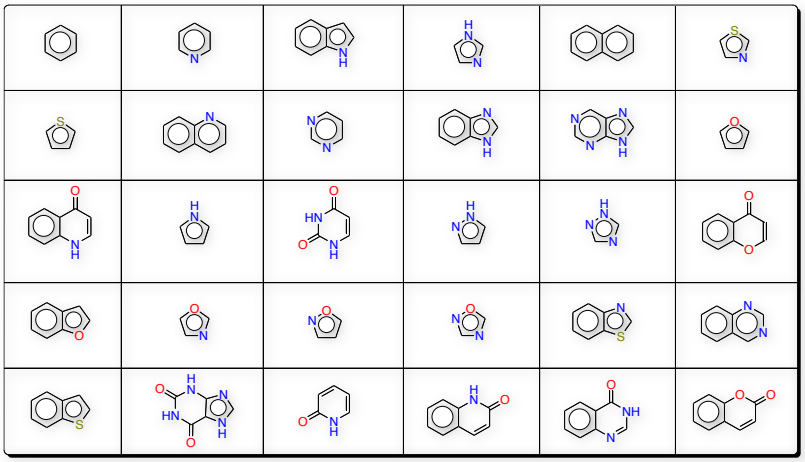
Heterocyclic Chemistry

Most Common Aromatic Scaffolds Present in Bioactive Molecules



Ertl, P.; Jelfs, S.; Muehlbacher, J.; Schuffenhauer, A.; Selzer, P., "Quest for the rings. In silico exploration of ring universe to identify novel bioactive heteroaromatic scaffolds." *J. Med. Chem.* **2006**, *49*, 4568-4573.

Properties, Reactivity and Reactions of Heterocycles

- Heterocycles can be classified into:

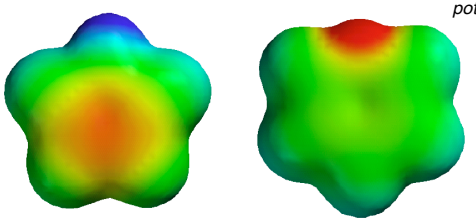
π-excessive

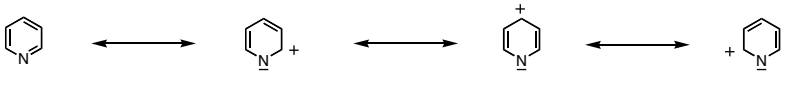
π-deficient

π-excessive:
the -NH- bonds not involved, N yes, in the π-system
excess electron density on carbons

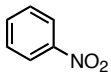
π-deficient:
decreased electron density in carbons

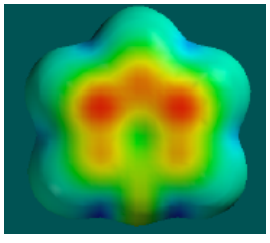
Electron-density surface encoded with the electrostatic potential



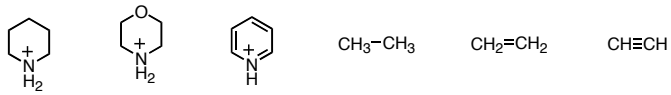


Electrophilic substitution is most difficult at C-2 or C-4
electrophilic substitution is difficult also at C-3

cf. 



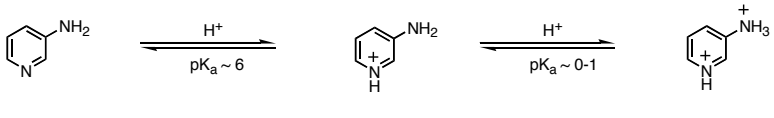
Electron-density surface encoded with the ionization potential



