renewable source has emerged to be the growing interest as it serves to be green and eco-friendly alternative with least chemical waste.

Gallic acid is an inexpensive antioxidant commonly found in considerable amounts in bio-wastes such as grape pomace or oak bark and gallnuts etc [25]. Recently, Yun et al.[26] have reported the preparation of Pd(0) nanoparticle from Pd(II) using gallic acid as both reducing and stabilizing agent. Recently, we have reported the gallic acid derived PdNPs-catalyzed Suzuki-Miyaura cross-coupling of aryl halides and arylboronic acid [27]. This led us to develop a mild and efficient Sonogashira protocol for the coupling of aryl halides with terminal alkynes to fulfill our objective of safe reaction strategy.

2. Experimental

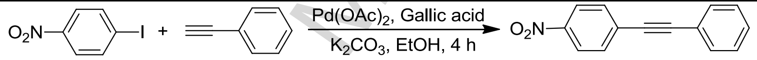
2.1. Catalytic Sonogashira Reaction

In a 50 ml round bottom flask, a mixture of aryl halide (0.5 mmol), terminal alkyne (0.65 mmol), $Pd(OAc)_2$ (1 mol%), gallic acid (1 mol%) and K_2CO_3 (1.5 mmol) in 4 ml EtOH was stirred at 40 °C. After completion (vide TLC); the reaction mixture was diluted with H_2O and extracted with ethyl acetate (3×10 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: Hexane) to give corresponding functionalized alkyne. Purity of isolated product was confirmed by comparing ^1H, ^{13}C NMR data with authentic compounds.

3. Results and Discussion

At the onset, to examine the effectiveness of gallic acid in Sonogashira reaction, we performed the reaction using 4-iodonitrobenzene, phenylacetylene, K_2CO_3 and $Pd(OAc)_2$ (1 mol%) with gallic acid (1 mol%) in ethanol (Table 1). Initial investigation at room temperature (*ca*. 27 °C) proceeds with the formation of 85% isolated product. However, on increasing the temperature to 40 °C, the reaction proceeds to completion and 95% coupling product was isolated (Table 1, entry 1-2). By lowering the Pd loading to 0.5 mol% poor conversion, even on increasing the reaction time up to 7 h, was observed (Table 1, entry 3). Optimization results showed nearly a quantitative formation of the cross-coupling product with equimolar loading of $Pd(OAc)_2$ and gallic acid (*i.e.* 1 mol%) under an environmentally preferred alcoholic reaction medium (Table 1, entry 2). On using higher gallic acid loading the reaction progress decreases significantly (Table 1, entries 5-6). High gallic acid loading prevents the increase in the size of PdNPs, because excess reducing agent diminishes the Ostwald ripening process [28, 29] by capping most of the free Pd surface sites and lowers the accessibility of the Pd particle at the surface for catalysis. When the reaction was performed without $Pd(OAc)_2$-gallic acid or base or with gallic acid without $Pd(OAc)_2$ no conversion was noticed, signifying the role of the catalyst and added base (Table 1, entries 7-9). The reaction gives low yield in the absence of gallic acid or with $PdCl_2$ (Table 1, entries 10 and 11). The lower activity with $PdCl_2$ could be due to different coordinating ability of anions to the nanoparticle surface [30]. The weak coordination of chloride ion to Pd compared to acetate ion decreases the stability of PdNPs. This enhances the rate of palladium leaching and thus lowers the reaction activity. It is noteworthy to mention here that the preformed PdNPs also deliver identical reactivity (Table 1, entry 12).

Table 1
Screening of catalytic effect on Sonogashira coupling[a]

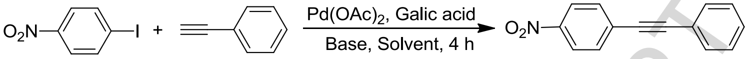


Entry	Catalyst (mol%)	Gallic acid (mol%)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$ (1)	1	5	85[c]
2	$Pd(OAc)_2$ (1)	1	5	95
3	$Pd(OAc)_2$ (0.5)	1	7	60
4	$Pd(OAc)_2$ (1)	0.5	12	50
5	$Pd(OAc)_2$ (1)	2	7	65
6	$Pd(OAc)_2$ (1)	5	7	50
7	-	-	24	-
8	$Pd(OAc)_2$ (1)	1	24	-[d]
9	-	1	24	-
10	$Pd(OAc)_2$ (1)	-	12	50
11	$PdCl_2$ (1)	1	6	70
12	PdNPs (preformed)		5	93

[a] Reaction conditions: 4-nitroiodobenzene (0.5 mmol), phenylacetylene (0.75 mmol), K_2CO_3 (1.5 mmol), EtOH (4 ml) at 40 °C. [b] Isolated yield, [c] at r.t. (*ca* 27 °C), [d] without base.

