Objective 9: Apply reactivity principles to Substitution reactions: identify structural features (alpha C, LG), use curved arrows to predict product, compare S_N1 vs. S_N2 mechanisms.

Quiz Practice problems

Key ideas:

Substitution reactions are used to convert one functional group to another.
In a substitution reaction, an alpha carbon, leaving group, and nucleophile are needed.
The alpha carbon is the carbon at which the substitution reaction occurs.
The alpha carbon is the carbon bonded to a leaving group.
A leaving group is a base – see pK_a table.
Leaving groups can be good or poor.
A good leaving group is a weak base. A good leaving group is needed for a substitution reaction to occur.
A poor leaving group can be made into a good leaving group.
A nucleophile reacts at the alpha carbon and substitutes for the leaving group.

Skills:

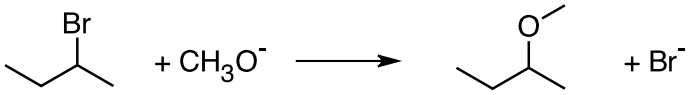
Identify alpha carbon in a compound.
Identify alpha carbon as 1^o, 2^o, 3^o.
Identify leaving group in a compound.
Identify leaving group as good or poor.
Describe how to make a poor leaving group into a good leaving group.
Identify a nucleophile as strong or weak.
Given reactants, use curved arrows to show how nucleophile reacts at alpha carbon to form substitution products.
Describe a subsitution reaction using a S_N1 mechanism. See stereochemistry.
Describe a subsitution reaction using a S_N2 mechanism. See stereochemistry.

0. We looked at 1^o, 2^o, 3^o carbons when we looked at alkanes. Alkyl halides and alcohols are classified as 1^o, 2^o, 3^o, too.
a. Ethanol is a 1^o alcohol. Why?
b. Rubbing alcohol is 2-propanol. Is rubbing alcohol a 1^o, 2^o, 3^o alcohol?
c. You looked at 1-bromobutane, 2-chlorobutane, 1-chloro-2-butene in Lab 4. Classify each alkyl halide as 1^o, 2^o, 3^o.

Answers:

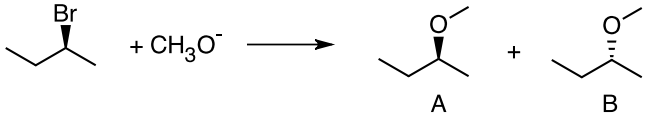
a. See the number of carbons bonded to the carbon bonded to the alcohol (OH) group.
Ethanol (CH_3CH_2OH) has 1 C bonded to the C bonded to the OH.
b. Rubbing alcohol (2-propanol) is a 2^o alcohol.
c. See the number of carbons bonded to the carbon bonded to the halide (X = F, Cl, Br, I) group.
1-bromobutane is a 1^o alkyl halide.
2-chlorobutane is a 2^o alkyl halide.
1-chloro-2-butene is a 1^o alkyl halide.

1. 2-bromobutane reacts with the methoxide ion in a substitution reaction.



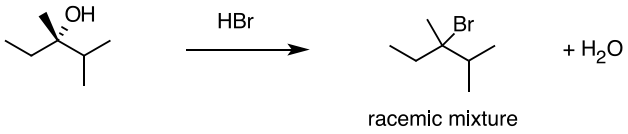
a. Circle the alpha carbon and leaving group in the reactants. Is the leaving group good or poor?
b. CH_3O^- is a nucleophile. Is this nucleophile strong or weak?
c. This reaction can occur by a S_N1 or S_N2 mechanism.
(i) Use curved arrows to show how reactants form products in a S_N1 mechanism.
(ii) Use curved arrows to show how reactants form products in a S_N2 mechanism.

d. (i) Is the configuration of 2-bromobutane shown below R or S?

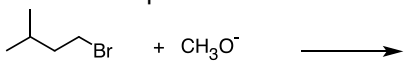


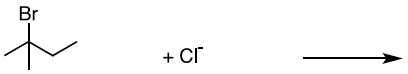
(ii) If the product distribution is 50% A and 50% B, the mechanism is ____.
(iii) If the product distribution is ___% A and ___% B, the mechanism is ____.

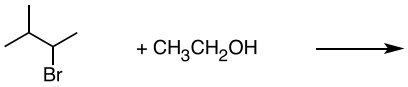
e. Explain the following observations. What is the mechanism type for each reaction?



f. Predict the product of each reaction.



