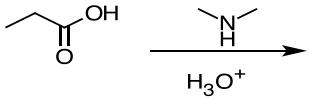
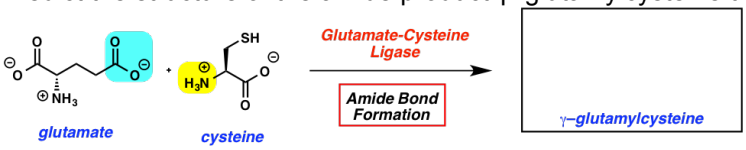
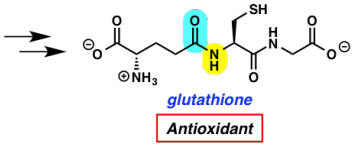
Objective 12b. Apply nucleophilic addition and elimination concepts to nucleophilic acyl substution of acids and derivatives (focus on amides)
Skills: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu^- and E^+, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.
Key ideas: Compare to Nu addn. Both have Td intermediate. No LG in Nu addn vs. LG in acyl sub.

Practice problems solutions:
1. An acid reacts with an amine in the presence of an acid catalyst to form an amide.
a. For the reaction below, use curved arrows to show how the amide product forms. What is the leaving group?
This reaction is reversible which means an amide undergoes hydrolysis to form an acid and amine. What bond forms? What bond breaks? This will help you on Question 2.

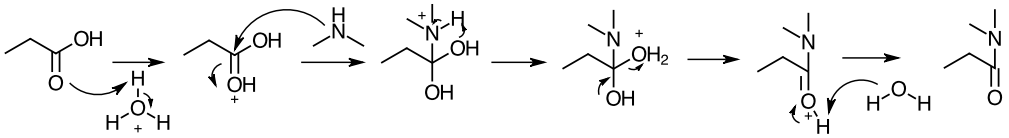


b. (From LearnBacon.com) Glutathione (antioxidant found in plants, animals, and fungi) synthesis.
Predict the structure of the amide product γ–glutamylcysteine that is formed after coupling of glutamate and cysteine.

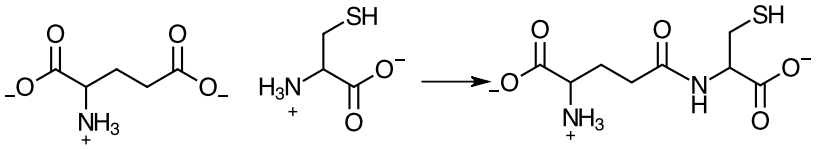




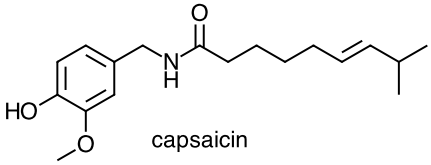
Answers:
a. acid + amine --> amide + water



b. acid + amine --> amide = γ–glutamylcysteine



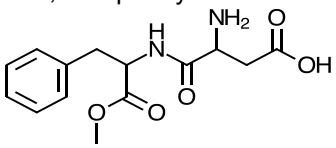
2. One way our body metabolizes chemicals is by hydrolysis of the amide group.
a. Capsaicin is found in chili peppers and is hot and spicy. It is also an anti-viral and is being investigated as a cancer drug.
(i) Draw the structure(s) of the metabolic (hydrolysis) product(s).



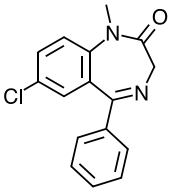
capsaicin

(ii) Milk or an adult beverage, like tequila, works better than water for relieving the burning sensation on your tongue. Explain why.

b. Aspartame is an artificial sweetener (Nutrasweet). In the body, aspartame is hydrolyzed to form methanol, aspartic acid, and phenylalanine. Draw the structures of aspartic acid and phenylalanine.



