Birch reduction of Heterocycles

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Gaich-Group Seminar
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1. General
   - Solvent
   - Reducibility
   - Mono-Protonation
   - Dianion-Formation
   - Dimerization
   - Cleavage

2. Examples/Applications
Review:

“Reduction of heterocyclic compounds by metal-ammonia solutions and related reagents”

Solvent system

- $e^-$ best solved in NH$_3$, more reactive in amines

- $A^*$ best solved & stabilized in amines

- Dielectric constant of co-solvent:
  
  THF: 7.6  
  HMPA: 30

- Co-solvents: THF, DME, dioxanes, HMPA $\rightarrow$ decreases metal solubility

- Temperature range:

  \[
  \begin{align*}
  \text{NH}_3 & : -80^\circ \rightarrow -33^\circ C \\
  \text{H}_2\text{NEt} & : -81^\circ \rightarrow 17^\circ C \\
  \text{H}_2\text{N-}(\text{CH}_2)_2-\text{NH}_2 & : 8^\circ \rightarrow 116^\circ C
  \end{align*}
  \]

  Li best soluble in amines
  Na/K alloy soluble in ethylene diamine

Reducibility

Lower LUMO $\rightarrow$ more rapid reduction

Reducibility

Reduction potentials $\rightarrow$ half wave potential ($E_{1/2}$)

in NH$_3$ not given for most cases $\rightarrow$ DMF or MeCN comparable

Reducibility

Stabilisation of A*-

17 > 18 > 19 > 20 > 21

→ More delocalization favours reduction
→ Benzyl groups (quinolines, indoles) & carboxyl substituents favours reduction

Arthur J. Birch, Jacob Slobbe, *Heterocycles* 1976, 5, 905-944
Acidic protons can prevent reduction:

\[ \text{9} \rightarrow \text{25} \]

$\rightarrow N$-alkyl substituents!

$\rightarrow$ Indoles work!

Positive charge favours reduction:

Reducibility

Experimental observations:

- Triazines, Pyridines, Pyrimidines, Pyridazines, Pyrazines, Quinolines & Indoles easy reducible
- Thiophenes reducible
- Furanes reducible under forcing conditions
- N-alkyl pyrrole carboxylic acids very slowly reducible
- Pyrroles not reducible
  Imidazoles only N-alkylated

Arthur J. Birch, Jacob Slobbe, *Heterocycles* 1976, 5, 905-944
Mono-protonation

Not irreversible like in carbocycles!

ESR studies and MO-calculations indicates protonation at position of highest electron spin density

\[ \rightarrow \text{Nitrogen special role!} \]

Protonation at nitrogen for pyridines & quinolines

Indoles protonated in benzene ring first!

Monoprotonated products can dimerize or add 2nd electron

Dianion Formation

\[
\text{A}^{2-} \xrightarrow{\text{e}^-} \text{A}^{\cdot-}
\]

Dianion formation is hindered \(\rightarrow\) reduction potential of \(\text{A}^{\cdot-}\) and the metal crucial

Product formation in some cases indicates dianion formation, at least in small amounts of an equilibrium

\(\rightarrow\) dianions highly basic, mostly irreversible protonated, even by \(\text{NH}_3\)

The more basic anion gets alkylated / protonated
Dimerization

Dependent on solvent system:

\[ 2 \text{A}^{2-} \rightleftharpoons \text{A}^{-} \text{A}^{-} \text{vs.} \text{A}^{-} + \text{A} \rightarrow \text{A}^{-} \text{A}^{-} \]

Dependent on presence of proton source:

Cleavage processes

Important for oxygen- and sulfur-containing heterocycles: \( S > O >> N \)

1. **Direct cleavage**: stabilisation of negative charge on hetero-atom
diaryl ethers, allyl ethers, benzyl ethers

![Chemical structures](image)

2. **Elimination**: \(-C-C-X\) \(\rightarrow\) \(C=C + X^-\)

![Chemical structures](image)

Arthur J. Birch, Jacob Slobbe, *Heterocycles* 1976, 5, 905-944
Cleavage processes: furanes

Cleavage processes: thiophenes

Arthur J. Birch, Jacob Slobbe, *Heterocycles* 1976, 5, 905-944
Examples/Applications

1) Pyridines
2) Pyrroles
3) Furanes
4) Thiophenes
1) Pyridines

Dihydropyridine derivatives tend to autoxidation and rearomatization → in-situ alkylation

