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

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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 reactants and catalysts.

Introduction

The Sonogashira cross-coupling reaction is the most useful tool for the formation of the C(sp^2)–C(sp) bond[1] and it is used as a key step in total synthesis.[2] 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,[3] 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:[4] unsymmetrically substituted diaryl alkynes were synthetised 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[5] or in continuous flow reaction systems,[6] and also for the preparation of symmetrical diaryl alkynes from aryl bromides[7] or aryl chlorides.[8] In 2011, Kim and co-workers described Sonogashira – homocoupling sequence from propiolic acid.[9] 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 phenylpropiolic 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.[10] Coupling between aryl chlorides and various alkynyl carboxylic acids has been catalyzed by cyclopalladated ferrocenylimine in the presence of phosphine ligand.[11] The use of palladium nanoparticles as catalysts combined with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided ligand-free decarboxylative coupling.[12] 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-phenathroline as the ligand, cesium carbonate as the base, and *N*,*N*-dimethylformamide as solvent at 130 °C.[13] 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.[14] Muthusubramanian and co-workers also developed a DCC reaction followed by cyclization in order to form heterocycles.[15] 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,[16] 1,1,1-trifluoro-2-iodoethane,[17] boronic acids,[18] or arene diazoniums[19] instead of classical aryl halides. Stereospecific decarboxylative coupling of benzyl esters of

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propiolic acids has recently been reported.[20] Mainly aryl alkynyl carboxylic acids are used, though some methodologies have been extended to alkyl alkynyl carboxylic acids.[10,11,13,14b,21]

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.

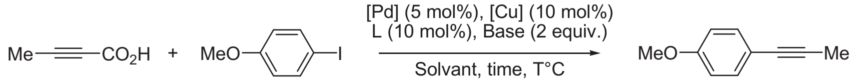
Results and discussion

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

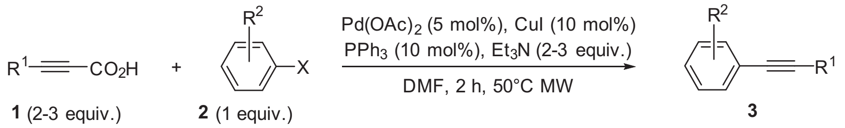


1a (1.2-3 equiv.) **2a** (1 equiv.) **3aa**

Entry	[Pd]	[Cu]	Ligand	Alkyne (equiv)	Base	Solvent	Temp (°C)	Time (h)	Conv.[a] (%)
1	–	CuI	PPh_3	1.2	Et_3N	DMF	rt	48	0
2	$PdCl_2(PPh_3)_2$	CuI	PPh_3	1.2	Et_3N	DMF	rt	16	15
3	$PdCl_2(MeCN)_2$	CuI	PPh_3	1.2	Et_3N	DMF	rt	16	15
4	$Pd(Ph_3)_4$	CuI	PPh_3	1.2	Et_3N	DMF	rt	16	20
5	Pd_2dba_3	CuI	PPh_3	1.2	Et_3N	DMF	rt	16	36
6	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	rt	16	50
7	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	rt	48	85
8	$Pd(OAc)_2$	–	PPh_3	1.2	Et_3N	DMF	rt	48	0
9	$Pd(OAc)_2$	$(CF_3SO_3)_2Cu$	PPh_3	1.2	Et_3N	DMF	rt	48	4
10	$Pd(OAc)_2$	$CuSO_4.5H_2O$	PPh_3	1.2	Et_3N	DMF	rt	48	10
11	$Pd(OAc)_2$	CuBr	PPh_3	1.2	Et_3N	DMF	rt	48	37
12	$Pd(OAc)_2$	CuI	–	1.2	Et_3N	DMF	rt	72	0
13	$Pd(OAc)_2$	CuI	Phenanthroline	1.2	Et_3N	DMF	rt	72	0
14	$Pd(OAc)_2$	CuI	L-Proline	1.2	Et_3N	DMF	rt	72	14
15	$Pd(OAc)_2$	CuI	PPh_3	1.2	i-Pr_2NH	DMF	rt	48	11
16	$Pd(OAc)_2$	CuI	PPh_3	1.2	K_2CO_3	DMF	rt	48	29
17	$Pd(OAc)_2$	CuI	PPh_3	1.2	DBU	DMF	rt	48	5
18	$Pd(OAc)_2$	CuI	PPh_3	1.2	–	DMF	rt	48	0
19	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	*i*-PrOH	rt	48	0
20	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	H_2O	rt	48	0
21	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	THF	rt	48	14
22	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	MeCN	rt	48	52
23	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	50 °C	24	60
24	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	MW 100 °C	0.5	–[b]
25	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	MW 50 °C	0.5	38
26	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	MW 50 °C	1	55
27	$Pd(OAc)_2$	CuI	PPh_3	1.2	Et_3N	DMF	MW 50 °C	2	65
28	$Pd(OAc)_2$	CuI	PPh_3	2	Et_3N	DMF	MW 50 °C	2	85
29	$Pd(OAc)_2$	CuI	PPh_3	3	Et_3N	DMF	MW 50 °C	2	100
30	$Pd(OAc)_2$	CuI	PPh_3	3	Et_3N	DMF	rt	48	100