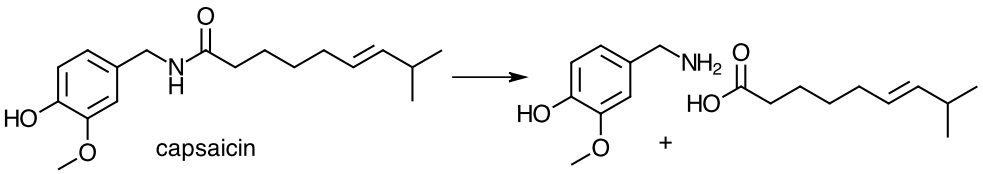
c. Valium is an anti-anxiety drug. Draw the structure of a metabolic (hydrolysis) products of this compound.



Diazapam (Valium)

Answers:

a. (i) amide + water --> amine + acid

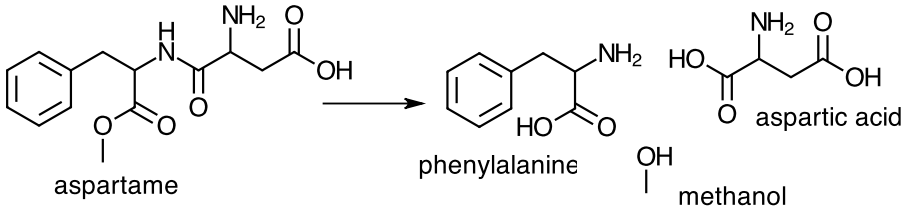


capsaicin

(ii) The non-polar hydrocarbon chain in capsaicin is soluble in the non-polar fat in milk or non-polar ethyl group in ethanol.

b. The ester group hydrolyzes to form an acid (phenylalanine) and alcohol (methanol).

The amide group hydrolyzes to form an acid (aspartic acid) and alcohol (phenylalanine).



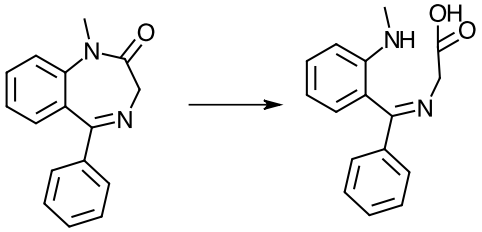
aspartame

phenylalanine

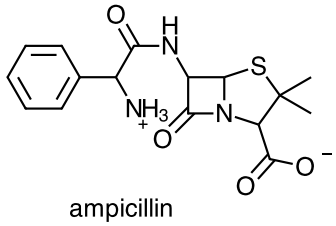
aspartic acid

methanol

c. amide + water --> amine + acid



3. Ampicillin is a beta-lactam (a beta-lactam is an amide group in a four sided ring) antibiotic. Beta-lactam antibiotics disrupt cell wall biosynthesis in bacteria by inactivating a transpeptidase enzyme. Assume this enzyme is ROH.



ampicillin

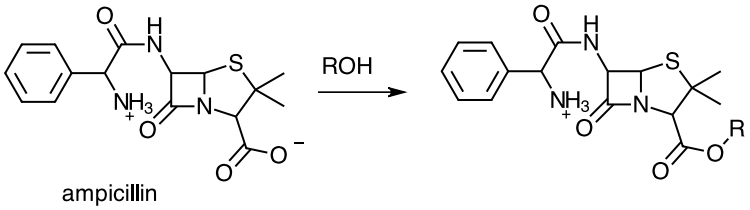
a. Ampicillin has two amide groups and an acid group. The amide group in the ring is the most reactive because _____.

b. Use curved arrows to show how ROH reacts with ampillicin. Draw the structure of the product.

