CHEMISTRY 2500

Topic #9: Nucleophilic Substitution Reactions of Alcohols

(more S_N1 and S_N2)

Fall 2014

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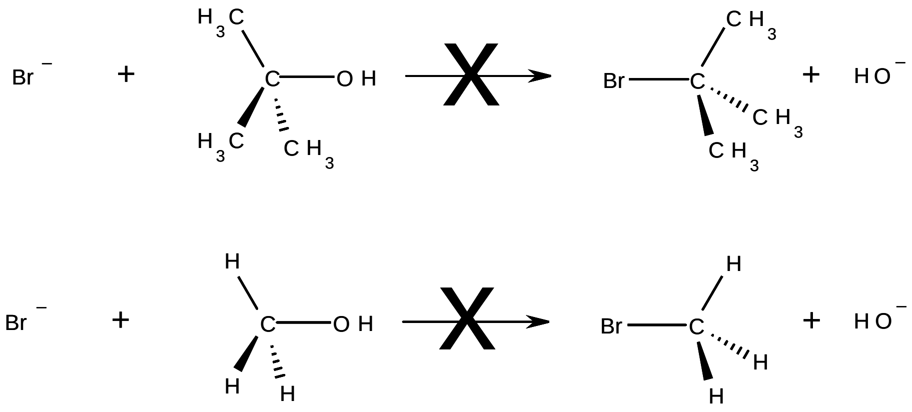
The Problem with Alcohols

- 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. Expect to see many different ways to make alcohols in CHEM 2600.

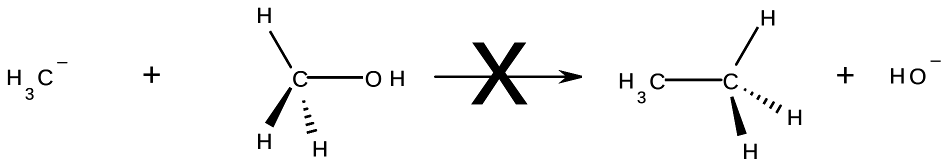
- Unfortunately, neither simple S_N1 nor simple S_N2 reactions are favoured for alcohols:



Why is this?

The Problem with Alcohols

- We could try using an extremely good nucleophile like H_3C^- . Then what would happen?



- So, if we want to use alcohols as starting materials for substitution reactions, we'll 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.

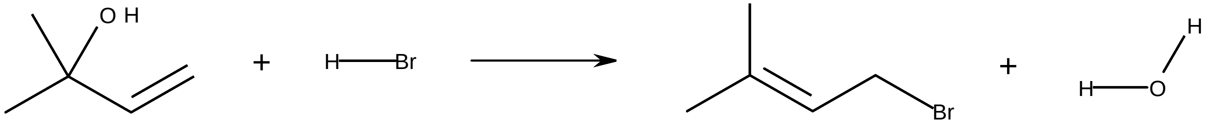
- There are many different leaving groups we could choose, most of which are oxygen-based:

- Another option, which we will explore later, is to convert the alcohol into the corresponding alkyl halide (Cl, Br or I – **NOT** F!)

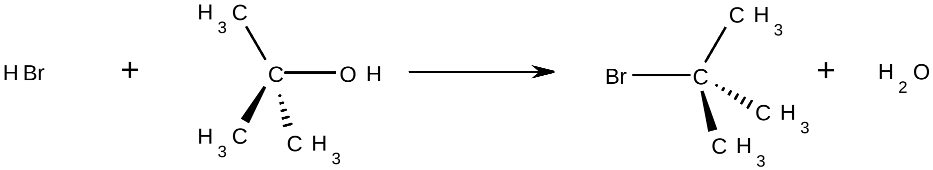
Solution #1: Make R-OH into R-OH_2^+

- If we want to use an alcohol in an S_N1 reaction, the usual practice is to convert R-OH into R-OH_2^+.

