

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° , 2° , 3° .

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 substitution reaction using a S_N1 mechanism. See stereochemistry.

Describe a substitution reaction using a S_N2 mechanism. See stereochemistry.

0. We looked at 1° , 2° , 3° carbons when we looked at alkanes. Alkyl halides and alcohols are classified as 1° , 2° , 3° , too.

a. Ethanol is a 1° alcohol. Why?

b. Rubbing alcohol is 2-propanol. Is rubbing alcohol a 1° , 2° , 3° alcohol?

c. You looked at 1-bromobutane, 2-chlorobutane, 1-chloro-2-butene in Lab 4. Classify each alkyl halide as 1° , 2° , 3° .

Answers:

a. See the number of carbons bonded to the carbon bonded to the alcohol (OH) group.

Ethanol ($\text{CH}_3\text{CH}_2\text{OH}$) has 1 C bonded to the C bonded to the OH.

b. Rubbing alcohol (2-propanol) is a 2° alcohol.

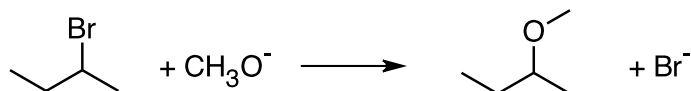
c. See the number of carbons bonded to the carbon bonded to the halide (X = F, Cl, Br, I) group.

1-bromobutane is a 1° alkyl halide.

2-chlorobutane is a 2° alkyl halide.

1-chloro-2-butene is a 1° 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?

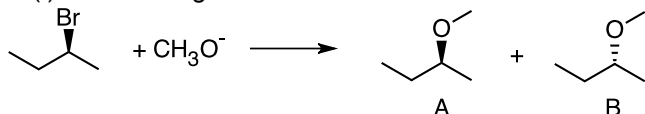
b. CH_3O^- is a nucleophile. Is this nucleophile strong or weak?

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.

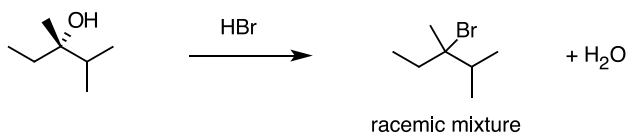
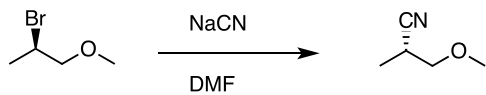
d. (i) Is the configuration of 2-bromobutane shown below R or S?



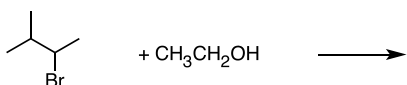
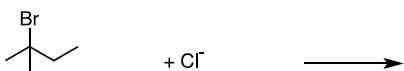
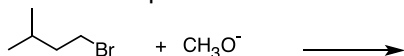
(ii) If the product distribution is 50% A and 50% B, the mechanism is _____.

(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.



Answers:

a. Br is a good leaving group.

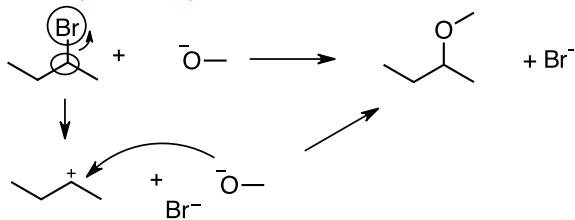
b. CH_3O^- is a strong nucleophile. See pK_a table – it is a strong base.

c. This reaction can occur by a $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism.

(i) Use curved arrows to show how reactants form products in a $\text{S}_{\text{N}}1$ mechanism.

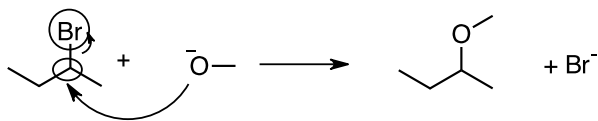
1st step: ionization of a leaving group to form carbocation.

2nd step: nucleophilic attack on electron deficient species.

