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A versatile synthesis of 17-heteroaryl androstenes via palladium-mediated Suzuki cross-coupling with heteroaryl boronic acids

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ABSTRACT

Suzuki coupling of 17-iodoandrosta-5,16-dien-3β-ol (**1**) and 17-iodoandrosta-4,16-dien-3-one (**2**) with nine heteroaryl boronic acids (mainly 2- or 3-furanyl, thienyl, benzofuranyl and benzothienyl boronic acid derivatives) were carried out under normal Suzuki condition ($Pd(PPh_3)_4$, 2 M Na_2CO_3 and MeOH), generally yielded C_{17}-heteroaryl steroids in moderate (10–60%) yields, but furanyl-2- and 5-chlorothienyl-2-boronic acid did not give any coupling product.

1. Introduction

Androgens have been implicated in the development and progression of common disorders of the prostate, most notably, benign prostatic hyperplasia (BPH) and prostatic cancer. Two important enzymes in the biosynthesis of androgens are 17α-hydroxylase/C17,20-lyase ($P450_{17\alpha}$) which regulates an early step in the biosynthesis of testosterone (T) and other androgens in both the testes and adrenal gland, and 5α-reductase (5α-R), which converts testosterone to the more potent androgen, dihydrotestosterone (DHT), in the prostate. Inhibitors of these enzymes have uses in the treatment of prostatic diseases [1]. To date, only ketoconazole [2,3], an imidazole antifungal agent, has been used for this purpose to treat patients with advanced prostatic cancer. However, this agent is neither selective nor very potent and has a number of significant side effects. Finasteride, an inhibitor of 5α-R, has been recently used as a treatment for BPH [4]. Finasteride only reduces DHT levels by −70% in these patients, but testosterone levels are often increased [5]. Although this is not a problem for BPH

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patients, it could result in growth stimulation of prostate cancers, since testosterone may bind to the androgen receptor, in the absence of DHT. Therefore, the development of new types of potent enzyme inhibitors that inhibit $P450_{17\alpha}$, as well as the 5α-R, could be effective in the treatment of prostatic cancer by achieving total androgen blockade. This new type of inhibitors would be a promising candidate in prostatic cancer therapy [6].

Recently, 17-heteroaryl substituted androstenes **(3** and **4)** have been found to have good inhibition activity against $P450_{17\alpha}$ [6]. We and others have reported that 17-(2′-imidazolyl), 4′-imidazolyl, 3′-pyrazolyl [1], as well as 1H-imidazolyl and 1H-1,2,3-triazolyl-androsta-5,16-dien-3β-ol [7] were very potent inhibitors for $P450_{17\alpha}$. 3′-Pyridyl-androsta-5,16-dien-3β-ol is already in clinical trials [6] and 17-(5′-isoxazolyl)-androsta-4,16-dien-3-one **(L-39)** which was both active against $P450_{17\alpha}$and 5α-R will soon enter phase I clinical trials [7]. From our experience, a 16,17-double bond would enhance inhibition activity, whereas the basic steroidal skeleton of 4-en-3-one, such as **L-39**, would also have inhibition activity against 5α-R [6].

One of the approaches to synthesize 17-heteroaryl androstene was cyclo-condensation of the appropriate constructed steroidal 17-side chain with some reagents. For examples, 4′-imidazole was synthesized via 21-acetoxy pregnenolone with formaldehyde and ammonia (Weigenhagen method), and 2′-imidazole was formed via 17-carboxaldehyde with glyoxal and NH_4OH [1]; Gabriel condensation gave 5′-substituted thiazole and Hantzch procedure yielded the 4′-substituted thiazole [8], while 21-bromo pregnenolone with thiourea afforded 2′-aminothiazole steroids [9]. But these cyclo-condensation approaches were not convenient and sometimes were rather tedious and gave the low yield, especially when there was 16,17-double bond. For example, 2′-imidazole was only obtained in less than 5% yield, although it was a very potent inhibitor [1].

