SYNTHESIS OF SOME 16,17-SECOANDROST-5-ENE DERIVATIVES

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UDC 547.92.057:615.2

Paper received: 12 February 2010

Paper accepted: 11 March 2010

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Abstract. Starting from 3β-acetoxyl-17-oxo-16,17-secoandrost-5-ene-16-nitrile (1), 3β-acetoxyl-16,17-secoandrost-5-ene-16-nitrile (4) was synthesized by a three-stage procedure. First, the formyl group of compound 1 was reduced, to yield the alcohol 2. Compound 2 was further transformed to the mesyloxy derivative 3, whose reduction with NaBH₃CN gave compound 4. Apart from compound 4 as the main reaction product, two additional products were obtained, for which the GC/MS analysis suggested that they are Δ⁸(¹⁴) and Δ¹⁴ derivatives of compound 4. Compound 4 was transformed into 3β-hydroxy-16,17-secoandrost-5-ene-16-nitrile (7), the Oppenauer oxidation of which afforded 3-oxo-16,17-secoandrost-4-ene-16-nitrile (8).

KEY WORDS: androst-5-ene derivatives, 16,17-seco steroids, reduction of aldehydes
INTRODUCTION

There are various ways of reducing the C=O group of aldehydes and ketones to a CH2 [1]. The two oldest methods are the Wolff-Kishner reduction and the Clemensen reduction. In the Wolff-Kishner reduction, the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). There are also a number of modifications of the Wolff-Kishner reaction, one of them being the Huang-Minlon reaction [2]. Another modification of the Wolff-Kishner reduction treats a ketone with hydrazine in toluene with microwave irradiation [3]. Also, a microwave-assisted Huang-Minlon procedure has been reported [4]. An indirect method of accomplishing the reaction is to use tosylhydrazones with NaBH₄, NaBH₃CN or BH₃ [5]. We have recently reported the reaction of reduction of tosylhydrazones, obtained from the corresponding steroidal 17-oxo-16,17-seco-16-nitriles with the aid of NaBH₄, which yielded the steroidal 16,17-triazoles [6]. Namely, the presence of the nitrile group close to the tosylhydrazone function facilitated the intramolecular 1,3-dipolar cycloaddition of the C≡N group onto the in situ generated diazo compound, which resulted in the formation of a triazole ring. Sulfonate esters, such as tosylates or mesylates, can also be reduced with NaBH₄ in polar aprotic solvents [7]. In this paper we used this indirect method for preparing a C-13 methyl derivative from the starting 3β-hydroxy-17-oxo-16,17-secoandrost-5-ene-16-nitrile by three synthetic steps.

EXPERIMENTAL

General procedure

Melting points were determined using a Büchi SMP 20 apparatus and are uncorrected. IR spectra (wave numbers in cm⁻¹) were recorded on a Nexus 670 FT-IR spectrometer. NMR
spectra were taken on a Bruker AC 250E spectrometer operating at 250 MHz (\(^1\)H) and 62.9 MHz (\(^{13}\)C) and are reported in ppm (\(\delta\)-scale), using standard Bruker software; the tetramethylsilane peak (\(\delta\) 0.00 ppm) was used as reference for \(^1\)H NMR, whereas the central carbon line of chloroform-\(d\) was set at 77.0 ppm for \(^{13}\)C NMR. GC/MS analyses were performed on an Agilent Technologies GC 6890N instrument with Mass Selective Detector 5973. High resolution mass spectra was recorded on a 6210 Time-of-Flight (TOF) LC/MS Agilent Technologies (ESI +) instrument. All solutions were dried over anhydrous Na\(_2\)SO\(_4\).

