Direct Conversion of Bromohydrins to Ketones by a Free Radical Elimination of Hydrogen Bromide[1]

Darko Dolenc* and Maja Harej[†]

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia

darko.dolenc@uni-lj.si

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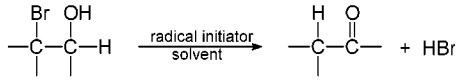
Abstract: Secondary β-bromo alcohols can be transformed directly to ketones in very good yields by a free radical process. Tertiary β-bromo alcohols do not react while the primary ones are transformed to aldehydes in lower yields. The reaction involves an abstraction of a hydrogen atom α to an OH group, followed by elimination of the bromine atom and subsequent tautomerization of an enol to a ketone.

Few procedures for direct transformation of halohydrins to carbonyl compounds have appeared in the literature. Most of them are based on reactions of halohydrins with bases and/or acids[2] or transition metal catalysts.[3] More recently, a photochemical transformation of bromohydrins to ketones in benzene or toluene was reported.[4] In our study of reactions of organic halogen compounds with radicals,[5] we have observed that bromohydrins eliminate hydrogen bromide in a free radical process, yielding ketones (Scheme 1).

Heating a mixture of *trans* 2-bromocyclohexanol and di-*tert*-butyl peroxyoxalate (DBPO)[6] in cyclohexane at 60−80 °C for a few minutes resulted in the formation of cyclohexanone in quantitative yield (see Table 1). White fumes of hydrogen bromide were also observed over the reaction mixture. Other secondary β-bromo alcohols reacted likewise. On the contrary, chloro and iodo analogues reacted differently. Under the same reaction conditions, *trans* 2-chlorocyclohexanol remained almost unreacted, yielding only trace amounts of cyclohexanol. The reaction of *trans* 2-iodocyclohexanol resulted mainly in deiodination, thus leading to the formation of cyclohexanol, accompanied by a small amount of cyclohexanone.

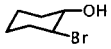
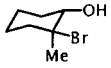
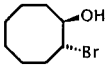
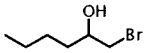
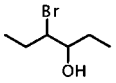
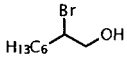
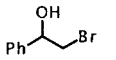
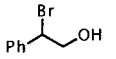
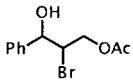
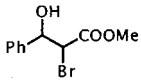
Tertiary β-bromo alcohols did not react at all; however, with primary bromohydrins, aldehydes were formed in relatively low amounts, probably due to further reactions. A pure aliphatic bromohydrin, 2-bromooctan-1-ol, yielded 61% of aldehyde, while 2-bromo-2-phenylethanol only gave tarry products.

Scheme 1



1a–10a **1b–10b**

Table 1. Reactions of Bromohydrins and DBPO in Cyclohexane[a]

Halohydrin		Product	Yield %[b]
	**1a**	**1b**	100 (89)[c]
	**2a**	**2b**	84
	**3a**	**3b**	93
	**4a**	**4b**	100
	**5a**	**5b**	93
	**6a**	**6b**	61
	**7a**	**7b**	89
	**8a**		0[d]
	**9a**	**9b**	80
	**10a**	**10b**	38[e]

[a] 0.2 mmol of halohydrin and 0.06 mmol of DBPO in 2 mL of cyclohexane, 60 °C to reflux, 10 min. [b] Determined by GC. [c] Isolated yield on 2 mmol scale. [d] Polymer. [e] 55% of acetophenone was also formed.

Elimination appeared to be severely affected by the solvent. The highest conversions and yields of ketones were obtained in cyclohexane and benzene. Conversions were significantly lower in other solvents (acetone, acetonitrile, AcOH); in those which are good hydrogen atom donors (EtOH, toluene, THF), the reaction did not take place at all.

The reaction seems to be initiated by the abstraction of the α-hydrogen atom from a halo alcohol by an electrophilic radical, which yields a stabilized α-hydroxy-

[†] Undergraduate student.

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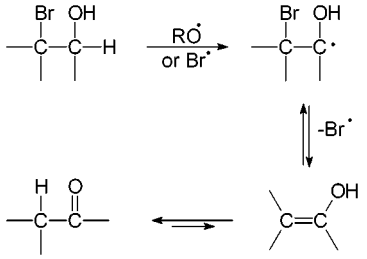
Scheme 2. Proposed Mechanism of Hydrogen Bromide Elimination from Bromohydrins



alkyl radical that in turn eliminates a β-halogen atom, thus forming a double bond (Scheme 2).

This process is feasible only in the case of bromohydrins since the enthalpy of a π-bond formation is comparable with C−Br bond dissociation energy.[7] In chlorohydrins, the C−Cl bond is considerably stronger, causing the elimination of a chlorine atom to be unfavorable. In iodohydrins, a competing abstraction of iodine atom predominates, at least in solvent cyclohexane, where nucleophilic cyclohexyl radicals are present.

The nature of the hydrogen abstracting radical is obviously electrophilic, in this case *tert*-butoxy radical or bromine atom. A Hammett plot for the elimination of HBr from substituted 1-aryl-2-bromoethanols (3-trifluoromethyl, H and 4-methyl) shows a linear correlation with $\rho = -1.0$, which is comparable to, for example, bromination of toluene.[8] Moreover, a nucleophilic alkyl radical would most probably abstract a halogen atom rather than an α-hydrogen.