As part of our ongoing medicinal chemistry program to search for more active $P450_{17\alpha}$ and 5α-R inhibitors, we are anxious to explore a convenient synthesis method which would introduce 17-heteroaryl groups into the androstene skeleton directly. In particular, we required a versatile and simple method of varying the 17-heteroaryl moiety in order to prepare scaffolds for chemical libraries. We noticed that the recent work described by Haidar et al. [10], who used lithium trimethoxy (5-pyrimidyl) boronate in the presence of bis-(triphenylphospphine) palladium(II) chloride as catalyst, to introduce the 5′-pyrimidyl group into the 17-position of androstene, and the approach was in a similar fashion as described by Potter et al. [11] who used lithium trimethoxy(4-pyridyl)boronate or diethyl(3-pyridyl)borane to synthesize 17-pyridyl androstenes. But these boronates have to be prepared in the lab [12,13]. Now, more and more heteroaryl boronic acids are becoming commercially available and have been established as an important reagent in the Suzuki coupling reaction [14]. Here we wish to describe a preliminary report to utilize commercially available heteroaryl boronic acids via the palladium-mediated Suzuki cross-coupling reaction, to synthesize the 17-heteroaryl androstenes. The reaction was depicted in the following Scheme 1.

2. Experimental

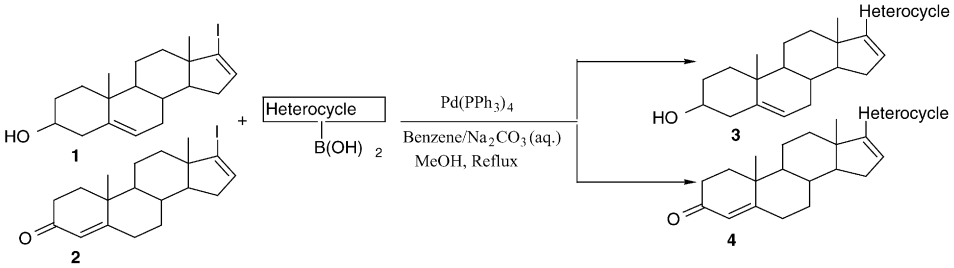
$Pd(PPh_3)_4$ and all nine heteroaryl boronic acids (mainly 2- or 3-furanyl, benzofuranyl, thienyl and benzothienyl boronic acid, etc. as shown in Table 1) were purchased from Aldrich without further purification. 17-Iodoandrosta-5,16-dien-3β-ol (**1**) was prepared by Potter's procedure as reported [11] with some modifications by us. Oppenauer oxidation of (**1**) gave 17-iodoandrosta-4,16-dien-3-one (**2**) in good yield. ^1H NMR spectra were recorded with a JOEL-AL300 or Bruker 500 instrument. FAB-MS were recorded on ZAB-HF-3FMS spectrometer, and ESI-MS were recorded on MDS SCIEX QSTAR spectrometer, Elemental analyses were performed on a Varo EL III elemental analyser. Melting points were determined on TX_4 melting point apparatus fitted with a microscope and are uncorrected.

2.1. *Representative procedure*

The synthesis of 17-iodoandrosta-5,16-dien-3β-ol (**1**) and 17-iodoandrosta-4,16-dien-3-one (**2**).

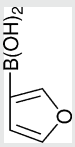
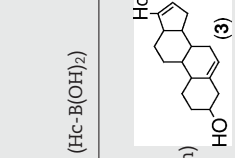
17-Iodoandrosta-5,16-dien-3β-ol (1)

