CHAPTER VII

SYNTHESIS OF BROMOHYDRINS USING NBS IN PRESENCE OF IODINE CATALYST
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Synthesis of bromohydrins using NBS in Presence of Iodine Catalyst

7.1. Introduction

To organic chemist, the vicinal functionalization of olefins by addition of water/alcohols and halogens in a highly regio and enantio selective manner appears to be very challenging and significant.\textsuperscript{1-4} Vicinal halohydrins are useful compounds in synthetic organic chemistry.\textsuperscript{5,6} The regioselective conversion of epoxides to halohydrins is a useful tool for regiospecific synthesis of halohydrins. Halohydrins are popularly used in the synthesis of pharmaceuticals, dyes, flame retardants, additives and plasticizers, agrochemicals used specially chemicals.\textsuperscript{8-13} Moreover, in medicinal and industrial chemistries, the important building blocks are halohydrins and alkoxy halides.\textsuperscript{8-13} $\alpha$-Halo-$\beta$-hydroxyderivatives can be readily transformed into epoxides, ketones and unusual $\beta$-hydroxy-$\alpha$-amines acids.\textsuperscript{14-18} But the most general method of preparing vic-halohydrins by ring opening of epoxides with halogen halides suffers from some serious disadvantages such as pharmacologically inactive halohydrins, unwanted byproducts and low regioselectivity.\textsuperscript{19-21} This has facilitated research in different directions starting from elemental halogens,\textsuperscript{22} metal halides such as LiX,\textsuperscript{23,24} TiCl$_4$-LiX,\textsuperscript{25} CeCl$_3$.7H$_2$O-Nal,\textsuperscript{26,27} to chlorosilanes,\textsuperscript{27} haloboranes\textsuperscript{28-30} etc. However these
reagents have disadvantages such as, preparation of reagents, longer reaction time, reflux temperatures, hygroscopic nature of catalysts etc. Elemental halogen, metal halides, hypohalous acids were also utilized as brominating agents. Oxidative halogenation reactions using different metal complexes have also been studied in recent years to understand the biosynthesis of many halogenated marine natural products like terpenes, indoles, phenols etc. in presence of haloperoxidases. Enantiomerically enriched phenyl glycidates, which is the precursors of the taxol C-13 phenylisoserine side chain and diltiazem, have been prepared by the kinetic resolution of anti-2-bromo-3-hydroxy phenylpropanoate. By halogen abstraction reaction, chiral radicals have been generated from β-oxy-α-bromo esters. In the synthesis of epoxides, bromohydrin, derivatives of precocene 1 (7 methoxy-2, 2 dimethyl chromene) is used which is highly reactive metabolites for the boil. On treatment with 1,2,4-triazole, bromohydrin of styrene derivative gives phenyl triazole which is useful fungicide. Different substituted product of benzopyrans is also used for the synthesis of bromohydrin, give the antihypertensive activity when aminated on the substituted pyrrolidine or piperidine. α, β-unsaturated carboxyl compounds and carboxylic acids have also been reported to undergo halohydrin reaction with N-halosuccinimide.

Carboxy halohydrins especially α-halo-β-hydroxycarboxylic acid derivatives are useful synthetic intermediates because of their transformation into important compounds and acts as precursors to many biologically active compounds.
Since bromohydrins acts as an important building block and has large application in organic, medicinal and industrial chemistry, therefore, a new effective method can be introduced for its synthesis.

7.2. Review of Literature:

N-Bromosuccinimide has been used as brominating agent for the synthesis of bromohydrins in moist-dimethyl sulfoxide as reaction medium. In this method the addition of HOBr to olefins, NBS act as source of positive bromine. I₂/H₂O Has also been used for the synthesis of iodohydrins and iodo ethers, especially cyclic ethers, from the corresponding olefins. Henry et al. first reported a palladium-(II)-catalysed enatioselective hydroxychlorination of terminal alkenes with a metal chloride and there is no involvement of halonium intermediate.

