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Sonogashira Coupling Reaction with Diminished Homocoupling

Arumugasamy Elangovan, Yu-Hsiang Wang, and Tong-Ing Ho*

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan R.O.C.

hall@ccms.ntu.edu.tw

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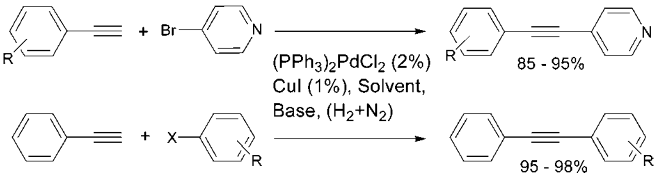
ABSTRACT



The side product from homocoupling reaction of two terminal acetylenes in the Sonogashira reaction can be reduced to about 2% using an atmosphere of hydrogen gas diluted with nitrogen or argon. Terminal arylethynes, diarylethynes, and a few new arylpyridylethynes with donor substituents have been synthesized in very good yields. Comparative control experiments suggest that the homocoupling yield is determined by concentration of both catalyst and oxygen.

Construction of π-conjugated aromatic compounds assumes significance in the wake of the application of these compounds in organic light-emitting diodes (OLEDs), in polymer LEDs, as nonlinear optical materials,[1] in carbohydrate sensing,[1g] and in molecular electronics.[2] Synthesis of arylethynyl compounds by catalytic crosscoupling of terminal acetylenes with aryl halides is an important step in this task.

Sonogashira coupling[3] is versatile and has been applied to prepare several terminal and internal acetylenes. The reaction conditions are mild, and many reactions can be performed at room temperature. But the reaction is fraught with a limitation, in that it often results in considerable yields of Hay coupling product (homocoupling of terminal acetylenes, also called Glaser coupling, vide infra).

In our continued endeavor of synthesizing new donor−acceptor molecular systems for optoelectronic applications,[4] we envisaged that Sonogashira coupling would enable us to realize aryl donors linked to aryl and heteroaryl acceptors via a triple bond. Initial attempts under original Sonogashira conditions[3b] resulted in lower yields of the cross-coupled products along with a considerable amount of homocoupling products.

In this paper, we present a method to diminish acetylene bicoupling and enhance the desired cross-coupling. A survey of the literature reveals that copper acetylide undergoes homocoupling when exposed to air, and the first observation to this effect was made by Glaser[5a,b] as early as 1869. Since then many groups have modified and improved the reaction to obtain useful symmetrical and unsymmetrical butadiynes.[5c] Use of a Cu^I salt in the presence of an amine solvent was an important modification (Hay condition)[5d] that promotes

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* To whom correspondence should be addressed. Fax: +886-2-2363-6359.

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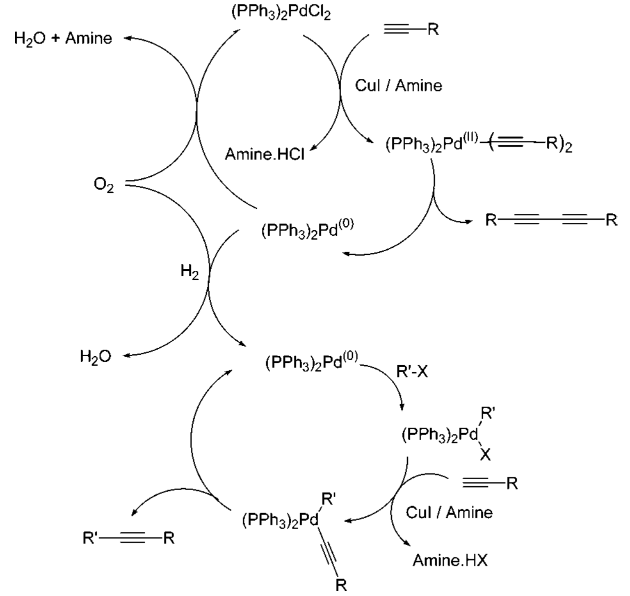
facile homocoupling of terminal ethynes at room temperatures in the presence of O_2. Later, use of palladium(0) complexes was invoked and optimized[5e,f] to obtain the butadiyne as the major product (a variant of Sonogashira reaction?!). From the foregoing discussions, it is clear that there remains, fundamentally, an urge to understand the mechanism underlying these reactions in the ever-evolving field of synthetic acetylenic chemistry especially of coupling reactions.

