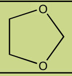
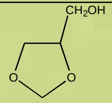
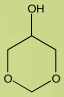
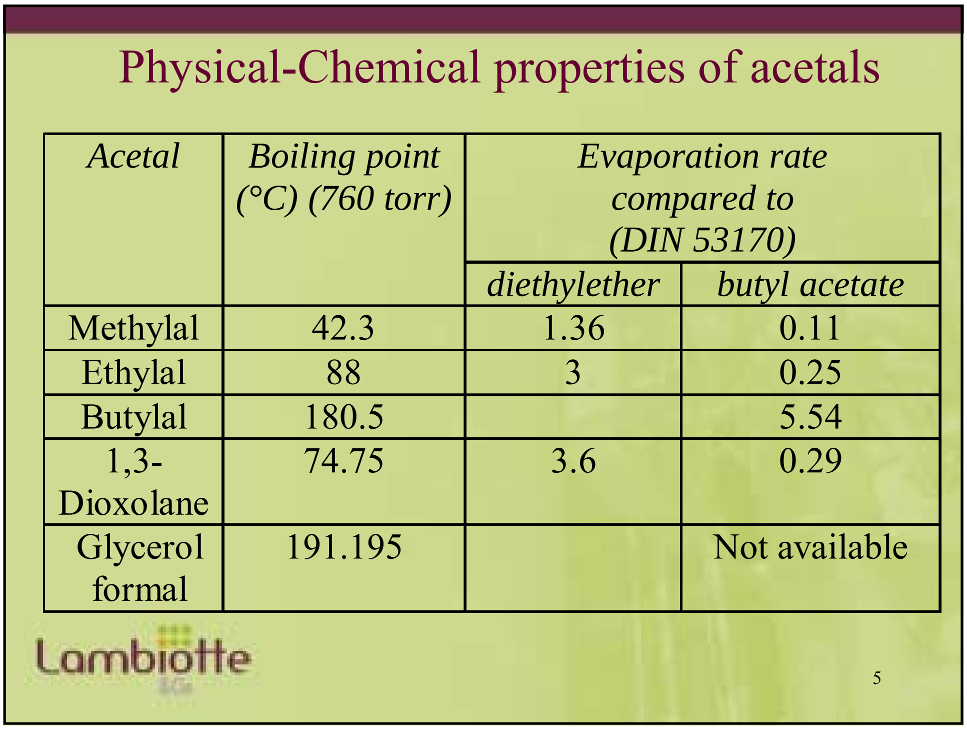
The use of acetals in the Pharmaceutical Industry

- Generalities
- Acetals in organic synthesis
  - Reagents
  - Solvents
- Acetals in purification processes
  - Extraction
  - Chromatography
  - Cristallization
- Acetals in galenic formulations

Generalities

Acetals produced by the Lambiotte company

Acetal	*Formula*	*CAS n°*	*EINECS n°*
Methylal	$CH_3-O-CH_2-O-CH_3$	109-87-5	203-714-2
Ethylal	$CH_3-CH_2-O-CH_2-O-CH_2-CH_3$	462-95-3	207-330-6
Butylal	$CH_3-CH_2-CH_2-CH_2-O-CH_2-O-CH_2-CH_2-CH_2-CH_3$	2568-90-3	219-909-0
1,3-Dioxolane		646-06-0	211-463-5
Glycerol formal	 	5464-28-8 4740-78-7	226-758-4 225-248-9



Physical-Chemical properties of acetals

Acetal	*Boiling point (°C) (760 torr)*	*Evaporation rate compared to (DIN 53170)*	
		diethylether	*butyl acetate*
Methylal	42.3	1.36	0.11
Ethylal	88	3	0.25
Butylal	180.5		5.54
1,3-Dioxolane	74.75	3.6	0.29
Glycerol formal	191.195		Not available

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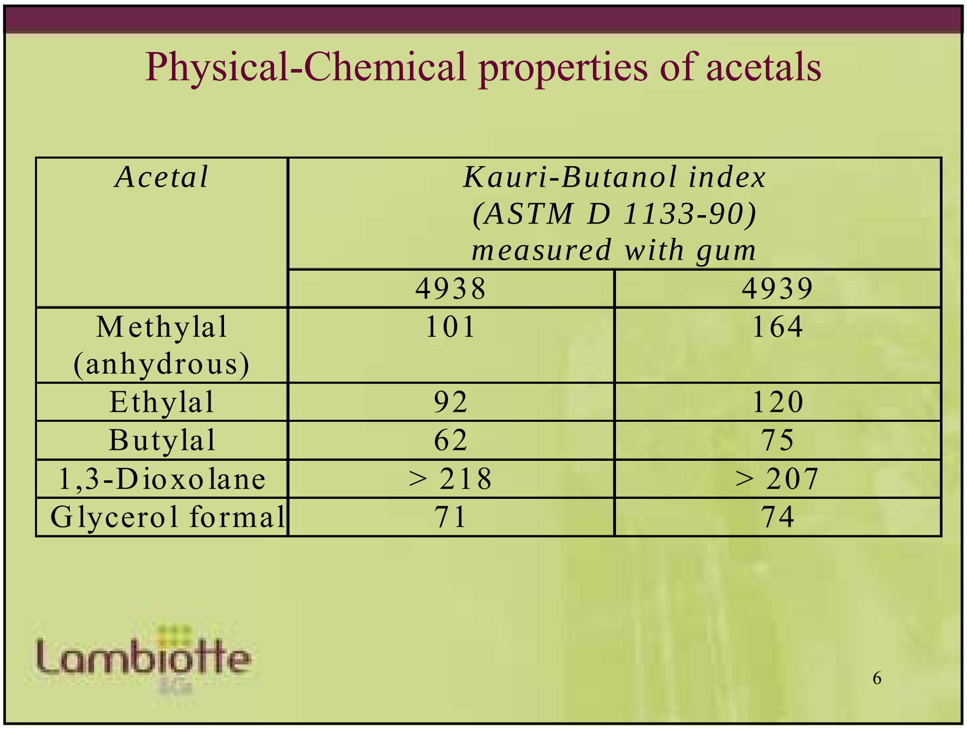

Physical-Chemical properties of acetals

Acetal	*Kauri-Butanol index (ASTM D 1133-90) measured with gum*	
	4938	4939
Methylal (anhydrous)	101	164
Ethylal	92	120
Butylal	62	75
1,3-Dioxolane	> 218	> 207
Glycerol formal	71	74

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Physical-Chemical properties of acetals

Acetal	*Solubility of the acetal in water (%)*	*Solubility of water in the acetal (%)*
Methylal	32.3	4
Ethylal	6.33	1.21
Butylal	Not soluble	0.24
1,3-Dioxolane	Fully miscible	Fully miscible
Glycerol formal	Fully miscible	Fully miscible

Physical-Chemical properties of acetals

Acetal	*Melting Point* (°C)	*Kinematic viscosity* (E-7 m^2/s) (25°C)	*Density* (g/cm^3) (20°C)
Methylal	- 104.8	3.71	0.861
Ethylal	- 66	5.07	0.83
Butylal	- 58.10	10.83	0.8354
1,3-Dioxolane	- 95	5.53	1.06
Glycerol formal	-58.10	117	1.203

Toxicology - Ecotoxicology

Toxicological profiles are well documented.
In general, the results are very good.

No records of any problems in the work place when used in industrial applications.
TLV (threshold limit value) or MAK of methylal : 1000 ppm.
Acetals have good ecotoxicological profiles.

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Atmospheric chemistry

Photochemical Ozone Creation Potential (POCP)

The atmospheric degradation of acetals has been fully investigated

The measured rates of reaction with the OH radical, which starts the atmospheric degradation, are in general very slow.

The rates are much slower than expected by calculation if acetals were considered as ethers. Therefore, possible emissions will only make a moderate contribution to the formation of tropospheric ozone.

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Atmospheric chemistry

Global Warming Potential (GWP)

Negligible.

Ozone Depletion Potential (ODP)

Due to the absence of a halogen atom, the ODP is zero.

Stability

Stability against hydrolysis

Acetals are stable in neutral and basic conditions, but in aqueous acidic conditions they may hydrolyse.

However, they show a very slow rate of hydrolysis : there were no traces of hydrolysis of methylal after 1 year at a pH level above 4.

At lower pH, rates remain slow.

Stability

Stability against peroxide formation

Methylal does not form any peroxides.

Therefore, methylal is not stabilized.

Other acetals may form a low level of peroxide and are stabilized.

Labelling

None of the acetals are labelled for toxicolgical reasons.

Methylal Ethylal 1,3-Dioxolane	are labelled as flammable products
Butylal Glycerol formal	do not require any labelling

Acetals
in
organic
synthesis

Methylal as reagent

- Transacetalizations
  - Simple
    - Aliphatic alcohols

$$HO-(CH_2)_9-Me \xrightarrow[\text{2. AcOEt}]{\text{1. MeOCH2OMe, ZrCl4}} MeO-CH_2-O-(CH_2)_9-Me$$

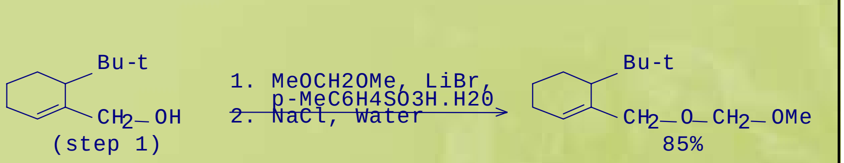
(step 1)

NOTE: no solvent

96%

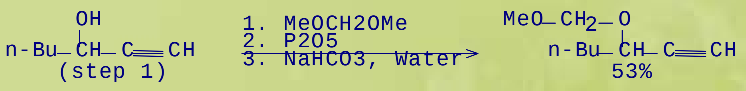
Methylal as reagent

- Allylic alcohols



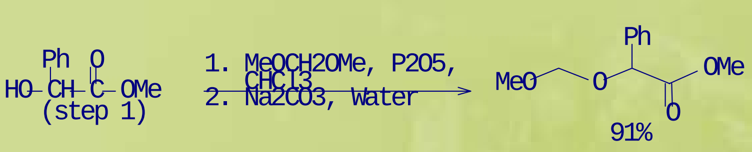
Methylal as reagent

- Propargylic alcohols



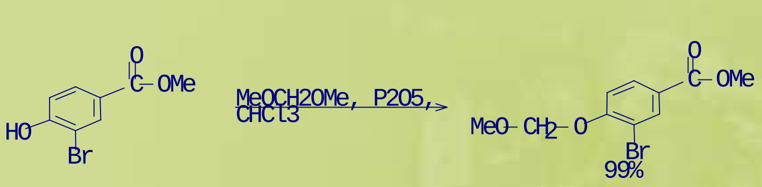
Methylal as reagent

- Benzylic alcohols



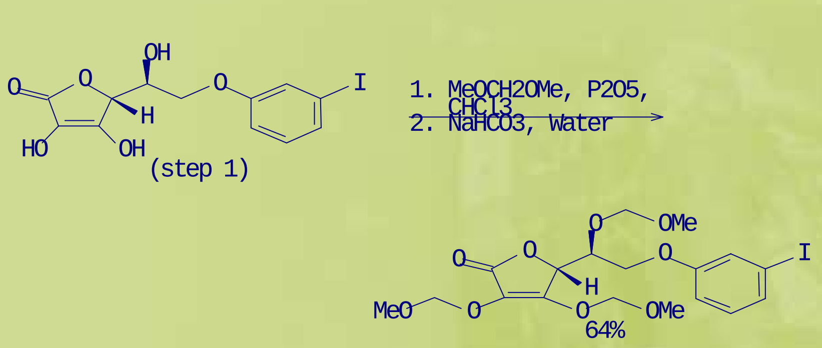
Methylal as reagent

- Phenols



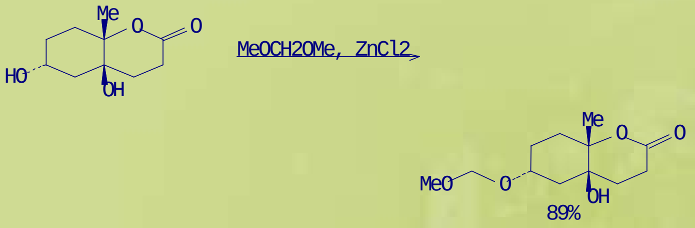
Methylal as reagent

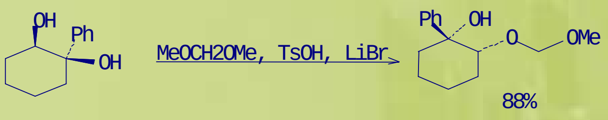
- Other alcohols



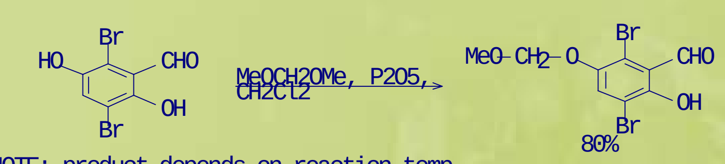
Methylal as reagent

- Examples of selectivities





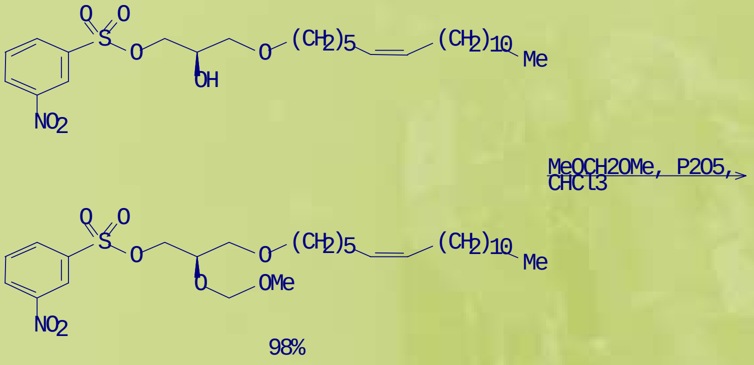
Methylal as reagent



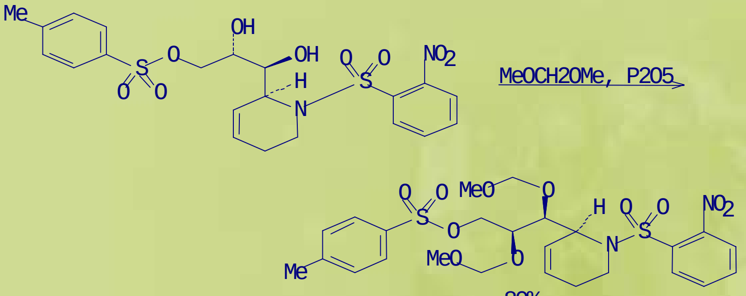
NOTE: product depends on reaction temp.

Methylal as reagent

- Other examples of transacetalizations



Methylal as reagent



80%

Methylal as reagent

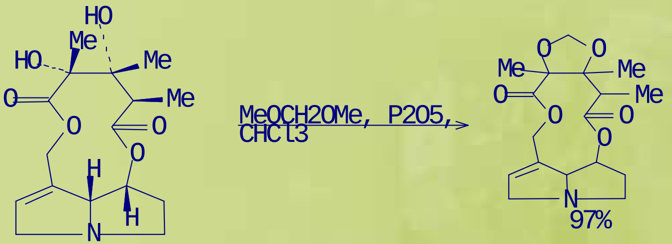
- Double

$$H_3C-O-CH_2-O-CH_3 \xrightarrow{\text{BuOH, TsOH}} n\text{-BuO}-CH_2-\text{OBu-}n$$

38%

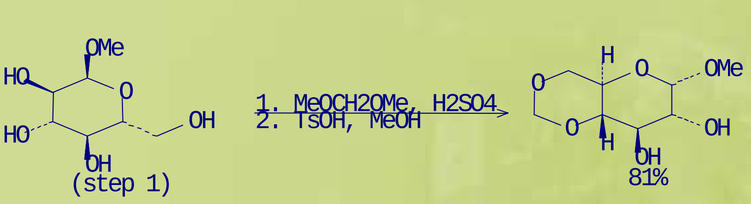
Methylal as reagent

– To cyclic acetals



Lambiotte

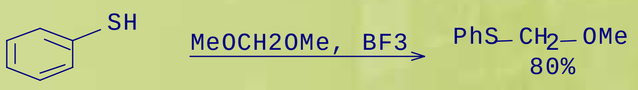
Methylal as reagent



Lambiotte

Methylal as reagent

- Transthioacetalizations
  - Simple



MeOCH2OMe, BF3

$PhS-CH_2-OMe$
80%

Methylal as reagent

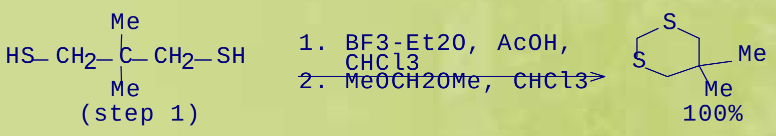
- Transthioacetalizations
  - Double

$$H_3C-O-CH_2-O-CH_3 \xrightarrow{\text{PhSH, HCl}} PhS-CH_2-SPh$$

100%

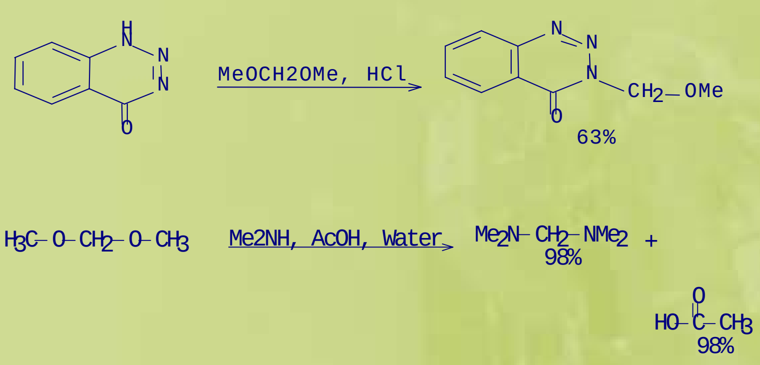
Methylal as reagent

- Transthioacetalizations
  - To cyclic thioacetal



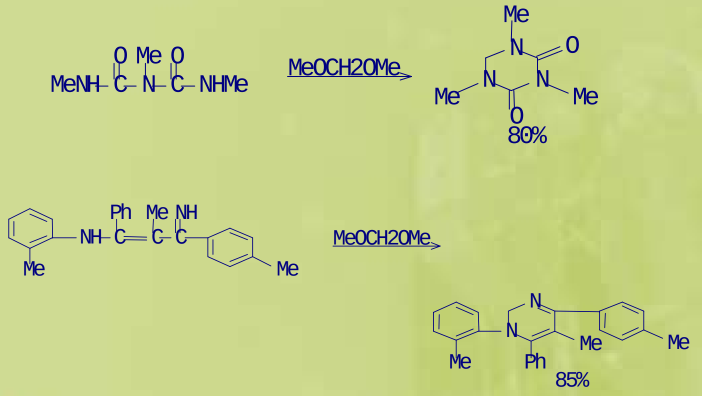
Methylal as reagent

- Reactions of methylal with nitrogen containing compounds



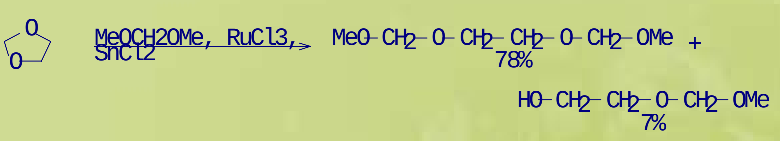
Methylal as reagent

- Reactions of methylal with nitrogen containing compounds to cyclizations



Methylal as reagent

- Reactions of methylal with acetals and thioacetals



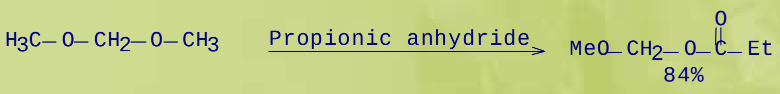
$EtS–CH_2–SEt \xrightarrow{MeOCH2OMe} EtS–CH_2–OMe$

Methylal as reagent

- Reactions of methylal with esters, anhydrides, carboxylic acids and their salts

$$\text{n-Pr–O–Ac} \xrightarrow{\text{MeOCH2OMe}} \underset{36\%}{\text{n-PrO–CH}_2\text{–OPr-n}}$$