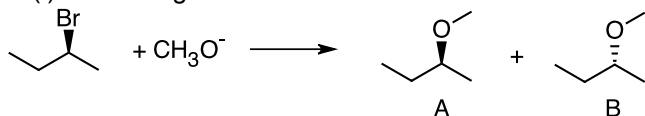


(ii) Use curved arrows to show how reactants form products in a $\text{S}_{\text{N}}2$ mechanism.

1st step: nucleophilic attack on carbon bonded to leaving group.



d. (i) The configuration of 2-bromobutane is **S**.



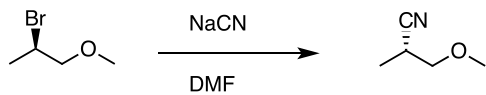
(ii) If the product distribution is 50% A and 50% B, the mechanism is $\text{S}_{\text{N}}1$.

Carbocation intermediate (from c(i)) has a trigonal planar shape with sp^2 hybridization. The (+) charge is an empty p orbital that is perpendicular to the plane of the atoms. The nucleophile (CH_3O^-) reacts with the carbocation on either side of the plane.

(iii) If the product distribution is 0% A and 100% B, the mechanism is $\text{S}_{\text{N}}2$.

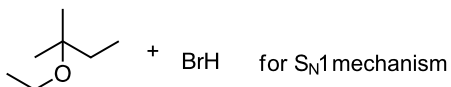
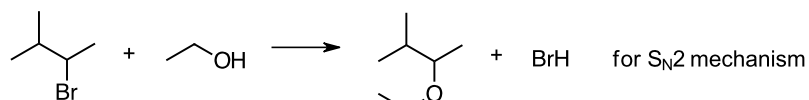
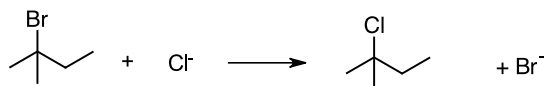
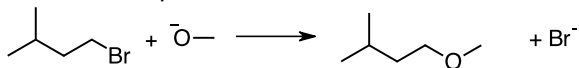
The nucleophile (CH_3O^-) reacts on the opposite side of the leaving group. The configuration of the product is the "inverse" of the reactant. (S)-2-bromobutane forms (R)-2-methoxybutane.

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



1st reaction shows inversion of configuration (R in reactant to S in product) so the mechanism is S_N2.
 2nd reaction shows a racemic mixture of products (50% R, 50% S) so the mechanism is S_N1.

f. Predict the product of each reaction.

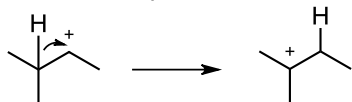


For S_N1 mechanism, a 2° carbocation intermediate forms. The 2° carbocation rearranges to a more stable 3° carbocation via a hydride shift.

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:

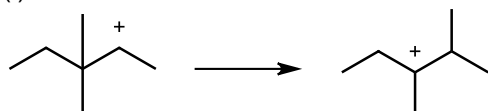
(i) what is the nucleophile in the curved arrow? What is the electrophile?



(ii) What type of carbocation forms?

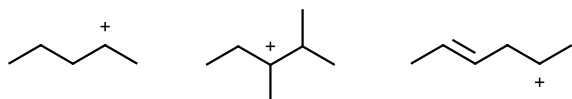
b. Alkyl shift:

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

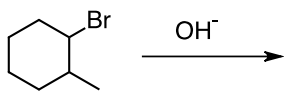


(ii) What type of carbocation forms?

c. Determine whether each carbocation can undergo rearrangement.



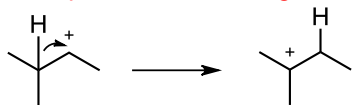
d. This reaction produces two organic substitution products. Draw the structures of each organic substitution product. (Hint: see Question 2a.)



Answers:

a. Hydride shift:

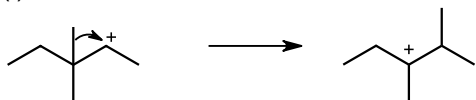
(i) The nucleophile is the C-H sigma bond. The electrophile is the carbocation.



(ii) A 3° carbocation forms.

