Chapter 3: Protecting Groups

I. Protecting Groups of Hydroxyl Groups

* Consider the stability and effect of anomeric group!
* Consider the solubility of starting material (the choice of solvent)!
* Consider the reactivity of different hydroxyl groups!

* DCM is common for pyranoses with 2-3 OH’s. For pyranose with more than 4 OH’s, use DMF or pyridine.

* Nucleophilicity of OH groups on pyranoses (chair conformation) (Carbohydr. Res. 1987, 162, 159.)

$1^\circ$ OH $>$ $2^\circ$ OH
Equatorial OH $>$ axial OH
Equatorial OH with vicinal axial OH (or OR) $>$ Equatorial OH without vicinal axial OH (or OR)

Examples:

Estimated order of nucleophilicity: $6$-OH $>$ $2$-OH $>$ $3$-OH $\sim$ $4$-OH

Estimated order of nucleophilicity: $6$-OH $>$ $3$-OH $>$ $2$-OH $>$ $4$-OH
(i) Alkyl ether type

Sug—OH  ➔  Sug—OR

Advantages:
* Relatively stable in harsh conditions (acidic, basic, reflux, etc.)
* Enhance the reactivity of glycosylation due to electron-donating effect
* More compatible to the conditions needed for deoxygenation or amino (azido) substitution
* Selective protection is possible

Disadvantages:
* Relatively harder to remove (deprotect)
* Conditions for protection and deprotection may not be compatible to other types of protecting groups

(a) R = methyl (CH₃, Me)

* Not commonly used due to the difficulty of deprotection
* Methoxy group can be found in naturally occurring unusual sugars

<table>
<thead>
<tr>
<th>Protection</th>
<th>Reagent/Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MeOTf, DCM, py., 80°C</td>
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<table>
<thead>
<tr>
<th>Deprotection</th>
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<tr>
<td></td>
<td>BBr₃, EtOAc or DCM</td>
<td><em>J. Org. Chem.</em> 1979, 44, 4863.</td>
</tr>
<tr>
<td></td>
<td>SiCl₄, NaH, DCM, CH₂CN</td>
<td><em>Synthesis</em> 1982, 1048.</td>
</tr>
<tr>
<td></td>
<td>AlCl₃, AlBr₃</td>
<td><em>Chem. Lett.</em> 1979, 97.</td>
</tr>
<tr>
<td></td>
<td>Ac₂O, FeCl₃, 80°C</td>
<td><em>J. Org. Chem.</em> 1974, 39, 3728</td>
</tr>
</tbody>
</table>

Examples:

1) CH₃I, NaH, THF  
2) AcOH, TFA, H₂O  

77%
(b) R = trityl, triphenylmethyl (Ph₃C, Tr)

* Excellent for selective protection of primary OH
* Stable in basic but very labile in acidic conditions
* Easy to observe with TLC
* Deprotection can be tricky

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<tr>
<td></td>
<td>HCl, CHCl₃, 0°C</td>
<td>* Carbohydr. Res. 1971, 17, 439.</td>
</tr>
<tr>
<td></td>
<td>BF₃, Et₂O</td>
<td>* Can. J. Chem. 1978, 56, 2700</td>
</tr>
</tbody>
</table>

Examples:
(c) \( R = \text{methoxymethyl (CH}_3\text{OCH}_2, \text{MOM)} \)

* Can be incorporated at relatively weak basic conditions (3° amine) but needs relatively strong acid (TFA) to remove
* Stable in basic conditions
* The reagent, MOMCl, is considered carcinogenic

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<tr>
<td></td>
<td>MOMCl, DIPEA, 0°C or r.t.</td>
<td><em>Synthesis</em> <strong>1975</strong>, 276.</td>
</tr>
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<tr>
<td></td>
<td>LiBF(_4), CH(_3)CN, 80°C</td>
<td><em>J. Org. Chem.</em> <strong>1986</strong>, 51, 635.</td>
</tr>
</tbody>
</table>

Examples:
(d) R = benzyl (C₆H₅CH₂, Bn)

- Can be traceless removed using hydrogenolysis
- Stable in basic conditions
- Relatively stable in acidic conditions
- Quenching excess reagent (BrBr) with MeOH can be tricky

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<tr>
<td></td>
<td>BnBr, Bu₂SnO or (Bu₃Sn)₂O, toluene, reflux</td>
<td>* J. Am. Chem. Soc. 1994, 116, 5647</td>
</tr>
</tbody>
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<th>Reference</th>
</tr>
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<tr>
<td></td>
<td>H₂, Pd/C or Pd(OH)₂/C</td>
<td>* J. Am. Chem. Soc. 1994, 1121</td>
</tr>
</tbody>
</table>

Examples:

(Synthesis 1994, 1121)

(Org. Lett. 2004, 6, 1365)
(e) R = p-methoxybenzyl (CH$_3$OC$_6$H$_4$CH$_2$, PMB)

* More prone to oxidative cleavage than Bn but less prone to reductive cleavage than Bn
* Stable in basic conditions
* Relatively stable in acidic conditions

