REVIEW IN FUNCTIONAL AND PROTECTING GROUPS

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ABSTRACT

In organic chemistry, many preparations of delicate organic compounds, some specific parts of their molecules cannot survive the required reagents or chemical environments. Then, these parts, or groups, must be protected. For example, lithium aluminum hydride is a highly reactive but useful reagent capable of reducing esters to alcohols. It will always react with carbonyl groups, and this cannot be discouraged by any means. When a reduction of an ester is required in the presence of a carbonyl, the attack of the hydride on the carbonyl has to be prevented.

KEYWORDS: Protecting, Function, Carbonyl Protected, Amine Protected

INTRODUCTION

Protecting groups are more commonly used in small-scale laboratory work and initial development than in industrial production processes because their use adds additional steps and material costs to the process, it is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction. It plays an important role in multistep organic synthesis.

Protecting Groups

- **Protecting groups** are used in synthesis to temporarily mask the characteristic chemistry of a functional group because it interferes with another reaction.
- A good protecting group should be easy to put on, easy to remove and in high yielding reactions, and inert to the conditions of the reaction required.
- For example, consider the following scenario: How can you perform the following reaction?

![Figure 1](image)

**Figure 1**

The overall transformation required is ester to primary alcohol. This is a reduction of the ester, which requires LiAlH₄, but that will reduce the ketone as well which we don't want. We can avoid this problem if we "change" the ketone to a different functional group first. Conceptually, this is like being able to put a cover (shown below) over the ketone while we do the reduction, then remove the cover.
Butyloxycarbonyl group is protecting group.

One of the purposes in protecting groups in organic synthesis is to eliminate unwanted side reactions. One of the major problems in organic synthesis is the suppression of unwanted side reactions. Frequently the desired reaction is accompanied by reaction at other parts of the molecule, especially when more than one functional group is present. Functional groups usually are the most reactive sites in the molecule, and it may be difficult or even impossible to insulate one functional group from a reaction occurring at another. Therefore any proposed synthesis must be evaluated at each step for possible side reactions that may degrade or otherwise modify the structure in an undesired way. To do this will require an understanding of how variations in structure affect chemical reactivity. Such understanding is acquired through experience and knowledge of reaction mechanism and reaction stereochemistry.

To illustrate the purpose and practice of protecting groups in organic synthesis, let us suppose that the synthesis of cis-2-octene, which we outlined in BUILDING THE CARBON SKELETON, has to be adapted for the synthesis of 5-octyn-1-ol. We could write the following: Stop Wearing Lame Shirts!

\[
\text{CH}_3\text{CH}_2\text{C}==\text{CH} \xrightarrow{\text{NaNH}_2} \text{CH}_2\text{CH}_2\text{C}==\text{C}:\text{Na} \xrightarrow{\text{BrCH}_3\text{CH}_2\text{CH}_2\text{OH}} \text{CH}_2\text{CH}_2\text{C}==\text{C}(\text{CH}_3)\text{OH}
\]

Figure: 3

However, the synthesis as written would fail because the alkyn is a weaker acid than the alcohol, and the alkynide anion would react much more rapidly with the acidic proton of the alcohol than it would displace bromide ion from carbon:

\[
\text{CH}_2\text{CH}_2\text{C}==\text{C}:\text{Na} + \text{HOCH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{} \text{CH}_2\text{CH}_2\text{C}==\text{CH} \xrightarrow{\text{NaO}(\text{CH}_2)\text{Br}} \text{CH}_2\text{CH}_2\text{C}==\text{C} + \text{Na}:\text{Br}
\]

Figure: 4

The hydroxyl group of 4-bromo-1-butanol therefore must be protected before it is allowed to react with the alkynide salt. There are a number of ways to protect hydroxyl groups, but one method, which is simple and effective, relies on the fact that unsaturated ethers of the type \( \text{RO} \), are very reactive in electrophilic addition reactions. An alcohol readily adds to the double bond of such an ether in the presence of an acid catalyst:

\[
\text{C}==\text{C} \xrightarrow{\text{H}^+} \text{C}==\text{C} \xrightarrow{\text{BrCH}_3\text{OH}} \text{C}==\text{C} \xrightarrow{\text{Br}/\text{CH}_3\text{O}} \text{C}==\text{C} + \text{H}^+
\]

