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Highly Efficient Synthesis of Steroidal Hydroxamic Acid Derivatives via Homogeneous Catalytic Carbonylation Reaction

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Abstract—Steroidal hydroxamic acid derivatives were synthesized in moderate to high yields by palladium-catalyzed carbonylation reactions of the corresponding iodo-alkenyl compounds or enol triflates in the presence of substituted hydroxylamines under mild reaction conditions. The effect of reaction parameters on the regioselectivity of carbonylation of *N*-substituted hydroxylamines is investigated in detail.

Introduction

Hydroxamic acids and their derivatives can be widely used in organic synthesis.[1] Although there is a great variety of reactions for the synthesis of hydroxamic acids,[2] the acylation[1] of hydroxylamine or its derivatives by conventional acylation reagents is still dominant. These reactions have been reported to lead to *N*-acylated derivatives[4,5] almost exclusively.

Previously, we have shown that various hydrazides can be synthesized under mild reaction conditions with high yields in homogeneous catalytic carbonylation reactions with substituted hydrazines as reagents.[6] At the same time, the only example of such a reaction using a hydroxylamine derivative as the nucleophile, was the carbonylation of a simple enol triflate with *N*,*O*-dimethyl-hydroxylamine in the presence of $Pd(PPh_3)_4$.[7]

Recently, we have reported our preliminary results on the facile synthesis of steroidal hydroxamic acid derivatives via the palladium-catalyzed functionalization of skeletons possessing iodo-alkene moieties.[8]

The main goal of this work is to present the results of a more detailed investigation which revealed that the regioselectivity of the acylation of the hydroxylamine derivatives highly depended on the structures of both reagents and on the various reaction parameters. Also, here we report on the scope and limitations of the above-mentioned reaction.

In addition to the great demand for a facile method for the synthesis of hydroxamic acid derivatives, the present work was initiated by the fact, that steroidal 17-carboxamides, the close analogs of steroidal hydroxamic acids, proved to be efficient 5α-reductase inhibitors.[9]

Results and Discussion

Carbonylation in the presence of *O*-substituted hydroxylamines

17-Iodo-androst-16-ene (**1**), 17-iodo-4-aza-4-methyl-androst-16-en-3-one (**2**), 17-iodo-4-aza-androst-16-en-3-one (**3**), 17-iodo-3-methoxy-estra-1,3,5(10),16-tetraene (**4**), 3-trifiloxy-17β-benzoyloxy-androst-2-ene (**5**) and 17-bromo-androsta-2,16-diene (**7**) (Fig. 1) were reacted with carbon monoxide and *O*-trimethylsilyl, *O*-benzyl- or *O*-methyl-hydroxylamine in the presence of palladium(II)-acetate, triphenylphosphine and triethylamine (Scheme 1).

While the substrates with the alkenyl iodide moiety could be totally converted into the desired products in 4–8 h, the enol triflate (**5**) reacted slowly and **5c** was only produced in moderate yield (60%). The bromo-derivative (**7**) was

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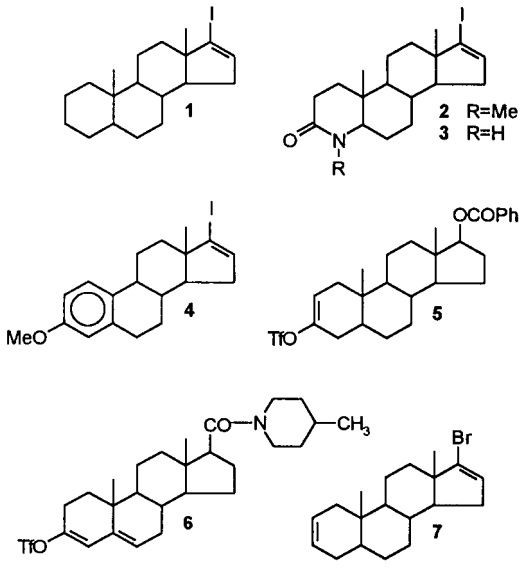


Figure 1. Steroidal substrates used in the carbonylation reaction.

found to be unreactive, no carbonylation product could be detected even after prolonged reaction times.

