Coupling Reaction of Acid Chlorides with Terminal Alkynes Catalyzed by Diatomite-Supported Palladium(II) Salophen Complex

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Abstract: A highly-efficient method for the copper- and solvent-free coupling reaction of acid chlorides and terminal alkynes catalyzed by diatomite-supported palladium(II) salophen complex is described. Acid chlorides are easily coupled with terminal alkynes, giving good to high yields in the presence of a low catalyst loading (1 mol% Pd) in DIEA at room temperature under aerobic conditions. After centrifugation, the supported catalyst is able to be recycled and reused for several times with only a slight decrease in activity.

Keywords: Copper-free, sonogashira reaction, supported catalyst, acid chlorides.

Alkynyl ketones are useful synthetic intermediates for the preparation of many biologically active compounds and heterocyclic derivatives [1]. The direct coupling of alkynyl palladium reagents with acid chlorides is an important method for the preparation of alkynyl ketones. However, these methods require anhydrous solvents and an inert atmosphere [2]. Moreover, these reactions require degassed organic solvents, and have to be carried out under an inert atmosphere. This is particularly inconvenient when the reactions are carried out in multiple vessels for library generation. In spite of the synthetic elegance of the construction of synthetically useful alkynyl ketones, these palladium-catalyzed reactions are usually carried out in a homogeneous phase, which makes the catalysts difficult to recover and reuse in subsequent reactions Hence, facile separation of catalysts and products for the recycling of the catalysts is rather important from the viewpoints of economical and environmental concern. For these reasons, heterogenization of such homogeneous catalysts used for alkynyl ketones formation is very valuable.

The use of heterogeneous catalysts for synthesis of alkynyl ketones has paid much attention to reducing waste, thus working toward an environmentally benign chemical process. Likhar and co-workers [3] have reported that acid chlorides could be coupled with terminal alkynes in the presence of 1 mol% of Pd/C under refluxing toluene, and the catalyst could be reused for five cycles with a 15% leaching of Pd.

Recently Chen *et al.* [4] have described the synthesis of alkynyl ketones by coupling acid chlorides with terminal alkynes catalyzed by a nanosized MCM-41 anchored palladium bipyridyl complex in the presence of PPh_3 and CuI at 50 °C in Et_3N as a solvent.

Very recently, we have reported the synthesis of the polystyrene-supported bidentate phosphine palladium(0) complex [PS-dpp-Pd(0)] and found that this complex is a highly active and recyclable catalyst for acylation of terminal alkynes with acid chlorides [5]. However, to the best of our knowledge, no Sonogashira coupling reaction of acid chlorides with terminal alkynes catalyzed by diatomite-supported palladium(II) salophen complex has been reported.

Diatomite ($SiO_2{\cdot}nH_2O$) or diatomaceous earth is a siliceous rock made up largely from the skeletons of aquatic plants called diatoms [6]. Due to the extremely porous structure, low density and high surface area of diatomite, there is a possibility to use it for the adsorption of organic and inorganic chemicals. Furthermore, these unique properties have led to its applications as filtration media in a number of industries. The diatom shell, which is composed of amorphous silica, has properties such as high porosity with strong adsorb ability and excellent thermal resistance. Hence, diatomite has been widely used as filter aid, catalytic support, and adsorbent [7].

In the present study, we wish to report the synthesis of diatomite-supported palladium(II) salophen complex and its catalytic properties in the copper- and solvent-free Sonogashira reaction of acid chlorides with terminal alkynes catalyzed under aerobic conditions.

The synthesis of the diatomite-supported Pd(II) salophen complex was carried out using a slight modification of the procedure previously reported for the synthesis of diatomite-supported Mn(II) salophen [8]. Specifically, 2.0 g of diatomite was added to 100 ml of ethanol together with 10.0 mmol of $PdCl_2(PhCN)_2$. After the mixture was refluxed for 6 h, 10.0 mmol of salophen was added to the suspension, and the mixture was further refluxed for 12 h. Then the mixture was cooled to room temperature, filtrated, and washed with ethanol. The catalyst was then obtained by drying the solid under vacuum at 100 °C for 12 h. The palladium content of diatomite-supported Pd(II) salophen, which was determined

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by inductively coupled plasma (ICP), was obtained to be 3.38 %. A comparison of the FT-IR spectrum for the encapsulated complex with that of the ''free complex'' [8] indicates the presence of the complex inside the diatomite cavities and pores. The IR spectra for diatomite-supported Pd(II) salophen show major bands at 3400, 3050, 1610, 1570, 1530, 1100, and 790 cm^{-1} which are absent in the diatomite IR spectrum.

