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Convenient Synthesis of 1,4-Naphthoquinones from Polymethoxynaphthalenes. Oxidative Demethylation with Silver-Catalyzed Ammonium Peroxodisulfate [1]

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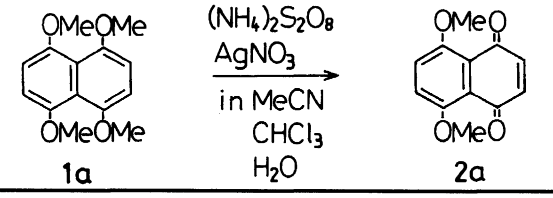
Synopsis. The oxidative demethylation of polymethoxynaphthalenes such as 1,4-di, 1,4,5-tri, 1,4,5,8-tetra, and 1,2,4,5,8-pentamethoxynaphthalenes with silver-catalyzed ammonium peroxodisulfate gave the corresponding 1,4-naphthoquinones in good yield under mild reaction conditions.

The oxidation of 1,4-dimethoxynaphthalene and *p*-dimethoxybenzene derivatives to the corresponding naphthoquinones and benzoquinones, respectively, has been accomplished using such oxidizing agents as silver(II) oxide[2] (AgO) and cerium(IV) ammonium nitrate[3] [$Ce(NH_4)_2(NO_3)_6$, CAN]. We have already reported that a two-step oxidative demethylation of 1,4,5,8-tetramethoxynaphthalene derivatives with CAN and AgO gave the corresponding naphthazarins.[4] Although the oxidations of aromatics, alcohols, and ketones with metal-catalyzed peroxodisulfate have been known,[5] to our knowledge no one has yet reported on the oxidative cleavage of methyl ether compounds by the reagent. We now wish to describe the oxidative demethylation of polymethoxynaphthalenes with silver-catalyzed ammonium peroxodisulfate.

Table 1. Demethylation of 1,4,5,8-Tetramethoxynaphthalene **1a**[a]



Entry	$(NH_4)_2S_2O_8$: $AgNO_3$ Molar ratio	Yield/%[b]	Recovered **1a**/%[b]
1	1 : 0.05	32	60
2	2 : 0.05	61	28
3	2.5 : 0.05	87	0
4	3 : 0.05	84	0
5	5 : 0	28	51
6	5 : 0.05	89	0
7	5 : 0.1	98	0
8	5 : 5	90	0
9	0 : 5	0	98
10	0.1 : 3	13	73
11[c]	1 : 1	17	70

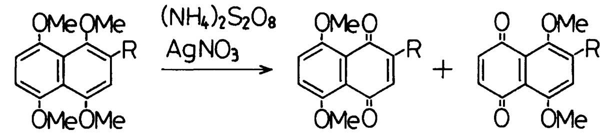
a) All reactions were carried out at room temperature for 18 h. b) Isolated yields. c) After a mixture of $(NH_4)_2S_2O_8$ and $AgNO_3$ in water was stirred at room temperature for 3 h, a solution of **1a** in CH_3CN–$CHCl_3$ was added and the mixture was stirred for 18 h.

Results and Discussion

In the course of our synthetic study of naphthoquinone derivatives, we found that silver-catalyzed ammonium peroxodisulfate oxidizes 1,4,5,8-tetramethoxynaphthalene (**1a**) to 5,8-dimethoxy-1,4-naphthoquinone (**2a**) in high yield. In attempting to examine the reaction system, several reactions of **1a** with ammonium peroxodisulfate were carried out in the presence of sil-

Table 2. Demethylation of 1,4,5,8-Tetra and 1,2,4,5,8-Pentamethoxynaphthalenes

Substrate Product (yield/%)[a]

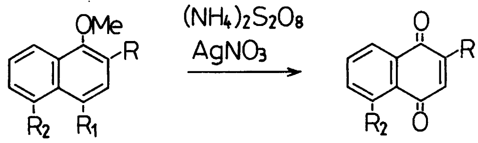


R	Type A	Type B
1a[8] : H	**2a** (98)	—
1b[9] : OMe	**2b** (69)	**3b** (20)
1c[4] : CH_2OH	**2c** (50)	**3c** (49)
1d[9] : Br	**2d** (6)	**3d** (87)
1e[8] : CHO	**2e** (0)	**3e** (89)

a) Isolated yields.

Table 3. Demethylation of 1,4-Di and 1,4,5-Trimethoxynaphthalenes

Substrate Product (yield/%)[a]



Substrate	Product
1f[10] : R=H, R_1=R_2=OMe	**2f** (65)
1g[11] : R=Me, R_1=OMe, R_2=H	**2g** (56)
1h[11] : R=R_2=H, R_1=OMe	**2h** (89)
1i[b] : R=R_2=H, R_1=OH	**2h** (76)

a) Isolated yields. b) A commercial reagent.