Figure: 5
The protected compound is a much weaker acid than the alkyne, and the displacement reaction can be carried out with the alkynide salt without difficulty. To obtain the final product, the protecting group must be removed, and this can be done in dilute aqueous acid solution by an S$_{N}$1 type of substitution:

\[
\begin{align*}
\text{CH}_2\text{C} & \equiv \text{C} & \text{CH}_2\text{C} & \equiv \text{C} \\
\text{RO} & \text{H} & \text{RO} & \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{C} & \equiv \text{C} & \text{CH}_2\text{C} & \equiv \text{C} & \text{H} \\
\text{RO} & \text{H} & \text{RO} & \text{H}
\end{align*}
\]

Protection of amines:

- Carbobenzyloxy (Cbz) group – Removed by hydrogenolysis
- p-Methoxybenzyl carbonyl (Moz or MeOZ) group – Removed by hydrogenolysis, more labile than Cbz
- tert-Butyloxy carbonyl (BOC) group (common in solid phase peptide synthesis) – Removed by concentrated strong acid (such as HCl or CF$_3$COOH), or by heating to $>$80 °C.
- 9-Fluorenylmethyloxycarbonyl (FMOC) group (Common in solid phase peptide synthesis) – Removed by base, such as piperidine
- Acetyl (Ac) group is common in oligonucleotide synthesis for protection of N4 in cytosine and N6 in adenine nucleic bases and is removed by treatment with a base, most often, with aqueous or gaseous ammonia or methylamine. Ac is too stable to be readily removed from aliphatic amides.
- Benzoyl (Bz) group is common in oligonucleotide synthesis for protection of N4 in cytosine and N6 in adenine nucleic bases and is removed by treatment with a base, most often with aqueous or gaseous ammonia or methylamine. Bz is too stable to be readily removed from aliphatic amides.
- Benzyl (Bn) group – Removed by hydrogenolysis
- Carbamate group – Removed by acid and mild heating.
- p-Methoxybenzyl (PMB) – Removed by hydrogenolysis, more labile than benzyl
- 3,4-Dimethoxybenzyl (DMPM) – Removed by hydrogenolysis, more labile than p-methoxybenzyl
- p-methoxyphenyl (PMP) group – Removed by ammonium cerium(IV) nitrate (CAN)
• Tosyl (Ts) group – Removed by concentrated acid (HBr, H₂SO₄) & strong reducing agents (sodium in liquid ammonia or sodium naphthalenide)
• Other Sulfonamides (Nosyl & Nps) groups – Removed by samarium iodide, tributyltin hydride.

CARBONYL PROTECTING GROUPS:

Protection of Carbonyl Groups:

- Acetals and Ketals – Removed by acid. Normally, the cleavage of acyclic acetals is easier than of cyclic acetals.
- Acylals – Removed by Lewis acids.
- Dithianes – Removed by metal salts or oxidizing agents.

CARBOXYLIC ACID PROTECTING GROUPS:

Protection of Carboxylic Acids

- Methyl esters – Removed by acid or base.
- Benzyl esters – Removed by hydrogenolysis.
- tert-Butyl esters – Removed by acid, base and some reductants.
- Esters of 2,6-disubstituted phenols (e.g. 2,6-dimethylphenol, 2,6-diisopropylphenol, 2,6-di-tert-butylphenol) – Removed at room temperature by DBU-catalyzed methanolysis under high-pressure conditions.
- Silyl esters – Removed by acid, base and organometallic reagents.
- Orthoesters – Removed by mild aqueous acid to form ester, which is removed according to ester properties.
- Oxazoline – Removed by strong hot acid (pH < 1, T > 100 °C) or alkali (pH > 12, T > 100 °C), but not e.g. LiAlH₄, organolithium reagents or Grignard (organomagnesium) reagents.

