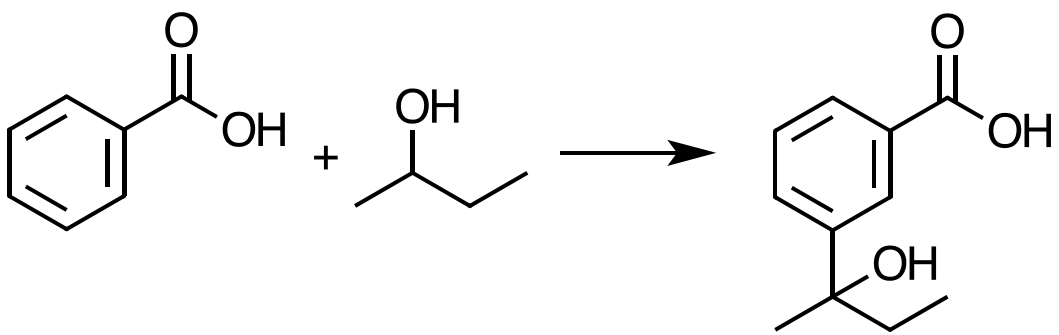
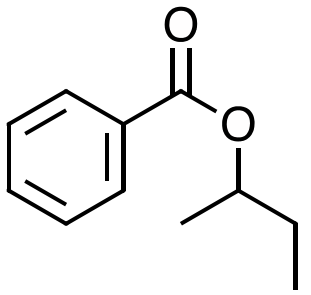
Nucleophilic Acyl Substitution Reactions

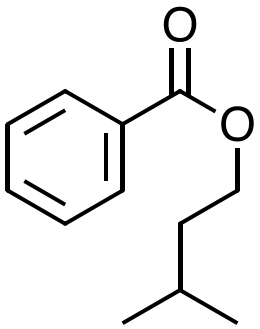
1. Predict the products:



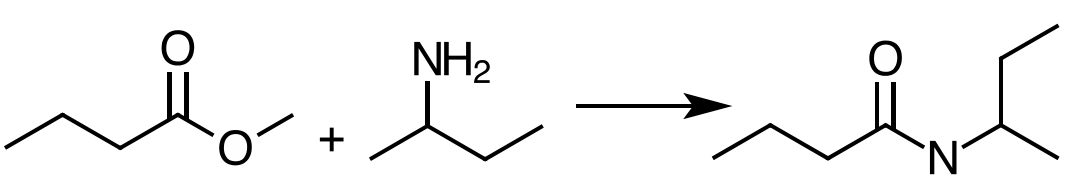
A



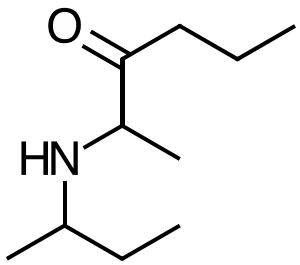
B



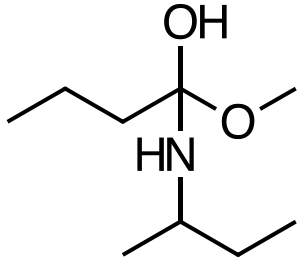
C



A



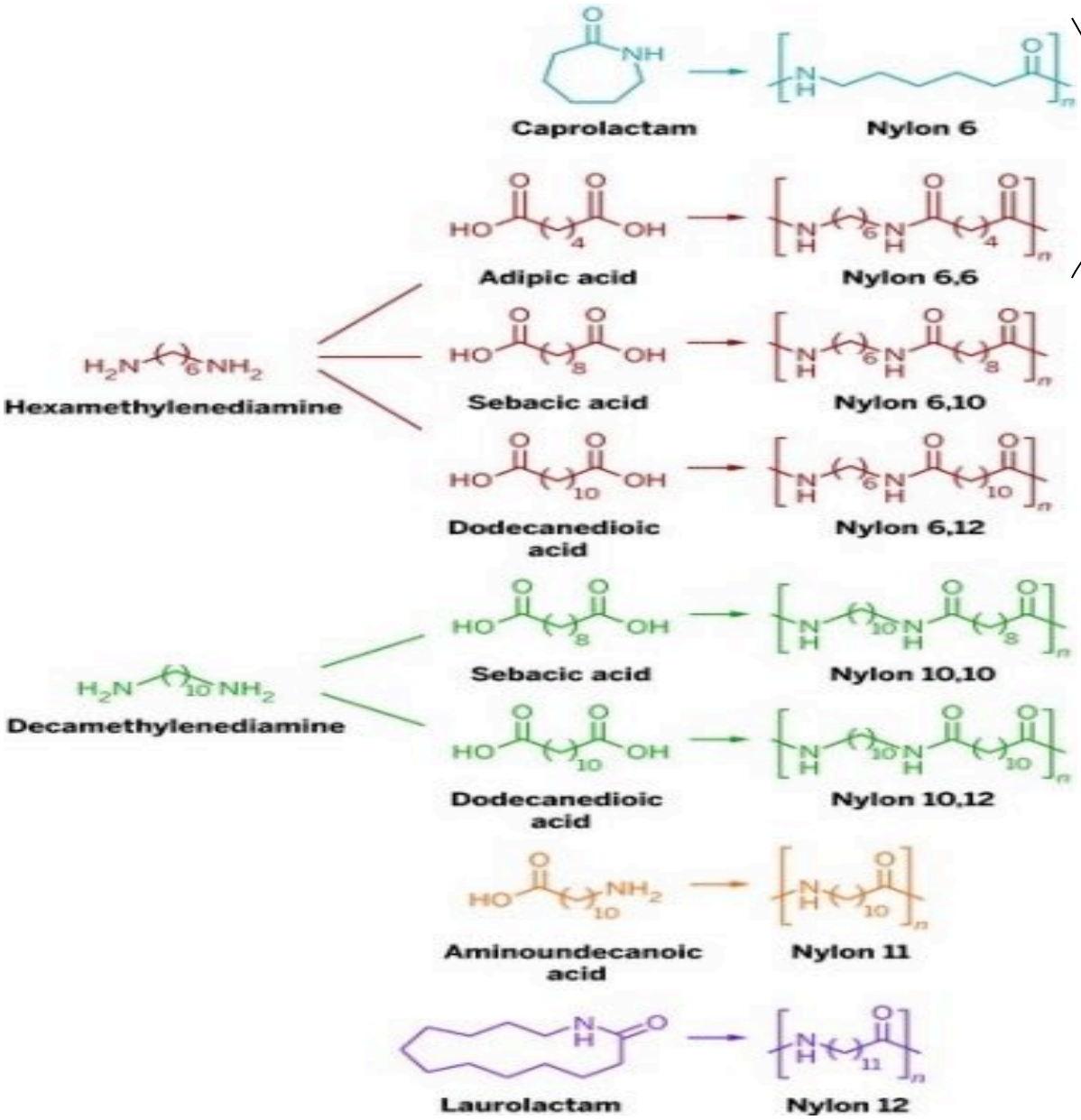
B



C

2. How are these two reactions similar?

Many Types of Nylon for Many Uses (CEN, 2/18/13, p. 28)

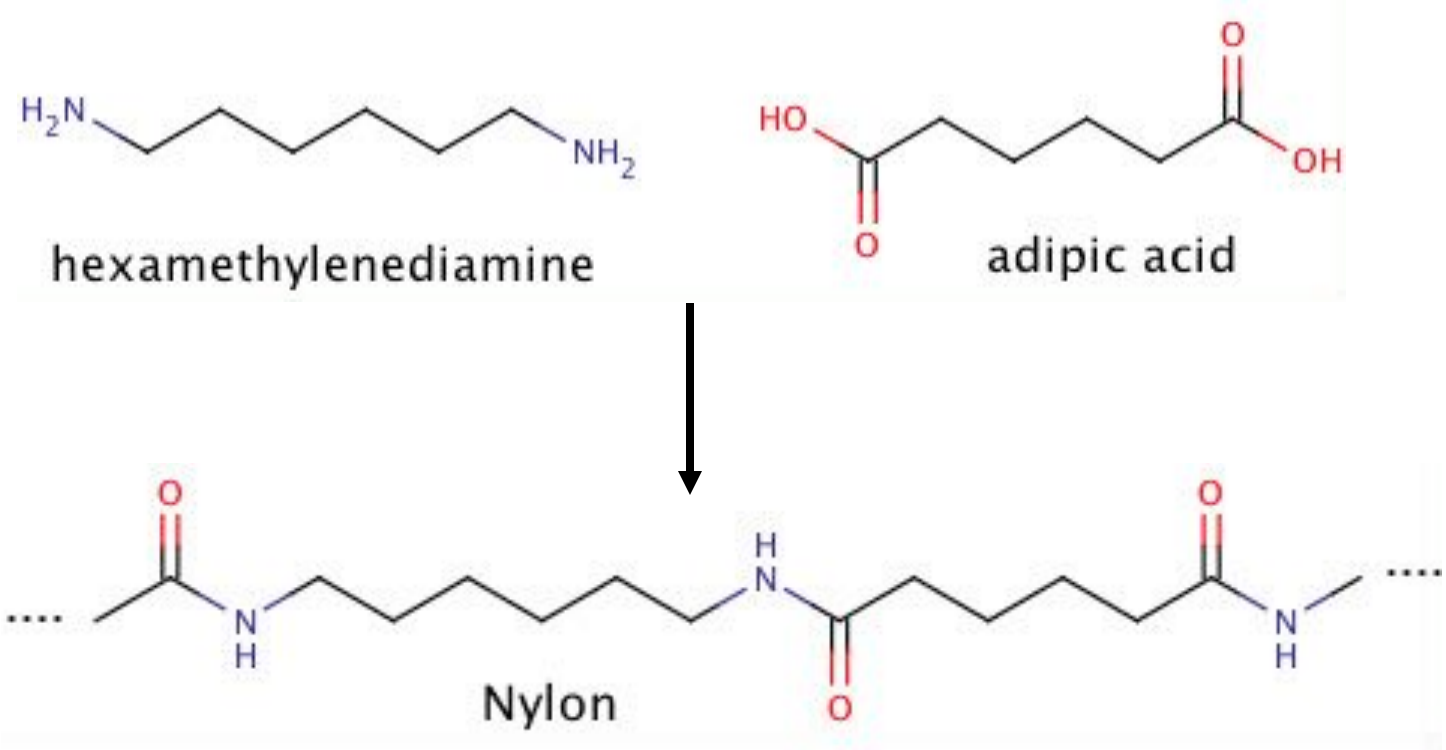


Carpets, fabric, food packaging, balloons

Flexible tubing in autos

As # of C's increase, chemical resistance and flexibility increase, specific gravity decreases

Brake and gas lines in cars



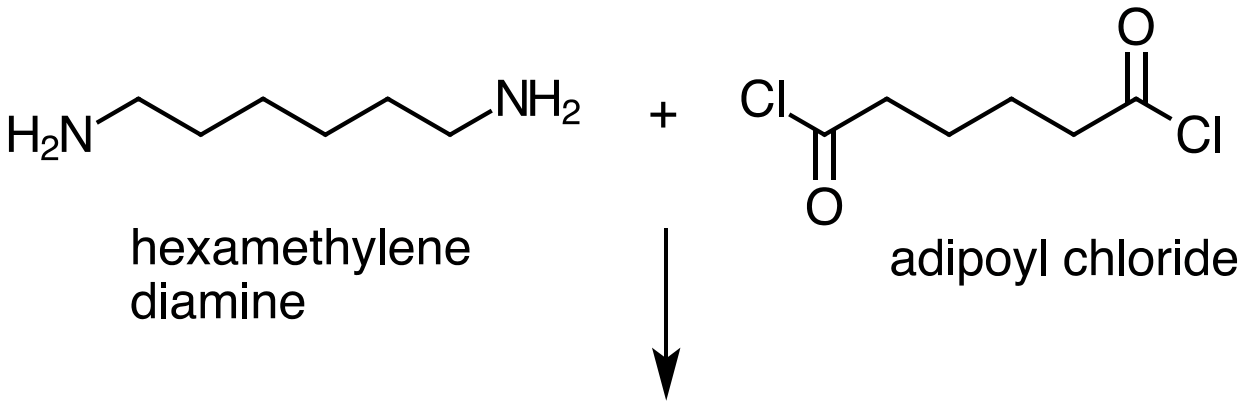
Nylon is a common plastic. (See Chang, 6th ed., Fig. 22.4, p. 765)

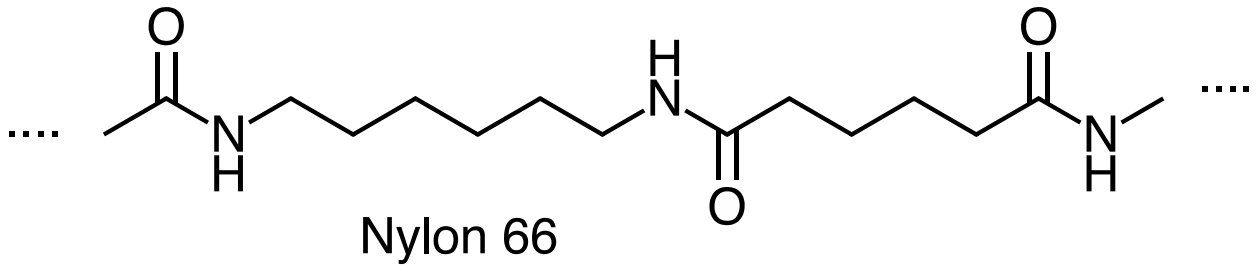
1. Identify the functional group(s) in nylon.
2. How is nylon made? Or How is this functional group made?
    a. Condensation (or reverse)
    b. alkene addition
    c. alcohol oxidation

Use curved arrows to show how nylon is produced.

