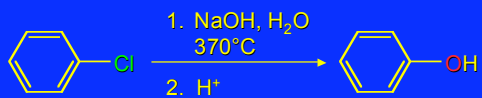


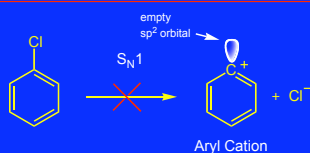
Nucleophilic Aromatic Substitution  
Aryl Halides & Benzynes

Chlorobenzene is very unreactive with nucleophiles



Not practical.  
Not sufficiently reactive.

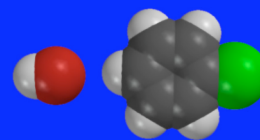
Reasons for Low Reactivity



$\text{S}_{\text{N}}1$  not reasonable because:

- 1) C—Cl bond is strong; therefore, ionization to a carbocation is a high-energy process
- 2) aryl cations are highly unstable

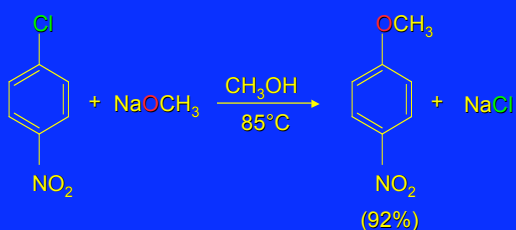
Reasons for Low Reactivity



$\text{S}_{\text{N}}2$  not reasonable because ring blocks attack of nucleophile from side opposite bond to leaving group

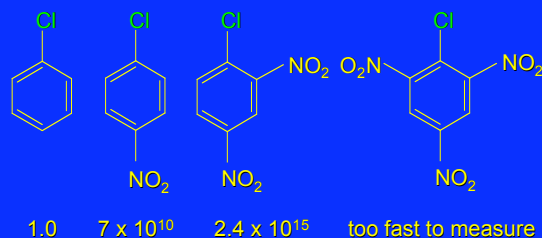
But...

nitro-substituted aryl halides do undergo nucleophilic aromatic substitution readily



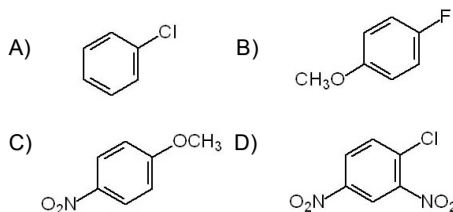
Effect of nitro group is cumulative

especially when nitro group is ortho and/or para to leaving group



### Question

Which compound will react faster with  $\text{NaOCH}_3$  in methanol ( $50^\circ\text{C}$ )?



### Kinetics


follows second-order rate law:  
 $\text{rate} = k [\text{aryl halide}][\text{nucleophile}]$

**inference:**  
both the aryl halide and the nucleophile are involved in rate-determining step

### Effect of leaving group

unusual order:  $\text{F} > \text{Cl} > \text{Br} > \text{I}$

X	Relative Rate*
F	312
Cl	1.0
Br	0.8
I	0.4



\* $\text{NaOCH}_3$ ,  $\text{CH}_3\text{OH}$ ,  $50^\circ\text{C}$

### General Conclusions About Mechanism

- bimolecular rate-determining step in which nucleophile attacks aryl halide
- rate-determining step precedes carbon-halogen bond cleavage
- rate-determining transition state is stabilized by electron-withdrawing groups (such as  $\text{NO}_2$ )

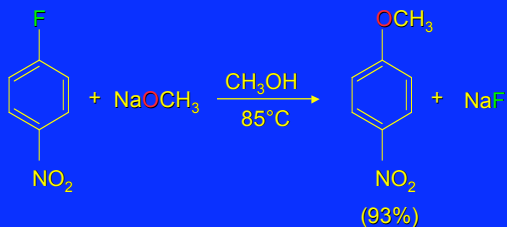
### The Addition-Elimination Mechanism of Nucleophilic Aromatic Substitution

### Addition-Elimination Mechanism

Two step mechanism:

- Step 1) nucleophile attacks aryl halide and bonds to the carbon that bears the halogen  
(slow: aromaticity of ring lost in this step)
- Step 2) intermediate formed in first step loses halide  
(fast: aromaticity of ring restored in this step)

### Reaction



### Question

How many signals would be observed in the  $^1\text{H-NMR}$  of the product isolated from the reaction of *p*-fluoronitrobenzene with potassium methoxide in methanol?

