Organic chemistry 1

- Oxidation – Reduction
- Protecting groups (total synthesis, carbohydrates chemistry, peptides…)
- Olefination reactions

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Chimioselective Nucleophilic Additions

Example

Acetal protection of the ketone (inert in presence of Grignard reagents)
Chimioselective Nucleophilic Additions

Example

Need acetal protection of the ketone (inert in presence of Grignard reagents)

7 tactical rules

1. Introduced easily & efficiently (high yield!).
2. Cheap and/or easily available.
3. Easy to characterize (avoid PG's introducing new stereogenic centres in the molecule).
4. Stable during purification
5. Stable within the broadest set of experimental conditions (Δ, aqueous, A or B, Ox or Red, …).
6. Removed easily and efficiently (high yield !) under very specific conditions.
7. By-products formed during the deprotection step should be easily separated.
1. Basic hydrolysis
2. Acid hydrolysis
3. Heavy metals deprotection
4. Fluoride deprotection
5. Hydrogenolysis
6. Transition metal catalysis
7. Photochemical deprotection
8. Enzymatic deprotection
9. .......
CARBONYL

dialkylacetal

1,3-dioxane
1,3-dioxolane

S,S'-dialkyldithioacetal

1,3-dithiane
1,3-dithiolane
1,3-oxathiolane
**O,O-acetals**

### Cyclic acetals

![Chemical reaction diagram]

**Deprotection**

**Relative hydrolysis**

1. Substituents that stabilize carbocation favored hydrolysis.
2. Ketals derived from ketones hydrolyse faster than aldehyde

### Preparation

- Acetals from aldehydes are formed faster than from ketones
- Enone system are less reactive due to the presence of the double bond
**O,O-acetals**

### Cyclic acetals

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{H}^+ \text{ or Lewis acid} & \quad \text{TMSO or OTMS} \\
\text{or} & \\
\text{HCl or APTS or PPTS (mild)} & \quad \text{solvent + H}_2\text{O}
\end{align*}
\]

**Deprotection**

**Relative hydrolysis**

1 2 31 13 16 172

**Note:**
- Substituents that stabilize carbocation favored hydrolysis.
- Ketals derived from ketones hydrolyse faster than aldehyde.

**Preparation**

- Acetals from aldehydes are formed faster than from ketones.
- Enone system are less reactive due to the presence of the double bond.

### Acyclic acetals

Less stable than cyclic acetals

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{HC(OMe)}_3 \text{ or PPTS} & \quad \text{TFA or APTS or PPTS (mild)} \\
\text{solvent + H}_2\text{O}
\end{align*}
\]
**O,O-acetals**

**Examples**

1. **TBSO**

    ![TBSO](image1)

    

    

    APTS (cat)

    Acetone

2. **CHO**

    ![CHO](image2)

    

    

    APTS

3. **K<sub>2</sub>CO<sub>3</sub>**

    ![K<sub>2</sub>CO<sub>3</sub>](image3)

    

    

    i. TMSOTf, DMS

    ii. TMSO~OTMS

    iii. K<sub>2</sub>CO<sub>3</sub>

**(-)-Jesterone synthesis**

![(-)-Jesterone synthesis](image4)

**Ph<sub>3</sub>COOH**

KHMDMS

**PPTS reflux**
**O,O-acetals**

**Examples**

- Selective deprotection of $\text{RO}$ donor for protection of $\text{S,S}-\text{acetal}$ are stable under acidic conditions.
S,S-acetals

**Drawbacks**
- thiols / dithiols have a nauseous smell
- deprotection with heavy metals → toxicity
- sulfur can poison catalysts such as Pd...

**Mechanism**
- Hydrolysis
- Ni Raney reduction affords the alkane
- S,S-acetals are useful for acyl anion equivalent (umpolung)

\[ \text{O} \quad \text{R}_1 \text{R}_2 \quad \text{H} \quad \text{S}_2 \quad \text{S} \quad \text{R}_1 \text{R}_2 \quad \text{O} \]

\[ \text{HS} \quad \text{SH} \quad \text{APTS or Lewis acid} \]

\[ \text{HgCl}_2, \text{Hg(ClO}_4\text{)}_2 + \text{base (CaCO}_3, \text{BaCO}_3...) \]
\[ \text{HgO, BF}_3, \text{Et}_2\text{O} \]

\[ \text{I}_2, \text{NaHCO}_3 \]
\[ \text{NBS, lutidine} \]
\[ \text{mCPBA} \]

\[ \text{Mel, CaCO}_3, \text{MeCN/H}_2\text{O ou Me}_3\text{OBF}_4, \text{MeOTf} \]
**S,S-acetals**

