ADDITION OF ARYLZIRCONIUM TRIBUTOXIDES TO 17-KETOSTEROIDS

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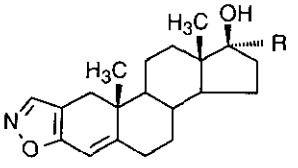
Abstract— Reaction of 17-oxoandrost-2,4-dieno[2,3-d]isoxazole **3** with arylzirconium tributoxides gives the corresponding C-17 aryl carbinols. Arylzirconium tributoxides are selective nucleophiles towards readily enolizable 17-ketosteroids and are less basic than lithium and Grignard reagents.

Danazol (**1**) is an orally active pituitary gonadotropin inhibitor with an unsubstituted isoxazole ring fused to the steroid A-ring.[1,2] For the purpose of exploring structure-activity relationships, we required a number of C-17 substituted compounds having the general structure **2**, in which the C-17 acetylene group of **1** is replaced by an aromatic or heteroaromatic ring.



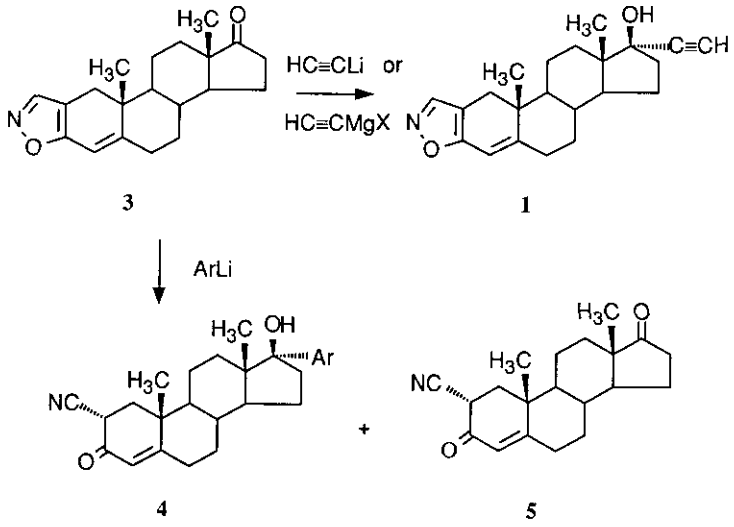
1 R = C≡CH

2 R = Ar

Formation of C-17 substituted steroids by the reaction of 17-ketosteroids with organolithium and Grignard reagents is well known[3,4] and this methodology has also been applied to 17-ketosteroids containing an isoxazole ring .[5] Reaction of 17-oxoandrost-2,4-dieno[2,3-d]isoxazole **3** with lithium acetylide or ethynylmagesium halide has to be carried out at -70 °C to -40 °C in order to minimize the base promoted cleavage of the isoxazole ring.

In our hands, aryllithium and aryl Grignard reagents failed to react with the ketone **3** at -70 °C. At higher

temperatures (-5 °C to 0 °C), for example phenyllithium, resulted in substantial amounts of the cyanoketones **4** (Ar=Ph, 28%) and **5** (39%) along with the recovered starting ketone **3** (17%).



3 **1** **4** **5**

Seebach and Reetz[6,7] have reported that organozirconium reagents are less basic than the corresponding lithium or Grignard reagents and undergo nucleophilic addition to aldehydes and ketones. We anticipated that as a result of the reduced basicity of zirconium reagents ring fragmentation of the isoxazole in **3** would not occur.

Arylzirconium reagents were prepared by a slight modification of the reported procedure[6]. Commercially available zirconium tetrabutoxide-n-butanol complex was decomposed by heating at 80-100°C with the removal of n-butanol at reduced pressure. Zirconium tetrabutoxide obtained in this manner was sufficiently pure (>95%, 60MHz ^{1}H-nmr) for subsequent reactions. An ethereal stock solution of chlorozirconium tributoxide was prepared from zirconium tetrabutoxide and zirconium tetrachloride according to Seebach's procedure.[6] A solution of organozirconium reagent **6** was then obtained by the addition of a solution of the appropriate aryllithium.

$$\text{Ar-Li} + \text{ClZr(OBu)}_3 \longrightarrow \text{Ar-Zr(OBu)}_3 + \text{LiCl}$$

6

Ketone **3** in dichloromethane was added to an ethereal solution of **6** to give the corresponding carbinols **2** (Table **1**). Grignard reagents may also be used to form **5** (Table **1**, products **2c** and **2d**). Moreover, the dianion prepared from 2-bromophenol and n-butyllithium[3] reacted with 2 moles of chlorozirconium tributoxide to give a reagent

which reacted with ketone **3** selectively to give **2e** (Table **1**).