pK_a	11	8	5	~42	~35	~25

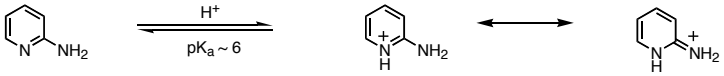
+ 1 pK unit/alkyl

decreases with number of alkyls, thus penta-Me ~ 8.5



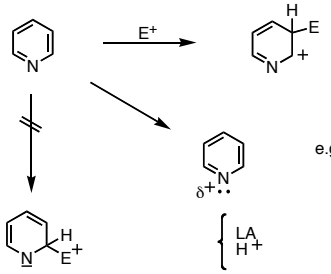
pK_a ~ 5

pK_a ~ 2-3

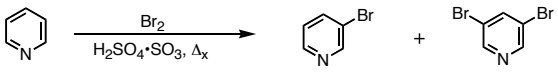


pK_a ~ 10

Pyridine: Electrophilic Substitution

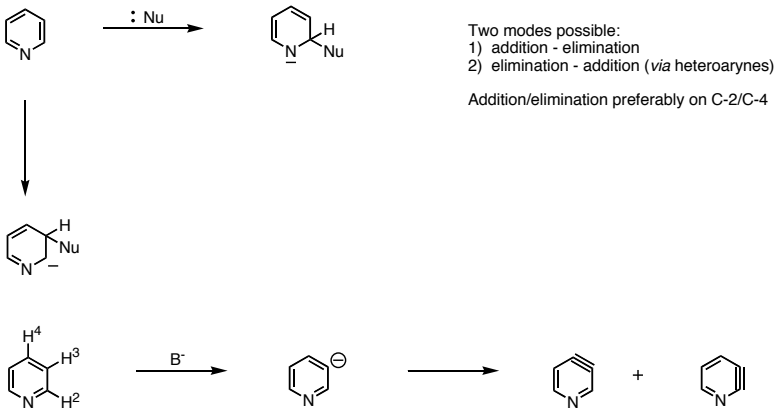


e.g. Friedel-Crafts on pyridine has not been achieved



Direct C-nitration of pyridine is very difficult to effect. Pyridine can be C-nitrated with nitric acid in sulfuric acid at 25 °C 10^8 times more slowly as compared with benzene. Thus, the C-nitration of pyridine has been effected only under extremely drastic conditions; i.e. treatment of pyridine with an alkali metal nitrate in fuming sulfuric acid at 300 °C is reported to afford 3-nitropyridine in 14% yield.

Pyridine: Nucleophilic Substitution

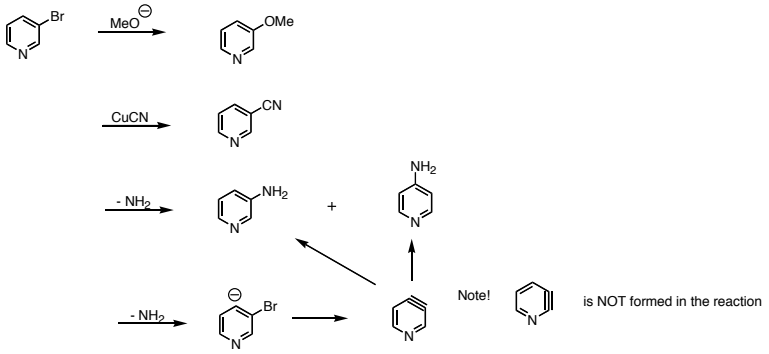


Two modes possible:
1) addition - elimination
2) elimination - addition (*via* heteroarynes)

Addition/elimination preferably on C-2/C-4

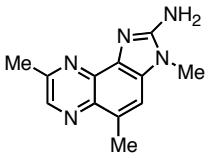
Most acidic hydrogen (H^3) is removed **?? - Kinetic Selectivity??**

Pyridine: Reactions



Note! is NOT formed in the reaction

How would you make this?



an aminoimidazoquinoxaline (IQx)

