Topic 5

Exam 1

5.1 Exam 1 Review Sheet

3/4:

- Important heterocycles and their key properties.
  - Pyridine.
    - π-deficient ring: δ^+ on α- and γ carbons, δ^- at β-carbon.
    - Reactivity.
      - EAS: Bad, except as *N*-oxide.
      - S_NAr: Good, especially at the α-carbons. Electrophile coordination can induce a 10 order of magnitude rate increase (see Figure 2.4), and can even drive dearomatization (as in NAD^+/NADH).
    - Acidity: $\gamma > \beta > \alpha$ (δ^+ without α-effect, no α-effect, α-effect).
    - Basicity: $pK_a \approx 5.5$ (modulated by substituents).
    - Nucleophilicity: Modulated by substituents (e.g., pyridine vs. DMAP).
    - Pyridine-containing drug: Nicotine.
  - Pyridone.
  - Quinoline.
    - Quinoline-containing drug: Quinine.
  - Isoquinoline.
    - Reactivity.
      - More reactive on non-heterocyclic portion.
      - EAS at 5- and 8-positions.
      - S_NAr *always* at 1-position.
  - Quinolone.
    - Quinolone-containing drug: Ciprofloxacin.
  - Pyridazine.
    - Reactivity: Easier to protonate because of unfavorable α-effect (in neutral form).
  - Pyrimidine.
    - Reactivity.
      - Relative to pyridine: Better at S_NAr, worse at EAS.
      - More reacrtive at 4- than 2-position (double α-effect is bad).
    - Pyrimidine-containing drug: Anti-asthma agents.
  - Pyrrole.

- Protonation at α-carbons ($pK_a = -3.8$).
- π-excessive ring: Slightly more reactive toward EAS at α- than β-carbons, though can vary depending on the type of carbocation formed??
- Pyrrole-containing drug: Lipitor.

– Imidazole.

- Hydrogen-bonds well.
- Undergoes tautomerization.
- $pK_{a\,1} = 14.5$, $pK_{a\,2} = 7.1$.
  - ➢ Oxazole's $pK_a = 0.8$, thiazole's $pK_a = 2.5$ (no equal-energy resonance form).
- Reactivity: Good at EAS (but not as good as pyrrole).
- Imidazole-containing natural product: Histidine.

– Pyrazole.

- Dimeric in solution (due to hydrogen bonding).
- Tautmerization: Hydrogen prefers to be farther away from bulky substituents.
- Reactivity.
  - ➢ EAS at 4-position (halogenation, formylation, etc.)
- Pyrazole-containing drug: DGAT-2 inhibitors.

– Indole.

- Reactivity.
  - ➢ 5-membered ring is most reactive.
  - ➢ EAS at 3-position.
  - ➢ Basic conditions can make N more nucleophilic than C3 (e.g., for acylation).
  - ➢ Alkylation: C3, C3 $\rightarrow$ C2, C3 $\rightarrow$ deprotonation, N.
  - ➢ Deprotonation at C2 (esp. with Boc DMG).
- $pK_a = 16.2$ for the nitrogen proton.
- Indole-containing natural product: Strychnine, tryptophan.

– Indazole.

- Indazole-containing drug: EGFR inhibitor.

– Thiophene.

- Thiophene-containing natural product: Echinothiophene.

– Furan.

- Acidity: $pK_a \approx 35.6$ (α-carbons).
- Furan-containing drug: Zantac.

• Pyridine reactivity.

– Directed metallation.

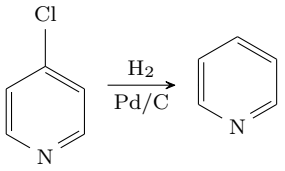
- Lithiation is reversible, hence why it is observed as occurring *thermodynamically* at the γ-position over *kinetically* at the α-position.
- DMGs: All the usual suspects (3° amides, methoxy, carbamates, etc.).
- DMGs (for π-deficient heterocycles): Halogens and pseudo-halogens (F, Cl, CF_3, CO_2^-).
  - ➢ Br sometimes included, but may prefer to do lithium/halogen exchange.
  - ➢ MeO is stronger than Cl as a DMG.
- β-DMGs direct γ (almost all) or α ($-$OEt).
- γ-DMGs direct β.
- α-DMGs direct β.

- Remember to do these reactions cold, in ethereal solvent (Et_2O or THF), and maybe with an additive (e.g., TMEDA).
- Lithium/halogen exchange.

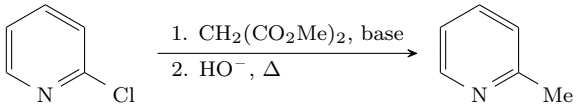
– Lateral deprotonation.
- pK_a's:
  - ➢ γ: 26.
  - ➢ α: 29.5.
  - ➢ β: 33.5.
- Thermodynamic conditions: $\gamma > \alpha > \beta$-positions.
- Kinetic conditions (e.g., with ^{n}BuLi): $\alpha > \gamma > \beta$-positions.
- Connection to decarboxylation at lateral positions.

– S_NAr is more probable than ketone addition.
- For example, aqueous ammonia will do S_NAr on pyridine before it adds to a bonded ketone.

– Hydrogenolysis of aryl chlorides.

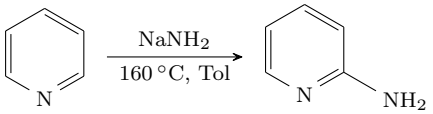


– Aryl chloride to methyl group.

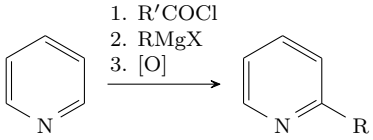


- See Figure 1.5.

– **Chichibabin** (reaction).

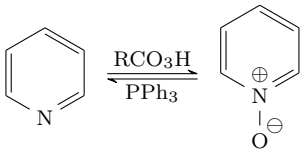


– 2-addition.



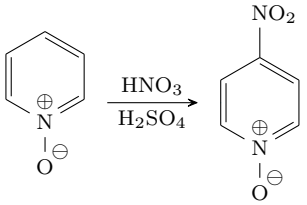
- The Grignard must be aryl, vinyl, or alkynyl.
- It's not clear what the final step oxidant would be, but perhaps DDQ??

– *N*-oxide formation and removal.

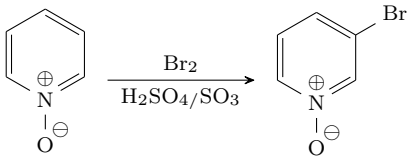


- Oxidants include *m*CPBA and H_2O_2.

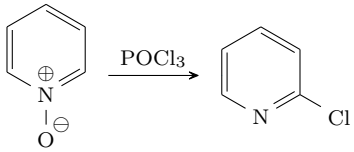
– *N*-oxide nitration.



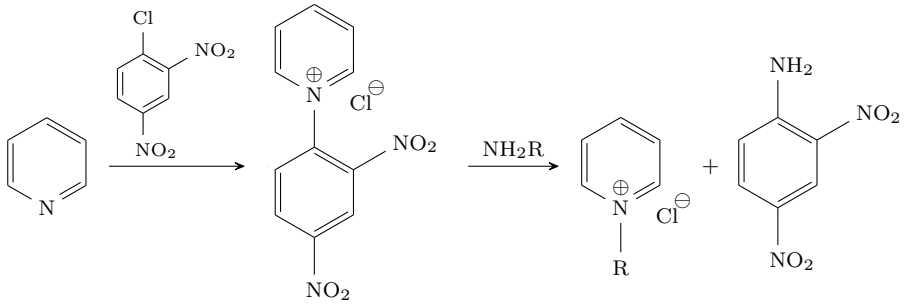
– *N*-oxide bromination.