- A) 2
- B) 3
- C) 4
- D) 5

### Question

Identify the rate law for the addition-elimination mechanism of nucleophilic aromatic substitution.

- A) Rate = [aryl halide]
- B) Rate = [aryl halide][nucleophile]
- C) Rate = [aryl halide][nucleophile]<sup>2</sup>
- D) Rate = [nucleophile]

### Mechanism

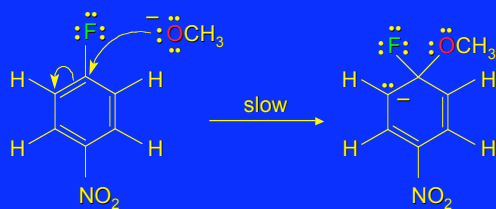
#### Step 1



bimolecular  
consistent with second-order kinetics; first order in aryl halide, first order in nucleophile

### Mechanism

#### Step 1

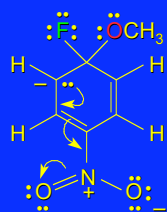


### Mechanism

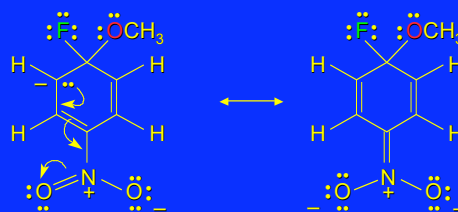
intermediate is negatively charged  
formed faster when ring bears electron-withdrawing groups such as  $\text{NO}_2$



Stabilization of Rate-Determining Intermediate by Nitro Group



Stabilization of Rate-Determining Intermediate by Nitro Group



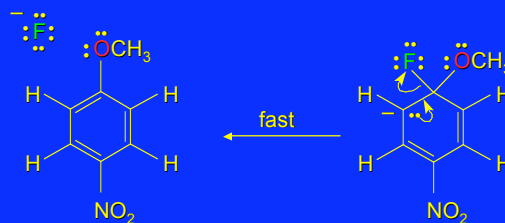
Mechanism

Step 2



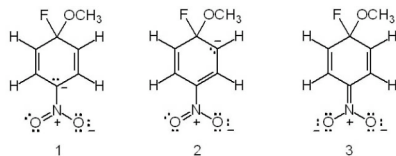
Mechanism

Step 2



Question

Which of the structures below is the most stable resonance structure for the reaction of *p*-fluoronitrobenzene with sodium methoxide?



- A) 1 only  
 B) 2 only  
 C) 3 only  
 D) 1 and 2

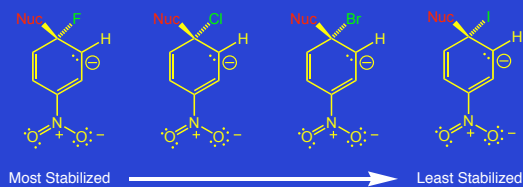
Leaving Group Effects

$F > Cl > Br > I$  is unusual, but consistent with mechanism

carbon-halogen bond breaking does not occur until after the rate-determining step

electronegative F stabilizes negatively charged intermediate

### The Role of Leaving Groups



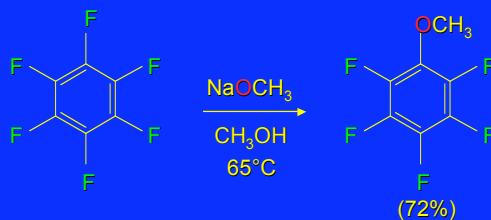
### Question

Which of the following compounds is the least reactive toward nucleophilic aromatic substitution?

- A) 1-chloro-4-nitrobenzene
- B) 1-iodo-2-nitrobenzene
- C) 1-fluoro-4-nitrobenzene
- D) 1-bromo-3-nitrobenzene

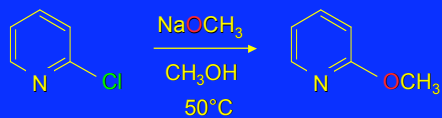
### Related Nucleophilic Aromatic Substitution Reactions

#### Example: Hexafluorobenzene



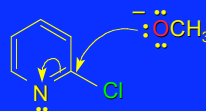
Six fluorine substituents stabilize negatively charged intermediate formed in rate-determining step and increase rate of nucleophilic aromatic substitution.