Although acetylene homocoupling reactions are generally useful in synthetic and application point of view, formation of *homo*coupling products while targeting *cross*coupling is undesirable. This is because the terminal acetylene is either very expensive or synthesized through several steps. Therefore, the formation of dimer is considered wasteful.

Hence, we carried out the Sonogashira reaction under dilute hydrogen atmosphere, and indeed, the yields of the bicoupling products have been found to be drastically diminished. Palladium(0), the active catalyst, is formed in situ from Pd^{II} only through the generation of the dimer as per the mechanism, and therefore, a small amount of the bicoupled product is always formed in the reaction. But the bicoupling may take place only as long as the palladium remains as Pd^{II} and yield the dimer in an amount equivalent to the molar stoichiometry of the catalyst. But in many cases, a considerable amount of dimer was formed in reality at the expense of crosscoupling product. The reason for the formation of excessive dimer and lower yields of the crosscoupled products in many reactions is to be addressed with appropriate justification. Although most of the reactions are performed in inert atmospheres, the reaction setup is not completely devoid of oxygen and as long as the oxygen remains in the reaction mixture, it may reoxidize the Pd^0 back to Pd^{II}, which in turn may catalyze bicoupling. This cycle seems to repeat again and again leading to the formation of predominantly homocoupling product until all of the oxygen is consumed. This can be controlled by using a reducing atmosphere for the elimination of excessive paramagnetic oxygen, which would otherwise be present in the reaction setup. The exact role of hydrogen is not fully clear; however, the reaction appears to follow one probable course depicted in Scheme 1. Hydrogen may reduce oxygen to form water in the vicinity of nascent Pd^0 [6] and thus reduce the concentration of oxygen in the reaction.

Although there are reports of slow addition of the acetylene[7] and use of phase-transfer conditions[8] to diminish homocoupling, it is worth mentioning that most of the organic reactions are slow and the homocoupling could take place even at later stages given a substantial concentration of O_2. It is also true that higher concentrations of acetylene at the early stages need not necessarily yield predominantly Hay coupling product if the concentration of oxygen is controlled. Further, it is worth mentioning that, under original conditions, the less the reactivity of the halide the more the yield of dimer.

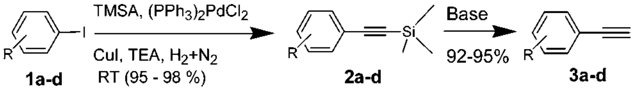
Scheme 1. Probable Mechanism[a]



[a] Evidence in support of the mechanism: (i) When the reaction (cf. Table 2, entry **e**) was carried out under identical conditions but with pure oxygen atmosphere instead of $N_2 + H_2$, diphenylbutadiyne was the only isolated product (92%) and little **4e** was isolated. (ii) When the reaction (cf. Table 3, entry **b**) was carried out with 10% palladium catalyst, 9.8% of the dimer was isolated along with 88% of **5b**.