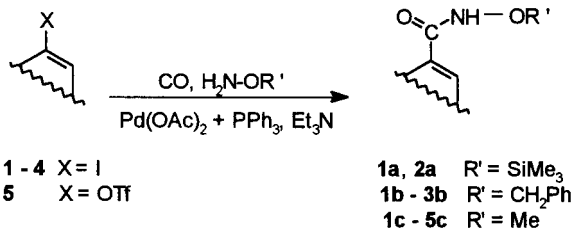
The *O*-substituted hydroxylamines gave comparable results with most of the steroidal substrates. Table 1 shows the results obtained after 1 h in order to compare conversions with that observed with *N*-substituted derivatives. However, in longer reactions total conversion of substrates with iodo-alkenyl moieties was achieved.

Carbonylation in the presence of *N*-substituted hydroxylamines

During the carbonylation of the same substrates (1–7, Fig. 1) with various *N*-substituted hydroxylamines (Scheme 2) the same order of substrate reactivity was observed as before. With steroidal alkenyl iodides and enol triflates complete conversion of the substrates could be achieved, in the latter cases with long reaction times. The bromo-derivative **7** was completely unreactive.

Reactivities of the hydroxylamine reagents are determined by the electron-donating/-withdrawing ability of the functional groups attached to the nitrogen (Table 1).

The most interesting point in this reaction is the regioselectivity of the reaction. Theoretically, the acylating agent (the palladium-acyl intermediate formed by oxidative addition



Scheme 1.

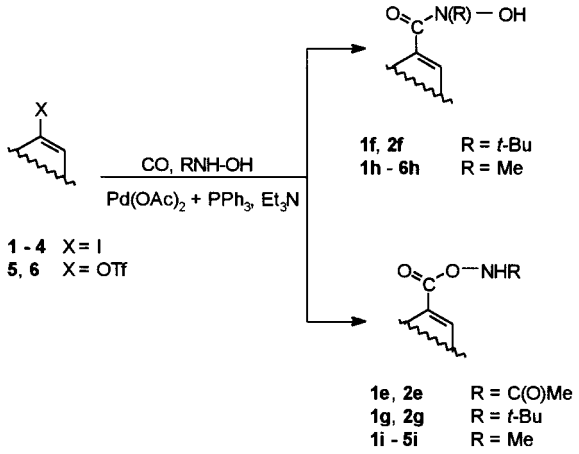
Table 1. Carbonylation of **1** in the presence of various hydroxylamine derivatives (RNH-OR′) (reaction conditions: 1 h, 60°C, in DMF, catalyst: $Pd(OAc)_2$+2 PPh_3. Conversions after 8 h are in brackets)

R	R′	Conv. (%)[a]
H	$SiMe_3$	92 (99)
H	CH_2Ph	85 (99)
H	Me	81 (98)
COMe	H	65 (95)
t-Bu	H	97 (99)
Me	H	91 (99)

[a] Determined by GC.

of the iodo-alkenyl substrate onto the palladium(0), followed by insertion of CO into the palladium–alkenyl bond) could react either with the NH or the OH functionality of the hydroxylamine derivative. Although *O*-acylation of arylhydroxylamines could be achieved with acyl cyanides[10,11] and in another case the formation of *N*-acylated derivatives was supposed to occur via the rearrangement of the primarily produced *O*-acylated compounds in the presence of an excess of hydroxylamine,[12] reactions of hydroxylamine derivatives with various acylating agents usually led to the corresponding hydroxamic acids.

According to our experiments, the site of acylation is determined by various factors: e.g. the structure of the reagent, the structure of the substrate and the solvent used (Table 2). As we have reported before,[8] the use of acetohydroxamic acid as the nucleophile led to the formation of the *O*-acylated derivatives exclusively. This can be explained by the strong electron-withdrawing effect of the acetyl group attached to the nitrogen. In the case of *N*-*t*-butyl-hydroxylamine *O*-acylation was still dominant, but here the steric properties seemed to outweigh electronic ones, resulting in 93 and 90% *N*-acylation in case of **1** and **2**, respectively. In spite of the electron donor ability of the *t*-Bu group, *N*-acylation was not favoured because of the steric bulk of the substituent. When *N*-methyl-hydroxylamine was used as the nucleophile, the regioselectivity of the reaction seemed to be strongly influenced by the structure of the substrate and the solvent.



