Pergamon

Tetrahedron Letters 41 (2000) 8089–8092

TETRAHEDRON LETTERS

Synthesis of 17α-4-amino- and 4-iodophenylestradiols

Nicolas Foy, Elie Stéphan* and Gérard Jaouen

Laboratoire de chimie organométallique-Ecole Nationale Supérieure de Chimie et CNRS, 11 rue Pierre et Marie Curie, 75005 Paris, France

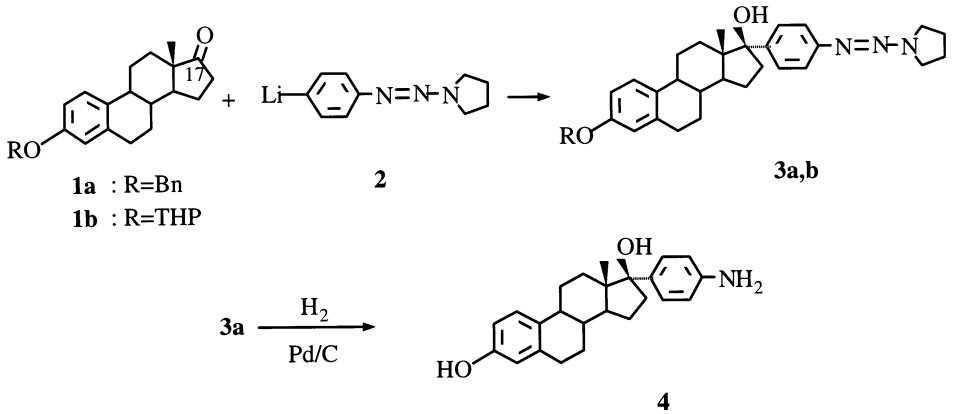
Received 15 June 2000; accepted 21 July 2000

Abstract

17α-(4-aminophenyl) estradiol **4** was prepared in three steps starting from commercial estrone. The key step is the addition of aryllithium **2** to the carbonyl at C17 on a protected estrone, which is only possible by activation. The adduct **3b** can be transformed into 17α-(4-iodophenyl) estradiol **7** by a Sandmeyer-type reaction with concomitant deprotection.

Keywords: arylation; biologically active compounds; lithiation; steroids; triazenes.

We have recently proposed a method to obtain 17α-arylestradiols in yields of 55–80% by the addition of aryllithiums to a protected estrone at the sterically hindered C17 carbonyl, in the presence of BF_3–Et_2O at low temperature.[1] A rigid structure of the arene type in the 17α position does not negatively affect estrogen hormone-receptor recognition[2] and we were particularly interested in preparing compounds substituted on the aromatic ring by amino and iodo functionalities, which are widely used in coupling and bioconjugation reactions.[3] The present study concerns first of all the synthesis of 17α-(4-aminophenyl)-estradiol **4** (Scheme 1),



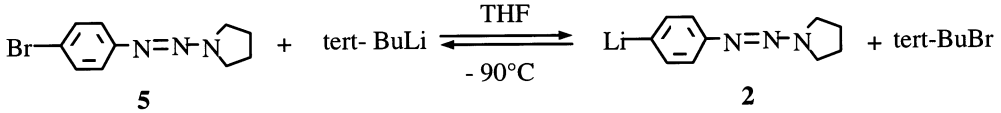
Scheme 1.

* Corresponding author. E-mail: stephan@ext.jussieu.fr

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01238-7

in three steps starting from commercial estrone. We now describe herein the efficient addition of aryllithium **2** to protected estrones **1**, in the presence of TMEDA at low temperature. The product **3a** gives estradiol **4** directly, by deprotecting both the phenol and the amine, in one step.

The synthesis of the aryllithium **2** has been described earlier by Gross.[4] This synthesis uses a halogen–metal exchange during the reaction of the bromo compound **5**, the latter being accessible in one step starting from 4-bromoaniline, with an excess of *sec*-BuLi (2.2 equiv.), in ether at −65°C (Scheme 2). We were constrained by the solubility of the steroids to use either THF or mixtures of solvents (such as THF or ether+toluene). Faced with reproducibility problems for the addition of the organo-lithium **2** prepared from *sec*-BuLi, we studied the exchange with *tert*-BuLi in an attempt to perturb the equilibrium with 2-*tert*-BuLi, according to Corey[5] and Seebach.[6]



Scheme 2.

The exchange shown in Scheme 2 occurs satisfactorily with one equivalent of *tert*-BuLi, as shown by the ^{1}H NMR spectrum of the crude reaction product obtained after treatment of the medium with D_2O (D incorporated *para* to the hydrogen). Using an excess of alkyllithium (2 equiv.) however gives a low rate of incorporation of D into the same position, and leads to side reactions.