The diatomite-supported Pd(II) salophen complex prepared was first used in the Sonogashira coupling reaction of acid chlorides with terminal alkynes. The coupling reaction of benzoyl chlorides with phenylacetylene was initially studied as a model reaction. The reaction conditions were systematically optimized, and the results were presented in Table **1**. As shown in this table, our initial goal was to optimize the reaction conditions for a copper- and solvent-free coupling of benzoyl chloride **1a** (1 mmol) and phenylacetylene **2a** (1mmol) in the presence of 1.0 mol% Pd. When the reaction was performed with DIEA as base, an excellent 98% yield of the product was obtained (entry 2). Increasing the amount of palladium catalyst (entry 8) and increasing the reaction time (entry 9) did not increase the yield of product further. Decreasing the reaction time (entry 10) decreased the yield of product. A low palladium concentration prolonged the reaction time and gave a decreased yield (entry 11).

After the optimized conditions were found, we explored the general applicability of the diatomite-supported Pd(II) salophen complex as a catalyst for copper- and solvent-free coupling reaction of acid chlorides **1** containing electron-withdrawing or donating substituents with different alkynes **2**. The results are shown in Table **2**. The coupling reaction of phenylacetylene with *p*-methyl and *p*-methoxy benzoyl chlorides bearing electron-donating groups at their *para*-positions gave the corresponding products **3b** and **3f** in 99% and 95% yields respectively (entries 2 and 6). *p*-nitro and *p*-chloro benzoyl chlorides having electron- electron-deficient aromatic rings also underwent the coupling reaction with phenylacetylene under similar conditions to afford the corresponding products **3d**, **3e** in excellent yield (99%).

The Sonogashira coupling reaction of the *ortho*-substituted electron rich benzoyl chlorides with terminal alkynes gave the corresponding coupling products in high yields owing to the steric hindrance of the *ortho*-substituents (entries 3 and 13).

When the less reactive acetylene, 1-hexyne, and 1-octyne were used, the coupling product was produced efficiently. The coupling of para-substituted benzoyl chlorides having methyl, methoxy, and chloro groups took place with 1-hexyne to give the corresponding products **3j-l** in 96%, 97%, and 99% yields, respectively (entries 10-12). Coupling reaction of 1-octyne with more reactive electron-withdrawing *p*-chlorobenzoyl chloride or the less active electron-rich *p*-methyl and *p*-methoxybenzoyl chlorides gave a high yields (entries 17-19). A hetero-aryl acid chloride such as 2-thiophene carbonyl chloride reacted with terminal alkynes to give the good products (entries 8, and 15). Under the same conditions as above, cyclohexane acid chloride also afforded the desired product in good to excellent yields (entries 7, 14, and 20).

The recyclability of the diatomite-supported Pd(II) salophen complex was examined in the coupling reaction of benzoyl chloride and phenylacetylene. The catalyst was separated from the reaction mixture by filtration after each experiment, washed with water and acetonitrile, and dried carefully before use in subsequent runs. Thus after the first reaction, which gave a quantitative yield of the coupling product **3a** (Table **2**, entry 1), the catalyst beads were recovered and successively subjected to four further runs under the same conditions to afford **3a** in 97–85% yields (Table **3**). It is to be mentioned that some information included in this article has previously been published [9].

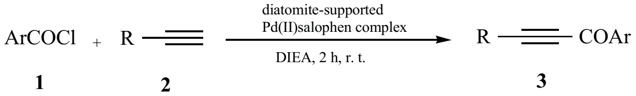
In conclusion, we have shown that diatomite-supported palladium(II) salophen complex is a highly efficient and recyclable catalyst for the copper- and solvent-free coupling

Table 1. Copper-and Solvent-Free Coupling Reaction of Benzoyl Chloride with Phenylacetylene[a]

Entry	Base	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	Et_3N	1.0	2	97
2	DIEA[c]	1.0	2	98
3	Pyrrolidine	1.0	2	97
4	Pyridine	1.0	2	65
5	Piperidine	1.0	2	97
6	Morpholine	1.0	2	95
7	Et_2NH	1.0	2	93
8	DIEA	2.0	2	98
9	DIEA	1.0	5	98
10	DIEA	1.0	1	86
11	DIEA	0.5	5	91

[a] Reaction conditions: benzoyl chloride (1.0 mmol), phenylacetylene (1.0mmol), base (1.0 mmol), room temperature, aerobic conditions.
[b] GC yield.
[c] Diisopropylethylamine.

