Synthesis of 1'-arylcarbamoylthiocarbonyl-3'-methyl-3-oxoandrost-4-eno[16α,17α-d]pyrazolines

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Abstract
A convenient four-step synthesis of progesterone fused to N-arylcarbamoylthiocarbonyl-pyrazoline at position 16,17 starting from 3β-acetoxypregna-5,16-dien-20-one was developed.

Keywords: Cyclization, heterocyclic steroid, N-aryl-2-hydrazinyl-2-thioxoacetamide, Oppenauer oxidation

Introduction

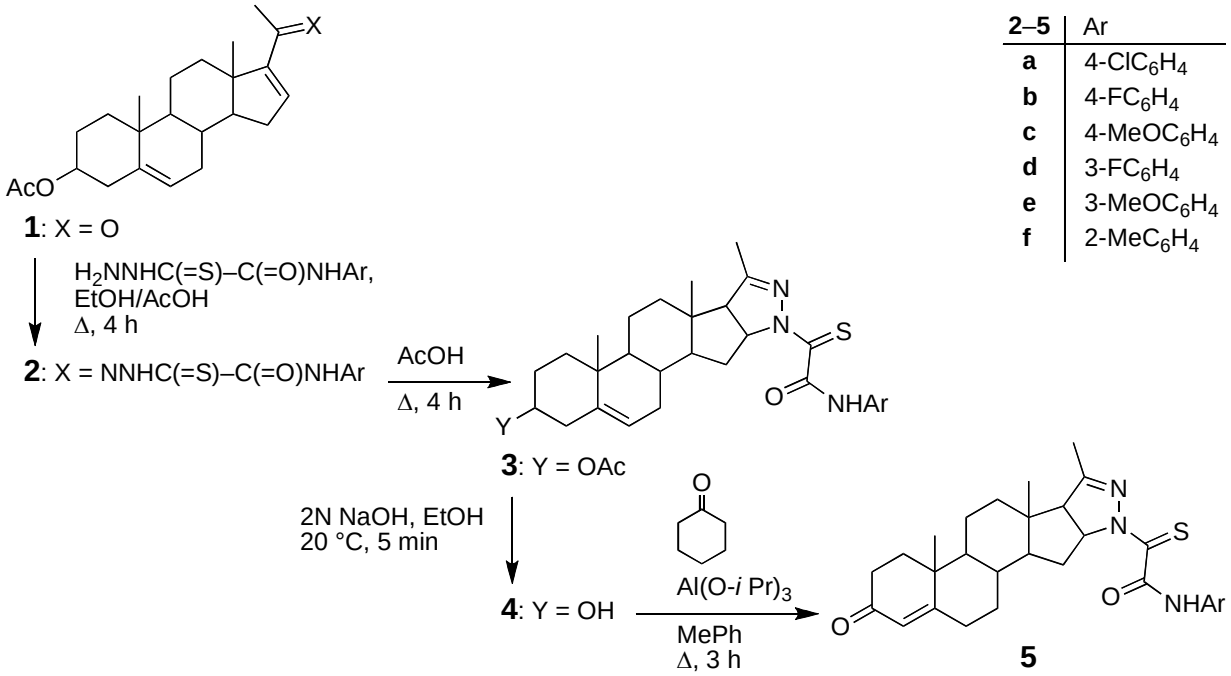
Steroids with a heterocyclic moiety have high biological activity and are of interest as potential drugs.[1] Therefore, we turned our attention to the synthesis of pyrazoline-containing compounds in order to study their structure-biological activity relationship. Such compounds can be synthesized by cyclization of 20-hydrazones bearing substituents.[1-5] 16,17-Heterocyclic steroids, prepared by cyclization of recently synthesized substituted steroid hydrazones derived from N-aryl-2-hydrazinyl-2-thioxoacetamide,[4,5] may be of particular interest. The chemical properties of oxamic acid thiohydrazides are determined by the difference in the reactivity of the oxamide and thiohydrazide groups. Due to the high polarizability of the π bond, the thiocarbonyl group reacts much more readily with nucleophiles than the carbonyl group. Combination of these groups with chiral steroid skeletons offers considerable scope for the systematic synthesis of heterocyclic steroids having valuable biological properties, which, in turn, can lead to the design of drugs.

