Reactions of 17-chloro-16-formylandrosta-5,16-diene with thiohydrazides of oxamic acids

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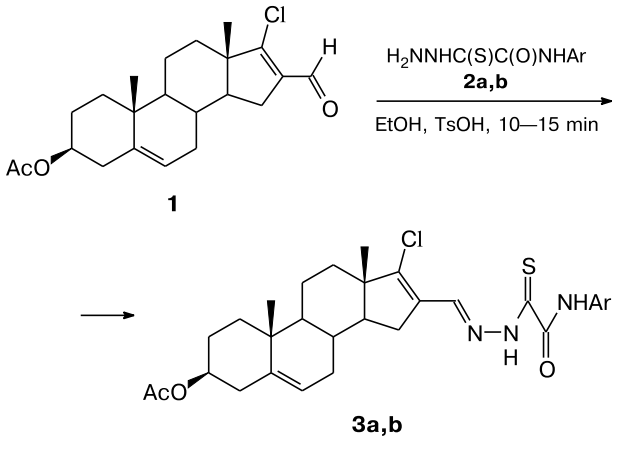
Reactions of thiohydrazides of oxamic acids with 17-chloro-16-formylandrosta-5,16-diene give the corresponding thiohydrazones at the formyl group. Their subsequent reactions with alkali (het)arenethiolates yield 17-het(aryl)thio derivatives, being accompanied by cyclization of the thiooxalylhydrazone fragment into a 1,3,4-thiadiazole ring.

Key words: androstane, thiohydrazides, oxamic acids, hydrazones, sulfides, 1,3,4-thiadiazoles, heterocyclization.

Continuing our investigations[1—3] into the synthesis of steroid derivatives containing heterocyclic fragments, we studied reactions of 17-chloro-16-formylandrostane with thiohydrazides of oxamic acids. According to the literature data,[4,5] reactions of such 17-chloro-16-formyl derivatives with hydrazines and hydrazides afford [17,16-*d*]-pyrazolines and pyrazoles fused to the corresponding steroid molecules.

Reactions of chloro aldehyde **1** with thiohydrazides of oxamic acids **2a**,**b** in ethanol in the presence of a catalytic amount of TsOH at 20 °C for 15 min give hydrazones **3a**,**b** in quantitative yields (Scheme 1).

Scheme 1

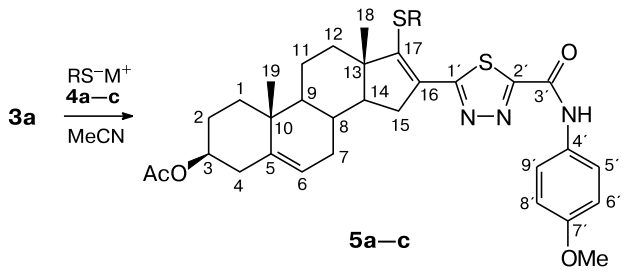


2, **3:** Ar = 4-$MeOC_6H_4$ (**a**), 4-ClC_6H_4 (**b**)

The structures of the hydrazones obtained were proved by spectroscopic methods and elemental analysis. Their ^1H and ^{13}C NMR spectra show characteristic signals at δ 8.3 (H(1′)) and 132.4 (C(16)). Compounds **3a**,**b** are very unstable and decompose within 3 h even at room temperature.

We studied reactions of hydrazone **3a** with (het)arenethiolates **4a**—**c** (Scheme 2). Variation of the solvents (DMSO, acetonitrile, and acetone) showed that acetonitrile ensures the highest yields of products **5a**—**c**. We also found that the sulfide bond formation is accompanied by cyclization of the thiooxalylhydrazone fragment into 1,3,4-thiadiazole. On using sodium pyrimidine-2-thiolate **4a**, compound **3a** is transformed into sulfide **5a** in 86% yield, which was isolated and characterized by ^1H and ^{13}C NMR and mass spectra and elemental analysis. Similar reactions with (het)arenethiolates **4b**,**c** produce complex mixtures of reaction products; we failed to isolate the target compounds **5b**,**c** in the individual state. However, their formation was confirmed by high-resolution mass spectra containing molecular ion peaks with *m*/*z* 656 and 647, respectively (see Scheme 2).

Scheme 2



4, **5:** R = pyrimidin-2-yl (**a**), Ph (**b**), 1,2,4-triazol-3-yl (**c**); M = Na, K

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2626—2627, December, 2013.