**Examples**

1. 
   \[
   \text{Hg(ClO}_4\text{)}_2, \text{CaCO}_3 \xrightarrow{\text{MeOH}}
   \]

2. 
   \[
   \text{NCS, AgNO}_3 \xrightarrow{\text{MeCN, H}_2\text{O}}
   \]

3. 
   \[
   \text{Mel (2 eq)} \xrightarrow{\text{CaCO}_3} \text{MeCN-H}_2\text{O}
   \]
DIOL

- methylidene acetal
- acetonide
- cyclohexylidene acetal
- benzyldine acetal
- \( p \)-methoxybenzyldine acetal (PMB)
- di-\( t \)-butylsilylene acetal
- cyclic carbonate

**Cleavages:**
- Cleaved by hydrogenolysis
- Cleaved with DDQ or CAN
- Cleaved with \( F^- \)
- Cleaved under basic conditions
Acetals are generally stable to base, and cleaved with acid catalyzed conditions (TFA-H₂O; Dowex + MeOH/H₂O; PPTS + MeOH...)

- 1,3-dioxanes hydrolyzed faster than 1,3-dioxolanes
- Possibility of orthogonal deprotection with TBS, using a thiol or iodine, CuCl₂, Zn(NO₃)₂, FeCl₃

Selectivity in 5/6/7 membered rings depends on experimentals conditions/substrate but, in general 5 membered rings are favored.

Cycloalkylidene

Same chemistry as isopropylidene but compounds are less solubles.
Acetals

Isopropylidene

General Conditions:

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Cycloalkylidene

Same chemistry as isopropylidene but compounds are less solubles.

Arylmethylene acetal

- Acid catalyzed deprotection
- Catalytic hydrogenation
- Lewis acid + hydride donor

Note for PMB derivative:
- PMB derivatives can be selectively deprotected with DDQ or CAN.
- Hydrolysis is 10x faster than benzylidene in acidic conditions
Acetals

Diol

Examples

1,3-dioxane hydrolyses faster than 1,3-dioxolane.

Selective deprotection of thiol, or iodine, CuCl₂, Zn(NO₃)₂, FeCl₃.

5-membered rings are favored.
ALCOHOL

Silyl ethers

Alkyl ethers

Alkyloxyalkyl ethers

Esters

Carbonates
Silyl protective groups

The conditions required for deprotection depend heavily on the specific silyl group and the steric environment of the silyl ether.

Selective deprotection of the more accessible of two silyl ethers is frequently possible.

All silyl groups are typically cleaved with $F^-$.
Silyl protective groups

Examples

\[
\text{I} - \text{OTBS} \xrightarrow{\text{PPTS}} \text{MeOH, rt, Ar, 2.5 h, light exclusion, 66\% (83\% b.o.r.s.m.)}
\]

\[
\text{TBDPSO} - \text{OTBS} \xrightarrow{\text{Cl}_3\text{CCO}_2\text{H}} \text{THF / H}_2\text{O}
\]

\[
\text{HO} - \text{Bn} - \text{BnO} - \text{Bn} - \text{Bn} \xrightarrow{\text{TBDPSCI imidazole}} \text{DMF}
\]
Silyl protective groups

Examples

\[
\text{I-} \quad \text{OTBS} \quad \xrightarrow{\text{PPTS}} \quad \text{MeOH, rt, Ar, 2.5 h, light exclusion, 66% (83% b.o.r.s.m.)} \quad \text{I-} \quad \text{OH} \quad \text{OTBS}
\]

\[
\text{TBDPSO} - \text{OTBS} \quad \xrightarrow{\text{Cl}_3\text{CCO}_2\text{H}} \quad \text{THF / H}_2\text{O} \quad \text{TBDPSO} - \text{OH} \quad \text{OTIPS}
\]

\[
\text{HO} - \text{BnO} - \text{BnO} \quad \xrightarrow{\text{TBDPSCl} \text{ imidazole}} \quad \text{DMF} \quad \text{TBDPSO} - \text{BnO} - \text{BnO} - \text{BnO}
\]