In certain cases we have observed a minor side reaction, namely the formation of a 2-bromoketone, which could be formed by the abstraction of a hydroxyl hydrogen atom from α-hydroxyalkyl radical by a bimolecular radical process and could therefore be suppressed by working at lower temperature. The most efficient procedure was found to be the warming of the reaction mixture in a water bath starting at 50−60 °C to reflux (of cyclohexane) during 15 min. In preparative runs or in cases of acid sensitive compounds, the reaction mixture was continuously purged with inert gas during the course of reaction.

The most suitable radical initiator proved to be di-*tert*-butyl peroxyoxalate, since it is a clean source of alkoxyl radicals. Initiation with dibenzoyl peroxide led to the formation of a complex mixture. The amount of initiator necessary for complete conversion is variable, but in most cases 10−20 mol % (based on the starting bromohydrin) is adequate.

The reaction may suggest a new efficient way for conversion of bromohydrins or, indirectly, even alkenes to ketones and is also successful with acid or base sensitive compounds, such as esters.

Experimental Section

General. Bromohydrins **4a**, **5a**, **7a**, **9a**, and **10a** were synthesized from alkenes and NBS or, preferably, *N*-bromosaccharin[9] in aqueous acetonitrile or DMSO[10] or by the reaction of corresponding epoxides with 48% HBr in diethyl ether (compounds **1a**−**3a**, **6a**, and **8a**).[11] 2-Chloro- and 2-iodocyclohexanol were prepared from cyclohexene oxide and the corresponding acid. Spectral and/or other data for halohydrins are reported elsewhere.[10,12−17]

2-Bromo-3-hydroxy-3-phenylpropyl Acetate (9a). A total of 2.0 mmol of (*E*)-3-phenylprop-2-en-1-yl acetate was added dropwise to the stirred solution of *N*-bromosaccharin (2.0 mmol) in 4 mL of acetonitrile−water mixture (3:1 v/v). The reaction mixture was stirred at room temperature for 1 h, diluted with diethyl ether, washed with sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by chromatography (silica gel, CH_2Cl_2) to afford 151 mg (55%) of 2-bromo-3-hydroxy-3-phenylpropyl acetate as a white solid which was recrystallized from CH_2Cl_2/hexane, mp 45−46 °C. The crystallized compound contains one molecule of water, otherwise it is an oil. ^{1}H NMR ($CDCl_3$, δ/ppm): 2.02 (s, 3H), 4.33 (dd, J = 11.5, 4.1 Hz, 1H), 4.44 (m, 1H), 4.52 (dd, J = 11.5, 6.6 Hz, 1H), 5.01 (d, J = 6.1 Hz, 1H), 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, δ/ppm): 20.6, 55.5, 64.2 74.9, 126.4, 128.3, 128.5, 139.5, 170.8. MS (EI): 274 (M^+ + 2, 0.8), 272 (M^+, 0.8), 193 (5), 149 (10), 133 (62), 107 (100), 105 (63), 91 (17), 79 (45), 77 (32). Anal. Calcd for $C_{11}H_{13}BrO_3 \cdot xH_2O$: C, 45.38; H, 5.19. Found: C, 45.29; H 5.43.

1-(3-Trifluoromethylphenyl)-2-bromoethanol. Oil (57%). ^{1}H NMR ($CDCl_3$, δ/ppm): 3.53 (dd, J = 10.6, 8.7 Hz, 1H), 3.66 (dd, J = 10.6, 3.4 Hz, 1H) 5.00 (dm, J = 8.5 Hz, 1H) 7.48−7.68 ppm (m, 4H). ^{13}C NMR ($CDCl_3$, δ/ppm): 39.7, 73.1, 122.9, 124.0 (q, J = 272 Hz), 125.2, 129.2, 129.4, 131.1 (q, J = 32 Hz), 141.5. ^{19}F NMR ($CDCl_3$, δ/ppm ($CFCl_3$)): −63.2 (s). MS (EI): 270 (M^+ + 2, 0.2), 268 (M^+, 0.2), 175 (100), 159 (8), 145 (16), 127 (50). Anal. Calcd for $C_9H_8BrF_3O$: C, 40.18; H, 3.00. Found: C, 39.90; H, 2.89.

Products were identified by NMR and/or GC-MS and data were compared with those of authentic materials or literature.

Eliminations: General Procedure. A total of 0.2 mmol of bromohydrin and 0.03 mmol of DBPO were dissolved in 2 mL of cyclohexane and placed in a flask, fitted with a reflux condenser. The solution was purged with argon and warmed in a water bath gradually from about 50 °C to reflux, during 15 min, and left at reflux for additional 10 min. The composition of the reaction mixture was then analized by GC. In preparative runs (2 mmol of bromohydrin, 0.3 mmol of DBPO in 5 mL of cyclohexane) the reaction mixtures were diluted with ether, washed with sodium hydrogen carbonate and water, and dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure.

Relative Rates of Elimination of HBr from Substituted 1-Phenyl-2-bromoethanols. A solution of substituted 2-bromo-1-phenylethanol (4-CH_3, 3-CF_3, 0.2 mmol), 2-bromo-1-phenylethanol (0.2 mmol), and DBPO (0.01 mmol) in 2 mL of cyclohexane was purged with argon, warmed as described above, and analyzed by GC. The relative rates k_X/k_H were calculated using the integrated rate equation $k_X/k_H = \ln(A/A_o)/\ln(B/B_o)$, where A is the amount of substituted bromohydrin and B is the amount of unsubstituted bromohydrin at the end of the reaction. A_o and B_o are the amounts of bromohydrins at the begining of the reaction. The measurement was made as a one-point kinetic determination and the values thus obtained are: k(4-Me)/k(H) = 1.52 and k(3-CF_3)/k(H) = 0.38.

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