Available online at www.sciencedirect.com
SCIENCE DIRECT
Steroids 70 (2005) 856–866
Steroids
www.elsevier.com/locate/steroids

Benzothieno and benzofurano annelated estranes

Masataka Watanabe [a], Shuntaro Mataka [b], Thies Thiemann [b,*]

[a] *Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Japan*
[b] *Institute of Materials Chemistry and Engineering, Kyushu University, 6-1, Kasuga-koh-en, Kasuga-shi, Fukuoka 816-8580, Japan*

Received 11 April 2005; received in revised form 24 May 2005; accepted 2 June 2005
Available online 19 July 2005

Abstract

The preparation of estrone derived benzothieno- and benzofurano fused steroids is described. Keystep is an intramolecular thienyl(/furyl)-ene-yne cyclization of 16-ethynyl-17-heterarylestra-1,3,5(10),16-tetraenes. The cyclization was carried out under Pt as well as under Ru catalysis.

Keywords: Synthesis; Estranes; Fused steroids; Heteroaryl-ene-ynes; Diene-ynes; Cyclization

1. Introduction

Recently, a number of ring annelated estranes have been synthesized. They include compounds with a heterocyclic as well as compounds with a carbocyclic E-ring, where the ring annelation has been fused to positions 16,17. Some of these pentacyclic molecules such as cyclopentano- and cyclohexano annelated 3,17β-estradiols, had a good binding affinity to the human estradiol or progesterone receptors and have been advanced as inhibitors of osteoporosis [1]. Ring annelation has been used to link bioactive molecules to estranes such as in the case of the synthesis of estrarubincin, which is a hybrid of estrane and anthraquinone [2]. Moreover, 16,17-ring annelated estranes have been used as key intermediates in the synthesis of natural occurring pentacyclic triterpenoids such as of alnusenone [3]. The routes to these ring annelated steroids have been many-fold and include Robinson annelation [4,5] for cyclohexeno-estranes and the intermolecular Diels Alder reaction with the steroid as diene [2] and, in the case of pyrazolo- and oxazoloestranes, intermolecular 1,3-dipolar cycloaddition reactions of estra-1,3,5(10),16-tetraenes [6] and intramolecular 1,3-dipolar cycloaddition reactions of tricyclic secosteroids [7,8]. Ring annelations at C-16,C-17 in steroids in the non-estrane series, were obtained through intermolecular Diels Alder reactions using the steroid as the ene component [9,10], through a combination of Heck reaction and triene cyclization [11–13]. From our previous experience, however, intermolecular reactions with estra-1,3,5(10),16-tetraenes, in which two bonds are formed, often proceed sluggishly. Thus, the 16,17-olefinic moiety often needs to be activated, especially in cycloaddition reactions. Combinations of Heck reactions with an intramolecular cyclization often suffer from low yields as the temperatures needed for the Heck reaction often induce the cyclization as follow-up reactions, but often without allowing for a completion of the second reaction. Furthermore, partial double bond migration within the newly formed ring system under the reaction conditions often leads to a number of isomeric by-products. In the following, the authors present a novel ring annelation procedure for steroids, which relies on a Suzuki reaction, but potentially can be expanded to other C–C bond forming reactions, in combination with the generally little known heteroaryl-ene-yne cyclization, closely related to the diene-yne cyclization, as the key step of the synthesis. Here, this procedure is used for the preparation of a number of novel 16,17-benzofurano- and benzothieno-annelated estranes.

* Corresponding author. Tel.: +81 92 583 7812; fax: +81 92 583 7894.
E-mail address: thies@cm.kyushu-u.ac.jp (T. Thiemann).

0039-128X/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2005.06.001

2. Experimental

Starting material estrone (**1**) (Wako Pure Chemical Industries Ltd.) was used as purchased. 3-*O*-Methylestrone (**2a**) (KOH, MeI, DMSO [14]), 3-*O*-benzylestrone (**2b**) (BnBr, NaH, dry DMF [15]), 16-hydroxymethylene-3-*O*-methylestrone (**3a**), 16-hydroxymethylene-3-*O*-benzylestrone (**3b**) (HCO_2Et, NaOMe, dry benzene [16]) and 17-bromo-16-formyl-estra-1,3,5(10),16-tetraen-3-ol (**9**) [17] were synthesized by procedures anaologous to ones found in the literature. Bis(η^6-*p*-cymene-dichlororuthenium) was synthesized according to the literature [18]. Ruthenium(III)chloride (Kishida), phellandrene (TCI) and NH_4PF_6 (Aldrich) were used as purchased. Anhydrous THF (stabilizer-free, KANTO) and anhydrous diethyl ether (KANTO) were used as purchased. Benzene, dichloromethane and dimethylformamide were dried over CaH_2. Ethyl formate was distilled over phosphorous pentoxide. Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. IR spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM machines. ^1H and ^{13}C NMR spectra were recorded with a JEOL EX-270 (^1H at 270 MHz and ^{13}C at 67.8 MHz) and JEOL Lambda 400 spectrometer (^1H at 395 MHz and ^{13}C at 99.45 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer [electron impact mode (EI), 70 eV or fast atom bombardment (FAB)]. Column chromatography was carried out on Wakogel 300.