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<tr>
<td>Deprotection</td>
<td>(NH$_3$)$_2$Ce(NO$_2$)$_6$, Ceric ammonium nitrate (CAN), CH$_3$CN, H$_2$O</td>
<td>J. Am. Chem. Soc. 1985, 107, 4586.</td>
</tr>
<tr>
<td></td>
<td>DDQ, DCM</td>
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</table>
(f) R = tetrahydropyranyl (THP)

* Stability similar to glycosidic bond
* Stable in basic conditions

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<tr>
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<tr>
<td>TsOH, MeOH, r.t.</td>
<td>J. Am. Chem. Soc. 1978, 100, 1942.</td>
<td></td>
</tr>
</tbody>
</table>

Examples:

(ii) Silyl ether type

\[
\text{Sug} \underset{OH}{\longrightarrow} X \quad + \quad \text{R}_3\text{Si} \quad \text{NR}_3^+ \quad \rightarrow \quad \text{Sug} \underset{\text{OSiR}_3}{\longrightarrow} + \quad \text{H} \quad \text{NR}_3^+ \quad \text{X}^- 
\]

* Stability varies

General reagents for protection: \( \text{R}_3\text{SiX} \) with 3° amines (DIPEA, TEA, imidazole, lutidine, pyridine, etc)
Common reagents for deprotection: TBAF, BF₃, KF, or pyridine-HF

<table>
<thead>
<tr>
<th>Silyl Ether Type</th>
<th>Protection Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Trimethylsilyl (TMS)</td>
<td>Can be cleaved with ( \text{K}_2\text{CO}_3 ), MeOH or citric acid</td>
</tr>
<tr>
<td>Triethylsilyl (TES)</td>
<td>Can be cleaved with ( \text{HOAc} )</td>
</tr>
<tr>
<td>Triisopropylsilyl (TIPS)</td>
<td>Possible for selective protection of 1° OH</td>
</tr>
<tr>
<td>( t )-Butyldimethylsilyl (TBS)</td>
<td>Selective protection of 1° OH</td>
</tr>
<tr>
<td>( t )-Butyldiphenylsilyl (TBDPS)</td>
<td>Selective protection of 1° OH  Relatively stable in basic condition</td>
</tr>
</tbody>
</table>
(iii) Ester type

\[
\text{Sug-OH} + R\text{C}_X \rightarrow \text{Sug-O-C}_R + HX
\]

(a) R = trifluoroacetyl (TFA)

General reagent for protection: trifluoroacetic anhydride with 3° amines (DIPEA, TEA, imidazole, lutidine, pyridine etc), DMAP as catalyst
Common reagent for deprotection: weak acids or bases

(b) R = acetyl (Ac)

General reagents for protection: Ac₂O with 3° amines (DIPEA, TEA, imidazole, lutidine, pyridine etc) or Ac₂O with cat. acids.
Common reagents for deprotection: K₂CO₃, MeOH, cat. NaOMe in MeOH, or LiOH, THF, H₂O (J. Org. Chem. 2004, 69, 1513)

* anomeric acetyl group can be selectively removed with H₂NNH₂-HOAc or BnNH₂

Examples:
(c) \( R = \text{trimethylacetyl (Piv)} \)

* Can be used for selective protection

General reagent for protection: pivaloyl chloride (PivCl) with \(3^\circ\) amines (DIPEA, TEA, pyridine etc)

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<td></td>
<td>Bu(_4\text{N}^+\text{OH}^-, \text{r.t.})</td>
<td><em>Tetrahedron Lett.</em> 1979, 20, 3561.</td>
</tr>
<tr>
<td></td>
<td>DIBAL</td>
<td></td>
</tr>
</tbody>
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Examples:

\[\text{OH}
\begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{HO} \\
\text{HO} \\
\text{OMe}
\end{array}
\xrightarrow{\text{PivCl (2 equiv.)}}
\begin{array}{c}
\text{HO} \\
\text{PivO} \\
\text{HO} \\
\text{PivO} \\
\text{OMe}
\end{array}
\]

\[\text{OH}
\begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{HO} \\
\text{HO} \\
\text{OMe}
\end{array}
\xrightarrow{\text{PivCl (2 equiv.)}}
\begin{array}{c}
\text{HO} \\
\text{PivO} \\
\text{HO} \\
\text{PivO} \\
\text{OMe}
\end{array}
\]

\[\text{OH}
\begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{HO} \\
\text{SPh}
\end{array}
\xrightarrow{\text{PivCl (2 equiv.)}}
\begin{array}{c}
\text{HO} \\
\text{PivO} \\
\text{HO} \\
\text{SPh}
\end{array}
\]

*(J. Org. Chem. 1998, 63, 6035)*
(d) R = Benzoyl (Bz)

* Can be used for selective protection

General reagent for protection: benzoyl chloride (BzCl) with 3° amines (DIPEA, TEA, pyridine etc)
* Less common method for protection: Benzoic acid, DEAD, PPh₃

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<tr>
<td></td>
<td>K₂CO₃, MeOH</td>
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<td></td>
<td>DIBAL</td>
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</table>

Examples:
II. Protecting Groups of 1,2- or 1,3-Dihydroxyl Groups

Consider the formation of acetal (ketal) from diol and aldehyde (ketone)!
Consider the solubility of ring or fused ring for selectivity!

