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An efficient synthesis of 5α-androst-1-ene-3,17-dione

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ARTICLE INFO

Article history:
Received 23 May 2006
Received in revised form
14 August 2006
Accepted 22 September 2006

Keywords:
5α-Androst-1-ene-3,17-dione
Bromination
Dehydrobromination
Synthesis

ABSTRACT

5α-Androst-1-ene-3,17-dione (**5**) as a prodrug of 1-testosterone (**4**) was prepared in four steps from 17β-Acetoxy-5α-androstan-3-one (stanolone acetate) (**1**) in high yield. Thus, stanolone acetate (**1**) was brominated in the presence of hydrogen chloride in acetic acid to give 17β-acetoxy-2-bromo-5α-androstan-3-one (**2**), which underwent dehydrobromination using lithium carbonate as base with lithium bromide as an additive to give 17β-acetoxy-5α-androst-1-en-3-one (**3**) in almost quantitative yield with 97% of purity. Compound (**3**) was hydrolyzed with sodium hydroxide to give 17β-hydroxy-5α-androst-1-en-3-one (4,1-testosterone), which was oxidized with chromium trioxide to afford 5α-androst-1-ene-3,17-dione (**5**). The overall yield of **5** was 78.2% with purity of 99%. In this method, the formation of 4-ene was diminished when 1-ene was introduced, and its mechanism was also discussed.

1. Introduction

5α-Androst-1-ene-3,17-dione (**5**), as a prodrug of 1-testosterone, can be converted to 17β-hydrxy-5α-androst-1-en-3-one (4,1-testosterone) in the body, which is an effective androgen [1]. The key step for synthesis of **5** is the formation of 1-ene. A few reports about the introduction of 1-ene have been described, either through bromination and dehydrobromination from 5α-androstane-3,17-dione [2] or stanolone acetate (**1**) [3], or via 1,2-dehydrogenating of 5α-androstane-3,17-dione by selenium compounds [4]. However, 4-ene formation was observed in previous bromination and dehydrobromination route, and the selenium routes also produced a mixture of 1-en-3-one, 1-chloro-2-en-3-one and 4-en-3-one besides selenium compounds are toxic agents themselves. Here, we reported a modified method using bromination and dehydrobromination to prepare the compound (**5**), in which the formation of 4-ene was diminished (Scheme 1).

2. Experimental

Mass spectrometry was carried out using a FINNIGAN MAT95XL spectrometer. High-pressure liquid chromatography was performed with column C_{18} on a HP1100-FINNIGAN LCQ (MeOH-H_2O grads system). ^1H NMR spectra was recorded on a BRUKER DPX 300 MHz spectrometer or a Mercury Plus 400 MHz spectrometer with TMS as an internal reference. Optical rotations were measured on a Horiba SEPA-200. All melting points were determined in open capillary tubes and are not corrected. Analytical thin layer chromatography was performed on Qingdao silica gel GF-254 precoated plates.

2.1. *17β-acetoxy-2-bromo-5α-androstan-3-one (2)*

To a mixture of **1** (57 g, 171.4 mmol) and hydrogen chloride (0.285 g) in acetic acid (399 ml), a solution of bromine (27.4 g, 171.5 mmol) in acetic acid (27.4 ml) was added dropwisely at 20–25 °C. The mixture was stirred for 1 h, and

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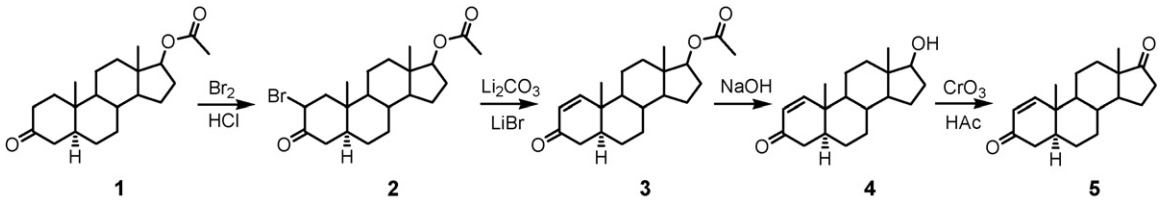
doi:10.1016/j.steroids.2006.09.008



Scheme 1 – Synthesis of 5α-androst-1-ene-3,17-dione (5) from stanolone acetate (1).