*Imidazole ?*
Silyl protective groups

Examples

Scheme 2. Reagents and conditions: a) TBSCl (1 equiv.), NaH, THF, RT, 1 h (60%); b) TsCl, Et₃N, DMAP (cat.), CH₂Cl₂, RT, overnight (86%); c) H₂C=CHCH₂MgBr, CuI, Et₂O, -20 °C → RT, 4.5 h (92%); d) TBAF, THF, RT, overnight (99%); e) PCC/Al₂O₃, NaOAc, CH₂Cl₂, RT, 3 h (80%).
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Ethers as protective groups

- methyl ether (Me)
- tert-Butyl ether (tBu)
- trityl ether (Tr)
- benzyl ether (Bn)
- p-methoxybenzyl (PMB) ether
- allyl ether (allyl)

Note: methyl ether are essentially used on phenol (deprotection with BX$_3$ or AlCl$_3$).

Formation by Williamson ether synthesis.

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**tBu ether**

Stable to basic conditions and to alkyl lithium nucleophilic attack.

**Déprotection**
- Acids and Lewis (strong): H$^+$, AL, TMSI
- TFA (anhydrous)
- HCl-dioxane 1M, Δ

**Formation**
- $\text{CF}_2\text{CF}_2\text{CF}_3$ , H$_2$SO$_4$
- $\text{Cl}_3\text{CCl}$, CH$_2$Cl$_2$-cyclohexane

---

**trityl ether**

Stable to basic conditions and to alkyl lithium nucleophilic attack but cleaved under mild acidic conditions.

**Déprotection**
- Acids and Lewis (mild): H$^+$, AL, resins
- Oxidant such as CAN, DDQ
- Na/NH$_3$

**Formation**
- Ph$_3$CCl, pyr, (DMAP cat)
- Ph$_3$COTf, 2,6-collidine

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mechanism
Ethers as protective groups

- methyl ether (Me)
- tert-Butyl ether (tBu)
- trityl ether (Tr)
- benzyl ether (Bn)
- p-methoxybenzyl (PMB) ether
- allyl ether (allyl)

- Bn, PMB and allyl ethers are robust; typically stable to acidic or basic conditions.
- Bn and PMB groups can be cleaved under orthogonal conditions.

**Benzyl derivatives**

General Conditions:

- **Déprotection for Bn and PMB:**
  - Hydrogenolysis: \( H_2 + \text{Pd/C} \) ou \( \text{Pd(OH)}_2 \) ou Rh/alumine
  - \( \text{Na, NH}_3 \) or \( \text{LiDBB} \)
  - \( \text{BX}_3, \text{DCM} \)
  - NBS

- **Orthogonal Déprotection for PMB:** \( \text{DDQ, CH}_2\text{Cl}_2 \) or \( \text{CAN, MeCN-H}_2\text{O} \)
  (compatible with acetal, MEM, MOM, THP, TBS, Ts)

**Allyl ether**

- Déprotection
  - Pd/C
  - Wilkinson (Rh) and in second step HCl or SeO\(_2\) or OsO\(_4\)…
  - Baudry (Ir)
Ethers as protective groups

**Examples**

1. \( \text{BnO} - \text{CH}_2 - \text{CH}_2 - \text{O} \) with \( \text{H}_2, \text{Pd/C} \) in \( \text{EtOH} \) gives 96% yield.

2. \( \text{OBN} - \text{CH}_2 - \text{CH}_2 - \text{O} \) with \( \text{NBS}, \text{CaCO}_3 \) in \( \text{hv} \) in \( \text{CCl}_4, \text{H}_2\text{O} \).

3. \( \text{MeO}_2\text{C} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{TBS} \) with \( \text{Cl}_3\text{C}(-\text{NH})\text{OCH}_2(p\text{-MeOPh}), \text{TfOH}, \text{CH}_2\text{Cl}_2, 0^\circ\text{C}, 3\text{ h} \) gives 75% yield.

4. \( \text{MeO} - \text{CH}_2 - \text{CH}_2 - \text{N}_{\text{Me}}\text{N} - \text{Me} \) with \( \text{DDQ}, \text{CH}_2\text{Cl}_2/\text{H}_2\text{O} \) at room temperature for 1 hr gives 84% yield.

5. \( \text{TBSO} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{OPMB} \) with \( 1. \text{Wilkinson} \) and \( \text{DABCO} \) followed by \( 2. \text{OsO}_4, \text{NMO} \).

