## Heterocycles

Saturated heterocycles are treated as derivatives of the related carbocycles. prefix: aza- for nitrogen; oxa- for oxygen; thia- for sulfur; phospha- for phosphorous



### **Reactions of Nonaromatic Heterocycles**



Oxacyclopentane (tetrahydrofuran, THF) and 1,4-dioxacyclohexane (1,4-dioxane) are used as solvents.



#### **Unsaturated Heterocycles**



#### **Aromatic 5-Membered Heterocycles**



### Preparations of Pyrroles, Furans, and Thiophenes



## Protonation and Deprotonation of Pyrrole



# **Properties of Furan**



Furan is protonated most easily at C2 as well, but hydrolysis probably takes place via an intermediate protonated at C3.

relative nucleophilicity: benzene << thiophene < furan << pyrrole inductive effect: O (3.5) > N (3.0) > S (2.6) resonance effect: N > O > S delocalization energy:

thiophene (121 kJ/mol<sup>-1</sup>) > pyrrole (88 kJ/mol<sup>-1</sup>) > furan (67 kJ/mol<sup>-1</sup>)

[benzene (151 kJ/mol<sup>-1</sup>); pyridine (96 kJ/mol<sup>-1</sup>)]

Furan possesses sufficient diene character to undergo Diels-Alder cycloadditions.



#### Electrophilic Aromatic Substitution (Pyrrole and Thiophene)



Strong acids must be avoided in the reactions of pyrrole to prevent polymerization.

Pyrrole is much more nucleophilic than benzene, so usually no acid catalyst is needed for electrophilic aromatic substitutions of pyrrole.



### Electrophilic Aromatic Substitution of Pyrrole

Pyrrole is so nucleophilic that it can undergo substitution reactions that are usually only feasible for electron-rich aromatic rings (e.g., phenols and *N*,*N*-dialkyl anilines).



## Reactions of Pyrrole, Thiophene, and Furan



**Furan** may undergo electrophilic substitutions similarly to pyrrole and thiophene (strongly acidic aqueous conditions should be avoided).





## **Reactions of Furan and Substitution Effect**

But when furan is subjected to electrophilic attack in the presence of a nucleophile, addition reactions usually occur, because furan is less aromatic. Addition product may then undergo elimination to give substitution product.



#### Other Reactions of Thiophene, Furan and Pyrrole



Thiophenes are less prone to undergo D-A reactions than furan. It only reacts with highly activated dienophiles and itself is a poor diene. When the reaction happens, the adducts are unstable and extrude sulfur.



#### Benzo-Fused 5-Member Ring Aromatic Compounds

10  $\pi$ -electron aromatic systems



Indole is related to pyrrole. It possesses many possible resonance forms, however, those disturbing the cyclic six- $\pi$ -electron of the fused benzene ring are less important.



#### **Preferred Electrophilic Substitution Sites**





Similar with indole, electrophilic aromatic substitution happens on C3 for benzothiophene, but for benzofuran substitution takes place on C2.





unstable due to strong electronegativity of O

# **Properties of Pyridine**



## **Pyridine Synthesis**

Hantzsch pyridine synthesis:



# **Pyridine Synthesis**

Modifications and variations of Hantzsch synthesis:



# **Properties of Pyridine**

Pyridines should show analogous properties of:

- *Tertiary amines*: reactions at the nitrogen lone pair, including protonation, alkylation, acylation, *N*-oxide formation, and coordination to Lewis acids, etc...
- Benzene: electrophilic substitution reactions
- Conjugated imines: susceptibility to attack by nucleophiles at the α- and γcarbon atoms



# **Properties of Pyridine**



Pyridine undergoes electrophilic aromatic substitution only under extreme conditions.

- Pyridine is electron-poor and therefore undergoes electrophilic aromatic substitution with great difficulty;
- The reaction is several orders of magnitude slower than for benzene and occurs only at C3;
- Halogenation, nitration, and sulfonation proceed under rather forcing conditions, and Friedel-Crafts alkylation and acylation do not take place;
- Reactivity for electrophilic substitution increases with the presence of EDG.



## **Electrophilic Aromatic Substitution of Pyridine**



# **Nucleophilic Substitution of Pyridine**

#### Pyridine undergoes relatively easy nucleophilic substitution.

- 1. Pyridine is electron deficient and therefore undergoes nucleophilic substitution more readily than does benzene;
- 2. Attack at C2 and C4 is preferred because the negative charge of the reaction intermediates is placed on the nitrogen atom (C2 is still preferred to C4 and substitution at C4 happens when C2s are occupied).



