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SHORT COMMUNICATIONS

Palladium-Catalyzed Synthesis of 3-Arylsteroids

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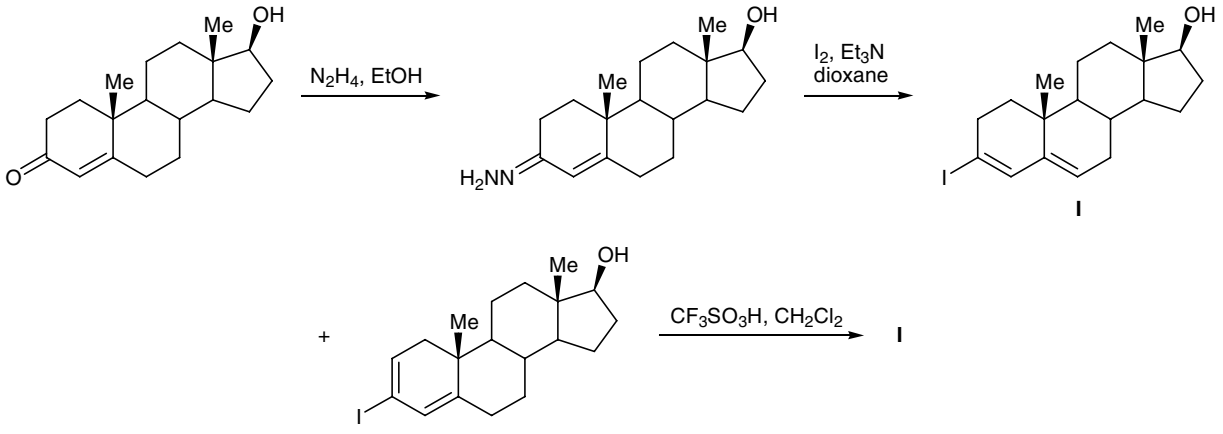
Application of classical methods of organic chemistry to syntheses of aryl- and hetaryl-substituted steroids implies the necessity of using a large number of protecting groups. New synthetic approaches to arylsteroids, based on catalytic formation of C–C bonds (cross coupling reactions), involve as a rule enol triflluoromethanesulfonates derived from keto steroids as initial compounds [1]. Reactions with iodosteroids are generally characterized by poor yields of arylsteroids, considerable amounts of by-products, and prolonged reaction times [2, 3]. We have recently shown that palladium-catalyzed cross coupling of 4- and 6-bromo- and -chlorosteroids with arylboronic acids provides a convenient synthetic route to arylsteroids [4, 5]. The developed procedure can be extended to 3-iodosteroids. Initial 3-iodoandrosta-3,5-dien-17-ol (**I**) was synthesized in a moderate yield by oxidation of testosterone hydrazone with iodine [6], followed by isomerization of steroid diene mixture by the action of trifluoromethanesulfonic acid. As a result, more stable isomer **I** was obtained (Scheme 1).

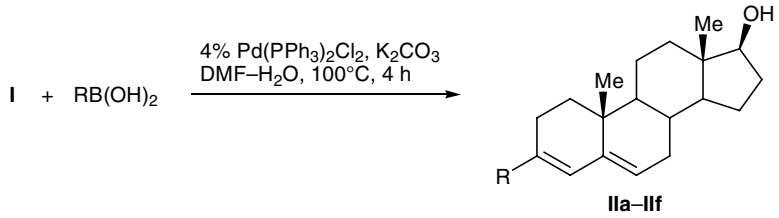
The arylation of compound **I** with aryl(or hetaryl)-boronic acids in aqueous DMF in the presence of 4 mol % of $Pd(PPh_3)_2Cl_2$ gave 50–77% of the corresponding 3-arylsteroids **IIa**–**IIf**. The cross coupling products were unambiguously identified by ^{1}H NMR spectroscopy and elemental analysis.

