Week 8

Amine Reactions and Carbohydrate Structure

8.1 Amines 2

5/17:

- Midterm 2.
  - Scores back after class.
  - Request a regrade (of your whole exam) ASAP if needed.
  - Raw score: 56 ± 24 (median 59).
  - Range: 0-99.
  - Adjusted: 70 ± 10.
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 20.4, 20.12, and 20.6-20.7.
  - Next time: Sections 22.1-22.2, 22.9A.
  - Practice problems: 20.19-20.24, 20.26, 20.34-20.36.
- Review of last lecture.
  - Basicity of amines.
  - Higher $pK_a(RNH_3{}^+)$ means more basic RNH_2.
  - Key: How willing is N to share its lone pair.
- Today, we will cover the following.

I. Properties of amines.
   B. Acid-base properties (cotd.).

II. Preparation of amines.
   A. Alkylation.
   B. Reduction.
   C. Hofmann rearrangement.
   D. Curtius rearrangement (review).

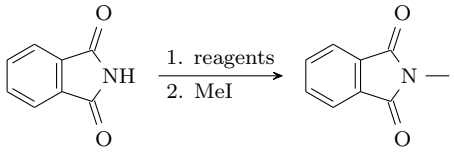
III. Reactions of amines.
   A. Hofmann elimination.
   B. Cope elimination.

- Acid-base properties (cotd.).
- Additional example amine pK_a's.
  - Py has p$K_a(PyH^+) = 5.3$.
    - Its basicity is intermediate between NH_3 and $PhNH_2$ due to its sp^2 hybridization.
  - Pyrrole has p$K_a(RH^+) = 0.4$.
    - Since nitrogen's lone pair here is fully incorporated into the aromatic system, it is not basic.
    - In fact, pyrrole has p$K_a(R) = 16.5$.
    - This means that its amine hydrogen is actually mildly acidic (about equivalent to ethanol's hydroxyl hydrogen).
  - Indole (left to us).
    - Indole is like pyrrole: To have $4n + 2$ aromatic electrons, it needs nitrogen's lone pair.
  - See the Aromaticity 2 lecture from Labalme (2022b) for more on aromatic pK_a's.
  - Amides.
    - An amide will coordinate a proton at its oxygen, not its nitrogen.
    - This protonated species will have p$K_a = 0$.
    - The reason for coordination at oxygen is that the resonance structure with a negative charge on oxygen makes a significant contribution to the overall molecule (oxygen is more electronegative than nitrogen). In fact, this resonance structure implies that the C–N bond in an amide is not rotatable, and thus the six atoms C–C(=O)–NH_2 are coplanar.
    - Additionally, the nitrogen protons are slightly acidic with p$K_a(RNH_2) = 18$.
    - Hence, if we react an amide with a Grignard, we will deprotonate the NH_2 portion.
- A note on how protonation can be used to isolate amines (and other basic species) when synthesizing them in the lab.
  - Begin by protonating the amines and performing an extraction.
  - The protonated amines will be attracted to the polar aqueous layer and all other organic compounds can be separated out with the organic layer.
  - Then we can deprotonate to recover our desired amines.
- Preparation of amines.
- Alkylation (direct).
- General form.

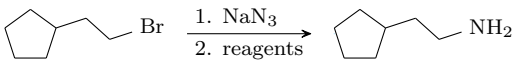
$$NH_3 \xrightarrow[2.\ NaOH]{1.\ MeI} MeNH_2$$

- Mechanism.
  - The first step proceeds via an S_N2 mechanism to yield a quaternary ammonium salt.
  - The second step (a basic workup) removes one of the three nitrogen protons, yielding $H_2O + NaI$ as side products.
- Problems with direct alkylation:
  - Even before the basic workup, we have base in solution (NH_3). This base can accomplish the second-step deprotonation, introducing $MeNH_2$ into our initial reaction mixture.
  - But adding alkyl groups (EDGs) creates more reactive amines, so $MeNH_2$ will preferentially attack CH_3I compared with NH_3.
  - Thus, with direct alkylation, we cannot stop at one particular stage; we will always get a mixture of NH_3, $MeNH_2$, Me_2NH, Me_3N, and Me_4NI.

