

Silica gel-Supported Palladium Catalyst for the Acyl Sonogashira Reaction

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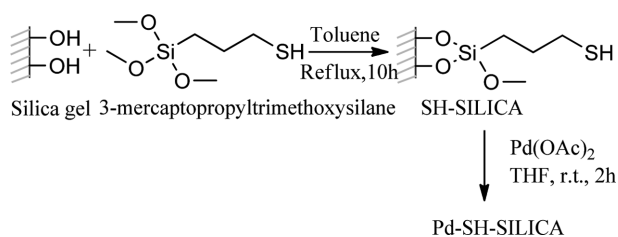
Key words: 3-Mercaptopropyltrimethoxysilane, Pd-incorporated silica, Acyl Sonogashira reaction, Pyrazole

The acyl Sonogashira reaction between acyl chlorides and terminal alkynes is one of the most useful method for the preparation of ynones which are important intermediates to prepare versatile pharmaceutically and biologically active heterocyclic compounds such as pyrroles,¹ pyrazoles,² furans,³ furanones,⁴ isoxazoles,⁵ pyrimidines,⁶ quinolines,⁷ indolizidinones.⁸ Due to the bifunctionality and broad applicability of ynones an efficient, mild and good heterogeneous catalyst for their preparation is highly desirable. The most straightforward method for the preparation of ynones utilizes palladium catalyst for the coupling of terminal alkynes with an acid chloride. In this case, variety of homogeneous catalysts has been employed.^{6,9} Homogeneous catalysis reactions are associated with many problems such as toxicity, reuse etc. Besides, the use of a copper co-catalyst in these coupling reactions facilitates the homocoupling of alkynes, which causes another problem to separate the products from the reaction mixture. Due to both environmental and economic issues, the attention has been increased to immobilize the metal complexes onto solid support materials to generate their heterogeneous forms. In order to successfully achieve this, a good choice of the support materials is required along with a good strategy for placing the active catalysts on the support materials. Among plenty of works on homogeneous catalysts, a few numbers of studies have been reported to heterogeneous catalyst. One such heterogeneous catalyst reported by J.-Y. Chen et al. where nanosized MCM-41 anchored palladium bipyridyl complex and CuI have been used for the coupling of acyl chlorides and terminal alkynes.¹⁰ Likhari's group reported that acyl chlorides could be coupled with terminal alkynes in presence of 1 mol % Pd/C under reflux of toluene and the catalyst could be reused for five cycles with a 15% leaching of Pd.¹¹ Another example of polymer supported palladium nanoparticles has been reported more recently as the copper

free catalyst for acyl sonogashira reactions.¹² This paper represent an extensive discussion on heterogeneously catalysis of Pd metal for this reaction. This palladium catalyst has been reported as the first recyclable catalyst in copper free reaction. However, the main goal of our study was to develop an active and selective catalyst that could be reused in acyl Sonogashira reaction. In this work, we selected a silica based sulfur palladium complex for this coupling reaction.

3-Mercaptopropyltrimethoxysilane and palladium supported silica has received considerable attention in organic synthesis for its availability, low cost, excellent heterogeneous nature, and ease of handling.¹³ It was effectively used in various organic syntheses.¹³⁻¹⁷ Despite various coupling reactions and exceptional heterogeneity, till now thiol containing palladium silica catalyst for ynones synthesis has not been reported. As a part of our continuous efforts in the development of a recyclable catalyst for carbon-carbon bond-forming reactions, we report herein a simple method for the coupling between various acyl chlorides and terminal alkynes catalyzed by Pd-SH-SILICA for the formation of ynones. For example, three component and sequential one-pot fashion, two pyrazoles were synthesized in high yields and illustrated the versatility of this modified acyl Sonogashira reactions.

The synthesis of silica functionalized organothiol groups was achieved by stirring with amorphous silica and excess amount of (3-mercaptopropyl)-trimethoxysilane in toluene at 100 °C for 10 h. The loading ratio of silica was confirmed to be 0.99 mmol gm⁻¹ of (3-mercaptopropyl)-trimethoxysilane via both elemental analysis and weight gain. Then the product thiol-functionalized amorphous silica was stirred with palladium acetate in tetrahydrofuran (THF) solution until the orange color of the solution was transferred to the silica gel to obtain the desired palladium catalyst, which was denoted as Pd-SH-SILICA



Scheme 1. Synthesis of the silica gel supported palladium catalyst.

