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Catalytic Processes of Oxidation by Hydrogen Peroxide in the Presence of Br_2 or HBr. Mechanism and Synthetic Applications

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Abstract:

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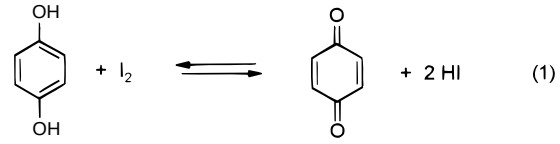
The mechanism and the synthetic applications for the oxidation of alcohols, ethers, and aldehydes by H_2O_2 catalyzed by Br_2 or Br^- in a liquid two-phase system (aqueous and organic) are reported. Aliphatic and benzylic primary alcohols and ethers show an opposite behavior, which has been rationalized on the ground of the different electronic configurations of the intermediate alkyl (π-type) and acyl (σ-type) radicals and their influence on enthalpic and polar effects. A two-phase system is particularly useful also for an efficient benzylic bromination by Br_2 or Br^-; the substitution of the benzyl bromide by OH, OR, and OCOR regenerates Br^-, which can be recycled. The evaluation of the relative reactivities of the involved substrates and intermediates has allowed to develop a variety of simple, facile, convenient, and selective syntheses of alcohols, aldehydes, ketones, esters, and benzyl bromides, which fulfill the conditions for practical applications.

Hydrogen peroxide is a valuable oxidant for several reasons: (i) low cost; (ii) low molar mass; (iii) high oxidation potential ($E° = 1.77$ V); (iv) formation of water as reduction product, thus avoiding the environmental problems which are frequently involved with other oxidants. However, a significant disadvantage is represented by the high activation energy required by many oxidations of organic compounds by H_2O_2. For this reason, catalysis is often necessary to activate H_2O_2 in these cases. The importance of bromine catalysis in the autoxidation for a variety of industrial processes is well-known.[1] In the past, we[2] have utilized catalysis by halogens or halogen halides to achieve selective oxidation of phenols to quinones, which do not occur in the absence of catalyst. Hydroquinone or catechol derivatives are not oxidized by H_2O_2 in the absence of catalyst, but the oxidation smoothly and selectively takes place in the presence of catalytic amount of I_2 or of HI; the actual oxidant is I_2 (eq 1).

The equilibrium of eq 1 is shifted at left because of the low redox potential ($E° = 0.54$ V) of I_2, but the presence of H_2O_2 determines the fast oxidation of HI (eq 2), shifting the

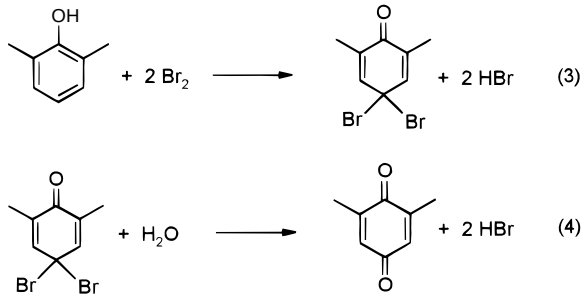


(1)

equilibrium of eq 1 at right.

$$2HI + H_2O_2 \rightarrow I_2 + 2H_2O \quad (2)$$

Similarly, the oxidation of phenols substituted in the 2 and 6 positions does not occur by H_2O_2 in the absence of catalyst, while it takes place with high selectivity in the presence of Br_2 or HBr; we[1] have interpreted the reaction according to eqs 3−5.



(3)

(4)

$$4HBr + 2H_2O_2 \rightarrow 2Br_2 + 4H_2O \quad (5)$$

I_2 and Br_2 are much less oxidizing than H_2O_2, but they are often more reactive and selective. Following a similar general criterion, other research groups[3−14] and, above all, the Interox Chemicals Ltd. researchers have developed a series of oxidation processes, which for their simplicity, selectivity, and cheapness appear to be useful for practical applications. Several of the reports from this group are patents[9−14] and, obviously, the reaction mechanisms were not discussed. In this paper, we attempt to rationalize the

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Table 1. **Oxidation of primary aliphatic alcohols to esters by H_2O_2, catalyzed by HBr (eq 6)**

alcohol	solvent	time (h)	convn (%)	yield (%)[a]
1-propanol	CH_2Cl_2/H_2O (1:1)	2	56	99
1-propanol	CH_2Cl_2/H_2O (1:1)	4	69	98
1-propanol	CH_2Cl_2/H_2O (1:1)	6	100	98
1-butanol	CH_2Cl_2/H_2O (1:1)	2	58	99
1-butanol	CH_2Cl_2/H_2O (1:1)	4	71	98
1-butanol	CH_2Cl_2/H_2O (1:1)	6	100	98
1-pentanol	CH_2Cl_2/H_2O (1:1)	6	100	97
1-hexanol	CH_2Cl_2/H_2O (1:1)	6	100	98
2-methyl-1-pentanol	CH_2Cl_2/H_2O (1:1)	6	100	95
1-heptanol	CH_2Cl_2/H_2O (1:1)	6	100	98
1-heptanol	hexane/H_2O (1:1)	6	61	97
1-heptanol[b]	hexane/H_2O (4:1)	6	58	95
1-heptanol[c]	hexane/H_2O (4:1)	24	91	91
1-heptanol	AcOEt/H_2O (1:1)	4	20	57
1-decanol	CH_2Cl_2/H_2O (1:1)	6	100	97

[a] Based on the converted alcohol. [b] 5% of heptanal is formed. [c] 9% of heptanal is formed.

involved overall reactivity and to show how the understanding of the structure−reactivity relationship can lead to further useful synthetic developments.