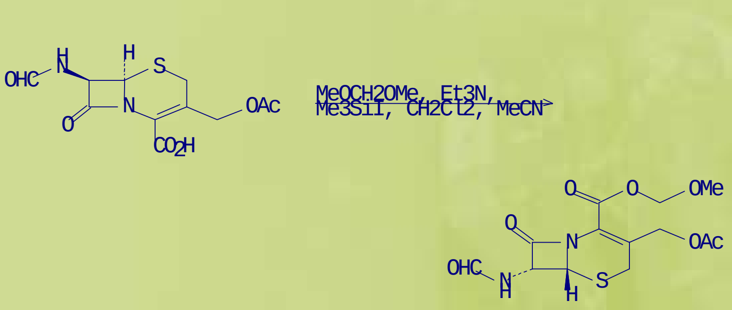
$$\text{Ac–O–Ac} \xrightarrow{\text{MeOCH2OMe, TsOH}} \underset{95\%}{\text{AcO–CH}_2\text{–OMe}}$$



$$\text{H}_3\text{C–O–CH}_2\text{–O–CH}_3 \xrightarrow{\text{Propionic anhydride}} \underset{84\%}{\text{MeO–CH}_2\text{–O–}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{–Et}}$$

Methylal as reagent

$$\text{HO–}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{–CH}_2\text{–CH}_3 \xrightarrow{\text{MeOCH2OMe}} \text{MeO–}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{–Et}$$

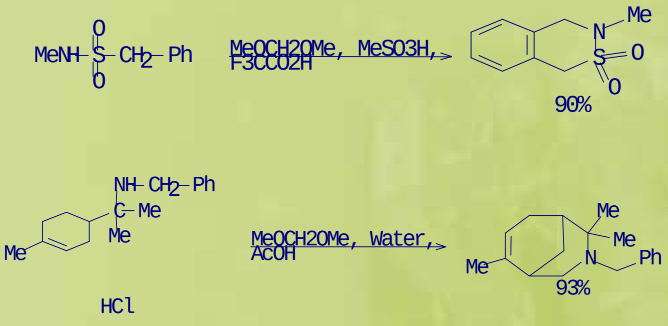


MeOCH2OMe, Et3N,
Me3SiI, CH2Cl2, MeCN

Methylal as reagent

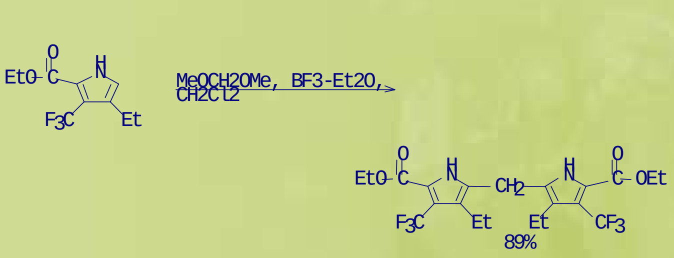
Methylal as reagent

- Methylal as a source of formaldehyde
  - In the synthesis of cyclic compounds



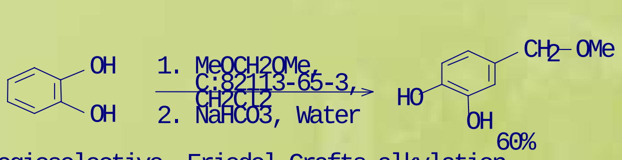
Methylal as reagent

- In the synthesis of “dimers”

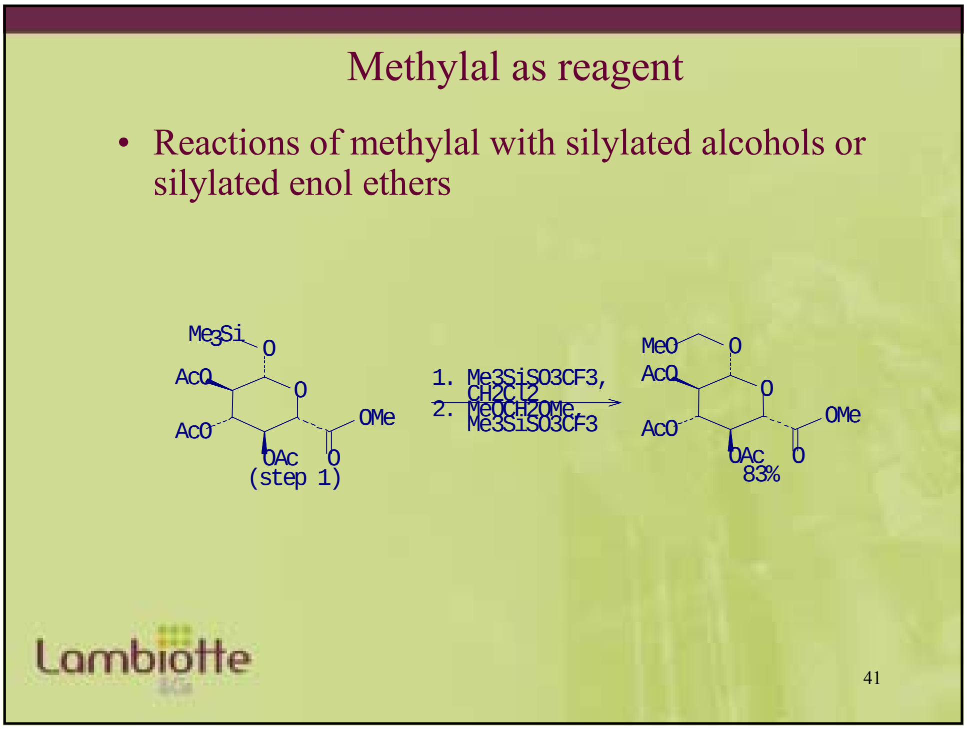


Methylal as reagent

- Methoxymethylations



NOTE: regioselective, Friedel-Crafts alkylation



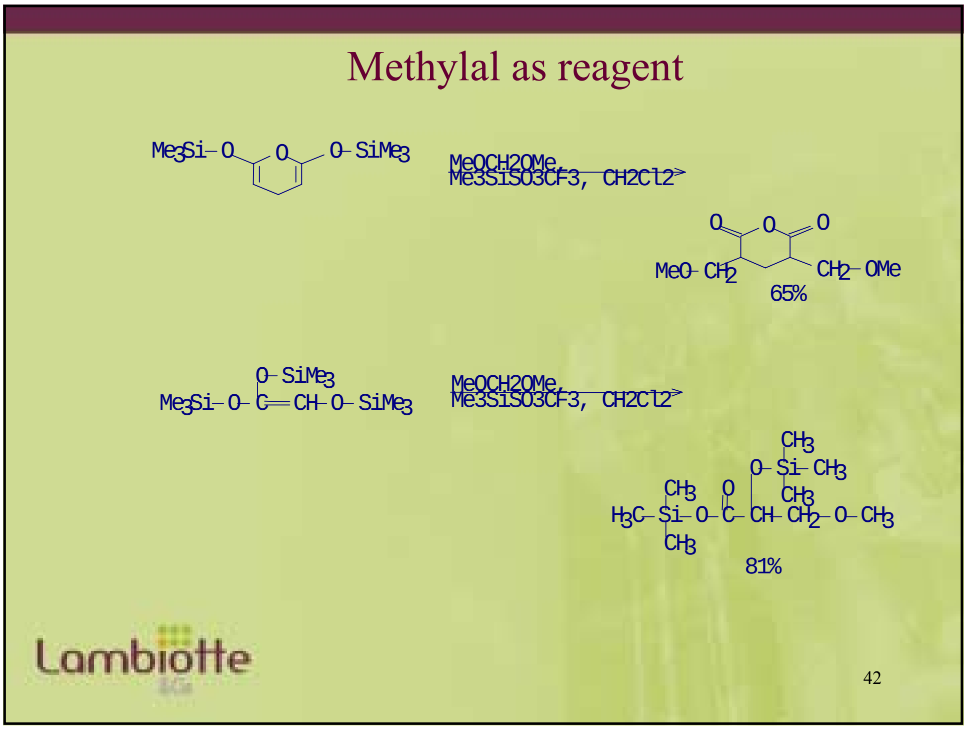
Methylal as reagent

- Reactions of methylal with silylated alcohols or silylated enol ethers

(step 1)

1. $Me_3SiSO_3CF_3$, CH_2Cl_2
2. $MeOCH_2OMe$, $Me_3SiSO_3CF_3$

83%



Methylal as reagent

$MeOCH_2OMe$, $Me_3SiSO_3CF_3$, CH_2Cl_2

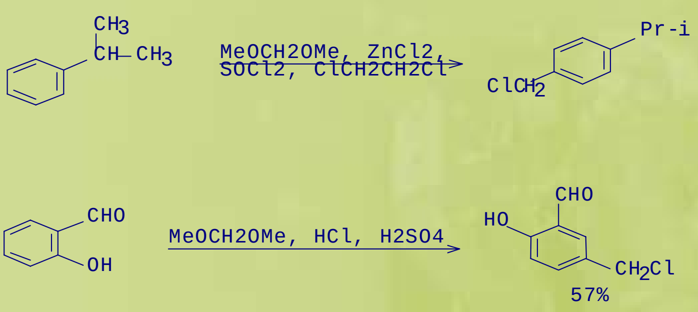
65%

$MeOCH_2OMe$, $Me_3SiSO_3CF_3$, CH_2Cl_2

81%

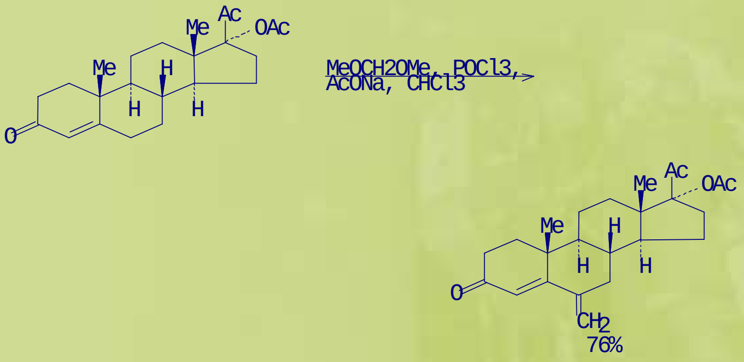
Methylal as reagent

- Chloromethylations



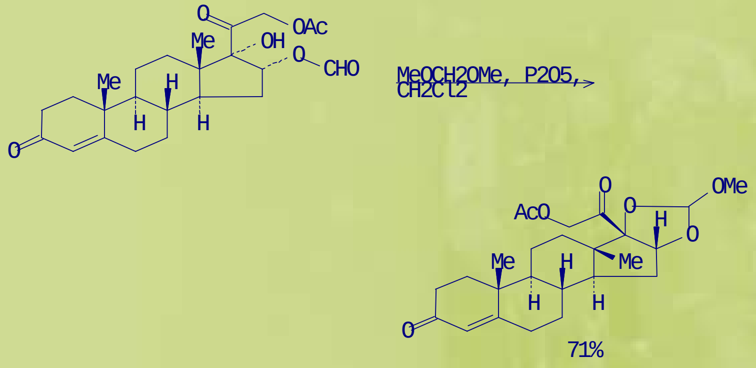
Methylal as reagent

- Methylenations

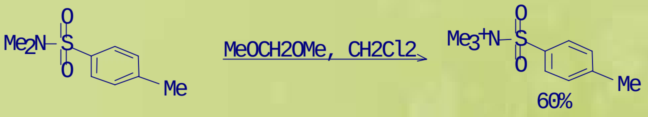


Methylal as reagent

- Methylations

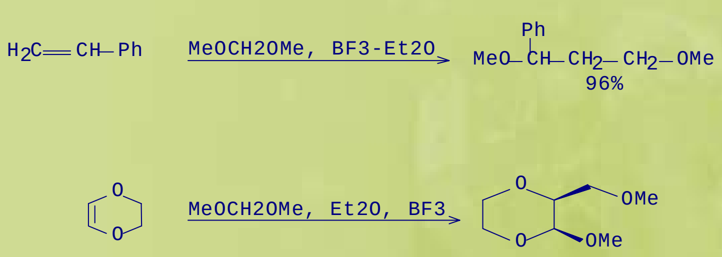


Methylal as reagent



Methylal as reagent

- Additions of methylal to carbon-carbon double bounds

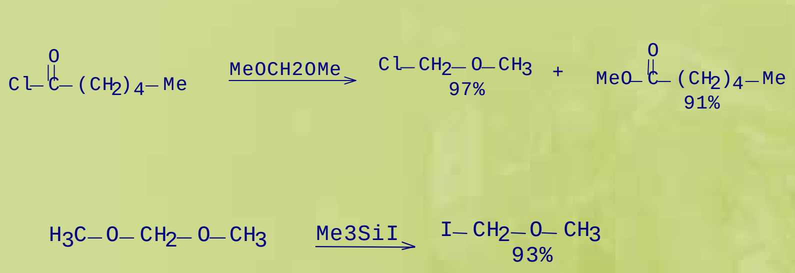


$$H_2C{=}CH{-}Ph \xrightarrow{MeOCH2OMe,\ BF3\text{-}Et2O} MeO{-}\underset{}{\overset{Ph}{CH}}{-}CH_2{-}CH_2{-}OMe \quad 96\%$$

$$\xrightarrow{MeOCH2OMe,\ Et2O,\ BF3}$$

Methylal as reagent

- Methylal in the synthesis of halogenomethylethers

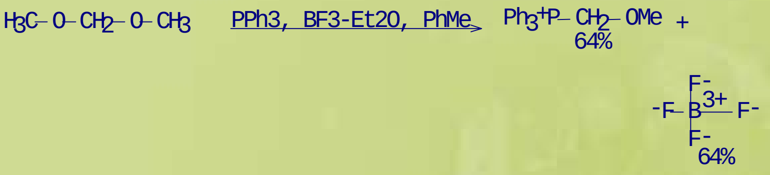


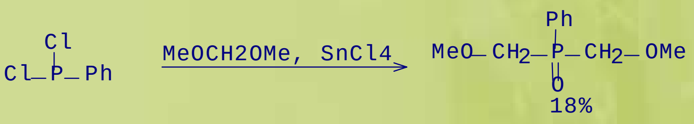
$$Cl{-}\overset{O}{\overset{\|}{C}}{-}(CH_2)_4{-}Me \xrightarrow{MeOCH2OMe} Cl{-}CH_2{-}O{-}CH_3 \ (97\%) + MeO{-}\overset{O}{\overset{\|}{C}}{-}(CH_2)_4{-}Me \ (91\%)$$

$$H_3C{-}O{-}CH_2{-}O{-}CH_3 \xrightarrow{Me3SiI} I{-}CH_2{-}O{-}CH_3 \quad 93\%$$

Methylal as reagent

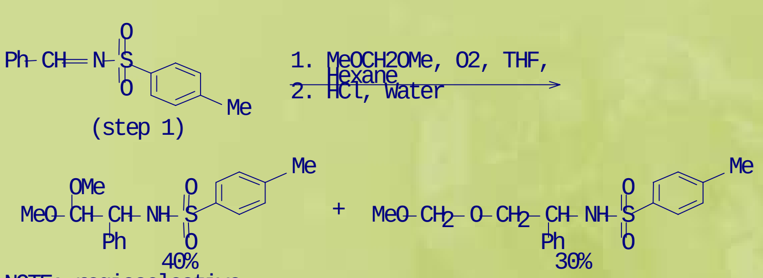
- Reactions of methylal with phosphorus compounds



