Four new mechanisms to learn: S_N2 vs E2 and S_N1 vs E1

S = substitution = a leaving group (X) is lost from a carbon atom (R) and replaced by nucleophile (Nu:)

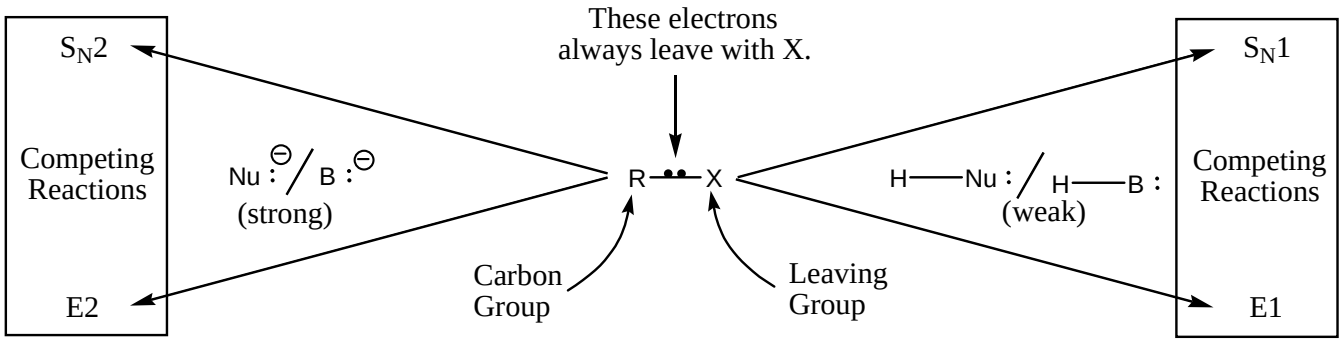
N = nucleophilic = nucleophiles (Nu:) donate two electrons in a manner similar to bases (B:)

E = elimination = two vicinal groups (adjacent) disappear from the skeleton and are replaced by a pi bond

1 = unimolecular kinetics = only one concentration term appears in the rate law expression, Rate = k[RX]

2 = bimolecular kinetics = two concentration terms appear in the rate law expression, Rate = k[RX] [Nu: or B:]

S_N2 competes with E2
S_N1 competes with E1



Nu: / B: = is an electron pair donor to carbon (= nucleophile) or to hydrogen (= base). It can be strong (S_N2/E2) or weak (S_N1/E1).

R = methyl, primary, secondary, tertiary, allylic, benzylic

X = -Cl, -Br, -I, $-OSO_2R$ (possible leaving groups in neutral, basic or acidic solutions)

X = $-\overset{\oplus}{O}H_2$ (only possible in acidic solutions)

The above pairs of reactions (S_N2/E2 and S_N1/E1) look very similar overall, but there are some key differences. The nucleophile/base is a strong electron pair donor in S_N2/E2 reactions (that's why they participate in the slow step of the reaction) and a weak electron pair donor in S_N1/E1 reactions (that's why they don't participate in the slow step of the reaction). This leads to differences in reaction mechanisms, which show up in the kinetics of the rate law expression (bimolecular = 2 and unimolecular = 1) and the possible reaction products obtained. It is recommended that you look at the reaction conditions first to decide what mechanisms are possible. You cut you choices in half when you decide that the electron pair donor is strong (S_N2/E2) or weak (S_N1/E1).

Important details to be determined in deciding the correct mechanisms of a reaction. (more details below)

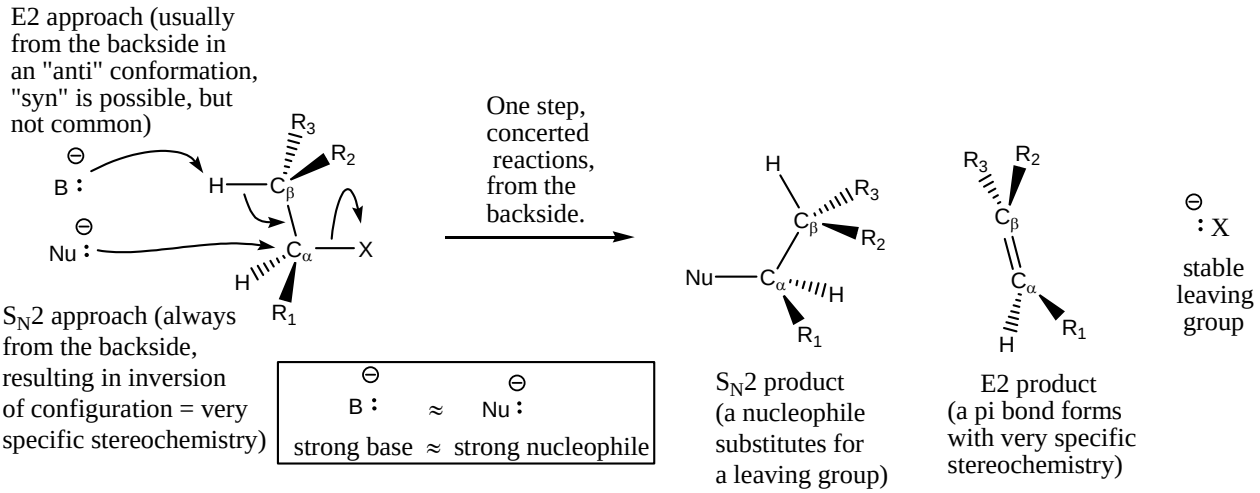
1. Is the nucleophile/base considered to be strong (anions, nitrogen, sulfur) or weak (neutral = H_2O, ROH, RCO_2H)?

2. What is the substitution pattern of the R-X substrate at the C_α carbon attached to the leaving group, X? Is it a methyl, primary, secondary, tertiary, allylic, or benzylic carbon? What about any C_β carbon atoms? How many additional carbon atoms are attached at a C_β position (none, one, two or three)?

3. Are the necessary " anti " C_β-H/C_α-X bond orientations possible to allow E2 reactions to occur?

S_N2 and E2 Competition – One Step Concerted Reactions

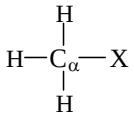
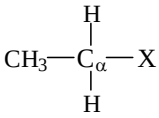
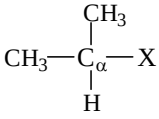
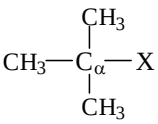
S_N2 and E2 reactions are one step reactions. The key bonds are broken and formed simultaneously, without any intermediate structures. These are referred to as *concerted reactions*. The S_N2 and E2 mechanisms compete with one another in consuming the R-X compound. Approach of the nucleophile/base is always from the backside in S_N2 reactions and mainly from the backside in E2 reactions (always from the backside in this chapter).



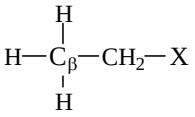
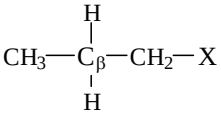
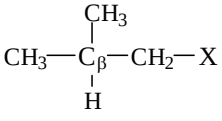
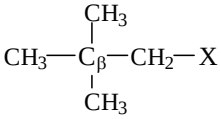
Terms
- S = substitution E = elimination Nu:⊖ = strong nucleophile B:⊖ = strong base X = leaving group
- 2 = bimolecular kinetics (second order, rate in slow step depends on RX and Nu:⊖/B:⊖)
- R-X = R-Cl, R-Br, R-I, R-OTs, ROH_2^+

Relative rates of S_N2 and S_N1 reactions with different substitution patterns at C_α and C_β of the R-X structure

Relative Rates of S_N2 Reactions - Steric hindrance at the C_α carbon slows down the rate of S_N2 reaction. (B:⊖ = Nu:⊖ = strong)

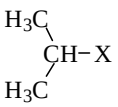
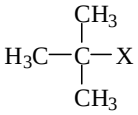
			
k ≅ 30	k ≅ 1	k ≅ 0.025 ≅ $\left(\frac{1}{40}\right)$	k ≅ 0
methyl (unique)	ethyl (primary) Reference compound	isopropyl (secondary)	t-butyl (tertiary) (very low)

Relative Rates of S_N2 Reactions - Steric hindrance at the C_β carbon also slows down the rate of S_N2 reaction. (B:⊖ = Nu:⊖ = strong)

			
k ≅ 1	k ≅ 0.4	k ≅ 0.03	k ≅ 0.00001
ethyl Reference compound	propyl	2-methylpropyl	2,2-dimethylpropyl (neopentyl)

All of these structures are primary R-X compounds at C_α, but substituted differently at C_β.

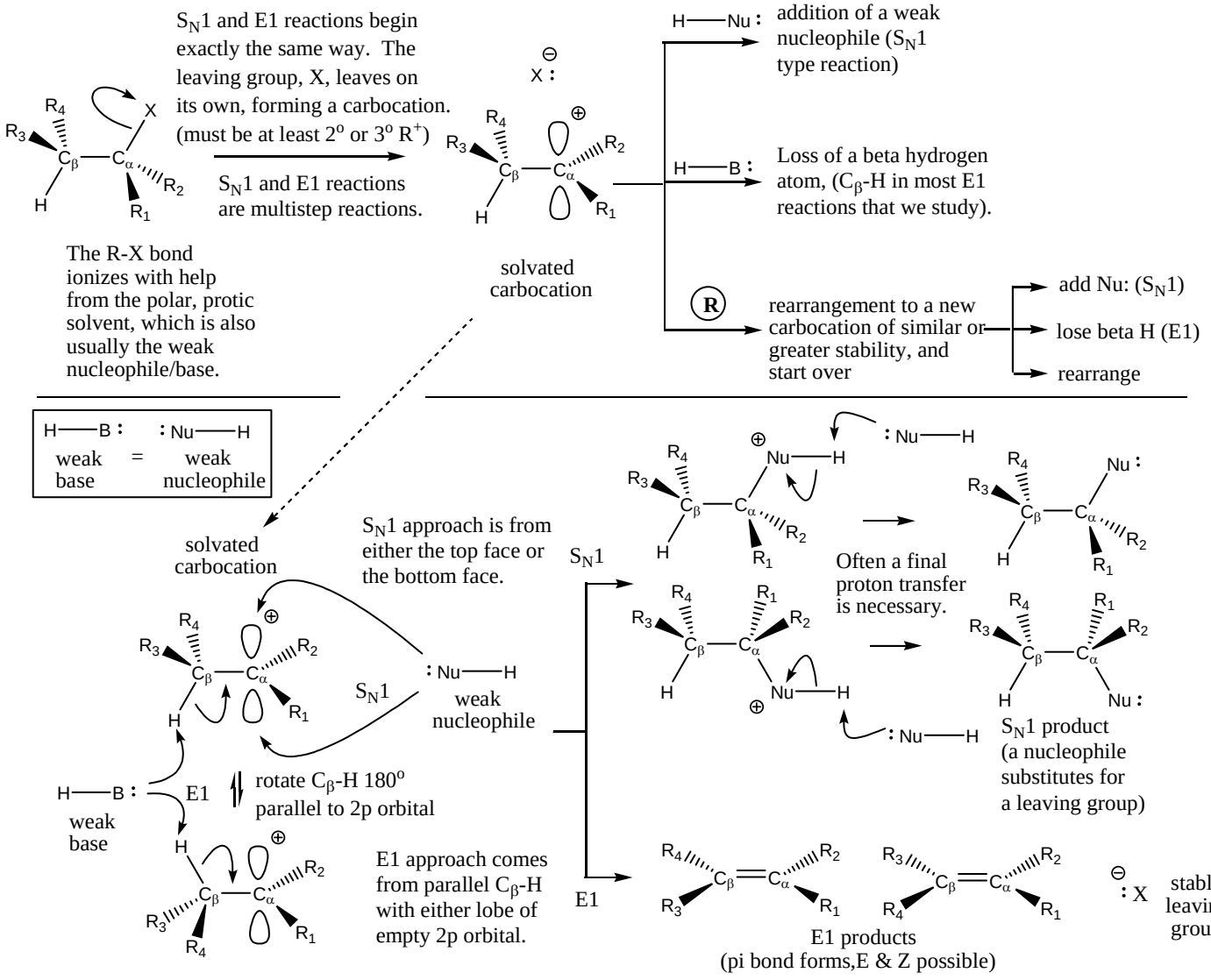
S_N1 (and E1) relative reactivities of R-X compounds: R-X ⟶ $R^\oplus$ ⟶ $S_N1 > E1$ (usually) (H-B: = H-Nu: = weak)

relative rates =	H_3C-X	CH_3CH_2-X		
	10^{-5}	10^{-4}	1.0	10^6 = 1,000,000
	these two rates are probably by S_N2 reaction		Reference compound	

(relative S_N1/E1 reactivity: methyl << primary << secondary < tertiary)

S_N1 and E1 Competition – Multistep Reactions

S_N1 and E1 reactions are multistep reactions and also compete with one another. Both of these reactions begin with the same rate-limiting step of carbocation formation from an R-X compound. Carbocations (R^+) are very reactive electron deficient carbon intermediates that typically follow one of three possible pathways leading to two ultimate outcomes: 1. add a nucleophile or 2. lose a beta hydrogen atom. The additional competing pathway for carbocation intermediates is rearrangement, in which atoms in a carbocation change positions to form a similar or more stable carbocation. Once formed, a new carbocation is analyzed in a similar manner to the previous one it came from. It may possibly rearrange again, but ultimately, the final step will be to either add a nucleophile at the carbocation carbon (S_N1) or to react with a base at a beta hydrogen atom (E1).