Table **1**

$Ar\text{-}Zr(OBu)_3$

3 ⟶ **2**

Product	R	% Yield[e]	Ratio C-17α to C-17β
a	C_6H_5	50	1:1[a,b]
b	4-FC_6H_4	51	1:1[a,b]
c	4-$CH_3C_6H_4$	87	α(38%), β(49%)[c,d]
d	4-$CH_3OC_6H_4$	42	α(15%), β(27%)[c,d]
e	2-HOC_6H_4	57	α only[c,d]
f	2-furyl	45	α only[c,d]
g	2-thienyl	27	3:1[a,b]

(*a*) Relative ratio was determined by ^{1}H-nmr(100MHz) integration of the isoxazole (N=CH) proton resonance signals. The isoxazole proton of the C-17β steroid is observed at lower field compared to C-17α steroid (see experimental).

(*b*) Non-separable mixture.

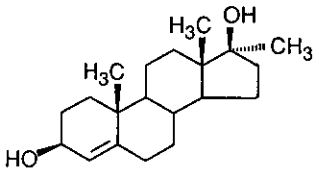
(*c*) Isolated yields in parenthesis.

(*d*) The structural assignment was made by comparison of the C_{18}- and C_{19}-CH_3 resonance signals of known C-17α and C-17β substituted steroids.[9]

(*e*) Overall isolated yield of addition product. Cyanoketone **5** was also isolated in 1-2% yield.

In most cases arylzirconium reagents were not as stereoselective in their addition to ketone **3** as the related lithium or Grignard reagents[3,4] which normally give the α-isomer. This might suggest that the large arylzirconium and its ligands chelate strongly with the 17-carbonyl oxygen and the transition state energy for reaction of the resulting complex may overcome the steric bias for α-selectivity posed by the C_{18}-CH_3 group, causing the loss of facial selectivity.[10] In contrast methylzirconium tributoxide was reported[6] to give only the α-isomer **7** when reacted with 3β-acetoxy-5-androstan-17-one followed by the basic hydrolysis of the intermediate. In accord with this report we also isolated the known 17α-methyl isomer[2] **8** in 80% yield when

methylzirconium tributoxide was reacted with ketone **3**. Thus the strain of the intermediary chelate may influence the stereoselectivity.



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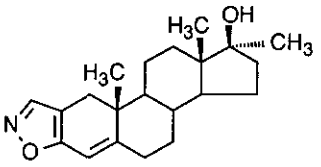

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Arylzirconium reagents were stereoselective when an oxygen atom was present next to the carbon bearing zirconium. In these examples only the α-isomers were obtained (Table **1, 2e** and **2f**). Possibly the intramolecular chelation between the adjacent oxygen and arylzirconium and its ligands may have weakened the zirconium/carbonyl chelation.

In conclusion, arylzirconium tributoxides have been demonstrated to be nucleophiles with reduced basicity as compared to aryllithium or Grignard reagents. This has allowed the facile preparation of a number of analogs containing the base sensitive isoxazole ring.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H Nmr spectra were recorded on a Hitachi Perkin-Elmer R-24B (60MHz) or a Varian Model HA-100 spectrometer with tetramethylsilane as an internal standard. Ir spectra were measured with a Perkin-Elmer Model 21 spectrophotometer. Mass spectra were determined using a Jeolco JMS-OISC model instrument. High pressure liquid chromatography was performed on a Waters Prep-500 instrument using standard silica Prep-pak cartridges.

