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Synthesis of Symmetrical Diarylalkynes by Double Stille Coupling of Bis(tributylstannyl)acetylene

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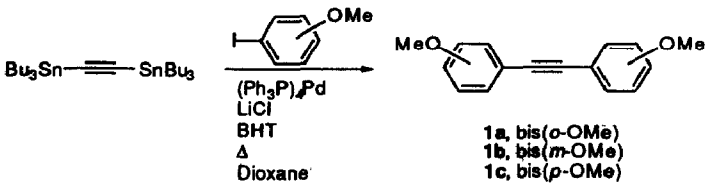
Abstract: Treatment of bis(tributylstannyl)acetylene with two equivalents of an aryl iodide in the presence of tetrakis(triphenylphosphine)palladium (0) affords good yields of the symmetrical diarylalkyne. This approach provides a convenient and safe alternative to the use of acetylene in the preparation of these compounds.

Recently we have been interested in bis(hydroxyphenyl)alkynes as molecules which, because they are hydroxyl-containing extended hydrocarbons, might have affinity for the estrogen receptor. Our strategy was to prepare the corresponding methoxylated diarylalkynes and then cleave the methyl ethers. Unsymmetrical diarylalkynes can be synthesized by two sequential arylations of an acetylene equivalent, while their symmetrical counterparts may prepared in a single step by copper and/or palladium catalyzed coupling of an aryl halide with acetylene. To avoid the hazard and inconvenience of employing gaseous acetylene, we explored other routes to these materials. We report herein that the palladium-catalyzed coupling of aryl iodides (in our case iodoanisoles) with bis(tributylstannyl)acetylene affords the symmetrical bis(methoxyphenyl)alkynes in good yields.

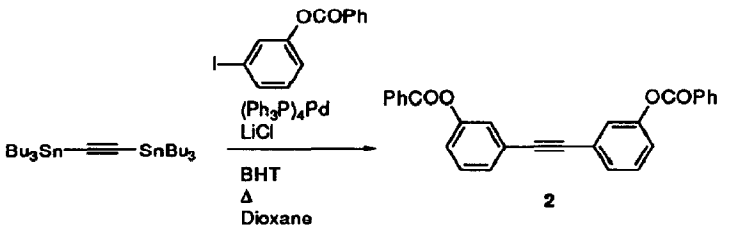
As stated above, the unsymmetrically methoxylated compounds are best prepared by arylation of trimethylsilylacetylene, removal of the silyl protecting group, and a second arylation.[1] Monoarylation of terminal alkynes is a well-known process,[2,3] and similar conditions will provide symmetrical diarylalkynes when acetylene itself is used as the substrate. Although tributylstannylalkynes have been coupled with aryl triflates,[4,5] we were surprised that no one had described any attempt to prepare diarylalkynes by a similar coupling of commercially available bis(tributylstannyl)acetylene. We have found that this procedure works quite well, even with the unactivated methoxy-substituted iodoanisoles). The conditions are quite similar to those of other stannane-aryl halide or triflate couplings:[4] the bis-stannane and two equivalents of the iodoanisole are combined in dioxane with a catalytic amount of tetrakis(triphenylphosphine)palladium and an excess of lithium chloride, and the reaction mixture is heated at reflux for five hours (Scheme 1).[6] Standard workup and chromatographic purification provides the diarylacetylenes (**1a**,[7,8] **1b**,[7,9] and **1c**[10,11]) in 85%, 70%, and 71% yields, respectively.



Scheme 1. Synthesis of symmetrical bis(methoxyphenyl) alkynes.

As we began examining the demethylation of these materials,[12] it became immediately clear that the use of boron tribromidewas too harsh, leading to decomposition in most cases. Only in the case of bis(*m*-methoxyphenyl)acetylene **1b** was it possible to isolate any cleavage product, and the yield was still quite low (28%). Other conditions were examined, but with limited success. Starting material was recovered when demethylation was attempted using boron tribromide-dimethylsulfide complex in refluxing 1,2-dichloroethane. Both iodotrimethylsilane and hydrobromic acid resulted in acetylene hydrolysis, providing benzylaryl ketone products. Treatment of bis(*p*-methoxyphenyl)acetylene 1c with lithium iodide in refluxing collidine did afford 17% of the desired bisphenolic acetylene, but it seemed prudent to begin examining the use a more readily cleavable protecting group. One possibility which stood out was the benzoate ester, which can be removed under quite mild conditions from phenols.

