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Facile Oxidation of Fused 1,4-Dimethoxybenzenes to 1,4-Quinones Using NBS: Fine-Tuned Control over Bromination and Oxidation Reactions

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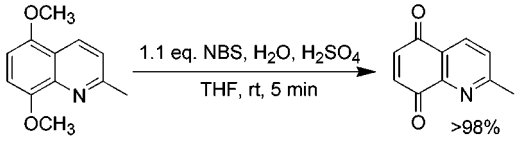
ABSTRACT



Fused 1,4-dimethoxybenzenes could be oxidized to benzoquinones by either direct oxidation or demethylation–oxidation. The oxidative demethylation of 5,8-dimethoxy-2-methylquinoline using 1.1 equiv of NBS in aqueous THF and a catalytic amount of H_2SO_4 at 20 °C for 5 min gave 2-methylquinoline-5,8-dione in 98% yield without bromination. Moreover, we can control either bromination or oxidative demethylation, or both reactions.

Compounds bearing the 1,4-quinone moiety are widespread in nature and have received much interest because of their physiological properties. 1,4-Dimethoxybenzenes and 1,4-hydroquinones are important precursors for 1,4-quinones. Thus, much attention has been focused on the facile oxidation of fused 1,4-dimethoxybenzenes to 1,4-quinones.

As shown in Figure 1, 1,4-dimethoxybenzenes could be oxidized to benzoquinones by either direct oxidation (path a) or demethylation−oxidation (path b).[1] Although oxidation of 1,4-hydroquinones is much easier than that of 1,4-dimethoxybenzenes, the direct oxidation route (path a) is much more attractive over path b as a result of the difficulty in the demethylation reaction and the isolation of 1,4-hydroquinones. Several examples of path a reported that oxidative demethylation[2] affords quinones from dimethoxybenzenes using ceric ammonium nitrate (CAN),[3] argentic oxide,[4] and concentrated nitric acid.[5] Oxidative demethylation using nitric acid gave low yield as a result of vigorous conditions and also side reactions such as nitration of the aromatic ring and oxidative demethylation. Argentic oxide works well, but the reagent has the disadvantage that it is not economically viable. Moreover, reactions using nitric acid or argentic oxide require a strong acidic condition, which may cause complication when a compound contains acid-sensitive functional groups. CAN has increasingly been used during the past decade in the synthesis of quinones,

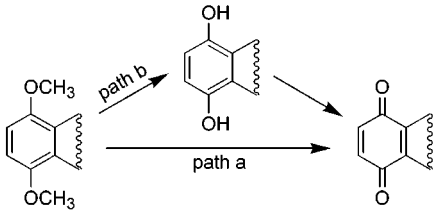


Figure 1. Two different reation paths from dimethoxybenzene to quinone.

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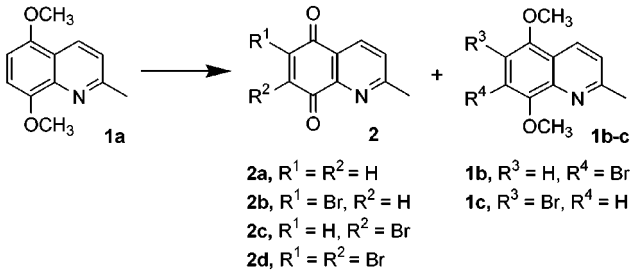
particularly as a means of effective oxidative demethylation of dimethoxybenzenes. However, because of its extremely limited solubility in common organic solvents, oxidation is often carried out in the mixed solvents. In addition, the reactions using CAN sometimes need a cooxidant for oxidation. Kubo et al.[3d−f] used CAN in the presence of 2,6-dicarboxylic pyridine acid *N*-oxide (DCPNO)[6] for oxidative demethylations of 5,8-dimethoxyquinoline derivatives to quinoline-5,8-dione derivatives in good yield. Using CAN in these reactions requires the inconvenience of DCPNO, which must be prepared from commercially available pyridine-2,6-dicarboxylic acid by *N*-oxidation.[6] *N*-Bromosuccinimide (NBS)[7] has been used for the preparation of brominated quinone compounds from 1,4-dihydroxyquinones[8a,b] and 1-hydroxy- or 1-hydroxy-4-alkoxybenzene compounds.[8c−f] There is no such report for the synthesis of 1,4-quinones from 1,4-dimethoxybenzenes using NBS. We have found that NBS in the presence of water and a catalytic amount of H_2SO_4 is a very efficient oxidative demethylation agent for fused 1,4-dimethoxybenzene systems. Moreover, we can also control either bromination or oxidative demethylation, or both reactions.