Oxidation of Alcohols and Aldehydes

Primary aliphatic alcohols, RCH_2OH, react with H_2O_2 under mild conditions in a liquid two-phase system (water and an organic solvent) in the presence of a catalytic amount of Br_2 or HBr to yield selectively the corresponding esters (eq 6).

$$2RCH_2OH + 2H_2O_2 \xrightarrow[\text{or HBr}]{Br_2} R{-}COO{-}CH_2R + 4H_2O \quad (6)$$

In the absence of Br_2 or HBr, no reaction occurs under the same conditions. The results obtained with a variety of primary alcohols are reported in Table 1. We explain the mechanism of the reaction by a free-radical chain process leading to the acyl bromide (eq 7−10) and the simultaneous alcoholysis of the acyl bromide (eq 11) and oxidation of HBr by H_2O_2.

$$R{-}CH_2OH + Br^{\bullet} \rightarrow R{-}\dot{C}HOH + HBr \quad (7)$$

$$R{-}\dot{C}HOH + Br_2 \rightarrow R{-}CHO + Br^{\bullet} + HBr \quad (8)$$

$$R{-}CHO + Br^{\bullet} \rightarrow R{-}\dot{C}O + HBr \quad (9)$$

$$R{-}\dot{C}O + Br_2 \rightarrow R{-}COBr + Br^{\bullet} \quad (10)$$

$$R{-}COBr + R{-}CH_2OH \rightarrow R{-}COO{-}CH_2R + HBr \quad (11)$$

To the best of our knowledge, the possibility to obtain esters from primary aliphatic alcohols by bromine-catalyzed H_2O_2 oxidation was mentioned by only one line of a report,[3] without any indication concerning the structure of the alcohols, the yields, the experimental conditions, the selectivity, or the mechanism.

The oxidation of the alcohol takes place in the organic phase (eqs 8−11), so that the competition of the hydrolysis of the acyl bromide to the corresponding carboxylic acid is minimized, whereas the oxidation of HBr by H_2O_2 (eq 12) occurs in the aqueous phase. In principle, the reaction could

$$2HBr + H_2O_2 \rightarrow Br_2 + 2H_2O \quad (12)$$

be carried out in three steps: (i) preparation of the acyl bromide by a stoichiometric amount of Br_2; (ii) alcoholysis of the acyl bromide; (iii) oxidation of HBr by H_2O_2. However, apart the complexity of the stoichiometric oxidation by Br_2, the large amount of HBr developed during the reaction leads to the bromination of the alcohol (eq 13), thus reducing the overall selectivity of the oxidation.

$$R{-}CH_2OH + HBr \rightarrow R{-}CH_2Br + H_2O \quad (13)$$

In the catalytic process the fast eq 12 keeps the stationary concentration of HBr very low and the reaction in eq 13 is practically absent.

The reaction can be carried out by Br_2 in the absence of H_2O_2 in a two-phase system; also in this case, the stationary concentration of HBr is very low in the organic phase, because of the much higher solubility of HBr in the aqueous phase. After Br_2 has reacted, the addition of H_2O_2 in the aqueous phase regenerates Br_2 by oxidation of HBr, thus making the overall process catalytic; in this way, the process is faster compared to the use of a catalytic amount of Br_2.

The reaction rate is directly related to the amount of Br_2 or HBr. It is convenient, from a practical standpoint, to use a relatively large amount of Br_2 or HBr, to obtain a fast reaction; after the separation of the organic phase, the aqueous phase can be recycled without loss of the catalytic activity.

The mechanism of eqs 7−10 assumes that the intermediate aldehyde, R−CHO, is more reactive toward bromine than the starting alcohol, $R{-}CH_2OH$. We have verified this assumption either by working at low conversion (by using a large excess of alcohol with respect to H_2O_2 no substantial amount of aldehyde was formed, but the ester is always the reaction product) or by oxidizing a mixture of aldehyde R−CHO and alcohol $R'{-}CH_2OH$; also in this latter case, the ester $RCOOCH_2R'$ was obtained with good selectivity (eq 14), which confirms that the aldehyde is much more reactive than the alcohol.

$$R{-}CHO + R'{-}CH_2OH + H_2O_2 \rightarrow R{-}COO{-}CH_2R' + 2H_2O \quad (14)$$

The higher reactivity of the aldehyde compared to the alcohol towards the free-radical bromination is justified by the enthalpic effect. The energy of the RCHOH−H bond is significantly larger (6−7 kcal/mol) than that of the RCO−H bond; this makes eq 9 almost thermoneutral, whereas eq 7 is an endothermic process. The polar effects are favorable

$$R{-}CH_2OH + Br^{\bullet} \rightarrow [R{-}C^{\delta+}HOH\cdots H\cdots Br^{\delta-}]^{\ddagger} \rightarrow R{-}\dot{C}HOH + HBr \quad (15)$$

$$R{-}CO{-}H + Br^{\bullet} \rightarrow [R{-}C^{\delta+}O\cdots H\cdots Br^{\delta-}]^{\ddagger} \rightarrow R{-}\dot{C}O + HBr \quad (16)$$

Table 2. Oxidation of secondary alcohols to ketones by H_2O_2, catalyzed by Br_2

alcohol	convn (%)	yield (%)[a]
2-hexanol	100	96
2-heptanol	98	99
2-decanol	99	98
cyclohexanol	94	87
cyclopentanol	96	91
2-adamantanol	100	96
Ph−CHOH−CH_3	100	95
Ph−CHOH−Ph	98	88

[a] Based on the converted alcohol.

Table 3. Oxidation of aliphatic aldehydes to esters in the presence of primary and tertiary alcohols

aldehyde	alcohol	convn (%)[a]	yield (%)[b]
1-heptanal	*n*-BuOH	96	92
1-heptanal	1-AdOH	89	87
1-heptanal	*t*-BuOH	92	84
1-pentanal	*n*-PrOH	87	91
1-pentanal	*n*-BuOH	91	89
1-pentanal	*t*-BuOH	83	87

[a] Converted aldehyde. [b] Based on the converted aldehyde.

(eqs 15 and 16) for both eqs 7 and 9, but they can be considered more pronounced with alcohols than with aldehydes, as will be discussed later. However, the more favorable polar effect with alcohols cannot balance the more favorable enthalpic effect with aldehydes.

By the same simple and convenient two-phase procedure secondary alcohols are selectively oxidized to the corresponding ketones (eq 17). The results are summarized in Table 2. Similar results were previously reported under more drastic conditions and under irradiation.[3,4]

$$\mathrm{R{-}CHOH{-}R' + H_2O_2 \xrightarrow[\text{or HBr}]{\mathrm{Br_2}} R{-}CO{-}R' + 2H_2O} \quad (17)$$

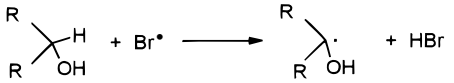
The new reaction (eq 14), based on the different reactivity of aldehydes and alcohols, makes the potential range for the synthesis of esters much larger, considering the great variety of available aldehydes and alcohols. Even an alcohol such as methanol, which is extremely soluble in water, can be successfully utilized for the preparation of methyl esters. Less water-soluble alcohols are even more effective, since the esterification takes place in the organic phase. A variety of esters obtained from aldehydes and alcohols are reported in Table 3. As far as we know, this is the first time that the synthesis of esters from aldehydes and alcohols is reported.

