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Investigation of sp^2–sp Coupling for Electron-Enriched Aryl Dihalides under Oxygen-Free Sonogashira Coupling Reaction Conditions Using a Two-Chamber Reaction System

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Organic sp^2-sp alternated π-conjugated systems are of interest due to their wide potential in applications such as field effect transistors (FET), light-emitting diodes (LEDs), nonlinear optical (NLO) materials, electrically conductive materials, and/or magnetic materials.[1] The Sonogashira coupling reaction[2] is well recognized as "the most popular procedure for alkynylation of aryl or alkenyl halides".[3] The characteristic of an aryl halide substrate is one of the crucial factors that governs the Sonogashira coupling reaction.[3] Aryl halides with electron-withdrawing groups are known to be much more reactive than their electron-enriched counterparts due to the lower electron density of their C−X bond.[3] Alkynylations of aryl dihalides are highly demanding with respect to the purity and cleanness of the reaction system when the goal is to achieve a high percentage of disubstitution product instead of the reaction being halted at the mono-substitution step. This has been further demonstrated by our synthesis of 1,3-bis{(6-methoxynaphthalen-2-yl)ethynyl}azulene. Consequently Sonogashira coupling reactions have seldom been applied to electron-enriched aryl dihalides, and no systematic study has been conducted to date. Particularly, alkynylation of 1,5-bis(alkoxy)-2,4-diiodobenzene has remained nearly unexploited. In our research, the initial aim in applying Sonogashira coupling reactions to alkynylations of electron-enriched aryldihalides was to develop a group of conjugated polymer systems having electromagnetic and/or optical properties as well as acceptable solubilities. However during our initial syntheses, significant challenges were encountered. Our syntheses of precursors, such as bisalkoxydiethynylbenzene and 1,3-diethynylazulene, and model compounds such as 1,3-bis(phenylethynyl)azulene, 1,3-bis(azulen-1-ylethynyl)benzene, and 1,4-bis(azulen-1-ylethynyl)benzene, were found to be complicated by competing homo-coupling reactions that occurred under the typical conditions of the Sonogashira reaction. Furthermore, homo-coupling is not acceptable for related reactions used to form ABAB types of polymers. Therefore we have proceeded to develop a reaction system that creates a significant change in the Sonogashira reaction conditions, and which is especially suitable for reactions with 1,5-bis(alkoxy)-2,4-diiodobenzene, azulene, and other electron-enriched aryl dihalides.

When exposed to oxygen, terminal acetylenes undergo a homo-coupling reaction in the presence of a copper(I) halide catalyst, which is known as the Glaser reaction.[4] Reagent-grade argon or nitrogen is typically used to provide the inert atmospheric conditions necessary to minimize the occurrence of the Glaser reaction. These inert gases normally contain only trace amounts of oxygen and are thus satisfactory for oxygen-sensitive reactions that occur at moderate rates. However, Sonogashira reactions with electron-enriched aryl halides as substrates are sluggish, so that a continuous flow of protection gas for prolonged periods can carry substantial amounts of oxygen to the reaction species. As a result, terminal acetylene can be consumed by oxygen to give a mono-substituted product as the major product instead of the desired disubstituted product. For example, in our syntheses of 1,3-bis{(6-methoxynaphthalen-2-yl)ethynyl}azulene, 1-iodo-3-{(6-methoxynaphthalen-2-yl)ethynyl}azulene was found unexpectedly to be the major product in 55% yield when 2-ethynyl-6-methoxynaphthalene and 1,3-diiodoazulene were allowed to react in a 2.1:1 ratio under conventional Sonogashira reaction conditions using ultrapure nitrogen as the protection gas (for details see Figure S8 in the Supporting Information).

In the case of a copper(I) halide catalyst as co-catalyst with palladium, two methods to avoid unwanted homo-coupling in moderately paced Sonogashira reactions have been

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proposed. The first calls for slowly adding the terminal alkynes, using a Pd^0 catalyst in the presence a phase-transfer reagent.[5] However for slow Sonogashira reactions, homocoupling is still not avoided by this method.[6] The second method calls for additionally mixing hydrogen gas with the inert gas to act as a reducing reagent.[6] However, in the presence of a palladium catalyst, hydrogen adds to the alkyne to form significant amounts of alkene and alkane side products. For example, in one of our syntheses using this method, a [previously unreported] 1,5-bisalkoxy-2,4-ethylbenzene side product was isolated in 15 % yield, (confirmed by its ^1H NMR spectrum; see Figure S4 in the Supporting Information), whereas the desired product 1,5-bisalkoxy-2,4-ethynylbenzene was obtained only as part of a complicated mixture that also included 1,5-bisalkoxy 2-ethylnyl-4-vinylbenzene, 1,5-bisalkoxy-2,4-divinylbenzene, and other structurally similar components which were almost impossible to separate under conventional workup conditions. Therefore Sonogashira coupling in a protecting atmosphere containing reducing hydrogen gas is impractical for sp^2–sp coupling of electron-enriched aryl dihalides.

