

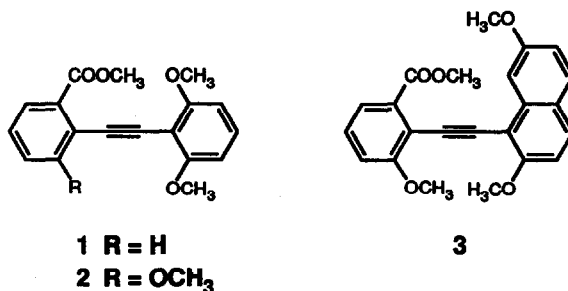
## MOLECULES FOR INTRAMOLECULAR RECOGNITION. SYNTHESIS AND STRUCTURES OF DIARYL- AND ARYLNAPHTHYLETHYNES

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*Summary:* While synthesizing models for intramolecular recognition, a simple and efficient method for forming terminal arylethyne was developed and palladium-catalyzed coupling chemistry of alkynes with either aryl iodides or aryl triflates was used to form crowded disubstituted alkynes.

Intramolecular recognition describes the interaction of two groups on the same molecule. As such it encompasses intramolecular catalysis in small molecules, proteins, and DNA, and non-covalent interactions that stabilize the tertiary structure of biopolymers and those that regulate nanometric devices. We are synthesizing a series of diaryl- and arynaphthylethyne, **1** - **3**, for studies of intramolecular recognition. Others have used this framework to anchor functional groups in a defined geometry for complexation of cations.<sup>3</sup> We report herein an efficient synthesis of these crowded ethynes by combining a modification of a classic method for the synthesis of terminal alkynes with a modern organometallic method for the synthesis of disubstituted alkynes.

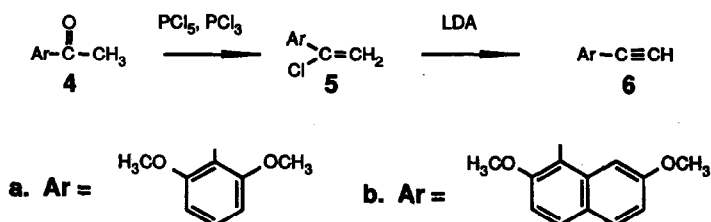


We have developed a simple method for synthesizing electron-rich arylethyne. (Scheme 1) Our first attempt to convert 2',6'-dimethoxyacetophenone **4a** into the corresponding alkyne **6a** following a classic procedure<sup>4</sup> resulted in undesired products. Two concurrent reactions took place between the electron-rich acetophenone **4a** and phosphorus pentachloride - - formation of a vinyl chloride and chlorination of the aromatic ring. Dehydrohalogenation of this product by lithium diisopropylamide produced 1-chloro-3-ethynyl-2,4-dimethoxybenzene<sup>5</sup>.

To prevent chlorinating the ring, a five- to seven-fold excess of phosphorus trichloride is mixed with the ketone in benzene before phosphorus pentachloride is added to the solution<sup>6</sup>. Quantitative conversion, based on NMR data, of the ketone into the vinyl chloride is accomplished without chlorinating the ring. We

have synthesized 2-(1-chlorovinyl)-1,3-dimethoxybenzene, **5a**, and 1-(1-chlorovinyl)-2,7-dimethoxynaphthalene<sup>7</sup>, **5b**, in 72.3% and 78.1% purified yields, respectively. The vinyl chlorides have been characterized by NMR<sup>8,9</sup>, IR, mass spec. and elemental analysis. The generality of this reaction has not been fully investigated, but it appears to be a useful method for the synthesis of electron-rich 1-arylviny chlorides from the aryl methyl ketones.

