A New and Efficient Transition Metal-Free Oxidation of Secondary Alcohols to Ketones Using Aqueous HBr and H_2O_2

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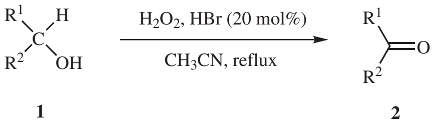
Received 24 August 2004

Abstract: Aqueous HBr/H_2O_2 was found to be an efficient and green system for the oxidation of secondary alcohols in excellent yields under very mild conditions.

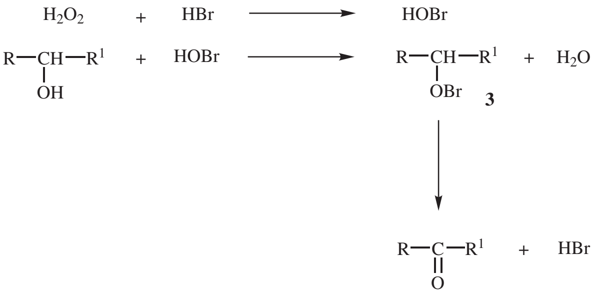
Key words: oxidation, secondary alcohols, ketones

The oxidation of secondary alcohols to carbonyl compounds is an important synthetic transformation[1] and in the recent past emphasis is being given towards the use of environmentally benign oxidants such as molecular oxygen with a view to developing green methodology.[2] In this context aerobic oxidation of secondary alcohols to ketones by using metal catalysts such as hydrated $RuCl_3$,[3] $RuO_2{\cdot}H_2O$,[4] a combination of cobalt and ruthenium,[5] tetrapropylammonium perruthenate,[6] Ru^{+3}-exchanged hydroxyapatite,[7] a ruthenium complex along with Co-salen,[8] Ru-Al-Mg hydrotalcites,[9] Pd (II) hydrotalcite[10] and cobalt complexes with 2-methylpropanal as the sacrificial aldehyde[11] have been reported in the literature. However, these procedures suffer from one or more drawbacks including the use of expensive metal catalysts such as ruthenium and palladium, oxidation of only activated alcohols such as benzylic and allylic alcohols, the need for a sacrificial aldehyde, and severe reaction conditions, for example, high pressure. The development of transition metal-free ecofriendly synthetic transformations is an area of current interest as such methods avoid the use of toxic and expensive metals and their complexes.

In this context, oxidation of secondary alcohols to ketones by using dimethyl sulfoxide, dicyclohexylcarbodiimide and various acids,[12] dimethyl sulfoxide activated with oxalyl chloride,[13] sodium hypochlorite in acetic acid,[14] $NaBrO_3$–NH_4Cl,[15] *N*-chlorosuccinimide with catalytic amounts of *N-tert*-butylbenzenesulfenamide[16] and molecular bromine with catalytic amounts of *N-t*-butyl-2-nitrobenzenesulfenamide[17] have been reported in the literature. A recent report by Neumann et al.[18] on the use of a combination of hydrogen peroxide and hydrohalic acid as a green halogenating agent for arenes inspired us to explore the potential of this transition metal-free system for oxidation of secondary alcohols. In this letter, we wish to report for the first time a new transition metal-free, efficient method for the oxidation of secondary alcohols to carbonyl compounds using aqueous HBr and H_2O_2 as green oxidant system under very mild reaction conditions (Scheme 1 and Scheme 2).



Scheme 1

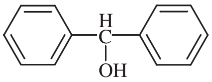
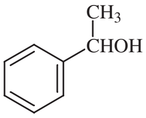
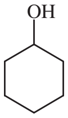
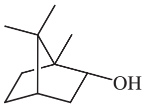
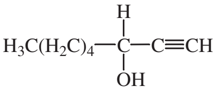
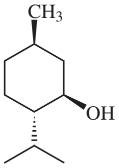
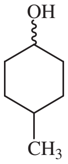
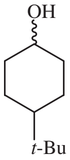
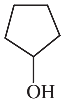
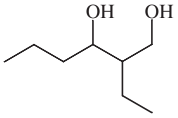
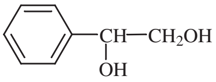
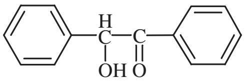
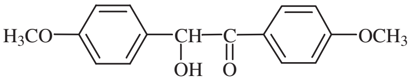
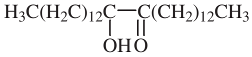
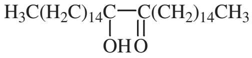