*2.1. 16-tert-Butoxymethylene-3-methoxyestra-1,3,5(10)-trien-17-one (**4a**)—general procedure A*

Hydroxymethylene ketone **3a** (14.04 g, 45 mmol) was added to a solution of *p*-TsOH–H_2O (425 mg, 2.23 mmol) and *tert*-BuOH (31 mL, 329 mmol) in benzene (200 mL). The solution was heated under reflux with the water formed distilled azeotropically and collected in a Dean–Stark condenser. After the reaction was complete, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with a conc. aqueous $NaHCO_3$ solution (100 mL) and then with water (3 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether:CH_2Cl_2 = 2:1:1) to give **4a** (11.08 g, 67%) as colorless prisms, mp: 149–151 °C; IR (KBr): 2926, 2853, 1712, 1637, 1574, 1496, 1464, 1425, 1371, 1278, 1256, 1246, 1201, 1154, 1128, 1101, 1052, 989, 965, 900, 872, 813 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 0.92 (s, 3H, CH_3, C-18), 1.32–2.40 (m, 19H), 2.66 (dd, 1H, ^3J 14.7Hz, ^4J 6.1Hz), 2.88–2.93 (m, 2H), 3.78 (s, 3H, OCH_3), 6.64 (d, 1H, ^4J 2.6Hz, C-4), 6.72 (dd, 1H, ^3J 8.6Hz, ^4J 2.6Hz, C-2), 7.21 (d, 1H, ^3J 8.6, C-1), 7.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.7, 24.7, 26.1, 26.8, 28.3, 29.7, 31.6, 37.9, 44.1, 48.7, 48.9, 55.2, 111.5, 113.9, 115.5, 126.3, 132.4, 137.8, 148.4, 157.5, 210.4; MS (70 eV): *m*/*z* (%) 368 (M^+, 70), 312 (100), 227 (86), 160 (55); HRMS found: 368.2347 calcd. for $C_{24}H_{32}O_3$: 368.2347; anal. calcd. for $C_{24}H_{32}O_3$: C 78.22, H 8.75; found: C 78.07 H 8.76.

*2.2. 3-Benzyloxy-16-tert-butoxymethylene-estra-1,3,5(10)-trien-17-one (**4b**)*

Hydroxymethylene ketone **3b** (10.0 g, 25.8 mmol) was reacted with *p*-TsOH–H_2O (245 mg, 1.29 mmol) and *tert*-BuOH (18 mL, 190 mmol) in benzene (100 mL) according to general procedure A. Column chromatography of the crude material on silica gel (hexane:ether:CH_2Cl_2 = 2:1:1) gave **4b** as colorless prisms (9.31 g, 81%); mp: 163–165 °C; IR(KBr): 3062, 3029, 2976, 2936, 2858, 1711, 1636, 1604, 1500, 1454, 1371, 1310, 1285, 1263, 1234, 1161, 1126, 1089, 1055, 1036, 993, 960, 914, 885, 860, 841, 820, 732, 693, 650 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$): δ_H 0.92(s, 3H, CH_3, C-18), 1.27–1.63 (m, 15H), 1.97–2.11 (m, 3H), 2.27–2.39 (m, 2H), 2.66 (dd, 1H, *J* 14.9 Hz, *J* 5.9 Hz), 2.87–2.92 (m, 2H), 5.03 (s, 2H, $PhCH_2O$), 6.73 (d, 1H, ^4J 2.5 Hz, C-4), 6.78 (dd, 1H, ^3J 8.4 Hz, ^4J 2.5 Hz, C-2), 7.20 (d, 1H, ^3J 8.4 Hz, C-1), 7.26–7.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.7, 24.7, 26.0, 26.8, 28.3, 29.7, 31.6, 37.9, 44.1, 48.7, 48.9, 70.0, 79.6, 112.3, 114.9, 115.5, 126.3, 127.4, 127.8, 128.5, 132.7, 137.3, 137.9, 148.4, 156.8, 210.4; MS (FAB, 3-nitrobenzyl alcohol): *m*/*z* (%) 445 (MH^+, 27), 444 (M^+, 17), 443 ($M^+ - 1$, 5); HRMS found: 445.2740 calcd. for $C_{30}H_{37}O_3$: 445.2743; anal. calcd. for $C_{30}H_{36}O_3$: C 81.04, H 8.16; found: C 81.10 H 8.12.

*2.3. 16-Formyl-3-methoxy-17-(thien-2′-yl)-estra-1,3,5(10),16-tetraene (**6a**)—general procedure B*

To a solution of 2-bromothiophene (0.77 mL, 8 mmol) in dry ether (20 mL) was added a solution of *n*-butyllithium in pentane (1.6 M, 5 mL) at −78 °C under an argon atmosphere. After 1 h at −78 °C, the solution was stirred for 30 min at 0 °C. Then, the pale yellow solution was cooled to −78 °C, and a solution of **4a** (1.47 g, 4 mmol) in THF (30 mL) was added and the resulting mixture was stirred at −0 °C for 5 h. Then, to the reaction mixture was added water (5 mL) and *p*-toluenesulfonic acid (1.52 g, 8 mmol) and the resulting reaction solution was stirred for 15 h. After the reaction was complete, the solution was poured into aqueous sodium bicarbonate solution (40 mL) and extracted with dichloromethane (3 × 60 mL. The organic phase dried over $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether:dichloromethane = 4:1:1) to give **6a** (1.22 g, 81%) as a greenish yellow powder; IR (KBr): 3074, 3032, 2928, 2901, 2846, 1650, 1617, 1573, 1496, 1457, 1431, 1376, 1319, 1279, 1250, 1227, 1168, 1123, 1091, 1017, 864, 939, 816, 787, 754, 735, 714, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.09 (s, 3H, CH_3, C-18), 1.20–2.44 (m, 10H), 2.74–2.96 (m, 3H), 3.78 (s, 3H, OCH_3), 6.65 (d, 1H, ^4J 2.5Hz, C-4), 6.71 (d.d., 1H, ^3J 8.4 Hz, ^4J 2.6 Hz, C-2), 7.10–7.20