Organic Chemistry
Mechanistic Patterns
(Ogilvie)
Chapter 11

CHEMISTRY 2600

Topic #4: Nucleophilic Substitution Reactions (S_N1 and S_N2)

Spring 2021

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Nucleophilic Substitution Reactions (S_N1/S_N2)

- Nucleophilic substitution reactions are reactions in which a leaving group attached to a **tetrahedral** carbon atom is displaced by a nucleophile. Consider the following reaction:

$$I^- + CH_3Br \rightarrow CH_3I + Br^-$$

- We can imagine three possible mechanisms for this reaction:
  - C-I bond is formed first then C-Br bond is broken:
  - C-Br bond is broken first then C-I bond is formed:
  - C-I bond is formed at the same time as C-Br bond is broken:

- One of these mechanisms can quickly be ruled out as impossible. Which one? Why?

Nucleophilic Substitution Reactions (S_N1/S_N2)

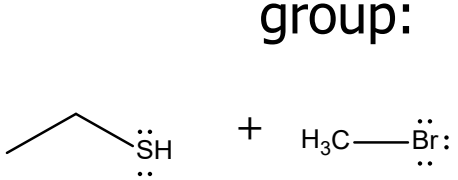
- The remaining two mechanisms are reasonable, and there are nucleophilic substitutions which proceed according to each.
  - Substitution reactions in which the leaving group leaves before the nucleophile attacks are referred to as S_N1 reactions.
  - Substitution reactions in which the leaving group leaves at the same time as the nucleophile attacks are referred to as S_N2 reactions.
- S = substitution. N = nucleophilic.
- The number refers to the number of molecules reacting in the rate-determining step. In substitution reactions, that's the step in which the leaving group leaves.

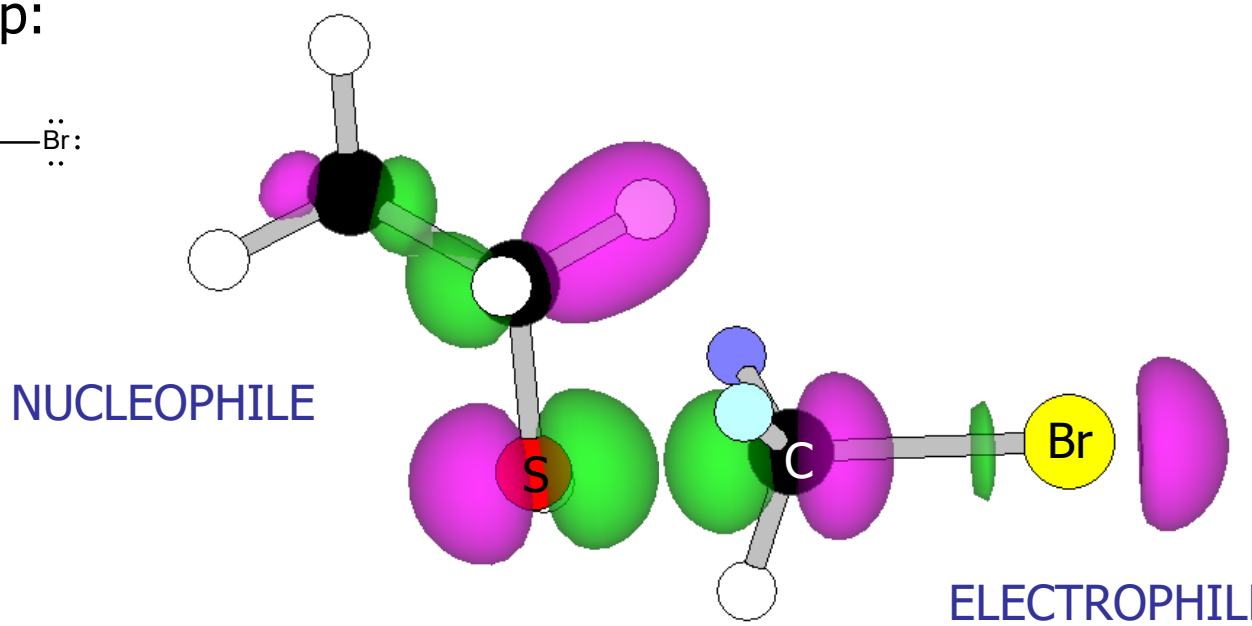
Nucleophilic Substitution Reactions (S_N1/S_N2)

- For most reactions, one mechanism will be preferred over the other. This particular reaction proceeds according to an S_N2 mechanism:

S_N2 Reactions

- S_N2 reactions are quite sensitive to steric effects. This is because they proceed via **backside attack** – which means that the nucleophile attacks the electrophile 180° from the leaving group:





- If one or more large groups were attached to the electrophilic C, it would be very difficult for a nucleophile to access it, and the reaction's activation energy would be very large.

S_N2 Reactions

- S_N2 reactions are therefore favoured by substrates that are not sterically hindered. e.g. primary (1°) substrates.

- The table below shows the relative rates of reaction for a variety of different alkyl bromides in S_N2 reactions.

Substrate	Relative Rate of S_N2 Reaction
CH_3Br	100
CH_3CH_2Br	1.31
$CH_3CH_2CH_2Br$	0.81
$(CH_3)_2CHBr$	0.015
$(CH_3)_3CBr$	0.004

S_N2 Reactions

- Here is another table showing relative rates of reaction for a variety of different alkyl bromides in S_N2 reactions.

Substrate	Relative Rate of S_N2 Reaction
CH_3Br	100
CH_3CH_2Br	1.31
$CH_3CH_2CH_2Br$	0.81
$CH_3CH_2CH_2CH_2Br$	0.52
$(CH_3)_2CHCH_2Br$	0.052
$(CH_3)_3CCH_2Br$	0.00001

Can you rationalize this data? Your model kit may be helpful…

S_N2 Reactions and Kinetics

- S_N2 reactions are referred to as **second order** reactions. This is because they involve two molecules colliding in the **rate determining step**.
- The rate of a reaction is generally measured as the change in concentration of one of the reactants over a given unit of time:

$$\text{average rate} = -\frac{\Delta[\text{reactant}]}{\Delta t}$$

- Or it can be reported in terms of product concentration:

$$\text{average rate} = \frac{\Delta[\text{product}]}{\Delta t}$$

- So, for our reaction between CH_3Br and I^-, we would report rate as either the consumption of CH_3Br or as the production of CH_3I. These are, of course, directly proportional!

S_N2 Reactions and Kinetics

- In an S_N2 reaction, the rate of reaction is directly proportional to the concentration of each of the two reactants.
- We can write a **rate law** for this reaction. A rate law is a mathematical equation relating the concentrations of each reactant to the overall rate of reaction. It involves a **rate constant** (k) which must be measured experimentally.
- The rate law for the reaction between CH_3Br and CH_3CH_2SH is:

- We already defined S_N2 reactions as **second order** based on the number of molecules colliding in the rate determining step. Another way to find the order of a reaction is to add the exponents on all concentrations in the rate equation. In this case, we can say that the reaction is first order in CH_3Br and first order in CH_3CH_2SH. Overall, it is **second order**.

S_N2 Reactions and Kinetics

- Rate laws and rate constants are determined experimentally. Known quantities of each reagent are mixed, and the initial rate of reaction is measured. By comparing reaction rates under different reaction conditions, reaction order and rate constant can be calculated.

- A mechanism is a hypothesis that must be consistent with all observed rate data!

- We can use rate data to test whether or not a given reaction might proceed via an S_N2 mechanism.

S_N2 Reactions and Kinetics

- Determine the rate law for this reaction. Calculate k.
- Might this reaction proceed via an S_N2 mechanism?

$[CH_3CH_2Br]$ (M)	**$[HO^-]$ (M)**	**Initial Rate (M/s)**
0.1	0.1	0.15
0.2	0.1	0.31
0.2	0.2	0.63

S_N2 Reactions and Kinetics

- Determine the rate law for this reaction. Calculate k.
- Might this reaction proceed via an S_N2 mechanism?