Into a 100 ml round-bottomed flask, fitted with a magnetic stirrer bar, was placed dehydroepiandrosterone (DHEA) (1.783 g, 6.19 mmol) and ethanol (40 ml), and then hydrazine hydrate (2.0 ml, 40 mmol) was added, followed by a solution of hydrazine sulfate (6 mg, 0.038 mmol) in water (2 ml). After stirring at room temperature for 4 days (TLC showed the reaction completed), the mixture was poured into cold water (80 ml) with stirring. The precipitate was dried at room temperature, dissolved in dioxane (38 ml), and triethylamine (7 ml, 51.8 mmol) added with stirring. Iodine (3.20 g, 25.2 mmol) was added in portions over 30 min and stirring continued for a further 1 h. The mixture was poured into 9% Na_2SO_3 (30 ml), and precipitate collected by filtration, washed with cold water (3 × 20 ml), and recrystallized from



Scheme 1

Table 1 – The results of cross-coupling of (1) and (2) with heterocyclic boronic acids

Bronic acid (Hc-B(OH)$_2$)										
Entry	1	2	3	4	5	6	7	8	9	
Refluxing (h)	11	18	22	28	22	14	18	19	17	
Yield[a] (%)	60.9	0[b]	29.4	31.1	0[c]	8.8	35.6	31.7	39.0	
Entry	10	11	12	13	14	15	16	17	18	
Refluxing (h)	16	23	23	23	22	30	28	28	23	
Yield[a] (%)	46.8	0[b]	0[b]	30.0	0[c]	11.3	22.6	11.4	31.6	

[a] Yields are those obtained after chromatographic separation.
[b] TLC showed that no significant amount of product was obtained.
[c] Only the starting material and deiodo steroid were recovered.

ethanol to give white needle crystals (**1**) (1.516 g, 62.0%) mp 174–176 °C (lit. [11] 175–176 °C).

17-Iodoandrosta-4,16-dien-3-one (2)

From a solution of (**1**) (200 mg, 0.503 mmol) in dry toluene (25 ml) and cyclohexanone (4 ml, 38.6 mmol) was distilled off part of the solvent (3–5 ml) to eliminate moisture. After allowing to cool to 90 °C, Al(O-i-Pr)$_3$ (220 mg, 1.12 mmol) was added and the mixture heated under reflux for 8 h, and then allowed to cool, poured into water (25 ml) with stirring. The organic solution was separated out and the aqueous solution was extracted with ether (3 × 25 ml). The combined organic solution was washed with water (3 × 20 ml) and brine (20 ml), and then dried over anhydrous Na_2SO_4, and concentrated. Chromatography, on elution with EtOAc/Petroleum ether (PE) (1/4, v/v), afforded **2** (198 mg). Recrystallized from acetone-PE to give **2,** crystals (150 mg, 75.4%). mp 165–168 °C. ^{1}H NMR($CDCl_3$): δ (ppm) = 6.12 (m, 1H, 16-H), 5.72 (s, 1H, 4-H), 1.19 (s, 3H, 19-CH_3), 0.76 (s, 3H, 18-CH_3). Anal. Calcd for ($C_{19}H_{25}OI$): C, 57.58; H, 6.36. Found: C, 57.58; H, 6.49.

2.1.1. *General procedure for Suzuki coupling with 17-iodoandrost-5,16-dien-3β-ol (1)*

A 25 ml flask equipped with a magnetic stirring bar and fitted with a condenser was charged with 17-iodoandrost-5,16-dien-3β-ol (**1**) (199 mg, 0.50 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), heteroaryl boronic acid (0.50 mmol), benzene (10 ml), MeOH (2 ml) and 2 M Na_2CO_3 (0.5 ml), and flushed with nitrogen. The reaction was monitored by TLC. After being stirred at 80 °C for the period shown in Table 1, the reaction mixture was treated with water (20 ml) at room temperature. The product was extracted with Et_2O (3 × 20 ml). The combined ether extracts were dried over $MgSO_4$. Flash column chromatography (FCC), eluted with EtOAc-PE (1/5, v/v) was employed to separate the product. The following compounds were prepared unless otherwise noted.

