

## Novel Synthesis of Unsymmetrical Diarylbutadiynes

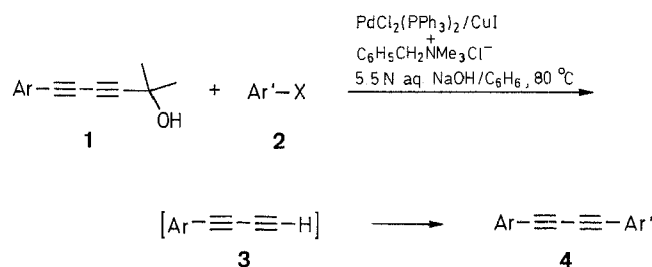
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Terminal arylbutadiynes, derived from 6-aryl-3,5-hexadiyn-2-ols, undergo a ready palladium-catalyzed coupling with activated aryl halides in the presence of a phase transfer catalyst to unsymmetrical diarylbutadiynes, not easily available by other coupling procedures.

Unsymmetrical butadiynes have been synthesized<sup>1,2</sup> in a variety of ways, the most common route being the Cadiot-Chodkiewicz reaction<sup>1</sup> involving a copper-catalyzed condensation of a terminal acetylene with a bromoacetylene. We have found that, while this reaction works favorably in some cases, its application to the synthesis of unsymmetrical diarylbutadiynes required in another study in our laboratory was unsuccessful. An alternate procedure developed by Negishi<sup>2</sup> has not yet found application in the synthesis of diarylbutadiynes.

Palladium-catalyzed coupling of activated aryl halides with terminal acetylenes has been reported<sup>3</sup> recently, and this coupling has been extended to terminal butadiynes.<sup>4</sup> Our attempts to make the required terminal aryl butadiynes in this way resulted in low yields, presumably due to polymerization, and we now describe a new, general synthesis of diarylbutadiynes utilizing phase transfer conditions.



1	Ar	2	Ar'	2	Ar'
a	2-Pyridyl	a	2-Pyridyl	d	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
b	C <sub>6</sub> H <sub>5</sub>	b	C <sub>6</sub> H <sub>5</sub>	e	2-Benzothiazolyl
c	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	c	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	f	2-Quinolyl
d	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>				

A variety of terminal arylbutadiynes, derived<sup>1</sup> *in situ* from 6-aryl-3,5-hexadiyn-2-ols/base, was coupled with activated aryl halides in the presence of base and catalyst. Thus, reaction of the arylhexadiynol **1** with a molar equivalent of the aryl halide **2** (X = Br for **2a**, **2e** and **2f**; X = I for **2b**, **2c** and **2d**) in refluxing benzene using benzyltrimethylammonium chloride as phase-transfer agent, aqueous sodium hydroxide solution as base, and a mixture of dichloropalladium bis(triphenylphosphine) and copper iodide as catalyst furnishes diarylbutadiynes **4** in moderate to good yields (Table). The reaction proceeds by an initial base-induced acetone cleavage to the intermediate arylbutadiyne **3** that immediately reacts with aryl halide **2** via palladium catalysis. We see no evidence for the buildup of **3** while following the reaction by high pressure liquid chromatography.

The arylhexadiynol **1** or the aryl halide **2** can contain the heteroarene portion of the diarylbutadiyne **4**. The general nature of the reaction is demonstrated by the synthesis of **4ab/4ba**,