$[(CH_3)_3CCl]$ (M)	$[H_2O]$ (M)	Initial Rate (M/s)
0.1	0.1	0.0068
0.2	0.1	0.014
0.2	0.2	0.014

S_N2 Reactions with Multiple Elementary Steps

- Not all S_N2 reactions proceed in one step, but they all have the same rate determining step, and they are all second order.
- Consider the following two-step S_N2 reaction:

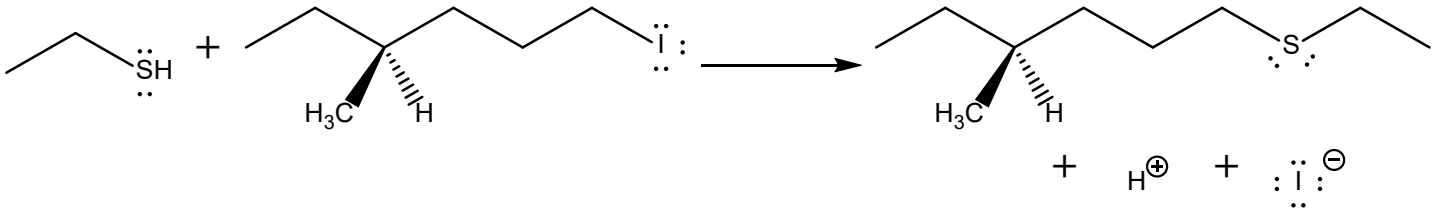
Provide a mechanism for this reaction and rationalize why the rate determining step is still the step in which the leaving group leaves.

S_N2 Reactions with Multiple Elementary Steps

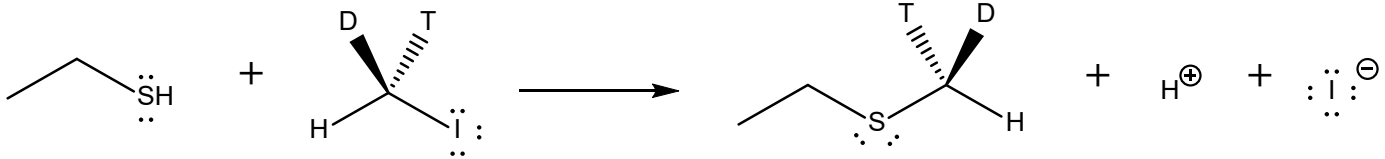
- Sketch a reaction profile diagram for the reaction on the previous page.

S_N2 Reactions and Stereochemistry

- So far, all the examples we have considered have involved achiral substrates. If we consider a chiral substrate, we discover that we must consider what happens to the stereochemistry in the reaction.
- If a chirality center is not the electrophilic site, then there is no change to its configuration:



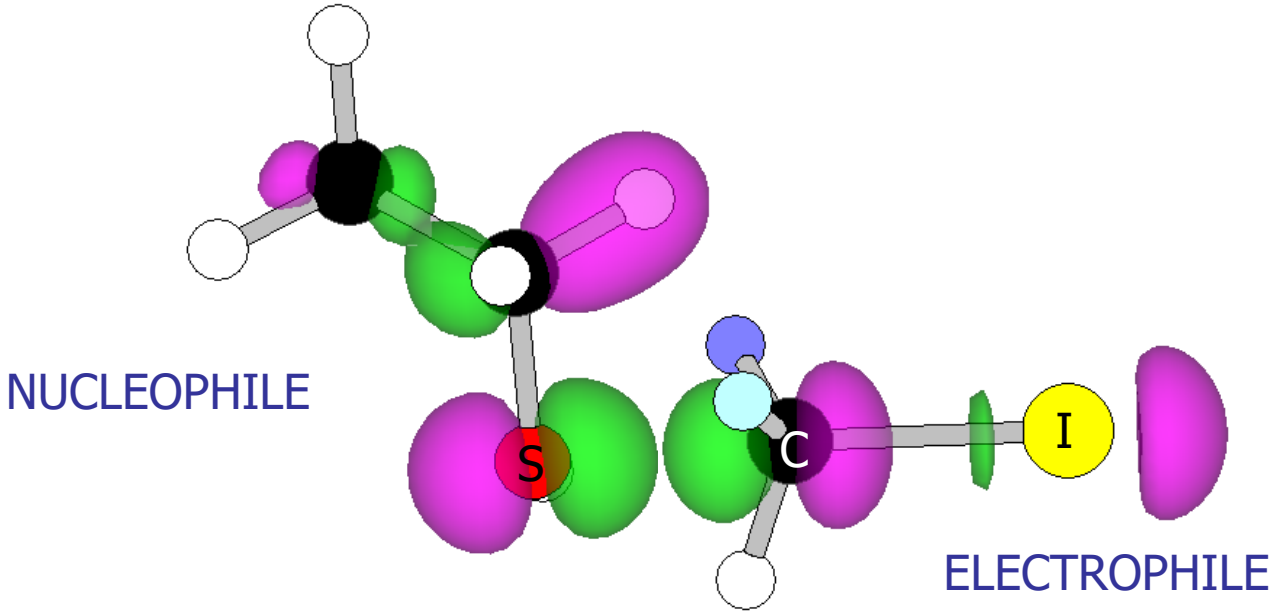
- If, however, the electrophilic site is a chirality center, it will be inverted:



This is because the reaction proceeds with **backside attack**.

S_N2 Reactions and Stereochemistry

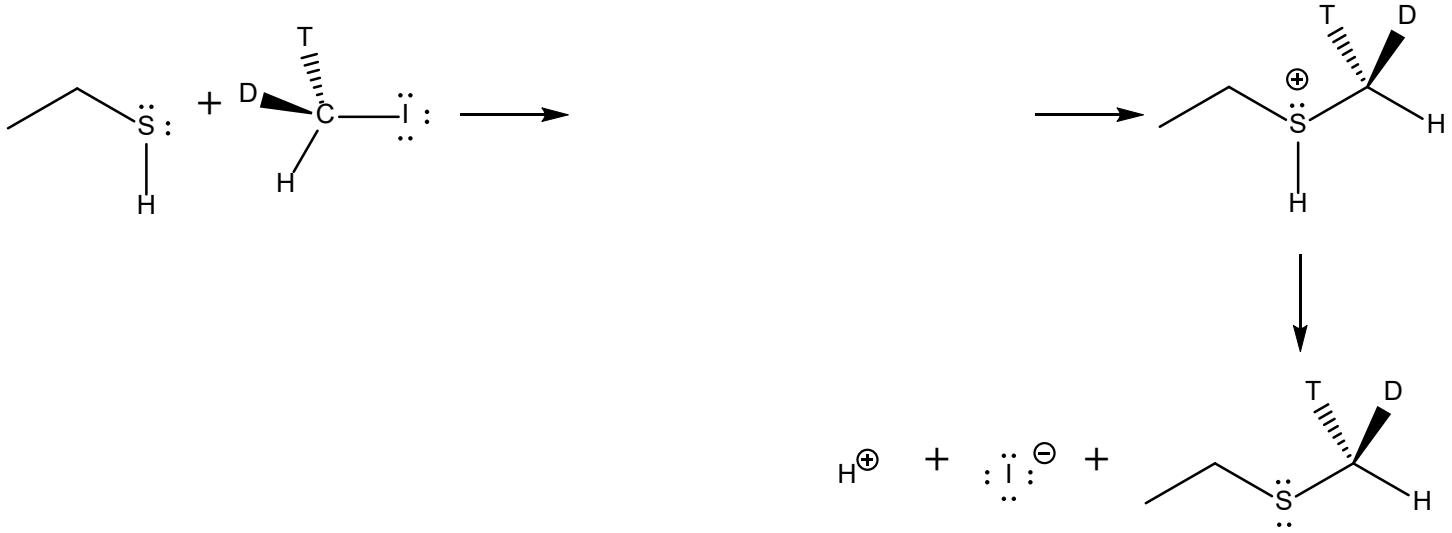
- Look at the HOMO for our nucleophile (CH_3CH_2SH) and the LUMO for our electrophile (CHDTI):



- The only way to get good overlap between these two MOs is for the nucleophilic site to attack the electrophilic site exactly opposite the leaving group. This results in inversion of the chirality center. This inversion always occurs in an S_N2 reaction but can only be observed when the electrophilic site is a chirality center.

S_N2 Reactions and Stereochemistry

- If we draw the reaction equation including the transition state, we can see how this inversion happens:



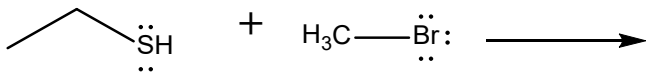
- If we imagine replacing the various hydrogen isotopes with larger groups, we can see that the nucleophile would have a difficult time approaching the electrophilic site and that the transition state would be relatively unstable due to steric effects. This confirms the observation that S_N2 reactions occur fastest at methyl electrophiles, reasonably fast at 1° electrophiles, very slowly at 2° electrophiles and not at all at 3° electrophiles.

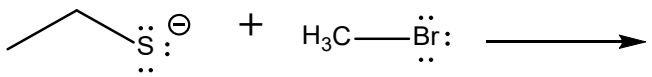
S_N2 Reactions and Reactivity

- Other factors to consider include the strength of the nucleophile (nucleophilicity) and leaving group ability.

- For each set of reactions, draw the S_N2 products. Then indicate which reaction should proceed more readily and why.

