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IBX in an ionic liquid: eco-friendly oxidation of 17α-methylandrostan-3β,17β-diol, an intermediate in the synthesis of anabolic oxandrolone

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Abstract—An easily available hypervalent iodine(V) reagent, 2-iodoxybenzoic acid (IBX) immobilized in the ionic liquid [bmim][Br] was found to be an efficient and eco-friendly protocol for the oxidation of 17α-methylandrostan-3β,17β-diol (**1**). At ambient temperature oxidation of **1** with IBX gave mestanolone (**2**) in good yield and with an increased stoichiometric amount of IBX, oxidation adjacent to the carbonyl functionality (α,β-unsaturation) occurred to give dehydrogenated 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) as the major product in a one-pot reaction. The product is easily obtained by extraction with diethyl ether and evaporation of the solvent.

Oxandrolone (17β-hydroxy-17α-methyl-2-oxa-5α-androsterone-3-one) is a well known 2-oxasteroid recognized for its anabolic activity with negligible side effects.[1] It is widely used in medicine as an anabolic drug,[2] for the promotion of weight gain following surgery and to improve muscle weakness.[3] It has also been recommended for the treatment of osteoporosis, HIV-wasting syndrome and HIV-associated muscle weakness. Oxandrolone was first prepared in 1962.[4] In its synthesis from dehydroepiandrosterone; 17α-methyl-androstan-3β,17β-diol (**1**), mestanolone (**2**) and 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**) are important intermediates. The synthesis of **3** from mestanolone is a regioselective transformation. In earlier reports bromination with molecular bromine followed by dehydrobromination was used to achieve this transformation, but the isomers were formed with poor regioselectivity. In another report, selective bromination with the bulky brominating agent phenyltrimethylammonium tribromide (PTT) was performed to improve the regioselectivity.[5] In all these earlier reported procedures hazardous molecular bromine was used in the synthesis.[6]

In the last two decades, hypervalent iodine reagents have enjoyed increasing popularity in organic synthesis.[7] The pentavalent iodine reagent, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (IBX) has been used for the oxidation of alcohols to carbonyl compounds,[8] oxidations adjacent to carbonyl groups to form α,β-unsaturated carbonyl systems[9] and in the synthesis of various heterocyclic compounds.[10] IBX has been known for more than a century,[11] although its presence in organic synthesis has remained limited primarily due to its remarkable insolubility in most organic solvents.[12,13] Very recently, Desai et al. reported the conversion of **2** into **3** using IBX in dimethyl sulfoxide (DMSO),[14] the only solvent in which IBX is appreciably soluble. As the recovery of product from this solvent is very difficult due to its high boiling point, it is an inconvenient solvent for the synthesis.

Ambient temperature ionic liquids especially those based on 1,3-dialkylimidazolium cations, are attracting growing interest as alternative reaction media for chemical and biochemical transformations.[15,16] Since they are nonvolatile in nature without any detectable vapor pressure, they have gained wide popularity in recent years as environmentally benign solvents and have been employed as reaction media for various organic reactions such as alkylation,[17] Heck reactions,[18] Suzuki reactions,[19] oxidation[20] and heterocyclization.[21]

In our efforts to synthesize anabolic steroids via eco-friendly methods with improved yields, we found that

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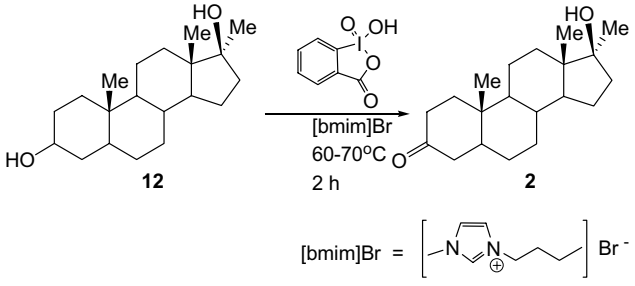
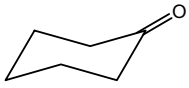
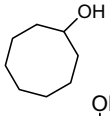
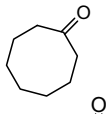
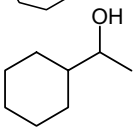
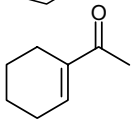
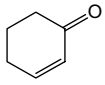
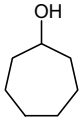
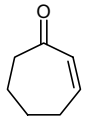
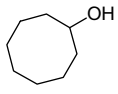
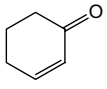
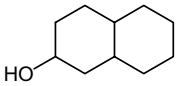
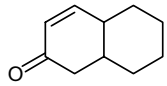


Scheme 1. Oxidation of **1** with 1.2equiv of IBX in ionic liquid.

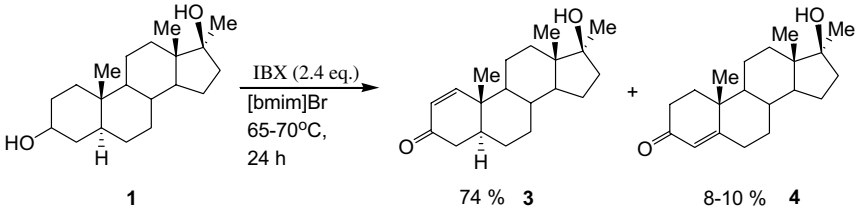
ionic liquids were excellent reaction media for the oxidation and dehydrogenation of steroids with 2-iodoxybenzoic acid. IBX dissolves in the ionic liquid [bmim][Br] to form a homogeneous mixture.[22] We report herein the synthesis of mestanolone (**2**) and 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**3**), important intermediates in the synthesis of the anabolic drug oxandrolone, by the oxidation and dehydrogenation of 17α-methylandrostan-3β,17β-diol (**1**) with 2-iodoxybenzoic acid (IBX) using 1-butyl-3-methylimidazolium bromide ([bmim][Br]) as the reaction medium (Scheme 1).