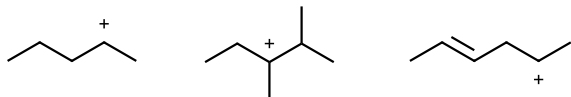
b. Alkyl shift:

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



(ii) A 3° carbocation forms.

c. Determine whether each carbocation can undergo rearrangement.



No

No

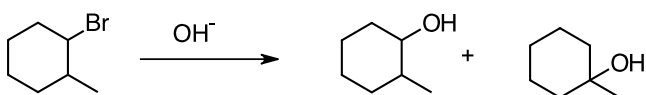
Yes

1st carbocation: 2° carbocation could form another 2° carbocation but no increase in stability (not thermodynamically favored) to no rearrangement.

Middle carbocation: carbocation is already a 3° carbocation. Alkyl shift could occur but product is another 3° carbocation.

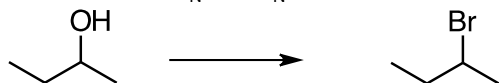
3rd carbocation: 2° carbocation forms a 2° allylic carbocation via a hydride shift. 2° allylic carbocation is more stable than a 2° carbocation.

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



2nd product forms from 3° carbocation intermediate that formed in a hydride shift of 2° carbocation in S_N1 mechanism.

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?



Answers:

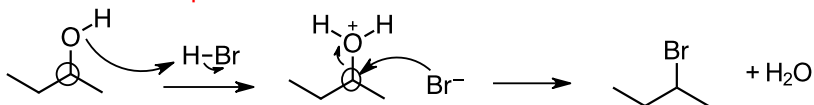
-OH is a poor leaving group because it is a strong base. So ROH will not react with Br⁻ in a substitution reaction.

HBr reacts with ROH to form ROH₂⁺; H₂O is a better leaving group because it is a weak base.

The alpha carbon is circled.

OH is the (poor) leaving group in ROH. H₂O is the (good) leaving group in ROH₂⁺.

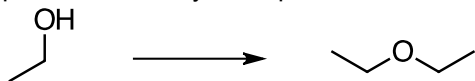
Br⁻ is the nucleophile.



We need to know the stereochemistry of the reactant and products to determine whether the mechanism is S_N1 or S_N2. Inversion of configuration for S_N2, e.g., R configuration for reactant → S configuration for product.

Racemic mixture for S_N1.

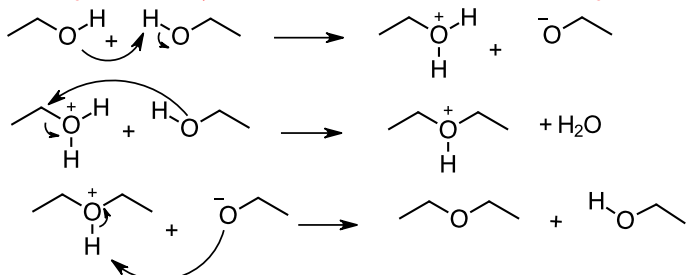
4. Would you use C_2H_5OH or $C_2H_5O^-$ to make this reaction occur? Use curved arrows to show how reactants form products. Identify the alpha carbon, leaving group, and nucleophile. Will the mechanism be S_N1 or S_N2 ?



Answers:

Use C_2H_5OH .

If $C_2H_5O^-$ is used, it reacts with the acidic H in C_2H_5OH to form $C_2H_5O^-$. Still need a good leaving group.



The alpha C is the C bonded to O.

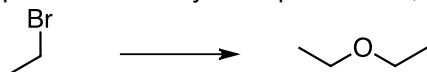
The leaving group is OH (poor LG) in C_2H_5OH and H_2O (good LG) in $C_2H_5OH_2^+$.

C_2H_5OH is the nucleophile.

The 1st step is an acid-base reaction. The equilibrium reaction favors the reactants. Not much $C_2H_5OH_2^+$ forms but this compound is needed because H_2O is a good leaving group.

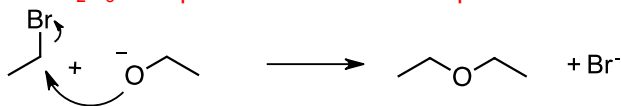
The mechanism is S_N2 because this reaction involves a primary (1°) alcohol.

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 ?