Benzylic alcohols behave quite differently from the aliphatic ones; secondary benzylic alcohols are much more reactive than are secondary aliphatic alcohols. The oxidation of mixtures of secondary benzylic and aliphatic alcohols leads to the selective oxidation of the benzylic derivatives to the corresponding ketones, indicating that the reactivity of the benzylic alcohol is >20 times higher than that of aliphatic alcohols. Also this behavior is simply explained on the basis of the enthalpic effect: the energy of the benzylic C−H bond

Table 4. Hyperfine coupling constants (*a*) of benzyl and benzoyl radicals

a	Ph−$CH_2^{\bullet}$	Ph−$CO^{\bullet}$
α_o-H	5.17	0.1
α_m-H	1.77	1.16
α_p-H	6.19	0.1

(ArC(R)(OH)−H) is 7−8 kcal/mol lower than that of the corresponding alkyl C−H bond (R_2COH−H), and this is reflected on the rate of hydrogen abstraction by $Br^{\bullet}$ (eq 18), which determines the chemoselectivity of the reaction.



(18)

The esters, $ArCOOCH_2Ar$, cannot be obtained from the corresponding primary benzyl alcohols, $ArCH_2OH$, according to eq 6, because the reactivity is opposite compared to primary aliphatic alcohols. Actually, benzyl alcohols are much more reactive than the corresponding aromatic aldehydes, so that the latter are not oxidized as long as the alcohols are present, whereas in the aliphatic series the aldehydes are much more reactive than the corresponding alcohols and it is not possible to stop the oxidation of alcohols to aldehydes. This inversion of reactivity could, in principle, be explained by three behaviors: (i) the primary benzyl alcohols are more reactive than the primary aliphatic alcohols; (ii) the aliphatic aldehydes are more reactive than the aromatic aldehydes; (iii) both behaviors are simultaneously operating.

By competitive kinetics, we have verified that the condition iii is fulfilled. The competitive reaction of benzyl alcohol and 1-heptanol selectively leads to the oxidation of benzyl alcohol, while a mixture of benzaldehyde and 1-heptanal leads with large prevalence to the oxidation of 1-heptanal.

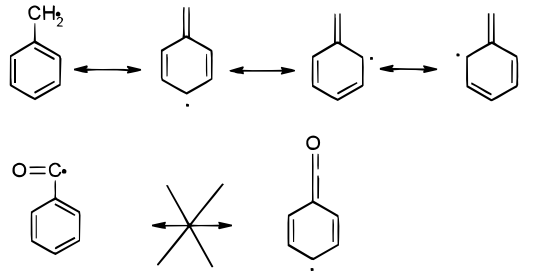
We explain this opposite behavior between aryl and alkyl derivatives by enthalpic and polar effects, as consequence of the electronic configurations of α-hydroxyalkyl and acyl radicals. Benzyl and alkyl radicals are π-type radicals, in which the unpaired electrons occupy p orbitals, while acyl radicals are σ-type radicals, with the unpaired electron located in hybrid orbitals of the carbon atom.[2] This is clearly shown by the hyperfine coupling of the ESR spectrum for the benzyl and benzoyl radicals (Table 4): the major proton hyperfine splitting is due to the meta hydrogen atoms in the benzoyl radical.[3] This is in contrast with the familiar para > ortho > meta trend observed with the benzyl π radical,[4] due to the resonance structures of eq 19, and it supports the lack of stabilization of the benzoyl radical, due to the absence of conjugation with the phenyl group (eq 20).

These electronic configurations are reflected in the bond strengths (Table 5); there is no influence on the strengths of the RCO−H bonds due to the substitution of a hydrogen atom on alkyl, vinyl, or aryl groups,[5] contrary to the behavior of alkyl radicals.[6]

Since the strengths of the Ar−CHOH−H and ArCO−H bonds are quite close, we explain the much higher reactivity

Table 5. Strengths (kcal/mol) of C−H bonds

CH_3-H	105	HCO−H	87.0
CH_3-CH_2-H	101	CH_3CO-H	87.0
Ph-CH_2-H	89	PhCO−H	86.9
$CH_2=CH-CH_2-H$	87	$CH_2=CH-CO-H$	87.1



(19)

(20)

of the benzyl alcohols, compared to that of the corresponding aldehydes, by the polar effect.[2,7] The s-electrons are, on the average, closer to the nucleus than are p-electrons; they therefore experience a greater interaction with nucleus, that is, s-orbitals have a higher electronegativity than p-orbitals. It is therefore easier to remove an electron from a p-orbital than from a s-orbital of the same quantum number in similar structures. The larger the contribution of s-character to a hybrid orbital, the greater the electronegativity of that hybrid orbital and the higher the energy required to remove an electron.

Thus, the contribution of polar forms to the transition state will be larger in hydrogen abstraction from ArCHOH−H (eq 15) than from ArCO−H (eq 16), that is, the polar effect is more marked in eq 15 than in eq 16. This larger charge separation is reflected in a lower activation energy and in a higher reactivity for hydrogen abstraction from benzylic alcohols than from aromatic aldehydes, even if the enthalpic effects are substantially equal. In conclusion, the *polar effect* determines the higher reactivity of primary benzylic alcohols compared to the corresponding aldehydes. On the other hand, primary benzylic alcohols are much more reactive than primary aliphatic alcohols exclusively for *enthalpic reasons* (different strength of the involved C−H bonds).

The higher reactivity of aliphatic aldehydes compared to aromatic aldehydes is exclusively due to the *polar effect* because the enthalpic effects are substantially equal (Table 5): alkyls are electron-releasing groups and so increase the contribution of polar forms to the transition states, while aryl groups are electron-withdrawing and decrease the charge separation in the transition state (eq 16).