2.1.1.1. 17-(3′-Furanyl)androsta-5,16-dien-3β-ol (Entry 1). mp 187–189 °C (lit. [9] 186–189 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 (s, 1H, 2′-H), 7.36 (t, 1H, J = 1.8 Hz, 5′-H), 6.48 (dd, 1H, J = 1.8 Hz, 4′-H), 5.83 (m, 1H, Δ^{16}-H), 5.38 (m, 1H, Δ^{6}-H), 3.53 (m, 1H, 3α-H), 1.08 (s, 3H, 19-CH_3), 0.96 (s, 3H, 18-CH_3).

2.1.1.2. 17-(3′-Thienyl)androsta-5,16-dien-3β-ol (Entry 3). mp 216–219 °C (lit. [9] 215–219 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (s, 1H, 2′-H), 7.23 (d, 1H, J = 0.6 Hz, 5′-H), 7.15 (dd, 1H, J = 0.6 Hz, 4′-H), 5.91 (m, 1H, Δ^{16}-H), 5.37 (m, 1H, Δ^{6}-H), 3.52 (m, 1H, 3α-H), 1.04 (s, 3H, 19-CH_3), 1.00 (s, 3H, 18-CH_3).

2.1.1.3. 17-(2′-Thienyl)androsta-5,16-dien-3β-ol (Entry 4). mp 192–195 °C (lit. [9] 190–195 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.14 (d, J = 0.3 Hz, 1H, 5′-H), 7.04 (d, 1H, J = 0.2 Hz, 3′-H), 6.97 (dd, 1H, J = 0.3, 0.2 Hz, 4′-H), 5.98 (m, 1H, Δ^{16}-H), 5.39 (m, 1H, Δ^{6}-H), 3.55 (m, 1H, 3α-H), 1.07 (s, 3H, 19-CH_3), 1.00 (s, 3H, 18-CH_3).

2.1.1.4. 17-(2′-Benzofuranyl)androsta-5,16-dien-3β-ol (Entry 6). mp 133–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, J = 0.6 Hz, 1H, 5′-H), 7.46 (d, 1H, J = 0.3 Hz, 8′-H), 7.30 (dd, 1H, J = 0.3, 0.2 Hz, 7′-H), 7.20 (dd, 1H, 0.6,0.2 Hz, 6′-H), 6.72 (s, 1H, 3′-H), 6.14 (m, 1H, Δ^{16}-H), 5.40 (m, 1H, Δ^{5}-H), 3.53 (m, 1H,

3α-H), 1.09 (s, 3H, 19-CH_3), 1.02 (s, 3H, 18-CH_3). FAB-MS: 389 ($M+H^+$).

2.1.1.5. 17-(2′-Benzothienyl)androsta-5,16-dien-3β-ol (Entry 7). mp 210–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 1.8 Hz, 1H, 8′-H), 7.70 (t, 1H, J = 1.1 Hz, 5′-H), 7.32 (dd, 1H, J = 1.8, 1.1 Hz, 6′-H), 7.27 (s, 1H, 3′-H), 7.23 (dd, 1H, J = 1.8, 1.1 Hz, 7′-H), 6.12 (m, 1H, Δ^{16}-H), 5.40 (m, 1H, Δ^5-H), 3.55 (m, 1H, 3α-H), 1.10 (s, 3H, 19-CH_3), 1.05 (s, 3H, 18-CH_3). Anal. Calcd. for ($C_{27}H_{32}OS$) C 80.15%, H 7.97%; Found: C 79.93%, H 7.84%.

2.1.1.6. 17-(3′-Benzothienyl)androsta-5,16-dien-3β-ol (Entry 8). mp 209–211 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.91 (d, J = 1.2 Hz, 1H, 8′-H), 7.85 (d, 1H, J = 1.0 Hz, 5′-H), 7.38 (s, 1H, 2′-H), 7.34 (dd, 1H, J = 1.0, 0.04 Hz, 6′-H), 7.32 (dd, 1H, J = 1.2, 0.04 Hz, 7′-H), 6.02 (m, 1H, Δ^{16}-H), 5.42 (m, 1H, Δ^5-H), 3.56 (m, 1H, 3α-H), 1.09 (s, 3H, 19-CH_3), 1.04 (s, 3H, 18-CH_3). Anal. Calcd. for ($C_{27}H_{32}OS$): C 80.15, H 7.97; Found: C 79.93, H 7.84.