- One potential solution.
  - In some cases, we can use excess amine and a bulky alkyl halide.
  - For example, mixing approx. 20 equivalents of $MeNH_2$ with BnCl yields fairly pure BnNMeH.
- Alkylation (Gabriel synthesis).
- General form.

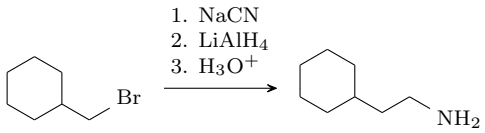


  - The Gabriel synthesis prepares primary amines.
  - The starting material is called **phthalimide**.
  - Reagents is either NaH (nice because it liberates $H_{2(g)}$ as an additional driving force) or K_2CO_3 (nice because it's not as strong as NaH).
- **Phthalimide**: A 2° amine, the lone hydrogen of which has has $pK_a = 8.3$ since it is subject to *two* EWG carbonyls and additional resonance with the aromatic ring. *Structure* see above left.
- Mechanism.
  - The first step is a deprotonation.
  - The second step proceeds via an S_N2 mechanism.
    - Thus, we preferentially use it in conjunction with primary alkyl halides.
    - Secondary, allylic, and benzylic alkyl halides will work.
    - An attempt to run this reaction with a tertiary alkyl halide will lead to elimination.
  - Notice that the product is a 3° amide and thus cannot react any further.
- There are three ways to recover the primary amine from the product above.
  1. Use H_2SO_4, H_2O, and heat.
     - This amide hydrolysis proceeds analogously to the last several steps of Figure 2.12.
     - A subsequent deprotonation of $MeNH_3^+$ will be required.
  2. Use NaOH, H_2O, and heat.
     - This amide hydrolysis proceeds analogous to the saponification mechanism.
  3. Use H_2NNH_2 and reflux.
     - See Solomons et al. (2016) for the mechanism.
- Reduction.
  - This method of preparation can proceed from a number of starting materials.
- From azides.



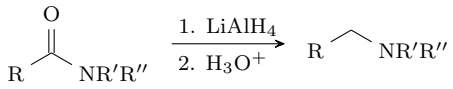
  - Begin with the desired alkyl group as an alkyl halide.
  - React it with an azide nucleophile via an S_N2 mechanism.
    - Azide is one of the few nucleophiles that is a very poor base, so it is very good for S_N2.
  - Reagents is either $LiAlH_4$ followed by an acidic workup or hydrogenation ($H_2 + Pd/C$).

- From nitriles.



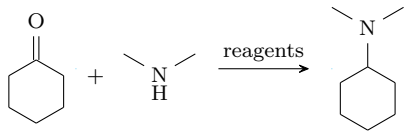
  - Take the desired alkyl group, S_N2 it with a cyanide nucleophile, and then reduce with $LiAlH_4$ as in Chapter 17.
  - Notice that this reaction adds an extra carbon before the amide, unlike with azides.

- From amides.



  - This is a review reaction; see the discussion associated with Figure 3.4.

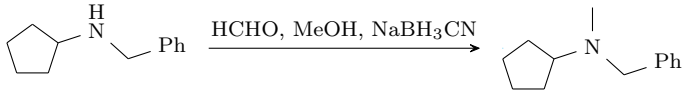
- From iminium ions (reductive amination).



  - This is a very useful reaction in the pharmaceutical industry.
  - Depending on the reagents, we can accomplish this reaction in a stepwise fashion or all at once.
  - Stepwise reagents.
    - Use mild H^+ followed by a mild hydride source, such as $NaBH_4$.
    - In the first step, we create an enamine in equilibrium with the corresponding iminium ion.
    - In the second step, hydride attacks the iminium ion's carbon, leading to the final product.
  - This set of reagents explains the name of the reaction: It is *amination* because we are replacing an oxygen with a nitrogen and *reductive* because we are reducing the iminium ion's double bond.
  - If we use these reagents, we must (in theory) perform the reaction stepwise because $NaBH_4$ can reduce any unreacted ketone.
    - In reality, there is a trick we can use to do this reaction all at once with these reagents.
  - One-step reagents.
    - Use sodium cyanoborohydride ($NaBH_3CN$) in alcoholic solvent (EtOH or MeOH).
  - $NaBH_3CN$ is a weaker hydride source (cyano groups are EWGs), so it can't react with the ketone because it's not electrophilic enough (the charged iminium ion is much more electrophilic).

