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Samarium Powder-Catalyzed Palladium-Free and Ligand-Free Sonogashira Coupling Reactions

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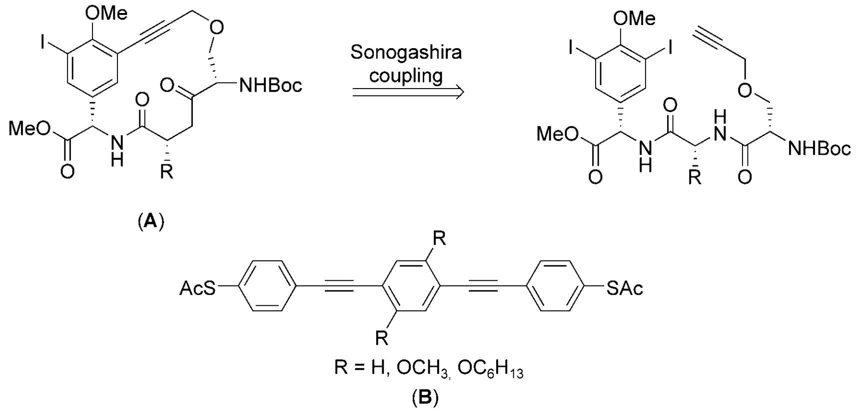
Abstract: A study of samarium powder-catalyzed cross-coupling reactions of aryl halides with terminal alkynes is described. The couplings performed in the polyethylene glycol PEG-600 provided the corresponding coupling products in good yields. The first example of palladium-free, copper-free and amine-free catalytic system for Sonogashira couplings is presented in the absence of ligand.

Keywords: aryl halides; cross-coupling; ligand-free; samarium powder; terminal alkynes

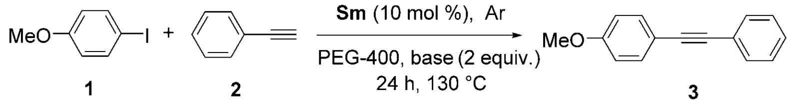
Transition metal-catalyzed cross-coupling reactions are the very useful processes for forming carbon-carbon bonds.[1] The Sonogashira-type coupling between terminal alkynes with ary or vinyl halides is one of the important and widely used procedures for the synthesis of molecules containing an acetylenic moiety, which is found in many fine chemicals and biologically active substances.[2] For example, the construction of arylalkynes plays an important part in prepation of macrocyclic peptide (**A**), which has gained pharmaceutical interest.[3] In recent years, arylalkynes (**B**) have been investigated as conjugated oligomers for reasearch on electrical conductance at the single molecule level.[4] Thus, it is obvious to show the importance and practicablity of such a coupling reaction as shown in Scheme 1.

Since its discovery, this alkynylation of aryl halides has gained great attention and various effective catalytic systems have been developed. The original Sonogashira coupling is carried out in the presence of $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$, or $Pd(PPh_3)_4$ together with CuI as the cocatalyst and a larger amount of amines as the solvents or cosolvents.[5] Based on this foundation, several modified protocols have been presented, including copper-free,[6] Pd/Ni bimetallic systems,[7] Au complex[8] and Ru/Al_2O_3 systems.[9] However, they were all limited for industrial use due to the high costs. To solve this problem, a low loading of palldium catalyst (10^{-4} mol%) was employed.[10] On the other



Scheme 1. Compounds containing an arylalkyne moiety.

Table 1. Screening catalytic conditions for samarium powder-catalyzed Sonogashira coupling between 4-iodoanisole and phenylacetylene.[a]