- We saw an example of this approach in the previous section when we looked at S_N1 reactions and rearrangements:

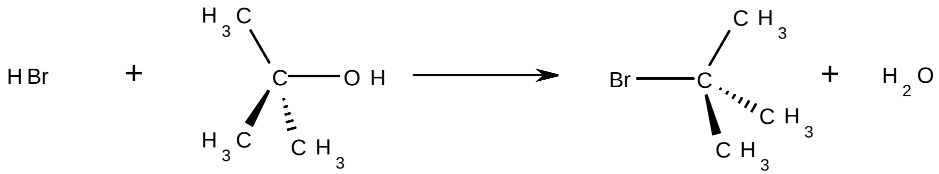


- A simpler example would be to consider the reaction of *t*-butanol (2-methylpropan-2-ol) with HBr:



This is a reaction has three elementary steps in its mechanism. Propose a reasonable mechanism for it on the next page.

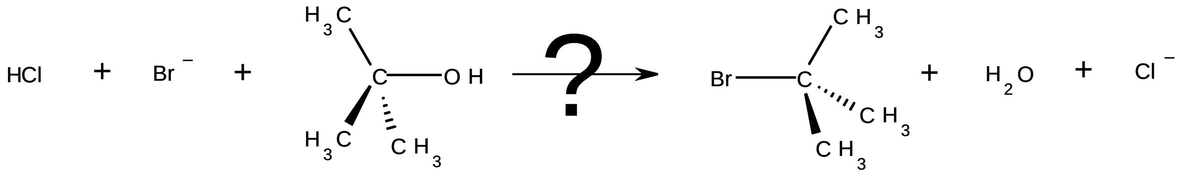
Solution #1: Make R-OH into R-OH_2^+



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

- The standard practice for these types of reaction is to use the acid whose conjugate base is the desired nucleophile. Why?

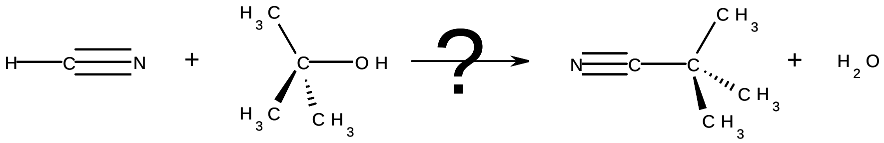
  Consider the reaction below...



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

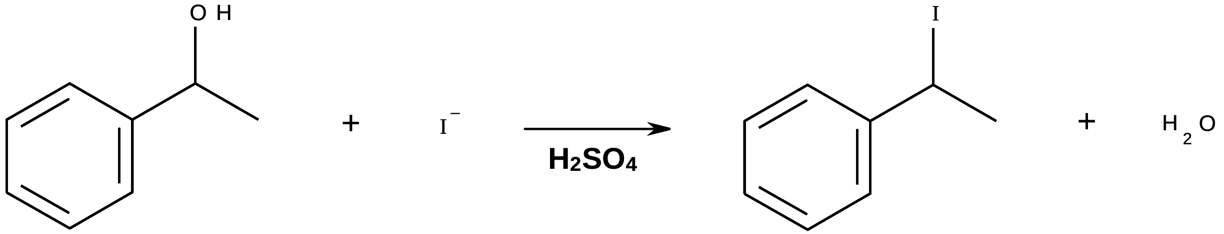
- This approach will only work if the acid in question is a strong acid. Why?

  Consider the reaction below...

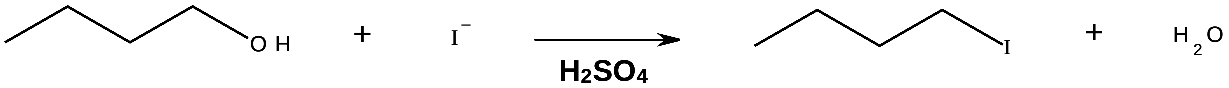


Solution #1: Make R-OH into R-OH_2^+

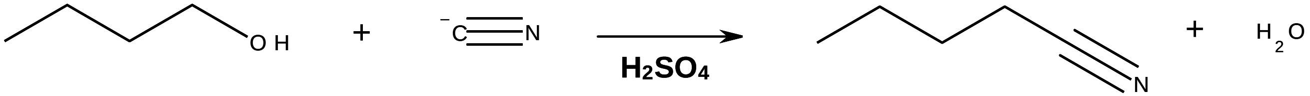
- Consider each of the following potential substitution reactions. Would it proceed as an S_N1 reaction, an S_N2 reaction, both or neither? Propose a mechanism justifying your choice.