(Scheme 1). Due to the higher uptake capacity of palladium acetate in mercaptopropyl silica gel, 0.40 mmol/gm palladium loading was achieved easily.^{18,13} Inductively coupled plasma (ICP) analysis also confirmed the palladium content. The structure of the catalyst can be found elsewhere that Pd(II) species coordinate to two sulfur ligands in the Pd-SH-SILICA catalysts.^{19,20} As it is mentioned in earlier reports that thiol-containing silica has particularly high affinity to the palladium metal so it can recapture at the end of the catalytic cycle easily and thus ensure low Pd contamination of the reaction mixture and products. In this case the reactions can occur likely in homogeneous mixture following a “release and catch” mechanism.^{19–23} As shown in Fig. 1, the SEM images of

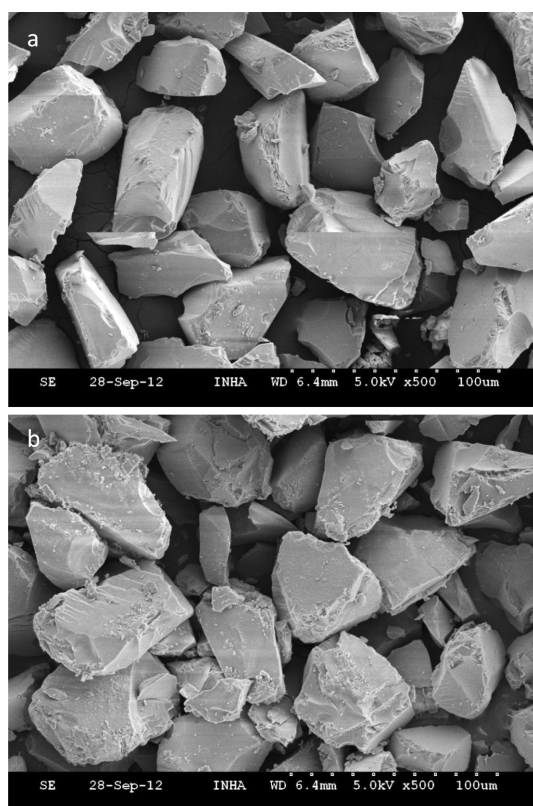


Figure 1. Scanning electron microscope (SEM) images of silica gel (a) produced Pd-SH-SILICA and (b) four times reused catalyst.

fresh sample and sample after the catalytic runs revealed that the shape and surface morphologies of catalyst remain almost same even after fourth catalytic cycle. It demonstrates that the particles of silica gel are performing with good stability in the catalytic reaction.

The efficient heterogeneous acyl Sonogashira coupling is still challenging. Moreover, the Pd catalysts under the stringent conditions suffer from Pd agglomeration, Pd leaching or structural damage of the supports. However, we observed a complete reaction at very mild reaction conditions. Various substrates were also examined with excellent yields and the experimental results are summarized in Table 1. The coupling reactions occurred smoothly at room temperature and fixed by applying the particular catalyst amount without copper co-catalyst. The reaction of benzoyl chloride with phenyl acetylene and base triethylamine was first examined using Pd-SH-SILICA catalyst at room temperature in toluene. The desired corresponding product was obtained in good yield (87%, entry 1, Table 1). After the completion of this reaction, the catalyst was recovered by simple filtration. The catalyst was rinsed

Table 1. Acyl Sonogashira reaction catalyzed by Pd-SH-SILICA

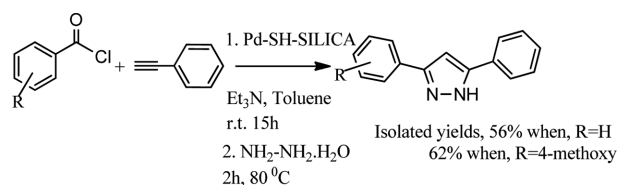
Entry	Acyl chloride	Product	Yield ^a (%)
1			87, 82 ^b , 79 ^c , 68 ^d
2			90
3			92
4			97
5			91
6			86

Reaction conditions: Pd-SH-SILICA catalyst 45 mg, phenyl acetylene (1 mmol), acid chloride (1.2 mmol), triethylamine (1.2 mmol), toluene (5 mL), ^aGC yields, ^bsecond catalytic run, ^cthird catalytic run, ^dfourth catalytic run.

