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Stereospecific Syntheses of Clomiphene and Tamoxifen via Stannylcupration of Diphenylacetylene

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STEREOSPECIFIC SYNTHESES OF CLOMIPHENE AND TAMOXIFEN *VIA* STANNYLCUPRATION OF DIPHENYLACETYLENE

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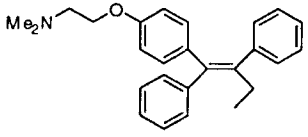
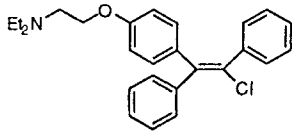
Abstract: Stereospecific *trans*-stannylcupration of diphenylacetylene affords a 1,2-dimetallostilbene which may be elaborated into either Clomiphene or Tamoxifen through palladium-catalyzed coupling with an aryl iodide.

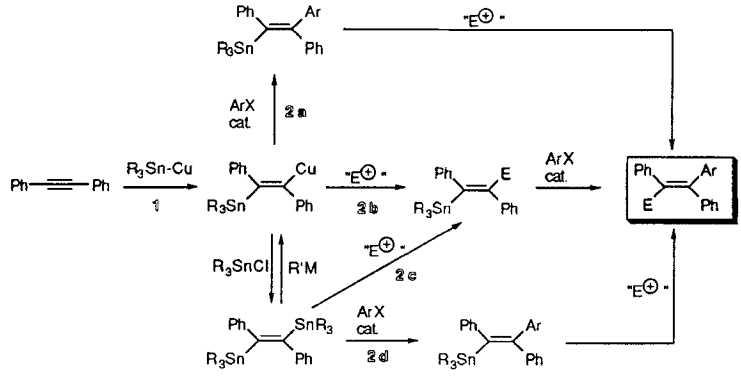
In a recent report we presented the results of our examination of the stannylmetallation of diphenylacetylene,[1] where we described the discovery of a method for the stereospecific preparation of *trans*-1-trialkylstannyl-2-metallo-1,2-diphenylalkenes *via* stannylcupration. This process is central to our proposed synthetic route to estrogenic and antiestrogenic triarylolefins. The present report will discuss our final studies regarding the application of this chemistry to the preparation of important triarylolefinic targets. Specifically, the successful conclusion of our efforts toward the synthesis of Tamoxifen (**1**) and Clomiphene (**2**) will be presented. Although syntheses of both **1**[2-5] and **2**[6,7] have been previously reported, the inability to readily establish the necessary stereochemistry has made these preparations long and, in some cases, required isomer separation.



1
Tamoxifen



2
Clomiphene



Scheme I. Stannylcupration approach to triarylolefins.

An overview of the synthetic strategy is shown in Scheme I. As stated previously,[1] we were unable to effect palladium-catalyzed coupling of the initial adduct with an aryl halide (Route 2a). Starting with a stannylmetalloalkene, Route 2b requires reaction with an electrophile, which for the ligands of interest would be an alkyl halide or a source of electropositive chlorine. Alkylations are well known for vinylcuprates, and chlorinations have also been reported.[8-10] Route 2c would probably be most useful for Clomiphene (E = Cl), and would afford the same advanced intermediate as Route 2b through halodestannylation of a bis-stannane. Finally, coupling of a bis-stannane (Route 2d) was previously attempted unsuccessfully, but could merit a reexamination.