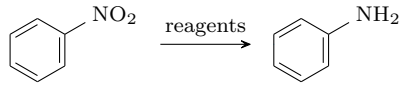
- Reductive amination describes the above reaction of a relatively complicated ketone with a relatively simple amine. If we use, instead, a relatively simple ketone and a relatively complicated amine, the reaction is called...

- Reductive alkylation.

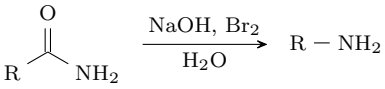


  - Remember that HCHO is formaldehyde, which is our carbon source here.

- Reductive amination/alkylation can be more controlled than alkylation.
  - This is because with alkylation, our final 3° amine could still form a quaternary ammonium salt in the presence of excess MeI.
  - However, a 3° amine can never form another iminium ion.
- From nitro groups.



  - Reagents is $H_2 + Pd/C$, $Fe + HCl$, or $Zn(Hg) + HCl$.
- Hofmann rearrangement.
- General form.



  - Whereas with azides and amides kept the number of carbons constant and nitriles added a carbon, here we lose a carbon.
  - This reaction is similar to the Curtius rearrangement.
  - The conditions are identical to those used in the haloform reaction, and we will see that there are homologies in the mechanisms, too.
- Mechanism.

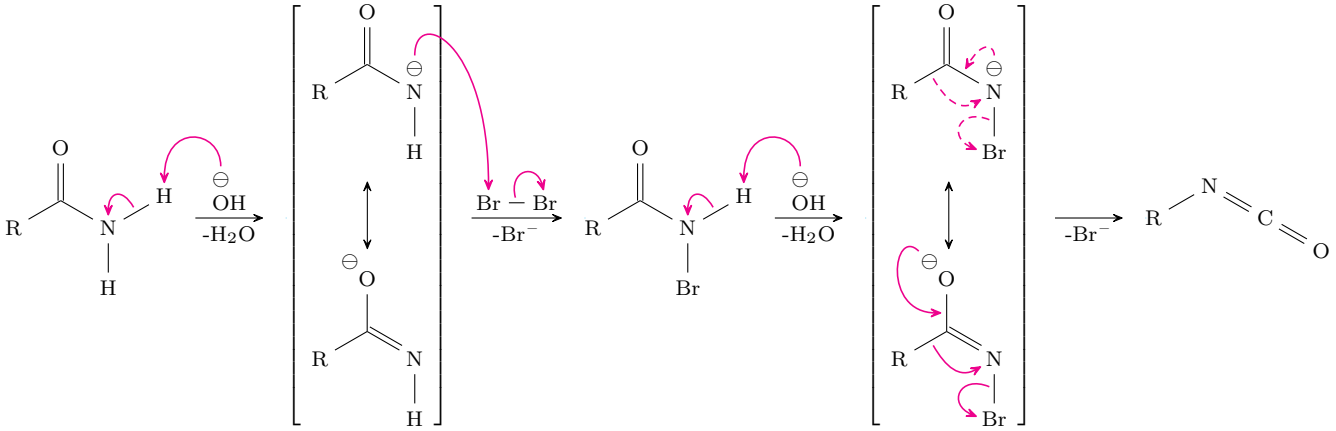


Figure 8.1: Hofmann rearrangement mechanism (isocyanate formation).

  - Many of these reactions are reversible, but the equilibria are not that important here.
  - The first two brominations proceed analogously to those in Figure 4.8.
    - Recall that the second bromination happens more readily because having bromine (an EWG) on the nitrogen makes the remaining hydrogen more acidic.
  - There are two possible rearrangement mechanisms after this for forming the isocyanate.
    - The two proceed from different resonance structures.
    - The one drawn in dashed lines is advocated for by Solomons et al. (2016). In it, the *nitrogen* lone pair kicks in, the alkyl group migrates to the nitrogen, and bromine leaves.

