Efficient Oxidizing Methods for the Synthesis of Oxandrolone Intermediates

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Mild, efficient and eco-friendly oxidation of 17α-methylandrostan-3β-17β-diol (1) has been studied with three different reagents *viz.* pentavalent iodine reagent 2-iodoxy benzoic acid (IBX) in DMSO at 65 °C, sodium hypochlorite and H_2O_2/Na_2WO_4 under phase transfer conditions to give 17β-hydroxy-17α-methylandrostan-3-one (mestanolone 2), a drug intermediate as oxidized product. The H_2O_2/Na_2WO_4/PTC gave mestanolone in high yield and purity whereas sodium hypochlorite/PTC system yielded some chlorinated material along with the mestanolone. However, 1 with 2.5 equivalent of IBX gave 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (3) under the similar reaction conditions in good yield and single step reaction.

Key words steroid; oxidation; 2-iodoxy benzoic acid (IBX); NaOCl; hydrogenperoxide; dehydrogenation

Steroid constitute an important group of chemical molecules that are known for their physiological properties in *Homo sapiens sapiens*. Some of the naturally occurring steroids are well known hormones like testosterone, estrogen, progesterone that regulate the growth and development of the body.[1,2] Owing to growth enhancing properties of naturally occurring steroids, a number of similar synthetic steroid molecules has emerged (*e.g.* oxandrolone, methyl testosterone) that are used as drug for the weight gain after surgery, treatment of trauma, birth control, regulation of inflammation and treatment of a number of various other diseases.[3]

Oxandrolone (17β-hydroxy-17α-methyl-2-oxa-5α-androsterone-3-one) is a 2-oxasteroid known to have very pronounced anabolic activity with much reduced androgenic and virilization effects.[4] It was first prepared in 1962 and found to be possessing potentially high anabolic activity. Since then it has been widely used as anabolic drug and has found specific applications such as therapy to promote weight gain following surgery, chronic infections and severe trauma, and to improve the thinness associated with muscle weakness. It has also been recommended for the treatment of osteoporosis, HIV wasting syndrome and HIV associated muscle weakness.

The synthesis of oxandrolone has always been a matter of interest to the chemists.[5,6] In general the synthesis of 2-oxasteroid is a tedious procedure having multiple step synthesis giving finally low yields. In its synthesis from dehydroepiandrosterone; 17β-methylandrostan-3β,17β-diol (**1**), mestanolone (**2**) and 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) are important intermediates. There are few methods in the literature related to the synthesis of 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) starting from mestanolone *viz*. bromination followed by dehydrobromination and by using 2-iodoxybenzoic acid. Mestanolone **2** has been obtained by the oxidation of **1** with CrO_3/acetic acid.[7] The earlier reported procedure has limitation of being low yielding and multiple step procedure.

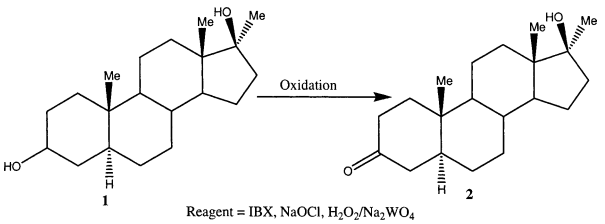

Chart 1. Oxidation of **1** with Various Reagents

Hypervalent iodine reagents have attracted increasing interest during the past decade because of their selective, mild and environment friendly properties as oxidizing agent in organic synthesis.[8—12] 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (IBX) has emerged as a mild and selective oxidant for the conversion of alcohols into aldehydes.[13] It has been used in various oxidative transformations leading to high yield of the product.[14] NaOCl and H_2O_2/Na_2WO_4 under phase transfer conditions have emerged as green oxidizing agents.[15] In this report we have studied the oxidative transformations of **1** with these oxidizing agents under different reaction conditions. In the process, we were able to synthesize **3** directly from **1** in very high yield *i.e.* one-pot synthesis of 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one starting from 17α-methylandrostan-3β,17β-diol in one step using IBX as an oxidizing agent (Chart 2).

