Modern Organic Synthesis II Problem set

Problems 1-7 are concerned with the useful Birch reduction process.

The reduction of aromatic rings with metals such as lithium, sodium, or potassium in liquid ammonia and in the presence of an alcohol accomplishes the formation of 1,4-cyclohexadienes and is known as the Birch reduction. Aromatic compounds bearing electron donating substituents such as alkyl or alkoxy groups are reduced more slowly than arenes that have electron withdrawing groups. Moreover, there is a relationship between the electronic character of a substituent on an aromatic ring and the regiochemical course of a Birch reduction. For example, a Birch reduction of an electron rich arene of type A generally favors a 1,4-cyclohexadiene of type B, while a Birch reduction of an electron deficient arene of type C favors a 1,4-cyclohexadiene of type D (see below).


Some real examples:

\[
\begin{align*}
\text{OMe} & \quad \xrightarrow{\text{Li}^0, \text{NH}_3(\text{liq.}), \text{EtOH (81-85\%)} } \quad \text{OMe} \\
\text{anisole} & \quad \text{(see JACS 1953, 75, 5360)} \\
\text{CO}_2\text{H} & \quad \xrightarrow{\text{Na}^0, \text{NH}_3(\text{liq.}), \text{EtOH (81-85\%)} } \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{(see Aus. J. Chem. 1954, 7, 256)}
\end{align*}
\]

Incidentally, lithium metal has a larger reduction potential (2.99 v) than sodium metal (2.59 v) and is generally preferred.

<table>
<thead>
<tr>
<th>relative rates of a Birch reduction of benzene</th>
<th>Li(^0)</th>
<th>Na(^0)</th>
<th>K(^0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>360</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Lithium metal is also more soluble in liquid ammonia than sodium.**
Problem #1

Provide reaction sequences that could allow the conversion of anisole to compounds 1 and 2.

\[
\text{anisole} \quad \xrightarrow{\text{steps}} \quad \text{compound 1} \quad \xrightarrow{\text{steps}} \quad \text{compound 2}
\]

Problem #2

Do you know the structures of the missing intermediates?

(see *Pure & Appl. Chem.* 1996, 68, 554)

Problem #3

Do you know the structures of the missing compounds?

(see *Chem. Commun.* 1971, 858)
Problem #4

Do you know the structures of the missing compound?

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{Li}^0, \text{NH}_3 (\text{I}), \\
\text{OMe} & \quad \text{THF; then Mel} \\
\to & \quad \text{A} \\
\end{align*}
\]


\textit{paniculide A}

Problem #5

Provide a reaction sequence that could convert compound 1 to compound 2:

\[
\begin{align*}
\text{OMe} & \quad \text{steps} \\
\text{Me} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

(see E.J. Corey et al. J. Am. Chem. Soc. 1968, 90, 5618)

Problem #6

How could syntheses of compounds A and B conceivably be achieved from the indicated starting materials?

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{A} \\
\text{OMe} & \quad \text{B} \\
\end{align*}
\]
Problem #7
Do you know the structures of the missing intermediates?

(see D.J. Hart et al. J. Am. Chem. Soc. 1989, 111, 7507)

**For interesting applications of the Birch reduction in enantioselective syntheses of chiral cyclohexanes, see: A.G. Schultz Acc. Chem. Res. 1990, 23, 207

Problem #8
Devises a retrosynthetic analysis for methyl homosecodaphniphyllate. If you need help, consult chapter 26 of Classics in Total Synthesis.

methyl homosecodaphniphyllate

Problem #9
Why is the β-lactam ring of the penicillins so susceptible to a destructive ring opening?

Problem #10
Propose a synthesis for the compound shown below. When you're finished, read J. Am. Chem. Soc. 1977, 99, 6066.