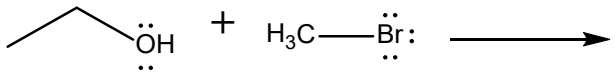
Reaction Set #1:

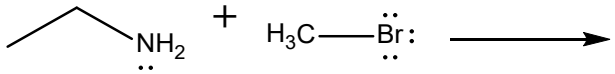




S_N2 Reactions and Reactivity

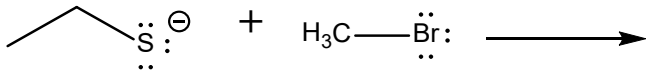
Reaction Set #2:

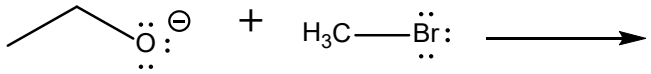




S_N2 Reactions and Reactivity

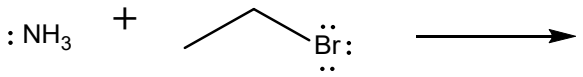
Reaction Set #3:

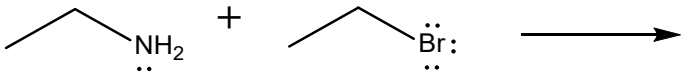


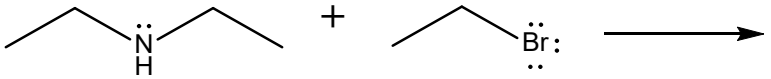


S_N2 Reactions and Reactivity

Reaction Set #4:



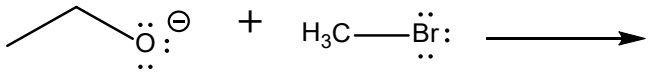


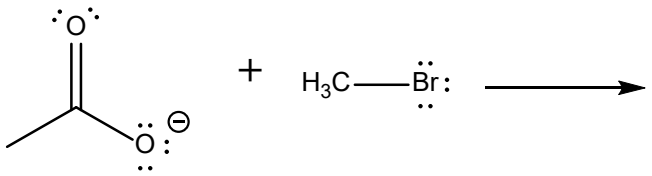


What does this tell you about would happen if you mixed ammonia and bromoethane with the hopes of making ethanamine?

S_N2 Reactions and Reactivity

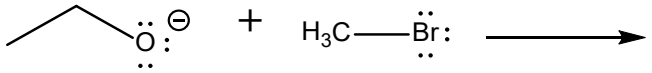
Reaction Set #5:

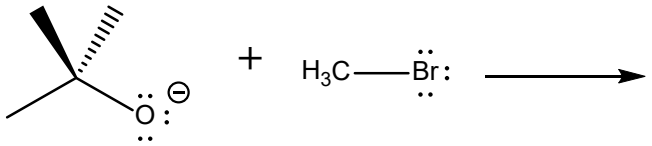




S_N2 Reactions and Reactivity

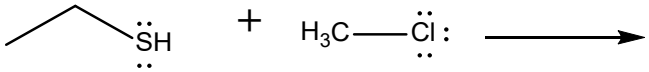
Reaction Set #6:

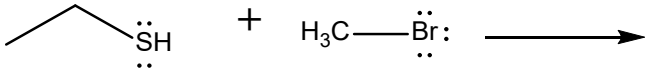


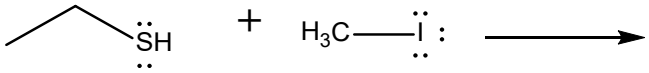


S_N2 Reactions and Reactivity

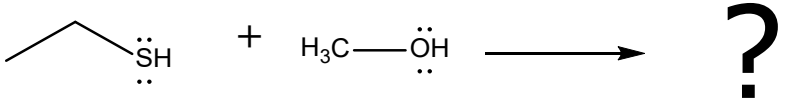
Reaction Set #7:







What about:

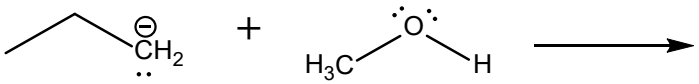


?

The Problem with Alcohols

- Alcohols are among the cheapest and most widely available starting materials for organic syntheses. This is, in part, because they can be prepared from so many different functional groups.

- Unfortunately, HO^- is a strong base and therefore a bad leaving group. One approach to dealing with a bad leaving group is to use a stronger nucleophile. In the case of alcohols, that doesn't tend to work very well. Why not?



- So, if we want to use alcohols as starting materials for substitution reactions, we have to be a little more creative…

The Problem with Alcohols: Solutions

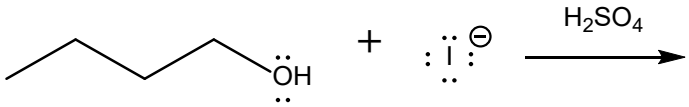
- In order to perform a substitution reaction beginning with an alcohol, we need to convert the hydroxy group into a better leaving group.

- There are many different leaving groups we could choose, most of which are oxygen-based:

- Another option would be to convert the alcohol into the corresponding alkyl halide (RCl, RBr or RI – **NOT** RF!).

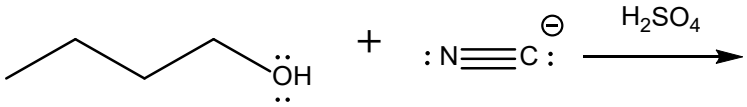
Solution #1: Make R-OH into R-OH_2^+

- Use of a strong acid to protonate the alcohol converts the poor leaving group into a good leaving group:



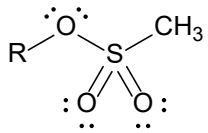
Solution #1: Make R-OH into R-OH_2^+

- This only works if the nucleophile is not basic. What happens if you try this approach with a basic nucleophile?

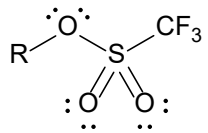


Solution #2: Make R-OH into Sulfonate Ester

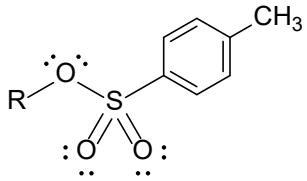
- If we wanted to make the nitrile attempted on the previous page, we'd have to take a different approach. A set of "base-friendly" leaving groups commonly prepared from alcohols are the sulfonate esters (R-O-SO_2R'):
  - If R' = CH_3, the group is a mesylate (R-OMs), short for "methanesulfonate ester":



  - If R' = CF_3 , the group is a triflate (R-OTf), short for "trifluoromethanesulfonate ester":

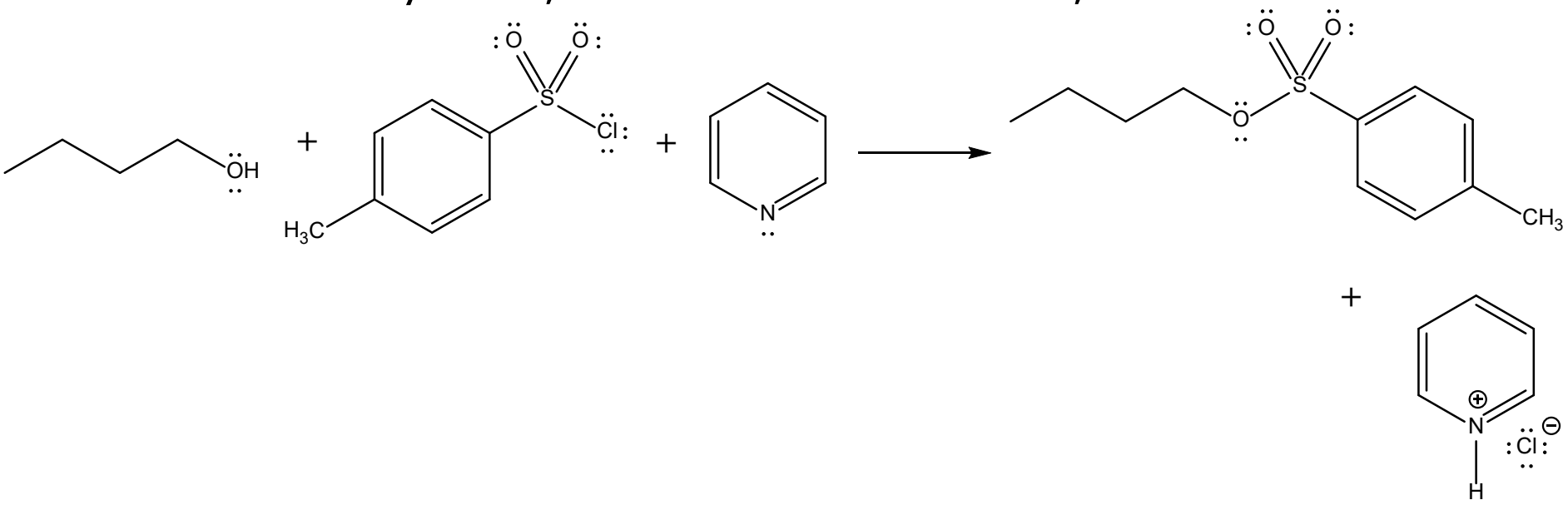


  - If R' = *p*-$C_6H_4CH_3$, the group is a tosylate (R-OTs), short for "1,4-toluenesulfonate ester":