    - The one drawn in solid lines is advocated for by Tang. In it, the *oxygen* lone pair kicks in, the alkyl group migrates to the nitrogen, and bromine leaves.
    - Tang will accept either on a test despite her preference for the latter.
  - Once we have an isocyanate, we remove it exactly as in Figure 3.13b.
    - The NHCOOH intermediate (intermediate 2 in Figure 3.13b) is a **carbamic acid**.
    - A possible intermediate between intermediate 1 and the carbamic acid is a resonance form of the former wherein we have kicked the oxygen lone pair in and used the double bond to create a lone pair on nitrogen, negatively charging it.
    - Note that Solomons et al. (2016) uses a simplified mechanism for these first two steps (isocyanate to carbamic acid). Therein the hydroxide attacks the isocyanate carbon and kicks the N=C electrons back onto nitrogen, forming the negatively charged nitrogen intermediate described above in one go. From here, the negative nitrogen can attack water to form the carbamic acid.
    - The mechanism of Solomons et al. (2016) is inaccurate, though, because when displaced the electrons will preferentially move toward the more electronegative oxygen.
    - Regardless, both mechanisms will be accepted as correct in this course.
  - Other comments.
    - Whereas we can isolate the isocyanate intermediate in the Curtius rearrangement, the conditions of the Hofmann rearrangement are such that it will continue reacting immediately upon being formed.
    - Even though CO_2 is released by this mechanism, we will not observe bubbling in the reaction mixture because the gas is absorbed by the basic media.
    - Overall, we form isocyanate and then perform two consecutive types of nucleophilic acyl substitution.

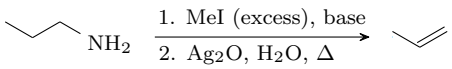
- An advantage of the Hofmann rearrangement is that it maintains the chirality in the R group.
  - In particular, we preserve the chirality at the carbon that ends up being α to the amine.
  - This differs from any of the reductive pathways that use S_N2, for instance.

- Comments on the Curtius rearrangement.
  - In the first step, heat is used to transform the (relatively stable) acyl azide into the isocyanate and liberate N_2 gas.
  - This detail was not mentioned in Lecture 6 and is not shown in Figure 3.13a.
  - You can hydrolyze the isocyanate with alcohol instead of water, leading to different products. We will explore this in PSet 5.

- Reactions of amines.

- Hofmann elimination.

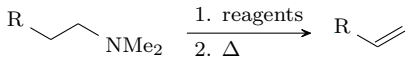
- General form.



  - This reaction solves the problem of how to turn NH_2 into a good leaving group so that we can eliminate it.
  - Example bases are NEt_3 or a NaOH pellet (it doesn't even have to be dissolved).
  - Yields the non-Zaitsev product[1] (less substituted alkene).

[1] This is why Mrs. Meer introduced the Zaitsev v. Hofmann product!

- Mechanism.
  - The first step makes the amide NH_2^- into a good leaving group by transforming it into a quaternary ammonium salt.
  - The second step causes the elimination. How it works centers around the dual role Ag_2O serves.
    - First, it relinquishes a silver cation to precipitate the iodide anion of the ammonium salt[2].
    - Second, the remaining AgO^- species acts as a strong bulky base.
- If we use a non-Hofmann elimination base (e.g., NaOEt) after forming the quaternary ammonium salt, then we get a mix of products with the Zaitsev product as the major product.
- Cope elimination.
- General form.



  - Reagents is mCPBA or H_2O_2.
  - We need heat around 150 °C in the second step.
- Mechanism.

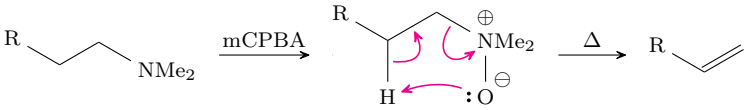


Figure 8.2: Cope elimination mechanism.

  - A concerted second step; hence, this is syn elimination.
- The Cope elimination is regioselective.

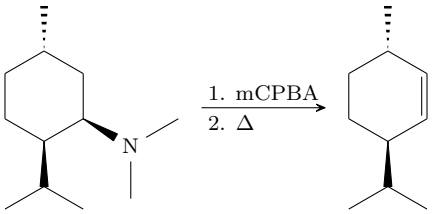


Figure 8.3: Cope elimination regioselectivity.

  - The hydrogen and oxygen need to be able to align (i.e., in the transition state). Thus, if they cannot, we will not get elimination there.
  - Guiding principle: The proton that you pull off has to point in the same direction as the nitrogen.

[2]Silver and iodide ions preferentially bond because of the HSAB principle from Labalme (2022a).