Table. Palladium Catalyzed Synthesis of Diarylbutadiynes 4

Reactants (1 + 2)	Product	Reaction Time (h)	Yield <sup>a</sup> (%)	mp (°C) <sup>b</sup> (solvent)	Molecular Formula <sup>c</sup> or Lit. mp (°C)	IR (KBr) <sup>d</sup> $\nu_{C\equiv C}$ (cm <sup>-1</sup> )	UV (CH <sub>3</sub> OH) <sup>e</sup> $\lambda_{max}$ (nm) (log $\epsilon$ )	<sup>1</sup> H-NMR (CDCl <sub>3</sub> /TMS) <sup>f</sup> $\delta$ , J (Hz)	<sup>13</sup> C-NMR (CDCl <sub>3</sub> ) <sup>g</sup> $\delta$	MS (70 eV) $m/z$ (%) <sup>h</sup>
<b>1a 2b</b> <b>1b 2a</b>	<b>4ab</b> <b>4ba</b> <sup>i</sup>	5 40	32 33	66–69 (pentane)	C <sub>15</sub> H <sub>9</sub> N (203.2)	2210	240 (4.65), 273 (4.45), 292 (4.54), 308 (4.63), 327 (4.55)	7.45 (m, 8H); 8.57 (dd, 1H, $J$ = 5.0, 1.0)	150.0, 142.0, 136.1, 132.5, 129.4, 128.3, 128.0, 123.3, 121.1, 82.5, 79.9, 73.9, 73.4	203 ( $M^+$ , 100); 176 (8); 150 (8); 126 (3); 101.5 ( $M^{++}$ , 4)
<b>1a 2c</b> <b>1c 2a</b>	<b>4ac</b> <b>4ca</b> <sup>j</sup>	24 24	37 43	128.5–130 (hexane)	C <sub>16</sub> H <sub>11</sub> N (217.3)	2215	275 (4.26), 296 (4.33), 313 (4.42), 332 (4.32)	2.35 (s, 3H); 7.40 (m, 7H); 8.52 (d, 1H, $J$ = 4.0)	150.1, 142.3, 139.8, 135.9, 132.4, 129.1, 127.8, 123.2, 118.1, 82.7, 79.8, 73.9, 72.9, 21.6	217 ( $M^+$ , 100); 189 (13); 163 (5); 139 (4); 108.5 ( $M^{++}$ , 4)
<b>1a 2d</b> <b>1d 2a</b>	<b>4ad</b> <b>4da</b> <sup>k</sup>	14 36	79 42	97.0–97.5 (hexane)	99–100 <sup>1,4</sup>	2207	216 (4.51), 243 (4.38), 255 (4.35), 287 (4.39), 298 (4.40), 318 (4.44), 341 (4.32), 228 (4.50), 280 (4.22), 312 (4.38), 333 (4.50), 357 (4.40)	3.85 (s, 3H); 6.85 (d, 2H, $J$ = 8.7); 7.20 (m, 1H); 7.47 (d, 2H, $J$ = 8.7); 7.53 (m, 2H); 8.57 (dd, 1H, $J$ = 1.0, 4.8)	160.6, 149.7, 142.0, 136.5, 134.3, 128.0, 123.2, 114.1, 113.0, 83.2, 79.1, 74.8, 72.3, 55.3	233 ( $M^+$ , 100); 218 (31); 190 (28); 164 (10); 140 (4.5); 116 ( $M^{++}$ , 3)
<b>1b 2e</b>	<b>4be</b>	37	50	116.5–117.5 (hexane)	C <sub>17</sub> H <sub>9</sub> NS (259.3)	2200	228 (4.50), 280 (4.22), 312 (4.38), 333 (4.50), 357 (4.40)	7.45 (m, 7H); 7.84 (m, 1H); 8.05 (m, 1H)	152.7, 147.1, 135.3, 132.6, 129.9, 128.4, 126.7, 126.5, 123.8, 121.1, 85.8, 80.3, 73.7, 72.8	259 ( $M^+$ , 100); 214 (21); 188 (3); 157 (2); 129.5 ( $M^{++}$ , 0.5)
<b>1b 2f</b>	<b>4bf</b>	22	39	128–129 (hexane)	C <sub>19</sub> H <sub>11</sub> N (253.3)	2220	213 (4.61), 246 (4.64), 256 (4.64), 283 (4.31), 313 (4.40), 351 (4.45)	7.15–7.90 (m, 9H); 8.12 (d, 2H, $J$ = 7.8)	148.1, 142.1, 136.2, 132.7, 130.3, 129.6, 129.2, 128.4, 127.5, 127.4, 127.3, 124.4, 121.2, 83.0, 80.6, 74.5, 73.6	253 ( $M^+$ , 100); 224 (7); 200 (2); 126 ( $M^{++}$ , 8)

<sup>a</sup> Yield of pure, isolated product.<sup>b</sup> Uncorrected, measured on a Thomas-Hoover melting point apparatus.<sup>c</sup> Satisfactory microanalytical data ( $\pm 0.4\%$  C, H, N) or high resolution mass spectral data were obtained for all compounds listed.<sup>d</sup> Recorded on a Perkin-Elmer Model 598 Infrared spectrophotometer.<sup>e</sup> Measured using a Shimadzu Model UV-240 UV spectrophotometer.<sup>f</sup> Obtained on a Varian 390 spectrometer.<sup>g</sup> Recorded on a Varian XL-300 spectrometer at 75.4 MHz.<sup>h</sup> Obtained on a Finnigan MAT 731.<sup>i</sup> Sample is identical to **4ab**.<sup>j</sup> Sample is identical to **4ac**.<sup>k</sup> Sample is identical to **4ad**.

