

Oxidation of Organic Sulfides by Br₂ and H₂O₂. Electrophilic and Free-Radical Processes

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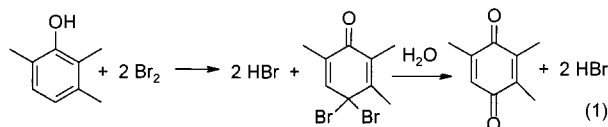
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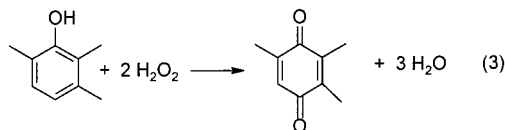
Bromine can be a selective oxidant for organic compounds; it can operate by an electrophilic or a free-radical mechanism. Its use, however, is not widespread because it is an expensive, environmentally unfriendly reagent; in addition, the formation of HBr as reduction product can affect the selectivity or even the occurrence of the oxidation itself.

We have recently introduced two developments that make Br₂ more attractive as an oxidant: (i) the use of an aqueous–organic two-phase system, in which the oxidation by Br₂ takes place in the organic phase while HBr is extracted by the aqueous phase, thus minimizing its possible negative effects; and (ii) the use of aqueous H₂O₂ to rapidly reoxidize HBr to Br₂, to keep the stationary concentration of HBr very low and to render the oxidation catalytic in Br₂ (the actual oxidant is, in this case, H₂O₂, much more convenient than Br₂ from every point of view).

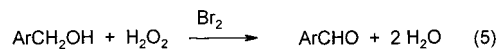
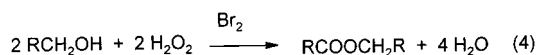
In the past^{1,2} we used Br₂ as electrophilic catalyst in the oxidation of 2,3,6-trimethylphenol by H₂O₂ to the corresponding trimethylbenzoquinone, an intermediate for the synthesis of vitamin E (eqs 1 and 2).



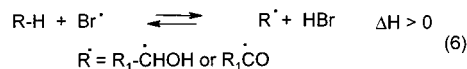
The overall stoichiometry is, therefore, shown by eq 3:



Another example, in which Br₂ acts as free-radical catalyst, involves the selective oxidation of primary alcohols to esters or aldehydes^{3,4} (eqs 4 and 5).



The selectivity is determined by the hydrogen abstraction from C–H bonds of alcohols or aldehydes, which is either endothermic or, in the most favorable cases, thermoneutral (eq 6).



In these cases, a low stationary concentration of HBr is very useful in order to shift the equilibrium of eq 6 to the right. The different behavior of aliphatic and benzyl alcohols is the consequence of the different electronic configurations of alkyl and acyl radicals, which are reflected on the energies of the involved C–H bonds and on the polar effects. With nonbenzylic alcohols, the strength of RC(O)–H bonds is much lower than that of R–CH(OH)–H bonds, so that aldehydes, being much more reactive than the corresponding alcohols, are never formed, even at low conversions. With benzylic alcohols, the strength of ArC(O)–H bonds is slightly higher compared to ArCH(OH)–H, as a result of the conjugation of the α-hydroxybenzyl radical (π-type) with the aromatic ring and the nonconjugation of the acyl radical (σ-type). Aromatic aldehydes are therefore less reactive than the corresponding alcohols, also because the polar effects in hydrogen abstraction by Br· are more marked with the alcohols.^{3,4}

We have now investigated the behavior of organic sulfides toward the Br₂-catalyzed oxidation. The results, summarized in the Table 1, show that both electrophilic and free-radical processes are involved and that the behavior is strongly depending on the structure of the sulfides.

Diaryl sulfides do not react with H₂O₂ and a catalytic amount of Br₂; the latter is consumed by electrophilic aromatic substitution and no further reaction occurs. By using stoichiometric amounts of Br₂, 4,4'-dibromodiphenyl sulfide was obtained in almost quantitative yield from diphenyl sulfide.