Next, we investigated the effect of different solvents on catalytic efficiency (Table 2) and the reaction proceeds efficiently in EtOH providing excellent isolated yield. This is in consistent with our earlier report on Sonogashira coupling [31]. The catalytic activity of the *in situ* catalyst was studied in water to follow green chemistry approach. However, catalytic efficiency decrease drastically in water and in aqueous alcohol (1:1) and lower yields were obtained upon prolonged reaction time (Table 2, entries 1-3). This discrepancy is may be due to the poor interactions between the low-polar reactants and active catalyst, which may form clusters during the reaction. Since, a well chosen base is often significant for the success of the cross-coupling reaction; we next studied the role of a number of bases under optimized reaction condition for a more improve coupling condition (Table 2). Upon optimizing the reaction, best result was obtained in ethanol at 40 °C with $Pd(OAc)_2$ (1 mol%) and gallic acid (1 mol%) using Cs_2CO_3 (2 equiv.) within 3 h (Table 1, entry 9).

Table 2
Screening the solvent and base.[a]

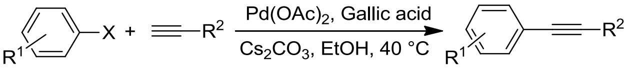


Entry	Solvent	Base (mmol)	Time(h)	Yield (%)[b]
1	H_2O	K_2CO_3 (1.5)	23	50
2	$EtOH/H_2O$	K_2CO_3 (1.5)	12	60
3	*i*$PrOH/H_2O$	K_2CO_3 (1.5)	12	50
4	EtOH	K_2CO_3 (1.5)	5	95
5	EtOH	K_2CO_3 (1)	6	60
6	EtOH	K_2CO_3 (2)	6	85
7	*i*PrOH	K_2CO_3 (1.5)	9	40
8	EtOH	NaOAc (1.5)	6	40
9	EtOH	Cs_2CO_3 (1)	3	97
10	EtOH	NaOH (1.5)	7	30
11	EtOH	Na_2CO_3	8	40

[a] Reaction conditions: 4-nitroiodobenzene (0.5 mmol), phenylacetylene (0.65 mmol), $Pd(OAc)_2$ (1 mol%), gallic acid (1 mol%), solvent (4 mL) at 40 °C. [b] Isolated yield.

Finally, to probe the scope of the catalytic system, using our standard conditions, we have evaluated various aryl halides and terminal alkynes (Table 3). The reaction system is compatible with a wide array of electronically diverse substituents. When investigating the influence of the nature of the halide (entries 1-5) as predicted a slight decrease in conversion was observed when going from iodide to bromide. In case of bromide, an increase in the reaction temperature improves the conversion with low reaction time. However, substitution at *para*-position drastically lowers the reaction yield even when the reaction time was increased to 6 h (Table 3, entries 3-5). Using substituted aryl iodide as substrate we evaluated coupling with various acetylene (Table 3, entries 6-17). Aryl iodides possessing an electron withdrawing group (*e.g.* NO_2) at *para*- or *meta*-position affords improved yield on coupling with phenyl acetylene (Table 3, entry 1 and 6). Conversions were always complete for *para*- and *meta*-substituted derivatives (Table 3, entries 1 and 6-10), but decreased efficiency was observed for 2-iodonitrobenzene, probably due to steric hindrance (Table 3, entry 13). The effectiveness of the present protocol was also studied for aliphatic alkynes, and to our delight moderate to high yield of cross-coupling products was observed in all cases (Table 3, entry 14-17). Moreover, the catalytic system also worked well with the coupling of 3-iodopyridine under present reaction conditions (Table 3, entry 18).

Table 3
Substrate scope of Sonogashira coupling [a]



Entry	X	R^1	R^2	Time(h)	Yield(%)[b]
1	I	4-NO_2	C_6H_5	3	97

2	Br	H	C_6H_5	7	70
3[c]	Br	H	C_6H_5	4	95
4[c]	Br	4-CH_3	C_6H_5	6	80
5[c]	Br	4-NO_2	C_6H_5	6	65
6	I	3-NO_2	C_6H_5	4	92
7	I	4-Me	C_6H_5	3	98
8	I	4-Me	4-MeC_6H_4	4	95
9	I	3-Me	C_6H_5	4	95
10	I	4-OMe	C_6H_5	4	80
11	I	H	C_6H_5	3	98
12	I	H	4-MeC_6H_4	5	97
13	I	2-NO_2	C_6H_5	8	40
14	I	H	*n*-octyl	5	80
15	I	H	*n*-butyl	5	85
16	I	H	cyclohexyl	5	90
17	I	4-Me	*n*-butyl	5	80
18	I	3-iodopyridine	C_6H_5	12	90

[a] Reaction conditions: aryl halide (0.5 mmol), acetylene (0.65 mmol), $Pd(OAc)_2$ (1 mol%), gallic acid (1 mol%), Cs_2CO_3 (1 mmol), EtOH (4 mL) at rt. [b] Isolated yield, [c] at 60 °C