RESULTS AND DISCUSSION

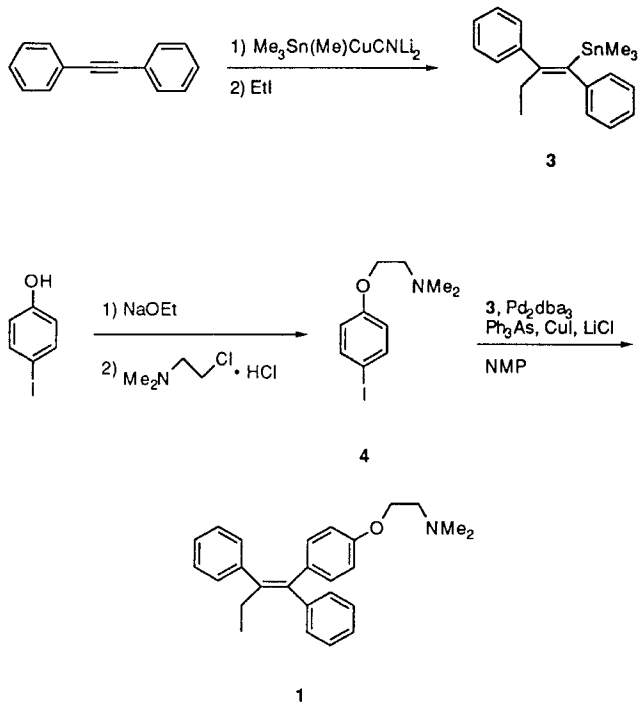
Tamoxifen

Upon examining the various synthetic options as presented in Scheme I, we felt that the most expeditious route would be 2b, in which the diphenylacetylene-stannylcuprate adduct would be trapped by ethyl iodide. In fact, both ethyl bromide and ethyl iodide are effective in quenching the vinyl anion, with the iodide providing a higher yield (58% *vs* 26%) of the desired product **3** (Scheme II). With

this product we were in the position of having three of the four olefinic substituents of Tamoxifen in place and with the correct stereochemistry. The synthesis of the final product required coupling of vinylstannane **3** with aryl iodide **4**, which was readily prepared from 4-iodophenol[6] (Scheme II). However, as before, the palladium-catalyzed coupling of this vinyl stannane was quite problematic. The use of standard Stille coupling catalysts such as tetrakis(triphenylphosphine)palladium (0) or bis(triphenylphosphine)palladium (II) chloride provided no coupling product. Equally unsuccessful were our attempts to employ other reagents which are known to promote such couplings (CuI, LiCl, Ph_3As). We would sometimes observe traces of the coupling adduct, but never preparatively useful amounts. However, the modification of some recently reported Stille coupling conditions[11] using tris(dibenzylideneacetone)dipalladium finally permitted the successful conclusion of this synthesis, providing Tamoxifen (1) in 52% yield. This material was identical to a commercial sample as judged by HPLC, TLC, and proton- and carbon-NMR spectra.

Clomiphene

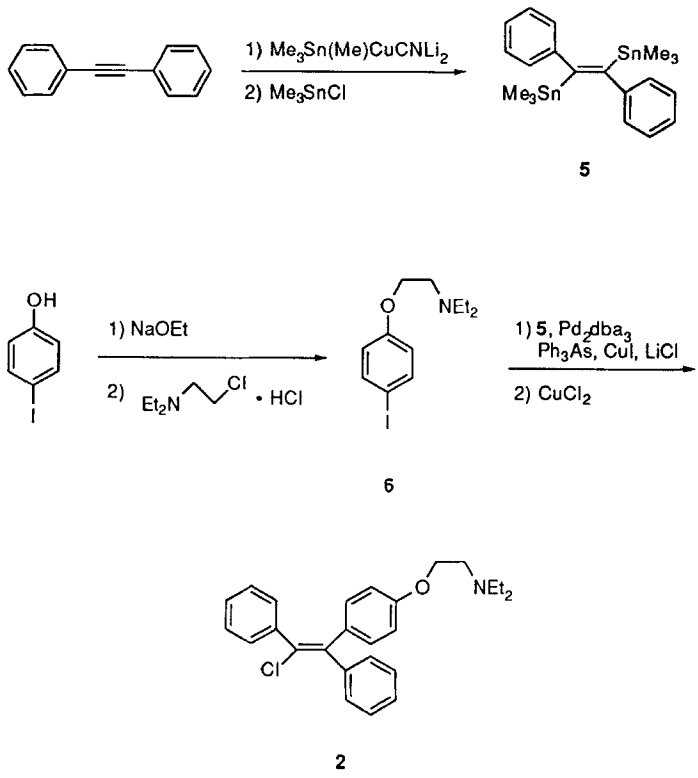
Our initial strategy for this target was essentially the same as for Tamoxifen, i.e., Route 2b, with the modification that the vinyl anion would be chlorinated rather than alkylated. However, despite the fact that the chlorination of vinylcuprates is known, only starting diphenylacetylene was recovered from the reaction of the vinylstannylcuprate intermediate with *N*-chlorosuccinimide (NCS). This is probably due to the rapid reaction of NCS with the starting stannylcuprate, which is in equilibrium with its diphenylacetylene adduct. Attempted iodinations with molecular iodine were equally unsuccessful. In an effort to bypass this problem, we prepared *trans*-bis-stannane **5** (Scheme III) as previously described,[1] to examine Route 2c. We reasoned that mono-halodestannylation of the bis-stannane would provide an alternative route to the desired 1-halo-2-stannylalkene. Unfortunately, both chlorodestannylation conditions ($CuCl_2$)[12] and iododestannylation condtions (I_2)[13] afforded diphenylacetylene as the only isolable product when **5** was the substrate. These results suggest that the 1-halo-2-stannylalkene undergoes extremely facile conversion to the 1,2-dihaloalkene under these conditions, and that this compound is unstable with respect to loss of molecular halogen, thus regenerating the halodestannylation agent. Alternatively,