Answers:

Use $C_2H_5O^-$. Alpha C is a weak electrophile so use the stronger nucleophile.



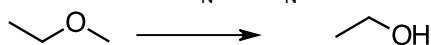
The alpha C is the C bonded to Br.

The leaving group is Br (good LG).

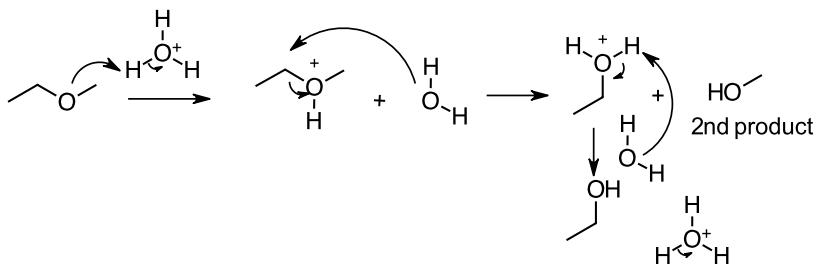
$C_2H_5O^-$ is the nucleophile.

The mechanism is S_N2 because this reaction involves a primary (1°) alkyl halide.

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 ?



Answers:



The alpha C is the C bonded to O – there are two alpha carbons.

The leaving group is OCH_3 (poor LG) in $C_2H_5OCH_3$ and $HOCH_3$ (good LG) in $C_2H_5(O^+H)CH_3$.

H_2O is the nucleophile.

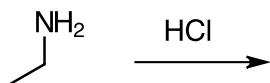
If H_2O reacts at the other alpha C, the leaving group is $HOCH_2CH_3$.

The mechanism is S_N2 because this reaction involves a primary (1°) alkyl halide.

This 1st and 3rd steps are acid-base reactions.

7. Ethyl amine sort of stinks. You can get rid of this smell with acid.

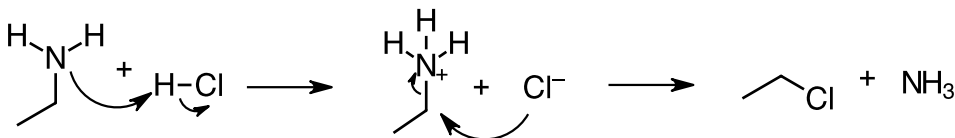
a. Use curved arrows to show how reactants form products. Identify the alpha carbon, leaving group, and nucleophile. Will the mechanism be S_N1 or S_N2?



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

Answers:

a.



The alpha C is the C bonded to N.

The leaving group is NH₂⁻ (poor LG) in C₂H₅NH₂ and NH₃ (good LG) in C₂H₅NH₃⁺.

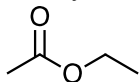
Cl⁻ is the nucleophile.

The mechanism is S_N2 because this reaction involves a primary (1°) alkyl halide.

b. Reaction is slower with vinegar because vinegar is a weaker acid than HCl.

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.

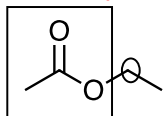


b. Is the leaving group good or poor? Give reasons.

c. Br⁻ reacts with ethyl acetate. Predict (draw the structure) the substitution product.

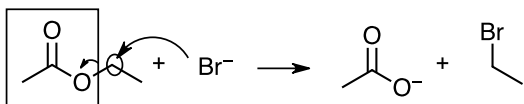
Answers:

a. The alpha C is circled and the leaving group (acetate ion, CH₃COO⁻) is boxed.

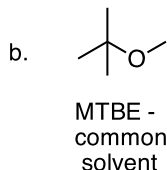
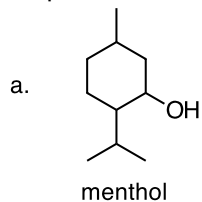


b. CH₃COO⁻ is a weak base to the leaving group is good.

c.