[a] Determined by ^1H NMR; only decarboxylative coupling products were observed.
[b] Degradation of the product was observed.

Table 2
Decarboxylative cross-coupling between alkynyl acids **1** and aryl halides **2**



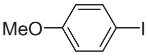
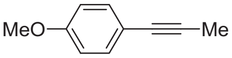
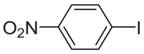
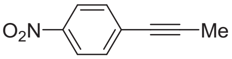
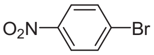
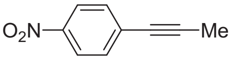
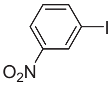
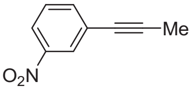
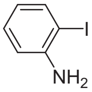
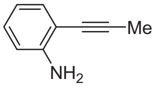
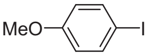
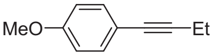
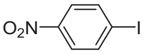
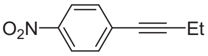
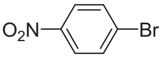
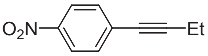
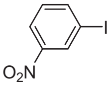
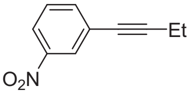
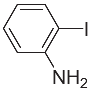
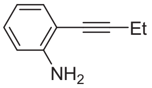
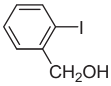
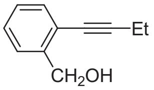
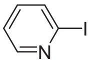
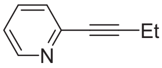
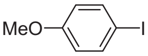
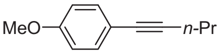
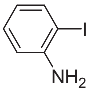
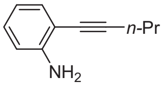
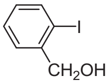
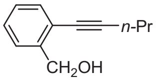
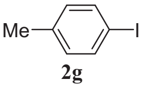
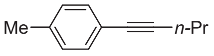
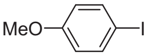
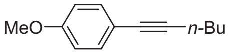
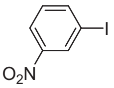
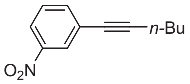
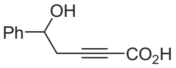
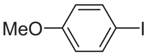
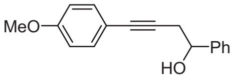
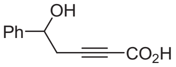
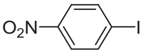
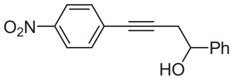
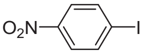
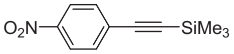
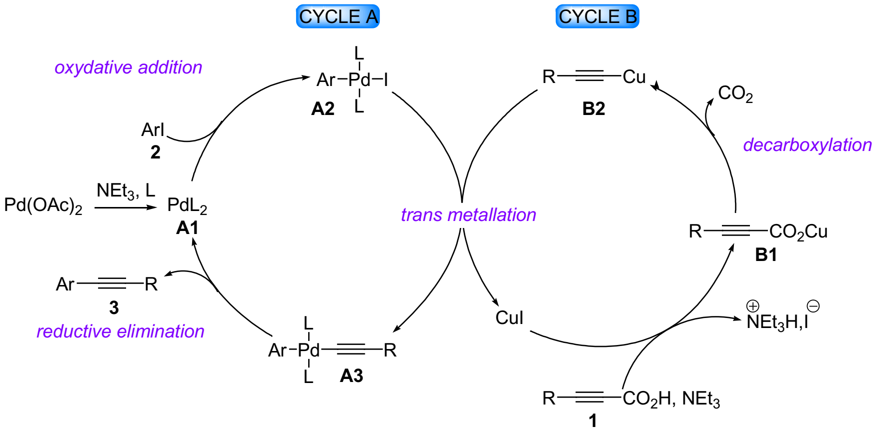
Entry	Alkynyl carboxylic acids	Aryl halides	Product	Yield[a] (%)
1	$\mathrm{Me{-}{\equiv}{-}CO_2H}$ **1a**	 **2a**	 **3aa**	41
2	$\mathrm{Me{-}{\equiv}{-}CO_2H}$ **1a**	 **2b**	 **3ab**	99
3	$\mathrm{Me{-}{\equiv}{-}CO_2H}$ **1a**	 **2’b**	 **3ab**	58
4	$\mathrm{Me{-}{\equiv}{-}CO_2H}$ **1a**	 **2c**	 **3ac**	86
5	$\mathrm{Me{-}{\equiv}{-}CO_2H}$ **1a**	 **2d**	 **3ad**	44[b]
6	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2a**	 **3ba**	85
7	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2b**	 **3bb**	99
8	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2’b**	 **3bb**	69
9	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2c**	 **3bc**	83
10	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2d**	 **3bd**	79
11	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2e**	 **3be**	66
12	$\mathrm{Et{-}{\equiv}{-}CO_2H}$ **1b**	 **2f**	 **3bf**	68
13	$\mathrm{{\mathit{n}}\text{-}Pr{-}{\equiv}{-}CO_2H}$ **1c**	 **2a**	 **3ca**	75
14	$\mathrm{{\mathit{n}}\text{-}Pr{-}{\equiv}{-}CO_2H}$ **1c**	 **2d**	 **3cd**	71
15	$\mathrm{{\mathit{n}}\text{-}Pr{-}{\equiv}{-}CO_2H}$ **1c**	 **2e**	 **3ce**	70

