Oxidative β-Halogenation of Alcohols: A Concise and Diastereoselective Approach to Halohydrins

Lingsheng Ai*, Weijin Wang*, Jialiang Wei*, Qing Li*, Song Song* a,b, Ning Jiao* a,b  

a State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, P. R. of China  
ssong@bjmu.edu.cn  
jiaoning@pku.edu.cn  
b State Key Laboratory of Drug Research Shanghai Institute of Materia Medical Chinese Academy of Sciences, Shanghai 201203, P. R. of China  

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Abstract β-Halohydrins bearing transformable halo- and hydroxyl groups, are easily converted into various valuable blocks in organic and pharmaceutical synthesis. A diastereoselective β-halogenation of benzyl alcohols was achieved under simple and low-cost conditions, which provided a direct synthesis of β-halohydrins. The simple reaction conditions, easily available reagents, high diastereoselectivities, and additional oxidant-free make this reaction very attractive and practical.

Key words halogenation, alcohols, dimethyl sulfoxide, halohydrins, oxidation

Organohalides are one of the most widespread and important chemicals and are present in more than 4500 natural products,1 as well as a great number of industrially valuable products such as pharmaceuticals, fire retardants, agrichemicals, and some new materials.2 In addition, it is no doubt that organohalides with their general reactivity make the chemical synthesis more simple, accessible, and valuable. β-Halohydrins, bearing a hydroxyl and halide functional group, are privileged building blocks in organic synthesis and could be conveniently converted into other significant organic intermediates such as azido alcohols, amino alcohols, and epoxides, all of which are widely used in the synthesis of many highly value-added chemicals.3 Up to date, halohydrins could be prepared by halohydroxylation of olefins,4 reduction of haloketones,5 ring-opening reaction of epoxides,6 and nucleophilic substitution of benzyl halides7 (Scheme 1, A). In most cases, the halo atom of halohydrins was introduced by the halo cation such as N-halosuccinimides and their analogues which are not good choices for large-scale halogenations because of expensive price and low atomic economy. Inspired by the enzyme-catalyzed aerobic oxidative halogenation in nature,8 a sophisticated approach by in situ generating the halogenating reagent from oxidant and halide salts is widely applied in halogenations9,10 especially in the oxidative halohydroxylation of olefins which provided a direct approach to halohydrins,10 although solvent, halide source, acid, oxygen source, and oxidant were required in these approaches.

Scheme 1 The synthesis of halohydrins
The β-halogenation of alcohols provides another direct approach to halohydrins. However, the reported β-halogenation of alcohols with halo cations always delivered mixtures of products (Scheme 1, B). As our continuous development of DMSO-based reactions, we herein reported our success in β-halogenation of alcohols with in situ generation of halo cation from sodium halides and DMSO (Scheme 1, C). The magic multiple role of DMSO as solvents, oxidant, stabilizer of halo cations, and nucleophile successfully enabled this novel transformation. Very importantly and interestingly, the diastereoselectivities of this transformation were very high (>25:1).

This reaction began with an unexpected bromination. As reported, the combination of aqueous HBr and DMSO showed high efficiency in the aromatic bromination of 2-naphthol to deliver aryl bromide in 79% yield (Scheme 2, eq 1). To our surprise, when changing the substituent of naphthalene from –OH to –CH(OH)CH₃, the aromatic bromination was totally suppressed, and aliphatic bromination at the methyl group occurred to afford bromohydrin in 33% yield (Scheme 2, eq 2). Due to the importance of the halohydrins, this bromination drew our great interest.

We then investigated the substrate scope of this novel bromination (Scheme 3). Various benzylic alcohols worked well under the standard conditions. It was noteworthy that when an electron-donating group such as methoxy, tert-butyl, or methyl was contained at the aryl ring, the corresponding bromohydrins were highly selectively obtained in good yields, respectively. The reported bromination on the electron-rich arenes was not detected in this protocol. In addition, heteroarenes such as benzothiophene and benzofuran-1-substituted alcohols were well tolerated in this transformation and converted into bromohydrins in moderate yields. Furthermore, the gram-scale reaction of 3a with 69% yield shows the potential application of this low-cost protocol. However, no bromohydrin was detected when alcohols without benzylic substituent were exposed under the standard conditions.

It is very challenging to control the diastereoselectivity of β-functionalization of alcohols. To our delight, the six-membered cyclic alcohols produced trans-bromohydrins as the sole product in high efficiency (Scheme 4). Although the five-membered and seven-membered cyclic alcohols afforded the target bromohydrins in moderate yields, the diastereoselectivities of these brominations were also very high (>25:1). The substituents on the phenyl ring had little influence on the efficiency and diastereoselectivity.