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



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

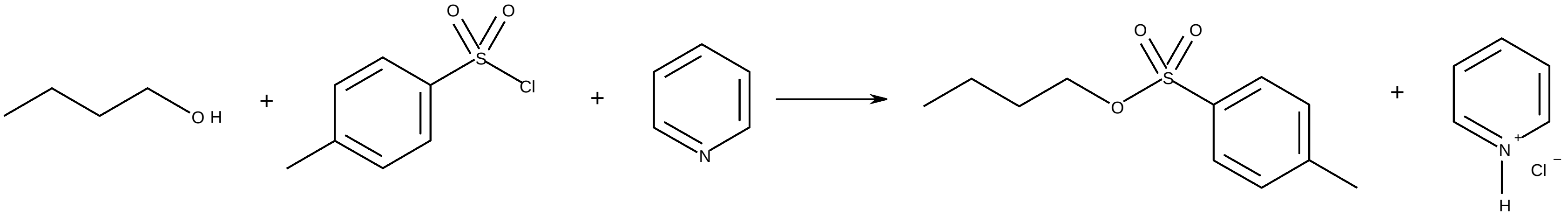


Solution #2: Make R-OH into Sulfonate Ester

- If we wanted to make the nitrile shown 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 ($R\text{-}O\text{-}SO_2R'$):
  - If R' = CH_3, the group is a mesylate (R-OMs), short for "<u>m</u>ethane<u>s</u>ulfonate ester":
  - If R' = CF_3 , the group is a triflate (R-OTf), short for "<u>t</u>ri<u>f</u>luoromethanesulfonate ester":
  - If R' = *p*-$C_6H_4CH_3$, the group is a tosylate (R-OTs), short for "1,4-<u>t</u>oluene<u>s</u>ulfonate ester":

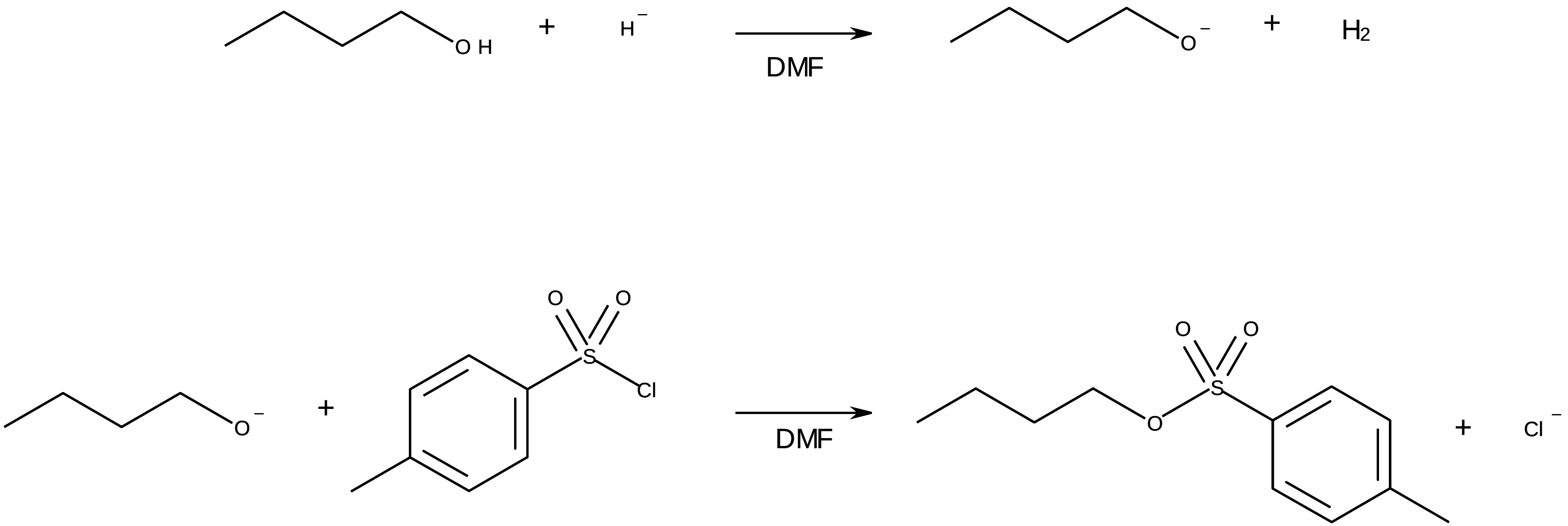
Solution #2: Make R-OH into Sulfonate Ester

