Notes

Electrophilic Destannylation: Stereospecific Introduction of Electrophiles at the 21 Position of (17α)-19-Norpregna-1,3,5(10),20-tetraene-3-17β-diols

Robert N. Hanson* and Hoda El-Wakil

Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115

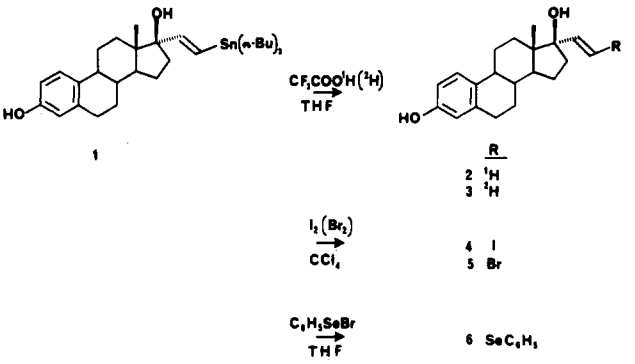
Received February 2, 1987

As part of our program to develop radiopharmaceuticals for the detection and diagnosis of estrogen-responsive breast cancer, we have focused on the use of organometallic substituents to facilitate the introduction of the radionuclide. As a result we initiated the application of organotin chemistry to the field of radiopharmaceutical chemistry in our preparation of the labeled antiestrogen [^{125}I]-iodotamoxifen.[1-3] In that synthesis we could selectively lithiate and subsequently stannylate ortho to the (dimethylamino)ethoxy group, and electrophilic radioiododestannylation proceeded rapidly and in very high yield. We have extended this approach in the field of estrogen receptor binding agents to the synthesis of radioiodinated 17α-[5-iodothien-2-yl][4] and 17α-(*E*)-iodovinyl estrogens.[5-9] Because of the availability of other radionuclides of potential in vitro or in vivo clinical interest, e.g., ^{3}H, ^{75}Br, ^{76}Br, and ^{73}Se, we have undertaken a preliminary examination of other electrophilic species containing these elements. This paper describes the results of this study in which a series of specifically substituted (17α,20*E*)-19-norpregna-1,3,5(10)20-tetraene-3,17β-diols (17α-vinylestradiols) were prepared and characterized.

Results and Discussion

The objectives of the study were to prepare the 17α-(*E*)-(tri-*n*-butylstannyl)vinylestradiol, to react the intermediate with H, D, Br, I, and SeC_6H_5 electrophiles, and to confirm the stereochemistry of the electrophilic destannylation. The first objective was achieved by utilizing the procedure that we previously reported.[6] The addition of (*E*)-tri-*n*-butylstannyl)lithium to estrone in THF at 0 °C provided the desired intermediate in a 29% yield. The ^{1}H NMR spectrum for the vinylic protons consisted of two doublets at δ 6.21 and 6.25 with a coupling constant of J = 20 Hz, consistent for the predicted *E* stereochemistry. The 17α-[(*E*)-(tri-*n*-butylstannyl)vinyl]estradiol was then subjected to destannylation with different electrophiles

Scheme I



(Scheme I). Protio- and deuteriodestannylation were achieved with trifluoroacetic acid and [1-^{2}H]trifluoroacetic acid, generated in situ with deuterium oxide and trifluoroacetic anhydride, at 0 °C, in less than 30 min to give essentially a quantitative yield of the desired product. The ^{1}H NMR spectra (300 MHz) confirmed the loss of the stannyl moiety and the introduction of a proton/deuteron. The stereochemistry was established with the (*E*)-[^{2}H]-vinylestradiol by the appearance of the two vinylic protons at δ 5.18 and 6.08 with a coupling constant of J = 17 Hz, consistant with the predicted *E* configuration.[7-12] Ipso halodestannylation was achieved in the manner previously described for the synthesis of the 17α-(*E*)-iodovinyl)estradiol.[6] The addition of 1 equiv of the iodine or bromine in carbon tetrachloride at ambient temperature gave a virtually instantaneous discharge of the color and produced a nearly quantitative yield of the 17α-(*E*)-(bromo- or -iodovinyl)estradiol. The vinylic portion of the ^{1}H NMR spectrum indicated a downfield shift of both protons, appearing as a pair of doublets, for the bromo derivative at δ 6.24 and 6.45 (J = 14 Hz) and for the iodo derivative at 6.30 and 6.87 (J = 14 Hz). The last reaction involved the addition of the pseudohalogen, phenylselenenyl bromide, generated in situ by the addition of bromine to diphenyl diselenide,[13] to the stannylvinyl intermediate at 0 °C for 5 h. The desired 17α-[(*E*)-(phenylseleno)vinyl]estradiol was isolated in a 76% yield by using flash chromatography. The ^{1}H NMR spectrum confirmed the introduction of the phenylselenenyl moiety via ipso substitution as characterized by the vinyl protons appearing as a pair of doublets at δ 6.23 and 6.60 (J = 16 Hz). This compound, unlike the other four, was relatively unstable and decomposed significantly over a period of several days.

