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Thermodynamic Meerwein-Ponndorf-Verley reduction in the diastereoselective synthesis of 17α-estradiol

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ABSTRACT

The synthesis of 17α-hydroxy steroids generally requires multiple synthetic manipulations. The synthesis of 17α-estradiol is no exception, as this process involves the protection and release of the 3-hydroxy functional group. The diastereoselective reduction of the 17-keto-steroid can be utilized to prepare 17α-hydroxy-steroids. Here, 17α-estradiol was synthesized from commercially available estrone under thermodynamic Meerwein-Ponndorf-Verley (MPV) conditions in a single step, followed by simple chromatographic separation over silica gel. The remaining mixture of unreacted estrone and estradiols was easily recycled through Oppenauer oxidation to estrone, with an overall yield of 68% 17α-estradiol.

1. Introduction

Estrogens are prescribed for hormone replacement therapy to manage menopausal symptoms, such as hot flashes and vaginal dryness, and these hormones have also been used for the prevention of osteoporosis [1–4]. A commonly used estrogen drug, Premarin™, contains approximately ten different biologically active estrogens [5], including estrone (**2**), 17β-estradiol (**3**) and 17α-estradiol (**1**). The estrogen molecule 17α-estradiol exhibits potential activity in menopause management and also shows a beneficial influence on the central nervous system [6]. The synthesis of 17α-hydroxy steroids is challenging, and most efforts have been devoted to the inversion of 17β-hydroxy steroids through Mitsunobu reactions [7,8] and the displacement of sulfonyl ester [9–12]. Both of these methods involve multiple steps, including the protection and removal of the protecting group using expensive or custom-synthesized reagents. Thus, a cheap, quick and economical method to manufacture large quantities of 17α-estradiol is needed. Herein, we report the one-step synthesis of 17α-estradiol from readily available estrone (**2**) through the reduction of the 17-carbonyl steroid using aluminum alkoxides (MPV reduction) [13–15] at an elevated temperature, in contrast to the inversion of the hydroxyl function. The use of aluminum isopropoxide has previously been reported for the reduction of estrone methyl ether [16] under kinetic conditions with modest yield and no stereochemical outcome (see Fig. 1).

2. Experimental methods

2.1. General methods

The nuclear magnetic resonance spectra were recorded on a Bruker ARX (300 MHz) spectrometer using deuterochloroform ($CDCl_3$) solutions and tetramethylsilane (TMS) as an internal standard (δ = 0), unless otherwise noted. High-performance liquid chromatography was performed on a Waters Alliance 2695 System with photodiode array (model 2996) on a Waters XTerra® RP_{18} column (3.5 μm, 4.6 × 150 mm). "Flash column" chromatography was performed on 32–64 μM silica gel (EM Science, Gibbstown, NJ). Thin-layer chromatography (TLC) was performed 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. 17α-Estradiol was purchased from Aldrich Chemical Company (Milwaukee, WI), 17β-estradiol was purchased from Berlichem Inc. (Wayne, NJ), estrone was purchased from Spectrum Chemical MFG Corp. (New Jersey) and aluminum isopropoxide and aluminum s-butoxide were purchased from Strem Chemicals Inc. (Newburyport, MA). All known products were compared with the corresponding authentic samples and reported spectroscopic data.

2.2. Synthesis

2.2.1. 17α-Estradiol (*1*)

Estrone (100 g) was added to the solution in an oven-dried 5-L four-necked RBF fitted with a mechanical stirrer and a condenser

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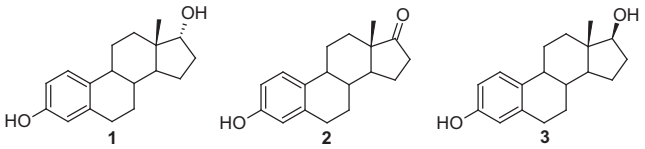

Fig. 1. Estrogens: 17α-estradiol (**1**), estrone (**2**) and 17β-estradiol (**3**).

under nitrogen, followed by the addition of 2-methyltetrahydrofuran (1.0 L) and 2-pentanol (80 mL, 2.0 eq.). This clear mixture was heated to reflux, and subsequently, aluminum s-butoxide (225 g, 2.47 eq.) was added using a Teflon tube cannula (5 mm wide) over 20 min at reflux. The reaction was refluxed for 18 hours with stirring, cooling to room temperature, and further cooling on an ice bath prior to quenching with 20% aq. sodium hydrogen sulfate hydrate (400 g in 2.0 L water, pH 2–3), dilution with ethyl acetate (1.0 L) and stirring for 30 min to dissolve the solids. The pH of the aqueous layer was 4. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (1 L). The combined organic layers were dried (sodium sulfate) and concentrated, and the crude was further dried on a vacuum pump overnight. The crude HPLC analysis showed a 45:55 α/β estradiol ratio from 4% estrone starting material. The mass of the crude product was approximately 110 g (110%).

The crude product was dissolved in THF (1 L), adsorbed on silica gel (400 g, 4 g silica gel per gram of estrone) and dried under vacuum. The large column containing 2.5 kg of silica gel was equilibrated with DCM (12 L), the adsorbed crude product was loaded, and sand was subsequently placed on top of the column. The analysis was run with the following solvents: (1) 6 L DCM, (2) 4 L 3% THF in DCM, (3) 4 L 4% THF in DCM, (4) 4 L 5% THF in DCM, and (5) 12 L 6% THF in DCM. The 500-mL fractions were collected, and the concentration of the fractions yielded 17α-estradiol as a white solid **1** (23.5 g, 99+%, mp 221.0–221.5 °C (lit. 219–222 °C [17]), $[\alpha]_D^{21}$ + 52.8 (c = 1.06, dioxane) (lit. +52.9U ± 1 (c = 0.9%, dioxane) [18])), estrone **2** (2.0 g) and a mixture of 17α/β-estradiol (74 g, 1:4 α:β).