Scheme II. Synthesis of Tamoxifen.

the 1-halo-2-stannylalkene may spontaneously eliminate trialkylstannyl halide to provide the observed alkyne product.

As a last resort, we turned our attention to Route 2d. As stated above, we had previously been unable to couple **5** with an aryl iodide. However, our success with the coupling conditions employed in the synthesis of Tamoxifen prompted us to reexamine them in this regard. The coupling partner in this case is iodide **6**, which was prepared from 4-iodophenol in the same fashion as was **4**.[6] Reasoning that the triarylvinylstannane adduct of **5** and **6** would be quite unstable, the crude product of this reaction was immediately subjected to chlordestannylation conditions (Scheme III). To our delight, Clomiphene (**2**) was obtained from this reaction after chromatographic purification. Although the yield was substantially lower in this case (15%), this was a two-step reaction and involved the coupling of a more hindered vinylstannane.



Scheme III. Synthesis of Clomiphene.

In summary, both Tamoxifen **1** and Clomiphene **2** have been prepared through an alkyne stannylcupration-Stille coupling process. The utility of this approach is based upon our discovery of *trans*-selective stannylcupration conditions. Neither of these syntheses has been optimized, and it is anticipated that such optimization would make these routes even more attractive for the preparation of Tamoxifen, Clomiphene, and other triarylolefins.

EXPERIMENTAL

General. All solvents were Fisher HPLC grade and were used without purification, except HPLC solvents which were degassed with helium. Flash

chromatography was performed according to the method of Still,[14] using 230-400 mesh silica gel (Merck Grade 60, 60Å, Aldrich Chemical Co.). Analytical thin layer chromatography was performed using 250-μ plates (Analtech, Inc.). Bis-stannane **5** was prepared as previously described.[1]

Proton and carbon-13 NMR spectra were obtained on a Varian VXR-300 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Gas chromatography was performed on a HP 5890A gas chromatograph with a 20 m J&W DB-5MS column.

