Studies on the reactivity of cis-4-benzyloxy-1,2-epoxycyclohexane

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Dedicated to Professor Joan Bosch on the occasion of his 60th birthday

Abstract
The reaction course of the selenation-oxidation-elimination sequence carried out from
cis-4-benzyloxy-1,2-epoxycyclohexane (cis-1) is studied. Contrary to literature precedents, this
transformation leads to an unexpected diastereomeric cyclohexenol, whose formation can be
interpreted by stereoelectronic grounds. In addition, the base induced rearrangement of cis-1
with lithium amide bases is also discussed. In the absence of external additives, a mixture of
cyclohexenols arising from the competition of syn and anti elimination processes is observed.
However, in the presence of Li salts, the corresponding cyclohexenol arising from an apparent
anti elimination pathway predominates. A mechanistic rationale is proposed to account for these
observations.

Keywords: Epoxide, nucleophilic attack, elimination, selenoxide, base induced rearrangement

Introduction

In the course of our recent research, the use of cis-4-benzyloxy-1,2-epoxycyclohexane (cis-1) has
disclosed interesting reactivity features that deserve some attention. Thus, a literature report1,2
describes the use of cis-1 as starting material for the synthesis of cis-5-benzyloxy-2-cyclohexenol
(cis-2) by phenyl selenation followed by oxidation to the corresponding selenoxide and in situ
elimination (Scheme 1).
Scheme 1. Proposed synthetic pathway for alcohol cis-2 from epoxide cis-1, according to reference 1.

Results and Discussion

Attempts to reproduce the above sequence required the preparation of epoxide cis-1, which was obtained uneventfully from 4-benzyloxydihydroxycyclohexene following literature protocols.\(^3\) Reaction of cis-1 with sodium phenylselenide (obtained in situ by reaction of diphenyl diselenide with NaBH\(_4\) in EtOH) was carried out as described in the literature.\(^1,2\) Mechanistic considerations concerning the putative reaction pathway involved in the transformation of cis-1 into the expected allylic alcohol cis-2, would require phenylselenide attack to afford phenylselenyl derivative 3 through a chelated reactive conformation cis-1A(Na), in agreement with the trans-diaxial attack imposed by the Fürst-Platner rule.\(^4\) The above reaction course would be imperative for the subsequent syn elimination of selenoxide 4 required to give alcohol cis-2 (see Scheme 2).

Scheme 2. Proposed mechanism to account for the formation of cis-2 by syn elimination of phenyl selenoxide intermediate 4.

However, taking into account the relatively low chelating ability of the Na ion to force the above reactive conformation cis-1A(Na),\(^6\) a thorough examination of the reaction outcome was undertaken. Thus, operation of a non-chelating reactive conformation cis-1B on reaction of cis-1
with phenylselenide would afford phenylselenide 5 (Scheme 3), whose oxidation to selenoxide 6, followed by \textit{syn}-elimination,\textsuperscript{5} would lead to the isomeric allylic alcohol \textit{cis}-7, as depicted in Scheme 3.

\begin{center}
\begin{tikzpicture}
\node[draw,shape=rectangle,inner sep=5] (a) at (0,0) {\textit{cis}-1B};
\node[draw,shape=rectangle,inner sep=5] (b) at (2,0) {5};
\node[draw,shape=rectangle,inner sep=5] (c) at (4,0) {5};
\node[draw,shape=rectangle,inner sep=5] (d) at (6,0) {6};
\node[draw,shape=rectangle,inner sep=5] (e) at (8,0) {\textit{cis}-7};
\draw[->,thick] (a) -- (b) node[midway,above] {NaPhSe};
\draw[->,thick] (b) -- (c) node[midway,above] {BnO};
\draw[->,thick] (c) -- (d) node[midway,above] {oxidation};
\draw[->,thick] (d) -- (e) node[midway,above] {\textit{syn} elimination};
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.} Proposed mechanism to account for the formation of \textit{cis}-7 by \textit{syn} elimination of phenyl selenoxide intermediate 6.