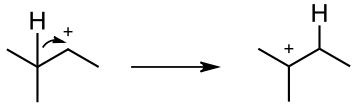




2. A carbocation intermediate forms in a S_N1 mechanism. A carbocation can rearrange to a more stable carbocation by a hydride ($H:^-$) shift or alkyl ($R:^-$) shift.

a. Hydride shift:

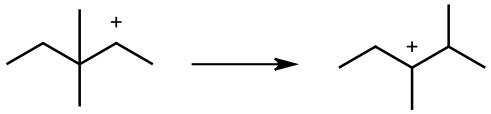
(i) what is the nucleophile in the curved arrow? What is the electrophile?



(ii) What type of carbocation forms?

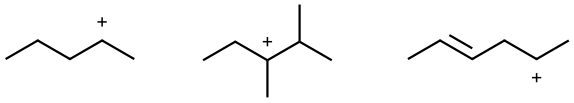
b. Alkyl shift:

(i) use curved arrows to show how this reaction occurs.

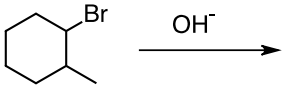


(ii) What type of carbocation forms?

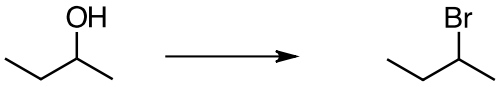
c. Determine whether each carbocation can undergo rearrangement.



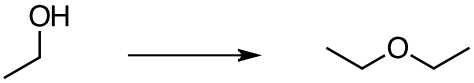
d. This reaction produces two organic substitution products. Draw the structures of each organic substitution product. (Hint: see Question 2a.)



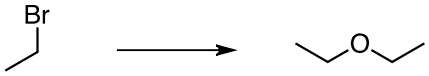
3. Explain why HBr is the other reactant and not Br^-. Use curved arrows to show how reactants form products. Identify the alpha carbon, leaving group, and nucleophile. What information do you need to know to determine whether the mechanism is S_N1 or S_N2?



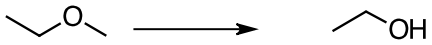
4. Would you use C_2H_5OH or $C_2H_5O^-$ to make this reaction occur? Use curved arrows to show how reactants form products. Identify the alpha carbon, leaving group, and nucleophile. Will the mechanism be S_N1 or S_N2?



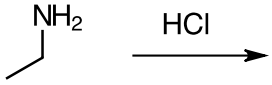
5. Would you use C_2H_5OH or $C_2H_5O^-$ to make this reaction occur? Use curved arrows to show how reactants form products. Identify the alpha carbon, leaving group, and nucleophile. Will the mechanism be S_N1 or S_N2?



6. An acid catalyst, e.g., H_3O^+, is needed for this reaction to occur. A 2nd organic product forms. Use curved arrows to show how reactants form the two organic products. Identify the alpha carbon, leaving group, and nucleophile. Will the mechanism be S_N1 or S_N2?

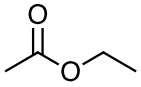


7. Ethyl amine sort of stinks. You can get rid of this smell with acid.
a. Use curved arrows to show how reactants form products. Identify the alpha carbon, leaving group, and nucleophile. Will the mechanism be S_N1 or S_N2?



b. Would this reaction be faster or slower if you used vinegar instead of HCl? Give reasons.

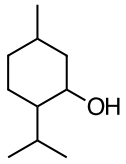
8. Ethyl acetate is a common solvent, e.g., in fingernail polish remover.
a. Ethyl acetate can undergo a substitution reaction. Identifying the alpha carbon and leaving group. Hint: see pK_a table.



b. Is the leaving group good or poor? Give reasons.
c. Br^- reacts with ethyl acetate. Predict (draw the structure) the substitution product.

9. Substitution reactions are used to convert one functional group to another. Identify the reactants to make the following compounds:

a.

