Topic 6

Azoles

6.1 Triazoles, Tetrazoles, Oxazoles, Thiazoles, and Combinations

3/6:

- Announcements.
  - Exam 1.
    - Spread: 57-96.
    - Median: 90.888
    - Mean: 88.
  - Exam 2 will be similar but cover some content that wasn't on Exam 1.
  - The presentations should be submitted to Dennis by Monday at noon; if that's a problem, let them know ASAP.
    - Let them know if we're not going to be here for any dates.
    - Order: The numbering of presentations. 1-7, 8-14, 15-21.
    - People tend to say the presentation is one of the things they get the most benefit out of in the course.
    - If we use a Mac, send as a PPTX or PDF file; PC, send as a PDF.
  - Today's slides are freshly edited!! Make sure you have the right copy from Canvas.
- We now begin lecture.
- Applications with diamine ligands.
  - Having an iodide source in solution cross-couples KI to the aryl bromide, forming an aryl iodide intermediate first.
- Cu-catalyzed coupling of α-amino acids.
  - Pioneer: Dawei Ma, Shanghai University.
    - Originally used palladium and copper, but "a sage reviewer (who was me)" told him that he probably didn't need the palladium.
  - Copper binds to carboxylate and does an intermolecular transfter.
  - Copper is good if you have *ortho*-carboxylates on an aryl chloride, even back in Ullmann's time.
  - Sometimes you also don't need any added ligand!
    - These are very efficient reactions because copper ligands are usually more expensive than the copper itself!
  - Copper oxide (Cu_2O) is also the cheapest form of copper to use at scale, if you're able to use it.

    - $Cu^{0/I/II}$ are all chemically competent in this reaction and interconvert.

- Cu-catalyzed C–N reactions with amines.
  - Dawei Ma's work again.
  - Originally used dimethylglycine or proline.
    - Moved on to inventing doubly deprotonated, anionic oxalamide ligands. These put more electron density onto the copper center than when you do the reactions with neutral diamine ligands. The difference between an anion and lone pair donation.
  - The interesting ones from a pharmaceutical perspective are the ones that tolerate heterocycles on both sides.
  - Quinazoline synthesis.
    - First step is Goldberg-type coupling, then condensation.
- Significant breakthrough: The Ma paper on Cu-catalyzed amination of (hetero)aryl chlorides.
  - This is still not ultra-user friendly (120 °C), but it does have relatively broad utility and scope.
  - Oxalamides are quite modular to put together: Amine plus oxalyl chloride. Thus, easy to do structure-activity relationships/high-throughput!
- Moving away from metal-catalyzed couplings.
- **Triazole**: A five-membered heterocycle with three nitrogens.
  - Lots of triazoles are fungicides.
  - Fungal infections in the hospital are a serious source of death, so there is a big need for such oral antifungals.
- **Contiguous** (triazoles): 1,2,3-triazoles.
  - There are also **1,2,4-triazoles**.
- Triazoles are actually super stable, despite all the nitrogens; can heat them up to 500 °C.
  - The click reaction is now omnipresent in biochemistry.
- Triazole chemistry.
  - Rapid tautomerization.
  - Amphoteric, like with imidazole. Protonated form has $pK_a = 1.2$.
    - Could I click together a DOT derivative??
- Synthesis of triazoles.
  - $[3 + 2]$ disconnections, predominantly.
    - It's important to remember the original progenitors of the work.
    - Huisgen did the original work; it was in the literature for 30-40 years before Sharpless figured out that copper could seriously accelerate the rate.
  - Aliphatic azides: Do S_N2.
  - Aryl azides: Go through diazoniums.
- Triazoles for click chemistry.
  - Sharpless really got people thinking about click chemistry (though everyone thought he was crazy when he first pitched it).

        - They have parking spots at Scripps for Nobel laureates, and now one for people with two (so Sharpless has his own).
        - Steve: "I hope that Barry doesn't drive, but ok."
    - Bertozzi is the one who realized the chemistry.
    - Copper catalytic cycle.
        - Make copper acetylide (as in Sonogashira chemistry), then coordinate the azide. Form the allene (maybe a diradical), ring contraction, then elimination.
        - This is relatively believed, but it could well be fantasy per Steve.
    - Ruthenium version.
        - From Fokin. Originally worked with Barry was critical to the chemistry, but they had a falling out and he moved to USC.
        - In this version, you get the 1,5-isomer. These are regio-complimentary processes.
        - Very good functional group compatibility.
        - Different mechanism, even from an early organometallic chemistry. Bind alkyne, displace a ligand with azide, cycloaddition to a compound that reductively eliminates to do C–N bond formation, and then falls off. Mechanistic hypothesis by Pierre Dixneuf.

