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Room-Temperature Oxidation of Secondary Alcohols by Bromate-Bromide Coupling in Acidic Water

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ROOM-TEMPERATURE OXIDATION OF SECONDARY ALCOHOLS BY BROMATE-BROMIDE COUPLING IN ACIDIC WATER

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GRAPHICAL ABSTRACT

$$\stackrel{OH}{R} \stackrel{R'}{\xrightarrow{}} \stackrel{BrOH/H_2O}{RT} \stackrel{O}{R} \stackrel{O}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{}} \stackrel{R'}{\xrightarrow{} \stackrel{R'}{\xrightarrow{}} \stackrel{R'$$

Abstract The use of environmentally benign reactions is currently an important topic in the field of synthetic chemistry. Here we report a high-yielding method to oxidize aliphatic or aromatic secondary alcohols into corresponding ketones using nonhazardous and inexpensive BrOH reagent at room temperature in water. BrOH reagent was derived from NaBr and NaBrO₃ in aqueous acid. Based on the presented results, a mechanism was proposed for this oxidation. The reported method offers a facile, efficient procedure to produce various ketones with a low amount of side products.

Keywords Alcohol oxidation; hypobromous acid; ketone; water

INTRODUCTION

Oxidation of primary or secondary alcohols to corresponding aldehydes or ketones is an important transformation reported in several reviews.^[1] Various reagents have been successfully used for that purpose.^[2]

These days it is important to plan synthetic strategies from an ecological point of view. The possibility of recycling reagents is also an important aspect. The optimum solution to minimize solvent wastes would be a solventless reaction.^[3] The use of environmentally friendly solvents, such as water, is preferable, as well.^[4] Additionally, catalytic reactions contain interesting possibilities for oxidation.^[5]

Recently, iodine-based reagents have been introduced as oxidizing agents with low toxicity, easy availability or handling, and high stability.^[6] Bromine compounds have been used in brominations as ecofriendly and safe reagents.^[7] Bromate has been reported to oxidize secondary alcohols in acidic solution^[8] and with metal catalysts.^[9]

Molecular bromine is a strong oxidant. A drawback of bromine oxidations of secondary alcohols in acidic solution is the formation of brominated by-products.

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Primary alcohols instead produce esters without side products.^[10] It has been proposed that in acidic bromate–bromide oxidation, hypobromous acid and bromine are in equilibrium and that hypobromous acid acts as the oxidizing species.^[11]

Bromate–bromide oxidation has been used to oxidize ethers to esters^[12] and in aqueous organic solvents secondary alcohols to ketones.^[11a,13a] Very recently, bromate has been successfully used to produce α -bromoketones from olefins.^[13b] The reaction was performed in a dioxane–water mixture and it contained bromohydrin as an intermediate, which further reacted with another BrOH equivalent.

In this article, we report a mild and simple method to oxidize various secondary alcohols to ketones at room temperature in plain water by using BrOH as the oxidizing agent. Hypobromous acid was generated from harmless NaBr with NaBrO₃ [Eq. (1)] in aqueous acid.^[13]

$$BrO_3^- + 2Br^- + 3H^+ \rightarrow 3BrOH \tag{1}$$

RESULTS AND DISCUSSION

In connection with our oxidation studies of 2-butanol by using bromide– bromate reagent in dioxane–water or tetrahydrofuran (THF)–water (1:4) mixture, it was noticed that the oxidation could be successfully performed in plain water. The oxidation produced, in addition to 2-butanone, brominated compounds 3-bromo-2-butanone and 1-bromo-2-butanone. To support the formation of 2-butanone, and simultaneously avoid the formation of undesired bromo compounds, the effect of the amount of BrOH, the addition rate of acid and the total reaction time on the product distribution was studied.

During the experiments it was noticed that the increased concentration of BrOH accelerated the oxidation of 2-butanol, but simultaneously increased the amount of bromo compounds. The addition rate of the acid affected the product distribution. A slow addition kept the oxidation rate low and decreased the formation of bromo compounds. The dilution of the concentration of BrOH reagent did not significantly affect the reaction rate and the additional advantage was that only trace amounts of brominated products formed.

It was concluded that optimum reaction conditions in water required 1.05 equiv. (0.21 mol/L) of active BrOH as prepared from bromide-bromate solution (2:1, respectively) with 10% H₂SO₄. The acid should be added slowly over the course of at least 2 h. These reaction parameters were applied to oxidations of various secondary alcohols, and their results are presented in Table 1.

The reaction time of the oxidations mainly varied between 2 h 15 min and 6 h. Electron-donating groups in the vicinity of the hydroxyl group shortened the oxidation time (Table 1, entries 3–5 vs. entry 1). Benzylic alcohols oxidized concurrently with the addition of the acid (Table 1, entries 7–10). An electron-withdrawing group next to the hydroxyl group (Table 1, entry 11) decreased the reaction rate remarkably, and the diol (Table 1, entry 12) did not react at all. Experiments with primary alcohols showed that they oxidized to esters as reported in the literature.^[11]

Results in Table 1 show that an electronic effect affects these oxidations. They indicate that the slow step of the reaction includes the generation of the positive

	Reaction products (%			Producto (/0)	Yield ^a	Purity
Entry	Time (h)	Alcohol (%)	Product	Side products	(%)	(%)
1 ^{<i>b</i>}	6	он Trace	≥99	O Br Trace	49	96
2 ^{<i>b</i>}	2.25	OH 	<u>۹6</u>	3 Br Br Br Br Br Br Br Br	90	96
3 ^{<i>b</i>}	4	OH K 8	91	O Br 1	71	92
4 ^{<i>b</i>}	3	OH —	97	Br	65	97
5 ^b	3.5	он 5	90 90	Br 5	52	92
6 ^{<i>c</i>}	4	ОН 16	69 69	Br 15		_
7	2.25	OH —	0 100		100	100
8	2.25	OH —	≥99	Br Br Br	>99	>99
9	2.25	OH		$\begin{array}{c} \begin{array}{c} & & \\ & & \\ & & \\ \end{array} \end{array} \xrightarrow{\begin{array}{c} \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{array}} \xrightarrow{\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	95	95

