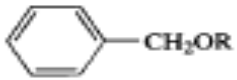
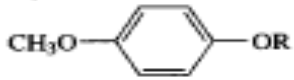
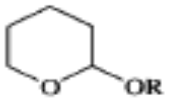
PROTECTIVE GROUPS

Principle of protection of alcoholic, amino, carbonyl and carboxylic groups

- A protective group is a derivative that can be put in place and then subsequently removed in order to prevent an undesired reaction.

HYDROXYL PROTECTIVE GROUPS

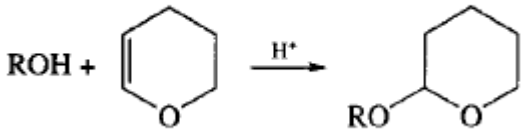
Structure	Name	Abbreviation
A. Ethers		
	Benzyl	Bn
	*p*-Methoxybenzyl	PMB
$CH_2{=}CHCH_2OR$	Allyl	
Ph_3COR	Triphenylmethyl (trityl)	Tr
	*p*-Methoxyphenyl	PMP
B. Acetals		
	Tetrahydropyranyl	THP
CH_3OCH_2OR	Methoxymethyl	MOM
CH_3CH_2OCHOR (CH$_3$ on CH)	1-Ethoxyethyl	EE
$(CH_3)_2COR$ (OCH_3 on C)	2-Methoxy-2-propyl	MOP
$Cl_3CCH_2OCH_2OR$	2,2,2-Trichloroethoxymethyl	
$CH_3OCH_2CH_2OCH_2OR$	2-Methoxyethoxymethyl	MEM
$(CH_3)_3SiCH_2CH_2OCH_2OR$	2-Trimethylsilylethoxymethyl	SEM
CH_3SCH_2OR	Methylthiomethyl	MTM
C. Silyl ethers		
$(CH_3)_3SiOR$	Trimethylsilyl	TMS
$(C_2H_5)_3SiOR$	Triethylsilyl	TES
$[(CH_3)_2CH]_3SiOR$	Triisopropylsilyl	TIPS
Ph_3SiOR	Triphenylsilyl	TPS
$(CH_3)_3CSi(CH_3)_2SiOR$	*t*-Butyldimethylsilyl	TBDMS
$(CH_3)_3CSi(Ph)_2SiOR$	*t*-Butyldiphenylsilyl	TBDPS
D. Esters		
CH_3CO_2R	Acetate	Ac
$PhCO_2R$	Benzoate	Bz
$CH_2{=}CHCH_2O_2COR$	Allyl carbonate	
$Cl_3CCH_2O_2COR$	2,2,2-Trichloroethyl carbonate	Troc
$(CH_3)_3SiCH_2CH_2O_2COR$	2-Trimethylsilylethyl carbonate	

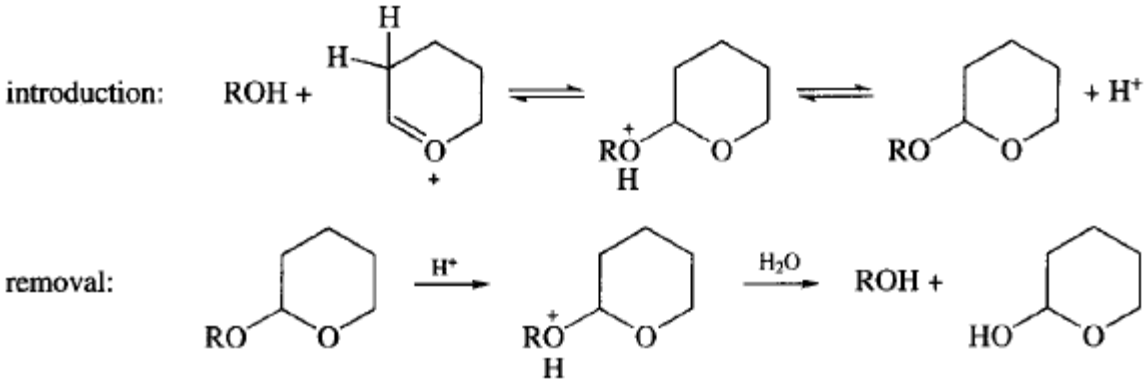
- Hydroxyl group is masked as a derivative lacking hydroxylic proton.
- Choice of a most appropriate ether group is dictated by the conditions the can be tolerated in subsequent removal of PG

ACETALS

THP (Tetrahydropyranyl group)

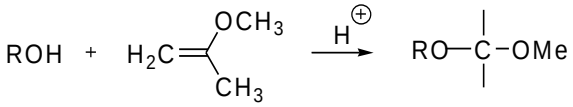
- When mildly acidic hydrolysis can be tolerated for protection, an important method is to form tetrahydropyranyl ether





Methoxy dimethyl ether

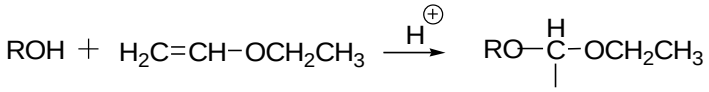
- We may use methyl 2-propenyl ether in place of dihydropyran