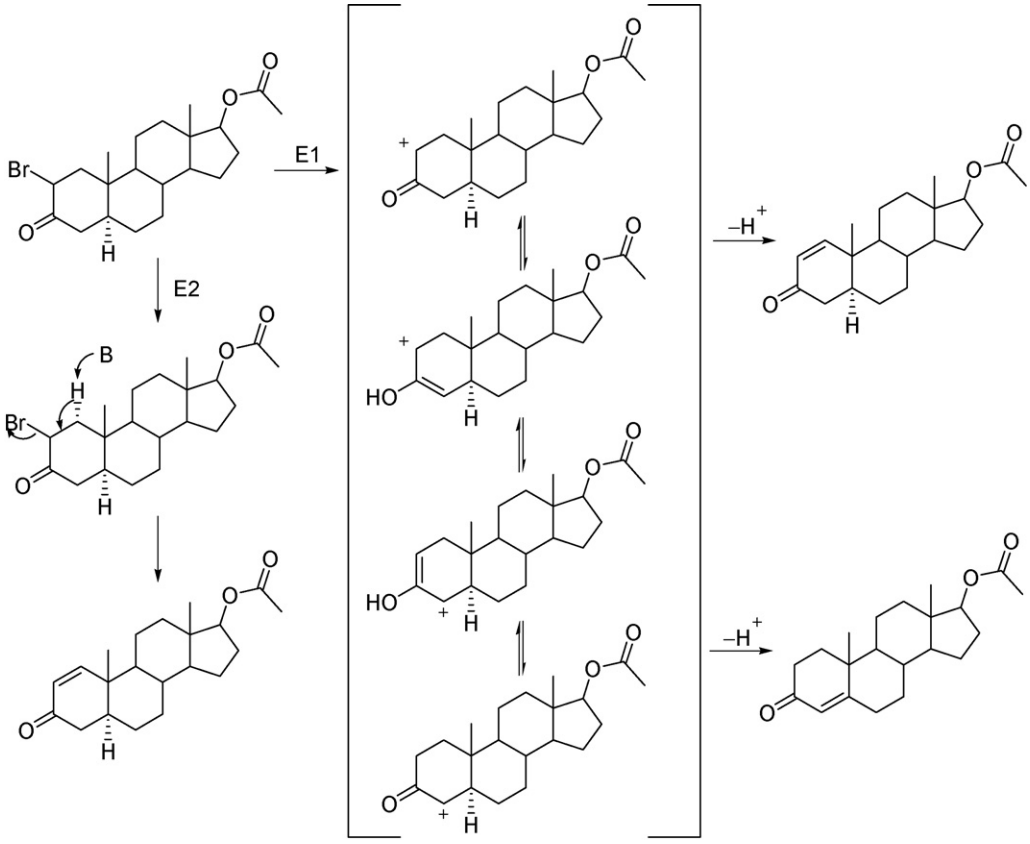
poured into water. The solid was collected by filtration, washed with water and dried to give **2** (62 g 88%). mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.81$ (s, 3H, C_{18}–CH_3), 1.10 (s, 3H, C_{19}–CH_3), 2.04 (s, 3H, 17–acetate–CH_3), 4.56–4.62 (dd, 1H, $J_1 = 7.80$ Hz, $J_2 = 9.09$, $C_{17\alpha}$–H), 4.72–4.79 (dd, 1H, $J_1 = 6.34$ Hz, $J_2 = 13.34$ Hz, C_2–H). IR(KCl): 1732.09, 1720.13 cm^{-1} ($\nu_{C_3,C_{acetate}=O}$).

2.2. 17β-acetoxy-5α-androst-1-en-3-one (3)

To a mixture of lithium bromide (31 g, 357 mmol) and lithium carbonate (31 g, 419.5 mmol) in *N*,*N*-dimethyl formaminde (1240 ml), **2** (62 g, 150.7 mmol) was added. The mixture was refluxed for 30 min, and poured into the solution of 10% hydrochloric acid (1500 ml). Resulting solid was filtered, washed with water till neutral, dried to give **3** (49.6 g, 99.6%). mp 123–126 °C; MS *m*/*z* 330 (M^+); UV (EtOH) λ_{max} (ε) = 229 nm (10,200). Purity 97% (HPLC). The crystals was recrystallizated with methanol to obtained the crystals: mp 127–129 °C. Lit[2] mp 125–130 °C. IR(KCl): 1729.53, 1684.69 cm^{-1} ($\nu_{C_{acetate},C_3=O}$).

2.3. 17β-hydroxy-5α-androst-1-en-3-one (4)

To a solution of sodium hydroxide (6.61 g, 165.3 mmol) in methanol (744 ml), **3** (49.6 g, 150.1 mmol) was added. The mixture was stirred at room temperature for 2 h, neutralized with acetic acid, concentrated under reduced pressure and poured into ice water. Resultant crystals were filtered, washed with water, dried to give **4** (43.2 g, 99.8%). mp 150–151 °C; MS *m*/*z* 288 (M^+); $[\alpha]_D^{25} = +54.5°$ (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.78$ (s, 3H, C_{18}–CH_3), 1.03 (s, 3H, C_{19}–CH_3), 3.66 (t, 1H, $C_{17\alpha}$–H, $J = 8$ Hz), 5.85 (d, 1H, C_2–H, $J = 10$ Hz), 7.15 (d, 1H, C_1–H, $J = 10$ Hz). Lit[5] mp 156–157 °C; ^{1}H NMR ($CDCl_3$) $\delta = 0.79$ (s, 3H, C_{18}–CH_3), 1.02 (s, 3H, C_{19}–CH_3), 3.64 (t, 1H, $C_{17\alpha}$–H, $J = 8$ Hz), 5.85 (d, 1H, C2–H, $J = 10$ Hz), 7.12 (d, 1H, C1–H, $J = 10$ Hz). IR(KCl): 3425.21 cm^{-1} (ν_{O-H}), 1668.35 cm^{-1} ($\nu_{C3=O}$).



