

Topic 2

N-Doped Heterocycles

2.1 Benzannulated Pyridine Derivatives

2/11: • 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**.

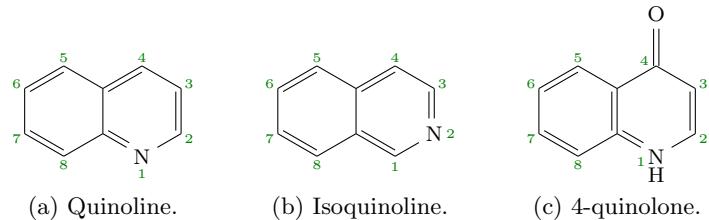


Figure 2.1: Key quinoline derivatives.

- 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.



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

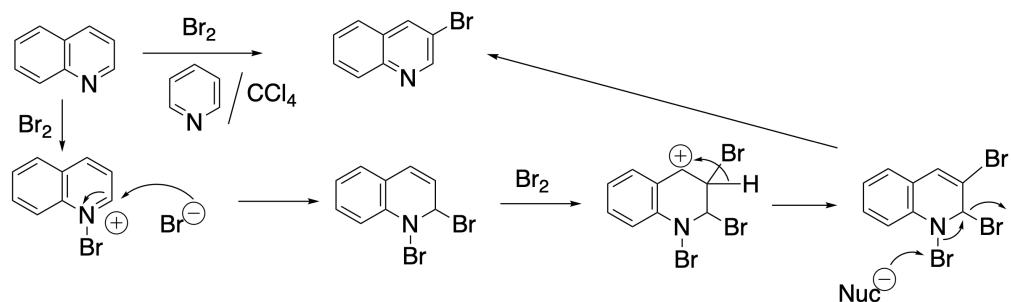


Figure 2.2: Quinoline 3-bromination mechanism.

- 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.

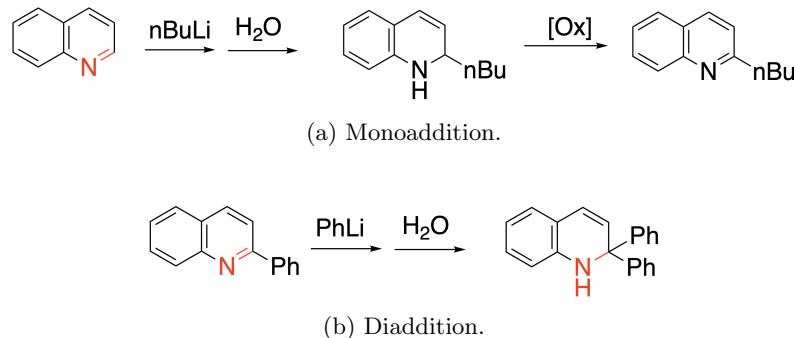


Figure 2.3: Lithiates add to quinoline.

- 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 H₂, you'll only hydrogenate the heterocyclic ring.
 - Under 70 atm of H₂, 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:** $\text{MeSO}_3\text{H} + \text{P}_2\text{O}_5$.
 - 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 aniline 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, CO₂, and acetone; evidently, only acetone gets kicked out here, not CO₂.^[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.
- POCl₃ 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 $\sigma_{\text{CH}} \rightarrow \pi_{\text{CO}}^*$ 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 chemistry (**Balz-Schiemann** reaction).

- Route A overview.
 - POCl₃ 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 POCl₃ 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 (all water-soluble!!).
 - 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.