Scheme 2.

Table 2. Regioselectivity of carbonylation in the presence of *N*-substituted hydroxylamines (RNH–OH)

Substrate	R	Solvent	Product distribution[a] (%)			
			N-acylation		*O*-acylation	
1	C(O)Me	DMF	**1d**	0	**1e**	100
1	*t*-Bu	DMF	**1f**	7	**1g**	93
1	*t*-Bu	Toluene	**1f**	4	**1g**	96
1	Me	DMF	**1h**	89	**1i**	11
1	Me	THF	**1h**	89	**1i**	11
1	Me	NEP[b]	**1h**	75	**1i**	25
1	Me	DMSO	**1h**	61	**1i**	39
1	Me	Toluene	**1h**	49	**1i**	51
2	C(O)Me	DMF	**2d**	0	**2e**	100
2	*t*-Bu	DMF	**2f**	10	**2g**	90
2	Me	DMF	**2h**	15	**2i**	85
2	Me	NEP	**2h**	36	**2i**	64
2	Me	Toluene	**2h**	41	**2i**	59
3	Me	DMF	**3h**	61	**3i**	39
4	Me	DMF	**4h**	87	**4i**	13
4	Me	Toluene	**4h**	58	**4i**	42
5	Me	DMF	**5h**	96	**5i**	4
6	Me	DMF	**6h**	100	**6I**	0

[a] Determined by ^{1}H NMR.
[b] 1-Ethyl-2-pyrrolidone.

Substrate structure and solvent effects in the carbonylation reaction of *N*-Me-hydroxylamine

While *N*-acylated hydroxylamines were synthesized with good selectivity in DMF as solvent using most of the substrates, surprisingly, reactions of steroidal derivatives with a lactame-structure in the A-ring also led to the *O*-acylated products in considerable amounts. In the case of **3** the two products (**3h**, **3i**) were produced in comparable amounts, but with **2** as substrate, **2i** was formed with good selectivity. No such phenomenon was observed with any of the other substrates, even when there was also an amide functionality in the molecule (**6**). Lower reactivity of 4-aza derivatives in various coupling reactions has been observed before.[13] This can be explained by the coordination of the lactame resulting in slower oxidative addition of the iodo-alkenyl moiety of the steroid to palladium. It is worth noting that no effect of the lactame ring of 2 or 3 on the selectivity of any coupling or carbonylation reactions has been observed before.

The use of an appropriate solvent is also a crucial point regarding the selectivity of the reaction. In DMF (or THF) the *N*-acylated products formed in good yields with **1** or **4** as substrates. The selectivity of the acylation decreased using other solvents in the order 1-ethyl-2-pyrrolidone (NEP), DMSO, toluene. In the latter case the two products could be found in almost equal amounts in the reaction mixtures. A similar, but reversed phenomenon was observed using **2** as substrate. While the *O*-acylated derivative was produced with good selectivity in DMF, the amount of the *N*-acylated product increased considerably using NEP or toluene. It should also be mentioned that product distribution did not change throughout the reaction. At the same time, toluene has no such effect in the reaction of **1** with *t*-Bu-hydroxylamine: the same selectivity was observed as in DMF.

Experiments were carried out to investigate if isolated **1i** could be converted into **1h** under the standard reaction conditions, but no such phenomenon was observed on heating **1i** neither in DMF nor in toluene.

No dependence of selectivity on the solvent was observed during acylation of *N*-methyl-hydroxylamine with benzoyl chloride: the *N*-acylated product was produced exclusively in both THF and toluene.

Conclusion

Steroidal hydroxamates and hydroxamic acids, the potential intermediates of further functionalized steroids were synthesized in moderate to high yields in palladium-catalyzed carbonylation reaction. The selectivities of the reactions show an unexpected dependence on substrate structure and solvents.

Experimental

All of the homogeneous catalytic experiments were carried out under carbon monoxide atmosphere. Solvents were dried with standard methods and distilled under argon. The ^{1}H and ^{13}C NMR spectra of the products were recorded on a VARIAN INOVA 400 spectrometer at 400 and 100.58 MHz, respectively. MS measurements were made with a VG 16-F spectrometer.