As expected from the above hypothesis, and contrary to literature precedents,\textsuperscript{1,2} \textit{alcohol \textit{cis}-7 was formed in this process instead of \textit{cis}-2}. Formation of \textit{cis}-7 was confirmed by comparison of its spectroscopical data with those described in the literature for this alcohol\textsuperscript{7} and isomeric \textit{cis}-2.\textsuperscript{8}

In light of these results, we explored the potential of epoxide \textit{cis}-1 as starting material for the synthesis of isomeric alcohols \textit{cis}-2 and \textit{cis}-7. In this context, synthesis of \textit{cis}-7 is described in the literature from base-induced rearrangement of epoxide \textit{cis}-1.\textsuperscript{7} However, despite the well recognised synthetic usefulness of this transformation,\textsuperscript{9,10} the reaction outcome can be dramatically affected by the nature of the base, the solvent, and the reaction temperature, among others.\textsuperscript{11,12} Thus, computational and experimental studies carried out on cyclohexane oxides have shown a switch from \textit{syn}-\textit{\beta} elimination in non polar solvents to a more energetically favourable \textit{anti}-\textit{\beta} elimination in polar solvents, such as HMPA.\textsuperscript{13} Our experiments carried out from epoxide \textit{cis}-1 under different reaction conditions (base, solvent, temperature, and LiClO\textsubscript{4} as chelating agent) are shown in Table 1. An initial experiment in LDA/E\textsubscript{2}O at rt (entry 1) showed the formation of a roughly 1:1 mixture of allylic alcohols \textit{cis}-2 and \textit{cis}-7, which can be interpreted as a result of the operation of competing \textit{anti} and \textit{syn} elimination processes, respectively, from the most stable conformation \textit{cis}-1\textit{B}, (Scheme 4).\textsuperscript{14} Based on our previous results,\textsuperscript{15} addition of LiClO\textsubscript{4} (5 equiv/mol) is known to drive the reaction mixture towards a chelated reactive conformation \textit{cis}-1\textit{A(Li)} (Scheme 5). This conformation was expected to favour the operation of a \textit{syn} elimination leading ultimately to \textit{cis}-2. However, contrary to our assumption, alcohol \textit{cis}-7 was the major one under the above conditions (entry 2). Similar results were obtained in the presence of THF as a solvent (entry 3), although unreacted starting epoxide \textit{cis}-1 was the major or exclusive one at lower temperatures (entries 5, 6).
Table 1. Reactivity of epoxide cis-1 under basic conditions in the presence of LiClO₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base (equiv/mol)</th>
<th>temp (°C)</th>
<th>t (h)</th>
<th>cis-7</th>
<th>cis-2</th>
<th>8</th>
<th>cis-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (a)</td>
<td>Et₂O</td>
<td>LDA (1.5)</td>
<td>25</td>
<td>16</td>
<td>25%</td>
<td>25%</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>Et₂O</td>
<td>LDA (1.5)</td>
<td>25</td>
<td>22</td>
<td>52%</td>
<td>&lt;5%</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>LDA (1.5)</td>
<td>25</td>
<td>24</td>
<td>35%</td>
<td>&lt;5%</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>LDA (3.0)</td>
<td>-78</td>
<td>4</td>
<td>58%</td>
<td>&lt;5%</td>
<td>19% (b)</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>LDA (1.5)</td>
<td>-20</td>
<td>22</td>
<td>30%</td>
<td>&lt;5%</td>
<td>46%</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>LDA (1.5)</td>
<td>reflux</td>
<td>5</td>
<td>33%</td>
<td>---</td>
<td>49% (b)</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>LiNEt₂ (1.5)</td>
<td>reflux</td>
<td>5</td>
<td>30%</td>
<td>---</td>
<td>32% (c)</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>LiNEt₂ (1.5)</td>
<td>reflux</td>
<td>5</td>
<td>30%</td>
<td>---</td>
<td>32% (c)</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>LiNEt₂ (1.5)</td>
<td>reflux</td>
<td>5</td>
<td>30%</td>
<td>---</td>
<td>32% (c)</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>Et₂O</td>
<td>LiN(C₆H₁₁)₂ (1.5)</td>
<td>25</td>
<td>3.5</td>
<td>46%</td>
<td>---</td>
<td>---</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

(a): No LiClO₄ was used in this experiment. (b): R=iPr. (c): R=Et.

The use of a larger excess LDA (3 equiv/mol, entry 4) was unsuccessful, since noticeable amounts of alcohol 8 (R=iPr) was also observed (see Scheme 5). This side reaction was even more important under reflux conditions, since 8 (R=iPr) was the major compound (entry 7). Moving from LDA to other lithium amide bases led to similar results, irrespective of their steric demand or reaction conditions (entries 8-10). In all cases, only alcohol cis-7 was formed as a result of a base-induced rearrangement process. Finally, contrary to literature precedents, the use of HMPA did not improve the reactivity of the lithium amides, since poor conversions were observed in all cases.