The protected estrones **1a** and **1b** are easily prepared by standard methods. Estrone benzyl ether (EBE)[7], prepared by reaction of its conjugated base (estrone+1 equiv. KOH) with BnBr (1 equiv.) at room temperature for 24 h in a dioxane/water (90/10) medium, is obtained in a yield of 88% after crystallization from ether. Tetrahydropyranyl estrone[8] is obtained in a yield of 80% after recrystallization from methanol.

Aryllithium **2** does not react with the estrones **1** unless activated. Activation of aryllithiums for addition onto the carbonyl of EBE was previously achieved using boron trifluoride, and with aryllithium **2** the adduct was obtained in 57% yield.[1] We also tested the activation by tetramethylethylenediamine, which gives a comparable yield of 60% (with 3 equiv. TMEDA per *tert*-BuLi). The procedure below describes the results obtained under optimal conditions.

Triazene **5** (2.57 g, 10.1 mmol) was dissolved in 150 mL anhydrous THF under an argon atmosphere. The medium was cooled to −90°C, then 10.1 mmol *tert*-BuLi (commercial solution in pentane) were added drop-wise while stirring. The reaction medium was stirred at −90°C for 3.5 h. TMEDA (4.57 mL, 30.3 mmol) was then added, followed by progressive addition of a solution of 1.3 g estrone benzyl ether (3.6 mmol) in 100 mL THF. Stirring was continued for 1.5 h at low temperature before hydrolysis. The THF was evaporated and the reaction medium extracted with dichloromethane. The crude product obtained after normal treatment was then chromatographed on a neutral alumina column using dichloromethane as an eluent. After evaporation of the solvent, 1.1 g estradiol **3a** was obtained as a solid (m.p. 134°C) in 60% yield. ^{1}H NMR (ppm) in $CDCl_3$: 7.4 (m, H arom.); 7.06 (1H, d, H-1); 6.72 (2H, m, H-2 and H-4); 5.02 (2H, s, CH_2–Ph); 3.8 (4H, m, CH_2–N); 1.08 (3H, s, CH_3-18).

The estradiol **3b** was prepared (and purified) under similar conditions, starting from estrone **1b**. Compound **3b** was obtained in 57% yield after chromatography (solid, m.p. 118°C).

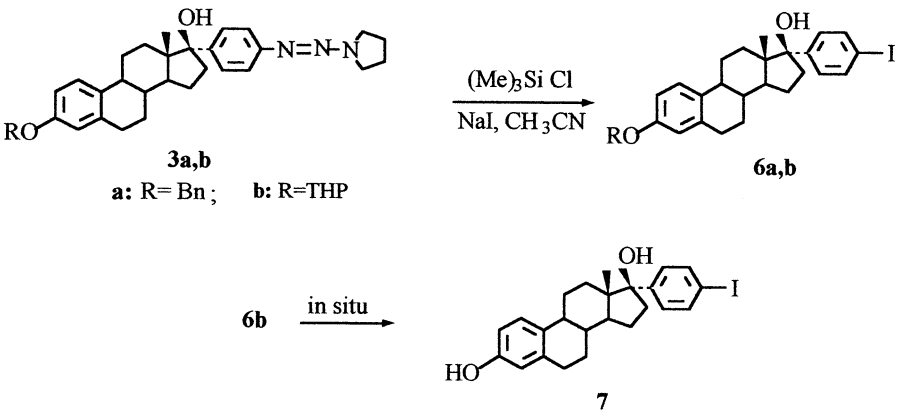
^{1}H NMR (ppm) in $CDCl_3$: 7.38 (m, H arom.), 7.08 (d, H-1), 6.79 (m, H-2 and H-4), 5.37 (m, O–CH–O), 3.8 (m, CH_2–N), 1.08 (s, CH_3-18).

Use of an Ni–Al alloy[9] has been proposed for reduction of triazenes to amines. Therefore hydrogenolysis of the triazene **3a** in the presence of an Ni–Al alloy was tested, however, this did not give satisfactory results in various solvents. The estradiol **4** was prepared by hydrogenation of **3a** in the presence of palladium on charcoal. Simultaneous debenzylation and reduction of the triazene function to amine was observed in the methanol–THF solution.

Steroid **3a** (0.13 g, 0.24 mmol) was dissolved in a mixture of methanol (10 mL) and THF (3 mL). Pd/C at 10% (0.13 g) was added and the medium hydrogenated under atmospheric pressure for 21 h. After filtration and evaporation of the solvents, the estradiol **4**, crystallized from a THF/pentane mixture, was obtained in a 67% yield. This is a solid (m.p. = 220°C) with low solubility in various solvents. ^{1}H NMR (ppm) in CD_3OD: 7.14 (d, H *meta* to NH_2), 7.0 (d, H-1), 6.70 (d, H *ortho* to NH_2), 6.44 (m, H-2 and H-4), 1.05 (s, CH_3-18).