- 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

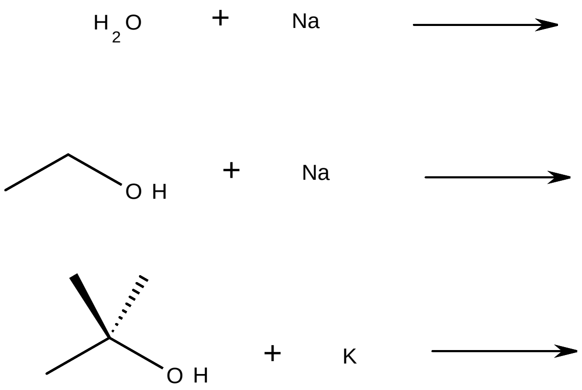
- An alternate approach is to react the alcohol with a strong base first then add the appropriate sulfonyl chloride ($ClSO_2R'$):



Solution #2: Make R-OH into Sulfonate Ester

- The alkoxide ion could alternately have been prepared by reacting the alcohol with sodium or potassium. This is usually done when the alcohol is also the solvent for the reaction.

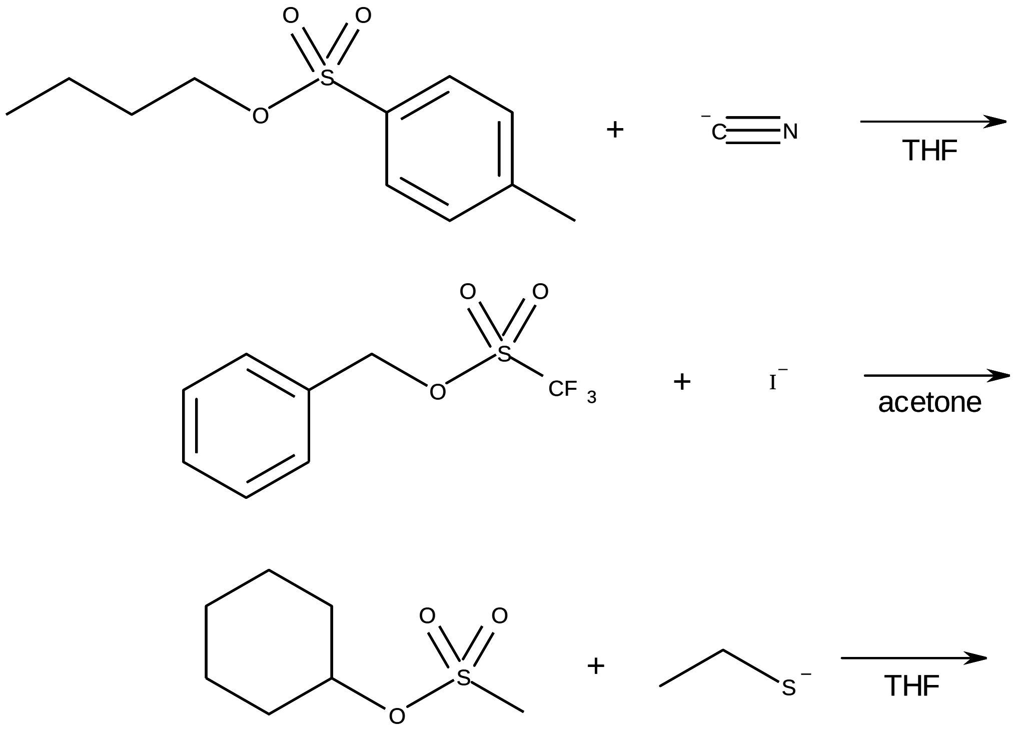
- These reactions are analogous to the reactions between alkali metals and water that you studied in CHEM 1000. Do you remember what the products were?