Table 1 summarizes the details of synthesis of aryl acetylenes **3** from aryl halides **1** via the formation of trimethylsilylethynyl derivatives **2**. Among the aryl halides used, the iodides required milder conditions. It is well-known that the relative reactivity of the halide is Ar−I ≫ Ar−Br > Ar−Cl. This fact is more appropriate for aryl halides or acetylenes with electron withdrawing substituents in which case the reaction rate of the coupling is faster than the reoxidation of Pd^0. But with electron-rich halides, the

Table 1. Synthesis of Terminal Acetylenes[a]



entry	phenyl iodide **1** (R)	reaction conditions	yield of **2** (%)	yield of **3** (%)
a	2,4-dimethyl	TEA, rt, 2 h	96	92
b	4-OMe	TEA, rt, 1.5 h	98	95^{9a}
c	4-NMe_2	TEA, rt, 1 h	$\sim$100	95^{9b}
d	4-NEt_2	TEA, rt, 1 h	$\sim$100	94

[a] 1.1 equiv of trimethylsilylacetylene (TMSA), 1% Pd, and 1% CuI were used in all cases.[11a]

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(6) Possibly, PPh_3-ligated Pd^0 may catalyze the reduction of O_2 at the molecular level. For palladium metal catalyzed reduction of O_2 into water, see: Nyberg, C.; Tengstål, C. G. *J. Chem. Phys.* **1984**, *80* (7), 3463−3468 and references therein.

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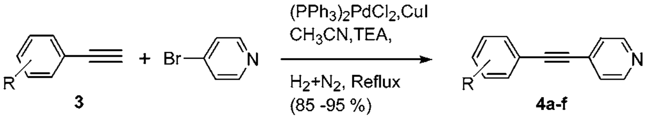
corresponding coupling reactions are rather slower. Two equivalents of trimethylsilylacetylene (TMSA) has to be used in such cases under usual conditions in order to get better yields.[9] Therefore, it may be inferred that the excess reagent was necessary in order to compensate for the loss incurred on account of the homocoupling.[10]

By using modified conditions, the reaction was found to be complete in 1 h with 1.1 equiv of the TMSA, and the crude was very neat and simple as evidenced from the NMR spectra. The product could be used in many cases for the next step without further purification.

Synthesis of **3c** (Table 1, entry **c**) has already been reported[9b] in high yields (90%), but we obtained only moderate yields (62%) as per the reported procedures with rest being bis(trimethylsilylbutadiyne). But using the modified conditions, we obtained quantitative yields from 4-iodo-*N*,*N*-dimethylaniline along with traces of dimer.

Table 2 shows the results of crosscoupling reactions. Triethylamine and piperidine were used as base individually but no apparent difference was noticed in the overall reaction and yields. No reaction was observed if THF was employed in place of acetonitrile. Therefore, acetonitrile was found to be the best solvent for the coupling reaction involving 4-bromopyridine hydrochloride. In all the reactions reported in Table 2 the yields of the cross-coupled products were increased at the expense of the homocoupling using the modified conditions whereas those of the homocoupling products were quite considerable when the reactions were carried out as per the original method.

Table 2. Synthesis of Internal Ethynes[a,b]



entry	phenylacetylene **3** (R)	yield of **4**[c,d] (%)		yield of dimer[c] (%)	
a	2,4-dimethyl	(89)	[59]	(1.90)	[33]
b	4-OMe	(91)	[64]	(1.88)	[28]
c	4-NMe_2	(94)	[63]	(1.78)	[35]
d	4- NEt_2	(95)	[55]	(2)	[30]
e	4-H	(88)	[45]	(2)	[45]
f	4-Me	(85)	[58]	(1.85)	[31]

[a] Mole ratio of acetylene to halide 1:1; CuI 1%; Pd 2%; base ~3 equiv; halide: 4-bromopyridine hydrochloride.[11b] [b] Conditions: (A) TEA, CH_3CN, reflux 8 h; (B) piperidine, CH_3CN reflux 8 h. [c] In parentheses: under the modified conditions. In square brackets: under original Sonogashira conditions.[3b] [d] Synthesis of compounds **4a**−**d**,**f** by catalytic crosscoupling is not known. The yields are the average of two runs and are of the isolated analytically pure compounds.