To a complete programming of the synthetic potentiality of these oxidations, it was also important to know the relative reactivities of aromatic aldehydes and aliphatic alcohols. We have verified, always by competitive kinetics, that aromatic aldehydes are much more reactive than methanol; clearly the *enthalpic effect* is responsible for this selectivity. The primary aliphatic alcohols are still somewhat less reactive than aromatic aldehydes, but the difference of reactivity is relatively small and the competitive oxidation of the two substrates takes place with partial selectivity; in this case, the *higher polar effect* for hydrogen abstraction from alcohols is balanced by the *more favorable enthalpic effect* for hydrogen abstraction from aldehydes.

Table 6. Synthesis of aldehydes $X-C_6H_4-CHO$ from $X-C_6H_4-CH_2OH$ by bromine-catalyzed H_2O_2 oxidation

X	ratio (alcohol:Br_2:H_2O_2)	convn (%)[a]	yields (%)[b]
H	1:0.05:2	92	98
H	1:0.15:1.5	100	93
o-Me	1:0.15:2	97	91
m-Me	1:0.15:2	94	96
p-Me	1:0.15:2	98	90
o-Cl	1:0.15:2	98	93
p-Cl	1:0.05:2	99	97
p-Cl	1:0.15:1	94	93
p-Br	1:0.05:2	98	98
p-COOEt	1:0.15:2	93	94
p-CN	1:0.2:2	94	92
o-NO_2	1:0.2:2	94	96
p-NO_2	1:0.15:2	81	95
p-Ph	1:0.15:2	98	94

[a] Conversion of the benzyl alcohol. [b] Yields based on the converted alcohol.

Table 7. Oxidation of benzyl alcohols $X-C_6H_4-CH_2OH$ to the corresponding methyl benzoates

X	convn (%)	yields (%)[a]
H	100	87
o-Me	100	83
p-Me	100	88
o-Cl	93	83
p-Cl	92	86

[a] Based on the converted benzyl alcohol.

The evaluation of the relative rates and their rationalization have allowed to develop the following three selective syntheses:

(i) A general method to oxidize primary benzyl alcohols to the corresponding aromatic aldehydes by always using the same two-phase system above-described under mild conditions and arresting the reaction when the benzyl alcohol has reacted. The mechanism is illustrated by eqs 7 and 8; the further oxidation does not occur owing to the lower reactivity of ArCHO compared to $ArCH_2OH$. The same synthesis is not possible with primary aliphatic alcohols. Several examples are reported in Table 6. The conversion can be increased by increasing the amount of H_2O_2. A few examples of oxidation by a similar procedure have been previously reported[3,4] without any mechanistic interpretation.

(ii) A general method to oxidize primary benzyl alcohols to the corresponding methyl benzoates in the presence of methanol, by using an excess of H_2O_2. The overall stoichiometry is shown by eq 21. Some examples are reported in

$$ArCH_2OH + CH_3OH + 2H_2O_2 \rightarrow Ar-COOCH_3 + 4H_2O \quad (21)$$

Table 7.

(iii) A general method to oxidize primary benzyl alcohols to benzoates of aliphatic alcohols (eq 22). Since the difference of reactivity between ArCHO and RCH_2OH is

Table 8. **Oxidation of benzyl alcohols X−C_6H_4−CH_2OH to alkyl benzoates X−C_6H_4−COOR**

X	R−OH	convn (%)[a]	yields (%)[b]
H	EtOH	93	84
H	*n*-BuOH	86	82
H	*t*-BuOH	91	93
o-Cl	*n*-BuOH	97	83
p-Cl	*n*-BuOH	92	88
o-Me	*n*-BuOH	98	81
o-Me	*t*-BuOH	78	94
p-Me	*t*-BuOH	81	96

[a] Conversion of benzyl alcohol. [b] Yields based on the converted benzyl alcohol.

$$ArCH_2OH + RCH_2OH + 2H_2O_2 \rightarrow Ar{-}COOCH_2R + 4H_2O \quad (22)$$

not large enough, a good selectivity is obtained by the slow addition of the alcohol RCH_2OH to the oxidizing two-phase system, to keep the stationary concentration of RCH_2OH relatively low during the reaction. The results are summarized in Table 8.

(iv) The synthesis of the same esters described by methods ii and iii can be achieved by starting from the corresponding aromatic aldehydes, which are intermediates in the reaction in eq 22. The results are reported in Table 9.

The latter three processes have never been previously reported, as far as we know; they are a direct consequence of our mechanistic interpretation.

An interesting aspect of all the syntheses above-reported is the fact that no chemical or photochemical initiation is necessary to start the radical chains of eqs 7−10. We explain this behavior by the formation of traces of Br_2O during the oxidation process; daylight is sufficient for the homolysis of the weak Br−O bond (eq 23).

$$Br{-}O{-}Br \rightarrow Br^{\bullet} + {}^{\bullet}O{-}Br \quad (23)$$

Oxidation of Ethers

Ethers are smoothly oxidized by H_2O_2 in a liquid two-phase system in the presence of catalytic amounts of Br_2 or HBr. The reaction products depend on the structure of the ether and the reaction conditions. Thus, methyl benzyl ether gives methyl benzoate according to eq 24.

$$PhCH_2OCH_3 + 2H_2O_2 \rightarrow Ph{-}COOCH_3 + 3H_2O \quad (24)$$

This appears to be a simple oxidation of a benzylic CH_2 group to carbonyl. However, the analysis of the reaction products during the reaction course (Table 10) revealed that benzaldehyde and methanol are initially formed and that only after all of the ether has reacted, benzaldehyde is further oxidized to methyl benzoate by procedure iv in the previous section. Thus, methyl benzyl ether can be oxidized in this way either to methyl benzoate (eq 24) or to benzaldehyde (eq 25).

$$PhCH_2OCH_3 + H_2O_2 \rightarrow Ph{-}CHO + CH_3OH + 3H_2O \quad (25)$$

Also in this case, the reaction can be carried out by Br_2 in a two-phase system, in the absence of H_2O_2; the aqueous HBr is then oxidized by H_2O_2.