- No new chiral centre is introduced
- The acetal is hydrolyzed under somewhat milder conditions than those required for THP ethers

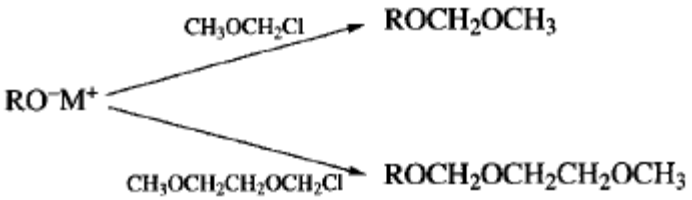
EE (ethoxyethyl ether)

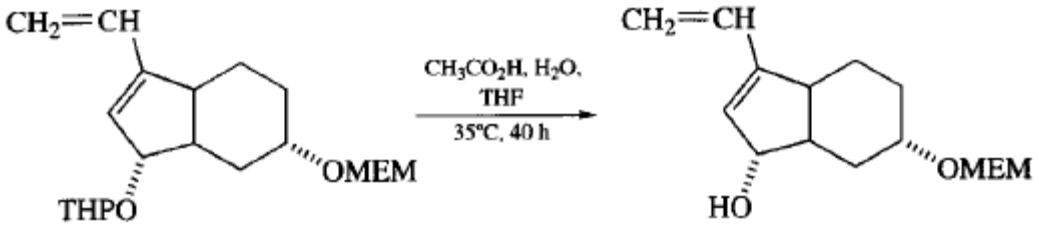
- Formed from ethyl vinyl ether



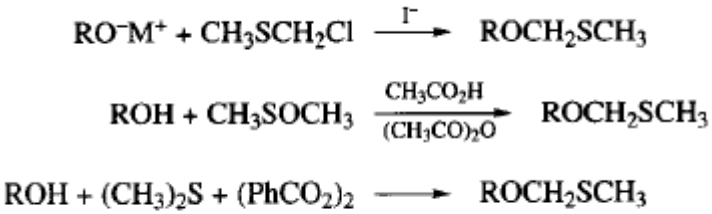
- EE group contains a stereogenic center

MOM and MEM


CH3OCH2Cl
ROCH2OCH3
RO⁻M⁺
CH3OCH2CH2OCH2Cl
ROCH2OCH2CH2OCH3

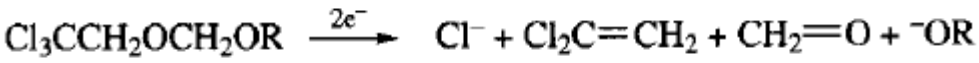

CH2=CH
OMEM
THPO
CH3CO2H, H2O,
THF
35°C, 40 h
CH2=CH
OMEM
HO

MTM (Methyl thiomethyl group)



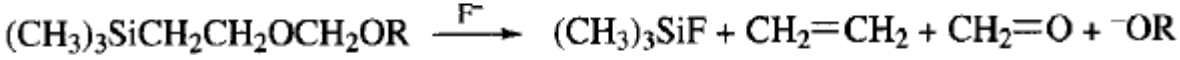
- Selectively removed under non acidic conditions in aq solutions containing Ag+ or Hg^{2+} salts
- THP and MOM are stable under these conditions.

2,2,2-Trichloroethoxymethyl group



- 2-Substituted alkoxymethoxy groups are designed for cleavage involving β-elimination
- Can be reduced by zinc, samarium diiodide and sodium amalgam
- β-Elimination results in the formation of formaldehyde hemiacetal which decomposes easily

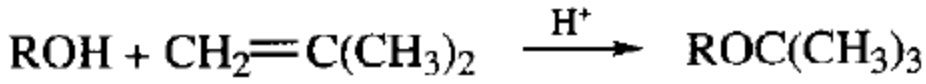
SEM [2-(Trimethylsilyl)ethoxymethyl]



Can be removed by various fluoride sources

ETHERS

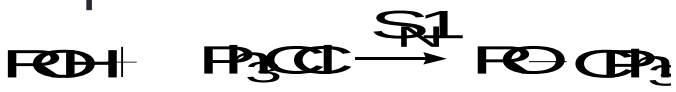
- Simple alkyl groups are generally not very useful.
- *t*-Butyl group has found some use as PG



- Because of the stability of the *t*-butyl cation, the *t*-butyl ethers can be cleaved under moderately acidic conditions.
- Trifluoroacetic acid in an inert solvent is frequently used.
- Can be cleaved by acetic anhydride –FeCl3 in ether
- Normally introduced by reaction of alcohol with isobutylene in the presence of acid catalyst. Acidic ion-exchange resins are effective catalysts.