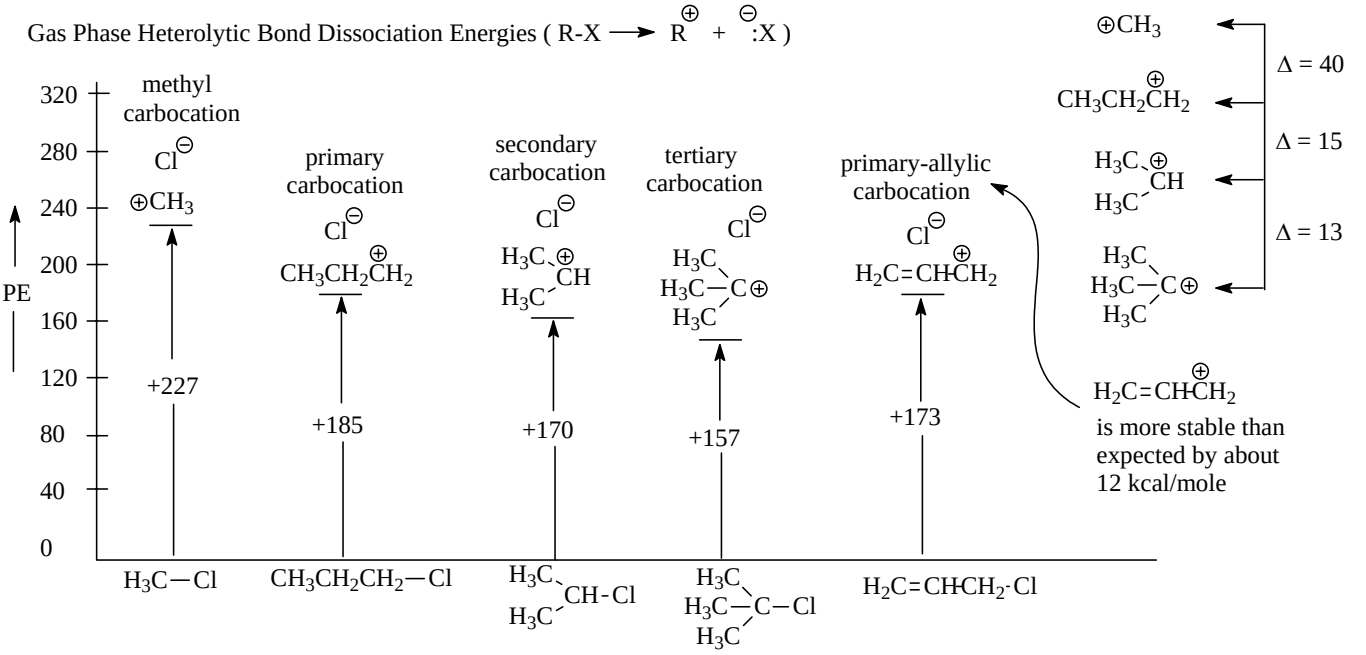


Terms

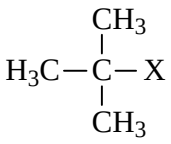
- S = substitution E = elimination H-Nu: = weak nucleophile H-B: = weak base X = leaving group
- 1 = unimolecular kinetics (first order reaction, the rate in the slow step depends only on RX)
- R-X = R-Cl, R-Br, R-I, R-OTs, ROH_2^+
- :Nu—H = H—B: = usually a polar, protic solvent (or mixture) of H_2O, ROH or RCO_2H

S_N1 and E1 reactions – the first step

Gas Phase Ionization Energies are known for R-Cl Bonds (and a lot of other bonds too, given in kcal/mol)

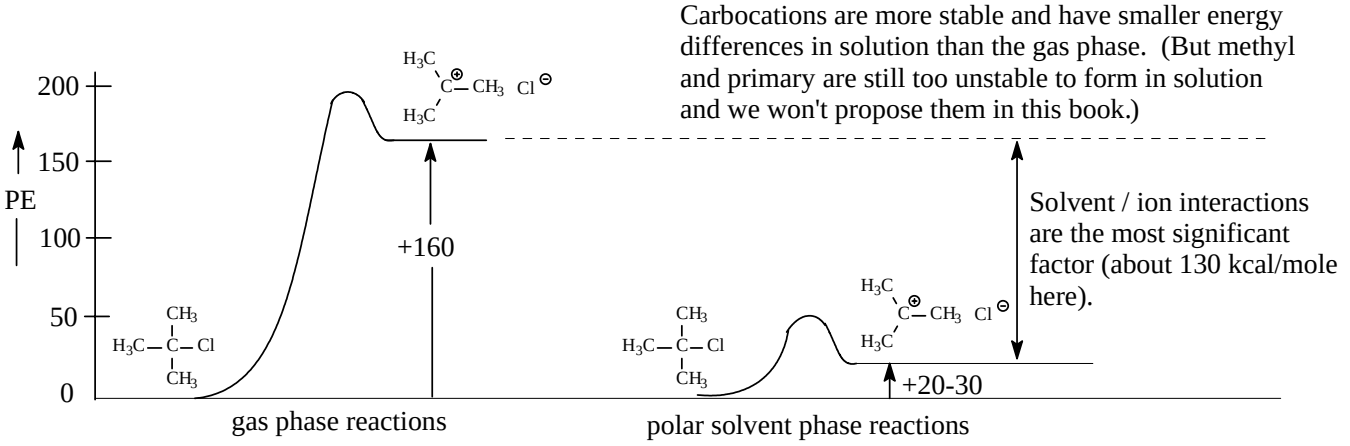


Lower charge density in the anions also makes it easier to ionize the C_α-X bond.

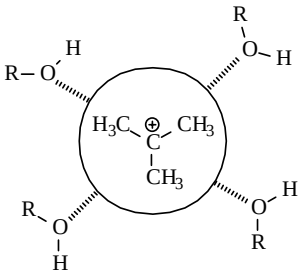


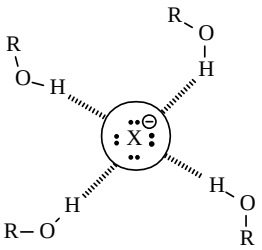
X =	Gas Phase B.E.
Cl	+157
Br	+149
I	+140

The activation energies for ionization in solvents are on the order of 20-30 kcal/mole (S_N1 and E1 reactions). It is clear from the difference in the gas phase energies of ionization that the solvent is the most stabilizing factor in ion formation. The magnitudes of these energies are compared in the potential energy diagram below.



Polar protic solvents are good for S_N1/E1 reactions because they allow for easier formation of cations and anions in solution, the first step of those mechanisms. Only secondary and tertiary carbocations are stable enough to form in solution (usually H_2O, ROH or RCO_2H, in our course, HX and H_2SO_4 acids work well too in reactions with alcohols).

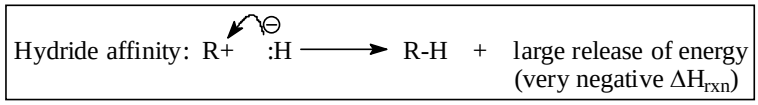


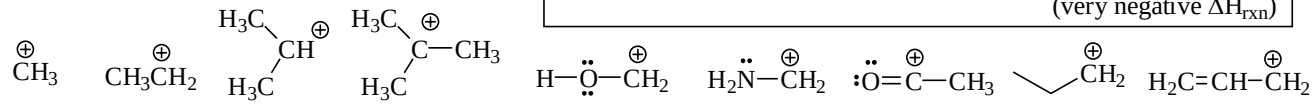


Many small solvent/ion interactions make up for a single, large covalent bond (heterolytic cleavage). A typical hydrogen bond is about 5-7 kcal/mole and typical covalent bonds are about 50-100 kcal/mole. In a sense the polar protic solvent helps to pull the C_α-X bond apart. The "polarized" protons tug on the "X" end and the lone pairs of the solvent molecules tug on the "C_α" end. If the carbocation is stable enough, the bond will be broken.

The large differences in carbocation energies provide a strong driving force to rearrange to a more stable carbocation. This complication is a very common side reaction whenever more stable carbocations can form.

Problem – A tremendous amount of energy is released when a hydride is allowed to combine with a carbocation in the gas phase (called hydride affinity). Explain the differences in the hydride affinities among the following carbocations.

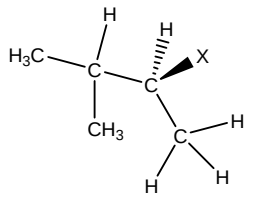




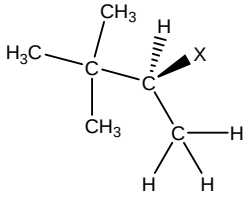
-315 -277 -249 -232 -248 -218 -230 -270 -256

Problem 5 - Consider all possible rearrangements from ionization of the following RX reactants. Which are reasonable? What are the possible S_N1 and E1 products from the reasonable carbocation possibilities? This is a long problem.

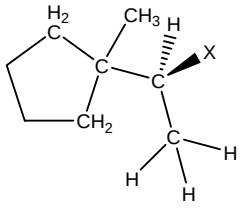
a.



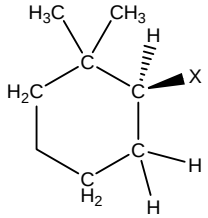
b.



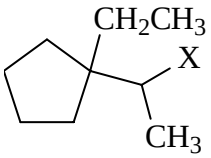
c.

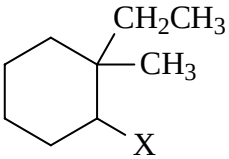


d.



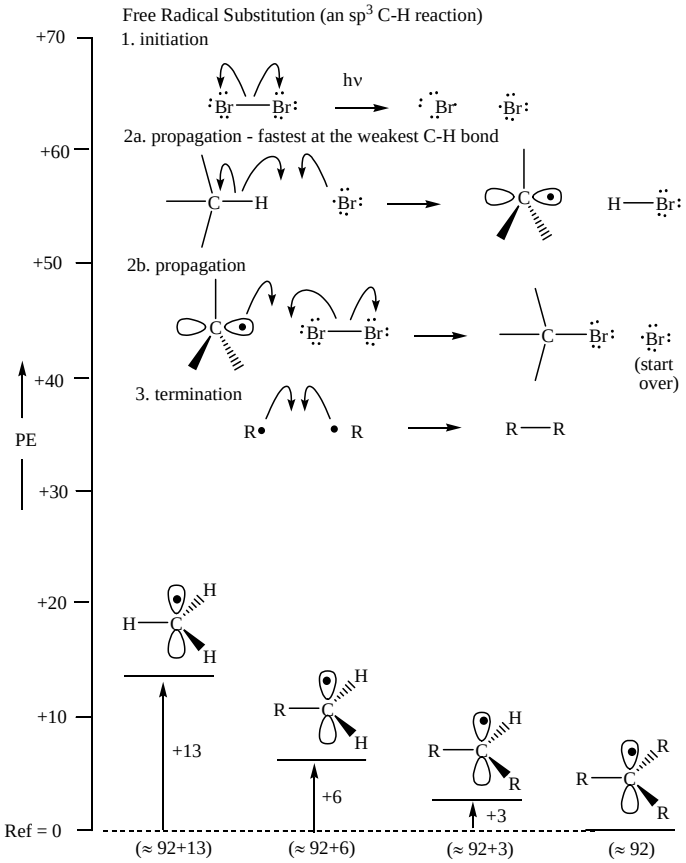
d. What would happen to the complexity of the above problems with a small change of an ethyl for a methyl? This problem is a lot more messy than those above, (which is the point of asking it). You do not have to redo the entire problem. Just consider where differences occur.



