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Efficient and convenient oxidation of organic halides to carbonyl compounds by H_2O_2 in ethanol

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Abstract—Various primary and secondary organic bromides were oxidized by hydrogen peroxide in refluxing ethanol to give the corresponding aldehydes/and ketones in high yield up to 94%; organic chlorides were oxidized to the corresponding aldehydes/and ketones by the same oxidant in ethanol in the presence of 10 mol % of KBr as the catalyst.

The oxidation of organic halides to the corresponding carbonyl compounds is a well known transformation in organic synthesis. In many cases, it affords more convenient access to the carbonyl compounds than the oxidation of the corresponding alcohols.

The oldest method for such a conversion constitutes the Hass–Bender reaction,[1] which involves O-alkylation of the nitronate anion followed by decomposition of the resulting intermediate. This method is only satisfied for *para*-substituted substrates. Sommelet reaction[2] is another classic method for this transformation. The reaction of the halides with hexamethylenetetramine gives the formaldehyde imine of the corresponding primary amine, which tautomerized into the methyl imine of the desired carbonyl compound. But benzaldehydes with electron-deficient or *ortho*-substituted rings are not satisfied.

Various reagents have been developed for this transformation in the ensuing decades. The Kröhnke[3] reaction and the Kornblum[4–6] reaction are the two most notable methods. Kröhnke reaction involves converting the halide to the pyridinium salt with *p*-*N*,*N*-dimethylnitroso-aniline to give a nitrone, which is hydrolyzed in aqueous acid to the carbonyl compounds. The Kornblum reaction is refluxing organic halide in DMSO along with sodium bicarbonate. A high reaction temperature is often required in both methods. Other notable methods to accomplish this conversion include the use of various amine N-oxide,[7–10] *N*-alkoxypyridinium salt,[11–14] $NaIO_4$–DMF,[15] selenium compounds,[16] oxodiperoxovanadate,[17] and IBX.[18] Masaki and co-workers[19] have reported the photo-oxidation of aryl bromides with mesoporous silica FSM-16, which uses oxygen as the oxidant. Selenium compounds are harmful to the environment, and the method of amine N-oxide is not conveniently enough. In this Letter, we report an efficient and convenient method for the oxidation of organic halides to the carbonyl compounds, wherein H_2O_2 in ethanol was used as the oxidant. The reaction proceeded well for various substituted benzylic halides affording high yields of aldehydes/or ketones (Table 1).

It was found that benzyl bromide could be oxidized to benzaldehyde by hydrogen peroxide in ethanol at reflux in 3 h.[20] In other solvents such as tetrahydrofuran, chloroform, and methylene chloride, much longer time was required and the conversion was poorer. The scope of this transformation was then investigated and the results are listed in Table 1.

Under the same conditions, various substituted benzylic bromides including 2-bromomethyl-naphthalene were readily oxidized to the corresponding aldehydes in high yields in a few hours (entries 1–7), whilst a strong electron-withdrawing nitro group at the *para*-position resulted in lower conversion, 70% of the starting material was recovered after 24 h (entry 8). Under the

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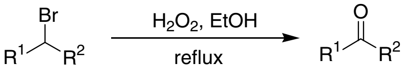
Table 1. Oxidation of primary and secondary organic bromides by H_2O_2 in ethanol[a]



Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	$PhCH_2Br$	PhCHO	3	89
2	4-Cl–$C_6H_4CH_2Br$	4-Cl–C_6H_4CHO	3.5	90
3	2-Cl–$C_6H_4CH_2Br$	2-Cl–C_6H_4CHO	3.5	93
4	4-CH_3–$C_6H_4CH_2Br$	4-CH_3–C_6H_4CHO	3	76
5	3,5-$(CH_3)_2$–$C_6H_4CH_2Br$	3,5-$(CH_3)_2$–C_6H_4CHO	6	85
6	3-Cl–$C_6H_4CH_2Br$	3-Cl–C_6H_4CHO	10	80
7	2-Naph–CH_2Br	2-Naph–CHO	3	83
8	4-NO_2–$C_6H_4CH_2Br$	4-NO_2–C_6H_4CHO	24	20[c]
9	$PhCHBrCH_3$	$PhCOCH_3$	1	91
10	Ph_2CHBr	Ph_2CO	0.5	94
11	4-F–$C_6H_4CHBrCH_3$	4-F–$C_6H_4COCH_3$	2	85
12	4-Br–$C_6H_4CHBrPh$	4-Br–C_6H_4COPh	2.5	86
13	$CH_3(CH_2)_3CH_2Br$	—	24	nd

[a] General reaction conditions: bromide (2 mmol), H_2O_2 (30%, 2 mL), ethanol (15 mL), reflux.

[b] Isolated yield.

[c] 70% of starting material was recovered.

reaction conditions (refluxing in ethanol), further oxidation of benzaldehyde to benzoic acid was not observed. However, on exposure to air, oxidation of benzaldehyde to benzoic acid occurred.