Because of the deficiencies of the above-mentioned two methods, recent efforts have focused on the development of copper-free Sonogoshira reactions that minimize the formation of diacetylene side products.[7] However, as a relatively new and only partially understood methodology, the mechanism of copper-free Sonogashira coupling is still under debate. For example, it has been reported that the formation of the $(\eta^2\text{-}RC{\equiv}CH)Pd^0L_2$ intermediate, along with the strong tendency for the Pd^0 complex to undergo ligand exchange in some cases, leads to the termination of the catalytic cycle prior to total conversion of the reactants.[8] To date there has not been any systematic study of the copper-free Sonogashira reaction applied to electron-enriched aryl halide substrates. Therefore there remains a significant demand for an ultra-clean, high-yield Sonogashira reaction.

The reaction system and conditions that we have developed and discussed herein address this demand. By providing a long-term, scrupulously oxygen-free and water-free environment, our novel two-chamber reaction system (Figure 1) renders nearly ideal reaction conditions for successfully completing even the slowest Sonogashira reactions with high yield. More specifically, since most Sonogashira reactions do not generate gaseous side products, and only moderate heat is released from the neutralization of HX with Et_3N, we have been able to use a totally sealed, two-chamber reaction system (Figure 1) to exclude oxygen. This system contains a solvent degas chamber D, a reaction chamber E, a reactant-addition passage C, and a solvent-addition passage B having a ground-glass joint connection A. Solid reactant is added to chamber E through passage C, which is then sealed (dashed line). Solvent and liquid reactants (trimethylsilylacetylene [TMSA], Et_3N) are then added through passage A to chamber D, after which chamber D is cooled to liquid nitrogen temperature, and the reaction system is connected to high vacuum (about 10^{-5} Torr). Solvent and liquid reactants are then subjected to three-to-four freeze–thaw cycles to eliminate any dissolved oxygen, following which passage B is sealed under vacuum. Finally, solvent and liquid reactants are delivered to reaction chamber E by vaper-phase solvent transfer.

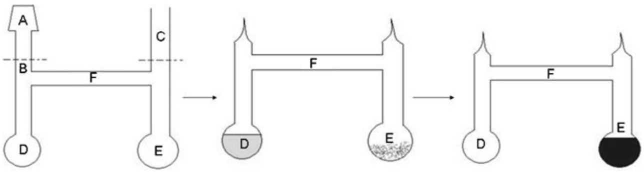


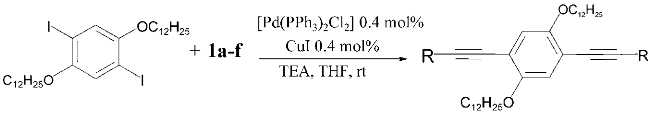
Figure 1. The two-chamber reaction system.

The mechanism for catalytic oxidation of terminal acetylene is still undetermined; however, there is no question that oxygen is involved as an oxidizing reagent.[6] Reaction yields are high for both azulene diiodide[10] and dialkoxybenzene diiodides (Table 1). For example, 1,3-ditrimethylsilylethynylazulene and 1,3-diphenylethylnylazulene are obtained with yields of 99 and 96 %, respectively, which are much higher than literature values (80–90 %).[11a,b] It has also been reported[5a] that a lower mole percentage of catalyst results in lower yields and longer reaction times and that under normal reaction conditions the catalyst can decompose to form a black-colored complex, either dissolved in solution or precipitated out. In our reaction system, just a small amount of catalyst can lead to completion of the reaction in good yield, since no catalyst is consumed by the oxidation during the reaction cycle. Thus a distinctive feature of our system is that after complete reaction the solution retains a light color due only to reaction product and residual catalyst complex, with triethylamine hydroiodide crystallized (Figure 2) on the bottom of chamber E.

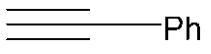
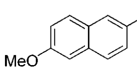
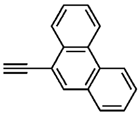
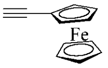
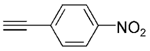
The completion of reactions was conveniently monitored by observing the formation of triethylamine hydroiodide crystals during the reaction process. When no more crystal growth was visible at the bottom of Chamber E, the reaction solution was carefully moved to a new glass surface; the approximate completion of the reaction was indicated when there were no more crystals depositing onto the new glass surface. Approximate reaction times could be determined with a precision of 8 h. The above monitoring method was checked in one case by comparison with a more precise method by sampling the reaction mixture in two-hour intervals followed by TLC analyses (see the Supporting Information for details). The reaction time in this case was determined with a precision of 2 h.

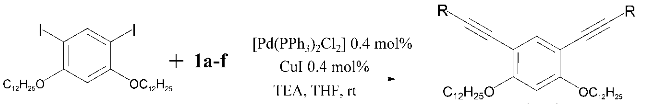
Our reaction system is well suited not only for syntheses using iodoazulenes but also for those using dibromoazulene.[12] The syntheses of 1-ethynylazulene and 1,3-diethynylazulene from corresponding iodoazulenes have been reported previously in 80–90 % yield,[11a,b,d] as have the syntheses of 2-ethynyl- and 6-ethynylazulene from 2-bromo- and 6-bromoazulene, respectively.[1a,11e] However, it is well known that it is difficult to obtain 1,3-diethynylazulene and its derivatives from 1,3-dibromoazulene, since the bromo group is a relatively poor leaving group, and the 1 and 3 positions

Table 1. Synthesis of bis(dodecyloxy)diethynylbenzene derivatives and 1,3-bis(ethynyl)azulene derivatives from the corresponding diiodides.