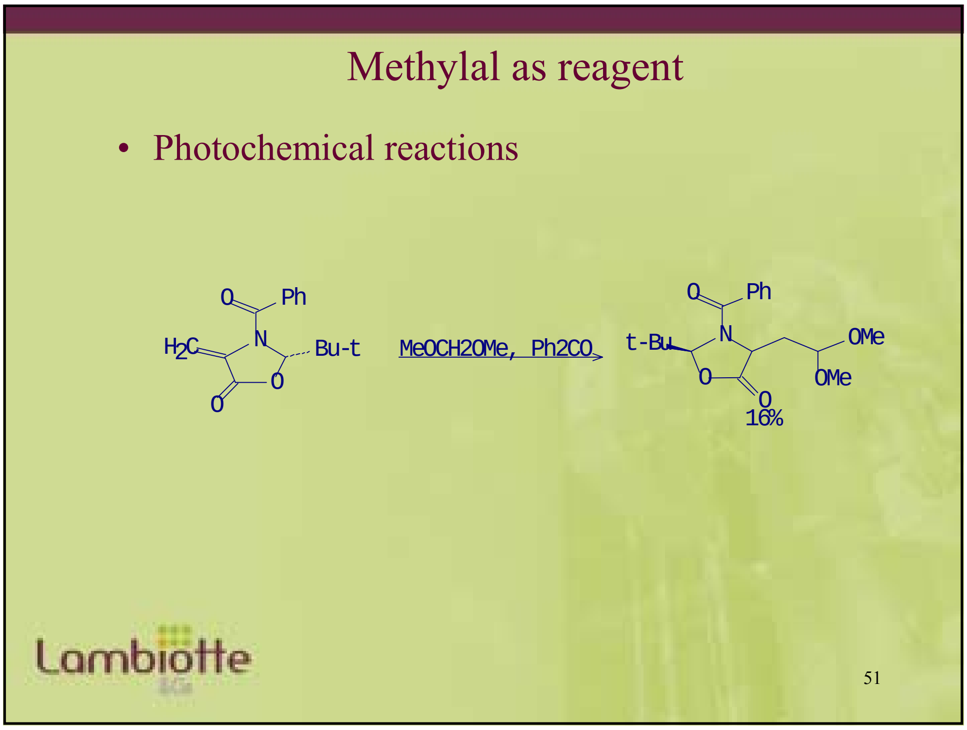


Methylal as reagent

- Radicalar reactions

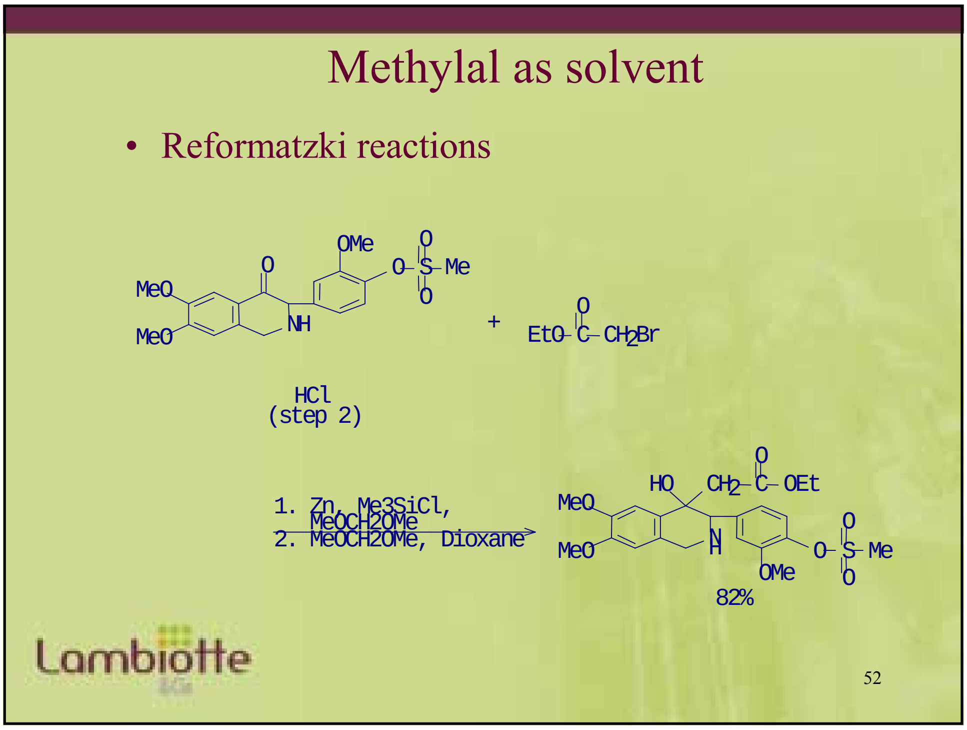


NOTE: regioselective



Methylal as reagent

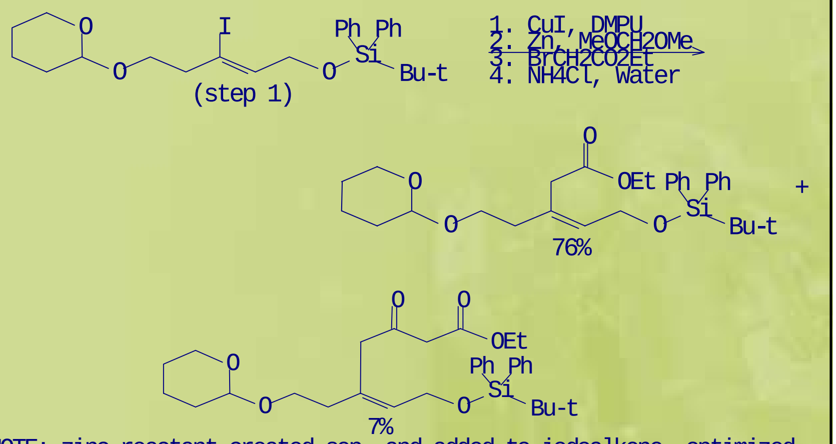
- Photochemical reactions



Methylal as solvent

- Reformatzki reactions

Methylal as solvent



NOTE: zinc reactant created sep. and added to iodoalkene, optimized conditions

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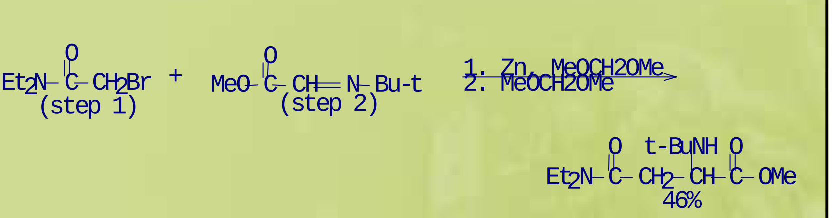
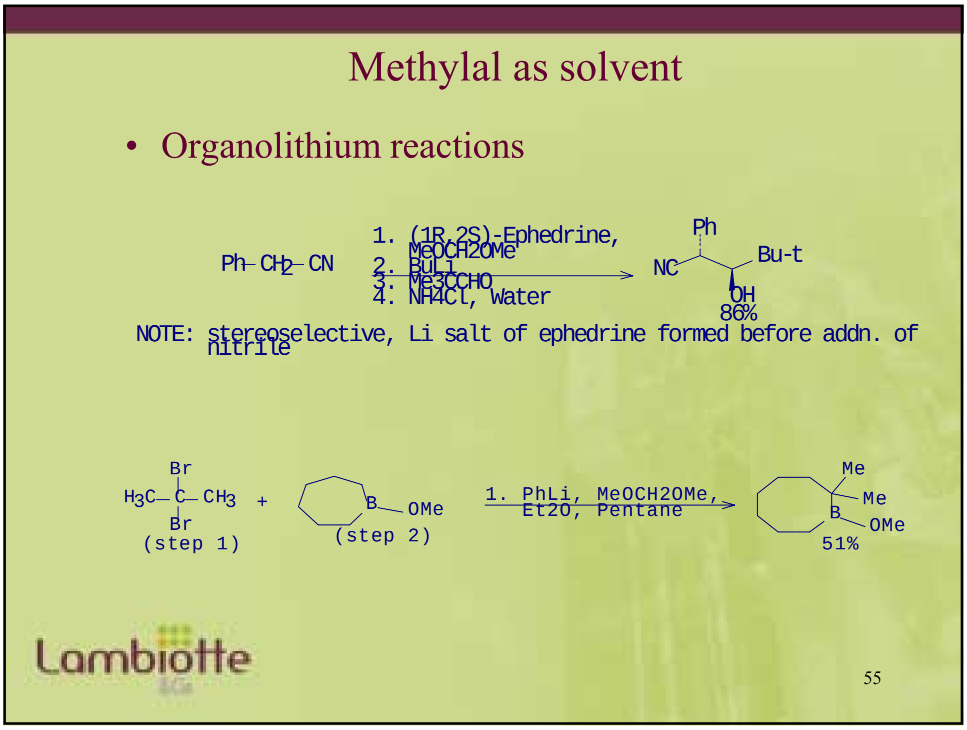
Methylal as solvent

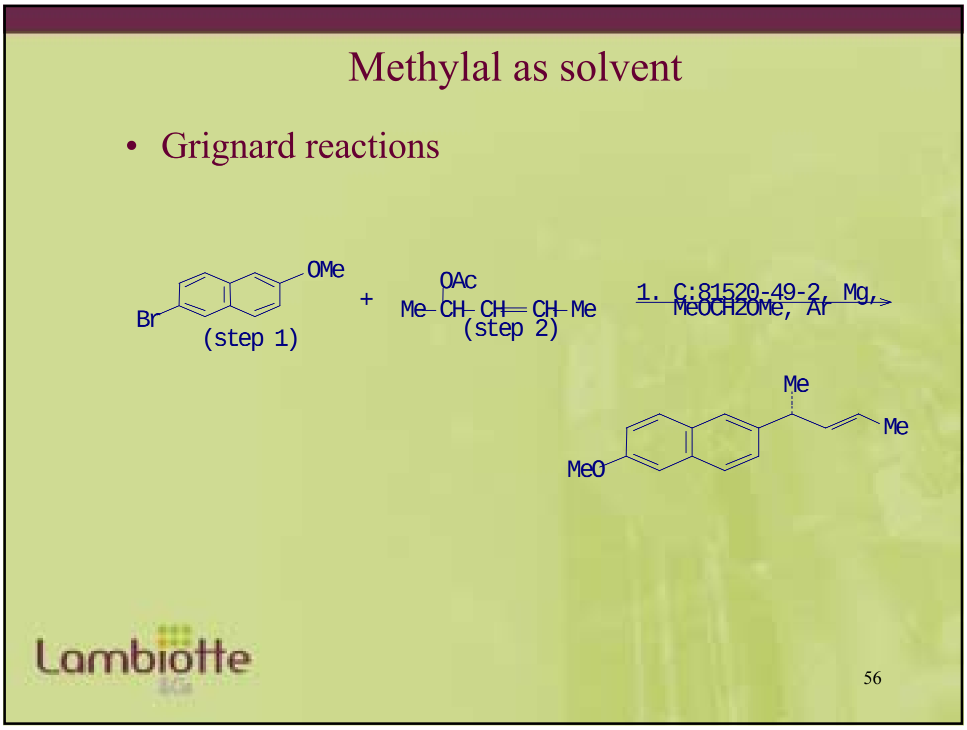

$$Et_2N-\overset{O}{\overset{\|}{C}}-CH_2Br + MeO-\overset{O}{\overset{\|}{C}}-CH{=}N-Bu\text{-}t \xrightarrow[\text{2. MeOCH2OMe}]{\text{1. Zn, MeOCH2OMe}} Et_2N-\overset{O}{\overset{\|}{C}}-CH_2-\overset{t\text{-}BuNH}{\overset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OMe$$



Methylal as solvent

- Organolithium reactions

NOTE: stereoselective, Li salt of ephedrine formed before addn. of nitrile

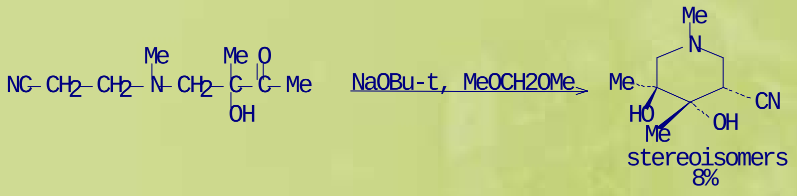


Methylal as solvent

- Grignard reactions

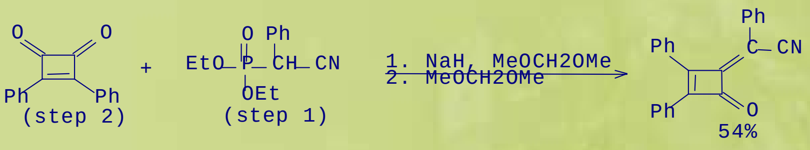
Methylal as solvent

- Reactions with alcoholates



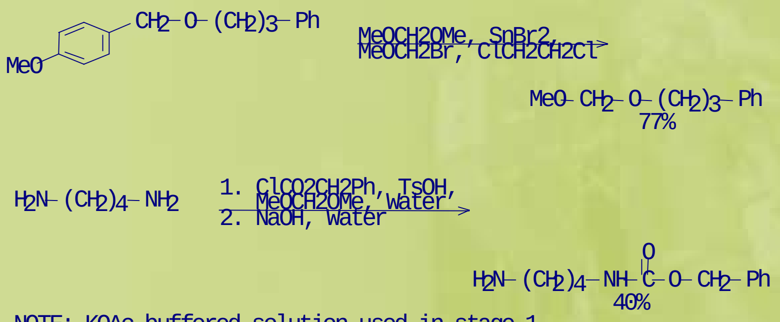
Methylal as solvent

- Reactions with hydrides



Methylal as solvent

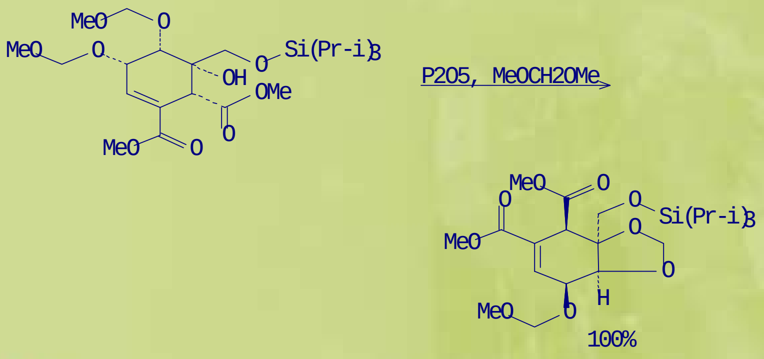
- Reactions with halogenomethylethers or chloroformates

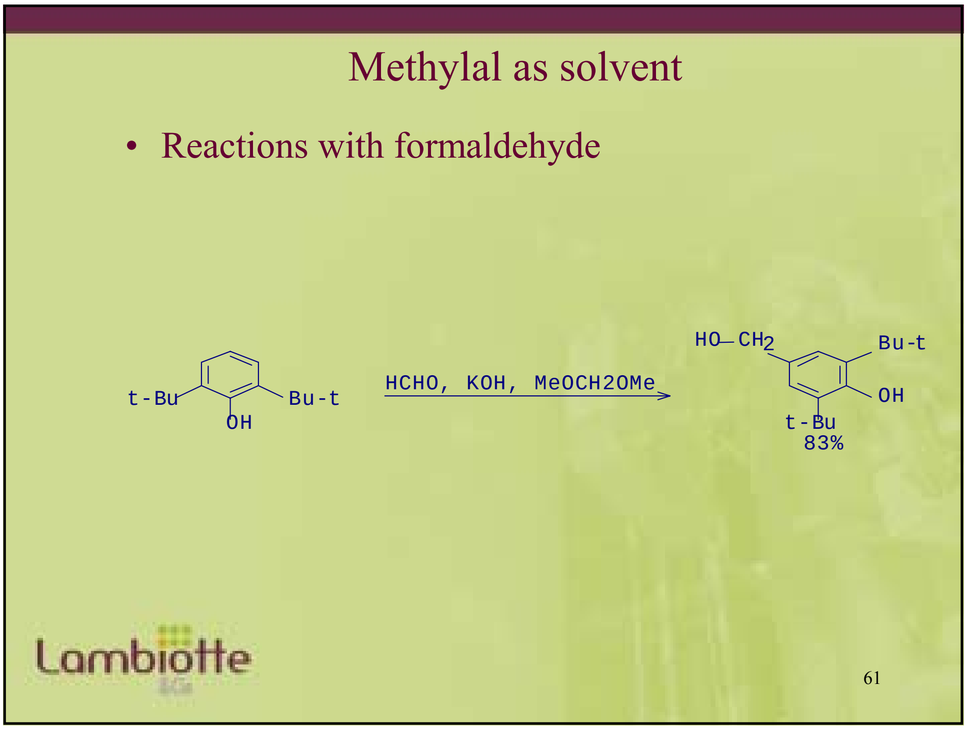


NOTE: KOAc buffered solution used in stage 1

Methylal as solvent

- Transacetalizations and internal transacetalizations



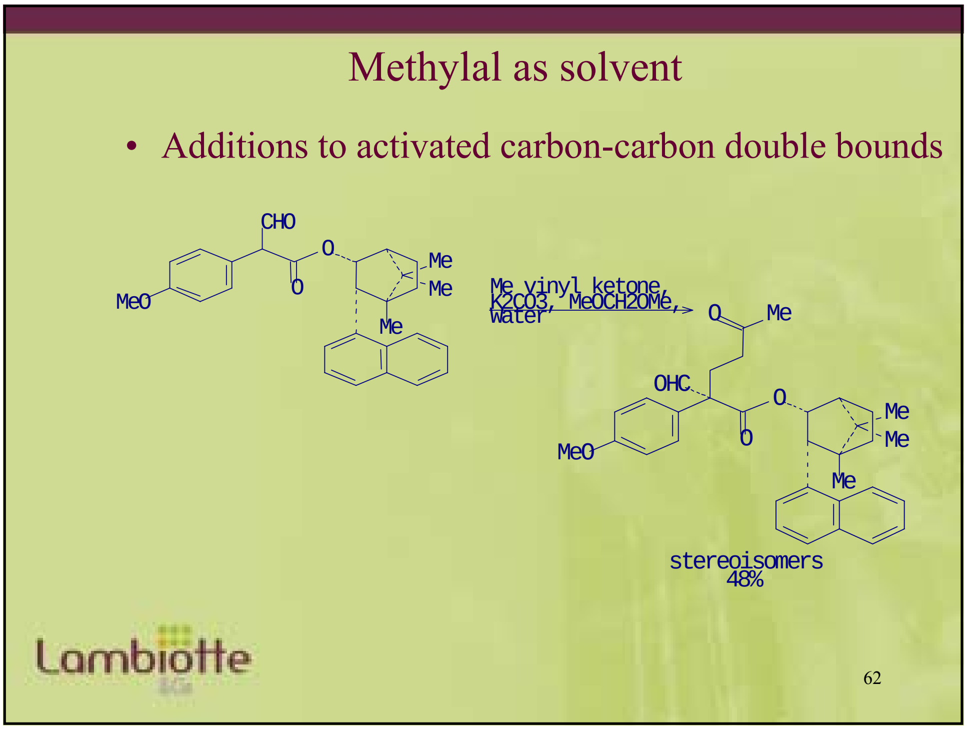


Methylal as solvent

- Reactions with formaldehyde

HCHO, KOH, MeOCH2OMe

83%



Methylal as solvent

- Additions to activated carbon-carbon double bounds

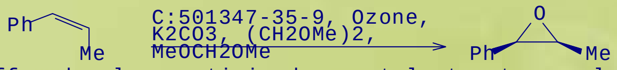
Me vinyl ketone, K2CO3, MeOCH2OMe, water

stereoisomers 48%

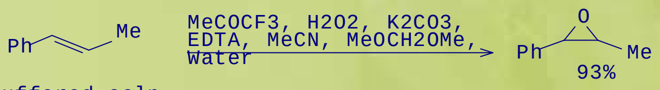
Methylal as solvent

Methylal as solvent

- Epoxidations of olefins



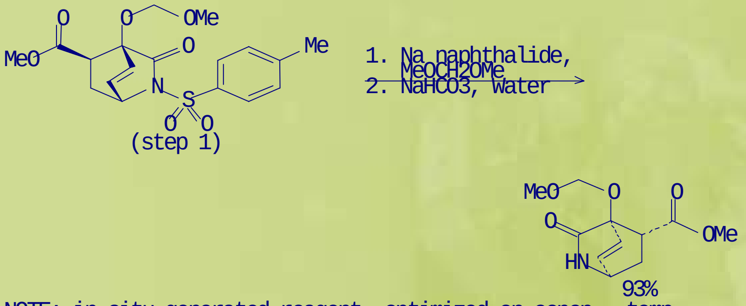
NOTE: buffered soln., optimized on catalyst, stereoselective



NOTE: buffered soln.

Methylal as solvent

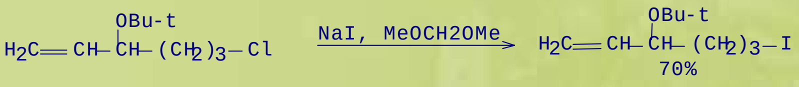
- Reductions



NOTE: in-situ generated reagent, optimized on concn., temp.

Methylal as solvent

- Halide exchanges

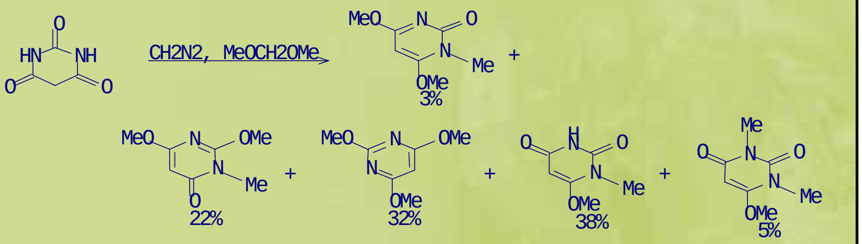


$$H_2C{=}CH{-}\underset{}{\overset{OBu\text{-}t}{CH}}{-}(CH_2)_3{-}Cl \xrightarrow{NaI,\ MeOCH2OMe} H_2C{=}CH{-}\overset{OBu\text{-}t}{CH}{-}(CH_2)_3{-}I$$

70%

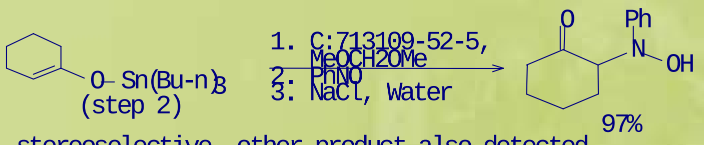
Methylal as solvent

- Reactions with diazomethane



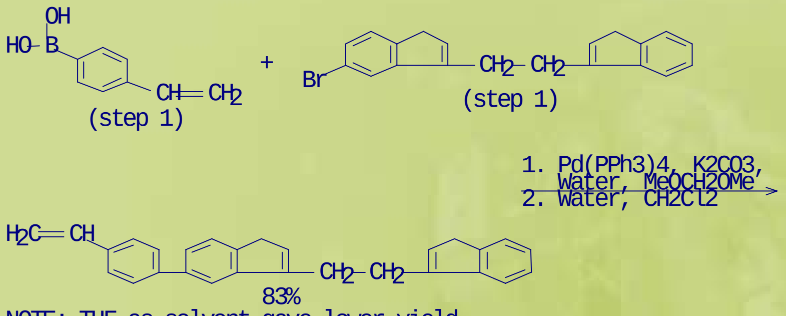
Methylal as solvent

- Reactions with organometallic compounds



NOTE: stereoselective, other product also detected

Methylal as solvent

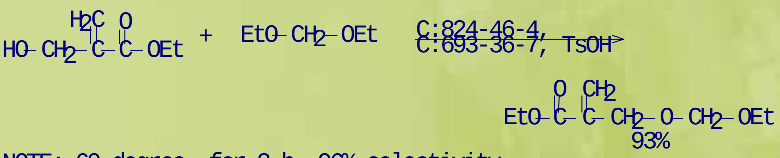


NOTE: THF as solvent gave lower yield

Ethylal as reagent

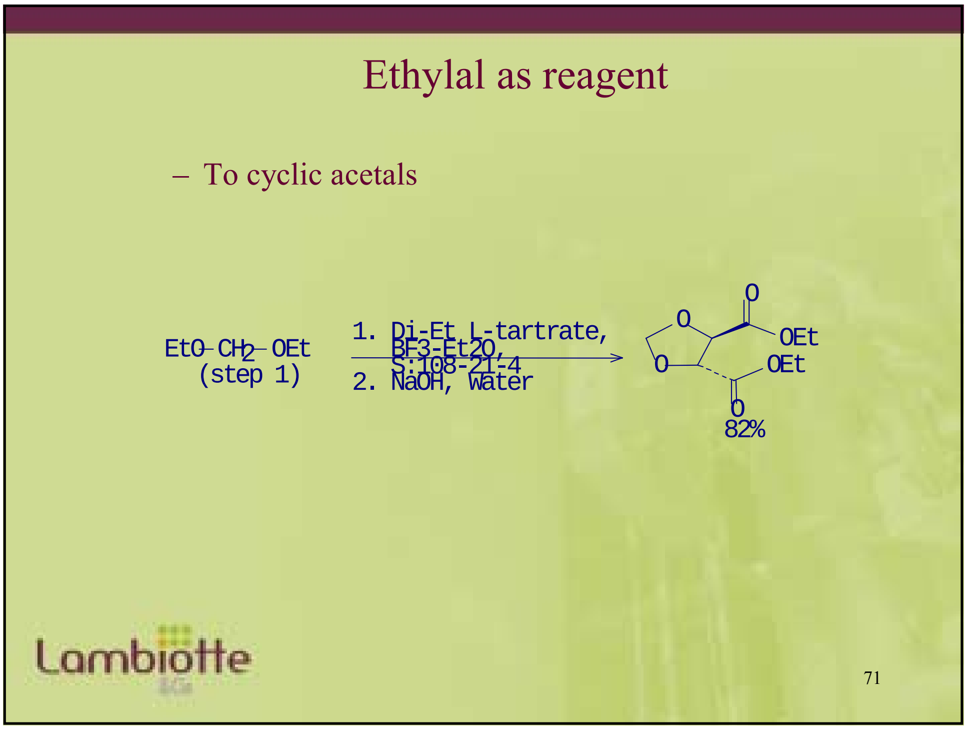
- Transacetalizations
  - Simple

$$EtO-CH_2-OEt \xrightarrow[\text{PhMe}]{\text{1-Octanol, Nafion H,}} EtO-CH_2-O-(CH_2)_7-Me \quad 89\%$$



