Synthetic Methods

Bromide-Assisted Oxidation of Substituted Phenols with Hydrogen Peroxide to the Corresponding *p*-Quinol and *p*-Quinol Ethers over WO_4^{2-}-Exchanged Layered Double Hydroxides**

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The selective oxidation of substituted phenols to yield 4-hydroxycyclohexa-2,5-dienones (*p*-quinols) and their ethers has been intensely investigated in view of their applications as antioxidants, antibiotics, and antitumor agents.[1,2] Besides electrolytic[3] and photosensitized[4] approaches, procedures for quinol preparation require stoichiometric amounts of oxidants, such as Bi^{III} or Tl^{III} salts,[5,6] oxygen at high pressure,[7] hydrogen peroxide,[8] or particularly electrophilic halogens,[9] such as I^{III} reagents, chlorine, or bromine. In view of the risks associated with handling such reactive species, much attention has recently been devoted to the in situ generation of halonium species from harmless halides by using oxygen or hydrogen peroxide.[10] As with haloperoxidase enzymes, this halide oxidation requires a catalyst. Most haloperoxidase mimics reported until now are only effective at extremely low pH values. However, we developed a heterogeneous haloperoxidase-like catalyst based on WO_4^{2-}-exchanged layered double hydroxides (WO_4^{2-}-LDH), which strongly accelerates the halide oxidation with hydrogen

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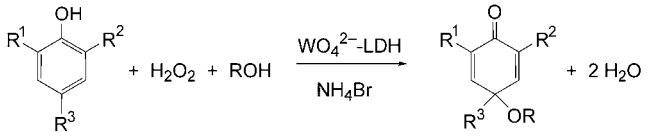
peroxide even at mild pH values.[11] Based on this method, we anticipated the overall transformation of substituted phenols to quinol ethers with hydrogen peroxide in the presence of a bromide salt, the WO_4^{2-}-LDH catalyst, and the appropriate alcohol. If successful, this one-pot synthesis could provide a new route towards the highly valuable *p*-quinol ethers:

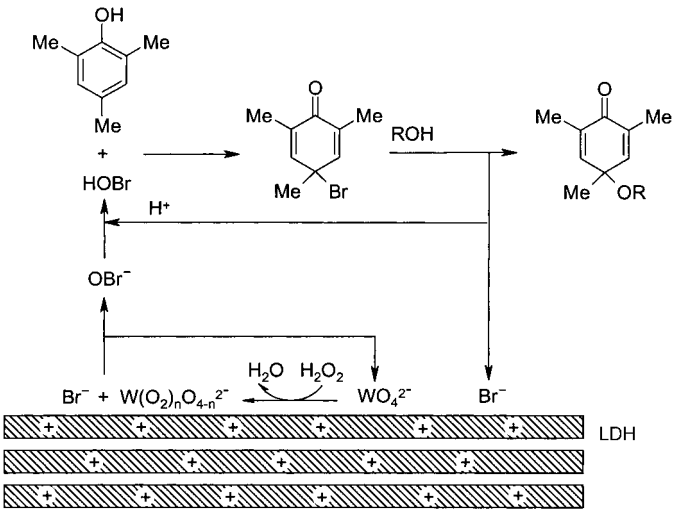


Initial investigations focused on the oxidative methoxylation of mesitol (**1**) with hydrogen peroxide in methanol in the presence of a bromide source and 1 mol% WO_4^{2-} exchanged on LDH (Table 1). Hydrogen peroxide was added slowly to the reaction mixture. We employed LDHs as supports with varying compositions $M^{II}_{1-x}M^{III}_x(OH)_2[(WO_4^{2-})_{xy/2}(A^-)_{x(1-y)}]\cdot m H_2O$ ($M^{II} = Zn^{II}$, Ni^{II}, Mg^{II}; $M^{III} = Al^{III}$, Ga^{III}; $A^- = Cl^-$, NO_3^-).[12] In our experience, the oxidative bromination proceeds fastest with LDHs with a large degree of isomorphous substitution ($x = 0.37$) and with tungstate contents of 20–25% of the total anion exchange capacity ($y = 0.25$–0.30). Ni^{II}- and NO_3^--containing LDHs have especially high productivities: quinol ether **1a** was produced in 87% yield within 30 min (Table 1, entry 1). With Mg^{II} in the hydroxide layers or with Cl^- as the counterion, the yield of **1a** is only slightly lower (Table 1, entries 2–3). In contrast, with the homogeneous catalyst Na_2WO_4, only 21% of **1a** is formed after 6 h (Table 1, entry 4). This result highlights the importance of the LDH support in facilitating the bromide oxidation (Scheme 1). Indeed, the cationic surface, decorated with peroxotungstate anions, attracts bromide anions and thus compensates for the repulsion between the negatively charged reaction partners Br^- and peroxotungstate. As a result, the bromide-oxidation rate is increased tremendously. In the absence of either WO_4^{2-}-LDH or Br^-, no product was observed after 12 h (Table 1, entries 5–6). As a solvent, a methanol/ethyl acetate mixture proved suitable, though satisfactory yields were also obtained in pure methanol or other methanol-containing mixtures (73–85%, data not shown). However, when acetone is used or when the water content is too high, the yields of **1a** drastically drop to lower values (32 and 72%; Table 1, entries 7–8).