Table 1. Oxidation of secondary alcohols (0.2 mol/L) in water at room temperature using 1.05 equiv. of BrOH reagent

(Continued)

	Time (h)	Alcohol (%)	Reaction products (%)		X7: 1 10	D
Entry			Product	Side products	- Y teld" (%)	Purity (%)
10	2.25	CI CI	ci		87	100
11 ^b	48	Br H	Br	Several minor products	_	_
12	24	но	No reaction			

Table 1. Continued

^aYield of isolated, properly characterized (¹H NMR, ¹³C NMR, MS) product.

^{*b*}Yield of the pure ketone was determined from the ¹H NMR spectrum of a mixture that contained CH_2Cl_2 based on the ratio of the integral of CH_2Cl_2 singlet (δ : 5.284 ppm) and $COCH_3$ singlet or $COCH_2$ quartet of the ketone.

^cOnly GC-MS analysis of the product mixture.

charge. Patil et al. has proposed that a reaction of alkene to α -bromoketone by using BrOH reagent happens via a bromohydrin intermediate.^[13b] Kajigaeshi et al. believe that the oxidizing species in their ketone- and ester-producing oxidations was molecular bromine or BrOH.^[11a] Farcas et al. has reported that in the oxidation of primary alcohols with bromine the formation of hypobromite ester (R-OBr) is the slow step.^[10a] However, Ogata et al. has pointed out that in the reaction mixture hypobromite ester and alcohol are in equilibrium.^[11b]

Based on these studies and our results in Table 1, we concluded that the oxidizing species Br^+ ion can be generated either from BrOH or Br_2 by the release of H_2O or HBr. It is believed, that H^- attacked Br^+ , resulting in a release of HBr in a slow step leading to the development of a partial positive charge on the carbonyl carbon (Scheme 1).

In Scheme 1, according to mechanism 1, the release of HBr in the slow step would generate the partial positive charge on carbonyl carbon although the adjacent



Scheme 1. Two alternative mechanisms for the oxidation of secondary alcohol by using BrOH reagent. The supposed slow step is marked with ‡ .

oxygen atom carries a positive charge. The slow step of mechanism 2 (Scheme 1) induces a rational charge distribution consistent with the results of Table 1. We believe that the reaction follows this mechanism. As a small species, Br^+ ion does not suffer any steric hindrance in this oxidation.

CONCLUSIONS

This study demonstrates that NaBr-NaBrO₃ salt mixture in acidic conditions can be used as a readily available, nontoxic, and low-cost oxidation system at room temperature in plain water. It provides an efficient, mild, and convenient method for the oxidation of aliphatic or benzylic secondary alcohols without any organic solvent.

The optimum oxidation conditions required 1.05 equiv. of active BrOH as dilute aqueous solution prepared from bromide–bromate mixture (2:1, respectively) with 10% H₂SO₄. It was essential for the clean room-temperature oxidation that the acid was slowly added over the course of at least 2 h. This, with the dilute reaction mixture, kept the amount of the oxidizing species low and thus reduced the possibility of side reactions.

With benzylic alcohols the isolated yields of corresponding ketones were good (87–100%) and with aliphatic alcohols were moderate to good (49–90%). Poor yields were obtained with highly evaporative ketones. Commonly, the purity of the products was good without further purification.

In summary, this study offers improvements in terms of simplicity, benign procedure, mild reaction conditions, commercially available reagents, and good yield of an isolated product with a small amount of side products. The method avoids the use of hazardous organic solvents and toxic metal catalysts and thus provides a clean and practical alternative to existing procedures.

EXPERIMENTAL

Materials and Product Analysis

All commercially available reagents (Aldrich, TCI, RdH) were used as purchased. Bromohydrin (entry 11, Table 1) was prepared from octene.^[14] ¹H and ¹³C NMR spectra were recorded on a Bruker DPX 200 spectrometer and are reported in parts per million (ppm) from tetramethylsilane (TMS) or solvent residue (CDCl₃, $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm) as an internal standard. Gas chromatograms were recorded on a Perkin-Elmer Auto System XL by using an OV-1 column equipped with a FI detector. Electron-impact (EI) mass spectra (GC-MS) were recorded at 70 eV ionization energies using a HP 5973 mass spectrometer and a HP 6890 series GC system with a DB-624 column. High-resolution mass spectra (ESI-MS) were recorded in positive mode on a Micromass LCT-TOF mass spectrometer. The purity of the products was determined by ¹H NMR and GC.

General Procedure for Oxidation of Secondary Alcohols

Alcohol (10 mmol), distilled water (40 mL), and aqueous solution (5 mL) containing a 2:1 molar ratio of NaBr (0.72 g, 7 mmol) and NaBrO₃ (0.528 g, 3.5 mmol) reagent were placed in a round-bottomed flask. The reaction mixture was stirred at room temperature, and 10% H₂SO₄ (5 mL, 5.25 mmol) was added within 135 min. The reaction was followed by GC-MS and was stopped by adding ca. 10 drops of saturated aqueous Na₂S₂O₃ solution. The aqueous solution was extracted with 3×50 mL CH₂Cl₂. The combined organic layers were washed with brine and dried with MgSO₄.

Spectral Data

All oxidation products are known compounds, and their recorded ¹H and ¹³C NMR as well HRMS [with <100 g/mol compounds MS(EI)] data were in good agreement with the values reported in the literature.

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