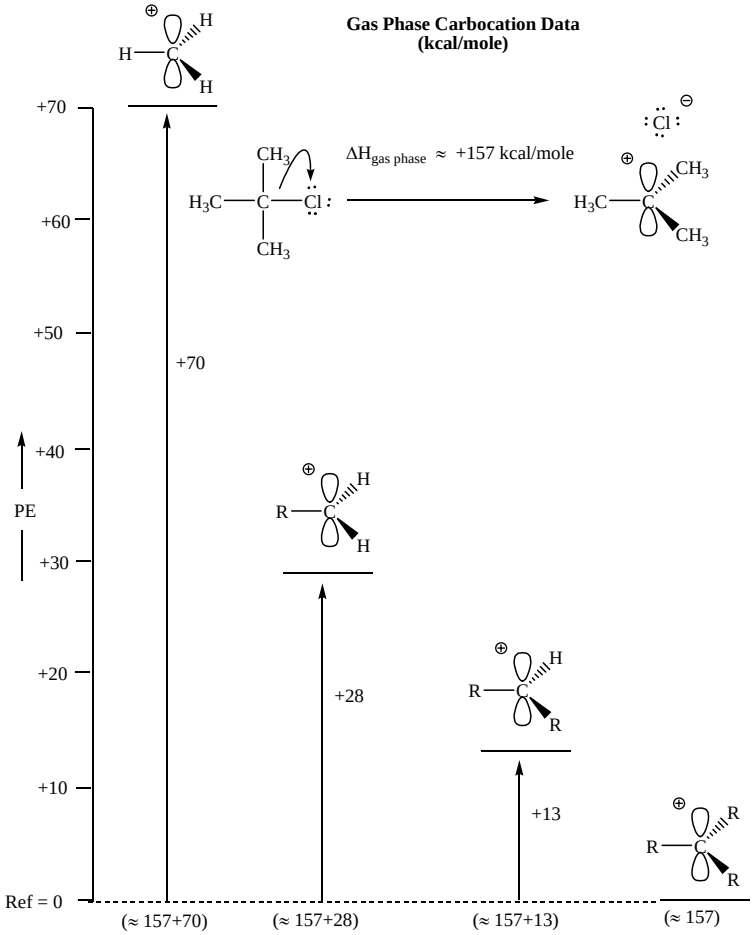


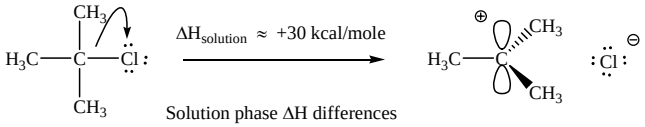
A comparison of free radical and carbocation intermediate stabilities

Gas Phase Free Radical Data (kcal/mole)



Gas Phase Carbocation Data (kcal/mole)





Solution phase ΔH differences

CH_3^+	+20
RCH_2^+	+9
R_2CH^+	+5
R_3C^+	0 (ref.)

Compare relative rates of reaction based on differences in ΔH

$$\frac{k_{methyl}}{k_{tiaary}} \approx 10^{\frac{-\Delta H}{(2.3)(R)(T)}} \approx 10^{\frac{-20{,}000}{(1380)}} \approx 10^{-14}$$

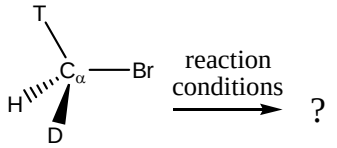
$$\frac{k_{primary}}{k_{tiaary}} \approx 10^{\frac{-\Delta H}{(2.3)(R)(T)}} \approx 10^{\frac{-9{,}000}{(1380)}} \approx 10^{-6.5} \approx 3.7\text{x}10^{-7} \approx \frac{1}{3{,}000{,}000}$$

$$\frac{k_{secondary}}{k_{tiaary}} \approx 10^{\frac{-\Delta H}{(2.3)(R)(T)}} \approx 10^{\frac{-5{,}000}{(1380)}} \approx 10^{-3.6} \approx 2.5\text{x}10^{-4} \approx \frac{1}{4000}$$

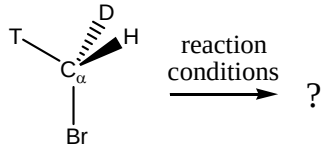
Generic Guidelines for RX patterns in our course (horizontal display and vertical display)

Example 1 - two possible perspectives (deuterium and tritium are isotopes of hydrogen that can be distinguished)

methyl RX example



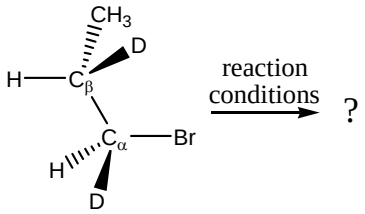
S-bromomethane



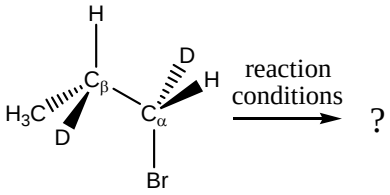
S-bromomethane

Example 2 - two possible perspectives (deuterium is an isotope of hydrogen that can be distinguished)

primary RX example



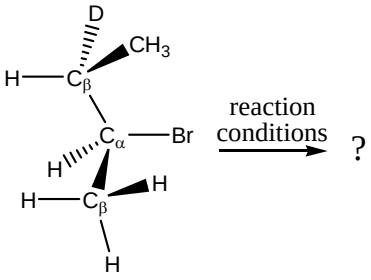
(1S,2S)- 1,2-dideuterio-1-bromopropane



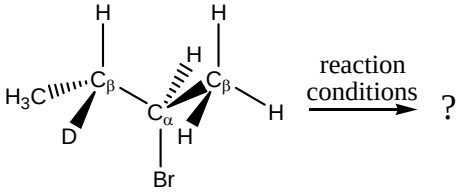
(1S,2R)- 1,2-dideuterio-1-bromopropane

Example 3 - two possible perspectives (deuterium is an isotope of hydrogen that can be distinguished)

secondary RX example



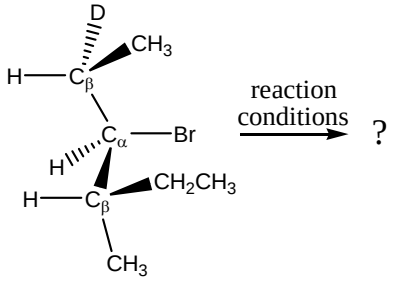
(2S,3R)-3-deuterio-2-bromobutane



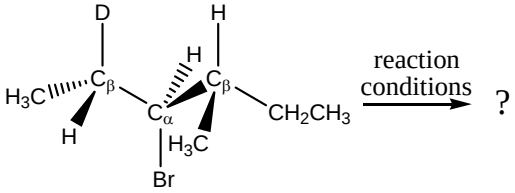
(2R,3R)-3-deuterio-2-bromobutane

Example 4 - two possible perspectives (deuterium is an isotope of hydrogen that can be distinguished)

secondary RX example



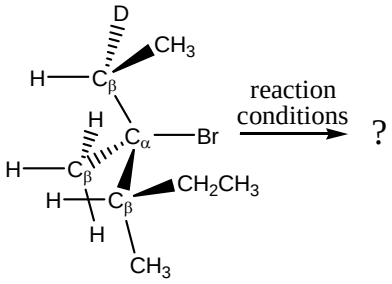
(2R,3R,4S)-2-deuterio-4-methyl-3-bromohexane



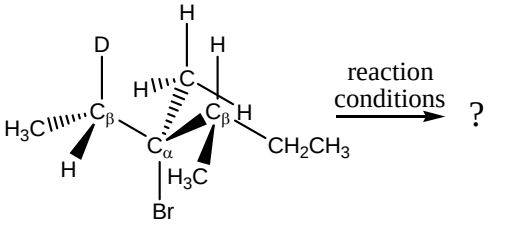
(2S,3S,4S)-2-deuterio-4-methyl-3-bromohexane

Example 5 - two possible perspectives (deuterium is an isotope of hydrogen that can be distinguished)

tertiary RX example



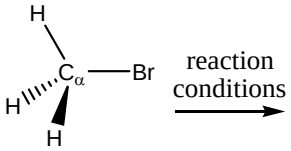
(2R,3R,4S)-2-deuterio-4-methyl-3-bromohexane



(2S,3S,4S)-2-deuterio-4-methyl-3-bromohexane

Predict the products

methyl RX example

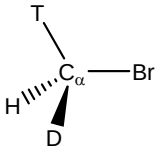


reaction conditions →

bromomethane

strong B:/Nu:
S_N2 = 1 product
E2 = 0 products

weak B:/Nu:
S_N1 = no reaction
E1 = no reaction



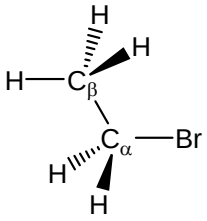
reaction conditions →

S-bromomethane

strong B:/Nu:
S_N2 = 1 product
E2 = 0 products

weak B:/Nu:
S_N1 = no reaction
E1 = no reaction

primary RX examples (simple and complicated)

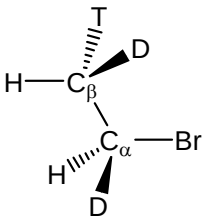


reaction conditions → ?

1-bromoethane

strong B:/Nu:
S_N2 = 1 product
E2 = 1 product

weak B:/Nu:
S_N1 = no reaction
E1 = no reaction



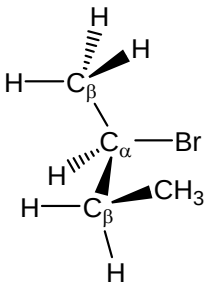
reaction conditions → ?

(1S,2S)- 1-bromo-1,2-dideuterio-2-tritioethane

strong B:/Nu:
S_N2 = 1 product
E2 = 3 products

weak B:/Nu:
S_N1 = no reaction
E1 = no reaction

secondary RX examples (simple and complicated)

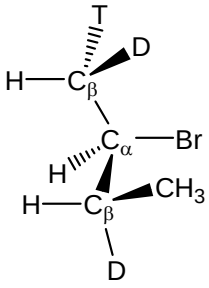


reaction conditions → ?

(2R)-2-bromobutane

strong B:/Nu:
S_N2 = 1 product
E2 = 3 products

weak B:/Nu:
S_N1 = 2 products
E1 = 3 products



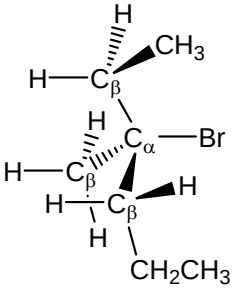
reaction conditions → ?

(1S,2R,3S)-1,3-dideuterio-1-tritio-2-bromobutane

strong B:/Nu:
S_N2 = 1 product
E2 = 5 products

weak B:/Nu:
S_N1 = 2 products
E1 = 10 products

tertiary RX examples (simple and complicated)

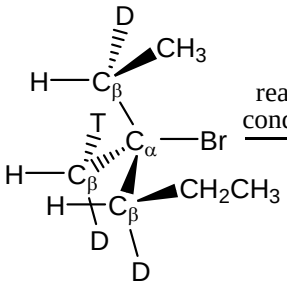


reaction conditions → ?