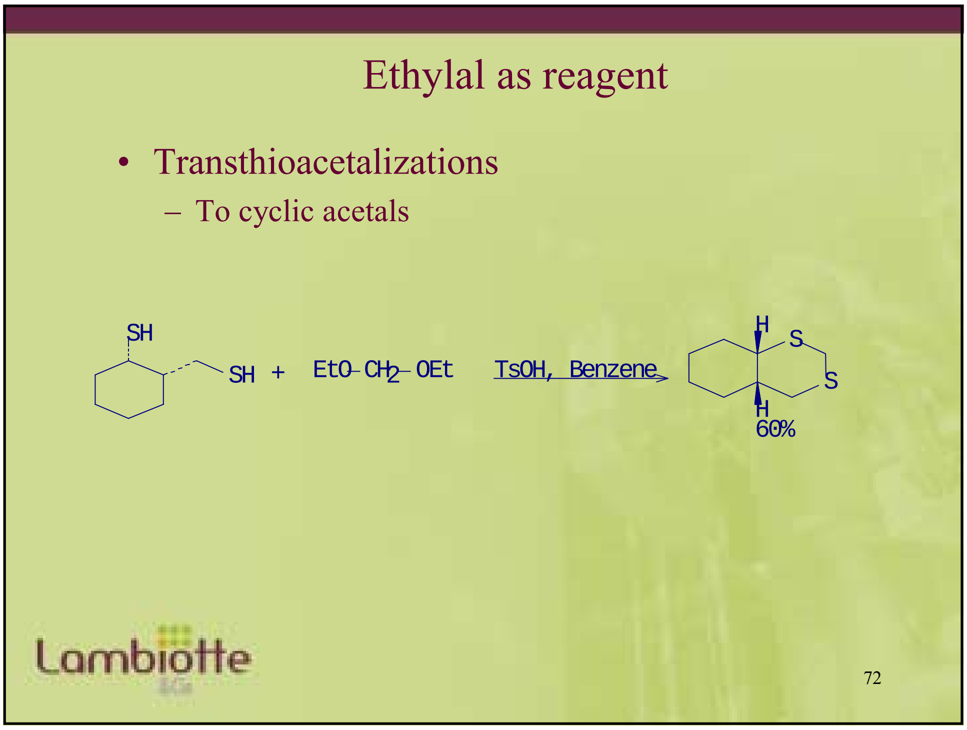
$$HO-CH_2-\overset{H_2C}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-OEt + EtO-CH_2-OEt \xrightarrow{\text{C:824-46-4, C:693-36-7, TsOH}} EtO-\overset{O}{\overset{\|}{C}}-\overset{CH_2}{\overset{\|}{C}}-CH_2-O-CH_2-OEt \quad 93\%$$

NOTE: 60.degree. for 3 h, 96% selectivity



Ethylal as reagent

- To cyclic acetals

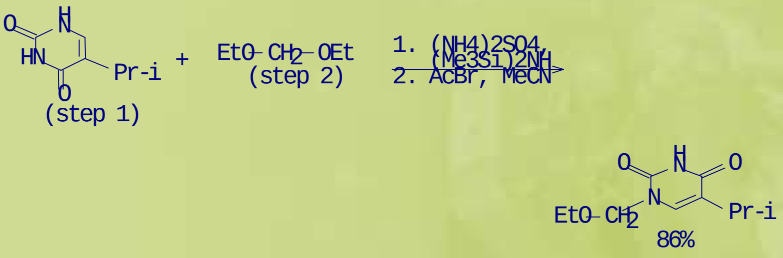


Ethylal as reagent

- Transthioacetalizations
  - To cyclic acetals

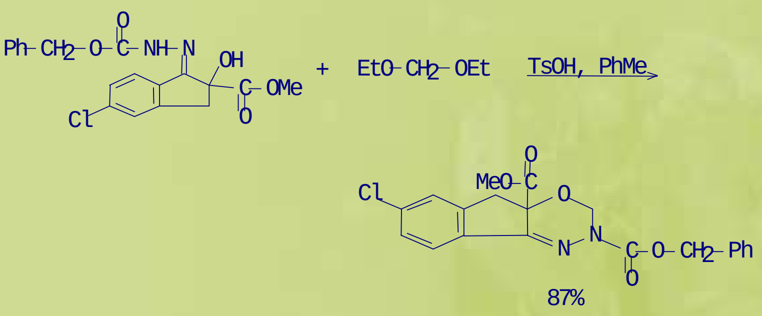
Ethylal as reagent

- Reactions of ethylal with nitrogen containing compounds



Ethylal as reagent

- Reactions of ethylal with nitrogen containing compounds to cyclizations



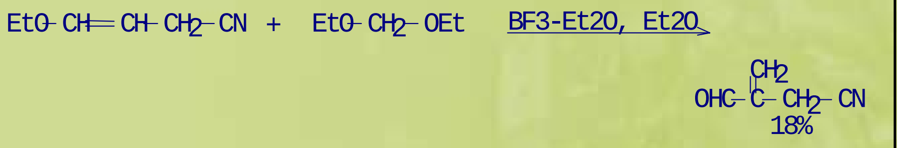
Ethylal as reagent

- Reactions of ethylal with thioacetals

$$EtO-CH_2-OEt + EtS-CH_2-SEt \longrightarrow \underset{15\%}{EtO-CH_2-O-CH_2-OEt}$$

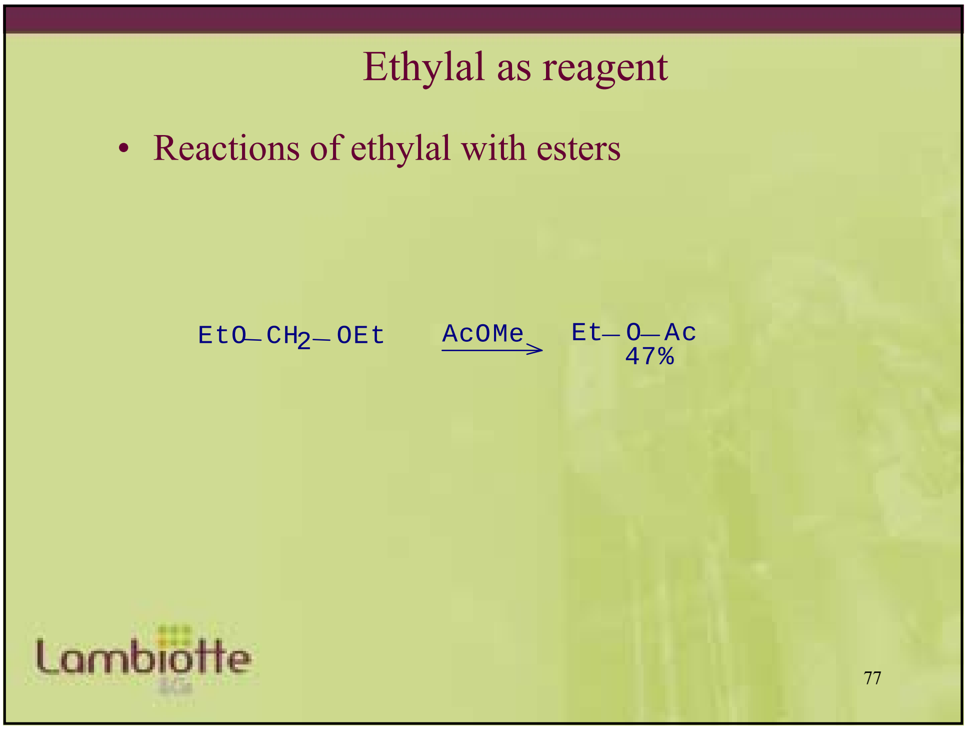
Ethylal as reagent

- Reactions of ethylal with enol ethers



$$EtO-CH=CH-CH_2-CN + EtO-CH_2-OEt \xrightarrow{\text{BF3-Et2O, Et2O}} OHC-\overset{\overset{\displaystyle CH_2}{\|}}{C}-CH_2-CN$$

18%

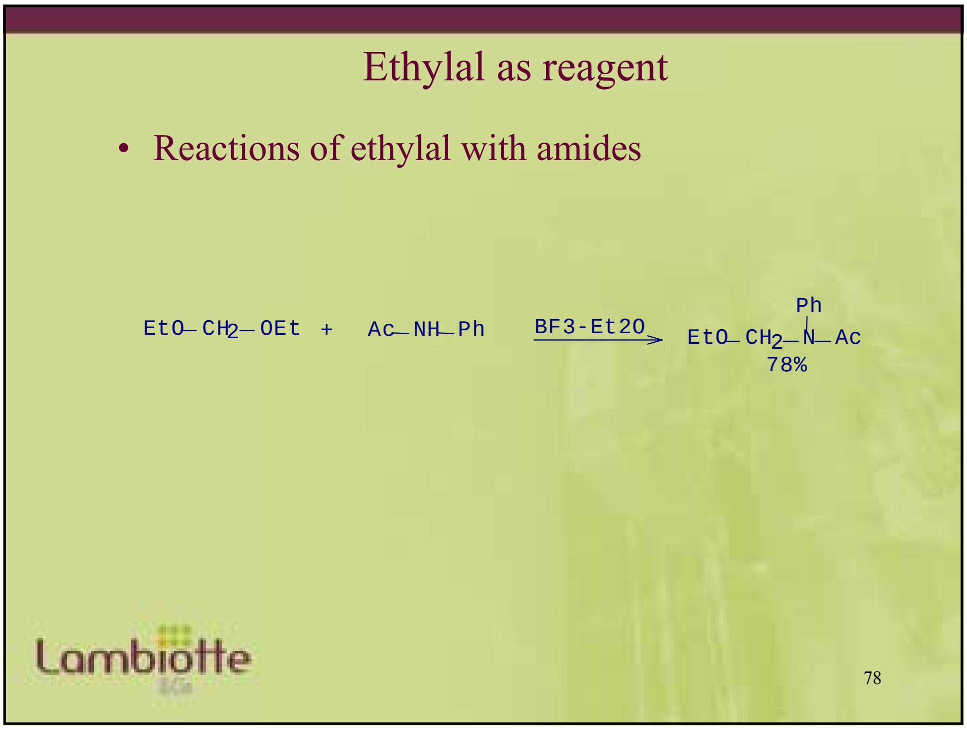


Ethylal as reagent

- Reactions of ethylal with esters

$$EtO-CH_2-OEt \xrightarrow{AcOMe} Et-O-Ac$$

47%



Ethylal as reagent

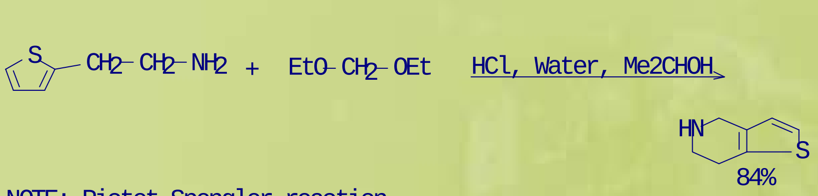
- Reactions of ethylal with amides

$$EtO-CH_2-OEt \;+\; Ac-NH-Ph \xrightarrow{BF3\text{-}Et2O} EtO-CH_2-\overset{\displaystyle Ph}{\overset{|}{N}}-Ac$$

78%

Ethylal as reagent

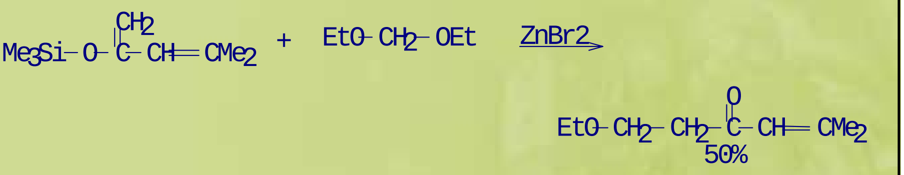
- Ethylal as a source of formaldehyde



NOTE: Pictet-Spengler reaction

Ethylal as reagent

- Reactions of ethylal with O-Si compounds



$$Me_3Si-O-\overset{CH_2}{\overset{\|}{C}}-CH=CMe_2 + EtO-CH_2-OEt \xrightarrow{ZnBr_2} EtO-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH=CMe_2$$

50%

Ethylal as reagent

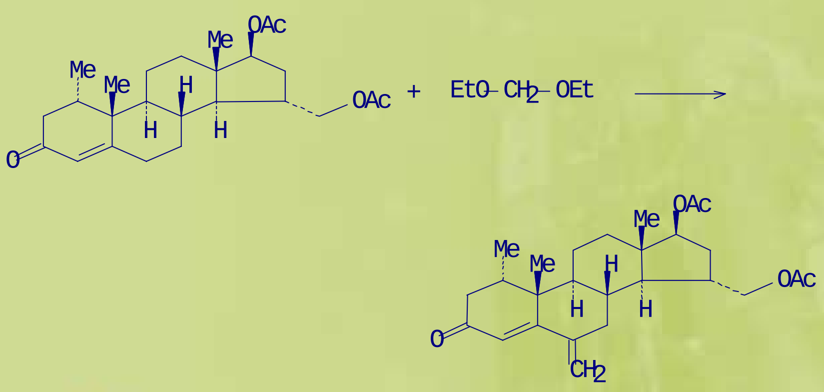
- Reactions of ethylal with Grignard reagents

$$\mathrm{EtO{-}CH_2{-}OEt} + \mathrm{Br{-}Mg{-}C{\equiv}C{-}Bu\text{-}n} \xrightarrow{\mathrm{Et2O}} \mathrm{EtO{-}CH_2{-}C{\equiv}C{-}Bu\text{-}n}$$

62%

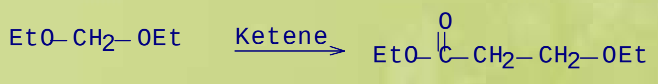
Ethylal as reagent

- Methylenations



Ethylal as reagent

- Reaction of ethylal with ketene



$$\mathrm{EtO{-}CH_2{-}OEt} \xrightarrow{\text{Ketene}} \mathrm{EtO{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}CH_2{-}OEt}$$

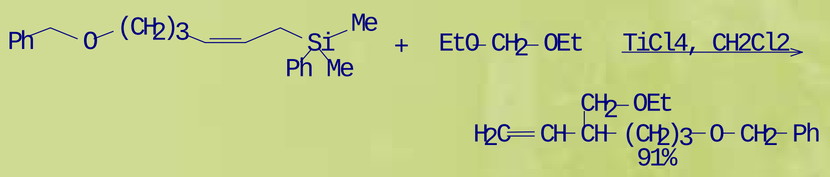
Ethylal as reagent

- Synthesis of ethyl halomethyl ethers

$$\mathrm{EtO{-}CH_2{-}OEt} \xrightarrow{\text{H2SO4, PhCOCl}} \underset{78\%}{\mathrm{H_3C{-}CH_2{-}O{-}CH_2{-}Cl}}$$

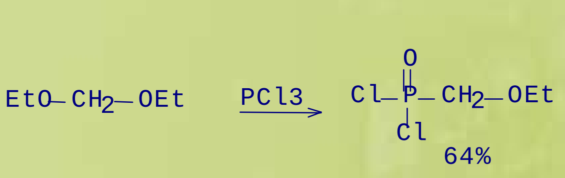
Ethylal as reagent

- Reaction of ethylal with organosilicon compounds



Ethylal as reagent

- Reaction of ethylal with phosphorus compounds

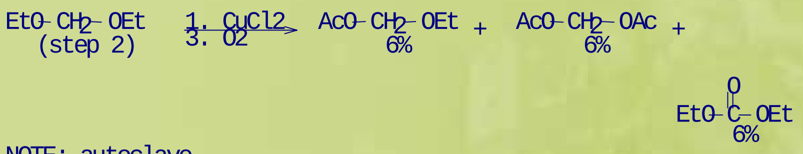


$$EtO{-}CH_2{-}OEt \xrightarrow{PCl_3} Cl{-}\overset{\overset{O}{\|}}{\underset{\underset{Cl}{|}}{P}}{-}CH_2{-}OEt$$

64%

Ethylal as reagent

- Oxydation

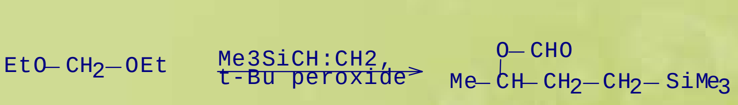


$$\underset{\text{(step 2)}}{EtO{-}CH_2{-}OEt} \xrightarrow[3.\ O_2]{1.\ CuCl_2} \underset{6\%}{AcO{-}CH_2{-}OEt} + \underset{6\%}{AcO{-}CH_2{-}OAc} + \underset{6\%}{EtO{-}\overset{\overset{O}{\|}}{C}{-}OEt}$$

NOTE: autoclave

Ethylal as reagent

- Radicalar reactions



$$EtO{-}CH_2{-}OEt \xrightarrow[\text{t-Bu peroxide}]{\text{Me3SiCH:CH2,}} Me{-}\overset{O{-}CHO}{\overset{|}{CH}}{-}CH_2{-}CH_2{-}SiMe_3$$

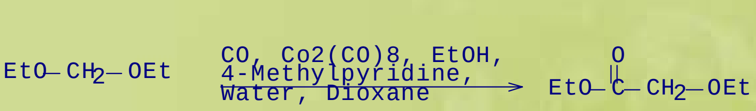
Ethylal as reagent

- Photochemical reactions

$$EtO-CH_2-OEt \xrightarrow[\text{t-Bu peroxide}]{\text{1-Hexene,}} Me-(CH_2)_6-Me$$

Ethylal as reagent

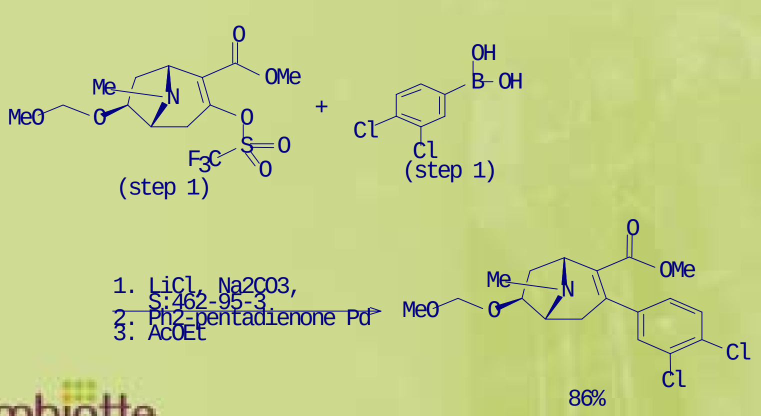
- Organometallic reactions



$$EtO-CH_2-OEt \xrightarrow[\text{Water, Dioxane}]{\text{CO, Co2(CO)8, EtOH, 4-Methylpyridine,}} EtO-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2-OEt$$

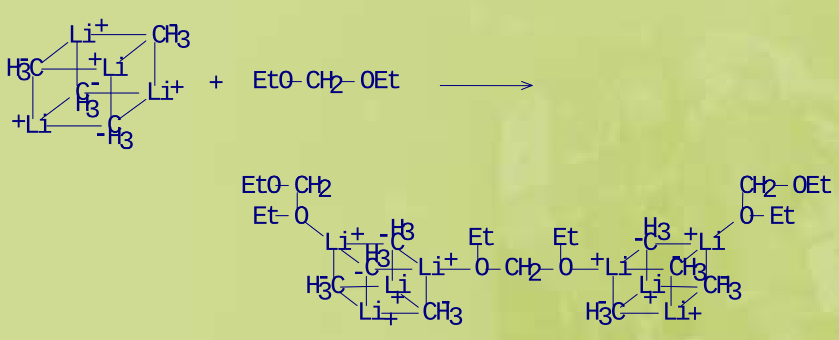
Ethylal as solvent

- Suzuki couplings

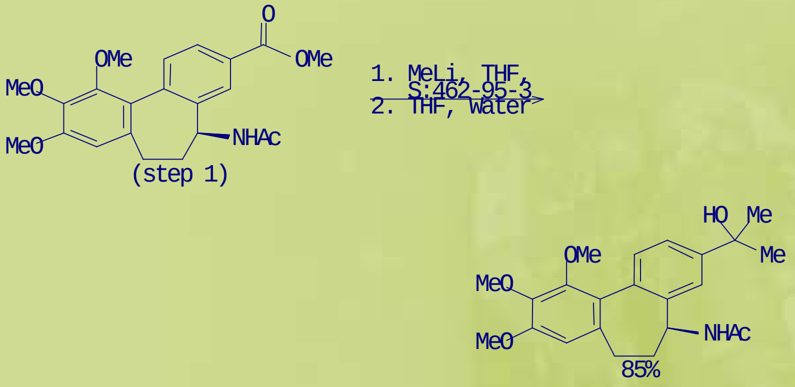


Ethylal as solvent

- Organolithium reactions



Ethylal as solvent



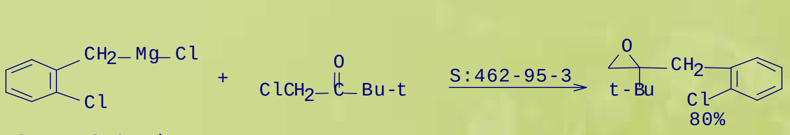
1. MeLi, THF, S:462-95-3
2. THF, water

(step 1)

85%

Ethylal as solvent

- Grignard reactions



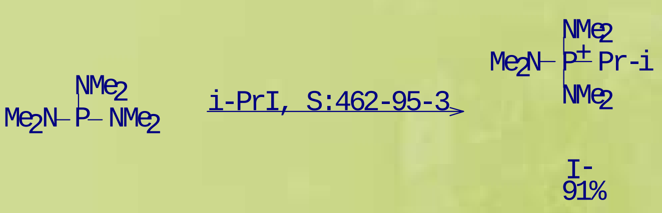
S:462-95-3

80%

NOTE: 10-25.degree.