– *N*-oxide chlorination.

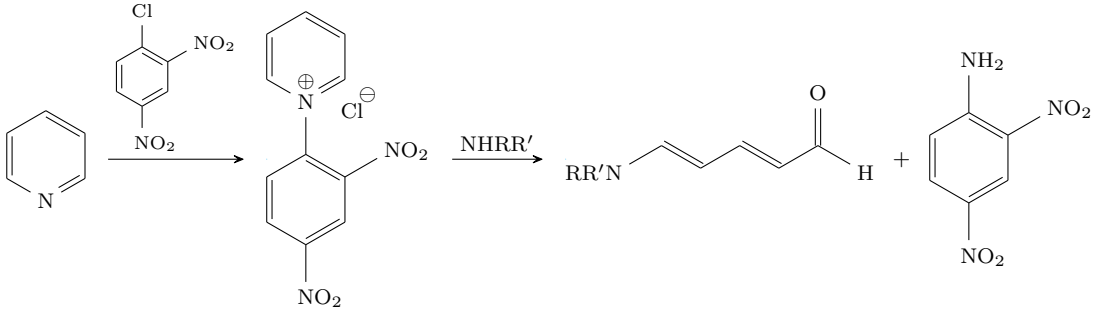


– **Zincke** (reaction).

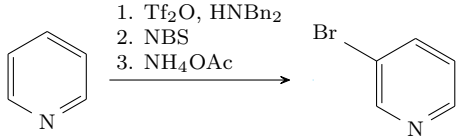


Zincke's salt

– **Zincke** (aldehyde formation).

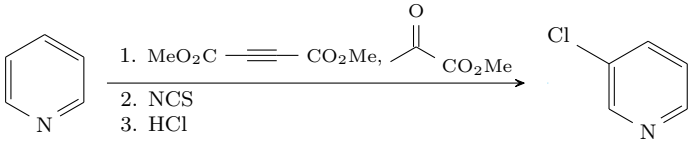


– Milder, Zincke-inspired *meta*-halogenation.



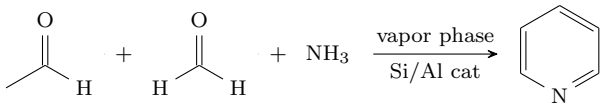
- Also works with NIS.
- Works with substituted pyridines, too.

– *meta*-halogenation via dearomatization.

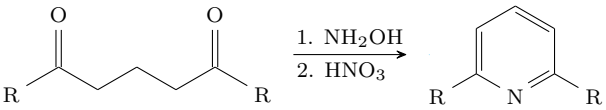


• Pyridine synthesis.

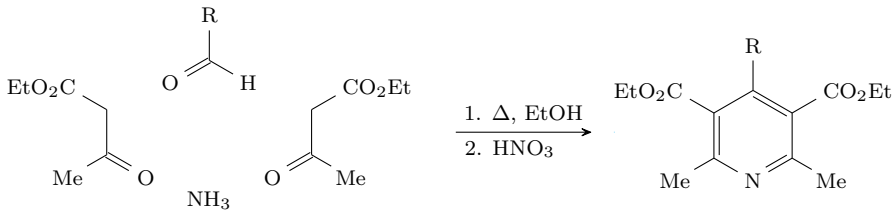
– Industrial pyridine synthesis.



– 1,5-dicarbonyl pyridine synthesis.



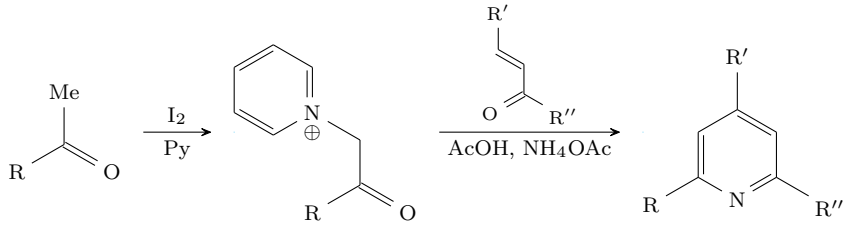
– **Hantzsch** (pyridine synthesis).



■ Mechanism is classic condensation reactions.

■ Asymmetric variant: Condense aldehyde and 1,3-dicarbonyl first, then condense with a **vinyligous urethane**. No last-step oxidation needed.

– **Kröhnke** (pyridine synthesis).

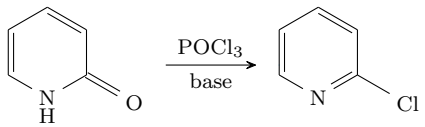


■ If R is enolizable (and not methyl), you will get regioisomers.

■ Can also start directly with an α-bromocarbonyl compound.

– $[2+2+2]$ pyridine syntheses: Cool, but limited synthetic utility.

- Some more important pK_a's.
  - ^{n}BuLi: 50.
  - LDA: 36.
  - $LiNEt_2$: 31.7.
- Pyridone.
  - Chlorination (see Figure 1.4).



- Cross-coupling.
  - Know generic mechanism.
    - Transmetallation typically occurs through σ-bond metathesis.
  - **Kumada** (coupling).

$$\mathrm{ArX} + \mathrm{RMgX} \xrightarrow{\mathrm{L}_n\mathrm{Pd}^0} \mathrm{Ar{-}R}$$

– **Negishi** (coupling).

$$\mathrm{ArX + RZnX \xrightarrow{L_nPd^0} Ar{-}R}$$

  - Common solvent: THF.
  - Ideal for coupling something to the pyridine α-position; 2-pyridylzincs are great.

– **Stille** (coupling).

$$\mathrm{ArX + RSnBu_3 \xrightarrow{L_nPd^0} Ar{-}R}$$

– **Suzuki-Miyaura** (coupling).

$$\mathrm{ArX + RB(OH)_2 \xrightarrow{L_nPd^0} Ar{-}R}$$

  - Common base: K_2CO_3.
  - Common ligands.
    - SPhos (see Figure 5.1b).
    - dppf (sp^3-hybridized boronates).
    - Heteroaryl couplings: PCy_3 or MIDA boronates.
  - Common solvent: ACN/H_2O.

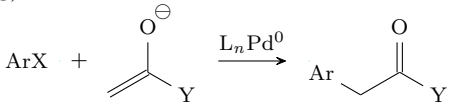
– **Sonogashira** (coupling).

$$\mathrm{ArX + R{-}{\equiv} \xrightarrow[Et_3N]{L_nPd^0,\,CuX} Ar{-}{\equiv}{-}R}$$

– **Hiyama** (coupling).

$$\mathrm{ArX + RSiMe_3 \xrightarrow[F^-]{L_nPd^0} Ar{-}R}$$

– **Carbonyl enolate** (coupling).