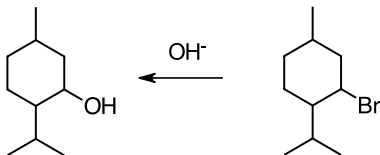


9. Substitution reactions are used to convert one functional group to another. Identify the reactants to make the following compounds:

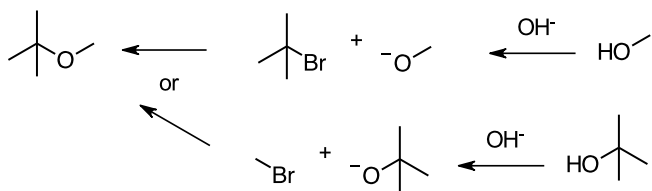


Answers:

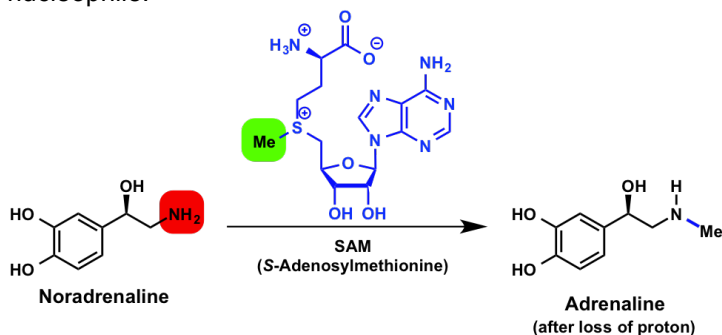
a.



b. We will find out in the next Objective why the 2nd reaction gives a higher yield of product.



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



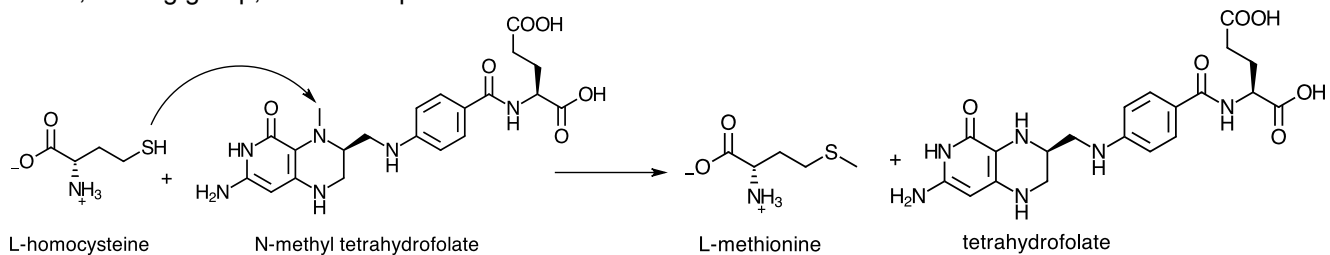
Answers:

Alpha C is the C bonded to S in SAM.

Leaving group is SAM without the Me (methyl) group.

Nucleophile is the lone pair on N in noradrenaline.

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.



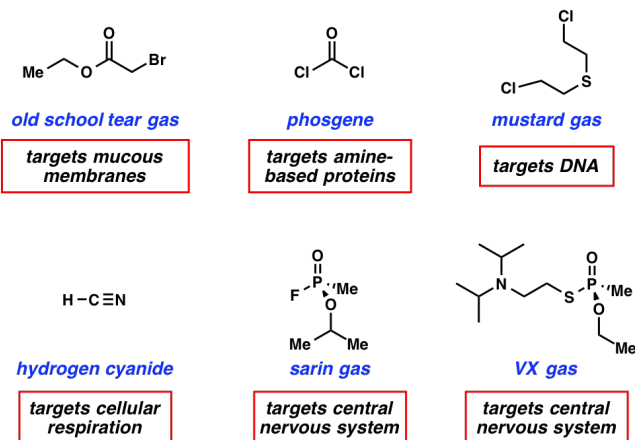
Answers:

Alpha C is the C (see arrow) bonded to N in N-methyl tetrahydrofolate.

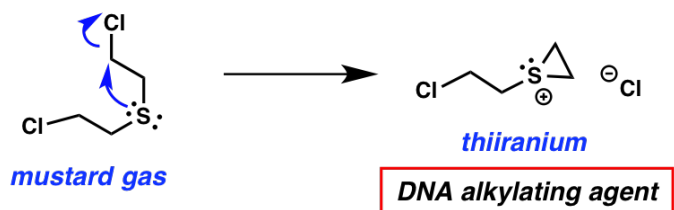
Leaving group is N-methyl tetrahydrofolate without the methyl group.