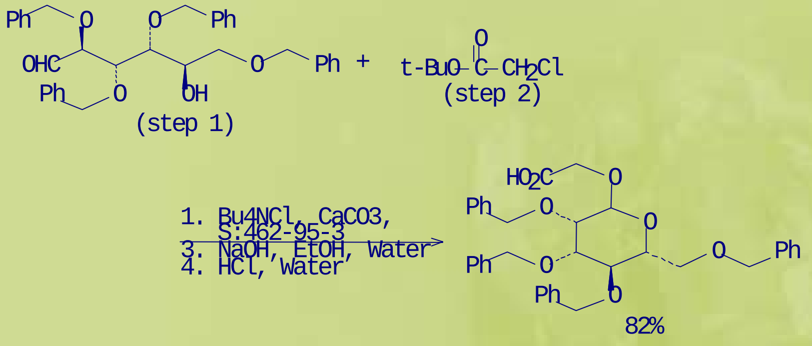
Ethylal as solvent

- Alkylations



Lambiotte

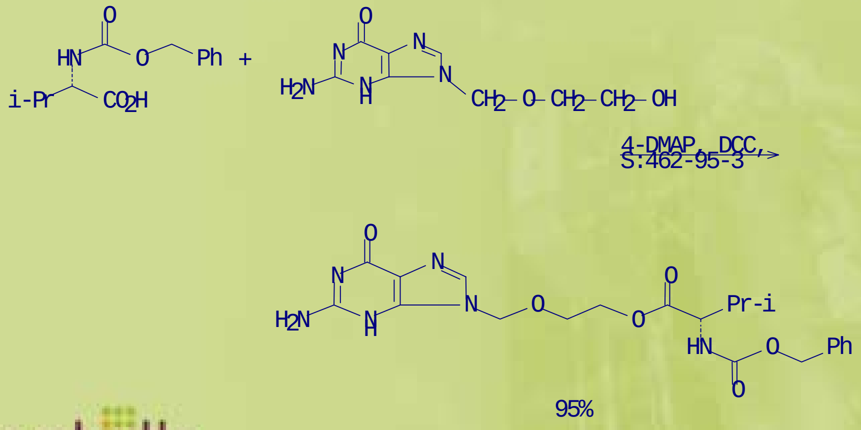
Ethylal as solvent



Lambiotte

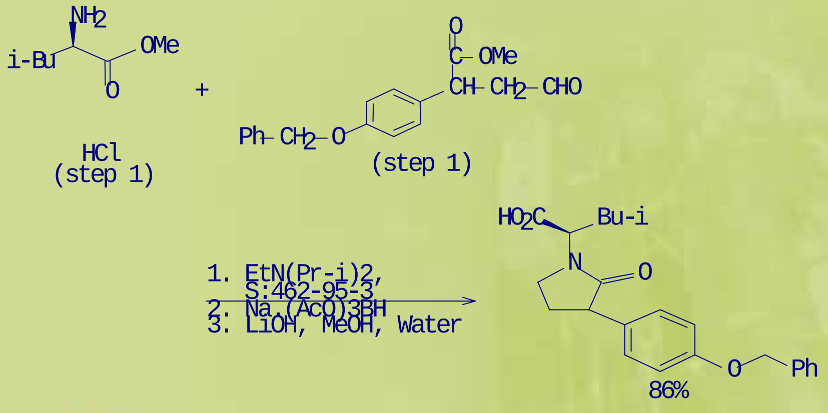
Ethylal as solvent

- Esterifications



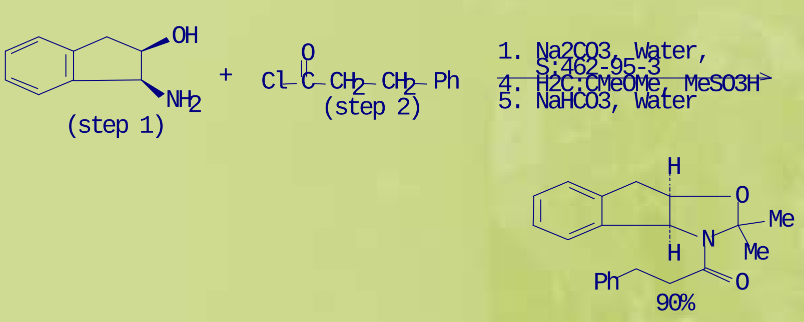
Ethylal as solvent

- Reactions amine + aldehyde



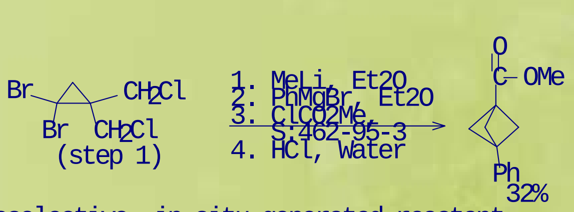
Ethylal as solvent

- Reactions amine + acid chloride

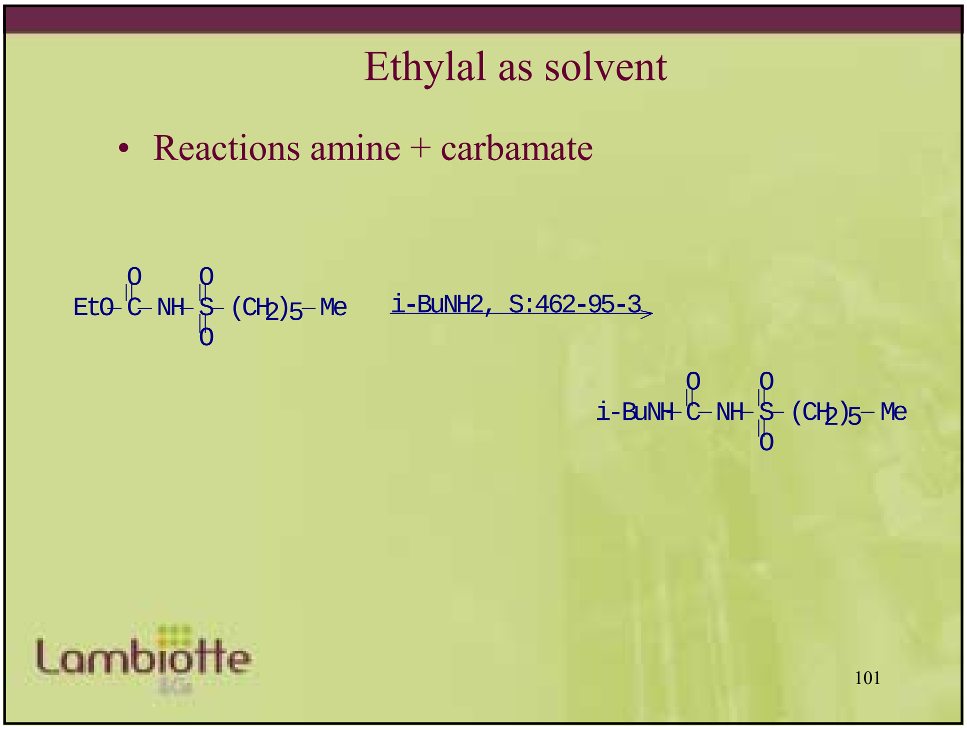


Ethylal as solvent

- Reactions amine + chloroformate



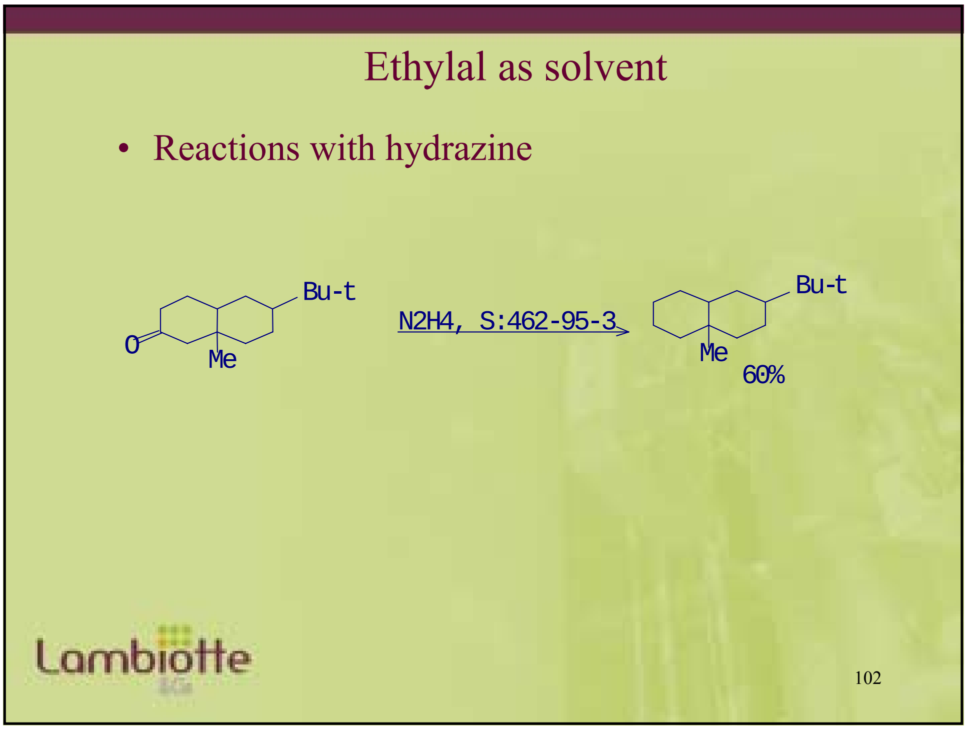
NOTE: regioselective, in-situ generated reactant



Ethylal as solvent

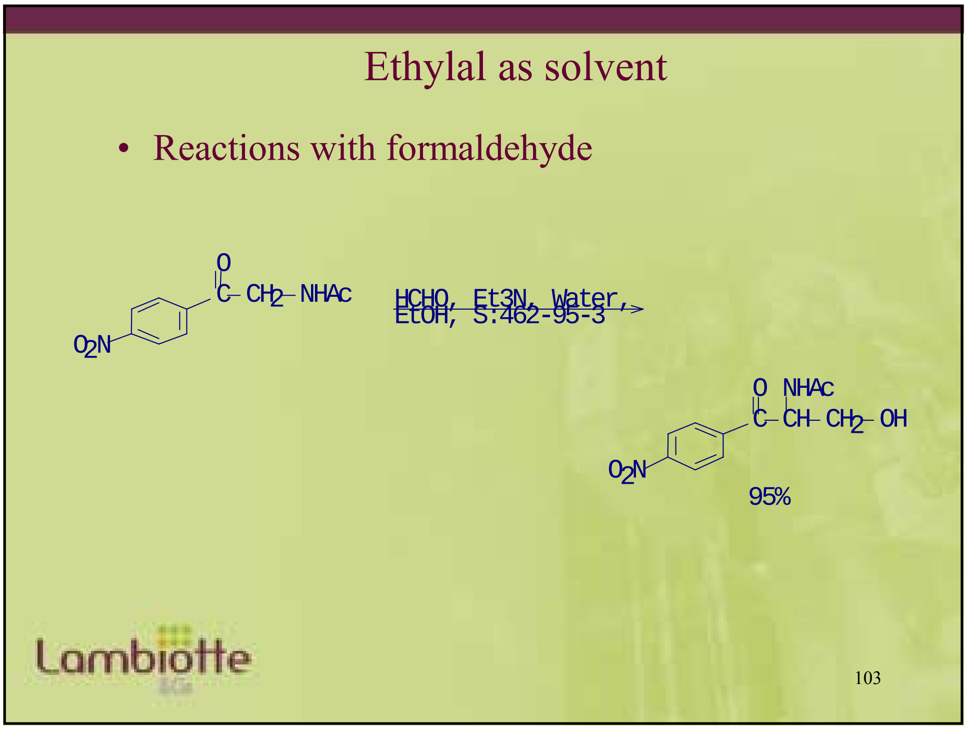
- Reactions amine + carbamate

$$\mathrm{EtO-\overset{O}{\overset{\|}{C}}-NH-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-(CH_2)_5-Me} \xrightarrow{\text{i-BuNH2, S:462-95-3}} \mathrm{i\text{-}BuNH-\overset{O}{\overset{\|}{C}}-NH-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-(CH_2)_5-Me}$$



Ethylal as solvent

- Reactions with hydrazine

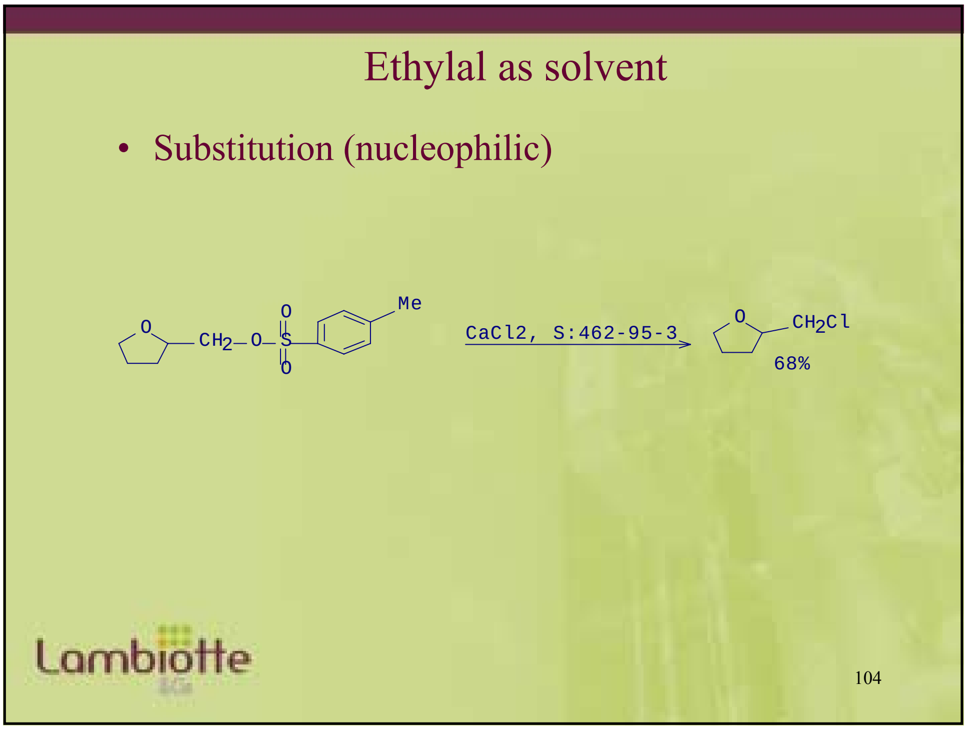


Ethylal as solvent

- Reactions with formaldehyde

HCHO, Et3N, Water, EtOH, S:462-95-3

95%



Ethylal as solvent

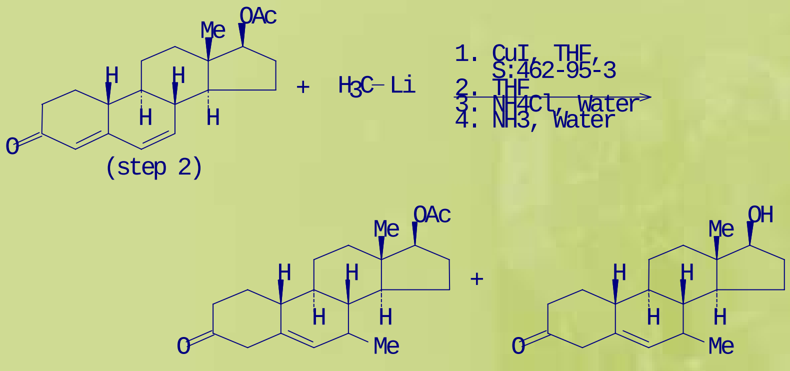
- Substitution (nucleophilic)

CaCl2, S:462-95-3

68%

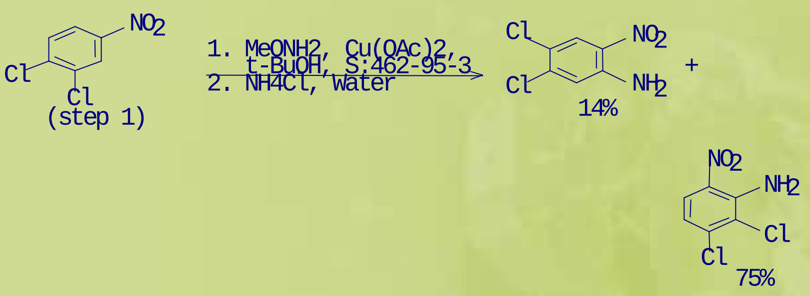
Ethylal as solvent

- Nucleophilic additions



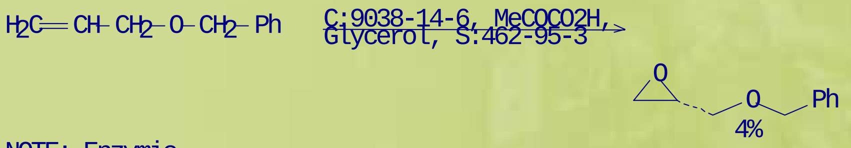
Ethylal as solvent

- Amination of nitroarene with O-alkylhydroxylamines



Ethylal as solvent

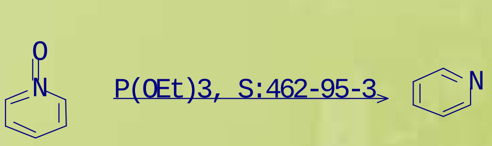
- Epoxydations of olefines



NOTE: Enzymic

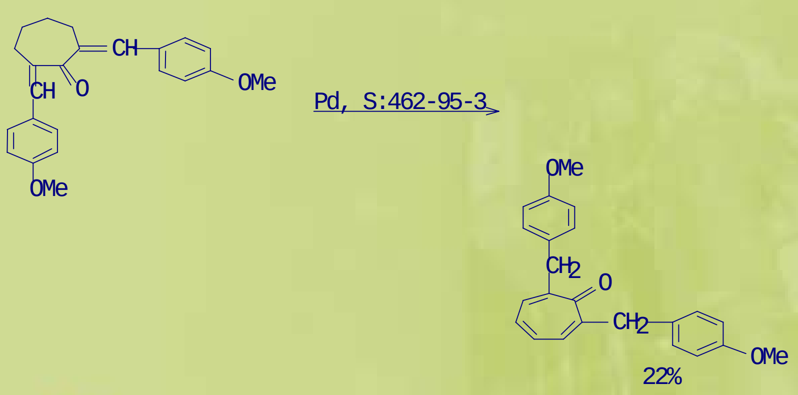
Ethylal as solvent

- Reductions



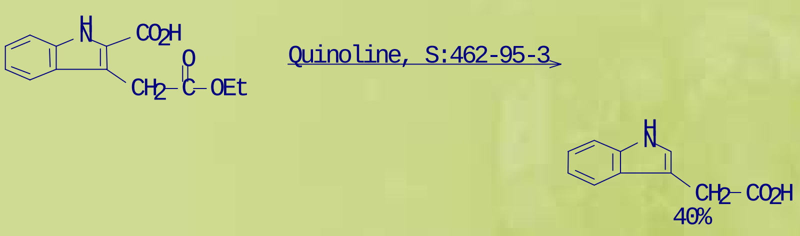
Ethylal as solvent

- Dehydrogenations - aromatizations



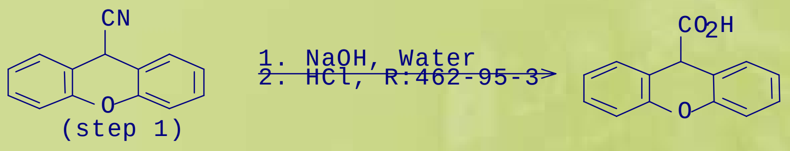
Ethylal as solvent

- Decarboxylations



Ethylal as solvent

- Acido-basic reactions



Butylal as reagent

- Transacetalizations

$$\text{n-BuO}-\text{CH}_2-\text{OBu-n} \xrightarrow{\text{1-Octanol, Nafion H}} \text{n-BuO}-\text{CH}_2-\text{O}-(\text{CH}_2)_7-\text{Me}$$

