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Regioselective Oxidation of Phenols to *o*-Quinones with *o*-Iodoxybenzoic Acid (IBX)

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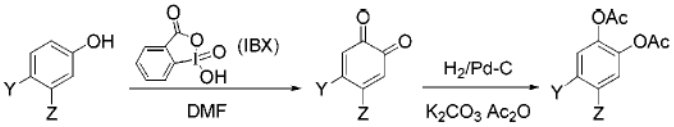
Abstract



An efficient regioselective method for oxidation of phenols to *o*-quinones is reported. When this procedure is combined with a subsequent reduction, it proves to be useful for the construction of a variety of catechols.

o-Quinones undergo a variety of reactions. For example, these species can be reduced to the corresponding catechol.[1,2] In addition, as a highly reactive 8π-electron system, *o*-quinones display two 4π components as potential sites for Diels–Alder reactions.[3] The selectivity between sites results from the polarizability of the complementary 2π component. For example, polarized alkenes such as enamines add to the external dione to restore aromaticity and yield a dioxin,[4] while less polarized alkenes such as styrene add to the cyclohexadiene portion to yield a [2.2.2]bicyclooctane.[5] Because *o*-quinones display four 2π components, there are varieties of [3 + 2] cycloaddition formats as well. The dipolar addition can be controlled so that either a carbonyl or an olefin moiety undergoes reaction.[6] In addition, there are many other reactions where the functional groups of *o*-quinones can be distinguished. For example, cesium fluorosulfate converts the most electrophilic carbonyl group of an *o*-quinone to 2,2-difluorocyclohexadienone,[7] while addition of a Wittig reagent can generate a benzopyran-2-one.[8] The ring olefins can be distinguished in nonsymmetric *o*-quinones: the most nucleophilic olefin is either oxidized or cleaved with peroxyacid[9] and Pb[10] reagents, respectively.

Such versatility clearly suggests that unsymmetric *o*-quinones should be of considerable synthetic use. However, a convenient means to access a range of differently substituted *o*-quinones has been lacking due in part to the difficulty in accessing the appropriately substituted catechol. A thorough survey of the literature reveals a few methods that allow for the regioselective conversion of a phenol to an *o*-catechol.[11] To the best of our knowledge, there are no previous examples of a regioselective procedure for the direct conversion of a phenol into an *o*-quinone. Oxidants such as Fremy's radical,[12] $MeReO_3$–H_2O_2,[13] dimethyldioxirane,[14] and benzeneseleninic anhydride[15] are indiscriminate or favor oxidation of the para position unless blocked with a substituent.

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Supporting Information Available: A general experimental procedure along with the crude ^{1}H NMR spectra used to estimate yields for *o*-quinones **4**, **6**, **8**, **11**, **13**, **15**, **17**, **19**, and **23** and full spectral characterization of **5**, **20**, **21**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

While investigating oxidative dearomatizations of 4-alkylated resorcinol derivatives[16] with hypervalent iodine reagents, we discovered another useful oxidative property of *o*-iodoxybenzoic acid, a reagent otherwise known as IBX (**1**).[17] Instead of the cyclohexa-2,5-dienone **3** observed with I^{III} reagents,[18] the *o*-quinone **4** smoothly emerged from phenol **2** in 69% yield (Figure 1).

Because of this unexpected yet pleasing transformation, we paused to investigate the potential of this novel transformation.

Table 1 illuminates the scope of this procedure. The oxidation of an array of phenols (0.1 M in a respective solvent) with a suspension of IBX (1 equiv) at room temperature was investigated. A double oxidation was found to ensue that produced a range of *o*-quinones. The reaction times varied from 6 to 53 h and depended primarily upon the polarity of the solvent and the functional groups distributed within the starting phenol. The transformation proved to be surprisingly general and regioselective, with the limitation that the starting phenol material must contain at least one electron-donating group.[19] Phenols without electron-donating substituents and those containing electron-withdrawing groups such as –C(O)R, –CHO, and $–NO_2$ failed to undergo oxidation.

Because most of the *o*-quinone products proved to be volatile and highly reactive, the overall yield for this process was estimated by ^{1}H NMR. This was accomplished by conducting the reactions in a deuterated solvent that was doped upon completion with 1 equiv of a ^{1}H NMR active standard such as EtOAc or DMF. The percent conversion was then estimated by comparing the integration of a proton of the product with a proton of the standard.[20]

DMF proved to be the superior solvent. For example, oxidation of **7** → **8** in $CDCl_3$ required 14 h and proceeded in 85% yield. Application of d_7-DMF speeded the conversion of **7** → **8** to 1.5 h in essentially quantitative yield. Similar improvements were observed in the conversion of **9** → **8** by exchanging d_7-DMF for $CDCl_3$. However, $CDCl_3$ worked well as a solvent in some instances. Oxidation of **5** → **6** in $CDCl_3$ required 19 h and afforded **6** in 92% yield, while oxidations of **10** → **11**, **12** → **13**, and **16** → **17** proceeded in 96, 84, and 99% yields, respectively. The low-yielding oxidation of **18** → **19** in both d_7-DMF and $CDCl_3$ is further evidence of the requirement that the starting substrate contain an electron-donating substituent, while the poor conversion of **14** → **15** is believed to reflect a solubility problem of **14**.