Answers:

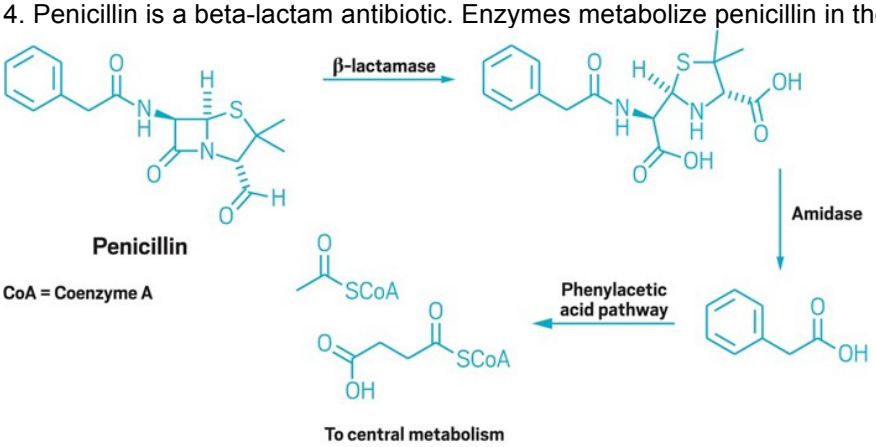
a. The 4 sided ring (square) has ring strain (90^{o} ring angle vs. 109^{o} tetrahedral or 120^{o} trigonal planar).

b. Acid + alcohol --> ester + water.

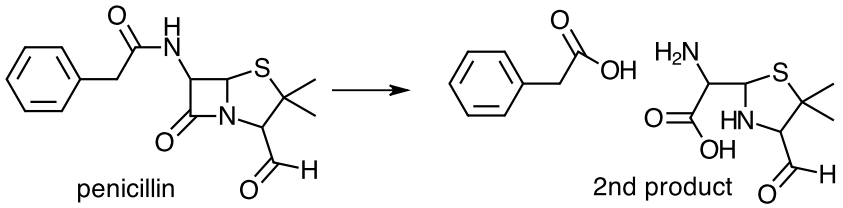


ampicillin

4. Penicillin is a beta-lactam antibiotic. Enzymes metabolize penicillin in the following series of reactions:

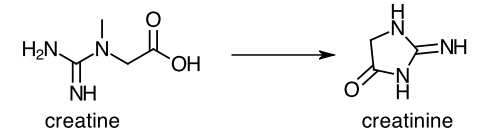


Reference: “Making of meal of penicillin,” CEN, 5/7/18, p. 11.
a. In the first reaction, identify the functional group conversion. What is the reaction type?
b. In the second reaction, identify the functional group conversion. Draw the structure of the second product.
Answers:
a. amide + water --> acid + amine. Amide hydrolysis is a nucleophilic acyl substitution reaction.
b. amide + water --> acid + amine. Amide hydrolysis is a nucleophilic acyl substitution reaction.
The second product is

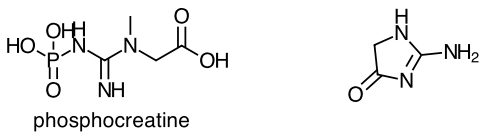


penicillin 2nd product

5. Creatine is found in vertebrates (mainly in skeletall muscle) and facilitates recycling of ATP. Creatine supplements are used by athletes to gain muscle mass. Creatine breaks down to creatinine.
Use curved arrows to show how creatine forms creatinine.

