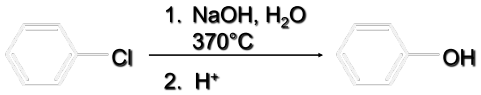
Nucleophilic Aromatic Substitution

Aryl Halides & Benzyne

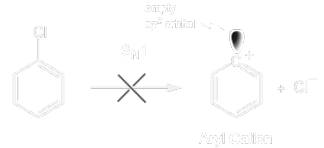
Chlorobenzene is very unreactive with nucleophiles



Not practical.

Not sufficiently reactive.

Reasons for Low Reactivity

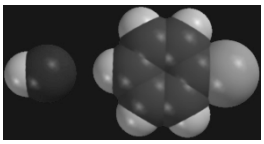


SN1 not reasonable because:

1) C—Cl bond is strong; therefore, ionization to a carbocation is a high-energy process

2) aryl cations are highly unstable

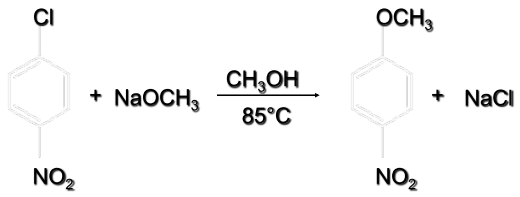
Reasons for Low Reactivity



S_N2 not reasonable because ring blocks attack of nucleophile from side opposite bond to leaving group

But...

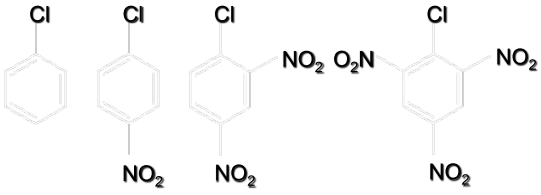
nitro-substituted aryl halides do undergo nucleophilic aromatic substitution readily



(92%)

Effect of nitro group is cumulative

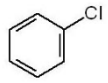
especially when nitro group is ortho and/or para to leaving group

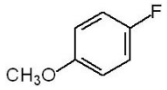


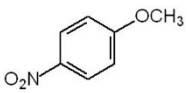
1.0 7×10^{10} 2.4×10^{15} too fast to measure

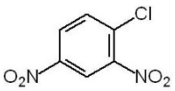
Question

Which compound will react faster with $NaOCH_3$ in methanol (50°C)?

A) 

B) 

C) 

D) 

Kinetics

follows second-order rate law:

rate = *k* [aryl halide][nucleophile]

inference:

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

Effect of leaving group

unusual order: F > Cl > Br > I

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

*$NaOCH_3$, CH_3OH, 50°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 NO_2)

The Addition-Elimination Mechanism of Nucleophilic Aromatic Substitution

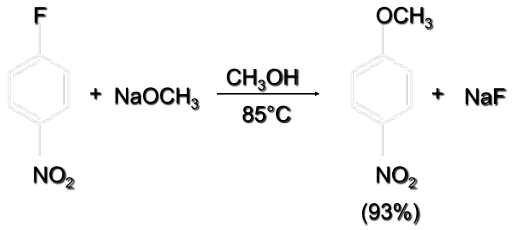
Addition-Elimination Mechanism

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}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

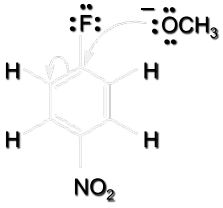
Question

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]^2
D) Rate = [nucleophile]

Mechanism

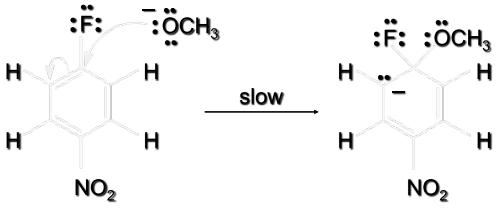
Step 1



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

Mechanism

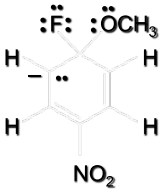
Step 1



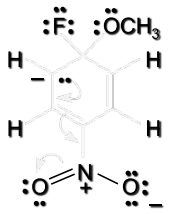
Mechanism

intermediate is negatively charged

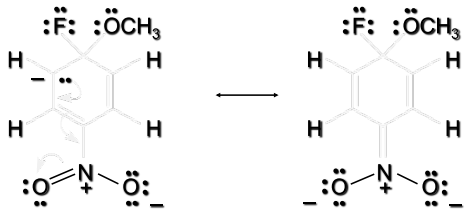
formed faster when ring bears electron -withdrawing groups such as NO_2



