

# Problem Set 1

## Carbocations, Carbanions, and Radicals

### 1.1 Problems 1, 2, and 6

9/4:

- Logistics.
  - The list of topics is the syllabus.
  - We'll cover everything we need to know in discussion, but we can supplement what we discuss here with our own readings.
    - Mo recommends the OChem II textbook.
  - Students: Frank, Christina, Jasmin, Alex (senior undergrad), and ??.
  - PSet 2 passed out on paper.
  - The locked door code for 18-578 is 9344, if we ever get here before him.
  - He'll ask us at the beginning of class which problems seem the most interesting to us.
  - We should try every problem on the PSet before class.
  - We'll probably put multiple problems up at the same time.
    - This is a team effort to sort out the board, not one person defending their solution.
  - We will not get through six problems every time.
  - These problems are basically ice breakers for discussion.
  - He encourages us to compare notes and compare solutions, but we must try all the problems first by ourselves.
    - Do not search for the solutions on Google; this takes away from the discussion.
  - Mo will send PSet 2 as a PDF!
  - These examples were chosen to start because Mo wants to begin with bond dissociation energy, carbocations, carbanions, and radical chemistry.
- We now begin discussing Problem 1.

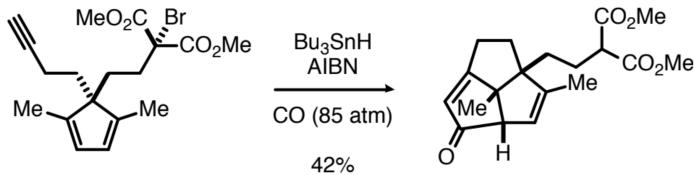
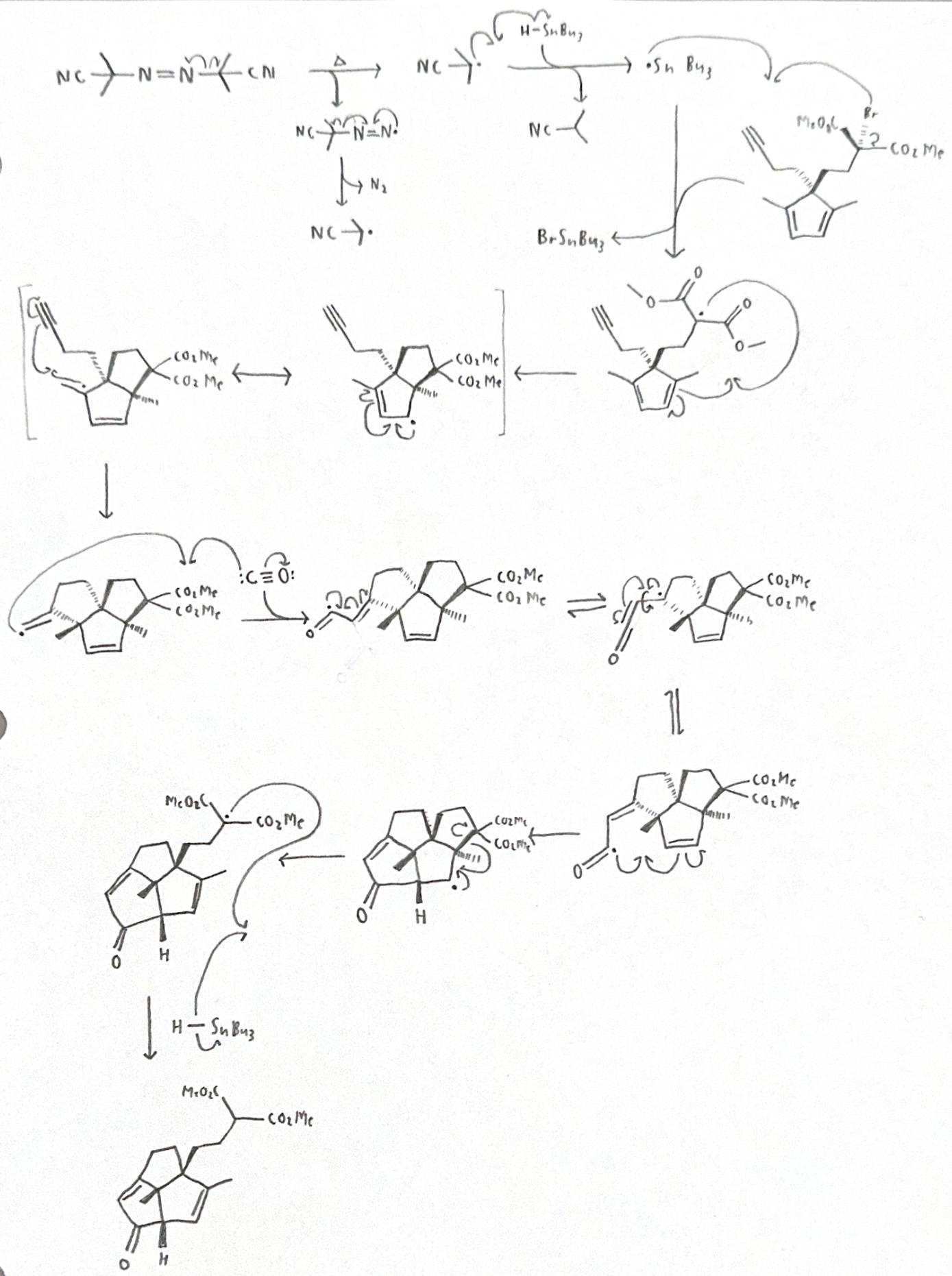


