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Synthesis of substituted estradiols by the selective aromatization of A-ring of steroidal 19-nor-Δ-4-3-ketones with phenylselenyl halides/hydrogen peroxide

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ABSTRACT

A range of 6-, 7-, and 11-substituted estradiols were synthesized by the selective aromatization of the A-ring of 19-nor steroids using phenylselenyl halides followed by oxidation with hydrogen peroxide. Established methods utilizing copper(II) halides failed or have given poor yields with these substrates.

1. Introduction

Estrogens are a class of physiologically active steroid molecules that play a crucial role in reproduction as well as in the maintenance of normal human physiology. Their widespread uses as pharmaceutical agents in hormonal birth control, hormone replacement therapy and for other gynecological indications make their synthesis attractive to date [1–4]. One of the key steps in the total synthesis of estrogens is the aromatization of the A-ring. A variety of methods are reported in the literature for the A-ring aromatization of 19-nor steroids, which spans from microbiological [5] to chemical methods, namely selenium dioxide and copper bromide [6,7]. As a part of an ongoing project for the development of new estrogens, we had to accomplish the selective aromatization of a number of highly substituted 19-nor steroids. Most of the conventional methods, however, failed or gave very poor yields when applied to our substrates. Herein we describe our efforts in the selective A-ring aromatization of 6-, 7-, and 11-substituted 19-nor steroids using a combination of phenylselenyl halides and hydrogen peroxide. Although the use of this methodology has been reported in the literature for the transformation of 19-nor testosterone to estrone [8], it gained very limited attention in steroid chemistry. We have investigated the scope and use of this reagent combination in the selective aromatization of a number of highly substituted 19-nor steroids where the standard methods failed and our results are summarized below.

2. Experimental

General: NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz, respectively, on a Bruker ARX-300 MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectral analysis was conducted on an Agilent 6224 ESI–TOF mass spectrometer with sample introduction by infusion. Melting points were recorded on a MEL-TEMP® 3.0 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo-Nicolet AVATAR 370 FT-IR machine. 'Flash column' chromatography was performed on 32–64-μm silica gel obtained from EM Science (Gibbstown, NJ). Thin-layer chromatography (TLC) analyses were carried out on silica gel GF (Analtech) glass plates (2.5 cm × 10 cm with 250 μm layer and pre-scored). Most chemicals and solvents were analytical grade and used without further purification. Commercial reagents were purchased from Aldrich Chemical Company (Milwaukee, WI). All experiments were carried out under inert atmosphere using dry nitrogen. For reactions that gave known compounds, the products were compared with reported spectroscopic data.

2.1. Synthesis of starting materials

All starting materials were prepared according to reported literature procedures. Compound **1** was synthesized from the known 3-methoxy-11β, 17β-dihydroxy estra-1,3,5(10)-tirene by a Birch reduction [9], benzylation of 11 and 17 hydroxyl groups followed by acid hydrolysis [10]. Compounds **3a**, **3b**, **3c**, **3d**[11], **5**[12] and **7**[13] were synthesized following reported procedures. Compound

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4a is a known compound and spectral data were found to be matching [14].

2.2. General procedure for the aromatization reaction

2.2.1. 11β,17β-Dibenzyloxy estra-1,3,5 (10)-triene-3-ol (2)