– **Heck** (coupling).

$$\mathrm{ArX + R{-}{=} \xrightarrow[Et_3N]{L_nPd^0} Ar{-}{=}{-}R}$$

– **Buchwald-Hartwig** (amination).

$$\mathrm{ArX + NHRR' \xrightarrow[base]{L_nPd^0} Ar{-}NRR'}$$

– **Carbonylation**.

$$\mathrm{ArX + CO + ROH \xrightarrow{L_nPd^0} ArCOOR} \qquad \mathrm{ArX + CO + NHRR' \xrightarrow{L_nPd^0} ArCONRR'}$$

  - Via an acyl palladide (ArCOPd) intermediate.

– **Ullmann** (coupling).

$$\mathrm{ArX + NHRR' \xrightarrow[base]{LCuX} Ar{-}NRR'}$$

– **Goldberg** (coupling).

$$\mathrm{ArX + RCONH_2 \xrightarrow[base]{LCuX} Ar{-}NHCOR}$$

– **Miyaura** (borylation).

$$\mathrm{ArX + B_2pin_2 \xrightarrow[base]{L_nPd^0} Ar{-}Bpin}$$

– **Cyanation**.

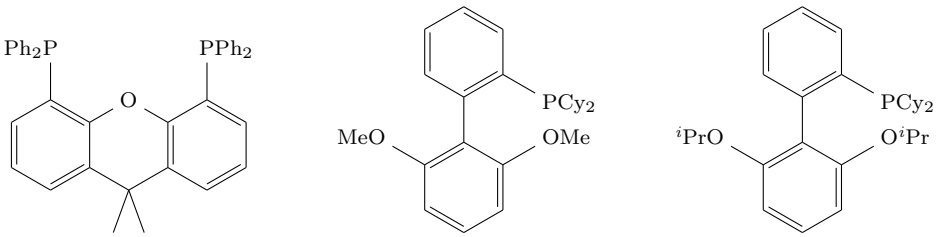
$$\mathrm{ArX} + \mathrm{CN}^- \xrightarrow{\mathrm{L}_n\mathrm{Pd}^0} \mathrm{ArCN}$$

– **C−O** (coupling).

$$\mathrm{ArX} + \mathrm{ROH} \xrightarrow[\text{base}]{\mathrm{L}_n\mathrm{Pd}^0} \mathrm{ArOR}$$

■ R can be alkyl or aryl.

– Ligands.

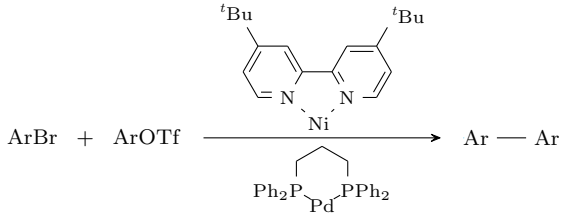


(a) Xantphos. (b) SPhos. (c) RuPhos.

Figure 5.1: Dialkylbiaryl phosphine ligands.

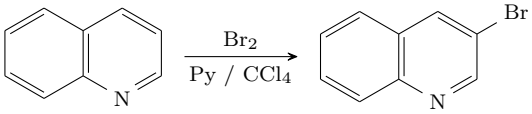
■ PPh_3.
■ Xantphos (Buchwald-Hartwig amination).
■ SPhos (Miyaura borylation and Suzuki-Miyaura borylation).
■ RuPhos (Negishi coupling).

– Direct cross-coupling of two (possibly hetero)aryl halides.



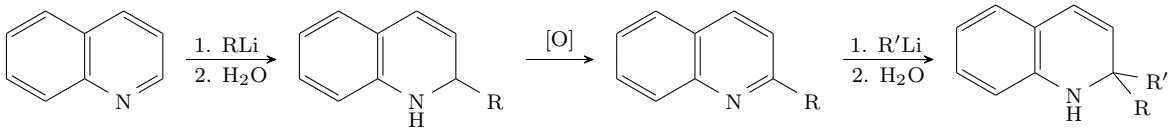
- Quinoline reactivity.

– *meta*-bromination.

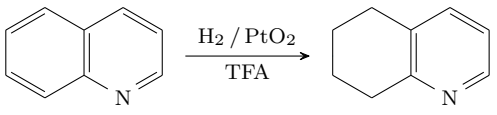


■ Proceeds through alternate mechanism.

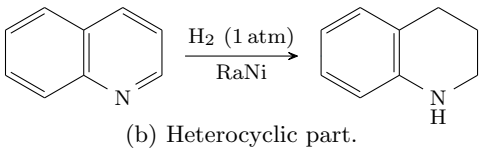
– 2-addition.



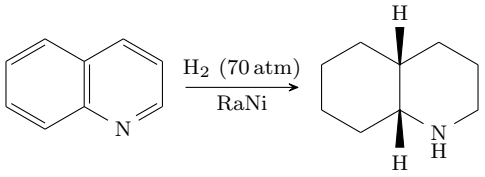
– Hydrogenations.



(a) Non-heterocyclic part.



(b) Heterocyclic part.

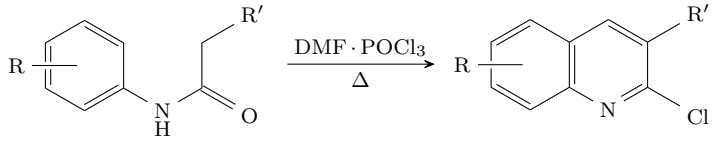


(c) Total.

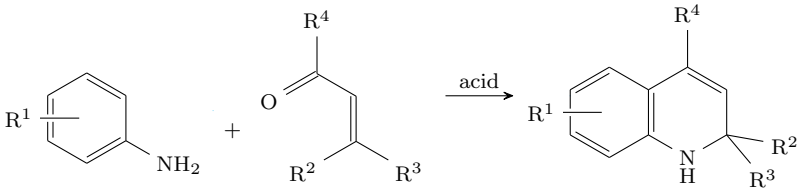
Figure 5.2: Quinoline hydrogenations.

- *cis*-decalin mostly formed in complete hydrogenation; some *trans*-though.

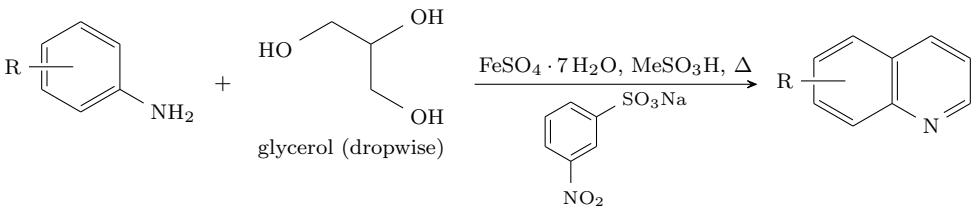
- Quinoline synthesis.
  - **Meth-Cohn** (quinoline synthesis): 3-substituted and 2-substitutable quinolines.



    - The starting material could come from the (possibly substituted) aniline and acid chloride (plus NEt_3).
    - Mechanism: Amide → chloroimine → enamine → attack on a Vilsmeier reagent → Friedel-Crafts.
  - **Skraup** (quinoline synthesis): No substitution, mix of (di-)2- and 4-substitution.



(a) Pyridine ring substiutions.



(b) No pyridine ring substitutions.

Figure 5.3: Skraup quinoline synthesis.