Results and Discussion

Earlier, we have carried out the reaction of 3β-acetoxypregna-5,16-dien-20-one (1) with monothiohydrazides of oxamides [$H_2NNHC(=S)$-$C(=O)NHR$] affording the corresponding 16,17-pyrazoline derivatives in low yields; in some cases attempts to perform the cyclization

failed.[4,5] In the present study, we developed a convenient route in four steps to progesterone analogs containing the N-arylcarbamoylthiocarbonylpyrazoline moiety fused to positions 16,17.

In the first step, the reaction of 3β-acetoxypregna-5,16-dien-20-one (**1**) with monothiohydrazides of oxamides in refluxing ethanol in the presence of a catalytic amount of glacial acetic acid produced 20-thiohydrazones **2a–f** in 80–85% yield (Scheme 1). In glacial acetic acid under reflux for 3 h, 20-thiohydrazones **2a–f** underwent cyclization to the corresponding (N-arylcarbamoylthiocarbonyl)pyrazolines **3a–f** in 77–80% yield. Hydrolysis of **3a–f** in 2N ethanolic NaOH at room temperature brought about removal of the 3β-acetyl group forming alcohols **4a–f**. Oppenauer oxidation of the 3β-hydroxy derivatives **4a–f** with cyclohexanone in the presence of $Al(Oi\text{-}Pr)_3$ afforded the desired Δ4-3-ketosteroid derivatives **5a–f** containing the (N-arylcarbamoylthiocarbonyl)pyrazoline moiety fused to positions 16α,17α in 64–69% yield.



Scheme 1

The structures of the reaction products were confirmed by elemental analyses, MS, ^{1}H and ^{13}C NMR. A series of 2D NMR experiments (COSY, TOCSY, ROESY, HSQS, HMBC) was used for the assignment of ^{1}H and ^{13}C NMR spectra as well as for the determination of the stereochemistry of the ring D/pyrazoline fusion.

The ^{1}H NMR spectra exhibit signals of one amide proton at δ 8.27, four aromatic protons in the range of δ 7.55–7.26, and four methine protons at δ 5.32, 5.08, 3.53 and 3.21. All other aliphatic protons signals are between δ 2.5 and 0.8; three methyl groups resonate at δ 2.10, 1.01 and 0.97. Isolated spin systems for rings A and all protons of rings B, C, and D of the steroid

were found in the TOCSY spectrum; the COSY spectrum enabled the proton assignment of each spin system. The ^{13}C spectrum of **5a** contains 27 different signals, which were assigned using the APT method. Three methyl, seven methylene, six methine, three protic sp^2-carbon atoms, two quaternary sp^3- and six aprotic sp^2 carbon atoms were identified.

Table 1. Yields, melting points, and elemental analysis data for products **2–5**

2–5	Yield [%]	mp [°C]	% Found/Calculated						Formula
			C	H	N	S	Cl	F	
2a	84	190–195 (dec.)	65.52 65.53	6.68 6.74	7.46 7.40	5.59 5.64	6.32 6.24	–	$C_{31}H_{38}ClN_3O_3S$
2b	82	187–191 (dec.)	67.45 67.49	6.81 6.94	7.58 7.62	5.75 5.81	–	3.58 3.44	$C_{31}H_{38}FN_3O_3S$
2c	85	185–188 (dec.)	68.10 68.18	7.20 7.33	7.46 7.45	5.55 5.69	–	–	$C_{32}H_{41}N_3O_4S$
2d	83	179–183 (dec.)	67.50 67.49	6.89 6.94	7.59 7.62	5.75 5.81	–	3.52 3.44	$C_{31}H_{38}FN_3O_3S$
2e	81	182–186 (dec.)	68.20 68.18	7.25 7.33	7.49 7.45	5.55 5.69	–	–	$C_{32}H_{41}N_3O_4S$
2f	80	173–177 (dec.)	70.20 70.17	7.25 7.54	7.49 7.67	5.55 5.85	–	–	$C_{32}H_{41}N_3O_3S$
3a	80	189–193 (dec.)	65.56 65.53	6.69 6.74	7.45 7.40	5.54 5.64	6.35 6.24	–	$C_{31}H_{38}ClN_3O_3S$
3b	76	185–190 (dec.)	67.47 67.49	6.81 6.94	7.60 7.62	5.77 5.81	–	3.56 3.44	$C_{31}H_{38}FN_3O_3S$
3c	78	183–187 (dec.)	68.15 68.18	7.36 7.33	7.38 7.45	5.72 5.69	–	–	$C_{32}H_{41}N_3O_4S$
3d	81	179–183 (dec.)	67.50 67.49	6.89 6.94	7.59 7.62	5.75 5.81	–	3.52 3.44	$C_{31}H_{38}FN_3O_3S$
3e	83	183–186 (dec.)	68.20 68.18	7.25 7.33	7.49 7.45	5.55 5.69	–	–	$C_{32}H_{41}N_3O_4S$
3f	77	171–177 (dec.)	70.20 70.17	7.25 7.54	7.49 7.67	5.55 5.85	–	–	$C_{32}H_{41}N_3O_3S$
4a	84	>196 (dec.)	66.31 66.20	6.85 6.90	8.03 7.99	5.97 6.09	6.73 6.74	–	$C_{29}H_{36}ClN_3O_2S$
4b	82	>187 (dec.)	68.41 68.34	6.96 7.12	8.34 8.24	6.35 6.29		3.63 3.73	$C_{29}H_{36}FN_3O_2S$
4c	85	>183 (dec.)	69.10 69.07	7.46 7.53	8.13 8.05	6.25 6.15	–	–	$C_{30}H_{39}N_3O_3S$