**mechanism**
Ethers as protective groups

Examples

1. BnO-ethyl ether

\[ \text{BnO} - \text{ethyl ether} \xrightarrow{H_2, \text{Pd/C}, \text{EtOH}} \text{EtO} - \text{ethyl ether} \]

2. 1,2-epoxybutane

\[ \text{1,2-epoxybutane} \xrightarrow{\text{NBS, CaCO}_3, \text{hv}} \text{glycidol} \]

3. 1,3-di-O-benzyl-2-O-TBS-D-glucofuranose

\[ \text{1,3-di-O-benzyl-2-O-TBS-D-glucofuranose} \xrightarrow{\text{Cl}_3\text{C}(=\text{NH})\text{OCH}_2(p-\text{MeOPh}), \text{TfOH, CH}_2\text{Cl}_2, 0 \degree \text{C, 3 h}} \text{1,3-di-O-benzyl-2-O-TBS-D-glucofuranose} \]

4. 6-amino-6-deoxy-1,3,4,6-tetradecahydro-2H-3,5-pyran-2-one

\[ \text{6-amino-6-deoxy-1,3,4,6-tetradecahydro-2H-3,5-pyran-2-one} \xrightarrow{\text{DDQ, CH}_2\text{Cl}_2/H_2\text{O, rt, 1 hr}} \text{pyranone} \]

5. 2,3-dideoxy-3-thio-4-O-pivaloyl-2,3,4,5-tetra-O-benzyl-D-arabinohex-2-ulose

\[ \text{2,3-dideoxy-3-thio-4-O-pivaloyl-2,3,4,5-tetra-O-benzyl-D-arabinohex-2-ulose} \xrightarrow{1. \text{Wilkinson DABCO, 2. OsO}_4, \text{NMO}} \text{2,3-dideoxy-3-thio-4-O-pivaloyl-2,3,4,5-tetra-O-benzyl-D-arabinohex-2-ulose} \]
Acetals for alcohol protection

- The above acetals can be cleaved under Bronsted or Lewis acidic conditions; conditions for selective cleavage are noted.
- Generally stable to base.
- Acetal protecting groups generally permit chelation.
- Disubstituted ethers (i.e. THP) are typically less stable to acid than mono-substituted ethers (i.e. MOM).
- Disubstituted ethers result in formation of a stereogenic center; this can sometimes complicate product analysis (if a diastereomeric mixture).

### General Conditions:

\[
\begin{align*}
\text{R-OH} + \text{Cl-OR'} & \xrightarrow{\text{DIPEA, CH}_2\text{Cl}_2} \text{R-O-OR'} \\
\text{or} & \xrightarrow{\text{NaH, THF}} \\
\text{or} & \xrightarrow{\text{BCl}_3, \text{CH}_2\text{Cl}_2, -78 \degree\text{C}} \\
\text{aq. HCl, THF} & \xrightarrow{\text{or}} \\
\end{align*}
\]

### Examples

- THPO
  - PPTS (cat) EtOH-H₂O

- HO
  - PPTS (cat)

- OAc
  - DCM
Esters and carbonates

- Acetate (Ac)
- Trichloroacetate
- Trifluoroacetate
- Pivolate (Piv)
- Benzoate (Bz)
- p-Bromobenzoate

Deprotection by saponification

General Conditions:

\[ \text{R'COCl, DMAP, Et}_3\text{N, CH}_2\text{Cl}_2 \]
\[ \text{or} \]
\[ \text{(R'CO)}_2\text{O, pyr, DMAP, CH}_2\text{Cl}_2 \]
\[ \text{or} \]
\[ \text{R'OCOCI, Et}_3\text{N, DMAP, CH}_2\text{Cl}_2 \]

\[ \text{R} \text{OH} \rightarrow \text{R} \text{O} \text{R'} \rightarrow \text{R} \text{OH} \]

- or -

\[ \text{aq. LiOH, MeOH} \]
\[ \text{or} \]
\[ \text{DIBAL, CH}_2\text{Cl}_2 \]

see above for orthogonal deprotection conditions

- Allyl carbonate (Alloc)
- 9-(fluorenymethyl) carbonate (Fmoc)
- tert-Butyl carbonate (Boc)
- 2-(trimethylsilyl)ethyl carbonate (Teoc)
- Benzyl carbonate (Cbz)
- 2,2,2-Trichloroethyl carbonate (Troc)

selective cleavage using Pd

cleaved using mildly basic conditions (piperidine)

cleaved under mildly acidic conditions

cleaved with F⁻

cleaved by hydrogenolysis

cleaved reductively using Zn/AgOH
CARBOXYLIC ACIDS

- $R\text{O}\text{Me}$
- $R\text{O}t\text{Bu}$
- $R\text{O}\text{alkene}$
- $R\text{O}\text{aryl}$
- $R\text{O}\text{SiR}_3$
- $R\text{O}R'$
- $R\text{O}R'$
Esters

