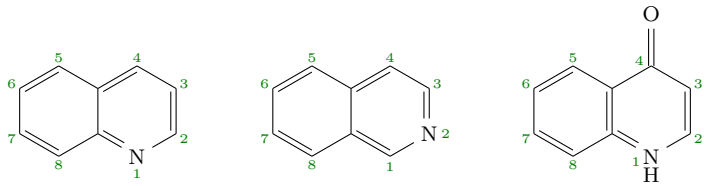
Topic 2

N-Doped Heterocycles

2.1 Benzannulated Pyridine Derivatives

1/11:

- Announcements.
  - Next week: Thursday lecture only.
  - Reiterates that we should try the problems, but don't fret.
- Today: An hour of lecture, and a half hour of problems.
- New heterocycles: **Quinoline** and **isoquinoline**.



(a) Quinoline. (b) Isoquinoline. (c) 4-quinolone.

Figure 2.1: Key quinoline derivatives.

  - Important subclass: Quinine- and **quinolone**-derived drugs.
  - Comparison with pyridine: Quinolines have two different aromatic regions.
- We'll now discuss some basic quinoline reactivity patterns.
- Relative EAS reactivity.

$$\text{Benzene} > \text{Isoquinolinium} > \text{Quinolinium} \gg \text{Pyridinium}$$

- Quinoline (dissolved in pyridine) can react to give the 3-bromoquinoline.

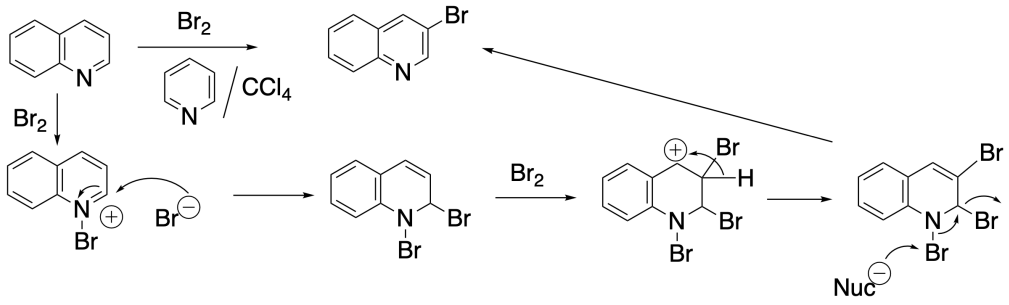
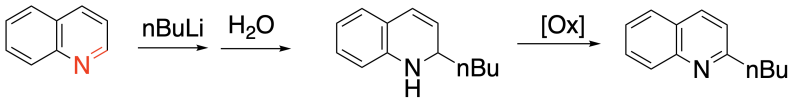


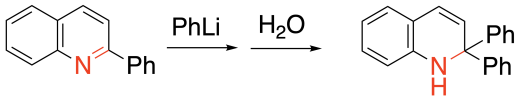
Figure 2.2: Quinoline 3-bromination mechanism.

  - However, the reaction mechanism is *not* EAS.
  - Indeed, this reaction is feasible only because a different mechanism is operational.

- Lithiates — followed by oxidation — add to quinoline at the 2-position.



(a) Monoaddition.



(b) Diaddition.

Figure 2.3: Lithiates add to quinoline.

  - We can also use analogous approaches to dearomatize the pyridine moiety by making a quaternary carbon.
  - Lithium-nitrogen coordination is critical to 2-addition; otherwise, we get 4-addition.

- Quinoline syntheses.
  - Many different ones, many from Germany.
  - Most common: **Skraup**, **Conrad-Limpach-Knorr**, and **Meth-Cohn** syntheses.
  - For most of these, you start with the aniline.
  - Common issues: Mixture of regioisomers.

- Meth-Cohn quinoline synthesis.
  - Proceeds via a mechanism analogous to the **Vilsmeier-Haack reaction**.
  - Driving force: P=O bond formation.
  - Amide → chloroimine, tautomerizes to enamine. Then an additional carbon comes from DMF.