Table 1. Continued

2–5	Yield [%]	mp [°C]	% Found/Calculated						Formula
			C	H	N	S	Cl	F	
4d	83	>189 (dec.)	68.45 68.34	7.19 7.12	8.38 8.24	6.25 6.29	–	3.56 3.73	$C_{29}H_{36}FN_3O_2S$
4e	81	>185 (dec.)	69.10 69.07	7.50 7.53	7.98 8.05	6.17 6.15	–	–	$C_{30}H_{39}N_3O_3S$
4f	80	>184 (dec.)	71.20 71.25	7.75 7.77	8.39 8.31	6.31 6.34	–	–	$C_{30}H_{39}N_3O_2S$
5a	68	>195 (dec.)	66.51 66.46	6.49 6.54	8.05 8.02	6.16 6.12	6.70 6.76	–	$C_{29}H_{34}ClN_3O_2S$
5b	69	>197 (dec.)	68.65 68.61	6.79 6.75	8.30 8.28	6.26 6.32	–	3.71 3.74	$C_{29}H_{34}FN_3O_2S$
5c	67	>195 (dec.)	69.30 69.33	7.20 7.18	8.06 8.09	6.15 6.17	–	–	$C_{30}H_{37}N_3O_3S$
5d	64	>199 (dec.)	68.58 68.61	6.80 6.75	8.31 8.28	6.35 6.32	–	3.63 3.74	$C_{29}H_{34}FN_3O_2S$
5e	66	>192 (dec.)	69.30 69.33	7.20 7.18	8.06 8.09	6.20 6.17	–	–	$C_{30}H_{37}N_3O_3S$
5f	68	>193 (dec.)	71.50 71.54	7.38 7.40	8.40 8.34	6.35 6.37	–	–	$C_{30}H_{37}N_3O_2S$

All correlations between carbons and protons through one bond were found in the HSQC spectrum. The HMBC spectrum permits the assignment of all quaternary atoms and inter-connections between the steroid and the N-(4-chlorophenyl)carbamoylthiocarbonylpyrazoline moiety. The stereochemistry was explored with 1D- and 2D-ROESY experiments. The ROESY spectrum revealed the correlations between H-16 and H-15, H-15', H-17, H-18 as well as between H-17 and H-18. These correlations are possible only in the case of the 16α,17α-configuration of ring D (Figure 1). No correlations between H-14 and H-16 or H-17 were found. The observed correlations between H-3 and H-1', H-2 and both H-4 and H-4' are possible only with the 3-OH group in β-position.

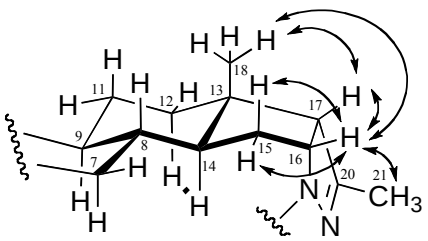


Figure 1. The most important ROESY correlations between protons of the steroidal ring D.