Na, NH₃, EtOH then H₃O⁺

Li, NH₃ 1eq EtOH then MeI

Pyridine access to Steroid skeletons

1) Pyridines

\[
\begin{align*}
\text{92} & \xrightarrow{\text{Na, NH}_3} \text{no defined products} \\
\text{93} & \xrightarrow{\text{Na, NH}_3} \text{no defined products} \\
\text{94} & \xrightarrow{\text{Na, NH}_3} \text{R} \\
\text{95} & \\
\text{96} & \xrightarrow{\text{Na, NH}_3} \text{iPrO}_2 \text{C} \\
\text{97} & + \\
\text{98} & \\
\end{align*}
\]

1) Pyridines

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1) Pyridines

\[ \text{CO}_2\text{Pr} \quad \text{CO}_2\text{Pr} \]

\[ \text{Na, NH}_3 \quad \text{I} \quad \text{Cl}_n \quad n = 1-3 \]

\[ \text{base} \]

\[ \text{H}_2 \quad \text{Pd/C} \]

\[ \text{H}_2 \quad \text{Pd/C} \]

\[ \text{MeI} \]

\[ \text{Na, NH}_3 \]

\[ \text{then MeI} \]

\[ \text{107} \rightarrow \text{108} \rightarrow \text{109} \rightarrow \text{110} \rightarrow \text{111} \rightarrow \text{112} \rightarrow \text{113} \]

\[ n = 1 \rightarrow \text{base: DBU, CH}_2\text{Cl}_2, \Delta; 95\% \]

\[ n = 2 \rightarrow \text{base: DBU, ac, } \Delta; 88\% \]

\[ n = 3 \rightarrow \text{base: KHMDS, 18-C-6, THF, } \Delta; 46\% \]

1) Pyridines

\[
\begin{align*}
\text{Pyridine} & \quad 1) \text{SOCl}_2, \text{NaBr} \quad \text{MeOH}, \Delta \quad 2) \text{Mel} \\
\text{Pyridine} & \quad 1) \text{SOCl}_2, \text{NaBr} \quad \text{MeOH}, \Delta \quad 2) \text{PMB-I}
\end{align*}
\]

DBB = di-\textit{tert}-butylbiphenyl
R = H, Me, \(\text{tBu}\), CO\textsubscript{2}Me, -(CH\textsubscript{2})\textit{n}-X

1) Pyridines

Transformations:

\[ \text{Li(secBu)}_3 \text{BH (THF), -78°C} \rightarrow \]

\[ \text{MeMgBr CuBr} \ast \text{SMe}_2 \text{BF}_3 \ast \text{OEt}_2, \text{(THF)} \text{-78°C to -10°C} \rightarrow \]

\[ \text{PhB(OH)}_2 \text{(DME/H}_2\text{O)} \rightarrow \]
1) Pyridines

- **127**: Treatment with Mel, Ag$_2$CO$_3$ in (CHCl$_3$), Δ produces 128.
- **128**: Further treatment with Mel, Δ yields 129, whereas treatment with MeOTf gives 130.
- **129**: Reaction with Li, DBB (THF), -78°C followed by Mel results in 131.
- **130**: Reaction with Na, naphthalene (THF), -78°C then R-X then H$_3$O$^+$ leads to 132.

References:

2) Pyrroles

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\[
\begin{align*}
&\text{N} \\
&\text{Boc} \\
&\text{CO}_2\text{iPr} \\
&133 \quad R = \text{Me}, \text{Et}, \text{iBu}
\end{align*}
\]

then R-X

\[
\begin{align*}
&\text{N} \\
&\text{Boc} \\
&\text{CO}_2\text{iPr} \\
&134
\end{align*}
\]

\[
\begin{align*}
&\text{Na, NH}_3 \\
&(\text{THF}), -78^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
&\text{N} \\
&\text{Boc} \\
&\text{CO}_2\text{cHx} \\
&135 \quad R = \text{H}, \text{Me}, \text{Bn}, \text{iBu}
\end{align*}
\]

then R-X

\[
\begin{align*}
&\text{N} \\
&\text{Boc} \\
&\text{CO}_2\text{cHx} \\
&136
\end{align*}
\]

\[
\begin{align*}
&\text{Li, NH}_3 \\
&-78^\circ\text{C}
\end{align*}
\]

then R-X

\[
\begin{align*}
&\text{N} \\
&\text{Boc} \\
&\text{O} \\
&\text{Me} \\
&137 \quad R = \text{H} \rightarrow \text{de} = 82% \\
&\text{R = Me} \rightarrow \text{de} = 50%
\end{align*}
\]