3\(\beta\)-Acetoxy-17-metanesulfonyloxy-16,17-secoandrostan-5-ene-16-nitrile (3)

Compound 2 (0.50 g, 1.45 mmol) in dry pyridine (16 ml) was stirred in an ice bath at 0\(^\circ\)C, while methanesulfonyl chloride (0.9 ml, 1.32 g, 11.5 mmol) was added. The reaction mixture was kept at 4\(^\circ\)C for 22 h and then poured into ice water (100 ml). After adding HCl (6 M) to pH 1, the precipitated crude product was purified by flash chromatography (toluene – ethyl acetate 3:1), affording a pure compound (0.53 g, 86%; mp 178-179\(^\circ\)C) after recrystallization from \(n\)-hexane – acetone in the form of white crystals.

IR (KBr): 3025, 2938, 2907, 2870, 2243, 1715, 1354, 1260, 1176, 965, 857. \(^1\)H NMR (CDCl\(_3\)): 1.05 (s, 6H, H-18 and H-19); 2.05 (s, 3H, CH\(_3\) from Ac); 3.06 (s, 3H, CH\(_3\) from Ms); 3.85 (d, 1H, \(J_{gem} = 10.7\) Hz, H-17a); 4.14 (d, 1H, \(J_{gem} = 10.7\) Hz, H-17b); 4.61 (m, 1H, H-3); 5.39 (m, 1H, H-6). \(^{13}\)C NMR (CDCl\(_3\)): 15.39 (C-15); 16.02 and 19.14 (C-18 and C-19); 19.77 (C-11); 21.38 (CH\(_3\) from Ac); 27.54 (CH\(_2\)); 31.73 (CH\(_2\)); 31.77 (C-10); 35.40 (CH\(_2\)); 36.57 (CH\(_2\)); 36.85 (C-13); 37.38 (CH\(_3\) from Ms); 37.67 (CH\(_2\)); 37.73 (Cq); 42.69 (CH); 48.78 (C-9); 73.52 (C-3); 75.75 (C-17); 118.81 (C=N); 121.14 (C-6); 139.42 (C-5); 170.51 (C=O). M (m/z): 364 (M\(^+\) + \(1\) - AcOH). Anal. calcd. for C\(_{22}\)H\(_{33}\)NO\(_3\)S (423.57): C, 62.38; H, 7.85; N, 3.31; S, 7.57; found: C, 62.17; H, 7.98; N, 3.31; S, 7.34.

3\(\beta\)-Acetoxy-16,17-secoandrostan-5-ene-16-nitrile (4), 3\(\beta\)-acetoxy-16,17-secoandrosta-5,8(14)-diene-16-nitrile (5) and 3\(\beta\)-acetoxy-16,17-secoandrosta-5,14-diene-16-nitrile (6)
To the solution of compound 3 (0.17 g, 0.4 mmol) in DMSO (2 ml), sodium cyanoborohydride (0.13 g, 3.7 mmol) was added, and the reaction mixture was stirred at 160°C for 15 h. After that, the reaction mixture was poured into water (40 ml) and acidified (6 M HCl) to pH 1. The solid product was purified by column chromatography (15 g, n-hexane – acetone 6:1), giving a mixture of compounds 4-6. Pure compound 4 was obtained after the recrystallization from n-hexane – acetone (45 mg, 34%, mp 153°C). The mixture of compounds 5 and 6 was straggled behind in the water liquor and could not be separated.

Compound 4: IR (KBr): 2966, 2942, 2895, 2852, 2237, 1731, 1244, 1041, 1030. $^1$H NMR (CDCl$_3$): 0.95 (s, 3H); 0.97 (s, 3H); 1.04 (s, 3H); 2.05 (s, 3H, CH$_3$ from Ac); 4.61 (m, 1H, H-3); 5.38 (m, 1H, H-6). $^{13}$C NMR (CDCl$_3$): 15.80 (C-15); 19.18, 20.11 and 20.59 (CH$_3$); 21.38 (CH$_3$ from Ac); 27.63; 30.75; 32.00; 32.60 (C-10); 33.77; 36.66; 36.90; 37.76; 41.21; 49.47; 49.63; 73.68 (C-3); 119.70 (C=N); 121.44 (C-6); 139.48 (C-5); 170.50 (C=O). HRMS (TOF) (m/z): C$_21$H$_{31}$NNaO$_2$[M+Na]$^+$; 352.22470; found 352.22427. GC/MS: 56.43%, 269 [M-AcOH]$^+$, ret. time 18.022 min.

