Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2847–2849

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of Nitrile Derivatives of Estrogens

Hasrat Ali and Johan E. van Lier*

CIHR Group in the Radiation Sciences, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada J1H 5N4

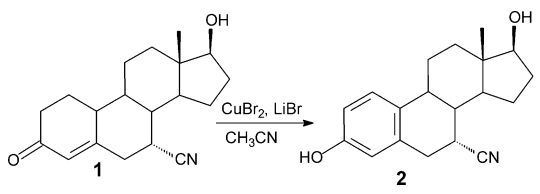
Received 21 June 2002; accepted 18 July 2002

Abstract—The first time synthesis of 7α- and 11β-nitrile estradiol is described. Reaction of 7α-cyano-19-nortestosterone with copper(II) bromide in acetonitrile at room temperature results in aromatization of the A-ring. Treatment of 11β-cyano-19-nortestosterone-17-one under similar condition does not induce A-ring aromatization but rather results in bromination at the 2β-position. However A-ring aromatized products are obtained when the latter compound is treated with Ac_2O-Py-AcOCl, NBS and HCl.

As a part of our investigation on new specific ligands for targeted radiotherapy and/or nuclear imaging of estrogen receptor (ER) rich tissues[1] we became interested in the synthesis of estradiol derivatives featuring a nitrile group at either the 7α- or 11β-position of estradiol. 7α-Substituted estradiol derivatives are a class of compounds of considerable pharmaceutical interest. Addition of a 7α-methyl group has been used to enhance receptor binding affinity and tissue specificity of estradiol derivatives designed as radiotracer for the imaging of ER positive breast tumors.[2] A number of estradiol derivatives substituted with a long aliphatic chain at the 7α-position exhibit pure antiestrogenic activity.[3] Likewise, 11β-substitution of estrogens provides a very potent class of hormone analogues. The ER is remarkably tolerant for relatively large substituents at the 11β-position. Overall, 11β-substitution imparts good binding affinity to ER, increases the stability of the ER-steroid complex while reducing nonspecific binding resulting in enhanced uptake by ER-rich target tissues.[4]

The starting material 7α-cyano-19-nortestosterone (**1**) was obtained from the known 4,6-estradien-17β-ol-3-one.[5] Reacting the latter with diethylaluminum cyanide[6] in THF introduces a cyano group selectively at the 7α-position to give **1** ($\lambda_{max} = 235$ nm; $\nu_{max} = 2240\,cm^{-1}$) in 77% yield. Three different methods for the A-ring aromatization of **1** to give 7α-cyano-estradiol (**2**) were evaluated. The first method consists of an oxidative aromatization of **1** using SeO_2 in *t*-butanol (25%).[7] The second method involves the conversion of **1** to its 3-enolacetate using Ac_2O-Py-AcOCl followed by treatment with *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) to give a 6-bromo derivative. Subsequent treatment with HCl in acetone followed by basic hydrolysis in 5% methanolic KOH yields **2** in 60%.[8] However, the best yield (80%) of **2** is obtained when the aromatization of **1** is carried out with copper(II) bromide and lithium bromide in acetonitrile at room temperature[9] (Scheme 1). Jones' oxidation of **2** in acetone provides a ketone at the C-17 position (80%), which on treatment with lithium acetylide ethylenediamine complex or lithium acetylide trimethylsilane followed by basic hydrolysis gives the 17α-ethynyl derivative (75%). Alternatively, the latter compound can also be obtained by treatment of 7α-cyano-19-nor-17α-ethynyltestosterone with copper(II) bromide and lithium bromide in acetonitrile at room temperature.