3-Iodoandrosta-3,5-dien-17-ol (I). A suspension of 3.39 g (11.8 mmol) of testosterone in 25 ml of 95% ethanol and 18 ml of 85% hydrazine hydrate was heated for 2 h under reflux with stirring. The resulting solution was diluted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in a mixture of 81 ml of dioxane and 18 ml of triethylamine, and 6.90 g (27.2 mmol) of iodine was slowly added to the solution. When gaseous products no longer evolved, the mixture was stirred for 30 min, treated with an aqueous solution of sodium sulfite, and extracted with methylene chloride. The extract was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent CH_2Cl_2–Et_2O, 20:1) to isolate 2.75 g of an equimolar mixture of $\Delta^{3,5}$- and $\Delta^{2,4}$-iodosteroids (according to the ^{1}H NMR data). The product mixture was dissolved in 10 ml of anhy-

Scheme 1.



Scheme 2.



IIa–IIf

R = 4-$MeOC_6H_4$ (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-FC_6H_4 (**d**), 3-$MeCOC_6H_4$ (**e**), 2-furyl (**f**).

drous methylene chloride, 20 mg of trifluoromethanesulfonic acid was added, and the mixture was stirred for 24 h at room temperature. Triethylamine, 1 ml, was added, the mixture was washed with water, the organic phase was separated, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel using methylene chloride as eluent to isolate 2.60 g (56%) of compound **I**, mp 155–157°C. ^{1}H NMR spectrum, δ, ppm: 6.53 s (1H), 5.35 m (1H), 3.63 m (1H), 3.47 d (1H, J = 4.6 Hz), 2.60 m (2H), 2.10 m (2H), 1.83 m (1H), 1.72–1.23 m (9H), 1.13–0.92 m (3H), 0.96 s (3H), 0.76 s (3H). Found, %: C 57.06; H 7.04. $C_{19}H_{27}IO$. Calculated, %: C 57.29; H 6.83.

3-Arylandrosta-3,5-dien-17-ols IIa–IIf (*general procedure*). A glass reactor equipped with a magnetic stirred was charged with 0.1 mmol of compound **I**, 0.11 mmol of the corresponding arylboronic acid, 0.2 mmol of K_2CO_3, and 4 μmol (4 mol %) of $Pd(PPh_3)_2Cl_2$, 1.9 ml of DMF and 0.1 ml of water were added under argon, the reactor was hermetically capped, and the mixture was stirred for 4 h at 100°C. It was then cooled to room temperature, transferred into a separatory funnel, diluted with methylene chloride, and washed with three portions of water, and the organic phase was dried over anhydrous Na_2SO_4 and evaporated at 45°C under reduced pressure. The residue was dissolved in 1.5 ml of methylene chloride, and the solution was applied to a column charged with silica gel. The column was eluted with methylene chloride–diethyl ether, 20:1.

3-(4-Methoxyphenyl)androsta-3,5-dien-17-ol (IIa) was synthesized from 39.8 mg (0.1 mmol) of compound **I** and 16.7 mg (0.11 mmol) of 4-methoxyphenylboronic acid. Yield 18.9 mg (50%), mp 188°C. ^{1}H NMR spectrum, δ, ppm: 7.39 d (2H, J = 8.9 Hz), 6.85 d (2H, J = 8.9 Hz), 6.34 s (1H), 5.51 m (1H), 3.79 s (3H), 3.66 t (1H, J = 8.4 Hz), 2.50 m (2H), 2.24 m (2H), 1.97 m (1H), 1.85 m (1H), 1.74–0.99 m (12H), 0.99 s (3H), 0.79 s (3H). Found, %: C 82.42; H 8.88. $C_{26}H_{34}O_2$. Calculated, %: C 82.49; H 9.05.