Dibenzyl sulfide reacts with H₂O₂ and a catalytic amount of Br₂, leading mainly to dibenzyl sulfoxide and minor amounts of benzyl bromide, benzyldisulfonic acid, benzyl alcohol, and benzaldehyde. Benzyl bromide and benzyldisulfonic acid were obtained in almost quantitative yield by using stoichiometric amounts of Br₂ in the absence of H₂O₂. Under the same conditions also dibenzyl sulfoxide and stoichiometric amounts of Br₂ led to benzyl bromide and benzyldisulfonic acid.

Our interpretation of these results involves both electrophilic and free-radical reactions. Initially the electrophilic attack of Br₂ on sulfur in the organic phase leads to the sulfoxide (eq 7):

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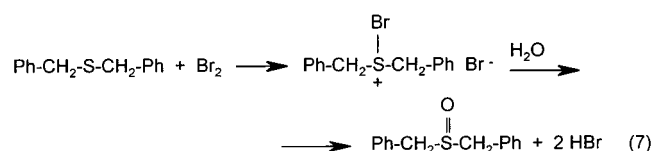
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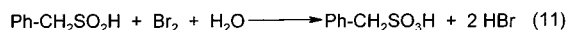
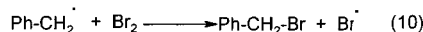
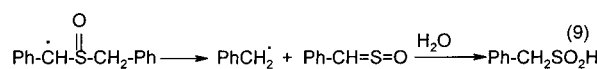
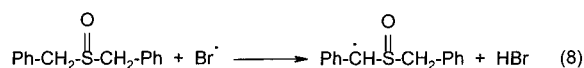
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Table 1. Oxidation of Organic Sulfides by H₂O₂ and Br₂ in a Two-Phase System (CH₂Cl₂/H₂O)

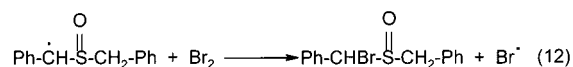
sulfide	H ₂ O ₂ (mmol)	Br ₂ (mmol)	CH ₂ Cl ₂ /H ₂ O	time (h)	conv (%)	products ^a (%)
diphenyl	1.8	0.2	5	24	8	4-Br-C ₆ H ₄ -S-Ph (98)
diphenyl		4	1	6	100	4-Br-C ₆ H ₄ -S-Ph (13); (4-Br-C ₆ H ₄) ₂ S (87)
dibenzyl	1.6	0.4	5	24	80	(PhCH ₂) ₂ SO (63); PhCH ₂ Br (20); PhCH ₂ SO ₃ H (17)
dibenzyl		4	1	2	100	PhCH ₂ Br (96); PhCH ₂ SO ₃ H (92)
PhCH ₂ SPh		2	1	24	64	PhCH ₂ SOPh (41); 4-Br-C ₆ H ₄ -SCH ₂ Ph (15)
Et-S-Ph	1.6	0.4	5	24	100	Ph-SO-Et (82)
Et-S-Ph		2	1	16	91	Ph-SO-Et (61); 4-Br-C ₆ H ₄ -S-Et (39)
Cl-(CH ₂) ₂ -SPh	1.6	0.4	5	24	100	Ph-SO-(CH ₂) ₂ -Cl (70)
Cl-(CH ₂) ₂ -SPh		2	1	21	84	Ph-SO-(CH ₂) ₂ -Cl (66); 4-Br-C ₆ H ₄ -S-(CH ₂) ₂ Cl (34)
di- <i>n</i> -butyl		2.2	1	24	83	(ⁱ Bu) ₂ SO (96)
di- <i>n</i> -butyl	1.8	0.3	4	24	87	(ⁱ Bu) ₂ SO (87)
di-(3-Me-butyl)	1.6	0.4	5	24	100	(3-Me-butyl) ₂ SO (82)
di-isopropyl	1.6	0.4	5	24	75	(ⁱ Pr) ₂ SO (93); Me ₂ CBr-S-CHMe ₂ (7)
di-isopropyl		2	1	24	92	(ⁱ Pr) ₂ SO (86); ⁱ PrBr (9); Me ₂ CBr-SO-CHMe ₂ (5)
di- <i>tert</i> -butyl	1.6	0.4	5	24	72	(<i>t</i> Bu) ₂ SO (70)
di- <i>tert</i> -butyl		2	1	24	81	(<i>t</i> Bu) ₂ SO (83)
methylbenzyl	1.6	0.4	5	24	84	Me-SO-CH ₂ Ph (82)
methylbenzyl		1.6	1	24	81	Me-SO-CH ₂ Ph (98)

^a Based on the converted substrate.