Experimental

Melting points were determined on a Boetius hot stage (heating rate near the melting point 4 °C min^{-1}) and are given uncorrected. High-resolution mass spectra (ESI) were recorded on a Bruker micrOTOF II instrument in the positive (capillary voltage 4500 V) or negative ion mode (capillary voltage 3200 V). The scan range was 50—3000 Da; the instrument was calibrated externally or internally using an Electrospray Calibrant Solution (Fluka). Solutions of samples in acetonitrile, methanol, or water were infused into the mass spectrometer through a syringe (flow rate 3 μL min^{-1}). Nitrogen was employed as a nebulizing gas (4 L min^{-1}); the interface temperature was 180 °C. ^{1}H NMR spectra were recorded on Bruker WM-300 (300 MHz) and Bruker DRX-500 instruments (500 MHz) at 303 K. ^{13}C NMR spectra were recorded on a Bruker WM-300 instrument (75 MHz). The signals of the solvents served as the internal standards. The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Kieselgel-G Si 254F plates (Merck) with hexane—ethyl acetate or light petroleum—ethyl acetate as an eluent; spots were visualized with a solution of $Ce(SO_4)_2$ in 10% H_2SO_4. For column chromatography, Acros 60A silica gel (0.060—0.200 mm) was used. Solvents were purified and dried according to standard procedures. Commercial chemicals (Acros) were employed. Thiohydrazides of oxamic acids **2a,b** were prepared as described earlier.[6]

Reactions of 17-chloro-16-formylandrostadiene 1 with thiohydrazides of oxamic acids 2a,b. Thiohydrazide of oxamic acid **2** (0.1 or 0.20 mmol) and a catalytic amount of TsOH were added at room temperature to a solution of 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene (**1**) (0.0376 g, 0.1 mmol) in ethanol (30 mL). The reaction mixture was stirred at room temperature for 10—15 min (monitoring by TLC) and poured into water (50 mL). The precipitate that formed was filtered off, washed with water (3×25 mL), and dried *in vacuo*. Products **3** were purified by column chromatography on silica gel with light petroleum—ethyl acetate as an eluent.

3β-Acetoxy-17-chloro-16-{2-[2-(4-methoxyphenylamino)-2-oxo-1-thioxoethyl]hydrazonomethyl}androsta-5,16-diene (3a). Yield 86%, m.p. 247—250 °C (ethyl acetate—hexane). Found (%): C, 63.64; H, 6.71; Cl, 6.12; N, 7.15; S, 5.58. $C_{31}H_{38}ClN_3O_4S$. Calculated (%): C, 63.74; H, 6.56; Cl, 6.07; N, 7.19; S, 5.47. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 0.92 (s, 3 H, C(19)H_3); 0.99 (s, 3 H, C(18)H_3); 1.29—1.92 (m, 9 H); 1.96 (s, 3 H, MeCO); 2.13—2.41 (m, 6 H); 2.78—2.91 (m, 2 H, C(15)H_2); 3.70 (s, 3 H, OMe); 4.42 (m, 1 H, C(3)H); 5.35 (s, 1 H, C(6)H); 6.86 (d, 2 H, H arom., J = 8.6 Hz); 7.59 (d, 2 H, H arom., J = 8.6 Hz); 8.78 (s, 1 H, C(1′)H); 10.33 (s, 1 H, NHCO); 13.70 (s, 1 H, NHCS). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 15.1 (C(19)), 19.0 (C(18)), 20.1 (C(11)), 21.2 (C$\underline{C}$$H_3$CO), 29.9 (C(15)), 27.5 (C(2)), 30.5 (C(7)), 32.7 (C(8)), 36.5 (C(1)), 37.8 (C(4)), 50.0 (C(10)), 33.0 (C(12)), 49.9 (C(9)), 49.5 (C(13)), 53.5 (C(14)), 55.4 (OMe), 73.3 (C(3)), 114.0 (C(6′)$_{Ar}$, C(8′)$_{Ar}$), 121.9 (C(5′)$_{Ar}$, C(9′)$_{Ar}$), 122.0 (C(6)), 131.42 (C(4′)$_{Ar}$), 133.1 (C(16)), 140.0 (C(5)), 150.7 (C(1′)), 152.6 (C(17)), 155.8 (C(7′)$_{Ar}$), 170.0 (Me$\underline{C}$O), 172.0 (C(3′)), 183.4 (C(2′)). MS (ESI), m/z: 585.