with acetone, water and again acetone and then dried at 50 °C following a new reaction with fresh solvent and reactants under the same reaction conditions. The silica material showed very minor loss in activity after the first reuse, and then the similar behavior persists in the next run. The catalyst is performing and maintaining its activity up to fourth catalytic cycle. The substituted acyl chlorides are observed to the corresponding products more efficiently. The *ortho* or *para*-substituted acyl chlorides did not show any difference on product yields. The reaction is tolerant over a wide range of functional groups on the acyl chlorides (Table 1), all of them results in high yields. This study shows the potential of this catalyst for practical synthetic application. Not only aryl acyl chlorides but also heteroaryl acyl chloride with phenyl acetylene is observed to produce high yield under the same reaction conditions.

In an effort to extend the range of potential organic synthesis, we illustrated three component pyrazole syntheses. Because of their wide-spread use in fields of pharmacy, synthetic and agro chemistry, a large variety of pyrazole derivatives have received much attention.²⁴ To date, the synthesis of these compounds has been somewhat limited by the available chemistry. By far the most common synthetic method for the preparation of substituted pyrazoles involves cyclocondensation of an appropriate hydrazine, which acts as a bidentate nucleophile, with other three-carbon units featuring two electrophilic carbons in a 1, 3-relationship.²⁵ Yet as shown earlier, an expedient, simple, and general method for the synthesis of pyrazoles is still being needed. Due to good activity of the Pd-SH-SILICA catalyst in acyl Sonogashira reaction, we further extended one-pot three component reactions. One-pot procedures involving multiple catalytic events are very useful from economical point of view²⁶ and also will not affect to the heterogeneous nature of the catalyst. Only one example H.-L. Liu and co-workers have been reported for the construction of pyrazole derivatives including one-pot three component fashion with acyl chlorides, alkynes and hydrazines.²⁷ In this case, the catalyst CuI and PdCl₂(PPh₃)₂ both were needed to achieve the desire product. We select a little different reaction condition to perform almost similar products avoiding CuI co-catalyst.

In the presence of hydrazine hydrate, the only product was the corresponding pyrazole in good yields. As shown in Scheme 2, the benzoyl chloride was firstly reacted with phenyl acetylene at room temperature in presence of triethylamine in toluene for 15 h. Then 2 equivalent hydrazine hydrate (in methanol solution) was added and stirred for an additional 2 h at 80 °C, which produce the pyrazole



Scheme 2. Pyrazole synthesis.

in 56% isolated yield. In the formation of pyrazoles, polar solvent was needed whereas hydrazine hydrate was non-soluble in toluene. For good solubility of hydrazine hydrate, methanol solution was added in the system. Under the same conditions, we carried out another example which also produce the desired product in 62% isolated yield (Scheme 2, R = 4-methoxy). Formation of pyrazole was observed by TLC analysis during the reaction. Thereby, the intermediate in the reaction mixture immediately reacts with hydrazine by accelerating the rate in the one-pot system. Further studies would be necessary for understanding of the reaction mechanism. Since our method proved successful with two examples of substituted pyrazoles, we envisaged that other interesting class of molecules with pharmacological activity might also be accessible.

It was described as copper free acyl Sonogashira reactions with silica based heterogeneous catalytic system and performed three component pyrazole synthesis in good yields. Although previously, one example was reported for acyl sonogashira reactions with nanosized MCM-41 anchored palladium bipyridyl complex to give good yields at 50 °C temperature in which a variety of alkynes and acyl chlorides were converted but it involves with poisonous phosphine ligand and CuI.¹⁰ Another example was reported the copper free catalytic acyl sonogashira reactions by palladium nanoparticles (PdNPs) embedded into a polymer matrix, PPS [PPS = poly(1,4-phenylene sulfide)], at 50 °C and high metal loading.¹² However, Pd-SH-SILICA exhibited improved catalytic performance for copper free acyl Sonogashira reactions under mild reaction conditions.

In conclusion, we have demonstrated an efficient and eco-friendly procedure for the synthesis of ynones using silica supported thiol-palladium complex as a recyclable catalyst under copper free mild reaction conditions. The material was synthesized by post grafting of 3-mercaptopropyltrimethoxysilane on amorphous silica and subsequently Pd(II) attached onto thiol groups. This synthetic method has notable advantages because it involves easily available, less costly and produces an easily recyclable catalyst in high yields of the products. The mild reaction conditions encouraged us to further extension for the devel-

opment of novel multicomponent reactions. Thus we have explained the three component synthesis of pyrazoles in one-pot fashion with good yields. Specifically, this simple procedure for the ynone synthesis and this approach to synthesize N-containing heterocycles may be valuable tool in future.