Table 9. **Oxidation of aromatic aldehydes, X−C_6H_4−CHO, to alkyl benzoates X−C_6H_4−COOR**

X	R−OH	convn (%)[a]	yields (%)[b]
H	MeOH	92	96
H	EtOH	94	84
H	*n*-BuOH	87	83
H	*t*-BuOH	72	94
o-Cl	MeOH	93	97
p-Cl	MeOH	91	89
o-Me	MeOH	92	87
p-Me	MeOH	89	91
p-Me	*n*-BuOH	91	78
p-Me	*t*-BuOH	81	96

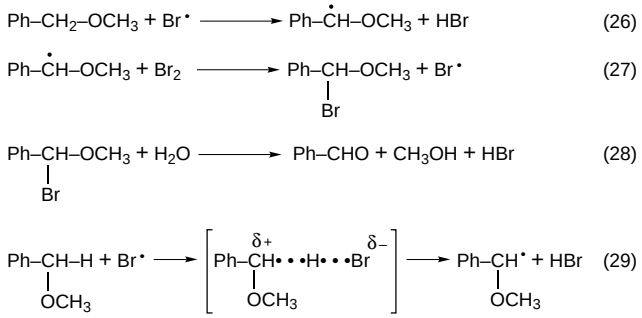
[a] Conversion of aldehyde. [b] Yields based on the converted aldehyde.

Table 10. **Oxidation of benzyl methyl ether to benzaldehyde (I), methyl benzoate (II), and mixed anhydride between benzoic and formic acids (III)**

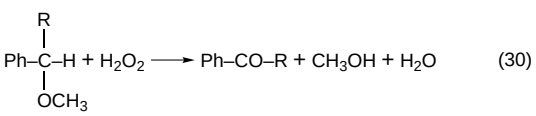
			yields[b]		
T (°C)	reaction time (h)	convn[a] (%)	I	II	III
18	0. 5	18	87		
18	1.3	32	91	2.1	
18	2	48	89	5.3	
18	3	70	87	9.1	
18	5.5	99.5	81	18.3	
18	26.5	100	20	60	
42	2	100	33	40	25
42	4	100		61	32

[a] Conversion of benzyl ether. [b] Yields based on the converted benzyl ether.

No reaction occurs under the same conditions in the absence of Br_2 or HBr, which indicates that the mechanism for the oxidation of ethers (eqs 26−29) is quite similar to the one discussed for alcohols (eqs 7−8). HBr is then



oxidized to H_2O_2 according to eq 12. The selectivity of the process is determined, also in this case, by combined favorable enthalpic (low energy of the benzylic bond) and polar (eq 29) effects. With secondary benzyl ethers, the corresponding ketones are obtained (eq 30).



The reaction represents a new general method for obtaining aromatic aldehydes, ketones or esters from benzyl ethers.

Table 11. Oxidation of secondary benzyl ethers, X−C_6H_4−CH(R)−OMe, to the corresponding ketones, X−C_6H_4−CO−R

X	R	convn[a] (%)	yields[b] (%)
H	Me	98	94
H	Et	96	97
o-Cl	Me	97	92
p-Cl	Et	99	89
o-Me	Me	96	91
p-Me	Me	92	94
p-Me	Et	96	98

[a] Conversion of benzyl ether. [b] Yields based on the converted benzyl ether.

Table 12. Oxidation of dialkyl ethers, R−CH_2−O−CH_2−R, to the corresponding esters, R−$COOCH_2$R (IV)

		yields[a] (%)		
R	convn (%)	IV	R−CH_2OH	R−COOH
n-Pr	94	65	10	8
n-Bu	92	73	7	6
n-hexyl	91	71	8	7
2-Me-pentyl	87	70	6	9
n-heptyl	89	71	9	8

[a] Yields based on the converted ether.

Some results are summarized in Tables 10 and 11. As for the corresponding alcohols, discussed in the previous section, also the oxidation of alkyl ethers is slower than that of benzyl ethers: both hydrogen abstraction (eq 26) and hydrolysis of the bromoethers (eq 28) are slower. Primary symmetrical alkyl ethers give the corresponding esters (eq 31).

$$R{-}CH_2{-}O{-}CH_2{-}R + 2H_2O_2 \rightarrow R{-}COO{-}CH_2R + 3H_2O \quad (31)$$

The reaction takes place by a mechanism identical to the one depicted in eqs 26−28, but the aliphatic aldehyde is much more reactive than both the alcohol R−CH_2OH and the starting ether, so that it is further oxidized to the ester by a reaction similar to eq 14. Some results are reported in Table 12.

Primary asymmetrical alkyl ethers, obviously, give two esters (eq 32). Secondary alkyl ethers lead to the corresponding ketones; the symmetric derivatives lead to only one ketone, while the asymmetric ethers give two different ketones (eq 33). Methyl alkyl ethers are oxidized to the corresponding methyl esters (eq 34), while methyl-*sec*-alkyl ethers give the ketone and methanol (eq 35).

$$R{-}CH_2{-}O{-}CH_2{-}R' + 2H_2O_2 \rightarrow R{-}COO{-}CH_2R' + RCH_2{-}OCOR' + 3H_2O \quad (32)$$
$$\sim 50\% \qquad\qquad \sim 50\%$$

$$R_2CH{-}O{-}CHR'_2 + 2H_2O_2 \rightarrow R{-}CO{-}R + R'{-}CO{-}R' + 3H_2O \quad (33)$$

$$R{-}CH_2{-}O{-}CH_3 + 2H_2O_2 \rightarrow R{-}COOCH_3 + 3H_2O \quad (34)$$

$$R_2CH{-}O{-}CH_3 + H_2O_2 \rightarrow R{-}CO{-}R + CH_3OH + H_2O \quad (35)$$

In all of these cases the selectivity is determined by the enthalpic effect, being the polar effect of the oxygen atom substantially identical; the high sensitivity of hydrogen abstraction by bromine atom to the bond strengths determines the selectivity among primary, secondary, and tertiary C−H bonds next to the oxygen atom. Cyclic ethers are oxidized to the corresponding lactones (eq 36). The results with a variety of ethers are reported in Table 13.

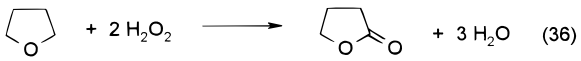


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Table 13. Oxidation of THF and other ethers

ether	product	time (h)	convn (%)[a]	yield (%)[b]
THF	γ-butyrolactone	1	34.2	98
THF	γ-butyrolactone	2	64.6	87
THF	γ-butyrolactone	4	92.4	81
methyl cyclooctyl ether	cyclooctanone	4	87	92
methyl cyclooctyl ether[c]	cyclooctanone	4	96	97
dicyclohexyl ether	cyclohexanone	4	98	93
methyl cyclohexyl ether	cyclohexanone	4	91	96

[a] Conversions based on the oxidant. [b] Yields based on the conversion. [c] The procedure is the same, with the difference that a stoichiometric amount of Br_2 was used in a two-phase system in the absence of H_2O_2.