Table 2. Copper- and Solvent-Free Sonogashira Reactions of Aroyl Chlorides with Terminal Alkynes[a]



Entry	Ar	R	Product	Yield[b] (%)
1	Ph	Ph	**3a**	98
2	4-Me-C_6H_4	Ph	**3b**	99
3	2-Me-C_6H_4	Ph	**3c**	98
4	4-NO_2-C_6H_4	Ph	**3d**	99
5	4-Cl-C_6H_4	Ph	**3e**	99
6	4-MeO-C_6H_4	Ph	**3f**	95
7	cyclohexyl	Ph	**3g**	91
8	2-thiophen	Ph	**3h**	92
9	Ph	*n*-C_4H_9	**3i**	97
10	4-Me-C_6H_4	*n*-C_4H_9	**3j**	96
11	4-MeO-C_6H_4	*n*-C_4H_9	**3k**	97
12	4-Cl-C_6H_4	*n*-C_4H_9	**3l**	99
13	2-Me-C_6H_4	*n*-C_4H_9	**3m**	95
14	cyclohexyl	*n*-C_4H_9	**3n**	98
15	2-thiophen	*n*-C_4H_9	**3o**	94
16	4-NO_2-C_6H_4	*n*-C_4H_9	**3p**	99
17	4-Cl-C_6H_4	*n*-C_6H_{13}	**3q**	99
18	4-Me-C_6H_4	*n*-C_6H_{13}	**3r**	95
19	4-MeO-C_6H_4	*n*-C_6H_{13}	**3s**	94
20	cyclohexyl	*n*-C_3H_7	**3t**	99

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), diatomite-supported palladium (II) salophen complex (0.01 mmol), DIEA (1 mmol), 2 h, room temperature, aerobic conditions.
[b] GC yield.

Table 3. Sonogashira Coupling Reaction of Benzoyl Chloride with Phenylacetylene Catalyzed by the Recycled Catalyst[a]

Entry	Catalyst	Yield(%)
1	first cycle	97
2	second cycle	95
3	third cycle	91
4	fourth cycle	85

[a] Reaction conditions; benzoyl chlorid (1.0 mmol), phenylacetylene (1.0 mmol), catalyst (0.01 mmol), Et_3N (1 mmol), room temperature, 2 h, aerobic conditions.
[b] GC yield.

reaction of a variety of acid chlorides and terminal alkynes leading to the formation of alkynyl ketones. The catalyst can be easily recycled by centrifugation and reused for several times with only a slight decrease in activity.

Typical Procedure for the Preparation of Diatomite-Supported Pd(II) Salophen Complex

To a 250-ml round bottom flask equipped with a magnetic stirrer bar, and containing EtOH (100 ml), were added 2.0 g of dried diatomite and 10.0 mmol (0.383 g) of $PdCl_2(PhCN)_2$, and the reaction mixture was refluxed for 6 h. Then 10.0 mmol (0.318 g) of salophen was added to the suspension, and the mixture was further refluxed for 12 h. The resulting product was filtered, washed with ethanol, and dried at 100 °C for 12 h to give diatomite-supported Pd(II) salophen complex.

Typical Procedure for the Coupling Reaction of Acid Chlorides with Terminal Alkynes Catalyzed by Diatomite-Supported Palladium(II) Salophen Complex

A round bottom flask was charged with an acid chloride (1.0 mmol), a terminal alkynes (1.0 mmol), catalyst (0.01

mmol), and DIEA (1.0 mmol). The mixture was stirred at room temperature for 2 h under aerobic conditions. Upon completion of the reaction, the reaction mixture was dissolved in chloroform (5 ml). The palladium catalyst was separated from the mixture by filtration, washed with water (10 ml) and acetonitrile (10 ml), and reused in the next run. The chloroform solution was then washed with water (5 ml) and dried over $MgSO_4$, and toluene (1.0 mmol) was added as internal standard for GC analysis. After GC analysis, the solvent was removed under vacuum, and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (97:5) as eluent to afford the pure product.

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