Experimental

All the chemicals and reagents used in the present study were of analytical reagent grade. Organic solvents were freshly distilled and purified before use. IBX was synthesized by the reported procedure.[11] The purity and homogeneity of all organic compounds was confirmed using the NMR and reverse phase HPLC. TLC were run on silica gel coated aluminum sheets (Silica gel 60 F_{254} EMerck, Germany) and visualized by spraying vanillin-phosphoric acid solution (10%) and then heating in hot air oven. Melting points were determined at Buchi B540 instrument. IR spectra were recorded on FTIR Perkin Elmer Spectrum BX spectrophotometer. NMR spectral characterizations of all the synthetic compounds were carried out on a JEOL 400 MHz and Bruker 300 MHz NMR instrument. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer.

Synthesis of 17β-Hydroxy-17α-methylandrostan-3-one (2) from 17α-Methyl Androstan-3β,17β-diol (1) Using 2-Iodoxy Benzoic Acid (IBX) 17α-Methylandrostan-3β,17β-diol (**1**) (1 g, 3.27 mmol) was dissolved in 15 ml of DMSO with stirring. To this solution, 2-iodoxy benzoic acid (IBX) (1.105 g, 3.94 mmol) was added in one lot. The solution was heated at 65 °C for 2 h and reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with 50 ml of diethyl ether. The organic layer was separated and washed with 5% $NaHCO_3$ solution (20 ml×2),

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water (20 ml×2) and then dried over Na_2SO_4. Solvent was evaporated *in vacuo* to get solid crude material 0.94 g (mp 181—186 °C). The crude product was purified on silica gel column (hexane : ethyl acetate 40 : 60 (v/v) to obtain pure 17β-hydroxy-17α-methylandrostan-3-one (0.88 g, 88%) mp 190—192 °C, $[\alpha]_D^{25}$ +10.5° ($CHCl_3$). IR (KBr) cm^{-1}: 3433, 1699, 1150. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.38—2.23 (3H, overlapping m), 2.11—2.09 (2H, m), 1.81—1.70 (3H, overlapping m), 1.61—1.24 (7H, overlapping m), 1.21 (3H, s), 1.03 (3H, s), 0.91 (1H, m), 0.87 (3H, s), 0.71 (1H, dt, J=3.68, 14.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 212.0 (C3), 81.6 (C17), 53.7 (C13), 50.4 (C4), 46.7 (C9), 45.4 (C14), 44.6 (C2), 38.9 (C10), 38.5 (C5), 38.1 (C16), 36.2 (C1), 35.7 (C8), 31.5 (C7), 31.3 (C12), 28.8 (C6), 25.7 (C11), 23.2 (C20), 21.0 (C18), 13.9 (C15), 11.4 (C19), *Anal*. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.88; H, 10.52. FAB$^+$-MS *m/z*: 305 (M+1).

Synthesis of 17β-Hydroxy-17α-methyl-Δ^1-androsten-3-one (3) from 17α-Methyl Androstan-3β,17β-diol (1) Using 2-Iodoxy Benzoic Acid (IBX) 17α-Methylandrostan-3β,17β-diol (**1**) (1 g, 3.27 mmol) was dissolved in 15 ml of DMSO. To this solution 2-iodoxy benzoic acid (IBX) (2.28 g, 8.16 mmol) was added in one lot. The solution was heated at 65 °C for 24 h and reaction was monitored by TLC. The reaction mixture was cooled to room temperature and diluted with 50 ml of diethyl ether. The organic layer was separated and washed with 5% $NaHCO_3$ solution (20 ml×2), water (20 ml×2) and then dried over Na_2SO_4. Solvent was evaporated *in vacuo* to get 0.90 g of brown colored solid crude material (91%, mp 125—130 °C). The crude product was purified by column chromatography (Silica gel, eluted with hexane/ethyl acetate 50 : 50 (v/v)) to obtain pure 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) (0.72 g, 74%), mp 154—155 °C (lit.[5] mp 153—154 °C, $[\alpha]_D^{25}$ +23° (EtOH). IR (KBr) cm^{-1}: 3517, 3030, 1663, 1066. ^{1}H-NMR (400 MHz, $CDCl_3$) (δ: 7.15 (1H, d, J=10.04 Hz), 5.85 (1H, d, J=10.24 Hz), 2.37 (1H, dd, J=3.4, 14.6 Hz), 2.22 (1H, dd, J=4.16, 14.6 Hz), 1.84—1.70 (6H, overlapping m), 1.59—1.23 (8H, overlapping m), 1.22 (3H, s), 1.03 (3H, s), 0.89 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 200.1 (C3), 158.3 (C1), 127.3 (C2), 81.4 (C17), 50.5 (C13), 49.9 (C4), 45.6 (C9), 44.3 (C14), 40.9 (C10), 38.9 (C5), 38.8 (C16), 36.4 (C8), 31.4 (C7), 30.9 (C12), 27.4 (C6), 25.8 (C11), 23.1 (C20), 20.8 (C18), 14.0 (C15), 12.9 (C19). *Anal*. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.39; H, 9.98. FAB-MS: 302.224 (M^+). 10% of Methyltestosterone **4** was present as by product. mp 161—162 °C (lit. 161—165 °C).