(Trityl, Tr, triphenylmethyl)

- Important protective group especially in carbohydrate chemistry
- Can be removed under even milder conditions than required for t-butyl group



- Hot aqueous acetic acid suffices to remove trityl group
- Ease of removal can be increased by addition of electron withdrawing groups

Benzyl group (Bn)

- Can serve as hydroxyl protection when acidic conditions for ether cleavage can not be tolerated.
- Benzyl C-O bond is cleaved by catalytic hydrogenolysis or by electron transfer reduction using Na/liq NH3 aromatic radical anions.
- Benzyl alcohols are converted to trichloroacetimidates which then react with alcohol to transfer benzyl group.



4-Methoxyphenyl (PMP)

- Find occasional use as PG
- Unlike benzylic groups, they can not be made directly from alcohol. Instead phenyl group must be introduced by a nucleophilic substitution.
- Can be cleaved by oxidation with CAN

Allyl ethers

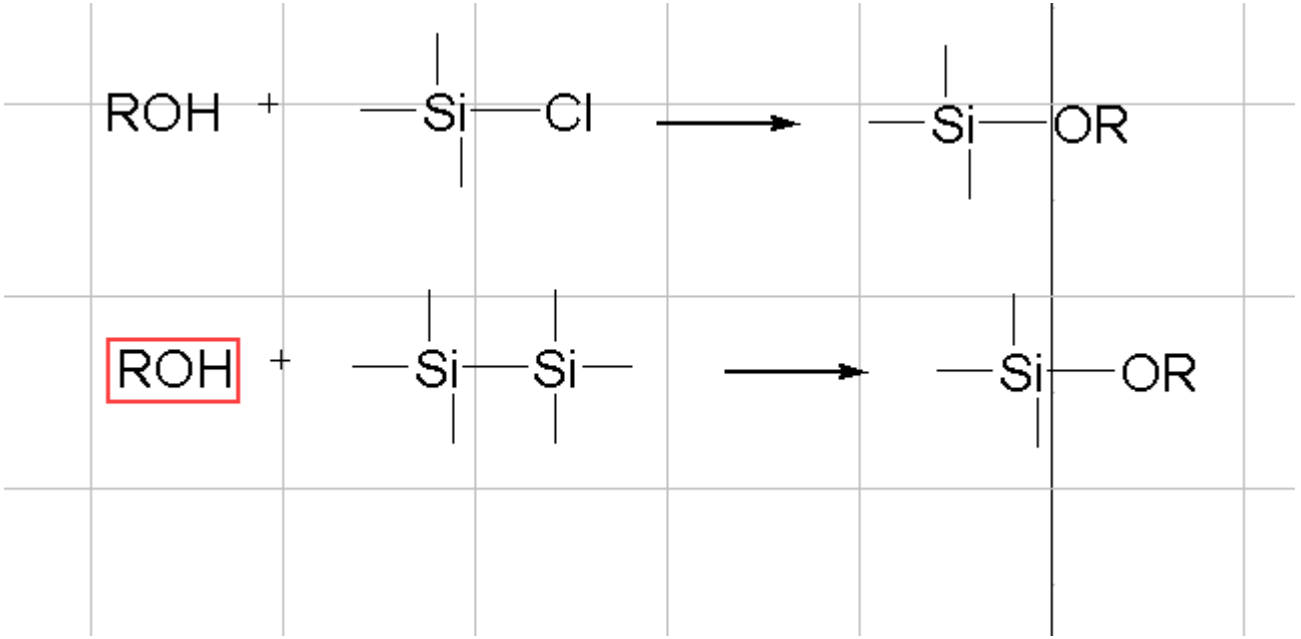
- Can be cleaved by conversion to propenyl ethers followed by acidic hydrolysis of the enol ether.



SILYL ETHERS

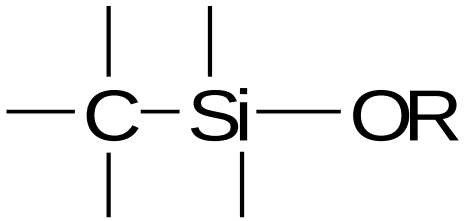
TMS

- Play important role as hydroxyl PG
- Alcohols can be easily converted to trimethylsilyl ethers (TMS) by reaction with trimethylsilyl chloride in the presence of amine or by heating with hexamethyldisilazane



TBDMS (t-butyldimethylsilyl)

- Increased steric bulk of the group increase its stability towards hydride reductions and Cr(VI) oxidations.

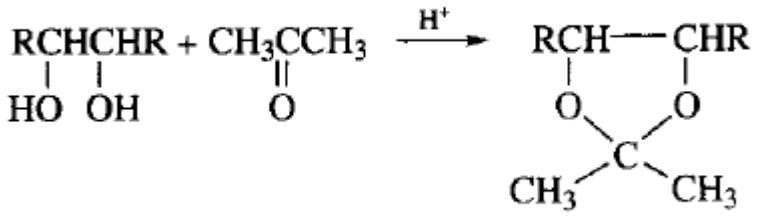


- Normally introduced using tertiary amines as a catalyst for the reaction of the alcohol with t-butyldimethyl silyl chloride or triflate (trifluoromethanesulfonate)