Figure 1.1: PSet 1, Q1.

- A key technique for thinking about, rationalizing, and solving this problem is **bond dissociation energy** (BDE).
  - In fact, we can apply BDE from the very beginning: AIBN's C–N bond is the first to break because its BDE is an extremely low  $\sim 30 \text{ kcal/mol}$ .
    - Additionally, AIBN's C–N bonds do not have to break symmetrically. Rather, one bond may break first (driven by its vibrational modes) to generate the stable tertiary carbon-centered radical *and* a nitrogen radical.
    - After some finite time (from picoseconds to much longer), the second C–N bond will split, off-gassing N<sub>2</sub>.
  - At this point, we must remember that this is a three-step radical reaction (initiation, propagation, termination), and AIBN is our initiator.
    - Thus, we don't have *equivalents* of AIBN to speak of, but rather a tiny amount in a sea of everything else.
  - Our AIBN radical is very stable, but the H–SnBu<sub>3</sub> bond is so weak that it will still break when the two bump into each other.
  - Indeed, BDE can justify why this bond breaks over any of the reactant C–H's.
    - H<sub>3</sub>C–H is 100 kcal/mol.
    - HR<sub>2</sub>C–H is  $\sim 90 \text{ kcal/mol}$ .
    - Tributyl tin hydride BDE is a whopping  $\sim 73 \text{ kcal/mol}$ .
    - Know BDEs!! [Here](#)'s a great resource for C–H bonds on Wikipedia.
  - The ·SnBu<sub>3</sub> radical is halophilic, and does indeed head straight for the bromine to form a resonance-stabilized radical on the reactant.
    - A typical C–Br BDE is 68 kcal/mol.
    - Why does AIBN pick off the H–SnBu<sub>3</sub> over the bromine, then??
      - Alexander Müller suggested it could be because tin and bromine are closer on the periodic table than they preferentially react (think hard/soft acid base theory).
  - Once we create the stabilized radical on the compound, we have to think about where it could go.
    - Do a C–H abstraction analysis to see what hydrogens the radical might be able to pick off.
    - The methyl hydrogens are relatively accessible and allylic, but the transition state would be seven-membered, which is less than ideal. Same with the propargyl hydrogens.
    - Indeed, 1,5-H atom transfer is the most favorable because it's a six-membered transition state.
      - Linear, intermolecular is the most stable transition state.
      - But when we get to 1,5-abstraction, intermolecular concentration dependencies (think chelate effect) start to compete with linearity.
      - However, 5-exo-trig is favorable addition chemistry.
        - 6-endo-trig will be more stable thermodynamically (secondary radical formation).
        - When 5-exo-trig is irreversible, we form that (the kinetic product).
        - When 5-exo-trig is reversible, we form exclusively the 6-endo-trig product.
      - Look up Baldwin's Rules!!
        - Exo/endo because the radical is outside/inside the formed ring.
        - dig/trig/tet naming is due to the hybridization of the carbon we're attacking (*sp*, *sp*<sup>2</sup>, *sp*<sup>3</sup> — respectively).
  - Be able to switch fluently between pK<sub>a</sub>'s and BDEs.