Scheme 4. Proposed reaction mechanisms to account for the formation of alcohols cis-2 and cis-7 from a common non-chelated reactive conformation cis-1B.
The above results, in the presence of LiClO$_4$ as chelating agent, can be interpreted by considering Scheme 5. Thus, due to the well recognized ability of Li ions to promote a reactive chelating conformation in epoxy cyclohexanes$^{6,15}$ conformation cis-$\text{1A(Li)}$ can account for the reactivity of epoxide cis-$\text{1}$ in the presence of LiClO$_4$ (5 equiv/mol). The commonly accepted syn elimination pathway for this kind of LDA promoted rearrangements would require a previous Li-ligand exchange to accommodate the amide base in a proper orientation for a subsequent abstraction of the vicinal pseudoaxial proton$^{10}$ (conformation cis-$\text{1C}$, Scheme 5). This exchange process might be slower than an alternative anti elimination pathway leading ultimately to major alcohol cis-$\text{7}$. This reactive conformation would also explain formation of amino alcohols $\text{8}$ as a result of nucleophilic attack of the amide base following a trans-diaxial pathway.

Scheme 5. Mechanistic interpretation to account for product distribution on reaction of epoxide cis-$\text{1}$ with LDA in the presence of LiClO$_4$.

In summary, the above results represent an additional proof of the generality of the Fürst-Platner rule on the reactivity of epoxy cyclohexane derivatives, as evidenced by the results obtained from epoxide cis-$\text{1}$ on reaction with phenyl selenide anion. On the other hand, studies on the base-induced rearrangement of epoxide cis-$\text{1}$ in the presence of LiClO$_4$ show the ability of this additive to facilitate an anti elimination process leading ultimately to allylic alcohol cis-$\text{7}$ as the major reaction product.
Experimental Section

General Procedures. Solvents were distilled prior to use and dried by standard methods. Melting points are uncorrected. FT-IR spectra are reported in cm$^{-1}$. $^1$H and $^{13}$C NMR spectra were obtained in CDCl$_3$ solutions at 300 MHz (for $^1$H) and 75 MHz (for $^{13}$C), respectively, unless otherwise indicated. Chemical shifts are reported in delta (δ units, parts per million (ppm) relative to the singlet at 7.24 ppm of CDCl$_3$ for $^1$H and in ppm relative to the center line of a triplet at 77.0 ppm of CDCl$_3$ for $^{13}$C.

cis-4-Benzyloxy-2-cyclohexenol (cis-7)$^7$
Sodium borohydride (950 mg, 25 mmol) is added portionwise to a solution of diphenyldiselenide (3.7 g, 12 mmol) in EtOH (10 mL) under nitrogen. The reaction mixture is stirred at rt for 10 min. The mixture is then treated with a solution of epoxide cis-1 (1g, 4.89 mol) in EtOH (5 mL). After stirring for 45 min at rt, the reaction mixture is diluted with THF (7 mL), treated with 30% H$_2$O$_2$ (5.2 mL added dropwise), and heated to reflux temperature with vigorous stirring. After 8h, the mixture is concentrated in vacuo, treated with H$_2$O (10 mL) and extracted with Et$_2$O (3 x 20 mL). The combined organic extracts are dried over MgSO$_4$, filtered and evaporated to afford a crude residue which was flash chromatographed on hexanes/EtOAc (2/1) to afford alcohol cis-7 (350 mg, 35 % yield).

$^1$H NMR (200 MHz, CDCl$_3$): δ 1.77-1.83 (4H, m, 2xH$_5$, 2xH$_6$), 3.89 (2H, m, H$_4$ and H$_1$), 4.12 (1H, d, J=12.2, CH$_2$-Ph), 4.60 (1H, d, J=12.2, CH$_2$-Ph), 5.91 (2H, broad, H$_2$, H$_3$), 7.34 (5H, m, Ar); $^{13}$C NMR (50 MHz; CDCl$_3$): δ 24.4 (C$_5$), 28.1 (C$_6$), 65.2 (C$_1$), 70.3 (CH$_2$-Ph), 71.5 (C$_4$), 127.4, 128.2, 128.9, 129.9, 133.0 (Ar), 138.4 (Cq); IR (cm$^{-1}$): 734, 1060, 1072, 2866, 2945, 3384; HRMS, Calculated for C$_{13}$H$_{16}$O$_2$: 204.1150; Found: 204.1158.

