Synthesis of 21-Aryl and Heteroaryl Ethisterones and the Corresponding A-Ring Substituted [2,3-*d*]Isoxazoles

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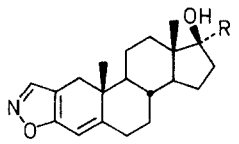
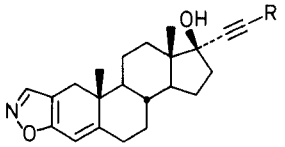
Palladium(0) catalyzed coupling reaction of ethisterone [**6**; (17α)-17-hydroxypregn-4-en-20-yn-3-one] with aromatic/heteroaromatic halides gave C-21 substituted derivatives **7**. Hydroxymethylation of the latter compounds followed by treatment with hydroxylamine hydrochloride resulted in the formation of 21-substituted (17α)-pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17-ols **3**.

In continuing our efforts to explore the structure–activity relationships of Danazol (**1**),[1] an orally active pituitary gonadotropin inhibitor, and to map the steric requirements at C-17 position of the progesterone, androgen and estrogen receptors, we recently reported the synthesis of C-17 substituted compounds of the general structure **2**.[2] Herein, we describe the synthesis of C-21 substituted derivatives of Danazol of the general structure **3** that involves a palladium(0) catalyzed cross-coupling reaction as the key step.



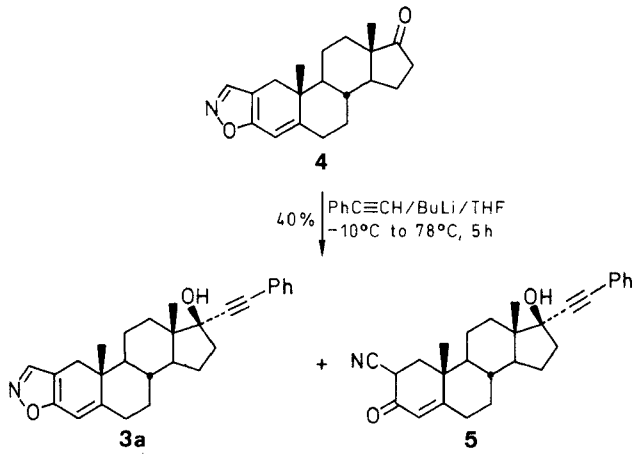
1 R = C≡CH
2 R = aryl, heteroaryl



3 R = aryl, heteroaryl

Terminal acetylenes are known[3–5] to be readily substituted with aromatic and heteroaromatic halides (Br, I) in the presence of catalytic amounts of the bis(triphenylphosphine)dichloropalladium(II), copper(I) iodide or other palladium(0) catalysts. These cross-coupling reactions are usually performed in low boiling amines (such as diethylamine, triethylamine, pyridine, etc.) as solvents. However, this methodology was not applicable for the synthesis of **3** directly from Danazol (**1**), due to the base sensitivity of the isoxazole ring. The predominant products were 2-cyano ketones **5**[2] when the reaction was run in triethylamine and a co-solvent such as tetrahydrofuran (Scheme 1).