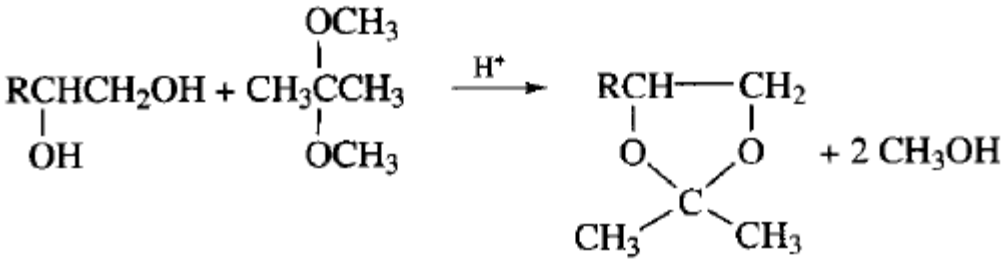
TIPS (triisopropylsilyl), TPS (triphenylsilyl), TBDPS (t-butyldiphenylsilyl)

- Other highly substituted silyl groups such as tri-isopropylsilyl are even more sterically hindered than TBDMS and can be used when more stability is required.
- The hydrolytic stability of the various silyl PGs is
- TMS<TBDMS<TIPS<TBDPS

- Diols represent a special case
- Both 1,2- and 1,3-diols easily from cyclic acetals with aldehydes and ketones.
- The isoproylidene derivatives (acetonides) are formed by reaction with acetone



- Isopropylidene group can also be introduced by acid catalyzed exchange with 2,2-dimethoxypropane



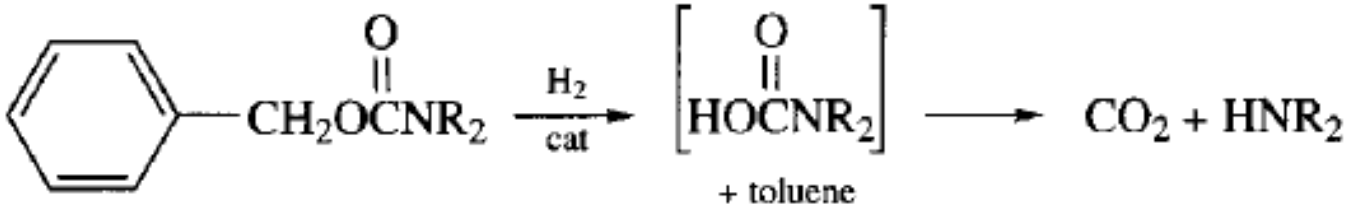
ESTERS

- Esterification sometimes offers advantages over the use of acetals or ether PGs
- Generally, ester groups are stable under acidic conditions
- Esters are especially useful in the protection during oxidations
- ACETATES and BENZOATES are most commonly used ester derivatives, they can be conveniently prepared by the reaction of unhindered alcohols with acetic anhydride or benzoyl chloride respectively in the presence of pyridine or other tertiary anions. 4-Dimethylaminopyridine (DMAP) is often used as a catalyst.catalyzed hydrolysis.
- Esters groups can be removed by base

AMINO PROTECTING GROUPS

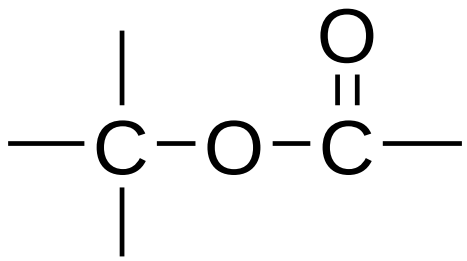
- Primary and secondary amino groups are nucleophilic and easily oxidized.
- If either of these types of reactivity will cause a problem, the NH2 group must be protected
- Most general of masking nucleophilicity is by acetylation, carbamates are particularly useful

Cbz (Carbobenzyloxy) group



Because of the lability of the benzyl C-O bond toward hydrogenolysis, amine can be regenerated by hydrogenolysis which is accompanied by spontaneous decarboxylation of the resulting carbamic acid.

t-Boc (t-butoxycarbonyl)



- Removal is done with an acid such as CF3COOH or p-TsOH
- t-Butoxycarbonyl groups are introduced by reaction of amines with t-butoxypyrocarbonate or the mixed carbonate ester “BOC-ON”.



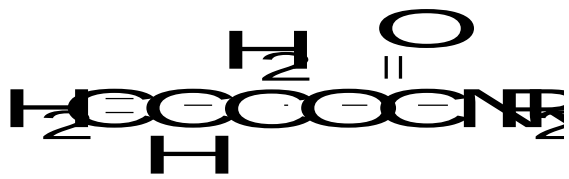
t-butyl pyrocarbonate



"BOC-ON"