EXPERIMENTAL SECTION

Preparation of Pd-SH-SILICA

A solution of 1 g silica in toluene (10 mL) was stirred with excess (3-mercaptopropyl)-trimethoxysilane (500 mg) at 100 °C for 10 h. The solution was filtered, and the residue was quickly washed with toluene and dichloromethane and air-dried (theoretical SH loading 0.99 mmol gm⁻¹). Then the dried solid material SH-SILICA (200 mg) was dispersed in a THF (2 mL) solution containing palladium acetate (20 mg) and stirred at room temperature until disappearance of yellow color.²⁰ The deep orange solid silica was filtered and the residue was washed with dichloromethane. The resulting solid material was dried in air (Pd loading 0.4 mmol gm⁻¹). It was denoted as Pd-SH-SILICA.

Catalytic Acyl Sonogashira Reaction

In a typical acyl Sonogashira reaction, the catalyst, Pd-SH-SILICA (45 mg) was added in dry toluene (5 mL), followed by alkynes (1 mmol), acyl chloride (1.2 mmol) and triethylamine (1.2 mmol) in a small glass vial. The resulting solution was stirred at room temperature for 15 h and monitored by thin-layer chromatography (TLC). After completion of the reaction, the product was monitored by GC analysis. All of the products were known. As an example, ¹H and ¹³C NMR of the compound (Table 1, entry 1) were observed and compared with literature. So, the reaction mixture was filtered and the solvent was completely evaporated under reduced pressure. The residue was extracted with ethyl acetate and washed twice with water, and concentrated under reduced pressure. The residue was then purified through column chromatography using the solvent ratio of hexane and ethyl acetate (10 : 1). 1, 3-diphenylprop-2-yn-1-one (table 1, entry 1)¹²: ¹H NMR (CDCl₃, 400 MHz): δ 8.23 (dd, *J* = 7.7 Hz, 2H), 7.69 (dd, *J* = 7 Hz, 2H), 7.64 (m, 1H), 7.42–7.55 (m, 5H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 178.0, 137.0, 134.1, 133.0, 130.8, 129.6, 128.7, 120.1, 93.1, 86.8 ppm. Anal. Calcd for C₁₅H₁₀O: C, 87.38; H, 4.85; Found: C, 87.27; H, 4.92.

Synthesis of Pyrazoles

After 15 h, explanation as above, without filtration the

mother solution was kept at 80 °C and added hydrazine hydrate (2 mmol in 1 mL methanol) solution. The reaction mixture was stirred for additional 2 h. After cooling to room temperature, the solvent was removed under reduced pressure and then the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (2×5 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/ethyl acetate, 4:1) to afford the pure pyrazoles. Both compound were characterized by spectral data and compared with literature. 3, 5-Diphenyl-1H-pyrazole (Scheme 1, R = H, 56% yield):^{28,29} ¹H NMR (CDCl₃, 400 MHz) δ 7.74 (d, *J* = 7.6 Hz, 4H) 7.34–7.45 (m, 6H), 6.85 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 148.8, 132.3, 128.8, 128.2, 125.7, 100.1 ppm. Anal. Calcd for C₁₅H₁₂N₂: C, 81.82; N, 12.73; H, 5.45; Found: C, 81.61; N, 12.82; H, 5.50. 3-Phenyl-5-(4-methoxyphenyl)-1H-pyrazole (Scheme 1, R=OMe, 62% yield):²⁸ ¹H NMR (CDCl₃, 400 MHz) δ 7.80 (d, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.40 (m, 3 H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1 H), 3.84 (s, 3 H) ppm; ¹³C NMR (CDCl₃): δ 148.9, 148.1, 159.8, 131.5, 128.7, 127.9, 126.9, 125.6, 123.6, 114.1, 99.5, 55.5 ppm. Anal. Calcd for C₁₆H₁₄N₂O: C, 76.80; N, 11.20; H, 5.60; Found: C, 76.75; N, 10.87; H, 5.82.

Catalyst Recycling

After the completion of a reaction, the mixture was centrifuged and toluene solution was decanted. The solids were washed with acetone, water and again acetone, isolated by centrifugation between washes, then dried at 50 °C and used for next run.

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