Nucleophile is the lone pair on S in L-homocysteine.

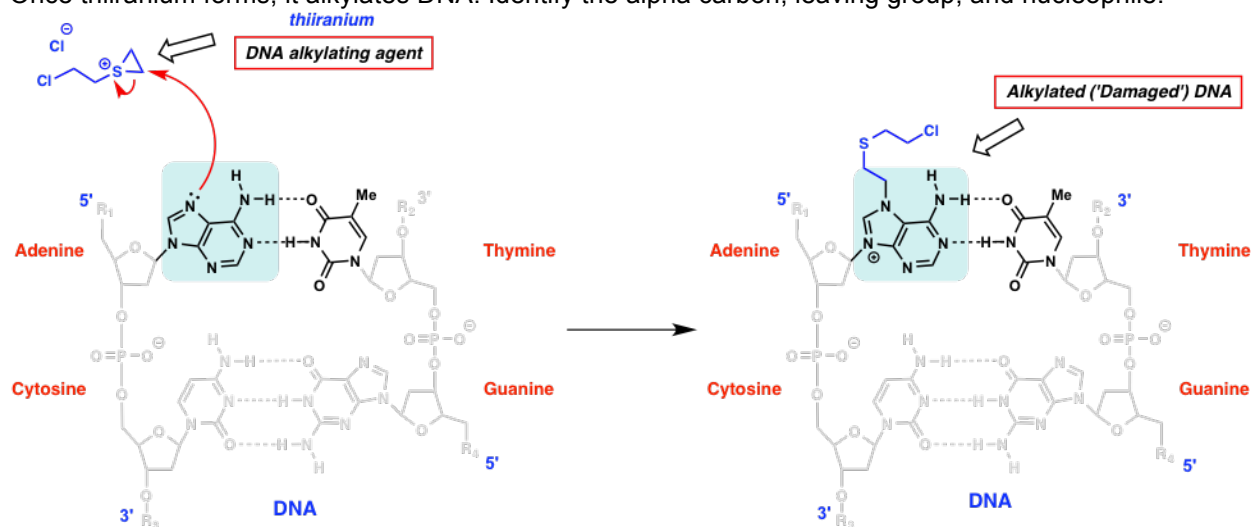
12. From LearnBacon.com: Chemical warfare and substitution reactions



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

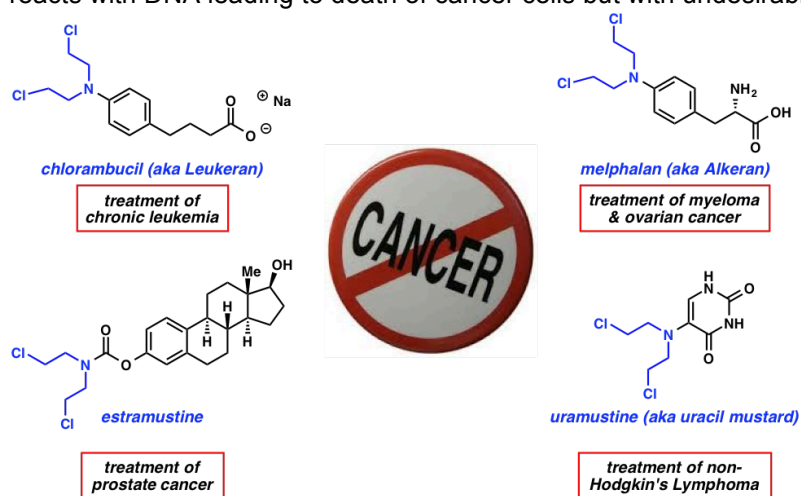


Once thiiranium forms, it alkylates DNA. Identify the alpha carbon, leaving group, and nucleophile.