- These reactions are quite exothermic so care must be taken to avoid causing a fire. They shouldn’t be done on very large scale.

Solution #2: Make R-OH into Sulfonate Ester

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



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

Solution #3: Make R-OH into R-X

- Sulfonate esters serve as leaving groups about as well as chlorides (since the pK_a values for HCl and RSO_3H are about -7). Therefore, if converting the alcohol into a sulfonate ester is helpful, it is reasonable to conclude that converting the alcohol into the corresponding alkyl halide would be equally helpful.
  - To convert an alcohol to the corresponding alkyl chloride, use either $SOCl_2$ or PCl_3
  - To convert an alcohol to the corresponding alkyl bromide, use either $SOBr_2$ or PBr_3

Solution #3: Make R-OH into R-X

- What is a reasonable reaction mechanism for the preparation of 1-chloropropane from by reacting 1-propanol with $SOCl_2$?

  The by-products are $SO_{2(g)}$, $H^{+}_{(propanol)}$ and $Cl^{-}_{(propanol)}$.

Solution #3: Make R-OH into R-X

- What is a reasonable reaction mechanism for the preparation of 1-chloropropane from by reacting 1-propanol with PCl_3?

  The by-products are $HPO(OPr)_{2(propanol)}$, $H^+_{(propanol)}$ and $Cl^-_{(propanol)}$.

P=O bonds are very strong, making this process favourable.

Solution #4: Use a Mitsonobu Reaction

- In a process very similar to the PCl_3 example, we can use a **Mitsonobu reaction**. This reaction also takes advantage of formation of a strong P=O bond; however, it does not require isolation of a product that is then reacted in an S_N2 reaction. Instead, the nucleophile is included as part of a reactant in the Mitsonobu reaction.

- A Mitsonobu reaction involves four main reactants:
  - The alcohol to be substituted
  - The conjugate acid of the desired nucleophile (e.g. HCl for Cl^-)
  - Triphenylphosphine ($Ph_3P = (C_6H_5)_3P$)
  - Diethyl azodicarboxylate (DEAD = $CH_3CH_2OC(O)NNC(O)OCH_2CH_3$)

Solution #4: Use a Mitsonobu Reaction

- The conjugate acid of the nucleophile does not have to be a strong acid. Commonly used nucleophile sources include:
  - HCl (for Cl^-)
  - HBr (for Br^-)
  - HI (for I^-)
  - HCN (for ^-CN)
  - RCO_2H (for RCO_2^-)
  - HN_3 (for N_3^-)
  - ArOH (for ArO^-)
  - ArSH (for ArS^-)

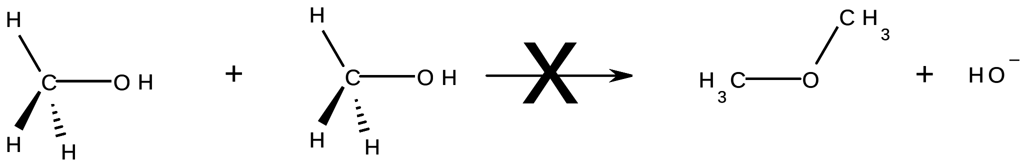
- The products include the desired substitution product as well as Ph_3PO (a *very* stable precipitate) and a hydrogenated DEAD ($CH_3CH_2OC(O)NHNHC(O)OCH_2CH_3$):

Solution #4: Use a Mitsonobu Reaction

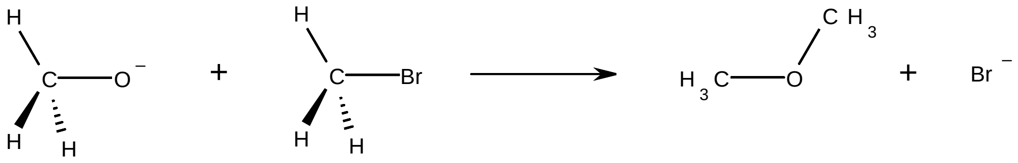
- What is the mechanism for the Mitsonobu reaction using ethanol as the alcohol and HBr as the nucleophile’s conjugate acid?