2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile

Allyl carbamates

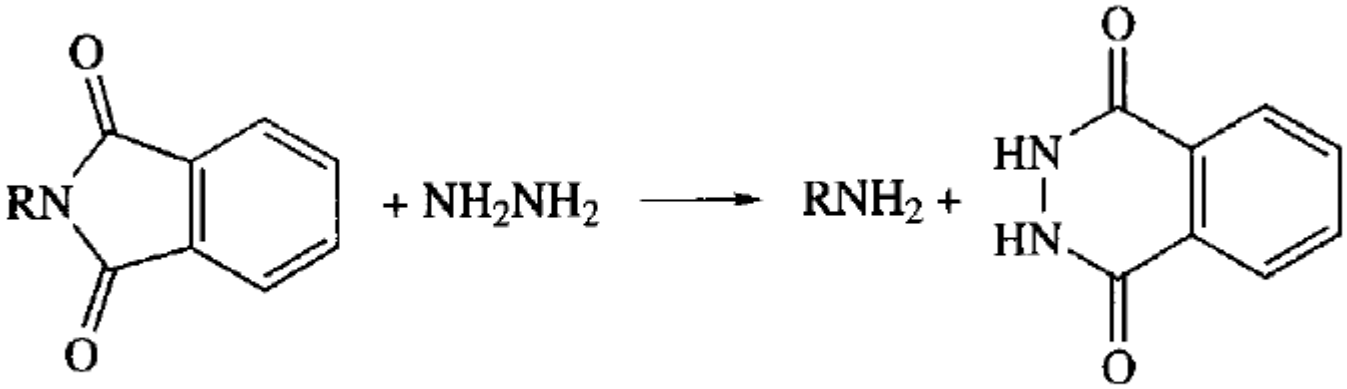


- Allyloxy group is removed by Pd-catalyzed reduction or nucleophilic substitution
- Allyl groups attached directly to amine or amide nitrogen can be removed by isomerization and hydrolysis
- N-Benzyl groups can be removed by reaction of amines with chloroformates (ClCO2Et)

- Amide nitrogens can be protected by 4-methoxyphenyl of 2,4-dimethoxyphenyl groups
- These PGs can be removed by oxidation with CAN
- 2,4-dimethoxyphenyl groups can be removed using anhydrous trifluoroacetic acid
- Simple amides are satisfactory PGs only if the rest of the molecule can resist the vigorous acidic or alkaline hydrolysis necessary for their removal
- For this reason, only amides that can be removed under mild conditions have been found useful as amino PGs