100%

solid-supported catalyst is SAC-13

(Nafion silica nanocomposite)

Butylal as reagent

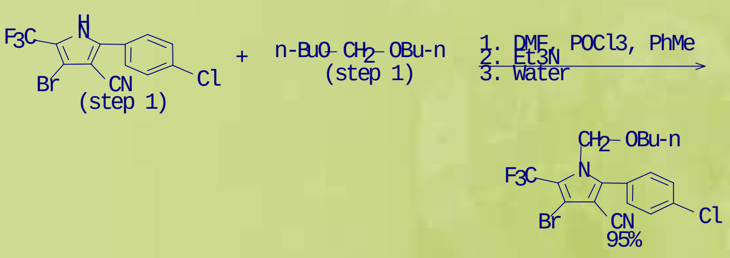
- Transthioacetalizations

$$n\text{-BuO}-\text{CH}_2-\text{OBu-}n \xrightarrow{\text{MeSH, BF}_3\text{-Et}_2\text{O, CHCl}_3} \text{H}_3\text{C}-\text{S}-\text{CH}_2-\text{S}-\text{CH}_3$$

32%

Butylal as reagent

- Reactions of butylal with nitrogen containing compounds



Butylal as reagent

- Reactions of butylal with acetals

$$\text{n-BuO}-\text{CH}_2-\text{OBu-n} \xrightarrow{\text{MeOCH2OMe, FeCl3}} \text{n-BuO}-\text{CH}_2-\text{OMe}$$

63%

Butylal as reagent

- Reactions of butylal with formaldehyde

$$\text{n-BuO}-\text{CH}_2-\text{OBu-n} \xrightarrow{\text{HCHO, H2SO4}} \text{n-BuO}-\text{CH}_2-\text{O}-\text{CH}_2-\text{OBu-n} +$$

$$\text{n-BuO}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{OBu-n} +$$

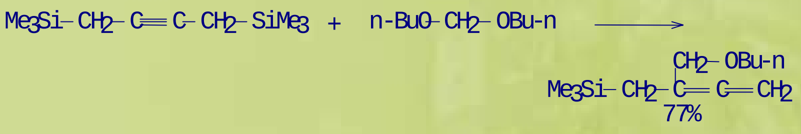
$$\text{n-BuO}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{OBu-n} +$$

$$\text{n-BuO}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{OBu-n}$$

NOTE: paraformaldehyde used; butanol also formed

Butylal as reagent

- Reactions of butylal with propargylsilanes



$$Me_3Si-CH_2-C\equiv C-CH_2-SiMe_3 + n\text{-}BuO-CH_2-OBu\text{-}n \longrightarrow Me_3Si-CH_2-\overset{CH_2-OBu\text{-}n}{C}=C=CH_2$$

77%

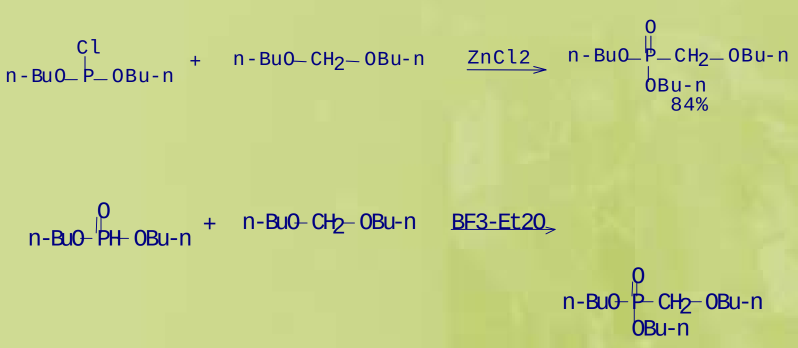
Butylal as reagent

- Synthesis of n- butyl halomethyl ethers

$$n\text{-}BuO-CH_2-OBu\text{-}n \xrightarrow{AcCl,\ BuOH} n\text{-}Bu-O-CH_2-Cl$$

Butylal as reagent

- Reactions of butylal with phosphorus compounds



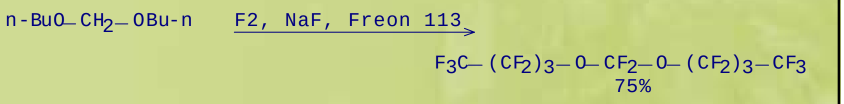
$$n\text{-BuO}-\overset{Cl}{\overset{|}{P}}-OBu\text{-}n \;+\; n\text{-BuO}-CH_2-OBu\text{-}n \xrightarrow{ZnCl2} n\text{-BuO}-\underset{OBu\text{-}n}{\overset{O}{\overset{\|}{P}}}-CH_2-OBu\text{-}n$$

84%

$$n\text{-BuO}-\overset{O}{\overset{\|}{PH}}-OBu\text{-}n \;+\; n\text{-BuO}-CH_2-OBu\text{-}n \xrightarrow{BF3\text{-}Et2O} n\text{-BuO}-\underset{OBu\text{-}n}{\overset{O}{\overset{\|}{P}}}-CH_2-OBu\text{-}n$$

Butylal as reagent

- Fluorinations



$$n\text{-BuO}-CH_2-OBu\text{-}n \xrightarrow{F2,\ NaF,\ Freon\ 113} F_3C-(CF_2)_3-O-CF_2-O-(CF_2)_3-CF_3$$

75%

Butylal as reagent

- Nitrations

$$n\text{-BuO}-CH_2-\text{OBu-}n \xrightarrow{N2O5,\ CH2Cl2} n\text{-BuO}-CH_2-O-NO_2 + n\text{-Bu}-O-NO_2$$

Butylal as reagent

- Radicalar reactions

$$n\text{-BuO}-CH_2-\text{OBu-}n \xrightarrow{CHCl3} H_3C-CH_2-CH_2-CH{=}O$$

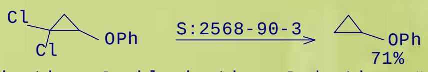
Butylal as reagent

- Organometallic reactions

$$\text{n-BuO}-\text{CH}_2-\text{OBu-n} \xrightarrow[\text{Co2(CO)8}]{\text{CO, HCHO, BuOH,}} \text{n-BuO}-\text{CH}_2-\text{CH}_2-\text{OH}$$

Butylal as solvent

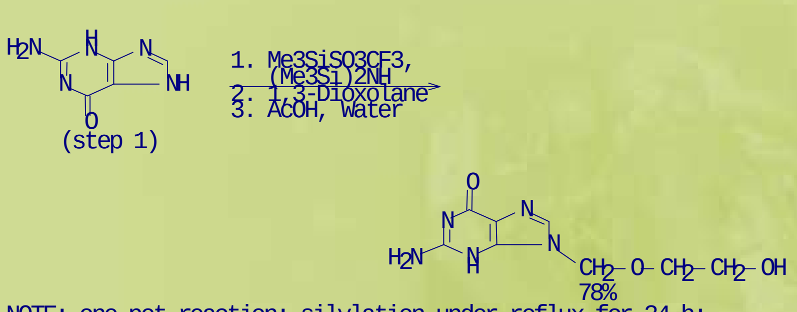
- Reductions with $LiAlH_4$



NOTE: Classification: Dechlorination; Reduction; # Conditions: LiAlH4; (n-BuO)2CH2; 110 deg; 110-115 deg 5h

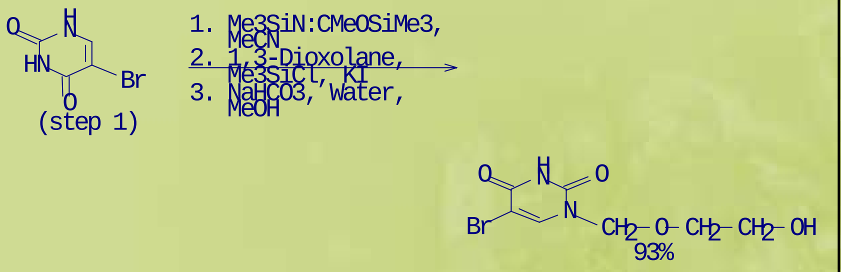
1,3-dioxolane as reagent

- Reactions with nitrogen containing compounds



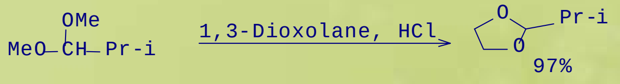
NOTE: one-pot reaction; silylation under reflux for 24 h;
regioselective alkylation under reflux for 16 h

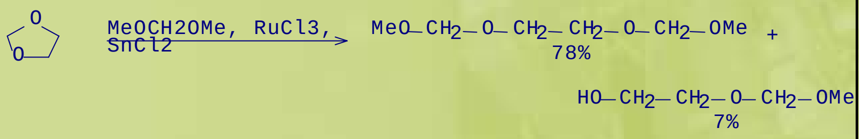
1,3-dioxolane as reagent



1,3-dioxolane as reagent

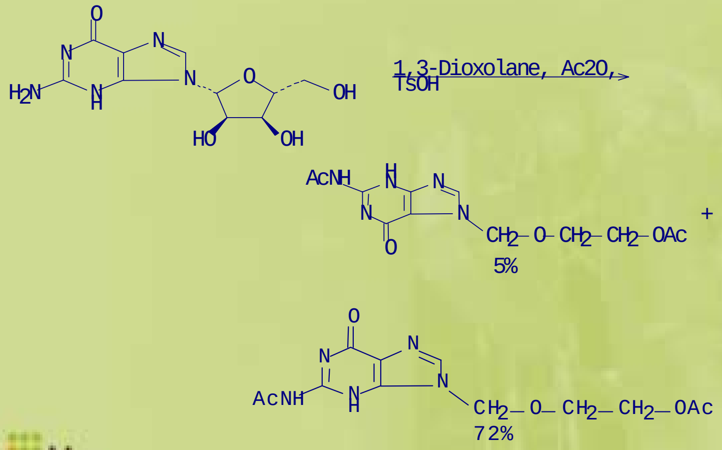
- Reactions with acetals





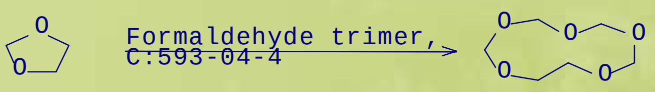
1,3-dioxolane as reagent

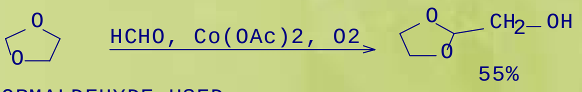
- Reactions with N-C-O containing products



1,3-dioxolane as reagent

- Reactions with formaldehyde

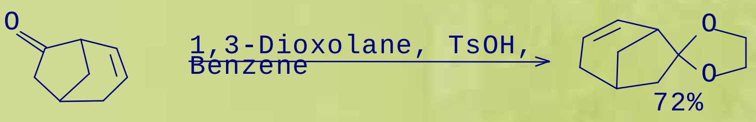




PARAFORMALDEHYDE USED

1,3-dioxolane as reagent

- Reactions with ketones



1,3-dioxolane as reagent

- Reactions with anhydrides

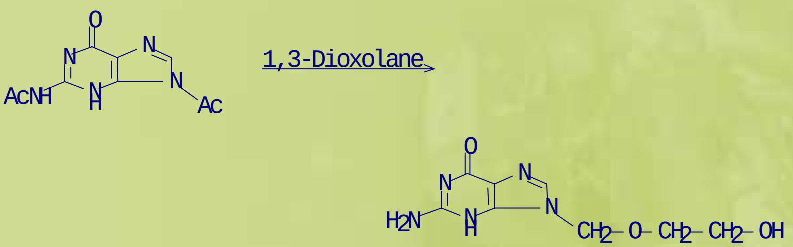
$$\mathrm{Ac{-}O{-}Ac} \xrightarrow{\text{1,3-Dioxolane}} \mathrm{AcO{-}CH_2{-}CH_2{-}O{-}CH_2{-}OAc}$$

87%

Lewis acid catalyst

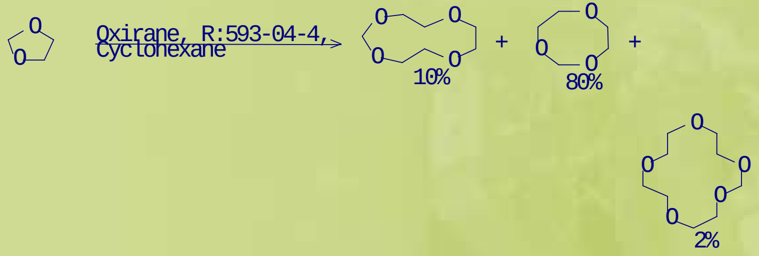
1,3-dioxolane as reagent

- Reactions with amides



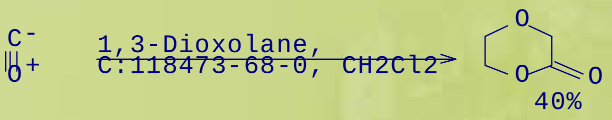
1,3-dioxolane as reagent

- Reactions with ethylene oxide



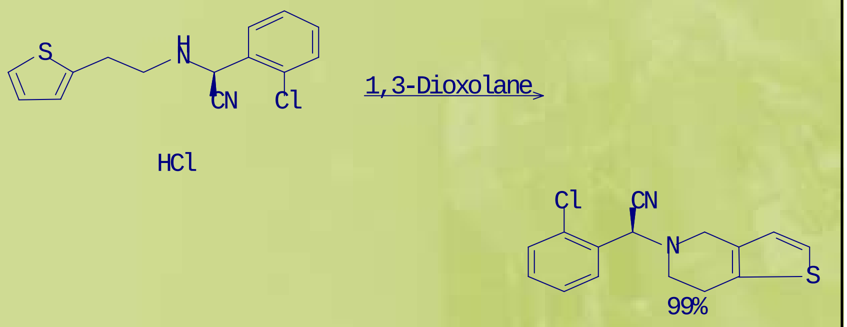
1,3-dioxolane as reagent

- Reactions with CO



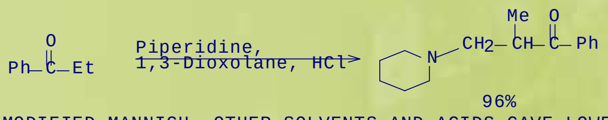
1,3-dioxolane as reagent

- Dioxolane as a source of formaldehyde



1,3-dioxolane as reagent

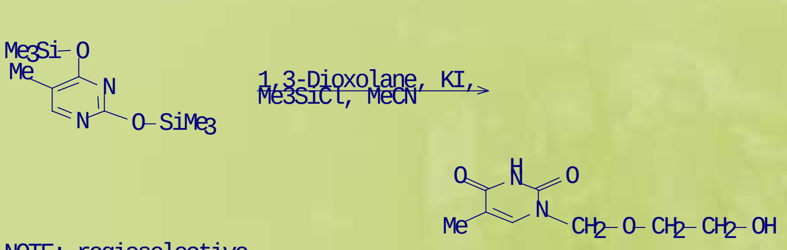
- Dioxolane in modified Mannich reactions



NOTE: MODIFIED MANNICH, OTHER SOLVENTS AND ACIDS GAVE LOWER YIELDS

1,3-dioxolane as reagent

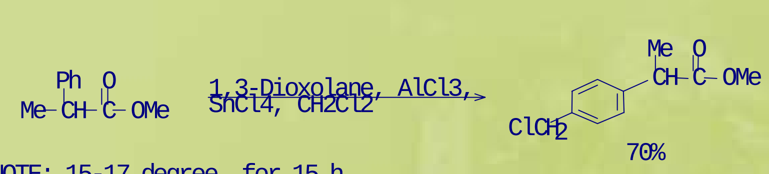
- Reactions of dioxolane with silylated alcohols



NOTE: regioselective

1,3-dioxolane as reagent

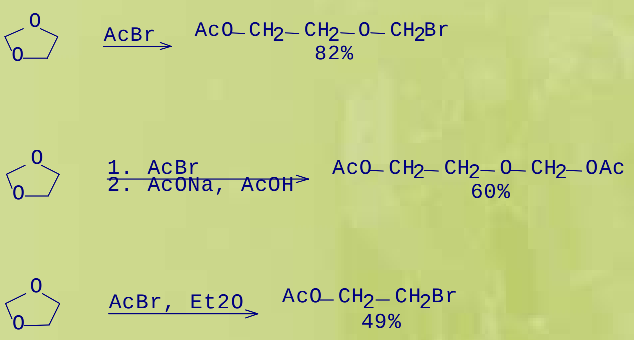
- Chloromethylations



NOTE: 15-17.degree. for 15 h

1,3-dioxolane as reagent

- Reactions with acyl halides

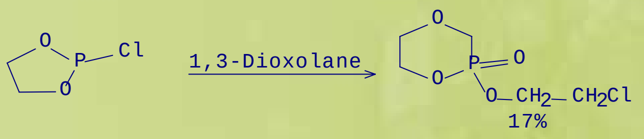


1,3-dioxolane as reagent

- Synthesis of halogenomethyl β-halogenomethyl ethers

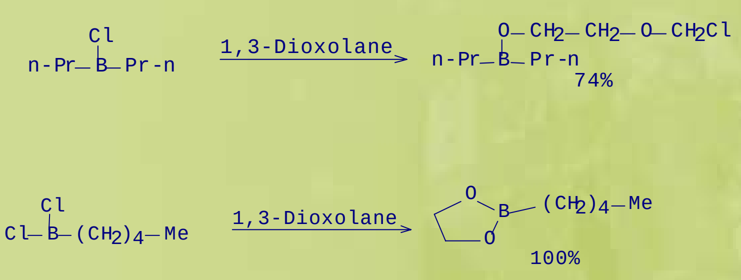
1,3-dioxolane as reagent

- Reactions with phosphorous containing compounds



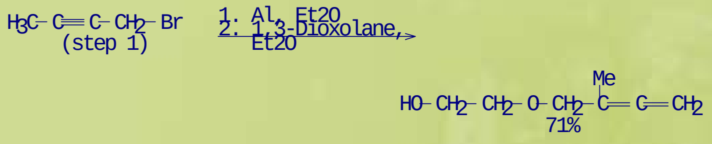
1,3-dioxolane as reagent

- Reactions with boron containing compounds

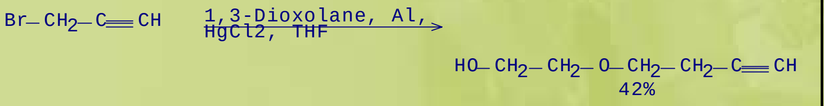


1,3-dioxolane as reagent

- Reactions with aluminium containing compounds



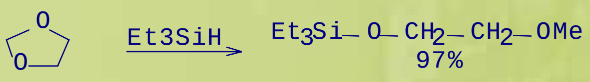
$H_3C-C\equiv C-CH_2-Br$ (step 1) $\xrightarrow[\text{Et2O}]{\text{1. Al, Et2O; 2. 1,3-Dioxolane,}}$ $HO-CH_2-CH_2-O-CH_2-\overset{Me}{C}=C=CH_2$ 71%