A solution of compound **1** (1 g, 2.12 mmol) in anhydrous THF (10 mL) was cooled to −78 °C and was treated dropwise with a 1 M THF solution of lithium bis(trimethylsilyl)amide (LiHMDS) (4.24 mL, 4.24 mmol). The resulting solution was stirred at −78 °C for 1.5 h. A solution of phenylselenyl chloride in anhydrous THF (10 mL) was added to the reaction mixture at −78 °C and was stirred for 3 h with warming to 0 °C. TLC showed complete conversion of starting material to the product. The reaction was quenched by the addition of saturated ammonium chloride (20 mL) and was extracted with EtOAc. The combined organic layers were washed with water, brine and were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford crude **1a** as a dark brown viscous liquid (1.25 g). The crude **1a** thus obtained was dissolved in THF (20 mL) and was treated with 30% hydrogen peroxide solution (0.5 mL, 4.24 mmol). The reaction mixture was stirred at room temperature for 3 h and was quenched by the addition of saturated $Na_2S_2O_3$ solution. The reaction mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give crude **2** (1 g) as a dark brown solid, which was purified by chromatography on a silica column eluting with 20% EtOAc–hexane solvent system. This gave the pure compound **2** as a pale yellow solid (530 mg, 53%) m.p. 152–153 °C IR (cm^{-1}) 3303, 2871, 1582, 1099, 1041, 701. ^1H NMR (δ, 300 MHz, $CDCl_3$) 1.10 (s, 3H, $-CH_3$), 3.48 (t, J = 8.4 Hz, –CHO), 4.28 (m, 1H, CHO), 4.36 (d, J = 11.7 Hz, 1H, $-OCH_2$), 4.58 (m, 3H, $-OCH_2$), 4.68 (s, 1H, –OH), 6.53 (m, 2H, ArH), 6.81 (d, J = 7.9 Hz, 1H, –ArH), 7.17 (m, 2H, ArH), 7.28 (m, 4H, –ArH), 7.37 (m, 4H, –ArH). ^{13}C NMR (75 MHz, $CDCl_3$) 13.3, 23.0, 27.2, 27.7, 29.7, 33.6, 38.6, 43.3, 49.5, 51.2, 59.4, 70.4, 71.6, 74.0, 88.7, 112.6, 115.5, 127.4, 127.5, 128.0, 128.3, 129.2, 138.4, 138.9, 139.3, 152.9. HRMS calculated for $C_{32}H_{35}O_3$ (M/Z−H) 467.2586. Found 467.2632.

2.2.2. 11β-Methyl-estra-1,3,5(10)-triene-3, 17β-diol (4a)

Compound **4a** was prepared from **3a** in 60% yield following the general procedure described for **2** except phenylselenyl bromide was used in place of phenylselenyl chloride and the following amounts of reagents were used: **3a** (288 mg, 1 mmol), phenylselenyl bromide (472 mg, 2 mmol), LiHMDS (5 mL, 5 mmol), 30% hydrogen peroxide (0.17 mL, 1.5 mmol). The product was purified using a silica column eluting with 30% EtOAc–hexane solvent system. **4a**: 170 mg, pale yellow amorphous solid. IR (cm^{-1}) 3336, 2908, 1616, 1246, 1058, 822. ^1H NMR (δ, 300 MHz, $CDCl_3$) 0.88 (m, 6H, 2× $-CH_3$), 3.71 (m, 1H, –CHO), 4.68 (s, 1H, –OH), 6.54 (m, 1H, –ArH), 6.63 (dd, J_1 = 2.7 Hz, J_2 = 5.7 Hz, –ArH), 7.05 (d, J = 8.3 Hz, –ArH). ^{13}C NMR (75 MHz, $CDCl_3$) 14.8, 17.3, 23.2, 26.8, 30.1, 30.4, 30.5, 33.8, 43.4, 44.4, 48.9, 51.6, 83.1, 112.9, 115.2, 128.1, 130.4, 139.1, 152.9.

2.2.3. 17β-tert-butyldimethylsilyloxy, 11β-methyl-estra-1,3,5(10)-triene-3-ol (4b)