Hydrogenation of **3a** was also carried out in the presence of $PdCl_2(CH_3CN)_2$, in ethanol/ethyl acetate (50/50; v/v). The triazene was then reduced selectively since the 3-*O*-benzyl ether of 17α-(4-aminophenyl) estradiol precipitated in this medium.

Barrio has previously described the halogenation of 1-aryl-3,3-dialkyltriazenes either in an acid medium[10] or in the presence of trimethylsilyl halides.[11] The second method was applied to the steroids **3** in order to obtain the 4-iodophenylated compounds **6** (Scheme 3).



Scheme 3.

The reaction shown above was first carried out with benzylated triazene. The estradiol formed, **6a** has a great tendency to dehydrate with heating. The dehydration can be limited at room temperature, and **6a** was thus obtained in 75% yield after purification by chromatography on a neutral alumina column.

Hydrogenolysis of the 3-*O*-benzyl ether of **6a** was difficult and deprotection by ethanethiol in the presence of BF_3–etherate[12] caused side reactions. The reaction shown in Scheme 3 was therefore carried out with the tetrahydropyranylated steroid **3b**. The Sandmeyer-type reaction is accompanied by deprotection of the phenol function in situ. In this way 17α-(4-iodophenyl)estradiol was prepared directly from **3b** according to the following method:

NaI (0.19 g, 1.26 mmol) was dissolved under an argon atmosphere in 1.5 mL acetonitrile, previously dried on a 4 Å filter. TMS–Cl (0.080 mL, 0.63 mmol) was added and the solution stirred at room temperature for several minutes. A solution of the steroid **3b** (0.15 g, 0.28 mmol) in 9 mL acetonitrile was then added and the mixture stirred for 17 h. After hydrolysis (saturated $NaHCO_3$) and evaporation of the acetonitrile, the residue was extracted with dichloromethane. After the usual treatment, the estradiol **7** was obtained as a solid (m.p.>300°C) in 90% yield.

^{1}H NMR (ppm) in DMSO-d_6: 8,9 (s, OH), 7.65 (d, H *ortho* to I), 7.15 (d, H *meta* to I), 6.89 (d, H-1), 6.4 (m, H-4), 0.95 (s, CH_3-18).

In summary, two new 17α-arylestradiols, **4** and **7**, have been prepared in three steps starting from commercial estrone. The key step is the condensation of a protected 4-lithioaniline onto a protected estrone, either in the presence of BF_3–Et_2O[1], or TMEDA as shown here. The intermediate triazene can be reduced to an amine or undergo a Sandmeyer-type reaction which permits access to a 4-iodophenylated estradiol at the 17 position. The compounds **3** undergo a Sandmeyer-type reaction with trimethylsilyl iodide to give 4-iodophenylated estradiols **6** (Scheme 3). 17α-(4-Iodophenyl) estradiol **7** is obtained by reaction of the tetrahydropyranylated compound **3b** with TMSI prepared in situ by reacting trimethylsilyl chloride with NaI. This synthesis therefore opens the way to the preparation of an estradiol **7** containing radioactive iodine, which, using isotopes such as ^{125}I or ^{131}I,[11] could be a good candidate for use as a readily-accessible radiopharmaceutical. To our knowledge, estradiols **4** and **7** have not been previously described in the literature. Measurements of biological affinity of the newly prepared estradiols for estradiol receptors are underway.

References

1. Stephan, E.; Affergan, T.; Weber, P.; Jaouen, G. *Tetrahedron Lett*. **1998**, *39*, 9427–9430.
2. Top, S.; El Hafa, H.; Vessières, A.; Quivy, J.; Vaissermann, J.; Hugues, D. W.; Mc Glinchey, M. J.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc*. **1995**, *117*, 8372–8380.
3. Arterburn, J. B.; Rao, K. V.; Perry, M. C. *Angew. Chem., Int. Ed*. **2000**, *39*, 771–772.
4. Gross, M. L.; Blank, D. H.; Welch, W. M. *J. Org. Chem*. **1993**, *58*, 2104–2109.
5. Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc*. **1972**, *94*, 7210–7211.
6. Seebach, D.; Neumann, H. *Chem. Ber*. **1974**, *107*, 847–853.
7. De Riccardis, F.; Meo, D.; Izzo, I.; Di Filippo, M.; Casapullo, A. *Eur. J. Org. Chem*. **1998**, 1965–1970.
8. Boucheau, V.; Renaud, M.; Rolland de Ravel, M.; Mappus, E.; Cuilleron, C. Y. *Steroids* **1990**, *55*, 209–221.
9. Lunn, G.; Sansone, E. B.; Keefer, L. K. *Synthesis* **1985**, 1104–1108.
10. Barrio, J. R.; Satyamurthy, N.; Ku, H.; Phelps, M. E. *J. Chem. Soc., Chem. Commun*. **1983**, 443–444.
11. Ku, H.; Barrio, J. R. *J. Org. Chem*. **1981**, *46*, 5239–5241.
12. Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem*. **1979**, *44*, 1661–1664.