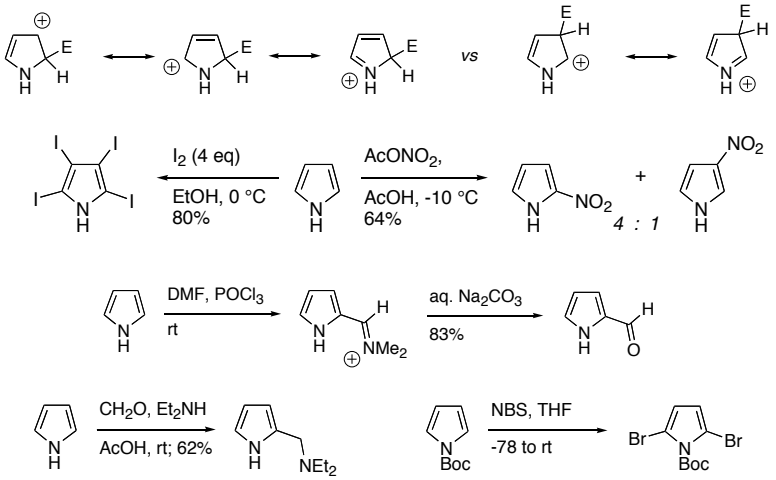
MeIQ$_x$

one of the most potent mutagens known;
100 000 rev/μg/plate in the Ames test
(aflatoxin 10 000!)

- Bierer, D. E.; O'Connell, J. F.; Parquette, J. R.; Thompson, C. M.; Rapoport, H., "Regiospecific synthesis of the aminoimidazoquinoxaline (IQx) mutagens from cooked foods." *J. Org. Chem.* **1992**, *57*, 1390-1405.

- The regioselective synthesis of 6 MeIQx was accomplished with this general strategy
- The key step involves the dehydrobrominative photocyclization (in 25-90% yield) of imidazolylpyrazinylethylenes - a previously unexplored transformation

Pyrrole: Electrophilic Aromatic Substitution



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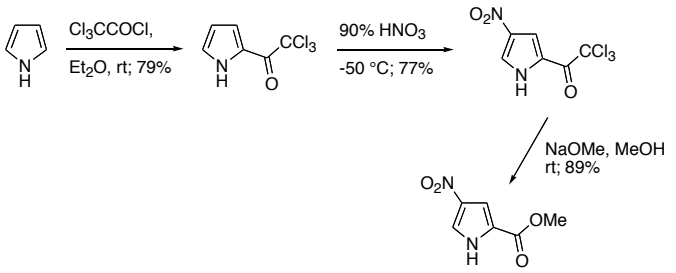
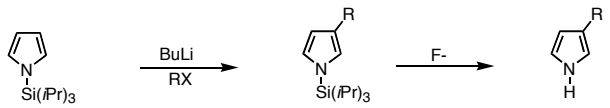
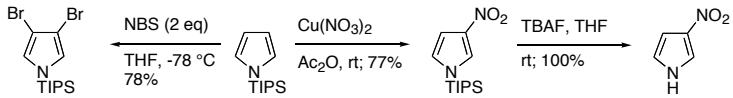


Pyrrole: Alkylation/Regiocontrol



TIPS shields from deprotonation at C-2's

Muchowski *Tetrahedron Lett.* **1983**, *24*, 3455.
Kozikowski *J. Org. Chem.* **1984** *49*, 3239.
Eschenmoser *Helv. Chim. Acta* **1987** *70*, 1115.
Stefan *Chem. Ber.* **1989** *122*, 169.
Muchowski *J. Org. Chem.* **1990** *55*, 6317.