Over hazardous molecular halogen, N-halosuccinimide, is better preferred for such transformations, yet this method has the disadvantages such as low yield and longer reaction time. Secondly, with electron deficient alkenes, this protocol does not work well. Using NBS in ionic liquid, Yadav et al. reported a modified procedure for hydrobromination of olefins. The shortcomings of this method is that in some cases bromohydrin formation takes place longer time and ionic liquids are more expansive. The oxidative halogenation methods as a halogen source require a metal salt, an oxidizing agent and a catalyst to perform the transformations. For such transformation using metal salts, such as LiX (X=Cl, Br) and NaX, as a halogenating agent in the presence of NaIO₄ as catalyst (Scheme 7.1).
The disadvantage of this method is the use of a high amount (25%) of the catalyst and a stoichiometric amount of 30% H$_2$SO$_4$ along with the metal halide (1.2 eq.). The another disadvantage of oxidative hydrohalogenation with hypohalous acid or bromates is that it takes longer reaction time and gives low yield.$^{2,33}$

Various reagents have found by different workers for halohydrin formation. Epoxides are versatile building blocks in organic synthesis and a large variety of reagents are known for the ring opening of these compounds.$^{59,60}$

H. Sharghi and his co-workers$^{61}$ reported the ring opening halogenations of epoxides by elemental halogens (l$_2$ or Br$_2$) in the presence of isonocotinic hydrazide (isoniazide) under mild reaction condition yield halohydrin (Scheme 7.2).

![Scheme 7.1](image_url)

![Scheme 7.2](image_url)
Another method for the synthesis of bromohydrins is the ring opening of epoxides\textsuperscript{62,67} by hydrogen halides or metal halides (Scheme 7.3).

\[
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{X} \\
\end{array}
\xrightarrow{\text{Nu}}
\begin{array}{c}
\text{Nu} \\
\text{OH} \\
\text{X} \\
\end{array}
\]

\textbf{Scheme 7.3}

Sharghi et al.\textsuperscript{68} reported another method for the synthesis of $\beta$-iodohydrin and $\beta$-bromohydrin by the direct ring opening of epoxides with elemental halogens in the presence of thiourea.

The method for stereospecific synthesis of diastereomeric "reverse" dihydrodiol epoxides of chrysene and picene has been reported by Wameling et al.\textsuperscript{69} For epoxidation, dimethyldioxirane (DMDO) is used in this process. In some media, Mitsuji and co-workers\textsuperscript{70} developed a reaction of 2-phospholene-1-oxides with bromine.

In the presence of magnesium nitrate catalyst, Suh et al.\textsuperscript{71} reported a highly regioselective conversion of epoxide to bromohydrins using tetrabutyl ammonium bromide. Coughlin\textsuperscript{72} and Bhuvaneswari\textsuperscript{73} reported biotransformation of alkenes by haloperoxidases for regiospecific bromohydrin formation from cinnamyl substrates in neutral aprotic media.

Kharasch\textsuperscript{74} first used $N,N$-dibromo-p-toluene-sulfonamide for the synthesis of 1-phenyl-2-$(p$-toluenesulfonamido)-1-bromomethane (Scheme 7.4). The same reagent was also used by Paul et al.\textsuperscript{75}
Phukan et al.\textsuperscript{76} also reported an efficient method for the regioselective and stereoselective synthesis of vicinal bromohydrins from olefin using \textit{N,N}-dibromo-\textit{p}-toluenesulfonamide (Scheme 7.5).

\begin{equation}
\begin{array}{c}
\text{TsNBr}_2 \\
\text{MeCN} : \text{H}_2\text{O (4:1), rt}
\end{array}
\end{equation}

\begin{align*}
R' &= \text{H, Ar, Ph (CH}_2\text{)}_2 - \\
R'' &= \text{H, CO}_2\text{Et, CO}_2\text{Me} \\
R', R'' &= - (\text{CH}_2)_4 -
\end{align*}

Scheme 7.5
7.3. Present Work

Objective

During past few years, a variety of reaction systems have been developed for the bromohydrin synthesis. In general, bromohydrin formation reaction using NBS require a catalyst. Many of these catalytic methods have one or more disadvantages such as longer reaction time, use of expansive catalysts etc. Iodine has been utilized as a very useful catalyst for various organic transformations. The objective of the present investigation is to examine the catalytic property of iodine for bromohydrin formation reaction using NBS as the brominating agent (Scheme 7.6). Our emphasis will be on the extension of the procedure for relatively inactive substrates such as cinnamic esters.

\[
\begin{align*}
R' \xrightarrow{NBS (1.2 \text{ eq.})} & \quad \text{OH} \\
& \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
R'' = & \quad \text{H, CO}_2\text{Et, CO}_2\text{Me} \\
R', R'' = & \quad -(\text{CH}_2)_4-
\end{align*}
\]

Scheme 7.6
7.4. Results and Discussion

Since we are more interested in studying the process for substrates like cinnamate, initial experiments were performed using ethyl cinnamate as the model substrate. In this reaction, ethylcinnamate (1 mmol) was added to a mixture of N-bromosuccinimide (1.2 mmol) and iodine (10 mol%) in 5 ml mixture of acetonitrile and water (4:1 ratio) at room temperature. Further improvement of yield was observed, when the reaction was performed at 0 °C. However 10 mol% results with good to excellent yield with exclusive anti-selectivity (Table 7.1). Moreover in absence of iodine catalyst reaction takes longer time with poor yield.

