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Rapid microwave-enhanced, solventless Sonogashira coupling reaction on alumina

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Abstract

A microwave-enhanced, solventless Sonogashira coupling reaction has been developed. Terminal alkynes couple with aryl or alkenyl iodide on palladium-doped alumina in the presence of triphenylphosphine and cuprous iodide to provide high yields of products. © 2000 Published by Elsevier Science Ltd.

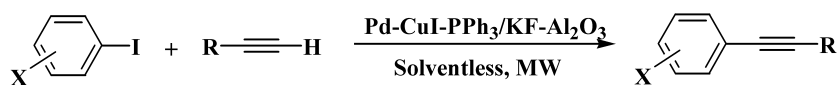
Keywords: coupling reactions; palladium; microwave heating; alkynes.

The Sonogashira coupling reaction of terminal alkynes and aryl or alkenyl halides provides an efficient route to aryl alkynes.^{1–4} Numerous applications to natural product syntheses have been reported, including the construction of complex enediyne antibiotics.^{5–7} The reaction is generally carried out in organic solvents such as amines, benzene, THF and DMF along with complex palladium catalysts which are soluble in these solvents. These soluble palladium reagents tend to be expensive and sometimes difficult to manipulate and recover. The solvents also pose recyclability (waste handling) problems of their own. In addition, amines such as piperidine, diethylamine and triethylamine are required in most Sonogashira reactions and they add to the environmental burden.

We have found alumina to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways which enhance its reactivity and it can be utilized to solve some of the environmental problems associated with organic reagents.^{8,9} For example, using a commercially available alumina potassium fluoride mixture, to which we added palladium powder (the least expensive form of palladium available), we were able to carry out Suzuki reactions on a wide variety of aromatic moieties without the use of solvents.⁹

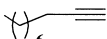
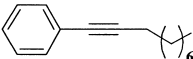
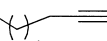
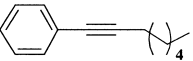
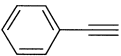
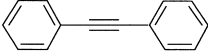
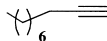
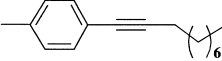
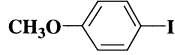
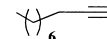
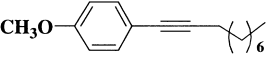
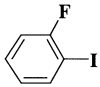
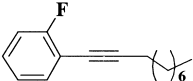
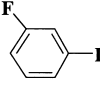
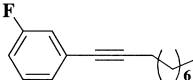
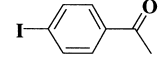
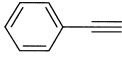
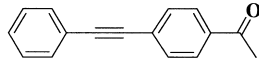
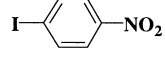
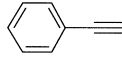
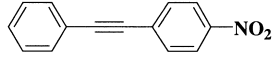
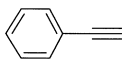
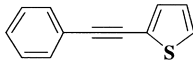
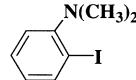
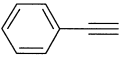
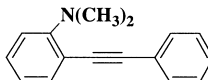
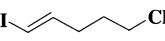
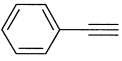
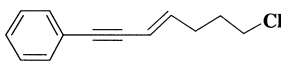
Microwave irradiation of organic reactions has gained in popularity in recent years since it was found to accelerate a wide variety of transformations.^{10,11} We now wish to report a microwave enhanced, energy efficient modification of a solid-state, Sonogashira reaction which enhances the reaction's eco-friendly attributes. The new methodology couples microwave irradiation with a solid-state, solvent free approach and leads to enhanced yields of the desired aryl alkynes.

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The results are summarized in Table 1. The data indicate that, under microwave irradiation in solvent free conditions, coupling readily occurs between a variety of aryl iodides, heteroaromatic iodides and vinyl iodides with terminal alkynes. However, aryl bromides and aryl chlorides do

Table 1
Sonogashira coupling reaction of organic halides with alkynes^a

Entry	RX	RC/CH	Product ^b	Yield(%) ^c
a				94 ^d , 0 ^e , 0 ^f 20 ^g
b				84
c				91
d				97 ^h
e				93 ^h
f				84 ^h
g				96 ^h
h				82
i				67
j				82
k				82
l				84 ^h

