Notes

Iron Powder-CuI Cooperative Catalytic System in Sonogashira Cross-Coupling Reaction

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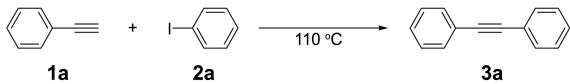
The transition metal-catalyzed sp-carbon-sp^2-carbon bond forming reaction by the cross-coupling of terminal alkynes with aryl and vinyl halides (or triflates) is well known as Sonogashira cross-coupling reaction.[1-4] This protocol has been widely used as a powerful synthetic tool for the synthesis of prevalent and valuable intermediates for pharmaceuticals and organic materials.[1-4] Since the coupling intrinsically catalyzed by Pd(PPh$_3$)$_4$ and CuI was discovered in 1975,[5] many elegant catalytic systems which facilitate such a coupling under the milder and cheaper conditions have been developed by the tuning of a ligand combined with the kind of palladium catalysts.[1-4] Furthermore, besides such palladium based systems, several catalytic systems which are inexpensive and benign to the environment have been developed for both an academic viewpoint and a large scale industrial application. For example, many copper salts combined with appropriate ligands have been used as an alternative to palladium based systems for Sonogashira cross-coupling reaction.[6-15] In connection with this report, iron salts have recently had an upsurge as a promising catalyst in carbon-carbon bond forming reactions due to their natural abundance, low cost and environmental friendliness.[16-20] Thus, a number of iron catalysts have also been applied to Sonogashira coupling. For representative examples, Mao and Vogel groups have reported that terminal alkynes are readily cross-coupled with aryl iodides in the presence of Fe(acac)$_3$ in combination with CuI without an additional ligand.[21-22] It was also disclosed by Liu group that Fe$_2$O$_3$/*N,N,N',N'*-tetramethylethylenediamine catalytic system can be used for such a coupling by the assistance of Cu(acac)$_2$ cocatalyst.[23] It is also worthy to note that terminal alkynes were found to be cross-coupled with aryl iodides in the presence of FeCl$_3$ combined with *N,N'*-dimethylethylenediamine or PPh$_3$ without further addition of a copper ancillary.[24,25] Under these circumstances, during the course of our ongoing studies on transition metal-catalyzed carbon-carbon and carbon-nitrogen bond forming reactions,[26-36] herein this report describes an efficient iron powder/CuI/PPh$_3$-catalyzed cross-coupling reaction between terminal alkynes and aryl iodides leading to coupled alkynes.

Phenylacetylene (**1a**) and iodobenzene (**2a**) were chosen as the model reactants for optimizing reaction conditions.

Several attempted representative results under various conditions are listed in Table 1. Treatment of **1a** with 1.2 equiv of **2a** in DMF in the presence of a catalytic amount of iron powder (10 mol % based on **1a**), PPh$_3$ (10 mol % based on **1a**) and CuI (10 mol % based on **1a**) along with K$_2$CO$_3$ for 10 h afforded diphenylacetylene (**3a**) in 95% isolated yield with complete conversion of **1a** and concomitant formation of a trace amount of 1,4-diphenylbuta-1,3-diyne by the homo-coupling of **1a** on GLC (run 1). Lower reaction rate and yield were observed in the absence of either PPh$_3$, or Fe powder, or CuI (runs 2-4). Even though the reaction proceeds in the absence of iron powder, the yield of **3a** was lower than that of the reaction by the addition of iron powder (run 3). It is known that CuI/PPh$_3$ catalytic system catalyzes cross-coupling of terminal alkynes and aryl iodides in H$_2$O at a higher temperature in a pressure tube.[37] It is worthwhile to note that the reaction proceeds even in the absence of CuI (run 4). These results indicate that the coexistence of Fe powder, PPh$_3$ and CuI is necessary for the effective

Table 1. Optimization of conditions for the reaction of phenylacetylene (**1a**) with phenyl iodide (**2a**)^a

Run	Catalytic systems	Bases	Solvents	Time (h)	Yield (%)
1	Fe powder/CuI/PPh$_3$	K$_2$CO$_3$	DMF	10	95
2	Fe powder/CuI	K$_2$CO$_3$	DMF	10	82
3	CuI/PPh$_3$	K$_2$CO$_3$	DMF	10	80
4	Fe powder/PPh$_3$	K$_2$CO$_3$	DMF	10	76
5	Fe powder/CuI/PPh$_3$	–	DMF	10	6
6	Fe powder/CuI/PPh$_3$	K$_3$PO$_4$	DMF	10	99
7	Fe powder/CuI/PPh$_3$	Cs$_2$CO$_3$	Toluene	1	73
8	Fe powder/CuI/PPh$_3$	Cs$_2$CO$_3$	Dioxane	1	64
9	Fe powder/CuI/PPh$_3$	Cs$_2$CO$_3$	PEG-400	1	19
10	Fe powder/CuI/PPh$_3$	Cs$_2$CO$_3$	DMF	1	99
11	CuI/PPh$_3$	Cs$_2$CO$_3$	DMF	10	77

^{a}Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), Fe powder (0.1 mmol), CuI (0.1 mmol), PPh$_3$ (0.1 mmol), base (2 mmol), solvent (2 mL), at 110 °C, under N$_2$.

formation of **3a** (runs 1-4). However, when the reaction was carried out in the absence of base under the employed conditions, **3a** was produced in only 6% yield with incomplete conversion of both substrates (run 5). Replacing K_2CO_3 by K_3PO_4 under the same reaction conditions resulted in quantitative yield of **3a** (run 6). As a result, after further elaborated tuning with base, reaction time and solvent, the best result in terms of both product **3a** yield and complete conversion of **1a** is best accomplished by the standard set of reaction conditions shown in run 10 of Table 1 (runs 7-11).