Six-membered ring: thermodynamically favored
Five-membered ring: kinetically favored

General Mechanism
(i) For selection between 1,3-diol and trans-1,2-diol

(ii) For selection between 1,3-diol and cis-1,2-diol

(iii) For selection between trans-1,2-diol and cis-1,2-diol
(iv) Acetonide (isopropylidene)

Common reagents for protection: acetone or Me₂C(OMe)₂ and acids (TsOH, PPTS, ZnCl₂ etc) with removal of water
Common reagents for deprotection: acids (TsOH, TFA, HCl etc) with addition of water

Examples:
(v) Benzylidene

Common reagents for protection: PhCHO or PhCH(OMe)₂ and acids (TsOH, PPTS, ZnCl₂ etc) with removal of water
Common reagents for deprotection: acids (TsOH, TFA, HCl etc) with addition of water

* Can be selectively converted into Bn or Bz

Examples:

(J. Org. Chem. 1969, 34, 1035)

(J. Org. Chem. 2000, 65, 2410)
(vi) Cyclohexane-1,2-diacetals (CDA)

\[
\begin{align*}
\text{MeOH, CH(O\text{Me})_3, cat. H}_2\text{SO}_4, \text{reflux} \quad & \quad \begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{CDA, MeOH, CH(O\text{Me})_3, cat. CSA, reflux} \quad & \quad \begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array}
\end{align*}
\]


Similar reagent: CH\text{3}(O\text{Me})_2C(O\text{Me})_2\text{CH}_3, or 2,3-butanedione

(vii) Silyl-based protecting group

Triisopropyldisilyl (TIPDS)

\[
\begin{align*}
\text{HO} & \quad \begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{Z}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{HO} \\
\text{OH}
\end{array}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{iPr} & \quad \begin{array}{c}
\begin{array}{c}
\text{Si} \\
\text{O}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{iPr} \\
\text{iPr}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{Z}
\end{array}
\end{array}
\end{align*}
\]

15
(viii) Other examples

\[
\begin{align*}
\text{Cyclohexone dimethyl ketal, TsOH-H}_2\text{O, CH}_3\text{CN} & \quad 41\% \\
\text{(Org. Lett. 2004, 3, 1381)}
\end{align*}
\]
III. Protecting Groups of Amino Groups

(i) Masking NH$_2$ (amino) as N$_3$ (azido)


Examples:


(Org. Lett. 2007, 9, 3797–3800)
The azido group can be converted (reduced) to amino group using the following methods:
(1) H₂, Pd/C; (2) PR₃, THF, H₂O; (3) LiAlH₄; (4) thiols (HSCH₂CH₂SH, HSCH₂CH₂OH, dithiothreitol etc)

* Hydrogenation can be

* Mechanism of Staudinger reaction

6,3',4'-tri-O-benzyl-tetraazidoneamine

Per-azido per-benzyl tobramycin

1) TFA/CH₂Cl₂
2) EDC, HOBt, Et₃N, NMP, DMF

28%
1.0 M PMe₃ in toluene (1.1 eq.), Boc-ON (2.4 eq.), toluene, -78°C to 10°C

31%

Boc-ON:

(ii) Phthalamide (intermediate involved in Gabriel amine synthesis)

Common reagents for protection: phthalic anhydride
Common reagents for deprotection: acids hydrazine, EtOH, reflux

Example:
(iii) Carbamate-type

\[ \text{R-NH}_2 + \text{Cl-OC(O)O} \text{R'} + :B \rightarrow \text{R-NOC(O)O} \text{R'} + \text{H}^+ \text{B-Cl}^- \]

* Solvent selection is important.

(a) 9-Fluorenylmethoxycarbonyl chloride (Fmoc-Cl)

* Stable in acidic and neutral conditions
* Easy to observe with strong UV absorption

Common reagents for deprotection: amines (piperidine)

(b) Di-tert-butyl dicarbonate, Boc anhydride (Boc₂O)

* Stable in basic and neutral conditions

Common reagents for deprotection: acids (TFA)
(c) Benzyl chloroformate, Carbobenzyloxy chloride (Cbz-Cl, Z-Cl)

* Stable in acidic, basic and neutral conditions

Common reagents for deprotection: hydrogenolysis (H\textsubscript{2}, Pd/C))

\[ \begin{align*}
\text{Cl} & \quad \text{O} \\
\text{O} & \quad \text{C} \\
\text{O} & \quad \text{H}
\end{align*} \]

(d) Allyl chloroformate (Alloc-Cl)

* Stable in acidic, basic and neutral conditions

Common reagents for deprotection: Pd(0) reagents

\[ \begin{align*}
\text{Cl} & \quad \text{O} \\
\text{O} & \quad \text{C} \\
\text{O} & \quad \text{C} \\
\text{C} & \quad \text{H}
\end{align*} \]