Synthesis of Ynones via Recyclable Polystyrene-Supported Palladium(0) Complex Catalyzed Acylation of Terminal Alkynes with Acyl Chlorides under Copper- and Solvent-Free Conditions

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Abstract: Herein, a highly efficient method for the copper- and solvent-free coupling reaction of acyl chlorides and terminal alkynes catalyzed by 1-phenyl-1,2-propanedione-2-oxime thiosemicarbazone-functionalized polystyrene resin-supported Pd(0) complex is described. Acyl chlorides are easily coupled with terminal alkynes, giving good to high yields in the presence of a low catalyst loading (1 mol% Pd) in Et₃N at room temperature under aerobic conditions. After centrifugation, the supported catalyst can be recycled and reused several times with only a slight decrease in activity.

Key words: copper-free, solvent-free, supported catalyst, Sonogashira coupling, acyl chloride, ynone

The synthesis of ynones has attracted considerable interest because of their appearance in a wide variety of biologically active molecules¹ and their utility as synthetic intermediates, particularly for the synthesis of natural products² and pharmaceutical molecules.³ A common route to ynones involves the acylation of alkynyl organometallic reagents based on silver,⁴ copper,⁵ lithium,⁶ zinc,⁷ silicon,⁸ and tin⁹ with acid chlorides. The coupling reaction of acyl chlorides and terminal alkynes catalyzed by palladium catalysts has received much attention of late. This reaction can be achieved under mild conditions with a wide range of functional groups on alkynes and enhanced chemoselectivity.¹⁰

In spite of the synthetic elegance of the construction of synthetically useful ynones, these palladium-catalyzed reactions are usually carried out in a homogeneous phase, which makes the catalysts difficult to recover and reuse in subsequent reactions.

The use of heterogeneous catalysts for the synthesis of ynones has paid much attention to reducing waste, thus working toward an environmentally benign chemical process. Likhar and co-workers have reported that acyl 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.¹¹

Recently, Chen et al.¹² have described the synthesis of ynones by coupling acyl chlorides with terminal alkynes catalyzed by a nanosized MCM-41 anchored palladium

SYNLETT 2011, No. 3, pp 0311–0314 Advanced online publication: 13.01.2011 DOI: 10.1055/s-0030-1259322; Art ID: D23310ST © Georg Thieme Verlag Stuttgart · New York bipyridyl complex in the presence of Ph_3P and CuI at 50 °C in Et₃N as 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.¹³ However, to the best of our knowledge, no Sonogashira coupling reaction of acyl chlorides with terminal alkynes catalyzed by polystyrene-supported palladium(0) complex has been reported.

Our approach was guided by three imperatives: (1) the support should be easily accessible; (2) the reaction should be carried out using readily available and cheap reagents; and (3) the ligand anchored on the support should be air-stable at room temperature, which should allow its storage in normal bottles with unlimited shelf-life.

In this paper, we wish to report the synthesis of the polystyrene-supported palladium(0) 1-phenyl-1,2-propanedione-2-oxime thiosemicarbazone complex [abbreviated as PS-ppdot-Pd(0)] and its catalytic properties in the copperand solvent-free Sonogashira reaction of acyl chlorides with terminal alkynes catalyzed under aerobic conditions. The ease of preparation of the complex, its long shelf-life, stability toward air, and compatibility with a wide variety of aryl halides and alkynes make it ideal for the abovementioned reactions.

We used a well-known chloromethylated polystyrene (2% DVB) as catalyst support because it is still one of the most popular polymeric materials used in synthesis due to its inexpensive, ready availability, mechanical robustness, and facial functionalization.

The immobilized Schiff base palladium PS-ppdot-Pd(0) can be prepared easily from a commercially available polymer. In this approach, the Schiff base palladium complex is attached, via a covalent bond, to a pendant chloromethyl group on the surface of the polymer resin particles. Reaction of polystyrene resin with 1-phenylpropane-1,2-dione-2-oxime thiosemicarbazone PPDOT¹⁴ (1) in DMF at 100 °C and then treatment of the PPDOT-functionalized polymer **2** with a solution of PdCl₂(PhCN)₂ in ethanol under reflux resulted in covalent attachment of the palladium complex. Reduction with hydrazine monohydrate gave the polystyrene-supported palladium(0)-complex catalyst [PS-ppdot-Pd(0)] **4** (Scheme 1).