General procedure for the carbonylation reaction

A mixture of the steroidal alkenyl iodide or enol triflate (1 mmol), was reacted with the hydroxylamine-derivative (5 mmol) and carbon monoxide in the presence of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol) and Et_3N (0.5 ml) in DMF or toluene at 60°C for 4–6 h. The mixtures were homogeneous at the reaction temperature. The reaction was monitored by GC or TLC. When the carbonylation was complete, the volatile components were removed in vacuo. The residue was dissolved in 30 ml of $CHCl_3$, washed with 30 ml 5% HCl, 30 ml of saturated aqueous $NaHCO_3$ and 30 ml of brine and dried over Na_2SO_4. The evaporation of the solvent and chromatography (aluminum oxide, chloroform/methanol=95/5) resulted in the products in good isolated yields. The structures of the minor products (**1f**, **2f**, **5i**) were determined from the reaction mixtures.

The compounds prepared by the above procedure are as follows. (Spectroscopic data for **1c**, **2c**, **1e**, **2e**, **1h** and **2i** have been reported elsewhere.[8])

17-(*N*-(Trimethylsilyloxy)carbamoyl)-androst-16-ene (1a). Pale yellow powder, mp 177–179°C, yield: 365 mg (94%). ^{1}H NMR (δ, $CDCl_3$): 6.40 (m, 1H); 5.54 (brs, 1H); 1.05–2.5 (m, 22H, ring protons); 0.90 (s, 3H); 0.78 (s, 3H); 0.02 (s, 9H). IR (KBr, ν(cm^{-1})): 3200 (NH); 1650 (C=O). MS *m*/*z* 299(36); 284(100); 257(20). Anal. Calcd for $C_{23}H_{39}NO_2Si$: C, 70.90; H, 10.09; N, 3.59. Found: C, 71.12; H, 10.24; N, 3.45.

17-(*N*-(Trimethylsilyloxy)carbamoyl)-4-aza-4-methyl-androst-16-en-3-one (2a). Pale yellow powder, mp 196–200°C, yield: 380 mg (91%). ^{1}H NMR (δ, $CDCl_3$): 6.37 (m,

1H); 5.35 (brs, 1H); 3.05 (m, 1H); 2.91 (s, 3H); 2.43 (m, 2H); 1.00–2.3 (m, 15H, ring protons); 0.98 (s, 3H); 0.91 (s, 3H); 0.02 (s, 9H). IR (KBr, $\nu(cm^{-1})$): 3160 (NH); 1660 (C═O); 1600 (C═O). Anal. Calcd for $C_{23}H_{38}N_2O_3Si$: C, 65.99; H, 9.15; N, 6.69. Found: C, 65.72; H, 9.27; N, 6.54.

17-(*N*-Benzyloxycarbamoyl)-androst-16-ene (1b). Pale yellow powder, mp 130–133°C, yield: 366 mg (90%). ^1H NMR (δ, $CDCl_3$): 8.09 (brs, 1H); 7.38 (m, 5H); 6.22 (m, 1H); 4.92 (m, 2H); 1.00–2.20 (m, 22H, ring protons); 0.92 (s, 3H); 0.79 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 164.90; 147.64; 137.07; 135.39; 129.33; 129.33; 128.69; 128.56; 128.56; 78.15; 56.60; 55.11; 47.20; 46.95; 38.43; 36.44; 34.70; 33.72; 31.92; 31.84; 28.99; 28.84; 26.75; 22.09; 20.58; 16.52; 12.14. IR (KBr, $\nu(cm^{-1})$): 3150 (NH); 1630 (C═O). MS *m/z* 407(2); 392(4); 329 (5); 285 (10); 91(100). Anal. Calcd for $C_{27}H_{37}NO_2$: C, 79.56; H, 9.15; N, 3.44. Found: C, 79.82; H, 8.98; N, 3.58.