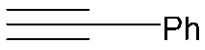
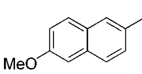
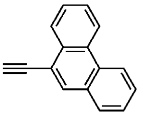
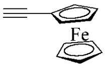
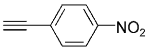


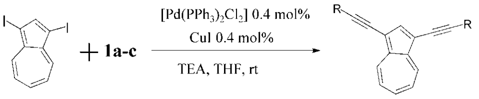
2a-f

Entry	Terminal alkyne	This work yield [%]	Literature yield [%]
1a	TMSA	99	80~92[9a,b]
1b		96	91[9c,d]
1c		89	N/A(new)[a]
1d		91	N/A(new)[a]
1e		94	N/A(new)[a]
1f		90	N/A(new)[a]

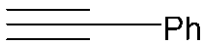
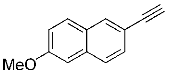


3a-f

Entry	Terminal alkyne	This work yield [%]	Literature yield [%]
1a	TMSA	99	N/A(new)[a]
1b		96	N/A(new)[a]
1c		89	N/A(new)[a]
1d		90	N/A(new)[a]
1e		91	N/A(new)[a]
1f		90	N/A (new)[a]



4a-c

Entry	Terminal alkyne	This work yield [%]	Literature yield [%]
1a	TMSA	99	80–90[11a,b]
1b		96	79[11c]
1c		90	N/A(new)[a]

[a] N/A = not available; reaction time: 8 days.

are the highest-electron-density positions of azulene. For example, synthesis attempts have been made using the Suzuki coupling reaction, for which only 8–35 % yields were reported.[11e,13] In contrast, in our sealed-reaction system, our first attempt at the Sonogashira reaction using 1,3-dibromoazulene as reactant resulted in a much higher yield of 65–70 % (Table 2).

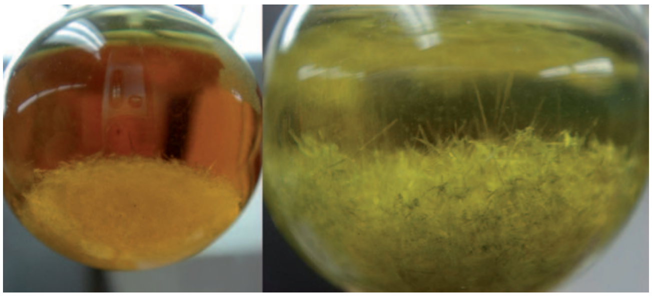
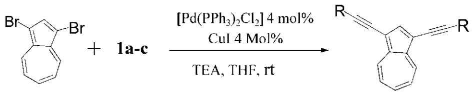
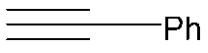
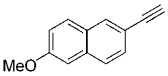


Figure 2. The reaction chamber E after reaction completion with product of **2b** (left) and **3c** (right). Crystals formed at the bottom are triethylamine hydroiodide.

Table 2. Synthesis of 1,3-bis(ethynyl)azulene derivatives from 1,3-dibromoazulene.



4a-c

Entry	Terminal alkyne	This work yield [%]	Literature yield [%]
1a	TMSA	65	25~37[11a,13]
1b		71	N/A[a]
1c		70	N/A(new)

[a] N/A = not available; reaction time: 30 days.

Generally when the Glaser (homo-coupling) side reaction is reduced to less than 2 %, the workup of the Sonogashira reaction products is greatly simplified. Since most of the desired products do not dissolve in methanol, and the solubilities of impurities such as Et$_3$NHI and Et$_3$N are very high in methanol, a workup including the vacuum evaporation of THF and triethylamine followed by several cycles of methanol wash or recrystallization with hte THF/methanol solvent pair is adequate for purification in many cases. Alternatively a minimum amount of methanol can be used in this last step by employing a Soxhlet extractor.

Finally, an additional benefit of the modified Sonogashira reaction is that it is environmentally friendly: Green chemistry is achieved by using a very low loading of catalyst, and by eliminating the waste solvent that would be otherwise generated as column eluent.

In summary, a sealed oxygen-free two-chamber reaction system for the Sonogashira coupling reaction with dihaloazulene and other electron-rich aryl halides as substrates was designed and employed to overcome the presence of homo-coupling side reactions. Approximate reaction times were determined in most cases by observing co-product crystal growth and was further determined in one corroborating case by a more precise method that included two-hour-sampling and monitoring by TLC. Simplified, reliable, environmentally friendly procedures were developed.

Keywords: C–C coupling · aryl dihalides · homogeneous catalysis · palladium · Sonogashira reaction · synthetic methods

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