Topic 3

π-Excessive Heterocycles

3.1 Imidazoles, Pyrazoles, and Indoles

2/20:

- Announcements.
  - PSet 2 will not be posted yet because most of the material won't be covered until next Tuesday.
    - We'll still have it a week before the exam, and the exam will not be so indole focused.
  - The practice exams are also still to come.
  - Lots of material and esoteric reactions in these slides; Steve will not discuss it all, nor expect that we remember it all.
- **Imidazole** and **benzimidazole**.
  - Important constituents in pharmaceuticals and biologically important substructures (e.g., histidine; nucleophile in salt bridges; constituent in DNA).
  - Proteins are often purified on nickel columns that act on histidines (see "HisTags").
- Structure and reactivity.
  - Often put into structures to increase water solubility (can completely hydrogen-bond; both donor and acceptor)!
  - Combination of pyridine and pyrrole: One lone pair orthogonal to the π-system, and one pyrrole-like pair that does not typically react with electrophiles.
  - Imidazole is less nucleophilic than pyrrole at carbon.
  - Rapid tautomerization complicates reactivity; if you want to target a particular site, you might get a surprise. But there are ways to overcome this that we'll discuss.
  - Imidazole is amphoteric: One H is moderately acidic (not super, but not like C–H either), and then can protonate. Much less acidic than oxazole or thiazole because of resonance.
  - Alkylation at nitrogen occurs, followed by deprotonation, followed by more reactivivity.
- Reactions of imidazole.
  - Deprotonation (with a strong base, e.g., NaH, LDA, NaHMDS) creates a strong base that monoalkylates.
  - Selective alkylation at nitrogen?
    - Target N^2 with protection (acylation), **ethyl Meerwein's reagent**, and deacylation.
    - Target N^1 with Buchwald amination (Steve: "I hate the amination, should've gotten rid of the amination").
  - EAS.

    - Better than benzene, worse than pyrrole.
    - Nitration breaks the symmetry of the molecule. Easier to put nitrogen group next to non-positively charged nitrogen.
    - Polybromination is also possible.
    - Selective bromination occurs analogously to with pyridine (see Figure **??**); attack at nitrogen, then carbon, then rearomatization.
    - More "trivial" reactions.
  - S_NAr.
    - Moves the lone pair onto the nitrogen, as we've seen.
  - Directed metallation.
    - SEM (popularized by Bruce Lipschutz at UC-Santa Barbara) is the best protecting group. Can be removed by fluoride, which induces a loss of ethylene and formaldehyde.
    - Selective deprotonation between the two nitrogens (fairly standard, steric factors considered).
    - Can then do again.
  - Lithium-halogen exchange.
    - LiX exchange occurs faster than deprotonation, then deprotonation occurs.
    - To ensure that everything occurs in the right order, people will often add a strong base (e.g., LiHMDS) first; then add butyl lithium to do the LiX exchange.
  - Radical chemistry, e.g., the Minisci reaction.
    - Photochemistry as well, but that would be a whole other course; Steve won't discuss, take 5.44 with Alison if you want to hear more.
    - Minisci (radical decarboxylation) predates photoredox catalysis for generation of carbon-centered radicals.
    - Second example: Nucleophilic radical can add to electron-deficient (because of the aldehyde) carbon center.
  - Quaternary imidazolium salts.
    - Subsequent base yields ylide, i.e., the NHC (NHCs ubiquitous in catalysis).

- Selected imidazole disconnections.
  - Some should look familiar, and some may not.
  - The first one to talk about individually is the **Debus-Radziszewski** (imidazole synthesis).
    - From a long, long time ago. First reported synthesis of imidazole.
    - Combines a 1,2-diketone, aldehyde, and ammonia.
    - Proposed mechanism has zero evidence, but some variation is probably correct.
      - ➢ Aldehyde is probably converted to imine *before* formation of the diimine on the 1,2-diketone.
      - ➢ Then condensation.
      - ➢ Then tautomerization.
  - Synthesis 1: Analogous to the Pinner reaction; very common.
  - Van Leusen: Analogous to the pyrrole synthesis of the same name.
  - Synthesis 4.
    - Aminoacetal an acetal for stability reasons.
    - Attack to imine and then cyclization.
  - Synthesis 6: Paal-Knorr type.

- Example synthesis: Conivaptan.