2.1.1.7. 17-[1′-(Phenylsulfonyl)-3′-indolyl]androsta-5,16-dien-3β-ol (Entry 9). mp 249–251 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.1 Hz, 1H, 2′-H), 7.88–7.85 (m, 2H, 2″-H), 7.71 (d, 1H, J = 6.9 Hz, 4″-H), 7.55–7.50 (m, 2H,3″-H), 7.46–7.41 (m, 2H, 4′,7′-H), 7.35–7.22 (m, 2H, 5′, 6′-H), 6.15 (dd, 1H, J = 3.0, 1.8 Hz, Δ^{16}-H), 5.40 (d, 1H, J = 5.4 Hz, Δ^5-H), 3.53 (m, 1H, 3α-H), 1.09 (s, 3H, 19-CH_3), 1.02 (s, 3H, 18-CH_3). Anal. Calcd. for ($C_{33}H_{37}O_3SN$): C 75.14, H 7.02, N 2.66; Found: C 75.23, H 6.87, 2.61.

2.1.2. General procedure for Suzuki coupling with 17-iodoandrost-4,16-dien-3-one (2)

A 25 ml flask equipped with a magnetic stirring bar and a condenser, was charged with 17-iodoandrost-4,16-dien-3-one (100 mg, 0.25 mmol), $Pd(PPh_3)_4$ (30 mg, 0.025 mmol), and heteroaryl boronic acid (0.25 mmol), benzene (6 ml), MeOH (2 ml) and 2 M Na_2CO_3 (0.5 ml), and flushed with nitrogen. the reaction was monitored by TLC. After being stirred at 80 °C for the period shown in the Table 1, the reaction mixture was treated with water (10 ml) at room temperature. The product was extracted with Et_2O (3 × 10 ml). The combined Et_2O solution was dried over $MgSO_4$. Flash column chromatography and eluted with EtOAc-PE (1/5, v/v) was employed to separate the products.

2.1.2.1. 17-(3′-Furanyl)androsta-4,16-dien-3-one (Entry 10). mp 110–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.47 (s, 1H, 2′-H), 7.37 (t, 1H, J = 1.8 Hz, 5′-H), 6.48 (dd, 1H, J = 1.8 Hz, 4′-H), 5.83 (m, 1H, Δ^{16}-H), 5.75 (m, 1H, Δ^4-H), 1.08 (s, 3H, 19-CH_3), 0.96 (s, 3H, 18-CH_3). ESI-MS: 337 ($M+H^+$).

2.1.2.2. 17-(2′-thienyl) androsta-4,16-dien-3-one (Entry 13). mp 139–141 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.15 (d, J = 5.1, 3.0 Hz, 1H, 5′-H), 7.04 (d, 1H, J = 3.0 Hz, 3′-H), 6.97 (dd, 1H, J = 5.1, 3.0 Hz, 4′-H), 5.97 (m, 1H, Δ^{16}-H), 5.75 (s, 1H, Δ^4-H), 1.22 (s, 3H, 19-CH_3), 1.05 (s, 3H, 18-CH_3). ESI-MS: 353 ($M+H^+$).

2.1.2.3. 17-(2′-Benzofuranyl)androsta-4,16-dien-3-one (Entry 15). mp 214–218 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, J = 0.6 Hz, 1H, 5′-H), 7.48 (d, 1H, J = 0.3 Hz, 8′-H), 7.26 (dd, 1H, J = 0.3, 0.2 Hz, 7′-H), 7.16 (dd, 1H, J = 0.6, 0.2 Hz, 6′-H), 6.83 (s, 1H, 3′-H), 6.38 (m, 1H, Δ^{16}-H), 5.76 (m, 1H, Δ^4-H), 1.28 (s, 3H, 19-CH_3), 1.03 (s, 3H, 18-CH_3). ESI-MS: 387 ($M+H^+$).

