Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3071–3073

TETRAHEDRON LETTERS

# An efficient synthesis of novel estrieno[2.3-*b*] and [3.4-*c*]pyrroles

Xuqing Zhang* and Zhihua Sui

*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 1000 Route 202, Box 300, Raritan, NJ 08869, USA*

Received 29 January 2003; revised 14 February 2003; accepted 24 February 2003

**Abstract**—An efficient protocol for the preparation of novel estrieno[2.3-*b*] and [3.4-*c*]pyrroles **1** and **2** using Pd(0)-catalyzed amination and Bischler indole synthesis is described. © 2003 Elsevier Science Ltd. All rights reserved.

Steroids bearing heterocycles fused to the A-ring of the steroid nucleus have been of pharmaceutical interest. There are a number of reports on the preparation of the steroids with the pyrazole, isoxazole or pyrimidine ring fused in the 2,3-position of the nucleus.[1] Many of these steroidal heterocycles have been found to possess potent biological activities, such as anti-microbial, anti-inflammatory hypotensive, hypocholesterolemic and diuretic activities.[2] An ongoing program in our laboratory is directed at the design and synthesis of novel estrogen receptor ligands for the treatment or prevention of disorders and diseases mediated by an estrogen receptor or as components of oral contraceptive regimens. In the course of our studies, we became interested in constructing novel estrieno[2.3-*b*] and [3.4-*c*]-pyrroles (**1** and **2** in Fig. 1) as targets to investigate the ability of the fused pyrrole group to function as a bioisostere of the phenol group of estradiol. Herein, we report a short and efficient synthetic pathway to regioisomers **1** and **2** through a Pd(0)-catalyzed amination–Bischler indole synthesis strategy.

The traditional transformation of estrone (**3**) into 3-aminoestrone (**5b**), a key intermediate for the preparation of **1** and **2**, is accomplished in three steps using either a Smiles[3] or Chapman-like[4] rearrangement in the key step. Since both of these pathways suffered from some drawbacks, such as high reaction temperature, long reaction time, poor yield and low product purity, it becomes desirable to develop a simple and efficient way to overcome these drawbacks. 3-Aminoestrone (**5b**) is a versatile precursor of a number of biologically active compounds containing nitrogen moiety. These *N*-containing compounds are found to exhibit a large spectrum of activities. During the last decade, the Pd(0)-catalyzed amination process has proven quite valuable because of the ease with which a variety of complicated *N*-containing heterocycles or carbocycles can be rapidly constructed in good yields utilizing mild reaction conditions.[5] Recently, Poirier and co-workers reported an efficient method for the preparation of 3-aminoestrone from estrone through a three-step sequence with a Pd(0)-catalyzed amination as the key reaction. [6] Given the distinct advantages of the Pd(0)-catalyzed amination reaction, we initiated our investigations by carrying out the transformation of phenol to aniline using the aryl triflate **4a** as the starting material (Scheme 1). Triflate **4a** was subjected to the standard Pd(0)-catalyzed amination condition [$Pd(OAc)_2$, BINAP, NaO-*t*-Bu in toluene 100°C, 24 h] using $BnNH_2$ as a $NH_2$ equivalent. However, the reaction resulted in very low yield of the desired aniline **5a** ($\sim$15%) with mostly recovering estrone (**3**), generated by the hydrolysis of the triflate **4a** under the alkaline reaction conditions. Due to the difficulty of handling a large scale reaction under strictly anhydrous conditions, we then abandoned the aryl triflates route in favor of the corresponding aryl nonaflates route.[7] These nonaflates, maintain the same chemical properties as aryl triflates but possess stronger stability toward base hydrolysis and are more reactive toward Pd(0)-insertion