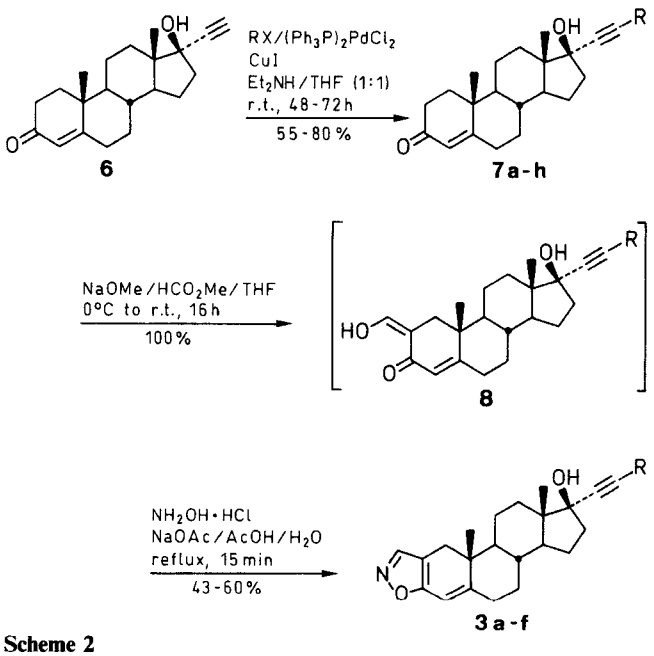
Recently Jordon and Koch[6] have reported estrogenic and antiestrogenic activities of various C-21 substituted ethynyl estradiols. These compounds could be synthesized by the addition of the corresponding sodium or lithium acetylides to the C-17 ketone, estrone.[7,8] Following these procedures, the addition of lithium phenylacetylide to 17-oxoandrosta-2,4-dieno[2,3-*d*]isoxazole **4**[2] was attempted to prepare the C-21 phenyl derivative (Scheme 1). When the reaction was run at −78 °C, the desired product **3a** (R = Ph) was isolated in only 40% yield along with 2-cyano ketone **5** (R = Ph, 30%) and the recovered starting material **4** (25%). At higher temperatures (−50 °C to 0 °C), the cyano ketone **5** (R = Ph) was the major product isolated.



Scheme 1

Even though we were able to prepare compound **3a** (R = Ph) in a reasonable yield by the above scheme, there are limitations to this route: not all the aromatic/heteroaromatic acetylenes are readily available and they need to be synthesized individually; the low yield of the final product is due to the competitive formation of the side product, 2-cyano ketone **5**.

To circumvent these problems we have devised a two-step procedure (Scheme 2) for the target compounds starting from the commercially available ethisterone, (17α)-17-hydroxypregn-4-en-20-yn-3-one (**6**). The C-21 hydrogen of ethisterone was reacted with various aromatic and heteroaromatic halides (Br, I) in the presence of



Scheme 2

Table 1. C-21-Substituted (17α)-17-Hydroxypregn-4-en-20-yn-3-ones **7**

Product	R	mp (°C)	Yield (%)[a]	IR (KBr) ν (cm^{-1})	MS (M$^+$)[b] m/z	^{1}H NMR ($CDCl_3$) δ, J (Hz)
7a	Ph	186–188 (Lit.[7], 185–187)	55	3480, 3000, 2800, 1660, 1615	388 ($C_{27}H_{32}O_2$)	0.80–3.00 (m, 20H), 1.00 (s, 3H), 1.22 (s, 3H), 5.80 (s, 1H), 7.20–7.60 (m, 5H)
7b	4-FC_6H_4	171–173	66	3420, 3020, 2830, 1658, 1612, 1600	406 ($C_{27}H_{31}FO_2$)	0.70–3.00 (m, 20H), 0.96 (s, 3H), 1.20 (s, 3H), 5.76 (s, 1H), 6.96 (d, J = 8.0, 2H), 7.39 (dd, J = 8.0, 6.5, 2H)
7c	2-pyridyl	222–224	65	3500, 3180, 2940, 1680, 1663, 1617	384 ($C_{26}H_{31}NO_2$)	0.80–3.10 (m, 20H), 0.98 (s, 3H), 1.22 (s, 3H), 4.66 (bs, 1H), 5.73 (s, 1H), 7.10 (t, J = 2.5, 4.5, 1H), 7.40 (d, J = 3.8, 1H), 7.80 (t, J = 2.4, 4.5, 1H), 8.55 (d, J = 3.5, 1H)
7d	4-$NO_2C_6H_4$	204–206	80	3350, 3100, 2940, 2220, 1658, 1615, 1512, 1342	433 ($C_{26}H_{31}NO_4$)	0.80–3.20 (m, 20H), 1.01 (s, 3H), 1.24 (s, 3H), 3.08 (s, 1H), 5.77 (s, 1H), 7.54 (d, J = 9.0, 2H), 8.13 (d, J = 9.2, 2H)
7e	4-$Me_2NC_6H_4$	190–192	72	3600, 3100, 2203, 1650, 1605	431 ($C_{29}H_{37}NO_2$)	0.70–2.80 (m, 20H), 0.96 (s, 3H), 1.20 (s, 3H), 2.95 (s, 6H), 5.76 (s, 1H), 6.58–7.30 (m, 4H)
7f	4-NCC_6H_4	218–220	70	3500, 3110, 2225, 1670, 1615	413 ($C_{28}H_{31}NO_2$)	1.00 (s, 3H), 1.30 (s, 3H), 1.25–2.60 (m, 20H), 5.70 (s, 1H), 7.40–7.55 (m, 4H)
7g	3-$F_3CC_6H_4$	175–177	68	3425, 3280, 1660, 1616	456 ($C_{28}H_{31}F_3O_2$)	1.00 (s, 3H), 1.20 (s, 3H), 1.30–2.70 (m, 20H), 5.85 (s, 1H), 7.30–7.70 (m, 4H)
7h	2-thienyl	170–172	72	3480, 3100, 1665, 1620	394 ($C_{25}H_{30}O_2S$)	0.88–2.80 (m, 20H), 0.92 (s, 3H), 1.15 (s, 3H), 5.80 (s, 1H), 7.10 (dd, J = 3.4, 4.0, 1H), 7.20 (d, J = 4.5, 1H), 7.30 (d, J = 4.0, 1H)

