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Palladium and Copper Catalyzed Sonogashira Decarboxylative Coupling of Aryl Halides and Alkynyl Carboxylic Acids

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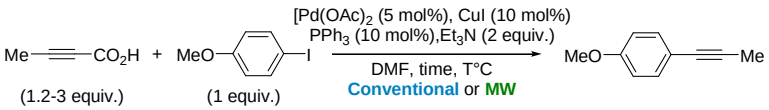
Sonogashira cross-coupling reaction is the most useful tool for the formation of C(sp^2) – C(sp) bond[1] and it is used as key step of total synthesis.[2] This reaction proceeds *via* palladium catalyzed coupling between aryl halides and terminal alkynes in the presence of copper salts as co-catalyst. A limitation of this coupling is the alkyne source in particularly the use of volatile terminal alkynes. Decarboxylative Sonogashira reaction between aryl halides and alkynyl carboxylic acids emerged as an alternative to Sonogashira reaction.[3] In this way, terminal alkynes are replaced by the corresponding alkynyl carboxylic acids that are easily available and stable for the handling and storage.
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.

(1) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922. (2) K. Park, S. Lee, *RCS Adv.* **2013**, *3*, 14165–14182. (3) K. Park, S. Lee, *RCS Adv.* **2013**, *3*, 14165–14182.

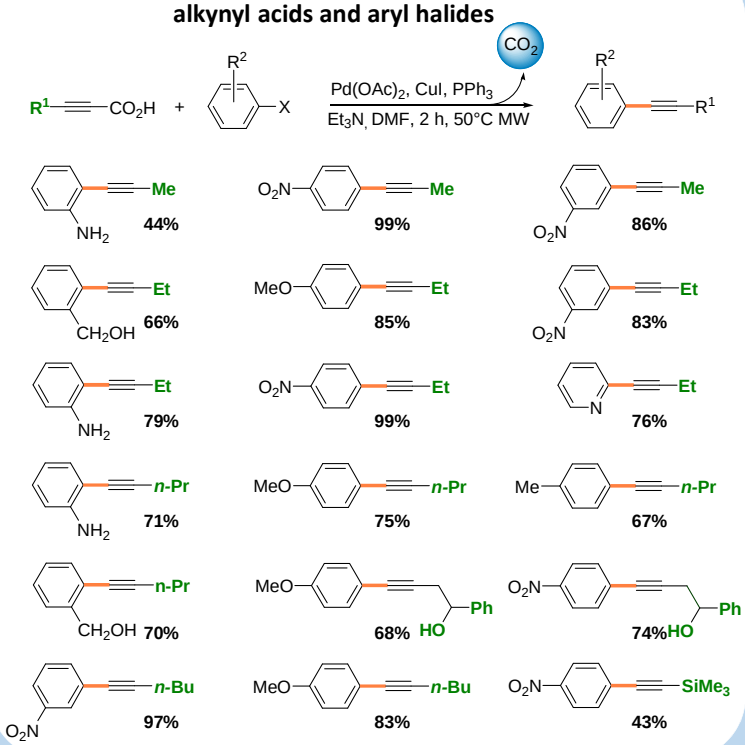
Optimization of reaction conditions



Alkyne (equiv.)	Temperature (°C)	Time (h)	Conv. (%)
1.2	rt	16 h	50 %
1.2	rt	48h	85 %
1.2	50°C	24 h	60 %
1.2	MW 100°C	0.5 h	-
1.2	MW 50°C	2	65 %
2	MW 50°C	2	85 %
3	**MW 50°C**	**2**	**100 %**
3	rt	48 h	100 %

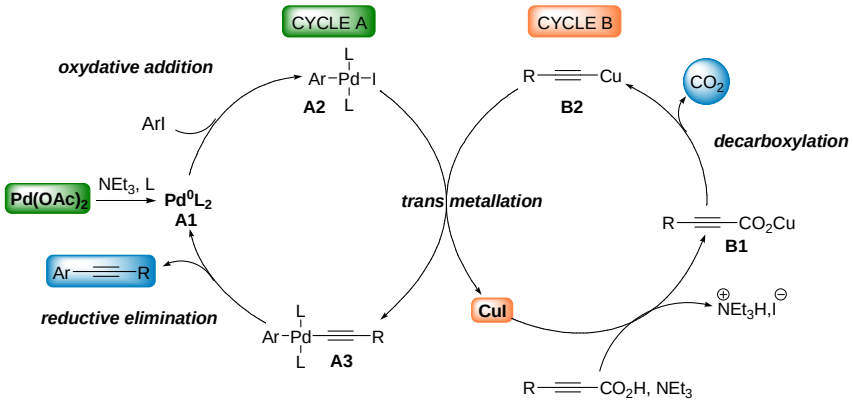
In a first time, the reaction was performed at room temperature to determine the most appropriate catalysts and reagents. A range of palladium catalysts, copper catalysts and ligands have been examined. The used of palladium and copper seems to be essentials to carry out the coupling reaction. The use of palladium (II) acetate, copper iodide and triphenylphosphine as the catalytic system provided a more effective reaction. Then, various organic and inorganic bases and solvents were tested. Triethylamine and dimethylformamide (DMF) are the most efficient base and solvent.

Decarboxylative cross-coupling between alkynyl acids and aryl halides



Mechanism

The mechanism is 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). Alkynyl carboxylic acid, in the presence of base and copper (I), leads to the formation of copper carboxylate **B1** which is subjected to decarboxylation.[4] The alkynyl copper **B2** formed is a well-known intermediate in Sonogashira reaction.[1] Palladium salts allow the formation of C-C bond *via* a classic mechanism: first an oxidative addition leads to intermediate **A2** followed by *trans*-metallation with alkynyl copper **B2** which brings to complex **A3**. Eventually, a reductive elimination furnishes the excepted compound and regenerates palladium (0) **A1**.



(4) T. Li, P. Sun, H. Yang, Y. Zhu, H. Yan, L. Lu, J. Mao, *Tetrahedron* **2012**, *68*, 6413–6419; W. Jia, N. Jiao, *Org. Lett.* **2010**, *12*, 2000–2003.

To conclude, we have developed an efficient method for the Sonogashira decarboxylative cross-coupling reaction between aryl halides and alkynyl carboxylic acids.[5] This reaction is easy to implement and uses common reactants and catalysts. It can be made either at room temperature or in microwaves conditions which allow shorter reactions times. This methodology is being used for the functionalization of various heterocyclic compounds.

(5) C. Maaliki, Y. Chevalier, E. Thiery, J. Thibonnet, *Tetrahedron Lett.* **2016**, *57*, 3358-3362.