Table 2. ^{1}H NMR and MS data for **2–5**

2–5	^{1}H NMR (500. MHz, $CDCl_3$): δ	MS: M+ m/z (%)
2a	0.97 (s, 3 H, 18-Me), 1.01 (s, 3H, 19-Me); 2.10 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 4.61 (m, 1H, 3-H), 5.32 (m, 1H, 6-H), 6.43 (m, 1H, 16-H), 7.25, 7.27 (AA', 2H, H_{Ar}), 7.54, 7.56 (BB', 2H, H_{Ar}), 10.20 (s, 1H, NH), 11.75 (s, 1H, NH).	567 (27)
2b	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 4.61 (m, 1H, 3-H), 5.40 (m, 1H, 6-H), 6.43 (m, 1H, 16-H), 7.10 (m, 2H, H_{Ar}), 7.70 (m, 2H, H_{Ar}), 10.20 (s, 1H, NH), 11.70 (s, 1H, NH).	551 (22)
2c	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.85 (s, 3H, OMe), 4.61 (m, 1H, 3-H), 5.40 (m, 1H, 6-H), 6.43 (m, 1H, 16-H), 6.59, 6.61 (AA', 2H, H_{Ar}), 7.59, 7.61 (BB', 2H, H_{Ar}), 10.10 (s, 1H, NH), 11.80 (s, 1H, NH).	563 (21)
2d	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 4.61 (m, 1H, 3-H), 5.40 (m, 1H, 6-H), 6.43 (m, 1H, 16-H), 6.81 (m, 1H, H_{Ar}), 7.22 (m, 2H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 10.10 (s, 1H, NH), 11.80 (s, 1H, NH).	551 (16)
2e	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.85 (s, 3H, OMe), 4.61 (m, 1H, 3-H), 5.40 (m, 1H, 6-H), 6.43 (m, 1H, 16-H), 6.70 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.03 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.20 (m, 1H, H_{Ar}), 7.36 (s,1H, H_{Ar}), 10.10 (s, 1H, NH), 11.80 (s, 1H, NH).	563 (23)
2f	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 2.32 (s, 3H, Me_{Ar}), 4.61 (m, 1H, 3-H), 5.40 (m, 1H, 6-H), 6.43 (m, 1H, 16-H), 7.10 (m, 1H, H_{Ar}), 7.22 (m, 2H, H_{Ar}), 7.93 (m, 1H, H_{Ar}), 10.10 (s, 1H, NH), 11.80 (s, 1H, NH).	547 (25)
3a	0.97 (s, 3 H, 18-Me), 1.01 (s, 3H, 19-Me, 2.10 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.21 (d, J = 8.2 Hz, 1H, 17-H), 4.61 (m, 1H, 3-H), 5.08 (t, J = 7.8 Hz, 1H, 16-H), 5.32 (m, 1H, 6-H), 7.25, 7.27 (AA', 2H, H_{Ar}), 7.54, 7.56 (BB', 2H, H_{Ar}), 8.27 (s, 1H, NH).	567 (19)
3b	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.22 (d, J = 8.21 Hz, H, 17-H), 4.61 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 7.10 (m, 2H, H_{Ar}), 7.70 (m, 2H, H_{Ar}), 8.20 (s, H, NH).	551 (28)
3c	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.85 (s, 3H, OMe), 4.61 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 6.59, 6.61 (AA', 2H, H_{Ar}), 7.59, 7.61 (BB', 2H, H_{Ar}), 8.10 (s, 1H, NH).	563 (22)