$Br-CH_2-C\equiv CH$ $\xrightarrow[\text{HgCl2, THF}]{\text{1,3-Dioxolane, Al,}}$ $HO-CH_2-CH_2-O-CH_2-CH_2-C\equiv CH$ 42%

1,3-dioxolane as reagent

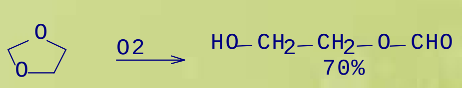
- Reductions of dioxolane

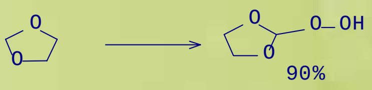


$\xrightarrow{\text{Et3SiH}}$ $Et_3Si-O-CH_2-CH_2-OMe$ 97%

1,3-dioxolane as reagent

- Oxidations of dioxolane

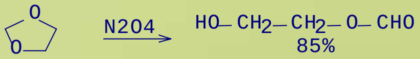


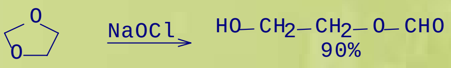


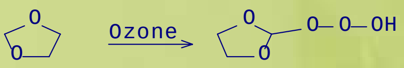
Conditions O_2

14H

1,3-dioxolane as reagent

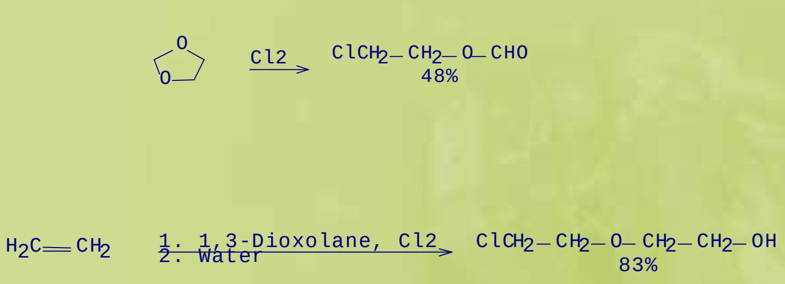






1,3-dioxolane as reagent

- Chlorinations

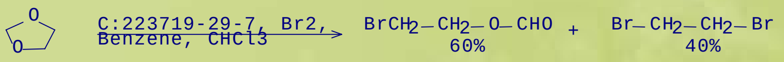


$\xrightarrow{Cl_2}$ $ClCH_2-CH_2-O-CHO$ 48%

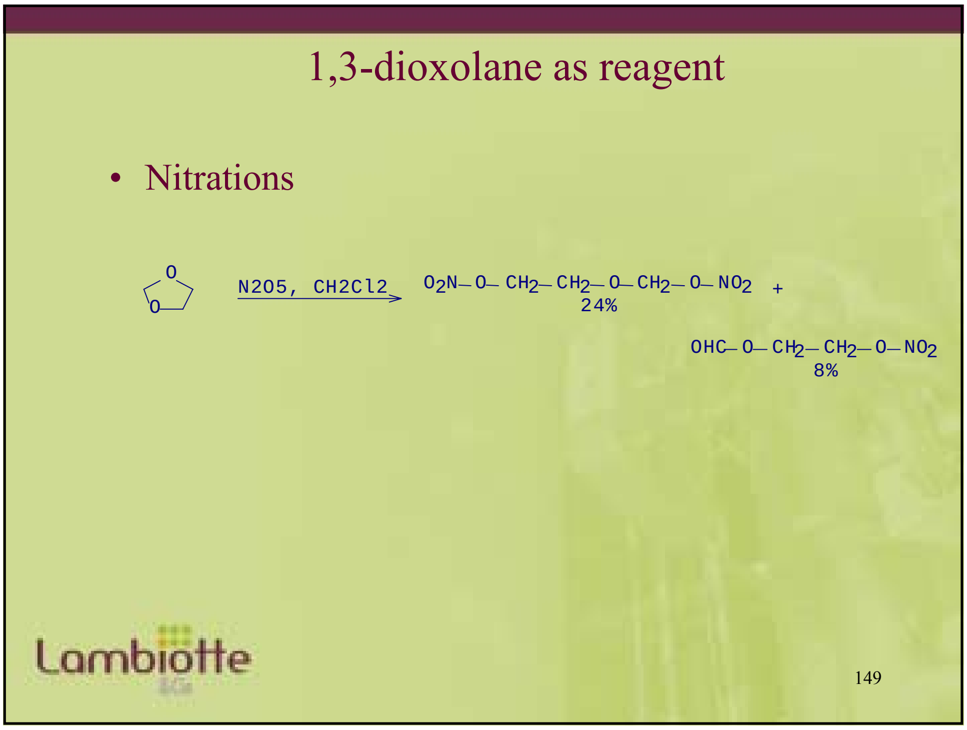
$H_2C{=}CH_2 \xrightarrow[\text{2. Water}]{\text{1. 1,3-Dioxolane, } Cl_2} ClCH_2-CH_2-O-CH_2-CH_2-OH$ 83%

1,3-dioxolane as reagent

- Brominations

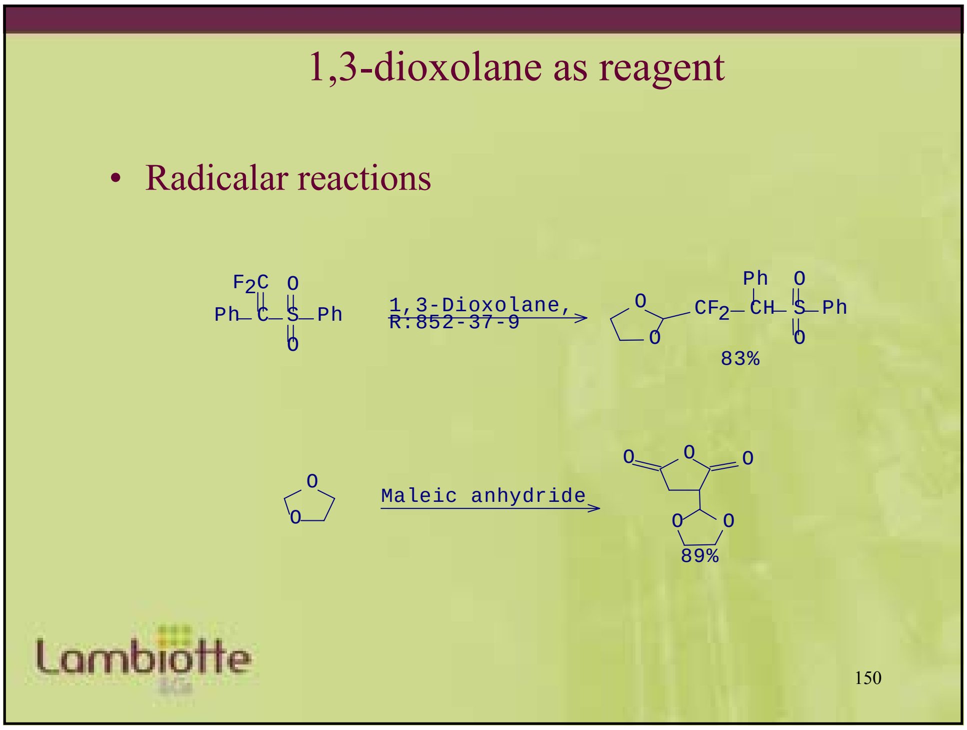


$\xrightarrow[\text{Benzene, } CHCl_3]{\text{C:223719-29-7, } Br_2\text{,}}$ $BrCH_2-CH_2-O-CHO$ 60% + $Br-CH_2-CH_2-Br$ 40%



1,3-dioxolane as reagent

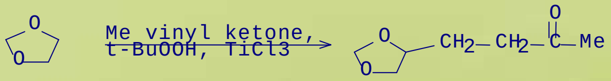
- Nitrations

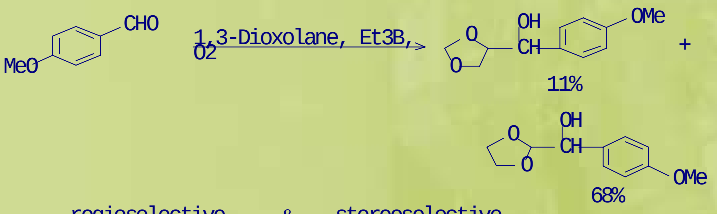


1,3-dioxolane as reagent

- Radicalar reactions

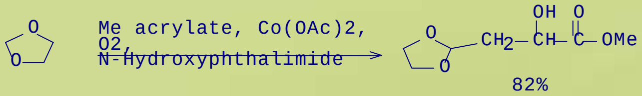
1,3-dioxolane as reagent

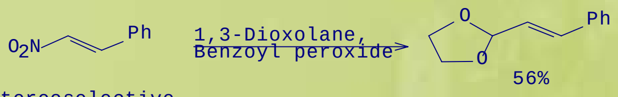




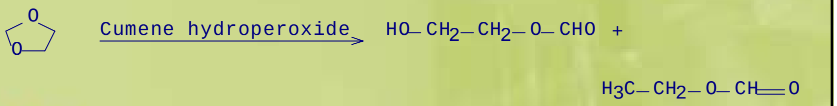
regioselective & stereoselective

1,3-dioxolane as reagent



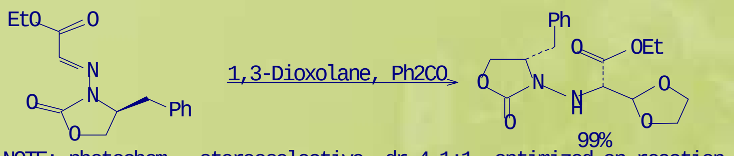


stereoselective



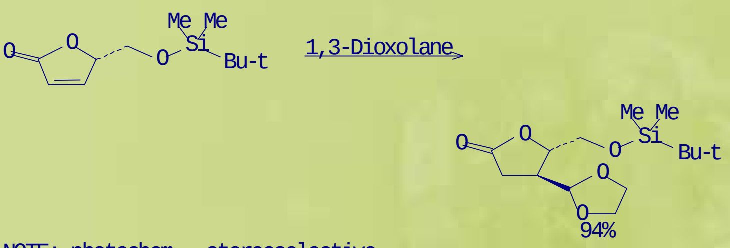
1,3-dioxolane as reagent

- Photochemical reactions



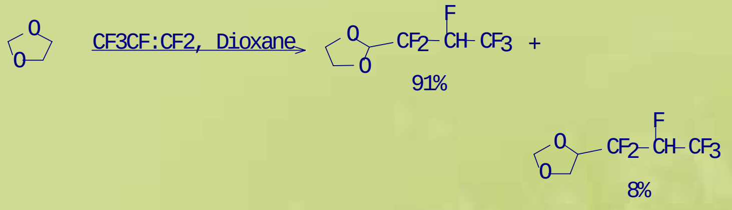
NOTE: photochem., stereoselective, dr 4.1:1, optimized on reaction time and temp.

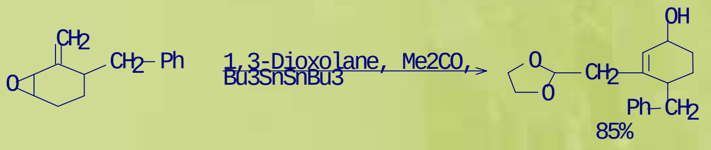
1,3-dioxolane as reagent



NOTE: photochem., stereoselective

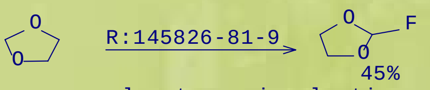
1,3-dioxolane as reagent





1,3-dioxolane as reagent

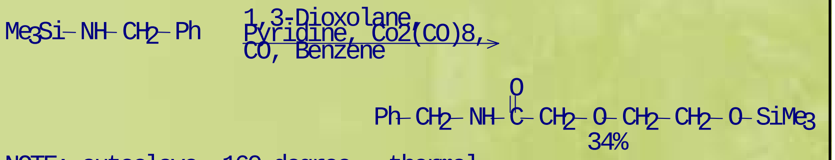
- Electrochemical reactions



NOTE: electrochem., no solvent, regioselective

1,3-dioxolane as reagent

- Organometallic reactions



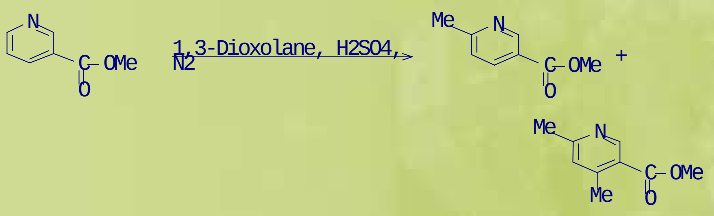
$$Me_3Si-NH-CH_2-Ph \xrightarrow[\text{CO, Benzene}]{\text{1,3-Dioxolane, Pyridine, Co2(CO)8,}} Ph-CH_2-NH-\overset{O}{\overset{\|}{C}}-CH_2-O-CH_2-CH_2-O-SiMe_3$$