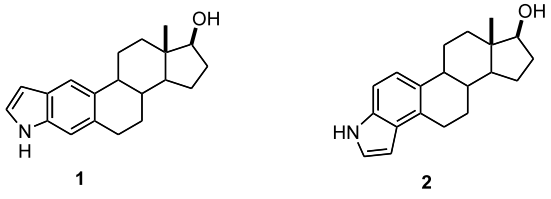
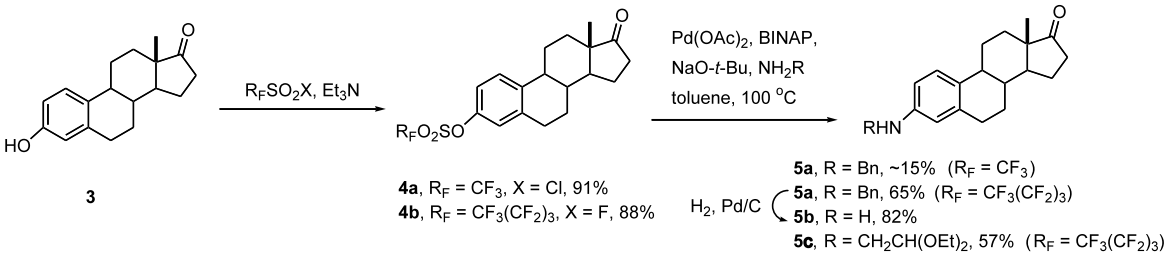


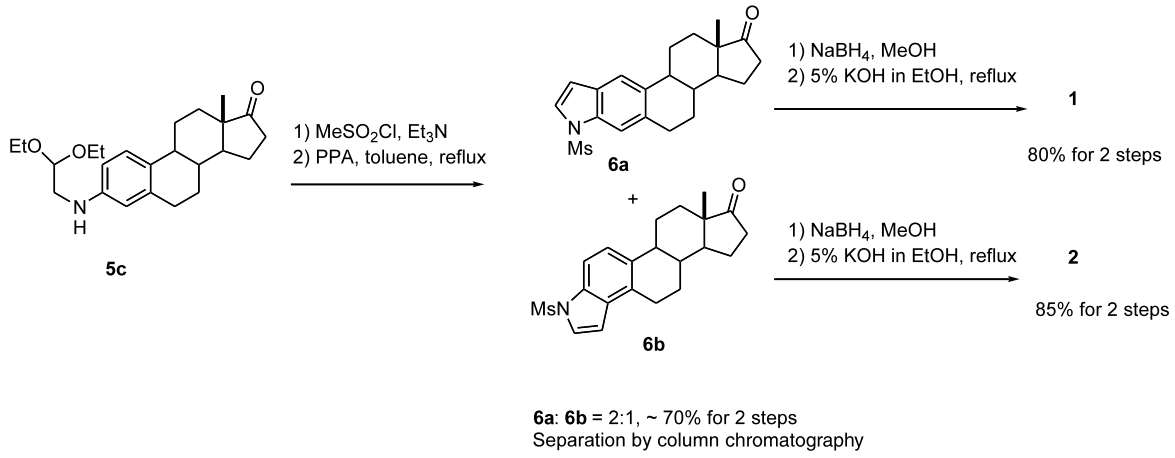

**Figure 1.**

* Corresponding author. Fax: +1-908-526-6469; e-mail: xzhang5@prdus.jnj.com

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)00541-0




**Scheme 1.**




**Scheme 2.**

due to their greater electron withdrawing capacity. Aryl nonaflate **4b** was readily prepared by the reaction of estrone (**3**) with commercially available $CF_3(CF_2)_3SO_2F$ in the presence of $Et_3N$ in 88% yield. Applying this strategy to our system, we were pleased to find that the nonaflate **4b** was smoothly transformed into the aniline **5a** in 65% yield without either starting material **4b** or the estrone (**3**) (Scheme 1). The reaction was conducted in toluene at 80–100°C for 2–6 h and could be readily scaled up to ~20 g without strictly anhydrous conditions. 3-Aminoestrone (**5b**) was then obtained by hydrogenation of the Bn protected aniline **5a** in 82% yield. In contrast to most previously described procedures, the present method allows lower temperatures, shorter reaction times and less strictly anhydrous solvents to 3-aminoestrone (**5b**) in good yield and high purity (>98% by HPLC).