The preparation of the benzoate analogue to bis(*m*-methoxyphenyl)alkyne 2 is presented in Scheme 2. The requisite *m*-iodophenyl benzoate[13] was prepared straightforwardly from *m*-iodophenol, and the coupling afforded alkyne 2 in 28% yield.



Scheme 2. Preparation of (benzoyloxyphenyl)alkynes

Cleavage of the bis(benzoyloxyphenyl)alkyne with propylamine in toluene[14] proved to be extremely facile, in contrast to the methoxy derivatives. The reaction is quite clean, and one need only separate the desired product from *N*-propylbenzamide by chromatography using 5% methanol in chloroform. The deprotection results are summarized in Table 1.

Table 1. Preparation of Bis(hydroxyphenyl)alkynes.

3a-b

Substrate	R_1	R_2	Method[a]	Product	R_1'	R_2'	% Yield
1b	*m*-OMe	*m*-OMe	A	3a[15]	*m*-OH	*m*-OH	28
1c	*p*-OMe	*p*-OMe	B	3b[16,17]	*p*-OH	*p*-OH	17
2[18]	*m*-O_2CPh	*m*-O_2CPh	C	3a[15]	*m*-OH	*m*-OH	87

[a]Method: A BBr_3/CH_2Cl_2
B LiI/Δ/Collidine
C Propylamine/Toluene

In conclusion, bis(tributylstannyl)acetylene can be coupled with oxygenated aryl iodides to provide symmetrical diarylalkynes. It seems likely that this process would also be effective with aryl iodides containing other substitutents, particularly electron-withdrawing groups,[19] and therefore should prove to be a useful alternative to arylation of acetylene. With respect to preparation of the (hydroxyphenyl)alkynes, the benzoate is a more readily removed protecting group, although the synthesis of the benzoyloxy compounds results in lower yields than for the corresponding methoxy derivatives.

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6. Bis(tributylstannyl)acetylene (1.00 g, 1.66 mmol) was combined with 2 equivalents of the iodoarene, 0.1 equivalent of tetrakis(triphenylphosphine)palladium (0), 6 equivalents of lithium chloride, and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in 10 mL of dioxane. The resulting suspension was heated at reflux under nitrogen for 5 hours, and then cooled to room temperature. Pyridine (1.5 mL) and 1.4 *M* pyridinium hydrofluoride in tetrahydrofuran (3 mL) was added, and stirring was continued for an additional 20 h. The reaction mixture was diluted with 50 mL of diethyl ether, was filtered through a pad of Celite, and the pad was washed with two 25-mL portions of diethyl ether. The filtrates were combined and washed with 50 mL of 1 *M* aqueous hydrochloric acid, 50 mL of water, and 50 mL of saturated aqueous sodium chloride, and were dried (Na_2SO_4). Filtration and evaporation of the solvent, followed by purification of the residue by flash chromatography on silica gel afforded the diaryl alkyne.
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8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, J=7.4, 1.4 Hz, 2H), 7.31-7.23 (m, 2H), 6.96-6.85 (m, 4H), 3.91 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 133.3, 129.4, 120.2, 112.6, 110.5, 89.7, 55.9.
9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.03 (m, 6H), 6.87 (dd, J=8.2, 1.7 Hz, 2H), 3.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 129.2, 124.0, 116.2, 114.8, 89.1, 55.2.
10. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J=8.6 Hz, 4H), 6.85 (d, J=8.6 Hz, 4H), 3.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.7, 115.5, 113.8, 87.9, 55.3.
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15. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.18 (t, J=7.8 Hz, 2H), 7.07-6.97 (m, 4H), 6.86-6.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 156.3, 129.4, 124.0, 123.2, 118.1, 115.8, 88.8.
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17. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.35 (dd, J=8.5, 2.8 Hz, 4H), 6.85 (dd, J=8.5, 2.8 Hz, 4H); ^{13}C NMR (75 MHz, acetone-d_6) δ 158.1, 133.4, 116.2, 115.2, 88.2.
18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J=7.4 Hz, 4H), 7.63 (t, J=7.4 Hz, 2H), 7.50 (t, J=7.6 Hz, 4H), 7.46-7.35 (m, 6H), 7.24-7.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 150.5, 133.5, 129.9, 129.2, 129.0, 128.9, 128.4, 124.6, 124.2, 121.9, 89.1.
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