To the best of our knowledge, the oxidation of ethers by H_2O_2, catalyzed by bromine has not been reported previously.

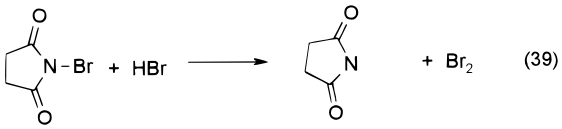
Benzylic Bromination in the Presence of H_2O_2

Free-radical bromination is one of the synthetic methodologies more widely utilized for the functionalization of alkyl aromatics because the easy nucleophilic substitution of the benzylic bromine atom allows for the synthesis of a large variety of derivatives, including alcohols, aldehydes, and esters. For practical applications, the high molar mass and cost of bromine are the main disadvantages. Molecular bromine can be utilized by a classical free-radical chain process (eqs 37 and 38).

$$Ar{-}CH_3 + Br^{\bullet} \rightleftarrows Ar{-}CH_2^{\bullet} + HBr \quad (37)$$

$$Ar{-}CH_2^{\bullet} + Br_2 \rightarrow Ar{-}CH_2{-}Br + Br^{\bullet} \quad (38)$$

Reaction 37 is almost thermoneutral (H−Br and benzylic C−H bonds have very close strengths) and reversible; thus, complete conversions are sometimes obtained with difficulty, particularly with the less reactive electron-deficient alkyl aromatics. To overcome this difficulty, the more expensive *N*-bromosuccinimmide, NBS, is often utilized, also for practical purposes. In this case, the stationary concentration of H−Br is always kept very low by its fast reaction with NBS (eq 39), minimizing in this way the reversibility (eq 40).



(39)

$$Ar{-}CH_2^{\bullet} + Br_2 \rightarrow Ar{-}CH_2Br + Br^{\bullet} \quad (40)$$

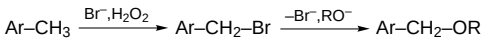
Similar results have been obtained by more simple and convenient procedures carried out with Br_2 or Br^- in the presence of H_2O_2[5,6,8−15] (eqs 41 and 42).

$$2Ar{-}CH_3 + Br_2 + H_2O_2 \rightarrow 2Ar{-}CH_2Br + 2H_2O \quad (41)$$

$$Ar{-}CH_3 + Br^- + H^+ + H_2O_2 \rightarrow Ar{-}CH_2Br + 2H_2O \quad (42)$$

These procedures offer seven advantages over the use of NBS or of Br_2 in a homogeneous system: (1) the molar mass and cost of H_2O_2 are much lower than those of NBS; (2) bromination in the presence of H_2O_2 allows complete utilization of bromine (eq 43) avoiding waste of one-half of the employed bromine atoms (eq 42); (3) the stationary concentration of HBr is always very low, due to the fast oxidation by H_2O_2 and the reversibility of eq 37 is minimized; (4) the experimental conditions and the separation of the reaction products are very simple. At the end of the reaction, the organic layer is separated and distillation of the solvent provides the benzyl bromides.

(5) No chemical or photochemical initiation is necessary, contrary to the bromination by NBS, because, as previously discussed, daylight is sufficient for the initiation (eq 23); (6) the two-phase system in the presence of H_2O_2 allows for the use not only of Br_2, but also of HBr or alkali bromide (eq 42) (this aspect is of particular interest in the synthesis of benzylic alcohols, ethers, and esters, since the latter can be easily obtained by nucleophilic substitution of benzyl bromides, which regenerates HBr, and can be recycled in aqueous acidic (H_2SO_4) medium, thus making the overall process catalytic in Br^- (eq 43)); (7) since benzyl alcohols and ethers can be further oxidized by H_2O_2 to aldehydes and esters under bromine catalysis, as discussed in previous sections, we can transform, e.g., a methyl aromatic into a methyl benzyl ether and further into aromatic aldehydes and esters, depending on the reaction conditions and the amount of H_2O_2 (eq 44).



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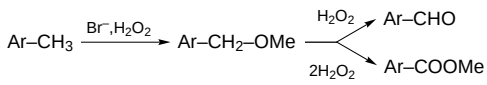

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The benzylic bromination in a two-phase system is a selective process, the only byprocess being the dibromination at complete conversion of the alkylaromatic. For the synthesis of aldehydes and esters, it is not necessary to separate mono- and dibromides, as the latter directly provide the aldehyde and HBr by hydrolysis (eq 45); HBr is then recycled by H_2O_2 oxidation (eq 12).

$$Ar{-}CHBr_2 + H_2O \rightarrow Ar{-}CHO + 2HBr \quad (45)$$

Table 14. **Bromination of 2-nitrotoluene (Ar−CH_3)**

brominating agent	$ArCH_3$:Br:H_2O_2	solvent	convn (%)	yields (%) of $ArCH_2Br$[a]
Br_2	1:1:0	CH_2Cl_2	traces	traces
Br_2	1:0.5:0	CH_2Cl_2/H_2O 1:1	20	99
Br_2	1:1.2:0	CH_2Cl_2/H_2O 1:2	91	89
Br_2/H_2O_2[b]	1:0.7:0	CH_2Cl_2	93	94
Br_2/H_2O_2	1:0.5:0.5	CH_2Cl_2/H_2O 1:1	34	98
Br_2/H_2O_2	1:0.7:10	CH_2Cl_2/H_2O 1:1	8	100
Br_2/H_2O_2[c]	1:0.7:1	hexane/H_2O 1:1		
HBr/H_2O_2	1:2:2	CH_2Cl_2/H_2O 1:2	87	93

[a] Based on the converted 2-nitrotoluene. [b] 36% aqueous H_2O_2. [c] 2- and 3-Bromohexanes are formed.