Dehydrohalogenation<sup>10</sup> by lithium diisopropylamide at room temperature quantitatively converts, based on NMR data, the vinyl chlorides, **5a** and **5b**, into 2-ethynyl-1,3-dimethoxybenzene, **6a** and 2,7-dimethoxy-1-ethynynaphthalene, **6b**. Overall isolated yields using crude vinyl chloride were 79.6% and 85.0%, respectively. The ethynes have been fully characterized by NMR<sup>11,12</sup>, IR, mass spec., elemental analysis, and X-ray crystal structures<sup>13,14</sup>.



**Scheme 1**

Recent synthetic procedures<sup>15</sup> for the coupling of either aryl iodides or aryl triflates with alkynes offer numerous possibilities for the coupling of alkynes **6a** and **6b**. In synthesizing our key synthons, **1** - **3**, we have shown that palladium-catalyzed coupling reactions work well even for the synthesis of crowded disubstituted alkynes. In the presence of palladium(0) and copper iodide as co-catalyst<sup>16</sup>, methyl 2-iodobenzoate and alkyne **6a** couple to yield methyl 2-[(2,6-dimethoxyphenyl)ethynyl]benzoate **1** in 56% isolated yield. The key synthon **1** has been characterized by NMR<sup>16</sup>, IR, mass spec., elemental analysis and X-ray crystal structure<sup>17</sup>.

Adapting the procedure by Chen and Yang<sup>18</sup>, alkynes **6a** and **6b** couple with 2-methoxy-6-methoxycarbonylphenyl trifluoromethanesulfonate<sup>18</sup> to yield methyl 2-[(2,6-dimethoxyphenyl)ethynyl]-3-methoxybenzoate<sup>19</sup> **2** and methyl 2-[(2,7-dimethoxynaphthyl)ethynyl]-3-methoxybenzoate **3** in 62% and 57% isolated yield, respectively. The synthons **2** and **3** have been fully characterized by NMR<sup>20,21</sup>, IR, mass spec., and elemental analysis. In the coupling reaction of alkyne **6a** with the triflate, *bis*-1,3-(2,6-dimethoxyphenyl)butenyne<sup>22</sup>, **7**, has been isolated as a side-product (~5%), probably because an excess of the alkyne is used. Trost et al. have shown that enynes can be synthesized by the direct coupling of two ethynes using palladium(II)<sup>23</sup>. Formation of the enyne **7** could probably be prevented by coupling a tin derivative of **6a** to the triflate; however, due to the difficulty of purifying the tributyltin derivative of **6a**, we've chosen to accept the formation of the enyne because it is easily separated by flash chromatography. The coupling reactions have not been optimized.