Compound 5: GC/MS: 27.63%, 267 [M-AcOH]$^+$, ret. time 18.262 min.

Compound 6: GC/MS: 15.94%, 267 [M-AcOH]$^+$, ret. time 18.393 min.

3β-Hydroxy-16,17-secoandrost-5-ene-16-nitrile (7)

To the solution of sodium ethoxide in ethanol (0.1 M, 1.7 ml) compound 4 (57 mg, 0.17 mmol) was added, and the reaction mixture was heated to 55°C with intensive stirring for 75 min. After that the mixture was poured to water (2 ml), acidified (6 M HCl) to pH 1, and extracted with dichlormethane (3 x 1 ml). The joined extracts were dried and the solvent removed. The crude product in the form of oil was chromatographed on silica gel (5 g, n-hexane – acetone 12:1), giving compound 7 in the form of a colorless oil. Yield: 71% (34.7 mg).

IR (film): 3404, 2964, 2931, 2901, 2862, 2240, 1424, 1368, 1075, 1053, 1030. $^1$H
NMR (CDCl₃): 0.94 (s, 3H); 0.97 (s, 3H); 1.02 (s, 3H); 3.54 (m, 1H, H-3); 5.37 (m, 1H, H-6).

¹³C NMR (CDCl₃): 15.81 (C-15); 19.24 (C-18); 20.06 (C-17); 20.59 (C-11); 30.73; 31.39; 31.95; 32.61 (C-10); 33.72; 36.73; 36.82; 41.14; 41.83; 49.42; 49.63; 71.55 (C-3); 119.84 (C≡N); 120.54 (C-6); 140.41 (C-5). MCI (m/z): 287 (M⁺).

**3-Oxo-16,17-secoandrost-4-ene-16-nitrile (8)**

Compound 7 (46.8 mg, 0.16 mmol) was dissolved in cyclohexanone (2.7 ml), and then aluminum isopropoxide (104.5 mg, 0.5 mmol) was added. The reaction mixture was heated at the boiling temperature for 3 hours. After that it was acidified (6 M HCl) to pH 3 and subjected to steam distillation. Upon the distillation and cooling the product was extracted with dichloromethane (3 x 10 ml). The joined extracts were dried and the solvent was removed. The crude product was purified by column chromatography on silica gel (3 g, n-hexane – acetone 8:1), giving compound 8 in the form of a colorless oil. Yield: 28% (7.1 mg).

IR (film): 2940, 2242, 1673, 1618, 1433, 1392, 1270, 1232, 1186, 865. ¹H NMR (CDCl₃): 0.98 (s, 6H); 1.21 (s, 3H); 5.76 (s, 1H, H-4). ¹³C NMR (CDCl₃): 15.96 (C-15); 17.56 (CH₃); 20.10 (CH₃); 20.67; 30.75; 31.56; 32.51; 33.81; 33.86; 35.47; 36.25; 38.66; 41.28; 48.55; 53.15; 119.54 (C≡N); 123.79 (C-4); 169.99 (C-5); 199.43 (C-3).