The benzylic bromination is particularly difficult with deactivated alkylbenzenes: in competitive bromination of equimolar amounts of *o*-nitrotoluene and toluene, we have observed that only the latter is substantially brominated. Thus, we have carefully investigated the bromination of *o*-nitrotoluene in different conditions, to recognize the factors which affect the reactivity and also because of the practical interest of the synthesis of *o*-nitrobenzaldehyde. The results, reported in Table 14, reveal three new important factors influencing the reaction: (1) the presence of water has a dramatic influence on the reaction; no substantial bromination takes place in the absence of water, whereas high conversions and yields are obtained under the same conditions in the presence of water; (2) an excess of H_2O_2 inhibits the bromination; (3) by using *n*-hexane as solvent in the presence of water, no bromination of *o*-nitrotoluene occurs, but 2- and 3-bromohexane are the only reaction products.

We have obtained similar results with 4-cyanotoluene.

Our interpretation is based on the reversibility of eq 37, which is more marked in the presence of electron-withdrawing groups (−NO_2, −CN); since HBr is much more soluble in water than in organic solvents, the aqueous phase extracts HBr from the organic phase, in which bromination takes place, thus minimizing the reversibility.

The inhibition, due to excess H_2O_2, must be related always to the reduced reactivity of *o*-nitrotoluene towards the bromine atom; this latter can abstract hydrogen atoms from H_2O_2, leading to its decomposition according to eq 46.

$$Br^{\bullet} + H_2O_2 \rightarrow HBr + HOO^{\bullet} \rightarrow O_2 \quad (46)$$

With deactivated alkyl aromatics it is more convenient to carry out the reaction by slowly adding the aqueous solution of H_2O_2 to the reacting mixture, to avoid the presence of excess H_2O_2, minimizing in this way eq 46.

The fact that in hexane solution the solvent is brominated in place of *o*-nitrotoluene indicates that the polar effect, as illustrated in eqs 15 and 16, is more important than the

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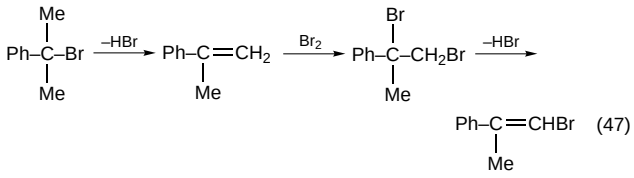
Table 15. **Bromination of alkylbenzenes**

substrate (S)	brominating agent	S:Br:H_2O_2	solvent	convn (%)	yields (%)[a]
toluene	Br_2/H_2O_2	1:0.7:1	CH_2Cl_2/H_2O 1:1	93	94
toluene[b]	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 1:1	100	70
toluene	$NaBr/H_2O_2$ H_2SO_4 (1)	1:2:2	CH_2Cl_2/H_2O 1:1	96	92
ethylbenzene	Br_2/H_2O_2	1:0.7:0.5	CH_2Cl_2/H_2O 1:1	87	92
ethylbenzene	$NaBr/H_2O_2$ H_2SO_4 (1)	1:2:2	CH_2Cl_2/H_2O 1:1	91	94
ethylbenzene	Br_2/H_2O_2	1:2:1.5	CH_2Cl_2/H_2O 1:1	93	89
cumene[c]	Br_2/H_2O_2	1:0.7:0.5	CH_2Cl_2/H_2O 1:1	60	5
p-CN-toluene	Br_2	1:1:0	CH_2Cl_2	traces	traces
p-CN-toluene	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 5:1	100	95
o-CN-toluene	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 5:1	97	98
o-Cl-toluene	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 1:1	100	94
p-Cl-toluene	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 1:1	100	93
p-Me-benzoic acid	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 1:1	100	87
Et-*p*-Me-benzoate	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 1:1	100	91
p-NO_2-toluene	Br_2	1:1:0	CH_2Cl_2	21	100
p-NO_2-toluene[d]	Br_2/H_2O_2	1:1:1	CH_2Cl_2	100	88
p-NO_2-ethylbenzene[d]	Br_2/H_2O_2	1:1:1	CH_2Cl_2	98	86
2-NO_2-4-MeO-toluene	Br_2/H_2O_2	1:1:1	CH_2Cl_2/H_2O 1:2	85	98

[a] Based on the converted alkylbenzene. [b] 28% of $PhCHBr_2$ is formed. [c] α-Methylstyrene and α-methyl-β-bromostyrenes are the main reaction products. [d] 36% aqueous H_2O_2 has been utilised.

enthalpic effect (the benzylic C−H bond is 8−10 kcal/mol weaker than the C−H bond in *n*-hexane). The results with a variety of alkyl aromatics are reported in Table 15; with deactivated substrates, the aqueous solution of H_2O_2 was slowly added to the reaction mixture.

Tertiary C−H bonds are not suitable for the bromination by this procedure, because HBr elimination takes place under the reaction conditions, leading mainly to α-methylstyrene and to *cis*- and *trans*-α-methyl-β-bromostyrenes (eq 47).



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Experimental Section

General Procedures. Mass spectra were performed on a GLC-MS Finnigan TSQ 70 instrument, using a Varian 3700 gas-chromatograph equipped with SBP-1 fused silica column (30 m × 0.2 mm i.d., 0.2 μm film thickness) and helium as carrier gas.

GC analyses were performed on a capillary gas-chromatograph equipped with SBP-5 fused silica column (25 m × 0.25 mm i.d., 1 μm film thickness) at a hydrogen flow rate of 8 cm^3 min^{-1}, PTV injector, and flame ionization detector.

Starting materials and reagents were purchased commercially and used without further purification.

All reaction products were known and were analyzed by GC and GC-MS and by comparison with authentic samples.

General Oxidation Procedures. *Oxidation of Primary Aliphatic Alcohols to Esters.* Five millimoles of the alcohol, dissolved in 7.5 mL of CH_2Cl_2, was stirred for 2 h at room temperature with 3 mmol of Br_2 and 7.5 mL of water; 6 mmol of H_2O_2 (30% aqueous solution) was added within 2 h. The organic phase was separated, washed with aqueous $NaHCO_3$ solution, and analyzed by GC (ethyl heptanoate as internal standard). The reaction products were identified by GC-MS analysis and by comparison with authentic samples. The results are reported in Table 1. The aqueous solution, containing HBr, has been utilized for a further oxidation of 5 mmol of alcohol in 7.5 mL of CH_2Cl_2 by the addition of 7.5 mmol of H_2O_2 over 4 h: the results are quite similar.