#### Example: 2-Chloropyridine



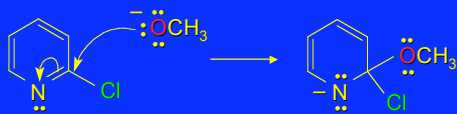
2-Chloropyridine reacts 230,000,000 times faster than chlorobenzene under these conditions.

#### Example: 2-Chloropyridine



Nitrogen is more electronegative than carbon, stabilizes the anionic intermediate, and increases the rate at which it is formed.

Example: 2-Chloropyridine



Nitrogen is more electronegative than carbon, stabilizes the anionic intermediate, and increases the rate at which it is formed.

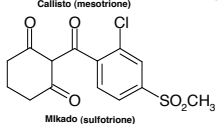
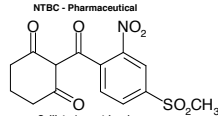
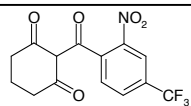
Nucleophilic Aromatic Substitution Reactions in Synthesis

Triketones

Herbicides that inhibit HPPD

Hydroxyphenyl pyruvate dioxygenase

NTBC - orphan drug for tyrosine anemia

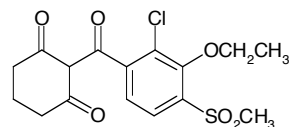


Triketones Continued

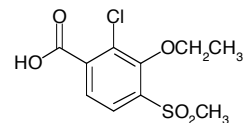
Inhibition of HPPD

Hydroxyphenyl pyruvate dioxygenase

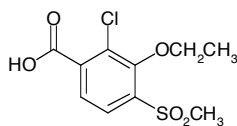
Third Generation



Synthetic Intermediate

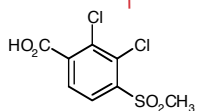


Triketones: Synthetic Intermediate



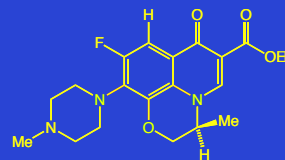
Starting from 2,3-dichlorothiophenol which is commercially available

- 1) S- methylation
- 2) EAS acylation
- 3) oxidation



Ofloxacin

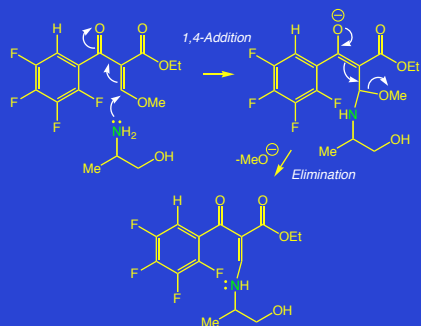
Ofloxacin (trade name Floxin) is a broad-spectrum quinolone antibiotic