2-methyl-2-bromohexane

strong B:/Nu:
S_N2 = 0 products
E2 = 5 products

weak B:/Nu:
S_N1 = 2 products
E1 = 5 products



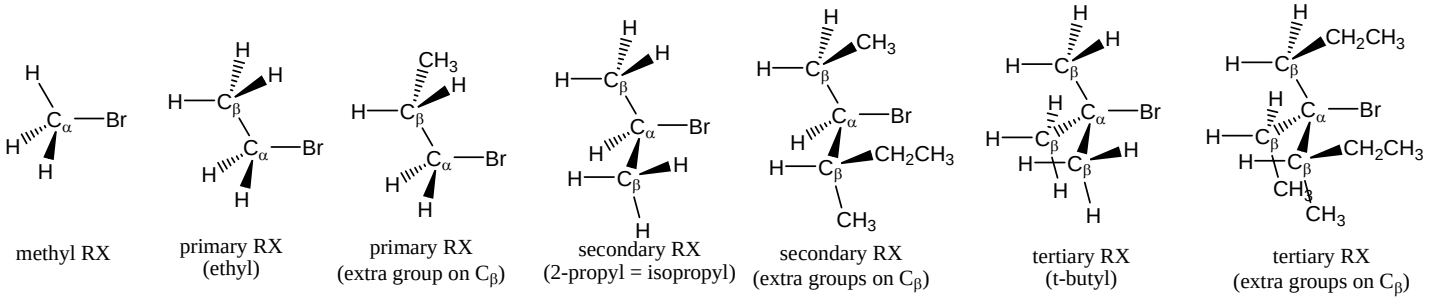
reaction conditions → ?

(2R,3R,4S)-2-deuterio-2-(R-deuteriotritiomethyl)-3-bromo-4-methylhexane

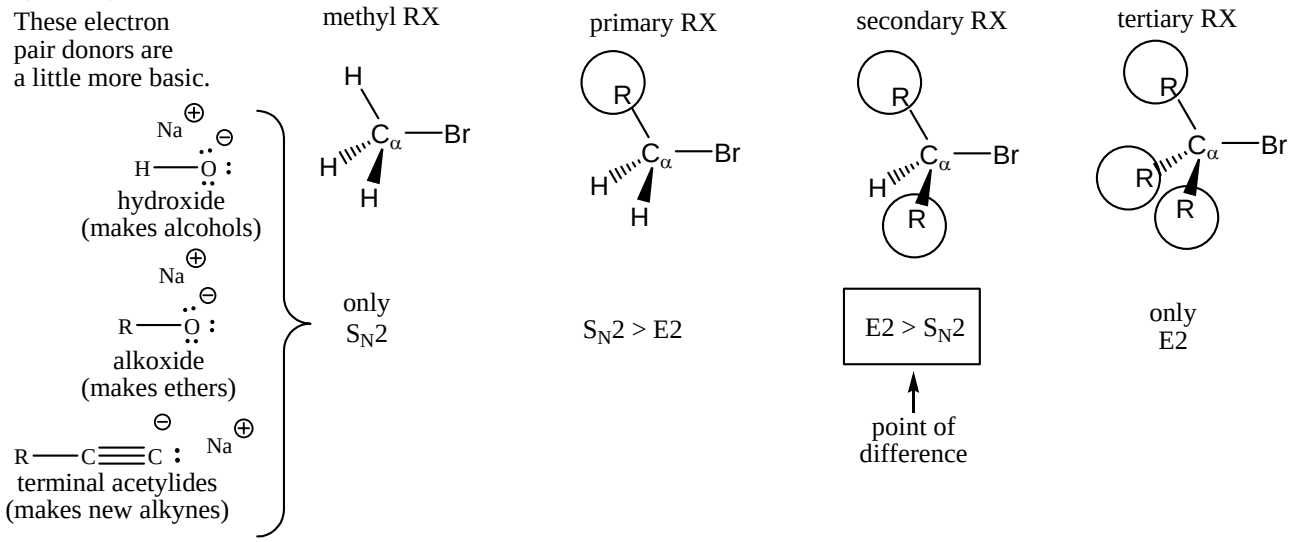
strong B:/Nu:
S_N2 = 0 products
E2 = 7 products

weak B:/Nu:
S_N1 = 2 products
E1 = 14 products

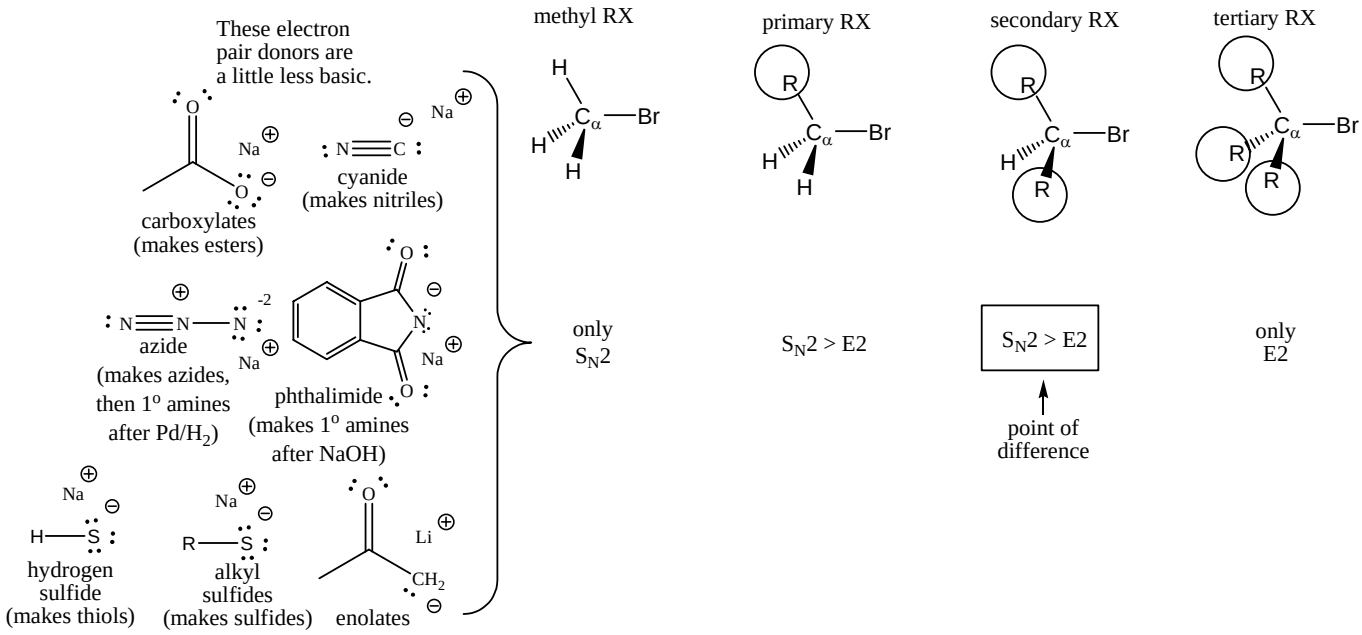
Possible reaction conditions with RX compounds (CH_3-X, RCH_2-X, R_2CH-X, R_3C-X, other patterns not included). If you notice the parallel bonds, it will help you draw the 3D structures.



1. strong base/nucleophile: hydroxide [$pK_a(H_2O) \sim 16$], alkoxides [$pK_a(ROH) \sim 16$] and terminal acetylides [$pK_a(RCCH) \sim 25$].

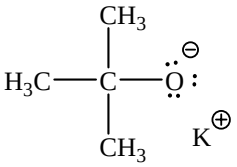


2. strong base/nucleophile: carboxylates [$pK_a(RCO_2H) \sim 5$], cyanide [$pK_a(HCN) \sim 9$], azide [$pK_a(HN_3) \sim 5$], phthalimidate [$pK_a \sim 8$] and hydrogen and alkyl sulfides [$pK_a(RSH) \sim 8$].

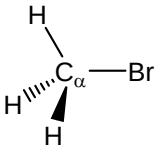


3. strong, sterically bulky bases: potassium t-butoxide [pK_a(ROH)~19] and lithium diisopropylamide [pK_a(R_2NH)~37]

We use potassium t-butoxide when we want to emphasize E2 reactions.

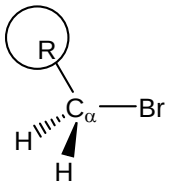


potassium t-butoxide



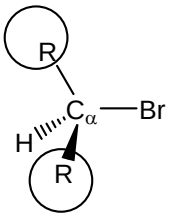
methyl RX

only S_N2



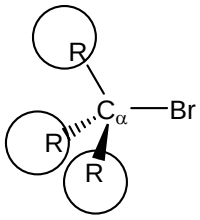
primary RX

$E2 > S_N2$



secondary RX

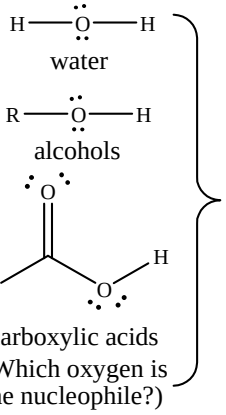
only E2



tertiary RX

only E2

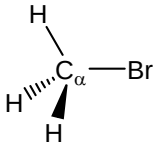
4. weak base/nucleophile (water, alcohols and liquid carboxylic acids), S_N1/E1 conditions, rearrangements possible



water

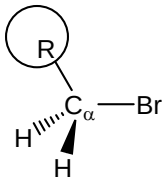
alcohols

carboxylic acids (Which oxygen is the nucleophile?)



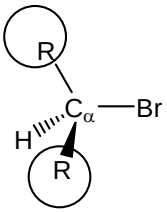
methyl RX

No Reaction



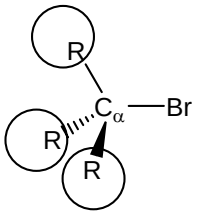
primary RX

No Reaction



secondary RX

$S_N1 > E1$



tertiary RX

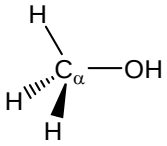
$S_N1 > E1$

These are mainly S_N1 conditions, with E1 side products. Rearrangements are a possible complication.

5. Alcohol (ROH) + HX acid (HX = HCl, HBr, HI) (S_N2 conditions at methyl and 1° RX or S_N1 at 2° and 3° RX)

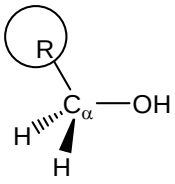
These are mainly S_N conditions.

H-X acids (HCl, HBr, HI)



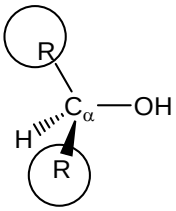
methyl RX

S_N2



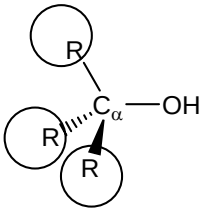
primary RX

S_N2



secondary RX

S_N1



tertiary RX

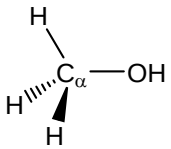
S_N1

The OH of an alcohol becomes a good leaving group (water) when protonated by a strong acid.

6. Alcohol (ROH) + H_2SO_4/Δ (E1 conditions, rearrangements are always a possibility with carbocations)

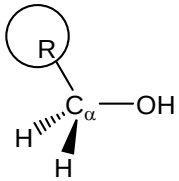
These are E1 conditions (very harsh).

H_2SO_4 / Δ ($-H_2O$)



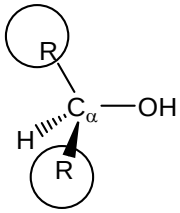
methyl RX

NA



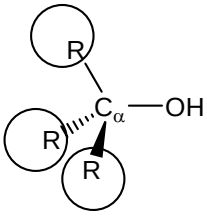
primary RX

E1



secondary RX

E1



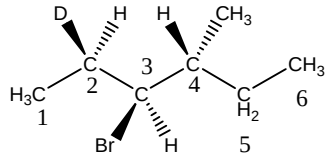
tertiary RX

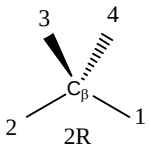
E1

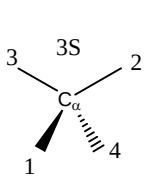
The OH of an alcohol becomes a good leaving group (water) when protonated by a strong acid.

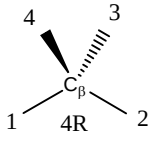
A possible approach to working S_N/E problems.

Write a 2D, then a 3D structure for the given name. (2R,3S,4R) 2-deuterio-3-bromo-4-methylhexane









All variations are shown below, which are enantiomers, diastereomers?