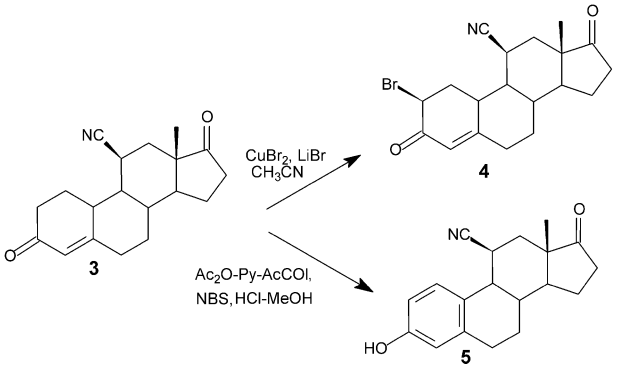
To prepare derivatives with the nitrile group at the 11β-position we started with the known nitrile **3**.[10] The latter is obtained as distereoisomers (α/β)cyano (1:3 ratio) by treatment of estr-5-ene-3,11,17-trione-3,17-bis(cyclic



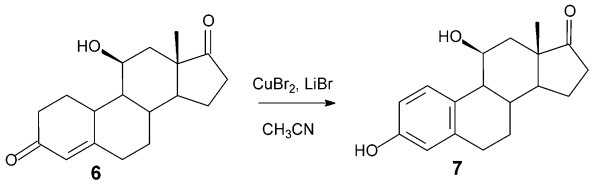
Scheme 1.

*Corresponding author. Tel.: +1-819-564-5409; fax: +1-819-564-5442; e-mail: johan.e.vanlier@usherbrooke.ca

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00634-0



Scheme 2.

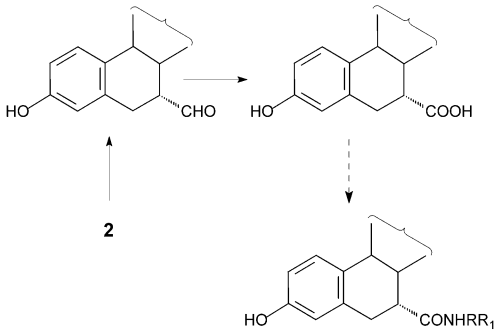


Scheme 3.

1,2- ethanediyl acetal) with tosylmethyl isocyanate in 1,2-dimethoxy ethane followed by deprotection of the acetal with dilute acid. The isomers were separated by chromatography. When the aromatization of **3** was attempted with copper(II) bromide and lithium bromide in acetonitrile at room temperature as described for **2**, one main product resulted featuring an electronic spectrum characteristic for the 4-en-3-one system.

The mass spectrum of this product showed peaks at *m/z* 357 and 359 of almost equal intensity corresponding to the presence of a bromine atom in the compound. The high resolution mass spectrum (HRMS) gave 375.0841 corresponding to the formula $C_{19}H_{22}BrNO_2$, that is structure **4**. The presence of the bromine atom at the axial C-2(β) was confirmed by the proton signal in the ^{1}H NMR spectrum at δ 5.03 as a triplet with $J = 2.9$ (Scheme 2). Prolonging the reaction time, changing the temperature or solvent, or varying the amount of the LiBr in the reaction mixture did not give the desired aromatic product but either unreacted starting material or side products. Initially, we assumed that the presence of an 11β-substituent prevented aromatization of the A-ring of 19-nor steroids. However, when we treated the 11β-hydroxy analogue **6** under the same conditions, the A-ring aromatized product **7** was obtained (Scheme 3). This indicates that the electron withdrawing capability of the 11β-substituent strongly affects the course of the reaction.

Alternatively, the synthesis of the 11β-nitrile **5** was achieved by converting **3** into the enol acetate in Ac_2O-Py-AcOCl and subsequently to the 6-bromo compound with NBS, following by treatment with HCl (40–50%). The assigned structure **5** was supported by the UV absorption maximum at 280 nm, which is characterstic for aromatic compounds, and the presence of characteristic peaks for the C-1, C-2 and C-4 protons at δ 6–6–7.2 in the ^{1}H NMR spectrum.[11] Treatment of **5** with lithium acetylide trimethylsilane followed by basic hydrolysis gave the 17α-ethynyl analogue.



Scheme 4.