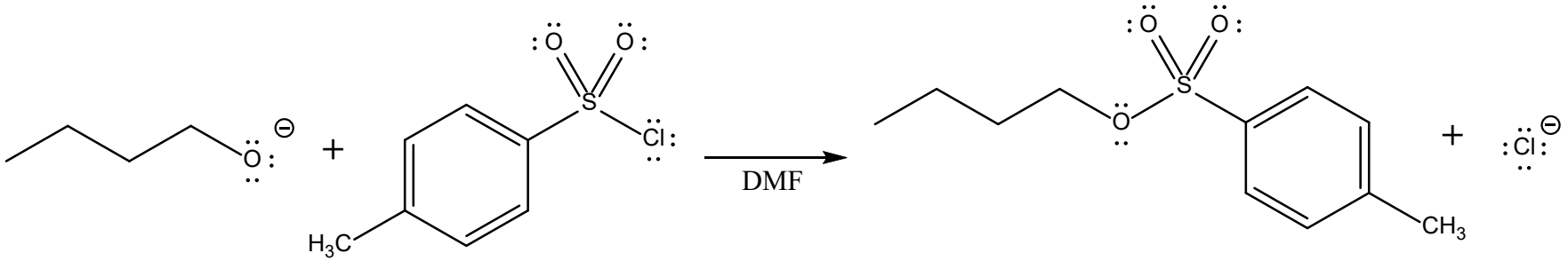
Solution #2: Make R-OH into Sulfonate Ester

- To prepare a sulfonate ester, react your alcohol of choice with the appropriate sulfonyl chloride ($ClSO_2R'$) in the presence of an amine such as pyridine *(shown below)*. The amine acts as both a catalyst and, at the end of the reaction, a base:



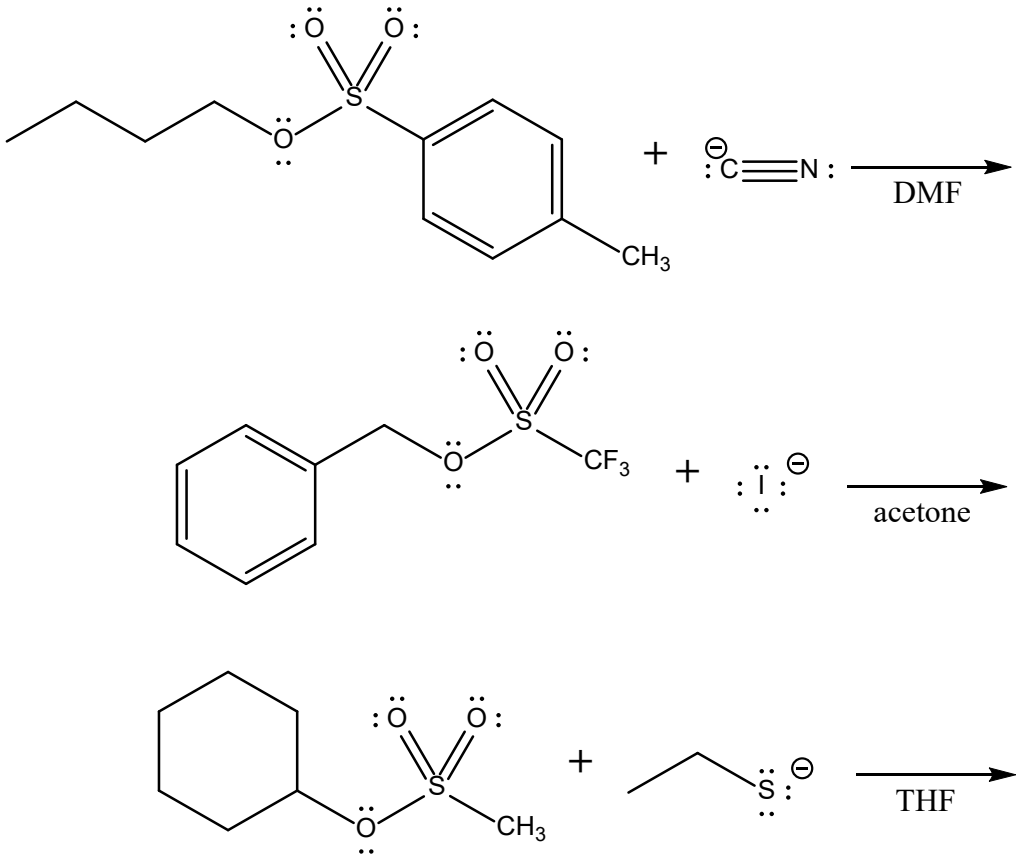
Solution #2: Make R-OH into Sulfonate Ester

- An alternative approach is to react the alcohol with a strong base first then add the appropriate sulfonyl chloride ($ClSO_2R'$):



Solution #2: Make R-OH into Sulfonate Ester

- The resulting sulfonate ester can then be used in an S_N2 reaction:



- Draw the products for each reaction above <u>and</u> identify the alcohol used to make each sulfonate ester.

S_N1 Reactions

- Previously, we considered the following reaction and determined that it would not proceed according to an S_N2 mechanism due to the steric bulk around the electrophilic site:

$$I^- + (CH_3)_3CBr \rightarrow (CH_3)_3CI + Br^-$$

S_N1 Reactions

$$I^- + (CH_3)_3CBr \rightarrow (CH_3)_3CI + Br^-$$

- This reaction still proceeds, but according to an alternative mechanism – the S_N1 mechanism. In an S_N1 reaction, there are always multiple steps.
  - In the rate determining step, the leaving group leaves, generating a carbocation:
  - After that, the nucleophile attacks the electrophilic carbocation:
  - There may be additional "set up" or "tidy up" steps involving protonation of a leaving group or deprotonation of a product.

S_N1 Reactions

- Draw a mechanism for the following S_N1 reaction:

$$H_2O + (CH_3)_3CBr \rightarrow (CH_3)_3COH + H^+ + Br^-$$

S_N1 Reactions and Reactivity

- In order for an S_N1 reaction to proceed, the leaving group must be **very** good. The pK_a of its conjugate acid should be no more than ~1.

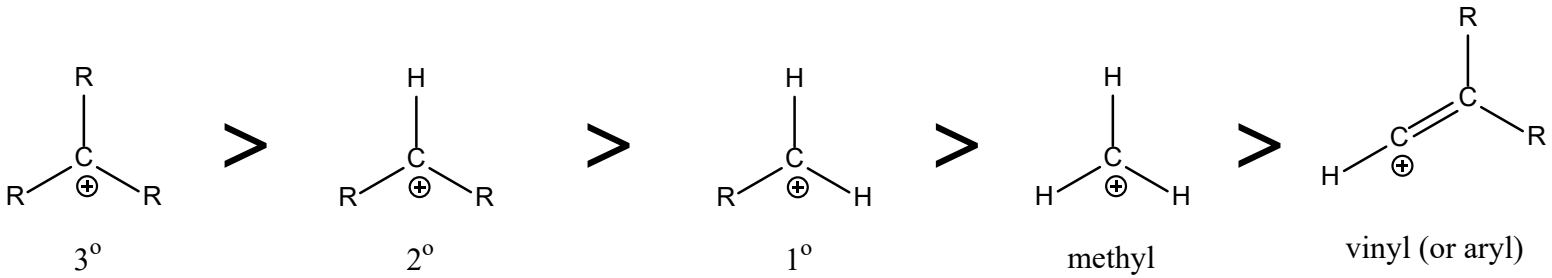
- Compare the first step of a hypothetical S_N1 reaction in which the substrate is 2-bromo-2-methylpropane vs. one in which the substrate is 2-methylpropan-2-ol:

Assume the only other reactant is a generic nucleophile (Nu^-) .

S_N1 Reactions and Reactivity

- In order for an S_N1 to proceed, the carbocation generated when the leaving group leaves must be relatively stable (compared to other carbocations; it can never be as stable as a neutral molecule).