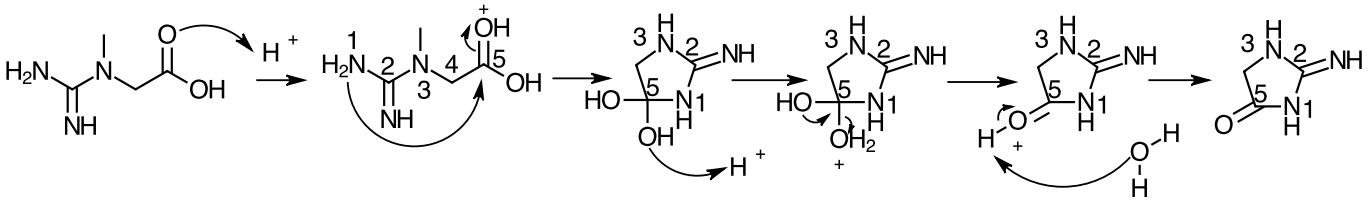


creatine creatinine

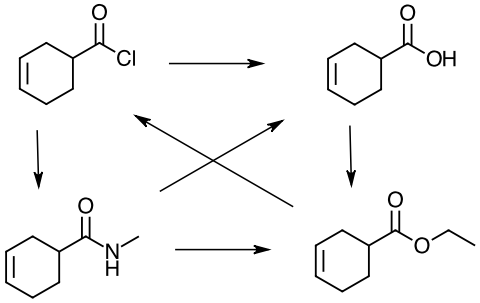


phosphocreatine

Answers: acid + amine --> amide + water
5 sided ring is stable – minimum ring strain.



6. Functional group conversions.
a. For each compound, identify the Nu:$^-$ and E^+. If there is more than one Nu:$^-$ or E^+., identify the strongest Nu:$^-$ or E^+.
b. Determine the reaction conditions for each reaction. Which reaction needs an acid catalyst? Why?
If a reaction does not need an acid catalyst, make sure the Nu:$^-$ is strong enough to react at the carbonyl C.
c. Draw the tetrahedral intermediate for each reaction. Circle the leaving group in each tetrahedral intermediate.

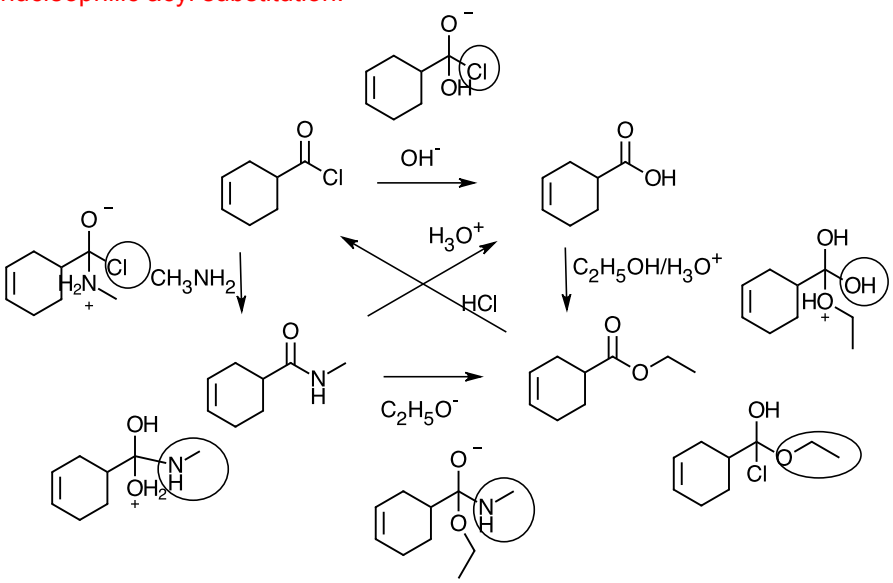


d. You want to form a C-C bond using CH_3MgBr. Which compound will <u>not</u> react with CH_3MgBr at the carbonyl C? Why?
e. Hydride, H:$^-$, (from $LiAlH_4$ or $NaBH_4$) is a good Nu:$^-$. Use curved arrows to show how hydride reacts with each compound. Draw the structure of each product.

Answers:

a. In each compound, the nucleophile is the carbonyl O and C=C pi bond. The lone pairs on the carbonyl O is a stronger Nu:$^-$ than the C=C pi bond.
In each compound, the electrophile is the carbonyl carbon.