Phosphate Protecting Groups:

- 2-cyanoethyl – removed by mild base. The group is widely used in oligonucleotide synthesis.
- Methyl (Me) – removed by strong nucleophiles e.g. thiophenole/TEA.
Terminal Alkyne Protecting Groups:

- propargyl alcohols in the Favorskii reaction,
- silyl groups, especially in protection of the acetylene itself.\(^4\)

**ALCOHOL PROTECTING GROUPS**

**Protection of Alcohols**

- Acetyl (Ac) – Removed by acid or base (see Acetoxy group).
- Benzoyl (Bz) – Removed by acid or base, more stable than Ac group.
- Benzyl (Bn, Bnl) – Removed by hydrogenolysis. Bn group is widely used in sugar and nucleoside chemistry.
- \(\beta\)-Methoxyethoxymethyl ether (MEM) – Removed by acid.
- Dimethoxytrityl, [bis-(4-methoxyphenyl)phenylmethyl] (DMT) – Removed by weak acid. DMT group is widely used for protection of 5'-hydroxy group in nucleosides, particularly in oligonucleotide synthesis.
- Methoxymethyl ether (MOM) – Removed by acid.
- Methoxytrityl [(4-methoxyphenyl)diphenylmethyl, MMT) – Removed by acid and hydrogenolysis.
- p-Methoxybenzyl ether (PMB) – Removed by acid, hydrogenolysis, or oxidation.
- Methylthiomethyl ether – Removed by acid.
- Pivaloyl (Piv) – Removed by acid, base or reductant agents. It is substantially more stable than other acyl protecting groups.
- Tetrahydropyranyl (THP) – Removed by acid.
- Tetrahydrofuran (THF) - Removed by acid.
- Trityl (triphenylmethyl, Tr) – Removed by acid and hydrogenolysis.
- Silyl ether (most popular ones include trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS), tri-isopropylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS) ethers) – Removed by acid or fluoride ion. (such as NaF, TBAF (Tetra-n-butylammonium fluoride, HF-Py, or HF-NEt\(_3\))). TBDMS and TOM groups are used for protection of 2'-hydroxy function in nucleosides, particularly in oligonucleotide synthesis.
- Methyl Ethers – Cleavage is by TMSI in DCM or MeCN or Chloroform. An alternative method to cleave methyl ethers is BBr\(_3\) in DCM.
Ethoxyethyl ethers (EE) – Cleavage more trivial than simple ethers e.g. 1N Hydrochloric acid$^{(1)}$

**BRIEFLY**

**Protecting of Alcohol:**
- Trimethylsilyl ether (TMS)
- Triethylsilyl ether (TES)
- Triisopropylsilyl ether (TIPS)
- tert-Butyldimethylsilyl ether (TBS, TBDMS)
- tert-Butylidiphenylsilyl ether (TBDPS)
- Acetate (Ac)
- Benzoate (Bz)
- Benzyl ether (Bn)
- 4-Methoxybenzyl ether (PMB)
- 2-Naphthylmethyl ether (Nap)
- Methoxymethyl acetal (MOM)
- 2-Methoxyethoxymethyl ether (MEM)
- Ethoxyethyl acetal (EE)
- Methoxypropyl acetal (MOP)
- Benzyloxymethyl acetal (BOM)
- Tetrahydropyranyl acetal (THP)
- 2,2,2-Trichloroethyl carbonate (Troc)
- Methyl ether

**Protecting of Phenol**
- Triisopropylsilyl ether (TIPS)
• tert-Butyldimethylsilyl ether (TBS, TBDMS)
• Methyl ether
• Benzyl ether (Bn)
• Methoxymethyl acetal (MOM)
• [2-(Trimethylsilyl)ethoxy]methyl acetal (SEM)

Protecting of Amine
• Trifluoroacetamide
• tert-Butyloxycarbamate (Boc)
• Benzylcarbonylcarbamate (CBz)
• Acetamide (Ac)
• Formamide
• Methyl carbamate
• 4-Methoxybenzenesulfonamide
• Benzylamine (Bn)

Protecting of Carboxylic Acid
• Methyl ester
• Benzyl ester

Protecting of Aldehyde and Ketone
• Dimethyl acetal
• Ethylene glycol acetal
• Neopentyl glycol acetal
• Trimethylsilyl cyanohydrin
• 1,3-Dithiane
• Diethyl acetal
• 1,3-Dithiolane