Entry	Cat. [mol%]	Base	Solvent	**1**:**2**	Yield [%][b]
1	Sm (10)	K_2CO_3	PEG-400	1:1.2	44
2	–	K_2CO_3	PEG-400	1:1.2	trace
3[c]	Sm (10)	K_2CO_3	PEG-400	1:1.2	trace
4	Sm (10)	K_2CO_3	PEG-200	1:1.2	18
5	Sm (10)	K_2CO_3	PEG-600	1:1.2	84
6	Sm (10)	K_2CO_3	PEG-1000	1:1.2	62
7	Sm (10)	K_2CO_3	DMF	1:1.2	trace
8	Sm (10)	K_2CO_3	DMSO	1:1.2	trace
9	Sm (10)	K_2CO_3	$C_6[min]PF_6$	1:1.2	trace
10	Sm (10)	K_2CO_3	glycol	1:1.2	trace
11[d]	Sm (10)	K_2CO_3	PEG-600	1:1.2	68
12	Sm (10)	K_3PO_4	PEG-600	1:1.2	trace
13	Sm (10)	Cs_2CO_3	PEG-600	1:1.2	trace
14	Sm (10)	KF	PEG-600	1:1.2	12
15	Sm (10)	Et_3N	PEG-600	1:1.2	NR
16	Sm (10)	KOH	PEG-600	1:1.2	trace
17	Sm (10)	K_2CO_3	PEG-600	1:1.5	67
18	Sm (10)	K_2CO_3	PEG-600	1:2	34
19	Sm (10)	K_2CO_3	PEG-600	1:3	17
20	Sm (20)	K_2CO_3	PEG-600	1:1.2	75
21	Sm (30)	K_2CO_3	PEG-600	1:1.2	40
22	Sm (50)	K_2CO_3	PEG-600	1:1.2	31
23[e]	Sm (10)	K_2CO_3	PEG-600	1:1.2	trace
24[f]	Sm (10)	K_2CO_3	PEG-600	1:1.2	32
25 g]	Sm (10)	K_2CO_3	PEG-600	1:1.2	NR
26	Sm_2O_3 (10)	K_2CO_3	PEG-600	1:1.2	NR
27	SmI_2 (10)	K_2CO_3	PEG-600	1:1.2	NR

[a] *Reaction conditions:* Ar, Sm (*ca.* 350 µm powder from Aldrich, 99% purity, 0.05 mmol), 4-iodoanisole (0.5 mmol), phenylacetylene (0.6 mmol), base (1.0 mmol), solvent (2 mL), 130 °C, 24 h.

[b] Isolated yield based on 4-iodoanisole.

[c] The catalytic reaction was performed in air.

[d] Sm (*ca.* 550 µm powder) was used instead of Sm (*ca.* 350 µm powder).

[e] I_2 (10 mol%) was employed as the additive.

[f] TBAB (10 mol%) was employed as the additive.

[g] LiCl (10 mol%) was employed as the additive.

hand, the use of a cheaper and lower-toxicity metal instead of palladium provides another possible route.[11] Thus, copper salts together with various ligands as novel catalytic systemes have been reported.[12] Recently, Bolm and co-workers have reported the $FeCl_3$-catalyzed Sonogashira coupling reaction using DMEDA as the ligand.[13] Meanwhile, we and other groups have demonstrated efficient Fe/Cu co-catalyzed alkynylations of aryl halides.[14] Differently, Wang has disclosed that the Sonogashria coupling was investigated in the presence of ultrafine nickel powder together with CuI and PPh_3.[14] Based on our interest on coupling reactions using easily available catalysts,[12i,j,14a,15] herein, we describe our recent finding that samarium powder could directly catalyze the alkynylation of aryl halides without using any ligands and co-catalysts.

Polyethylene glycol (PEG) is widely considered as a good recyclable solvent with a low environmental impact. It is interesting to find that PEG usually afforded better results than the commonly used solvents.[16] This is perhaps attributable to its special role in the catalysis relative to classical phase-transfer catalysts. Thus, the coupling between 4-iodoanisole and phenylacetylene as the model reaction was carried out in PEG-400 in the presence of 10 mol% of samarium powder (*ca.* 350 µm). The respective results are listed in Table 1. To our delight, only the exclusive desired coupling product was obtained in promising yield (44%) (Table 1, entry 1). However, as we know that for the copper-mediated alkynylation of aryl halides, it is unavoidable to get the self-coupling of alkynes as the possible by-products. Therefore, the coupling with our protocol was highly selective. When the reaction was carried out in air or in the absence of base, no product was obtained (entries 2 and 3). PEGs with different molecular weights have been employed in the reaction (entries 4–6) and PEG-600 gave the best result of 84% yield (entry 5). Other common solvents including DMF, DMSO and glycol were sceened and only traces of product were obtained (entries 7–9). In addition, an ionic liquid, such as $C_6[min]PF_6$, was a suitable choice for the possible solvent (entry 10). Different sizes of the samarium powder did not give enhanced results (entry 11). Subsequently, various inorganic and organic bases have been investigated in the coupling reaction. However, none of them gave better result than K_2CO_3 (entries 12–16). Changing the ratios between the two substrates did not favor the reactions (entries 17–19). Increase of the samarium loading did not result in enhanced results (entries 20–22). Various additives, such as iodine, TBAB (n-Bu_4NBr) and LiCl, have been employed in the reactions and disappointing results were obtained (entries 23–25). Other forms of samarium were not favorable for the catalytic reaction (entries 26 and 27).