- 1,2,4-triazole synthesis.
    - Paal-Knorr-type mechanism.
        - Cyclodehydration using P_4O_{10} (a non-HCl-producing version of $POCl_3$).
        - Method is not mild: 250 °C.
    - *Sym*-triazine (etymology is unknown to Steve) plus primary hydrazine makes a 1,2,4-triazole.
        - Mechanistically interesting: Carbons are rarely activated for attack. Then electrocyclic ring-opening. Then intramolecular attack to form a species that ejects the simple amidide.
    - Acyl hydrazides and chloroimidates.
        - Heating in the presence of base leads to cyclization, after activation.
    - Pinner strategy.
        - Nitrile to a Pinner salt, condense with hydrazine, and add one carbon with an orthoester.
        - Know how to write the mechanism for orthoester stuff (could be on Exam 2)!!

- Example synthesis: 1,2,4-triazole.
    - S_NAr synthesis of triazoles.
        - Gives a 3:2 mixture of different isomers. Selectivity from sterics of the methyl group.
        - Then S_NAr with MeO^- and removing the methyl group with BBr_3.
    - Other strategy: Multicomponent synthesis.
        - Nitrogen-nitrogen bond formation is an unmet need in organic chemistry!
        - Here you do displacement with a nitrogen nucleophile and nitrogen electrophile??

- We'll not discuss pentazoles, but...

- Tetrazoles.
    - Tetrazoles are pharmaceuticals substitutes for carboxylic acids!
        - Very acidic.
        - But slower pharmacokinetics; the body excretes carboxylic acids very fast.
    - Rapid tautomerization.

- Making tetrazoles without azides is very difficult.

  - Can do with triflic anhydride to form an activated intermediate that can do addition-elimination, then intramolecular displacement of nitrogen onto the end.
    - Note: Using an azide with DCM forms a small amount of 1,1-diazidomethane, which is a contact explosive and can blow up and cause a secondary explosive from the azide. So don't repeat this procedure!
  - Stannyl tetrazole.
    - This is one exception where alkyltin reagents can be used on scale because higher molecular weight azides are safer than low molecular weight azides, even though we don't typically like tin chemistry at scale.
    - Maybe do my DOT synthesis with tributyltin azide instead of HN_3??
  - Classic methods, rejuvenated during the heyday of combinatorial chemistry.
  - **Passerini** (tetrazole synthesis).
    - Don't do in general because HN_3 is a very explosive compound. In small amounts in flow, it's probably fine, but not good in big amounts.
    - Proposed mechanism: Nitrilium??

- Example synthesis: Biggest selling tetrazole of all time (Novartis chemical; billions of dollars per year): Sartans, esp. valsartan. Huge for high blood pressure, heart failure, and kidney disease caused by diabetes.
  - Benzylic bromination radical reaction.
  - Displace with valine (protected as butyl ester).
  - **Schotten-Baumann** (amide synthesis): The classic way to make amides. Interfacial reaction: Amide bond formation is faster than hydrolysis of the acid chloride. Amine is more soluble in the organic layer than the water is. Very efficient: Shake two things together, then filter off the organic layer and you have all the product!
  - Heated with tributylstannyl azide in xylene to form the triazole, then reduce the ester.

- Example synthesis: 6 nitrogens and 7 carbons.
  - Claisen condensation to diketone, then condense with hydrazine to make the pyrazole carboxylic ester.
  - Hydrolyze under standard conditions. Treat with CDI (safer phosgene), then ammonia.
  - Amide dehydration (this time with TFAA).
  - *In situ*-generated zinc azide does the cyclization to the tetrazole.

- Example synthesis: Key step related to an Exam 1 problem.
  - Amino-chlorodipyrimidine. Think about how to make this!!
  - *para*-methoxybenzylchloride made fresh, because very reactive and produces HCl.
  - Kumada coupling to vinyl pyrimidine acts like an α,β-unsaturated carbonyl. Can do nucleophilic attack.
  - Iodinated under acidic conditions.
  - Copper-catalyzed C–C coupling. Hydrolysis/decarboxylation.
  - TMS-azide with triethyl orthoformate (alternative to Bu_3SnN_3??)

- Oxazoles.
  - **Kemp elimination** (named after MIT's Dan Kemp): Ring-opening under strongly basic conditions.
  - Nitrogen is mildly basic; poor resonance.

  - Very common in pharmaceuticals.
  - Aromaticity: Nitrogen is pyridine-like, one oxygen lone pair in the aromatic system (sp^2-hybridized oxygen).
  - Relatively acidic at the 2-position. Can be deprotonated with standard bases (e.g., LDA).
  - Generally do not undergo EAS.