- Quinoline hydrogenations.
  - You can get some interesting chemoselectivity, enabling you to reach basically whatever you want!
  - Reducing the benzene ring.
    - Completely counterintuitive result: In the presence of an acid, you reduce the non-heterocyclic part of the quinoline heterocycle.
  - Reducing the heterocyclic ring, or everything: Use Raney nickel (RaNi).
    - RaNi is a pyrophoric, extremely active form of nickel used for very difficult hydrogenations and desulfurizations.
    - Under 1 atm of H_2, you'll only hydrogenate the heterocyclic ring.
    - Under 70 atm of H_2, you'll hydrogenate everything (typically to the *cis*-decalin derivative, but you can get some isomers).

- Most famous quinoline synthesis: The Skraup quinoline synthesis.
  - Michael addition, Friedel-Crafts type cyclization, and oxidation.
  - A series of conditions for this reaction have been optimized over time.

  - Classic Skraup.
    - Reagents: Glycerol, sulfuric acid, and As_2O_5 (oxidizing agent).
    - Under acidic conditions, glycerol will lose 2 equivalents of H_2O to generate acrolein *in situ*.
      - ➢ Following protonation, the first step involves a hydride shift to β-hydroxyaldehyde.
      - ➢ Then we get E_1 via the electron conduit to acrolein.
    - Why don't we just add acrolein directly?
      - ➢ Glycerol is really safe and cheap, but acrolein will "polymerize if you look at it sideways."
      - ➢ Substituted acrolein derivatives (e.g., other Michael acceptors) can be added directly with sulfuric or tosylic acid, but acrolein, itself, needs these conditions.
    - Using Skraup methodology, we can synthesize 1,10-phenanthroline from 8-aminoquinoline.
    - But not super scalable: Reaction "often resulted in uncontrolled violence."
  - Scalable Skraup.
    - Alternative: Use glycerol in the presence of iron sulfate, a strong acid (e.g., methane sulfonic acid), and a strong oxidant (deprotonated sulfonic acid).
      - ➢ The use of this particular oxidant makes separation easier at the end.
      - ➢ This is an unusual use of a nitro group as an oxidizing agent; not often used, but was recently by Baran.
    - Once acrolein is generated *in situ*, it undergoes Michael addition. Then we get Friedel-Crafts reactivity, followed by oxidation.
    - This method was used to synthesize a PDE4 inhibitor.

- Misc. quinoline derivative syntheses.
  - **Combes** (quinoline synthesis): Aniline condenses with a β-diketone, followed by intramolecular acid-promoted Friedel-Crafts cyclization.
  - **Conrad-Limpach-Knorr** (quinolone synthesis): The mechanism involves a Combes-analogous condensation with a β-ketoester, followed by Friedel-Crafts cyclization.
    - Sulfuric acid gives the 2-quinolone product.
    - Heat gives the 4-quinolone product.
    - We'll discuss this difference later!
  - Used to make compounds that fight botulism, malaria, and ebola.
    - One important reagent used in some syntheses is **Eaton's reagent**.

- **Eaton's reagent**: $MeSO_3H + P_2O_5$.
  - This is a variation on PPA from last time. Easier to work with an quantitate.

- Making a KRAS inhibitor.
  - KRAS is a particularly virulent form of cancer for which inhibitors have not come on the market until recently.
  - The starting material is a trisubstituted anline that is probably not cheap.
  - Selectively (or selectively enough) chlorinate this SM.
    - On an exam, Steve will never ask us to think that we could do this selectively.
    - It's not obvious to him that we would chlorinate where we do, but we *should* be able to draw a mechanism!! (This is basically 5.12 chem.)
  - **Meldrum's acid** and a trimethyl orthoester condense into a new reagent.
    - This reagent is very prone to nucleophilic attack, so we get a Michael-type addition-elimination condensation with the aniline.

