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An expedient one-pot entry to catecholestrogens and other catechol compounds via IBX-mediated phenolic oxygenation

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Abstract—A one-pot procedure for the preparation of catecholestrogens in over 90% yield is reported, involving oxygenation of 17β-estradiol or estrone with *o*-iodoxybenzoic acid (IBX) followed by reduction with methanolic $NaBH_4$. The procedure, which was extended to the *o*-hydroxylation of a number of representative phenols in good-to-high yields, expands significantly the scope of phenolic oxidation mediated by IBX.

1. Introduction

The catecholestrogens (**3/4** and **5/6**) are important products of metabolic transformation of the estrogens arising by P450-mediated hydroxylation of 17β-estradiol (**1**) and estrone (**2**), respectively, at the 2- and 4-positions of the phenolic A-ring.[1] Because of their implication in the mechanisms of estrogen-related carcinogenesis,[2] for example, in breast cancer, the catecholestrogens have been the focus of considerable interest for toxicological studies and as starting materials for novel steroidal derivatives with antiestrogenic properties. Their availability, however, is currently limited by the lack of a facile and expeditious preparative procedure.[3] For example, classical approaches based on phenolic nitration involve at least three steps and, for the synthesis of 2-hydroxy-17β-estradiol (**3**) and 4-hydroxy-17β-estradiol (**4**), reductive conversion of the 17-oxo group of an estrone derivative.[3c] Moreover, protection/deprotection steps with chromatographic separations are often required.

In connection with our studies on the oxidation of estrogens,[4] we have now developed a simple and convenient one-pot procedure for the preparation of the catecholestrogens **3/4** or **5/6**, which involves use of the hypervalent iodine reagent *o*-iodoxybenzoic acid (IBX)[5] under carefully controlled reaction and work-up conditions.

In a typical procedure, solid IBX (2.5 equiv) was added to a solution of **1** or **2** (200 mg) in $CHCl_3$/MeOH 3: 2 v/v (40 mL) at −25 °C. A yellow-to-orange color developed and the mixture was stirred for 24 h. Methanolic $NaBH_4$ (15 mg in 1 mL) was then added at −25 °C under vigorous stirring until the color disappeared (usually within 5 min). After mild acidification with acetic acid (200–500 μL) to remove excess $NaBH_4$, the mixture was washed five times with equal volumes of a saturated NaCl solution containing 10% sodium dithionite buffered at pH 7.0 with sodium phosphate. Evaporation of the organic layer eventually furnished the desired products **3/4** or **5/6**, which could be separated by preparative TLC (benzene/ethyl acetate/acetic acid 1/1/0.01) on silica.

This procedure differs from previous IBX-mediated oxidations[6–8] in that the key steps are run in the cold, to prevent quinone conversion to intractable materials in the chloroform-containing medium,[9] and the critical reductive treatment is efficiently carried out with methanolic $NaBH_4$ under homogeneous phase conditions. The latter treatment allowed product recovery in good-to-high yields, without affecting the carbonyl at C-17 of estrone substrates **5** and **6**. Chemoselective reduction of the quinone moiety, sparing the carbonyl function of **5** and **6**, was made possible by the low temperature maintained during $NaBH_4$ treatment and the cold acid quenching of the mixture; partial reduction occurred when the treatment was performed at room temperature and/or the cold acid quenching step was omitted prior to solvent evaporation.

Keywords: Estrogens; IBX; Catechols.
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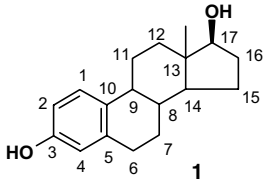
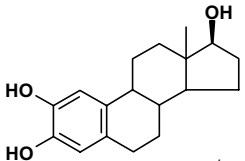
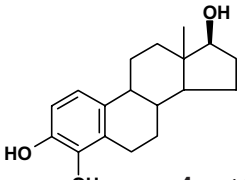
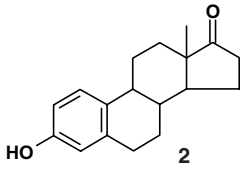
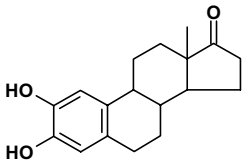
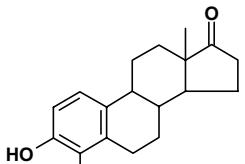
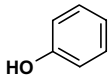
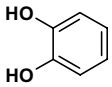
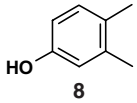
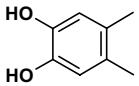
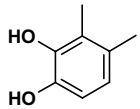
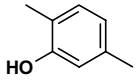
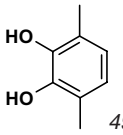
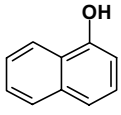
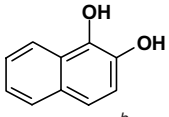
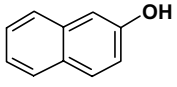
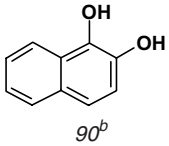
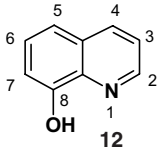
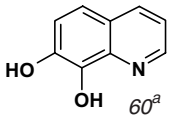
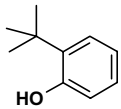
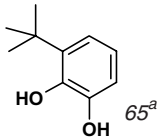
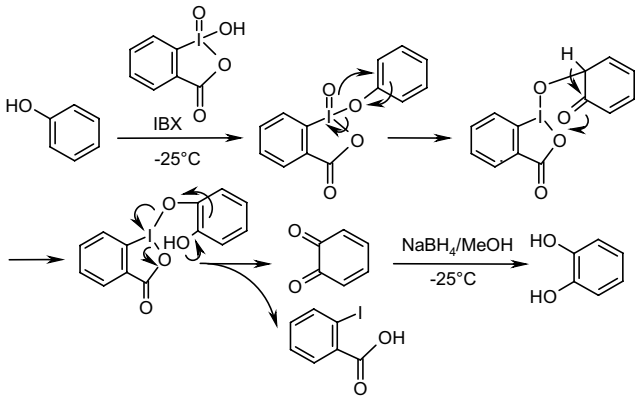
For comparative purposes, and to assess its potential and scope for phenolic oxidation, the procedure was extended to a number of representative substrates. These included the parent phenol (**7**), 3,4-dimethylphenol (**8**), 2,5-dimethylphenol (**9**), 1-naphthol (**10**), 2-naphthol (**11**), 8-hydroxyquinoline (**12**), and 2-*tert*-butylphenol (**13**). Reaction conditions, products[10] and yields are provided in Table 1.

The reaction proceeded smoothly with complete substrate consumption in all cases and resulted in good-to-high product yields. Data in Table 1 indicate that

Table 1. IBX-promoted *o*-hydroxylation of estrogens and other phenols

Substrate	Concn (mM)/ IBX equiv	Solvent	Reaction time	Product(s)/yield(s) (%)[a,b]
 **1**	20/2.5	$CHCl_3$/MeOH 3/2	24 h	 **3** *42[a] 49[b]*  **4** *44[a] 48[b]*
 **2**	20/2.5	$CHCl_3$/MeOH 3/2	24 h	 **5** *45[a], 50[b]*  **6** *47[a], 48[b]*
 **7**	90/2.0	$CHCl_3$/MeOH 4/1	20 min	 *97[b]*
 **8**	100/1.5	$CHCl_3$	12 h	 *38[a], 45[b]*  *35[a], 40[b]*
 **9**	100/1.5	$CHCl_3$	12 h	 *49[a]*
 **10**	70/1.5	$CHCl_3$	12 h	 *96[b]*
 **11**	70/1.5	$CHCl_3$	12 h	 *90[b]*
 **12**	60/2.0	$CHCl_3$/MeOH 4/1	1 h	 *60[a]*
 **13**	60/2.0	$CHCl_3$/MeOH 4/1	1 h	 *65[a]*

[a] Determined on products isolated by TLC on silica (impurities below ^1H NMR detection limits).
[b] Formation yield (determined by HPLC by comparing peak areas with external calibration curves).



Scheme 1.

the reaction allows for the regioselective conversion of monophenols to *o*-diphenols (catechols), and that in few cases, that is, **1**, **2**, and **8**, two *ortho* regioisomers are produced in comparable yields. This is a reflection of the comparable steric hindrance and reactivity on the two positions *ortho* to the OH group.

The IBX-induced conversion of phenol to catechol with a brief mechanistic description[6,8] is illustrated in Scheme 1.

Use of cold methanolic $NaBH_4$ after oxidation of phenols **7–13** proved to be critical for efficient quinone reduction since, with $CHCl_3$ or a $CHCl_3$/MeOH mixture as the solvent, a simple reductive work-up with sodium dithionite at room temperature[6] was not entirely satisfactory leading in some cases to a poor recovery of the catechol products. In a previous paper[7] Quideau et al. reported oxidation of 2,5-dimethylphenol (**9**) with Stabilized IBX (SIBX), a non-explosive alternative to IBX, in THF to give as main product a dimeric species arising from hydroxylation at the carbon bearing the methyl group. We did not notice the presence of that dimer in our mixture, so it is likely that the different regioselectivity observed in the present study reflects the change of solvent and/or temperature favoring attack of the oxygen to the unsubstituted position of the aromatic ring.