- In CHEM 2500, you learned that the inductive effect and hyperconjugation stabilized carbocations, leading to a general ranking of carbocation stability:



- **JUST AS YOU <u>CANNOT</u> DO AN S_N2 REACTION AT A NON-TETRAHEDRAL CARBON, YOU <u>CANNOT</u> DO AN S_N1 REACTION AT A NON-TETRAHEDRAL CARBON.**

S_N1 Reactions and Reactivity

- S_N1 reactions are therefore favoured by 3° substrates and those which produced resonance-stabilized carbocations (including allylic and benzylic alkyl halides).
  - Draw all resonance structures for the carbocation generated from 3-chloropropene:

  - Draw all resonance structures for the carbocation generated from chloromethoxymethane:

S_N1 Reactions and Reactivity

- Draw all resonance structures for the carbocation generated from benzyl chloride ($C_6H_5CH_2Cl$)

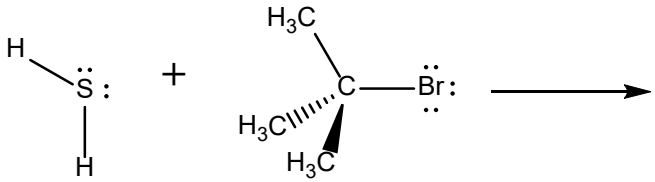
S_N1 Reactions and Reactivity

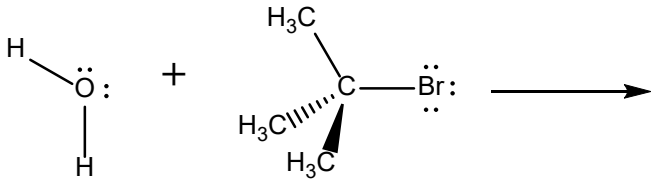
- Note that vinyl and aryl carbocations **cannot** be resonance stabilized because the positive charge is perpendicular to the pi system. As such, it is NOT part of the pi system and cannot be delocalized:

S_N1 Reactions and Reactivity

- For an S_N1 reaction to be favourable, it is necessary to:
  - have a good leaving group, and
  - form a stabilized carbocation

- How does the strength of the nucleophile affect the rate of an S_N1 reaction? Compare the following two S_N1 reactions:





S_N1 Reactions and Kinetics

- In an S_N1 reaction, the rate determining step is the one in which the leaving group leaves. The nucleophile is not involved in this step. As such, the rate of an S_N1 reaction depends only on the concentration of electrophile.

- The rate law for the S_N1 reaction between $(CH_3)_3CBr$ and H_2O is:

- S_N1 reactions are **first order** based on the number of molecules involved in the rate determining step. Looking at this rate law, we can see that the reaction is first order in $(CH_3)_3CBr$ and zero order in H_2O. Overall, it is **first order**.

S_N1 Reactions and Kinetics

- On slide 12, we saw experimental rate data for the substitution reaction between 2-chloro-2-methylpropane and water:

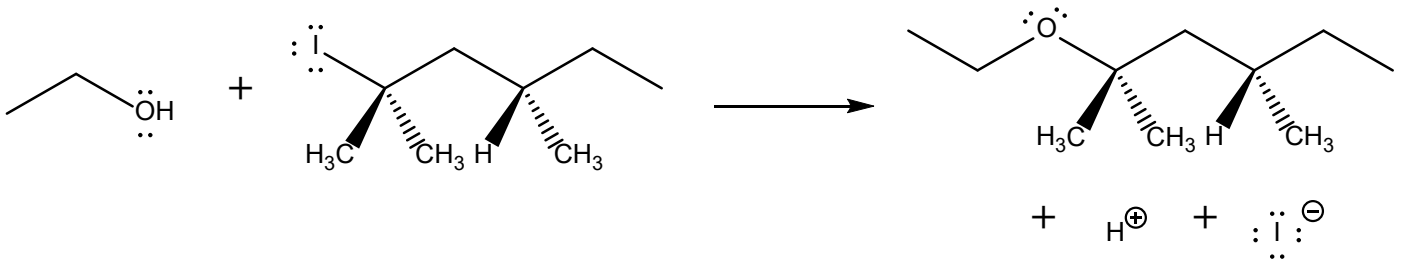
$[(CH_3)_3CCl]$ (M)	$[H_2O]$ (M)	Initial Rate (M/s)
0.1	0.1	0.0068
0.2	0.1	0.014
0.2	0.2	0.014

We determined that the rate law was $rate = 0.07\frac{1}{s}[(CH_3)_3CCl]$ and that this reaction could not proceed via an S_N2 mechanism. Could it proceed via an S_N1 mechanism?

S_N1 Reactions and Stereochemistry

- So far, all the examples we have considered have involved achiral substrates. If we consider a chiral substrate, we discover that we must consider what happens to the stereochemistry in the reaction.

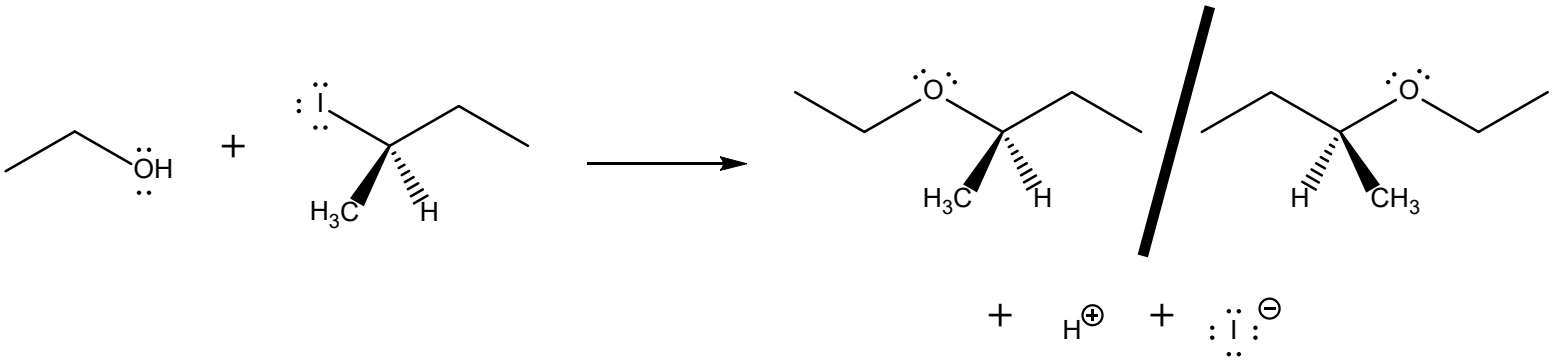
- If a chirality center is not the electrophilic site, then there is no change to its configuration:



This is consistent with what we saw for S_N2 reactions.

S_N1 Reactions and Stereochemistry/Isomers

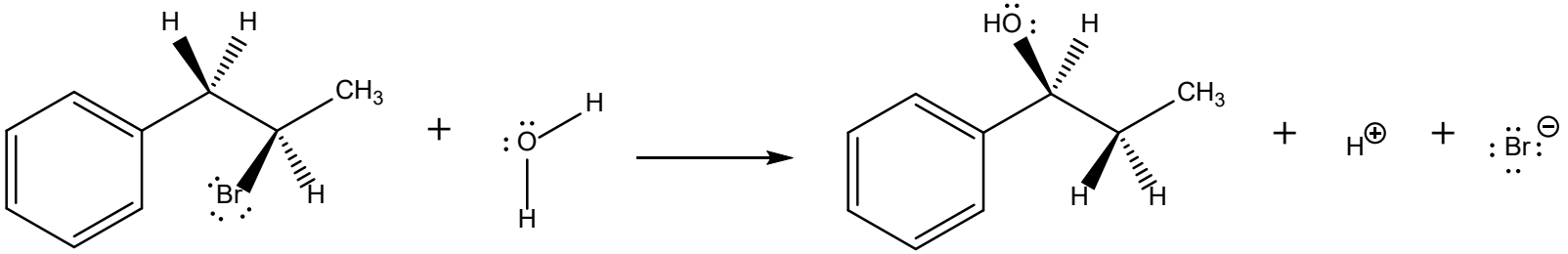
- If, however, the electrophilic site is a chirality center, its configuration will not be retained:



This was not the case for S_N2 reactions. Given the mechanism for an S_N1 reaction, why do you think this occurs?

S_N1 Reactions and Stereochemistry/Isomers

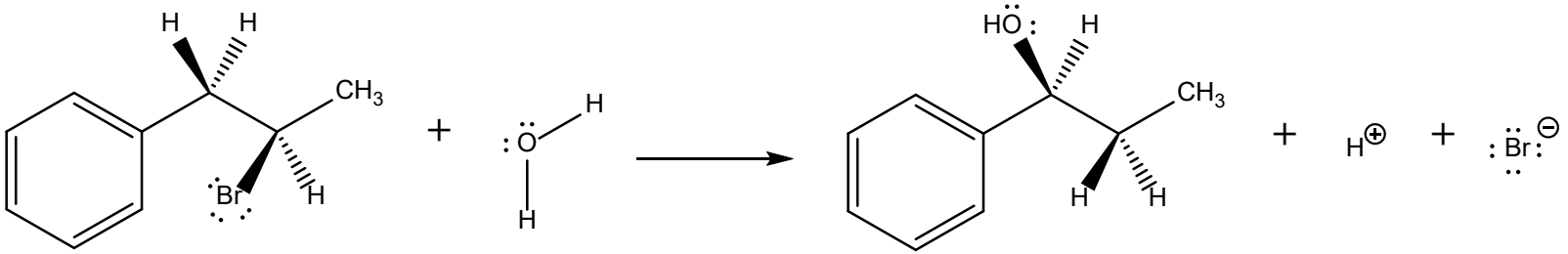
- Another interesting consequence of the S_N1 reaction mechanism is that, occasionally, the product is a constitutional isomer of the one we'd initially expect.