**RESULTS AND DISCUSSION**

The starting compound in this synthesis was 3β-acetoxy-17-oxo-16,17-secoandrost-5-ene-16-nitrile (1), whose synthesis was described previously [8]. Compound 1 was reduced first with sodium borohydride (NaBH₄) and thus transformed to compound 2 [8].
compound 3 (Scheme 1). With the aim of obtaining a methyl group at the C-13 position, compound 3 was subjected to the reduction with sodium borohydride in dimethylsulfoxide. This reducing agent was chosen because of the presence of cyano group in compound 3, since it is known that in a polar aprotic solvent it reduces selectively sulfonate esters in the presence of a number of functional groups, such as the ester, carboxylic, amide, nitrile, nitro, olefine, aldehyde, keto, and epoxide [7]. The reaction was performed at 160°C during 15 hours, and it yielded 3β-acetoxy-16,17-secoandrosten-5-ene-nitrile (4) in the mixture with another two compounds, 5 and 6, which could not be separated by column chromatography. Pure compound 4 was obtained after recrystallization, but the compounds 5 and 6 remained in the mother liquor, and could not be separated. The GC/MS analysis showed that these two compounds differ from compound 4 only by two mass units. We suppose that compounds 5 and 6 contain a double bond, that is that they are Δ⁸(14) and Δ¹⁴ derivatives of compound 4.

Scheme 2 shows the postulated mechanism of formation of compounds 5 and 6. According to this mechanism, in the first phase the disruption of the C₁₇-O bond takes place, followed by the elimination of the mesyloxy group and formation of the primary carbocation 3a. The rearrangement of the hydride anion from the C-14 atom yields the more stable, tertiary carbocation 3b. The elimination of the proton from the C-8 atom (direction a) yields the formation of the Δ⁸(14) double bond, whereas the elimination of the proton from the C-15 atom yields the Δ¹⁴ double bond (direction b).

Scheme 2.

The deprotonation of compound 4 was carried out under basic reaction conditions with sodium ethoxide in ethanol, and the resulting 3β-hydroxy derivative 7 was subjected to the Oppenauer oxidation with cyclohexanone and aluminum isopropoxide, rendering 3-oxo-
16,17-secoandrost-4-ene-16-nitrile (8).

CONCLUSION

The paper describes a multistage synthesis of D-seco compounds 2-8, starting from compound 1. By reducing the OH group of compound 2 with sodium borohydride and of mesyloxy group in compound 3 with sodium cyanoborohydride in dimethylsulfoxide, a methyl group was introduced at the C-13 position (compound 4). Apart from the expected 16,17-seco derivate 4, two additional products were obtained, for which it was supposed that they contain $\Delta^{8(14)}$ (5) and $\Delta^{14}$ (6) double bonds. The proposed mechanism of formation of compounds 5 and 6 is based on the assumption of the rearrangement of the hydride anion from the C-14 atom to the intermediate primary carbocation 3a, with further elimination of the proton from the C-8, i.e. C-15, atom.

Acknowledgement

The authors thank the Ministry of Science and Technological Development of the Republic of Serbia for financial support (Grant No. 142052).

REFERENCES


NAUČNI RAD

SINTEZA DERIVATA 16,17-SEKOANDROST-5-ENA

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IZVOD


KLJUČNE REČI: derivati androst-5-ena, 16,17-seko steroidi, redukcija aldehida
Scheme 1.

Scheme 2.
Scheme 1. Synthesis of compounds 3-8. Reagents and reaction conditions: a) NaBH₄, EtOH, rt, 30 min; b) MsCl, Py, 4°C, 22h; c) NaBH₃CN, DMSO, 160°C, 15 h; d) EtONa, EtOH, 55°C, 75 min; e) cyclohexanone, Al(iPrO)₃, refluks, 3 h.

Šema 1. Sinteza jedinjenja 3-8. Reagensi i reakcioni uslovi: a) NaBH₄, EtOH, st, 30 min; b) MsCl, Py, 4°C, 22h; c) NaBH₃CN, DMSO, 160°C, 15 h; d) EtONa, EtOH, 55°C, 75 min; e) cikloheksanon, Al(iPrO)₃, refluks, 3 h.

Scheme 2. Proposed mechanism for the formation of compounds 5 and 6

Šema 2. Pretpostavljeni mehanizam građenja jedinjenja 5 i 6