General procedure for the reactions of epoxide cis-1 with lithium amide bases
Lithium amide bases were typically prepared by treatment at -78ºC of a solution of the corresponding amine (4.5 mmol) in the required solvent (4 mL) with BuLi (2.5 mL of a 1.6 N solution in hexanes). This affords a solution containing 4 mmol LDA, approximately. The above mixture is allowed to warm to the required temperature and next treated with a solution of epoxide cis-1 (500 mg, 2.45 mmol for a base/substrate ratio of 1.5) containing LiClO$_4$ (1.3 g, 12.25 mmol) in the required solvent (6 mL). The reaction mixture was quenched by careful addition of H$_2$O (1 mL). The organic phase was extracted, dried, and evaporated in vacuo to afford a residue which was purified by flash chromatography to afford the reaction products (see Table 1).

cis-5-Benzylolxy-2-cyclohexenol (cis-2)$^8$

$^1$H NMR (200 MHz, CDCl$_3$): δ 1.99 (2H, t, 2xH$_6$), 2.21 (2H, m, 2xH$_4$), 3.80 (1H, q, H$_3$), 4.18 (1H, m, H$_1$), 4.99 (2H, s, CH$_2$-Ph), 5.65 (1H, m, H$_3$), 5.84 (1H, m, H$_2$), 7.26 (5H, complex, Ar). $^{13}$C NMR (50.4 MHz; CDCl$_3$): δ 30.1 (C$_1$), 30.1 (C$_6$), 35.7 (C$_4$), 64.7 (C$_1$), 70.4 (CH$_2$-Ph), 72.4
(C5), 127.3, 127.5, 128.3 (CH Ar), 125.1, 130.1 (C3, C2), 138.2 (Cq); HRMS, Calculated for C_{13}H_{18}O_{2}: 204.1150; Found: 204.1142.

**c-5-benzyloxy-t-2-diethylamino-r-cyclohexanol (8, R=Et)**

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.03 (6H, t, CH$_3$), 1.35 (2H, m, 2xH$_4$), 1.70 (1H, complex, H$_6$), 2.10 (1H, m, H$_6$), 2.36-2.45 (5H, m, 2xN-CH$_2$ and H$_2$), 2.62 (2H, m, H$_3$), 3.30 (2H, complex, H$_1$ and H$_5$), 4.50-4.52 (2H, broad, CH$_2$-Ph), 7.27 (5H, complex, Ar); $^{13}$C NMR (50.4, CDCl$_3$): $\delta$ 14.5 (CH$_3$), 19.2 (C$_4$), 31.4 (C$_3$), 38.6 (C$_6$), 43.2 (N-CH$_2$), 65.5 (C$_2$), 66.5 (C$_1$), 70.0 (CH$_2$-Ph), 74.8 (C$_5$), 127.4 and 128.2 (CH Ar), 138.6 (Cq); HRMS, Calculated for C$_{17}$H$_{28}$NO$_2$: 278.2042 (M+1)$^+$; Found: 278.2033.

**c-5-benzyloxy-t-2-diisopropylamino-r-cyclohexanol (8, R=iPr)**

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.06 (12H, d, CH$_3$), 1.55 (2H, m, 2xH$_4$), 1.90-2.30 (2H, m, 2xH$_6$), 2.67-3.02 (5H, m, 2xN-CH, H$_2$ and 2xH$_3$), 3.35 (m, 2H, H$_1$ and H$_5$), 4.40-4.65 (2H, broad, CH$_2$-Ph), 7.35 (5H, complex, Ar); $^{13}$C NMR (50.4, CDCl$_3$): $\delta$ 20.4 (C$_3$), 22.1 (CH$_3$), 30.7 (C$_4$), 37.5 (C$_6$), 47.7 (N-CH), 60.3 (C$_1$), 62.2 (C$_2$), 72.5 (CH$_2$-Ph), 75.8 (C$_5$), 127.0 and 129.5 (CH Ar), 137.5 (Cq); HRMS, Calculated for C$_{19}$H$_{32}$NO$_2$ (M+1)$^+$: 306.2355; Found: 306.2366.

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**References and Notes**

2. The authors described the formation of a diastereomeric mixture of alcohols *cis*-2 and *trans*-2 from a mixture of epoxides *cis*-1 and *trans*-1, respectively.
14. Despite formation of cis-2 can also be interpreted as a result of a syn elimination from a putative chelated conformation cis-1A (Li) (Scheme 5), operation of this reactive conformation usually requires a higher concentration of Li ions (see text).