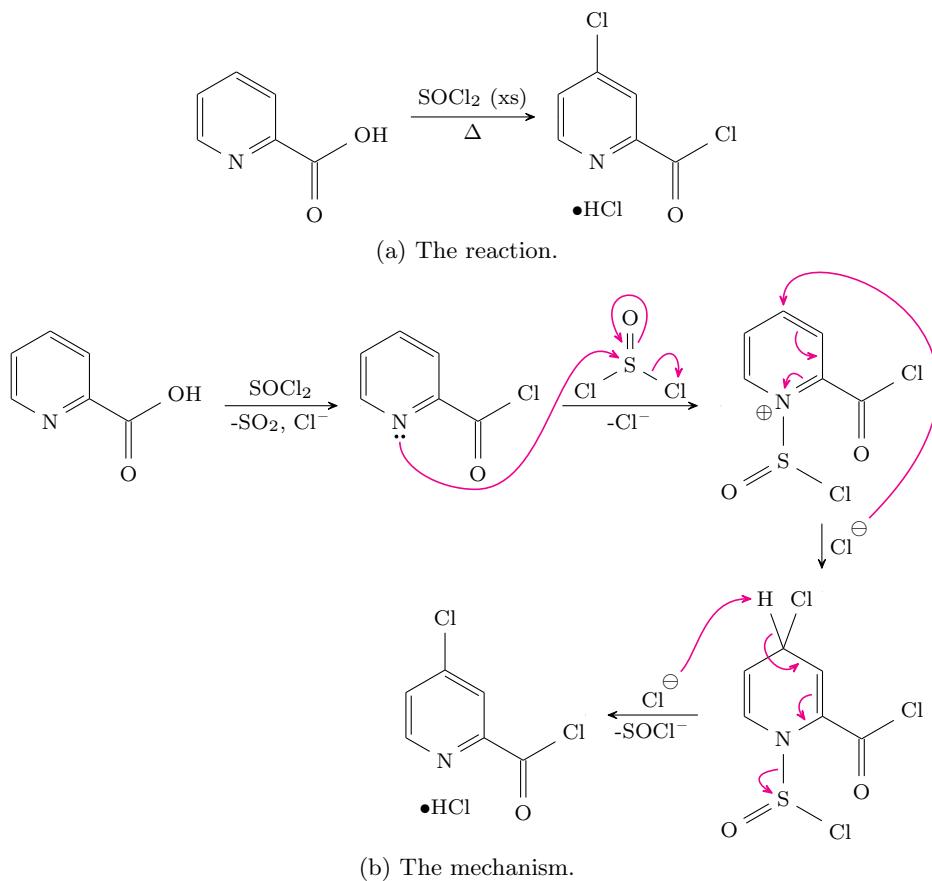
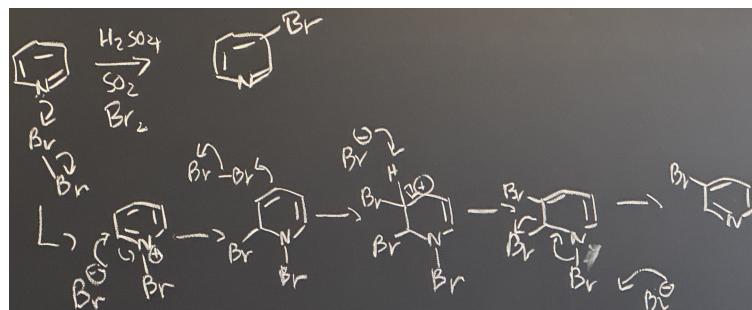


Figure 2.4: TTQ: Pyridine 4-chlorination.

- 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.

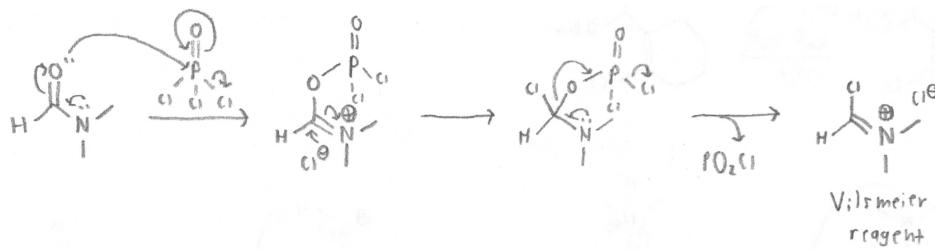
Figure 2.5: TTQ: Pyridine *meta*-bromination.