Oxidation of Secondary Alcohols to Ketones. Procedure A was utilized by employing half of the oxidant. The results are reported in Table 2.

Oxidation of Aliphatic Aldehydes in the Presence of Alcohols. Five millimoles of the aldehyde, 15 mmol of the alcohol, and 2.5 mmol of Br_2 dissolved in a mixture of 7.5 mL of CH_2Cl_2 and 7.5 mL of water were refluxed for 1 h; 2.5 mmol of H_2O_2 was added, and the mixture was refluxed for an additional hour. The organic phase was separated and analyzed by GC and GC-MS; authentic samples were utilized for the identification and analysis of the reaction products. The results are reported in Table 3.

Oxidation of Benzyl Alcohols to Aldehydes. Two millimoles of the alcohol, dissolved in 10 mL of ACOEt and 2 mL of water, together with Br_2 and H_2O_2 in the ratios reported in Table 6, was refluxed for 4 h. The organic phase was separated, washed with aqueous $NaHCO_3$ solution, and analyzed by GC (*p*-chlorobenzaldehyde as internal standard; with *p*-chlorobenzyl alcohol, *o*-chlorobenzaldehyde was utilized as internal standard). The reaction products were identified by GC-MS analysis and by comparison with authentic samples. The results are reported in Table 6.

Oxidation of Benzyl Alcohols to Methyl Benzoate. Five millimoles of benzyl alcohol, 20 mmol of CH_3OH, and 5 mmol of Br_2 in 10 mL of CH_2Cl_2 and 10 mL of water were refluxed for 2 h; 6 mmol of H_2O_2 were then added under reflux over a 2 h period. The organic phase was separated

and analyzed by GC (ethyl benzoate as internal standard) by using authentic samples and GC-MS analysis for the identification of the reaction products. The results are reported in Table 7.

Oxidation of Benzyl Alcohols to Alkyl Benzoates. Procedure E has been utilized with benzyl alcohols and tertiary aliphatic alcohols. With primary aliphatic alcohols, the procedure has been modified as follows: 5 mmol of benzyl alcohol, 1 mmol of aliphatic alcohol, and 5 mmol of Br_2 in 10 mL of CH_2Cl_2 and 10 mL of water were refluxed. Over 4 h, 6 mmol of H_2O_2 and 4 mmol of aliphatic alcohol were added. The organic phase was separated and analyzed by GC and GC-MS. The results are reported in Table 8.

Oxidation of Aromatic Aldehydes to Alkyl Benzoates. Procedures E and F were utilized by using half of the oxidant. The results are reported in Table 9.

Competitive Oxidations. One millimole of benzyl alcohol and 2 mmol of 1-heptanol in 7 mL of CH_2Cl_2 were stirred for 24 h at room temperature with 0.2 mmol of Br_2 and 2 mmol of H_2O_2 (30% aqueous solution). The GC and GC-MS analyses of the organic solution revealed the presence of 1-heptanol (36%), benzaldehyde (40%), benzyl alcohol (1.5%), 1-heptyl benzoate (9%), and 1-heptyl heptanoate (4%). The results indicate that benzyl alcohol is more than 20 times more reactive than 1-heptanol.

Two millimoles of benzaldehyde, 2 mmol of 1-heptanal, and 6 mmol of methanol in 7 mL of CH_2Cl_2 were stirred for 24 h at room temperature with 0.2 mmol of Br_2 and 2 mmol of H_2O_2 (30% aqueous solution). The analysis of the organic solution revealed the presence of benzaldehyde (40%), 1-heptanal (3.5%), methyl heptanoate (29%), and methyl benzoate (11%).

Two millimoles of benzaldehyde and 2 mmol of 1-heptanol in 7 mL of CH_2Cl_2 were stirred for 24 h at room temperature with 0.2 mmol of Br_2 and 2 mmol of H_2O_2. The analysis showed the presence of 1-heptanol (35%), benzaldehyde (24%), 1-heptyl benzoate (25%), and 1-heptyl heptanoate (8%).

Oxidation of Ethers. Alkylbenzyl Ethers. Two millimoles of methyl benzyl ether in 7.5 mL of CH_2Cl_2 were stirred for 24 h at room temperature with 0.2 mmol of Br_2 and 4 mmol of H_2O_2 (30% aqueous solution). The mixture was analyzed during the reaction course after 0.5, 1.3, 2, 3, 5.5, and 26.5 h, and the results are reported in Table 10.

Di-n-alkyl Ethers. Two millimoles of di-*n*-alkyl ether, 0.2 mmol of Br_2, and 4 mmol of H_2O_2 (30% aqueous solution) were stirred for 4 h at room temperature in 7.5 mL of CH_2Cl_2. The organic phase was separated and analyzed. The results are reported in Table 12.

Oxidation of Tetrahydrofuran (THF) to γ-Butyrolactone. Ten millimoles of THF and 4 mmol of Br_2 were refluxed for 1 h in a mixture of 5 mL of CH_2Cl_2 and 5 mL of water. Four millimoles of H_2O_2 was added, and the mixture was refluxed for 1 h; an additional 4 mmol of H_2O_2 was added, and the mixture was refluxed for 2 h. The mixture was analyzed after 1, 2, and 4 h, and the results are reported in Table 13.

The same procedure was utilized with other ethers, and the results are summarized in Table 13.

Bromination of Alkylbenzenes. Five millimoles of alkylbenzene, dissolved in 15 mL of a CH_2Cl_2/H_2O mixture containing the other reagents in the ratios reported in Tables 14 and 15, were refluxed for 4 h. The CH_2Cl_2 solution was separated from the aqueous phase and directly analyzed by GC and GC-MS, by using *p*-chlorobenzyl bromide as internal standard (with *p*-chlorotoluene the internal standard was *o*-chlorobenzyl bromide) and authentic samples of the benzyl bromides for the characterization. With substrates deactivated by the presence of $-NO_2$, $-CN$, and $-COOR$ groups, H_2O_2 was slowly added to the reacting mixture.

In competitive bromination of equimolar amounts of *o*-nitrotoluene and toluene, only the latter is substantially brominated. With cumene, only 5% of cumyl bromide was formed; the main reaction products were α-methylstyrene (72%) and a 1:1 mixture of *cis*- and *trans*-α-methyl-*β*-bromostyrenes (21%). The products were characterized by comparison (GC-MS) with authentic samples.

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