Scheme 1

Successful functionalization of the polymer was confirmed by elemental analysis. The N content of the resin was found to be 4.77% (0.82 mmol/g), which indicates that only 60% of total chlorine is substituted by amine. The metal loading of the polymer-supported palladium complex, determined by inductively coupled plasma (ICP), was found to be 4.38% (0.41 mmol/g). In the IR spectrum of the polymer-bound PPDOT obtained, the sharp C–Cl peak (due to CH₂Cl groups) at 1264 cm⁻¹ in the starting polymer was practically omitted or was seen as a weak band after introduction of PPDOT and palladium on the polymer. In addition, the IR spectrum of the polymer-anchored PPDOT showed new absorption bands at 3400 (OH), 3340 (NH), and 1678 cm⁻¹ (C=N), which were absent in the IR spectrum of the pure polymer beads. This confirms the formation of the metal complex on the surface of the polymer.

The catalytic activity of the PS-ppdot-Pd(0) complex 4 (1 mol%) was studied at room temperature under aerobic conditions in a copper-free coupling reaction using phenylacetylene and benzoyl chloride. As shown in Table 1, our initial goal was to optimize the reaction conditions for a copper- and solvent-free coupling of benzoyl chloride **5a** (1 mmol) and phenylacetylene **6a** (1 mmol) in the presence of 1 mol% Pd [as in PS-ppdot-Pd(0)]. When the reaction was performed with Et₃N as base, an excellent 99% yield of the product was obtained (entry 2). When the reaction was conducted with common inorganic bases such as K₂CO₃ and Cs₂CO₃, low GC yields were obtained (entries 8 and 9). Using lower palladium loadings mostly led to a longer reaction time, which was consistent with our experimental results (entries 10 and 11).

After optimized conditions were found, a variety of acyl chlorides were coupled with terminal alkynes in the presence of 1 mol% of PS-ppdot-Pd(0) under copper- and solvent-free conditions (Table 2). These results show that the reaction is equally facile with both electron-donating and electron-withdrawing substituents present on the aroyl chloride and the terminal alkyne resulting in excellent yields of ynones.

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 **7b** and **7f** in 98% yield (entries 2 and 6). *p*-Nitroand *p*-chlorobenzoyl chlorides having electron-deficient aromatic rings also underwent the Sonogashira coupling

 Table 1
 Copper- and Solvent-Free Coupling Reaction of Benzoyl

 Chloride with Phenylacetylene^a

Entry	Base	Catalyst (mol%)	Time (h)	Yield (%) ^b
1	DIPEA	1.0	0.5	98
2	Et ₃ N	1.0	0.5	99
3	pyrrolidine	1.0	0.5	95
4	pyridine	1.0	0.5	50
5	Et ₂ NH	1.0	0.5	85
6	morpholine	1.0	0.5	68
7	piperidine	1.0	0.5	92
8	K ₂ CO ₃	1.0	0.5	10
9	Cs ₂ CO ₃	1.0	0.5	5
10	Et ₃ N	0.5	2	87
11	Et ₃ N	0.2	5	80

^a Reaction conditions: benzoyl chloride (1.0 mmol), phenylacetylene (1.50 mmol), base (1.0 mmol), r.t., aerobic conditions.

^b GC yield.

with phenylacetylene under similar conditions to afford the corresponding products **7d**,**e** in excellent yield (99%), respectively (entries 4 and 5).

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

When the less reactive acetylenes 1-hexyne and 1-pentyne were used, the coupling products were produced efficiently. The coupling of *para*-substituted benzoyl chlorides having methyl-, methoxy-, and chloro-substituents took place with 1-hexyne to give the corresponding products **7j–l** in 98%, 98%, and 99% yields, respectively (entries 10–12). Coupling reaction of 1-pentyne with more reactive electron-deficient *p*-chlorobenzoyl chloride or the less reactive electron-rich *p*-methyl- and *p*-methoxybenzoyl chlorides gave excellent yields of the coupled products (entries 17–19). Copper-free coupling reactions of aroyl halides with trimethylsilylacetylene also took place

Table 2 Copper- and Solvent-Free Sonogashira Reactions of AcidChlorides with Terminal Alkynes^a

