Lecture 1: General Reactivity 1

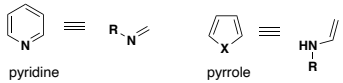


pyriDOGE

- You are MINING pyriDOGE in this class!
- Market value determined right before the midterm and final
- Use you pyriDOGE for:
  - Points on exams / homeworks
  - Heterocycles Merchandise (coming soon!)
- Transferable between students!



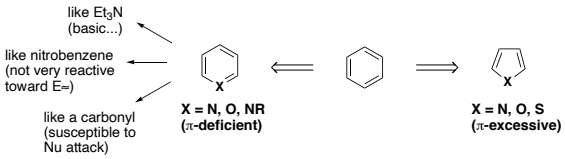
Not all nitrogens are created equal

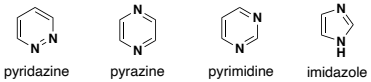


Four main types of heteroaromatic compounds:

greater aromaticity — less aromaticity

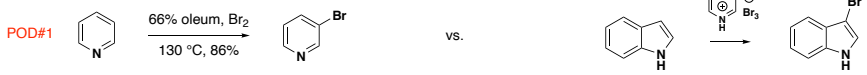
pyridine-like N < pyrrole N < sulfur < oxygen





Aromaticity as a uesful qualitative guide to predict: reactivity, tautomerism, substituent reactivity, retrosynthesis

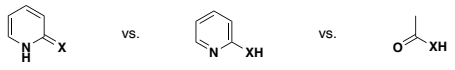
A Tendency to give addition rather than substitution increaces as aromaticity decreases



B Cyclic transition state reactions (pericyclic) increases are aromaticity decreases



C dominant tautomeric structure related to degree of aromaticity



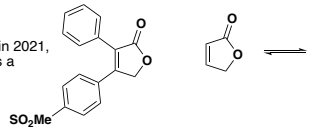
B A

dominant form:

O	carboxylic acid
N	amide
C	ketone

tautomerism and aromaticity in heterocyclic chemistry review: Chem. Rev. 2004, 104, 2777

As a medicinal chemist in 2021, what would you view as a potential metabolic liability of Vioxx?



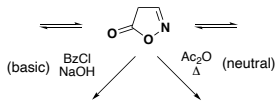
Corey, *Tetrahedron. Letters.* **2005**, 46, 927

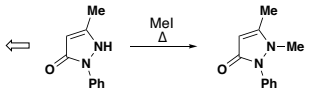
POD #2

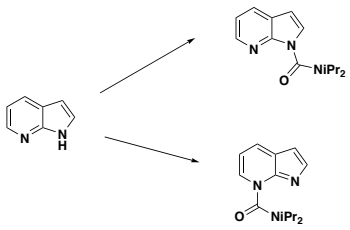


different reactivity via different tautomeric forms
(tuning the reaction conditions...)

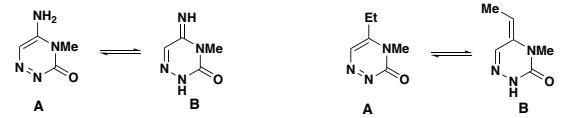
POD #3



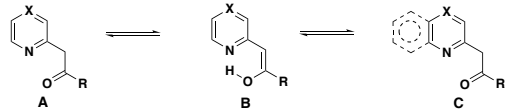




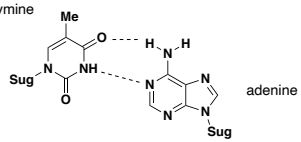
tautomeric forms:



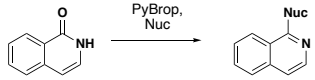
hydrogen bonding also impacts tautomeric forms



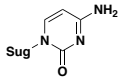
thymine



adenine

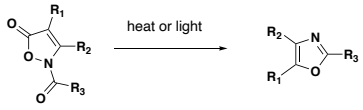


JOC, **2007**, *72*, 10194

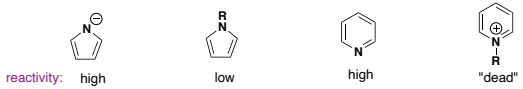


cytosine

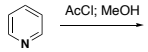
(D) Facility of unimolecular reactions increaces as aromaticity decreases



Attack of E^+ on Nitrogen:

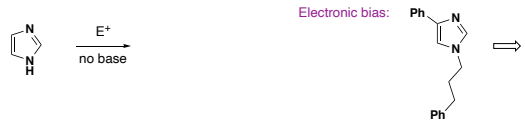


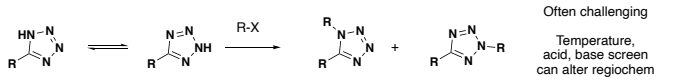
POD #4



Consulting corner: strategies to control regioselective N-alkylation

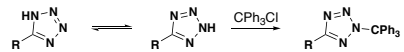
The case of imidazole, pyrazole, and tetrazole for N-selectivity in alkylations



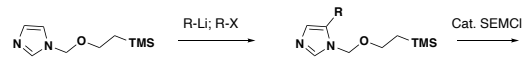


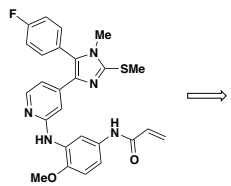
Eur. J. Org. Chem. **2012**, 6101

Steric blocking



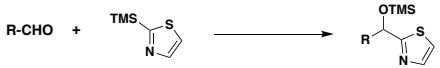
SEM-trick



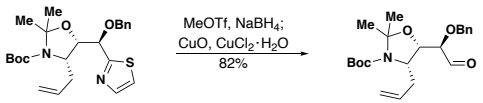


EGFR Mutant Inhibitors
J. Med. Chem. **2020**, *63*, 4293

POD #5



JOC, 1994, 54, 3656; Chem. Rev., 2004, 104, 2557



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OL, **2001**, *3*, 2677