Table 2. Continued

2–5	^{1}H NMR (500. MHz, $CDCl_3$): δ	MS: M+ m/z (%)
3d	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 4.61 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 6.81 (m, 1H, H_{Ar}), 7.22 (m, 2H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 8.10 (s, 1H, NH).	551 (18)
3e	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.85 (s, 3H, OMe), 4.61 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 6.70 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.03 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.20 (m, 1H, H_{Ar}), 7.36 (s, 1H, H_{Ar}), 8.10 (s, 1H, NH).	563 (26)
3f	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.20 (s, 3H, OAc), 2.32 (s, 3H Me_{Ar}), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 4.61 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H,), 5.40 (m, 1H, 6-H), 7.10 (m, 1H, H_{Ar}), 7.22 (m, 2H, H_{Ar}), 7.93 (m, 1H, H_{Ar}), 8.10 (s, 1H, NH).	547 (17)
4a	0.97 (s, 3 H, 18-Me), 1.01 (s, 3H, 19-Me), 2.10 (s, 3H, 21-Me), 3.21 (d, J = 8.2 Hz, 1H, 17-H), 3.53 (m, 1H, 3-H), 5.08 (t, J = 7.8 Hz, 1H, 16-H), 5.32 (m, 1H, 6-H), 7.24, 7.26 (AA', 2H, H_{Ar}), 7.54, 7.56 (BB', 2H, H_{Ar}), 8.27 (s, 1H, NH).	525 (28)
4b	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.52 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 7.10 (m, 2H, H_{Ar}), 7.70 (m, 2H, H_{Ar}), 8.20 (s, 1H, NH).	509 (27)
4c	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.52 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.4 (m, 1H, 6-H), 6.89, 6.91 (AA', 2H, H_{Ar}), 7.59, 7.61 (BB', 2H, H_{Ar}), 8.00 (s, 1H, NH).	521 (23)
4d	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.52 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 6.81 (m, 1H, H_{Ar}), 7.22 (m, 3H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 8.10 (s, 1H, NH).	509 (14)
4e	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.85 (s, 3H, OMe), 3.52 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 6.70 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.03 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.20 (m, 1H, H_{Ar}), 7.36 (s, 1H, H_{Ar}), 8.10 (s, 1H, NH).	521 (24)
4f	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21Me), 2.32 (s, 3H Me_{Ar}), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.52 (m, 1H, 3-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.40 (m, 1H, 6-H), 7.10 (m, 1H, H_{Ar}), 7.22 (m, 2H, H_{Ar}), 7.93 (m, 1H, H_{Ar}), 8.10 (s, 1H, NH).	505 (16)

Table 2. Continued

2–5	^{1}H NMR (500. MHz, $CDCl_3$): δ	MS: M+ m/z (%)
5a	0.97 (s, 3 H, 18-Me), 1.01 (s, 3H, 19-Me), 2.10 (s, 3H, 21-Me), 3.21 (d, J = 8.2 Hz, 1H, 17-H), 5.75 (s, 1H, 4-H), 5.08 (t, J = 7.8 Hz, 1H, 16-H), 7.25, 7.27 (AA', 2H, H_{Ar}), 7.54, 7.56 (BB', 2H, H_{Ar}), 8.27 (s, 1H, NH).	523 (27)
5b	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.75 (s, 1H, 4-H), 7.10 (m, 2H, H_{Ar}), 7.70 (m, 2H, H_{Ar}), 8.20 (s, 1H, NH).	507 (17)
5c	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.75 (s, 1H, 4-H), 6.89, 6.91 (AA', 2H, H_{Ar}), 7.59, 7.61 (BB', 2H, H_{Ar}), 8.00 (s, 1H, NH).	519 (23)
5d	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.75 (s, 1H, 4-H), 6.81 (m, 1H, H_{Ar}), 7.22 (m, 3H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 8.10 (s, 1H, NH).	507 (16)
5e	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 3.85 (s, 3H, OMe), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.75 (s, 1H, 4-H), 6.70 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.03 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.20 (m, 1H, H_{Ar}), 7.36 (s, 1H, H_{Ar}), 8.10 (s, 1H, NH).	519 (22)
5f	1.05 (s, 3 H, 18-Me), 1.10 (s, 3H, 19-Me), 2.05 (s, 3H, 21-Me), 2.32 (s, 3H Me_{Ar}), 3.22 (d, J = 8.2 Hz, 1H, 17-H), 5.15 (t, J = 7.8 Hz, 1H, 16-H), 5.75 (s, 1H, 4-H), 7.10 (m, 1H, H_{Ar}), 7.22 (m, 2H, H_{Ar}), 7.93 (m, 1H, H_{Ar}), 8.10 (s, 1H, NH).	503 (14)

Table 3. ^{13}C NMR data for **4a**

Atom number	δ_{13C}	Atom number	δ_{13C}	Atom number	δ_{13C}	Atom number	δ_{13C}
1	37.16	8	31.73	15	32.80	22	183.85
2	31.39	9	49.41	16	65.70	23	162.07
3	71.46	10	36.45	17	65.75	24	165.90
4	42.09	11	20.81	18	20.74	25	136.17
5	140.43	12	35.74	19	19.28	26	121.02
6	121.09	13	46.54	20	165.98	27	128.81
7	31.84	14	50.40	21	17.38	28	129.48