ArCOCI 5	+ R [PS	-ppdot-Pd(0)] N, r.t., 0.5 h	→ ArCO 	—R
Entry	Ar	R	Product	Yield (%) ^b
1	Ph	Ph	7a	99
2	$4-MeC_6H_4$	Ph	7b	98
3	$2-MeC_6H_4$	Ph	7c	97
4	$4-O_2NC_6H_4$	Ph	7d	99 (95)
5	4-ClC ₆ H ₄	Ph	7e	99
6	4-MeOC ₆ H ₄	Ph	7f	98 (93)
7	cyclohexyl	Ph	7g	99
8	2-thienyl	Ph	7h	99
9	Ph	<i>n</i> -Bu	7i	99
10	4-MeC ₆ H ₄	<i>n</i> -Bu	7j	98
11	4-MeOC ₆ H ₄	<i>n</i> -Bu	7k	98
12	4-ClC ₆ H ₄	<i>n</i> -Bu	71	99 (94)
13	2-MeC ₆ H ₄	<i>n</i> -Bu	7m	97
14	cyclohexyl	<i>n</i> -Bu	7n	99
15	2-thienyl	<i>n</i> -Bu	70	99
16	Ph	<i>n</i> -Pr	7 p	99
17	$4-ClC_6H_4$	<i>n</i> -Pr	7q	99
18	4-MeC ₆ H ₄	<i>n</i> -Pr	7 r	98
19	4-MeOC ₆ H ₄	<i>n</i> -Pr	7s	98 (93)
20	cyclohexyl	<i>n</i> -Pr	7t	99
21	Ph	TMS	7u	99
22	$4-MeOC_6H_4$	TMS	7w	98
23	$4-O_2NC_6H_4$	TMS	7x	99 (95)
24	2-thienyl	TMS	7y	98

^a Reaction conditions: 5 (1.0 mmol), 6 (1.0 mmol), [PS-dppot-Pd(0)]
(0.01 mmol), Et₃N (1.0 mmol), 0.5 h, r.t., aerobic conditions.
^b GC yield. Numbers in parentheses are isolated yields.

under similar conditions to give products **7u**, **7w**, and **7x** in excellent yields (entries 21–23).

A heteroaryl acyl chloride such as 2-thiophene carbonyl chloride also reacted with terminal alkynes to give the products in near quantitative yields (entries 8, 15, and 24). Under the same conditions as above, cyclohexane carbonyl chloride also afforded the desired coupling products in excellent yield (entries 7, 14, and 20).

The recyclability of the PS-ppdot-Pd(0) catalyst **4** was examined in the Sonogashira coupling reaction of benzoyl

chloride with 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 **7a** (Table 2, entry 1), the catalyst beads were recovered and successively subjected to four further runs under the same conditions to afford **5a** in 99–90% yields (Table 3).

 Table 3
 Copper-Free Coupling Reaction of Benzoyl Chloride with Phenylacetylene Catalyzed by the Recycled Catalyst^a

Entry	Cycle	Yield (%) ^b
1	1st	99
2	2nd	97
3	3rd	93
4	4th	90

^a Reaction conditions: benzoyl chloride (1.0 mmol), phenylacetylene (1.0 mmol), catalyst (0.01 mmol), Et_3N (1 mmol), r.t., 0.5 h, aerobic conditions.

^b GC yield.

In conclusion, we have shown that PS-ppdot-Pd(0) is a highly efficient and recyclable catalyst for the copper- and solvent-free coupling reaction of a variety of acyl chlorides and terminal alkynes leading to the formation of ynones. The catalyst can be easily recycled by centrifugation and reused several times with only a slight decrease in activity.

Preparation of Polymer-Anchored PS-ppdot-Pd(0) 4

To a 250 mL round-bottom flask equipped with a magnetic stirrer bar, and containing DMF (100 mL), were added chloromethylated polystyrene (2 g, 1.25 mmol/g of Cl) and PPDOT (7.5 mmol), and the reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was filtered and washed thoroughly with DMF, and dried in vacuo for 12 h. The PPDOT-functionalized polymer 2 (1.5 g) was treated with EtOH (50 mL) for 30 min. An ethanolic solution of PdCl₂(PhCN)₂ (0.12 g) was added, and the resulting mixture was heated to 70 °C for 6 h. The resulting bright yellow colored polymer, impregnated with the metal complex, was filtered and washed with EtOH, and then stirred with hydrazine monohydrate (2 g) and EtOH (20 mL) at 50 °C under Ar for 5 h. The resulting product was filtered, washed with EtOH, and dried at 50 °C to give PS-ppdot-Pd(0) (Scheme 1).