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**References and notes:**

1. NSF Research Experience for Undergraduates participant, summer 1990.
2. Project SEED participant, summer 1989.
3. Letsinger, R. L.; Nazy, J. R. *J. Am. Chem. Soc.* **81**, 3013-3017 (1959); Letsinger, R. L.; Oftedahl, E. N.; Nazy, J. R. *J. Am. Chem. Soc.* **87**, 742-749 (1965); Vögtle, F.; Schaefer, H.; Ohm, C. *Chem. Ber.* **117**, 955-958 (1984).
4. Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc. Perkin Trans. I*, 2443-2446 (1985).
5. Evans, K. L.; Fronczek, F. R.; Gandour, R. D. *Acta Cryst.* **C45**, 1831-1832 (1989).
6. **Typical procedure:** To a solution of 2',6'-dimethoxyacetophenone (21.62 g, 0.12 mol) and  $\text{PCl}_3$  (57.6 ml, 0.66 mol) in 180 mL of benzene was added  $\text{PCl}_5$  (27.49g, 0.13 mol). The flask was flushed with nitrogen and magnetically stirred overnight at room temperature. The solution was poured over ice (~300 g). The organic layer was washed with  $\text{H}_2\text{O}$  ( $3 \times 100$  mL), saturated  $\text{NaHCO}_3$  solution (100 mL), and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure yielding 23.12 g of a pale yellow oil that solidified upon standing. Flash chromatography (6/1 hexane/ethyl acetate) yielded white crystals.
7. Crystal structure of **5b**: Prince, P.; Evans, K. L.; Boss, K. R.; Fronczek, F. R.; Gandour, R. D. *Acta Cryst.* **C46**, 1150-1152 (1990).
8. **5a:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.25 (t, 1H,  $J=8.35$  Hz, C5), 6.55 (d, 2H,  $J=8.35$  Hz, C4 and C6), 5.73 (d, 1H,  $J=1.00$  Hz,  $=\text{CH}_2$ ), 5.33 (d, 1H,  $J=1.00$  Hz,  $=\text{CH}_2$ ), 3.83 (s, 6H,  $\text{OCH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 157.6 (C1 and C3), 132.0 ( $>\text{C}=\text{}$ ), 130.3 (C5), 118.4 ( $\text{CH}_2$ ), 116.9 (C2), 103.9 (C4 and C6), 56.0 ( $\text{OCH}_3$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{11}\text{O}_2\text{Cl}$ : C, 60.46; H, 5.58. Found: C, 60.19; H, 5.42.
9. **5b:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.75 (d, 1H,  $J=8.98$  Hz, C4), 7.66 (d, 1H,  $J=9.03$  Hz, C5), 7.26 (d, 1H,  $J=2.45$  Hz, C8), 7.09 (d, 1H,  $J=8.98$  Hz, C3), 7.02 (dd, 1H,  $J=9.03$  and 2.45 Hz, C6), 5.94 (d, 1H,  $J=1.00$  Hz,  $=\text{CH}_2$ ), 5.47 (d, 1H,  $J=1.00$  Hz,  $=\text{CH}_2$ ), 3.96 (s, 3H,  $\text{C2-OCH}_3$ ), 3.91 (s, 3H,  $\text{C7-OCH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 158.8 (C7), 154.6 (C2), 134.6 ( $>\text{C}=\text{}$ ), 133.3 (C8a), 130.5 (C4), 129.6 (C5), 124.2 (C4a), 120.9 (C1), 119.0 ( $=\text{CH}_2$ ), 116.7 (C6), 110.5 (C3), 102.5 (C8), 56.6 ( $\text{C2-OCH}_3$ ), 55.2 ( $\text{C7-OCH}_3$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{O}_2\text{Cl}$ : C, 67.61; H, 5.27. Found: C, 67.65; H, 5.25.
10. **Typical procedure:** A 2M solution of butyllithium in hexanes (150 mL, 0.3 mol) was added slowly under nitrogen to a solution of diisopropylamine (50.45 mL, 0.36 mol) in 120 mL THF at  $-78^\circ\text{C}$ . The temperature was raised to  $0^\circ\text{C}$  for 20 minutes, and then cooled back to  $-78^\circ\text{C}$ . The crude 2-(1-chlorovinyl)-1,3-dimethoxybenzene (23.12 g, 0.116 mol) dissolved in 120 mL THF was added slowly to the lithium diisopropylamide solution. The cold bath was removed and the solution was stirred for 5 hours. The reaction was quenched with water (100 mL), and the organic layer was washed with water ( $2 \times 100$  mL), 2N HCl ( $3 \times 100$  mL), water ( $1 \times 100$  mL) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure. The product, **6a**, was purified by sublimation yielding 15.53 g of white crystals.
11. **6a:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.25 (t, 1H,  $J=8.50$  Hz, C5), 6.54 (d, 2H,  $J=8.50$  Hz, C4 and C6), 3.89 (s, 6H,  $\text{OCH}_3$ ), 3.57 (s, 1H,  $\equiv\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 162.1 (C1 and C3), 130.2 (C5), 103.4 (C4 and C6), 100.2 (C2), 85.3 ( $-\text{C}\equiv$ ), 76.2 ( $\equiv\text{CH}$ ), 56.0 ( $\text{OCH}_3$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{10}\text{O}_2$ : C, 74.06; H, 6.21. Found: C, 74.33; H, 6.28.