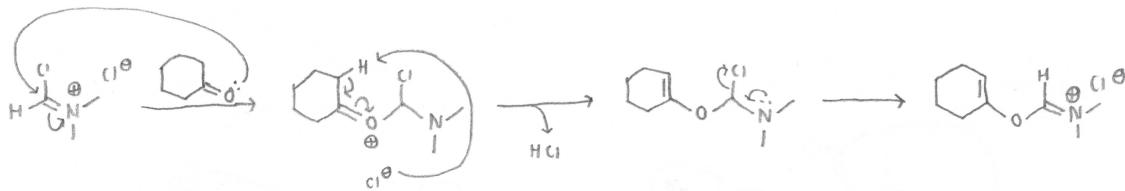
- Uses bromination mechanism from class (see Figure 2.2).
- Oleum could be SO_2 or SO_3 .
- Br^- can remove either bromine in the last step.
- This gets full credit; it is great, but for the second bromination, it may make more sense to put the bromine on the other side of the compound; the 1,2-dibromide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

2.2 Pyrimidines and Pyrroles

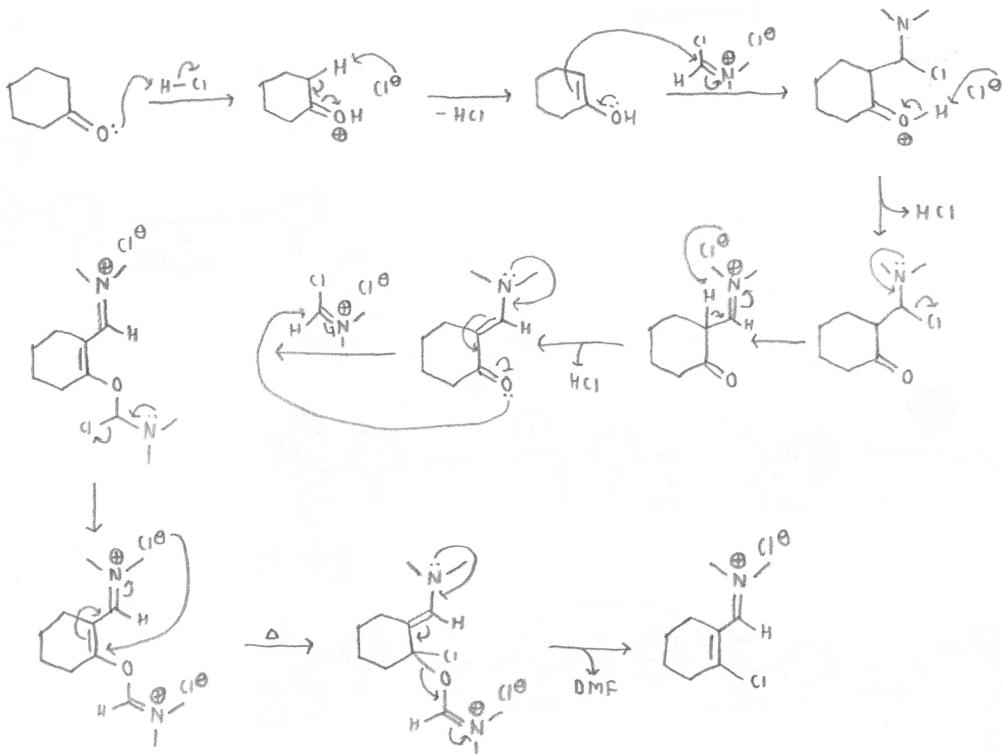
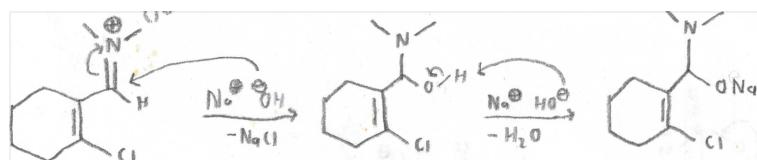
2/13:

- Syntheses of pyrimidines.
 - Several disconnections once again.
 - Most important ones: The [3 + 3] disconnections, especially the **Pinner reaction**.
 - Pinner reaction.
 - You make an **amidine**, typically by adding a sodamide (NH_2^-) to a nitrile.
 - **Grimaux** (pyrimidine synthesis).
 - Makes barbituric acid (part of barbituates).
 - Equivalent of a diacid chloride plus a urea.
 - Then can be converted into halides using reactions we've discussed such as POCl_3 .
 - **Biginelli** (pyrimidine synthesis).
 - Ignored for 125 years.
 - Became popular when people wanted libraries of heterocycles.
 - Popular because you can mix and match β -ketoesters, aldehydes, and ureas.
 - Mechanistically, you begin with a **Knoevenagel condensation** (aldol variant). This gives a species very activated toward Michael addition, so urea can add twice.
 - “Urea has the solubility of brick dust,” so you need a quite active solvent mixture to get at least some of it in solution.
 - **Ziegenbein-Franke** (pyrimidine synthesis).
 - Very young; about 60 years old.
 - Think about the mechanism of ketone to β -chloroaldehyde (once again, a 1,3-biselectrophile)!!
 - The β -chloroaldehyde is then pyrolyzed with formamide.
 - Mechanism: Michael addition, transitive imine formation, addition-elimination to lose H_2O .
 - **Pinner** (reaction).
 - Acidic reaction with a nitrile gives a **Pinner salt**.
 - Either hydrolyse or convert to the amidine.
 - Several 1,3-bisnucleophiles can be treated with 1,3-biselectrophiles (typically a β -dicarbonyl, but can be others) in this manner.
- Addendum: Vilsmeier-Haack type chloroformylation mechanism.

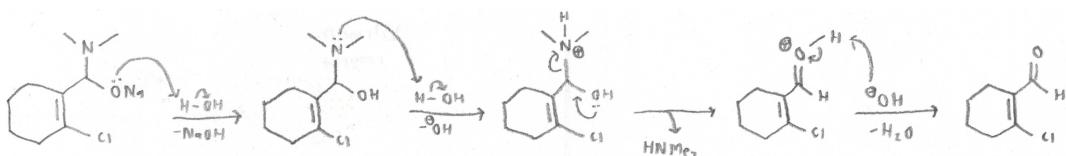




(b) Hydrochloric acid libration for autocatalysis of the keto-enol tautomerization.

(c) Formation of the β -chloroacryliminium chloride salt.

(d) Basic hydrolysis.



(e) Neutral/acidic hydrolysis.

Figure 2.6: Vilsmeier-Haack chloroformylation mechanism.

– **Vilsmeier reagent** prep (Figure 2.6a).

- To a solution of excess DMF, POCl_3 is added. Thus, POCl_3 will react completely with DMF to form the Vilsmeier reagent (and PO_2Cl byproduct). Said reagent will then be solubilized in the leftover DMF. This all occurs without competing reactivity with the ketone.
- Even if a ketone was present, POCl_3 would prefer to react with DMF over the ketone because DMF's carbonyl is more reactive than the ketone's owing to the conjugated nitrogen lone pair.
- DMF also reacts exclusively through its oxygen instead of its nitrogen because its nitrogen is dialkylated, so it cannot undergo amide-iminol tautomerization.

– Liberation of HCl (Figure 2.6b).

- When the ketone is added to solution, very little of it (about one molecule in a million) will be in the reactive enol form. Thus, the element most susceptible to immediate electrophilic attack by the Vilsmeier reagent is the ketone's lone pairs.
 - It is interesting that DMF does not attack the Vilsmeier reagent; or perhaps it only does so reversibly.
 - Perhaps this reaction is unfavorable because the resulting iminium ion would have DMF as a much better leaving group (entropically and enthalpically in a polar aprotic solvent) than chloride.
- Regardless, once the ketone attacks the Vilsmeier reagent, the resulting oxocarbenium ion's α -protons are greatly activated toward deprotonation, perhaps by the chloride formerly of the Vilsmeier reagent salt. This leads to HCl liberation.
- Now that there is no risk of forming an enthalpically unfavorable dication, the nitrogen lone pair is free to remove the chloride ion, reforming the more stable iminium salt (in a kind of no-bond resonance). The resultant species will not react further productively.

– However, the damage is done, and the liberated HCl can now catalyze the main sequence of steps.

– The main reaction (Figure 2.6c).