- Figure 5.3a.
  - ➢ If at least one of $R^2, R^3 = H$, then acid = H_2SO_4 and the system is oxidized to a quinoline.

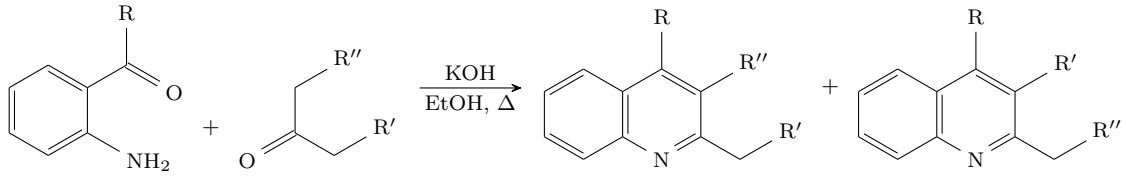
➢ If both $R^2, R^3 \neq H$, then acid = pTsOH and the system is *not* oxidized.

■ Figure 5.3b.

➢ Acrolein generated *in situ* from glycerol.

■ Mechanism: Michael addition, Friedel-Crafts, dehydration, oxidation.

– **Friedlander** (quinoline synthesis): 2-, 3-, and 4-substitution (or mix and match).

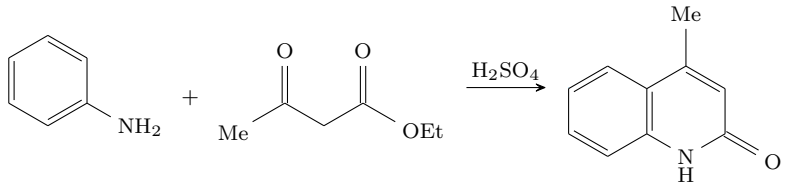


■ Mechanism: Imine condensation, followed by enamine attack on the aldehyde/ketone.

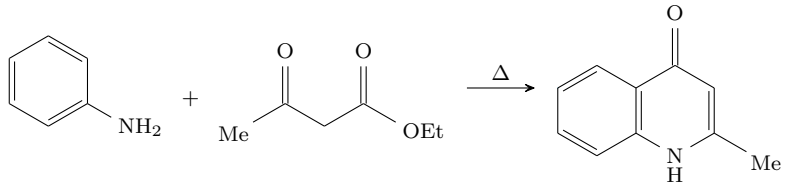
■ Regioisomer problems: Just reject the unwanted side product.

• Quinolone synthesis.

– **Conrad-Limpach-Knorr** (quinolone synthesis).



(a) 2-quinolones.



(b) 4-quinolones.

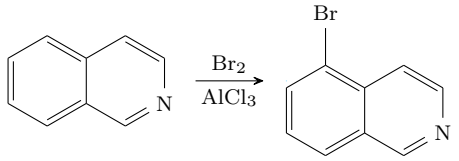
Figure 5.4: Conrad-Limpach-Knorr quinolone synthesis.

■ Presumably also works with substituted variants.

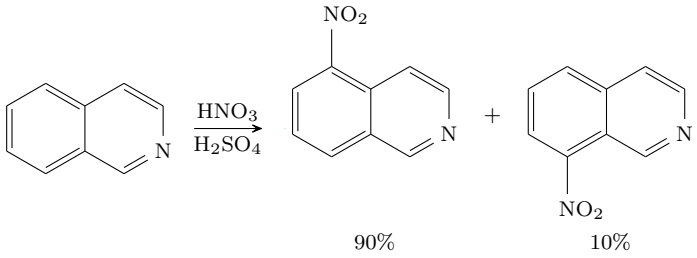
■ Acid protonates the more electron-rich ester; heat provides energy for attack at the more electrophilic ketone.

• Isoquinoline reactivity.

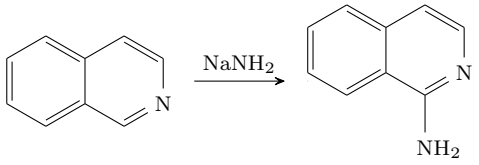
– 5-bromination.



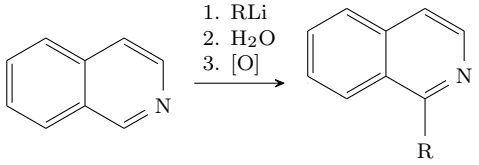
– 5- and 8-nitration.



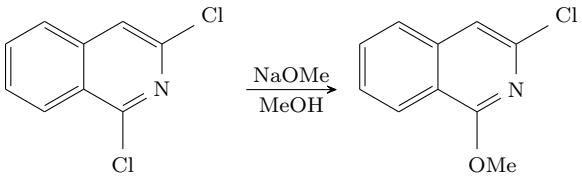
- Chichibabin reaction.



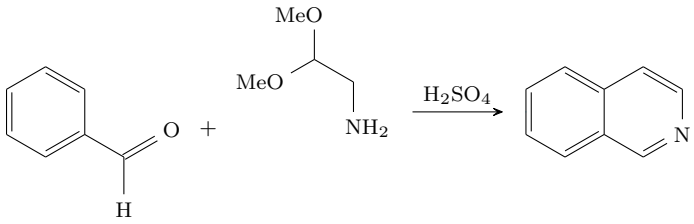
- 1-addition.



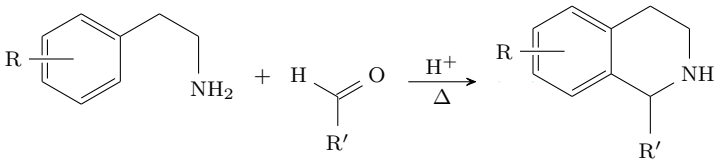
- 1-selective S_NAr.



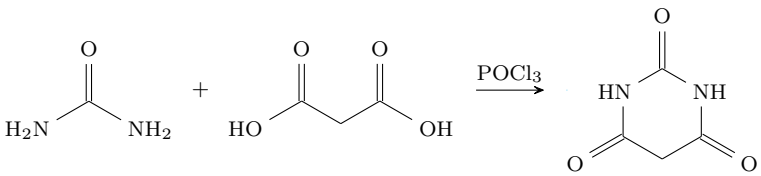
- Isoquinoline synthesis.
  - **Pomeranz-Fritsch** (isoquinoline synthesis): Anything can be substituted.



    - Can use methyl or ethyl acetal.
  - **Bischler-Napieralski** (isoquinoline synthesis): Enables formation of same derivatives.
  - **Pictet-Gams** (isoquinoline synthesis): Enables formation of same derivatives.
- **Pictet-Spengler** (reaction): A β-arylethylamine undergoes condensation with an aldehyde or ketone followed by ring closure.

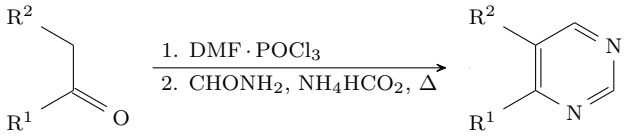


  - Mechanism can be Friedel-Crafts or involve shifts (depending on the most nucleophilic position).
- Pyrimidine synthesis.
  - **Grimmaux** (pyrimidine synthesis): 3 carbonyls.



