

# Advanced Organic Chemistry/ Organic Synthesis – CH 621 Protecting Groups

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# **Protecting Groups – Strategy**



To protect one sensitive group, while the "active" group should remain unchanged.

- (Selective reactions)
- Protecting groups, when the above is not possible

Ideal protection:

- Introduce under mild conditions
- Stable under the target reaction conditions
- Removable under mild conditions

- Orthogonal protection



#### **Protection of Alcohols**

# Formation of ethers

Ether protective groups for alcohols

Group	Structure	Abbreviation	Normal metho removal
Benzyl	OCH <sub>2</sub> Ph	OBn	H2, cat. Pd/C
p-Methoxybenzyl	OCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	OPMB	DDQ or Ce(NH <sub>4</sub> ) <sub>3</sub> (NC
Trityl	OCPh <sub>3</sub>	OTr	CH <sub>3</sub> CO <sub>2</sub> H or CF <sub>1</sub> CO <sub>2</sub> H
t-Butyl	OC(CH <sub>3</sub> ) <sub>3</sub>	OBu <sup>t</sup>	HCl or HBr o CF1CO1H
Allyl	OCH <sub>2</sub> CH=CH <sub>2</sub>	-	cat. $(Ph_3P)_3R$ then $Hg^{2+}$ , H
Methoxymethyl	OCH <sub>2</sub> OCH <sub>3</sub>	OMOM	HCl or CF <sub>3</sub> C
Methylthiomethyl	OCH2SCH3	OMTM	HgCl <sub>2</sub>
Methoxyethoxymethyl	OCH2OCH2CH2OCH3	OMEM	TiCl4 or ZnB1
1-Ethoxyethyl	OCH(CH <sub>3</sub> )OC <sub>2</sub> H <sub>5</sub>		CH <sub>3</sub> CO <sub>2</sub> H

(a) Benzyl unaffected by these conditions.

(b) Causes isomerization to the enol ether, OCH=CHCH3, which is then easily hydrolysed.





# **Protection of Alcohols**

# Formation of silyl ethers

Table 10.2 Silyl ether prote	tive groups for alcohols
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Group	Structure	Abbreviation
Trimethylsilyl	OSi(CH <sub>3</sub> ) <sub>3</sub>	OTMS
t-Butyldimethylsilyl	OSi(CH <sub>3</sub> ) <sub>2</sub> C(CH <sub>1</sub> ) <sub>3</sub>	OTBS or OTBDMS
Triisopropylsilyl	OSi(CH(CH <sub>3</sub> ) <sub>2</sub> ) <sub>3</sub>	OTIPS
t-Butyldiphenylsilyl	OSiPh <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	OTBDPS
Trimethylsilylethoxymethoxy	OCH2OCH2CH2Si(CH3)3	OSEM



# **Protection of Alcohols**

#### Formation of esters

Group	Structure	Abbreviation	Normal method of removal
Acetyl	OCOCH3	OAc	Base, e.g. K <sub>2</sub> CO <sub>3</sub> , CH <sub>2</sub> OH
Trifluoroacetyl Trimethylacetyl (pivaloyl) Benzoyl 2,4,6-Trimethylbenzoyl	$OCOCF_3$ $OCOC(CH_3)_3$ OCOPh $OCOC_6H_2(CH_3)_3$	OPiv OBz OCOMes	Mild base NaOH NaOH or (C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> LiAlH <sub>4</sub>

Table 10.3 Ester protective groups for alcohols



# **Protection of Alcohols**

# Formation of esters



# **Protecting Groups – Carboxylic acids**



#### Formation of esters

Group	Structure	Abbreviation
Benzyl	OCH <sub>2</sub> Ph	OBn
p-Methoxybenzyl	OCH2C6H4OCH3	OPMB
Trityl	OCPh <sub>3</sub>	OTr
t-Butyl	OC(CH <sub>3</sub> ) <sub>3</sub>	OBu <sup>t</sup>
Allyl	OCH2CH=CH2	-
Methoxymethyl	OCH <sub>2</sub> OCH <sub>3</sub>	OMOM
Methylthiomethyl	OCH <sub>2</sub> SCH <sub>3</sub>	OMTM
Methoxyethoxymethyl	OCH2OCH2CH2OCH3	OMEM
1-Ethoxyethyl	OCH(CH <sub>3</sub> )OC <sub>2</sub> H <sub>5</sub>	-

# **Protecting Groups – Carboxylic acids**



# Formation of *ortho* esters



# **Protecting Groups – Thiols**



# Formation of ethers

Avoid oxidative conditions (S oxidation)

Group	Structure	Abbreviation
Benzyl	OCH <sub>2</sub> Ph	OBn
p-Methoxybenzyl	OCH2C6H4OCH3	OPMB
Trityl	OCPh <sub>3</sub>	OTr
t-Butyl	OC(CH <sub>3</sub> ) <sub>3</sub>	OBu <sup>t</sup>
Allyl	OCH2CH=CH2	-
Methoxymethyl	OCH <sub>2</sub> OCH <sub>3</sub>	омом
Methylthiomethyl	OCH2SCH3	OMTM
Methoxyethoxymethyl	OCH2OCH2CH2OCH3	OMEM
1-Ethoxyethyl	OCH(CH <sub>3</sub> )OC <sub>2</sub> H <sub>5</sub>	-

#### **Protecting Groups – Aldehydes and Ketones**







#### **Protecting Groups – 1,2- and 1,3-diols**



Acetals



# **Protecting Groups – Amines**





Usually: - N-benzyl - N-trityl - N-allyl

# **Protecting Groups – Amines**



# **N-Acylation**

Usually:

- N-benzoyl
- N-acetyl
- N-trifluoroacetyl



# **Protecting Groups – Amines**



# Formation of carbamates





Group	Structure	Abbreviation	Normal i of remov
Ethoxycarbonyl	$N{-}CO_2C_2H_5$	-	C <sub>3</sub> H <sub>7</sub> SLi HBr, CH
Benzyloxycarbonyl	N-CO2CH2Ph	N-Cbz <sup>(a)</sup>	H2, cat. 1
t-Butoxycarbonyl	N-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	N-Boc	HCl
Allyloxycarbonyl	N-CO <sub>2</sub> CH <sub>2</sub> CH=CH <sub>2</sub>	N-Alloc	Cat. (Ph then H
9-Fluorenylmethoxy- carbonyl	25	N-Fmoc	Piperidin morpholi
Trimethylsilylethoxy- carbonyl	N-CO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub>	-	F

(a) Or simply N-Z.

(b) Causes isomerization to N-CO2CH=CHCH3, which is then easily hydrolysed.























