- An *sp* carbanion is more stable because we're holding that electron density tight near the positive nucleus.
  - An *sp* radical is extremely unstable because it has nowhere to draw electron density from.
  - Hyperconjugation stabilizes a primary radical over the methyl radical.
  - The AIBN radical is not stabilized by an EWG (EWGs destabilize radicals), but it is stabilized by resonance with the cyano group.
- So if hydrogen abstraction is less than ideal, let's think about what other kinds of chemistry radicals can do.
  - Addition chemistry is one major such option! Double bonds are nucleophilic sites that a radical will naturally be attracted to, so our achiral compound can undergo a radical attack at either of the quaternary carbons with essentially the same effect.
    - Thus, we will have a racemic mixture of products, but the stereochemistry of each molecule will be set by this attack.
    - That's why Mo wanted the stereochemistry indicated; to show that the attack will lead to a syn product.
    - Indeed, the *cis*-fused 5-membered ring is 15 kcal/mol more stable than the *trans* equivalent.
  - We can now resonate the radical over to the more stable tertiary position.
  - Now we begin the abstraction analysis over again.
    - No good-looking hydrogens to abstract, so it's probably addition chemistry again.
    - If we add into the alkyne, we can do a kinetically favored 5-exo-dig.
    - Additionally, there *will* be a thermodynamic driving force for this reaction: Compare bond energies! A C–C  $\sigma$ -bond is stronger than a C≡C  $\pi$ -bond.
  - Maxim: Whenever we have the opportunity to form a C–C  $\sigma$ -bond, we like to do that.
  - Now is a good time to pick up a CO.
    - Again, we are thermodynamically driven by the breaking of a C≡O triple bond to form a C–C single bond.
    - How about the stereochemistry?
      - We need the *Z* alkene to complete the cyclization, but in fact, the *Z* and *E* alkenes are equivalent! This is because resonance with the radical allows unrestricted rotation around the “alkene” bond in the other resonance structure.
      - Note that equilibrium arrows are good for E/Z isomerism because we are moving the atoms, not just the electron density as in resonance.
  - The rate of cyclization of the acyl radical must outcompete reduction by the tin hydride.
  - Then we can break a bond to form a more stable radical.
  - Finally, we can react with tributyltin hydride in a propagation step.
  - Altogether, the full solution to PSet 1, Q1 is on the next page.



- We now begin discussing Problem 2.

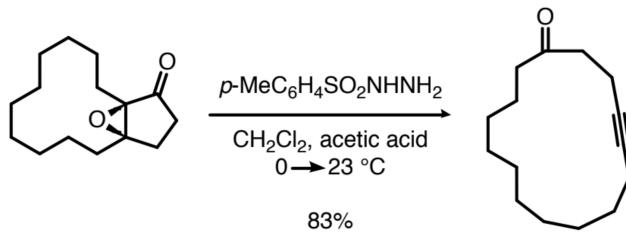
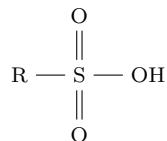
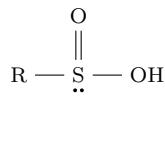


Figure 1.2: PSet 1, Q2.

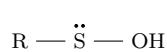
- Aside: The naming of the reagent.



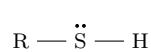
(a) Sulfonic acid.



(b) Sulfinic acid.



(c) Sulfenic acid.



(d) Thiol.

Figure 1.3: The oxidation states of sulfur.

- There are four different oxidation states of sulfur.
- They are referred to as (from most oxidized to most reduced) **sulfonic acid**, **sulfinic acid**, **sulfenic acid**, and **thiol**.
- Now back to the problem at hand.
- In acidic solution, the first thing we can do is make the carbonyl more reactive via protonation.
  - Note that the hydrazide may get protonated with the acid (and perhaps 90% of it will be!), which would shut down nucleophilicity.
  - But whatever hydrazide remains can do the demonstrated chemistry.
- Then our hydrazine species can come in and add via nucleophilic addition.
- After this, we're fairly stable. But a negatively charged oxygen (like the epoxide) in acidic species can be protonated!
- After protonation, we'll want to break the epoxide ring. But where can we draw the electron density from?
  - Looking around, notice that the second hydrazine nitrogen has a lone pair that can be used!
  - Additionally, we can start building toward our alkyne located three carbons away from the position that could become the ketone after our new alcohol undergoes some modification.
- Specifically, that modification will be kicking down the oxygen electrons to form the triple bond, kick out the leaving group, and break the leaving group in half all in one concerted step. This bond breaking process is still favorable because...
  - The relevant orbitals align in an **antiperiplanar** fashion;
  - We are strengthening and weakening consecutive bonds;
  - Antibonding molecular orbitals receive donations of electron density, specifically the  $\sigma^*$ -antibonding orbital of the S–N bond;