3-(4-Chlorophenyl)androsta-3,5-dien-17-ol (IIb) was obtained from 39.8 mg (0.1 mmol) of steroid **I** and 17.2 mg (0.11 mmol) of 4-chlorophenylboronic acid. Yield 21.9 mg (57%), mp 232°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.50 d (2H, J = 8.6 Hz), 7.35 d (2H, J = 8.6 Hz), 6.50 s (1H), 5.60 m (1H), 3.45 s (1H), 2.44 m (2H, obscured by the solvent), 2.23–0.95 m (19H), 0.91 s (3H), 0.68 s (3H). Found, %: C 78.46; H 7.85. $C_{25}H_{31}ClO$. Calculated, %: C 78.43; H 8.10.

3-(4-Methylphenyl)androsta-3,5-dien-17-ol (IIc) was prepared from 59.6 mg (0.15 mmol) of iodide **I** and 24.5 mg (0.18 mmol) of 4-tolylboronic acid. Yield 38.3 mg (70%), mp 181°C. ^{1}H NMR spectrum, δ, ppm: 7.35 d (2H, J = 8.1 Hz), 7.12 d (2H, J = 8.1 Hz), 6.39 s (1H), 5.53 m (1H), 3.65 t (1H, J = 8.5 Hz), 2.52 m (2H), 2.32 s (3H), 2.26–2.03 m (2H), 1.97 m (1H), 1.85 m (1H), 1.74–0.99 m (12H), 0.99 s (3H), 0.79 s (3H). Found, %: C 86.18; H 9.34. $C_{26}H_{34}O$. Calculated, %: C 86.19; H 9.39.

3-(4-Fluorophenyl)androsta-3,5-dien-17-ol (IId) was obtained from 39.8 mg (0.1 mmol) of steroid **I** and 15.4 mg (0.11 mmol) of 4-fluorophenylboronic acid. Yield 28.0 mg (77%), mp 224°C. ^{1}H NMR spectrum, δ, ppm: 7.40 m (2H), 6.98 m (2H), 6.34 s (1H), 5.54 m (1H), 3.66 t (1H, J = 8.4 Hz), 2.48 m (2H), 2.27–0.99 m (16H), 0.99 s (3H), 0.79 s (3H). Found, %: C 81.98; H 8.15. $C_{25}H_{31}FO$. Calculated, %: C 81.85; H 8.46.

1-[3-(17-Hydroxyandrosta-3,5-dien-3-yl)phenyl]-ethanone (IIe) was prepared from 39.8 mg (0.1 mmol) of **I** and 18.0 mg (0.11 mmol) of 3-acetyl-phenylboronic acid. Yield 20.9 mg (54%), mp 175°C. ^{1}H NMR spectrum, δ, ppm: 8.04 s (1H), 7.78 d (1H, J = 7.6 Hz), 7.66 d (1H, J = 7.6 Hz), 7.39 t (1H, J = 7.6 Hz), 6.48 s (1H), 5.61 m (1H), 3.66 t (1H, J = 8.5 Hz), 2.60 s (3H), 2.56 m (2H), 2.29–1.85 m (4H), 1.78–1.02 m (12H), 1.00 s (3H), 0.80 s (3H). Found, %: C 82.79; H 8.70. $C_{27}H_{34}O_2$. Calculated, %: C 83.03; H 8.77.

3-(2-Furyl)androsta-3,5-dien-17-ol (IIf) was synthesized from 39.8 mg (0.1 mmol) of compound **I** and 12.3 mg (0.11 mmol) of 2-furylboronic acid. Yield

22.4 mg (66%), mp 132°C. ^{1}H NMR spectrum, δ, ppm: 7.33 d (1H, J = 1.3 Hz), 6.48 s (1H), 6.36 m (1H), 6.23 d (1H, J = 3.3 Hz), 5.56 m (1H), 3.65 t (1H, J = 8.4 Hz), 2.46–0.99 m (18H), 0.98 s (3H), 0.78 s (3H). Found, %: C 81.47; H 9.14. $C_{23}H_{30}O_2$. Calculated, %: C 81.61; H 8.93.

The ^{1}H NMR spectra were recorded from solutions in $CDCl_3$ (except for **IIb**) on a Bruker Avance 400 spectrometer (400 MHz) using HMDS as reference.

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