12. **6b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.75 (d, 1H,  $J=8.90$  Hz, C4), 7.66 (d, 1H,  $J=8.82$  Hz, C5), 7.55 (d, 1H,  $J=2.35$  Hz, C8), 7.08 (d, 1H,  $J=8.90$  Hz, C3), 7.03 (dd, 1H,  $J=8.82$  and 2.35 Hz, C6), 4.02 (s, 3H, C2-OCH<sub>3</sub>), 3.95 (s, 3H, C7-OCH<sub>3</sub>), 3.77 (s, 1H,  $\equiv\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 160.4 (C2), 159.4 (C7), 136.5 (C8a), 130.4 (C4), 129.7 (C5), 123.9 (C4a), 117.1 (C6), 109.6 (C3), 103.9 (C1), 103.4 (C8), 86.4 ( $\equiv\text{CH}$ ), 78.6 ( $-\text{C}\equiv$ ), 56.5 (C2-OCH<sub>3</sub>), 55.3 (C7-OCH<sub>3</sub>). Anal. Calcd for  $\text{C}_{14}\text{H}_{12}\text{O}_2$ : C, 79.23; H, 5.70. Found: C, 79.38; H, 5.69.
13. Crystal structure of **6a**: Evans, K. L.; Horn, G. W.; Fronczek, F. R.; Gandour, R. D.; Watkins, S. F. *Acta Cryst.* **C46**, 331-332 (1990).
14. Crystal structure of **6b**: Prince, P.; Fronczek, F. R.; Gandour, R. D. *Acta Cryst.* **C46**, 1720-1723.
15. a. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* 4467-4470 (1975). b. Chen, Q.-Y.; He, Y.-B. *Tetrahedron Lett.* **27**, 1171-1174 (1986). c. Dieck, H. A.; Heck, R. F. *J. Organometal. Chem.* **93**, 259-263 (1975). d. Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **25**, 508-524 (1986). e. King, A. O.; Negishi, E.; Villani, F. J., Jr; Silveira, A., Jr. *J. Org. Chem.* **43**, 358-360 (1978). f. Garst, M. E.; McBride, B. J. *J. Org. Chem.* **54**, 249-250 (1989).
16. **1**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.93 (dd, 1H,  $J=7.86$  and 1.14 Hz, C2), 7.70 (dd, 1H,  $J=7.67$  and 1.03 Hz, C5), 7.43 (dt, 1H,  $J=7.52$ , 7.67, and 1.14 Hz, C4), 7.31 (dt, 1H,  $J=7.86$ , 7.52, and 1.03 Hz, C3), 7.19 (t, 1H,  $J=8.35$  Hz, C4'), 6.51 (d, 2H,  $J=8.35$  Hz, C3', C5'), 3.93 (s, 3H, C(O)OCH<sub>3</sub>), 3.87 (s, 6H, C2', C6'-OCH<sub>3</sub>).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  166.7 (C=O), 161.3 (C2', C6'), 133.9 (C3), 131.2 (C1), 129.9 (C6), 129.8 (C4'), 127.2 (C5), 124.1 (C2), 103.2 (C3', C5'), 101.4 (C1'), 96.3 (C6-C $\equiv$ ), 87.0 (C1'-C $\equiv$ ), 55.7 (OCH<sub>3</sub>), 51.6 (C(O)OCH<sub>3</sub>). Anal. Calcd for  $\text{C}_{18}\text{H}_{16}\text{O}_4$ : C, 72.96; H, 5.44. Found: C, 72.88; H, 5.39.
17. Crystal structure of **1**: Huang, E. T.; Evans, K. L.; Fronczek, F. R.; Gandour, R. D. *Acta Cryst.* submitted.