^aReaction conditions: aryl or alkenyl iodide (1.00 mmol), alkyne (1.05mmol), Pd powder (40mg), CuI (70 mg), PPh₃ (180mg), KF (40% by weight)/Al₂O₃ (1.0 g). A 1000 watt microwave oven (Sharp Model R-4A38) was used at 100% power for 2.5 minutes. ^bAll reaction products exhibited physical and spectral characteristics in accord with literature values. ^cIsolated yields. ^dNo palladium was added. ^eNo triphenylphosphine was added. ^fNo CuI was added. ^gNo alumina was added and the 1000 watt microwave oven was used at 30% power for 3 minutes. ^hSatisfactory elemental analysis was obtained.

not react and the starting materials are recovered unchanged. Substituent effects were also examined. The results indicate that an electron-donating group on the aromatic ring enhances the reaction and leads to the desired product in excellent yields (97 and 93%, respectively, entries d and e). Strong electron-withdrawing groups, lead to more moderate yields (82 and 67%, respectively, entries h and i). It is interesting to note that a bulky group on the *ortho*-position of the benzene ring did not inhibit the reaction (82%, entry k).

During the investigation, we found that the reaction did not occur in the absence of palladium, cuprous iodide, or triphenylphosphine (entry a). CAUTION, the microwave reaction should not be attempted in the absence of alumina which apparently acts as a temperature moderator.¹² Without alumina, the liquid reactants can react uncontrollably in the presence of metallic palladium (DANGER).

Larock and his co-worker have reported that indoles and benzofurans can be prepared by the coupling terminal alkynes with *o*-iodoaniline and *o*-iodophenol, respectively, using palladium and copper reagents.^{13,14} We found that coupling *o*-iodophenol with terminal alkyne produced the cyclized product, benzofuran, in moderate yield. The coupling reaction of *o*-iodoaniline with terminal alkynes is dependent on the reaction conditions. If a 1:1 ratio of *o*-iodoaniline to alkyne is used, only the coupling product is obtained, and no cyclization product forms. This differs from previously reported results.¹⁴ When the ratio of *o*-iodoaniline to alkyne is 2:1, a mixture of cyclization and coupling products is formed (Fig. 1).

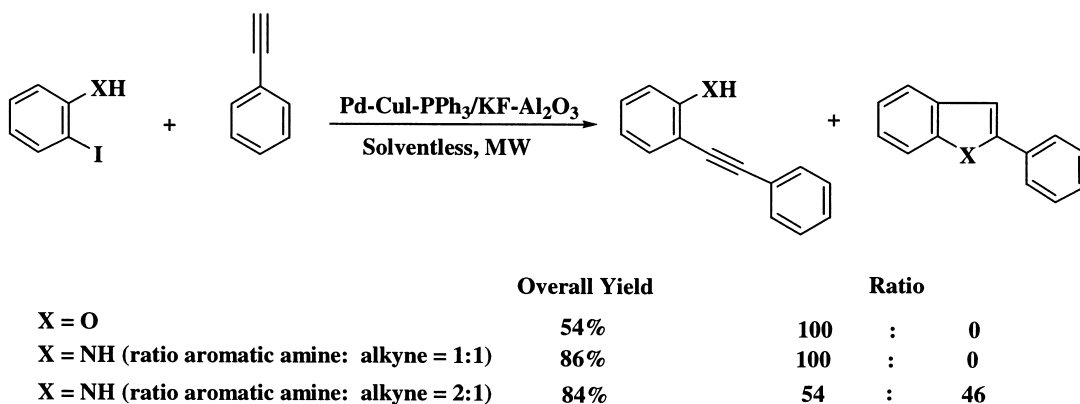


Figure 1.

The synthesis of 1-phenyl-1-decyne is representative. Iodobenzene (0.204 g, 1.000 mmol) and 1-decyne (0.145 g, 1.050 mmol) were added to a mixture of KF/Al₂O₃ (1.000 g, 40% by weight), palladium powder (0.040 g, 0.376 mmol, 99.9+% as a submicron powder), cuprous iodide (0.070 g, 0.368 mmol) and triphenylphosphine (0.180 g, 0.686 mmol) contained in a clean, dry, 25 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave and irradiated at 100% power for 2.5 min. After cooling, hexane (5 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product was purified by flash chromatography to yield 0.201 g of 1-phenyl-1-decyne (94%). The same reaction was carried out on a 10 mmol scale and resulted in slightly higher yields.

In summary, a reliable, rapid and practical procedure for the synthesis of arylacetylenes via a Sonogashira coupling reaction was developed which involves the use of a solvent-free mixture of potassium fluoride on alumina under microwave irradiation conditions. The reaction is environmentally friendly, and results in high yields of the desired product.

Acknowledgements

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