Compound **4b** was prepared from **3b** in 79% yield following the general procedure described for **2** except phenylselenyl bromide was used in place of phenylselenyl chloride and the following amounts of reagents were used: **3b** (403 mg, 1 mmol), phenylselenyl bromide (283 mg, 1.2 mmol), LiHMDS (3 mL, 3 mmol), 30% hydrogen peroxide (0. 13 mL, 1.2 mmol). The product was purified using a silica column eluting with 10% EtOAc–hexane solvent system. **4b**: 320 mg, white amorphous solid. IR (cm^{-1}) 3303, 2883, 1603, 1251, 1087, 827. ^1H NMR (δ, 300 MHz, $CDCl_3$) 0.02 and 0.04 (2s, 6H, $-Si(CH_3)_2$, 0.80 (d, J = 7 Hz, 3H, $-CH_3$), 0.89 (m, 12H, 4× $-CH_3$), 3.60 (t, J = 8.5 Hz, 1H, –CHO), 6.57 (m, 1H, –ArH), 6.66 (dd, J_1 = 3 Hz, J_2 = 6 Hz, 1H, –ArH), 7.01 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) −4.8, −4.5, 15.1, 17.3, 18.1, 23.4, 25.9, 26.9, 30.2, 30.5, 30.9, 36.7, 43.7, 45.0, 51.3, 83.0, 91.9, 113.2, 115.4, 127.9, 129.7, 138.9, 153.8. HRMS calculated for $C_{25}H_{39}O_2Si$ (M/Z−H) 399.2718. Found 399.2719.

2.2.4. 17β-tert-Butyldimethylsilyloxy,7α,11β-dimethyl-estra-1,3,5(10)-triene-3-ol (4c)

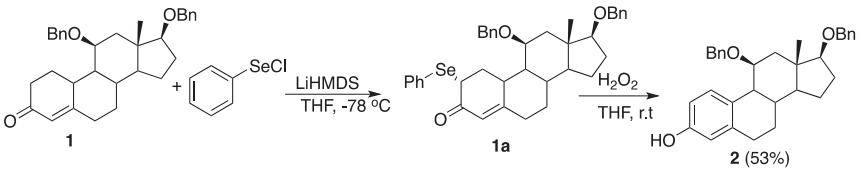
Compound **4c** was prepared from **3c** in 69% yield following the general procedure described for **2** except phenylselenyl bromide was used in place of phenylselenyl chloride and the following amounts of reagents were used: **3c** (353 mg, 0.85 mmol), phenylselenyl bromide (401 mg, 2 mmol), LiHMDS (2.6 mL, 2.6 mmol), 30% hydrogen peroxide (0.13 mL, 1.1 mmol). The product was purified using a silica column eluting with 10% EtOAc–hexane solvent system. **4c**: 180 mg, white crystalline solid. m.p. 179–181 °C. IR (cm^{-1}) 3307, 2900, 1502, 1246, 1112, 839. ^1H NMR (δ, 300 MHz, $CDCl_3$) 0.03 (2s, 6H, $-Si(CH_3)_2$), 0.80 (d, J = 7 Hz, 3H, $-CH_3$), 0.85 (m, 6H, 2× $-CH_3$), 0.9 (s, 9H, 3× $-CH_3$), 3.62 (t, J = 8.1 Hz, 1H, –CHO), 6.52 (m, 1H, –ArH), 6.62 (dd, J_1 = 3 Hz, J_2 = 6 Hz, 1H, –ArH), 7.03 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) −4.7, −4.5, 12.3, 15.0, 17.4, 18.1, 22.7, 25.9, 27.7, 30.8, 30.9, 35.8, 38.2, 42.5, 43.9, 44.9, 45.7, 48.2, 83.0, 113.0, 116.0, 127.9, 130.0, 137.6, 152.9. HRMS calculated for $C_{26}H_{41}O_2Si$ (M/Z−H) 413.2876. Found 413.2874.

2.2.5. 13β-Ethyl-11-methylene-18-nor-estra-1,3,5(10)-triene-3,17β-ol (6a)