1-Trimethylstannyl-1,2-diphenylbutene (3). To a stirred suspension of 1.382 g (15.4 mmol) of copper (I) cyanide in 75 mL of tetrahydrofuran at - 40 °C under nitrogen was added 22.04 mL (30.9 mmol) of a 1.4 *M* solution of methyllithium in diethyl ether. The solution was stirred for 15 min, 5.055 g (15.4 mmol) of hexamethylditin was added, and stirring was continued for 1 h. A solution of 2.500 g (14.0 mmol) of diphenylacetylene in 5 mL of tetrahydrofuran was added, the cooling bath was removed, and stirring was continued for 2 h. The reaction was then quenched by addition of 2.468 Ml (4.813 g, 30.9 mmol) of ethyl iodide. The reaction mixture was poured into 100 mL of 9:1 saturated aqueous ammonium chloride:concentrated aqueous ammonium hydroxide and extracted with two 100-mL portions of diethyl ether. The organic extracts were combined and dried (Na_2SO_4). Filtration and evaporation at reduced pressure on a rotary evaporator afforded a residue which was purified by flash chromatography on silica gel using hexane as eluant to provide 3.08 g (58%) of vinylstannane **3** as a colorless oil. Gas chromatographic analysis indicated a purity of 96%, wtih the remaining 4% being bis-stannane **5**: R_F 0.33 (hexane); ^1H NMR ($CDCl_3$) δ 7.64-7.22 (m, 10H), 2.58 (q, J = 7.5 Hz, 2H), 1.03 (t, J = 7.5 Hz, 3H), -0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.6, 145.7, 145.2, 144.2, 128.8, 128.1, 127.1, 126.9, 124.8, 28.5, 13.4, -7.9.

4-[2-(Dimethylamino)ethoxy]iodobenzene (4). A mixture of 0.313 g (13.6 mmol) of sodium metal and 30 mL of ethyl alcohol were stirred under nitrogen until all of the sodium was consumed. A solution of 1.000 g (4.54 mmol) of 4-iodophenol in 30 mL of ethyl alcohol was added, and then a solution of 0.982 g (6.82 mmol) of dimethylaminomethyl chloride hydrochloride in 30 mL of ethyl alcohol was added. The reaction solution was heated at reflux for 16 h, was cooled to room temperature, and was quenched by the addition of 200 mL of water. The mixture was extracted with two 100-mL portions of diethyl ether, and the organic

extracts were combined, washed with two 100-mL portions of 1 *M* aqueous sodium hydroxide, and dried (Na_2SO_4). Filtration and evaporation of the solvent a pale yellow oil which was purified by flash chromatography on silica gel using 10% methanol in chloroform as eluant to provide 0.986 g (75%) of aryl iodide **4** as a colorless oil. Gas chromatographic analysis indicated a purity of 98%: R_F 0.52 (10% methanol in chloroform); ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 2.71 (t, J = 5.7 Hz, 2H) 2.32 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 158.4, 137.9, 116.8, 82.8, 66.2, 58.2, 46.0.

Tamoxifen (1). To a solution of 0.076 g (0.26 mmol) of aryl iodide **4** in 2 mL of degassed *N*-methylpyrrolidone under nitrogen was added sequentially 0.012 g (0.013 mmol) of tris(dibenzylideneacetone)dipalladium, 0.016 g (0.052 mmol) of triphenylarsine, 0.005 g (0.026 mmol) of copper (I) iodide, 0.089 g (2.10 mmol) of lithium chloride, and 0.200 g (0.52 mmol) of vinylstannane **3**. The resulting suspension was heated at 45° C for 48 h. After being cooled to room temperature, the mixture was diluted with 10 mL of water and was extracted with two 10-mL portions fo diethyl ether. The organic extracts were combined, dried (Na_2SO_4), filtered, and evaporated to afford an amber oil, which was purified by flash chromatography on silica gel using 10% methanol in chloroform as eluant to provide 0.050 g (52%) of triarylolefin (**1**) as a pale yellow solid: mp 94.5-97.5° C (lit.[15] mp 96-98° C); R_F 0.50 (10% methanol in chloroform). The ^1H and ^{13}C NMR spectral properties of this material were identical with those of an authentic sample of Tamoxifen.