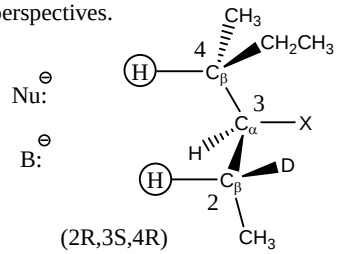
(2R,3S,4R)	(2S,3R,4S)
(2R,3S,4S)	(2S,3S,4R)
(2S,3S,4S)	(2R,3R,4R)
(2R,3S,4S)	(2S,3R,4R)

(2R,3S,4R) 2-deuterio-3-bromo-4-methylhexane

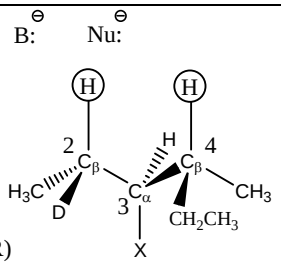
What are the expected products if hydroxide is the electron donor? How would the expected products change if hydroxide were changed to ethoxide (?), ethanoate (acetate)(?), t-butoxide(?), azide(?), cyanide(?), terminal acetylide(?) water (?), ethanol(?) or ethanoic acid(?). Write a separate mechanism showing the formation of each possible product. Which are major? Which are minor? How would the problem change if the bromine, deuterio and/or methyl were moved to another position?

How would this problem change if (2R,3S,4R) 2-deterio-4-methylhexan-3-ol were mixed with concentrated HBr (?) or H_2SO_4/Δ(?).

Two possible perspectives.

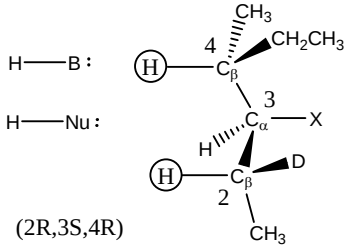


(2R,3S,4R)

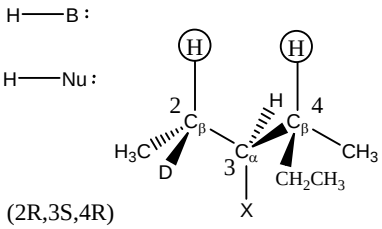


(2R,3S,4R)

Two additional perspectives, with slightly different conditions.



(2R,3S,4R)



(2R,3S,4R)

Method for filling in the blanks on a structure from the name of the structure.

1. Draw C_α = C3 (in this problem) first in its proper configuration (R or S).

2. Add in groups on C_β carbons in any manner. It is convenient to put an anti C_β-H to C_α-X for E2 reactions. If you are lucky, they will be in the correct R/S configuration. If you are wrong, then switch two convenient groups.

3. If there is a strong nucleophile/base, then write out all of the S_N2/E2 possibilities. The S_N2 product will form only by inversion of configuration via attack from the backside at C_α-X. Any E2 products require an anti C_β-H and C_α-X conformation. You must look at every possible anti C_β-H to determine all of the possible alkene products. You should draw every possible conformation and examine the predicted alkene that forms. This will determine the configuration of any alkene products. More preferred alkene products are, generally, more substituted and "E" > "Z", whether an E2 or E1 mechanism.

4. If there is a weak nucleophile/base, then write out all of the S_N1/E1 possiblities. The first step for both mechanisms is loss of the leaving group which forms a carbocation. The two ultimate choices are $S_N1$and E1 reactions, but rearrangements must be considered along the way with every carbocation that forms. To keep our life simple, we will only consider rearrangements to more stable carbocations when predicting reactions. To explain a result we may have to invoke rearrangements to similarly stable carbocations. For S_N1 products add the :Nu-H from the top and bottom faces of the carbocation. If C_α is a chiral center, there will be two different products (R/S). It is also possible that there are two products in a ring with cis/trans possibilities and no chiral centers. You will also have to take off the extra proton on the attacking nucleophile via an acid/base reaction to get a neutral product. For E1 products you will have to remove any C_β-H (no anti requirement, top or bottom face). Make a double bond between all different C_β carbons and the C_α carbon. Switch the two groups on either of the carbons of any double bonds to see if different stereoisomers are formed. The possible outcomes are that the switch produces no change or that E/Z stereoisomers are formed. Any possible outcome is a predicted result in E1 reactions based on the generic alkene stabilities listed in point 3.

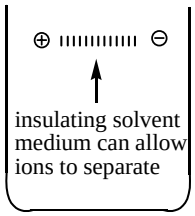
Solvents

Ions are often involved in solution phase reactions and the solvent must allow for their solubility. A reasonable amount of solvent polarity is necessary to make this possible. Solvents used in these sorts of reactions are often divided into two broad classes: polar protic and polar aprotic. Polar solvents (protic and aprotic) have moderate to large dielectric constants ($\varepsilon \geq 15$), which allows for charge separation at lower energy expense.

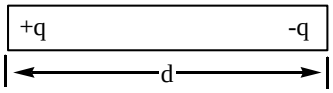
ε =	dielectric constant (bulk solvent property)	$\frac{1}{\varepsilon} \approx$	work necessary to separate charge in the solvent
μ =	dipole moment (molecular property)	$\approx$	an indication of charge separation in a molecule

ε = dielectric constant = bulk solven property, indication of amount of work necessary to separate charges in a solvent enviroment

μ = dipole moment = individual "molecule" property



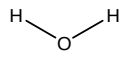
The work to separate charge = $1/\varepsilon$. ($\varepsilon_{air} = 1$, as a reference, and $\varepsilon_{H2O} = 78$, for comparison, e.g. it is 78 times easier to separate charge in water than in air)



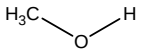
The diople moment, μ, is dependent upon the charge imbalance in a molecule (q) and the distance of separation (d).

Protic solvents have a polarized hydrogen attached to an electronegative atom (usually, oxygen as O-H or, less commonly, nitrogen as N-H). This polarized hydrogen atom is good at hydrogen bonding with partially or fully negative sites, which helps to stabilize the anions in solution, but leads to anions encumbered by solvent molecules. Polar aprotic solvents do not have a polarized hydrogen atom and don't have the ability to interact strongly with negative charge. While hydrogen bonding is good for dissolving an anion in protic solvents, it inhibits the anion's ability to attack another atom in a reaction, more so in S_N2 than E2.

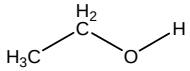
Polar protic solvents - the protic part is the polarized hydrogen atom attached to oxygen



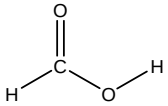
ε = 78
μ = 1.8 D



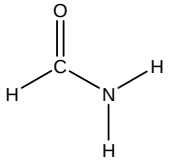
ε = 33
μ = 1.7 D



ε = 25
μ = 1.7 D



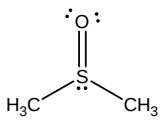
ε = 59
μ = 1.4 D



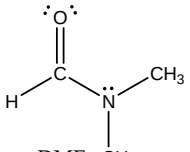
ε = 111
μ = 3.8 D

Polar protic solvents are good at solvating anions (with their hydrogen ends) and cations (with their oxygen ends). They tend to inhibit S_N2 reactions because solvent molecules are strongly solvating the nucleophile preventing easy approach to the backside of the C_α carbon.

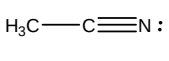
Polar aprotic solvents - aprotic means there is no polarized hydrogen atom attached to oxygen



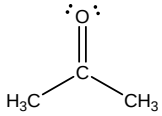
DMSO
dimethyl sulfoxide
ε = 47
μ = 3.9 D



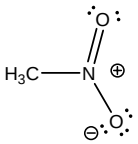
DMF
dimethyl formamide
ε = 37
μ = 3.9 D



AN
acetonitrile
ε = 38
μ = 3.9 D



acetone
ε = 21
μ = 2.9 D



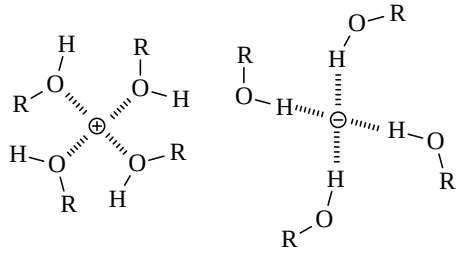
nitromethane
ε = 36
μ = 3.5 D

Polar aprotic solvents do not have any polarized hydrogen atom to solvate anions. They do usually have a very strong, concentrated partial negative end that is good at solvating cations. Cations are tied up with the solvent, while anions (nucleophiles/bases) are relatively unsolvated and much more reactive than in polar protic solvents. These are very good solvents for S_N2 reactions.

Both protic and aprotic polar solvents usually have a concentrated negatively polarized oxygen or nitrogen which can interact strongly with cationic species. Polar aprotic solvents have similar dielectric constants to polar protic solvents. So, the main difference is that polar aprotic solvents do not have any polarized hydrogen to solvate anions. This leads to poorer solvation of anions which makes them much better nucleophiles in S_N2 reactions. A more exposed anion is a more reactive electron pair donor, which is a good thing for S_N2 reactions. Polar aprotic solvents like DMSO, DMF and acetone are therefore preferred for S_N2 reactions.

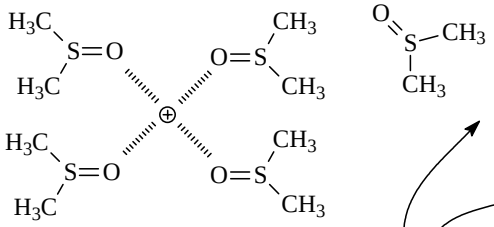
Cation/anion solvation shells in polar protic and aprotic solvents

polar protic solvents

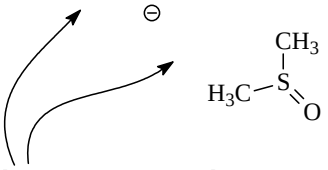


Strong solvent interaction with both cations and anions. The anion/solvent shell must be shed before a reactive encounter with the RX substrate can occur to induce an S_N2 reaction. A more basic anion is more hydrogen bonded.

polar aprotic solvents



Strong solvent interaction with cations.



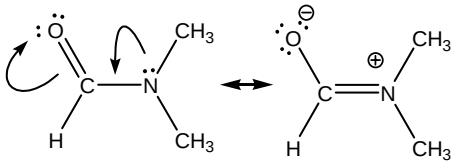
Weak solvent interactions with anions. Electron pair donation (S_N2) is much easier than in protic solvents. Direct reaction with the RX substrate is possible from the more "free" lone pairs, so a more basic anion is also a more nucleophilic anion.

Activation energy is a measure of the energy barrier that must be overcome for a successful reaction. Higher activation energies produce slower rates of reaction. The following differences in activation energy, E_a, for S_N2 reactions with the given nucleophiles and methyl iodide (CH_3I) indicate differing rates of reaction. Show the mechanisms with curved arrows and explain the differences in the E_a (rates of reaction).

Nucleophile	$(CH_3)_2NCHO$ (ε = 37) E_a in DMF (kcal/mol)	(CH_3OH) (ε = 33) E_a in methanol (kcal/mol)
$:Cl:^-$	16.9	25.0
$:Br:^-$	17.3	23.0
$:I:^-$	20.9	18.0

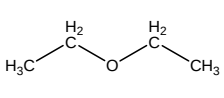
$Nu:^- + CH_3\text{-}I \longrightarrow$?

DMF = dimethyl formamide
(a polar aprotic solvent)

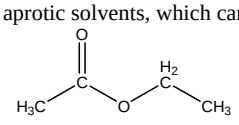


The second resonance structure shows concentrated negative charge on oxygen (interacts well with positive charge) and difuse positive charge at nitrogen end (interacts poorly with negative charge).

A few examples of nonpolar and aprotic solvents, which can work well for reactions where charge is not a factor or phase transfer catalysis is possible.

