



## Palladium and copper catalyzed Sonogashira decarboxylative coupling of aryl iodides and alkynyl carboxylic acids



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### ARTICLE INFO

#### Article history:

Received 9 May 2016

Revised 15 June 2016

Accepted 16 June 2016

Available online 17 June 2016

#### Keywords:

Palladium

Copper

Decarboxylative coupling

Alkynyl carboxylic acids

Aryl halides

### ABSTRACT

A mild procedure of palladium and copper catalyzed decarboxylative cross-coupling reaction of aryl halides and alkynyl carboxylic acids has been developed. Low molecular weight acids, to introduce small building blocks, were specifically used. This methodology is easy to implement and uses common reagents and catalysts.

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### Introduction

The Sonogashira cross-coupling reaction is the most useful tool for the formation of the C(sp<sup>2</sup>)-C(sp) bond<sup>1</sup> and it is used as a key step in total synthesis.<sup>2</sup> This reaction proceeds via palladium catalyzed coupling between aryl halides and terminal alkynes in the presence of copper salts as co-catalysts. One limitation of this coupling is the alkyne source, in particular the use of volatile terminal alkynes. The decarboxylative Sonogashira reaction between aryl halides and alkynyl carboxylic acids has emerged as an alternative to the Sonogashira reaction,<sup>3</sup> and terminal alkynes are replaced by the corresponding alkynyl carboxylic acids that are easily available and stable for handling and storage. Lee and co-workers reported the first decarboxylative coupling of alkynyl carboxylic acids and aryl halides in 2008:<sup>4</sup> unsymmetrically substituted diaryl alkynes were synthesised from propiolic acid via the consecutive reactions of the Sonogashira reaction and the decarboxylative coupling (DCC) reaction using palladium salts in the presence of a phosphine ligand and a base to catalyze the two couplings. This methodology has been developed for the preparation of unsymmetrical diaryl alkynes, one pot<sup>5</sup> or in continuous flow reaction systems,<sup>6</sup> and also for the preparation of symmetrical diaryl alkynes from aryl bromides<sup>7</sup> or aryl chlorides.<sup>8</sup> In 2011, Kim and co-workers described Sonogashira – homocoupling sequence from propiolic acid.<sup>9</sup> After the coupling between propiolic acid and aryl iodides under Sonogashira conditions, addition of silver carbonate provided a

homocoupling reaction for the formation of corresponding diynes. Lee and co-workers extended palladium-catalyzed DCC reactions between phenylpropionic acid or oct-2-ynoic acid with aryl halides in the presence of a phosphine ligand and tetrabutylammonium fluoride as the base at 90 °C.<sup>10</sup> Coupling between aryl chlorides and various alkynyl carboxylic acids has been catalyzed by cyclopalladated ferrocenylimine in the presence of phosphine ligand.<sup>11</sup> The use of palladium nanoparticles as catalysts combined with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided ligand-free decarboxylative coupling.<sup>12</sup> Development of this methodology achieved a palladium-free DCC reaction with copper (I) as the catalyst. Using this approach, Xue and co-workers reported the coupling between aryl halides and alkynyl carboxylic acids catalyzed by copper iodide in the presence of 1,10-phenanthroline as the ligand, cesium carbonate as the base, and *N,N*-dimethylformamide as solvent at 130 °C.<sup>13</sup> Another example was reported by Mao and co-workers. The reaction was performed by copper iodide in the presence of triphenylphosphine as the ligand, potassium carbonate as the base, and dimethylsulfoxide or water as the solvent at 100 °C.<sup>14</sup> Muthusubramanian and co-workers also developed a DCC reaction followed by cyclization in order to form heterocycles.<sup>15</sup> This strategy was used with aryl alkynyl carboxylic acids and substituted 2-iodotrifluoroacetanilide in the presence of copper (I)/*L*-proline as the catalytic system. Moreover, a decarboxylative coupling reaction was developed with various substrates such as benzyl halides,<sup>16</sup> 1,1,1-trifluoro-2-iodoethane,<sup>17</sup> boronic acids,<sup>18</sup> or arene diazoniums<sup>19</sup> instead of classical aryl halides. Stereospecific decarboxylative coupling of benzyl esters of

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propionic acids has recently been reported.<sup>20</sup> Mainly aryl alkynyl carboxylic acids are used, though some methodologies have been extended to alkyl alkynyl carboxylic acids.<sup>10,11,13,14b,21</sup>

We focused on using alkynyl carboxylic acids, in particular the alkynyl alkyl acids, in the decarboxylative Sonogashira reaction. But-2-ynoic acid and pent-2-ynoic acid were of particular interest since they allow the introduction of propyne and butyne that are more difficult to handle under the usual Sonogashira cross-coupling conditions. We present here a new methodology for the alkynylation of aryl halides under microwave conditions.