138

2) Pyrroles

\[
\text{139} \xrightarrow{\text{Li, NH}_3, (\text{THF}), -78^\circ C \text{ (MeOCH}_2\text{CH}_2)_2\text{NH}} \xrightarrow{\text{then isoprene then R-X}} \text{140}
\]

\[
\text{R = Me} \rightarrow 78\% \text{ ee}
\]
\[
\text{Et} \rightarrow 86\% \text{ ee}
\]
\[
\text{iBu} \rightarrow 90\% \text{ ee}
\]
\[
\text{Bn} \rightarrow 90\% \text{ ee}
\]

\[
\text{141}
\]

\[
\text{142} \xrightarrow{\text{1) Li, NH}_3, (\text{THF}), -78^\circ C \text{ (MeOCH}_2\text{CH}_2)_2\text{NH}} \xrightarrow{\text{then isoprene then R-X (excess)}} \xrightarrow{\text{2) TFA, (CH}_2\text{Cl}_2}} \text{143}
\]

\[
\text{R = Me, Bn}
\]

Two different electrophiles also possible!


2) Pyrroles

**Aldol reaction:**

\[ \text{N}\text{Boc CO}_2\text{Pr} \xrightarrow{\text{Li, NH}_3, \text{(THF), -78°C}} \xrightarrow{\text{then isoprene then RCHO}} \text{N}\text{Boc CO}_2\text{Pr} \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>CHO</td>
<td>91%</td>
</tr>
<tr>
<td>147</td>
<td>CHO</td>
<td>90%</td>
</tr>
<tr>
<td>148</td>
<td>CHO</td>
<td>94%</td>
</tr>
<tr>
<td>149</td>
<td>CHO</td>
<td>78%</td>
</tr>
</tbody>
</table>

Only one example with furane

\[ \text{CHO} \xrightarrow{\text{Li, NH}_3, \text{(THF), -78°C}} \xrightarrow{\text{then isoprene then PhCHO}} \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>151</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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3) Furanes

3) Furanes

\[
\begin{align*}
\text{160} & \xrightarrow{\text{Na, NH}_3, \text{then Mel}} \text{dr = 41:59} \\
\text{161} & \\
\text{162} & \xrightarrow{\text{Na, NH}_3, \text{then Mel}} \text{dr = 30:1} \\
\text{163} & \\
\text{164} & \xrightarrow{\text{Na, NH}_3, \text{then R-X}} \text{de = 94\%} \\
\text{165} & \xrightarrow{6\text{M HCl}} \\
\text{166} & \\
\end{align*}
\]

\[R = \text{Me, Et, }\text{iBu, Bn, CH}_2\text{OMe, (CH}_2\text{)}_3\text{Cl, allyl}\]

Thiophenes

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R\(^1\) = Me, nPr, nC\(_9\)H\(_{19}\), cHx, OH, nC\(_7\)H\(_{15}\)
R\(^2\) = H, Me, Bu
R\(^3\) = Me, Bn, allyl, Bn

Thiophenes

\[
\begin{align*}
\text{173} & \xrightarrow{\text{Li, } \text{NH}_3, \text{NH}_4\text{Cl}} \text{174} \\
\text{174} & \xrightarrow{1) \text{ DCC, MeOH}} \xrightarrow{2) \text{ LAH}} \xrightarrow{3) \text{ Ac}_2\text{O, pyr}} \text{175} \\
\text{176} & \xrightarrow{\text{PFL lipase}} \\
\text{177} & \xrightarrow{1) \text{ OsO}_4, \text{NMO}} \xrightarrow{2) \text{ Ac}_2\text{O, pyr}} \\
\text{178} & \xrightarrow{\text{MeOH, } \text{Na}_2\text{CO}_3} \xrightarrow{\text{AcO}} \\
\end{align*}
\]

thio-\(D\)-ribose derivative

→ Birch reduction of hetero cycles much more complicated than carbocycles
→ Many variables to consider

\[
A \overset{e^-}{\longrightarrow} A^- \overset{\text{e}^-}{\longrightarrow} A-A^- \\
XH \overset{-X^-}{\longrightarrow} \overset{e^-}{\longrightarrow} A^{2-} \overset{XH}{\longrightarrow} -AH \overset{XH}{\longrightarrow} AH_2 \\
\overset{-X^-}{\downarrow} \quad \overset{-X^-}{\downarrow} \quad \overset{-X^-}{\downarrow} \\
A^{2-} \overset{\text{e}^-}{\longrightarrow} A'H \overset{XH}{\longrightarrow} A'H_2
\]

→ Very useful procedures under right conditions, especially under alkylation conditions!