Experimental Section

General Procedures. All solvents were dried by standard methods. NMR spectra of $CDCl_3$ solutions were recorded with a Bruker DRX-500 instrument (500 MHz) at 303K. The residual proton and carbon signals of $CDCl_3$ (δ_H 7.27, δ_C 77.0) were taken as the internal standards. 2D experiments were performed using standard Bruker software. The TOCSY spectra were recorded with 200 ms duration of MLEV-17 spin-lock, the ROESY spectra were recorded with 200 ms duration of spin-lock. 1D-selective ROESY spectra were recorded using 50 ms shaped pulse. The HMBC spectrum was optimized for the coupling constant of 8 Hz. The mass spectra were obtained on a Kratos instrument using a direct inlet system; ionization energy 70 eV; accelerating voltage 1.75 kV. Melting points were measured with a Boetius hot-stage apparatus. All reaction mixtures were analyzed; the purity of the products was checked by TLC (Silica gel 60 F_{254}, Merck, ethyl acetate /hexane, 1:1 v/v, as the eluent). Silica gel 60 (0.04-0.063 mm. Merck-Schuchardt) was used for column chromatography. Starting materials **1**[6] and **2a–f**[7] were prepared by literature procedures. All other reagents are commercially available and were used as received.

N-Aryl-2-thioxoacetamido-2-hydrazones of 3β-acetoxypregna-5,16-dien-20-one (2a–f). General procedure

A solution of 3β-acetoxypregna-5,16-dien-20-one (**1**) (2.14 g, 6 mmol) and the corresponding N-aryl-2-hydrazinyl-2-thioxoacetamide (6 mmol) was refluxed in ethanol (20 mL) in the presence of glacial acetic acid (1 mL) for 4 h. After cooling the resulting light yellow solid was sucked off, washed with ethanol, dried in vacuo, and recrystallized from ethanol to give pure bright yellow crystals **2a–f** (Tables 1 and 2).

1'-Arylcarbamoylthiocarbonyl-3'-methyl-3β-acetoxyandrost-5-eno[16α,17α-d]pyrazolines (3a–f). General procedure

A solution of hydrazone **2a–f** (6 mmol) was refluxed in glacial acetic acid (70 mL). After 4 h, the reaction mixture was cooled, diluted with water (300 mL) and left at room temperature for 16 h. The precipitate formed was sucked off, washed with water and heptane, and dried in vacuo. Purification by column chromatography on silica gel (hexane/ethyl acetate 4:1 as eluent) gave light yellow crystals **3a–f** (Tables 1 and 2).

1'-Arylcarbamoylthiocarbonyl-3'-methyl-3β-hydroxyandrost-5-eno[16α,17α-d]pyrazolines (4a–f). General procedure

A solution of acetate **3a–f**, (6 mmol) in 2N NaOH in ethanol (50 mL) was stirred at room temperature for 5 min. The reaction mixture was diluted with water (500 mL). The resulting precipitate was sucked off and dried on air. The product was purified by column chromatography (silica gel, hexane/ethyl acetate 3:1 as eluent) to give light yellow crystals **4a–f** as (Tables 1 and 2). The ^{13}C-NMR spectrum of **4a** is listed in Table 3.

1'-Arylcarbamoylthiocarbonyl-3'-methyl-3-oxoandrost-4-eno[16α,17α-d]pyrazolines (5a–f). General procedure

To a solution of 3β-hydroxyandrost-5-eno[16α,17α-d]pyrazolines **4a-f** (2 mmol) in dry toluene (40 mL) and freshly distilled cyclohexanone (15 mL) was added a solution of aluminum isopropoxide (817 mg, 4 mmol) in toluene (30 mL). The resulting solution was refluxed for 3 h. Excess of aluminum isopropoxide was destroyed by adding aqueous acetic acid (30%, 600 mL). The toluene layer was separated and washed with satd. aq. $NaHCO_3$ solution. The aqueous phase was extracted with chloroform and washed with satd. aq. $NaHCO_3$ solution. The organic extracts were combined, washed with water, dried (Na_2SO_4), and evaporated in vacuo; cyclohexanone was removed by steam distillation. The product was purified by column chromatography (silica gel, hexane/ethyl acetate 3:1 as eluent) to give light yellow crystals **5a–f** (Tables 1 and 2).

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