Reduction of the *o*-quinone product occurs upon hydrogenation or exposure to $Na_2S_2O_4$ (Figure 2). After an oxidation conducted in DMF was complete, K_2CO_3 (2.5 equiv), Ac_2O (2.1 equiv), and Pd/C (5 mol %) were added to the crude product mixture and the resulting suspension was stirred under a hydrogen atmosphere for 24 h. The bisacetylated catechol that emerged facilitated isolation. The protected hydroquinone proved to be much more stable and less volatile than the corresponding *o*-quinone and catechol precursors. *Since oxidation, reduction, and acylation occur successively in the same pot, this procedure embodies a high-yielding 1-pot conversion of an electron-rich phenol into a catechol*. The isolated yields of the bis-acylated products **20** and **21**, 87 and 76%, respectively, substantiated the validity of our ^{1}H NMR method for estimating the yields of the *o*-quinones.

This highly regioselective oxidation of phenols to *o*-quinones with IBX (**1**) is remarkable because it represents a double oxidation; a hydroxy residue is regioselectively installed, and the resulting catechol intermediate is oxidized. The process most likely follows the pathway shown in Figure 3. The starting material combines with IBX to extrude H_2O producing the I^V intermediate **A**, which serves to intramolecularly deliver the oxygen to the most nucleophilic and least congested ortho site on the starting phenol. During this delivery process, the I^V atom is concurrently reduced to the I^{III} species **B**, which in turn undergoes tautomerization to intermediate **C**. The oxidation of catechols to *o*-quinones by I^{III} reagents is well documented.

[21] These types of reactions are believed to proceed by exchange of an I^{III} ligand for the phenol to produce a structure similar to **C** that oxidatively collapses with concurrent reduction of the iodine atom to produce an *o*-quinone and an I^{I} reagent.

To test the validity of this mechanism, the phenol **22** was exposed to IBX (**1**) (Figure 4). Because phenol **22** has no α-hydrogens, the cyclohexa-2,4-dienone cannot tautomerize and further oxidize. Instead, structure **23**, which results from a Diels–Alder dimerization of the corresponding methylated intermediate **B**, emerges as the sole diastereomeric product. This I^{III} dimer could be isolated but proved to be unstable toward chromatography. Reduction of **23** with sodium dithionite ($Na_2S_2O_4$) furnished diol **24** in 51% (isolated yield), and this structure was fully characterized. A ^1H NOE study of compound **24** established the relative stereochemical configuration to be that which emerges from dimerization of the cyclohexa-2,4-dienone intermediate on the face of the alkoxy residue.

In conclusion, the regioselective oxidation of electron-rich phenols with IBX (**1**) proves to be useful as an efficient method for the construction of a variety of catechols and o-quinones using mild, nontoxic conditions. Furthermore, such a procedure might find application in syntheses of dimeric structures such as bisorbicillinol and trichodimerol.

Acknowledgements

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16. a Van De Water RW, Magdziak D, Chau J, Pettus TRR. J Am Chem Soc 2000;122:6502–6503. b Jones RM, Van De Water RW, Lindsey CC, Hoarau C, Ung T, Pettus TRR. J Org Chem 2001;66:3435–3441. [PubMed: 11348127]

17. IBX (1), which is best known as the penultimate [$I^{(V)}$] intermediate in the synthesis of Dess–Martin periodinane, has gained popularity in its own right as a mild oxidant for alcohols, particularly diols, and for the selective oxidations of the carbon atom adjacent to aromatic systems, when 1 is applied in polar solvents: (a) ChaudhariSSSynlett20002278 b Nicolaou KC, Baran PS, Zhong YL. J Am Chem Soc 2001;123:3183–3185. [PubMed: 11457049]IBX is easily formulated by treatment of 2-iodobenzoic acid with oxone. See Frigerio M, Santagostino M, Sputore S. J Org Chem 1999;64:4537–4538.

18. Pettus LH, Van de Water RW, Pettus TRR. Org Lett 2001;3:905–908. [PubMed: 11263912]

19. Phenol itself failed to undergo oxidation with IBX.

20. No correction was made for differences between the relaxation times of the examined proton in the product and standard. However, protons with similar characteristics and in similar chemical environments were compared if possible. The crude spectra that are available for 6, 8, 11, 13, 15, 17, and 19 contain the 2-iodobenzoic acid byproduct of IBX.