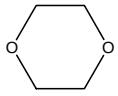


ε = 4
μ = 1.4 D



ε = 6
μ = 1.8 D

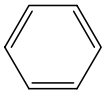
ε = 8
μ = 1.6 D



ε = 2
μ = 0.0 D

CH_2Cl_2

ε = 9
μ = 1.6 D

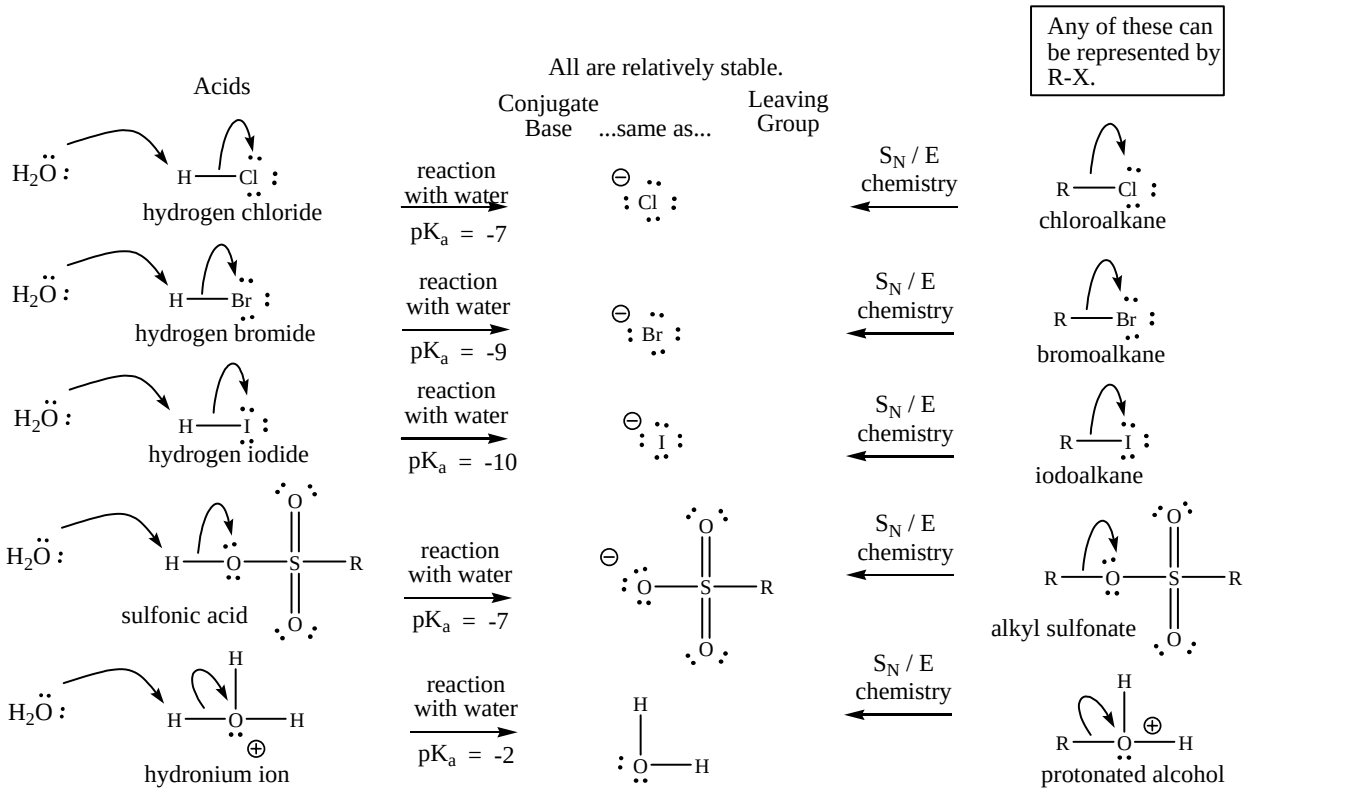


ε = 2
μ = 0.0 D

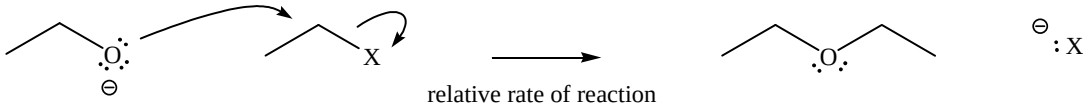
Good Leaving Groups

A leaving group has to be a reasonable, stable entity (usually anionic) so that the overall reaction thermodynamics are favorable. Initially, we will begin using five different variations of leaving groups in our course (there are many others). While there are differences in leaving group ability, we will consider all of them "good" and represent them with "X", as in R-X compounds. Four of our leaving groups leave as anions (similar to their conjugate acids) and one of our leaving groups leaves as a neutral molecule, water (from a protonated alcohol). The pK_a of an acid can provide a comparison of how well its conjugate base leaves a proton and, while not exactly the same, we can use that number as an indication of how well a leaving group leaves a carbon atom. A low pK_a for an acid should indicate a stable conjugate base, and thus a good leaving group in S_N/E reactions.

Our five good leaving groups (for now) – all considered as "X" in our course

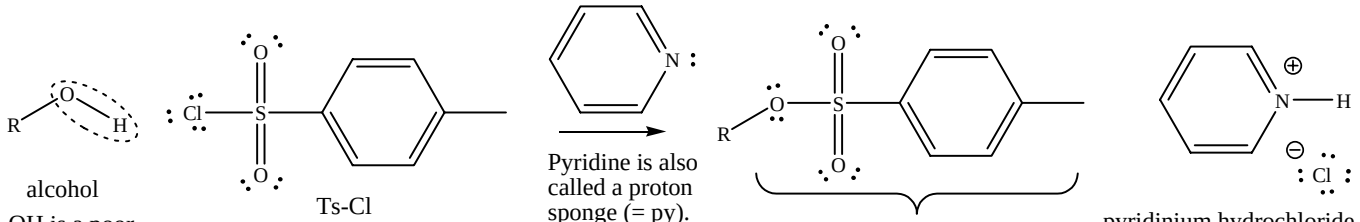


Leaving group ability in S_N2 reactions with ethoxide nucleophile.



X =	relative rate of reaction
-F	0
-Cl	1
-Br	830
-I	1210
-OTs	1500

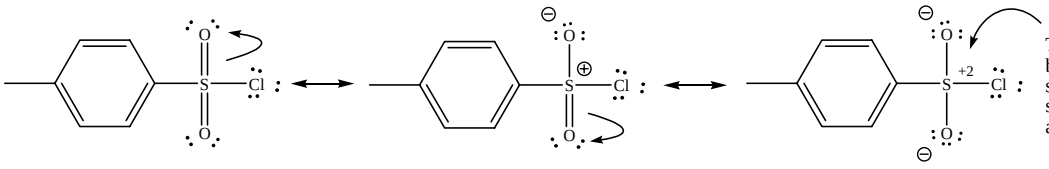
How to make an alkyl sulfonate from an alcohol, and turn the lousy OH leaving group of an alcohol into an excellent leaving group.



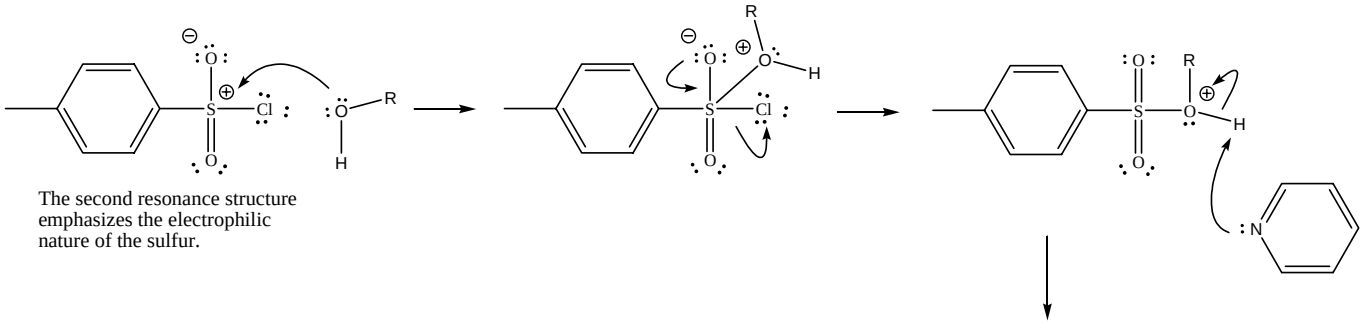
There are many variations of sulfonic acids, but we will only use toluenesulfonate esters, also called tosylates and represented as R-OTs. They can be made from toluenesulfonyl chloride (Ts-Cl), and alcohols (ROH), with pyridine serving to neutralize the H-Cl co-product.

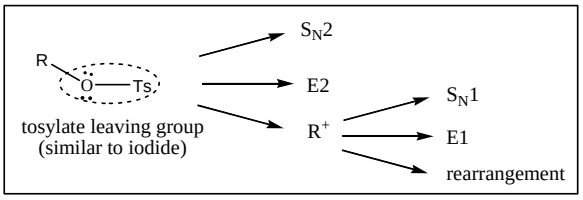
Possible Mechanism for Tosylate Formation from an Alcohol and Tosyl Chloride

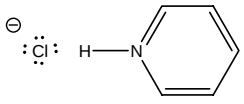
Resonance structures of tosyl chloride before attack of alcohol

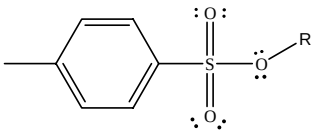


Possible Mechanism – addition of nucleophile before leaving group leaves



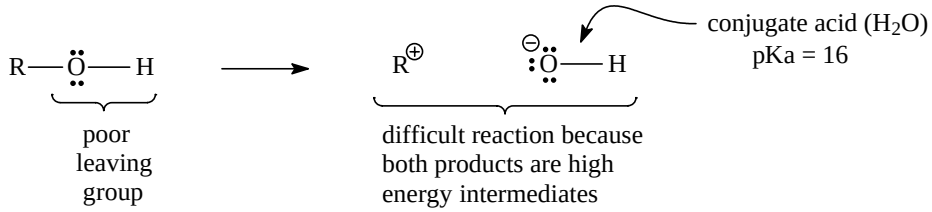


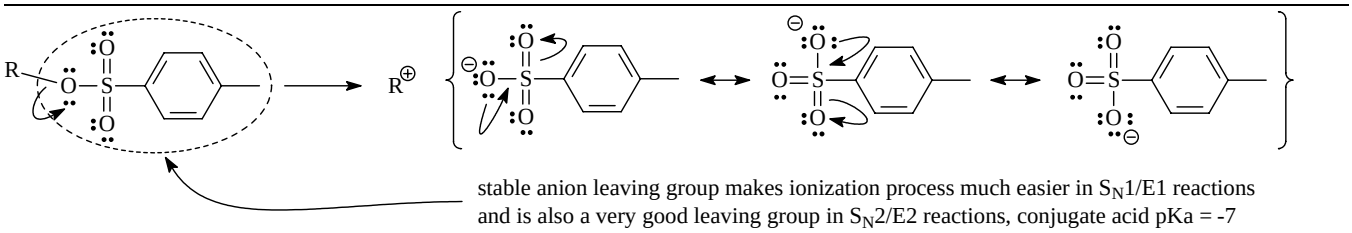




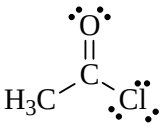
The reaction presented above is a general reaction of acid chlorides, which produces esters (of carbon = organic, nitrogen = inorganic, sulfur = inorganic, phosphorous = inorganic and others). The oxygen(s) and chlorine inductively pull electron density from the central atom (C, N, S or P) and make it very partial positive. This inductive effect is reinforced by a resonance effect, which in C and N is somewhat less important due to the lack of an octet, but in sulfur and phosphorous is very reasonable since those atoms retain an octet.

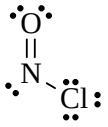
Once the alcohol oxygen is attached to the sulfonyl portion, the oxygen becomes a good leaving group and can leave as a very stable anion. (Think again of a stable base vs. its strong acid K_a/pK_a.)

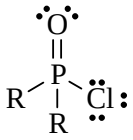




Problem – a. Show analogous resonance structures for the carbon, nitrogen and phosphorous acid chlorides to those given above for tosyl chloride which emphasizes their electrophilic character.

a 

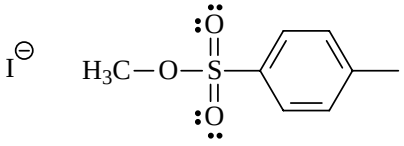
b 

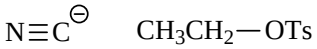
c 

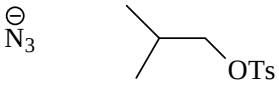
b. Show a similar mechanism of substitution (to that of tosyl chloride, above) for each of the above acid chlorides with methanol as the attacking alcohol. What is the nucleophile? What is the electrophilic atom in each example? What is the leaving group in each example?

c. Show a similar mechanism of substitution (to that of tosyl chloride, above) for each of the above acid chlorides with methylamine as the attacking compound. What is the nucleophile? What is the electrophilic atom in each example? What is the leaving group in each example?