Table 2 (*continued*)

Entry	Alkynyl carboxylic acids	Aryl halides	Product	Yield[a] (%)
16	n-Pr—≡—CO_2H **1c**	 **2g**	 **3cg**	67
17	n-Bu—≡—CO_2H **1d**	 **2a**	 **3da**	83
18	n-Bu—≡—CO_2H **1d**	 **2c**	 **3dc**	97
19	 **1e**	 **2a**	 **3ea**	68
20	 **1e**	 **2b**	 **3eb**	74
21	Me_3Si—≡—CO_2H **1f**	 **2b**	 **3fb**	43

[a] Isolated yield.
[b] Degradation of the product after 24 h.



Scheme 1. Plausible mechanism of decarboxylative Sonogashira reaction.

eliminated during the purification. Aryl bromide **2′b** was used in DCC reaction with acids **1a**, **1b,** instead of aryl iodide **2b** (entries 3 and 8): the coupling products **3ab** and **3bb** were obtained in lower yields. No conversion was achieved with aryl chlorides. The use of 2-iodopyridine **2f** in the coupling with 2-pentynoic acid **1b** yielded 68% of the product although the conversion was not total (conv = 72%, entry 13). The coupling of 3-(trimethylsilyl)propiolic acid **1f** and aryl iodide **2b** did not lead to total conversion (conv = 57%) but in this case the coupling product **3fb** could be isolated in 43% yield (entry 22).

On the basis of our results and of the literature, the mechanism reaction shown in Scheme 1 was proposed. The requirement of palladium and copper salts suggests that each has a distinct function. We therefore proposed a mechanism based on two catalytic cycles: one for the C–C bond coupling involved the palladium salts (Cycle A), the other one for the decarboxylation of alkynyl carboxylic acid catalyzed by copper salts (Cycle B). In the presence of base and copper (I), alkynyl carboxylic acid **1** led to the formation of copper carboxylate **B1** which was subjected to decarboxylation.[14b,22] The alkynyl copper **B2** formed is a well-known intermediate in Sonogashira reaction.[1] Palladium salts allowed the formation of C–C bond via a classic mechanism: first an oxidative addition leading to intermediate **A2** followed by a *trans*-metallation with alkynyl copper **B2** which resulted in complex **A3**. Eventually, a reductive elimination provided the expected compound **3** and regenerated palladium (0) **A1**.

Conclusion

To conclude, we have developed an efficient method for the Sonogashira decarboxylative cross-coupling reaction between aryl halides and alkynyl carboxylic acids. This reaction is easy to implement and uses common reactants and catalysts. It can be performed either at room temperature or under microwave conditions, the latter requiring shorter reaction times. A range of aryl alkynyl compounds and aryl halides were prepared in modest to good yields.

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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.2016.06.073.

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