Among the features required for a general radiolabeling method are (1) that the reaction proceed rapidly, i.e., in less than an hour; (2) that the reaction yields a single product; and (3) that the product possesses the nuclide in the desired locus. Our research has demonstrated that the electrophilic radiohalodestannylation of substituted tri-

(1) Seitz, D. E.; Tonnesen, G. L.; Hellman, S.; Hanson, R. N.; Adelstein, S. J. *J. Organonomet. Chem.* **1980**, *186*, C33.
(2) Tonnesen, G. L.; Hanson, R. N.; Seitz, D. E. *Int. J. Appl. Radiat. Isol.* **1981**, *32*, 171.
(3) Hanson, R. N.; Seitz, D. E. *Int. J. Appl. Radiat. Isot.* **1982**, *33*, 105.
(4) Lee, S.-H,; Hanson, R. N.; Seitz, D. E. *Tetrahedron Lett.* **1984**, *25*, 1751.
(5) Hanson, R. N.; Seitz, D. E.; Bottaro, J. C. *J. Nucl. Med.* **1982**, *23*, 43.
(6) Hanson, R. N.; Seitz, D. E.; Bottaro, J. C. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 810.
(7) Hanson, R. N.; Franke, L. A. *J. Nucl. Med.* **1984**, *25*, 998.
(8) Franke, L. A.; Hanson, R. N. *J. Nucl. Med.* **1984**, *25*, 1116.
(9) Nakatsuka, I.; Ferriera, N. L.; Eckelman, W. C.; Francis, B. E.; Rzeszotarski, W. J.; Gibson, R. E.; Jagoda, E. M.; Reba, R. C. *J. Med. Chem.* **1984**, *27*, 1287.
(10) Hoyte, R. M.; Rosner, W.; Johnson, I. S.; Zielinski, J.; Hochberg, R. B. *J. Med. Chem.* **1985**, *28*, 1695.
(11) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'Der, Ya. L. *Synthesis* **1986**, 496.
(12) Hofmeister, H.; Laurent, H.; Schulze, P.-E.; Wiechert, R. *Tetrahedron* **1986**, *35*, 75.
(13) Sharpless, K. B. *J. Org. Chem.* **1974**, *39*, 429.

0022-3263/87/1952-3687$01.50/0

alkylarylstannanes is such a method. The corresponding versatility of the trialkylvinylstannanes has been less well defined. In the present study we have clearly demonstrated that a polyfunctional precursor, the (*E*)-21-(tri-*n*-butylstannyl)-(17α)-19-norpregna-1,3,5(10),20-tetraene-3,17β-diol, which can be prepared in good yields with the defined *E* stereochemistry, undergoes facile ipso substitution with a variety of electrophiles. These reactions which include protonation, deuteriation, halogenation, and phenylselenation proceed at ambient temperatures or lower, within 1–30 min, except in the case of the phenylselenation. In all cases a single product resulting from ipso substitution is obtained in isolated yields of 76–97%. The compounds could be identified by the mass spectra which provided the parent ions, and the stereochemistry could be clearly assigned as the basis of the vinylic coupling constants. No evidence of electrophilic reactions of electrophilic reactions on the unprotected phenolic A ring could be detected. This supports our selection of the trialkylstannyl moiety for activation of sp^2 carbon bonds toward electrophilic substitution in the development of radiopharmaceuticals labeled with the radionuclides of hydrogen, selenium, bromine, or iodine.

Experimental Section

General Methods. IR spectra were obtained via a Perkin-Elmer Model 599B infrared spectrophotometer. ^1H and ^{13}C NMR spectra were taken at ambient temperature in $CDCH_3$, CD_3CO-CH_3, or CD_3OD, with tetramethylsilane as an internal standard on a Varian 300-MHz instrument. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Flash chromatography employed silica gel (230–400 mesh) as the absorbent. Thin layer chromatography was performed on both normal (silica gel) and reverse phase (C-18) plates using chloroform/ethyl acetate (9:1) and ethanol/water (9:1) as the eluents. The *n*-butyllithium, trifluoroacetic acid, trifluoroacetic anhydride, deuterium oxide, diphenyl diselenide, iodine, and bromine were obtained commercially from Aldrich Chemical Co. and used without further purification.