  - Then heating the mixture to boiling using Dowtherm as a solvent causes the substrate to collapse to the quinolone.
    - The mechanism for this is at the bottom in the box.
    - Note that at high temperatures, Meldrum's acid is known to undergo a pericyclic decomposition to a ketene, CO_2, and acetone; evidently, only acetone gets kicked out here, not CO_2.[1]
    - In fact, it appears that the whole mechanism in the box plausibly occurs via a sequence of pericyclic reactions.
  - Nitric acid then gives nitration.
  - $POCl_3$ chlorinates the ketone and aromatizes the system.
  - Pretty selective S_NAr occurs, even with a hindered piperazine.
  - A note of the mechanism of action: Acrylimides (top of the finished molecule) are thought to give Michael addition with DNA.

- **Friedlander** (quinoline synthesis).
  - Retrosynthetic disconnections: An alkene disconnects into a carbanion equivalent and a carbonyl, and an imine disconnects into an amine and a carbonyl.
    - Very rational.
  - Subject to regiocontrol issues.
    - McWilliams (at Pfizer) did a very careful study, and was able to use an organocatalyst to get 90% selectivity for one regioisomer.
  - Aside: Scalability.
    - 90% selectivity may not sound great to us.
    - But as long as we can reject the unwanted isomer via recrystallization or derivitization (not chromatography), this is much better than a 4-step synthesis that requires complicated/expensive reagents or conditions.
  - This chemistry is generalizable, as well; see the reaction at the bottom of the slide.
  - Anytime the symbol "OEi" appears in a slide, that means "Δ."

- Example synthesis: A MS drug by UCB (a Belgian pharmaceutical company).
  - Starting material: A nitro-phenylalanine derivative.
  - Condensation to the amide with a variant of Yamaguchi's reagent.
  - Reduction of the nitro group to the corresponding aniline.
  - Condensation with a dichlorobenzaldehyde to form the imine.
  - **Pavarov reaction** with a good leaving group.
    - Specifically, 2-pyrrolidone leave under oxidative conditions.
  - Lastly, we hydrolyze the ester to an acid.
  - Two solvent swaps.
    - These are supposed to purge impurities using washes; we rarely do this in academia.
    - Switching to ACN gets rid of water, and switching to heptane gets rid of the ACN because nonpolar molecules don't stick to polar molecules and can thus be removed well under vacuum.

- This concludes our discussion of quinolines for the time being.

- We now discuss isoquinolines.

[1] Wikipedia. Note also that Meldrum's acid is so strong because the conformational restriction caused by the ring forces the α-proton to undergo $\sigma_{CH} \to \pi^*_{CO}$ donation.

- Isoquinolines.
  - It's easier to do chemistry on their nonheterocyclic part.
    - For example, nitration and bromination most frequently occur at the 5- and 8-positions.
  - Unsurprisingly, the Chichibabin and lithiate/oxidation reactions work again.
    - Nucleophiles will *always* add at the position between the nitrogen and other aromatic ring.
    - With the dichloro species, you should be very confident you can do the addition to this position.
    - This may show up on an exam!!
- Isoquinoline syntheses.
  - **Pomeranz-Fritsch** (isoquinoline synthesis): A condensation/Friedel-Crafts between an aldehyde and the synthetic equivalent of 2-aminoacetaldehyde.
    - Like acrolein, we can't use 2-aminoacetaldehyde raw because it self-condenses.
    - Treatment with acid forms the heteroatom-stabilized carbocation that then does Friedel-Crafts chemistry.
  - We can also do C−N cross-coupling (which we'll discuss later).
  - **Bischler-Napieralski** (isoquinoline synthesis).
    - Make an amide.
    - Then use $POCl_3$ to access the nitrilium ion via a chloroimine-type mechanism.
    - The chloroimine is in no-bond resonance with the nitrilium ion, which is very active in Friedel-Crafts type chemistry.
  - **Pictet-Gams** variation of the Bischler-Napieralski reaction.
    - Start with a benylic alcohol.
    - Thus, you've pre-installed your oxidation! That's the advantage.
    - The disadvantage is getting the substrate.
- **Pictet-Spengler** reaction.
  - From early 20th century Germany.
  - Phenethyl amine and an aldehyde condense and cyclize.
  - Generalizable to other substrates.
  - Proposed mechanism: The iminium ion produced during condensation cyclizes.
    - This can occur via Friedel-Crafts type chemistry, or via a more complicated mechanism with shifts depending on the substrate.
    - In the example shown, it does make more sense that the more nucleophilic position would initially attack the iminium ion, before rearrangement!
- Example synthesis: Idorisia needed to make a pretty simple compound, but making it at scale was hard.
  - Process groups "compete" multiple routes for cost-efficiency, safety, and reliable access to reagents from multiple sources.
    - Because the bigshots will say, "we need 5 kilos in 3 months. If that goes well, 50 kilos 6 months after that. If that goes well, a tonne a year after that."
    - Then the process chemists will start with what they know works, and then they'll refine at cost, scale (e.g., issues with exotherms), issues with buying materials or catalysts, etc.
  - Route-scouting summary.
    - None of the routes use particularly fancy chemistry. Route A uses really old chemisty (**Balz-Schiemann** reaction).