General Procedure for the Coupling Reaction of Acid Chlorides with Terminal Alkynes Catalyzed by PS-ppdot-Pd(0)

A round-bottom flask was charged with an acid chloride (1.0 mmol), a terminal alkyne (1.0 mmol), [PS-ppdot-Pd(0)] (0.01 mmol), and Et_3N (1.0 mmol). The mixture was stirred at r.t. for 30 min under aerobic conditions. Upon completion of the reaction, the mixture was extracted with EtOAc (2 × 10 mL). The organic layer was washed with H₂O to remove the amine hydrochloride byproduct. The organic layer was separated, dried over MgSO₄, filtered, and concentrated in vacuo to afford the crude product. The residue was purified by column chromatography using CHCl₃–MeOH (98:2) as eluent to afford the pure product.

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References

- (1) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011; and references therein.
- (2) (a) Dodero, V. I.; Koll, L. C.; Faraoni, M. B.; Mitchell, T. N.; Podesta, J. C. J. Org. Chem. 2003, 68, 10087. (b) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A. Angew. Chem. Int. Ed. 2004, 43, 3947. (c) Trost, B. M.; Ball, Z. T. J. Am. Chem. Soc. 2004, 126, 13942.
- (3) (a) Trost, B. M.; Schmidt, T. J. Am. Chem. Soc. 1988, 110, 2301. (b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. J. Am. Chem. Soc. 2001, 123, 2074. (c) Sheng, H.; Lin, S.; Huang, Y. Tetrahedron Lett. 1986, 27, 4893. (d) Kel'in, A. V.; Gevorgyan, V. J. Org. Chem. 2002, 67, 95.
- (4) Davis, R. B.; Scheiber, D. H. J. Am. Chem. Soc. **1956**, 78, 1675.
- (5) Logue, M. W.; Moore, G. L. J. Org. Chem. 1975, 40, 131.
- (6) Schmit, U.; Schwochau, M. Chem. Ber. 1964, 97, 1649.
- (7) Vereshchagin, L. I.; Yashina, O. G.; Zarva, T. V. Zh. Org. Khim. 1966, 2, 1895.
- (8) Walton, D. R. M.; Waugh, F. J. Organomet. Chem. 1972, 37, 45.

- (9) Logue, M. W.; Teng, K. J. Org. Chem. 1982, 47, 2549.
- (10) (a) Tohda, Y.; Sonogashira, K.; Hagihara, N. Synthesis 1977, 777. (b) Wang, J.-X.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. Synth. Commun. 2001, 31, 3337. (c) Yin, J.; Wang, X.; Liang, Y.; Wu, X.; Chen, B.; Ma, Y. Synthesis 2004, 331. (d) Alonso, D. A.; Nájera, C.; Pacheco, M. C. J. Org. Chem. 2004, 69, 1615. (e) Chen, L.; Li, C.-J. Org. Lett. 2004, 6, 3151. (f) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. Chem. Commun. 2005, 1037. (g) Palimkar, S. S.; Kumar, P. H.; Jogdand, N. R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Tetrahedron Lett. 2006, 47, 5527. (h) Palimkar, S. S.; Lahoti, R. J.; Srinivasan, K. V. Green Chem. 2007, 9, 146. (i) Liu, H.-L.; Jiang, H.-F.; Zhang, M.; Yao, W.-J.; Zhu, Q.-H.; Tang, Z. Tetrahedron Lett. 2008, 49, 3805. (j) Lv, Q.-R.; Meng, X.; Wu, J.-S.; Gao, Y.-J.; Li, C.-L.; Zhu, Q.-Q.; Chen, B.-H. Catal. Commun. 2008, 9, 2127. (k) Nishihara, Y.; Inoue, E.; Okada, Y.; Takagi, K. Synlett 2008, 3045.
- (11) Likhar, P. R.; Subhas, M. S.; Roy, M.; Roy, S.; Kantam, M. L. *Helv. Chim. Acta* 2008, *91*, 259.
- (12) Chen, J.-Y.; Lin, T.-C.; Chen, S.-C.; Chen, A.-J.; Mou, C.-Y.; Tsai, F.-U. *Tetrahedron* **2009**, *65*, 10134.
- (13) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Rajaie, M. *Tetrahedron Lett.* **2010**, *51*, 33.
- (14) Reddy, K. H.; Prasad, N. B. L.; Reddy, T. S. *Talanta* **2003**, 59, 425.

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