17-(*N*-Benzyloxycarbamoyl)-4-aza-4-methyl-androst-16-en-3-one (2b). Pale yellow powder, mp 136–139°C, yield: 403 mg (92 %). ^1H NMR (δ, $CDCl_3$): 8.45 (brs, 1H); 7.32 (m, 5H); 6.20 (m, 1H); 4.92 (m, 2H); 3.05 (m, 1H); 2.89 (s, 3H); 1.00–2.45 (m, 17H, ring protons); 0.92 (s, 3H); 0.81 (s, 3H). IR (KBr, $\nu(cm^{-1})$): 3150 (NH); 1630 (C═O); 1600 (C═O). Anal. Calcd for $C_{27}H_{36}N_2O_3$: C, 74.28; H, 8.31; N, 6.42. Found: C, 74.02; H, 8.51; N, 6.28.

17-(*N*-Benzyloxycarbamoyl)-4-aza-androst-16-en-3-one (3b). Pale yellow powder, mp 144–146°C, yield: 368 mg (87%). ^1H NMR (δ, $CDCl_3$): 8.18 (brs, 1H); 7.32 (m, 5H); 6.17 (m, 1H); 5.79 (brs, 1H); 4.90 (m, 2H); 3.00 (m, 1H); 1.00–2.40 (m, 17H, ring protons); 0.93 (s, 3H); 0.87 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 172.30; 164.81; 147.41; 136.34; 135.34; 129.33; 129.33; 128.73; 128.57; 128.57; 78.22; 65.29; 60.74; 55.83; 51.60; 47.18; 35.92; 33.35; 33.13; 31.78; 29.34; 28.50; 27.22; 20.91; 16.48; 11.31. IR (KBr, $\nu(cm^{-1})$): 3150 (NH); 1630 (C═O); 1600 (C═O). Anal. Calcd for $C_{26}H_{34}N_2O_3$: C, 73.90; H, 8.11; N, 6.63. Found: C, 73.58; H, 8.27; N, 6.55.

17-(*N*-Methoxycarbamoyl)-4-aza-androst-16-en-3-one (3c). Pale yellow powder, mp 183–186°C, yield: 304 mg (88 %). ^1H NMR (δ, $CDCl_3$): 8.17 (brs, 1H); 6.28 (m, 1H); 5.43 (brs, 1H); 3.78; (s, 3H); 3.06 (m, 1H); 2.40 (m, 2H); 1.00–2.25 (m, 15H, ring protons); 0.99 (s, 3H); 0.92 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 172.41; 164.88; 147.36; 136.20; 64.43; 60.74; 55.84; 51.65; 47.22; 35.90; 34.25; 33.36; 33.18; 31.83; 29.36; 28.58; 27.19; 20.91; 16.49; 11.31. IR (KBr, $\nu(cm^{-1})$): 3220 (NH); 1650 (C═O); 1610 (C═O). Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.01; H, 8.52; N, 8.17.

17-(*N*-Methoxycarbamoyl)-3-methoxy-estra-1,3,5(10),16-tetraene (4c). Pale yellow powder, mp 169–172°C, yield: 316 mg (93%). ^1H NMR (δ, $CDCl_3$): 8.21 (brs, 1H); 7.18 (d, 8.4 Hz, 1H); 6.70 (dd, 2.8 Hz, 8.4 Hz, 1H); 6.62 (d, 2.8 Hz, 1H); 6.34 (m, 1H); 3.79 (s, 3H); 3.76 (s, 3H); 1.2–3.00 (m, 13H, ring protons); 1.00(s, 3H). IR (KBr, $\nu(cm^{-1})$): 3240 (NH); 1640 (C═O). MS *m/z* 309(100); 294(10). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.08; H, 7.72; N, 4.32.

3-(*N*-Methoxycarbamoyl)-17β-benzoyloxy-androst-2-ene (5c). Pale yellow powder, mp 164–166°C, yield: 272 mg (60%). ^1H NMR (δ, $CDCl_3$): 8.44 (brs, 1H); 8.01 (d, 7.2 Hz, 2H); 7.53 (t, 7.2 Hz, 1H); 7.41 (t, 7.2 Hz, 2H); 6.51 (m, 1H); 4.82 (m, 1H); 3.77 (s, 3H); 1.00–2.30 (m, 20H, ring protons); 0.92 (s, 3H); 0.73 (s, 3H). IR (KBr, $\nu(cm^{-1})$): 3250 (NH); 1700 (C═O); 1640 (C═O). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.75; H, 8.08; N, 3.27.