Table 7.1. Synthesis of bromohydrin from ethylcinnamate under various conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp.</th>
<th>Catalyst (m mol)</th>
<th>NBS (mmol)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>% of anti product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>0.1</td>
<td>1.2</td>
<td>2</td>
<td>68</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0°C</td>
<td>0.1</td>
<td>1.2</td>
<td>1</td>
<td>79</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>0°C</td>
<td>0.1</td>
<td>1.1</td>
<td>1</td>
<td>70</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Reaction conditions: solvent: MeCN–H2O (4:1), 5mL; ethylcinnamate, 1mmol

After optimizing the reaction conditions we explained the procedure using different olefins, styrene etc. The results are summarized in Table 7.2.
Table 7.2. Synthesis of bromohydrin from various olefins

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin/ Styrene</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(\text{OH} \quad \text{O} \quad \text{Br} )</td>
<td>(\text{OH} \quad \text{O} \quad \text{Br} )</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td>2.</td>
<td>(\text{Me} \quad \text{Cl} \quad \text{O} \quad \text{Me} )</td>
<td>(\text{Me} \quad \text{Cl} \quad \text{Br} \quad \text{O} \quad \text{Me} )</td>
<td>1.5</td>
<td>72</td>
</tr>
<tr>
<td>3.</td>
<td>(\text{CH}_2 \quad \text{O} )</td>
<td>(\text{Br} \quad \text{O} \quad \text{Me} )</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>4.</td>
<td>(\text{OH} \quad \text{O} \quad \text{Me} )</td>
<td>(\text{OH} \quad \text{O} \quad \text{Br} \quad \text{O} \quad \text{Me} )</td>
<td>2.5</td>
<td>67</td>
</tr>
<tr>
<td>5.</td>
<td>(\text{Me} \quad \text{O} \quad \text{Me} )</td>
<td>(\text{Me} \quad \text{O} \quad \text{Br} \quad \text{O} \quad \text{Me} )</td>
<td>1.3</td>
<td>83</td>
</tr>
<tr>
<td>6.</td>
<td>(\text{Ph} \quad \text{(\text{Ph})} )</td>
<td>(\text{Ph} \quad \text{(\text{Ph})} \quad \text{Br} )</td>
<td>1.5</td>
<td>75</td>
</tr>
<tr>
<td>7.</td>
<td>(\text{O} \quad \text{O} \quad \text{Cl} )</td>
<td>(\text{O} \quad \text{O} \quad \text{Br} \quad \text{Cl} )</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>8.</td>
<td>(\text{OH} )</td>
<td>(\text{Br} )</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>9.</td>
<td>(\text{OH} )</td>
<td>(\text{Br} )</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>10.</td>
<td>(\text{OH} )</td>
<td>(\text{Br} )</td>
<td>1</td>
<td>81</td>
</tr>
</tbody>
</table>

From Table 7.2 it can be concluded that the yield of bromohydrin synthesized from ethyl cinnamate, methyl cinnamate, trans-stilbene, styrene, indene and
1,2-dihydro naphthalene gives excellent yield. In all cases, the rate of reaction is fast. However in case of chalcones (Entry 7), usually undergo slow bromohydrin reaction with lower yield. In all cases, the reaction shows high regioselectivity.

Products were characterized by analyzing the NMR spectroscopic data. In $^1$H NMR spectrum, the CH proton connected to oxygen of OH gives a doublet due to coupling with coupling constant 9Hz in the chemical shift range 3.5-4.5 ppm. However in some cases this signal is appearing as multiplet. The CH proton connected to bromine gives a doublet with coupling constant value around 9 Hz in the chemical shift range 4.5-5.5 ppm. But in some cases it is appearing as multiplet. The OH proton in some compound is appearing at a variable chemical shift range of 2.5-3 ppm. The aromatic proton signal appears as multiplet in the range between 7.2-8.1 ppm.

