# Undergraduate Experiments with a Long-Lived Radical (Fremy's Salt)

## Synthesis of 1,4-Benzoquinones by Degradative Oxidation of *p*-Hydroxybenzyl Alcohols

**J. Morey**
Universitat de les Illes Balears, E. 07071 Palma de Mallorca, Spain

As their name implies, long-lived radicals such as nitroxides[1] are kinetically stable species, that is, they react slowly with other radicals or spin-paired molecules. Thus, in spite of being high-energy, odd-electron species, they usually behave as very selective reagents for their radical centers are sterically protected from attack.

Fremy's salt (potassium nitrosodisulfonate, FS)[2] is a typical long-lived radical that can be easily prepared. FS needs to be manipulated with care since acid and nitrite impurities promote its decomposition. Consequently, FS is usually stored in a desiccator containing ammonium carbonate and calcium oxide, where it remains for several months without decomposition.

When employed in aqueous buffered solutions, FS is a smooth oxidant (redox potential: 0.24 V versus SCE, measured at pH = 10) capable of oxidizing phenols and anilines of appropriate redox potentials to the corresponding quinones. Contrary to expectations it has recently been proved that *p*-hydroxybenzylalcohols undergo FS-promoted degradative oxidation thus yielding the corresponding 1,4-benzoquinones instead of 1,2-benzoquinones[3].

Available information regarding this interesting process suggests a mechanistic pathway (see Fig. 1) involving three steps: (1) one-electron oxidation of the phenol by FS, (2) cross-coupling of the so-generated phenoxide radical with FS, at the site of highest odd-electron density (C-4), and (3) fragmentation of the cyclohexadienone intermediate as shown (see Fig. 1).

The present communication describes a series of experiments planned for a practical course in undergraduate organic chemistry, generally devoid of experiments involving radical chemistry.

The key step in each of these synthetic sequences (see Fig. 2) is the FS degradative oxidation of a bromo-4-hydroxybenzylalcohol. It should also be emphasized that the required isomeric bromoalcohols are available from a common and cheap starting material: vanillin (3-methoxy-4-hydroxybenzaldehyde). Thus, *o*-bromination is achieved by direct treatment of this phenol with bromine, whereas clean *p*-bromination is accomplished by appropriate modification (acetylation) of the strongly directing phenolic group.

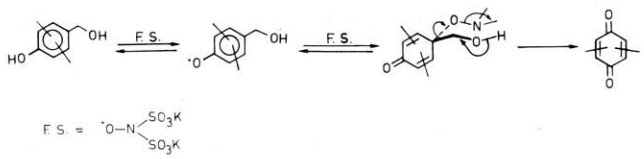


Figure 1. Fremy's salt oxidative degradation of phenolic substrates.

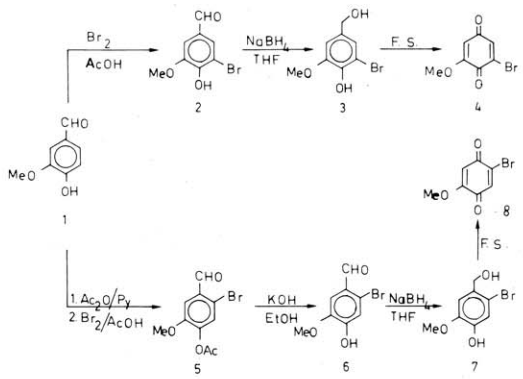


Figure 2. Synthesis of 2-bromo-6-methoxy and 2-bromo-5-methoxy-1,4-benzoquinone.

## Experimental

### *Preparation of Potassium nitrosodisulfonate (Fremy's salt, ·O–N–(SO$_3$K)$_2$*

Fremy's salt has been prepared, recrystallized, and stored as reported in the literature[2]. Violent decomposition—apparently due to acid impurities—of FS has been noticed by several workers. We have found that this can be avoided by controlling the pH of the solution during the $KMnO_4$ oxidation, so that it is maintained around 9 by adding ammonium hydroxide to the solution when necessary. If required, FS can be smoothly destroyed simply by dissolving it in 0.1 N HCl. The violet color vanishes completely in about 30 min.

### *3-Bromo-4-hydroxy-5-methoxybenzaldehyde (**2**)*

The synthesis of the title compound should be carried out in a well-ventilated hood.

In a 50-mL flask, 2.5 g of commercial vanillin were dissolved, with magnetic stirring, in 12.5 mL of glacial acetic acid. Then, 3 g of liquid bromine was added dropwise from a 10-mL separatory funnel. After the addition was completed, the orange–brown solution was stirred for an additional hour. Workup was carried out by pouring the resulting solution into a 250-mL beaker over cracked ice (40 g). The precipitate formed was then filtered using a Buchner funnel. The resulting cake was washed repeatedly with cold water (5 × 125 mL) and air dried. Recrystallization in hot water yielded 3.6 g (95%) of the title compound, mp 160–162 °C.