  - Pinner-type synthesis.
- Example synthesis: Estrogen receptor.
  - N^- adds to nitrile.
  - Workup to amidine.
  - Condense with α-bromoacetaldehyde to form the imidazole.
- Example synthesis: Obesity.
  - α-bromopyruvate.
- Van Leusen.
  - TosMIC: Stabilized isocyanide.
  - Easily deprotonated, add to the imine, attack at carbene, proton transfer, losing the sulfonate.
- COX-2 inhibitors.
  - Historically important chemistry.
    - Merck billion-dollar molecule.
    - Has to do with pain.
    - Aspirin (but disrupts stomach) $\rightarrow$ NSAIDs (ibuprofen, endoproxin) $\rightarrow$ tylenol (but dissolves liver) $\rightarrow$ opioids (but addictive).
    - Most things inhibit both pathways (COX-1 and COX-2), but this drug was selective for COX-2, specifically. But this (Vioxx) causes heart-valve problems (and Merck had to pull it from the market at great loss).
    - Celebrex as well, but the company died and had to be sold to Pfizer.
- Example synthesis: Like Lipitor, another statin compound.
  - Glycine benzyl ester is a fairly standard protected amino acid.
  - Treat it to form something, which after cleavage can be acylated.
  - Ester to benzylamine.
  - Cyclize with a primary amine to stitch in the nitrogen.
  - Cyclize (fairly typical with statins).
- Example synthesis: Debus-Radziszewski chemistry.
  - Microwave chemistry was huge, but the bubble has burst at this point. You still see it here and there, but not much.
  - Get to the asymmetric α-diketone with a SeO_2 oxidation.
  - What method you'll use commonly depends on what you have and what you have successfully been able to do previously.
  - Ester, cross-Claisen, hydrolysis/decarboxyliation could also allow you to make a series of different imidazoles.
- Example synthesis: pan-JAK inhibitor.
  - Lab synthesis.
    - Buy the phenol and protect it as the SEM.
    - Miyaura borylation, Suzuki-Miyaura coupling, Pinner salt formation, convert to the imidium system.
    - Cleave with acid to liberate the carbonyl and do the intramolecular cyclization.

  - Scale synthesis.
    - Removed Miyaura borylation with Grignard, etc.
    - Gets a byproduct, but it's inactive.
    - Many telescoped steps.
    - You need to worry about the form of the crystal that recrystallizes (there is a whole field of **crystal engineering**); is it too big, too small, etc.?

- Example synthesis: P13K β-Sparing.
  - No lateral deprotonation, despite intuition!
  - Weinreb amide (for adding carbanions to carbonyl derivatives).
  - Alkylate on nitrogen, do S_NAr (could also be benzyne).
  - Palladium catalyst for final Suzuki-Miyaura cross-coupling.
    - Can do it in the presence of *a lot* of basic functional groups.
    - More evidence why this chemistry won the Nobel prize.

- 1,2-azoles.
  - We'll talk mostly about pyrazole, but there's also isothiazole and isoxazole.
  - Dimeric structure in solution.
  - Also has tautomerization.

- A few reactions (similar again).
  - N lone pair in and out of the aromatic system.
  - Acylation $\rightarrow$ deprotonation again.
  - Selective halogenation can be rationalized based on arrow-pushing and charges.
  - Can acylate on carbon by sterically blocking the site that will typically react first; thus, more engineered and less useful.
  - Under neutral conditions, alkylation occurs at the lone pair.
    - Under basic conditions, we form the thermodynamic product.
  - Lots of companies have wanted to *N*-arylate at the thermodynamically unfavored nitrogen recently, and have needed catalysts to do that.
  - Lithiation.

- Pyrazole syntheses.
  - More condensation chemistry.
    - Always look for bisnucleophiles and biselectrophiles!
    - This is a very common disconnection.
  - Dipolar cycloadditions can also be employed (not as common, but occur on occasion).
  - Knorr gets his own synthesis.
    - This is good for symmetric pyrazoles.
  - Propynyl ketones act as the synthetic equivalent of a β-dicarbonyl.
  - Cyclopropane thing synthesis.
    - Take the diketone, halogenate in between, nucleophilic displacement. α-aryloxy ketone could feed into a cross-Claisen condensation.
  - Aside: Whenever you see a structure, think about whether you can get to it using chemistry that you learned in first-year organic; that's what people want to use.