What is the *Leaving Group* in the *Tetrahedral* intermediate?

Another way to make Nylon: use adipoyl chloride instead of adipic acid. Which reaction is faster?



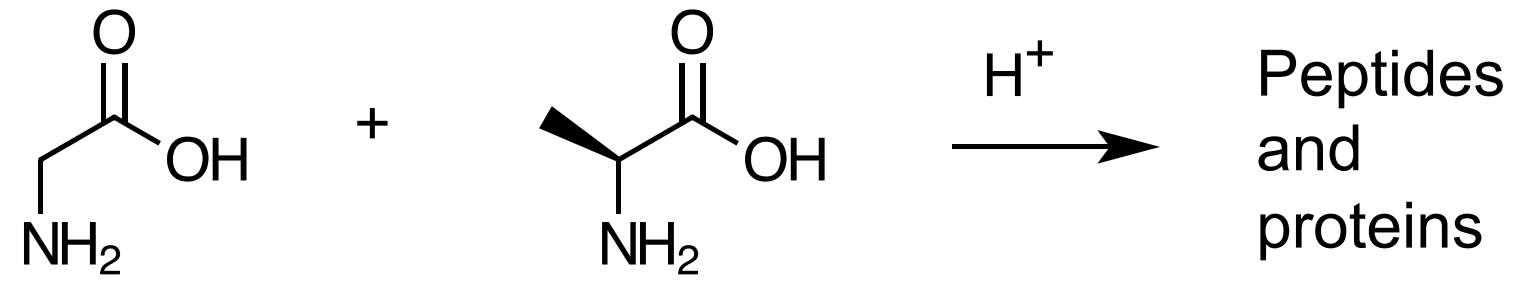


What is the *Leaving Group* in the *Tetrahedral* intermediate? What bonds break? What bonds form?

Objective: Predict product of $Nu:^-$ acyl substitution reaction

E.g., $Nu:^-$ = RNH_2 (_____ formation)

$RCOOH + RNH_2$ -- H^+ catalyst →



glycine alanine

What is the *Leaving Group* in the *Tetrahedral* intermediate?
What bonds break? What bonds form?

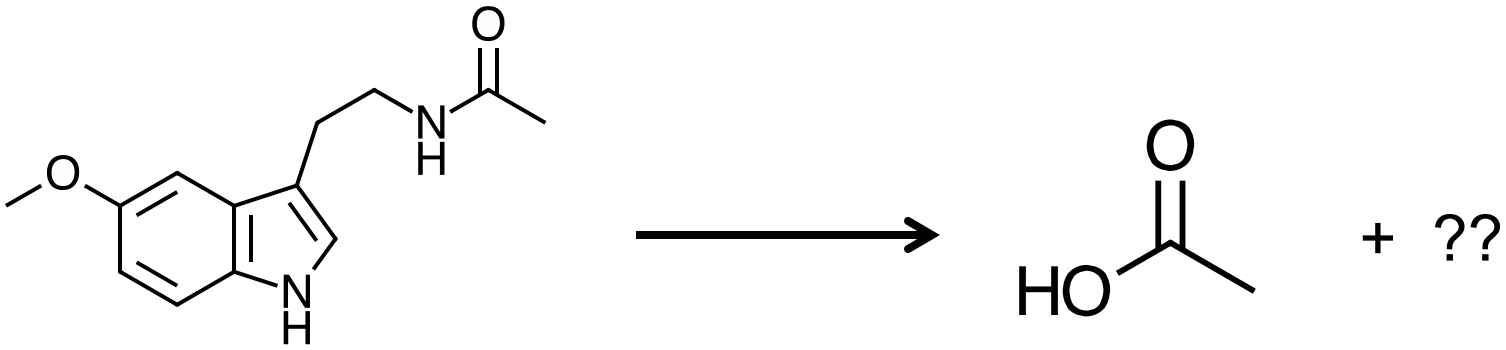
Amides: used in Sedatives (Klein, "Organic Chemistry", p. 981)

One way our body metabolizes chemicals is by hydrolysis of the amide group.

One metabolic product of melatonin is acetic acid.

Draw the structure of the other metabolic product.

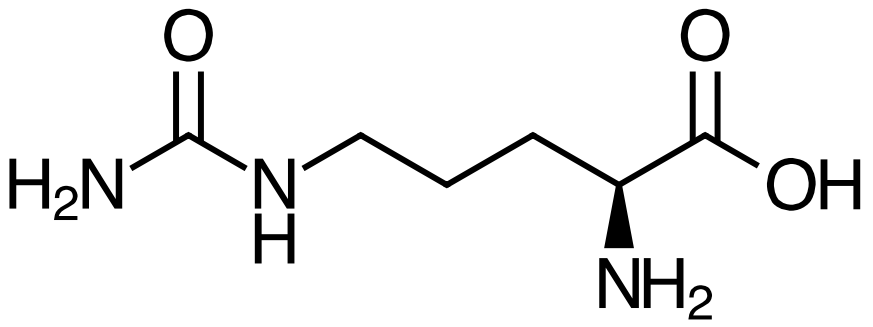
Hint: What bond breaks? What bond forms?



Melatonin
(regulates sleep)

Eating Watermelon May Prevent Muscle Soreness

Watermelon juice contains L-citrulline



L-citrulline

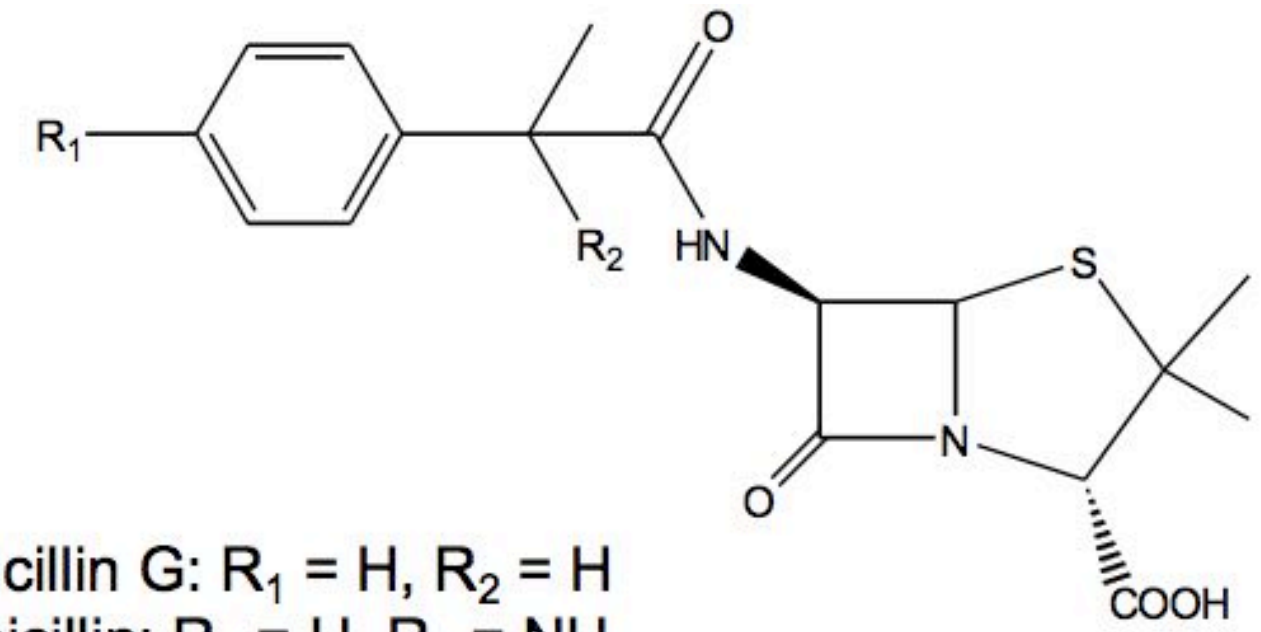
What are the metabolic products?

C&EN, 8/5/13, p. 30,
http://cen.acs.org/articles/91/i31/Watermelon-Juice-Wards-Off-Muscle.html

Biology: Cyclic Amides (Lactams) Are Found in Antibiotics

β-Lactams = 4 sided ring

Reference: Carey, 8th ed., p. 847



Penicillin G: R_1 = H, R_2 = H

Ampicillin: R_1 = H, R_2 = NH_2

Amoxicillin: R_1 = OH, R_2 = NH_2

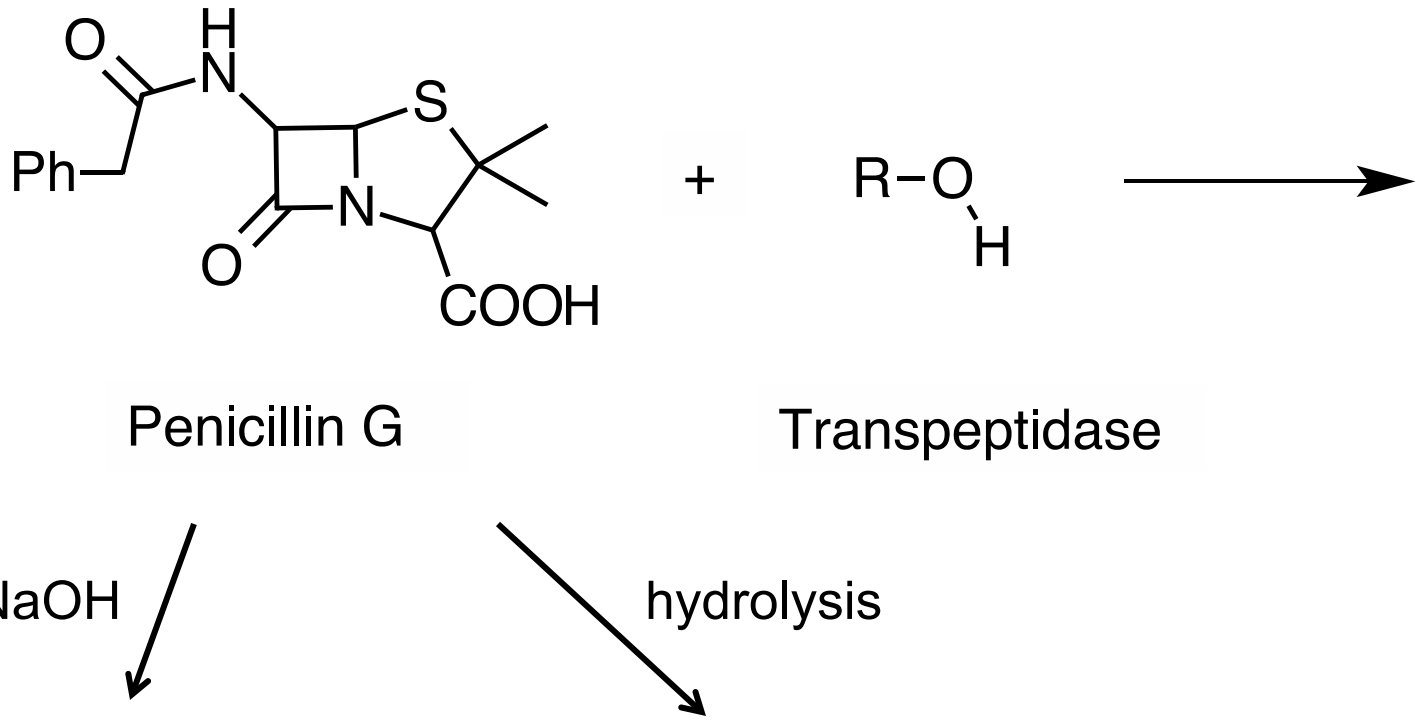
At which atom will nucleophilic acyl substitution occur?