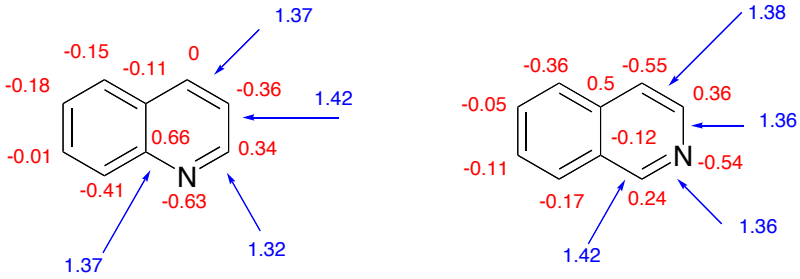


Reactions of Quinolines & Isoquinolines

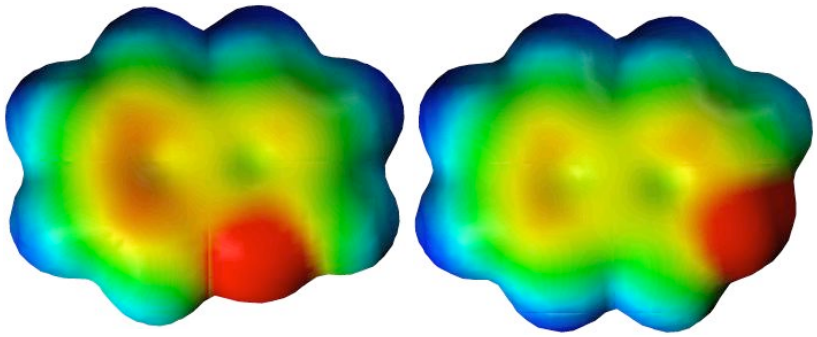
• Structural and electronic properties:

• Quinoline is a π-deficient heterocycle, related to pyridine but with a slightly lower pKa = 4.9 (pyridine has a pKa = 5.2). The pKa of isoquinoline is 5.1.

• The following electrostatic charges and bond distances were calculated at the DFT/BLY3P/ 6-31G* level:

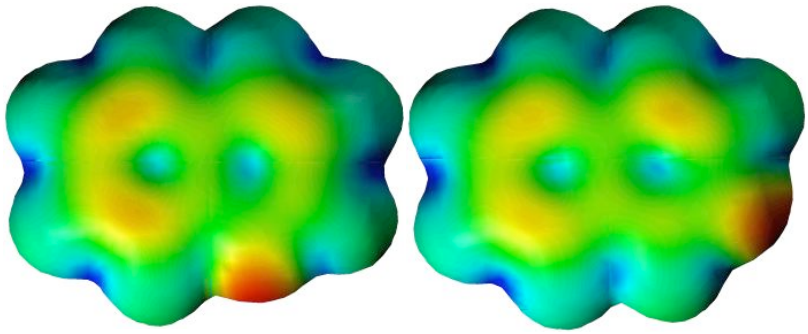


• Structural and electronic properties (cont):



Electron-density surface encoded with the electrostatic potential

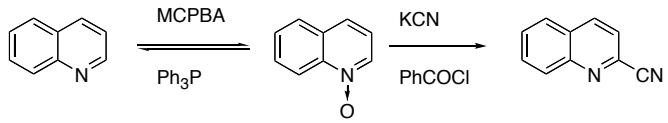
• Structural and electronic properties (cont):



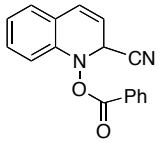
Electron-density surface encoded with the ionization potential

• Chemical properties of quinolines and isoquinolines

• 2-Cyanoquinoline is obtained from quinoline *N*-oxide by treatment with cyanide/benzoyl chloride with deoxygenation and alpha-substitution. O-Acylation is the first step; this is followed by addition of cyanide to the 1-benzyloxy quinolinium ion to give the 1,2-dihydroquinoline, which eliminates benzoic acid



via



Syntheses of Methoxatin

Zhang, Z.; Tillekeratne, L. M. V.; Hudson, R. A., "Synthesis of isomeric analogs of coenzyme pyrroloquinoline quinone (PQQ)." *Synthesis* **1996**, 377-382.
MacKenzie, A. R.; Moody, C. J.; Rees, C. W., "Synthesis of the bacterial coenzyme methoxatin." *Tetrahedron* **1986**, *42*, 3259-3268.
Buchi, G.; Botkin, J. H.; Lee, G. C. M.; Yakushijin, K., "A synthesis of methoxatin." *J. Am. Chem. Soc.* **1985**, *107*, 5555-5556.
* Gainor, J. A.; Weinreb, S. M., "Synthesis of the bacterial coenzyme methoxatin." *J. Org. Chem.* **1982**, *47*, 2833-2837.
* Hendrickson, J. B.; DeVries, J. G., "A convergent total synthesis of methoxatin." *J. Org. Chem.* **1982**, *47*, 1148-1150.