Table 1: Br^--assisted oxidation of mesitol (**1**) to 4-methyoxy-4-methylcyclohexa-2,5-dienone (**1a**).[a]

Entry	Catalyst, conditions	Yield[b] (Conversion) [%]	*t* [h]	*p*/*o*[c]
1	NiAl[NO_3^-, WO_4^{2-}]	91 (100)	0.5	25:1
2	NiAl[Cl^-, WO_4^{2-}]	84 (97)	0.5	24:1
3	MgAl[NO_3^-, WO_4^{2-}]	86 (92)	0.5	21:1
4	$Na_2WO_4\cdot 2H_2O$	21 (28)	6	23:1
5	no WO_4^{2-} catalyst	0 (<1)	12	–
6	no NH_4Br	0 (<1)	12	–
7	5 vol% water	72 (95)	1	24:1
8	acetone instead of ethyl acetate	32 (34)	1	24:1

[a] Conditions, unless mentioned otherwise: WO_4^{2-}-LDH ($Ni_{0.64}Al_{0.36}(OH)_2[(WO_4^{2-})_{0.045}(NO_3^-)_{0.27}]\cdot 0.6\,H_2O$) (17 mg), MeOH/EtOAc/$H_2O$ (10 mL; 30:68.5:1.5 vol%), NH_4Br (0.15 M), **1** (0.06 M), aqueous H_2O_2 (35 wt%; added at 2.8 mmol h^{-1}), 60°C. Product yields and identities were determined by GC and GC–MS, and, after product extraction with diethyl ether, by ^1H and ^{13}C NMR spectroscopic analysis. [b] Yield of *p*- and *o*-quinol ethers. [c] Molar ratio of *p*- and *o*-quinol ethers.

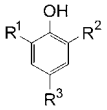
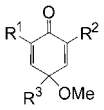
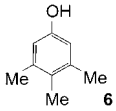
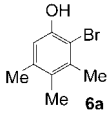
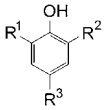
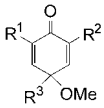
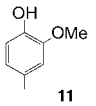
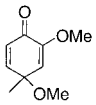
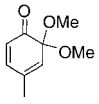


Scheme 1. Bromide-assisted oxidation of mesitol with H_2O_2 to the corresponding *p*-quinol (ether) over WO_4^{2-}-exchanged layered double hydroxide.

The synthetic utility of this heterogeneous tungstate-catalyzed oxidation was evaluated with a wide range of variously substituted phenols (Table 2). Alkylated phenols undergo the Br^--assisted oxidative methoxylation in moderate to excellent yields, especially when the *ortho* and *para* positions are substituted (Table 2, **1–4**; 81–91%). However, when the *ortho* or *para* positions are unsubstituted, stable brominated phenols are the main products (**5–6**). This limitation does not hold for the *p*-alkoxylated phenols (**7–10**), and high yields of the *p*-benzoquinone monoketals are obtained, irrespective of the substitution pattern. A considerable benefit of the catalytic procedure is that the products are not transketalized. Thus, the WO_4^{2-}-LDH can be used for the synthesis of mixed ketal 4-ethoxy-4-methoxycyclohexa-2,5-dienone (**8a**). When Tl salts are used as the oxidant, **8a** is not accessible because of Tl^{III}-induced transketalization.[6,13] Reactions with *o*-alkoxylated phenols, **11**, are less selective and give rise to a mixture of products, including the *o*-quinone monoketal **11b**. The latter is unstable and dimerizes through a Diels–Alder mechanism.[9f]

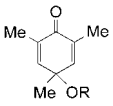
Finally, the use of various alcohol nucleophiles was evaluated in Table 3. If the bromide salt is sufficiently soluble in the solvent mixture and the alcohol is not too bulky (as for example, *tert*-butyl alcohol), many alcohol reagents lead to the quinol ether products in good yields (75–91%). The oxidative alkoxylation is highly *para*-selective, with *p*/*o* ratios >20:1, in contrast to most existing procedures.[9,14]

Table 2: Oxidation of substituted phenols to quinol ethers.[a]