## Results and discussion

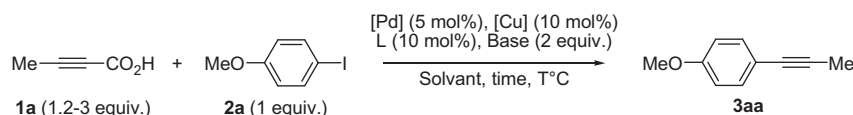
In order to optimize the reaction protocol, we examined a range of palladium and copper catalysts, ligands, bases, and solvents, using the coupling of but-2-ynoic acid **1a** with 1-iodo-4-methoxybenzene **2a** as the test reaction (Table 1). It should be noted that the conversion must be complete as the starting material **2a** and product **3aa** cannot be separated by chromatography on silica gel. The reaction was performed initially at room temperature to determine the most appropriate catalysts and reagents (entries 1–22). A range of palladium catalysts (entries 1–6), copper catalysts (entries 8–11) and ligands (12–14) were examined. The use of palladium and copper seemed to be essential to carry out the coupling reaction (entries 1 and 8). The use of palladium (II) acetate, copper iodide, and triphenylphosphine as the catalytic system provided the most effective reaction (entries 6 and 7). Various organic and inorganic bases (entries 15–18) and solvents (entries

19–22) were then tested. Triethylamine and *N,N*-dimethylformamide (DMF) were the most efficient base and solvent respectively (entry 7). In order to obtain a total conversion, the reaction was performed under conventional heating or under microwave irradiation (entries 23–27). Conversion was only 60% at 50 °C for one day (entry 23). Heating at 100 °C under microwave irradiation led to degradation of the product (entry 24).

However, similar conversion was achieved by conventional heating at 50 °C for 1 day and under at 50 °C under microwave irradiation for 2 h (entries 23 and 27). Finally, the amount of acid **2a** was increased to 3 equiv to obtain total conversion at 50 °C MW for 2 h (entry 29) or at room temperature for 2 days (entry 30). The time saved obtained under microwave irradiation encouraged us to develop this reaction under these conditions.

Various available aryl halides and alkyl alkynyl carboxylic acids were used to investigate the scope of the decarboxylative Sonogashira reaction and the results are summarized in Table 2. First the reaction was developed with but-2-ynoic acid **1a** and *ortho*-, *meta*-, or *para*-substituted aryl iodides **2** (entries 1, 2, 4, and 5). The corresponding decarboxylative coupling product was isolated in modest to good yields. With pent-2-ynoic acid **1b** (entries 6–11), hex-2-ynoic acid **1c** (entries 13–16), hept-2-ynoic **1d** (entries 17 and 18), or 5-hydroxy-5-phenylpent-2-ynoic acid **1e** (entries 19 and 20), only 2 equiv of these acids were required to obtain total conversion. Coupling of these acids with various aryl iodides provided the expected product in good yields. In the case of *o*-iodoaniline **2d** (entries 5, 10, 14), some amidation of the amine group (5–10%) was observed in the crude but this by-product was easily

**Table 1**  
Optimization of reaction conditions



Entry	[Pd]	[Cu]	Ligand	Alkyne (equiv)	Base	Solvent	Temp (°C)	Time (h)	Conv. <sup>a</sup> (%)
1	—	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	48	0
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	16	15
3	PdCl <sub>2</sub> (MeCN) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	16	15
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	16	20
5	Pd <sub>2</sub> dba <sub>3</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	16	36
6	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	16	50
7	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	48	85
8	Pd(OAc) <sub>2</sub>	—	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	48	0
9	Pd(OAc) <sub>2</sub>	(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub> Cu	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	48	4
10	Pd(OAc) <sub>2</sub>	CuSO <sub>4</sub> ·5H <sub>2</sub> O	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	48	10
11	Pd(OAc) <sub>2</sub>	CuBr	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	rt	48	37
12	Pd(OAc) <sub>2</sub>	CuI	—	1.2	Et <sub>3</sub> N	DMF	rt	72	0
13	Pd(OAc) <sub>2</sub>	CuI	Phenanthroline	1.2	Et <sub>3</sub> N	DMF	rt	72	0
14	Pd(OAc) <sub>2</sub>	CuI	L-Proline	1.2	Et <sub>3</sub> N	DMF	rt	72	14
15	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	<i>i</i> -Pr <sub>2</sub> NH	DMF	rt	48	11
16	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	K <sub>2</sub> CO <sub>3</sub>	DMF	rt	48	29
17	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	DBU	DMF	rt	48	5
18	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	—	DMF	rt	48	0
19	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	<i>i</i> -PrOH	rt	48	0
20	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	H <sub>2</sub> O	rt	48	0
21	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	THF	rt	48	14
22	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	MeCN	rt	48	52
23	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	50 °C	24	60
24	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	MW 100 °C	0.5	— <sup>b</sup>
25	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	MW 50 °C	0.5	38
26	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	MW 50 °C	1	55
27	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	1.2	Et <sub>3</sub> N	DMF	MW 50 °C	2	65
28	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	2	Et <sub>3</sub> N	DMF	MW 50 °C	2	85
29	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	3	Et <sub>3</sub> N	DMF	MW 50 °C	2	100
30	Pd(OAc) <sub>2</sub>	CuI	PPh <sub>3</sub>	3	Et <sub>3</sub> N	DMF	rt	48	100

<sup>a</sup> Determined by <sup>1</sup>H NMR; only decarboxylative coupling products were observed.

<sup>b</sup> Degradation of the product was observed.

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