In a systematic study, we investigated the efficacy of the oxidation of cyclic secondary alcohols with IBX in an ionic liquid (Table 1). The reactions were performed under different conditions by dissolving the alcohol in [bmim]Br followed by addition of IBX. The representative substrates cyclohexanol (entry 3) and cyclooctanol (entry 4) were oxidized at room temperature with 1.2equiv of IBX to give cyclohexanone and cycloocta-

Table 1. Oxidative transformations with IBX in the ionic liquid [bmim]Br

Entry	Substrate	Product	Conditions	Yield[a] (%)
1	**1**	**2**	IBX (1.2equiv), 65 °C, 2h	88 82[b]
2	**1**	**3**	IBX (2.4equiv), 65 °C, 22h	74[c] 71[b,c]
3			IBX (1.2equiv), 25 °C, 2.5h	87
4			IBX (1.2equiv), 25 °C, 6h	92
5			IBX (3equiv), 80 °C, 4h	82
6			IBX (1.4equiv), 75 °C, 7h	84
7			IBX (1.8equiv), 75 °C, 8h	86
8			IBX (2.6equiv), 75 °C, 8h	78
9			IBX (2.8equiv), 75 °C, 14h	82
10			IBX (2.5equiv), 75 °C, 11h	80
11			IBX (2.5equiv), 85 °C, 11h	74

[a] Yield determined by gas chromatography.
[b] Reaction repeated in recovered ionic liquid.
[c] Methyltestosterone (8–10%) is also present.



Scheme 2. One-pot synthesis of **3** via IBX-mediated oxidation of **1** in the ionic liquid [bmim][Br].

none as the sole products. Further additional portionwise addition of IBX at the same temperature did not lead to further oxidation of the product. However, dehydrogenation adjacent to the carbonyl functionality occurred at elevated temperature. Replacing the alcohol reaction mixture with pure cyclohexanone (entry 6) also led to a similar observation. When the initial temperature of the reaction mixture was kept at 70–80 °C, the portionwise continuous addition of 1.2 equiv of IBX yielded the corresponding ketone in much reduced time, although a minor amount of the α,β-unsaturated ketone was obtained due to further oxidation. With a stoichiometric increase of IBX with respect to the reactant, oxidation with simultaneous dehydrogenation occurred giving the corresponding α,β-unsaturated ketone directly from the alcohols (entries 8–10). Having gained the key information regarding the scope of this methodology, we turned our attention to more complex substrate, the steroid alcohol **1**. Steroid molecules were considered to be the best testing ground for evaluation of the efficacy of the developed system. Mestanolone was the product ketone obtained on oxidation of 17α-methylandrostan-3β,17β-diol (**1**) with 1.2 equiv of IBX. Previously this transformation was achieved with CrO_3/acetic acid.[23]

With the higher stoichiometric ratio of IBX **1** was smoothly converted into **3** in one pot. Testosterone **4**, the regioisomer of **3** was formed in 8–10% during this process (Scheme 2). Formation of **3** as the major isomer shows the regioselectivity of this reaction. The tertiary alcohol group present in alcohol **1** remained unaffected during this oxidation, a necessary requirement for a higher yield of the product. When compared with earlier reports, this oxidative protocol is highly efficient and very high yielding. In earlier reports, **3** was synthesized by a multiple step process using hazardous chemicals in 48% overall yield. While using this method, **3** has been synthesized by a single step and environment friendly procedure in 74% overall yield.

After extraction of the oxidized product with diethyl ether, the iodosobenzoic acid (IBA) resulting from the reduction of IBX was removed by adding excess water and filtration of the precipitated solid. The IBA so obtained can be reoxidized to IBX by standard procedures.[24] The ionic liquid can be recovered by simply concentrating the filtrate under vacuum and reused in up to three recycles without affecting the yield of the product.

In conclusion, this report describes an elegant and efficient protocol for the oxidative transformation of secondary alcohols using the mild and inexpensive reagent IBX at ambient temperature in the environmentally benign ionic liquid [bmim][Br].[25] With the prospect of recycling the ionic liquid and excellent yield of the products, this protocol will be potentially beneficial for chemists for the synthesis of other steroid drugs.

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25. Representative general procedure: 17α-methylandrostan-3β,17β-diol **1** (1 g, 3.27 mmol) was dissolved in 3 mL [bmim][Br] with stirring. To this solution 1.2 equiv (1.105 g, 3.94 mmol)/2.4 equiv (2.21 g, 7.88 mmol) of 2-iodoxybenzoic acid was added in one portion. The solution was heated at 65 °C and the reaction was monitored by TLC (or GC in the case of other alcohols). On completion, the reaction mixture was cooled to room temperature and extracted with diethyl ether (4 × 10 mL). The organic layer was separated and washed with 5% $NaHCO_3$ solution (5 mL), water (5 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give a solid crude product, which was purified by silica gel column chromatography.