Table 4. The Physical Data of the Quinone Product

Product	Crystal color and form	Solvent of recrystallization	Mp/°C	Lit, Mp/°C
2a	Reddish-orange needles	Ligroin–benzene (3 : 1)	159—160	157[12]
2b	Orange needles	Ethylacetate	163—165	165,[13] 165—170[14]
	Orange plates	Benzene–hexane (3 : 1)	175—176.5	
3b	Orange needles	Benzene–hexane (3 : 1)	144—145	126,[15] 144—146[14]
2c	Orange needles	Ethanol	180.5—182	176—176.5[4]
3c	Yellow needles	Ethanol	175—176	135—136[4]
2d	Reddish-orange solids	Benzene–ligroin (10 : 1)	155—157	160[16]
3d	Yellowish-orange leaflets	Benzene–hexane (1 : 1)	143.5—144	—
3e	Yellow solids	Ligroin–benzene (5 : 1)	175—175.5	177—178[17]
2f	Yellowish-orange solids	Benzene–hexane (2 : 1)	182—183.5	180—185[18]
2g	Pale yellow solids	Hexane	102.5—105.5	105—106[19a]
2h	Yellow leaflets	Ligroin	123—124	125.2[19b]
5	Yellow plates	Sublimation	111—113[a]	117[20]

a) In a sealed tube.

ver nitrate at room temperature for 18 h; the results are listed in Table 1. These results suggest that the reaction system requires 2.5—5 molar amounts of ammonium peroxodisulfate and 0.05—0.1 molar amounts of silver nitrate to the substrate (**1a**). It has been reported that the peroxodisulfate ion, $S_2O_8{}^{2-}$ provides a sulfate radical anion, $SO_4^{-\bullet}$ [6] in the presence of a silver(I) ion. Their reports and our results seem to indicate that the sulfate radical anion oxidizes substrate **1a** to give quinone **2a**.

We next applied oxidative demethylation to several polymethoxynaphthalenes and dimethoxybenzenes. Although this reaction proceeded smoothly for such polymethoxynaphthalenes as 1,4-di, 1,4,5-tri, 1,4,5,8-tetra, and 1, 2, 4, 5, 8- pentamethoxynaphthalenes (Tables 2 and 3), no reaction occurred in cases of hydroquinone dimethyl ethers, such as 2,5-dimethoxybenzyl alcohol and 2,5-dimethoxybenzaldehyde, except for 1,4-dimethoxybenzene (**4**). The oxidative demethylation of **4** was unsuccessful at room temperature, but gave 1,4-benzoquinone (**5**) in 43% yield under reflux for 2 h. Upon demethylation of 2-substituted 1,4,5,8-tetramethoxynaphthalenes (Table 2), substrates (**1b** and **1c**) having an electron-donating group gave, principally, type-A quinones (**2b** and **2c**); the minors were type-B (**3b** and **3c**). On the other hand, substrates (**1d** and **1e**) bearing an electron-withdrawing group preferentially afforded type-B quinones (**3d** and **3e**).

Although oxidative demethylation requires a longer reaction time[7] using ammonium peroxodisulfate than that employing CAN, the former is equal or superior to the latter in the yield for demethylation of the tetramethoxynaphthalene derivatives. Furthermore, ammonium peroxodisulfate is much cheaper than CAN and may be convenient for large-scale preparations. Although oxidative demethylation using AgO requires a strong acid, a reaction employing ammonium peroxodisulfate as well as CAN occurs under mild reaction conditions.

In conclusion, we found that silver-catalyzed ammonium peroxodisulfate is an effective reagent for the oxidative demethylation of polymethoxynaphthalenes to obtain 1,4-naphthoquinones.

Experimental

The melting points were determined using a Yanagimoto micromelting- point apparatus, and were uncorrected. ^{1}H NMR spectra were taken on a JEOL JNM-60 in a $CDCl_3$ solution using Me_4Si as an internal standard. The mass and IR spectra were obtained using a JEOL DX-300 spectrometer, and a Simadzu IR 470 spectrometer, respectively. Since products **2**, **3**, and **5** are known compounds, except for **3d**, such physical data as the melting points, crystal colors and forms are given in Table 4.

General Procedure for the Oxidative Demethylation of Polymethoxynaphthalenes 1. A solution of ammonium peroxodisulfate (2 mmol) in water (1 ml) and silver nitrate (0.04 mmol) in water (1 ml) was added to a solution of **1** (0.4 mmol) in acetonitrile (10 ml), or in a mixture of acetonitrile/chloroform (5 : 1). After stirring at room temperature for 18 h, the starting material completely disappeared (monitored by TLC). The mixture was diluted with water (30 ml) and extracted with chloroform (3×50 ml). The extract was washed with brine (30 ml) and dried with anhydrous sodium sulfate. The solvent was evaporated and the crude product was chromatographed on silica gel [TLC, 20×20 cm, layer 0.7 mm, Merck 60 $PF_{254+366}$, $CHCl_3/C_2H_5OH$ (100 : 5)].

3d: IR (KBr) 1659 (C=O), 1612, 1241, and 1035 cm^{-1}; ^1HNMR $\delta=3.89$, 3.97 (each s, 3H, OCH_3), 6.80 (s, 2H, quinonoid ring H), and 7.55 (s, 1H, benzenoid ring H); MS *m/z* 298 (M^++2, 100%) and 296 (M^+, 95). Found: C, 48.98; H, 3.43%. Calcd for $C_{12}H_9O_4Br$; C, 48.51; H, 3.05%.

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