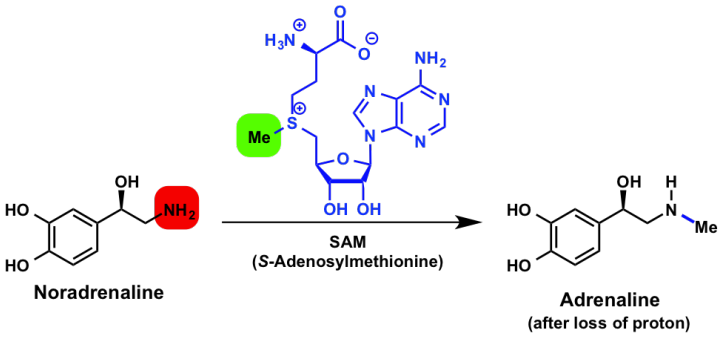


menthol

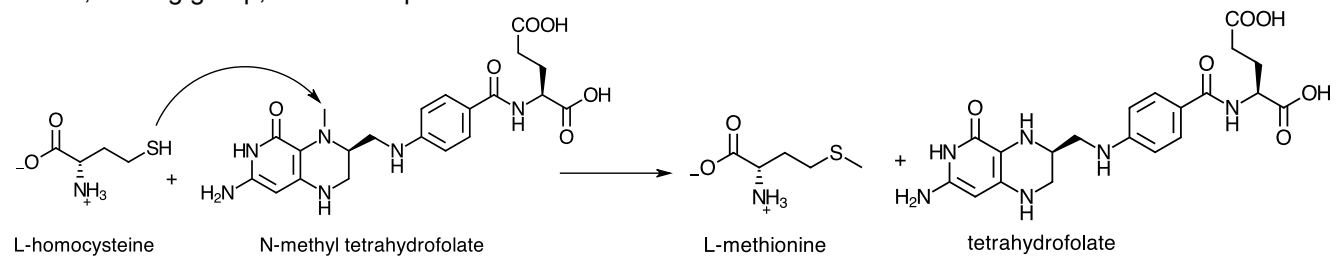
b.

MTBE - common solvent

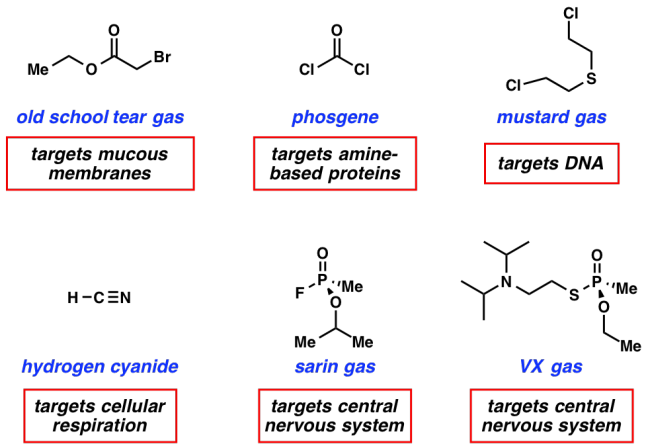
10. From LearnBacon.com: Adrenaline is produced in a substitution reaction. Identify the alpha carbon, leaving group, and nucleophile.



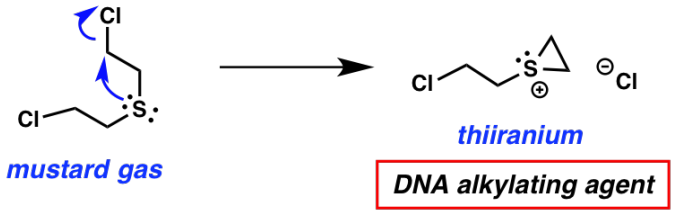
11. Methionine is the most common eukaryote start codon in process of translation of mRNA to protein. Identify the alpha carbon, leaving group, and nucleophile.