HBr is oxidized to Br₂ by H₂O₂ in the aqueous phase (eq 2), thus generating a catalytic process. The sulfoxide undergoes a free-radical chain process leading to benzyl bromide and benzenesulfonic acid (eqs 8–11):



The β-scission in eq 9 appears to be a very fast process, as it successfully competes with the fast bromine atom transfer (eq 12):

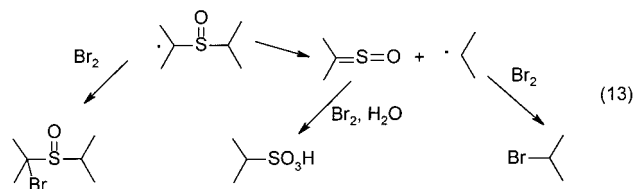


Phenylalkyl sulfides show both behaviors; benzylphenylsulfoxide is the main reaction product from benzylphenyl sulfide, but 4-bromophenylbenzyl sulfide is also significantly formed. The electrophilic aromatic substitution competes with the electrophilic attack on sulfur. Similar results we obtained from phenylethyl and phenyl-2-chloroethyl sulfides.

Dialkyl sulfides give the corresponding sulfoxides with good selectivity by bromine-catalyzed oxidation with H₂O₂ and also with stoichiometric Br₂ in the two-phase system; the oxidation appears to have a general character with primary, secondary, and tertiary alkyl groups. The process can be made substantially catalytic in Br₂; also, when this latter is initially utilized in a stoichiometric amount, the formed HBr is extracted by the aqueous

phase and oxidized to Br₂ by H₂O₂. Thus the aqueous phase can be continuously recycled without limitations, and H₂O₂ is the only oxidant consumed.

With secondary alkyl groups, such as isopropyl, the free-radical processes leading to isopropyl bromide and α-bromoisopropyl sulfoxide compete to a much lesser extent with the electrophilic oxidation compared to dibenzyl sulfide (eqs 8 and 9). Moreover secondary alkyl radicals undergo both β-scission and bromine atom transfer (eq 13), whereas benzyl radicals only undergo β-scission. This is clearly due to the higher stability of benzyl radical.



Alkyl sulfoxides have attracted much attention as intermediates in synthetic transformations;⁵ therefore the oxidation of sulfides to sulfoxides has been studied extensively using a large variety of oxidation protocols and is of continuous interest in organic chemistry.^{5–11}

The oxidations described in this note represent, in our opinion, useful synthetic procedures, in addition to providing elements for the mechanistic interpretation of the behavior of organic sulfides with Br₂ and H₂O₂.

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Experimental Section

All reagents were purchased from Aldrich and used without further purification. The reactions were carried out at room temperature by using 15 mL of solvents for 2 mmol of substrate (ratios of solvents and reagents and reaction times are reported in Table 1). The reaction mixtures were analyzed by GC using a capillary gas chromatograph equipped with a SBP-5 fused silica column (25 m \times 0.25 mm i.d., 1.0 μ m film thickness) at a hydrogen flow rate of 8 cm³ min⁻¹, PTV injector, and flame ionization detector. The products were characterized by GLC-MS, using a gas chromatograph equipped with a SBP-1 fused silica column (30 m \times 0.2 mm i.d., 0.2 μ m film thickness) and

helium as carrier gas, and by NMR spectroscopy, and they were identified by comparison with authentic samples.

Quantitative analyses of sulfoxides were performed by GLC, using diphenyl sulfoxide as internal standard. For the more selective examples reported in Table 1, such as for di-*n*-butyl sulfide, diisopropyl sulfide and methyl benzyl sulfide, the reactions were also carried out on a larger scale (20 mmol) and the products were isolated simply by evaporating the organic solvent (CH₂Cl₂). In every case the weight of the crude product corresponds to the quantitative GLC analysis. The products were purified by flash chromatography (hexane/ethyl acetate 4:1).

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