- HCl has $\text{pK}_a = -6.3$, comparable to a protonated ketone's -6 to -8 . Thus, HCl can now easily protonate a ketone in solution, accelerating keto-enol tautomerization.
 - HCl could surely protonate many other species, too, but this is the only productive reactivity so it will predominantly control experimental results.
- Keto-enol tautomerization yields an alkene that is sufficiently nucleophilic to attack another equivalent of the Vilsmeier reagent.
- The protonated ketone can then be deprotonated (liberating more HCl), and an iminium chloride salt reformed.
- The β -ketoiminium chloride has a *significantly* acidic α -proton, and a base in solution (shown as chloride, for the sake of balancing everything) can deprotonate it to yield another equivalent of HCl, as well as a conjugation-stabilized vinylgous amide.
 - The increasing concentration of HCl in solution results in an experimentally observable autocatalytic rate increase.
 - It is important to remember that conjugated alkenes are more stable than unconjugated ones, hence why the vinylgous amide is more thermodynamically stable than the β -ketoiminium ion.
 - This vinylgous amide intermediate can actually be isolated in some schemes!
- We now want to get rid of the ketone oxygen. To do so, another equivalent of the Vilsmeier reagent will be used to turn it into a better leaving group. This leads to the formation of a labile (unstable) bisiminium chloride.
 - Note that in much the same way that DMF's oxygen is activated toward nucleophilic attack by its nitrogen, the vinylgous amide's oxygen is activated by the further away, conjugated nitrogen.

- Under the heated conditions of the reaction, the bisiminium chloride is subject to attack at the β -position of the conjugated iminium ion, followed by a collapse that kicks out DMF as a great leaving group (strong C=O bond formation, amide-type conjugation, entropically favorable dissolution in the DMF solvent, etc.).
- We have now arrived at a species that is stable until workup.
- In most procedures, basic workup appears to be a prerequisite to neutralization (Figure 2.6d).
- Then, under acidic or neutral conditions, we get the collapse to the aldehyde (Figure 2.6e).
 - Note that this sequence of collapse to an aldehyde holding off until neutral or acidic conditions is reminiscent of Figure 3.7 in Labalme (2024).
 - Indeed, under basic conditions, an anion is more stable on oxygen than nitrogen; but under acidic conditions, a nitrogen is more easily protonated (and hence used as a leaving group) than an oxygen.
- It is worth noting that salt formation appears to be a driving force to be aware of, perhaps due to Coulombic attraction being more thermodynamically stable than covalent bond formation in some cases.
- References.
 - Marson (1992, pp. 3663–3665) — review with currently accepted reaction mechanism outline.
 - Virgilio and Heilweil (1981, pp. 12–13) — standard prep for Vilsmeier-type chloroformylation.
- Now some older chemistry.
 - Pyrimidines can be anti-asthma reagents.
 - **Dimroth rearrangement** is quite interesting, but we don't have to know it (it's pretty esoteric).
- Skipping Biginelli.
- Example synthesis: An α_1 -Adrenoceptor Antagonist.
 - Useful reagent, POCl_3 , $\text{S}_{\text{N}}\text{Ar}$, deprotection.
 - Aside: We should be saying in this class, “this again?!”
 - Lots of condensations, $\text{S}_{\text{N}}\text{Ar}$, dehydrations, etc.
- Example synthesis: GABA $\alpha 2/3$ agonist.
 - Europe is on the move to ban all fluorine-containing drugs.
 - But how do you make CF_3 -containing compounds?
 - CF_3^- equivalents are really expensive to use on a large scale.
 - Ideally, use TFA or anhydride; can also use CF_3H , but this is a greenhouse gas 500–2000 times worse than CO_2 .
 - They use the anhydride; Friedel-Crafts type reaction with ethyl vinyl ether.
 - Michael addition with guanidinium ion produces the core structure next.
 - Next reagent is the synthetic equivalent of α -bromoacetaldehyde.
- Example (medchem) synthesis: DNA-dependent kinase inhibitor.
 - Steve loves these compounds with high densities of nitrogens; this one has 8.
 - Strategy: Break into smaller heterocycles and use C–N cross-coupling.
 - The first reagent is an amide acetal (specifically, the dimethyl acetal of DMF, analogous to **Brederech's reagent**). It makes nitrogen into an electrophile; you acylate this, and then get intramolecular $\text{S}_{\text{N}}2$.
 - ??, Curtius rearrangement, C–N coupling with a Buchwald ligand (BrettPhos) on a palladium catalyst.