- The entropic gain in going from one molecule to three favors this step thermodynamically.
- Aside: 4-membered transition states.

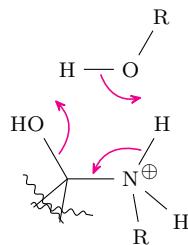
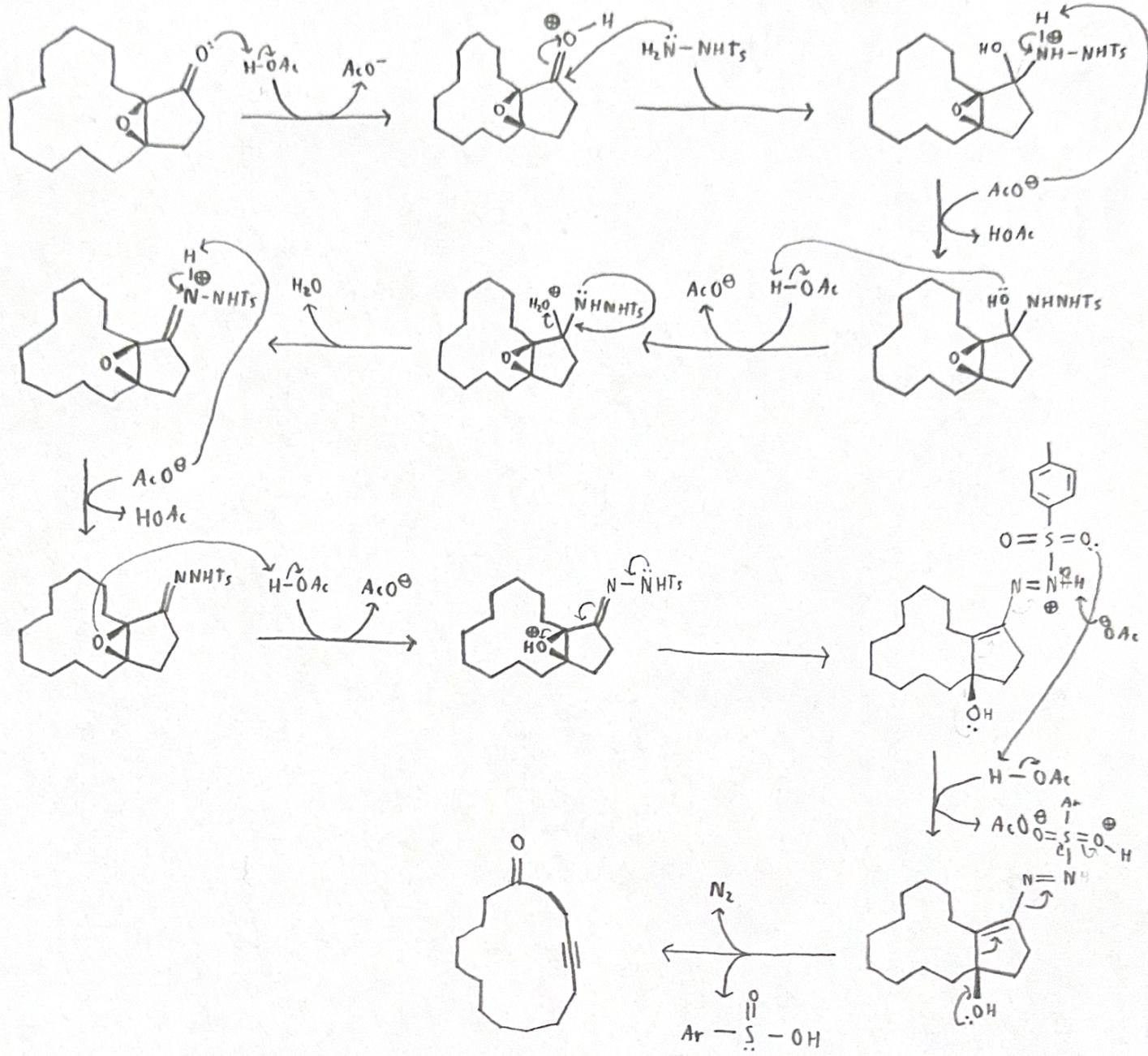


Figure 1.4: Using an acid as a proton transfer agent.