2.1.2.4. 17-(2′-Benzothienyl)androsta-4,16-dien-3-one (Entry 16). mp 203–205 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (d, 1H, J = 1.8 Hz, 8′-H), 7.67 (t, 1H, J = 1.1 Hz, 5′-H), 7.33 (dd, 1H, J = 1.8, 1.1 Hz, 6′-H), 7.27 (s, 1H, 3′-H), 7.22 (dd, 1H, J = 1.8, 1.1 Hz, 7′-H), 6.12 (m, 1H, Δ^{16}-H), 5.76 (m, 1H, Δ^4-H), 1.25 (s, 3H, 19-CH_3), 1.10 (s, 3H, 18-CH_3). Anal. Calcd. for ($C_{27}H_{30}OS$): C 80.55, H 7.51; Found: C 80.63, H 8.00.

2.1.2.5. 17-(3′-Benzothienyl)androsta-4,16-dien-3-one (entry17). mp 230–232 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, 1H, J = 1.2 Hz, 8′-H), 7.85 (t, 1H, J = 1.0 Hz, 5′-H), 7.39 (s, 1H, 2′-H), 7.37 (d, 1H, J = 1.0 Hz, 6′-H), 7.32 (dd, 1H, J = 1.2, 0.1 Hz, 7′-H), 6.01 (m, 1H, Δ^{16}-H), 5.77 (m, 1H, Δ^4-H), 1.22 (s, 3H, 19-CH_3), 1.05 (s, 3H, 18-CH_3). FAB-MS: 403 ($M+H^+$).

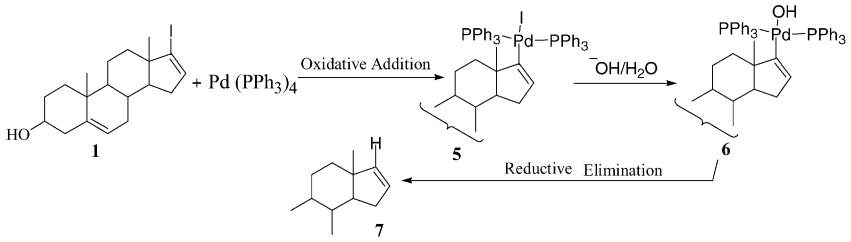
2.1.2.6. 17-[1′-(Phenylsulfonyl)-3′-indolyl]androsta-4,16-dien-3-one (Entry 18). mp 155–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.5 Hz, 1H, 2′-H), 7.88 (d, J = 7.5 Hz, 2H, 2″-H), 7.71 (d, 1H, J = 8.0 Hz, 4″-H), 7.55–7.52 (m, 2H, 3″-H), 7.46–7.43 (m, 2H, 4′,7′-H), 7.35–7.32 (m, 1H, 6′-H), 7.27–7.24 (m,1H, 5′-H), 6.15 (s, 1H, Δ^{16}-H), 5.77 (s, 1H, Δ^4-H), 1.26 (s, 3H, 19-CH_3), 1.04 (s, 3H, 18-CH_3). FAB-MS: 526 ($M+H^+$).

3. Results and discussion

The 17-iodoandrostene (**1**) was prepared by the method of Potter et al. [11] reported in 1997 with the following improvements. Dehydroepiandorstone was treated with hydrazine to give the 17-hydrazone which on treatment with iodine in the presence of 1,1,3,3-tetramethylquanidine. However, this two step procedure was tedious and 1,1,3,3-tetramethylquanidine expensive. We then discovered that the 17-hydrazone could be decomposed directly with I_2 and triethylamine to give similar yields and the procedure was both simple and economical.