- Example synthesis: Fungicidal compound.
 - Key disconnection is a Suzuki-Miyaura cross-coupling.
 - 2-iodo-5-bromopyridine isn't too hard to access. Then you make the 2-metallocypyridine with **turbogrignard** (isopropyl magnesium chloride); negative charge attacks the halide (Br or I) to form the more stable anion.
 - This anion attacks PivCl.
 - Then lithiation and attack at the ketone.
 - Other route: Sequential alkylation to form the cyclobutane, even in the presence of a fairly weak base.
 - Then more turbogrignard (this time with the bromide) to generate the boronic acid. We can do this in the presence of a nitrile, presumably because the nitrile is so hindered.
- We now move onto 5-membered heterocycles.
 - Steve loves these, particular ones with multiple heteroatoms.
 - Their reactions are typically more challenging, so most people avoid them. They're also of great interest in many applications.
- **Pyrrole.** *Etymology* from Greek “bright red color which pyrrole imparts to pinewood shavings moistened with concentrated hydrochloric acid.”^[3]
 - Most chemistry started in Germany, because they had a huge coal industry and most heterocycles were originally isolated from coal tar.
 - PE and PP were invented (by accident) at the Max Planck institute, specifically the Ziegler-Natta polymerization; at Max Planck, they only call it the “Ziegler” polymerization.
 - Pyrrole is π -excessive; it's more electron-rich. Unlike in pyridine, the nitrogen lone pair is *part* of the aromatic system. This leads to anionic charges all throughout the ring.^[4]
 - pK_a of protonated pyrrole is -3.8 , and the proton actually resides on carbon (because the pyrrole nitrogen is so nonbasic).
 - Not quite as aromatic as benzene, but still pretty aromatic.
 - Tetramethylpyrrole has $pK_a = 3.7$ (methyl groups' hyperconjugation induces seven orders of magnitude difference). Also, now we protonate on the nitrogen (different in slides)??
- Very susceptible to EAS.
 - α -position is slightly more active than β -position (4 : 1 ratio in nitration).
 - So electrophilic that bromination (even under mild conditions) goes straight to tetrabrominated material.
 - Monobromination can be accomplished with an alternative electrophilic bromine equivalent to NBS, called **dibromodimethylhydantoin**.
 - Boc protection allows you to do mono- or di- α -brominated pyrrole.
 - TIPS protection allows you to do mono- or di- β -brominated pyrrole.
- When you do something to the nitrogen, you do not disrupt aromaticity.
- **Vilsmeier** is classic; this is the best way to make 2-pyrrolylaldehydes.
- Electrocyclic reactions.
 - Pyrrole is a very poor diene.

³Steve wonders, “How do you think to do that?!”

⁴If so electron rich, could help prevent thionolactonization tautomerization??

- Decarboxylation can be nice; can be much easier to synthesize carboxylated than decarboxylated version.
- Cross-coupling reactivity of pyrrole.
 - The choice of protecting group is key, and TIPS is usually best.
 - Protecting group-dependent coupling applies to the Miyaura borylation and everything else.
- Selected pyrrole syntheses.
 - Classic disconnections give unstable precursors (esp. the dialdehyde), so we need synthetic equivalents.
 - Pyrrole is no longer made from coal tar; it is today made commercially from furan.
 - Alternative big synthesis: Pyrolyzing the sugar derivative, **ammonium mucate**. This is entropically very favorable.
 - Classic way for an organic or medicinal chemist to do this: **Paal-Knorr synthesis**.
 - There are, in fact, lots of Knorr syntheses.
 - The issue is that you can't buy that many 1,4-dicarbonyl compounds.
 - Enamines (in mild acid) protonate at carbon (they protonate at nitrogen in strong acids). Pyrrole is essentially an enamine!
 - **Knorr** (pyrrole synthesis).
 - α -aminocarbonyl and β -ketoEWG (e.g., β -ketoester).
 - Imine formation, followed by aldol-like condensation.
 - Example: 2-aminoacetone and an activated system; activated because you don't want self-condensation.
 - Saponify the methyl ester selectively, distill to remove CO_2 .
 - Write mechanisms for all transformations!!
 - **Hantzsch** (pyrrole synthesis).
 - α -halocarbonyl (no self-condensation!) and β -ketoEWG.
 - Alkylation followed by ammonia.
 - Example given.
 - **van Leusen** (pyrrole synthesis).
 - More unusual.
 - There are also several van Leusen syntheses of 5-membered heterocycles, all using TosMIC (an **isocyanide**, which is a type of heteroatom-stabilized carbene).
 - Mechanism: After deprotonation of the acidic TosMIC α -proton, Michael addition occurs. The resultant enolate adds at the isocyanide carbon to make the imino carbanion. Following protonation, the activated α -proton of the β -iminoketone gets deprotonated, generating an electron conduit through which to eject a tosyl leaving group. Finally, intramolecular proton transfer gives the desired pyrrole derivative.
 - Compatible with HWE to introduce functional groups at C3 and C4 from an aldehyde and phosphonate ester.
 - Pyrrole is a great nitrogen protecting group; what else doesn't have a free NH? This is a quite common protecting group, even in Steve's collaboration with BMS.
 - Example synthesis: Remdesivir (COVID-19 drug).
 - Required an efficient route to a certain heterocycle (on a 100 ton scale).
 - Has to be done efficiently, cheaply, reliable, no bad waste stream, and SMs are basically “air, earth, fire, and water;” things you can get very cheaply from a variety of sources.