The potential of IBX for the conversion of phenols to *o*-quinones and catechols was also underscored in a recent paper,[8] in which a number of phenols substituted with electron-donating groups were shown to undergo regioselective oxidation. The procedure described herein not only stands comparison with the previous one, as judged from the reported oxidation of **11** in $CDCl_3$,[8] but expands its scope to include the estrogens and several other phenolic compounds.[11] Particularly worthy of note is the conversion in good yield of phenol itself, for which the IBX-mediated hydroxylation was reported to be unsuccessful.[8]

Acknowledgements

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10. 2-Hydroxy-estra-1,3,5(10)-trien-3,17β-diol (**3**). Pale yellow powder. UV (MeOH): λ_{max} 281 nm. ESI/MS *m/z*: 287 [M−H$^+$]; ESI-HRMS calculated for $C_{18}H_{23}O_3$ (M−H$^+$) 287.1647, found 287.1649. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 0.78 (s, 3H, C*H*$_3$), 3.73 (t, *J* = 8.8 Hz, 1H, C*H*OH), 6.58 (s, 1H), 6.81 (s, 1H).
4-Hydroxy-estra-1,3,5(10)-trien-3,17β-diol. (**4**) Pale yellow powder. UV (MeOH): λ_{max} 280 nm. ESI/MS *m/z*: 287 [M−H$^+$]; ESI-HRMS calculated for $C_{18}H_{23}O_3$ (M−H$^+$) 287.1647, found 287.1648. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 0.77 (s, 3H, C*H*$_3$), 3.73 (t, *J* = 8.8 Hz, 1H, C*H*OH), 6.69 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H).
2-Hydroxyestrone (**5**). Pale yellow powder. UV (MeOH): λ_{max} 282 nm. ESI/MS *m/z*: 285 [M−H$^+$]; ESI-HRMS calculated for $C_{18}H_{21}O_3$ (M−H$^+$) 285.1491, found 285.1491. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 0.78 (s, 3H, C*H*$_3$), 6.61 (s, 1H,), 6.82 (s, 1H).
4-Hydroxyestrone (**6**). Pale yellow powder. UV (MeOH): λ_{max} 282 nm. ESI/MS *m/z*: 285 [M−H$^+$]; ESI-HRMS calculated for $C_{18}H_{21}O_3$ (M−H$^+$) 285.1491, found 285.1490, found 288.1725. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 0.77 (s, 3H, C*H*$_3$), 6.67 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H).
Catechol. Brownish powder. UV (MeOH): λ_{max} 280 nm. ESI/MS *m/z*: 109 [M−H$^+$]; ESI-HRMS calculated for $C_6H_5O_2$ (M−H$^+$) 109.0289, found 109.0291.
4,5-Dimethylcatechol. Pale brown powder. UV (MeOH): λ_{max} 280 nm. ESI/MS *m/z*: 137 [M−H$^+$]; ESI-HRMS calculated for $C_8H_9O_2$ (M−H$^+$) 137.0603, found 137.0604. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 2.20 (s, 6H, C*H*$_3$), 5.51 (s, 2H).

3,4-Dimethylcatechol. Pale brown powder. UV (MeOH): λ_{max}280 nm. ESI/MS *m/z*: 137 [M−H$^+$]; ESI-HRMS calculated for $C_8H_9O_2$ (M−H$^+$) 137.0603, found 137.0605. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 2.21 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 5.53 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H).

3,6-Dimethylcatechol. Pale brown powder. UV (MeOH): λ_{max} 281 nm. ESI/MS *m/z*: 137 [M−H$^+$]; ESI-HRMS calculated for $C_8H_9O_2$ (M$^+$) 137.0603, found 137.0604. ^{1}H NMR ($CDCl_3$), δ (ppm) selected signals: 2.22 (s, 6H, CH_3), 6.61 (s, 2H).

1,2-Dihydroxynaphthalene. Pale blue powder ESI/MS *m/z*: 159 [M−H$^+$]; ESI-HRMS calculated for $C_{10}H_7O_2$ (M−H$^+$) 159.0446, found 159.0449.

7,8-Dihydroxyquinoline. Pale red powder ESI/MS *m/z*: 160 [M−H$^+$]; ESI-HRMS calculated for $C_9H_6O_2N$ (M−H$^+$) 160.0398, found 160.0403. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.22 (d, J = 8.8 Hz, 1H), 7.29 (dd, J = 8.4, 4.4, Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 8.16 (dd, J = 8.4, J = 1.6, Hz, 1H), 7.29 (dd, J = 4.4, J = 1.6, Hz, 1H).

3-*tert*-Butylcatechol. Pale brown powder. UV (MeOH): λ_{max} 281 nm. ESI/MS *m/z*: 165 [M−H$^+$]; ESI-HRMS calculated for $C_{10}H_{13}O_2$ (M−H$^+$) 165.0915, found 165.0917. ^{1}H NMR (CD_3OD_3), δ (ppm): 1.40 (s, 9H, CH_3), 6.55 (dd, J = 8.0, J = 7.5, Hz, 1H), 6.64 (dd, J = 8.0, J = 1.5, Hz, 1H), 6.70 (dd, J = 7.5, J = 1.5, Hz, 1H).

11. NOTE ADDED IN PROOF, Saeed, M.; Zahi, M.; Rogan, E.; Cavalieri, E. *Steroids* **2005**, *70*(3), 173–178.