On the other hand, the certificate of analysis of commercial Fe powder (99.9%, Strem Chemicals, Inc.) shows several elements such as As (< 3 ppm), Pb (< 4 ppm) and

Hg (< 2 ppm) along with insoluble materials in aqueous acid (0.05%). We also confirmed that no Pd contaminant in Fe powder was observed by ICP-AES (inductively coupled plasma-atomic emission spectroscopy). However, even though Cu was detected in 9 ppm by ICP-AES, similar treatment of **1a** with **2a** under the catalytic system of CuI (1500 ppm based on **1a**)/PPh_3/Cs_2CO_3/DMF afforded **3a** in only 6% yield.

For investigating the reaction scope, the optimized condition was subjected to the reaction of various terminal alkynes **1** with aryl iodides **2** and several representative results are summarized in Table 2. Phenylacetylene (**1a**) reacted with an array of aryl iodides (**2a-g**) having electron-donating and -withdrawing substituents on the aromatic ring to afford the corresponding coupled alkynes (**3a-g**) in quantitative isolated yields. The product yield was considerably affected by the position of the substituent on **2**, whereas the electronic nature of that had no relevance to the product yield. With *ortho*-substituted aryl iodide **2b**, the coupled product yield was lower than that when *meta*- and *para*-substituted aryl iodides (**2c-g**) were used. Thus, a longer reaction time was actually needed for the satisfactory coupling with **2b**. In the reaction of vinyl alkyne, 1-ethynylcyclohex-1-ene (**1b**) with several aryl iodides, the corresponding coupled alkynes were also obtained in quantitative yields. Here again, lower reaction rate was observed with **2d** and **2g**. Lower reaction rate and yield were observed with alkyl alkyne **1c** when compared with those of aryl and vinyl alkynes. The coupling of **1c** with several aryl iodides afforded coupled alkynes (**3k-n**) in the range of 84-97% yields for a longer reaction time. From the reaction between 2-ethynylnaphthalene (**1d**) and **2a**, the corresponding coupled alkyne **3o** was also produced in quantitative yield. Heteroaryl alkyne, 2-ethynylpyridine (**1e**) was also cross-coupled with **2a** to give 2-(2-phenylethynyl)pyridine (**3p**) in 76% yield for 10 h.

In summary, we have demonstrated that the cross-coupling of aryl, vinyl, alkyl substituted terminal alkynes with aryl iodides was catalyzed by Fe powder/PPh_3/CuI. The present reaction provides a cheaper cooperative catalytic system in Sonogashira cross-coupling reaction and further study for a catalytic role of iron powder is currently under investigation.

Table 2. Fe powder/PPh_3/CuI-catalyzed Sonogashira cross-coupling of terminal alkynes **1** with aryl iodides **2**[a]

R≡ + I—Ar $\xrightarrow[\text{DMF}]{\text{Fe powder/CuI/PPh}_3\text{, Cs}_2\text{CO}_3}$ R≡—Ar

(R = aryl, heteroaryl, vinyl, alkyl)

Terminal alkynes 1	Ary liodides 2	Coupled alkynes 3	Yield (%)
1a	**2a**	**3a**	99
1a	**2b**	**3b**	85[b]
1a	**2c**	**3c**	96
1a	**2d**	**3d**	97
1a	**2e**	**3e**	99
1a	**2f**	**3f**	95
1a	**2g**	**3g**	99
1b	**2a**	**3h**	95
1b	**2d**	**3i**	95[b]
1b	**2g**	**3j**	99[b]
1c n-C$_6$H$_{13}$	**2a**	**3k**	85[c]
1c	**2d**	**3l**	97[c]
1c	**2f**	**3m**	84[c]
1c	**2g**	**3n**	97[c]
1d	**2a**	**3o**	99
1e	**2a**	**3p**	76[b]

[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Fe powder (0.1 mmol), PPh_3 (0.1 mmol), CuI (0.1 mmol), Cs_2CO_3 (2 mmol), DMF (2 mL), at 110 °C, for 1 h, under N_2. [b]For 10 h. [c]For 20 h.

Experimental Section

Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. GLC analyses were carried out with a Shimadzu GC-17A instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as carrier gas. The isolation of pure products was carried out *via* column (silica gel 60, 70-230 mesh, Merck) or thin layer (silica gel 60 GF$_{254}$, Merck) chromatography. Iron powder (99.9%) was purchased from Strem Chemicals Inc. Commercially available organic and inorganic compounds were used without further purification except for solvents, which were distilled prior to use.

General Procedure for Fe Powder/PPh₃/CuI-Catalyzed Cross-Coupling Reaction of Terminal Alkynes with Aryl Iodides. A mixture of alkyne (1 mmol), aryl iodide (1.2 mmol), iron powder (0.0056 g, 0.1 mmol), PPh₃ (0.026 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol), Cs₂CO₃ (0.652 g, 2 mmol) and DMF (2 mL) was placed in a sealable reactor with Teflon cap (Radleys Discovery Technologies). After the system was flushed with N₂, the mixture was stirred at 110 ᵒC for a required time. After the reaction mixture was cooled down to room temperature, it was filtered through a short silica gel column (ethyl acetate as eluent) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by column or thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give coupled alkynes **3**. All coupled alkynes prepared by the above procedure were characterized by GLC and melting point comparison with authentic samples synthesized by known methods and purchased from chemical companies.

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