- Chlorosulfonylisocyanate is a quite old reagent. Installs a nitrile (good to draw mechanism!!). Then Pinner-type reagent.
- This was ok for the first few tons (33% yield over 4 steps).
- Take pyrrole itself (write mechanism for Vilsmeier-type reaction!!) Intermediacy of an oxime, followed by dehydration of the oxime).
- Then N–N bond from chloramine.
- Two telescoped transformations increases yield by about 50%!
- Addendum: CSI-type nitrile installation.

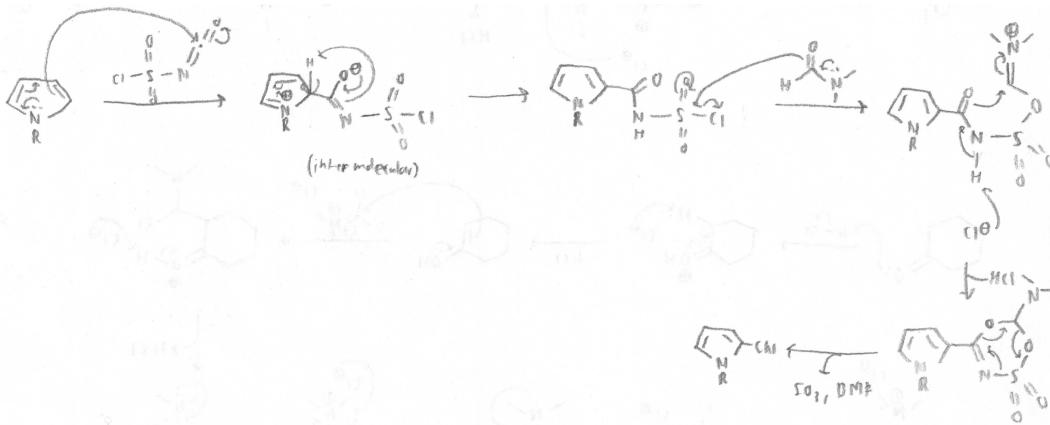
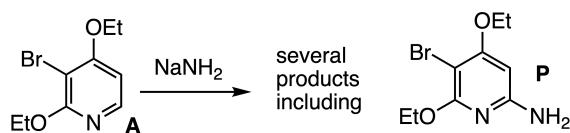


Figure 2.7: Chlorosulfonylisocyanate-induced nitrile installation.