17-(*N*-*t*-Butylaminoxy-carbonyl)-androst-16-ene (1g). Pale yellow powder, mp 174–177°C, yield: 317 mg (85%). ^1H NMR (δ, $CDCl_3$): 6.21 (m, 1H); 5.44 (brs, 1H); 0.90–2.30 (m, 22H, ring protons); 1.35 (s, 9H); 0.94 (s, 3H); 0.79 (s, 3H). IR (KBr, $\nu(cm^{-1})$): 3330 (NH); 1630 (C═O). Anal. Calcd for $C_{24}H_{39}NO_2$: C, 77.16; H, 10.52; N, 3.75. Found: C, 76.99; H, 10.62; N, 3.88.

17-(*N*-*t*-Butylaminoxy-carbonyl)-4-aza-4-methyl-androst-16-en-3-one (2g). Pale yellow powder, mp 188–192°C, yield: 325 mg (81%). ^1H NMR (δ, $CDCl_3$): 6.17 (m, 1H); 5.43 (brs, 1H); 3.04 (m, 1H); 2.91 (s, 3H); 2.43 (m, 2H); 1.00–2.25 (m, 15H, ring protons); 1.35 (s, 9H); 0.97 (s, 3H); 0.90 (s, 3H). IR (KBr, $\nu(cm^{-1})$): 3360 (NH); 1630 (C═O); 1600 (C═O). Anal. Calcd for $C_{24}H_{38}N_2O_3$: C, 71.60; H, 9.51; N, 6.96. Found: C, 71.42; H, 9.75; N, 6.82.

17-(*N*-Hydroxy-*N*-methylcarbamoyl)-4-aza-4-methyl-androst-16-en-3-one (2h). Pale yellow powder, mp 146–149°C, yield: 114 mg (32%). ^1H NMR (δ, $CDCl_3$): 5.99 (m, 1H); 3.38 (s, 3H); 3.03 (m, 1H); 2.91 (s, 3H); 2.43 (m, 2H); 1.05–2.35 (m, 16H, ring protons); 1.04 (s, 3H); 0.90 (s, 3H). IR (KBr, $\nu(cm^{-1})$): 3420 (OH); 1610 (C═O). Anal. Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95; N, 7.77. Found: C, 70.15; H, 9.11; N, 7.52.

17-(*N*-Hydroxy-*N*-methylcarbamoyl)-4-aza-androst-16-en-3-one (3h). Pale yellow powder, mp 150–152°C, yield: 188 mg (54%). ^1H NMR (δ, $CDCl_3$): 5.98 (m, 1H); 5.62 (brs, 1H); 3.37 (s, 3H); 3.05 (m, 1H); 1.05–2.45 (m, 18H, ring protons); 1.04 (s, 3H); 0.92 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 172.5; 163.8; 145.9; 134.4; 65.3; 60.8; 55.5; 51.4; 48.2; 36.8; 33.8; 33.0; 32.8; 31.9; 28.8; 28.1; 27.5; 20.8; 16.3; 11.1. IR (KBr, $\nu(cm^{-1})$): 3420 (OH); 1610 (C═O). Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.57; H, 8.88; N, 7.91.

17-(*N*-Hydroxy-*N*-methylcarbamoyl)-3-methoxy-estra-1,3,5(10),16-tetraene (4h). Pale yellow powder, mp 136–139°C, yield: 267 mg (78%). ^1H NMR (δ, $CDCl_3$): 7.15 (d, 8.5 Hz, 1H); 6.88 (dd, 2.8 Hz, 8.5 Hz, 1H); 6.60 (d, 2.8 Hz, 1H); 6.00 (m, 1H); 3.74 (s, 3H); 3.39 (s, 3H); 1.2–3.00 (m, 14H, ring protons); 1.04 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 163.55; 157.52; 145.81; 137.72; 135.33; 126.07; 113.88; 111.42; 55.84; 55.20; 48.81; 44.26; 37.42; 37.00; 34.29; 32.18; 29.61; 27.78; 26.29; 16.61. IR (KBr, $\nu(cm^{-1})$): 3420 (OH); 1620 (C═O). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.05; H, 7.68; N, 3.89.

