

Efficient Sonogashira Coupling Reaction Catalyzed by Copper (I) Iodide in the Presence of $\text{KF}/\text{Al}_2\text{O}_3$

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Abstract

We have developed a convenient and efficient method for coupling of aryl iodides and bromides with terminal alkynes. The protocol uses CuI as catalyst, 1, 10-phenanthroline as ligand, $\text{KF}/\text{Al}_2\text{O}_3$ as base and toluene as solvent. The method is suitable for the synthesis of functionalized aryl-alkynes.

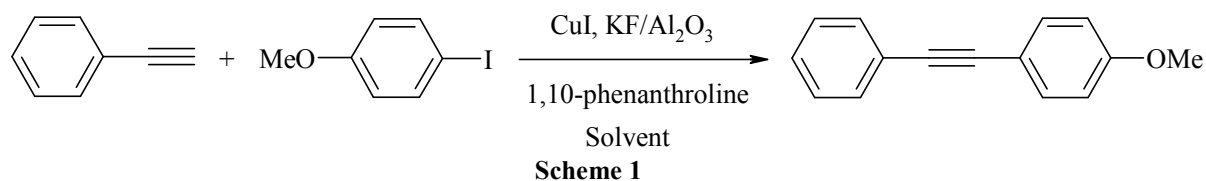
Keywords: CuI , Coupling reaction, Sonogashira reaction, Aryl iodides, Aryl bromides, Terminal alkynes.

Introduction

The acetylenic moiety is an important unit found in many compounds that are of pharmaceutical, biological, and material interest.¹ The selective method for the synthesis of these compounds is the Sonogashira reaction,² which involves the Pd/Cu-mediated formation of a $\text{C}(\text{sp}^2)\text{-C}(\text{sp})$ bond. A major drawback of this process for industrial use is the use of two metal catalysts, making recovery of the expensive palladium difficult. Thus it is worthwhile to search for cheaper and less toxic catalysts for the aryl-alkyne couplings. In 1992 Okuro *et al.* found that aryl halides can couple with terminal alkynes with CuI in the presence of Ph_3P .³ Wang *et al.* reported later that the $\text{CuI}/\text{Ph}_3\text{P}$ -catalyzed aryl-alkyne coupling can also be performed under microwave irradiation.⁴ Compared to the Sonogashira reaction, the $\text{CuI}/\text{Ph}_3\text{P}$ -catalyzed aryl-alkyne coupling has advantage due to the low price of Cu. However, in Okuro and Wang's procedures the use of toxic Ph_3P is not desirable. On the other hand, the application of $\text{KF}/\text{Al}_2\text{O}_3$ to organic synthesis also has

provided new methods for the wide range of organic reactions, many of which are staples of synthetic organic chemistry.⁵ KF/Al₂O₃ as a base in the presence of CuI was chosen as we have recently used this system for C-N and C-O bond formation in *N*-amidation and *O*-arylation.⁶