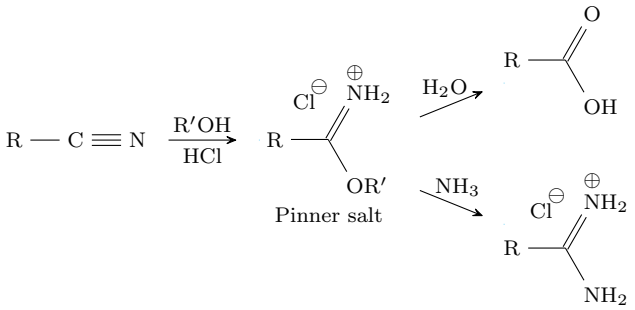
    - Can also use NaOR/ROH and di-R malonate esters.

- **Ziegenbein-Franke** (pyrimidine synthesis): 5- and 6-substituted pyrimidines.



  - Will have regioselectivity issues if $R^1 \neq R^2$.
- $[3+3]$ (pyrimidine syntheses).
  - Bis-nucleophile: Pinner product, or other group in the middle besides alkyl.
  - Bis-electrophile.
    - 4(5)6-substitution: β-diketone.
    - (5)6-substitution, 4-one: β-ketoester.
    - 4(5)-substitution: α,β-unsaturated ketone with β-leaving group.
    - 6-substitution, 4-one: Propynyl ester.
    - (5)-substitution: Vinamidium salt.
    - (5)6-substitution, 4-amine: β-ketonitrile.

- **Pinner** (reaction).

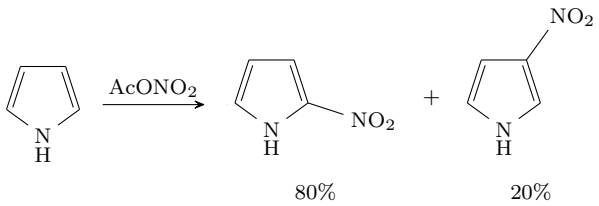


  - Forms **Pinner salts**, which are readily derivatized.

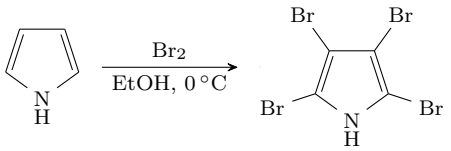
- **Turbogrignard**: The compound ^{i}PrMgCl, which is useful for converting R–X to Grignards.
- $KOH + H_2O/THF$ can sometimes be used to convert chloro-heterocycles to carbonyl groups.
- Boc protection/deprotection.

$$R_2NH \xrightarrow[Et_3N,\,DMAP]{Boc_2O} R_2N{-}Boc \xrightarrow{TFA} R_2NH$$

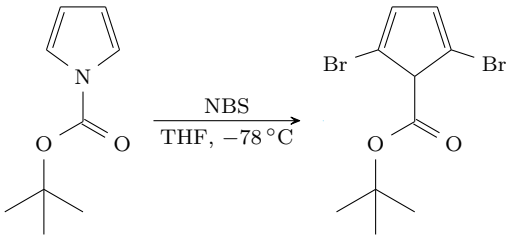
- Pyrrole reactivity.
  - 2- (and partial 3-) nitration.



    - $AcONO_2$ is a source of NO_2^+; made from $HNO_3 + Ac_2O$.
  - Perbromination.

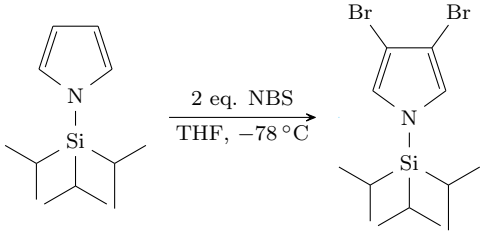


– 2,5-bromination.



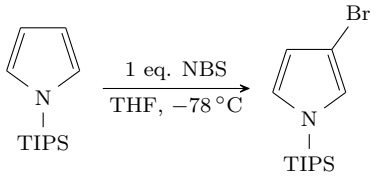
■ Boc-protection.

– 3,4-bromination.

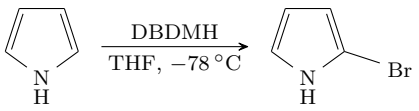


■ TIPS-protection.

– 3-bromination.

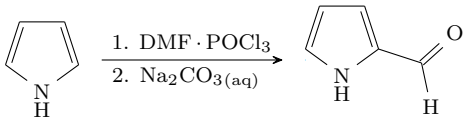


– 2-bromination.



■ Dibromodimethylhydantoin is an alternative Br^+ equivalent.

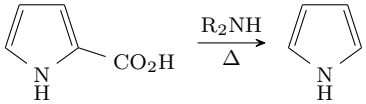
– Vilsmeier formylation.



– Can get reactivity at N by deprotonating with NaH.

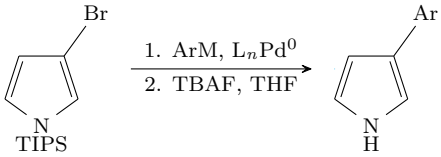
– Diels-Alder reactivity: Possible with Boc (EWG) protection and *very* activated dienophiles.

– Decarboxylation.



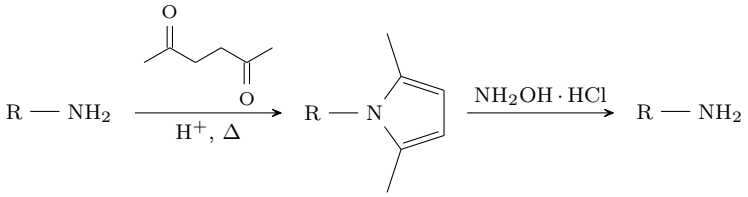
■ Carboxylic acids can be used as removable C2-blocking groups.

– Cross-coupling.

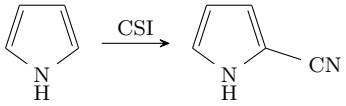


- Big, bulky protecting group needed (TIPS best).

– 2,5-dimethylpyrrole protection/deprotection.

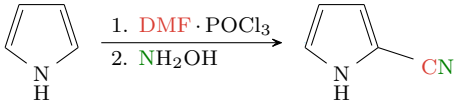


– 2-nitrilation (with CSI).



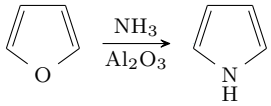
- DMF-induced pericyclic reactions can help in workup.

– 2-nitrilation (with Vilsmeier-type chemistry).

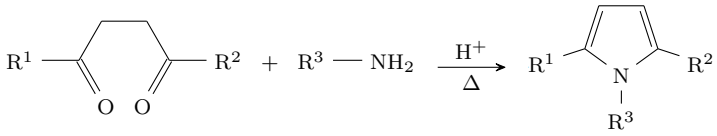


- Pyrrole synthesis.

– Industrial pyrrole synthesis.