Solution #5a: Use RO$^-$ as the Nucleophile

- If the goal is to make an ether, reacting two alcohols in a substitution reaction won't work:



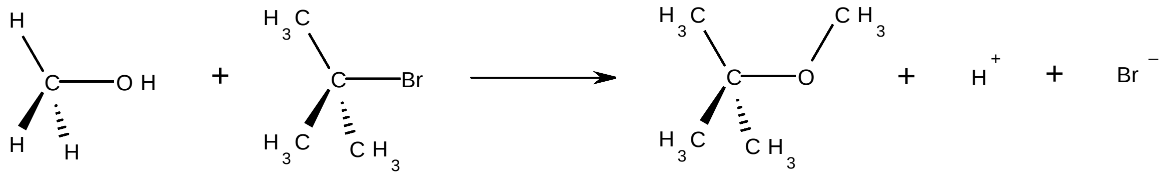
- It is, however, possible to prepare the alkoxide anion from one alcohol then react that with an alkyl halide to generate the ether shown above:



- This is known as the Williamson Ether Synthesis and it is an example of an ________ reaction.

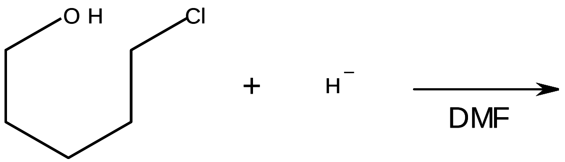
Solution #5b: Use ROH as the Nucleophile

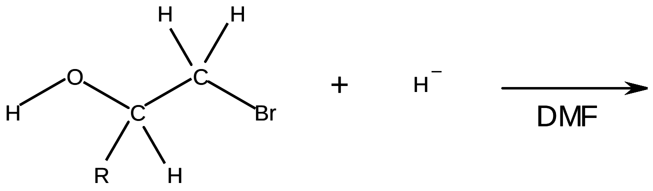
- It is also possible to prepare ethers via an analogous ________ reaction:



Solution #5: Use ROH/RO$^-$ as the Nucleophile

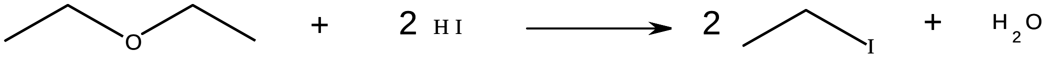
- Note that the nucleophilic site and electrophilic site do not have to be in different molecules. We can make cyclic ethers too:





More on Ethers and Epoxides

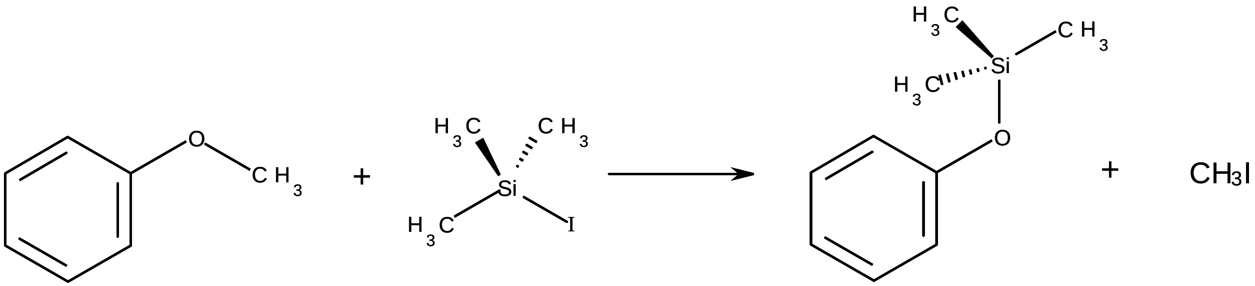
- Cleavage of ethers is done via substitution reactions as well. Consider the following reaction:



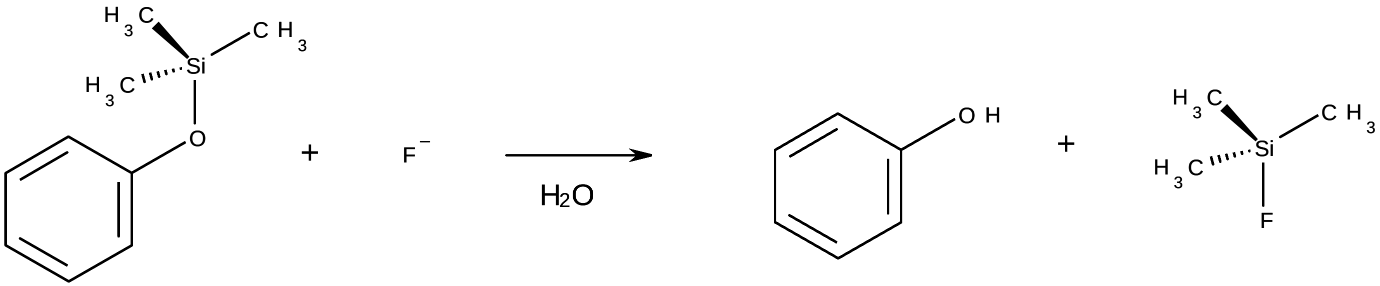
Propose a reasonable mechanism and conclude whether it is an S_N1 or S_N2 process.

More on Ethers and Epoxides

- A similar ether cleavage reaction uses trimethylsilyl iodide (TMSI) as the electrophile:



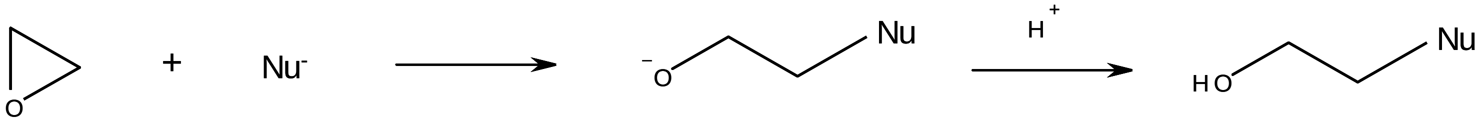
- The silyl ether can then be cleaved using F⁻ in another substitution reaction:



More on Ethers and Epoxides

- While, in most cases, ethers are poor electrophiles for substitution reactions:

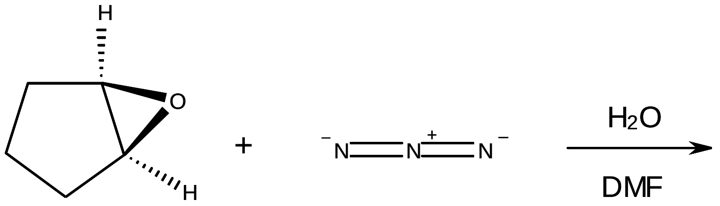
epoxides are the exception to the rule:

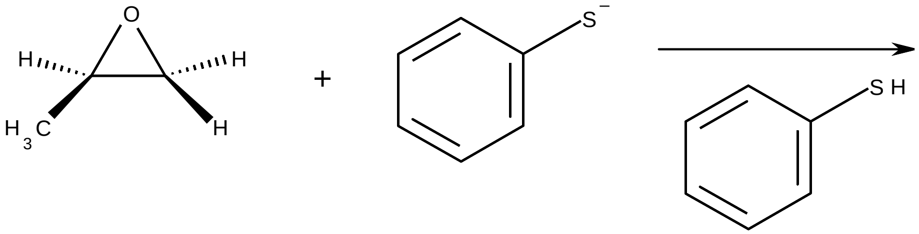


Why is this?

More on Ethers and Epoxides

- Under neutral or basic conditions and in the presence of a good nucleophile, an epoxide will readily undergo an S_N2 reaction.
- Carefully considering regiochemistry and stereochemistry, give the product(s) of each reaction below.





More on Ethers and Epoxides

- Under acidic conditions and in the presence of a nucleophile, an epoxide will readily undergo an S_N1 reaction.

- Carefully considering regiochemistry and stereochemistry, give the product(s) of the reaction below.