Scheme 2 – The mechanism of dehydrobromination.

Table 1 – The conditions and results of dehydrobromination

Entry	Base[a]	Br^{-}[a]	Ratio of 1-ene[b] (%)	Ratio of 4-ene[b] (%)
1	Li_2CO_3	LiBr	97	1
2	Li_2CO_3	–	91	7
3	$CaCO_3 + 4\%H_2O$	LiBr	94	4
4	$CaCO_3$	NaBr	61	37
5	$CaCO_3$	–	53	45

The reaction substrate was the compound (**3**) using the same batch.

[a] The quantities of carbonate and bromide were 2.78 and 2.38 mol to 1 mol of **3**.

[b] The ratio was measured by HPLC.

2.4. *5α-androst-1-ene-3,17-dione (5)*

To a solution of **4** (43.2 g, 149.8 mmol) in acetic acid (432 ml), a solution of chromium trioxide (17 g, 170.0 mmol) in water (17 ml) was added slowly with stirring. The reaction mixture was stirred at 25–30 °C for 1 h, poured into a solution of sodium sulfite in ice water (2000 ml). Resultant crystals were filtered, washed with water, dried to obtain **5** (42.7 g) (crude). Then, the crude was recrystallized from ethyl acetate to form **5** (38.4 g, 88.9%). mp 139.5–140.5 °C; MS *m/z* 286 (M^+); $[\alpha]_D^{25} = +140°$ (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 0.91$ (s, 3H, C_{18}–CH_3), 1.04 (s, 3H, C_{19}–CH_3), 5.87 (d, 1H, C_2–H, $J = 10$ Hz), 7.13 (d, 1H, C_1–H, $J = 10$ Hz). Lit[4] mp 139–140 °C; ^1H NMR ($CDCl_3$) $\delta = 0.91$ (s, 3H), 1.05 (s, 3H), 5.86 (d, 1H, $J = 10$ Hz), 7.12 (d, 1H, $J = 10$ Hz). IR(KCl): 1739.52 and 1671.92 cm^{-1} ($\nu_{C_{17},C=O}$).

3. Results and discussion

In the synthesis of 5α-androst-1-ene-3,17-dione (**5**) from stanolone acetate (**1**), the key step is the introduction of 1-ene moiety. We chose the bromination and dehydrobromination route in this study.

Typically, the dehydrobromination at 4,5-position proceeded more easily than at 1,2-position, likely because the intermediate tertiary cation is more stable than the corresponding secondary cation, and/or the resultant 4-ene product is chemically more stable than it 1-ene product. The formation pathway of these two regioisomers involved E1 mechanism proceeding through either a direct elimination of proton or sequential 1,3-proton transfer (or hydride shift) before elimination as highlighted in Scheme 2.

We believed that if we could somehow inhibit the formation of carbonium ion, an important intermediate for the E1 elimination, by careful selection of reaction conditions to force the elimination go through E2 pathway (Scheme 2), the formation of 4-ene regioisomer could be diminished.

Previous dehydrobromination studies suggested that basic conditions such as sodium carbonate, 2-methyl pyridine, 2,4,6-trimethyl pyridine, etc., could facilitated the E1-elimination pathway to give a mixture of 1-ene and 4-ene regioisomers [6,7].

Based on our previous experience in the elimination of the related 2,4-dibromo compounds [8], we hypothesized that increasing the basicity of the reaction system via addition of soluble bromide salts as additives could facilitated the E2 pathway and thus diminished the by-products. Thus, we compared the effect of lithium carbonate and calcium carbonate with and without the corresponding additive lithium bromide and sodium bromide. The results are summarized in Table 1.

It is interesting to note that the best condition seemed to be of lithium carbonate as base ab lithium bromide as an additive (entry **1** in Table 1). The yield was almost quantitative and the conversion of 1-ene compound reached to 97%, comparing to sodium carbonate as base with no additive (entry **5** in Table 1) in which substantial amount of 4-ene regioisomer (45%) was obtained.

In summary, 5α-androst-1-ene-3,17-dione (**5**) was prepared by bromination, dehydrobromination, hydrolysis and oxidation from stanolone acetate (**1**) in high yield. This route might be suitable for industrial scale synthesis.

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