[a] Yields are of isolated pure products.
[b] Satisfactory microanalysis obtained: C ± 0.4, H ± 0.4, N ± 0.4, F ± 0.4, S ± 0.4.

bis(triphenylphosphine)dichloropalladium(II), copper(I) iodide, diethylamine/tetrahydrofuran (1:1) to give the C-21 substituted ethisterone derivatives **7a–h** (Table 1). Due to the insolubility of ethisterone in diethylamine, tetrahydrofuran was added as a co-solvent to expedite the reaction. A similar reaction was carried out by Arcadi and co-workers[9,10] during the palladium-catalyzed reductive addition of aryl iodides to various propargyl alcohols. The palladium-catalyzed coupling reaction tolerated a wide range of electron-withdrawing or electron-donating functional groups (Table 1). Hence this methodology should be widely applicable in the synthesis of the C-21 substituted steroids.

Hydroxymethylation with sodium methoxide and methyl formate in tetrahydrofuran of representative examples of **7** gave the intermediate **8** which was reacted with hydroxylamine hydrochloride and sodium acetate in acetic acid and water following the known procedure[1] resulting in the formation of [2,3-*d*]isoxazole steroids **3a–f** (Table 2).

In conclusion, we have reported an efficient method to introduce aromatic and heteroaromatic groups at the C-21 position of the steroids.

Melting points were taken using a Mel Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Model HA-100 or Bruker-AC 200 Spectrometer with TMS as an internal standard. IR spectra were obtained on a Perkin-Elmer Model 21 spectrometer. Mass spectra were determined using a Jeolco JMS-OISC Model instrument. TLC was performed on E. Merck 5 × 20 cm Kieselgel 60F-254 plates. The products were purified on a Waters Prep-500 instrument using standard silica Prep-Pak cartridges.

21-Substituted- (17α)-17-Hydroxypregn-4-en-20-yn-3-ones 7a–h; General Procedure:

To a solution of ethisterone (0.03 mol) in freshly distilled Et_2NH (50 mL) and anhydr. THF (50 mL) was added the aromatic/heteroaromatic bromides or iodides (0.036 mol) followed by bis(triphenylphosphine)dichloropalladium(II) (0.28 mmol) and CuI (0.16 mmol). After stirring under Ar at r.t. for 48–72 h, the mixture was filtered and evaporated to dryness. The residue was partioned between CH_2Cl_2 and H_2O. The organic layer was separated, washed with salt solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product which was then purified using HPLC (hexanes/EtOAc, 4:1) affording **7a–h** (Table 1).