Remember: Cyclic Esters = Lactones

Stability: amides > esters so lactams > lactones

β-Lactam antibiotics work by deactivating a transpeptidase enzyme, which is required for biosynthesis of bacterial cell walls.

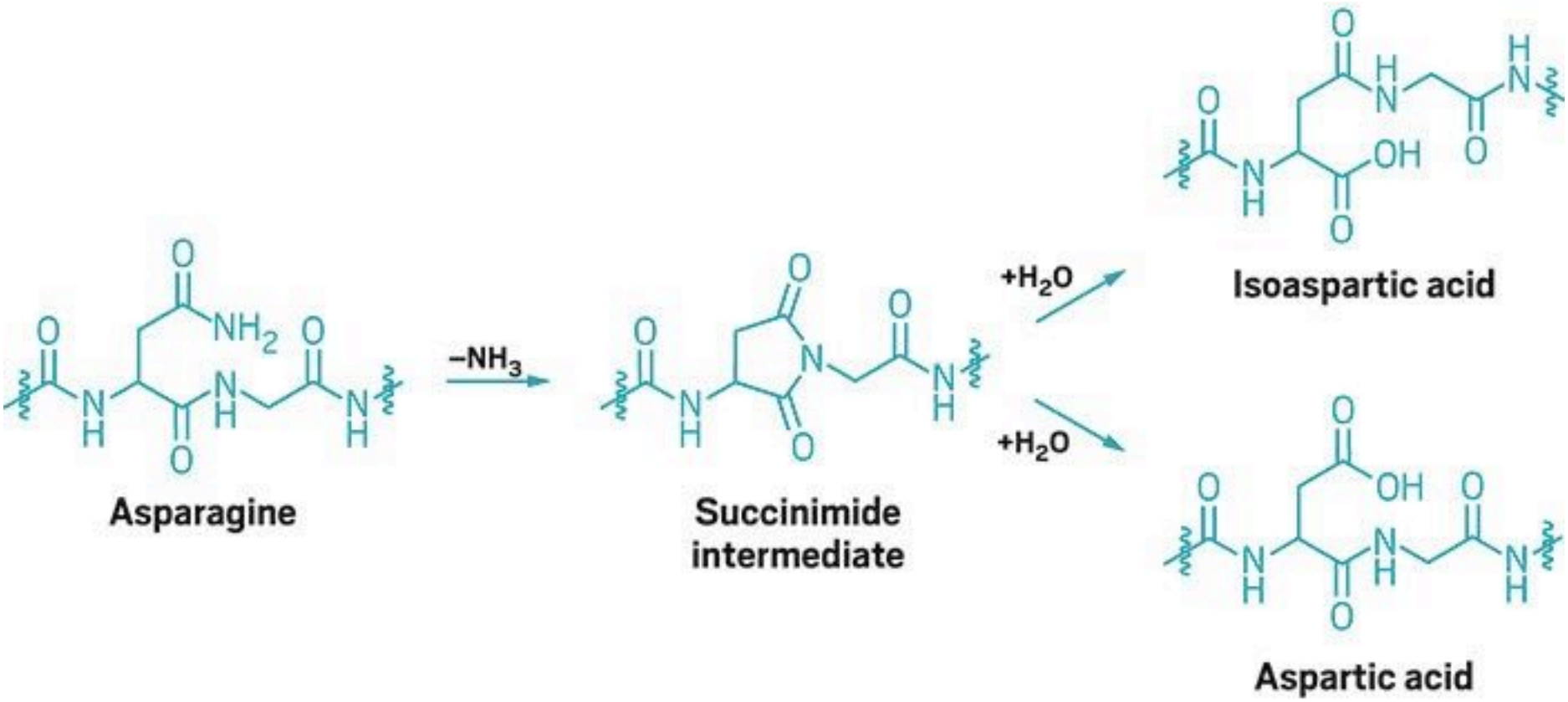
Draw the structure of the product.



CEN, 5/30/16, Protein drugs

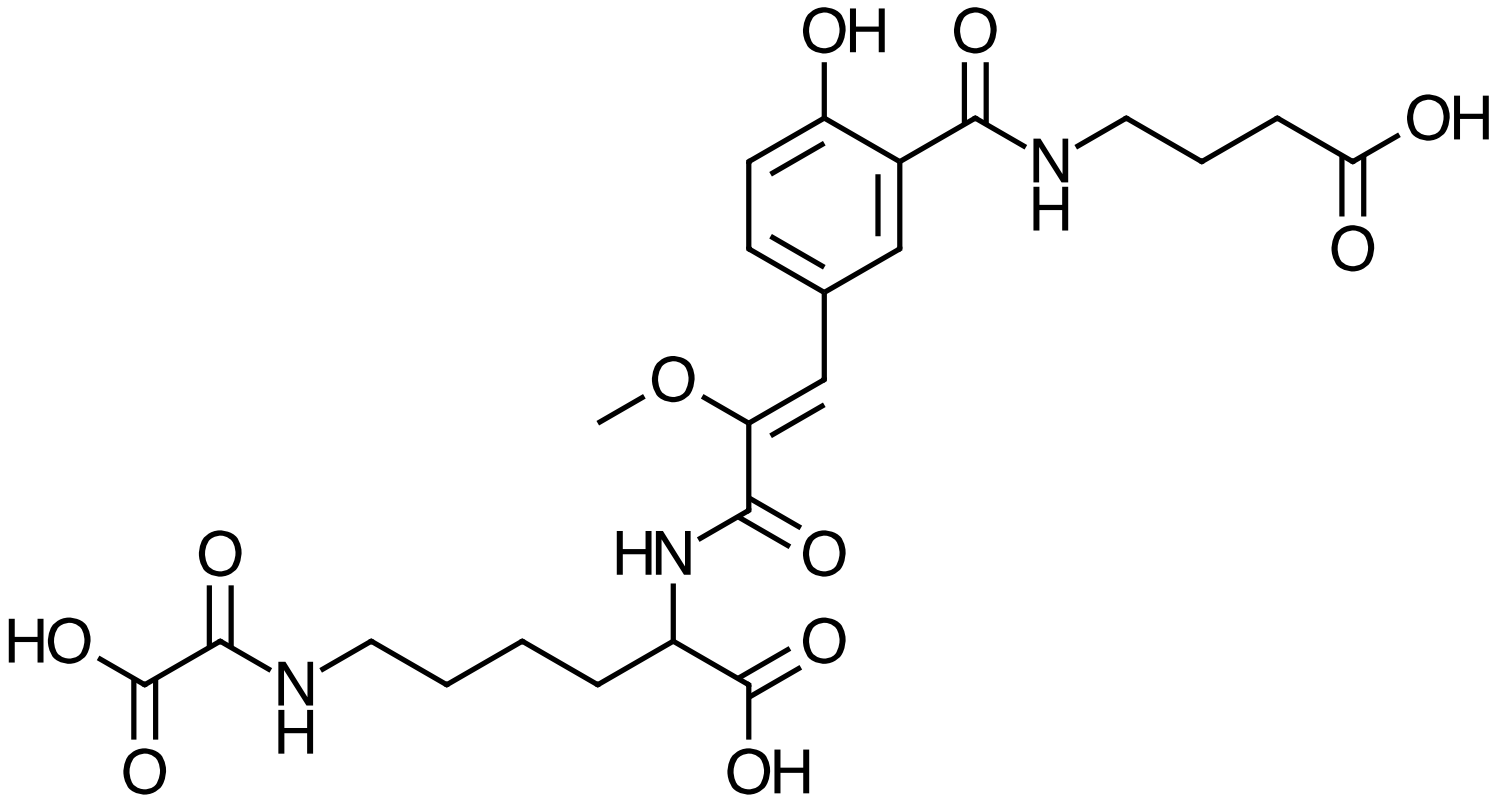
http://cen.acs.org/articles/94/i22/Mass-spec-weighs-protein-therapeutics.html

Deamidation, in which an asparagine residue is spontaneously converted to either aspartic acid or isoaspartic acid, is a common degradation mechanism in protein therapeutics.



Use curved arrows to show bonds breaking and forming.

CEN, 4/28/14, p. 26 Luciferin causes earthworms to glow

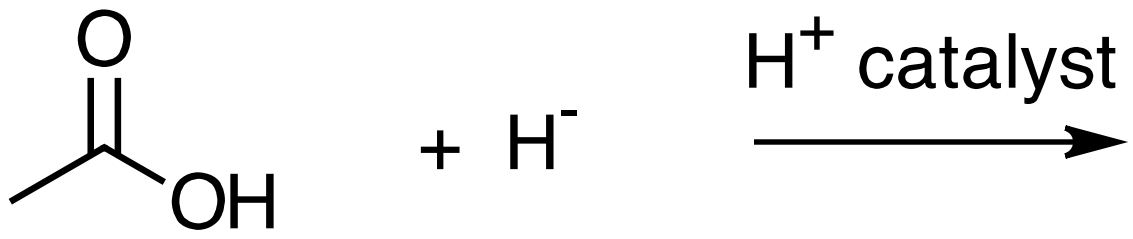


Draw the structure(s) of the hydrolysis product(s).
At which atom will a $Nu:^-$ most likely react?
At which atom will a E^+ most likely react?

Objective: Predict product of $Nu:^-$ acyl substitution reaction

E.g., $Nu:^-$ = $H:^-$ (hydride from $LiAlH_4$ or $NaBH_4$)

RCOOH + H^- -- H^+ catalyst -->

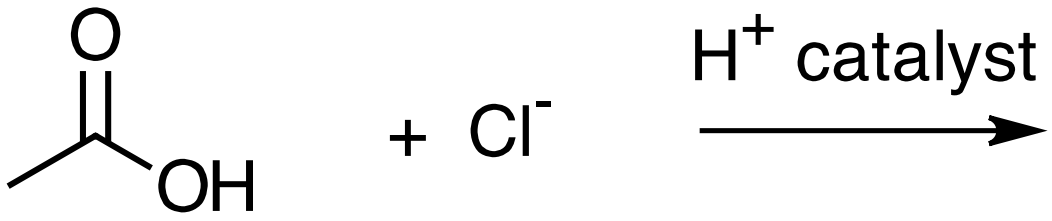


What is the *Leaving Group* in the *Tetrahedral* intermediate?

Objective: Predict product of $Nu:^-$ acyl substitution reaction

E.g., $Nu:^-$ = Cl^- (from $SOCl_2$)

RCOOH + Cl^- -- H^+ catalyst -->

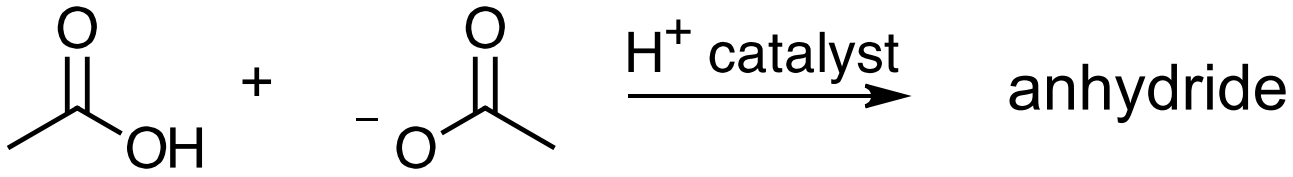


What is the *Leaving Group* in the *Tetrahedral* intermediate?