With a reliable method to synthesis the 3-amino analogs of estrone secured, we turned our attention to the preparation of estrieno[2.3-*b*] and [3.4-*c*]pyrroles **1** and **2**. Bischler indole synthesis is a practical method for the synthesis of various substituted or unsubstituted indoles.[8] Applying our palladium-catalyzed amination of **4b** with $NH_2CH_2CH(OEt)_2$ as amine source afforded **5c** in 57% yield.[9] The aniline derivative **5c** was then protected as the sulfonamide and subjected to the acid-catalyzed Bischler condition (PPA, toluene, reflux, 1 h) to afford the protected estrieno[2.3-*b*]pyrrole **6a** and its regio-isomer [3.4-*c*]pyrrole **6b** in ~2:1 ratio (Scheme 2). The regio-isomers **6a** and **6b** could be easily separated by column chromatography and reduction of the separated isomers by $NaBH_4$ in MeOH at 0°C followed by deprotection of the sulfonamide by 5% KOH in EtOH afforded the final products estrieno[2.3-*b*]pyrrole **1** (80% for two steps) and estrieno[3.4-*c*]pyrrole **2** (85% for two steps).[10]

In conclusion, we have reported a mild, efficient and straightforward method for the synthesis of the estrieno[2.3-*b*] and [3.4-*c*]pyrroles, **1** and **2**. The Pd(0)-catalyzed amination utilizing the aryl nonaflates as the precursors provides a reliable way in the preparations of some pharmaceutically useful amino steroids.

## References

1. (a) Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Beyler, A. L.; Potts, G. O.; Arnold, A. *J. Am. Chem. Soc.* **1959**, *81*, 1513; (b) Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Neumann, H. C.; Christiansen, R. G.; Clarke, R. L.; Ackerman, J. H.; Page, D. F.; Dean, J. W.; Dickinson, W. B.; Carabateas, C. *J. Am. Chem. Soc.* **1961**, *83*, 1478; (c) Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Chrstiansen, R. G.; Beyler, A. L.; Potts, G. O.; Arnold, A. *J. Org. Chem.* **1961**, *26*, 279; (d) Ackerman, J. H.; Potts, G. O.; Beyler, A. L.; Clinton, R. O. *J. Med. Chem.* **1964**, *7*, 238; (e) Camoutsis, C. *J. Heterocyclic Chem.* **1996**, *33*, 539; (f) Laitonjam, W. S.; Rajkumar, T. S.; Chingakham, B. S. *Steroids* **2002**, *67*, 203.