- At a minimum, look to add an O–H to the ring to make it a six-membered transition state.
- We could also do this in a two-step intermolecular process.
- As a specific example, amide bond hydrolysis under basic conditions is more reminiscent of the six-membered ring, though.
- Aside: Protonation and  $pK_a$ 's.
  - Ketones are much harder to protonate than comparable species.
    - $pK_a$  of hydronium is  $-1.7$ .
    - $pK_a$  of protonated ethylene oxide (the simplest epoxide) is  $-2$ .
    - $pK_a$  of protonated carbonyl is  $-6$  to  $-8$ .
  - Protonated THF is more easily stabilized by solvation effects than protonated diethyl ether because the “arms” are being held back in THF, so the oxygen lone pairs are more accessible.
  - Carboxylic acid derivatives vary in terms of how hard they are to protonate.
    - Acid chloride is  $-9$ .
    - Amide is  $0$  (resonance stabilization of the positive charge to the nitrogen).
    - Ether is in the middle (still has resonance stabilization, but oxygen is more electronegative).
- Random note: Strain for a 5-membered ring is about  $5\text{ kcal/mol}$ .
- Altogether, the full solution to PSet 1, Q2 is on the next page.



- We now begin discussing Problem 6.

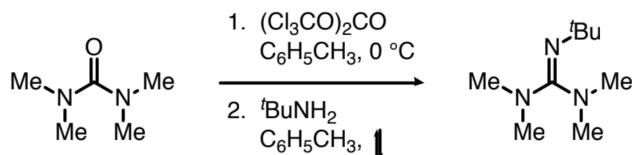
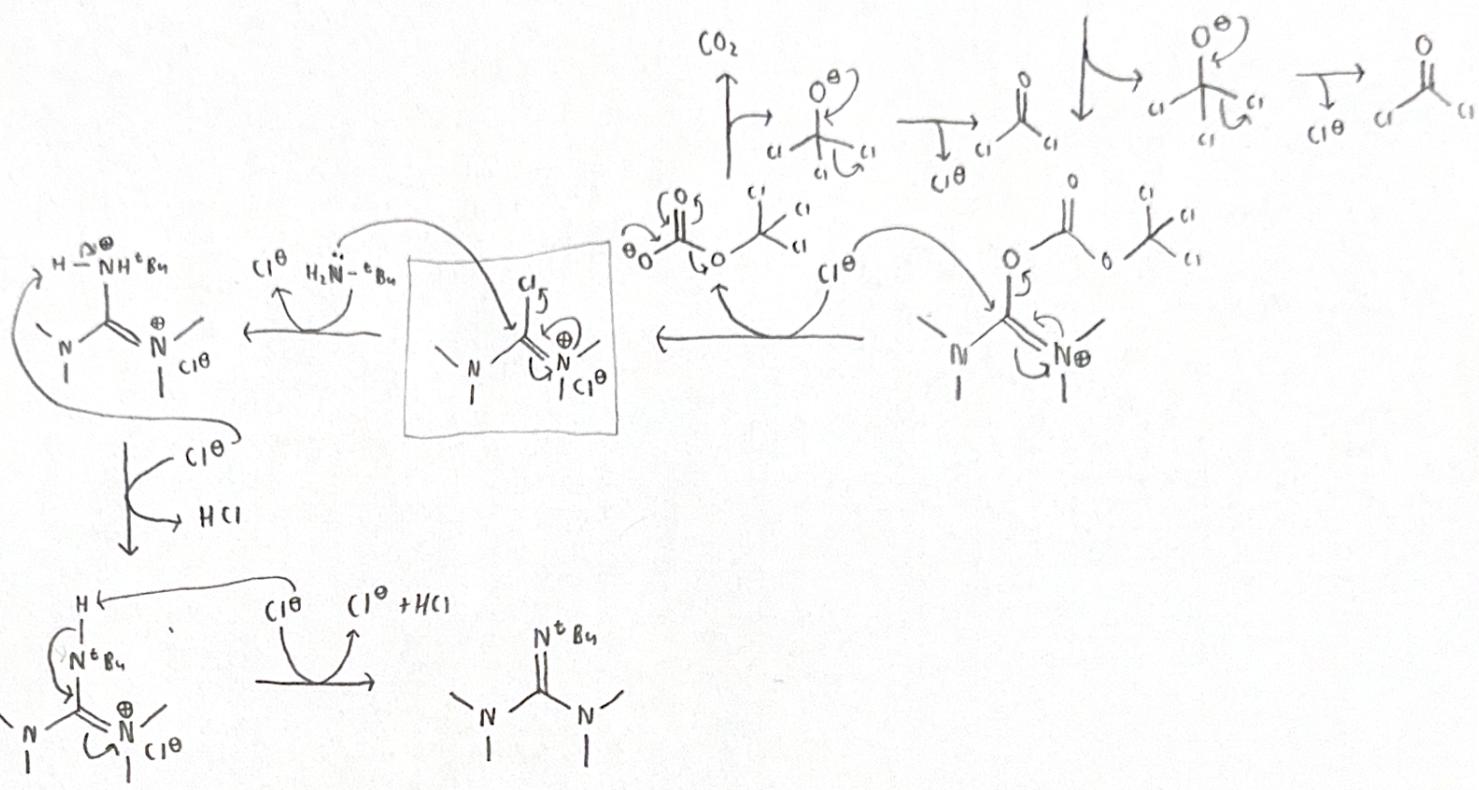
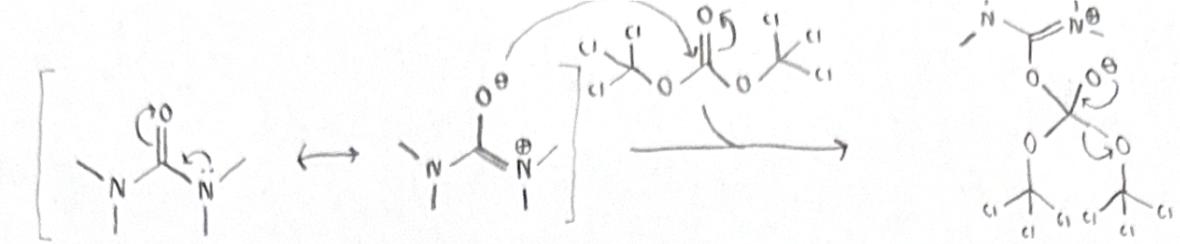


Figure 1.5: PSet 1, Q6.

- The first reagent is triphosgene. We use it because...
  - It is far less toxic than phosgene;
  - It generates phosgene *in situ*.