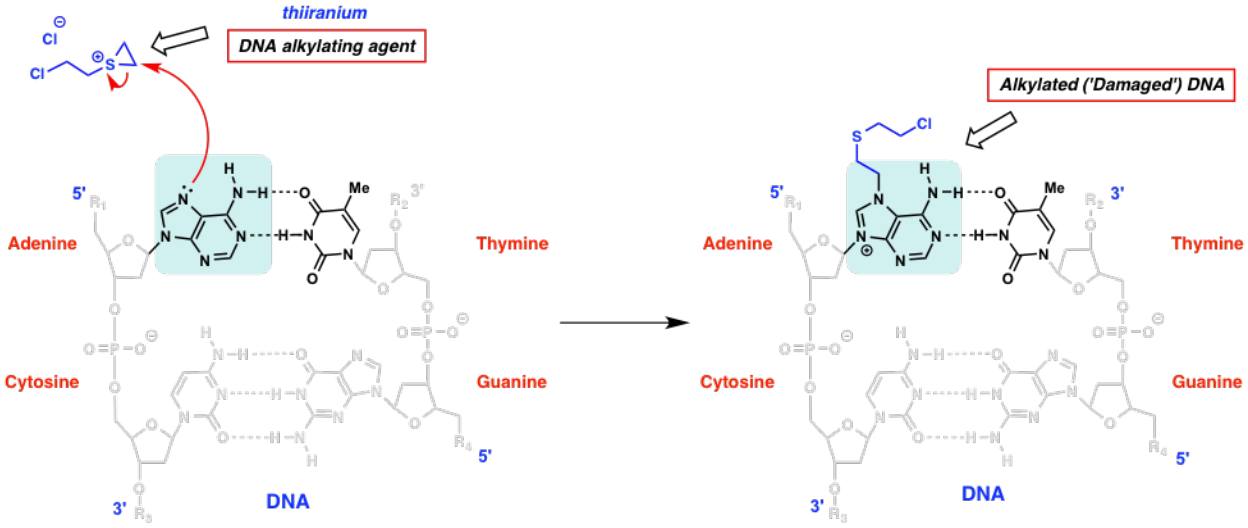
12. From LearnBacon.com: Chemical warfare and substitution reactions



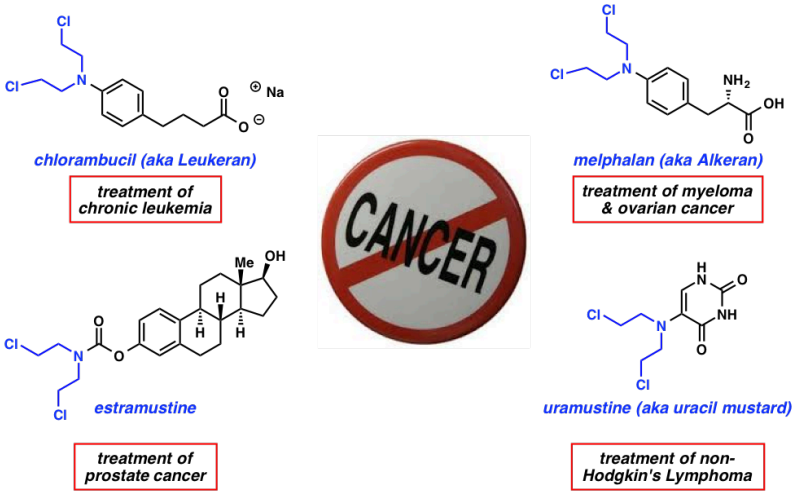
The reaction below is a S_N2 reaction. Identify the alpha carbon, leaving group, and nucleophile.



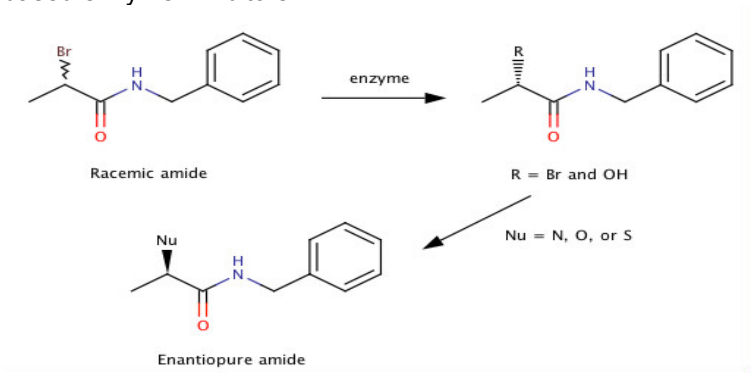
Once thiiranium forms, it alkylates DNA. Identify the alpha carbon, leaving group, and nucleophile.



Nitrogen mustard (analog of sulfur mustard) used as cancer treatment.
Nitrogen mustard derivatives, e.g., chlorambucil, melphalan, estramustine, uramustine, are anti-cancer drugs, which reacts with DNA leading to death of cancer cells but with undesirable side effects.



13. C&EN, 10/10/11 "*Chemoenzymatic Path Yields Chiral Amides*"
α-Substituted amides are important building blocks in medicinal chemistry for the synthesis of antibiotics and peptide-based enzyme inhibitors.



a. What type of reaction is the 2nd step?
b. What is the mechanism type?