The synthesis of 4-phenylethynylpyridine **4e** (Table 2, entry **e**) has been reported[12] in 85% yield, but we could obtain only about half as much under the reported conditions along with an equal amount of diphenylbutadiyne, whereas using the modified conditions we were able to achieve higher yields of **4e** with the formation of traces of the diphenylbutadiyne nearly corresponding to the stoichiometric amount of the palladium catalyst.

To test the viability of the present method for generality, we chose a few known systems such as the coupling of phenylacetylene with different haloarenes, and the results are summarized in Table 3. It is clear that the method is

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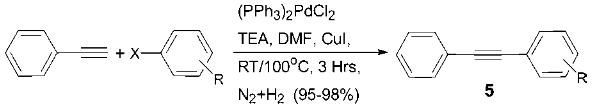
(11) **Typical Experimental Procedure. (a) Synthesis of 3c (Table 1, Entry c).** A 100 mL flask was charged with 4-iodo-*N*,*N*-dimethylaniline (**1c**) (2.47 g; 10 m mol), dichlorobis(triphenylphosphine)palladium(II) (70 mg; 1 mol %), and CuI (20 mg; 1 mol %), degassed, and back-filled three times with a mixture of H_2 and N_2/Ar. TEA (previously purged with N_2 + H_2, 50 mL) was introduced into the reaction flask. Then TMSA (1.08 g; 11 m mol) was added with stirring under the reducing atmosphere. After the mixture was stirred for 1 h, the solvents were evaporated and the residue was shaken with saturated $NaHCO_3$ solution and ether. After the usual workup, evaporation of ether left a brown residue that was chromatographed on a short neutral alumina column using hexane eluant to get 2.16 g (99.5%) of **2c**. ^{1}H NMR ($CDCl_3$, 400 MHz $CHCl_3$ internal standard δ=7.24 ppm): δ = 7.31 (d, J = 9.0 Hz, 2H); 6.57(d, J = 9.0 Hz, 2H); 2.95 (s, 6H); 0.22 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.1 MHz): 150.01, 132.97, 111.49, 109.79, 106.47, 91.12, 40.25, 0.39. This was stirred in MeOH with 4 g of potassium carbonate for 2 h and then the methanol was evaporated, the residue shaken with water and the product was taken in ether. The combined ether solutions were washed with brine, dried over Na_2SO_4 and then passed through a short alumina column. Evaporation of the solvent afforded analytically pure **3c** (1.38 g; 95%). ^{1}H NMR ($CDCl_3$ 400 MHz): δ (ppm) = 7.34 (d, J = 8.8 Hz, 2H); 6.6 (d, J = 8.8 Hz, 2H); 2.957 (s, 1H); 2.952 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 150.19, 133.05, 111.58, 108.65, 84.82, 74.75, 40.25. **(b) Synthesis of 4c (Table 2 entry c).** 4-Bromopyridine hydrochloride (1.94 g; 10 m mol), the palladium catalyst (140 mg; 2 mol %), and CuI (20 mg 1 mol %) were placed in a flask and degassed as before. To the reaction flask was added piperidine (0.3 mL) or TEA (0.2 mL). The acetylene **3c** was added to the reaction mixture in CH_3CN (previously purged with N_2 + H_2) at about 80 °C. The reaction was stirred at reflux for 8 h under the reducing atmosphere. After the base workup followed by silica gel chromatography, the byproduct bis(4-*N*,*N*-dimethylaminophenyl)butadiyne (58 mg) and the cross-coupled product **4c** (2.1 g, 94%) were isolated. ^{1}H NMR ($CDCl_3$ 400 MHz): δ (ppm) = 8.52 (d, J = 6.1 Hz, 2H); 7.40 (d, J = 9.0 Hz, 2H); 7.31 (d, J = 6.1 Hz, 2H); 6.64 (d, J = 9.0 Hz, 2H); 2.99 (s, 6H). ^{13}C NMR δ (ppm) = 150.48, 149.25, 133.06, 132.43, 125.08, 111.60, 108.36, 96.16, 85.22, 40.19. High mass (*m*/*z*): (M^+) 222.123; (M + 1) 223.1322.

