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Tetrahedron Letters 45 (2004) 3237–3239

Tetrahedron Letters

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Copper-catalyzed cross-coupling of aryl iodides and aryl acetylenes using microwave heating

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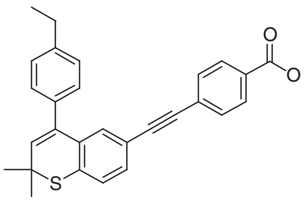
Received 13 February 2004; accepted 25 February 2004

Abstract—An efficient copper-catalyzed cross-coupling of aryl iodides with aryl acetylenes under microwave irradiation is described. The reaction proceeds under microwave heating with 10 mol % CuI and 2 equiv Cs_2CO_3 in 43–87% yields.

Biaryl alkynes moieties exist in a variety of natural and unnatural products of biological and pharmaceutical importance. These compounds include AGN-194310[1] (Fig. 1), a RAR antagonist for the treatment of mucocutaneous toxicity currently in Phase III clinical trials, as well as other compounds with potential as immunomodulators,[2] antifungal,[3] antipsoriatic,[1] and antiarthritic agents.[2]



AGN-194310

Figure 1.

The most widely used method for constructing biaryl alkynes involves cross-coupling of aryl halides with terminal aryl acetylenes. Sonogashira et al.[4] first reported the palladium/copper-catalyzed cross-coupling of aryl halides with terminal acetylenes. Recent advances of Sonogashira reaction include development of conditions with metals other than copper[5] and a copper-free protocol.[6] Unfortunately, procedures with other metals normally require a stoichiometric amount of the metal, thus producing concerns of cost efficiency and toxicity. These concerns have been obviated in the copper-free protocol using (allyl $PdCl)_2$,[6] but there is still a pressing need for the development of methods for catalytic coupling reactions using transition metals other than palladium. Thus, Okuro et al. developed a CuI-catalyzed coupling reaction of aryl and vinyl halides with terminal alkynes.[7] However, this reaction required the addition of triphenylphosphine and extended reaction time (80–120 °C, 10–40 h).[7] Recently, Wang et al. reported a microwave-assisted version of this reaction.[8] Herein, we wish to report an efficient microwave-assisted copper-catalyzed cross-coupling reaction of aryl iodides with terminal alkynes that, unlike the Wang procedure, does not require addition of any ligands.

A typical procedure involves irradiation of a mixture of aryl iodide (**1**), aryl acetylene (**2**), catalytic CuI (10 mol %), and 2 equiv of Cs_2CO_3 in *N*-methylpyrrolidinone (NMP) under microwave at 195 °C for 2–6 h followed by purification of the crude products by silica gel flash chromatography (Table 1).[9] The isolated yields of coupling products **3a–o** ranged from 43% to 87%.[10] For example, the coupling reaction of 1-*tert*-butyl-4-iodo-benzene with 1-ethnyl-2-fluorobenzene (Table 1, entry h) provided an 87% yield of product under microwave conditions. When the same reaction was carried out using a preheated oil bath under otherwise identical conditions (10 mol % CuI, 2 equiv Cs_2CO_3, 195 °C, 2.5 h), a lower yield (71%) was obtained. Without CuI catalysis, no reaction occurred under microwave irradiation. In the absence of Cs_2CO_3, only

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Keywords: Microwave; Aryl acetylenes; Cross-coupling; Aryl iodide.

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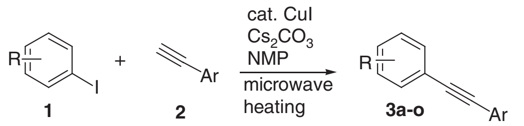
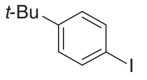
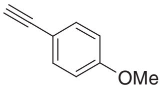
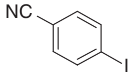
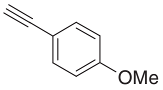
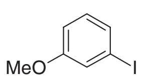
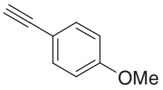
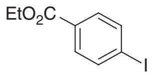
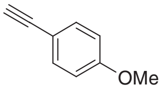
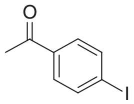
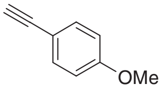
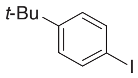
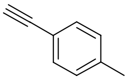
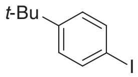
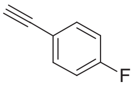
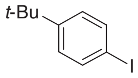
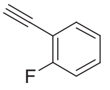
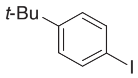
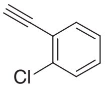
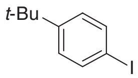
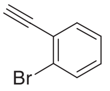
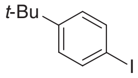
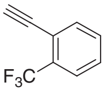
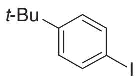
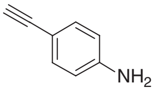
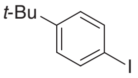
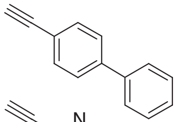
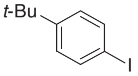
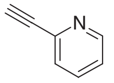
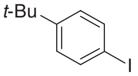
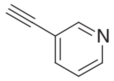
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.124