Objective: Predict product of Nu:$^{-}$ acyl substitution reaction

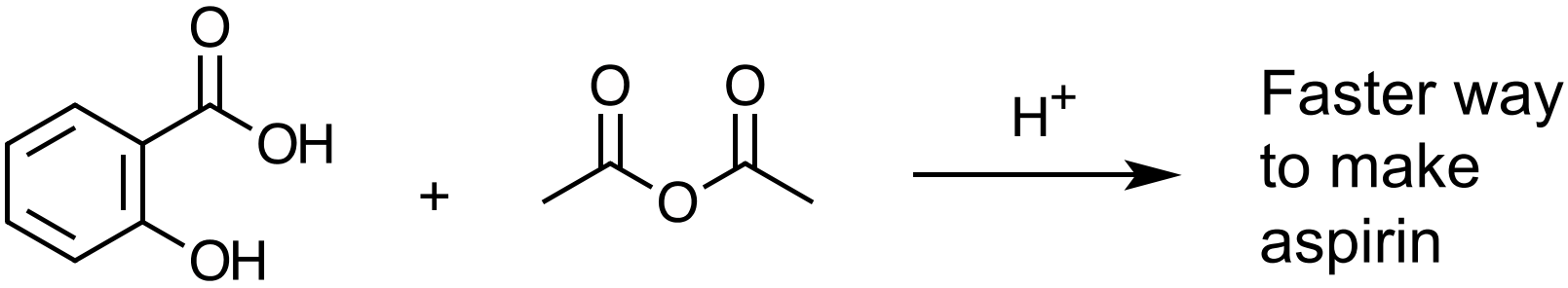
E.g., Nu:$^{-}$ = $^{-}$OCOR

RCOOH + RCOO^{-} -- H^{+} catalyst -->



Anhydride is more reactive than acid
So instead of RCOOH + ROH, use

RCOOCOR + ROH -- H^{+} catalyst -->

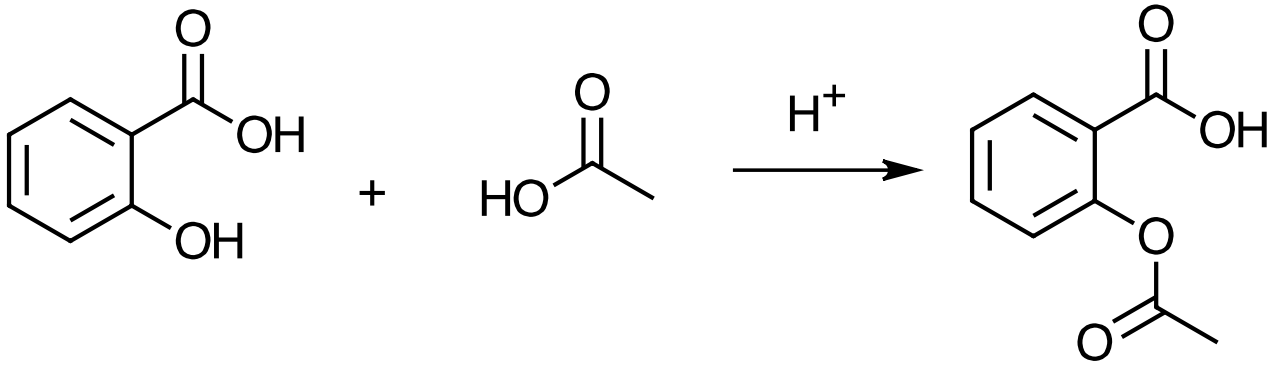


Objective: Predict product of $Nu:^-$ acyl substitution reaction

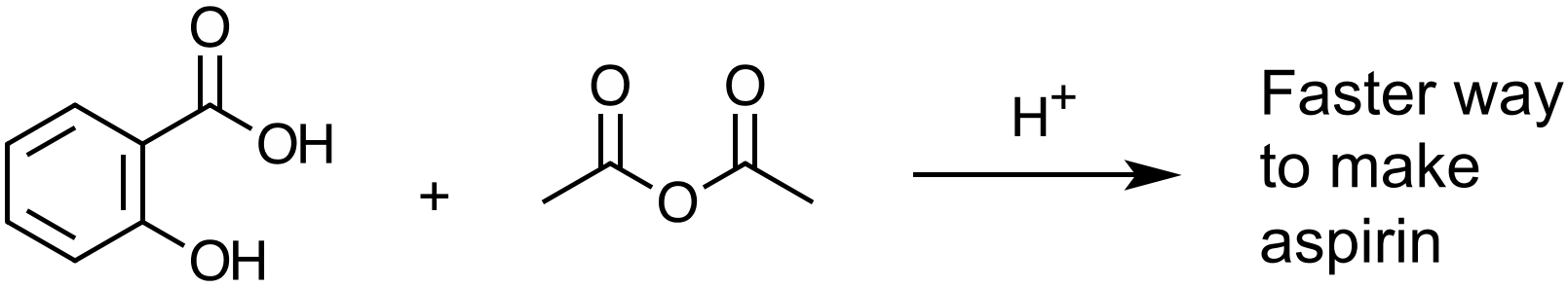
Anhydride is more reactive than acid

e.g., instead of RCOOH + ROH --H^+ catalyst --> RCOOR

use RCOOCOR + ROH -- H^+ catalyst --> RCOOR



aspirin



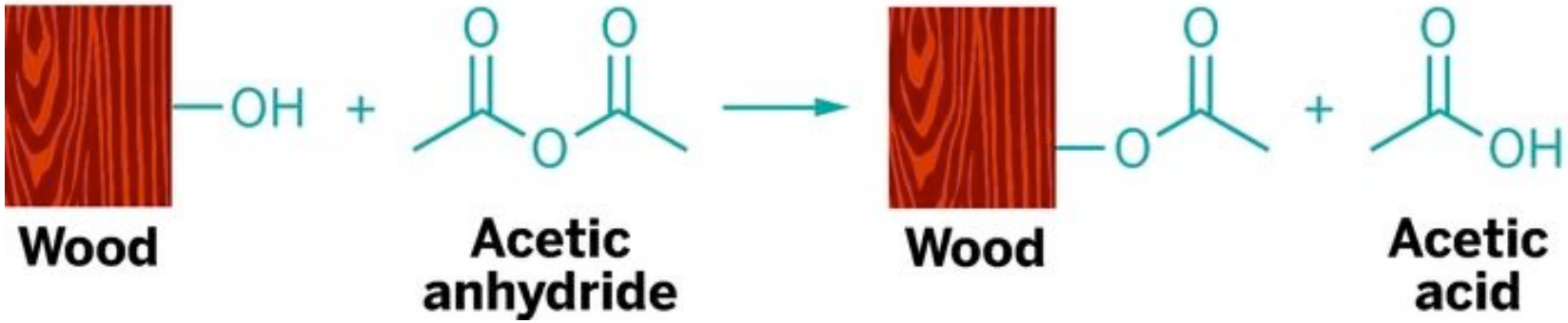
Faster way to make aspirin

http://cen.acs.org/articles/90/i32/Making-Wood-Last-Forever-Acetylation.html

8/6/12, CEN, p. 22 “Making Wood Last Forever With Acetylation”

Pressure Treatment: preservatives, such as ammoniacal copper quaternary compounds, are infused into wood

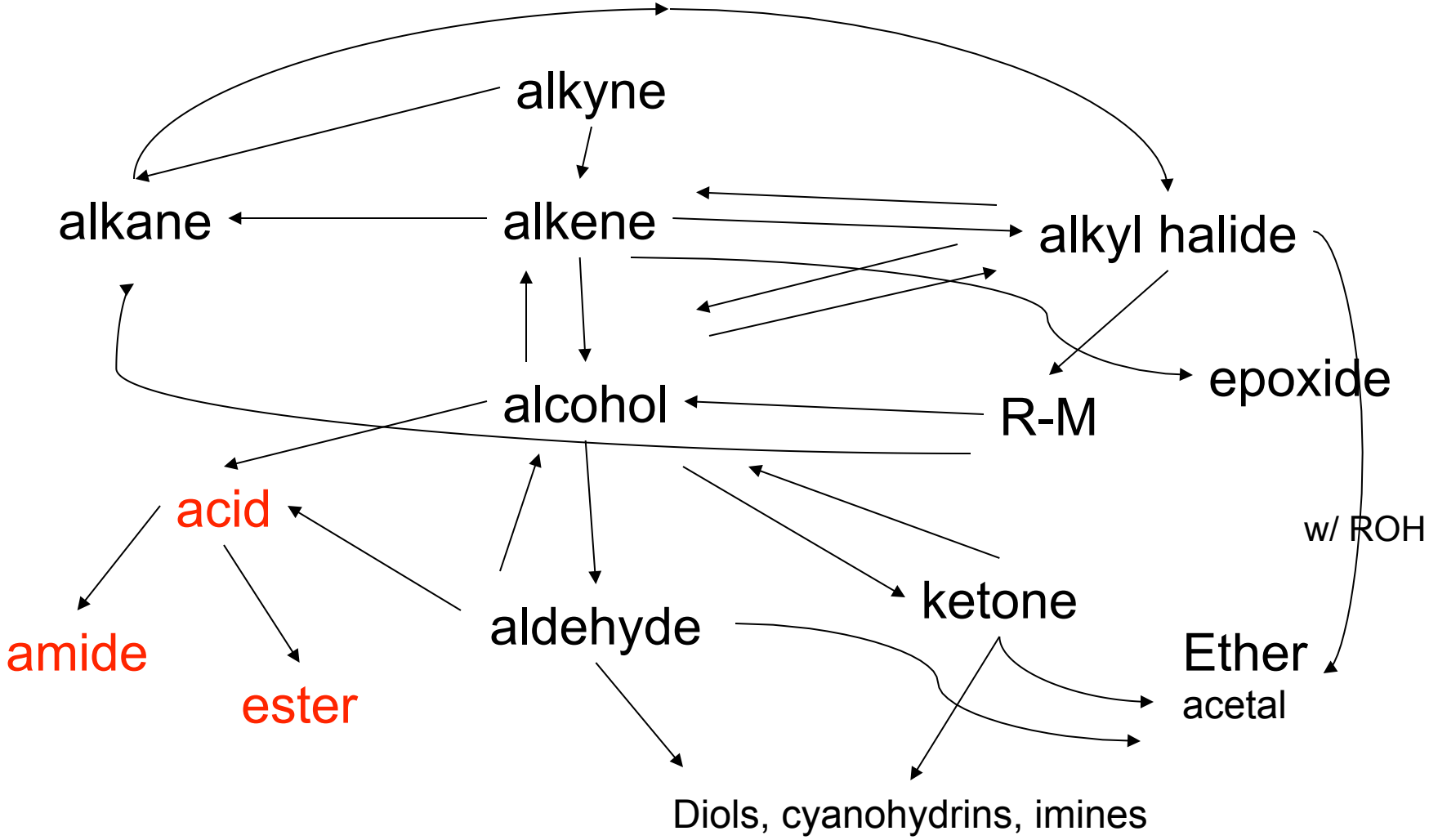
Acetylation: chemically modifies wood - acetic anhydride reacts with the Lignin and hemicellulose (in wood plant cell wall) contain hydroxyl groups.



Same chemistry employed since the early part of the last century for making cellulose acetate—acetylated wood pulp—for photographic film, wedding dress fabric, cigarette filters, and playing cards.

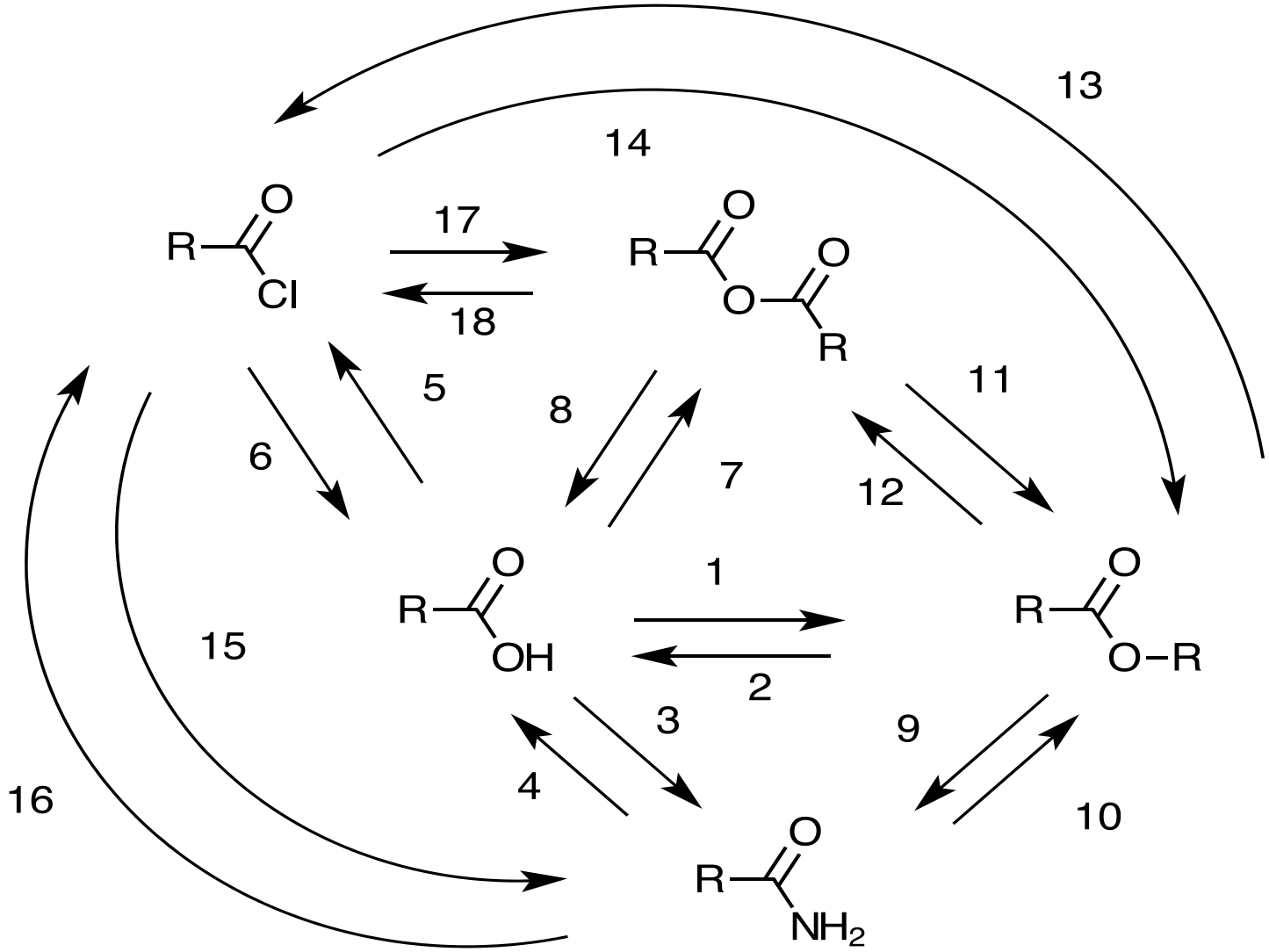
Reaction Roadmap:

What group undergoes Nu:$^-$ acyl substitution? And what group is produced? What are β-keto acids used for?

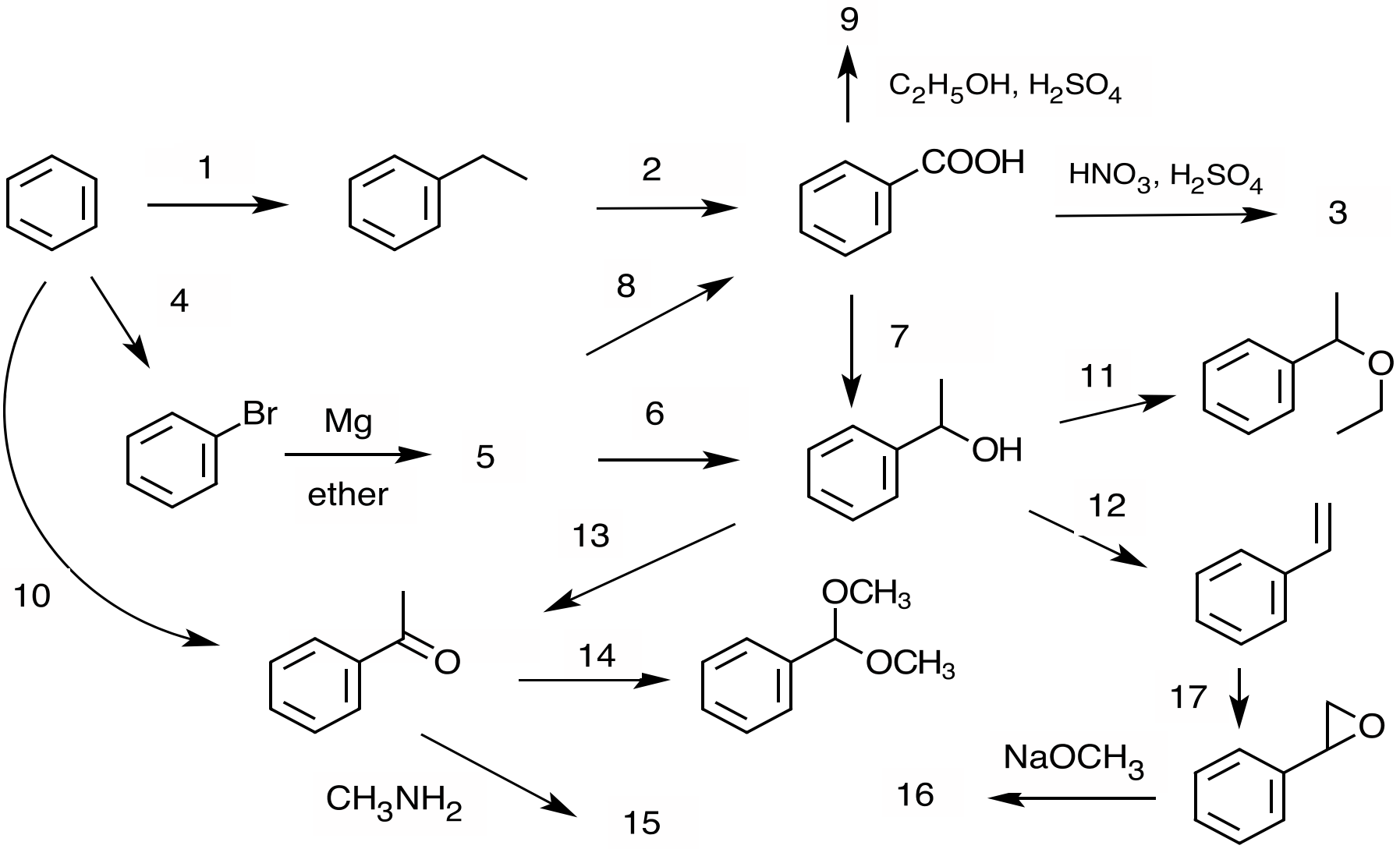


Objective: Convert one acid derivative to another

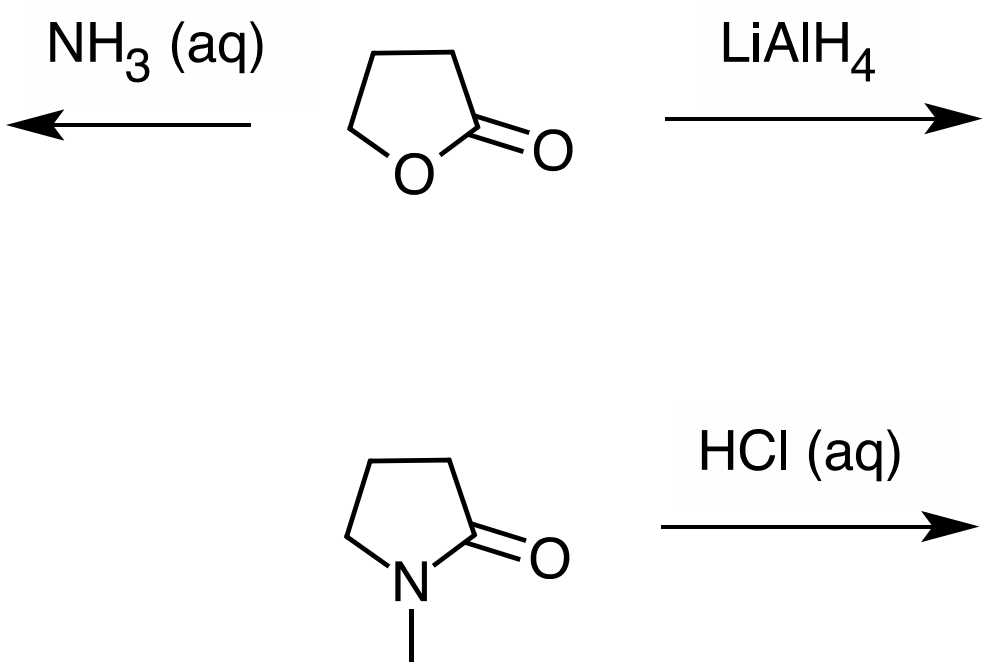
Identify the Reaction Conditions to Convert One Functional Group to Another **(**Hint: **What Nu:$^-$ to use?)**



ID structure or reaction conditions.
Which reactions involve a carbonyl carbon?
Which reactions make a C-C bond?

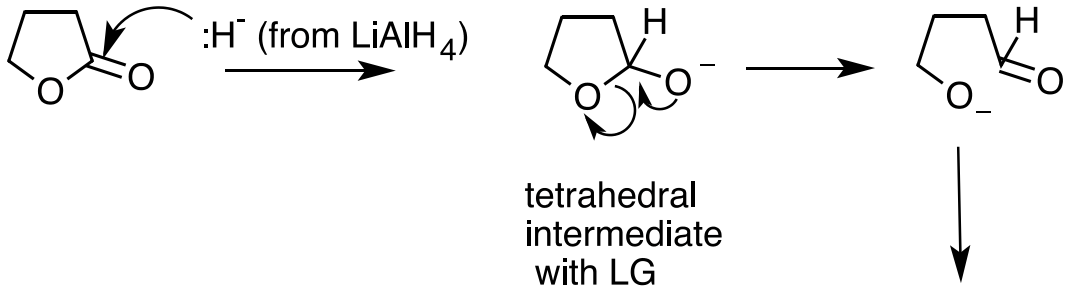


Predict the product in each reaction:

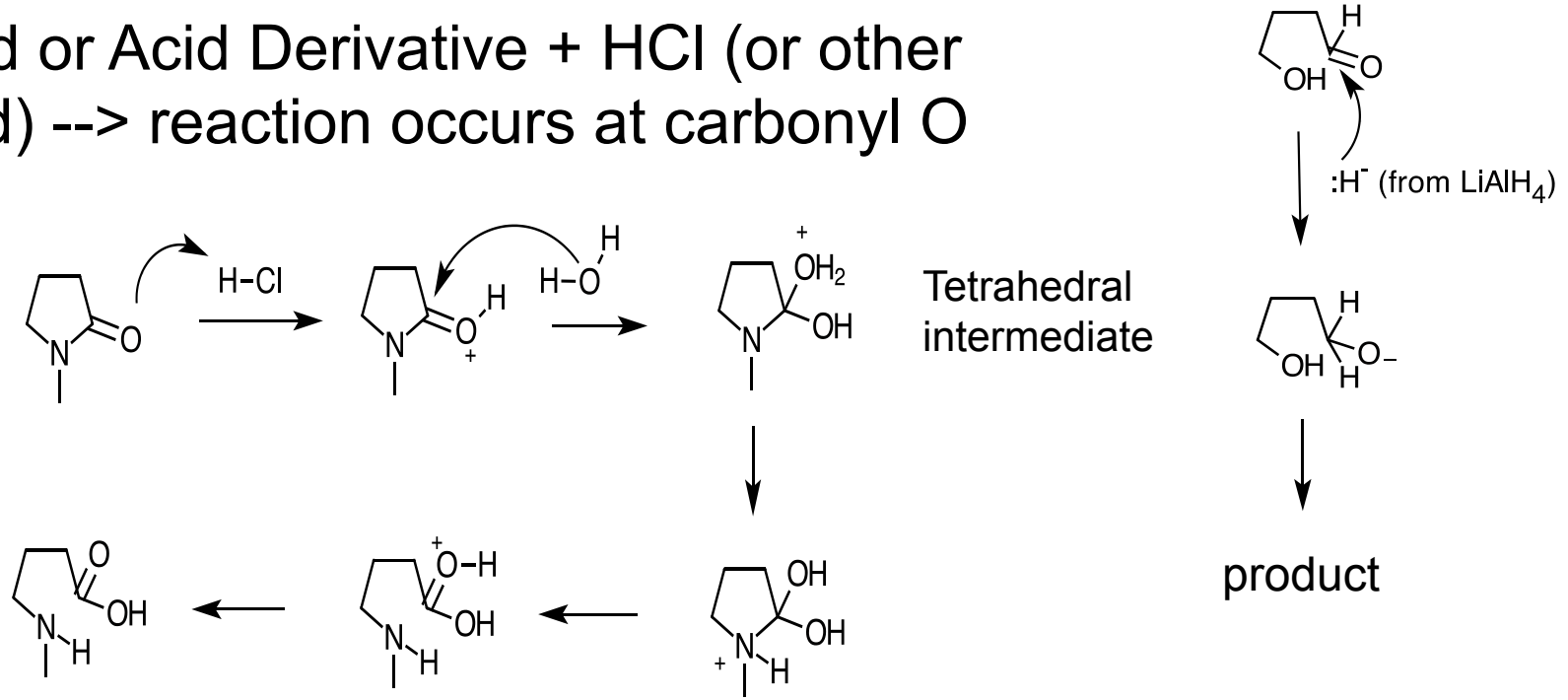


Acid or Acid Derivative + Nu:$^-$ --> reaction occurs at carbonyl C

Nu:$^-$ = H^- (from $LiAlH_4$ or $NaBH_4$), N (from amine), O (from ROH), etc.