- The mechanism begins as you'd expect; however, once the carbocation is generated, it rearranges to form a more stable carbocation. This is a very fast process and will occur before the nucleophile can attack.

S_N1 Reactions and Stereochemistry/Isomers

- In this example, the initial carbocation is secondary but with no resonance stabilization. A hydride shift gives a carbocation that is benzylic in addition to being secondary:

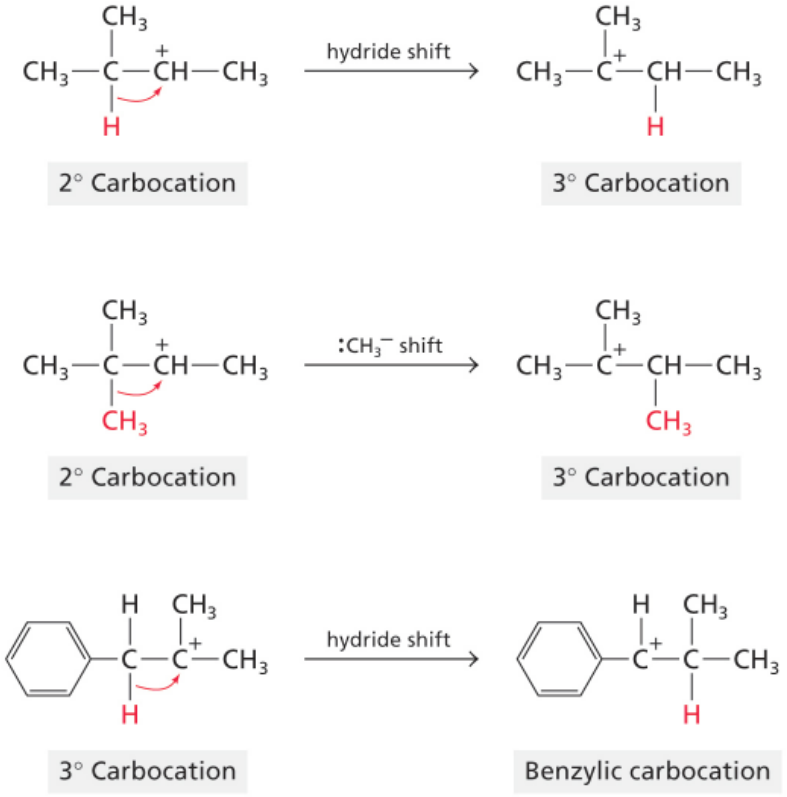


S_N1 Reactions and Stereochemistry/Isomers

- Carbocation rearrangements are not limited to S_N1 reactions. Any time you propose a reaction mechanism involving a carbocation intermediate, look to see if it can be made significantly more stable through a carbocation rearrangement.

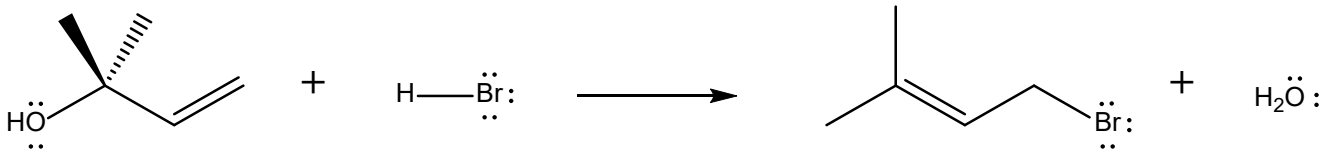
- It is also worth noting that carbocation rearrangements can involve shifting either a hydride ion or a methyl anion.

- Pay close attention to the way the curly arrows are drawn in the figure at the right. We should be able to tell if you're proposing a hydride shift or generation of a pi bond by where the arrow points!



S_N1 Reactions and Stereochemistry/Isomers

- The following S_N1 reaction has been used to make a precursor to *trans*-chrysanthemic acid in a senior organic lab at the U of C.



Propose a mechanism consistent with the product formed.

- Note that this is <u>not</u> a carbocation rearrangement. What is it?

S_N1 vs. S_N2 Reactions: Solvent Effects

- The reaction on the previous page was done using 50% $HBr_{(aq)}$ as the solvent. **S_N1** reactions are usually done in **polar protic** solvents because they help to stabilize the developing charge in the transition state (facilitating formation of the carbocation intermediate):

- Common polar protic solvents include:

S_N1 vs. S_N2 Reactions: Solvent Effects

- **S_N2** reactions are usually done in **polar aprotic** solvents. The solvent must be polar enough to dissolve the nucleophile, but should not be so polar as to render the nucleophile unreactive. (The more stable a compound is, the less reactive it is.)

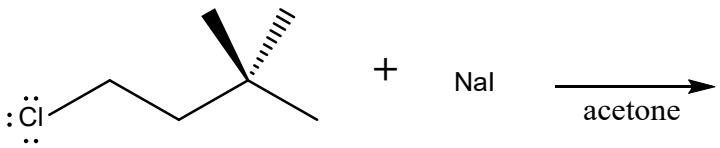
- Common polar aprotic solvents include:

S_N1 vs. S_N2 Reactions: Comparison

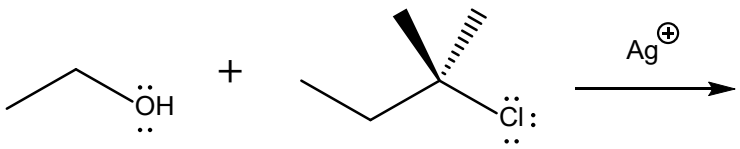
	S_N2	S_N1
Reaction Order	second order reaction	first order reaction
Minimum # Steps	1 or more steps	2 or more steps
Intermediates?	not necessarily	carbocation
Stereochemical Consequences	stereospecific inversion of configuration at electrophilic site	racemization (full or partial) at electrophilic site
Importance of Nucleophile Strength	very important; no reaction for weak nucleophiles like H_2O	unimportant
Importance of Leaving Group	very important; no reaction for weak leaving groups like HO^-	very important; no reaction for weak leaving groups like HO^-
Substrate Structure Dependence	avoid steric hindrance; CH_3 > 1° > 2°(slow) > 3° (no); no reaction for aryl/vinyl	need carbocation stabilization; 3° > 2° (slow) > 1° (no); resonance stabilization helps; no reaction for aryl/vinyl
Solvent	polar aprotic	polar protic
Competing Reactions	E2	E1, E2, rearrangement

S_N1 vs. S_N2 Reactions

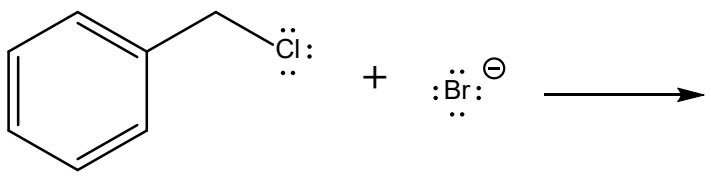
- For each of the reactions on the following pages, suggest whether you'd expect it to proceed via S_N1, S_N2, both or neither then draw the appropriate product(s).