The Suzuki cross-coupling of heteroaryls, although a process of great synthetic potential [15,16], has not been used to its full extent due to the unavailability of the corresponding heteroaryl boronic acids. Hence, our experiments only start on those heteroaryl boronic acids which are commercially available. They are mainly furan and thiophene derivative as shown in Table 1.

Palladium-mediated reaction of 17-iodoandrostenes (**1**) and (**2**) with the boronic acid derivatives under the Suzuki arylation condition (cat. Pd $(PPh_3)_2$, Na_2CO_3/MeOH) mostly led to the desired cross-coupled product in moderate yield (see Table 1). 17-(3′-Furanyl)-, (3′ or 2′-thienyl)-androsta-5,16-dien-3β-ol (Entries 1, 3 and 4) were identical with that reported by Burkhart et al. [9], which were obtained by reacting with a 17-keto steroid with lithiofuran or lithiothiophene and dehydration of the resulting tertiary alcohol in two steps. Although the total yields were similar, Suzuki coupling was direct and convenient. Generally, the 5-ene-3β-ol (**1**) gave better yields than the 4-ene-3-one (**2**) (compare Entries 1–10; 7–16; 8–17 and 9–18). Among these coupling reactions 3-furan boronic acids afforded the highest yield (60%, Entry 1), whereas 2-furan boronic acids failed to give any coupling product (Entries 2 and 11), however, 2-benzofuran boronic acid did give the cou-



Scheme 2

pling product albeit in poor yield (ca.10%, Entries 6 and 15). The 2-and 3-thienyl and benzothienyl boronic acids, as well as 3-indolyl boronic acid yielded the Suzuki product in about 30% yield. Surprisingly, the 4-ene-3-one (**2**) did not yield any of the desired product with 3-thienyl boronic acid (Entry 12) or 5-chloro-2-thienyl boronic acid (Entry 14). These results can be explained as indicated below:

3.1. *The deiodination of 17-iodoandrostenes (1) and (2)*

Recently, dehalogenation has been reported in the Suzuki reaction [17,18] and we observed that the deiodination reaction side reaction was rather large in our case because the iodo compound is not stable. Quite a lot of the 17-deiodo byproduct was recovered in almost every reaction. For example, up to 25% and 18% yield of the 17-deiodo compound was recovered in Entries 6 and 13, respectively, A possible mechanism of its formation is shown in Scheme 2.

3.2. *The deboronation of heteroaryl boronic acid*

The protodeboronation was recognized as a problem for heteroaryl boronic acids when the boronic acid was in the *ortho* position to heteroatom. 2-Pyridine boronic acid is unstable especially in protic solvents, while its 3- and 4-pyridyl species are stable [19]. This would explain the coupling reaction with furan boronic acid. Furan-3-boronic acid gave a highest yield (60%) in our case (Entry 1), while its 2-boronic acid failed to yield any product as the boronic acid in 2-furanboronic acid is adjacent to oxygen. But benzofurano-2-boronic acid, in which the benzene ring might disperse the electronegative effect of oxygen, did give 10% yield. Because the electron withdrawing effect of sulfur is less then oxygen, 2-thienyl boronic acid did yield a coupling product in moderate yield (30%, Entries 4 and 13) while a strong electron withdrawing chlorine at the 5-position (Entries 5 and 14) failed to yield any coupled product except the deiodo steroid (**7**) after 22 h reflux. If the reaction proceeded at room temperature for 45 h only trace amounts of coupled product could be detected on TLC.

In summary, we have utilized herteroaryl boronic acids via palladium-mediated Suzuki cross-coupling reaction with 17-iodoandrostene and found that it would be a simple and convenient alternative for introduce heteroaryl group into 17-position of steroid. The yields were moderate (from 10% to 60%) although it has not been optimized. The yield might be poor to nil, especially when the boronic acid is at the *ortho* position to heteroatom, This is the preliminary report and the further work on Suzuki coupling of steroids with imidazole or pyrimidine boronic acids is on going.

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