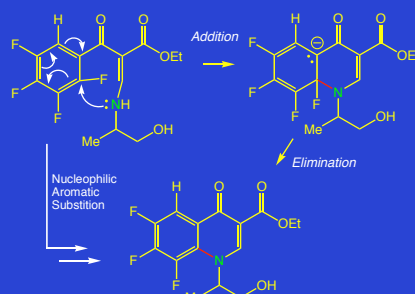
Ofloxacin

<http://www.ofloxacin.com/>

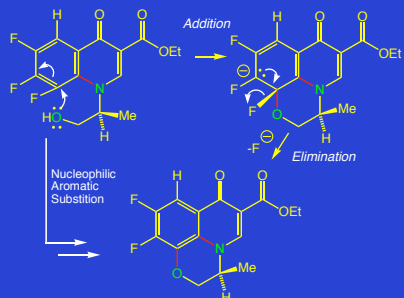
### Synthesis of Ofloxacin, Part 1



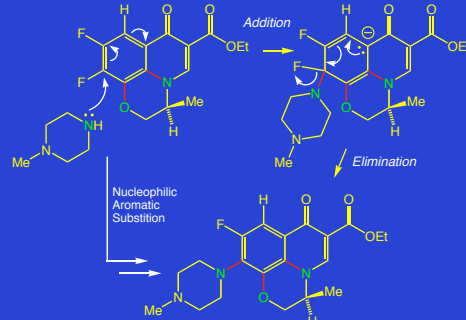
### Synthesis of Ofloxacin, Part 2



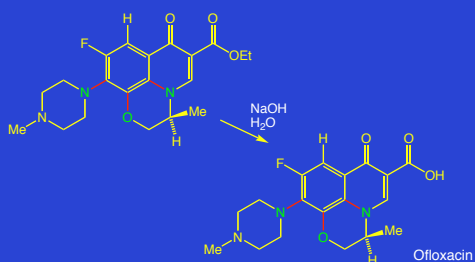
### Synthesis of Ofloxacin, Part 3



### Synthesis of Ofloxacin, Part 4

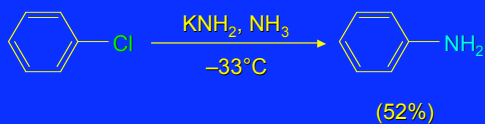


### Synthesis of Ofloxacin, Part 5



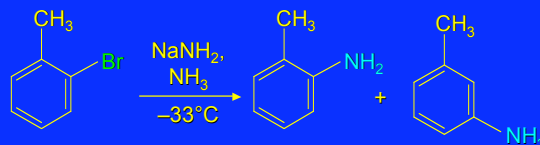
The Elimination-Addition Mechanism  
of Nucleophilic Aromatic Substitution:  
Benzyne

*Aryl Halides Undergo Substitution When Treated With Very Strong Bases*



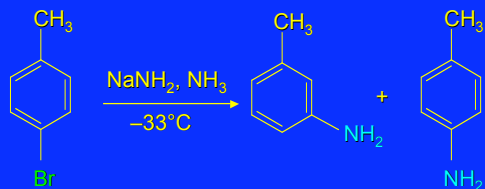
*Regiochemistry*

new substituent becomes attached to either the carbon that bore the leaving group or the carbon adjacent to it

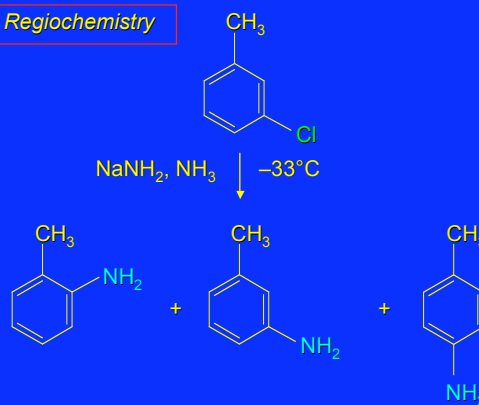


*Regiochemistry*

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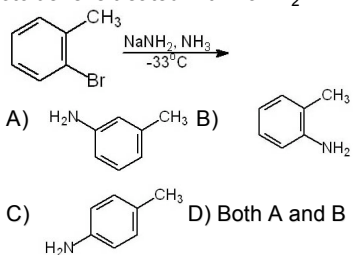


*Regiochemistry*

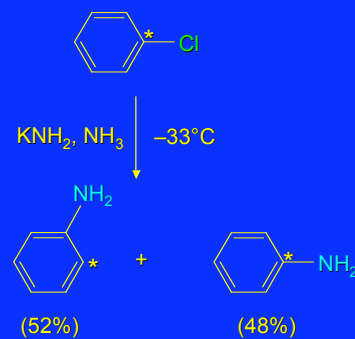


**Question**

What product will be isolated when *o*-bromotoluene is treated with  $\text{NaNH}_2$  in  $\text{NH}_3$ ?



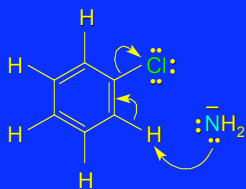
*Same result using  $^{14}\text{C}$  label*





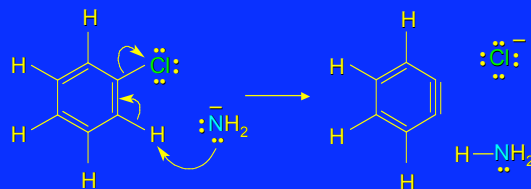
### Mechanism

#### Step 1



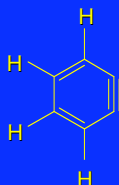
### Mechanism

#### Step 1



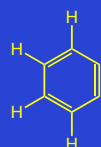
compound formed in this step is called *benzyne*

### Benzyne

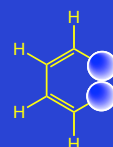


Benzyne has a strained triple bond.  
It cannot be isolated in this reaction, but is formed as a reactive intermediate.