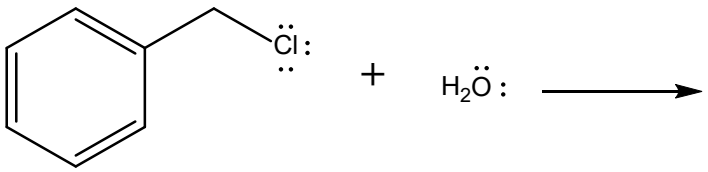
S_N1 vs. S_N2 Reactions



S_N1 vs. S_N2 Reactions

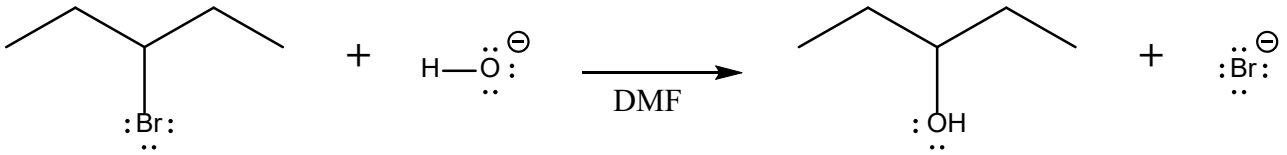


S_N1 vs. S_N2 Reactions

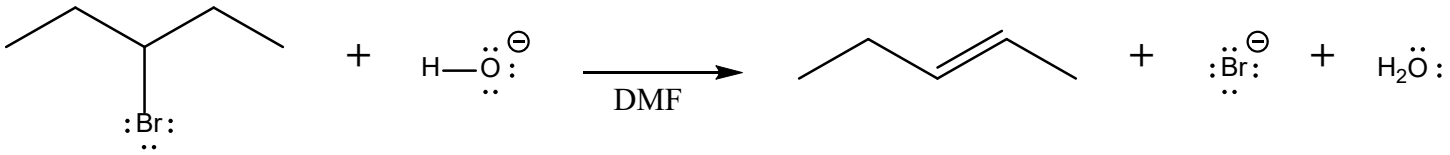


Special Nucleophiles: Alcohols from Acetate

- We might want to make an alcohol by doing an S_N2 reaction between an alkyl halide and a hydroxide ion:

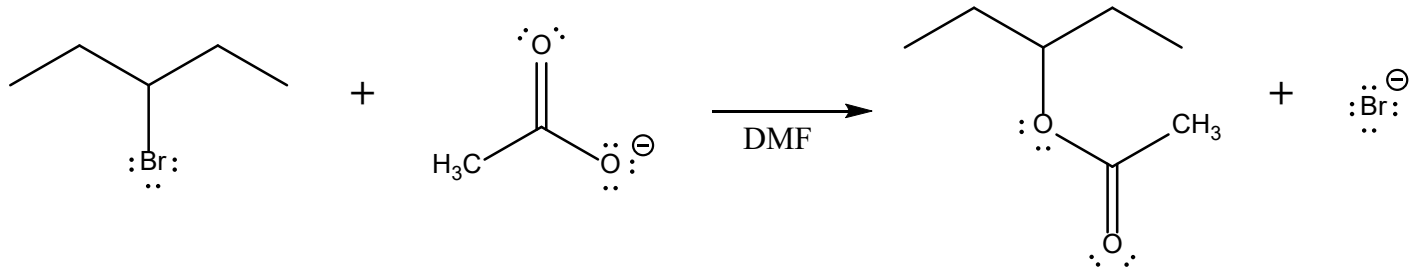


- Unfortunately, hydroxide is a strong base as well as a strong nucleophile. This can lead to side reactions like eliminations (which are the focus of the next chapter):

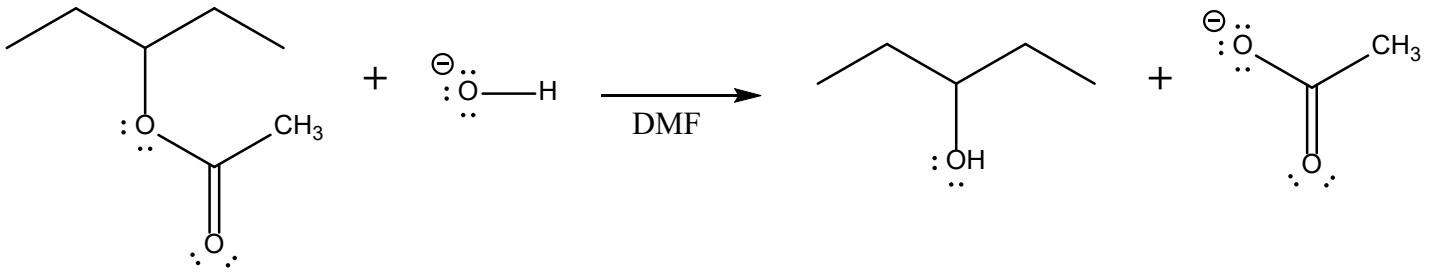


Special Nucleophiles: Alcohols from Acetate

- While it is possible to promote substitution by tinkering with the reaction conditions, it is also possible to use a two-step process to arrive at the same alcohol with fewer risk of side reactions:
  - Step 1: React the alkyl halide with an acetate ion



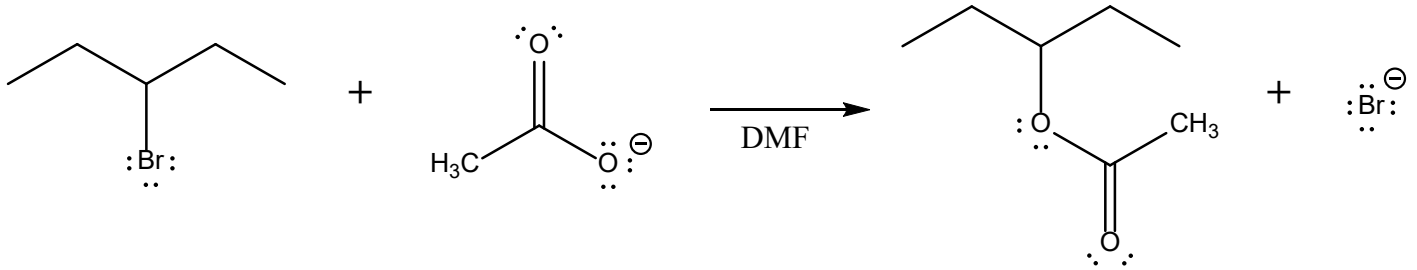
  - Step 2: React the resulting ester with a hydroxide ion



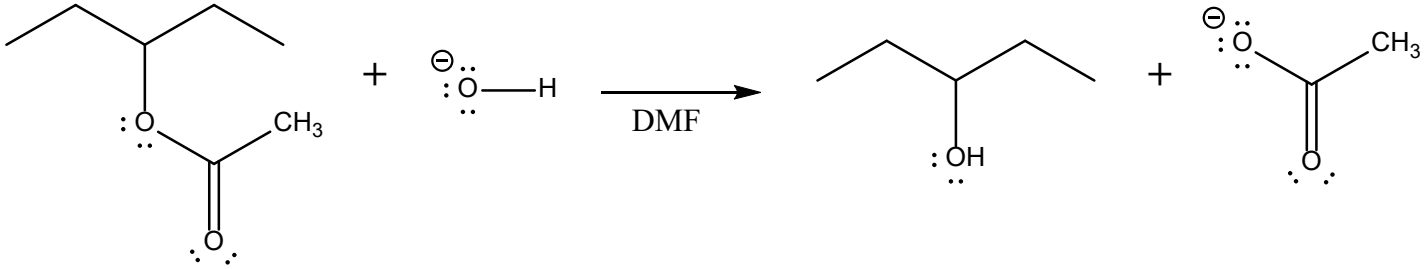
- Why are side reactions of less concern with this approach?

Special Nucleophiles: Alcohols from Acetate

- Propose a mechanism for each step on the previous page:
  - Step 1:



  - Step 2:



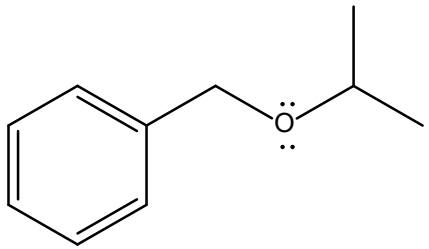
Special Nucleophiles: Ethers from Alkoxides

- Ethers can be prepared by reaction of an alkyl halide with an alkoxide. Again, you should consider the possibility of side reactions since alkoxides and hydroxide are equally strong bases.

- Alkoxides are readily made by deprotonating alcohols. We saw this reaction when we made sulfonate esters from alcohols:

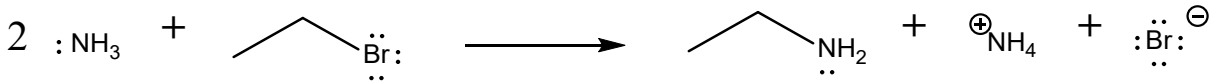
Special Nucleophiles: Ethers from Alkoxides

- When making an ether that is not symmetric, you also have to decide which "half" of the ether came from the alkoxide and which "half" came from the alkyl halide.
- What are the two options for making the following ether from an alkoxide and an alkyl bromide? Which seems better?



Special Nucleophiles: Making Amines

- On page 21 of these notes, we encountered the problem with attempting to prepare a primary amine from ammonia and an alkyl halide:

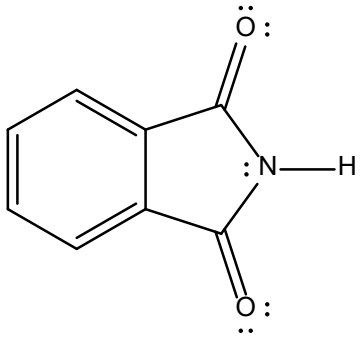


- What was the problem?

