



Copper-catalyzed alkyne–aryne coupling reaction under microwave conditions: preparation of unsymmetric and symmetric di-substituted alkynes

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ABSTRACT

Several unsymmetric and symmetric alkynes were prepared excellent to modest yields by generating benzyne from the reaction of 2-(trimethylsilyl)phenyl triflate with CsF in the presence of CuI and terminal alkyne under microwave heating for 30 min at 150 °C. Using conventional heating, the reactions required 24 h reaction time.

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In the words of Meyers and co-workers,¹ 'Aromatic substitution has occupied a central role in organic chemistry for over 100 years with one of its major achievements being the advent of a benzyne² intermediate in certain aromatic nucleophilic substitutions.³ Until 1983, the generation of benzyne required harsh conditions such as the reaction of haloarenes with strong bases (e.g., LDA and alkali amides), the reaction of 1,2-dihaloarenes with Mg, and the oxidation of 1-aminobenzothiazines. The scope of the benzyne reaction using classical harsh conditions is limited, especially in its failure (unlike alkynes) to participate in transition-metal-mediated cross-coupling reactions involving C(sp)–C(sp²) bond formation. However, in 1983 an exciting, mild method for the preparation of arynes in situ at moderate temperatures from commercially available *o*-silyl aryl triflates⁴ came on the scene allowing the scope of benzyne reactions to be greatly extended. These aryne-mediated reactions initially were found to occur with high efficiency using Pd as catalyst.⁵

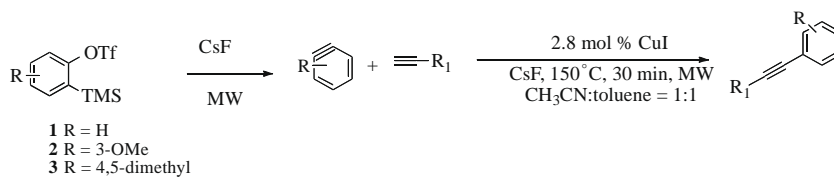
We were intrigued by a recent report⁶ that benzyne, generated by the reaction of 2-(trimethylsilyl) phenyltriflate and CsF, is an efficient intermediate in the copper-catalyzed two-component coupling reaction with alkynes. These reactions require a temperature of 110 °C and 24 h reaction times. With our long-time (>50 years) interest in benzyne chemistry in synthesis combined with our recent interest in microwave-assisted reactions,⁷ it occurred to us that the aforementioned coupling reaction might serve to merge our two interests. Such a combination would represent, to

our knowledge, the first example of microwave-assisted benzyne chemistry.

Initially, we performed the reaction of benzyne generated in situ from 2-(trimethylsilyl) phenyl triflate (**1**) and phenyl acetylene in the presence of CuI catalysis with microwave heating. After many experiments in which reaction temperatures and times were varied, we found that the highest yield was obtained when the microwave heating was carried out for 30 min at a temperature of 150 °C in a 1:1 acetonitrile/toluene solvent mixture (Scheme 1). The microwave reactions were performed in a CEM Discover Model microwave apparatus. The reactions were run in a sealed tube at 101 PSI and power at 200 W with rapid stirring. Plots of temperatures versus time, pressure (psi) versus time, and wattage (W) versus time are given in the Supplementary data.

As shown in Table 1, the reaction of **1** with 10 terminal alkynes gave the corresponding 2-substituted 1-phenylacetylene (entries 1–10) (with the exception of the ester entry 5, which was formed in 63% yield) in yields ranging from 95% to 70%. The reaction of **2** gave 2-substituted 3-methoxyphenylacetylenes as expected⁸ (entries 11–18). 3-Methoxy phenylacetylene and 3-methoxy *p*-nitro phenyl acetylene (entries 11 & 18) were formed in 97% yield, while the remaining 3-methoxy analogs were produced in significantly lower yields ranging from 59% to 79%. The reaction of **3** with terminal alkynes gave the corresponding 4,5-dimethylphenyl acetylenes (entries 19–25). Four of the products (entries 19–22) were formed in the range of 97–84% yields, while the ester (entry 23) was obtained in 65%. The results also indicate that acetylenes possessing an ether, ester, a nitro, or a halogen group as well as a pyridine ring tolerate the conditions of the microwave reactions. However (not indicated in the Table 1), the reactions of hydroxy and amino-

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
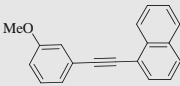
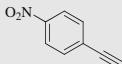
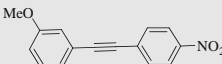

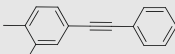
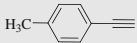
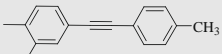
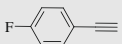

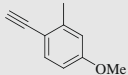
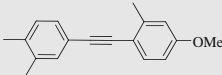

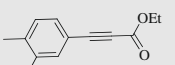
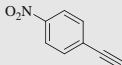
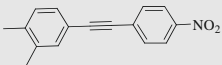

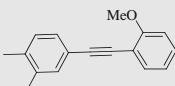


Scheme 1.

Table 1
The copper-catalyzed two-component coupling reaction

Entry	R	Alkyne	Product	Yield ^a (%)
1	H			90
2	H			95
3	H			86
4	H			84
5	H			63
6	H			70
7	H			82
8	H			86
9	H			77
10	H			94
11	3-OMe			97
12	3-OMe			79
13	3-OMe			76
14	3-OMe			65
15	3-OMe			72
16	3-OMe			78

Table 1 (continued)

Entry	R	Alkyne	Product	Yield ^a (%)
17	3-OMe			59
18	3-OMe			97
19	4,5-Dimethyl			89
20	4,5-Dimethyl			96
21	4,5-Dimethyl			92
22	4,5-Dimethyl			97
23	4,5-Dimethyl			65
24	4,5-Dimethyl			97
25	4,5-Dimethyl			84

Reaction conditions: benzyne precursor (1.2 equiv), terminal alkyne (1.0 equiv), CsF (2.4 equiv), CuI (0.1 equiv), toluene/CH₃CN 3:3 mL, 150 °C, 30 min.

^a Isolated yield.

substituted acetylenes with benzyne undergo decomposition to give complex reaction mixtures. A typical procedure is given in Ref. 9.

In summary, we have demonstrated a facile synthetic copper-catalyzed alkyne–aryne method for the one-pot synthesis of symmetric and unsymmetrical diary alkynes using microwave heating. By modulating the generation of arynes from 2-(trimethylsilyl) phenyl trifluoromethane-sulfonate and its 3-methoxy derivative with CsF under various conditions, we were able to obtain a significantly faster strategy for constructing sp²–sp² carbon bonds.

Acknowledgment

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- Typical procedure*: Preparation of 1,2-diphenylethyne: Phenyl acetylene (0.028 g, 0.274 mmol), CuI (5.2 mg, 0.0274 mmol), and CsF (0.099 g, 0.652 mmol) were charged with an oven-dried tube under the protection of nitrogen. Then, 2-(trimethylsilyl) phenyl triflate (0.1 g, 0.335 mmol) was added by syringe to a mixture of CH₃CN and toluene (2:2 mL). The reaction mixture was stirred at 150 °C for 30 min under microwave heating. The suspension was filtered and concentrated under reduced pressure. The residue was purified by preparative chromatography on TLC-Silica Gel 60 F₂₅₄ to provide 44 mg (90%) of 1,2-diphenylethyne.