(17α,20*E*)-21-(Tri-*n*-butylstannyl)-19-norpregna-1,3,5(10),20-tetraene-3,17-diol (1). This compound was synthesized from estrone and (*E*)-1,2-bis(tri-*n*-butylstannyl)ethene according to the procedure of Hanson et al:[6] ^1H NMR ($CDCl_3$) δ 0.67–2.67 (41, H, m, steroid nucleus plus $(n\text{-}C_4H_9)_3$, 2.67–2.93 (3 H, m), 6.12 (d, J = 20 Hz, 1 H, C_{21}-H, 6.25 (d, J = 20 Hz, 1 H, C_{20}-H) 6.55 (d, J = 3 Hz, 1 H, C_4-H), 6.70 (d, J = 8 Hz, J = 3 Hz, 1 H, C_2-H), 7.15 (d, J = 8 Hz, C_1-H); MS (EI), m/e 530 ($M^+ - C_4H_9$).

(17α,20*E*)-19-Norpregna-1,3,5(10),20-tetraene-3,17-diol (2). To a suspension of 1 (100 mg, 0.17 mmol) in THF at 0 °C was added dropwise a solution of CF_3CO_2H in THF. The resulting solution was stirred at 0 °C for 30 min, then quenched with 7 N methanolic KF, and neutralized by the addition of 6 N aqueous sodium hydroxide. The reaction mixture was extracted with ethyl acetate; the organic layer was washed sequentially with water and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was purified by flash chromatography on silica gel using dichloromethane–ethyl acetate (9:1) as the solvent. The product was obtained in 95% yield (50 mg, 0.16 mol): TLC SiO_2 = 0.29, C-18 = 0.73; ^1H NMR (CD_3OD) 0.95 (5, 3 H, C_{18}-H), 1.24–2.50 (m, 11 H, steroid nucleus), 2.75–2.78 (m, 3 H, C_6-H, C_{10}-H), 5.09–5.19 (m, 2 H, C_{21}-H), 6.06–6.12 (m, 1 H, C_{20}-H), 6.47 (d, J = 3 Hz, C_4-H) 6.55 (dd, J = 8 Hz, J = 3 Hz, 1 H, C_2-H), 7.09 (d, J = 8 Hz, 1 H, C_1-H); ^{13}C NMR (CD_3OD) 14.4, 23.88, 27.19, 28.37, 30.35, 33.02, 36.01, 40.72, 44.58, 47.76, 50.10, 84.63, 113.30, 115.63, 126.76, 132.15, 138.34, 144.18, 155.20 ppm; mass spectrum (EI) m/e 298 (M^+).

(17α,20*E*)-21-Deuterio-19-norpregna-1,3,5(10),20-tetraene-3,17-diol (3). To a suspension of trifluoroacetic anhydride (3.84 mmol, 13.6 mmol) in 5 mL of THF at 0 °C was added deuterium oxide (0.54 mL, 13.6 mmol). The resulting solution was added to a THF solution containing the vinylstannane 1 (0.200 g, 0.34 mmol). The reaction proceeded as for 2. The product was isolated in a 90% yield as a white solid (0.092 g, 0.31 mmol): TLC SiO_2 = 0.29, C-18 = 0.73; ^1H NMR (CD_3OD) δ 0.96 (s, 3 H, $C_{18}H_3$), 1.45–2.50 (m, 11 H, steroid nucleus), 2.75–278 (m, 3 H) 3.3 (s, 1 H), 5.18 (d, J = 17 Hz, C_{21}-H), 6.08 (d, J = 17 Hz, C_{20}-H), 6.55 (d, J = 3 Hz, C_4-H), 6.62 (dd, J = 3 Hz, J = 8 Hz, C_2-H), 7.10 (d, J = 8 Hz, C_1-H); ^{13}C NMR (CD_3OD) 14.53, 23.90, 27.12, 28.30, 30.37, 33.01, 36.04, 40.47, 44.60, 47.25, 49.50, 84.71, 113.33, 115.76, 126.86, 131.28, 138.48, 143.83, 155.23 ppm; mass spectrum (EI), m/e 299 (M^+).