Table 1 illustrates the differences between the reactions of 5,8-dimethoxy-2-methylquinoline (**1a**) using NBS depending on the reaction conditions. The optimized condition for oxidative demethylation (entry 1)[9] was that **1a** was added to a well-stirred mixture of 1.1 equiv of NBS in aqueous THF and a catalytic amount of H_2SO_4 (0.05 mL) at 20 °C for only 5 min to prevent bromination at the C6 or C7 position of **1a**. This reaction[7] gave 2-methylquinoline-5,8-dione (**2a**) in 98% yield, and then NBS under this reaction condition acted as an oxidative demethylation agent. In entry 2, since 1.1 equiv of NBS in the absence of water as well as a catalytic amount of H_2SO_4 acted as a bromination agent, we obtained 6-bromo-5,8-dimethoxy-2-methylquinoline (**1b**, 54%) and 7-bromo-5,8-dimethoxy-2-methylquinoline (**1c**, 30%). In entry 3, the reaction using NBS (1.1 equiv) in the presence of water without a catalytic amount of H_2SO_4 gave **1b** (53%), **1c** (28%), and **2a** in a trace amount. This result means that the reaction rate of bromination is faster than that of oxidative demethylation under this reaction condition. Therefore, we could find that a small amount of H_2SO_4 plays a role of catalyst in oxidative demethylation. When an excess of NBS (3.5 equiv) was added to the solution of aqueous THF with stirring at 20 °C over a period of approximately 2 days (entry 4), we obtained 6,7-dibromo-2-methylquinoline-5,8-dione (**2d**, 65%) as a major product, with 6-bromo-2-methylquinoline-5,8-dione (**2b**, 7%), **1b** (8%), and **1c** (7%). A trace amount of 7-bromo-2-methylquinoline (**2c**) was detected. In this procedure, we thought that **1a** might be brominated by a bromonium cation at C6 (**1b**) or C7 (**1c**) and that a second bromination of **1b** and **1c** proceeded to **2d** by Michael-type addition at C7 or C6 after the oxidative demethylation of **1b** or **1c**. Despite using an excess of NBS (3.3 equiv) with water and a catalytic amount of H_2SO_4 (entry 5), we obtained 95% yield of **2a**, similar to the result of entry 1 without the formation of brominated products.

The plausible mechanism of this reaction would be as shown in Figure 2. This mechanism of reaction is similar to the mechanism proposed by Cohen et al.[10]

Table 1. Differences in Reactions Using NBS Depending on Reaction Conditions[a]



entry	mol % of NBS	H_2O (mL)	H_2SO_4 (mL)	reaction time	yield of product (%)[b] 2a	2b	2c	2d	1b	1c
1[c]	110	5	0.05	5 min	98					
2[d]	110	0	0	10 min					54	30
3	110	5	0	5 min	tr				53	28
4	350	5	0	2 day		7	tr	65	8	7
5	350	5	0.05	5 min	95					

[a] All reactions were performed with a 1.0 mmol of 5,8-dimethoxy-2-methylquinoline (**1a**) in THF (25 mL) at 20 °C. [b] Isolated yield. [c] The optimized reaction condition of oxidative demethylation. [d] The optimized reaction condition of bromination.

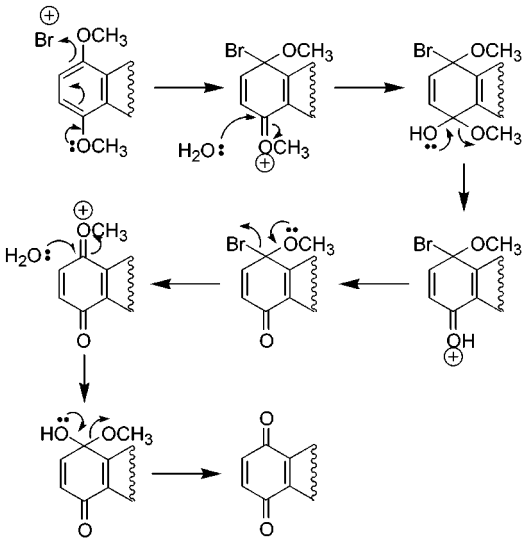
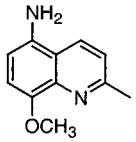
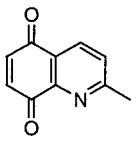
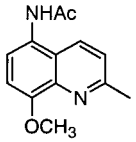
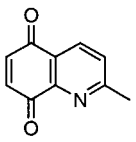
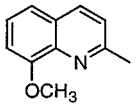
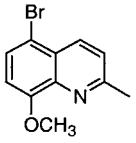
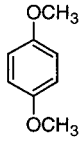
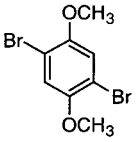
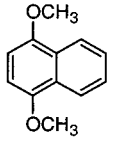
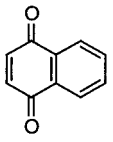
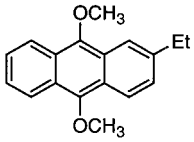
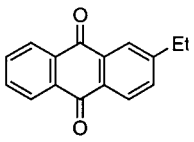