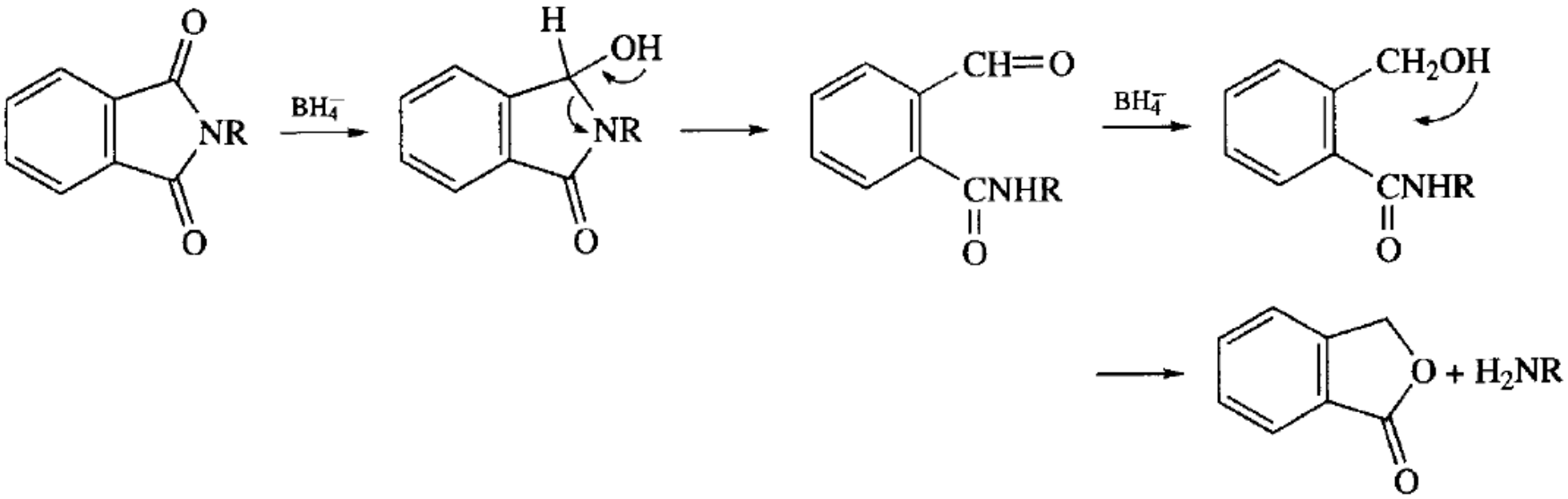
Phthalimides

- Used to protect primary amines
- Can be cleaved by treatment with hydrazine

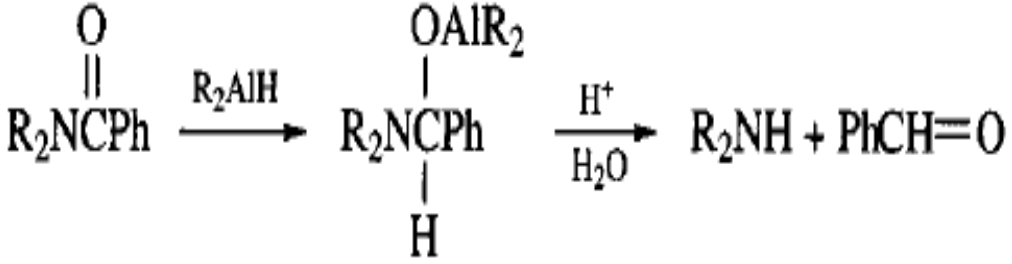


Phthalimides

- Reduction by NaBH4 in aq EtOH is an alternative method for deprotection

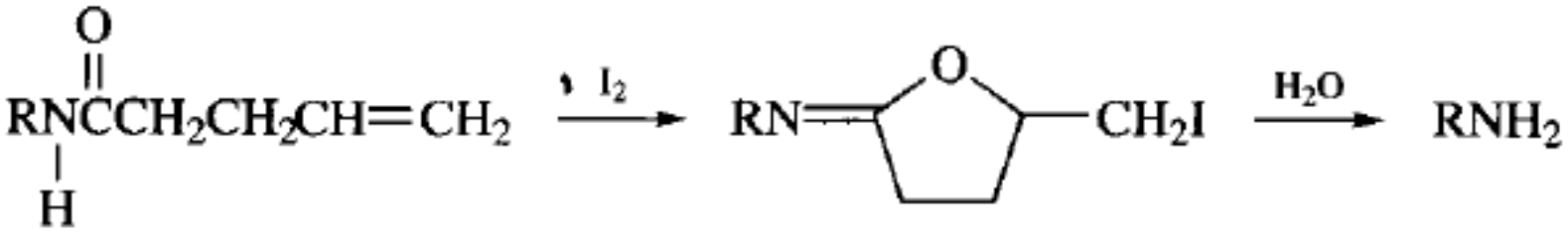


Amides can also be removed by partial reduction. If the reduction proceeds only to the carbinolamine stage, hydrolysis can liberate the deprotected amine. Trichloroacetamides are readily cleaved by sodium borohydride in alcohols by this mechanism.[84] Benzamides, and probably other simple amides, can be removed by careful partial reduction with diisobutylaluminum hydride.[85]

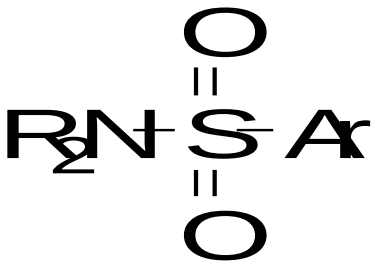


Amide with 4-Pentenoyl group

- The PGs can be removed by the mechanism involving iodocyclization and hydrolysis of the resulting iminolactone



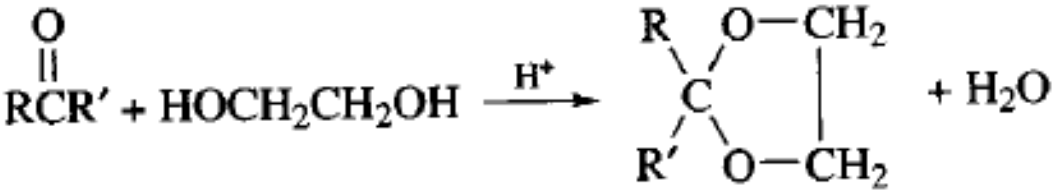
Sulfonamides



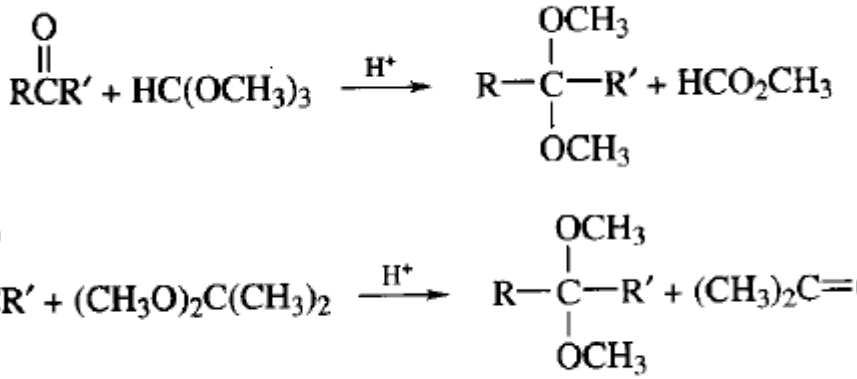
- Simple sulfonamides are difficult to hydrolyze