Acid or Acid Derivative + HCl (or other acid) --> reaction occurs at carbonyl O



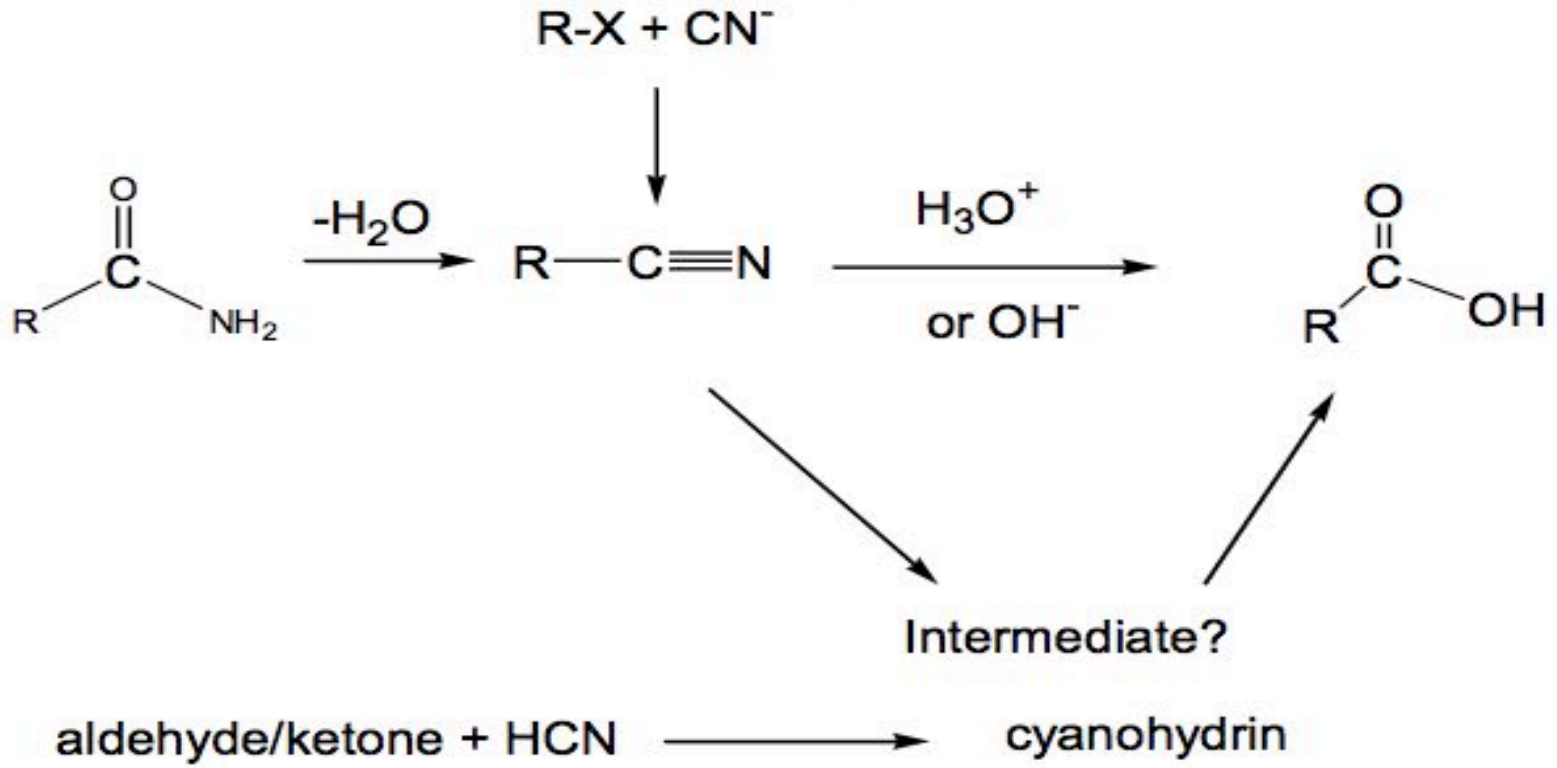
Objective: predict reactions of nitriles

Nitriles (which don't have a carbonyl group) Are Often Treated As An Acid Derivative

The Nitrile Carbon Behaves Like a Carbonyl Carbon

Nitriles undergo Hydrolysis to Form Acids.

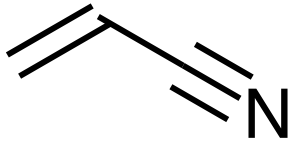
What functional group is formed as the intermediate?

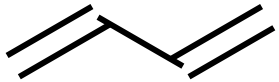


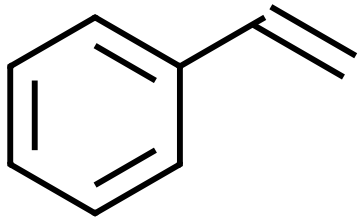
Carey, 8th ed., Problem 19.29t, u, and v

3D printer filament: ABS

A = acrylonitrile B = butadiene S = styrene





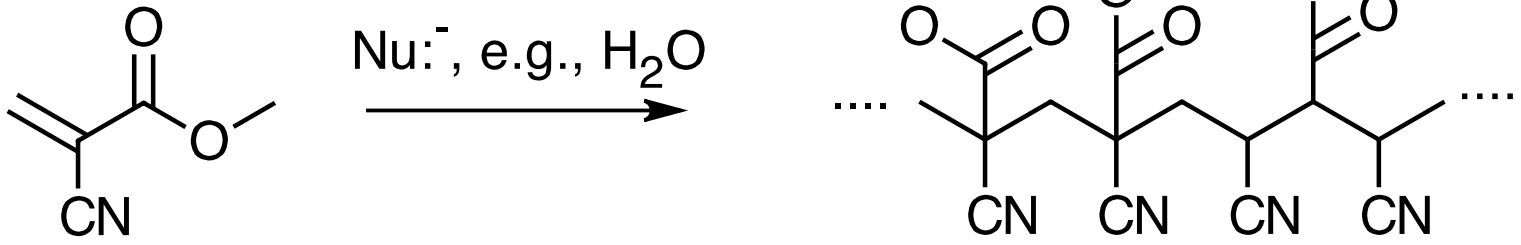


ABS is a terpolymer made by polymerizing acrylonitrile with styrene in the presence of polybutadiene.

High impact resistance ➔ better mechanical properties than PLA

Super Glue comes from methyl cyanoacrylate

http://i.ebayimg.com/images/i/112054913021-0-1/s-l1000.jpg

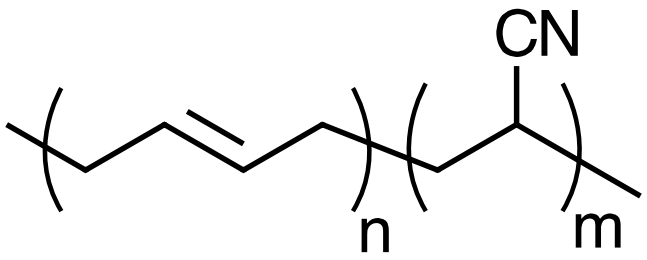


methyl methacrylate
α,β-unsaturated ester
Michael addition

Super Glue

Michael addition: Nu:⁻ reacts at vinyl C
But C=C pi bond is a Nu:⁻.
Resonance structures show vinyl C can have (+) charge.

Nitrile gloves comes from acrylonitrile butadiene rubber



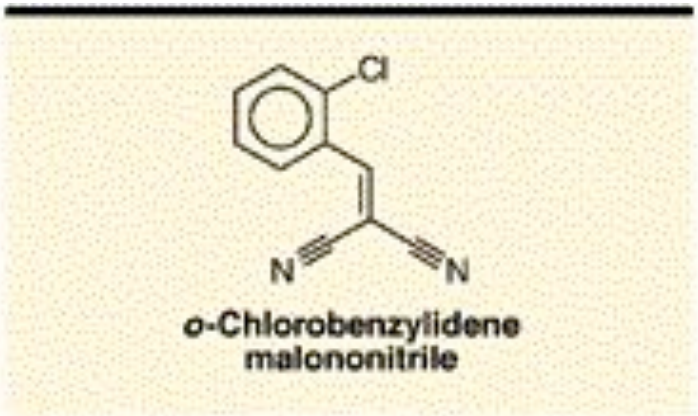
https://www.gloveclub.co.uk/media/catalog/product/cache/1/image/650x650/c5620bcfa0160be1509233fa8dad160e/8/1/813bodsownl._sl1500__1.jpg

High tensile strength, good resistance to oils, dilute acids and bases

Anatomy of a tear gas (http://pubs.acs.org/cgi-bin/bottomframe.cgi?7751gov1box)

Police in Seattle released copious quantities of tear gas in their efforts to disperse demonstrators at the World Trade Organization meeting.

The tear gas they used contained o-chlorobenzylidene malononitrile, according to a Seattle police spokeswoman. The substance is called CS after the two men who developed it in 1928, Ben B. Corson and Roger W. Stoughton. CS, a white crystalline solid at room temperature, is classified as an "antiriot agent" by the U.S. military. Law enforcement agencies in the U.S. began using CS tear gas in the 1960s, and now police around the world use it.



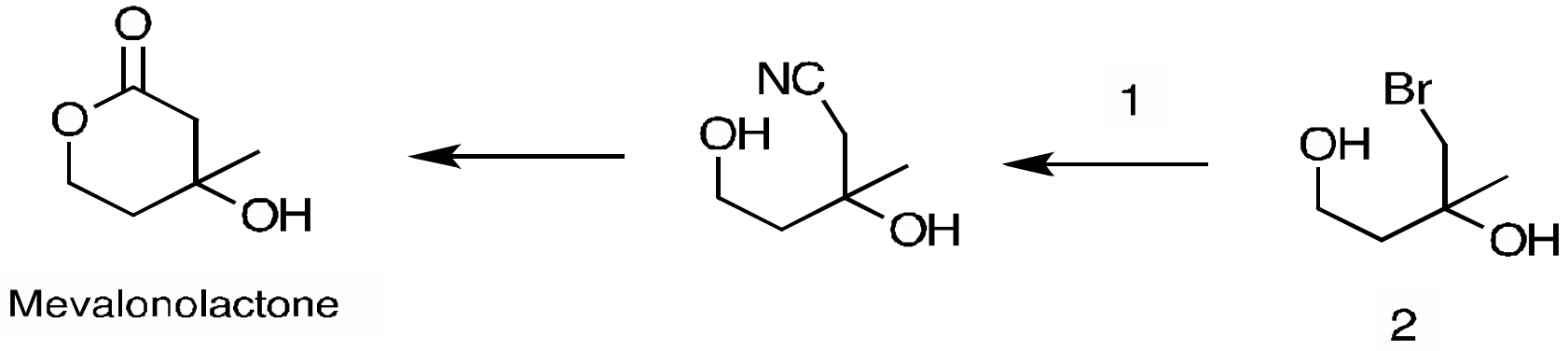
U.S. sales of CS powder and munitions containing it, such as grenades and projectiles, are limited to law enforcement agencies. However, small aerosol cans containing a formulation of CS are available to the U.S. public.

According to the Army, exposure to CS causes pain and burning in the eyes and skin within seconds. The chemical is an alkylating agent that reacts readily at nucleophilic sites, and sulfhydryl-containing enzymes such as those found in the eye are a prime target, the Army says. What is the Electrophile?

Effects of CS exposure include an extreme burning sensation in the eyes with a copious flow of tears, coughing, sneezing, a perception of chest tightness, and dizziness. Most of these effects subside within 30 minutes of exposure. High concentrations may trigger nausea and vomiting.

A study by the National Toxicology Program found no evidence of carcinogenic activity in mice and rats exposed to CS for up to two years.

<u>Mevalonolactone</u> is an intermediate in the biosynthesis of terpenes and steroids.



a. For (1), would you use HCN or NaCN? Give reasons.
b. Use curved arrows to show how mevalonolactone is formed.