Synthesis of 17β-Hydroxy-17α-methylandrostan-3-one (2) Using NaOCl/TBABr 17α-Methylandrostan-3β,17β-diol (**1**) (1 g, 3.2 mmol) was taken in 14 ml of acetic acid (glacial). Added tetrabutyl ammonium bromide (2 mg) and cooled the reaction mixture to 15 °C in water bath and added sodium hypochlorite 0.5 M (8.4 ml) drop-wise while maintaining the temperature of waterbath 15—18 °C. Stirred the reaction mixture at same temperature for 16 h. After completion of reaction (TLC) evaporated the acetic acid *in vacuo* and then coevaporated with ethanol/water (70 : 30 v/v). The solid was crystallized using ethanol : water (70 : 30) as a solvent to get **2** (0.67 g, 68%), mp 188—190 °C.

Synthesis of 7β-Hydroxy-17α-methylandrostan-3-one (2) Using H_2O_2/Na_2WO_4/CTMAHSO$_4$ 17α-Methylandrostan-3β,17β-diol (**1**) (1 g, 3.2 mmol) was taken in 80 ml of toluene. Added Na_2WO_4 (0.25 g) and cetyltrimethylammonium hydrogensulphate ($CTMAHSO_4$) (0.28 g). Cooled the reaction mixture in ice bath and added H_2O_2 (30% solution) (4.2 ml, 4.8 mmol) drop-wise with fast mechanical stirring (1000 rpm). After addition of H_2O_2, the reaction mixture was slowly heated to 95 °C. Reaction mixture was stirred at same temperature for 24 h. After completion of reaction (TLC), toluene was completely removed *in vacuo*. Solid product obtained was crystallized from water : *t*-butanol (3 : 50 v/v), first refluxing the mixture to clear solution and then cooling at 4 °C to afford **2** (3.65 g, 80%) mp 190—192 °C.

Result and Discussion

Despite their ubiquity and utility in organic chemistry the synthesis of Oxandrolone is tedious and involve challenging transformations. Several methods to effect this operation have been developed over the years. Most of these protocols rely on highly toxic reagents and laborious low yielding procedures. Our recent explorations for a cheap and non-toxic oxidizing reagent led us to propose the IBX as a suitable candidate to effect the oxidation of **1** to **2** and **3**. Since IBX is known to oxidize alcohols, the prospect of accomplishing multiple oxidative processes in one operation was particularly enticing. Aqueous H_2O_2 is an ideal oxidant when coupled with a tungstate complex and quaternary ammonium hydrogen sulfate as an acidic phase transfer catalyst. Hence we have used NaOCl and H_2O_2/Na_2WO_4 under phase transfer conditions for the oxidation of **1**.