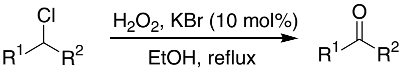
Secondary bromides such as (1-bromoethyl)benzene (entry 9), benzhydryl bromide (entry 10), 1-(1-bromoethyl)-4-fluorobenzene (entry 11), and 1-bromo-4-(bromo-(phenyl)-methyl)benzene (entry 12) were readily oxidized to the corresponding ketones in high yields. The reaction rate of secondary bromide was obviously faster than that of primary bromide.

Alkyl bromide such as *n*-pentyl bromide (entry 13) was found inert to this reaction, no product was detected.

When these reaction conditions were applied to benzyl chloride, no desired product was obtained. Since the conversion of benzylic or allylic chloride to the corresponding bromide by KBr occurs readily, addition of catalytic amount of KBr may be helpful to this reaction. Indeed, in the presence of 10 mol % of KBr, benzyl chloride could be oxidized to benzaldehyde by H_2O_2 in refluxing ethanol. Similarly, conversion of a series of benzylic chlorides to the corresponding aldehydes/ketones was achieved using KBr as the catalyst[21] (Table 2).

A plausible mechanistic pathway for the oxidation of bromides, similar to that of alcohol, proposed by Sain and co-workers,[22] is shown in Scheme 1. Hydrolysis of starting material **1** yielded the corresponding alcohol **2**, which was then oxidized to hypobromite **3** by the hypobromous acid, formed in situ by the reaction of hydrobromic acid with hydrogen peroxide. This hypobromite species, on abstraction of hydrogen, provided the final product, with regeneration of HBr. In the oxidation of organic chlorides, addition of catalytic amount of KBr was desired, to produce the actual oxidizing agent, hypobromous acid. It looks likely that the hydrolysis of the organic halide is the rate-determining step.

Table 2. KBr catalyzed oxidation of organic chlorides by H_2O_2 in ethanol[a]



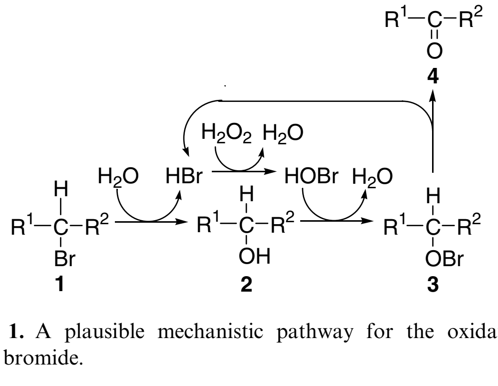
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	$PhCH_2Cl$	PhCHO	3.5	82
2	4-Br–C_6H_4–CH_2Cl	4-Br–C_6H_4–CHO	24	70
3	4-Cl–C_6H_4–CH_2Cl	4-Cl–C_6H_4–CHO	4	90
4	Ph_2CHCl	Ph_2CO	1	90
5	$PhCHClCH_3$	$PhCOCH_3$	1.5	82
6	4-F–C_6H_4–$CHClCH_3$	4-F–C_6H_4–$COCH_3$	2.5	83
7	4-Br–C_6H_4–CHClPh	4-Br–C_6H_4–COPh	2.5	88

[a] General reaction conditions: chloride (2 mmol), KBr (0.2 mmol), H_2O_2 (30%, 2 mL), ethanol (15 mL), reflux.

[b] Isolated yield.

Secondary halides hydrolyzed faster than primary ones, so that they were oxidized faster.

In conclusion, we have discovered an efficient and convenient method for the transformation of organic halides to carbonyl compounds, though it is not satisfied for aliphatic bromides. It provides an easy way to



Scheme 1. A plausible mechanistic pathway for the oxidation of organic bromide.

prepare substituted benzaldehydes. Employment of clean oxidant H_2O_2 together with nontoxic solvent ethanol makes it friendly to the environment.

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20. *General procedure for the oxidation of organic bromides to carbonyl compounds using benzyl bromide as an example*: Benzyl bromide (340 g, 2.0 mmol) was taken in a round bottom flask along with hydrogen peroxide (30%, 2 mL). The above mixture was dissolved in 15 mL of ethanol and the mixture was heated at reflux. The progress of the reaction was monitored by thin layer chromatography. The reaction was completed in 3 h. The ethanol was removed under reduced pressure and the residue was treated with 20 mL of water and then extracted with ethyl acetate (2 × 30 mL). The combined ester layers were dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed to give the desired product.
21. *General procedure for the oxidation of organic chlorides to carbonyl compounds*: To a round bottom flask was added benzyl chloride (250 mg, 2.0 mmol), KBr (24 mg, 0.2 mmol), and hydrogen peroxide (30%, 2 mL) in 15 mL ethanol. The mixture was refluxed for the time given in Table 2 and worked up as described for the oxidation of organic bromides.
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