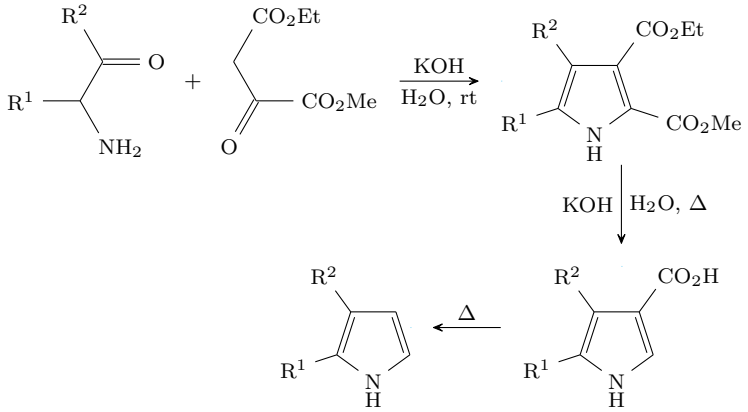


– **Paal-Knorr** (pyrrole synthesis): (1)(2)(5)-substitution.

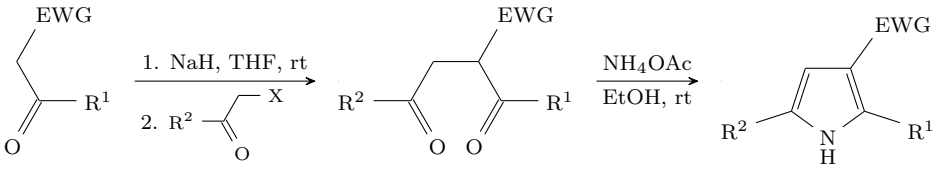


- To avoid R^3, use NH$_3$.
- To avoid R^1, R^2, or both, use the corresponding acetal(s). 2,5-dimethoxyTHF may be useful.

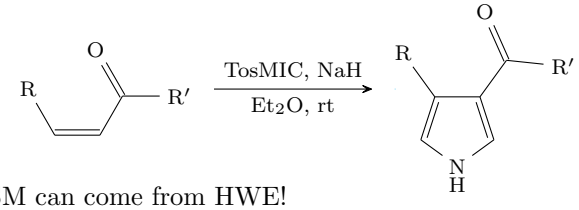
– **Knorr** (pyrrole synthesis): (2)3-substitution; can keep an ester or carboxylic acid at the 4- and/or 5-position.



- **Hantzsch** (pyrrole synthesis): 235-substitution.

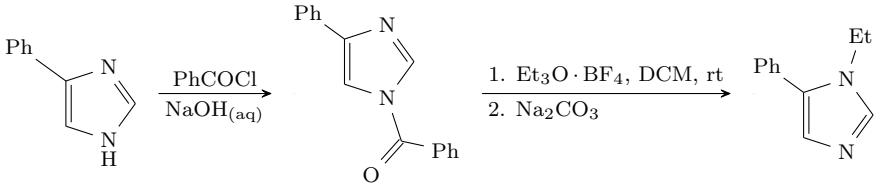


- **van Leusen** (pyrrole synthesis): 34-substitution.

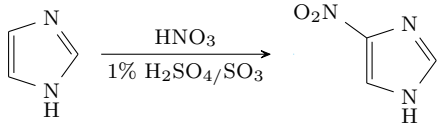


  - α,β-unsaturated SM can come from HWE!

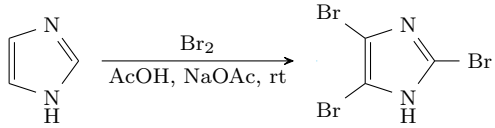
- $POBr_3$ does the same thing as $POCl_3$ (e.g., can brominate something).
- Imidazole reactivity.
  - Alkylation under neutral conditions: MeI adds to one, both, or neither nitrogen.
  - Alkylation under basic conditions (LDA, NaH, NaHMDS): Deprotonation and alkylation.
  - Selective N^2 alkylation.



  - 4-nitration.

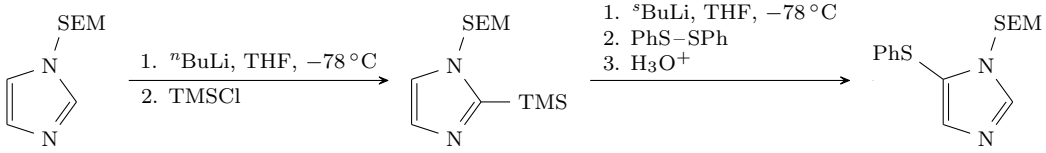


  - Perbromination.

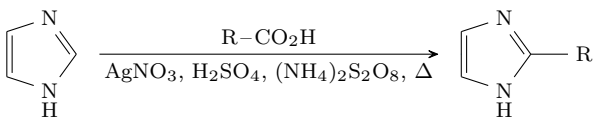


    - Can also do 2-bromination with just Br_2??

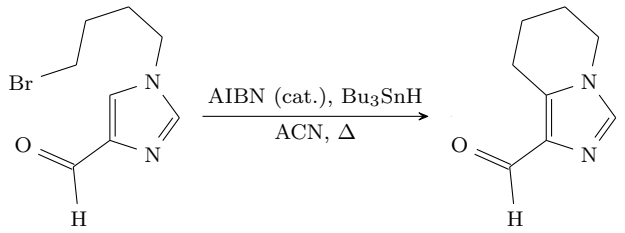
  - Directed metallation.



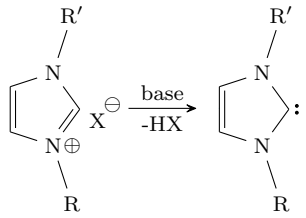
    - Protect with SEM (deprotonation, SEM-Cl).
    - Direct to C2, which can also be protected/deprotected to direct C4.
  - Lithium/halogen exchange: Consider adding a strong base before ^{n}BuLi to ensure ordering.
  - **Minisci** (reaction).



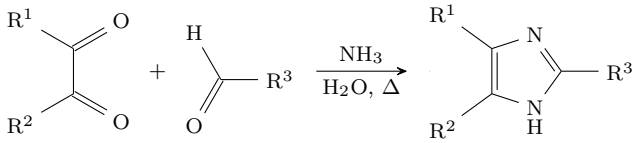
- Radical addition to electrophilic sites.



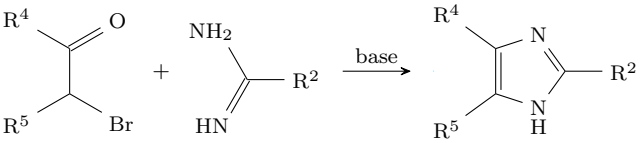
- Quaternary imidazolium salts to *N*-heterocyclic carbenes.



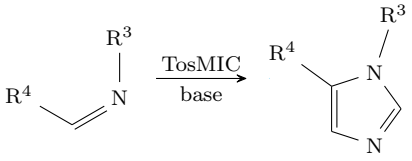
- Imidazole synthesis.
  - **Debus-Radziszewski** (imidazole synthesis): (2)45-substitution.



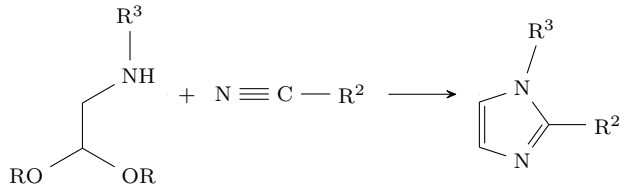
  - Pinner-type (imidazole synthesis): (2)4(5)-substitution.