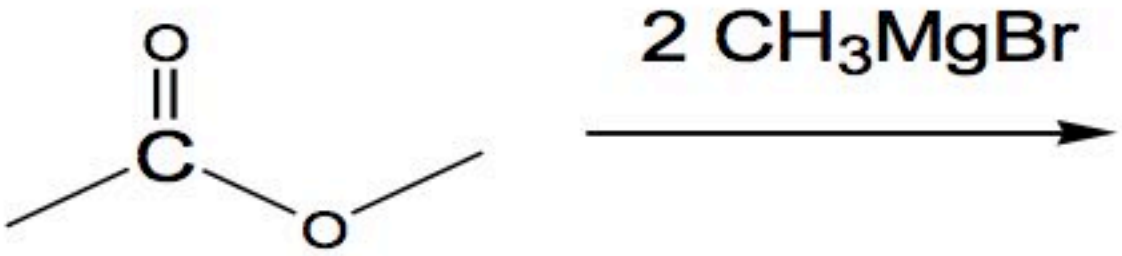
c. Suggest a synthesis of (2). Use ethylene or propylene as your source of carbon atoms and any necessary inorganic reagents.

So far, **Nucleophiles that React with Acids and Acid Derivatives are**: OH, OR, OCOR, NHR, NR_2

Other **Nucleophiles**, e.g., RMgX and hydride ($LiAlH_4$ and $NaBH_4$), react at carbonyl carbon in acid and acid derivatives.

Remember: aldehyde/ketone + RMgX or $H:^-$ → alcohol

Predict the product:

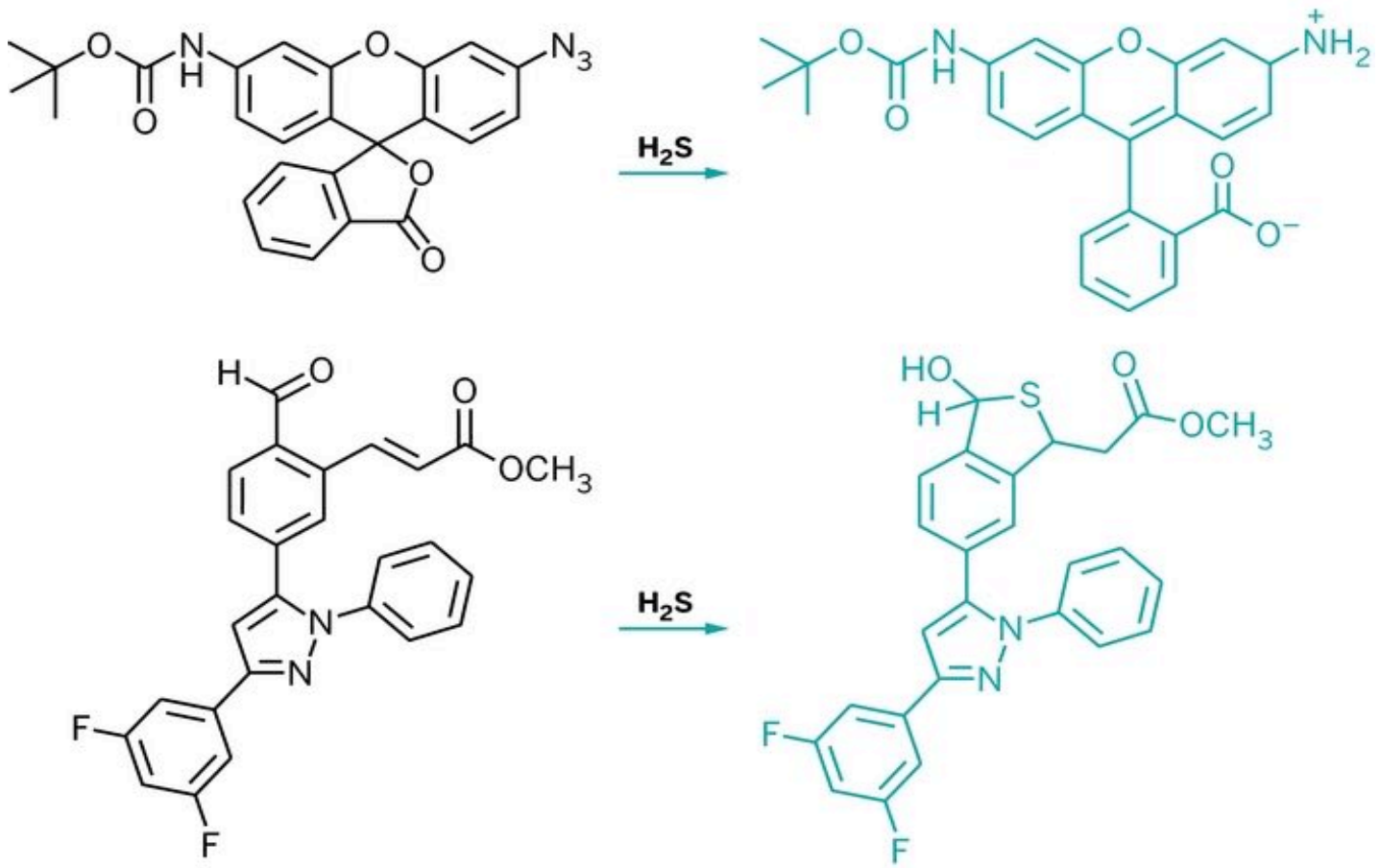


Klein, Ch. 21.50e and h, 65e

http://cen.acs.org/articles/89/i42/Detecting-H2S-Vivo.html

10/17/13, CEN, p. 60 Detecting H_2S in vivo

H_2S plays a role in cell signaling: it mediates blood pressure, metabolic rate, angiogenesis, and anti-inflammatory effects

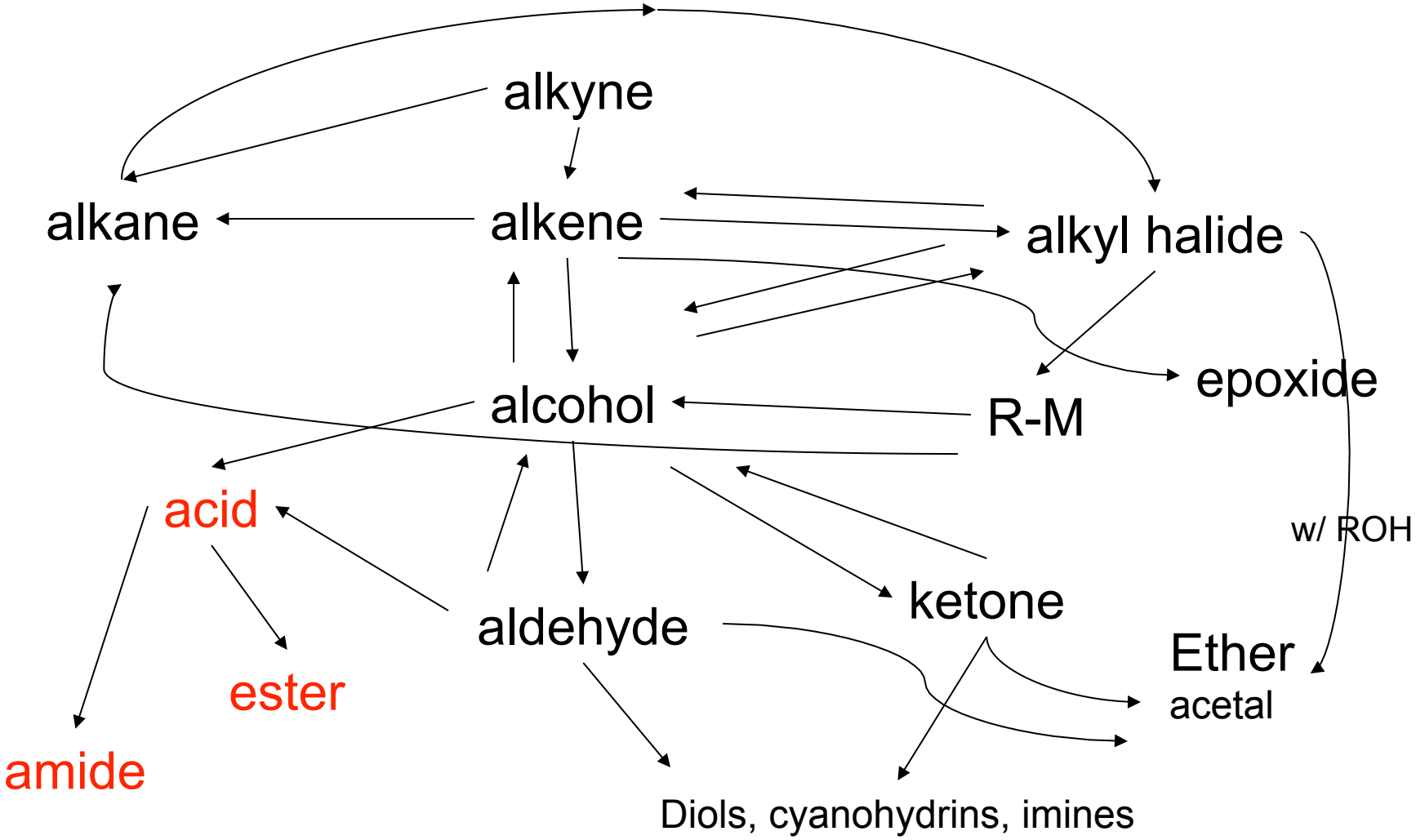


Sulfidefluor-1 (top left) reacts selectively with H_2S in vivo to generate an amine that fluoresces (blue). The He group's SFP-1 (bottom left) captures sulfide selectively in vivo, also yielding a fluorescent species.

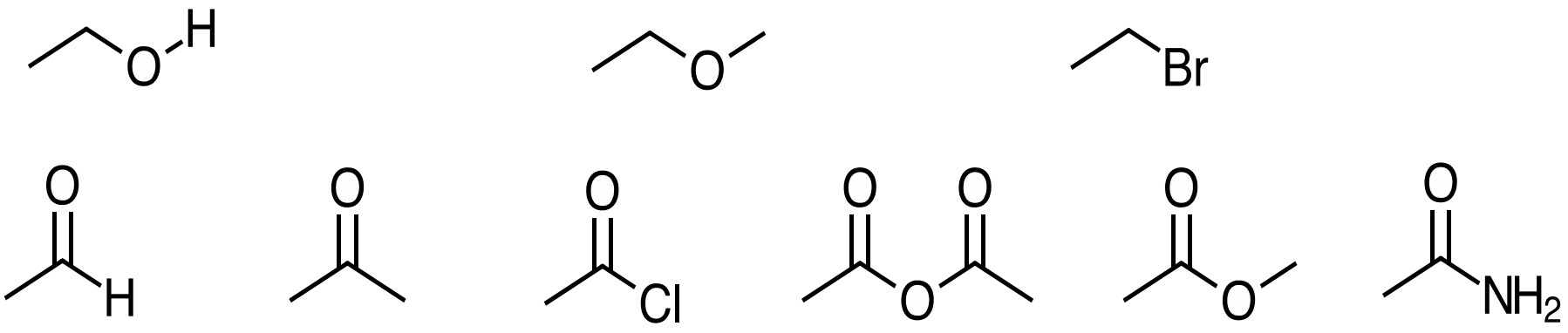
Reaction Roadmap:

Acid derivatives: acyl chlorides, anhydrides, esters, amides

What group makes nitriles? What group is made from nitriles?



