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Microwave-assisted copper- and palladium-catalyzed sonogashira-type coupling of aryl bromides and iodides with trimethylsilylacetylene

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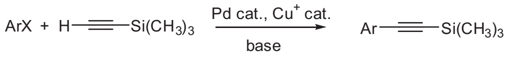
ABSTRACT

An efficient and rapid method was developed for the synthesis of 1-aryl-2-(trimethylsilyl)acetylene. Copper and palladium-catalyzed sonogashira-type coupling of trimethylsilylacetylene and aryl bromides or iodides in the presence of triethylamine as base under microwave irradiation in acetonitrile afforded the desired 1-aryl-2-(trimethylsilyl)acetylene. The use of microwave was found to significantly improve the reaction yield and shorten the reaction time.

Arylalkynes are important intermediates for the preparation of a variety of target compounds. Recent examples include heterocyclic compounds,[1] cathepsin inhibitors,[2] naphthalene derivatives,[3] conjugated alkenes,[4] enediyne antibiotics,[5] bioactive natural products, and pharmaceuticals.[6] Most of these compounds were provided by sonogashira coupling (Scheme 1), which is a palladium (0)-catalyzed coupling reaction of terminal alkynes and aryl iodides in the presence of copper iodide and a base. Recently, several sonogashira coupling methods using less reactive aryl bromides have been developed.[7,8] For example, Anne and co-workers used dichlorobis(triphenylphosphine)palladium and copper iodide as catalysts, triethylamine as the base to prepare the arylalkynes;[7] similarly, Comoy and co-workers used dichlorobis(triphenylphosphine)palladium and copper iodide as catalysts, triethylamine as the base to produce alkyne.[8] All these developed methods are typical sonogashira coupling, drawback of these approaches, such as the demand for a reactive arene derivative, long reaction times, and the limited choice of reaction medium, lead us to improve this reaction.

Currently, microwave-assisted organic synthesis (MAOS) has been a powerful and useful tool for rapid organic synthesis, and has attracted great interests of many academic and industrial research groups. Comparing with classical methods, MAOS has significant advantages that include simplicity in operation, increasing reaction rates, and improving reaction yields.[9] Unexceptionally, microwave irradiations have been applied to sonogashira coupling reaction for diarylacetylene and arylfuropyridones and others.[10] Here, we focused our attention on the use of microwave irradiation to Sonogashira coupling, and developed an efficient and rapid method for the synthesis of 1-aryl-2-(trimethylsilyl)acetylene.



Scheme 1. Sonogashira coupling reaction of terminal alkynes and aryl halides.

Initially, to investigate and optimize the copper and palladium-catalyzed sonogashira-type coupling of trimethylsilylacetylene and aryl bromides under microwave irradiation for the synthesis of the representative 1-aryl-2-(trimethylsilyl)acetylene **2a**, 4-bromobenzonitrile **1a** was chosen as the model substrate. The effects of different catalysts, bases, solvent, temperatures, and reaction times were examined on the model reaction and the results are listed in Table 1.

First we performed the reaction in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and triethylamine in acetonitrile under microwave irradiation at 80 °C in 2 min. The reaction did take place but only 70.3% yield of product **2a** was observed (Table 1, entry 1). With the hope of increasing the yield we tried the reaction under different increased

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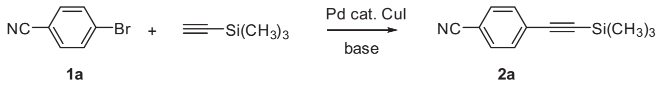
Table 1
Microwave-assisted sonogashira-type coupling of 4-bromobenzonitrile **1a** to 4-((trimethylsilyl)ethynyl)benzonitrile **2a**



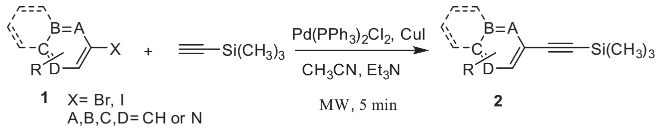
Entry[a]	*t* (min)	*T* (°C)	Solvent	Base[b]	Pd cat.	Yield[c] (%)
1	2	80	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	70.3
2	2	100	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	80.4
3	2	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	85.7
4	2	130	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	85.5
5	3	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	88.5
6	5	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	95.8
7	10	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	95.4
8	5	120	CH_3OH	Et_3N	$Pd(PPh_3)_2Cl_2$	43.8
9	5	120	H_2O	Et_3N	$Pd(PPh_3)_2Cl_2$	40.5
10	5	120	DMF	Et_3N	$Pd(PPh_3)_2Cl_2$	80.4
11	5	120	1,4-Dioxane	Et_3N	$Pd(PPh_3)_2Cl_2$	50.2
12	5	120	THF	Et_3N	$Pd(PPh_3)_2Cl_2$	75.0
13	5	120	CH_3CN	K_2CO_3	$Pd(PPh_3)_2Cl_2$	64.9
14	5	120	CH_3CN	NaOAc	$Pd(PPh_3)_2Cl_2$	33.1
15	5	120	CH_3CN	DMAP	$Pd(PPh_3)_2Cl_2$	62.9
16	5	120	CH_3CN	TBAOH	$Pd(PPh_3)_2Cl_2$	-
17	5	120	CH_3CN	DIPEA	$Pd(PPh_3)_2Cl_2$	78.7
18	5	120	CH_3CN	Et_2NH	$Pd(PPh_3)_2Cl_2$	15.1
19	5	120	CH_3CN	-	$Pd(PPh_3)_2Cl_2$	-
20	5	120	CH_3CN	Et_3N	$Pd(OAc)_2$	8.1
21	5	120	CH_3CN	Et_3N	$Pd(PPh_3)_4$	85.4
22	5	120	CH_3CN	Et_3N	$Pd(PhCN_2)Cl_2$	25.2
23[d]	480	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	85.0
24[e]	5	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	95.3
25[f]	8	120	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	94.9

