COPPER- AND AMINE-FREE SONOGASHIRA–HAGIHARA COUPLING REACTION CATALYZED BY Pd(0) NANOPARTICLES SUPPORTED ON MODIFIED CROSSLINKED POLYACRYLAMIDE

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Pd(0) nanoparticles supported on modified crosslinked polyacrylamide containing phosphinite ligand was prepared. The complex was a highly efficient catalyst for the Sonogashira– Hagihara coupling reaction in the absence of a copper cocatalyst and an amine base under aerobic condition. This protocol can be applied for different aryl halides including chloroarenes. The catalyst can be reused several times without any considerable decrease in its activity because of low leaching of palladium metal from the support. Transmission electron microscopy (TEM) analysis of the catalyst revealed the formation of stable and polydispersed Pd(0) nanoparticles.

Keywords: C–C Coupling; Heterogeneous catalysis; Palladium nanoparticle; Polyacrylamide support; Sonogashira coupling; Leaching.

Sonogashira coupling reaction of terminal alkynes with aryl or vinyl halides is a powerful method in organic synthesis for construction of carbon– carbon bond¹. The reaction directly provides an efficient rout to unique organic compounds having the $C(sp^2)-C(sp)$ bond which has been widely utilized in areas such as natural product synthesis, pharmaceutical and material science².

Since its first report in 1975³, the reaction has been well studied. The most commonly used catalytic systems for this transformation include variety of homogenous palladium complexes together with copper salt as a cocatalyst and large amount of amine as the solvent or cosolvent⁴. Although, the presence of the copper salts facilitates the coupling reaction by generation of copper acetylide, it can also induce a Glaser-type oxidative homocoupling of the terminal acetylene to the corresponding symmetrical diyne⁵. In order to reduce diacetylene formation, various copper-free methodologies have been reported^{6,7}. However, many of these methodologies 1968

may suffer from different problems. Most of them involve the use of amines such as piperidine, triethylamine or pyrrolidone in large excess or as a solvent⁸. The reactions are generally performed in the presence of homogenous palladium catalysts, which make the catalyst recovery a tedious procedure and may result in contamination of products by metallic species. Furthermore, many of these methods are applied for aryl iodides and activated aryl bromides but rarely for aryl chlorides. Other drawbacks can be: using high palladium catalyst loading, performing the reaction under anaerobic condition and using palladium complex or ligand that are expensive or hard to make. In this regard, numerous modifications have been reported for the Sonogashira coupling reactions recently. Some of them are: reactions in ionic liquid⁹, reactions in neat water¹⁰, use of palladacycle catalyst or N-heterocyclic carbene (NHC) ligands¹¹, incorporating mesoporous material such as MCM-41¹², solvent-free condition¹³, microwave irradiation¹⁴, phase transfer catalytic reaction condition¹⁵, use of fluorous biphasic catalysis (FBC) system¹⁶, reactions under ligand-free condition¹⁷, or microemulsion systems¹⁸, etc. In view of all these facts, despite that the Sonogashira coupling reaction has been intensively studied; there are only few examples of the heterogeneous palladium catalyst systems for the Sonogashira coupling of aryl chlorides which can act under copper-free condition¹⁹. Thus, the study of new types of polymer-supported palladium catalysts which might be suitable for the Sonogashira reaction of all aryl halides especially less active ones has practical significance.

In continuation of our previous studies on the use of modified polyacrylamide resins as heterogeneous supports²⁰, we recently introduced novel Pd(0) nanoparticles supported on modified crosslink polyacrylamide as a catalyst for the Heck and Suzuki coupling reactions²¹. Hereby, we present new application of this catalyst for a highly efficient copper- and amine-free Sonogashira reaction of a wide variety of aryl halides including aryl chlorides.

RESULTS AND DISCUSSION

Phosphinites are potential ligands for the formation of palladium complexes that can be used as catalysts in carbon-carbon bond formation reactions²². These ligands stabilize palladium and increase its reactivity. They indebted their efficiency in these reactions to their bulkiness and electronrichness. In this study, we have introduced palladium nanoparticles supported on modified crosslinked polyacrylamide containing phosphinite ligand as an efficient polymeric catalyst for Sonogashira–Hagihara coupling reactions. The polymeric phosphinite ligand was obtained by transamidation reaction of crosslinked polyacrylamide (5% with *N*,*N*'-methylenebis-acrylamide) with hydroxylamine and its subsequent reaction with chlorodiphenylphosphine. This polymeric ligand was complexed with Pd(OAc)₂ to obtain the heterogeneous catalytic system (Scheme 1). Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images of the catalyst showed palladium dispersion with a well degree of homogeneity in nanometer size²¹. The formation of active Pd(0) nanoparticles was revealed by its X-ray diffraction (XRD), TEM image and UV-Vis diffuse reflectance spectrum (UVDR) in our previous report²¹. The XRD patterns of the catalyst showed the characteristic bands for the formation of Pd(0) at (111), (200), (220) and (311) crystallographic planes. The absence of d \rightarrow d transition in UVDR spectrum was also attributed to metallic Pd(0) complex²¹.



