Note

Oxidation of Allylic Sulfides with Corynebacterium equi.*

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It has been demonstrated in our laboratory that Corynebacterium equi IFO 3730 has an enzyme system which can oxidize alkyl aryl sulfides to result in the corresponding sulfones and chiral sulfoxides.1,2 The susceptibility for oxidation and the ratio of oxidized products depend on the structure of the starting sulfides. Because sulfones and sulfoxides are important compounds in organic chemistry, it should be instructive to examine the applicability of this reaction for a wide number of compounds. Thus, we chose allylic sulfides as the substrates from two points of view. One is that allylic sulfides have two oxidizable functional groups, i.e., a C=C double bond and a sulfur atom, and it would be useful to develop a way for chemoselective oxidation of the sulfur atom without injuring the carbon–carbon double bond.2) The other aspect is that allylic sulfoxides are useful synthons for allylic alcohols,3> chiral sulfoxides being applicable to the asymmetric synthesis of chiral allylic alcohols.4) Here we wish to report our observations that the enzyme system of C. equi has shown a reactivity to allylic sulfides and sulfoxides different from that of alkyl aryl compounds.

Corynebacterium equi IFO 3730 was inoculated to a medium consisting of inorganic salts and 2% of hexadecane.1) The allylic sulfides 1 listed in Table I were added to the medium at the same time with inoculation. The substrates were oxidized to the corresponding sulfoxides 2 and sulfones 3 by cultivation for 3 days at 30°C as in the case of the alkyl aryl sulfides.1) In all cases, a lower concentration of substrates was preferable for high conversion.

\[
\text{ArSCH} = \text{CHR} \xrightarrow{C. \text{ equi}} \text{ArSOCH} = \text{CHR} + \text{ArSO}_2\text{CH} = \text{CHR}
\]

Compared to the alkyl aryl compounds, the allylic sulfides were generally more resistant to oxidation, while the relative reactivity of the sulfoxides was higher than that of the sulfides. Accordingly, the yield of sulfones was high compared with that of sulfoxides. The most representative is the case of cinnamyl phenyl sulfide (1d). When the concentration of the substrate was 0.2% (v/v), almost all the starting sulfide was converted to the corresponding sulfone 3d. The introduction of a methoxy group to the \(\text{para}\)-position of the phenyl group attached to sulfur markedly inhibited the formation of sulfone, resulting in the formation of sulfoxide to high selectivity (Table I, e).

The reason for this selectivity is not clear at present, it being supposed that the enriched electron density on the

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**Table I. Oxidation of Allylic Sulfides with C. equi**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ar</th>
<th>R</th>
<th>Concentration (%)</th>
<th>Recovered (%)</th>
<th>Sulfoxide (%)</th>
<th>Sulfone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>H</td>
<td>0.2</td>
<td>36</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>Me</td>
<td>0.2</td>
<td>43</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>n-Pr</td>
<td>0.4</td>
<td>84</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>Ph</td>
<td>0.2</td>
<td>52</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>Ph</td>
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<td>57</td>
<td>8</td>
<td>35</td>
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<tr>
<td>f</td>
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<td>Ph</td>
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<td>6</td>
<td>7</td>
<td>87</td>
</tr>
<tr>
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<td>Ph</td>
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<td>56</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>h</td>
<td>Ph</td>
<td>Ph</td>
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<td>58</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>i</td>
<td>Ph</td>
<td>Ph</td>
<td>0.2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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* Cultivation was carried out at 30°C for 3 days.
* Concentration of substrates in v/v.
* The ratio of recovered starting material and oxidation products. As the total recovery of sulfur-containing compounds was nearly quantitative, the ratios shown in this table are almost equal to the yield of each compound.

Studies on Enzymatic Oxidation of Sulfides. Part III. For Part II, see ref. 1b.
sulfur atom by the effect of the methoxy group might be responsible for the change in reactivity. The ortho-methoxy derivative 1f was entirely recovered after a 3-day cultivation with the bacterium. In this case, the steric hindrance around the sulfur atom is considered to be the main reason.

The smaller number of carbons in the allylic chain also raised the selectivity for the formation of sulfoxides vs. sulfone. Thus, allyl phenyl sulfide (1a) formed the sulfoxide 2a in about a 40% yield. In one experiment, 2a was isolated in a yield as high as 56%. The optical purity of this sulfoxide was determined to be 100% by HPLC using a Pirkle column. It showed a specific rotation of +176° (EtOH, c = 2.02), indicating that this sulfoxide had an (R) absolute configuration. This stereoselectivity is the same as was the case with oxidation of the allyl aryl sulfides. It is noteworthy that the optical purity of 2a was extremely high, in spite of the fact that allylic sulfoxides have been shown to be liable to racemize through an equilibrium with the sulenate ester 4.6. The fact that practically no equilibrium was set up between 2a and 4 during the cultivation period would be due to the high polarity of the reaction medium.7 Allyl p-tolyl sulfide (5) also gave a fairly good yield of the corresponding sulfoxide 6 (57%), together with only 9% of allyl p-tolyl sulfone (7) and 20% of the starting material. The optical yield of the sulfoxide 6 was revealed to be 93.2%, by HPLC, being slightly lower than allyl phenyl sulfoxide (2a).

Benzylc sulfide was also oxidized smoothly by the enzyme system of C. equi. When benzyl decyl sulfide (8) was submitted to the biochemical reaction (a concentration of 0.2%), it resulted in the formation of benzyl decyl sulfoxide (9) as the sole product (an isolated yield of 73%). Formation of the corresponding sulfone and recovery of the starting sulfide 8 were not detected by NMR. Again, the optical purity of the sulfoxide 9 was confirmed to be 100% by HPLC. The absolute configuration was estimated to be (R), because only the peak of an enantiomer with a longer retention time was observed similarly to the other sulfoxides, such as 2a and the alkyl aryl sulfoxides.1b

In conclusion, the enzyme system of C. equi showed different reactivities to a variety of allylic and benzylic sulfoxides. In cases when allylic phenyl sulfides with a long carbon chain were employed as substrates, the major products were the corresponding sulfones. On the other hand, allyl phenyl and alkyl benzylic sulfides mainly resulted in the formation of sulfoxides in high enantiomeric excess.

**EXPERIMENTAL**

**Spectroscopic measurement.** Spectral data were obtained as previously reported.8)

**Medium.** The basal medium already reported was supplemented with 2% of hexadecane.1

**Cultivation.** To a 500-ml Sakaguchi flask, 45 ml of medium, 5 ml of seed culture in the same medium, and 0.1 to 0.2 ml of sulfides were added and shaken at 30°C for 3 days. The after-treatments were carried out according to the methods already described.1b

**Determination of the ratio of sulfur-containing compounds and the optical purities of sulfoxides.** The same methods used in earlier experiments were also applied in these studies.

**Preparation of sulfides.** Allylic sulfides were prepared by the reaction between allylic halides and sodium arenc-thiolates in ethanol, or under a two phase system catalyzed by cetyltrimethylammonium bromide.10)

1-Chloro-(-)2-butene, 1-chloro-(-)2-hexene, and 1-chloro-3-phenyl-(-)2-propene were obtained by chlorination of the corresponding alcohol with carbon tetrachloride and triphenylphosphine at room temperature.11) Neither migration of the double bonds nor E-Z isomerization were observed.

**Preparation of authentic sulfoxides and sulfones.** Authentic dl-sulfoxides12) and sulfones13) were synthesized by oxidation of sulfides with hydrogen peroxide.

**REFERENCES**


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