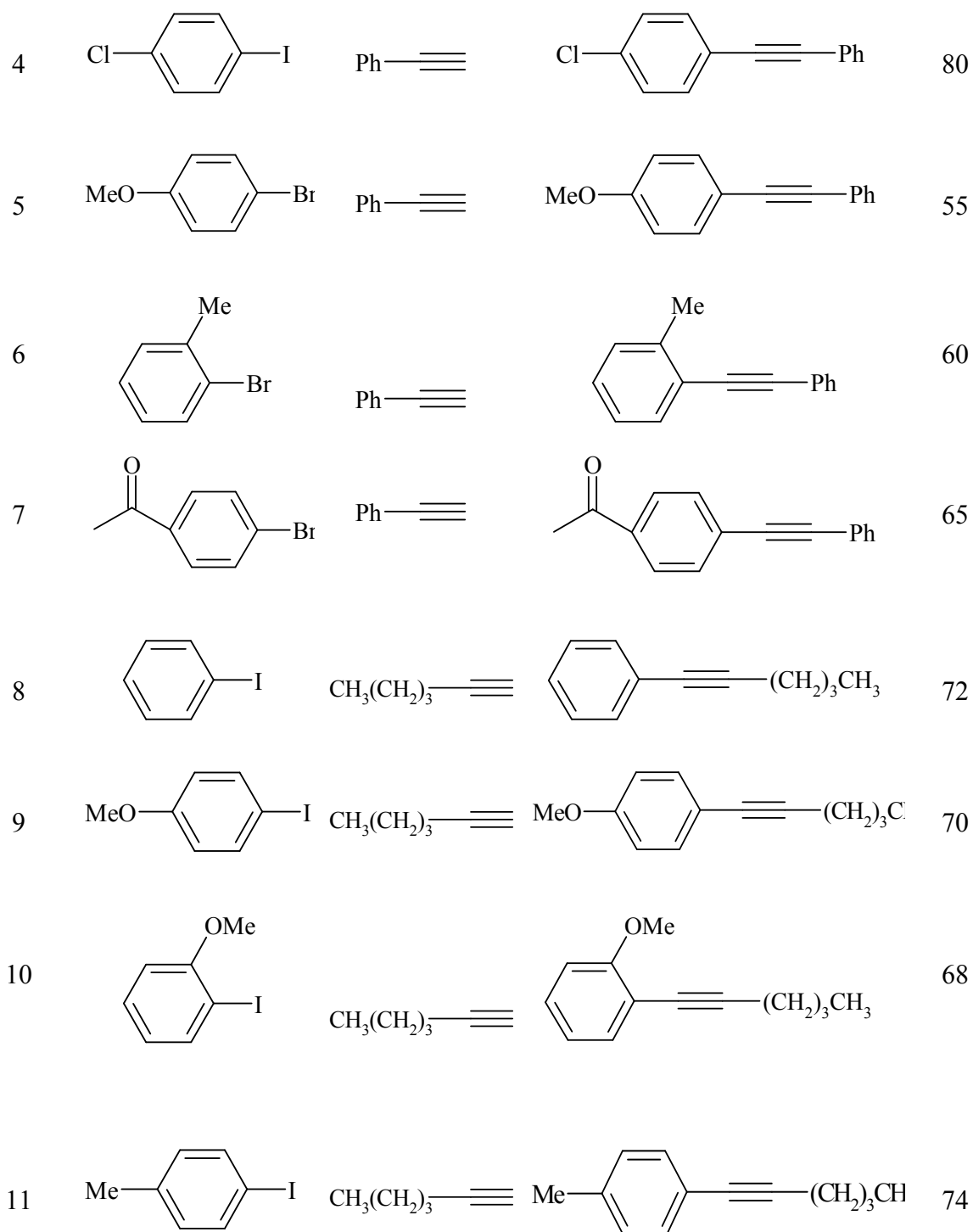
Initially, we employed CuI-catalyzed coupling reaction of phenylacetylene with 4-iodoanisole as a model reaction to optimize the reaction conditions (scheme 1).



Variation of solvent, temperature, and molar ratio of the substrates revealed that a molar ratio of 1.2:1 phenyl acetylene to 4-iodoanisole and 1,10-phenanthroline (30 mol%), CuI (10 mol%), and KF/Al₂O₃ (5 equivalent) in toluene at 110 °C gives the highest yield of the 1-Methoxy-4-phenylethynyl benzene (78%) after 24 hours. To show the generality of this method, we subjected a series of aryl halides with terminal alkynes and the results are summarized in Table 1.

Table 1: Copper-catalyzed coupling of aryl halides with terminal alkynes^a

| Entry | Aryl halide | Alkyne | Product | Yield (%) ^b |
|-------|-------------|----------|---------|------------------------|
| 1 | | Ph—C≡C—H | | 81 |
| 2 | | Ph—C≡C—H | | 78 |
| 3 | | Ph—C≡C—H | | 75 |



^a Reaction conditions: Aryl iodide (1 mmol), alkyne (1.2 mmol), CuI (0.1mmol), 1,10-phenanthroline (0.3 mmol), KF/Al₂O₃ (5 mmol) in 5 mL of toluene, 110 °C; or aryl bromide (1 mmol), alkyne (1.2 mmol), CuI (0.15 mmol), 1,10-phenanthroline (0.45 mmol), KF/Al₂O₃ (5 mmol) in 5 mL of toluene, 110 °C, 24 h.