It is well established from the literature that well dispersed PdNPs are formed from Pd(II) with gallic acid wherein gallic acid acts as both reductant and stabilizer [26]. In order to further clarify the active species in the present Sonogashira reaction, transmission electron microscope (TEM) was used for the analysis of the size and distribution of PdNPs. TEM images showed that the PdNPs were well fabricated and are average dimension of the spherical particles (mean diameter 13.7 nm) after completion of the reaction (**Figure S1, see ESI†**). This stabilization of PdNPs by gallic acid is thought to be due to the high anionic charge of the gallate ions [32, 33]. Thus, it is obvious that the active catalytic species of the reaction is the *in situ* formed PdNPs. To identify the true active catalytic species, we performed the mercury-poisoning test [34, 35]. For this, gallic acid and $Pd(OAc)_2$ were stirred in ethanol containing Cs_2CO_3 and excess of Hg(0) (molar ratio to [Pd] ~400) for 30 min prior to addition of the reacting substrates. After 3 hours of adding the reactants, negligible amount of coupling product formation was observed. This suggested that the PdNPs is acting as a true heterogeneous catalyst, and the reaction is occurring on the molecular surface. To further verify the reducing role of gallic acid in the formation of PdNPs, we have prepared PdNPs using gallic acid and $Pd(OAc)_2$ without adding the substrates. For this, $Pd(OAc)_2$ (5 mg) and gallic acid (5 mg) were mixed in EtOH (4 mL) at room temperature under aerobic conditions. Instant change in colour of the resulting solution from orange to black indicates the reduction of Pd(II) ions to Pd(0). In UV/Vis analysis, the disappearance of a peak at 281 nm, due to $Pd(OAc)_2$, confirms the reduction of Pd(II) ions to Pd(0). Moreover, appearance of a characteristic absorption peak at 361 nm attributes the formation of Pd(0) particles (**Figure S3-S4, see ESI†**). Powder X-ray diffraction (PXRD) measurements of the black palladium particles were consistent with the formation of Pd(0) clusters, and matches well with the standard XRD database (JCPDS card no. 89-4897). The diffraction peak observed at 40.11°, 46.66° and 68.12° corresponds to the crystal plane (111), (200), (220) reflections, respectively (**Figure S5, see ESI†**). The reduction of Pd(II) ions was further confirmed by the appearance of significant vibration bands in the FT-IR spectrum (**Figure S6, see ESI†**). The observation of a peak at 1664 cm^{-1} and the disappearance of vibrational peaks at 1602 cm^{-1} (due to Pd-O), 1570 cm^{-1} (due to the C=O) and 1424 cm^{-1} (due to acetate) signifies the perfect interaction between gallic acid and Pd(II) ions. These data are consistent with the literature reports [26] and confirms the reducing-capping role of gallic acid in the formation mono-sized PdNPs.

From the green chemistry viewpoint, the major challenge of a metal catalysis is its ability for recycling. The reusability of the PdNPs was investigated by consecutive Sonogashira coupling reactions of iodobenzene and phenylacetylene. After the first catalytic cycle, the reaction mixture was extracted with ethyl acetate and centrifuged and the organic fraction was removed for purification and the recovered residue was directly used for further catalytic cycle by the addition of fresh reactants. Identical results were obtained upto 2nd run, thereafter the yields gets slightly decrease in 3rd and 4th cycles (**Table S1, see ESI†**). TEM image showed that the size of nanoparticles get reduced (mean diameter 4.7 nm) after 2nd cycle (**Figure S2, see ESI†**). This could be due to the aggregation and precipitation of the large sized nanoparticles, which leaves smaller nanoparticles in solution [29]. This decrease of active particles from the surface may lowered the catalytic activity of the coupling reaction. Moreover, the accumulation of salt byproducts during the successive catalyst recycling may also lower the catalytic efficiency.[27] To ensure reproducibility for practical industrial applications, we performed a large scale Sonogashira coupling with 10 mmol 4-iodonitrobenzene loading. The cross-coupling preceded smoothly giving 99% isolated yield of the desired product. In contrast to the earlier reported methods on PdNPs, these results are superior in terms of palladium loading, reactions conditions and yields (see **Table S2**, **ESI†**).

4. Conclusion

In conclusion, a simple, efficient and sustainable method for the use of gallic acid-derived PdNPs in the Sonogashira reaction between aryl halides and terminal acetylene derivatives was developed. The *in situ* formed spherical PdNPs showed excellent catalytic activities in ethanol, under aerobic conditions, with low catalyst loading (1 mol% Pd) with four times recyclability. Overall, good to excellent yields were achieved with various electronically diverse substrates under optimum thermal conditions. The catalytic system is easily accessible, environmentally benign and avoids the use of unfavorable ligands and toxic solvent.

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Highlights

1. Gallic acid derived *in situ* PdNPs is developed as reusable catalyst for Sonogashira reactions.
2. Natural feedstock is used as additive
3. The catalyst is easily accessible, mild and avoids use of unfavorable ligands and toxic solvent
4. The new catalyst is effective for diverse range aryl halides and terminal acetylenes