Protecting of Sulfonamide
• tert-Butyloxycarbamate (Boc)

Protecting of 1,2-Diol
• Acetonide
• Benzaldehyde acetal
• Carbonate

Protecting of Acetylene

• Trimethylsilane (TMS)

Protecting of Indole

• tert-Butoxy carbamate (Boc)
• N-(4-Methoxybenzyl)indole (PMB)
• Methoxymethyl aminal (MOM)

General Characteristics

Carbonyl groups are generally protected as acetals under acidic conditions. Acetals are stable under reductive, basic, nucleophilic, and oxidizing (nonacidic) conditions.

Reaction Mechanism

Acetalization is naturally reversible. Use of the alcohols in excess and/or efficient removal of water from the system become important to push the reactions to completion.

![Figure: 11](image1)

The order of reactivity for carbonyl compounds is roughly as follows.

![Figure: 12](image2)

Examples

The total synthesis of saxitoxin\(^1\): Taking advantage of the fact that oxygens are more easily activated by hard Lewis acids or Brønsted acids than sulfurs, the O-acetal was directly converted into the S-acetal.

![Figure: 13](image3)
The Noyori conditions\textsuperscript{[2]}. Acetals or ketals can be synthesized in high yield using the bis-TMS ether reagent and catalytic TMSOTf. This reaction works even at cryogenic temperatures. The disiloxane (TMSOTMS) byproduct is stable and unreactive that the reverse reaction does not occur, allowing for kinetically-controlled protection.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure14.png}
\caption{Figure: 14}
\end{figure}

The Otera catalyst\textsuperscript{[3]}. Otera’s distannoxane catalyst mediates acetalization of acid-sensitive compounds. It is proposed that the catalyst forms a nucleophilic tin alkoxide as well as acting as a mild Lewis acid. This reaction does not require any dehydration apparatus.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure15.png}
\caption{Figure: 15}
\end{figure}

Ketone-selective acetalization in the presence of aldehyde\textsuperscript{[4]}. The example shown here uses treatment with dimethylsulfide and TMSOTf, followed by the Noyori conditions.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure16.png}
\caption{Figure: 16}
\end{figure}

The protection of cyclohexanone with ethylene glycol\textsuperscript{[5]}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure17.png}
\caption{Figure: 17}
\end{figure}

The most popular acetal protecting groups are shown below. The hydrolysis of six-membered ring acetals is faster than that of five-membered ring acetals.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure18.png}
\caption{Figure: 18}
\end{figure}
Thioacetals are Deprotected Mainly by

- Methylation then hydrolysis.
- Oxidation (e.g. by hypervalent iodine) then hydrolysis.
- Hydrolysis using Hg(II).

**Two protecting groups for alcohols:**
- Trimethylsilyl ether formation using trimethylsilyl chloride (TMS-Cl) and triethylamine (NET₃).
- Easily removed by aqueous acid (H₃O⁺) or fluoride (F⁻).

\[
\text{R-O-H} \xrightarrow{\text{NET}_3, \text{TMS-Cl}} \text{R-O-TMS}
\]

**Two protecting groups for alcohols:**
- Dihydroxypropyl (DHP) and an acid catalyst (H⁺) will react to form a tetrahydroxypropyl protecting group (THP).
- Easily removed by aqueous acid (H₃O⁺).

\[
\text{R-O-H} \xrightarrow{\text{H}^+} \text{R-O-THP}
\]

**For more than one alcohol...**

...remember that there is an order in which alcohols are protected, beginning with primary alcohols (least sterically hindered), then secondary alcohols (more sterically hindered) and finally tertiary alcohols:

- Remember the order for protecting alcohols is always going to show reactivity on the 1°, then 2° and then 3°.

Thus: \[\text{primary} \rightarrow \text{secondary} \rightarrow \text{tertiary}\]
REFERENCES


2. Moussa, Ziad; D. Romo (2006). "Mild deprotection of primary N-(p-toluenesufonyl) amides with SmI₂ following