^b Isolated yield; products were characterized by ¹H NMR and m.p.

As can be seen in Table 1, it was found that either electron-deficient or electron-rich aryl iodides reacted with phenyl acetylene to give the corresponding cross coupling products in 75-81% yields (entries 1–4). More importantly, we were pleased to observe that aryl bromides also worked well for this reaction, although higher catalyst loading (15 mol% CuI and 45 mol% 1,10-phenanthroline) was required to obtain satisfactory yields (entries 5–7). Substituent effects indicate that the reaction is relatively insensitive to the electronic characteristics of a substituent as well as its location. Aliphatic alkynes were also suitable substrates for this reaction besides aryl alkynes. For examples, 1-hexyne coupled with aryl iodides in good yields to provide aliphatic alkynes (entries 8–11).

In summary, we have developed an operationally simple and efficient method for the copper-catalyzed coupling of a variety of aryl halides with terminal alkynes using KF/Al₂O₃ as a base and CuI as the catalyst and 1,10-phenanthroline as the ligand. We believe that potassium fluoride supported on alumina (KF/Al₂O₃) provides an excellent complement to the other base such as Cs₂CO₃ in copper-catalyzed methodology that has already been utilized in a number of applications.

Experimental

General procedure: A mixture of aryl halide (1 mmol), alkyne (1.2 mmol), CuI (10 mol% for aryl iodides and 15 mol% for aryl bromides), 1,10-phenanthroline (30 mol% for aryl iodides and 45 mol% for aryl bromides), KF/Al₂O₃ (5 equivalents) and toluene (5 ml) was stirred at 110 °C for 24 h. The progress of the reaction was monitored by TLC. After the reaction was finished, diethyl ether was poured into the mixture, then washed with water, extracted with diethyl ether, dried with anhydrous MgSO₄, evaporated under vacuum, and the residue was purified by column chromatography on silica gel using hexane as eluent to afford the pure products. The spectroscopic data and melting points for known products compared well with the reported data. Selected physical and spectral data:

1-Methoxy-4-phenylethynyl benzene (table 1, entries 2 and 5): m.p. 56-57 °C (lit.^[7a] 58-60 °C); ¹H NMR (500 MHz, CDCl₃): δ 7.57-7.51 (m, 4H), 7.40-7.30 (m, 3H), 6.93-6.92 (m, 2H), 3.88 (s, 3H).

1-(4-Chlorophenyl)phenylacetylene (table 1, entry 4): m.p. 78-80 °C (lit.^[3] 81-82 °C); ¹H NMR (500 MHz, CDCl₃): δ 7.59-7.57 (m, 2H), 7.52-7.50 (m, 2H), 7.42-7.37 (m, 5H).

1-(4-Acetylphenyl)phenylacetylene (table 1, entry 7): m.p. 94-95 °C (lit.^[7b] 95-96 °C); ¹H NMR (300 MHz, CDCl₃): δ 7.92 (d, *J*=8.4 Hz, 2H), 7.59 (d, *J*=8.4 Hz, 2H), 7.55-7.52 (m, 2H), 7.37-7.34 (m, 3H), 2.58 (s, 3H)

1-(Hex-1-ynyl)-4-methyl benzene (table 1, entry 11) : Oil ^[7c]; ¹H NMR (500 MHz, CDCl₃): δ 7.33 (d, *J*=7.1 Hz, 2H), 7.12 (d, *J*=7.8 Hz, 2H), 2.44 (t, *J*=7.1 Hz, 2H), 2.37 (s, 3H), 1.65-1.60 (m, 2H), 1.56-1.52 (m, 2H), 0.99 (t, *J*=7.3 Hz, 3H).

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