  - Diazomethane can be generated in flow now, so it can be used on scale.
    - Explosive and toxic; precursors are also nasty (mutagenic), so bad on lab scale, too.
  - What if the condensation has 2 : 1 selectivity in the wrong direction?
    - Try a dipolar cycloaddition.
    - Treat a thing with base to do a 1,3-elimination. Then do this with an aryl acetylene (looks good, but hard to handle and explosive, so use an equivalent).
    - As an equivalent, use the enamine, which is an elimination away from the acetylene.
    - They did this chemistry on a huge scale, which is wild to Steve.
  - In process chemistry, they will do almost anything (as long as its legal), even using brutal conditions, if necessary.

- DGAT-2.
  - Cyclopropanated benzimidazole derivative.
  - Reduce to the 1,2-diamino derivative. Then other piece for condensation.
  - Other piece: α-alkylation twice. Can't do S_N2 with cyclopropanes because the transition state wants to be 120°, but the cyclopropane is 60°.
  - GMP (General Manufacturing Procedure) synthesis (control access to the reactors, everyone is in clean suits, etc.). Very expensive, but makes sense if the compound is going into a person.
  - Got starting material from γ-bromocarboxylic acid via Hell-Volhard-Zelinsky reaction, in Steve's guess.
  - Cleave the ester under acidic conditions; in basic, you would have competitive S_NAr?? (easier to control the quality of acetyl chloride and methanol than gaseous chloride, so as to generate HCl *in situ*).
  - Do this in the presence of Boc-anhydride to form the Boc-amide.
  - Use T3P (a reagent to make amides).
  - Then cleave the Boc.

- Indoles.
  - Jeremy Knowles (Steve's doctoral advisor) used to make fun of people who made indoles, yet Steve ended up making them regardless.
  - Most widely occuring ones: (*S*)-tryptophan and seratonin (responsible for sleep, depression, anxiety, etc.).
  - SSRIs: Selective seratonin uptake inhibitors.
    - Triptans are antimigrane drugs, very structurally related to seratonin.
    - Migraines are financially huge to pharmaceutical companies. No generally successful solutions yet.
  - LSD.

- Reactions of indoles.
  - 5-membered ring is always the most reactive part.
  - 6 M sulfuric acid reveals that protonation at C3 is most favorable.
    - $pK_a = -3.5$, so does not protonate easily.
  - React with electrophiles at C3.
    - Example: Halogenation occurs at C3.
  - Acylation.
    - Acidic conditions: C3.

        - Basic conditions: At the nitrogen.
        - C3-blocking leads to C2 reactivity next.
    - Excess of methyl iodide and heat leads to tetramethylated isoindole structure. Write how this forms!!
        - Skatole (one of the worst smelling compounds in the world) is the product; look it up!
    - BF_3-etherate.
        - Proceeds through spirocyclic intermediate (very common chemistry for indoles), as proven by isotopic labeling.
        - Aside: On mechanisms.
            - ➢ You used to have cumulative exams and 2 foreign languages as PhD requirements.
            - ➢ Frank Westheimer (famous guy who invented chemical biology) was one of Steve's "cumes." One question he gave was "cite the original experimental evidence for these 20 famous findings;" Steve had no idea.
    - Mannich-type reactions.
        - pH = 6 is the Goldilocks range.
        - Pictet-Spengler type transformation, historically used in alkaloid synthesis.
    - With base.
        - NaH is fine, but not great on scale (usually shipped as mineral oil dispersion).
        - EtMgI is shipped around in tank cars and it forms a base just fine.
    - Directed metallation.
        - BOC is DMG, then deprotonate at C2, then electrophile.
        - Cooler way: Throw dry ice in (CO_2 source). Treat with more to form dianion, then deprotect.
- Reactions of gramine.
    - Tryptophan.
        - Put something on that isn't a great leaving group.
        - Put on an electron conduit that allows you to push out bad leaving groups.
        - This is a way to make racemic tryptophan.
    - N-methylation.
        - TIPS (big) allows for C4 lithiation.
        - This is important because the **Fischer indole syntehsis** (typical) is not good at making 4-substituted indoles.
- We'll start with indole synthesis next time.
- Next Tuesday, after class: PSet 2 and previous years' exams.