(17α,20*E*)-21-Bromo-19-norpregna-1,3,5(10),20-tetraene-3,17-diol (5). To a solution of 1 (0.100 g, 0.17 mmol) in CCl_4 was added dropwise a 0.02 M solution of bromine in CCl_4 until the color of bromine persisted. To the reaction mixture was added 1 mL of 7 N KF in methanol and 1 mL of a 5% aqueous sodium bisulfate solution. The mixture was extracted with ether, and the organic phase was dried over $MgSO_4$ (anhydrous), filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel using dichloromethane/ethyl acetate (9:1) as the solvent. The product was isolated as a white solid in a 90% yield (0.058 g, 0.15 mmol): TLC SiO_2 = 0.35; C-18 = 0.69; ^1H NMR (CD_3OD–$CHCl_3$) δ 0.96 (s, C_{18}-H), 1.24–2.43 (m, 11 H, steroid nucleus), 2.75–2.78 (m, 3 H), 3.3 (s, 1 H), 6.24 (d, J = 14 Hz, C_{21}-H), 6.45 (d, J = 14 Hz, C_{20}-H), 6.51 (d, J = 3 Hz, C_4-H, C_2-H, C_1-H, 6.63 (dd, J = 8 Hz, J = 3 Hz, C_2-H), 7.10 (d, J = 8 Hz, C_1-H); ^{13}C NMR (CD_3OD–$CDCl_3$) 14.32, 23.69, 26.96, 28.10, 30.22, 33.07, 36.39, 40.30, 44.37, 47.77, 50.02, 85.61, 113.26, 115.69, 126.80, 130.08, 138.39, 143,50, 155.09 ppm; mass spectrum (EI), m/e 376,374 (M^+) 1:1 for Br isotopes.

(17α,20*E*)-21-(Phenylseleno)-19-norpregna-1,3,5(10),20-tetraene-3,17-diol (6). To a solution of diphenyl diselenide (0.120 g, 0.38 mmol) in THF was added 0.34 mmol of bromine in THF. The solution, which turned from yellow to brown upon formation of the phenylselenenyl bromide, was added dropwise to a solution of the vinylstannane 1 (0.150 g, 0.25 mmol) in THF at 0 °C. The reaction turned green as it was stirred at 0 °C for 5 h. The reaction was quenched by the addition of 7 N aqueous KF and extracted with ethyl acetate. The organic phase was washed with saturated NaCl and water, dried over sodium sulfate (anhydrous), filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel to yield on oil that solidified on standing: yield 76% (0.087 g, 0.19 mmol); TLC SiO_2 = 0.43, C-18 = 0.67; ^1H NMR (CD_3OD) 0.95 (s, C_{18}-H), 1.25-2.40 (m, 11 H, steroid nucleus), 2.70-284 (m, 3 H), 6.23 (d, J = 16 Hz, C_{21}-H), 6.44 (d, J = 3 Hz, C_4-H), 6.47 (dd, J = 3 Hz, J = 3 Hz, C_2-H), 6.60 (d, J = 16 Hz, C_{20}-H), 7.10 (d, J = 8 Hz, C_1-H), 7.21–7.46 (m, 5 H, Se-C_6H_5); ^{13}C NMR (CD_3OD) 14.80, 24.25, 27.60, 28.81, 30.74, 33.65, 36.82, 41.10, 45.20, 49.51, 50.55, 85.98, 113.75, 116.42, 127.23, 128.11, 130.32, 132.47, 133.17, 138.73, 144.09, 155.89 ppm; mass spectrum (EI), m/e 456, 455, 454, 452 (M^+), multiplicity of Se isotopes.

Acknowledgment. We gratefully acknowledge the Public Health Service through the NIH Grants 1RO1 CA31624 and 1 RO1 CA41399 for their support of this research.

Registry No. 1, 82123-95-3; 2, 7678-95-7; 3, 108561-03-1; 5, 103924-36-3; 6, 108561-04-2; estrone, 53-16-7; (*E*)-1,2-bis(tri-*n*-butylstannyl)ethene, 14275-61-7.

The Pyrolysis of *S*-Alkyl Dimethylthiocarbamates

Douglas E. Johnson,* James C. DeLane, and Eric E. Wisted

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

Received August 8, 1986

Thiocarbamate herbicides are used extensively worldwide for controlling the growth of undesirable plant species. These herbicides are relatively nonpersistent in the environment, but the preferred mode of degradation is not well established.[1,2] Thermal reactions could be an

0022-3263/87/1952-3688$01.50/0