Scheme 1

Optimization of Reaction Condition for Sonogashira Reaction

To optimize the reaction condition, we chose iodobenzene and phenylacetylene as a model coupling partners. Initial screening of the reaction revealed that 0.5 mole % of the catalyst was sufficient to induce coupling reaction for aryl iodides and bromides, while 1 mole % is necessary for coupling of less active aryl chlorides. Furthermore, the reactions need tetrabutylammonium bromide (TBAB) (Jeffery catalyst) as an additive. Although the effect of TBAB in the coupling reactions is not completely clear, but it acts as a base and phase transfer catalyst to accelerate these reactions. In addition, TBAB facilitate the regeneration of the zerovalent palladium in the catalytic cycles²³. The influence of solvent on the Sonogashira coupling reaction of the model substrates was examined over the catalyst as shown in Table I. Among the solvents used, high catalytic activity was observed in NMP and DMF. However, the reaction in DMF produced homo-coupled dialkyne and needed longer reaction time. The use of EtOH and THF as solvents led to slower reaction, and no product was obtained when the reaction was carried out in CH_3CN . Table II shows the influence of base for the model reaction. As mentioned in the literature, the use of a base in the Sonogashira reaction not only is necessary for absorption of hydrogen halides, but also is important in inhibiting homo-coupling product formation²⁴. No coupling reaction occurred in the absence of a base. Among

TABLE I

Effect of different solvents on the Sonogashira coupling of iodobenzene with phenylacetylene $\!\!\!^a$

Entry	Solvent	Time, h	Conversion, % ^b
1	DMF	6	100
2	NMP	4	100
3	THF	6	75
4	EtOH	6	70
5	CH ₃ CN	6	trace

 a Reaction condition: aryl halide (1.0 mmol), phenylacetylene (1.2 mmol), $\rm K_2CO_3$ (2.0 mmol), Pd catalyst (0.5 mole %), TBAB (5 mole %) in solvent (5 ml) at 100 °C. b Conversion based on iodobenzene.

TABLE II Effect of different bases on the Sonogashira coupling of iodobenzene with phenylacetylene^{*a*}

Entry	Base	Time, h	Conversion, % ^b
1	_	6	trace
2	Et ₃ N	6	60
3	K ₂ CO ₃	4	100
4	KF	6	50
5	$Na_3PO_4 \cdot 12H_2O$	6	100

^{*a*} Reaction condition: aryl halide (1.0 mmol), phenylacetylene (1.2 mmol), base (2.0 mmol), Pd catalyst (0.5 mole %), TBAB (5 mole %) in NMP (5 ml) at 100 °C. ^{*b*} Conversion based on iodobenzene.

bases tested, K_2CO_3 was the best choice. It gave quantitative conversion of iodobenzene without considerable formation of homo-coupling product. Other bases such as Et₃N, KF and Na₃PO₄·12H₂O were explored and proved to be inferior. In all, 0.5 mole % of polymeric catalyst/K₂CO₃/5 mole % TBAB in NMP at 100 °C considered as an optimum catalyst system for aryl iodides and bromides and 1 mole % of the catalyst loading for aryl chlorides.

The Sonogashira–Hagihara Coupling Reaction of Aryl Halides with Terminal Alkynes

To examine the scope and limitation of Sonogashira coupling reaction, a variety of aryl halides were coupled with terminal alkynes under optimized condition and produced excellent to moderate yield of the coupling products (Scheme 2), although, homo-coupled product was also formed to an extent of 6–9%. The results are recorded in Table III. It is observed that the process tolerates both electron-donating and electron-withdrawing groups in the aryl halides. Heterocyclic substituent was also tolerated (entry 13). The reactions of less active aryl chlorides need longer reaction times and more palladium loading (entries 14–17).

$$\begin{array}{c}
X \\
R^{1} \\
R^{2} \\
R^$$

Scheme 2

A Pd(0) species stabilized by ligands is proposed in the catalytic cycle of Sonogashira reaction. In our catalytic cycle, the formation of such Pd(0) nanoparticles was revealed by TEM analysis of the catalyst after a Sonogashira reaction between iodobenzene and phenyl acetylene (Fig. 1). The TEM image shows the presence of polydispersed Pd(0) nanoparticles varying in size from 30–50 nm.