CARBONYL PROTECTIVE GROUPS

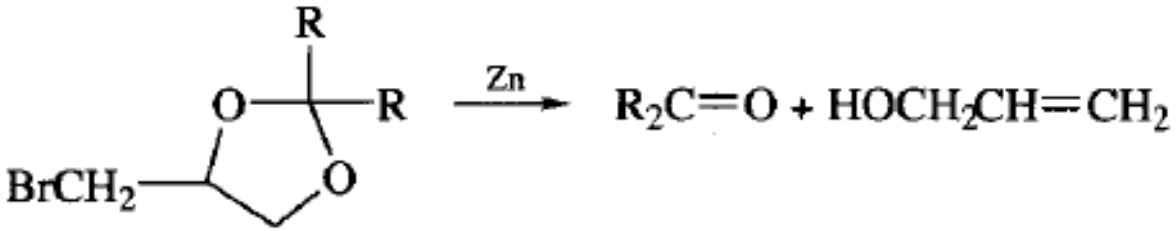
Dioxolane derivative

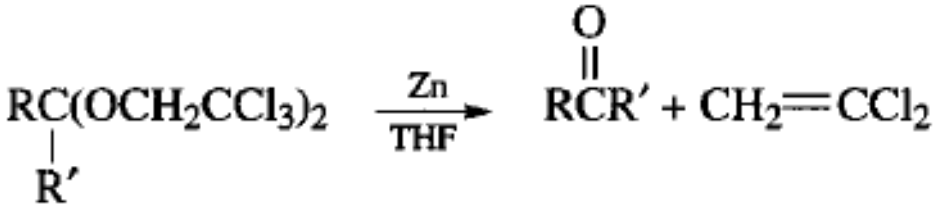


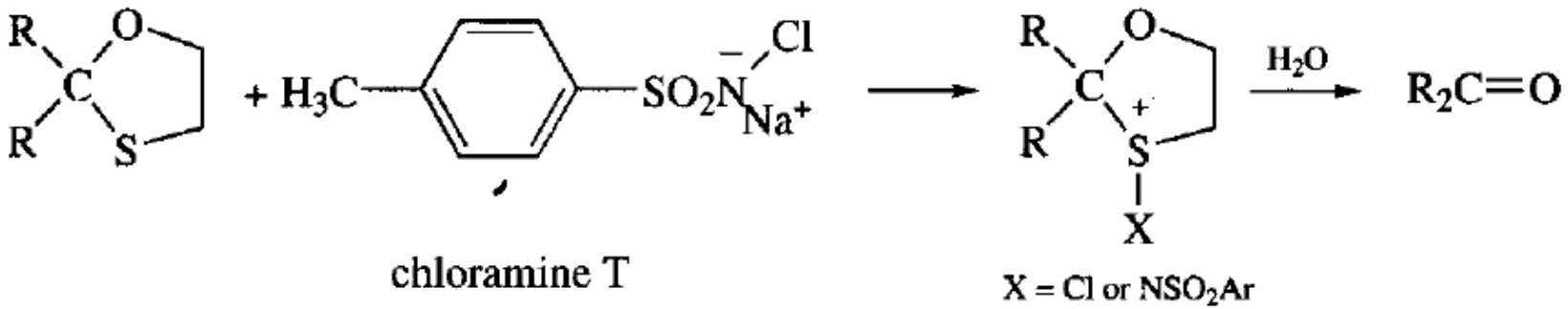
Dimethyl or diethyl acetals/ketals

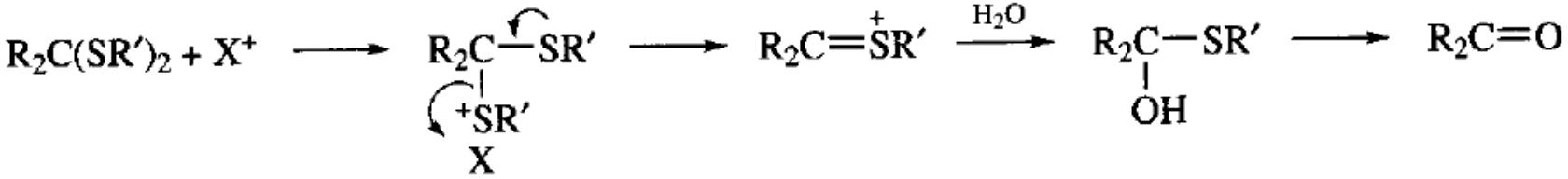


- If carbonyl group must be regenerated under non hydrolytic conditions, β-haloalcohols such as 3-bromo-1,2-dihydroxypropane or 2,2,2-trichloroethanol can be used for acetal formation. These groups can be removed by reduction with zinc which proceeds with β-elimination.