General procedure for the preparation of a C-17 substituted steroid from organozirconium reagent. To a solution of chlorozirconium tributoxide (74 ml, 0.148 mol) in anhydrous ether (200 ml) at -10 °C under argon atmosphere was added either an organolithium or a Grignard reagent (0.144 M) in anhydrous ether (70 ml). The mixture was stirred for 1 h at 0°C, a solution of **3** (15g, 0.048 mol) in dry dichloromethane (100 ml) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into 20% aqueous potassium fluoride solution (400 ml) and ether (400 ml) and acidified with 6N aqueous hydrochloric acid to pH 6.0. The ether layer was separated, washed with water and saturated salt solution, and dried over anhydrous magnesium sulphate. Removal of solvent gave the crude product which was purified by hplc. In each case varying amounts of starting material (**3**) (10-15%) and the cyanoketone (**5**) (1-2%) were also isolated.[11]

(17ξ)-17-Phenylandrost-2,4-dieno[2,3-d]isoxazol-17-ol (**2a**). Light yellow powder, yield (9.5 g, 50%) (ethyl acetate:hexane, 1:1); mp 145-148 °C; ms (m/z) 389 (M^+), 371 (M^+-H_2O); ir vmax (KBr) 3400 (OH), 1630 (C=N), and 1600 cm^{-1} (C=C); ^1H nmr ($CDCl_3$) δ 0.98 (3H, bs, C_{18}-CH_3), 1.10 (3H, s, C_{19}-CH_3), 1.20-2.80 (17H, m), δ 3.55 (1H, bs, OH), 6.10 and 6.18 (1H, s, C_4-H, α and β isomers), 7.00-7.60 (5H, m, ArH), and 7.88 and 7.94 (1H, s, N=CH, α and β isomers). Anal. Calcd for $C_{26}H_{31}NO_2.0.25\ H_2O$: C, 79.29; H, 8.00; N, 3.56. Found: C, 79.58; H, 8.29; N, 3.44.

(17ξ)-17-(4-Fluorophenyl)androst-2,4-dieno[2,3-d]isoxazol-17-ol (**2b**). Yellow powder, yield (10.1 g, 51%) (dichloromethane: hexane, 1:1); mp 195-200 °C; ms (m/z) 407 (M^+), 389 (M^+-H_2O); ir vmax (KBr) 3340-3410 (OH), 1632 (C=N), and 1603 cm^{-1} (C=C); ^1H nmr ($CDCl_3$) δ 1.00 (3H, bs, C_{18}-CH_3), 1.08 (3H, s, C_{19}-CH_3), 1.20-2.90 (17H, m), 6.12 and 6.16 (1H, s, C_4-H, α and β isomers), 6.80-7.20 (2H, t, J=4.0Hz, ArH), 7.20-7.7 (2H, m, ArH), and 7.96 and 8.00 (1H, s, N=CH, α and β isomers). Anal. Calcd for $C_{26}H_{30}FNO_2$: C, 76.63; H, 7.42; N, 3.44; F, 4.66. Found: C, 76.45; H, 7.52; N, 3.29; F, 4.50.

(17β)-17-(4-Methylphenyl)androsta-2,4-dieno[2,3-d]isoxazol-17-ol (**2c**). Bright yellow powder, yield (9.5 g, 49%) (ethyl acetate: hexane, 1:1); mp 110-112 °C (d); ms (m/z) 403 (M^+), 385 (M^+-H_2O); ir vmax (KBr) 3430 (OH), 1640 (C=N), and 1600 cm^{-1} (C=C); ^1H nmr ($CDCl_3$), δ 0.97(3H, s, C_{18}-CH_3), 1.09 (3H, s, C_{19}-CH_3), 1.15-2.60 (17H, m), 2.32 (3H, s, Ar-CH_3), 6.09 (1H, s, C_4-H), 7.00-7.40 (4H, m, ArH), and 7.85 (1H, s, N=CH). Anal. Calcd for $C_{27}H_{33}NO_2\ .0.25\ H_2O$: C, 79.46; H, 8.27; N, 3.43. Found C 79.75; H, 8.54; N, 3.26.