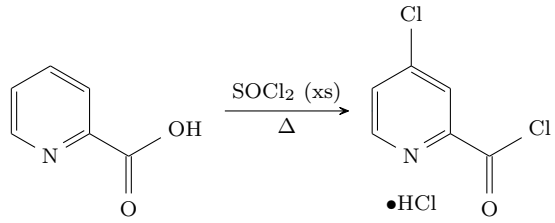
  - Route A overview.
    - $POCl_3$ probably gave a side product that was hard to reject, so they use $POCl(OPh)_2$.
    - Lots of energy put into optimizing this route, so Steve guesses it must have been a really desirable starting material.
    - Primary amide to Hofmann rearrangement.
    - Diazitized, then classic Balz-Schiemann.
  - Route B.
    - On small scale, we can do a Stille reaction.
      - ➢ We could also do tin/lithium exchange and something else (??) to get to a more scalable intermediate.
      - ➢ Then we can get to a desired α-fluoro reagent.
    - However, there's a better bucket chemistry approach.
      - ➢ Carboxylic acid to acyl malonate. Very acidic, hence easily able to fluorinate.
      - ➢ Then double hydrolysis/decarboxylation to form the α-fluoro intermediate.
    - We then use an amide acetal, a species analogous to an orthoester that is derived from DMF. This forms a **vinylogous**[2] amide, an enamine-type compound.
    - Then under hydrogenation conditions, a quinoline N-oxide is formed. This then gets hydrogenated down to form another intermediate.
    - At this point, we excise the alcohol OH with $POCl_3$ and reduction.
      - ➢ This is a **transfer hydrogenation**, with formate is a hydrogen source
    - Aside: Pharma companies have tight controls on hydrogen; you can't even use a balloon unless you go to a special room. Avoid until scale-up!
  - In the end, they chose to use Route C.
    - It's better to not use (very expensive) Selectfluor.

- We now move onto diazenes.
  - Key diazenes.
    - Benzene derivatives: Pyridazine, pyrimidine, pyrazine.
    - Quinoline derivatives: Cinnoline, phthalazine, quinazoline, quinoxaline.
    - The benzene derivatives aren't too common, but the benzanulated heterocycles are very common in pharmaceuticals.
  - Important characteristics.
    - All of the effects of adding one nitrogen to benzene to make pyridine are intensified.
    - Pyridazine, pyrimidine, and pyrazine are colorless liquids that are water soluble.
    - Nucleophilic addition is much easier.
    - Electrophilic addition is much harder.
    - The compounds are much less nucleophilic and basic.
  - The α-effect in pyridazine makes it easier to protonate than pyrimidine.