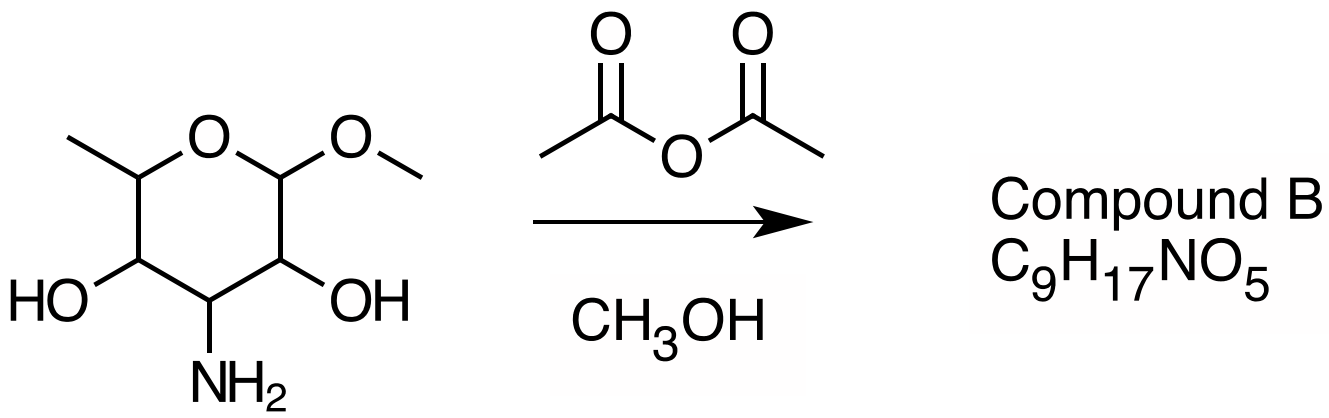
Knowing Reactive Sites of a Functional Group Helps ID Product



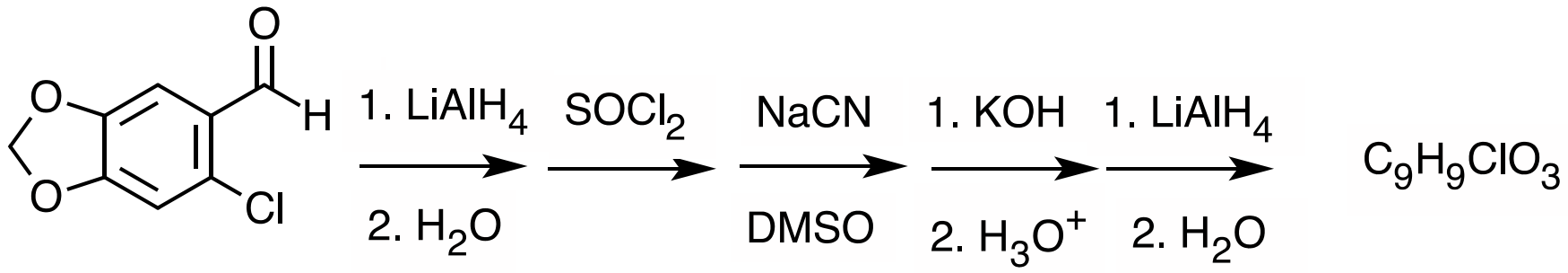
How are the compounds in the top row similar?
What reaction type do these compounds undergo?

How are the compounds in the bottom row similar?
What reaction type do these compounds undergo?

Compound A is a derivative of the carbohydrate perosamine, which is found in the antibiotic perimycin. When A is treated with excess acetic anhydride in methanol, a mono-acyl derivative B ($C_9H_{17}NO_5$) in 73% yield. Draw the structure of B. (Hint: consider that methanol reacts with acetic anhydride.)



1. The compound shown was subjected to the following series of reactions to give a product having the molecular formula, $C_9H_9ClO_3$. What is this product?



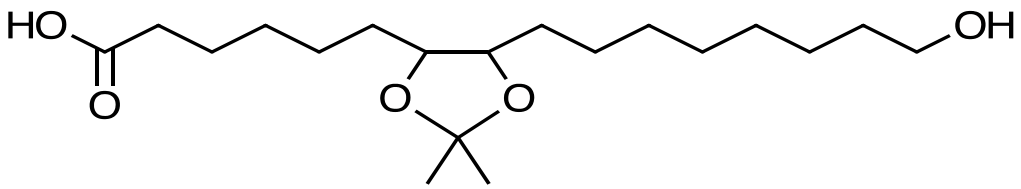
2. Write a structural formula for the principle product or products of the following reaction:

propanoyl chloride and sodium propanate

Carey, 8th ed. Problem 19.40

Ambrettolide ($C_{16}H_{28}O_2$) has a musk-like odor and is obtained from hibiscus. Its synthesis consists of 7 steps:

Step	Reactant	Reagents	Product
1	A	H_2O, H^+, heat	$C_{16}H_{32}O_5$ (B)
2	B	HBr	$C_{16}H_{29}Br_3O_2$ (C)
3	C	Ethanol, H_2SO_4	$C_{18}H_{33}Br_3O_2$ (D)
4	D	Zinc, ethanol (converts vicinal dibromides to alkenes)	$C_{18}H_{33}BrO_2$ (E)
5	E	$NaCH_3COO$, CH_3COOH	$C_{20}H_{36}O_4$ (F)
6	F	KOH, C_2H_5OH, then H^+	$C_{16}H_{30}O_3$ (G)
7	G	Heat	Ambrettolide

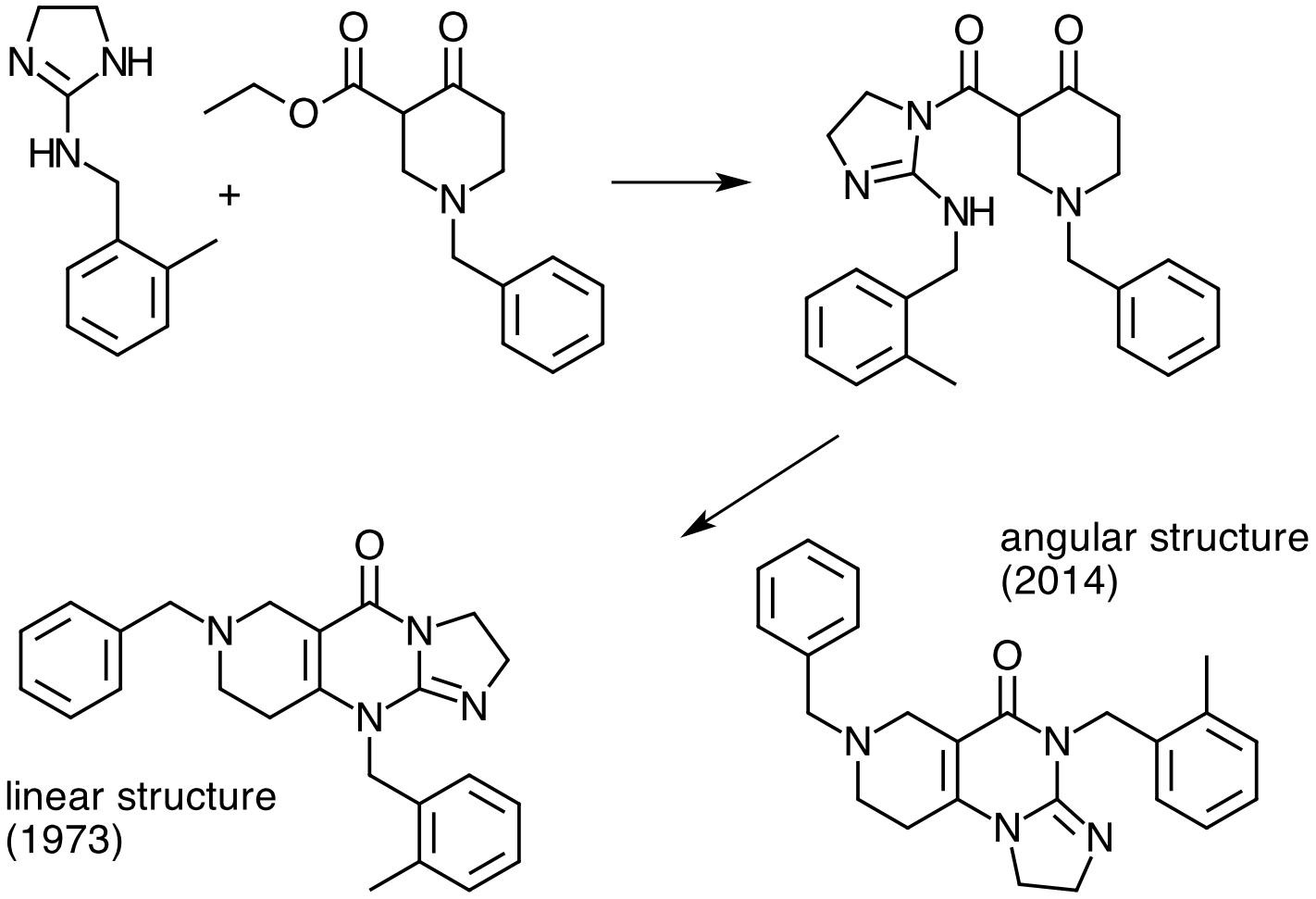


Compound A

Determine the structures of Compounds B through G.

C&EN, 6/9/14, p. 32 (http://cen.acs.org/articles/92/i23/Fog-Clearing-TIC10-Drug-Development.html)

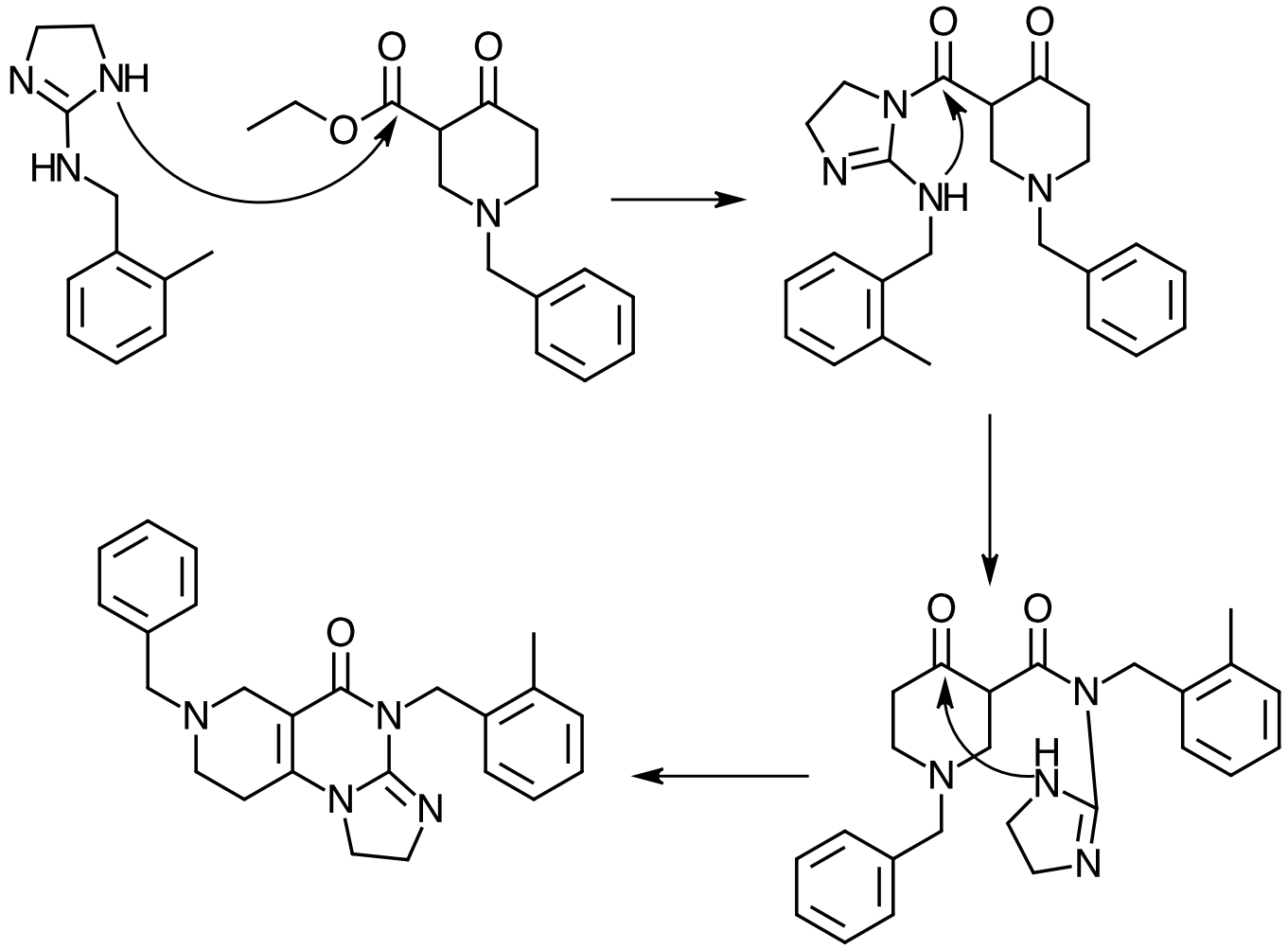
Anti-cancer drug, TCI10, structure correction (Bio Ind rxn app)



What reaction type occurs in each step?

C&EN, 6/9/14, p. 32 (http://cen.acs.org/articles/92/i23/Fog-Clearing-TIC10-Drug-Development.html)

Anti-cancer drug, TCI10, structure correction



What reaction type occurs in each step? Nu:$^{-}$ acyl sub