(17α)-17-(4-Methylphenyl)androsta-2,4-dieno[2,3-d]isoxazol-17ol (**2c**). Yellow powder, yield (7.5 g, 38%) (dichloromethane: hexane, 1:1); mp 218-220 °C; ms (m/z) 403 (M^+), 385 (M^+-H_2O), 370 (M^+-H_2O + CH_3); ir vmax (KBr) 3400 (OH), 1643 (C=N), and 1610 cm^{-1} (C=C); ^1H nmr (60MHz, $CDCl_3$) δ 0.45 (3H, s, C_{18}-CH_3), 0.99 (3H, s, C_{19}-CH_3), 1.15-2.90 (17H, m), 2.30 (3H, s, Ar-CH_3), 6.15 (1H, s, C_4-H), 7.25 (4H, m, ArH), and 7.92 (1H, s, N=CH). Anal. Calcd. for $C_{27}H_{33}NO_2$: C, 80.36; H, 8.24; N, 3.47. Found: C, 80.45; H, 8.32; N, 3.49.

(17β)-17-(4-Methoxyphenyl)androsta-2,4-dieno[2,3-d]isoxazol-17-ol (**2d**). White powder, yield (5.11 g, 27%) (ethanol); mp 146-150 °C; ms (m/z) 419 (M^+), 401 (M^+-H_2O); ir vmax (KBr) 3063 (OH), 1637 (C=N), and 1605 cm^{-1} (C=C); ^1H nmr ($CDCl_3$) δ 0.98 (3H, s, C_{18}-CH_3), 1.09 (3H, s, C_{19}-CH_3), 1.15 -2.65 (17H, m), 3.78 (3H, s, Ar-OCH_3), 6.10 (1H, s, C_4-H), 6.82 (2H, d, J = 4.5 Hz, ArH), 7.24 (2H, d, J = 4.5 Hz, ArH), and 7.85 (1H, s, N=CH). Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.34. Found: C, 77.33; H, 8.27; N, 3.25.

(17α)-17-(4-Methoxyphenyl)androsta-2,4-dieno[2,3-d]isoxazol-17-ol (**2d**). Off-white powder, yield (3.0 g, 15%) (ethyl acetate); mp 157-163 °C; ms (m/z) 419 (M^+), 401 (M^+-H_2O), 386 (M^+-H_2O + CH_3); ir vmax (KBr) 3052 (OH), 1637 (C=N), and 1608 cm^{-1} (C=C); ^1H nmr ($CDCl_3$) δ 0.46 (3H, s, C_{18}-CH_3), 1.00 (3H, s, C_{19}-CH_3), 1.10-2.90 (17H, m), 3.80 (3H, s, Ar-OCH_3), 6.16 (1H, s, C_4-H), 6.16 (1H, s, C_4-H), 6.88 (2H, d, J = 4.0 Hz, ArH), 7.40 (2H, d, J = 4.0 Hz, ArH), and 7.92 (1H, s, N=CH). Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.34. Found: C, 77.39; H, 8.06; N, 3.37.

(17β)-17-(2-Hydroxyphenyl)androsta-2,4-dieno[2,3-d]isoxazol-17-ol (**2e**). White powder, yield (11;2 g, 57%) (ethyl acetate); mp 215-216 °C (d); ms (m/z) 405 (M^+), 390 (M^+-CH_3), 387 (M^+-H_2O); ir vmax (KBr) 3280 (OH), 1640 (C=N), and 1600 cm^{-1} (C=C); ^1H nmr ($CDCl_3$) δ 0.98 (3H, s, C_{18}-CH_3), 1.10 (3H, s, C_{19}-CH_3), 1.15-2.80 (17H, m), 6.01 (1H, s, OH), 6.10 (1H, s, C_4-H), 6.60-7.30 (4H, m, Ar-H), 7.90 (1H, s, N=CH) and 9.80 (1H, s, Ar-OH). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.70; N, 3.45. Found: C, 76.84; H, 7.82; N, 3.42.