### Table 1 Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Br] (equiv)</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)b</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>KBr (2)</td>
<td>–</td>
<td>DMSO</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>KBr (2)</td>
<td>H₂SO₄ (2)</td>
<td>DMSO</td>
<td>60</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>NaBr (2)</td>
<td>H₂SO₄ (2)</td>
<td>DMSO</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>NaBr (2)</td>
<td>TsOH (2)</td>
<td>DMSO</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>NaBr (2)</td>
<td>MsOH (2)</td>
<td>DMSO</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>NaBr (2)</td>
<td>TFOH (2)</td>
<td>DMSO</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>NaBr (2)</td>
<td>H₂SO₄ (2)</td>
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<td>40</td>
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</tr>
<tr>
<td>8</td>
<td>NaBr (2)</td>
<td>H₂SO₄ (4)</td>
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<td>80</td>
<td>mess</td>
</tr>
<tr>
<td>9</td>
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<td>H₂SO₄ (4)</td>
<td>DMSO</td>
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<td>73</td>
</tr>
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<td>H₂SO₄ (4)</td>
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<td>60</td>
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</tr>
<tr>
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<td>H₂SO₄ (4)</td>
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<td>60</td>
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</tr>
<tr>
<td>13</td>
<td>NaBr (2)</td>
<td>H₂SO₄ (4)</td>
<td>THF</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: The solution of 3a (0.5 mmol), bromide source, and additive in solvent (1 mL) was stirred under air for 24 h.
b Isolated yields.

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We then optimized the bromination conditions (Table 1). The reaction did not work when changing aqueous HBr to KBr (Table 1, entry 1). This experiment revealed the acidic conditions were essential for this reaction. When HBr was generated by KBr and H₂SO₄ in situ, 4a could be obtained in 38% yield (Table 1, entry 2). The yield increased to 44% using NaBr instead of KBr (Table 1, entry 3). Other organic acids such as TsOH, MsOH, or TFOH showed lower efficiency than that of H₂SO₄ (Table 1, entries 3–6). The amount of acidic additive influenced the yield strongly. Compound 4a was obtained in 73% yield when 4 equiv of H₂SO₄ were employed (Table 1, entry 9). When the reaction preformed with 1.2 equiv of NaBr, only 46% yield of 4a was obtained (Table 1, entry 11). Compound 4a was not detected when the reaction was carried out in other solvents (Table 1, entries 12 and 13). These results indicated that DMSO was indispensable in this bromination.
The bromohydrin 4a was conveniently converted into other valuable products (Scheme 6). Azido alcohol 7, the key intermediate of β-blocker pronethalol19a and other bioactive molecules,19b was synthesized in 98% yield by stirring 4a with NaN₃ at 60 °C in DMSO. Exposure of 4a with aqueous NaOH solvent in THF afforded epoxide 8 in 95% yield, which could easily react with amines to produce amino alcohol drugs.19c Amino alcohol 9 also could be synthesized by treating 4a with ammonium hydroxide in MeOH. The reaction of 4a and CO₂ in the presence of NMe₅HCO₃ provided carboxylic ester 10 in 97% yield.

To investigate the mechanism of this bromination, control experiments were performed. Ethyl naphthalene 11 could not be brominated under the standard conditions, indicating the hydroxyl was indispensable for present bromination (Scheme 7, eq 5). Treatment of alcohol 3a under standard conditions in the absence of NaBr afforded alkene 12 in 39% yield (Scheme 7, eq 6). Subjecting the obtained alkene 12 back to the standard conditions led to 4a in 76% yield, which indicated that alkene 12 might be the key intermediate of this transformation (Scheme 7, eq 7).

Previous studies reported that the hydrobromic acids could be oxidized by DMSO to molecular bromine (Scheme 7, eq 8).11 If Br₂ was generated, it would readily react with...
the in situ generated alkene 12 to afford a trans-dibrominated product 13.13d However, exposure of trans-13 under the conditions for 24 h provided the product 4p only in 27% yield and showed much lower diastereoselectivity (trans/cis = 9:1, Scheme 7, eq 9). This experiment demonstrated that the corresponding dibromination was not involved in this process. We therefore suspected that the HBr was oxidized to bromonium (Br+) which was stabilized by DMSO through coordination (Scheme 7, eq 10).10j

On the basis of the above experimental results and previous reports,18,20 we proposed the mechanism of this haloamination by DMSO to give (DMSO)nBr+DMS (n = 1–3).10j The electrophilic addition of Br+ to alkene A delivers the alkoxysulfonium B which quickly decomposes to produce trans-bromohydrin 4u.10j,16a

In conclusion, we have developed a novel β-halogenation of benzylic alcohols for the efficient synthesis of high-value halohydrins. The simple reaction conditions, easily available reagents, and high diastereoselectivity control make this protocol very attractive and practical. Mechanistic studies reveal that halocation (X+) rather than molecular halogen is involved in the transformation. This reaction demonstrates a new application of DMSO and HX in organic synthesis and would promote the application of the alkene in situ generation strategy.

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Supporting Information

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References