34%

NOTE: autoclave, 160.degree., thermal

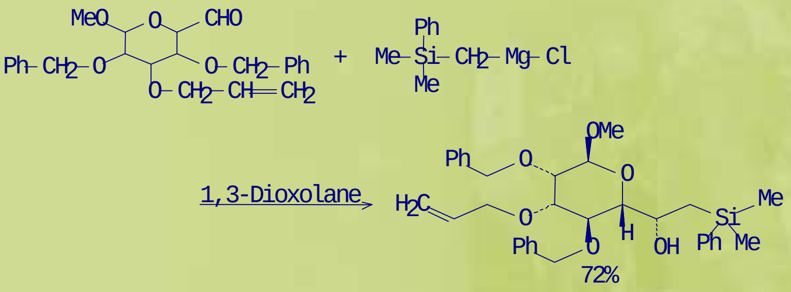
1,3-dioxolane as reagent

- Radiochemical reactions



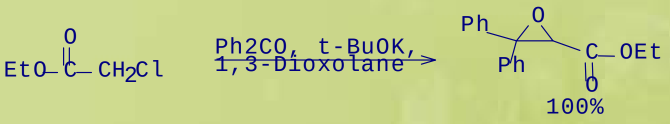
1,3-dioxolane as solvent

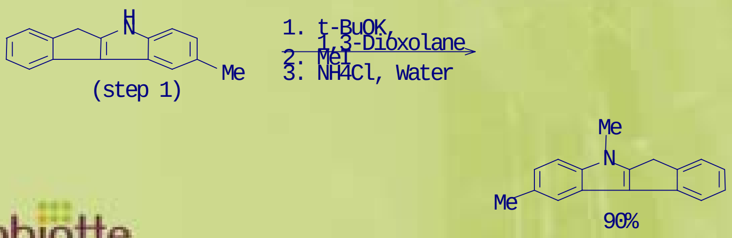
- Grignard reactions



1,3-dioxolane as solvent

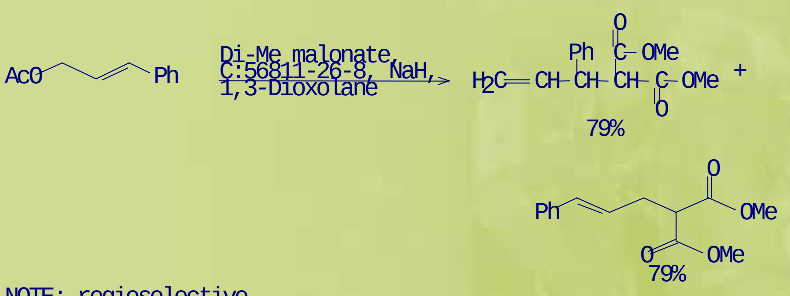
- Reactions with alcoholates





1,3-dioxolane as solvent

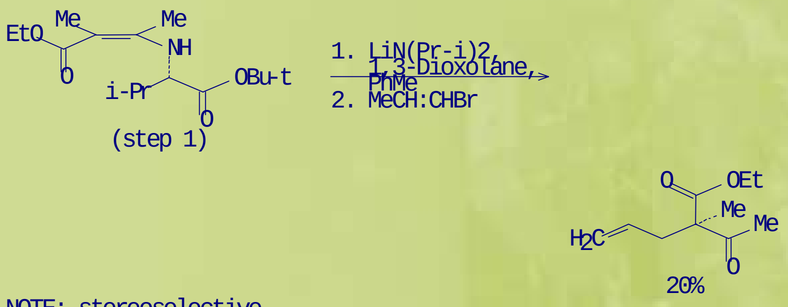
- Reactions with hydrides



NOTE: regioselective

1,3-dioxolane as solvent

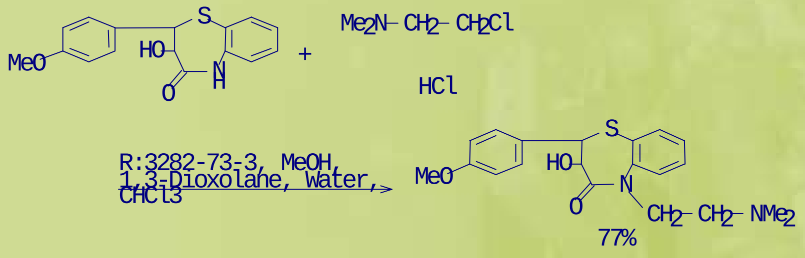
- Reactions with Li-diisopropylamide



NOTE: stereoselective

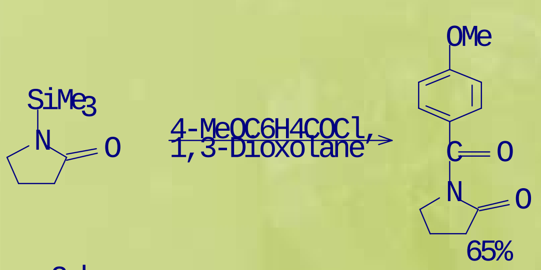
1,3-dioxolane as solvent

- Alkylations of amides with alkyl halides



1,3-dioxolane as solvent

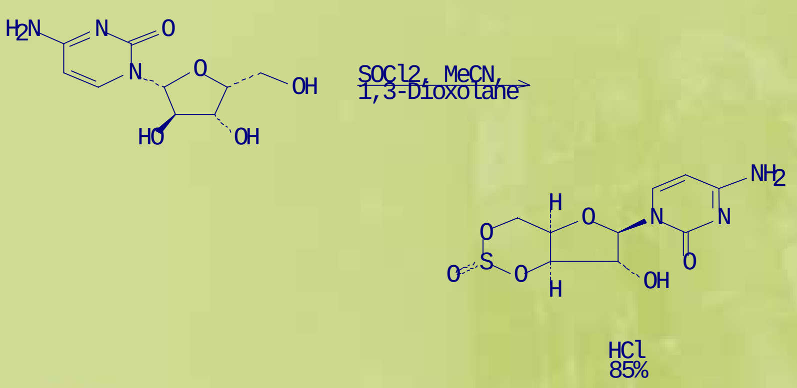
- Reactions with acyl halides



NOTE: 40.degree. 2 h

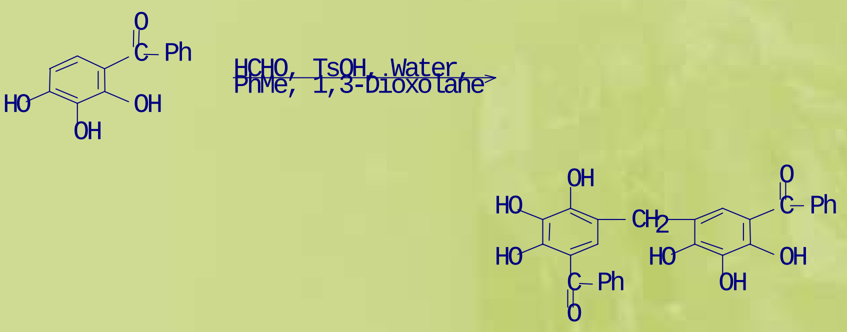
1,3-dioxolane as solvent

- Reactions of alcohols with thionyl chloride



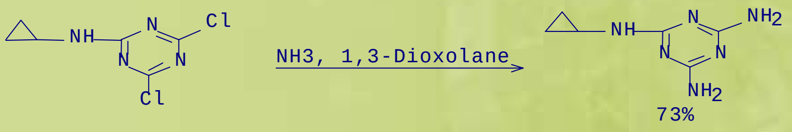
1,3-dioxolane as solvent

- Reactions with formaldehyde



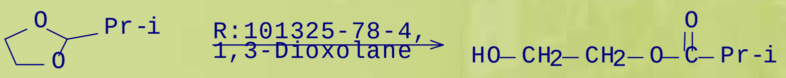
1,3-dioxolane as solvent

- Aromatic nucleophilic substitutions



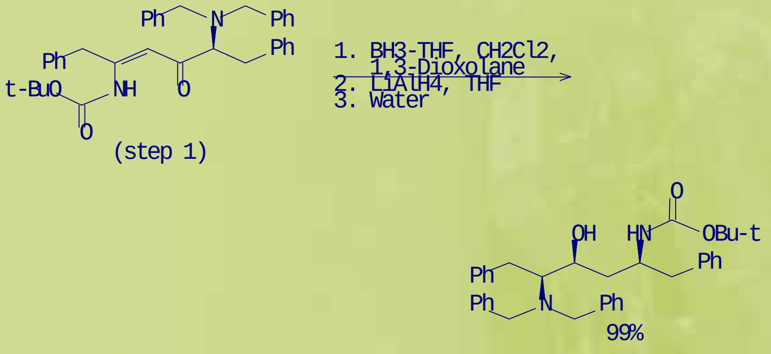
1,3-dioxolane as solvent

- Oxidations



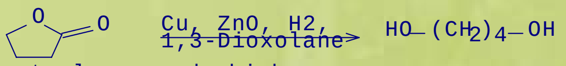
1,3-dioxolane as solvent

- Reductions



1,3-dioxolane as solvent

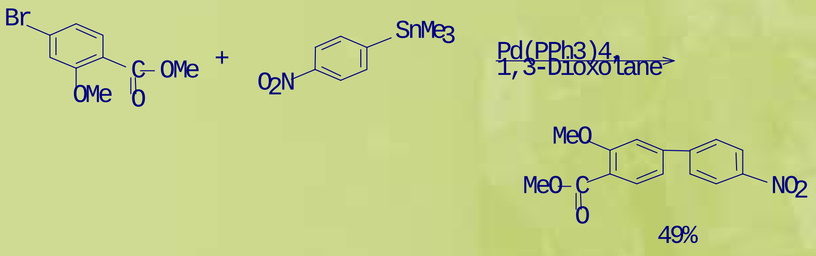
- Hydrogenations



NOTE: batch autoclave used, high pressure

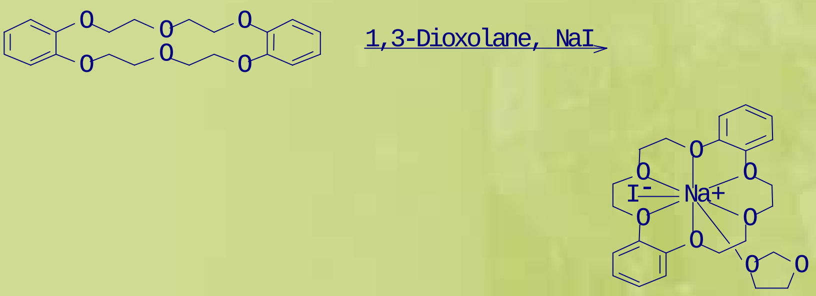
1,3-dioxolane as solvent

- Organometallic reactions



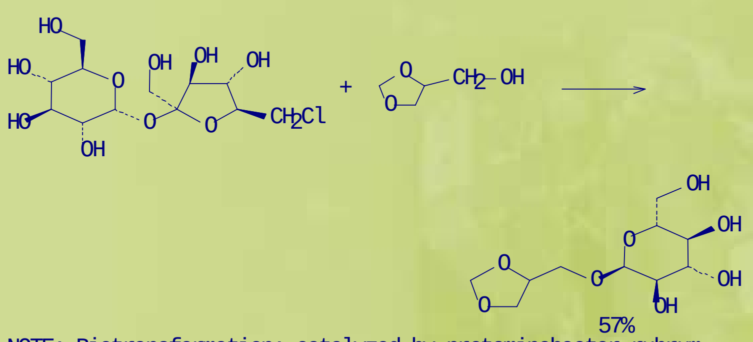
1,3-dioxolane as solvent

- NaI crown ethers complexes



Glycerol formal as reagent

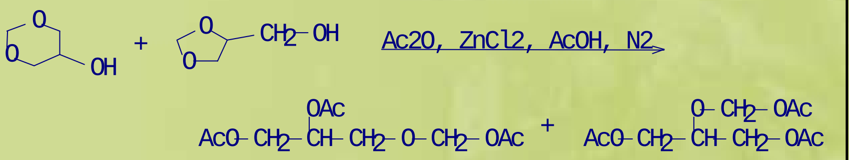
- Transacetalizations (biological)



NOTE: Biotransformation: catalyzed by protaminobacter rubrum

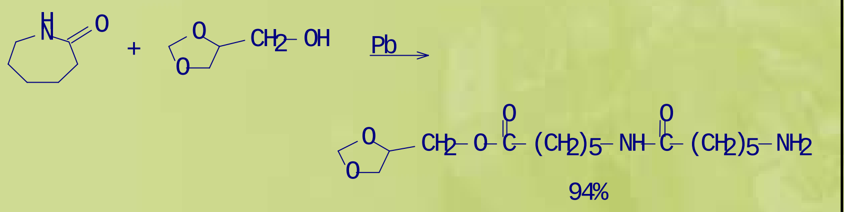
Glycerol formal as reagent

- Reactions with anhydrides



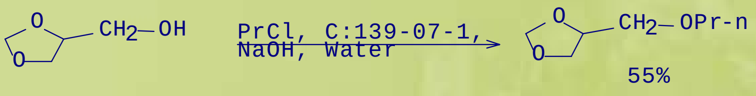
Glycerol formal as reagent

- Reactions with lactames



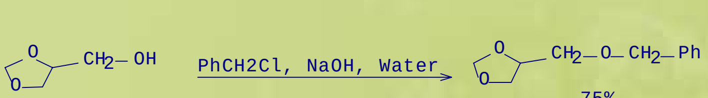
Glycerol formal as reagent

- Reactions with alkyl halides

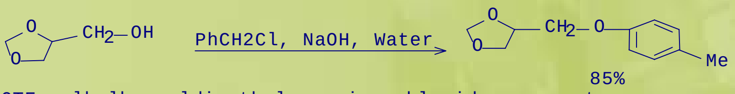


Glycerol formal as reagent

- Reactions with benzylic halides



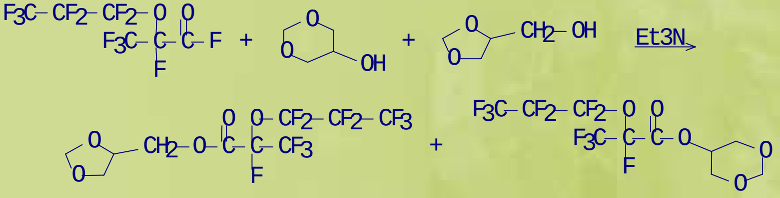
NOTE: Katamin AB catalyst



NOTE: alkylbenzyldimethylammonium chlorides present

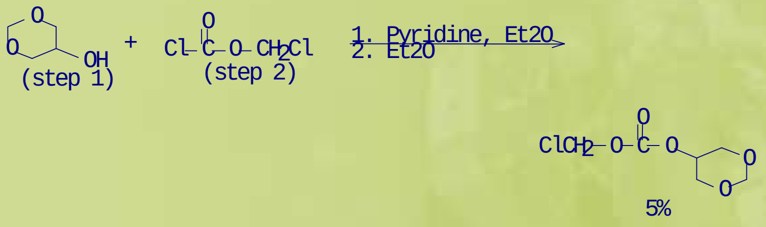
Glycerol formal as reagent

- Reactions with acyl fluorides



Glycerol formal as reagent

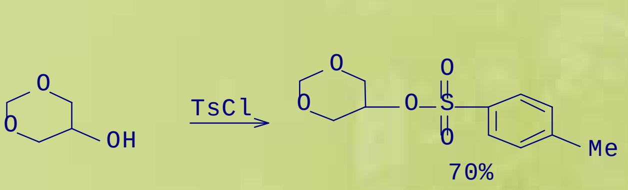
- Reactions with chloroformates



Lambiotte

Glycerol formal as reagent

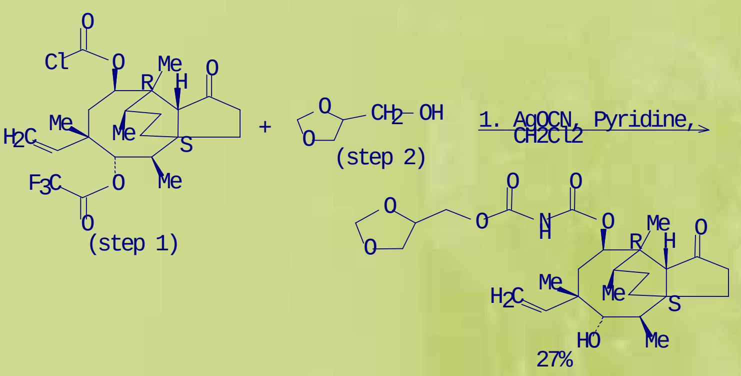
- Reactions with tosyl chloride



Lambiotte

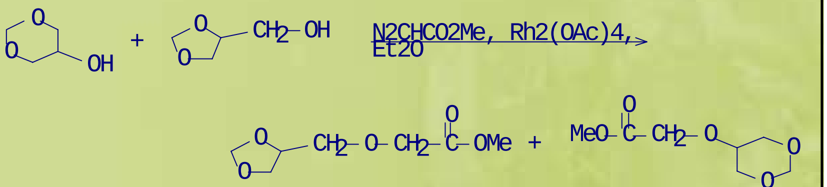
Glycerol formal as reagent

- Reactions with isocyanates



Glycerol formal as reagent

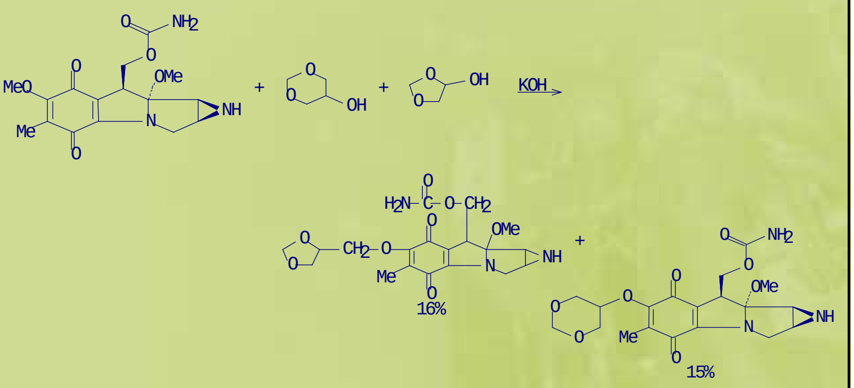
- Reactions with diazo esters



NOTE: 90% overall yield

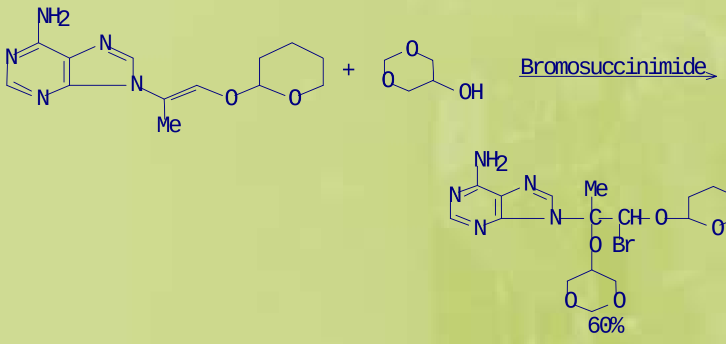
Glycerol formal as reagent

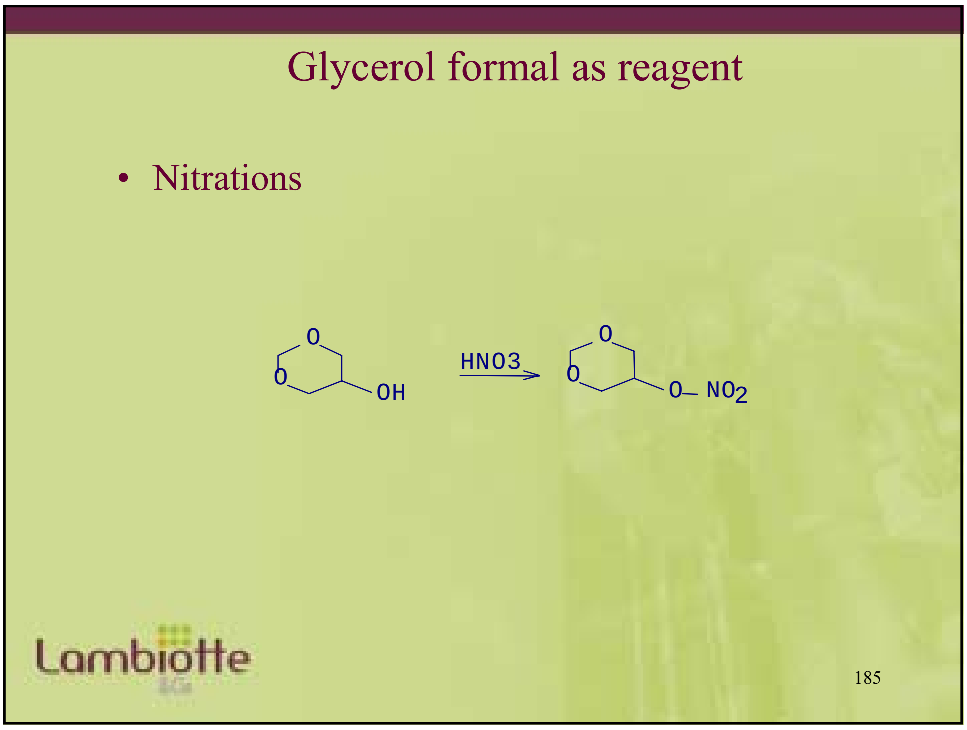
- Nucleophilic substitutions (addition – elimination)



Glycerol formal as reagent

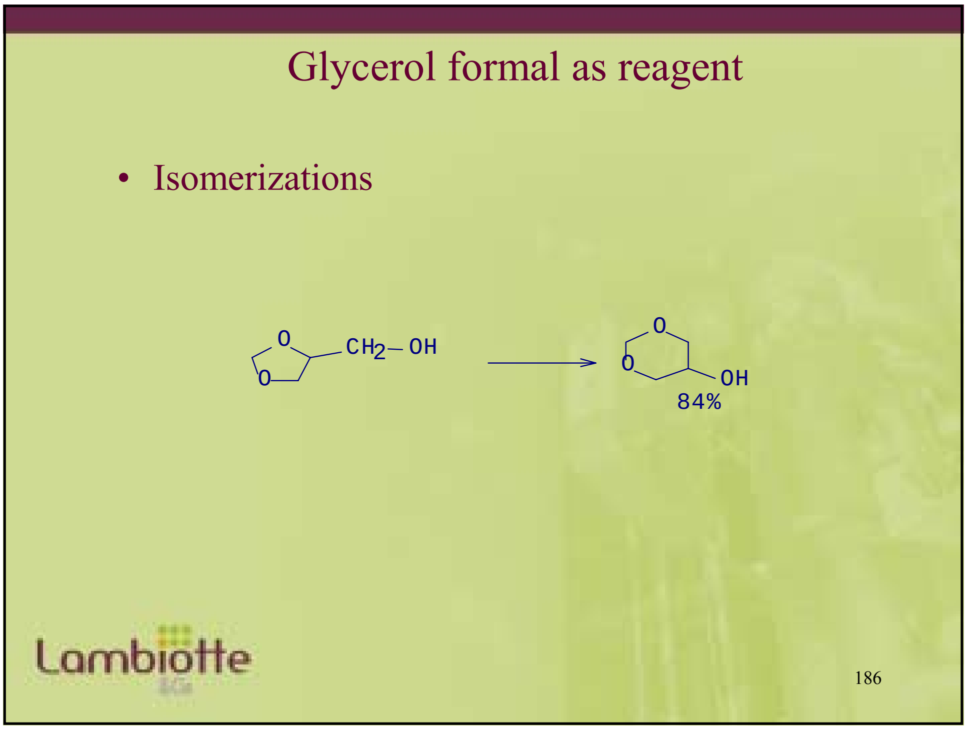
- In alkoxybrominations of olefins





Glycerol formal as reagent

- Nitrations



Glycerol formal as reagent

- Isomerizations

Acetals in purification processes

Extraction

Some examples of selectivities with acetals have been found.

For example, methylal selectively extract caffeic acid from *Echinacea angustifolia* leaving caftaric and cichoric acids which are extracted by water or ethanol / water (70/30) mixture.

Chromatography

Thin Layer Chromatography (TLC)

Methylal gives round elution spots and avoids trails.

This property extrapolated to column chromatography reduces

the wanted product recovery time

and

the volume of solvent used.

Chromatography

HPLC – normal phase

Methylal, in a first approach, gives better results than ethylal and dioxolane.

Methylal, as co-solvent, has a particular behaviour : it behaves
either as a polar solvent
or as a non-polar solvent.

In other words, added to the main solvent, it is equivalent, depending on the cases, to an addition of e.g. hexane, or to an addition of e.g. methanol.

Chromatography

HPLC – reverse phase

Reverse phase HPLC solvents are water combined with methanol, acetonitrile and sometimes tetrahydrofurane.

Methanol and acetonitrile must be labelled as toxic.

Methylal and dioxolane easily substitute methanol and acetonitrile.

Further to the obvious advantage to use products without labeling for toxicological concerns, there are technical and economical advantages.

Chromatography

Elution power of acetonitrile is higher than that of methanol. A blend 40/60 acetonitrile / water has the same elution power as a blend 50/50 methanol / water. With acetonitrile, the percentage of water can be higher.

With methylal, the percentage of water can still be higher. A blend 30/70 methylal / water has the same elution power than the above mentioned blends.

Chromatography

On the other hand, in blends with the same percentage of solvents, methylal elutes faster than acetonitrile, itself faster than methanol.

This means the peaks are thinner with methylal.

Thinner peaks have also been observed with dioxolane, as well as more symmetrical peaks.

Chromatography

Gel Permeation Chromatography

In comparison with a blend cycolohexane / MTBE (60 : 40) , dioxolane, but mainly methylal, give a very flat base line (with less noise).

Methylal give higher peaks.

Crystallization

Acetals are used as solvent for recrystallization

Acetals
in
galenic
formulations

Methylal in galenic formulations

- Transcutaneous antiseptics

Methylal is an excipient in transcutaneous form of antiseptics (e.g. Hexomedine)

Composition of Hexomedine :

Hexamedine	
Methylal	10 %
Isopropanol	38%
Propyleneglycol	29 %
Water	23%

Methylal in galenic formulations

- Haemostatic sprays

Methylal is used in haemostatic sprays based on oxidized cellulose

Methylal in galenic formulations

- Cooling sprays

Ingredients	%
Methylal	42.0
Ethanol	25.55
Camphor	1.05
Menthol	1.05
Methyl salicylate	0.35
Propane Butane 3.2 bar	30

Methylal in galenic formulations

- Bandaging sprays

Ingredients	%
Luviflex VBM 35	10.0
Luvimer 100 P	1.0
AMP 100	0.6
Onyxide 3300	0.2
Polyethylene glycol 400	1.0
Benzocaine	0.2
Ethyl alcohol	35.0
Methylal cosmetic grade	22.0
DME	15.0
LPG	15.0

Glycerol formal in galenic formulations

- Antiherpetic cream

  Glycerol formal is a constituent of an antiherpetic cream based on acyclovir

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Glycerol formal in galenic formulations

- Veterinary injectables

  Glycerol formal is used as a solvent for the following active ingredients in veterinary injectables :

  abamectine
  chloramphenicol
  enrofloxacin
  ivermectine
  oxytetracycline
  sulfadiazine
  sulfadoxine
  sulfamethoxazole
  trimethoprime

  Glycerol formal is also used to dissolve preservatives for injectables : methyl and propyl p.hydroxybenzoate