On the basis of the general mechanism reported earlier in the literature^{13b,23b,24c}, a mechanism for this Sonogashira cross-coupling reaction is outlined in Scheme 3. The Pd(0) species could be generated from the reaction of Pd(OAc)₂ with polymeric ligand (L) in step 1. After oxidative addition of aryl halides to Pd(0) in step 2, insertion of the triple bond to

1972

TABLE III

Palladium catalyzed Sonogashira coupling reaction of aryl halides with terminal alkynes^a

	RI	$ \begin{array}{c} X \\ + R^2 \longrightarrow \frac{Pd}{K_2C} \end{array} $	cat. (0.5-1 mol%) 'BAB (5 mol%) O ₃ /NMP/100 °C	$\rightarrow R^1 - $	≡−R ²
Entry	Aryl halide	R ²	Product	Time, h	Yield, % ^b
1		Ph	1a	4	90
2		CH ₂ OH	1b	5	85
3	MeOI	Ph	1c	7	89
4	MeO-V-I	CH ₂ OH	1d	7	80
5	Br Br	Ph	1a	8	87
6	Br	CH ₂ OH	1b	12	82
7	O ₂ N-Br	Ph	1e	4	75
8	O ₂ N-Br	CH ₂ OH	1f	5	80
9	NC Br	Ph	1g	4	86

16	MeOC — </th <th>`}—CI</th> <th>Pn</th> <th>31</th> <th></th>	`}—CI	Pn	31	
	\	/			

17 ^c	Me CI	Ph	3j	24	70

 a Reaction condition: aryl halide (1.0 mmol), terminal alkyne (1.2 mmol), K₂CO₃ (2.0 mmol), Pd catalyst (0.5–1 mole %), TBAB (5 mole %) in NMP (5 ml) at 100 °C. b Isolated yield. c Pd catalyst (1 mole %).

Collect. Czech. Chem. Commun. 2011, Vol. 76, No. 12, pp. 1967-1978

Sonogashira React	on Catalyzed	by Supported	Catalyst
0	~	· · · ·	

TABLE III (Continued)

Entry	Aryl halide	R ²	Product	Time, h	Yield, % ^b
10	ClBr	Ph	1h	6	85
11	MeOC Br	Ph	1i	7	80
12	Me Br	Ph	1j	12	80
13	MBr	Ph	1k	8	85
14 ^{<i>c</i>}	CI	Ph	3a	24	70
15 ^c	O ₂ N-CI	Ph	3e	9	78
16 ^c	MeOC CI	Ph	3i	18	72
17 ^c	Me-CI	Ph	3j	24	70

Ar-Pd-X generates the alkenylpalladium (step 3) which undergoes β -hydride elimination (step 4) to afford disubstituted alkynes. The Pd(0) species is regenerated by reductive elimination of the Pd(II) compound in the presence of a base in the final step 5. TBAB has promoting influence in this cycle by assistance in the regeneration of zerovalent palladium catalyst in step 5. Several possible mechanisms proposed by Jeffery in this matter²³.



Scheme 3





The Recyclability and Heterogeneity Test of the Catalyst

We also examined the reuse of the catalyst in the reaction of iodobenzene with phenylacetylene. The catalyst was recycled for five cycles in this reaction to record a TON of 860 and average TOF (h^{-1}) of 31.8 in total for five runs. The yield of the product gradually decreased from 91% for the first run to 82% for the fifth run as shown in Fig. 2. Therefore, there is no significant loss of the catalytic activity during these cycles and the catalyst showed good reusability.

Immobilized metal catalysts often suffer from leaching of metal species during the course of reaction. To probe the issue of palladium leaching in our system, the filtrate of the reaction between iodobenzene and phenylacetylene was analyzed by ICP. Analysis of the crude reaction mixture indicates a total leaching of 4.8% of the palladium for the whole recycling processes. These results indicate low leaching of palladium into the solution.