(17β)-17-(2-Furanyl)androsta-2,4-dieno[2,3-d]isoxazol-17-ol (**2f**). Light brown powder, yield (8.28, 45%) (dichloromethane: hexane, 1:1); mp 120-122 °C (d); ms (m/z) 379 (M^+-H_2O + CH_3); ir vmax (KBr) 3470 (OH), 1632 (C=N), and 1607 cm^{-1} (C=C); ^1H nmr ($CDCl_3$) δ 1.00 (3H, s, C_{18}-CH_3), 1.05 (3H, s, C_{19}-CH_3), 1.10-3.00 (17H, m), 6.14 (1H, s, C_4-H), 6.20-6.35 (2H, m), 7.36 (1H, m), and 7.92 (1H, s, N=CH). Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.49; H, 8.16; N, 3.65.

(17ξ)-17-(2-Thienyl)androsta-2,4-dieno[2,3-d]isoxazol-17-ol (**2g**). Pale yellow powder, yield (5.1 g, 27%) (dichloromethane: ether, 1:1); mp 185-188 °C; ms (m/z) 395 (M^+-H_2O), 362 (M^+-H_2O+CH_3); ir vmax (KBr) 3380 (OH), 1632 (C=N), and 1603 cm^{-1} (C=C); ^1H nmr ($CDCl_3$ + DMSO-d_6) δ 1.01 (3H, bs, C_{18}-CH_3), 1.08 (3H, s, C_{19}-CH_3), 1.15-2.90 (17H, m), 6.14(1H, bs, C_4-H), 6.70-7.2 (3H, m), and 7.92 and 7.96 (1H, s, N=CH, α and β isomers). Anal. Calcd for $C_{24}H_{29}NO_2S$: C, 72.88; H, 7.39; N, 3.54. Found: C, 72.95, H, 7.64; N, 3.18.

(2α,17β)-17-Hydroxy-3-oxo-17-phenylandrost-4-ene-2-carbonitrile (**4**) and 3,17-Dioxoandrost-4-ene-2-carbonitrile (**5**). To a solution of phenyllithium (73 g, 83.8 mmol) in dry tetrahydrofuran (180 ml) at -70 °C under a nitrogen atmosphere was added a solution of the ketone **3** (20.0 g, 64.30 mmol) in dry tetrahydrofuran (500 ml) over a period of 1 h. The reaction mixture was stirred at -70°C for 2 h and then 2 h at 0 °C. The organic layer was separated after quenching the reaction mixture with saturated ammonium chloride solution, dried over anhydrous magnesium sulphate, and evaporated to dryness to give a yellow foam. The crude product was separated by hplc (solvent, ethylacetate: hexane, 1:1) to afford three compounds. The first material was recovered ketone **3** (5.25 g, 17%). The second product was the 17α-phenyl compound (**4**) (7.0 g, 28%) as a yellow solid (from ethyl acetate: hexane, 1:1); mp 209-210 °C; ms (m/z) 389 (M^+); ir vmax (KBr) 2255 (C=N) and 1680 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 0.80-2.80 (17H, m), 1.10 (3H, s, C_{18}-CH_3), 1.20 (3H, s, C_{19}-CH_3), 3.54 (1H, dd, $J_{a,e}$=5.0 Hz,$J_{a,a}$=15.0Hz,C_2-H), 5.72 (1H, s, C_4-H), and 7.28 (5H, s, ArH). Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 79.94; H, 8.15; N, 3.45. The third compound was the cyanoketone (**5**) (7.8 g, 39%). The cyanoketone (**5**) has identical (^1H nmr and ir spectra) with the compound prepared from the base promated cleavage of the isoxazole ketone (**3**): ir vmax ($CHCl_3$), 2235 (C=N), 1730 (C=O), and 1680 cm^{-1}(C=C-C=O); ^1H nmr (60MHz, $CDCl_3$) δ 0.88 (3H, s, C_{18}-CH_3), 1.25 (3H, s, C_{19}-CH_3), 1.10-2.70 (17H, m), 3.70 (1H, dd, $J_{a,e}$=5.0 Hz, $J_{a,a}$=14.4 Hz, C_2-H), and 5.72 (1H, s,C_4-H). Similar results were obtained with phenylmagnesium bromide.

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11. To minimize the formation of cyanoketone during the workup, the reaction mixture was poured into ice-cold 20% aqueous potassium fluoride solution and acidified at 0 °C.

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