18. To a solution of methyl 3-methoxysalicylate (6.46 g 35.44 mmol) in 20 mL of  $\text{CH}_2\text{Cl}_2$  and 5.7 mL of  $\text{NEt}_3$  at  $-15^\circ\text{C}$  under nitrogen was added triflic anhydride (11.23 g, 39.80 mmols) at such a rate to maintain the temperature between  $-15$  to  $-10^\circ\text{C}$ . The solution was placed in a refrigerator ( $1^\circ\text{C}$ ) overnight. The solvent was removed under reduced pressure and bulb-to-bulb distillation in a Kugelrohr apparatus yielded 96.5% yield of a colorless oil. Complete characterization of triflate was obtained.
19. Evans, K. L.; Horn, G. W.; Fronczek, F. R.; Gandour, R. D. *Acta Cryst.* **C46**, 502-504 (1990).
20. **2**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.49 (dd, 1H,  $J=7.89$  and 0.87 Hz, C6), 7.28 (dd, 1H,  $J=7.89$  and 8.27 Hz, C5), 7.22 (t, 1H,  $J=8.41$  Hz, C4'), 7.03 (dd, 1H,  $J=8.27$  and 0.87 Hz, C4), 6.54 (d, 2H,  $J=8.41$  Hz, C3' and C5'), 3.95 (s, 3H, C3-OCH<sub>3</sub>), 3.94 (s, 3H, C(O)OCH<sub>3</sub>), 3.93 (s, 6H, C2', C6'-OCH<sub>3</sub>).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 167.3 ( $>\text{C}=\text{O}$ ), 161.6 (C2' and C6'), 160.7 (C3), 133.7 (C1), 129.8 (C4'), 128.2 (C5), 122.0 (C6), 113.9 (C4), 113.7 (C2), 103.6 (C3' and C5'), 102.4 (C1'), 92.0 and 91.8 (C $\equiv\text{C}$ ), 56.5 (C3-OCH<sub>3</sub>), 56.2 (C2', C6'-OCH<sub>3</sub>), 52.0 (C(O)OCH<sub>3</sub>). Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{O}_5$ : C, 69.93; H, 5.56. Found C, 69.95; H, 5.76.
21. **3**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.11 (d, 1H,  $J=2.48$  Hz, C8'), 7.74 (d, 1H,  $J=8.98$  Hz, C4'), 7.66 (d, 1H,  $J=8.75$  Hz, C5'), 7.58 (dd, 1H,  $J=7.74$  and 0.99 Hz, C6), 7.32 (dd, 1H,  $J=7.87$  and 7.74 Hz, C5), 7.11 (dd, 1H,  $J=7.87$  and 0.99 Hz, C4), 7.10 (d, 1H,  $J=8.98$  Hz, C3'), 7.05 (dd, 1H,  $J=8.75$  and 2.48 Hz), 4.09 (s, 3H, C2'-OCH<sub>3</sub> or C7'-OCH<sub>3</sub>), 4.08 (s, 3H, C2'-OCH<sub>3</sub> or C7'-OCH<sub>3</sub>), 4.02 (s, 3H, C3-OCH<sub>3</sub>), 3.93 (s, 3H, C(O)OCH<sub>3</sub>).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  166.5 (C=O), 160.7 (C3), 159.8 (C2'), 159.3 (C7'), 136.6 (C8a'), 132.7 (C1), 130.1 (C4'), 129.3 (C5'), 128.1 (C5), 123.9 (C4a'), 122.1 (C6), 116.9 (C6'), 114.03 (C2), 113.96 (C3'), 110.0 (C4), 106.0 (C1'), 104.6 (C8'), 94.7 and 93.0 (C $\equiv\text{C}$ ), 56.6 (OCH<sub>3</sub>), 56.4 (OCH<sub>3</sub>), 55.6 (OCH<sub>3</sub>), 51.9 (C(O)OCH<sub>3</sub>). Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{O}_5$ : C, 73.39; H, 5.36. Found: C, 73.74; H, 5.47.
22. Crystal structure of **7**: Evans, K. L.; Fronczek, F. R.; Gandour, R. D. *Acta Cryst.* submitted.
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