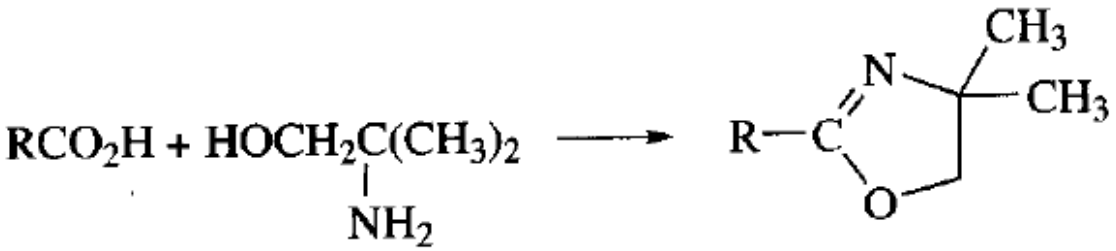


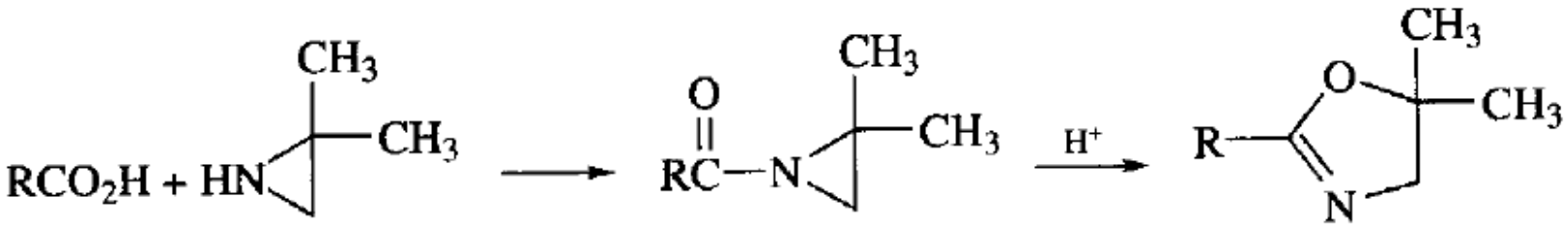


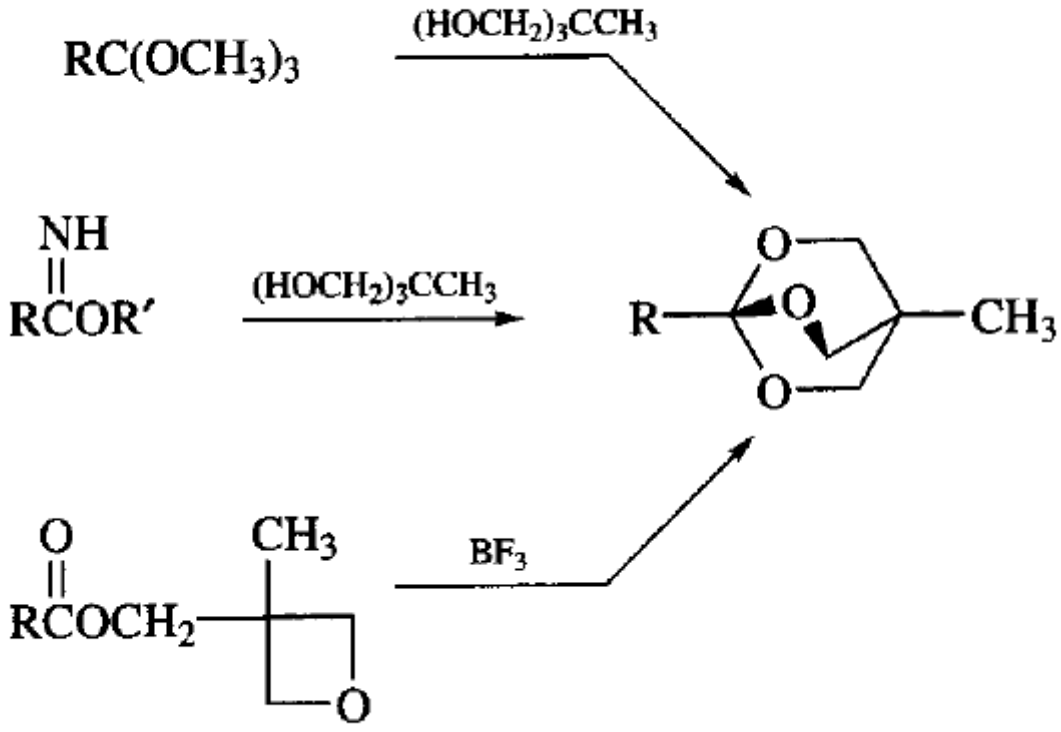

R
O
C
R
S
+ H3C
SO2N
Cl
Na+
chloramine T
R
O
C
+
R
S
X
X = Cl or NSO2Ar
H2O
R2C=O


R2C(SR′)2 + X+
R2C
SR′
+SR′
X
R2C=+SR′
H2O
R2C
SR′
OH
R2C=O

CARBOXYL PROTECTIVE GROUPS


RCO2H + HOCH2C(CH3)2
NH2
CH3
N
CH3
R
C
O


CH3
RCO2H + HN
CH3
O
CH3
RC
N
CH3
H+
CH3
O
CH3
R
N


RC(OCH3)3
(HOCH2)3CCH3
NH
RCOR′
(HOCH2)3CCH3
O
R
O
CH3
O
O
CH3
O
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O
BF3