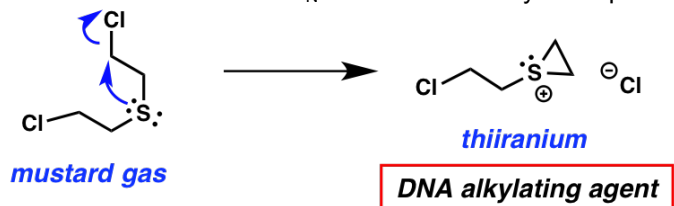
Nitrogen mustard (analog of sulfur mustard) used as cancer treatment.

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.



Answers:

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

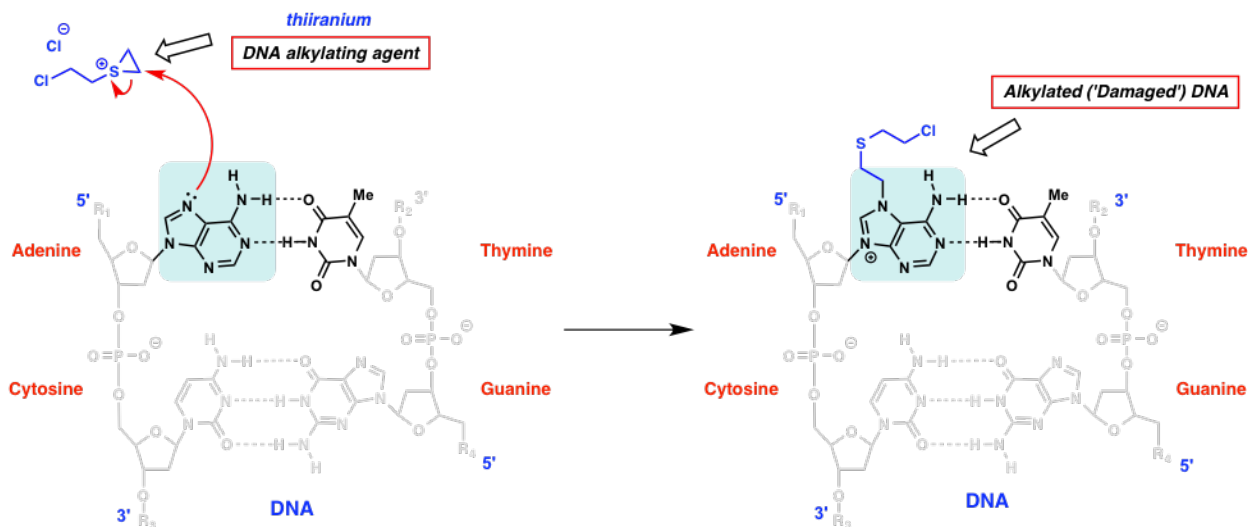


Alpha C is the C (see arrow) bonded to Cl in mustard gas.

Leaving group is Cl.

Nucleophile is the lone pair on S in mustard gas.

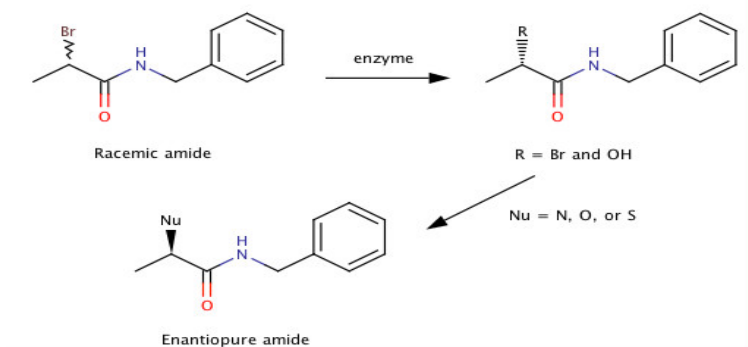
Once thiiranium forms, it alkylates DNA. Identify the alpha carbon, leaving group, and nucleophile.



Alpha C is the C (see arrow) bonded to S in thiiranium.
 Leaving group is S and the rest of thiiranium.
 Nucleophile is the lone pair on N in adenine base in DNA.

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.



- What type of reaction is the 2nd step?
- What is the mechanism type?

Answers:

- Substitution – Nu substitutes for R. Note R = Br or OH in this reaction. Usually R indicates an alkyl group.
- S_N2 mechanism –dash in reactant and wedge in product indicates inversion of configuration.