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

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

Received September 13, 2001

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 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 or transition metal catalysts. More recently, a photochemical transformation of bromohydrins to ketones in benzene or toluene was reported. In our study of reactions of organic halogen compounds with radicals, 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 peroxoyxalate (DBPO) 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.

Table 1. Reactions of Bromohydrins and DBPO in Cyclohexane

<table>
<thead>
<tr>
<th>Halohydrin</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1b</td>
<td>100 (89)</td>
</tr>
<tr>
<td>2a</td>
<td>2b</td>
<td>84</td>
</tr>
<tr>
<td>3a</td>
<td>3b</td>
<td>93</td>
</tr>
<tr>
<td>4a</td>
<td>4b</td>
<td>100</td>
</tr>
<tr>
<td>5a</td>
<td>5b</td>
<td>93</td>
</tr>
<tr>
<td>6a</td>
<td>6b</td>
<td>61</td>
</tr>
<tr>
<td>7a</td>
<td>7b</td>
<td>89</td>
</tr>
<tr>
<td>8a</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9a</td>
<td>9b</td>
<td>80</td>
</tr>
<tr>
<td>10a</td>
<td>10b</td>
<td>38</td>
</tr>
</tbody>
</table>

* 0.2 mmol of halohydrin and 0.06 mmol of DBPO in 2 mL of cyclohexane, 60 °C to reflux, 10 min. ‡ Determined by GC. † Isolated yield on 2 mmol scale. ‡ Polymer. † 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-
alkyl radical that in turn eliminates a \( \beta \)-halogen atom, thus forming a double bond (Scheme 2).

This process is feasible only in the case of bromohydrins since the enthalpy of a \( \alpha \)-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 \( \alpha \)-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 hydroxy hydrogen atom from \( \alpha \)-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 peroxoxyxalate, 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 \( \text{E}-\)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 \( \nu / \nu \)). 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\(_2\)Cl\(_2\)/hexane) to afford 151.9 mg (35%) of 2-bromo-3-hydroxy-3-phenylpropyl acetate as a white solid which was recrystallized from CH\(_2\)Cl\(_2\)/hexane, mp 45–46 °C. The crystallized compound contains one molecule of water, otherwise it is an oil. \( ^{1} \)H NMR (CDCl\(_3\), 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 (dd, \( J = 6.1 \) Hz, 1H), 7.35 (m, 5H). \(^{13}\)C NMR (CDCl\(_3\), ppm): 20.6, 55.5, 64.2 74.9, 126.4, 128.3, 128.5, 139.5, 170.8. MS (EI): 274 (M\(^+\)).

**Notes**


**Relative Rates of Elimination of HBr from Substituted 1-Phenyl-2-bromoethanols.** A solution of substituted 2-bromo-1-phenylethanol (4-CH\(_3\), 3-CH\(_3\)F, 0.2 mmol), 2-bromo-1-phenylethanol (0.2 mmol), and DBPO (0.01 mmol) in 2 mL of cyclohexane were warmed at 50 °C and left at reflux for additional 10 min. The composition of the reaction mixture was then analyzed 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.

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