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

Yonghua Lei<sup>a,†</sup>, Tianhan Hu<sup>a,†</sup>, Xingsen Wu<sup>a</sup>, Yue Wu<sup>a</sup>, Hua Xiang<sup>a</sup>, Haopeng Sun<sup>a</sup>, Qidong You<sup>a,\*</sup>, Xiaojin Zhang<sup>a,b,\*</sup>

<sup>a</sup> Jiangsu Key Laboratory of Drug Design and Optimization, and State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China <sup>b</sup> Department of Organic Chemistry, School of Science, China Pharmaceutical University, Nanjing 210009, China

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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.

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Arylalkynes are important intermediates for the preparation of a variety of target compounds. Recent examples include heterocyclic compounds,<sup>1</sup> cathepsin inhibitors,<sup>2</sup> naphthalene derivatives,<sup>3</sup> conjugated alkenes,<sup>4</sup> enediyne antibiotics,<sup>5</sup> bioactive natural products, and pharmaceuticals.<sup>6</sup> 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.<sup>7,8</sup> For example, Anne and co-workers used dichlorobis(triphenylphosphine)palladium and copper iodide as catalysts, triethylamine as the base to prepare the arylalkynes;<sup>7</sup> similarly, Comoy and co-workers used dichlorobis(triphenylphosphine)palladium and copper iodide as catalysts, triethylamine as the base to produce alkyne.<sup>8</sup> 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

\* Corresponding authors.

<sup>†</sup> These two authors contributed equally to this work.

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

research groups. Comparing with classical methods, MAOS has significant advantages that include simplicity in operation, increasing reaction rates, and improving reaction yields.<sup>9</sup> Unexceptionally, microwave irradiations have been applied to sonogashira coupling reaction for diarylacetylene and arylfuropyridones and others.<sup>10</sup> 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.

Initially, to investigate and optimize the copper and palladiumcatalyzed 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  $Pd(PPh_3)_2Cl_2$ , Cul, 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

E-mail addresses: youqd@163.com (Q. You), zxj@cpu.edu.cn (X. Zhang).

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#### Table 1

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

NC	Br +		Si(CH <sub>3</sub> ) <sub>3</sub>	Pd cat. Cul base	NC	──Si(CH <sub>3</sub> )₃
Entry <sup>a</sup>	t (min)	T (°C)	Solvent	Base <sup>b</sup>	Pd cat.	Yield <sup>c</sup> (%)
1	2	80	CH₃CN	Et₃N	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	70.3
2	2	100	CH₃CN	Et₃N	$Pd(PPh_3)_2Cl_2$	80.4
3	2	120	CH <sub>3</sub> CN	Et₃N	$Pd(PPh_3)_2Cl_2$	85.7
4	2	130	CH₃CN	Et₃N	$Pd(PPh_3)_2Cl_2$	85.5

4	2	130	$CH_3CN$	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	85.5
5	3	120	CH₃CN	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	88.5
6	5	120	CH₃CN	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	95.8
7	10	120	CH₃CN	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	95.4
8	5	120	CH₃OH	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	43.8
9	5	120	$H_2O$	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	40.5
10	5	120	DMF	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	80.4
11	5	120	1,4-Dioxane	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	50.2
12	5	120	THF	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	75.0
13	5	120	CH₃CN	$K_2CO_3$	$Pd(PPh_3)_2Cl_2$	64.9
14	5	120	CH₃CN	NaOAc	$Pd(PPh_3)_2Cl_2$	33.1
15	5	120	CH₃CN	DMAP	$Pd(PPh_3)_2Cl_2$	62.9
16	5	120	CH₃CN	TBAOH	$Pd(PPh_3)_2Cl_2$	-
17	5	120	CH <sub>3</sub> CN	DIPEA	$Pd(PPh_3)_2Cl_2$	78.7
18	5	120	CH <sub>3</sub> CN	Et <sub>2</sub> NH	$Pd(PPh_3)_2Cl_2$	15.1
19	5	120	CH <sub>3</sub> CN	-	$Pd(PPh_3)_2Cl_2$	-
20	5	120	CH <sub>3</sub> CN	Et <sub>3</sub> N	$Pd(OAc)_2$	8.1
21	5	120	CH <sub>3</sub> CN	Et <sub>3</sub> N	$Pd(PPh_3)_4$	85.4
22	5	120	CH <sub>3</sub> CN	Et <sub>3</sub> N	$Pd(PhCN_2)Cl_2$	25.2
23 <sup>d</sup>	480	120	CH <sub>3</sub> CN	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	85.0
24 <sup>e</sup>	5	120	CH₃CN	Et <sub>3</sub> N	$Pd(PPh_3)_2Cl_2$	95.3
25 <sup>f</sup>	8	120	CH₃CN	Et₃N	$Pd(PPh_3)_2Cl_2$	94.9

<sup>a</sup> Reaction conditions: (**1a**) 4-bromobenzonitrile (1.5 mmol), trimethylsilylacetylene (1.5 mmol), base (7.2 mmol), Pd catalysts (5 mol %), Cul (10 mol %), solvent (1.0 mL) at the specified temperature and reaction time. Microwave irradiation (MWI) power = 150 W.

<sup>b</sup> DMAP: 4-dimethylaminopyridine; TBAOH: tetrabutylammonium hydroxide; DIPEA: *N*,*N*-diisopropylethylamine.

<sup>c</sup> Yield of isolated product.

<sup>d</sup> Reaction was carried out under conventional heating in a sealed tube.

<sup>e</sup> Microwave irradiation power = 300 W.

<sup>f</sup> Microwave irradiation power = 100 W.