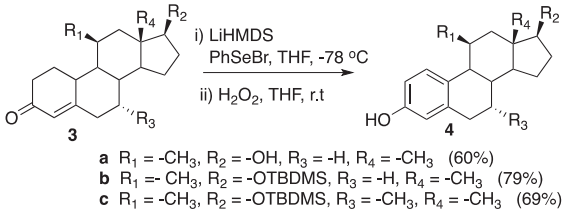
Compound **6a** was prepared from **5a** in 59% yield following the general procedure described for **2** except phenylselenyl bromide was used in place of phenylselenyl chloride and the following amounts of reagents were used: **5a** (460 mg, 1.5 mmol), phenylselenyl bromide (722 mg, 3.1 mmol), LiHMDS (7.7 mL, 7.7 mmol), 30% hydrogen peroxide (0.17 mL, 1.5 mmol). The product was purified using a silica column eluting with 30% EtOAc–hexane solvent system. **6a**: 260 mg, pale yellow amorphous solid. IR (cm^{-1}) 3320, 2938, 1616, 1288, 1058, 801. ^1H NMR (δ, 300 MHz, $CDCl_3$) 1.07 (t, J = 7.5 Hz, 3H, $-CH_3$), 3.93 (t, J = 7.9 Hz, 1H, –CHO), 4.74 (bs, 1H, –OH), 4.87 (s, 1H, =CH), 4.98 (s, 1H, =CH), 6.58 (s, 1H, –ArH), 6.63 (dd, J_1 = 3 Hz, J_2 = 6 Hz, 1H, –ArH), 7.21 (d, J = 8.2 Hz, 1H, –ArH). ^{13}C NMR (75 MHz, $CDCl_3$) 9.2, 18.8, 22.0, 26.8, 30.7, 31.3, 41.6, 44.3, 47.2, 51.3, 52.2, 83.3, 109.0, 112.4, 115.4, 127.9, 131.4, 139.5, 147.5, 153.2. HRMS calculated for $C_{20}H_{25}O_2$ (M/Z−H) 297.1855. Found 297.1860.

2.2.6. 13β-Ethyl-11-methylene-18,19-dinor-17α-pregna-1,3,5(10)-triene-20-yne-3,17β-ol (6b)

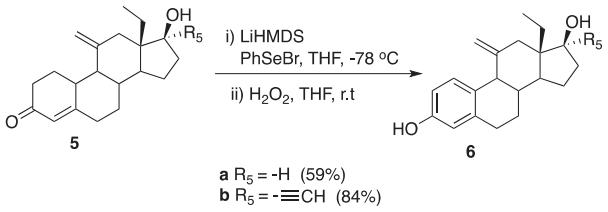
Compound **6b** was prepared from **5b** in 84% yield following the general procedure described for **2** except phenylselenyl bromide was used in place of phenylselenyl chloride and the following amounts of reagents were used: **5b** (324 mg, 1 mmol), phenylselenyl bromide (472 mg, 2 mmol), LiHMDS (5 mL, 5 mmol), 30% hydrogen peroxide (0. 22 mL, 2 mmol). The product was purified using a silica column eluting with 40% EtOAc–hexane solvent system. **6b**: 270 mg, pale yellow amorphous solid. IR (cm^{-1}) 3301, 2940, 2245, 1611, 1246, 1053, 905. ^1H NMR (δ, 300 MHz, $CDCl_3$) 1.06 (t, J = 7.2 Hz, 3H, $-CH_3$), 2.05 (s, 1H), 3.03 (d, J = 10 Hz, 1H), 4.72 (s, 1H, –OH), 4.88 (s, 1H, =CH), 5.00 (s, 1H, =CH), 6.56 (d, J = 2.6 Hz, 1H, –ArH), 6.63 (dd, J_1 = 2.6 Hz, J_2 = 6 Hz, 1H, –ArH), 7.21 (d, J = 8.4 Hz, 1H, –ArH). ^{13}C NMR (75 MHz, $CDCl_3$) 9.3, 19.9, 21.7, 26.9, 30.7, 40.0, 40.4, 42.0, 50.9, 52.1, 74.2, 81.1, 87.8, 109.2, 112.5, 115.3, 127.8, 131.3, 139.5, 147.8, 153.1.