# **Nucleophilic Substitution of Pyridine**

Reactions similar to the Chichibabin reaction take place between pyridine and Grignard or organolithium reagents:



Most nucleophilic substitutions of pyridines involve halides as leaving groups, the 2- and 4-halopyridines being particularly reactive.



## **Oxidation and Reduction of Pyridine**



Pyridine N-oxide can undergo both electrophilic and nucleophilic substitutions.



## Reactions of Pyridine $\alpha$ -Proton



#### **Quinolines and Isoquinolines: Syntheses**

#### Quinolines:



#### **Isoquinolines:**



## **Quinolines and Isoquinolines: Properties**

Basicity: quinoline < pyridine < isoquinoline



(iso)quinoline N-oxide



Similar with naphthalene:



## Electrophilic Aromatic Substitution of Quinoline and Isoquinoline

Electrophilic substitutions on quinoline and isoquinoline take place on the benzene ring: pyridine is electron-poor compared to benzene.

Substitution at carbons next to the ring fusion is kinetically favored, as in the naphthalene



## **Nucleophilic Substitutions**

Nucleophiles react preferentially at the electron-poor pyridine nucleus. These reactions are analogous in mechanism to those with pyridine itself.



## **Nucleophilic Addition Reactions**



Reactions of  $\alpha$ -proton (similar reactions as with pyridine)

Reduction



## Diazines, Triazines, and Tetrazines

Higher aza analogs of pyridine behave in a similar manner but show the increasing effect of aza substitution: increasing electron deficiency



#### **Electrophilic and Nucleophilic Substitutions of Diazines**

- Diazine, triazine, and tetrazines are stronger bases than pyridine
- With the number of nitrogen atoms increases from one to higher, electrophilic attack on the ring carbon atoms becomes increasingly difficult and nucleophilic attack becomes easier.



### **Diels-Alder Reactions with Heterocycles**





#### **2-pyranone:**







#### Syntheses of 2-pyranone:









## Syntheses of Azole Compounds



1,3-dipolar addition



## **Properties of Azole Compounds**

In comparison with pyrrole, thiophene and furan, the additional nitrogen in the rings has important effects.

Tautomerism of imidazole and pyrazole





No separate existence

two equivalent resonance forms



**pyridine N alike: basic** (lone pair not involved in conjugation) and **electron withdrawing** 



Like a pyrrole N: nonbasic (lone pair involved in conjugation) and electron donating

## **Reactions of Azole Compounds**

Due to the electron-withdrawing effect of the additional N, azole compounds are less reactive toward electrophilic substitutions compared to corresponding 5-membered cyclic molecules with one heteroatom, but they can be expected to undergo these reactions under common conditions for aromatic compounds.

Electrophilic substitution of imidazole:



A complication of imidazole is the ease with which N-3 is protonated or attacked by electrophilic reagent; Friedel-Craft alkylation and acylation at Cs generally fails for this reason and nitration in sulfuric acid is difficult but viable; sulfonation only takes place with hot oleum to give C-4 substituted product.

# Reactions of Azole Compounds

But tribromo substituted product can be easily obtained by reacting with bromine in the absence of catalyst (nearly neutral conditions); and imidazolide anion undergo coupling reaction with  $PhN_2^+$  (basic conditions).



Electrophilic substitution with pyrazole takes place at C-4:



Alkylation of imidazole:



Alkylation is often

# Acylation of Imidazole

As imidazole is both a good nucleophile and good leaving group, *N*-acylimidazole is a good "acyl transfer" reagent. The usual amide stabilization through nitrogen lone pair is much less effective with N-acylimidazole because the lone pair is part of the aromatic sextet.



Being an "acyl transfer" reagent, imidazole can catalyze the hydrolysis of esters and other acyl derivatives.



## Catalysis Effect of DMAP

The rate of this rxn is 10<sup>4</sup> times faster when 4-dimethylaminopyridine (DMAP) is present.



## Nucleophilic Substitution of Azole Compounds

X = 0. S



Similar with pyridine, nucleophilic substitution takes place most readily at C-2 with imidazole, but the displacement is not easy, unless in the presence of additional activating group(s).

Oxazole and thiazole undergo nucleophilic addition more easily.



(PhCHO, CO<sub>2</sub>, Me<sub>2</sub>NCHO, etc.)