(12) Nishikawa, S.; Sato, M.; Kojima, H.; Suzuki, C.-e.; Yamada, N.; Inagaki, M.; Kashimura, N.; Mizuno, H. *J. Agric. Food Chem.* **1996**, *44*, 1337−134.

(13) All reactions except entry **b** were carried out at 100 °C for 3 h with added DMF without which longer duration was required. Entry **b** was carried out at rt (see the Supporting Information). **Typical Procedure. Synthesis of 5b.** 4-Iodoanisole (234 mg), catalyst (14 mg), and CuI (2 mg) were taken in a flask and degassed as for **2** and **4**. TEA (10 mL) and phenylacetylene (102 mg) were introduced subsequently. The reaction mixture was stirred at rt for 3 h. When the starting anisole disappeared (TLC), TEA was evaporated and the residue purified by column chromatography Yield: diphenylbutadiyne: 4 mg; **5b**: 203.8 mg (98%); mp 60.62 °C; R_f 0.77 (10% ethyl acetate/hexane). ^{1}H NMR: δ (ppm) = 7.48−7.51 (m, 2H); 7.45 (d, 2H, J = 8.8 Hz); 7.32−7.23 (m, 3H); 6.86 (d, 2H, J = 8.8 Hz). The term "original method" refers to the method given in ref 3b (under nitrogen atmosphere), and all reactions under original method were done after flushing the reaction setup with pure nitrogen.

Table 3. Synthesis of Diarylethynes[a]



entry	phenyl halide (R)	X	yield of **5**[b] (%)	yield (%) of diphenylbutadiyne[b]
a	2,4-dimethyl	I	(96) [72]	(2) [20]
b	4-OMe	I	(98) [70]	(1.9) [23]
c	4-CN	Br	(98) [68]	(1.8) [25]
d	4-NO_2	I	(95) [75]	(1.8) [25]
e	4-CHO	Br	(98) [73]	(1.9) [23]
f	4-$COCH_3$	Br	(96) [76]	(1.8) [20]

[a] Mole ratio of ethyne to halide is 1:1; Pd catalyst, 2%; CuI, 1%.[13] [b] Values in parentheses and square brackets correspond to the yields in the present and original methods, respectively.

tolerant to a variety of substrates, and the yields are very good irrespective of the nature of the halide. Also, *no* adverse effect such as reduction of triple bond or other reducible groups by hydrogen in the presence of Pd^0 was noticed. Therefore, the present method appears to be benign toward a vast number of substrates. Upon carrying out the reactions in Table 3 in the presence of air (without degassing) but with a balloon filled with a mixture of nitrogen and hydrogen over the reaction flask, very little improvement was noticed. Therefore, it is essential that the reaction setup is completely degassed and back-filled with the gaseous mixture before adding the terminal acetylene. This ensures better diffusion of hydrogen into the reaction mixture and thus favors reduction of oxygen. This situation does not seem possible if the system is not degassed and back-filled with reducing gas mixture.

Approximately 10−40% hydrogen in an inert gas can be used for degassing reactants and solvents as well as for maintaining the reducing atmosphere during reaction. Hydrogen without diluting with nitrogen was also found to work the same way. However, for safety reasons of both person and reaction we recommend dilution with nitrogen or argon to a maximum of 1:1.

Thus, we have employed a reducing atmospheric condition to control and minimize oxidative homocoupling of terminal acetylenes and thereby increase the targeted cross-coupling in the highly versatile and useful palladium-catalyzed Sonogashira reaction generally utilized to synthesize acetylene compounds. Synthesis and photophysical studies of more new donor−acceptor acetylenes are underway and will be published soon.

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Supporting Information Available: Synthetic procedures and spectral data for compounds **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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