Table 1. Cross-coupling of aryl iodides with aryl acetylenes

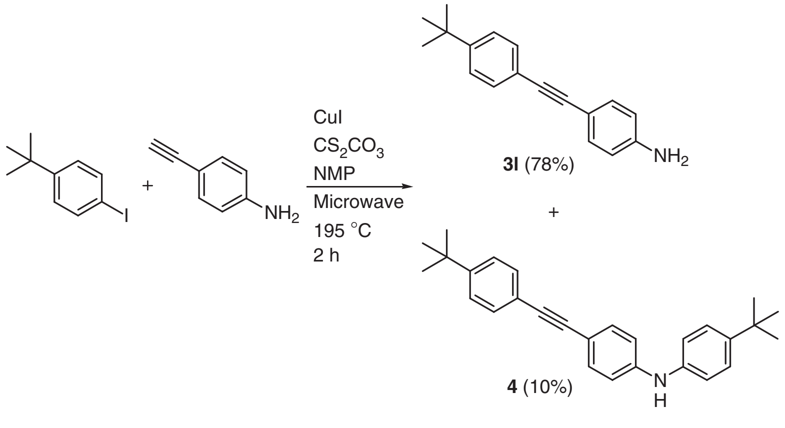


Entry	Ar–I (**1**)	Alkynes (**2**)	Reaction time (h)	Yield % (**3a–o**)
a			4	76
b			2	71
c			3	68
d			2	54
e			2	43
f			2.5	85
g			4	83
h			2.5	87
i			2.5	72
j			2.5	63
k			2	81
l			2	78
m			2	72
n			6	79
o			4	79

5% conversion was observed as indicated by HPLC analysis of the reaction mixture. Thus, the CuI catalyst and Cs_2CO_3 play critical roles in this coupling reaction.

For the aryl iodide component, a variety of functional groups were tolerated, although lower yields were obtained with ester and ketone derivatives (entries d and e), presumably due to degradation of the starting materials under the basic reaction conditions. For the aryl acetylenes, electron-withdrawing and electron-neutral groups generally provided slightly higher yields than those with electron-donating groups (entries f, g, h, and k vs a and l). This may be ascribed to the reduced acidity of aryl acetylenes with electron-donating substituents. Fluoro-, chloro-, and bromo-phenylacetylenes were well tolerated (entries h–j) under these microwave conditions, thus providing coupling products suitable for further functionalization. Decreasing isolated yields (entries h>i>j) were observed with increasing sizes of *ortho*-halogens (F<Cl<Br). Of particular interest is the finding that coupling of 4-ethynyl-phenylamine with 1-*tert*-butyl-4-iodo-benzene (entry l) furnished 78% yield of the desired product **3l** along with 10% yield of di-arylamine **4** due to further N-arylation of **3l** (Scheme 1). Thus, the coupling of aryl iodides appears to be selective with phenylacetylenes over the N-arylation of phenylamines. When 1-ethynyl-4-nitrobenzene was treated with 1-*tert*-butyl-4-iodo-benzene for 2 h, we observed 80% starting material along with 20% of the reduced product. Thus, nitro group does not seem to be tolerated under these conditions. In addition to phenyl acetylenes, we also investigated pyridyl acetylenes (entries n and o). Both 2- and 3-ethynyl-pyridines worked well but required longer reaction time (4–6 h) to go to completion.

Other variations of this reaction were briefly investigated. Alkyl alkynes may not be suitable as no reaction was observed with aryl iodides and benzylacetylene or trimethyl-prop-2-ynyl-silane. In addition, sluggish reactions were observed with aryl bromides. For example, only 5% conversion was observed after 4 h microwave heating with 1-bromo-4-*tert*-butyl-benzene and 1-ethnyl-2-fluorobenzene compared with the 87% yield obtained with the aryl iodide (entry h). Use of NaO*t*-Bu instead of Cs_2CO_3 increased the conversion to 20% after



Scheme 1. Synthesis of **3l**.

4 h, but also increased the extent of the oligomerization of 1-ethnyl-2-fluorobenzene.[11]

In summary, we have developed an operationally simple and efficient methodology for the copper-catalyzed cross-coupling reactions of aryl iodides with aryl acetylenes using microwave heating.

Acknowledgement

We thank Dr. Joanne Bronson for critical reading of the manuscript.

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9. Representative procedure: To a solution of 1-*tert*-butyl-4-iodo-benzene (130 mg, 0.5 mmol) and 1-ethnyl-2-fluorobenzene (63 mg, 0.53 mmol) in *N*-methylpyrrolidinone (0.67 mL) in a microwave vial were added cesium carbonate (325 mg, 1.0 mmol), and copper(I) iodide (9 mg, 0.05 mmol). The vial was sealed and heated in a Smith Creator at 195 °C for 2.5 h. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The reaction mixture was cooled down to room temperature and purified by silica gel flash chromatography (5% acetone/95% hexanes) to yield **3h** as white crystalline material (107 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H), 7.10 (m, 2H), 7.31 (m, 1H), 7.37 (d, 2H, $J = 8.4$ Hz), 7.50 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.2, 34.8, 82.0, 94.6 (d, $J = 10$ Hz), 112.2 (d, $J = 20$ Hz), 115.5 (d, $J = 20$ Hz), 119.9, 123.9 (d, $J = 4$ Hz), 125.4, 129.8 (d, $J = 10$ Hz), 131.5, 133.4, 151.9, 162.6 (d, $J = 250$ Hz).
10. All new compounds (**3a**–**o**) have spectral and analytical data in agreement with the indicated structure.
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