Problem –
a. Show how each of the following compounds can react in an S_N2 reaction (mechanism). Identify the nucleophile, substrate, leaving group and product in each equation (-$OSO_2C_6H_4CH_3$ = -OTs)

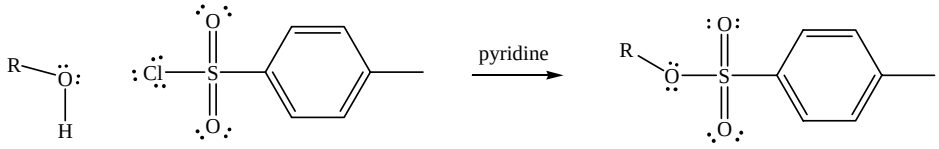
a 

b 

c 

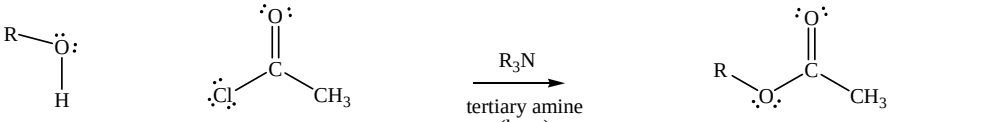
b. What alcohol and reactions would generate each of the above tosylate esters? Write out the reaction equation, including the necessary reagents to produce the desired transformation.

Problem - Alcohols can be converted into inorganic esters and organic esters. An example of each possibility is shown below.



alcohol — toluenesulfonyl chloride (tosyl chloride) — alkyl tosylate (an inorganic ester)

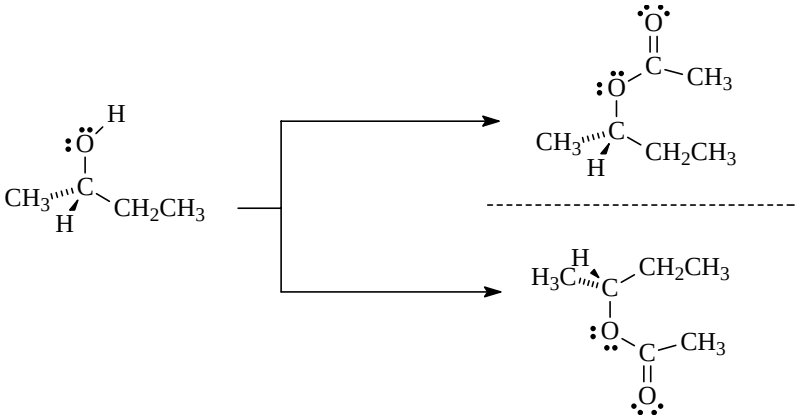
mechanism = acyl-like substitution



alcohol — acetyl chloride (an acid chloride) — alkyl ethanoate (an organic ester)

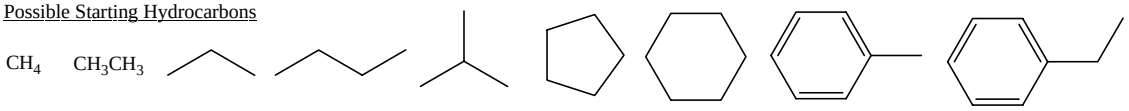
mechanism = acyl substitution

Use these two reactions and the fact that -OTs is a good leaving group and $CH_3CO_2^{--}$ is a good nucleophile to propose a synthesis of both enantiomers shown below from the chiral alcohol shown. Classify all chiral centers as R or S.

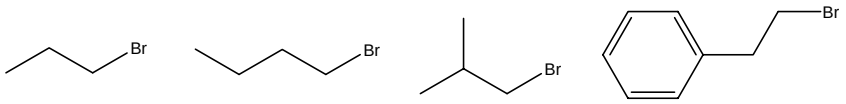


Available chemicals from the catalog

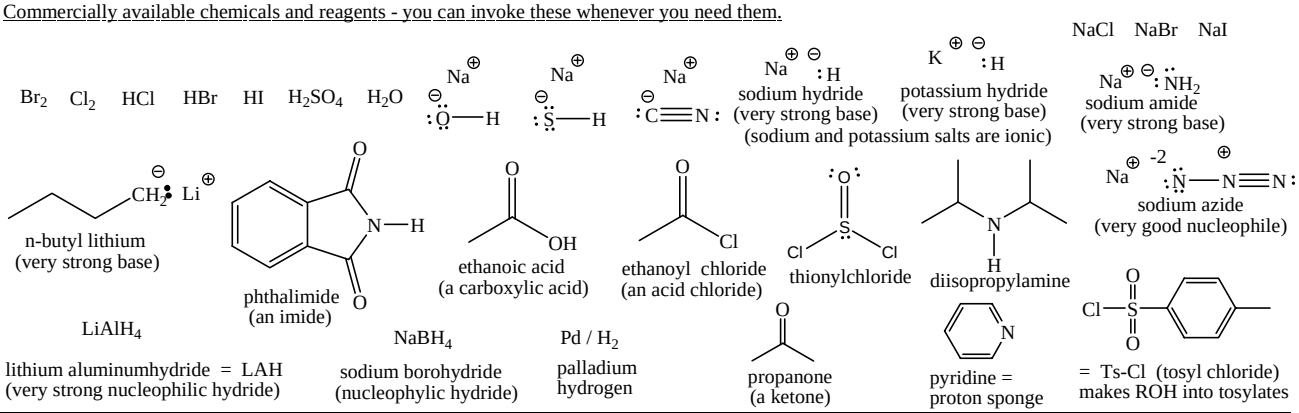
Possible Starting Hydrocarbons



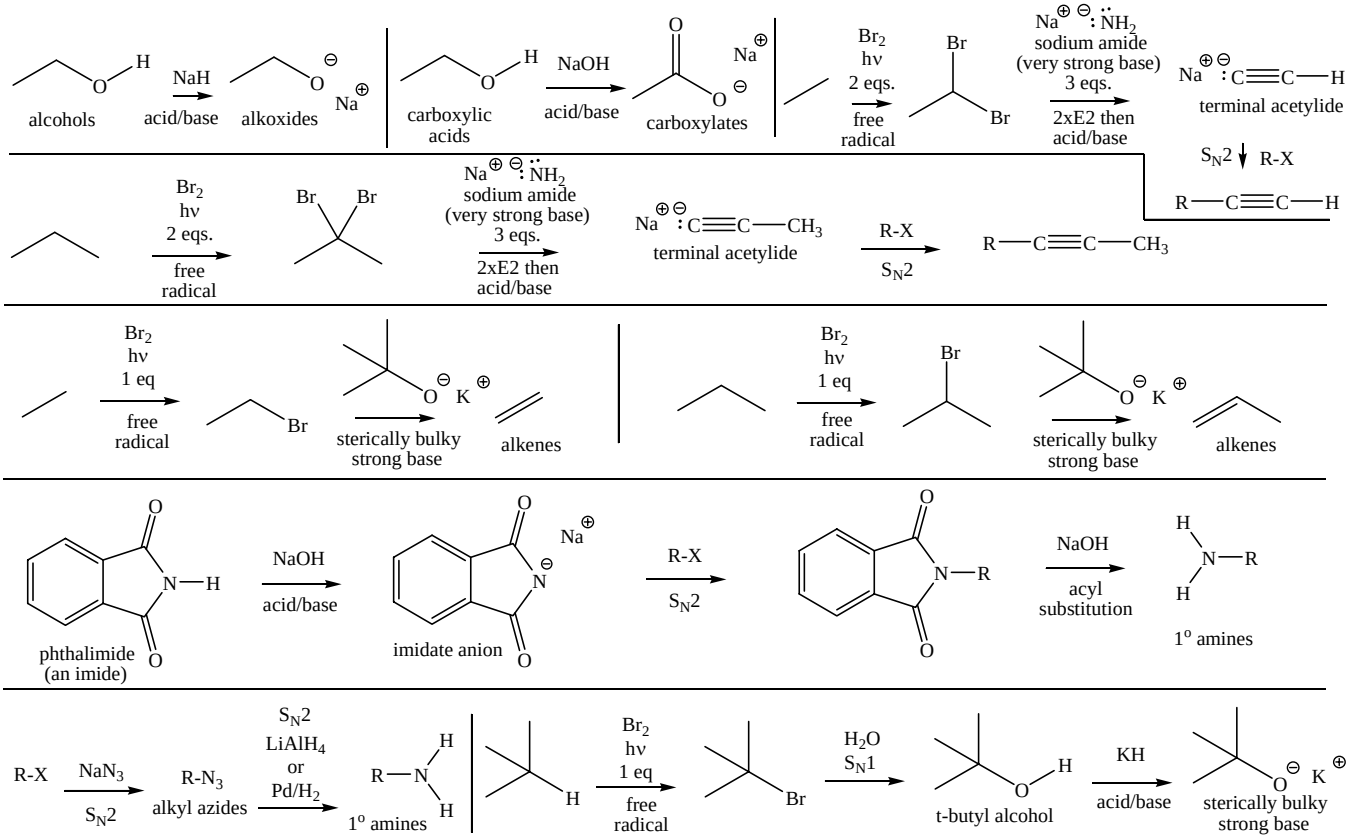
For now, these primary RX compounds are available. Later you will have to make them.



Commercially available chemicals and reagents - you can invoke these whenever you need them.

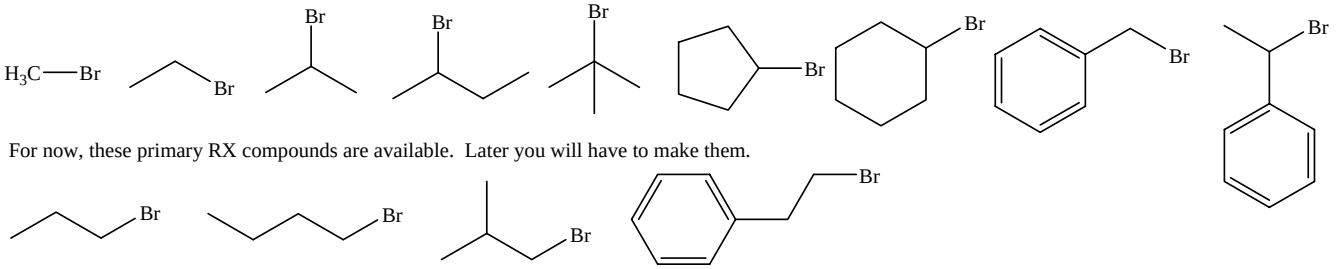


Make these from above reagents -examples are provided in the pages that follow.



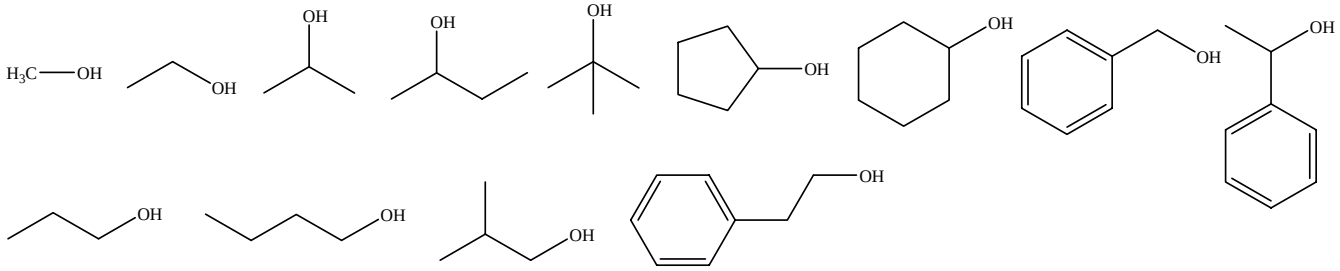
Synthetic targets we can make.

Make these from free radical bromination of alkanes

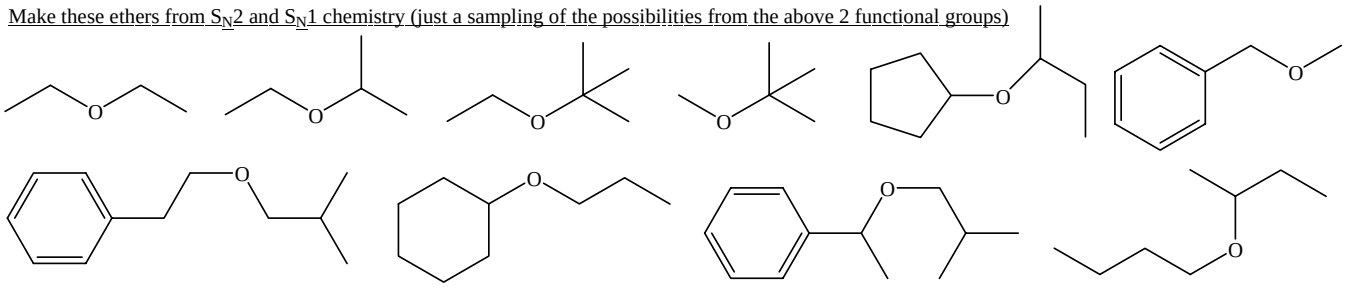


For now, these primary RX compounds are available. Later you will have to make them.