In $^{13}$C NMR spectrum, the CH carbon connected to bromine gives its signal at about 50-55 ppm whereas the CH carbon near OH gives its signal at about 70-75 ppm. The signal at 194 ppm is due to carbonyl group present in the compound. The aromatic ring carbon signals appear in between 120-140 ppm.
Fig. 7.1: $^1$H NMR Spectra of Ethyl 2-bromo-3-hydroxy-3-phenyl propanoate (Entry 1)

Fig. 7.2: $^{13}$C NMR Spectra of Ethyl 2-bromo-3-hydroxy-3-phenyl propanoate (Entry 1)
Fig. 7.3: $^1$H NMR Spectra of Methyl 2-bromo-3-hydroxy-3-phenyl propanoate (Entry 3)

Fig. 7.4: $^{13}$C NMR Spectra of Methyl 2-bromo-3-hydroxy-3-phenyl propanoate (Entry 3)
Fig. 7.5: $^1$H NMR Spectra of 2-bromo-3-hydroxy-1, 3-diphenyl propan-1-one (Entry 7)

Fig. 7.6: $^{13}$C NMR Spectra of 2-bromo-3-hydroxy-1, 3-diphenyl propan-1-one (Entry 7)
7.5. Conclusion

In conclusion, we have developed an efficient and general catalytic method for the bromohydrin reaction of various olefinic substrates in the presence of iodine using NBS as brominating agent with good to excellent yield. The important features of this methodology are mild reaction condition, cleaner reaction profile, operational simplicity and cheap, non-toxic and readily available catalyst.

7.6. Experimental Section

General procedure for the synthesis of bromohydrins:

To a solution of olefin (1 mmol) and NBS (1.2 mmol), in acetonitrile-water (4:1) (5ml) in a 25ml round-bottom flask was added iodine (0.1 mmol) at 0°C. The mixture was stirred at 0°C using a magnetic stirrer for the appropriate time as monitored the progress of the reaction by TLC from time to time till completion. After completion of the reaction, the reaction mixture was washed with 10% aqueous Na₂S₂O₃ (10 ml). Ethyl acetate was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and combined organic extract was washed with brine solution. The organic layer thus obtained was dried over anhydrous Na₂SO₄ and evaporated to give crude bromohydrin. The product(s) was purified by column chromatography on silica gel (230-400 mesh) with petroleum ether – EtOAC as eluent gave the pure product.
Experimental Data:

Entry 1: Ethyl 2-bromo-3-hydroxy-3-phenyl propanoate

White crystalline

MP: 79 -80°C [Lit. 75 - 77°C]

IR (neat cm⁻¹): 3450, 2979, 2930, 1719, 1430, 1285, 1020

¹H NMR (CDCl₃, 300 MHz): δ 1.28 (t, J=6 Hz, 3H), 4.22 - 4.29 (q, J=2 Hz, 2H), 4.36 - 4.38 (d, J=9.6Hz, 1H), 5.03 - 5.08 (m, 1H), 7.31 (m, 5H).

¹³C NMR (CDCl₃, 75 MHz): δ 13.7, 47.6, 62.2, 74.9, 126.8, 128.5, 138.9, 169.3.

Entry 2: Methyl 2-bromo-3-chloro-4-methoxy phenyl-3-hydroxy propanoate.

Thick Oil

¹H NMR (CDCl₃, 300 MHz): δ 3.70 (s, 3H), 3.73 (s, 3H) 4.23 (d, J=9 Hz, 1H), 4.9 (d, J=8.7Hz, 1H), 6.84 (d, J=8.4Hz, 1H), 7.16 (d, J=8.4Hz, 1H), 7.34 (s, 1H).

¹³C NMR (CDCl₃, 75 MHz): δ 14.1, 21.0, 47.7, 53.3, 56.1, 74.0, 111.7, 122.2, 128.8, 132.4, 154.9.
Entry 3: Methyl 2-bromo-3-hydroxy-3-phenyl propanoate.

\[
\begin{align*}
\text{White crystalline} \\
\text{MP: 64 - 65°C [Lit 63°C]} \\
\text{IR (neat, cm}^{-1}\text{): 3466, 2954, 2916, 1732, 1442, 1280, 1022.} \\
\text{\textsuperscript{1}H NMR (CDCl}_3\text{, 300 MHz):} \\
\delta 
\begin{align*}
3.76 \text{ (s, 3H), } & 4.35 \text{ (d, J=8.7 Hz, 1H), 5.01 - 5.1} \text{ (m, 1H), 7.33 - 7.42 (m, 5H).} \\
\text{\textsuperscript{13}C NMR (CDCl}_3\text{, 75 MHz):} \\
\delta 
\begin{align*}
47.4, 53.0, 74.9, 126.9, 128.3, 128.6, 138.9, 169.8. 
\end{align*}
\end{align*}
\]