### *2-Bromo-4-hydroxymethyl-6-methoxyphenol (**3**)*

To a tetrahydrofuran (23 mL) solution of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (**2**) (3 g) in a 100-mL flask, 0.6 g of $NaBH_4$ were added in one portion. After the initial reaction subsided, the mixture was gently refluxed for 2 h. Workup was carried out by pouring the solution into cold 5% HCl (45 mL). The heterogeneous mixture was thoroughly extracted with ether (3 × 20 mL). The combined extracts were then washed with brine (3 × 15 mL) and

[1] Davies, D. I.; Parrot, M. J. *Free Radicals in Organic Synthesis*; Springer-Verlag: New York, 1978.

[2] Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971,** *71,* 229–246.

[3] Saá, J. M.; Morey, J.; Costa, A. *Tetrahedron Lett.* **1986,** *27,* 5125–5128.

dried over anhydrous $Na_2SO_4$. Evaporation of the solvent yielded an oily residue that solidified. Final recrystallization in hot water yielded 2.25 g (74% yield) of the title alcohol, mp 132–134 °C.

### *2-Bromo-6-methoxy-1,4-benzoquinone (**4**)*[4]

To 250 mL of buffered aqueous solution (78.8 mL of 0.2 M $Na_2HPO_4$ and 171.2 mL of 0.2 M $NaH_2PO_4$) of FS (8 g), a methanolic solution (10 mL) of 1.54 g of 2-bromo-4-hydroxymethyl-6-methoxyphenol (**3**) was added in one portion. The original violet color of FS rapidly changed to brown, and a yellow precipitate slowly formed. Stirring was continued for 1 h and then the quinone was filtered, washed with cold water, and air dried. Recrystallization in methanol gave yellow–orange needles (0.94 g, 65%), mp 166–167 °C.

### *3-Methoxy-4-acetoxy-benzaldehyde*

A mixture of 5.0 g of commercial vanillin (**1**), 5 mL of acetic anhydride, and 5 mL of pyridine was left overnight at room temperature in a well-ventilated hood. Evaporation under reduced pressure left an oily residue that was dissolved in 15 mL of dichloromethane. The resulting solution was washed with a 5% $CuSO_4$ aqueous solution (4 × 20 mL), brine (2 × 20 mL), and finally dried over anhydrous $Na_2SO_4$. Removal of the solvent left an oily residue that solidified. The title compound crystallized in ether (5.3 g, 83% yield), mp 76–77 °C.

### *2-Bromo-4-acetoxy-5-methoxybenzaldehyde (**5**)*

3.7 g (53% yield) of the title compound, mp 101–103 °C (ethanol), were obtained from 5 g of 3-methoxy-4-acetoxy-benzaldehyde by using the procedure employed for the preparation of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (**2**).

### *2-Bromo-4-hydroxy-5-methoxybenzaldehyde (**6**)*

A solution of 3.0 g of 2-bromo-4-acetoxy-5-methoxybenzaldehyde in 10% (by weight) ethanolic KOH was refluxed for 1.5 h. Careful acidification with 10% HCl yielded a precipitate, which was filtered and washed with cold water. Crystallization in ethanol yielded 2.4 g (94% yield) of the title compound (**6**), mp 179–180 °C.

### *2-Methoxy-4-hydroxymethyl-5-bromophenol (**7**)*

$NaBH_4$ reduction of 2-bromo-4-hydroxy-5-methoxybenzaldehyde (2.4 g) under identical conditions as those described for the preparation of 2-bromo-4-hydroxymethyl-6-methoxyphenol (**3**), yielded 1.7 g (71%) of the title compound, mp 153–154 °C (water).

### *2-Bromo-5-methoxy-1,4-benzoquinone (**8**)*

Fremy's salt oxidation of 2-methoxy-4-hydroxymethyl-5-bromophenol (**7**) was carried out by using the same procedure as above. The title compound was obtained (0.84 g, 58% yield) as orange–yellow needles, mp 193–194 °C (methanol).

## Discussion

The synthetic strategy employed for the preparation of isomeric bromo quinones from a common starting material is a general one, that is, the modification of orientation (regioselectivity) in the electrophilic aromatic substitution. The isomeric bromophenols (after basic hydrolysis of the acetate group) are obtained by moving from a strong activating and ortho/para directing group (–OH) to a moderately activating group ($-OCOCH_3$).

To benefit from the above regioselective control, the isomeric *p*-hydroxybenzaldehydes are then reduced (THF is the best choice of solvent for the $NaBH_4$ reduction) to the corresponding alcohols, which finally undergo the FS-promoted degradative oxidation, under very mild conditions.

Quinones are highly sensitive materials. Therefore they must be crystallized promptly and stored appropriately.

In summary *p*-hydroxybenzylalcohols should be considered as useful *p*-benzoquinones synthons.


## Acknowledgment

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[4] Oxidative degradations by FS can be done on a microscale basis.