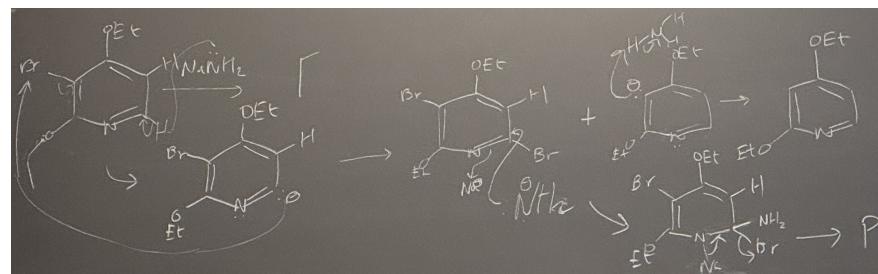
- CSI's electrophilic isocyanate induces EAS-type reactivity from the nucleophilic pyrrole.
- Then PT occurs to the more nucleophilic isocyanate nitrogen (most likely intermolecular, contrary to how it's drawn). This also has rearomatization as a favorable driving force.
- At this point, we're pretty stable, but the solvent DMF can get involved. A few pericyclic reactions later, we get DMF back, strong S=O bond formation in SO_3 , HCl catalyst formation, and our nitrile.
- Reference: Vorbrüggen and Krolikiewicz (1994, p. 6553).
- **Volumetric productivity:** How much material can you get through your reactors in a given day? The better you do, the less the cost of your reactor dilutes the cost of your pharmaceutical.
 - When you get to a certain scale, labor costs fall out of the equation.
- Academics should spend less time on the cost and more time on the novelty of the chemistry.
- Six steps for a practical synthesis of the fluoro/ethyl ester.
 - Aza-Michael addition.
 - Protect nitrogen as Boc.
 - Claisen to β -ketoester.
 - Treatment with DAST (not particularly nice or cheap, but is effective).
 - Pyrrolidine to dihydropyrrole, then a base as weak as Et_3N can form the shown product.
- Lipitor.
 - Largest-selling pharmaceutical (in terms of dollars) in the history of the world.

- Discovered at Park-Davis in Ann Arbor, a relatively small company. They partnered with Pfizer for the sales and marketing. They worked out a deal where they did well at low sales, but poorly at high sales; but this ended up being bad, and Pfizer acquired the company.
- Bruce Roth (the inventor) got laid off after 5 years, which kind of sucked.
- Classic example of a statin.
- Along with penicillin antibiotics, statins changed the world more than almost any other pharmaceutical class.
- Original synthesis: Paal-Knorr, enolate reduction, lactonization.
- β -ketoacids and esters are great substrates for asymmetric Noyori/Sharpless/Knowles chemistry.
- **Stetter** species reacts to form a carbon-carbon bond, then Michael addition.
- This material prepared from isoascorbic acid (available for 11 cents/gram).

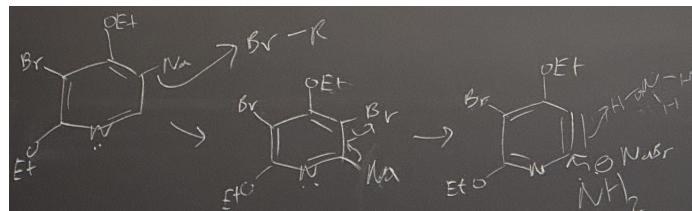
- Problem 3.



(a) The reaction.



(b) A defensible mechanism.



(c) Another defensible mechanism.

Figure 2.8: TTQ: Non-Chichibabin pyridine amination.

- Hint: This reaction does *not* proceed through a Chichibabin-type mechanism.
- Defensible mechanism 1 (Figure 2.8b).
 - If we're not starting with addition chemistry, then let's start with abstraction/deprotonation chemistry!
 - The *meta*-position is usually more acidic in pyridines, but the alkoxides both add electron density to it. Thus, the *ortho*-position is now more acidic.
 - Deprotonating there gives an anion; now we have a species that *cannot* be acted upon by a nucleophile.

- Additionally, this anion is destabilized by the α -effect.
 - So, in the spirit of turbogrignard, we react at the bromide (through an ate complex) to form a new, more stable anion.
- Then the new anion does intermolecular proton abstraction from the NH_3 we produced.
- But now the 2-bromoposition is activated in the molecule that abstracted a bromide, so we can do a more classic Chichibabin with our better leaving group.
 - Note that the second equivalent of NH_2 attacks C2 instead of C5 because we can delocalize the C2 charge onto the nitrogen but not a hypothetical C5 charge.
- Follow-up question: What happens if we deprotonate at the other pyridine hydrogen position?
- Defensible mechanism 2 (Figure 2.8c).
 - We start with the same type of bromine abstraction.
 - This is followed by benzyne-type formation. We're under brutal conditions, so sodamide can act as a base again!
 - From benzyne, the sodamide might attack it and then pick up a proton from the NH_3 .
- Differentiating the two mechanisms.
 - KIEs could work.
 - Selective deuteration of one position would also allow you to look at the product distribution and see whether the proton or deuteron got removed. In one, the deuteron will hang around; in the other, not.