Scheme 1. Synthesis of compound **2**



Scheme 2. Syntheses of compounds **4a**, **4b** and **4c**



Scheme 3. Syntheses of compounds **6a** and **6b**

2.2.7. 17β-tert-Butyldimethylsilyloxy, 6,6-cyclopropyl-estra-1, 3,5(10)-triene-3-ol (8)

Compound **8** was prepared from **7** in 37% yield following the general procedure described for **2** except phenylselenyl bromide was used in place of phenylselenyl chloride and the following amounts of reagents were used: **7** (580 mg, 1 mmol), phenylselenyl bromide (396 mg, 1.2 mmol), LiHMDS (3 mL, 3 mmol), 30% hydrogen peroxide (0. 23 mL, 2.1 mmol). The product was purified using a silica column eluting with 40% EtOAc–hexane solvent system. **8**: 210 mg, pale yellow amorphous solid. IR (cm^{-1}) 3362, 2921, 1620, 1251, 1099, 839. ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 0.04 (s, 3H, –$Si(CH_3)_2$), 0.05 –$Si(CH_3)_2$), 0.77 (s, 4H, –CH_2), 0.79 (s, 3H, –CH_3), 0.91(s, –Si–C–$(CH_3)_3$) 3.65 (t, J = 8.1 Hz, 1H), 4.8 (bs, 1H, –OH), 6.12 (d, J = 2.5 Hz, 1H, –ArH), 6.58 (dd, J_1 = 3 Hz, J_2 = 5.6 Hz, 1H, –ArH), 7.15 (d, J = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) −4.8, −4.5, 11.3, 16.7, 18.1, 18.5, 23.2, 23.5, 25.3, 25.6, 30.9, 34.7, 37.9, 39.8, 43.5, 44.7, 49.3, 81.7, 108.4, 111.9, 126.2, 133.2, 143.7, 153.8. HRMS calculated for $C_{26}H_{39}O_2Si$ (M/Z−H) 411.2720. Found 411.2715.

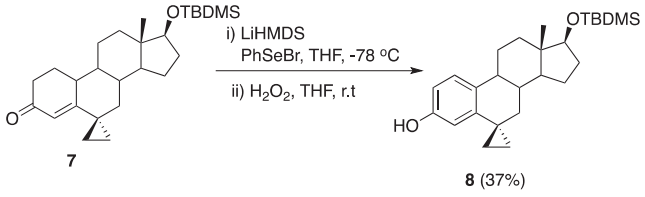
3. Results and discussion

Our studies commenced with the aromatization of 11,17-dibenzyloxy 19-nor steroid derivative **1** (Scheme 1).

As shown in the above scheme, substrate **1** was deprotonated at C-2 with LiHMDS at −78 °C and the resulting enolate was trapped with phenylselenyl chloride. The resulting phenylselenyl adduct was oxidized using hydrogen peroxide to afford the 11-, 17-dibenzyloxy estradiol derivative **2** in 53% yield. Comparable yield of **2** was obtained when phenylselenyl bromide and hydrogen peroxide were used as the reagents. This method has been widely used for the conversion of ketones to α,β-unsaturated ketones [15–17]. This selective aromatization of substrate **1** with reagents such as copper(II) bromide and selenium dioxide gave a complex reaction mixture. It is already reported in the literature that selective aromatization of 3-keto-Δ-4, 19-nor steroids are substrate dependent and conventional reagents like copper bromide fails in substrates having bulky substituents at position 11 and other positions [18].

With the encouraging results obtained in the case of substrate **1**, we extended the present study to 11-substituted derivatives and the results are summarized in the following scheme (Scheme 2).

This methodology was successfully applied for the A-ring aromatization of 13-ethyl, 19-nor Δ-4-3-ketones (Scheme 3), a notable example being etonogestrel (**5b**), a steroidal progestin largely used in hormonal birth control. The A-ring aromatized etonogestrel derivative **6b** was obtained in an excellent yield of 84%. It should be noted that this transformation was previously achieved only through microbial oxidation [19].



Scheme 4. Synthesis of compound **8**

This methodology was also tried on 6-substituted 3-keto-Δ-4, 19-nor steroid **7**. All conventional methods of aromatization failed when applied to this substrate. As shown in Scheme 4, the corresponding estradiol derivative was obtained in a moderate yield of 37%.

In conclusion, we studied the scope of using phenylselenyl halides and hydrogen peroxide for the selective A-ring aromatization of substituted 19-nor steroids. It is also established that, this methodology is substituent independent and gave moderate to excellent yields of a variety of substituted estradiol derivatives.

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