Stabilization of Rate-Determining Intermediate by Nitro Group

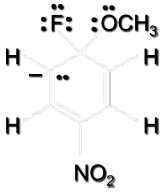


Stabilization of Rate-Determining Intermediate by Nitro Group



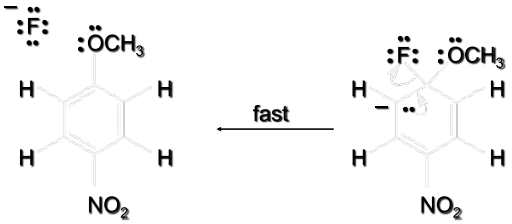
Mechanism

Step 2



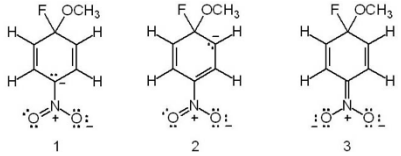
Mechanism

Step 2



Question

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



1 2 3

A) 1 only B) 2 only

C) 3 only D) 1 and 2

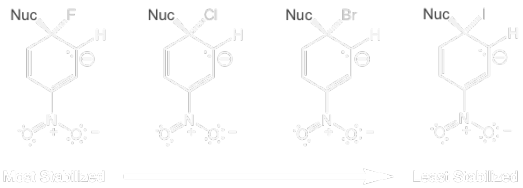
Leaving Group Effects

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

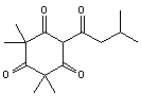
Which of the following compounds is the least reactive toward nucleophilic aromatic substitution?

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

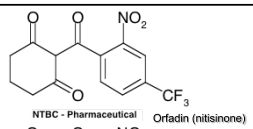
Nucleophilic Aromatic Substitution Reactions in Synthesis

http://chemconnections.org/organic/chem298/bottlebrush.html

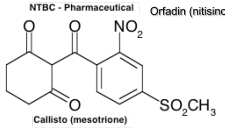
Plant Natural Products: Triketones



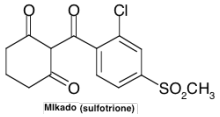
leptospermone



NTBC - Pharmaceutical Orfadin (nitisinone)



Callisto (mesotrione)



Mikado (sulfotrione)

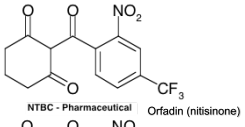
Triketones

Orfadin- orphan drug for tyrosine anemia

Herbicides that inhibit HPPD

Hydroxyphenyl pyruvate dioxygenase
Not to be confused with:

Hallucinogen Persisting Perceptual Disorder



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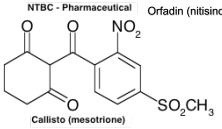
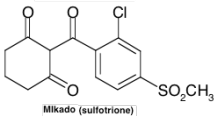
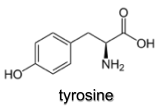


Callisto (mesotrione)

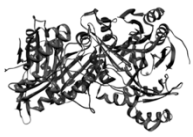


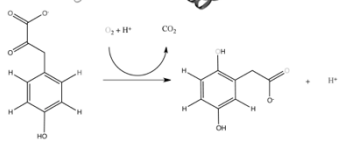
Mikado (sulfotrione)