*2.2.2. Estrone (**2**)*

The estradiols (mixture of α/β; 74 g, 1 eq.) were initially dissolved in 2-methyltetrahydrofuran (390 mL) at room temperature under nitrogen with stirring. Benzaldehyde (83.6 g, 2.9 eq.) and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT, 1.5 g, 0.025 eq.) were added and dissolved. Aluminum isopropoxide (27.7 g, 0.5 eq.) was subsequently added, and the resulting light brown solution/slurry was stirred for 4 h at an ambient temperature. The crude HPLC analysis showed 95% conversion. The reaction was quenched with aq. sodium hydrogen sulfate (70 g in 1 L water) and extracted with ethyl acetate (2 × 400 mL). The combined organic layer was dried over sodium sulfate and subsequently filtered and concentrated. The HPLC analysis showed 95% yield of the desired product **1**. The residue was dissolved in DCM (100 mL) and triturated with hexanes (700 mL); the white product was collected on filter paper and washed with hexanes (3 × 40 mL) to yield 43.3 g estrone **2** (58%). Additional product was observed in the mother liquor, which required recrystallization or further chromatography. The excess benzaldehyde and benzyl alcohol formed during the reaction reduced the recrystallization of the product (see Scheme 1).

3. Results and discussion

Traditional reducing agents, such as sodium borohydride and lithium aluminum hydride, were initially employed at ambient temperature to monitor the scope of the diastereospecificity in the direct reduction of estrone to estradiol (Table 1). Previous studies and entries 1 and 2 showed that under kinetic reaction conditions, 17β-estradiol is predominantly produced from the less steric alpha face of estrone after the addition of hydride. A modest yield of 17α-estradiol was encouraging (entry 3) when sodium borohydride was added to the reaction after refluxing estrone in isopropanol, suggesting that the use of a suitable reducing agent under thermodynamic conditions results in the formation of a 17α-estradiol/17β-estradiol mixture directly from estrone with an excellent yield. With the increasing popularity of modern separation techniques, such as HPLC, one-step synthesis followed by chromatographic separation could represent an attractive alternative to tedious and low-yield stereoselective synthesis.

To examine this hypothesis, we utilized the Meerwein-Ponndorf-Verley (MPV) reduction, which generally employs aluminum isopropoxide for the chemoselective reduction of aldehydes and ketones to alcohols [13–15]. The addition of aluminum isopropoxide (0.5 eq.) to refluxing estrone in isopropanol resulted in a 3:7 α/β ratio of 17-hydroxy-estradiol (entry 4), with only 7% conversion. The increase in the α/β ratio after hydride addition was a promising outcome, although the conversion was low, and the low conversion was subsequently addressed using various stoichiometric quantities of the reducing agent (entries 5, 6, and 7). The best yield (83%) was achieved using toluene as a solvent, which boils at a higher temperature (110 °C) than isopropanol (82 °C), with a product ratio of 1/3 in favor of 17α-estradiol (entry 7).

It was evident that running this reaction under thermodynamic MPV conditions with increasing reaction temperature is beneficial for the reaction yields and desired product ratios. Acetone was produced during the reaction with aluminum isopropoxide, which decreased the internal reaction temperature to a value lower than the solvent boiling temperature, resulting in lower yields and product ratios. Next, aluminum s-butoxide was examined as a reducing agent (entry 8), resulting in 83% conversion, with 44% desired product. Notably, this reaction produced butanone, which has a higher boiling point than acetone. The use of excess reducing agent improved the conversion but did not affect the product ratio (entry 10), and the use of higher boiling solvents, such as xylenes, also increased the product yield to 99% but did not influence the product ratio (entry 11). Notably, simple silica gel chromatography is sufficient to separate the two diastereoisomers of this estradiol.

Once the conditions were optimized, the large-scale synthesis of 17α-estradiol was initiated with 100 g of estrone according to the conditions in entry 10. Surprisingly, a solid precipitate was formed within a few minutes after the addition of aluminum s-butoxide with solvent, which separated, and mechanical stirring, which stopped working. We assumed that the unprotected 3-hydoxyl and 17-hydroxyl of the newly produced estradiols formed oxygen-aluminum-oxygen bonds (insoluble solid polymer), causing the mechanical stirrer to fail. Even with no stirring, similar reaction products were obtained, but on a smaller scale. For further optimization, we used 2-methyltetrahydrofuran, a more polar solvent than toluene, and a higher-boiling additive co-solvent, 2-pentanol, which disrupts the formation of the polymer. Under these conditions, the large-scale reaction with 100 g of estrone was successful, without stirring failure. The crude HPLC analysis showed a 45:55 α/β estradiol ratio using 4% estrone starting material. The purification of the crude residue under regular silica gel chromatography resulted in a 23.5% yield using estrone (2%) and a mixture of estradiols (74%). We propose that improving chromatographic techniques would yield even higher amounts of 17α-estradiol from this reaction.

The mixture of estradiols, predominantly 17β-estradiol, can be recycled back to estrone under Oppenauer oxidation conditions with benzaldehyde as the sacrificial oxidant instead of acetone. Thus, the estradiols were treated with aluminum isopropoxide in