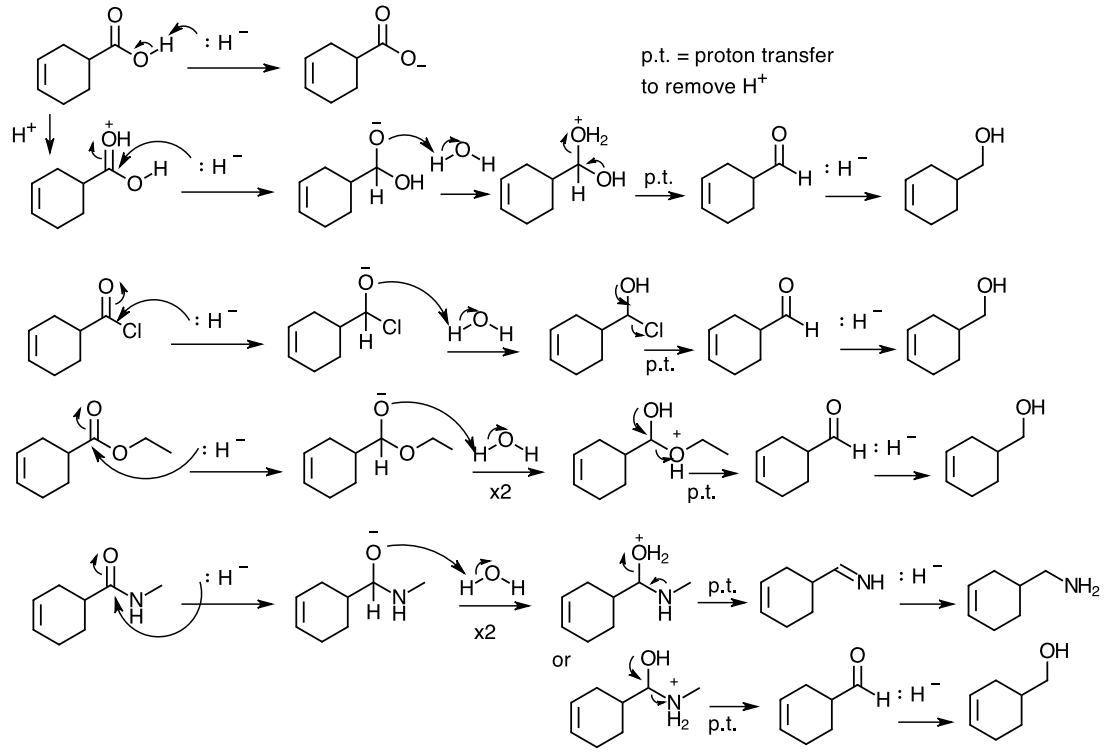
b. The carbonyl carbon in the acyl chloride is the most electrophilic and nucleophilic acyl substitution can occur without an acid catalyst. The acid, ester, and amide need an acid catalyst to make the carbonyl carbon a better electrophile for nucleophilic acyl substitution.



c. A tetrahedral intermediate may have two or more groups that can be leaving groups.
The leaving group needs to be a good leaving group (weak base) to form the desired product for a nucleophilic acyl substitution reaction.
When the good leaving group forms, a lone pair on O forms a pi bond on the tetrahedral C and then the leaving group leaves.

d. The acid group will not react with CH_3MgBr at the carbonyl C. CH_3MgBr reacts at the acidic H (H bonded to O in acid group) because the acidic H is a better electrophile.

e. Hydride reacts at carbonyl carbon to form tetrahedral intermediate.
The tetrahedral intermediate has two leaving groups.
One leaving group leaves to form an aldehyde.
So the hydride reduces the acid, acid chloride, and ester to an aldehyde.
The hydride reduces the amide to an imine – see last reaction.
The aldehyde or imine reacts with another hydride to form a 1^{o} alcohol (or amine from imine).
The hydride reacts at carbonyl carbon to form tetrahedral intermediate, etc.
https://en.wikipedia.org/wiki/Reductions_with_metal_alkoxyaluminium_hydrides



7. Aliskiren hemifumarate is an active pharmaceutical ingredient (API) to make Tekturna, a cardiovascular drug. The process is shown below (http://cen.acs.org/articles/92/i21/EndEnd-Chemistry.html).
The first compound is a lactone. Use curved arrows to show how the lactone undergoes aminolysis to form the second compound.