HPPD



tyrosine



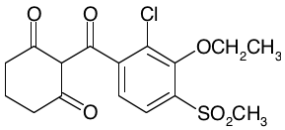


http://en.wikipedia.org/wiki/4-Hydroxyphenylpyruvate_dioxygenase

Triketones Continued

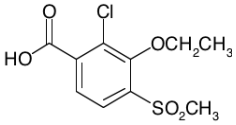
Inhibition of HPPD

Hydroxyphenyl pyruvate dioxygenase

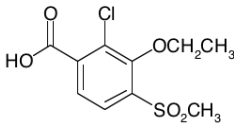


http://en.wikipedia.org/wiki/P-hydroxyphenylpyruvate_dioxygenase_inhibitor

Synthetic Intermediate

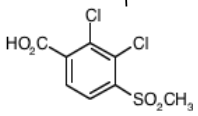


Triketones: Synthetic Intermediate



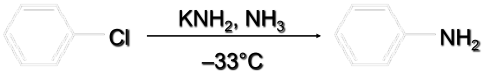
Starting from 2,3-dichlorothiophenol which is commercially available

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



The Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution: Benzyne

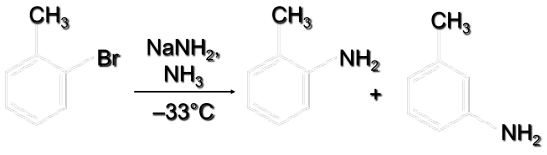
Aryl Halides Undergo Substitution When Treated With Very Strong Bases



(52%)

Regiochemistry

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



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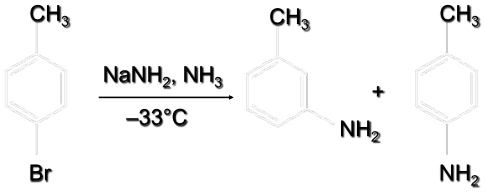
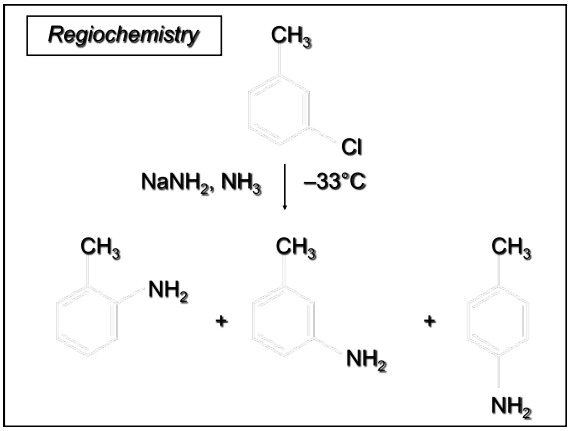
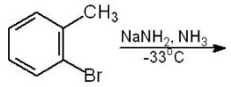


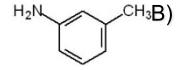
Regiochemistry

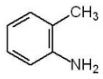


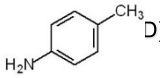
Question

What product will be isolated when *o* -bromotoluene is treated with $NaNH_2$ in NH_3?



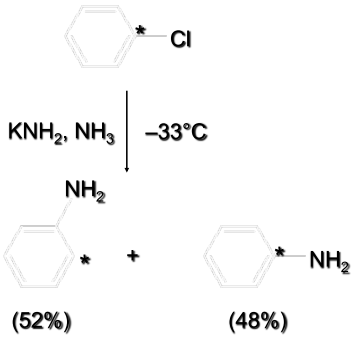
A) 

B) 

C) 

D) Both A and B

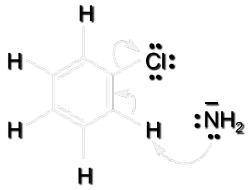
Same result using ^{14}C label



(52%) (48%)

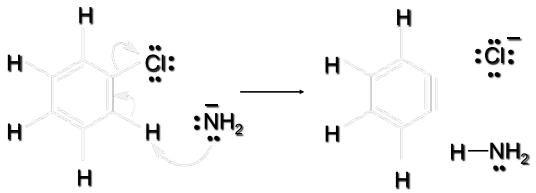
Mechanism

Step 1



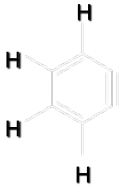
Mechanism

Step 1



compound formed in this step is called *benzyne*

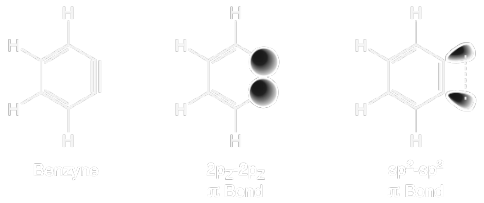
Benzyne



Benzyne has a strained triple bond.