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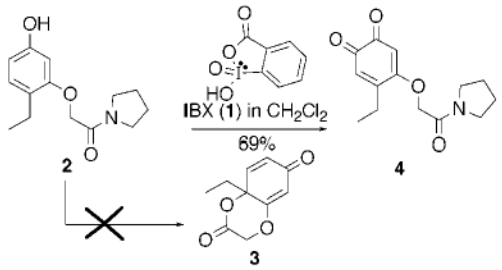


Figure 1.
An undesired but useful result.

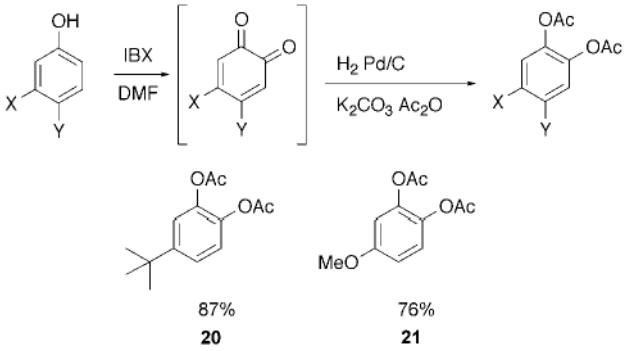


Figure 2.
One-pot procedure converting phenols to catechols.

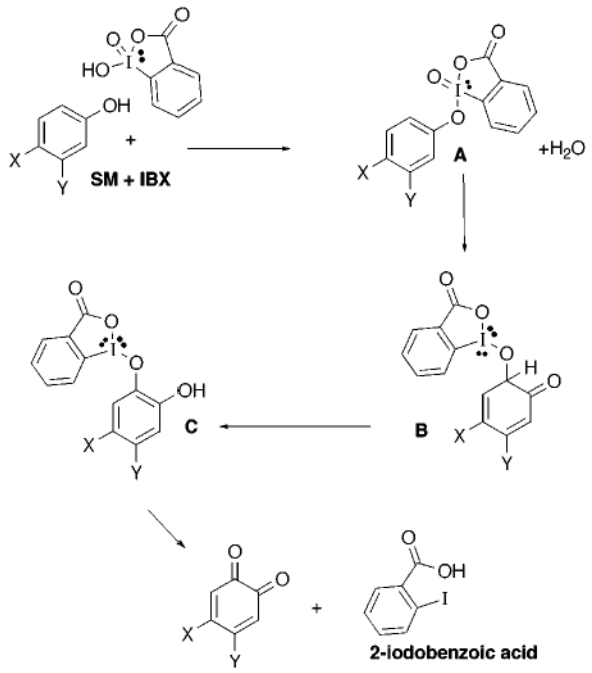


Figure 3.
Plausible mechanism.

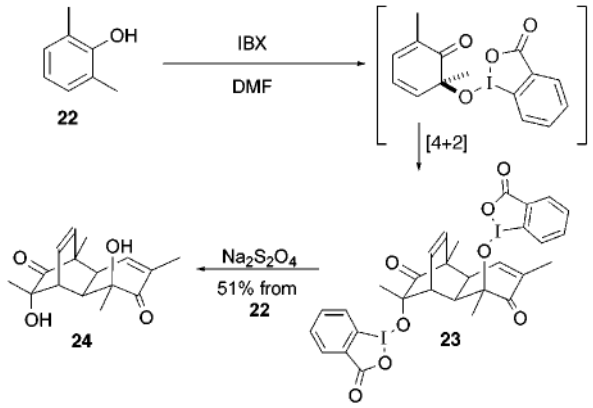
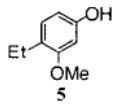
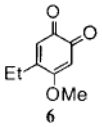
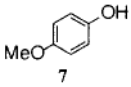
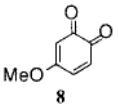
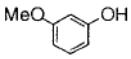
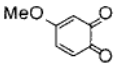
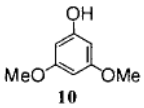
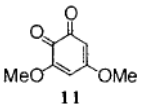
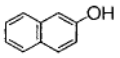
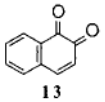
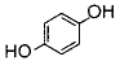
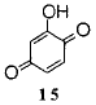
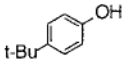
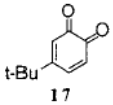


Figure 4.
Evidence for the proposed mechanism.

Table 1

Oxidations of Phenols with IBX at 25 °C

entry	*phenol*	*solvent*	*time(h)*	*o-quinone*	*yield*
1	 **5**	$CDCl_3$	19	 **6**	92%
2	 **7**	$CDCl_3$	14	 **8**	85%
3		d_7-DMF	1.5		99%
4	 **9**	$CDCl_3$	48	 **8**	16%
5		d_7-DMF	8		99%
6	 **10**	$CDCl_3$	21	 **11**	96%
7	 **12**	$CDCl_3$	10	 **13**	84%
8	 **14**	d_7-DMF	24	 **15**	20%
9	 **16**	$CDCl_3$	53	 **17**	99%
10	 **18**	$CDCl_3$	20	 **19**	33%
11		d_7-DMF	6		41%