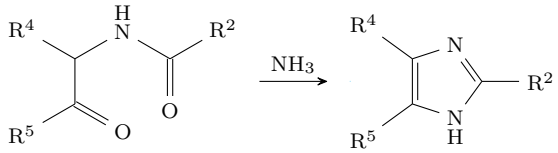
  - **van Leusen** (imidazole synthesis): (3)4-substitution.



  - Synthesis 4: 2(3)-substitution.

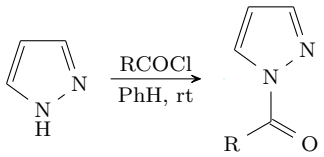


  - Paal-Knorr-type (imidazole synthesis): 24(5)-substitution.



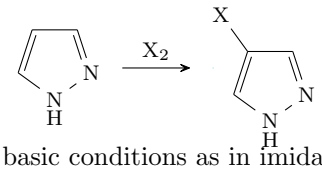
- Pyrazole reactivity.

- Acylation.



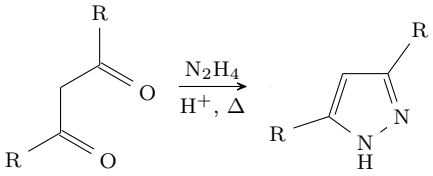
  - Mechanism probably proceeds through reversible acylation at the other nitrogen first.

- 4-halogenation.



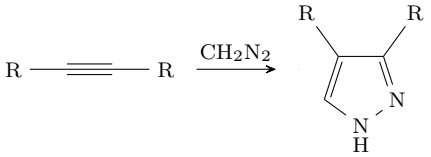
- *N*-alkylation varies in neutral vs. basic conditions as in imidazole.
- 5-directed metallation upon N–H protection.

- Pyrazole synthesis.
  - **Knorr** (pyrazole synthesis): (2)35-substitution.



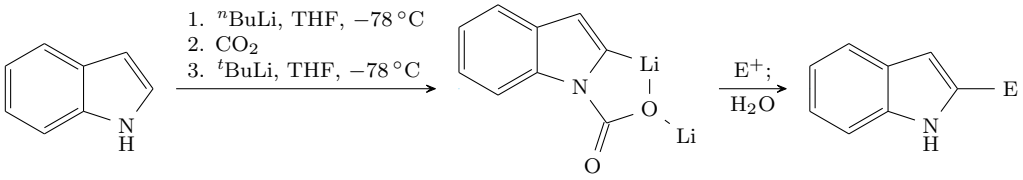
    - Regioisomer issues if asymmetric, unless extreme mismatch in electrophilicity/nucleophilicity is induced.

  - Dipolar cycloaddition method: 34-substitution.



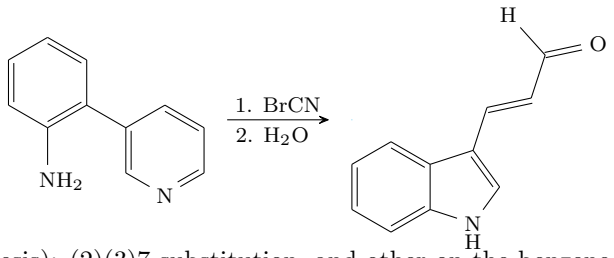
    - May have regioisomer issues. Can be partially overcome by introducing electronic biases.

- Indole reactivity.
  - **Mannich** (reaction): Formaldehyde and dialkylamines add at C3.
  - C2 lithiation.

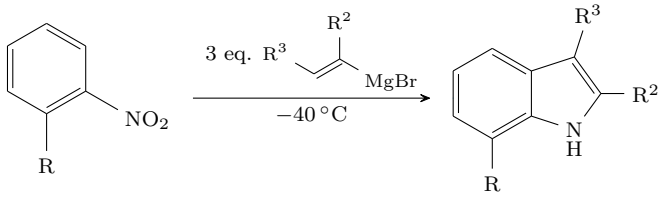


  - Gramine (from Mannich reaction) can be methylated and leave to allow other nucleophiles to attach to the offshot position.
  - 4-lithiation of gramine with TIPS protection.

- Indole synthesis.
  - **Zincke** (indole synthesis): 3-substitution.



– **Bartoli** (indole synthesis): (2)(3)7-substitution, and other on the benzene ring.

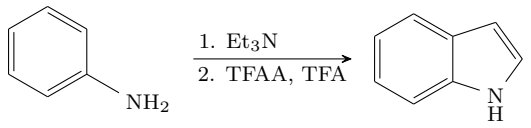


■ *Requires* bulky 7-group.

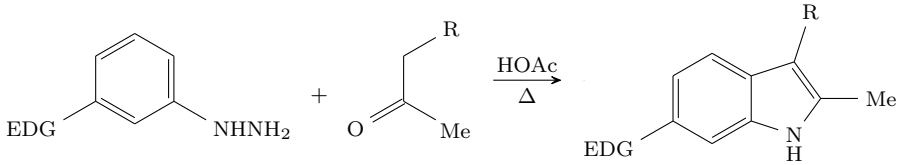
– **Leimgruber-Batcho** (indole synthesis): (3)-substitution, and other on the benzene ring.

■ Does not need a bulky 7-group.

– **Bischler** (indole synthesis): Aniline starting material.



– **Fischer** (indole synthesis).

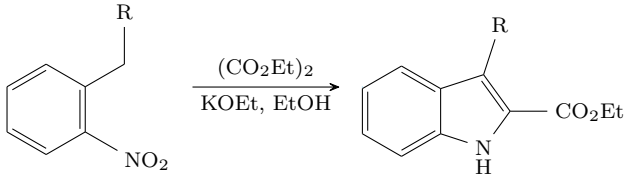


■ Regioisomer problems: Enolization both ways, substituents on the ring.

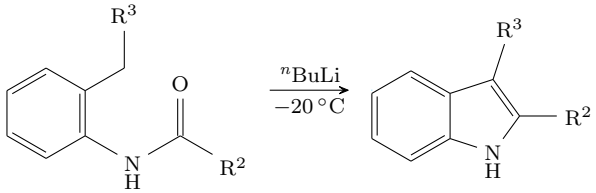
■ *meta*-EDG selective for 6-substitution.

■ Weak acid selective for thermodynamic enolization; strong acid selective for kinetic enolization.

– **Reissert** (indole synthesis): 2-ester-(3)-substitution, and other on the benzene ring.



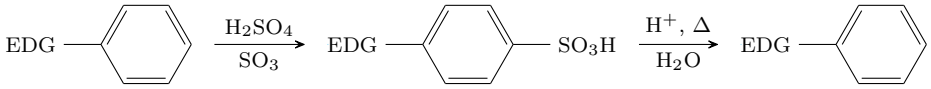
– **Madelung** (indole synthesis): 2(3)-substitution, and other on the benzene ring.



- Could prepare starting material from Fridel-Crafts, Clemmensen, bromination, Goldberg (or nitration, reduction, acylation).

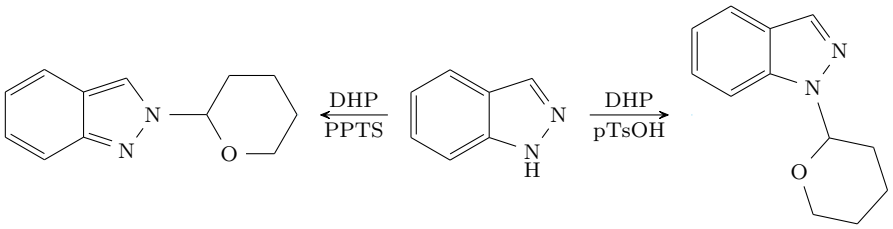
– **Hemetsberger** (indole synthesis): 2-ester-substitution.