- Oxazole reactions.
  - Can get S_NAr if good leaving group.
  - C-metallations: 2-lithio compound is in equilibrium with ring-opened enolate isocyanide; can be trapped as O–TMS ether. If you heat that, it (remarkably) rearranges to what you thought you were gonna make in the first place!
    - Exclusive C-silylation: More hindered, but triflates react more rapidly. Perhaps this reaction is done reliably cold, instead of while heating, wonders Steve?
  - Lateral deprotonation.

- John Cornforth: Another big chemist who helped invent chemical biology.
  - Won the Nobel prize with Prelog.
  - Incredibly talented (and deaf!).
  - One reaction (not his NP one) was the **Cornforth rearrangement**.
    - Occurs via ring-opening to pseudo-symmetric intermediate, from which you can close back equally well.
    - CH_3 vs. CD_3 R-groups would give a 50/50 mixture.

- Synthesis.
  - The usual suspects.
  - **Robinson-Gabriel** (oxazole synthesis): α-amino ketone, acylate it, and dehydrogenate with P_2O_5 (which, remember, is really P_4O_{10}).
    - Acid-promoted cyclization and loss of water.
    - Driving force: Making phosphoric acid. P_2O_5 is like a phosphorous anhydride, so you're forming stronger P=O bonds in this reaction.
  - **Blümlein-Lewy** (oxazole synthesis).
    - Steve goes over mechanism.
    - Can also push arrows from the nitrogen and lose water afterwards.
  - **Fischer** (oxazole synthesis): Condensation of a cyanohydrin with an aldehyde under HCl conditions.
    - Cyanohydrins in basic conditions release cyanide, so keep it acidic!
  - **Van Leusen** (oxazole synthesis): Skipping mostly. *Also known as* **Schölkopf**.

- Isoxazole synthesis.
  - N–O bonds makes these difficult to work with in a lot of cases.
  - Synthesis by dipolar cycloaddition.
    - Can make nitrile oxides from 1,3-elimination or dehydration of nitro compounds.
    - Dipolar cycloaddition on enamine example: May be E2; may be anomeric effect from oxygen kicking out the amine, followed by loss of the proton.

- Thiazoles.

  - More basic than oxazoles (because sulfur is less electronegative).
  - Very common in drugs and dyes.
  - More aromatic than oxazoles (again, sulfur is less electronegative).
  - Thiazoliums are precurors to organocatalysts, e.g., thiamine pyrophosphate
  - Analogous electronic structure (pyridine nitrogen, sp^2 sulfur) to oxazole.

- Thiazole reactivity: EAS has preferential sites, even though it's not very common.

- Thiazole syntheses.

  - The usual suspects: Hantzsch, Van Leusen, Robinson-Gabriel.
  - **Hantzsch** (thiazole synthesis): Thioamide. Electrophile attacks at the sulfur because it's polarizable and nucleophilic.
    - Then...
    - Used in the total synthesis of Pomothlocin A.
  - **Van Leusen** (thiazole synthesis): Always start with TosMIC, deprotonation, addition to an electrophile, and then cyclization back onto the isonitrile carbon. Can acylate the S^-, though it probably wouldn't survive workup.
  - **Cook-Heilbron** (thiazole synthesis): Many thiazole syntheses use CS_2. CS_2 used to be a common solvent, and it smells horrible.
    - Again, CS_2 looks like CO_2 in terms of reactivity: Attack at the central carbon.
    - Sulfur adds to pendant nitrile, then tautomerization to substituted thiazole.
    - Variation with α-haloketones as well.
  - **Robinson-Gabriel** (thiazole synthesis): Use P_4S_{10}, or Lawesson's reagent for a gentler method. Then cyclization with loss of water.

- Example synthesis: Sodelglitazar.

  - Get to thioamide, treat with α-chloro-β-ketoester.
  - Very good, old-fashioned chemistry.

- Oxadiazoles.

  - Purported to be more important in the future.
  - Showing up more and more, e.g., in a new explosive.

- 1,3,4-oxadiazole synthesis.

  - Hydrazine solution and hydrazine hydrate are more stable than anhydrous hydrazine.
  - Substitute to form hydrazide, trap with something else, then dehydrate (Robinson-Gabriel type).

- 1,2,4-oxadiazole synthesis.

  - Pinner-type chemistry.

- Example synthesis: PPAR-a agonist.

  - Covers this.

- Example synthesis: Apelin receptor (APJ) agonist.

  - Ethoxylated ethyl acetoacetate, convert to vinyligous urethane, treat with diethyl malonate to make hydroxy-pyridone. Halogenate.
  - Negishi coupling.
  - Treat with hydrazide to form an intermediate that they can then dehydrate with T3P.