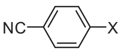
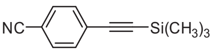
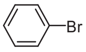
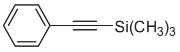
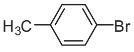
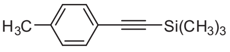
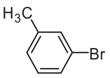
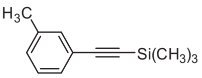
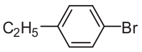
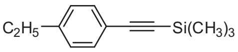
[a] Reaction conditions: (**1a**) 4-bromobenzonitrile (1.5 mmol), trimethylsilylacetylene (1.5 mmol), base (7.2 mmol), Pd catalysts (5 mol %), CuI (10 mol %), solvent (1.0 mL) at the specified temperature and reaction time. Microwave irradiation (MWI) power = 150 W.
[b] DMAP: 4-dimethylaminopyridine; TBAOH: tetrabutylammonium hydroxide; DIPEA: *N*,*N*-diisopropylethylamine.
[c] Yield of isolated product.
[d] Reaction was carried out under conventional heating in a sealed tube.
[e] Microwave irradiation power = 300 W.
[f] Microwave irradiation power = 100 W.

temperature and reaction time. As shown in Table 1, entries 2–7, the reaction went better with higher temperature. The product **2a** was obtained at 120 °C in 85.7% yield (Table 1, entry 3). And it was found that 120 °C was the fitness temperature, further increasing the temperature contributed little to improve the yield. Notably, when the reaction time was prolonged from 2 min to 5 min, the substrate **1a** could be completely converted into **2a** in a high yield of 95.8% (Table 1, entry 6). Further prolonging the reaction time to 10 min did not contribute to the yield (Table 1, entry 7). In order to find an optimal solvent, we tried different solvents such as methanol, water, DMF, 1, 4-dioxane, and THF. As shown in Table 1, entries 8–12, our experiments indicated that acetonitrile is the optimal solvent of this reaction. In addition, we tried the coupling reaction in the presence of different inorganic bases such as K_2CO_3, NaOAc, as well as organic bases such as DMAP, TBAOH, DIPEA, and Et_2NH (Table 1, entries 13–18). And without the bases the reaction did not occur (Table 1, entry 19). With the optimal solvent and base in hand, three other common palladium catalysts $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(PhCN_2)Cl_2$ were screened (Table 1, entries 20–22). Among them, $Pd(PPh_3)_2Cl_2$ provided the best reactivity under otherwise an identical condition. In addition, the influence of MWI power on the reaction was also tested. Further increasing the MWI power from 150 W to 300 W contributed little to the reaction (Table 1, entry 24). However, when the MWI power was decreased to 100 W, it should take more reaction time (8 min) to make the reaction completed (Table 1, entry 25). It must be emphasized that the reaction gave only 85.0% yield of product **2a** when carried out under conventional heating using the same sealed microwave tube at 120 °C after a greatly prolonged reaction time of 480 min (8 h) (Table 1, entry 23). This suggested that the sonogashira coupling reaction could be significantly accelerated by MWI.

With the optimized conditions in hand (Table 1, entry 6), we next began to extend the scope of this microwave-assisted sonogashira coupling reaction to a variety of substrates. As shown in Table 2, these substrates were efficiently converted into the desired 1-aryl-2-(trimethylsilyl)acetylene products in excellent yields within a short reaction time under MWI.[11] Compared to

Table 2
Synthesis of 1-aryl-2-(trimethylsilyl)acetylene derivatives



Entry[a]	Substrate **1**	Product **2**	Yield[b] (%)
1	 **1a** X = Br **1aa** X = I	 **2a**	95.8 96.2[c]
2	 **1b**	 **2b**	92.0
3	 **1c**	 **2c**	95.0
4	 **1d**	 **2d**	91.1
5	 **1e**	 **2e**	95.0

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