Entry 4: Methyl 2-bromo-3-hydroxy-3-(3-methoxy phenyl) – propanoate

\[
\begin{align*}
\text{White crystalline} \\
\text{MP: 75-77\textdegree C} \\
\text{\textsuperscript{1}H NMR (CDCl}_3\text{, 300 MHz):} \\
\delta 
\begin{align*}
3.82 \text{ (s, 6H), } & 6.36 \text{ (d, J=15.9 Hz, 1H), 6.7-6.89 (m, 1H), 7.09-7.10 (m, 1H), 7.47} \text{ (d, 9 Hz, 1H), 7.9 (d, 15.9Hz, 1H).} \\
\text{\textsuperscript{13}C NMR (CDCl}_3\text{, 75 MHz):} \\
\delta 
\begin{align*}
51.7, 55.3, 112.3, 117.4, 120.5, 133.8, 143.0, 158.8, 166.6. 
\end{align*}
\end{align*}
\]
Entry 5: Methyl 2-bromo-3-hydroxy-3-(4-methoxyphenyl) propanoate

Thick Oil

\[ \text{POH O} \]

\[ \text{MeO} \]

\[ \text{Br} \]

\[ \text{OMe} \]

\( \delta 3.55 - 3.82 \text{ (m, 6H)}, 4.21 - 4.35 \text{ (m, 1H)}, 4.82 - 5.0 \text{ (m, 1H)}, 6.86 \text{ (d, } J=6Hz, 2H), 7.26 \text{ (d, } J=6Hz, 2H). \)

\( \delta 47.7, 53.0, 55.0, 74.5, 113.7, 128.1, 131.1, 159.5, 169.8. \)

Entry 6: 2-bromo-1, 2-diphenylethanol

White solid

MP : 83 – 86°C [Lit 83-84°C]

\( \delta 2.47 \text{ (bs, 1H)}, 5.1 \text{ (d, 6 Hz, 1H)}, 5.21 \text{ (d, 6Hz, 1H)}, 7.26 - 7.62 \text{ (m, 10H)}. \)

\( \delta 56.8, 78.0, 127.8, 128.1, 128.4, 128.7, 128.8, 128.9, 139.6, 139.9. \)
Entry 7: 2-bromo-3-hydroxy-1, 3-diphenyl propan-1-one

White solid

MP: 109-111°C

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.5 (bs, 1H), 5.14 (d, $J$=8.5 Hz, 1H), 5.32 (d, $J$=8.1 Hz, 1H), 7.21 - 7.69 (m, 7H), 8.02 (d, $J$=7.2 Hz, 2H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 47.7, 74.0, 128.7, 128.8, 129.04, 134.3, 134.4, 137.9, 194.4.

Entry 8: 2-bromo-1-phenylethanol

Thick oil

IR (neat, cm$^{-1}$): 3408, 2935, 2952, 1600, 1460, 1062, 708.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.1 (bs, 1H), 3.51 - 3.67 (m, 2H), 4.92 - 4.95 (m, 1H), 7.26 - 7.39 (m, 5H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 40.7, 73.8, 125.9, 128.5, 128.7, 140.1.
Entry 9: 2-bromo-2, 3-dihydro-1 H-inden-1-ol

![Chemical structure](image)

White solid
MP : 124-125°C

^1H NMR (CDCl₃, 300 MHz): δ 3.15 - 3.2 (m, 1H), 3.5 - 3.62 (m, 1H), 4.2 - 4.30 (m, 1H), 5.27 - 5.32 (m, 1H), 7.15 - 7.5 (m, 4H).

^13C NMR (CDCl₃, 75 MHz): δ 40.5, 54.5, 83.4, 124.1, 124.6, 127.6, 129.0, 139.8, 141.7.

Entry 10: 2-bromo-1, 2,3,4-tetrahydron phthalen-1-ol

![Chemical structure](image)

^1H NMR (CDCl₃, 300 MHz): δ 2.41 - 2.7 (m, 2H), 2.85 - 3.1 (m, 2H), 4.21 - 4.5 (m, 1H), 4.85 - 5.1 (m, 1H), 7.12 - 7.25 (m, 2H), 7.47 - 7.53 (m, 2H).

^13C NMR (CDCl₃, 75 MHz): δ 28.1, 29.8, 56.3, 74.1, 126.8, 128.2, 128.6, 135, 135.5.
7.7 References