Scheme 2

Treatment of a variety of secondary alcohols both activated and non-activated with a catalytic amount of aqueous HBr (20 mol%) and H_2O_2 (2 mmol) in acetonitrile yielded the corresponding ketones in very good yields.[19] All the alcohols studied were smoothly converted to the corresponding ketones in excellent yields, (see Table 1). Among the various alcohols studied, benzoins were found to be the most reactive and required shorter reaction times for their oxidation (Table 1, entries 12 and 13). Furthermore, aromatic substituted alcohols were found to be more reactive than aliphatic alcohols (Table 1, entries 1 and 2). Oxidation of 2-ethyl-1,3-hexanediol and 1-phenyl-1,2-ethanediol under these conditions yielded corresponding hydroxyl-ketones, 2-ethyl-1-hydroxy-3-hexanone and 2-hydroxy-1-phenylethanone, respectively, in good yields showing the usefulness of this method for the selective oxidation of secondary alcohols in the presence of primary alcohols (Table 1, entries 10 and 11). To evaluate the effect of solvent, aerobic oxidation of benzhydrol was carried out under similar reaction conditions but using different solvents. Among the various solvents such as xylene, acetonitrile, methanol, toluene and 1,2-dichloroethane studied, acetonitrile was found to be the most suitable for this transformation. The oxidation of secondary alcohols to the corresponding ketones was found to be very slow at room temperature and could be carried out more efficiently in refluxing acetonitrile.

SYNLETT 2005, No. 1, pp 0173–0175
Advanced online publication: 29.11.2004
DOI: 10.1055/s-2004-836047; Art ID: D24704ST

Table 1 Oxidation of Secondary Alcohols to Ketones Using H_2O_2/HBr System[a]

Entry	Substrate	Reaction time (h)	Yield (%)
1		0.75	92[20]
2		1.00	90[20]
3		3.00	78[20]
4		5.00	82[21]
5	 $H_3C(H_2C)_4-\overset{H}{\underset{OH}{C}}-C\equiv CH$	5.00	70
6		5.50	65[21]
7		3.50	75[22a,23a]
8		7.00	65[22c,23b]
9		7.00	70[22c,23c]
10		7.50	65[14b]
11		2.5	80[21]
12		0.50	96[20]
13		0.17	97[24]
14	 $H_3C(H_2C)_{12}\underset{OH}{C}-\underset{O}{\overset{\|}{C}}(CH_2)_{12}CH_3$	3.00	85[25]
15	 $H_3C(H_2C)_{14}\underset{OH}{C}-\underset{O}{\overset{\|}{C}}(CH_2)_{14}CH_3$	3.50	75[25]

[a] Reaction conditions: secondary alcohol (1 mmol), 30% H_2O_2 (2 mmol), 48% HBr (20 mol%) in MeCN (5 mL) at reflux temperature under atmospheric pressure.

Although the mechanism of this reaction is not clear at this stage, the reaction probably involves the formation of hypobromous acid by the reaction of aqueous hydrogen peroxide with hydrobromic acid,[18] which then reacts with the secondary alcohol **1** to afford hypobromite species **3** followed by the abstraction of hydrogen to yield the corresponding ketone.

In summary, we have developed a simple oxidation procedure for the selective oxidation of both activated and non-activated secondary alcohols to the corresponding ketones. The simplicity of the system and the versatility of the method towards a range of activated and non-activated alcohols make the HBr/H_2O_2 system an attractive, metal-free, synthetic tool for the oxidation of secondary alcohols to ketones.

Acknowledgment

We are thankful to the Director, IIP for his kind permission to publish these results. Suman L. Jain, Vishal B. Sharma are grateful to CSIR, New Delhi for the award of Research Fellowships.

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(19) **General Experimental Procedure**: To a stirred solution of secondary alcohol (1 mmol) and 30% H_2O_2 (2 mmol) in MeCN (5 mL) was added drop wise aq 48% HBr (20 mol%) and the reaction mixture was refluxed for the time as given in Table 1. The progress of the reaction was monitored by TLC (SiO_2). At the end of reaction the excess H_2O_2 was destroyed by the addition of aq bisulfite followed by the filtration through a small Buchner funnel. After filtration, the reaction mixture was purified by the solvent extraction with CH_2Cl_2 (3 times) and the solvent was evaporated under vacuum. The residue thus obtained was purified by column chromatography on silica gel using EtOAc–hexane (1:4) as eluent. Evaporation of the solvent yielded corresponding ketones. The reaction times and yields of the products are presented in the Table 1. The products were identified by comparing their physical and spectral data with those of authentic compounds reported in literature.

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