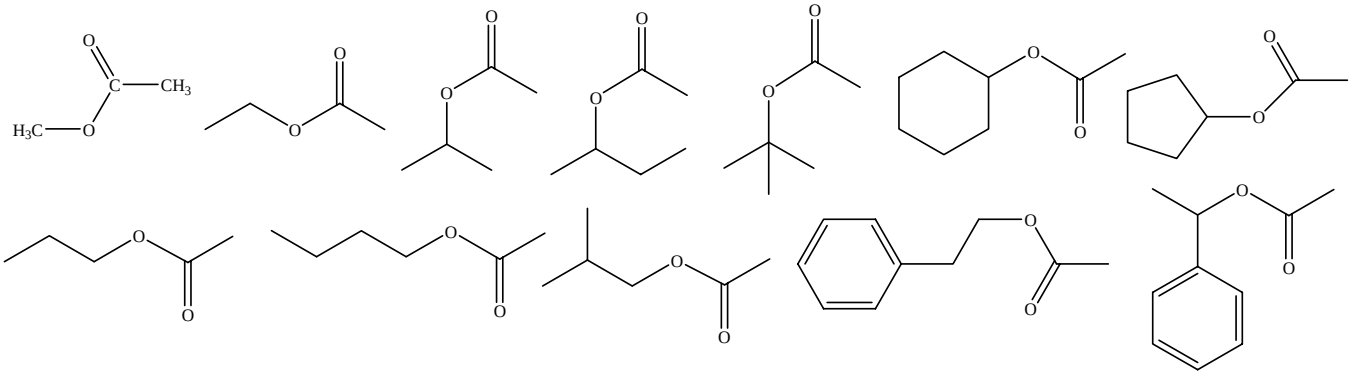
Make these alcohols from S_N2 and S_N1 chemistry



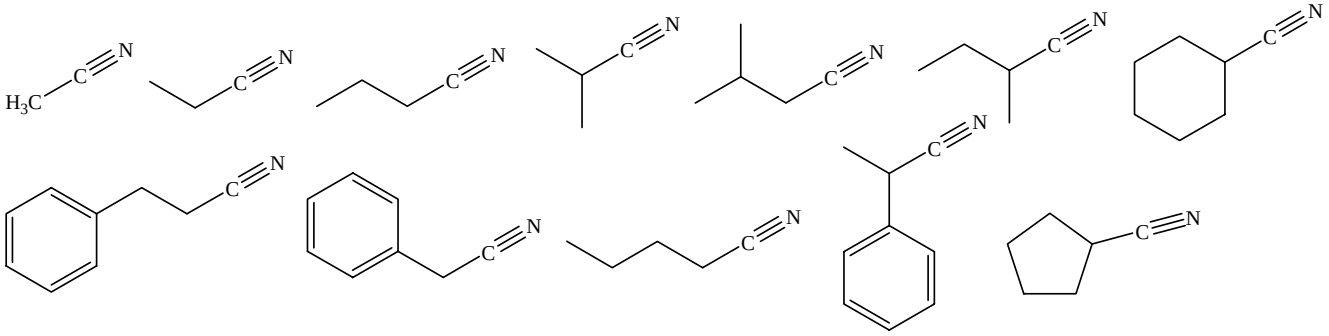
Make these ethers from S_N2 and S_N1 chemistry (just a sampling of the possibilities from the above 2 functional groups)



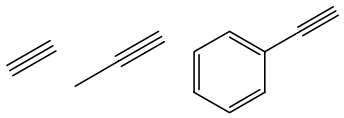
Make these esters from S_N2 and S_N1 chemistry (make 2° alcohols using acyl substitution, not possible using S_N2 and RX + $HO^{\ominus}$)



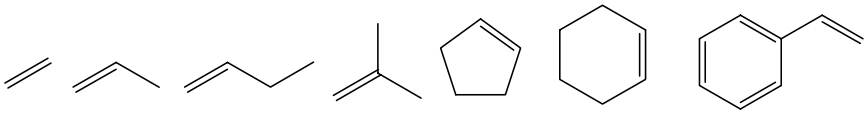
Make these nitriles from S_N2 chemistry



Make these alkynes from E2 chemistry (twice)

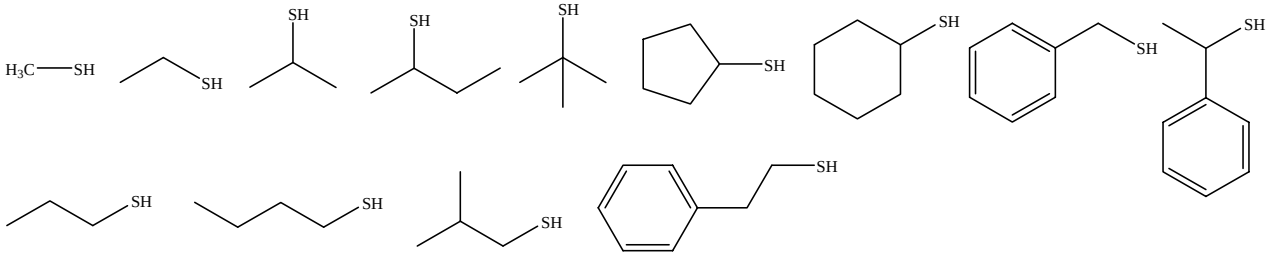


Make these alkenes from E2 chemistry once)

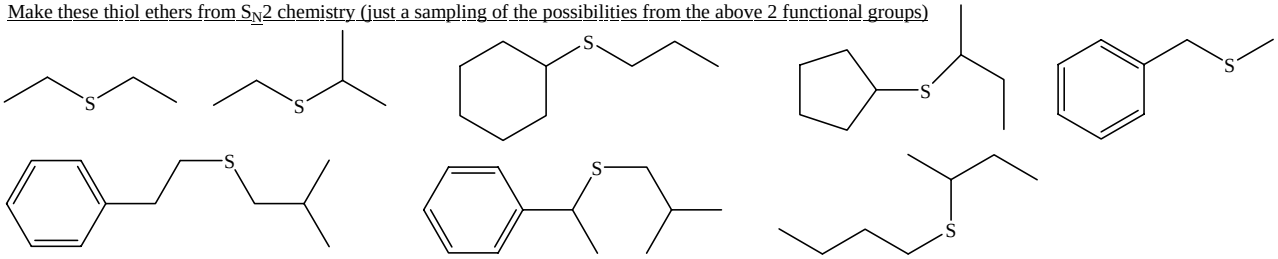


Make these alkynes from S_N2 chemistry

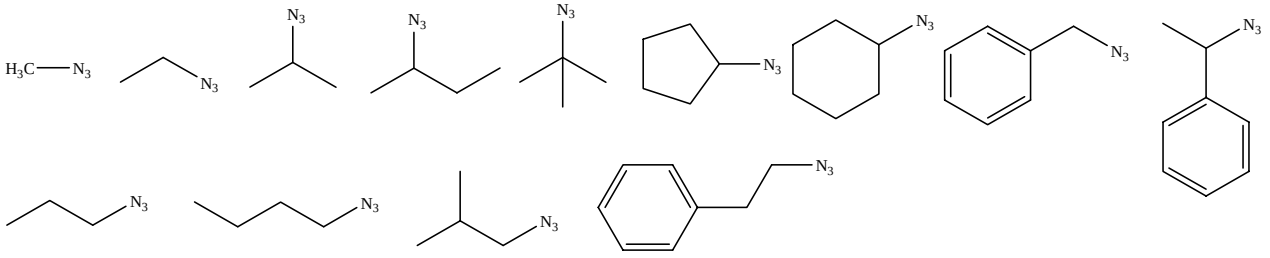
Make these thiols from S_N2 chemistry



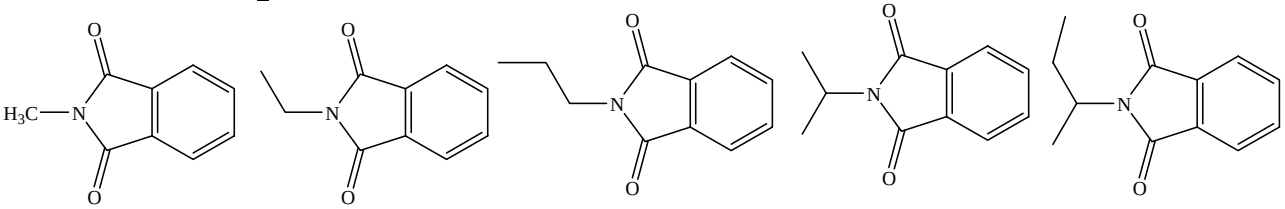
Make these thiol ethers from S_N2 chemistry (just a sampling of the possibilities from the above 2 functional groups)



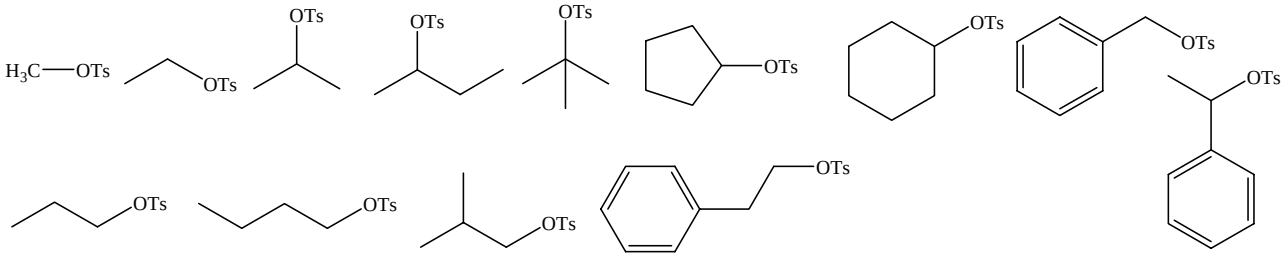
Make these azides fromS_N2 chemistry (made in 1º amines in one more step = $LiAlH_4$ or Pd / H_2)



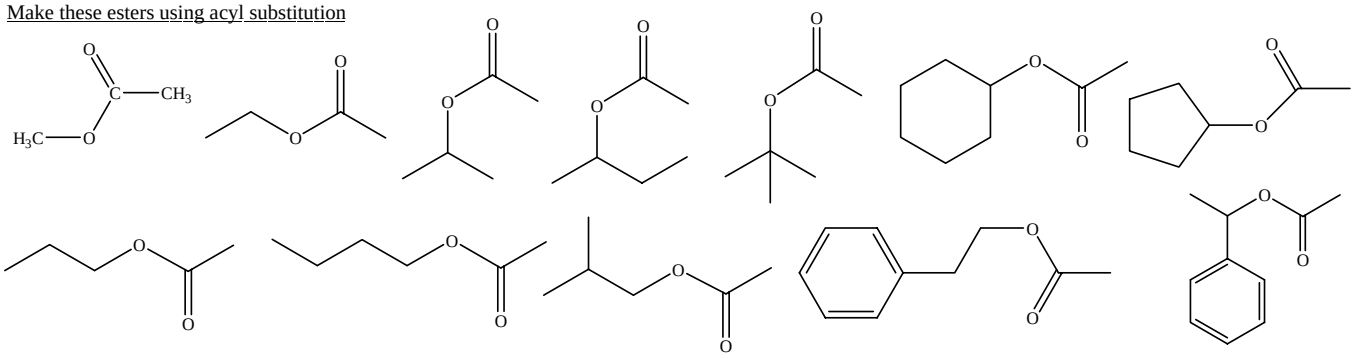
Make these phthalimides fromS_N2 chemistry (made in 1º amines in one more step = NaOH)



Make these tosylates from alcohols and tosyl chloride / pyridine



Make these esters using acyl substitution



Make these amides using acyl substitution