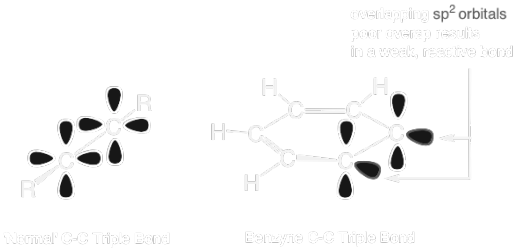
It cannot be isolated in this reaction, but is formed as a reactive intermediate.

Benzyne - A Reactive Molecule With an Abnormal π-Bond



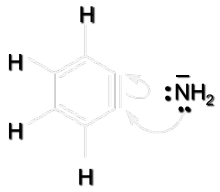
Benzyne has a reactive triple bond.
It cannot be isolated in this reaction, but is formed as a reactive intermediate.

Benzyne - A Reactive Aromatic Molecule With An Abnormal, In-Plane π-Bond



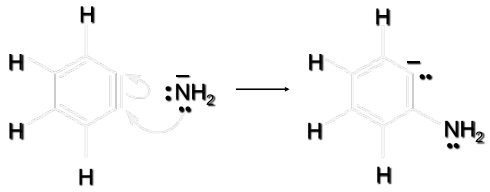
Mechanism

Step 2



Mechanism

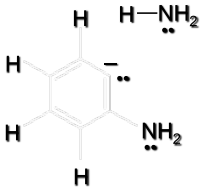
Step 2



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

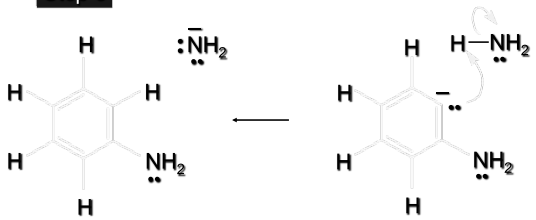
Mechanism

Step 3



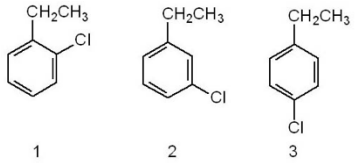
Mechanism

Step 3



Question

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



1 2 3

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

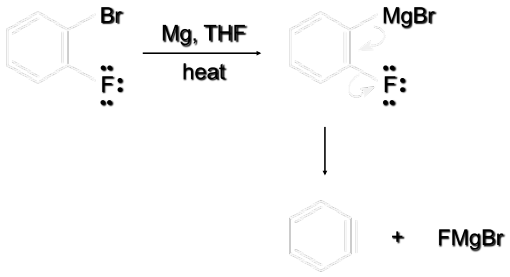
Diels-Alder Reactions of Benzyne

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.

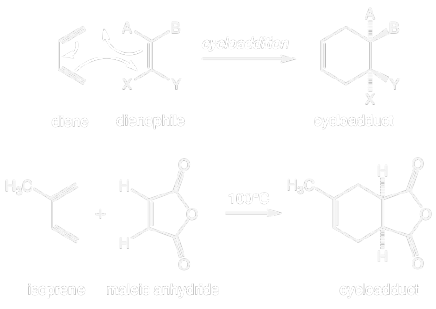
Other Routes to Benzyne



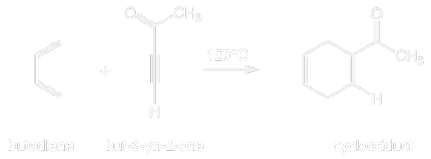
Benzyne as a Dienophile

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

The Diels-Alder Reaction



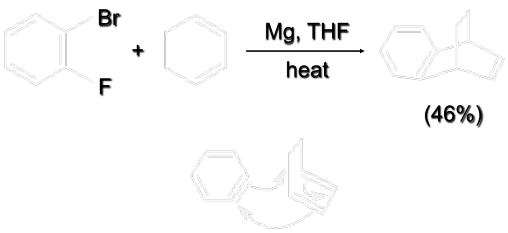
Electron-Deficient Alkynes Behave as Dienophiles



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



(46%)

Diels Alder Reaction

Benzyne as a Dieneophile