2. (a) Hirschmann, R.; Buchschacher, P.; Steinberg, N. G.; Fried, J. H.; Ellis, R.; Kent, G. J.; Tischler, M. *J. Am. Chem. Soc.* **1964**, *86*, 1520; (b) Gupta, R.; Pathak, D.; Jindal, D. P. *Eur. J. Med. Chem.* **1996**, *31*, 241; (c) Manson, A. J.; Stonner, F. W.; Neumann, H. C.; Christiansen, R. G.; Clarke, R. L.; Ackerman, J. H.; Page, D. F.; Dean, J. W.; Phillips, D. K.; Potts, G. O.; Arnold, A.; Beyler, A. L.; Clinton, R. O. *J. Med. Chem.* **1963**, *6*, 1; (d) Wang, S.; Xie, F.; Song, K. *Chem. Abstr.* **1993**, *119*, 203669y; (e) Hirschmann, R.; Steinberg, N. G.; Buschacher, P.; Fried, J. H.; Kent, G. J.; Tishler, M. *J. Am. Chem. Soc.* **1963**, *85*, 120.
3. (a) Levi, A. A.; Rains, H. C.; Smiles, S. *J. Chem. Soc.* **1931**, 3264; (b) Evans, W. J.; Smiles, S. *J. Chem. Soc.* **1936**, 329; (c) Weidner, J. J.; Weintraub, P. M.; Schnettler, R. A.; Peet, N. P. *Tetrahedron* **1997**, *53*, 6303.
4. (a) Scherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1972**, *37*, 1681; (b) Morrow, D. F.; Butler, M. E. *J. Org. Chem.* **1964**, *29*, 1893; (c) Morrow, D. F.; Hofer, R. M. *J. Med. Chem.* **1966**, *9*, 249; (d) Conrow, R. B.; Bernstein, S. *Steroids* **1968**, *11*, 151.
5. (a) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367; (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413; (c) Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417; (d) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.
6. Radu, I.; Poirier, D.; Provencher, L. *Tetrahedron Lett.* **2002**, *43*, 7617.
7. Knochel, P.; Rottlander, M. *J. Org. Chem.* **1998**, *63*, 203.
8. Sundberg, R. J.; Laurino, J. P. *J. Org. Chem.* **1984**, *49*, 249.
9. *Typical procedure for Pd(0)-catalyzed amination of the aryl nonaflate—the preparation of* ***5c***. A three-necked flask was charged with $Pd(OAc)_2$ (0.655 mmol, 148 mg), BINAP (0.72 mmol, 432 mg) and NaO-*t*-Bu (45.86 mmol, 4.39 g). The reaction mixture was stirred in toluene (400 mL) for 10 min at 80°C. A mixture of $NH_2CH_2CH(OEt)_2$ (39.31 mmol, 5.72 mL) and **4b** (32.76 mmol, 18.0 g) in toluene (20 mL) was then slowly added dropwise via syringe to the reaction mixture. After addition, the mixture was heated at 80°C with stirring for 2 h. The reaction mixture was cooled to room temperature. $Et_2O$ and water were added and the solution was partitioned between $Et_2O$ and water. The $Et_2O$ layer was washed with brine, dried over anhydrous $Na_2SO_4$ and concentrate to yield **5c** as a crude solid. The crude product was purified by column chromatography using 4:1 hexanes/EtOAc to yield **5c** as a colorless oil (7.16 g, 57%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.12 (d, $J=8.8$ Hz, 1H), 6.53 (d, $J=8.8$ Hz, 1H), 6.38 (s, 1H), 4.68 (t, $J=6.0$ Hz, 1H), 3.80 (br, s, 1H), 3.75 (m, 2H), 3.60 (m, 2H), 3.22 (d, $J=6.0$ Hz, 2H), 2.91 (m, 2H), 2.50 (dd, $J=18.0$, 8.8 Hz, 1H), 2.42 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 2.15–1.94 (m, 3H), 1.72–1.38 (m, 6H), 1.25 (t, $J=7.6$ Hz, 6H), 0.98 (s, 3H); MS ($m/z$) 408, $[M+Na]^+$.
10. *Spectral data for* ***1*** *and* ***2***. **1**: white solid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.01 (br, s, 1H), 7.68 (s, 1H), 7.14 (s, 1H), 7.12 (m, 1H), 6.45 (m, 1H), 3.75 (t, $J=8.5$ Hz, 1H), 3.05–2.95 (m, 2H), 2.52 (m, 1H), 2.43 (m, 1H), 2.15 (m, 1H), 2.05–1.88 (m, 2H), 1.80–1.58 (m, 2H), 1.55–1.28 (m, 6H), 0.85 (s, 3H); MS ($m/z$) 318, $[M+Na]^+$; 296, $[M+H]^+$. Anal. calcd for $C_{20}H_{25}NO\cdot 0.2\ H_2O$: C, 80.33; H, 8.56; N, 4.68. Found: C, 80.46; H, 8.42; N, 4.61. **2**: white solid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05 (br, s, 1H), 7.15 (d, $J=6.0$ Hz, 1H), 7.13 (d, $J=6.0$ Hz, 1H), 7.12 (m, 1H), 6.45 (m, 1H), 4.65 (t, $J=9.5$ Hz, 1H), 3.10–2.90 (m, 2H), 2.40–2.28 (m, 2H), 2.20–2.08 (m, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.60–1.28 (m, 6H), 0.85 (s, 3H); MS ($m/z$) 318, $[M+Na]^+$.