Substrate	Product	R^1	R^2	R^3	H_2O_2 [equiv]	Yield (Conv.) [%]
						
1	**1a**	Me	Me	Me	2.3	91 (100)
2	**2a**	*i*Pr	*i*Pr	Me	3.0	88 (100)
3	**3a**	*t*Bu	*t*Bu	Me	3.2	87 (96)
4	**4a**	*t*Bu	*t*Bu	*t*Bu	6.0	81 (94)
5	**5a**	H	Me	Me	4.0	21 (100)[b]
 **6**	 **6a**				2.3	71 (100)[c]
						
7	**7a**	H	H	OMe	2.3	94 (100)
8	**8a**	H	H	OEt	2.3	92 (100)
9	**9a**	H	Cl	OMe	2.3	92 (99)
10	**10a**	Me	Me	OMe	2.3	89 (100)
 **11**	 **11a**  **11b**				4.0	56 (96)[d]

[a] Conditions as in Table 1; 0.5–1 h. [b] 2-Brominated product (m/z = 200–202): 59% yield. [c] m/z = 214–216. [d] $p/o \approx 8{:}1$; to be taken with caution because of considerable dimerization of the *ortho* product.

Table 3: WO_4^{2-}-LDH-catalyzed oxidative alkoxylation of mesitol (**1**) with various alcohols.[a]

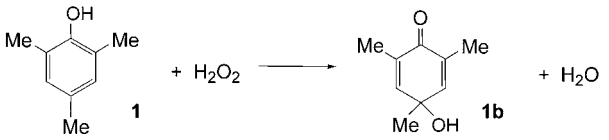
Entry	Alcohol (ROH)	Products	H_2O_2 [equiv]	*p*/*o*	Yield (Conv.) [%]
1	MeOH		2.3	25:1	91 (100)
2	EtOH		2.3	26:1	89 (100)
3	*n*PrOH		2.3	24:1	86 (100)
4	*n*BuOH		3.2	25:1	84 (100)
5	*n*HexOH		3.2	n.d.	21 (68)
6	AllylOH		3.2	n.d.	81 (100)
7	AmylOH		3.2	n.d.	82 (98)
8	*i*PrOH		3.2	27:1	75 (99)
9	*i*BuOH		3.2	30:1	78 (95)
10	*t*BuOH		3.2	n.d.	3 (85)

[a] Conditions as in Table 1, except that methanol is replaced by other alcohols.

As is known from previous mechanistic work,[11b] hydrogen peroxide is activated by the tungstate to give peroxotungstates, which in turn oxidize Br^- into hypobromite. As shown in Scheme 1 and in agreement with literature reports,[15,16] subsequent electrophilic bromination of mesitol (**1**) by HOBr generates the 4-bromocyclohexa-2,5-dienone intermediate, which in some reactions was detected as a transient product in small amounts by GC–MS. Under neutral conditions, this compound rapidly reacts with the alcohol to form the quinol ether,[15,17] and the eliminated HBr can participate in a new catalytic cycle. Under acidic conditions, the same 4-Br compound rearranges into the stable 3-bromomesitol.[9e] Clearly, for the success of the overall transformation, it is essential to avoid acidity, which underlines again the need for a haloperoxidase mimic capable of halide oxidation under neutral conditions.

Regarding the efficiency of hydrogen peroxide, it is important to avoid the unproductive reduction of OBr^- by excess hydrogen peroxide, which yields singlet oxygen. Whether this occurs depends on the hydrogen peroxide concentration, the pH value of the reaction conditions, and the reactivity of the phenol. In the case of **1** in 0.15 M NH_4Br, dropwise addition of hydrogen peroxide at a maximum rate of 500 mol (mol W)$^{-1}$ h^{-1} resulted in reasonable yields based on the concentration of hydrogen peroxide.

Careful analysis of the products from **1** showed that the *p*-quinol 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (**1c**) was always formed in small amounts. Since **1b** is a drug and vitamin E precursor,[2] we briefly investigated its formation. In reaction conditions similar to those given in Table 3, and in a water/THF solvent mixture (9:1), **1c** is produced in 91% yield, with only 2,6-dimethylquinone as a minor byproduct.



In conclusion, we have designed a one-pot metal-catalyzed procedure for the synthesis of 4-alkoxy- or 4-hydroxy-substituted cyclic 2,5-dienones in good yields from a broad range of phenol substrates. Although this particular class of phenol oxidations has often been performed with stoichiometric oxidants, we propose a metal-catalyzed route based on the clean oxidant hydrogen peroxide. A unique feature of the WO_4^{2-}-LDH/NH_4Br/H_2O_2 catalytic system is that high bromide-oxidation rates are decoupled from strong acidity which allows a high chemoselectivity for the desired quinol products to be reached.

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