- *para*-sulfonyl protecting group installation and removal.



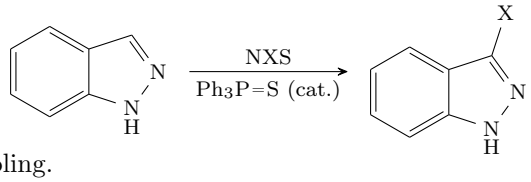
- Indazole reactivity.

– N^1- and N^2-THP protection.



- Deprotect with pTsOH in MeOH.

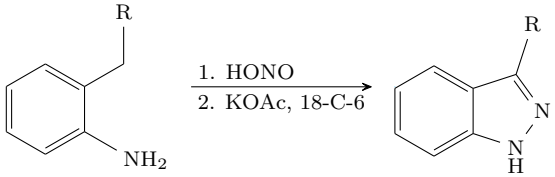
– 3-halogenation.



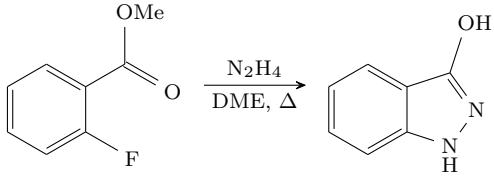
- Feeds into cross-coupling.

- Indazole synthesis.

– Route 1: (3)-substitution, and other on the benzene ring.



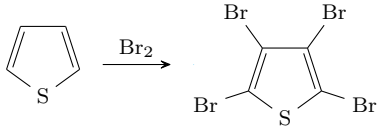
– Route 3: (3)-substitution, and other on the benzene ring.



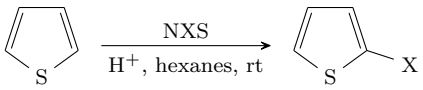
- Can put nothing (aldehyde), amine (nitrile), or hydroxyl (ester) on the 3-position.

- Thiophene reactivity.

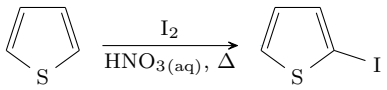
– Perbromination.



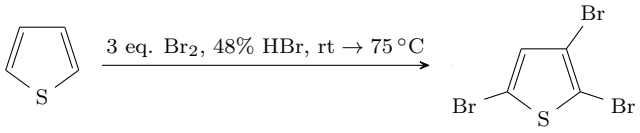
– 2-bromination/chlorination.



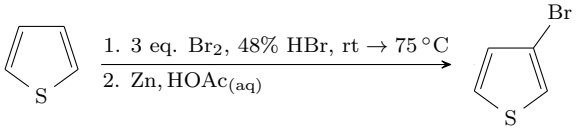
- 2-iodination.



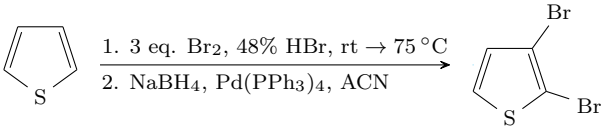
- 2,3,5-tribromination.



- 3-bromination.



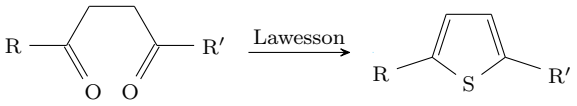
- 2,3-dibromination.



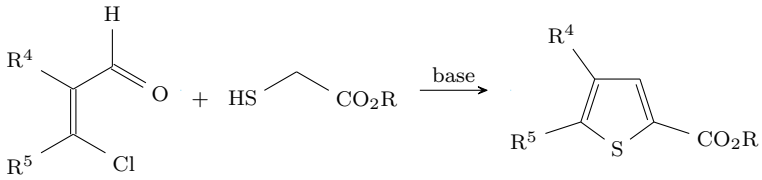
- Thiophene synthesis.
  - Industrial thiophene synthesis.

$$\mathrm{BuH} + \mathrm{S_8} \xrightarrow[600\,^\circ\mathrm{C}]{\text{cat.}} \text{thiophene}$$

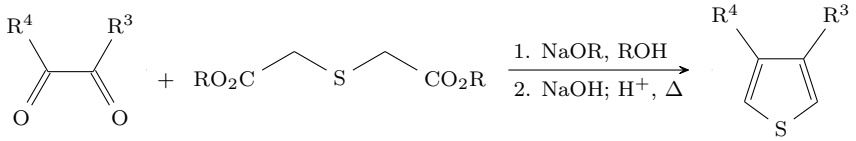
  - **Paal-Knorr** (thiophene synthesis): 25-substitution.



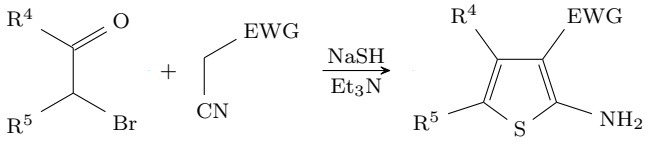
  - **Fiesselmann** (thiophene synthesis): 2-ester-45-substitution.



    - Can also use esters or nitriles as in indazole route 1.
    - Can saponify ester to 2,3-substituted derivative.
  - **Hinsberg** (thiophene synthesis): 34-substitution.

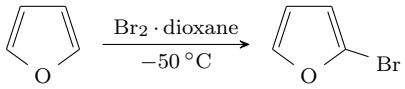


  - **Gewald** (thiophene synthesis): 2-amino-3-EWG-45-substitution.

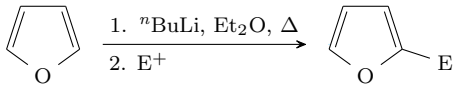


- Knoevenagel-type mechanism.
- Remember that S_1 is more active than S_n.

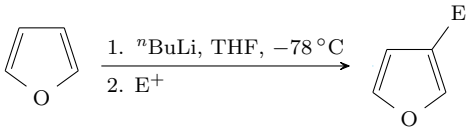
- Furan reactivity.
  - 2-bromination.



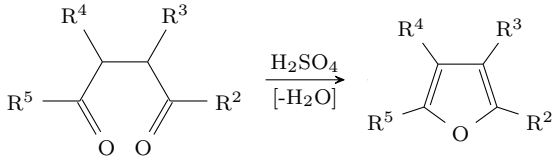
  - 2-addition.



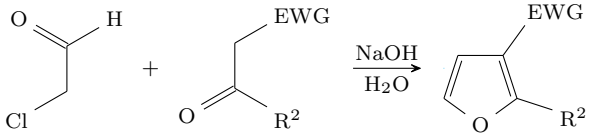
  - Diels-Alder with highly activated dienophiles.
  - Mannich reaction: 2-substitution.
  - 3-addition.



- Furan synthesis.
  - **Paal-Knorr** (furan synthesis): 2(3)(4)5-substitution.



  - **Feist-Benary** (furan synthesis - aldehydes): 23-substitution.



  - **Feist-Benary** (furan synthesis - ketones): 235-substitution.