#### Table 2

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

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<sub>2</sub>CO<sub>3</sub>, NaOAc, as well as organic bases such as DMAP, TBAOH, DIPEA, and Et<sub>2</sub>NH (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)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Pd(PhCN<sub>2</sub>)Cl<sub>2</sub> were screened (Table 1, entries 20–22). Among them, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> 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 sono-gashira 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.<sup>11</sup> Compared to

Si(CH<sub>3</sub>)



Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>,

CH<sub>3</sub>CN, Et<sub>3</sub>N

R'D

Si(CH<sub>3</sub>)<sub>3</sub>

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### Table 2 (continued)

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Entry <sup>a</sup>	Substrate 1	Product 2	Yield <sup>b</sup> (%)
6	H <sub>3</sub> CO-CBr 1f	H <sub>3</sub> CO- Si(CH <sub>3</sub> ) <sub>3</sub>	90.2
7	OCH3 2g X=Br 2gg X=I	CCH <sub>3</sub> Si(CH <sub>3</sub> ) <sub>3</sub> 2g	87.9
8	H <sub>3</sub> CO X 2h X=Br	H <sub>3</sub> CO Si(CH <sub>3</sub> ) <sub>3</sub> 2h	95.1 97.0 <sup>c</sup>
9	$2hh X=1$ $CI \longrightarrow Br$ $1i$	CI-SI(CH <sub>3</sub> ) <sub>3</sub>	93.9 97.0 <sup>c</sup>
10	Br 1j	Si(CH <sub>3</sub> ) <sub>3</sub>	91.5
11		CI Si(CH <sub>3</sub> ) <sub>3</sub> 2k	90.6
12	F-Br 11	FSi(CH <sub>3</sub> ) <sub>3</sub>	95.1
13	F 1m	$ \begin{array}{c} & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & $	92.0
14	In N	∑	93.0
15	Io N	20 N	89.9
16	NC-W-Br N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-	NC-(/	91.2
17	$H_{3C} _{N} Br$	$H_{3C} _{N} Si(CH_{3})_{3}$ $2q$	92.2
18		Si(CH <sub>3</sub> ) <sub>3</sub>	88.0
19	Br 1s	Si(CH <sub>3</sub> ) <sub>3</sub>	83.6 81.5 <sup>d</sup>
20	H <sub>3</sub> C CH <sub>3</sub> Br 1t	H <sub>3</sub> C CH <sub>3</sub> Si(CH <sub>3</sub> ) <sub>3</sub> 2t	80.3

<sup>a</sup> Reaction conditions: substrate (1) (1.5 mmol), trimethylsilylacetylene (1.5 mmol), Pd catalysts (5 mol %), CuI (10 mol %), Et<sub>3</sub>N (7.2 mmol), acetonitrile (1.0 mL), 120 °C. Reaction time: 5 min. MWI power = 150 W. <sup>b</sup> Yield of isolated product.

<sup>c</sup> Reaction time: 2 min.
 <sup>d</sup> Reaction time: 10 min.

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4-bromobenzonitrile substrate 1a, 4-iodobenzonitrile (1aa) substrate also afforded quantitative yields (Table 2, entry 1). Moreover, several functional groups such as methyl, ethyl, methoxyl, ethoxyl, and chloro or fluoro were well tolerated under our conditions and excellent yields were obtained in all the cases (Table 2, entries 2-13, 20). Among them, sterically crowded acetylenes produced the coupled product in slightly lesser yields, as shown in (Table 2, entries 7, 11, 20). Good results were also obtained from heterocyclic aryl halides or naphthalene halides (Table 2, entries 14–19). The two pyridine derivatives **2n** and **2o** and the two pyrimidine derivatives 2p and 2q were prepared from their corresponding bromides **1n**, **1o** and **1p**, **1q** in a high yield. Lower yields were obtained in the case of 4-bromoisoqunoline (1r) and 2bromonaphthalene (1s). The naphthalene derivative 2s was obtained in lesser yield than others, even after continuing the reaction to 15 min. Furthermore, it should be mentioned that both phenvl bromide and phenvl iodide can give the desired products, and phenyl iodide is known to be a more efficient substrate. As shown in Table 2, entries 7, 8, the desired products 2gg, 2hh were produced by the two phenyl iodide substrates 1gg and 1hh in quantitative yield in 2 min.

In summary, we have developed an efficient and high yielding method based on copper and palladium-catalyzed sonogashiratype coupling processes under microwave-assisted irradiation in short reaction time to access to the appealing 1-aryl-2-(trimethylsilyl)acetylene from the corresponding aryl iodides or bromides and trimethylsilylacetylene. This method provides excellent yields and purities of products in a short time, making it a useful strategy for the synthesis of structurally diverse 1-aryl-2-(trimethylsilyl)acetylene.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01. 088.

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- 11. General procedure for the rapid synthesis of 1-aryl-2-(trimethylsilyl)acetylene under MWI in acetonitrile in the presence of triethylamine: A sealed 10 mL glass tube containing substrate 1a-1s (1.5 mmol), trimethylsilylacetylene (1.5 mmol), triethylamine (7.5 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol %), Cul (10 mol %), and acetonitrile (1 mL) was placed in the cavity of a microwave reactor and irradiated for 2–10 min, at 120 °C and power 150 W. After cooling to room temperature by an N<sub>2</sub>-flow, the tube was removed from the rotor. The reaction mixture was combined with dichloromethane (30 mL) and water (30 mL), dried over sodium sulfate, and concentrated. Purification by column chromatography, eluting with petroleum ether gave 1-aryl-2-(trimethylsilyl)acetylenes (2a-2s) as coloured oils or solids. All the products 2a-2s were characterized by <sup>1</sup>H NMR and El-MS. (See Supporting Information file for characterization data of <sup>1</sup>H NMR and El-MS spectrum.)