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THE SONOGASHIRA REACTION IN WATER *VIA* AN AMPHIPHILIC RESIN-SUPPORTED PALLADIUM-PHOSPHINE COMPLEX UNDER COPPER-FREE CONDITIONS

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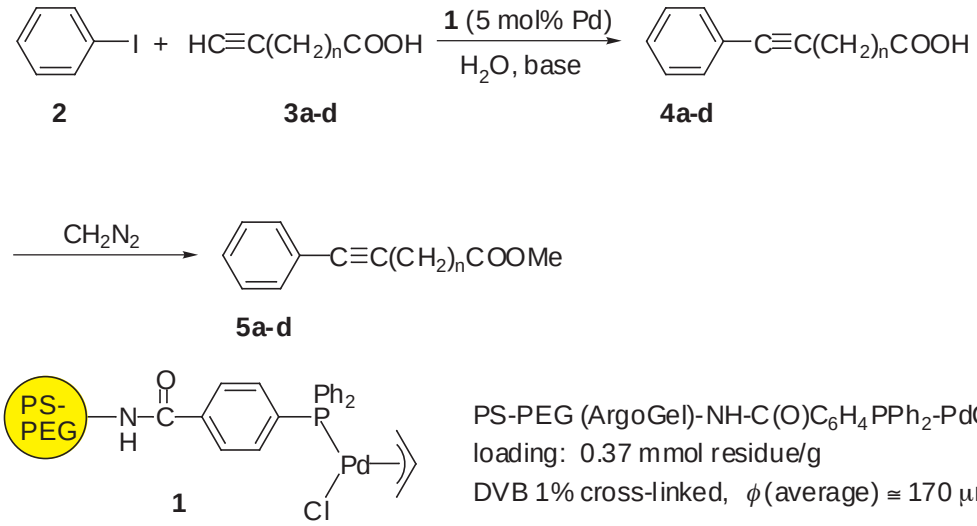
Abstract – The Sonogashira reaction of aryl halides with terminal alkynes was catalyzed by an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium-phosphine complex in water to give the corresponding aryl-substituted alkynes in high yields under copper-free conditions. Reaction of *o*-iodophenol with terminal alkynes under Sonogashira conditions gave benzofuran derivatives in one step.

The palladium-catalyzed coupling of an aryl halide with a terminal alkyne promoted by CuI and an amine base, the so-called Sonogashira reaction,[1] is recognized not only as the most successful method for producing arylacetylene derivatives but is also a key step in the preparation of benzofurans or indoles.[2] However, one of the major problems associated with it lies in the reaction conditions where a copper reagent is frequently required to promote the reaction.[3] The solid-phase Sonogashira reaction, on the other hand, has recently been thoroughly investigated for the coupling of resin-supported halobenzenes with various terminal alkynes to meet the requirement of combinatorial synthesis.[4,5,6] High-throughput synthesis by solution-phase catalysis has also been recognized as a useful methodology with the advent of efficient methods for compound purification. One approach employs supported catalysts that can be readily removed by simple filtration. We have previously reported that an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium-phosphine complex (**1**) catalyzed various palladium-mediated reactions smoothly in water where the advantages of both a water-based environmentally benign reaction and heterogeneous catalysis have been combined in one system.[7] As part of our effort to demonstrate the wide utility of this catalyst system, we decided to examine the Sonogashira reaction in water[8,9] catalyzed by a palladium complex of amphiphilic PS-PEG-supported phosphine under copper-free conditions. We report herein this reaction and its use for the preparation of benzofuran derivatives.

This manuscript is dedicated to Prof. Yuichi Kanaoka on the occasion of his 75th birthday.

Scheme 1



The Sonogashira reaction of iodobenzene (**2**) with 2 equiv of the terminal alkynes (**3**) was carried out in water in the presence of the amphiphilic PS-PEG resin-supported palladium complex (**1**) (5 mol % Pd) (Scheme 1). The catalyst resin was filtered off and rinsed with a small portion of sat. $NaHCO_3$. The combined aqueous filtrate was acidified and extracted with ether to give the phenyl-substituted alkynecarboxylic acids (**4**). The carboxylic acids (**4**) were isolated as their methyl esters from (**5**) after treatment with diazomethane. Representative results are summarized in Table 1. It was found that the Sonogashira reaction takes place under aqueous alkaline conditions in the presence of the PS-PEG

Table 1. The Sonogashira Reaction in Water with the Resin-Supported Complex (**1**).[a]