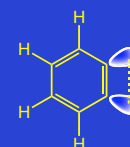
### Benzyne - A Reactive Molecule With an Abnormal $\pi$ -Bond



Benzyne



$2p_z$ - $2p_z$   
 $\pi$  Bond

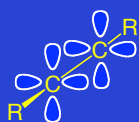


$sp^2$ - $sp^2$   
 $\pi$  Bond

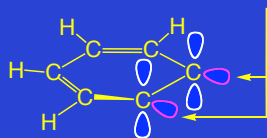
Benzyne has a reactive triple bond.  
It cannot be isolated in this reaction, but is formed as a reactive intermediate.

### Benzyne - A Reactive Aromatic Molecule With An Abnormal, In-Plane $\pi$ -Bond

overlapping  $sp^2$  orbitals  
poor overlap results  
in a weak, reactive bond



'Normal' C-C Triple Bond



Benzyne C-C Triple Bond

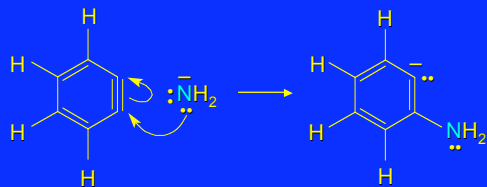
### Mechanism

#### Step 2



### Mechanism

Step 2



Angle strain is relieved. The two  $sp$ -hybridized ring carbons in benzyne become  $sp^2$  hybridized in the resulting anion.

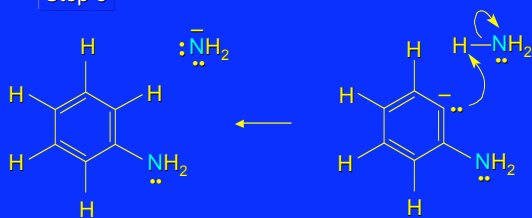
### Mechanism

Step 3



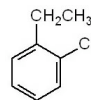
### Mechanism

Step 3

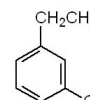


### Question

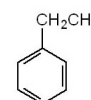
Which of the following compounds give a single benzyne intermediate on reaction with sodium amide?



1



2



3

A) 1 only  
C) 3 only

B) 1 and 3  
D) 1 and 2

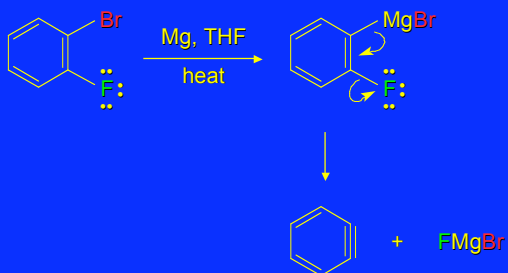
Diels-Alder Reactions of Benzyne

### Other Routes to Benzyne

Benzyne can be prepared as a reactive intermediate by methods other than treatment of chlorobenzene with strong bases.

Another method involves loss of fluoride ion from the Grignard reagent of 1-bromo-2-fluorobenzene.

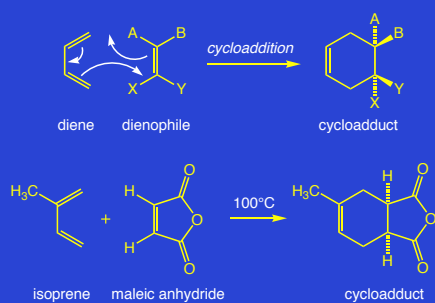
### Other Routes to Benzyne



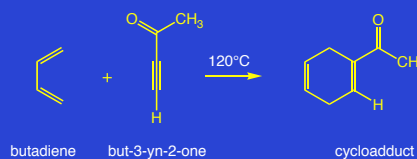
### Benzyne as a Dienophile

Benzyne is a fairly reactive dienophile, and gives Diels-Alder adducts when generated in the presence of conjugated dienes.

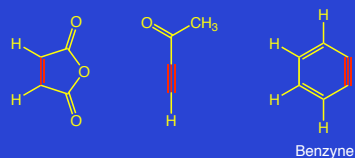
### The Diels-Alder Reaction Revisited



### Electron-Deficient Alkynes Behave as Dienophiles



### Benzyne Behaves as a Dienophile



Benzyne is a fairly reactive dienophile, and gives Diels-Alder adducts when generated in the presence of conjugated dienes.

### Benzyne as a Dienophile