21-Substituted- (17α)-Pregna-2,4-dien-20-yno[2,3-d]isoxazol-17-ols 3a–f; General Procedure:

To a solution of the steroid **7** (0.053 mol) in anhydr. THF (50 mL), cooled to 0°C, was added a suspension of NaOMe (0.137 mol) in MeOH (5 mL). After stirring for 10 min at this temperature, methyl formate (0.27 mol) was added dropwise within 5 min. The ice-bath was removed and the mixture was stirred for an additional 16 h at r.t., H_2O (60 mL) was added slowly and the mixture was neutralized with 12 N HCl. The THF layer was separated and dried ($MgSO_4$) and evaporated to give a yellow foam. The ^{1}H NMR showed the

Table 2. C-21-Substituted (17α)-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17-ols **3**

Product	R	mp (°C)	Yield (%)[a]	IR (KBr) ν (cm^{-1})	MS (M^+)[b] *m/z*	NMR ($CDCl_3$) δ, *J* (Hz)
3a	Ph	175–177	48	3400, 3300, 2840, 1612, 1572, 1490	413 ($C_{28}H_{31}NO_2$)	0.97 (s, 3 H), 1.04 (s, 3 H), 1.10–2.70 (m, 19 H), 6.16 (s, 1 H), 7.20–7.50 (m, 5 H), 7.96 (s, 1 H)
3b	4-FC_6H_4	182–184	60	3350, 2980, 2840, 1600, 1505	431 ($C_{28}H_{30}FNO_2$)	0.78 (s, 3 H), 1.04 (s, 3 H), 1.20–3.20 (m, 19 H), 6.20 (s, 1 H), 6.80 (m, 2 H), 7.25–7.60 (m, 2 H), 7.95 (s, 1 H)
3c	2-pyridyl	222–224	45	3480, 3000, 2840, 1610, 1530	414 ($C_{27}H_{30}N_2O_2$)	1.00 (s, 3 H), 1.05 (s, 3 H), 1.25–2.85 (m, 19 H), 6.20 (s, 1 H), 7.20 (t, J = 2.5, 4.8, 1 H), 7.45 (d, J = 4.0, 1 H), 7.60 (t, J = 2.4, 4.5, 1 H), 8.00 (s, 1 H), 8.55 (d, J = 4.0, 1 H)
3d	3-$F_3CC_6H_4$	179–181	52	3420, 3300, 2230, 1615, 1535	481 ($C_{29}H_{30}F_3NO_2$)	1.00 (s, 3 H), 1.10 (s, 3 H), 1.20–3.85 (m, 19 H), 6.20 (s, 1 H), 7.30–7.85 (m, 4 H), 7.97 (s, 1 H)
3e	4-$NO_2C_6H_4$	155–157 (d)	43	3200, 3100, 2840, 2220, 1630, 1520, 1475, 1445	458 ($C_{28}H_{30}N_2O_4$)	1.00 (s, 3 H), 1.15 (s. 3 H), 1.30–2.90 (m, 19 H), 6.15 (s, 1 H), 7.50 (d, J = 8.5, 2 H), 7.98 (s, 1 H), 8.15 (d, J = 8.0, 2 H)
3f	2-thienyl	158–160	44	3460, 3100, 2840, 1605, 1518, 1472	419 ($C_{26}H_{29}NO_2S$)	0.88 (s, 3 H), 1.00 (s, 3 H), 1.10–2.90 (m, 19 H), 6.20 (s, 1 H), 7.00 (dd, J = 3.6, 4.0, 1 H), 7.20 (d, J = 4.5, 1 H), 7.35 (d, J = 4.2, 1 H), 8.15 (s, 1 H)

[a] Yield of isolated pure products after two steps.
[b] Satisfactory microanalysis obtained: C ± 0.4, H ± 0.4, N ± 0.4, F ± 0.4, S ± 0.4.

2-hydroxymethylene derivative **8** (δ, br s, 7.50) which was sufficiently pure to be used directly in the next step.

A mixture of 2-hydroxymethylene derivative **8** (0.052 mol), $NH_2OH \cdot HCl$ (0.057 mol) and anhydr. NaOAc (0.062 mol) in AcOH (150 mL) and H_2O (12 mL) was refluxed for 15 min. The yellow solution was then poured into an excess of ice-water and the resulting solid was filtered off and dried. The product was then purified either on a Florosil column (CH_2Cl_2) or on HPLC (hexanes/EtOAc, 7:3) to give the isoxazole **3a–h** (Table 2).

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