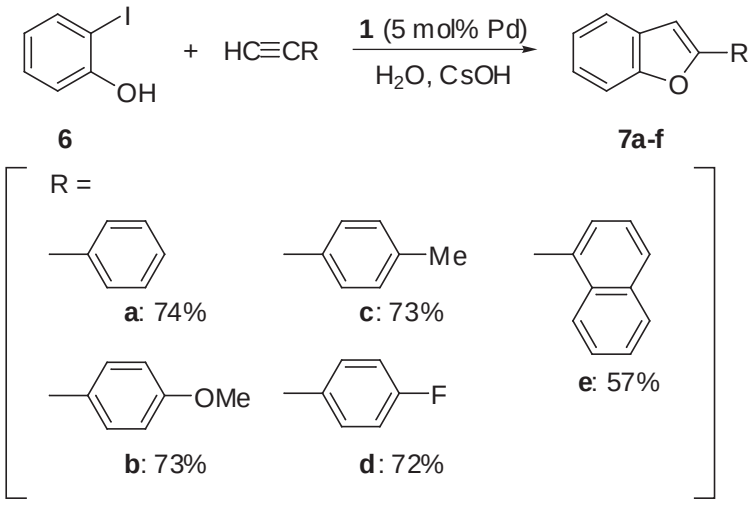
entry	alkyne	base	equiv of base	product	yield[b] (%)
1	HC≡C$(CH_2)_4$COOH (**3a**)	CsOH	3.0	**4a**	74
2	HC≡C$(CH_2)_4$COOH (**3a**)	Et_3N/CuI[c]	3.0	**4a**	70
3	HC≡C$(CH_2)_4$COOH (**3a**)	Et_3N	3.0	**4a**	35
4	HC≡C$(CH_2)_4$COOH (**3a**)	Cs_2CO_3	3.0	**4a**	44
5	HC≡C$(CH_2)_4$COOH (**3a**)	LiOH	3.0	**4a**	59
6	HC≡C$(CH_2)_4$COOH (**3a**)	KOH	3.0	**4a**	65
7	HC≡C$(CH_2)_4$COOH (**3a**)	$Ba(OH)_2$	3.0	**4a**	35
8	HC≡C$(CH_2)_4$COOH (**3a**)	CsOH	5.0	**4a**	83
9	HC≡CCOOH (**3b**)	CsOH	5.0	**4b**	58
10	HC≡C$(CH_2)_2$COOH (**3c**)	CsOH	5.0	**4c**	68
11	HC≡C$(CH_2)_8$COOH (**3d**)	CsOH	5.0	**4d**	41

[a] All reactions were carried out in water with shaking at 60 °C for 12 h. The ratio of **2** (mol)/**3** (mol)/**1** (Pd equiv)/H_2O (L) = 1.0/2.0/0.05/4.0. [b] Isolated yield of the corresponding methyl ester (**5a-d**). [c] 0.05 equiv to **2** of CuI was used.

supported palladium complex (**1**). The combination of the resin-catalyst (**1**), cesium hydroxide and water is essential to promote coupling under copper-free conditions.[10] Thus, a mixture of **2**, **3a** and **1** was shaken in water in the presence of 3 equiv. of cesium hydroxide at 60 °C for 12 h to give **4a** in 74% yield (Table 1, entry 1). The reaction with Et_3N/CuI, the most frequently used reagent system for the Sonogashira reaction, gave **4a** in 70% yield under otherwise similar reaction conditions (entry 2). Coupling in the presence of Et_3N, Cs_2CO_3, LiOH, KOH, or $Ba(OH)_2$ gave **4a** in 35%, 44%, 59%, 65% and 35% yields, respectively, also under similar conditions (entries 3-7). The chemical yield of **4a** was increased with 5 equiv of cesium hydroxide to 83% yield (entry 8). The coupling of **2** with propiolic acid (**3b**), pentynoic acid (**3c**) and undecynoic acid (**3d**) gave **4b**, **4c** and **4d** in 58%, 68% and 41% yields, respectively.

Using the copper-free conditions to promote the Sonogashira reaction identified above, a one-step preparation of the benzofurans (**7**) was achieved in water *via* coupling of 2-iodophenol (**6**) and the terminal alkynes (Scheme 2). A mixture of the iodophenol (**6**) with 4 equiv. of phenylacetylene in water was agitated in the presence of 5 mol % palladium of the PS-PEG resin-supported complex (**1**) and 5 equiv of CsOH at 60 °C for 12 h to give 2-phenylbenzofuran (**7a**) in 74% isolated yield. The reactions of 4-methoxyphenylacetylene, 4-methylphenylacetylene, 4-fluorophenylacetylene and 1-naphthylacetylene gave the corresponding benzofurans (**7b**, **c**, **d** and **e)** in 73%, 73%, 72% and 57% yields, respectively,[11] under the same reaction conditions.

Scheme 2



In summary, the Sonogashira reaction was found to proceed in aqueous alkaline solution under copper-free conditions by use of an amphiphilic PS-PEG resin-supported palladium complex. A one-step preparation of benzofurans bearing 2-substituents was achieved under similar conditions in high yields. Further studies on the water-based Sonogashira reaction and the related heterocyclization with various aryl halides and terminal alkynes are currently underway in our laboratory.

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