Figure 2. Proposed mechanism of oxidative demethylation using NBS.

We performed the oxidative demethylation reactions of several compounds involving mono- or dimethoxy groups to corresponding quinones under optimized condition as for entry 1 in Table 1 (Table 2). The oxidative demethylation of 5-amino-8-methoxy-2-methylquinoline and 5-(*N*-acetylamino)-8-methoxy-2-methylquinoline proceeded under the optimized conditions, providing **2a** (80%, entry 1, and 90%, entry 2, respectively). In the case where the C5 position of quinoline does not have any substituent (entry 3), the

Table 2. the Oxidative Demethylations of 1,4-Methoxybenzenes under Optimized Conditions[a]

Entry	compound	yield[b] (%)	product
1		80	
2		90	
3[c]		80	
4[c]		> 10[d]	
5		98	
6		99	

[a] All reactions were performed with a 1.0 mmol reaction scale using 1.1 equiv of NBS in the presence of THF (25 mL), water (5 mL), and H_2SO_4 (0.05 mL) for 5 min at 20 °C. [b] Isolated yield. [c] Reaction time was 15 min. [d] Reactant was recovered yield of >80%.

oxidative demethylation did not proceed. In addition, for 1,4-dimethoxybenzene, which is not a fused system, the oxidative demethylation did not occur at all (entry 4). The oxidative demethylation of 1,4-dimethoxynaphthalene and 2-ethyl-9,10-dimethoxyanthracene, which has no pyridine moieties, could proceed and gave 98% and 99% yield of 1,4-naphthoquinone and 2-ethyl-9,10-anthraquinone. Although the electron density on the benzene ring of 1,4-dimethoxybenzene is higher than that of the benzene ring of fused systems such as 1,4-dimethoxynaphthalene and 5,8-dimethoxyquinoline, the oxidative demethylation reaction of 1,4-dimethoxybenzene did not proceed. This suggests that the reaction sites are the benzylic positions on the fused ring and that the reaction intermediate would be somewhat stabilized by the fused ring.

In summary, we have demonstrated a mild oxidative demethylation of fused 1,4-dimethoxybenzenes to 1,4-quinones using NBS in the presence of aqueous THF and a catalytic amount of sulfuric acid. We can also control two reactions, bromination or oxidative demethylation, because different pathways are followed depending on the presence or absence of a catalytic mount of sulfuric acid. However, the oxidative demethylation of an unfused ring system such as 1,4-dimethoxybenzene does not proceed under the optimized reaction conditions. Further studies on synthetic applications to various anticancer and antibiotic agents such as lavendamycin and streptonigrin derivatives,[11] as well as on the development of the diagnostic agent of quinoline-5,8-dione derivatives as a tumor marker, are in process in our laboratories.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **2**, **2c**, 1,4-naphthoquinone, and 2-ethyl-9,10-anthraquinone. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **Typical Procedure.** 5,8-Dimethoxy-2-methylquinoline (**1**, 203 mg, 1.0 mmol) was added to a well-stirred mixture of NBS (196 mg, 1.1 mmol) in a solution of THF (15 mL), water (5 mL), and sulfuric acid (0.05 mL) at 20 °C. The mixture was stirred over 5 min and basified with aqueous $NaHCO_3$ (10 mL). The mixture was extracted from aqueous phase with EtOAc (20 mL x 3). The organic layer was dried over sodium sulfate anhydrous and evaporated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/Hx) to obtain 169 mg (98%) of 2-methylquinoline-5,8-dione (**2**).

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