- This problem can be resolved by choosing a different source of nucleophilic nitrogen then converting the resulting product into the desired amine. This approach is similar to the "use acetate as the nucleophile then hydrolyze the ester to an alcohol" approach to synthesis of an alcohol from an alkyl halide that we saw on pages 48-50 of these notes.

Special Nucleophiles: Amines from Phthalimide

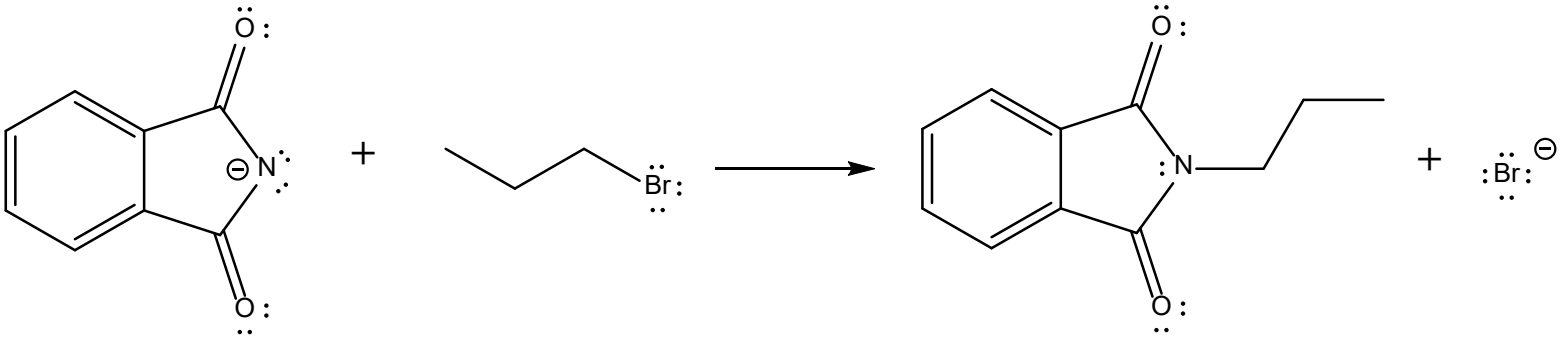
- One source of nucleophilic nitrogen is phthalimide:



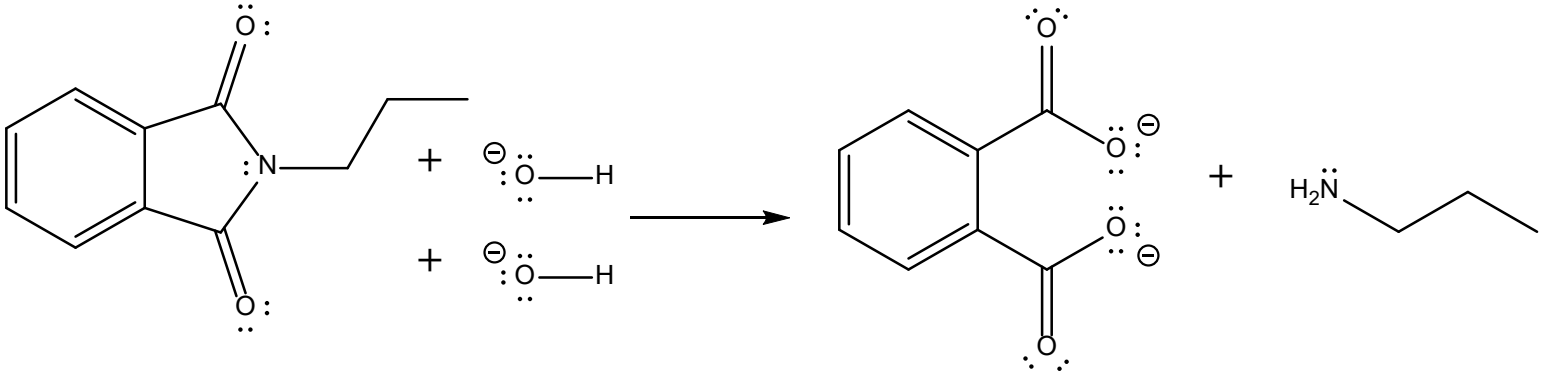
- The hydrogen atom explicitly drawn in the diagram above is rather more acidic than most NH groups, and phthalimide can be deprotonated using hydroxide. Why?

Special Nucleophiles: Amines from Phthalimide

- Step 1: React the conjugate base of phthalimide with an alkyl halide:



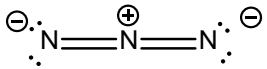
- Step 2: Convert this product to the corresponding amine by heating it with either hydroxide or hydrazine (NH_2NH_2):



- Do you think Step 1 proceeded via an S_N1 or S_N2 mechanism? Why?

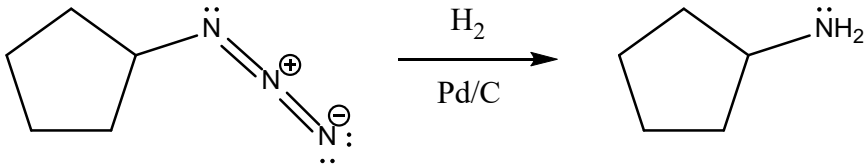
Special Nucleophiles: Amines from Azide

- Another source of nucleophilic nitrogen is the azide ion (N_3^-):



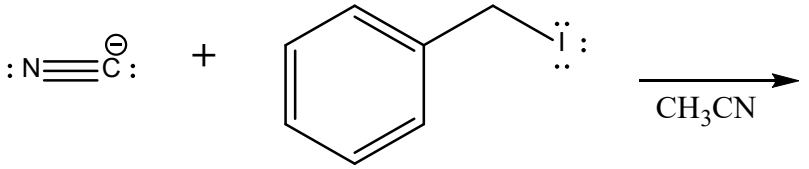
  - Step 1: React the azide ion with an alkyl halide:

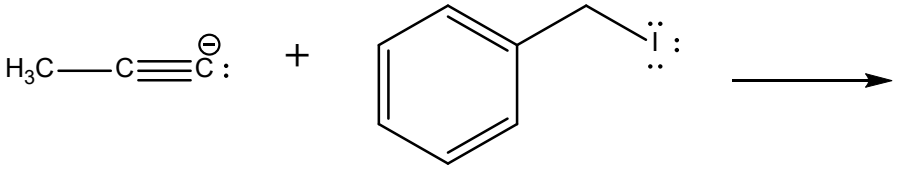
  - Step 2: React the resulting alkyl azide with hydrogen gas in the presence of a transition metal catalyst (the same reaction conditions used to hydrogenate alkenes; see Chapter 8 of Ogilvie).



Special Nucleophiles: Acetylides and Cyanide

- The ability to form carbon-carbon bonds is essential to making any large organic molecule from smaller components. In Chapter 7 of Ogilvie, you learned about acetylide ions and cyanide, both of which are sources of nucleophilic carbon.
- Predict the products of the following S_N2 reactions:





Special Nucleophiles: Acetylides and Cyanide

- Use of cyanide as a nucleophile gives us yet another way to access amines via substitution reactions. How?
  - Hydrogenation of a nitrile gives an amine:
  - Reduction of a nitrile with a hydride source gives an amine:

Special Electrophiles: Epoxides

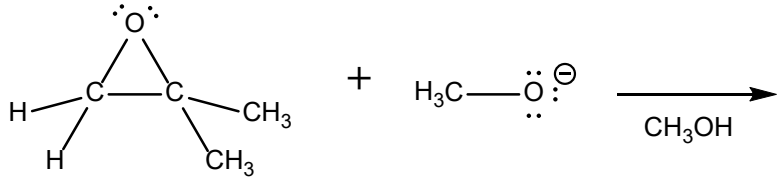
- In Chapter 8 of Ogilvie you saw that, unlike most other ethers, epoxides are reasonably good electrophiles. Why is this?

- Depending on the reaction conditions, substitution reactions of epoxides can proceed via either an S_N2 mechanism or an S_N1-like mechanism. For an epoxide which is not symmetric, the dominant mechanism determines which side of the epoxide the nucleophile attacks.

Special Electrophiles: Epoxides

- Under basic conditions, substitution reactions of epoxides proceed predominantly via a S_N2 mechanism.

- Given what you know about S_N2 reactions, which side of the epoxide would you expect the nucleophile to attack? What is the product of this reaction?



Special Electrophiles: Epoxides

- Under acidic conditions, substitution reactions of epoxides proceed predominantly via an S_N1-like mechanism.

- Given what you know about S_N1 reactions, which side of the epoxide would you expect the nucleophile to attack? What is the product of this reaction?