Under the same conditions, different common metal powders have been used in the alkynylation of 4-iodoanisole. From Figure 1 it can be seen that besides samarium, copper, zinc, nickel, iron, indium powders also showed promising catalytic activities. Compartively, samarium gave the best result. In order to control for issues of potential metal contamination, we carried out experiments in new flasks with new stirring bars and new caps. We also ensured that all of reagents including aryl halides, alkynes, K_2CO_3 and PEG-600 had the low levels of Pd (below 10 ppb) as measured by ICP-MS.[17] Therefore, we will apply this optimal catalytical system to the couplings of different substrates.

A wide array of substrates was subjected to the optimized reaction conditions as shown in Table 2. To our delight, we found that for the aryl iodides, all transformations proceeded well, giving the corresponding products **3–12** with moderate to good yields (Table 2, entries 1–15). In regard of the alkynylation of aryl bromides, promising results were also obtained (entries 16 and 17).

Subsequently, catalyst recycle experiments were also carried out based on the alkynylation of 4-iodoanisole. The way to recover the catalytic system was very simple, only by adding diethyl ether to the reaction and decanting the upper layer. The residue was added to the substrates for the second run. All the work-up should be performed under an atmosphere of argon. However, to our astonishment, only 40% yield of the desired coupling product was obtained.

Scanning electron microsope (SEM) studies of both fresh and used catalysts were carried out to understand the shape and size of the particles. Figure 2a and Figure 2b show the SEM images of the fresh and used catalyst after the first cycle, respectively. It is obviously seen that after the reaction the size of samarium powder became smaller, which shows that smaller size is not beneficial for the efficiency of catalyst.

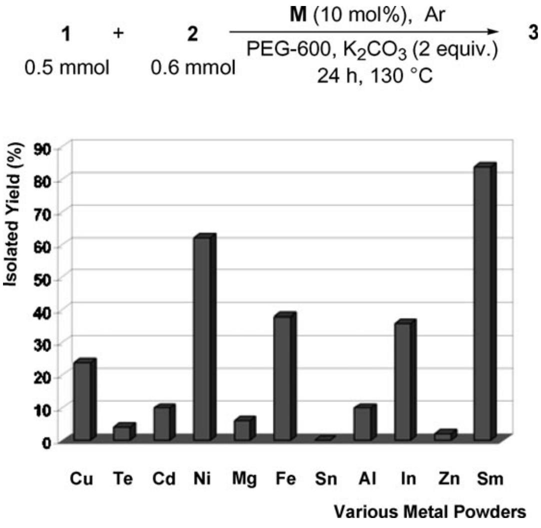


Figure 1. Various metal powders were employed in the Sonogashira coupling of 4-iodoanisole and phenylacetylene.