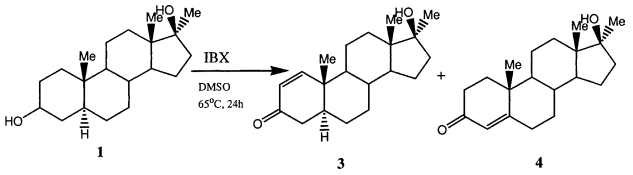

Chart 2. Oxidation of 17α-Methylandrostan-3β,17β-diol **1** with IBX (2.5 Equivalent)

17α-Methylandrostan-3β,17β-diol (**1**) was obtained by the reaction of MeMgI with epiandrosterone using a standard procedure.[17] **1** on oxidation with iodoxybenzoic acid in dimethyl sulfoxide gave 17β-hydroxy-17α-methylandrostan-3-one (**2**) in very high yield in 2 h. When the same reaction was done with higher amount of IBX (2.5 equivalent), dehydrogenated product 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) is obtained in high yield. In this method, 10—15% methyltestosterone **4** is also formed (Chart 2). The products **3** and **4** were isolated by column chromatography. Formation of **3** in major amount in this method indicate that after oxidation of hydroxyl group the abstraction of hydrogen (dehydrogenation) from α,β-position to carbonyl group by bulky 2-iodoxybenzoic acid take place from the less sterically hindered side of the reactant. The approach of 2-iodoxybenzoic acid to carbon C1 and C2 will be comparatively easier to that of C4 and C5. It is interesting that by this reagent we can directly convert 17α-methylandrostan-3β,17β-diol **1** to 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) in single step reaction, avoiding the multiple step of oxidation, bromination and dehydrobromination and thus obtaining **3** in much higher yield and easier way.

Desai *et al*. have reported the synthesis of 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one using IBX as reagent for dehydrogenation.[5] They have started from mestanolone while we have used 17α-methylandrostan-3β,17β-diol as starting material and directly converted it into 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one. Hence one step is reduced in our synthetic procedure and secondly 17α-methyl androstan-3β,17β-diol is less costly. Reduction of one step leads to increase in overall yield. Cabaj *et al*. have used a different approach for the synthesis of **3**.[6] They first brominated the mestanolone regioselectively and then dehydrobrominated the intermediate to give product **3**. The earlier reported procedures are multiple step reactions and molecular bromine, a highly harmful chemical was used for the synthesis. The overall yield of product **3** was low. In this report (Chart 2), we have eliminated the multiple steps, used mild and environment friendly reagents and overall yield is higher to that of earlier reports.

Oxidation of **1** with sodium hypochlorite has been reported with very low yield of the mestanolone.[18] Lee *et al*. used the sodium hypochlorite with phase transfer catalyst for the oxidation of alcohols and amines and has reported high yield of the oxidized product.[19] Oxidation of **1** with sodium hypochlorite under phase transfer condition gave the 100% conversion of **1** but after crystallization the mestanolone was

Table 1. % Yield of Products Obtained from Oxidation of **1** with Different Oxidizing Agents

Sr. No.	Reagent	Equivalent of reagent used	Reaction time (h)	Yield (%) of product **2**	Yield (%) of product **3**
1	IBX	1.2	2	88	4—5[b)]
2	NaOCl	1.4	16	68	—
3	H_2O_2/Na_2WO_4	1.5	24	82	—
4	IBX	2.5	24	—	74[a)]

a) isolated product yield, *b*) yield by gas chromatography.

obtained in 68% yield. A careful examination of mother liquor showed presence of chlorinated side products.

Hydrogen peroxide with heteropolycations under phase transfer conditions has been reported as environment friendly green oxidizing reagent. Noyori *et al*. has used hydrogen peroxide with sodium tungstate as catalyst and methyltrioctylammonium hydrogen sulfate as phase transfer catalyst for the oxidation of various primary and secondary alcohols.[15)] We have used toluene as reaction media and easily available cetyltrimethyl ammonium hydrogen sulfate for the conversion. With this reagent, the mestanolone was obtained in high yield and purity.

In summary, oxidative transformation of **1** with 2-iodoxybenzoic acid, sodium hypochlorite and hydrogen peroxide gave mestanolone in good to high yield. With hydrogen peroxide, mestanolone has been obtained in environment friendly procedure. **3** has been obtained in a single pot reaction from **1** using IBX.

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