3-(*N*-Hydroxy-*N*-methylcarbamoyl)-17β-benzoyloxy-androst-2-ene (5h). Pale yellow powder, mp 133–137°C, yield: 385 mg (85%). ^1H NMR (δ, $CDCl_3$): 8.01 (d, 7.4 Hz, 2H); 7.53 (t, 7.4 Hz, 1H); 7.41 (t, 7.4 Hz, 2H); 5.93 (m, 1H);

4.82 (m, 1H); 3.37 (s, 3H); 1.00–2.35 (m, 21H, ring protons); 0.92 (s, 3H); 0.78 (s, 3H). IR (KBr, ν(cm^{-1})): 3420 (OH); 1705 (C═O); 1610 (C═O). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.29; H, 8.06; N, 3.15.

3-(*N*-Hydroxy-*N*-methylcarbamoyl)-17β-(3′-methyl-pentane-1′,5′-diyl)carboxamido-androst-3,5-diene (6h). Pale yellow powder, mp 149–152°C, yield: 414 mg (91%). ^{1}H NMR (δ, $CDCl_3$): 6.17 (m, 1H); 5.62 (m, 1H); 4.62 (m, 2H); 3.98 (m, 2H); 3.38 (s, 3H); 0.90–3.00 (m, 24H, ring protons); 0.91 (s, 3H); 0.89 (d, 6.4 Hz, 3H); 0.72 (s, 3H). IR (KBr, ν(cm^{-1})): 3410 (OH); 1620 (C═O); 1600 (C═O). Anal. Calcd for $C_{28}H_{42}N_2O_3$: C, 73.97; H, 9.31; N, 6.16. Found: C, 74.12; H, 9.25; N, 6.28.

17-(*N*-Methylaminoxy-carbonyl)-androst-16-ene (1i). Pale yellow powder, mp 158–160°C, yield: 124 mg (37%). ^{1}H NMR (δ, $CDCl_3$): 6.26 (m, 1H); 5.68 (brs, 1H); 2.81 (d, 4.8 Hz, 3H); 1.00–2.35 (m, 22H, ring protons); 0.96 (s, 3H); 0.80 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 166.72; 150.72; 135.39; 56.78; 55.13; 47.22; 46.52; 38.44; 36.43; 35.00; 33.78; 31.92; 31.54; 29.00; 28.88; 26.76; 25.93; 22.10; 20.65; 16.54; 12.15. IR (KBr, ν(cm^{-1})): 3315 (NH); 1630 (C═O). Anal. Calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.34; H, 10.15; N, 4.11.

17-(*N*-Methylaminoxy-carbonyl)-4-aza-androst-16-en-3-one (3i). Pale yellow powder, mp 1654–168°C, yield: 106 mg (31%). ^{1}H NMR (δ, $CDCl_3$): 6.26 (m, 1H); 5.62 (brs, 1H); 5.61 (brs, 1H); 3.05 (m, 1H); 2.82 (d, 4.8 Hz, 3H); 1.00–2.50 (m, 17H, ring protons); 0.98 (s, 3H); 0.92 (s, 3H). ^{13}C NMR (δ, $CDCl_3$): 172.6; 166.5; 150.5; 134.0; 65.0; 61.1; 55.5; 51.0; 46.6; 34.0; 33.2; 32.7; 32.2; 29.0; 28.2; 27.4; 25.7; 20.8; 16.0; 11.1. IR (KBr, ν(cm^{-1})): 3320 (NH); 1630 (C═O); 1600 (C═O). Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.15; H, 8.62; N, 7.95.

17-(*N*-Methylaminoxy-carbonyl)-3-methoxy-estra-1,3,5(10),16-tetraene (4i). Pale yellow powder, mp 154–156°C, yield: 112 mg (33%). ^{1}H NMR (δ, $CDCl_3$): 7.18 (d, 8.7 Hz, 1H); 6.90 (dd, 2.6 Hz, 8.7 Hz, 1H); 6.62 (d, 2.6 Hz, 1H); 6.29 (m, 1H); 5.64 (brs, 1H); 3.76 (s, 3H); 2.85 (d, 4.4 Hz, 3H); 1.2–3.00 (m, 13H, ring protons); 0.98 (s, 3H). IR (KBr, ν(cm^{-1})): 3320 (NH); 1630 (C═O). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.71; H, 7.85; N, 4.25.

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