**4ac/4ca** and **4ad/4da**, and there is every reason to believe that this reaction can be extended for use with a variety of heteroarenes and/or activated arenes. The arylhexadiynols are readily available by copper-catalyzed condensation of ethynylarenes with 1-bromo-3-hydroxy-3-methyl-1-butyne (Experimental Section), establishing this present procedure as a very convenient route to unsymmetrical diarylbutadiynes. Symmetrical diethynylbutadiynes, however, such as **4aa** [1,4-di(2-pyridinyl)buta-1,3-diyne] are more conveniently prepared by oxidative coupling of 2-ethynylpyridine in the presence of copper chloride, oxygen and *N,N,N',N'*-tetramethylenediamine (69% yield).

#### Arylhexadiynols 1; General Procedure:

A solution of 1-bromo-3-hydroxy-3-methyl-1-butyne<sup>5</sup> (1.63 g, 10 mmol) in MeOH or *N*-methylpyrrolidinone (5 mL) is added to a rapidly stirred mixture of ethynylarene (10 mmol), Cu<sub>2</sub>Cl<sub>2</sub> (0.019 g, 0.2 mmol), a 70% aqueous solution of ethylamine (1.15 mL, 18 mmol), NH<sub>2</sub>OH · HCl (0.027 g, 0.4 mmol) in MeOH or *N*-methylpyrrolidinone (10 mL) over 30 min. After stirring for an additional 24 h, the mixture is poured into saturated NH<sub>4</sub>Cl solution (20 mL) and extracted with ether (3 × 50 mL). The crude product is chromatographed on silica gel using

EtOAc/hexane as eluent. Removal of solvent provides products which are > 98% pure by HPLC analysis. Analytically pure samples can be obtained by recrystallization from an EtOAc/hexane mixture.

*5-Hydroxy-5-methyl-1-(2-pyridinyl)hexa-1,3-diyne (1a)*; yield: 51%; m.p. 112.5–115 °C (Lit.<sup>6</sup> m.p. 113–114 °C).

*5-Hydroxy-5-methyl-1-phenylhexa-1,3-diyne (1b)*; yield: 57%; m.p. 55–56 °C (Lit.<sup>1</sup> m.p. 56 °C).

*5-Hydroxy-5-methyl-1-(4-methylphenyl)hexa-1,3-diyne (1c)*; yield: 58%; m.p. 75–76 °C.

C<sub>14</sub>H<sub>14</sub>O calc. C 84.81 H 7.12  
(198.3) found 84.84 7.40

IR (KBr):  $\nu$  = 3240, 2227 cm<sup>-1</sup>.

UV (CH<sub>3</sub>OH):  $\lambda_{max}$  = 224 (log  $\epsilon$  = 4.35); 244 (3.90); 257 (4.21); 272 (5.35); 288 nm (4.28).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>/TMS):  $\delta$  = 1.60 (s, 6H); 2.10 (s, 1H); 2.37 (s, 3H); 7.07 (d, 2H,  $J$  = 8.4 Hz); 7.35 (d, 2H,  $J$  = 8.4 Hz).

*5-Hydroxy-5-methyl-1-(4-methoxyphenyl)hexa-1,3-diyne (1d)*; yield: 45%; m.p. 64.5–65.5 °C.

C<sub>14</sub>H<sub>14</sub>O<sub>2</sub> calc. C 78.47 H 6.59  
(214.3) found 78.51 4.45

IR (KBr):  $\nu = 3390, 2240 \text{ cm}^{-1}$ .

UV (CH<sub>3</sub>OH):  $\lambda_{\text{max}} = 206$  (log  $\epsilon = 4.41$ ), 230 (4.22), 262 (4.20), 276 (4.41), 290 nm (4.35).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>/TMS):  $\delta = 1.53$  (s, 6 H); 3.77 (s, 3 H); 6.73 (d, 2 H,  $J = 8.0$  Hz); 7.73 (d, 2 H,  $J = 8.0$  Hz).

#### Diarylbutadiynes 4; General Procedure:

A de-aerated mixture of arylhexadiynol **1**, (10 mmol) and aryl halide **2**, (10 mmol) in benzene (25 mL) is rapidly added to a mixture of dichloropalladium bis(triphenylphosphine) (0.28 g, 0.4 mmol), CuI (0.077 g, 0.4 mmol) and a 50 % aqueous solution of benzyltrimethylammonium chloride (125 mL, 0.34 mmol). De-aerated aqueous 5.5 N NaOH solution (4.5 mL, 25 mmol) is added and the resulting mixture stirred under reflux in a nitrogen atmosphere for 5–40 h. The reaction is monitored by HPLC analysis (Dupont ODS column acetonitrile/H<sub>2</sub>O). When there is no trace of starting materials, a solution of saturated NH<sub>4</sub>Cl (25 mL) is added and after stirring for 1 h at room temperature, the mixture is extracted with ether (3 × 50 mL), filtered and concentrated. The crude residue is chromatographed in silica gel using EtOAc/hexane as eluent (Table).

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