In order to extend the use of nitrile groups for the attachment of different substituents such as the amide group, the cyano group was reduced with diethyl aluminum hydride to the aldehyde (67%). The aldehyde was oxidised to a carboxylic acid group, which can subsequently be used for coupling via an amide linkage to other desired functional groups (Scheme 4). Such modifications can include long-chain aliphatic chains to yield pure antiestrogenic drugs.

In conclusion, we have reported a convenient method for the synthesis of 7α- and 11β-nitrile derivatives of estradiol. We also observed that aromatization of 19-nortestosterone to estradiol is strongly influenced by the nature of the substituent at the 11β-position.

Acknowledgements

This work was supported by the Canadian Institutes for Health Research grant no. MOP-37768.

References and Notes

1. (a) Gantchev, T. G.; Ali, H.; van Lier, J. E. *J. Med. Chem.* **1994**, *37*, 4164. (b) Nachar, O.; Rousseau, J.; Ouellet, R.; Rioux, A.; Lefebvre, B.; Ali, H.; van Lier, J. E. *J. Nucl. Med.* **2000**, *41*, 1324. (c) Seimbille, Y.; Ali, H.; van Lier, J. E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 657.
2. (a) Ali, H.; Rousseau, J.; Ghaffari, M. A.; van Lier, J. E. *J. Med. Chem.* **1991**, *34*, 854. (b) Ali, H.; Rousseau, J.; van Lier, J. E. *J. Med. Chem.* **1993**, *36*, 3061.
3. (a) Bowler, J.; Lilley, T. J.; Pittam, J. D.; Wakeling, A. E. *Steroids* **1989**, *54*, 71. (b) Wakeling, A. E.; Dukes, M.; Bowler, J. *Cancer Res.* **1991**, *51*, 3867.
4. Raynaud, J. P.; Ojasoo,T. In *Innovative Approaches in Drug Research*; Harms, A. F., Ed.; Elsevier: Amsterdam, 1986; p 47.
5. Bucourt, R.; Vignau, M.; Torelli, V.; Richard-Foy, H.; Getnet, C.; Seco-Millet, V.; Redeuith, G.; Baulieu, E.-E. *J. Biol. Chem.* **1978**, *253*, 8221.
6. Nagat, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4654.
7. Ali, H.; van Lier, J. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2485.
8. HPLC (55:45 MeOH/H_2O) $t_R = 15$ min; white crystalline solid (80%): recrystallized from methanol; mp 263–264 °C; $\lambda_{max} = 282$ nm; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 0.67 (s, 3H, 18-CH_3), 3.1–3.2 (m, 1H; 7β-H), 3.56 (t, 1H, $J = 7$ Hz; 17α-H),

4.58 (brs, 1H; OH), 6.45 (d, $J=2.5$ Hz, 1H, 4-CH), 6.58 (dd, $J=2.5$ and 8 Hz, 1H, 2-CH), 7.12 (d, $J=8$ Hz, 1H, 1-CH); MS m/z (rel inten) 297 (M^+, 100); HRMS 297.1729 calcd for $C_{19}H_{23}NO_2$. Found 297.1726.

9. Rao, P. N.; Cessaqc, J. W.; Kim, H. K. *Steroids* **1994**, *59*, 621.

10. Schwede, W.; Cleve, A.; Ottow, E.; Wiechert, W. *Tetrahedron Lett*. **1993**, *34*, 257.

11. HPLC (70:30 MeOH/H_2O) $t_R=10$ min; white crystalline solid (50%): recrystallized from methanol; mp 265 °C decom; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 0.77 (s, 3H, 18-CH_3), 2.65 (m, 1H; 11α-H), 6.56 (d, $J=2.6$ Hz, 1H, 4-CH), 6.62 (dd, $J=2.6$ and 8.4 Hz, 1H, 2-CH), 7.12 (d, $J=8.4$ Hz, 1H, 1-CH); MS m/z (rel int.) 295 (M^+, 100); HRMS 295.1572 calcd for $C_{19}H_{21}NO_2$. Found 295.1581.