For further investigation, in order to ascertain whether the catalyst was behaving in a truly heterogeneous manner, or whether it is merely a reservoir for more active soluble form of Pd, hot filtration test was performed²⁵. We repeated the reaction between iodobenzene and phenylacetylene and filtered the catalyst after 25% conversion, and allowed the reaction to continue in the absence of catalyst. No additional conversion was seen after filtration of the catalyst²⁶. This confirmed the heterogeneous character of the catalytically active species in this reaction.



FIG. 2

Reusability of polymer supported Pd(0) catalyst in the Sonogashira coupling reaction. Reaction condition: iodobenzene (1.0 mmol), phenylacetylene (1.2 mmol), K_2CO_3 (2.0 mmol), Pd catalyst (0.5 mole %), TBAB (5 mole %) in NMP (5 ml) at 100 °C

CONCLUSION

In conclusion, we have shown the applicability of zerovalent Pd nanoparticles supported on modified crosslinked polyacrylamide as an efficient and practical catalyst for the copper- and amine-free Sonogashira reaction in NMP under aerobic condition. This catalyst can be recovered and reused several times without considerable loss of activity because of negligible leaching of palladium from supported system. The TEM image of the catalyst shows the presence of polydispersed Pd(0) nanoparticles for the reaction.

EXPERIMENTAL

General

Acrylamide (Fluka) was recrystallized from chloroform. Other reagents and solvents were of commercial reagent grade and obtained from Merck, Fluka or Aldrich companies and used without further purification. All products were characterized by comparison of their FT-IR and NMR spectra and physical data with those reported in the literature. All yields refer to the isolated products. Progress of reactions were followed by TLC on silica-gel Polygram SILG/UV 254 plates or by GC on a Shimadzu model GC 10-A instrument with hydrogen flame ionization detector. IR spectra were run on a Shimadzu FT-IR-8300 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX instrument (250 MHz). The Pd analysis and leaching test was carried out by ICP-OES analyzer (Varian, Vista-Pro). TEM analyses were performed on a Philips model CM 10 instrument.

Preparation of the Supported Palladium Catalyst

The polymer supported palladium catalyst was prepared as described in our previous paper²¹. The polymeric phosphinite ligand was obtained by transamidation reaction of polyacrylamide (5% crosslinked with *N*,*N*'-methylene-bis-acrylamide) with hydroxylamine in ethanol at 90–100 °C and its subsequent reaction with chlorodiphenylphosphine/Et₃N in THF at 0 °C. This polymeric ligand was complexed with Pd(OAc)₂ to obtain the heterogeneous catalytic system. ICP analysis revealed that the catalyst contained an average of 0.15 mmol/g of Pd.

Sonogashira-Hagihara Coupling Reaction. General Procedure

A suspension of aryl halide (1.0 mmol), K_2CO_3 (2.0 mmol, 0.276 g), Pd complex (0.5–1 mole %, 0.033–0.067 g), tetrabutylammonium bromide (TBAB) (5 mole %, 0.016 g) and NMP (3 ml) were mixed in a 10 ml round-bottomed flask and phenylacetylene (1.2 mmol, 0.122 g) was added. The reaction mixture was stirred at 100 °C. Progress of the reaction was monitored by TLC (or GC if necessary). On completion of the reaction, the mixture was filtered and the filtrate poured into water (50 ml) and extracted with ethyl acetate (3 × 15 ml). Combined organic phases were dried over Na₂SO₄, filtered and evaporated in vacuum. Products were isolated by flash chromatography using petroleum ether, ethyl acetate, or their mixture

as eluents. Characterization of products was performed by comparison of their FT-IR, ¹H NMR, ¹³C NMR, and physical data with those of the authentic samples.

Reuse of the Catalyst

When the Sonogashira reaction according to the procedure described above was finished, the suspension was cooled down to room temperature and filtered off. The polymeric complex was washed with NMP, water and acetone and dried under vacuum. It was then used in the next reaction cycle with a new portion of reagents.

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- 26. In a typical experiment, Pd compelx (0.5 mole %, 0.033 g), iodobenzene (1.0 mmol, 0.204 g), phenylacetylene (1.2 mmol, 0.122 g), K_2CO_3 (2.0 mmol, 0.267 g), TBAB (5 mole %, 0.016 g) and NMP (3 ml) were taken in a round-bottomed flask and stirred at 100 °C for 1 h. At this stage (25% conversion), the catalyst was filtered off and the experiment was continued with the filtrate for another 24 h. There was no detectable increase in the product concentration, as is evident from the GC analysis.