3β-Acetoxy-17-chloro-16-{2-[2-(4-chlorophenylamino)-2-oxo-1-thioxoethyl]hydrazonomethyl}androsta-5,16-diene (3b). Yield 89%, m.p. 234—236 °C (ethyl acetate—hexane). Found (%): C, 61.31; H, 5.83; Cl, 12.13; N, 7.04; S, 5.52. $C_{30}H_{35}Cl_2N_3O_3S$. Calculated (%): C, 61.22; H, 5.99; Cl, 12.05; N, 7.14; S, 5.45. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 0.92 (s, 3 H, C(19)H_3); 0.99 (s, 3 H, C(18)H_3); 1.29—1.92 (m, 9 H); 1.96 (s, 3 H, MeCO); 2.13—2.41 (m, 6 H); 2.78—2.91 (m, 2 H, C(15)H_2); 4.42 (m, 1 H, C(3)H); 5.35 (s, 1 H, C(6)H); 7.38 (m, 2 H, H arom.); 7.63 (m, 2 H, H arom.); 8.45 (s, 1 H, C(1′)H); 10.15 (s, 1 H, NHCO); 13.67 (s, 1 H, NHCS). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 15.6 (C(19)), 19.5 (C(18)), 20.3 (C(11)), 21.5 (C$\underline{C}$$H_3$CO), 29.9 (C(15)), 27.5 (C(2)), 30.5 (C(7)), 32.7 (C(8)), 36.5 (C(1)), 37.8 (C(4)), 50.0 (C(10)), 33.0 (C(12)), 49.9 (C(9)), 49.5 (C(13)), 53.5 (C(14)), 73.2 (C(3)), 121.7 (C(16)), 122.0 (C(6)), 122.7 (C(5′)$_{Ar}$, C(9′)$_{Ar}$), 127.8 (C(6′)$_{Ar}$, C(8′)$_{Ar}$), 129.9 (C(4′)$_{Ar}$), 140.0 (C(5)), 141.3 (C(7′)$_{Ar}$), 153.8 (C(1′)), 152.6 (C(17)), 170.2 (Me$\underline{C}$O), 165.4 (C(3′)), 188.2 (C(2′)). MS (ESI), m/z: 589.

3β-Acetoxy-16-{5-[*N*-(4-methoxyphenyl)carbamoyl]-1,3,4-thiadiazol-2-yl}-17-(pyrimidin-2-ylsulfanyl)androsta-5,16-diene (5a). 2-Mercaptopyrimidine (0.0778 mmol) was dissolved in acetonitrile (4 mL). Sodium carbonate (0.0856 mmol) was added. The mixture was stirred at room temperature for 2 h (monitoring by TLC) and concentrated *in vacuo* to give sodium pyrimidine-2-thiolate (**4a**). Then thiolate **4a** (0.155 mmol) was suspended in acetonitrile (10 mL), and a solution of hydrazone **3a** (0.171 mmol) in acetonitrile (10 mL) was slowly added. The reaction mixture was stirred at 20 °C for 10—15 min (monitoring by TLC) and diluted with water (20 mL). The product was extracted with ethyl acetate (3×20 mL). The combined extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with ethyl acetate—hexane as an eluent. The yield of product **5a** was 86%, m.p. 154—157 °C (ethyl acetate—hexane). Found (%): C, 63.81; H, 6.09; N, 10.54; S, 9.82. $C_{35}H_{39}N_5O_4S_2$. Calculated (%): C, 63.90; H, 5.98; N, 10.65; S, 9.75. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.03 (s, 3 H, C(19)H_3); 1.12 (s, 3 H, C(18)H_3); 1.29—1.93 (m, 7 H); 2.08 (s, 3 H, MeCO); 2.12—2.43 (m, 6 H); 2.74—2.88 (m, 2 H, C(12)H_2); 3.30—3.39 (m, 2 H, C(15)H_2); 3.85 (s, 3 H, OMe), 4.62 (m, 1 H, C(3)H); 5.44 (s, 1 H, C(6)H); 7.07 (t, 1 H, C(5″)H, pyrimidine); 7.37 (d, 2 H, H arom., J = 8.6 Hz); 7.66 (d, 2 H, H arom., J = 8.6 Hz); 8.55 (d, 2 H, C(4″)H, C(6″)H, pyrimidine, J = 4.9 Hz); 9.13 (s, 1 H, NHCO). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.1 (C(19)), 19.0 (C(18)), 20.1 (C(11)), 21.2 (C$\underline{C}$$H_3$CO), 27.5 (C(2)), 30.5 (C(7)), 32.7 (C(8)), 36.5 (C(1)), 37.8 (C(4)), 39.9 (C(15)), 50.0 (C(10)), 33.0 (C(12)), 49.9 (C(9)), 49.5 (C(13)), 53.5 (C(14)), 55.4 (OMe), 73.3 (C(3)), 114.4 (C(6′)$_{Ar}$, C(8′)$_{Ar}$), 117.2 (C(5″), pyrimidine), 121.5 (C(5′)$_{Ar}$, C(9′)$_{Ar}$), 122.0 (C(6)), 131.42 (C(4′)$_{Ar}$), 138.7 (C(16)), 140.0 (C(5)), 145.2 (C(17)), 155.8 (C(7′)$_{Ar}$), 156.5 (C(4″), C(6″), pyrimidine), 163.2 (C(3′)), 164.3 (C(2′)), 164.7 (C(1′)), 170.6 (Me$\underline{C}$O), 175.2 (C(2″), pyrimidine). MS (ESI), m/z: 658.

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Received November 11, 2013