4-[2-(Diethylamino)ethoxy]iodobenzene (6). A mixture of 0.313 g (13.6 mmol) of sodium metal and 30 mL of ethyl alcohol were stirred under nitrogen until all of the sodium was consumed. A solution of 1.000 g (4.54 mmol) of 4-iodophenol in 30 mL of ethyl alcohol was added, and then a solution of 1.173 g (6.82 mmol) of diethylaminomethyl chloride hydrochloride in 30 mL of ethyl alcohol was added. The reaction solution was heated at reflux for 16 h, was cooled to room temperature, and was quenched by the addition of 200 mL of water. The mixture was extracted with two 100-mL portions of diethyl ether, and the organic extracts were combined, washed with two 100-mL portions of 1 *M* aqueous sodium hydroxide, and dried (Na_2SO_4). Filtration and evaporation of the solvent a pale yellow oil which was purified by flash chromatography on silica gel using 10% methanol in chloroform as eluant to provide 0.883 g (61%) of aryl iodide **6** as a colorless oil. Gas chromatographic analysis indicated a purity of > 99%: R_F 0.49

(10% methanol in chloroform); ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.2 Hz, 2H), 2.85 (t, J = 6.2 Hz, 2H) 2.62 (q, J = 7.1 Hz, 4H), 1.06 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 158.4, 137.9, 116.8, 82.6, 66.8, 51.7, 47.9, 12.1.

Clomiphene (2). To a solution of 0.079 g (0.25 mmol) of aryl iodide **4** in 2 mL of degassed *N*-methylpyrrolidone under nitrogen was added sequentially 0.023 g (0.024 mmol) of tris(dibenzylideneacetone)dipalladium, 0.030 g (0.097 mmol) of triphenylarsine, 0.009 g (0.049 mmol) of copper (I) iodide, 0.168 g (3.95 mmol) of lithium chloride, and 0.250 g (0.49 mmol) of vinylstannane **5**. The resulting suspension was heated at 45° C for 96 h. After being cooled to room temperature, the mixture was diluted with 10 mL of water and was extracted with two 10-mL portions fo diethyl ether. The organic extracts were combined, dried (Na_2SO_4), filtered, and evaporated to afford an yellow oil. The oil was dissolved in 2 mL of tetrahydrofuran and 0.146 g (1.09 mmol) of copper)II) chloride was added. After being stirred under nitrogen for 18 h the mixture was diluted with 20 mL of diethyl ether, was washed with 20 mL of water, and was dried (Na_2SO_4). Filtration and evaporation of the solvent afforded a yellow oil, which was purified by flash chromatography on silica gel usingj 5% methanol in chloroform as eluant to provide 0.015 g (15%) of triarylolefin (**2**) as a colorless oil: R_F 0.50 (10% methanol in chloroform). The ^{1}H and ^{13}C NMR spectral properties of this material were identical with those of an authentic sample of Clomiphene. Treatment of an ethanolic solution of this material with anhydrous hydrogen chloride afforded the hdyrochloride salt: mp 147-150.5° C (lit.[16] mp 149-150.5° C).

REFERENCES

1. Cummins, C. H.; Gordon, E. J. *Tetrahedron Lett.* **1994**, *35*, 8133-8136.
2. Al-Hassan, M. I. *Synthesis* **1987**, 815-816.
3. Al-Hassan, M. I. *Syn. Comm.* **1987**, *17*, 1247-1251.
4. Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121-2123.
5. Potter, G. A.; McCague, R. *J. Org.Chem.* **1990**, *55*, 6184-6187.
6. Al-Hassan, M. I. *Syn. Comm.* **1987**, *17*, 1787-1796.
7. Al-Hassan, M. I. *Org. Prep. Proc. Int.* **1991**, *23*, 116-118.
8. Westmijze, H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1977**, 2023-2026.

9. Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 168-171.
10. Levy, A. B.; Talley, P.; Dunford, J. A. *Tetrahedron Lett.* **1977**, 3545-3548.
11. Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613-5614.
12. Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563-6566.
13. Ali, H.; Rousseau, J.; Ghaffari, M. A.; van Lier, J. E. *J. Med. Chem.* **1991**, *34*, 854-860.
14. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
15. Harper, M. J. K. *Nature* **1966**, *212*, 87.
16. Ernst, S.; Hite, G.; Cantrell, J. S.; Richardson, A. J.; Benson, H. D. *J. Pharm. Sci.* **1976**, *65*, 148-150.

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