- First, make the reactant more nucleophilic via resonance.
- The reactant then attacks the reagent.
  - Note that Mo is fine with us drawing out a nucleophilic substitution as electrons kicking up and back down in one step instead of in two (as Levin required). As such, I have done a bit of both in the final mechanism for this problem.
- The leaving group is unstable, and undergoes  $\alpha$ -elimination of one chlorine.
- Chloride then attacks the positive center, kicking electrons up and down and kicking out a leaving group.
- $\text{CO}_2$  then leaves, and we get another phosgene and chloride.
- The chloride salt is where we end (the boxed intermediate in the final mechanism).
  - Note that overall at this point, we've generated 2 equivalents of phosgene and 1 equivalent of  $\text{CO}_2$ ; all chloride generated has been reincorporated into the molecule.
- Now we add the second species.
  - It attacks the iminium ion and kicks out the chloride.
  - Chloride then neutralizes the molecule, generating  $\text{HCl}$ .
  - Finally, one more chloride attacks the remaining nitrogen hydrogen.
    - Decide which way we go based on the  $\text{p}K_a$ 's of the relevant acids.
- Note that we need one extra equivalent of *tert*-butylamine to sequester the  $\text{HCl}$ .
- Altogether, the full solution to PSet 1, Q6 is on the next page.



- Next time.
  - We'll start next time with problems 4-5 of PSet 1.
  - First 5 sessions are with Mo, then Alison has 6-10.
  - 10 total sessions in this class.
- Memorize more  $pK_a$ 's!!