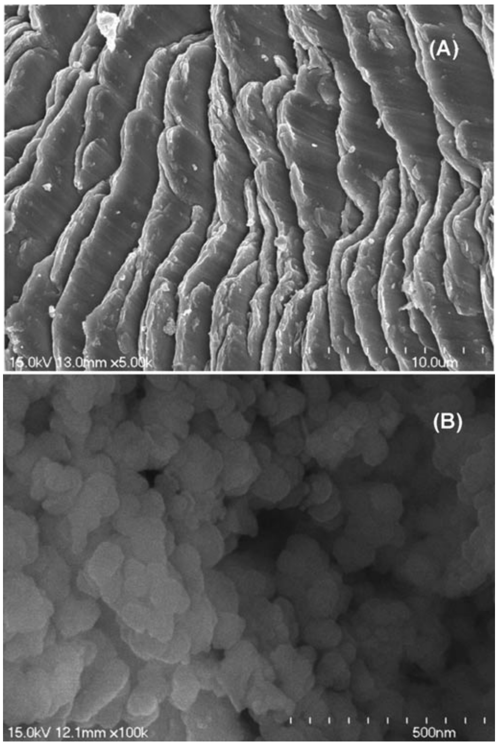
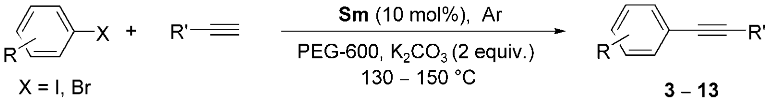
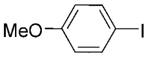
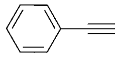
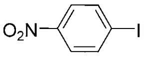
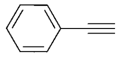
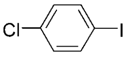
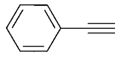
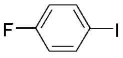
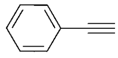
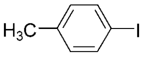
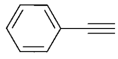
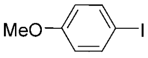
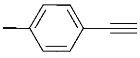
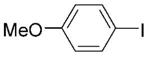
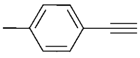
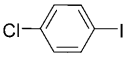
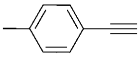
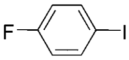
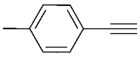
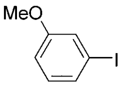
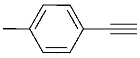
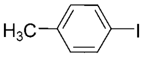
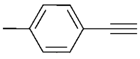
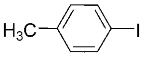
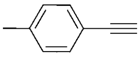
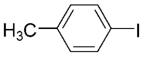
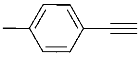
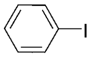
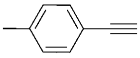
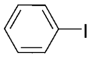
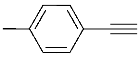
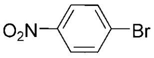
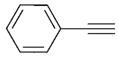
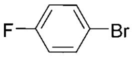
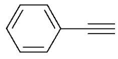


Figure 2. SEM images of samarium powders.

Table 2. Sm powder-catalyzed Sonogashira coupling of alkynes and aryl halides.[a]



Entry	RX	R′C≡CH		Temperature [°C]	Yield [%][b]
1			**3**	130	84
2			**4**	140	64
3			**5**	130	86
4			**6**	130	84
5			**7**	130	87
6			**8**	130	63
7			**8**	140	76
8			**9**	140	87
9			**10**	140	82
10			**11**	140	62
11			**12**	130	78
12			**12**	140	80
13			**12**	150	83
14			**7**	140	80
15			**7**	150	85
16			**4**	140	41
17			**6**	140	46

[a] *Reaction conditions:* Ar, Sm (*ca.* 350 μm powder from Aldrich, 99% purity, 0.05 mmol), aryl halide (0.5 mmol), alkyne (0.6 mmol), K_2CO_3 (1.0 mmol), PEG-600 (2 mL), 130–150 °C, 24 h.

[b] Isolated yield based on aryl halide (average of three runs).

However, on the other hand, it suggested a practical and alternative way to prepare the metal powders with smaller size.

In summary, we have developed a very practical and efficient protocol for the alkynylation of aryl iodides and bromides catalyzed by samarium powder in PEG-600. Features worth noting include 1) the coupling reactions between various alkynes and substituted aryl halides proceeded efficiently to afford valuable compounds; 2) the catalytic system is ligand-free, palladium-free, copper-free and amine-free; 3) the coupling reactions afforded the exclusive product without generating homocoupling of alkynes as the possible by-products; 4) the procedure is simple to perform in the absence of any additives. The scope, mechanism, and synthetic applications of this reaction are under further investigation.

Experimental Section

General Procedures

A mixture of aryl halide (0.5 mmol), alkyne (0.6 mmol), Sm powder (40 mesh, 99%, from Aldrich, 10 mol%), K_2CO_3 (2 equiv.), and PEG-600 (2 mL) in a Schlenk tube was stirred under an argon atmosphere at 130–150 °C for the desired time until complete consumption of starting material as monitored by TLC. After that the mixture was poured into ether, then washed with water, extracted with ethyl acetate, dried by anhydrous $MgSO_4$, then filtered and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products.

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