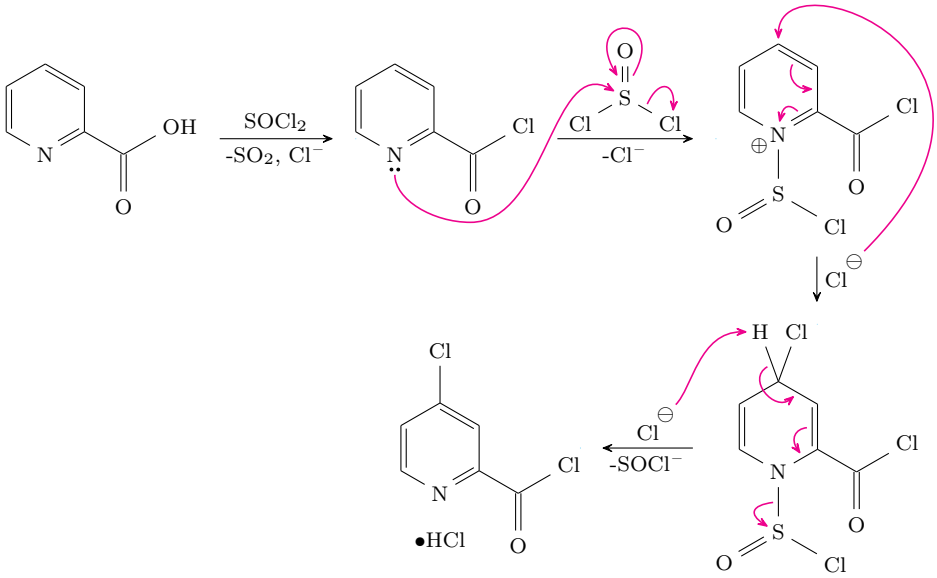
- Halo-diazenes.
  - For the purposes of this class, assume that 4-chloro will react faster than 2-chloro.
    - Sharon Neufeldt (Montana State) had a nice paper in JACS recently with an exception to this (Jackson et al., 2025).
  - These can be very fast S_NAr reactions.
  - Handwavey reason: Double α-effect is worse than one lone pair Coulombic problem.

[2] Wikipedia.

- Problem 1.



(a) The reaction.



(b) The mechanism.

Figure 2.4: TTQ: Pyridine 4-chlorination.

  - Convert to the acid chloride.
  - Activate the pyridine by reacting it with the best electrophile in solution; experimental studies show that it's not protonation here! Plus, protonation would make hydride your leaving group, which is much worse than $SOCl^-$.
  - Chloride may not be the base that does the final deprotonation, but we want the hydrochloride in the end so it's good to show that. If not chloride, subsequent proton exchange gives hydrochloride.
  - Fate of sulfur compound is unknown, so $SOCl^-$ is some kind of leaving group. That was our hint to use a sulfur electrophile to activate the ring.

- Problem 2.

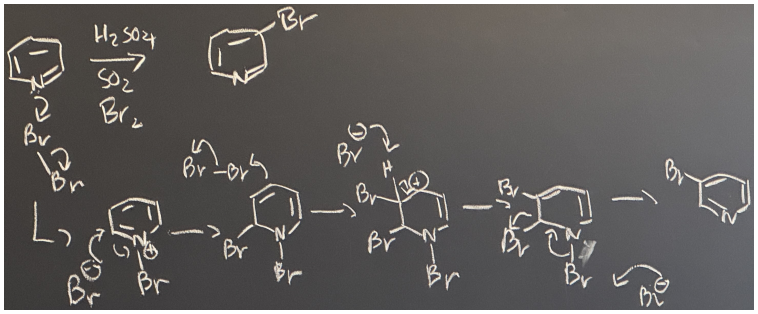


Figure 2.5: TTQ: Pyridine *meta*-bromination.

- Uses bromination mechanism from class (see Figure 2.2).
- Oleum could be SO_2 or SO_3.
- Br^- can remove either bromine in the last step.
- This gets full credit; it is great, but for the second bromination, it may make more sense to put the bromine on the other side of the compound; the 1,2-dibromide is unfavorable.
  - Principle: Large halides on contiguous carbons is just very challenging.
- Unclear what the SO_2 does.
- Electrophilic reaction $\rightarrow$ nucleophilic reaction with dearomatization.