Few words on ester preparation

**Classic conditions for ester preparation**

![Reaction diagram]

Note:
- CH$_2$N$_2$ (TMSCHN$_2$, commercial)
- TMSCl, AcCl / MeOH
- K$_2$CO$_3$, Mel

**Deprotection (and orthogonal conditions)**

![Deprotection reactions]

MOM, MEM, SEM… derived esters are deprotected using alcohols previous conditions.

**Silyl esters** are very sensitive and can be used for in situ protection to prevent reduction.

**Orthoesters**

![Orthoesters synthesis]

_Formation of classic orthoester via nitrile and alcohol reaction_
AMINES

Imide / Amide

Alkyl

Carbamates
Amine protecting groups

Phthalimide: Pht

Phthalimide can be introduced by Mitsunobu reaction (inversion of stereochemistry)

Trifluoroacetamide

Formation: TFAA + Et₃N, DCM 0°C

Deprotection: basic conditions (K₂CO₃, LiOH, MeOH-H₂O)

Carbamates

- **(Boc)**: R'RNCOO
  - KOH, ethylene glycol 100°C
  - K₂CO₃, H₂O-MeOH
  - nPrSLi, HMPA

- **(CbZ or Z)**: R'RNCOO
  - H₂ (or 1,4-cyclohexadiene), Pd/C
  - Li or Na, NH₃

- **(Aloc)**: R'RNCOO
  - Pd(PPh₃)₄ + (Nu)
  - hydride + Pd (0)

- **(Fmoc)**: R'RNCOO
  - Base (piperidine, NH₃, morpholine...)

- **(Teoc)**: R'RNCOO
  - Cleavage with F- β-elimination

- **(Troc)**: R'RNCOO
  - Cleavage with Zn, AcOH β-elimination
Amine protecting groups

**Sulfonamide**

Very resistant protecting group. Formation from the corresponding chlorinated reagent or anhydride

*Tosyle (Ts)*

\[
\begin{align*}
R & \quad \text{Na or Li, } NH_3 - THF
\end{align*}
\]

2-*(trimethysilyl)ethylsulfonyle (SES)*

Cleavage with F- β-elimination

**N-Alkyl**

(See alcohol section for protection and deprotection conditions)

**N-Silyl**

\[\text{Me}_2\text{Si} - \text{N} - \text{Br} \]
Orthogonal conditions (reminder)

a. Basic hydrolysis

\[ R^1\text{CO}R^2 \xrightarrow{K_2CO_3, MeOH \text{ ou } NH_3, MeOH} R^1\text{OH} \]

Amides need stronger conditions (except CF\textsubscript{3}-acetamide)

b. Acidic hydrolysis

\[ R^1\text{CO}R^2 \xrightarrow{HX} R^1\text{COOH} \]

\[ \text{O,S-acetal et S,S-acetal} \]

c. Heavy metals

\[ \text{O,S-acetal et S,S-acetal} \]

d. Fluorine

\[ \text{ROSiMe}_3 \xrightarrow{\text{ROH}} \]

e. Hydrogenolysis

\[ RO\text{CPh} \xrightarrow{H_2, \text{Pd/C}} \text{ROH} \]

f. Transition metal

\[ R^1\text{CO}R^2 \xrightarrow{\text{Pd}(0)} R^1\text{COH} \]

\[ \text{RO}\text{CPh} \xrightarrow{\text{RhCl(PPh}_3)_3} \text{ROH} \]

g. Other methods

- Zn/AcOH
- Na/NH\textsubscript{3}
- light
- enzyme
Influence of protecting groups

- **Transprotection**
  - Reaction with TBSOTf and Et$_3$N in CH$_2$Cl$_2$
  - Structure shown:

- **Neighboring groups participation**
  - Reaction with TsCl and DMAP in Et$_3$N
  - Structure shown:

- **Conformational and electronic effects**
  - Reaction with LDA in THF at -78 °C
  - Structure shown:

- **Coordination**
  - Reaction with MOMCl and base, followed by nBuLi
  - Structure shown: