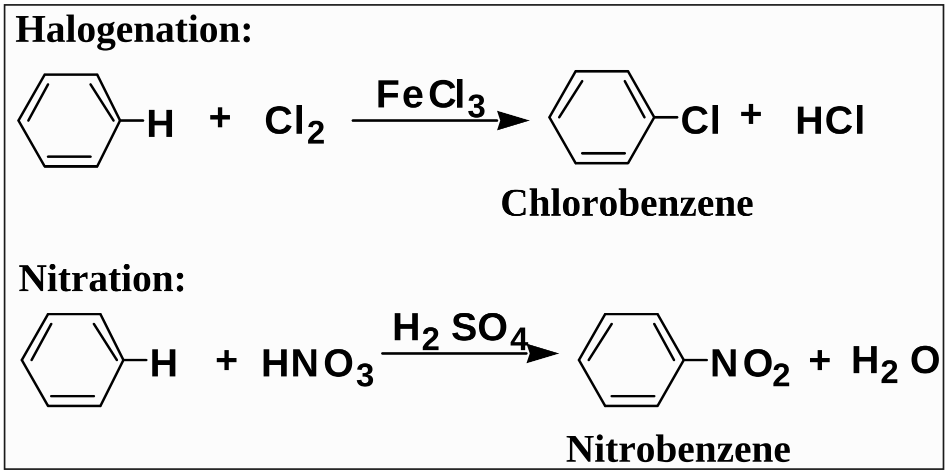
Reactions of Benzene & Its Derivatives

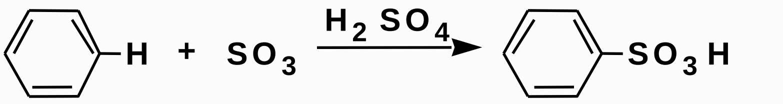
Reactions of Benzene

The most characteristic reaction of aromatic compounds is substitution at a ring carbon:



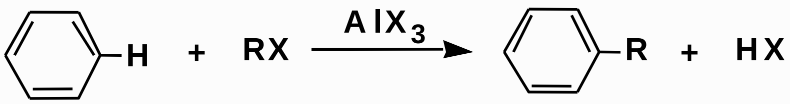
Reactions of Benzene

Sulfonation:



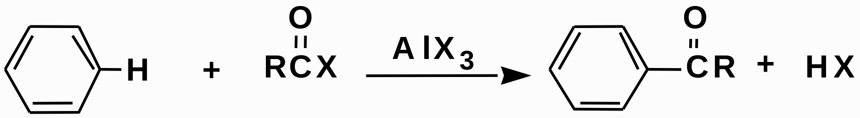
Benzenesulfonic acid

Alkylation:

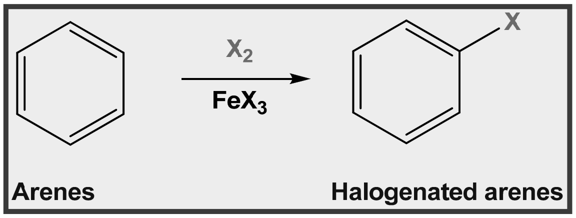


An alkylbenzene

Acylation:

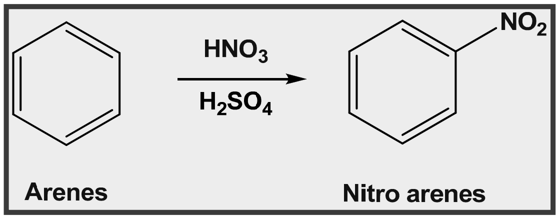


An acylbenzene



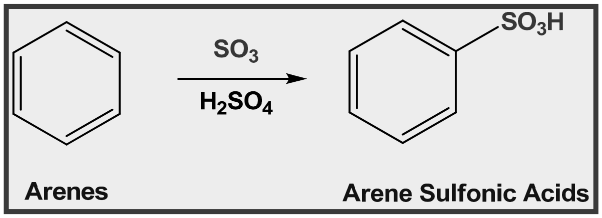
Arenes

Halogenated arenes



Arenes

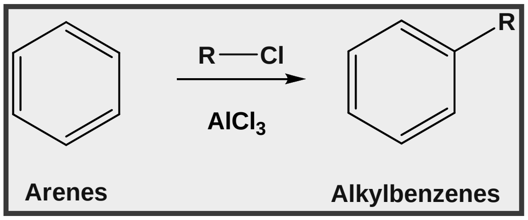
Nitro arenes



Arenes

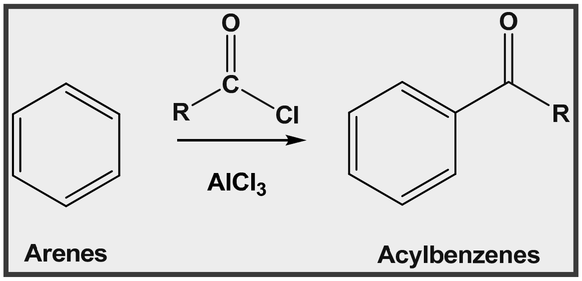
Arene Sulfonic Acids

Carbon-Carbon Bond Formations:



Arenes

Alkylbenzenes

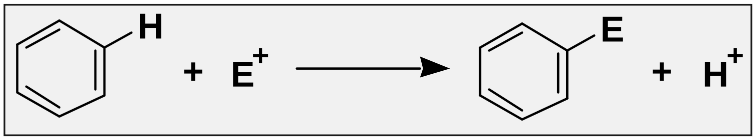


Arenes

Acylbenzenes

Electrophilic Aromatic Substitution

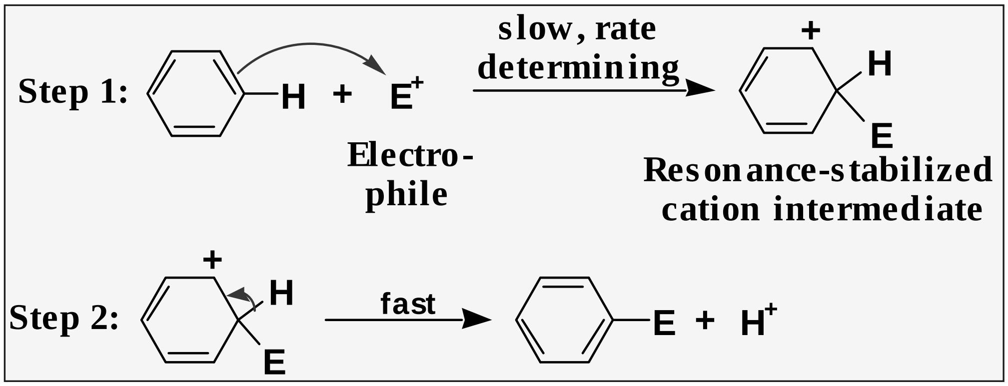
- Electrophilic aromatic substitution: a reaction in which a hydrogen atom of an aromatic ring is replaced by an electrophile



- In this section:
  - several common types of electrophiles
  - how each is generated
  - the mechanism by which each replaces hydrogen

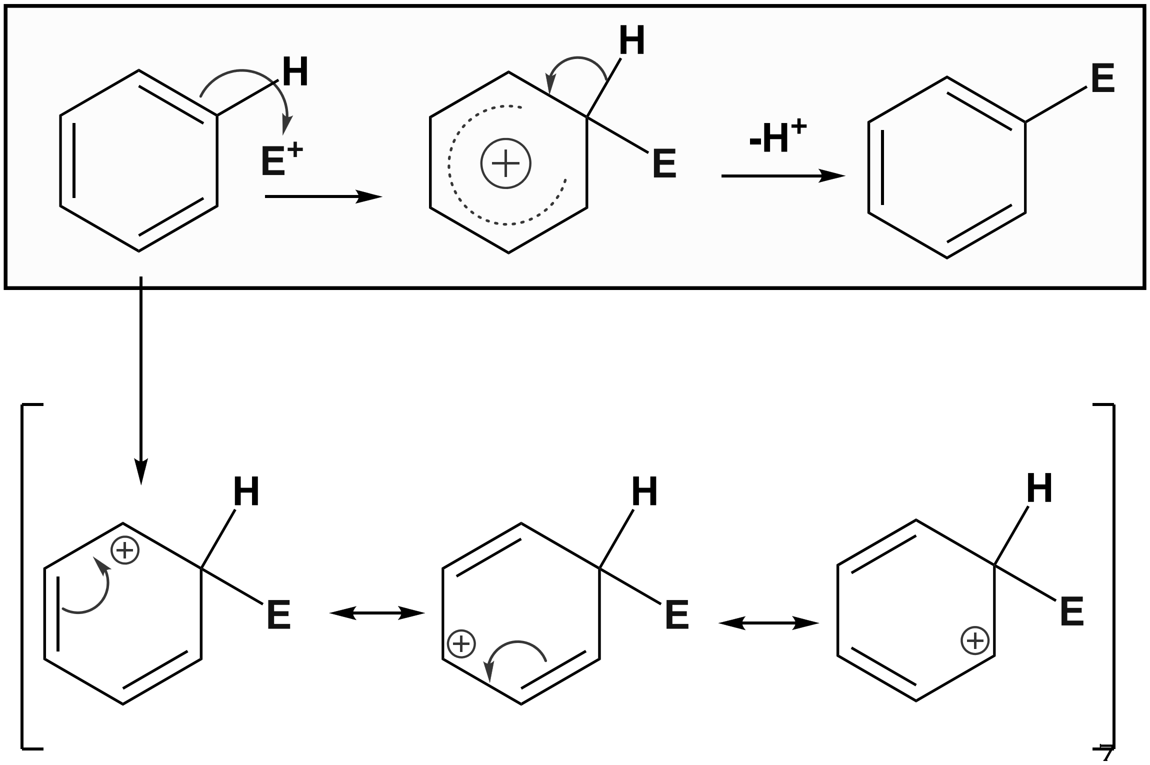
EAS: General Mechanism

- A general mechanism



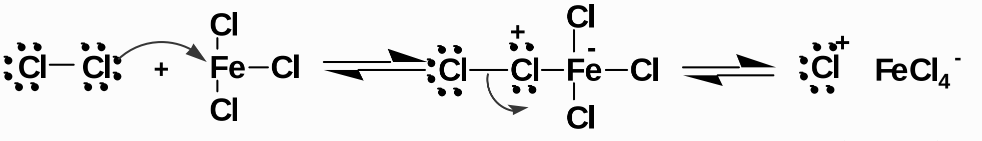
- Key question: What is the electrophile and how is it generated?

Electrophilic Aromatic Substitution (EAS)



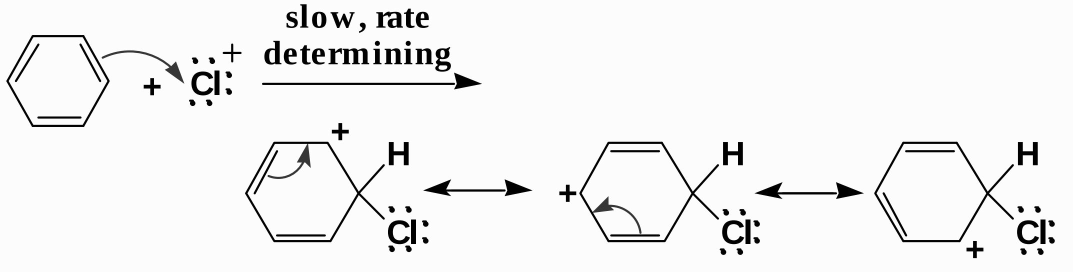
Chlorination

Step 1: formation of a chloronium ion



Chlorine (a Lewis base)	Ferric chloride (a Lewis acid)	A molecular complex with a positive charge on chlorine	An ion pair containing a chloronium ion

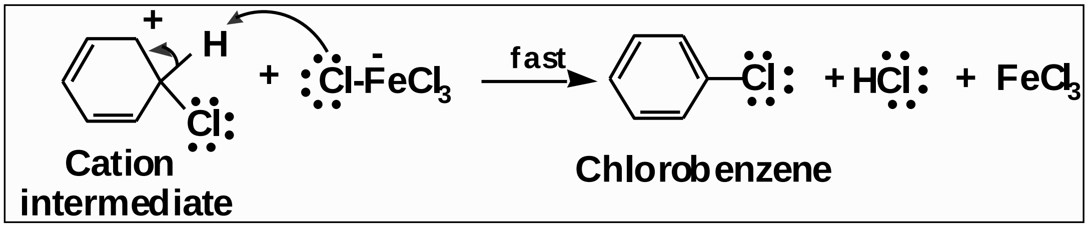
Step 2: attack of the chloronium ion on the ring



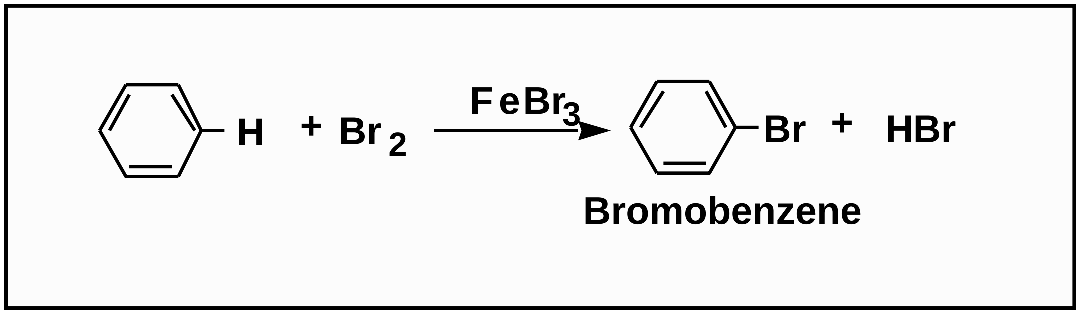
Resonance-stabilized cation intermediate; the positive charge is delocalized onto three atoms of the ring

Chlorination

Step 3: proton transfer regenerates the aromatic character of the ring



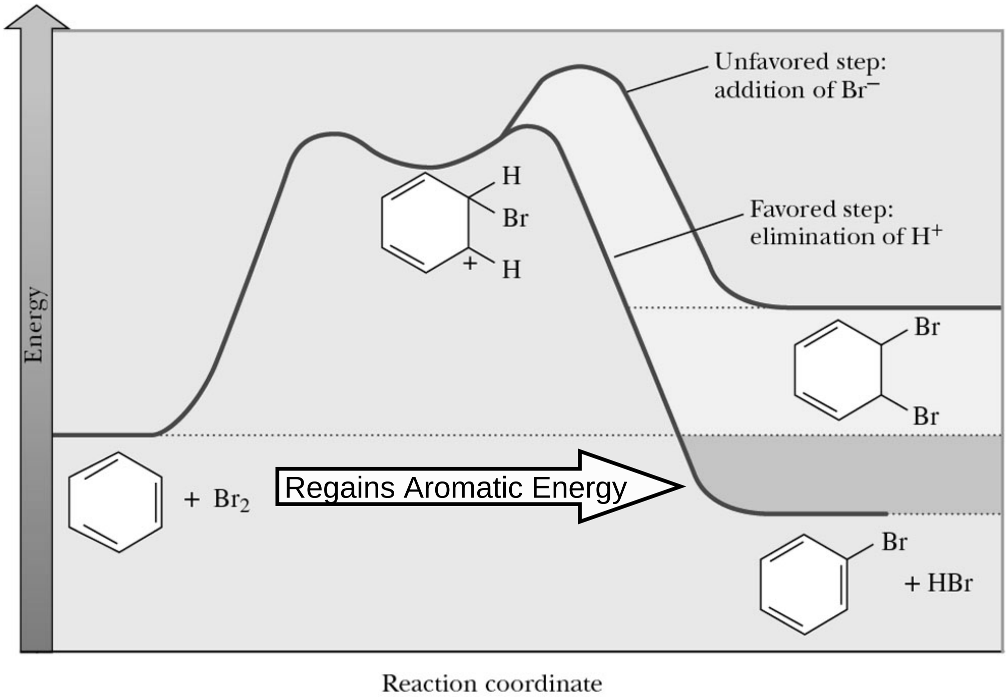
Bromination



This is the general method for Substitution of halogen onto a benzene ring

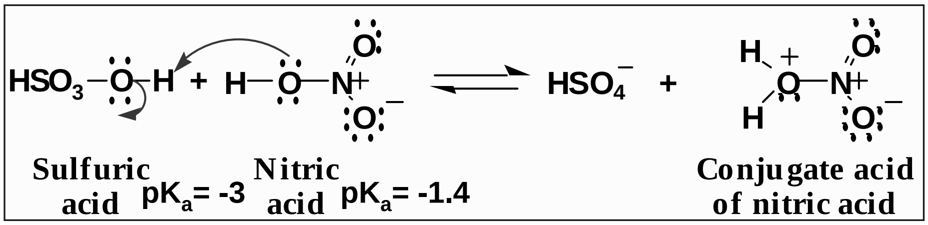
(CANNOT be halogenated by Free Radical Mechanism)

Bromination-Why not addn of Br_2?

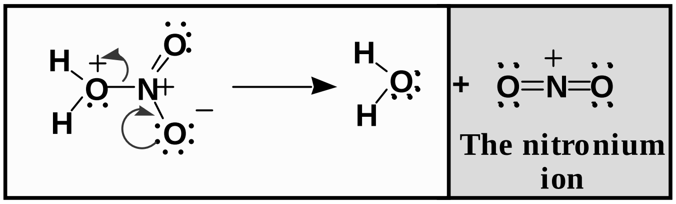


Nitration

- Generation of the nitronium ion, NO_2^+
  - Step 1: proton transfer to nitric acid

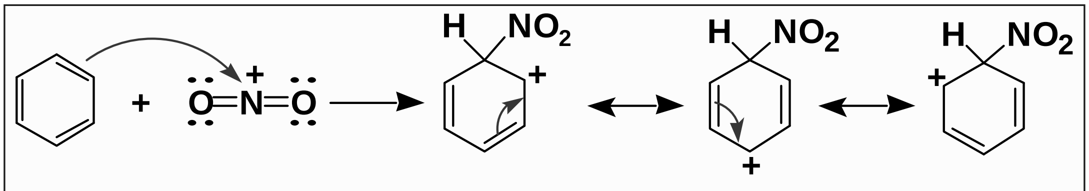


  - Step 2: loss of H_2O gives the nitronium ion, a very strong electrophile



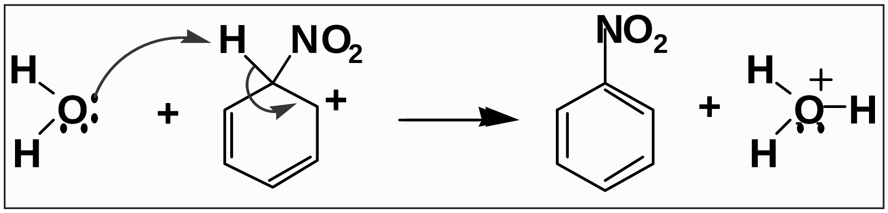
Nitration

Step 1: attack of the nitronium ion (an electrophile) on the aromatic ring (a nucleophile)



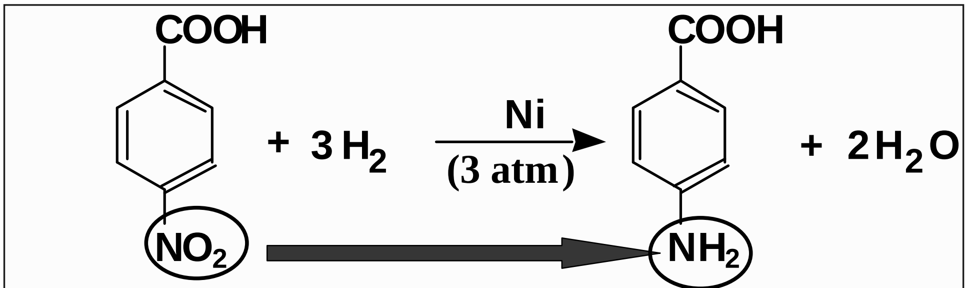
Resonance-stabilized cation intermediate

Step 2: proton transfer regenerates the aromatic ring



Nitration

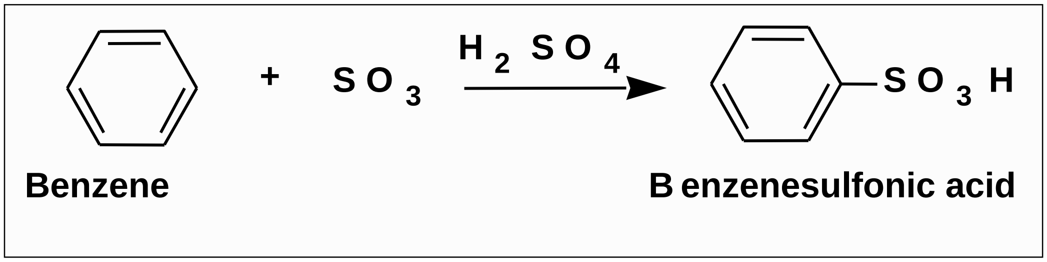
- A particular value of nitration is that the nitro group can be reduced to a 1° amino group



4-Nitrobenzoic acid **4-Aminobenzoic acid**

Sulfonation

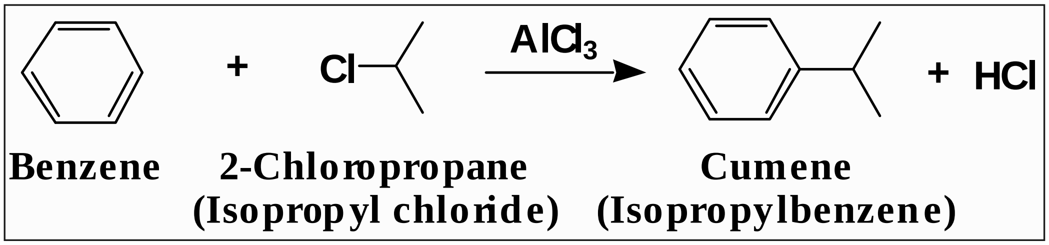
- Carried out using concentrated sulfuric acid containing dissolved sulfur trioxide



(SO$_3$ in H$_2$SO$_4$ is sometimes called "fuming" sulfuric acid.)

Friedel-Crafts Alkylation

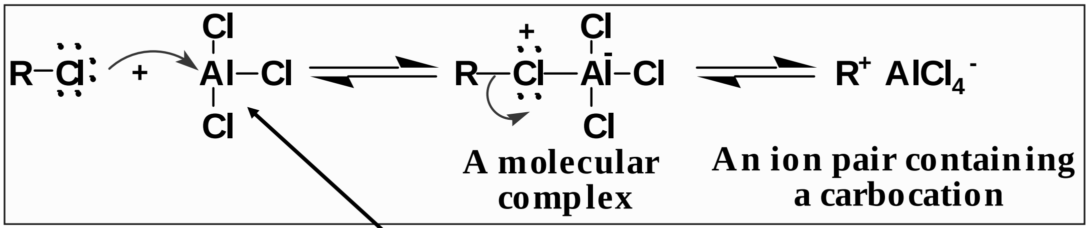
- Friedel-Crafts alkylation forms a new C-C bond between an aromatic ring and an alkyl group



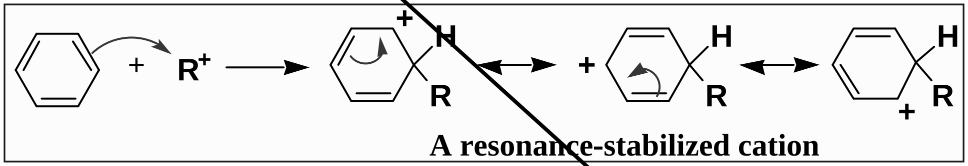
The electrophilic partner is a carbocation;
it will arrange to the most stable ion: allylic>3^o>2^o>1^o

Friedel-Crafts Alkylation

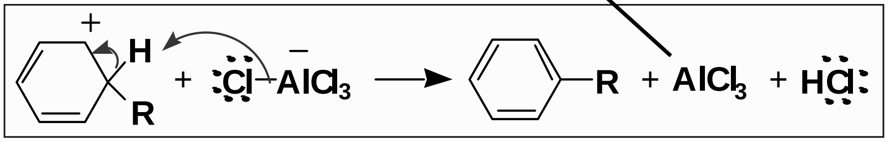
Step 1: formation of an alkyl cation as an ion pair



Step 2: attack of the alkyl cation on the aromatic ring



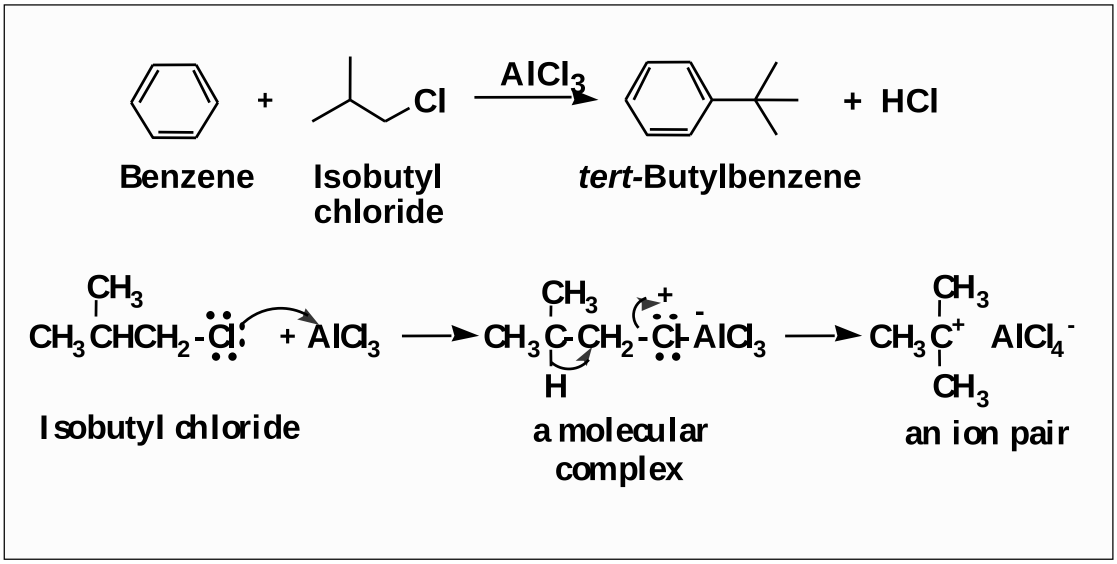
Step 3: proton transfer regenerates the aromatic ring



Friedel-Crafts Alkylation

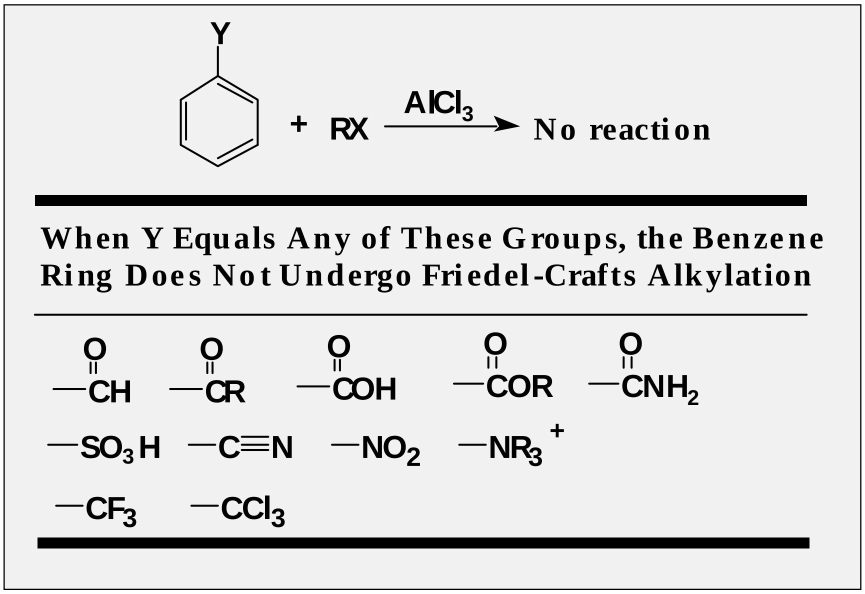
There are two major limitations on Friedel-Crafts alkylations:

1. carbocation rearrangements are common:



Friedel-Crafts Alkylation

2. F-C alkylation fails on benzene rings bearing one or more of these strongly **electron-withdrawing groups**

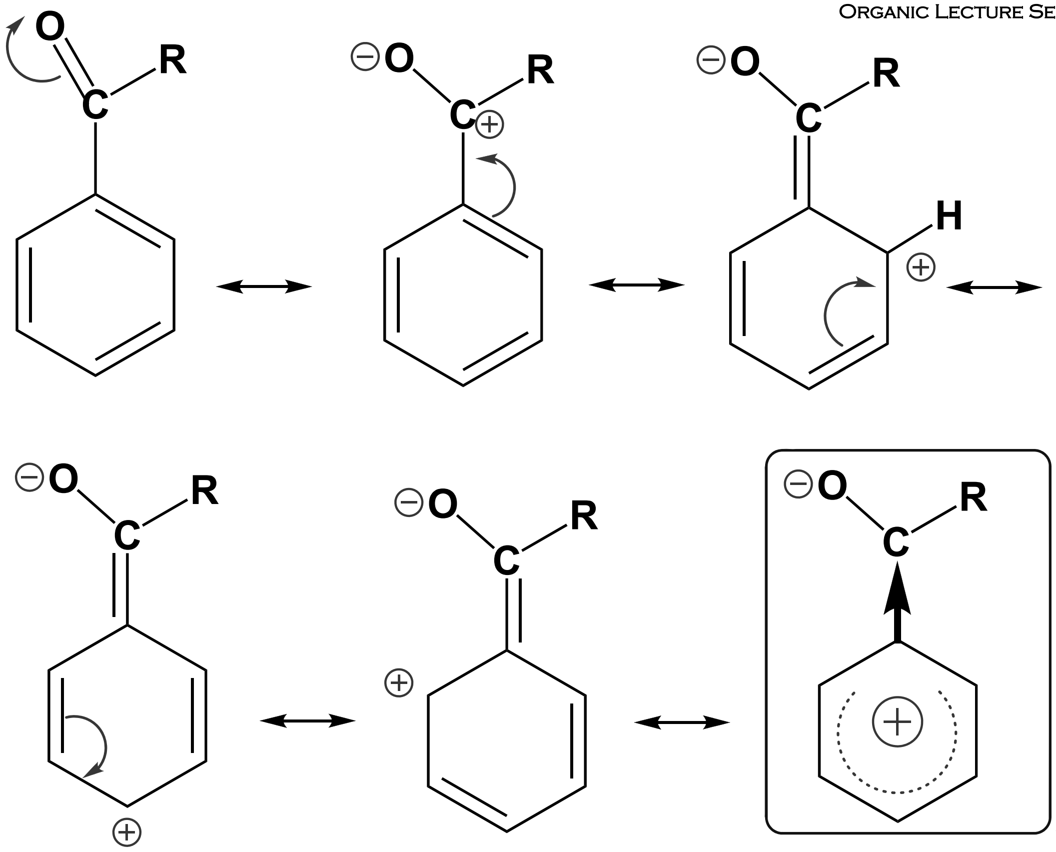


When Y Equals Any of These Groups, the Benzene Ring Does Not Undergo Friedel-Crafts Alkylation

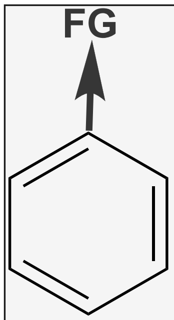
$-\overset{O}{\overset{\|}{C}}H$ $-\overset{O}{\overset{\|}{C}}R$ $-\overset{O}{\overset{\|}{C}}OH$ $-\overset{O}{\overset{\|}{C}}OR$ $-\overset{O}{\overset{\|}{C}}NH_2$

$-SO_3H$ $-C\equiv N$ $-NO_2$ $-NR_3^+$

$-CF_3$ $-CCl_3$



The “De-activation” of Aromatic Systems

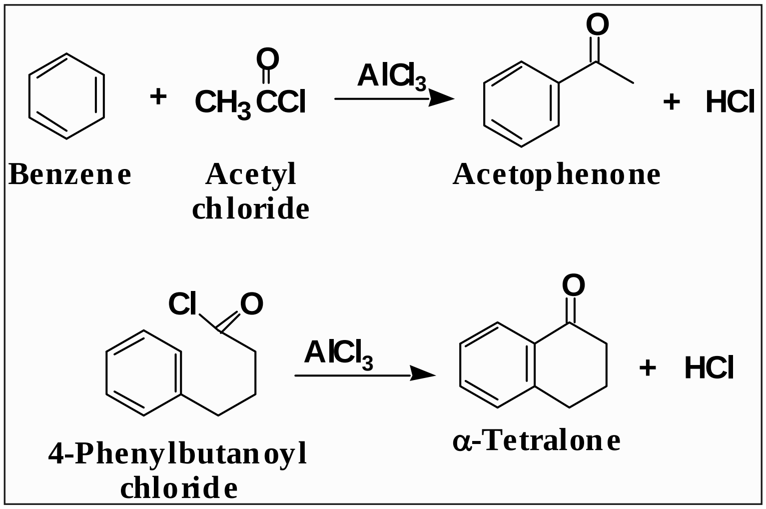


If the FG is an e^- withdrawingsubstitutent, then the ring system becomes more electron poor and is said to be "deactivated" towards electrophilic aromatic substitution. EAS occurs at a slower rate.

Note: deactivation refers to the **rate** of EAS

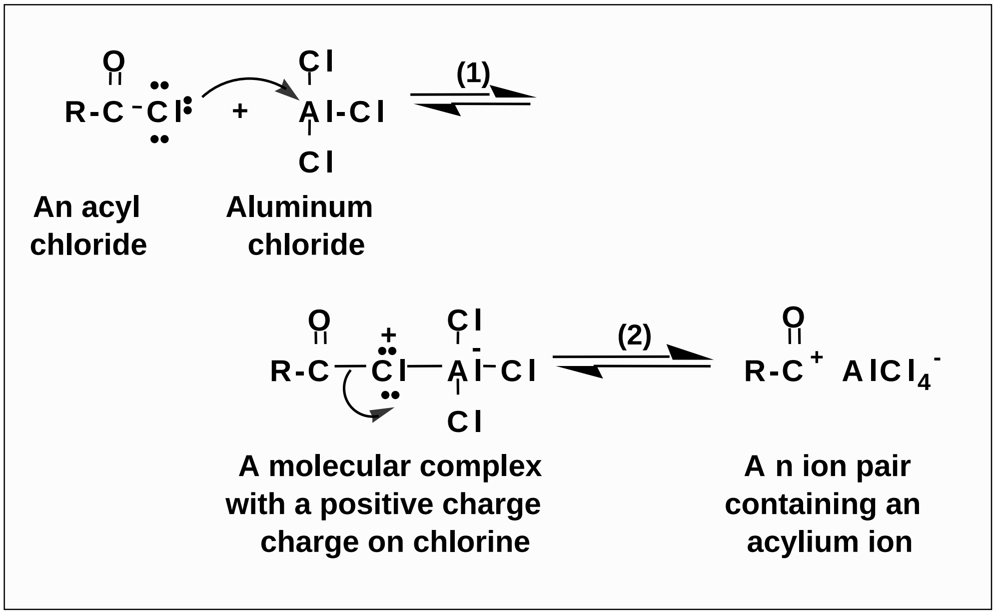
Friedel-Crafts Acylation

- Friedel-Crafts **acylation** forms a new C-C bond between a benzene ring and an acyl group:



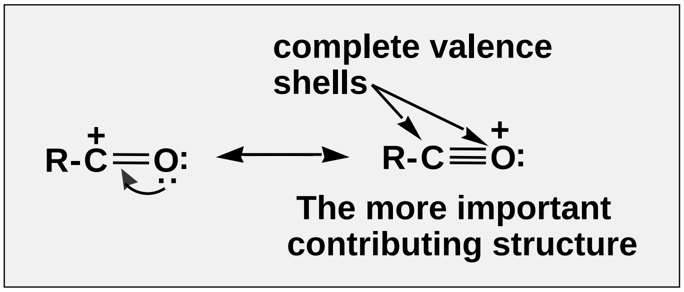
Friedel-Crafts Acylation

- The electrophile is an **acylium ion**



Friedel-Crafts Acylation

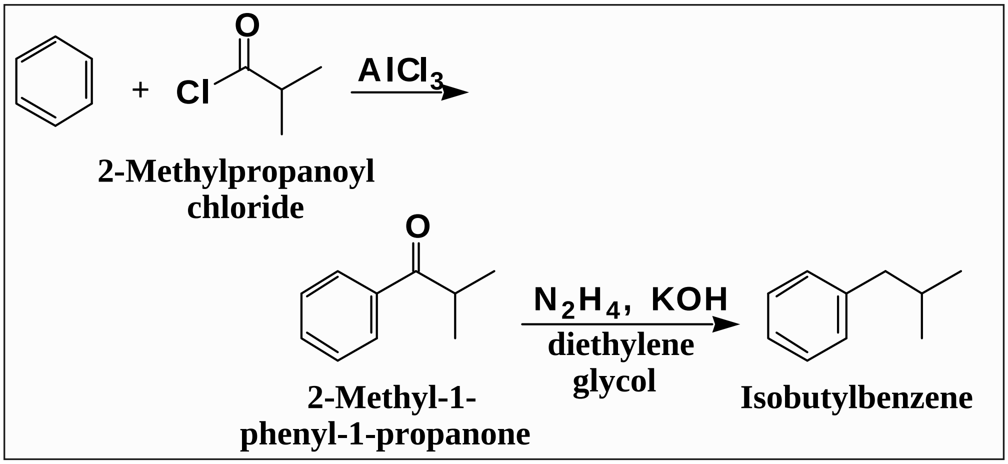
– an acylium ion is a resonance hybrid of two major contributing structures



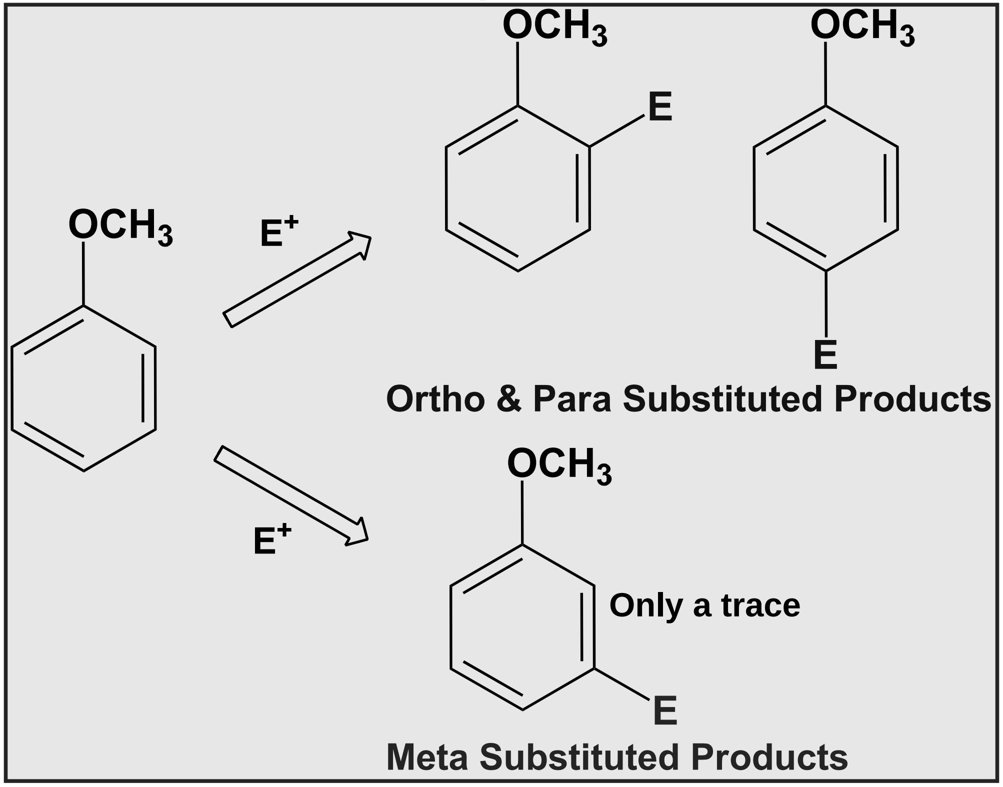
- F-C acylations are free of a major limitation of F-C alkylations; **acylium ions do not rearrange.**

Friedel-Crafts Acylation

A special value of F-C acylations is preparation of **unrearranged** alkylbenzenes:



Di- and Polysubstitution



Di- and Polysubstitution

Orientation on nitration of monosubstituted benzenes:

Substituent	ortho	meta	para	ortho + para	meta
$-OCH_3$	44	-	55	99	trace
$-CH_3$	58	4	38	96	4
$-Cl$	70	-	30	100	trace
$-Br$	37	1	62	99	1
$-COOH$	18	80	2	20	80
$-CN$	19	80	1	20	80
$-NO_2$	6.4	93.2	0.3	6.7	93.2

Di- and Polysubstitution

- **Orientation**:
  - certain substituents direct preferentially to ortho & para positions; others to meta positions
  - substituents are classified as either **ortho-para directing or meta directing** toward further substitution

Di- and Polysubstitution

- **Rate**
  - certain substituents cause the rate of a second substitution to be greater than that for benzene itself; others cause the rate to be lower
  - substituents are classified as **activating** or **deactivating** toward further substitution

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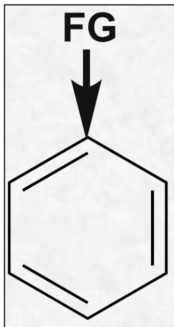
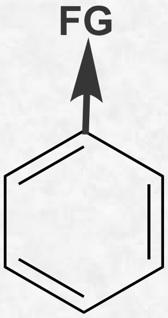


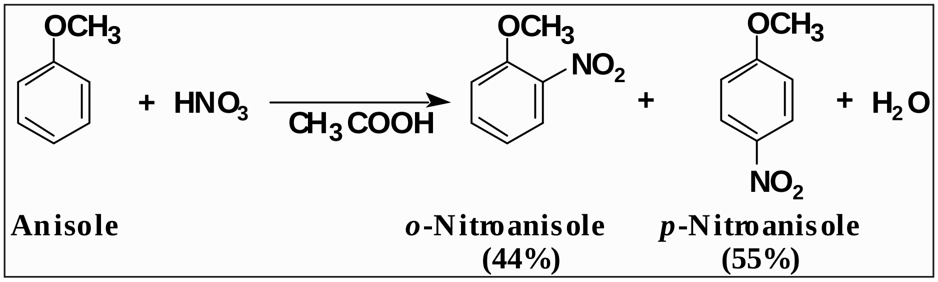
If the FG is an e$^-$ donating substitutent, then the ring system becomes more electron rich and is said to be "activated" towards electrophilic aromatic substitution. EAS is at a faster rate.



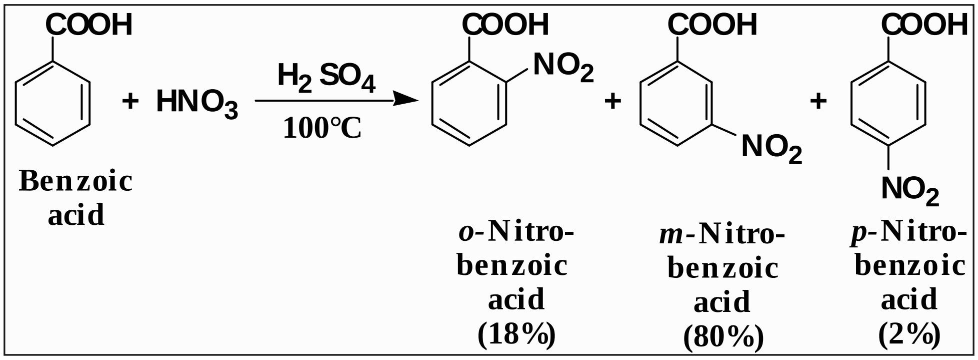
If the FG is an e$^-$ withdrawingsubstitutent, then the ring system becomes more electron poor and is said to be "deactivated" towards electrophilic aromatic substitution. EAS occurs at a slower rate.

Di- and Polysubstitution

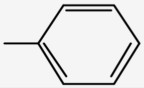
- $-OCH_3$ is ortho-para directing:



- $-CO_2H$ is meta directing

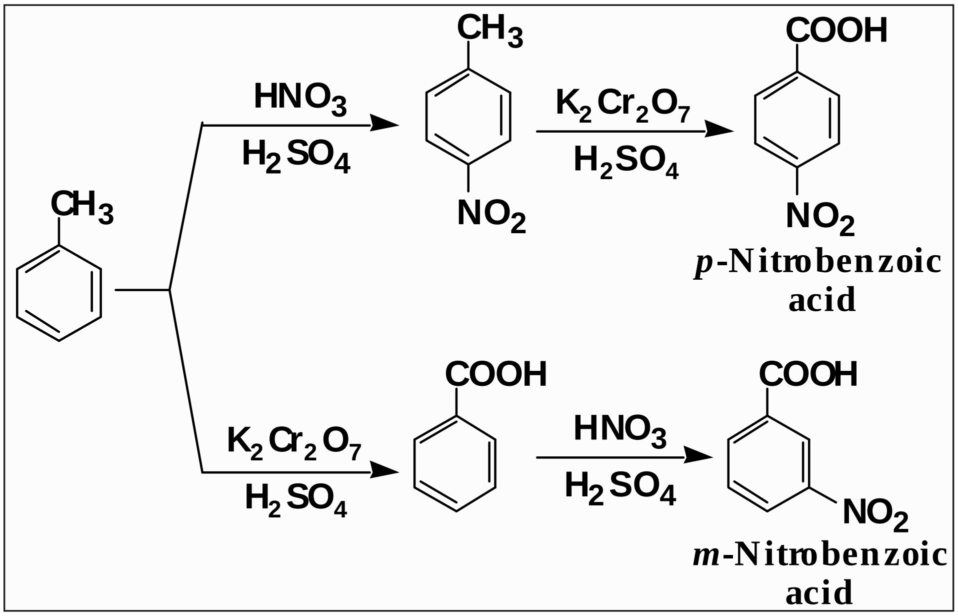


Di- and Polysubstitution

Ortho-para Directing	Strongly activating	$-\ddot{N}H_2$	$-\ddot{N}HR$	$-\ddot{N}R_2$	$-\ddot{\underset{..}{O}}H$	$-\ddot{\underset{..}{O}}R$
	Moderately activating	$-\ddot{N}H\overset{\overset{O}{\|}}{C}R$	$-\ddot{N}H\overset{\overset{O}{\|}}{C}Ar$	$-\ddot{\underset{..}{O}}\overset{\overset{O}{\|}}{C}R$	$-\ddot{\underset{..}{O}}\overset{\overset{O}{\|}}{C}Ar$	
	Weakly activating	$-R$				
	Weakly deactivating	$-\ddot{\underset{..}{F}}:$	$-\ddot{\underset{..}{Cl}}:$	$-\ddot{\underset{..}{Br}}:$	$-\ddot{\underset{..}{I}}:$	
Meta Directing	Moderately deactivating	$-\overset{\overset{O}{\|}}{C}H$	$-\overset{\overset{O}{\|}}{C}R$	$-\overset{\overset{O}{\|}}{C}OH$	$-\overset{\overset{O}{\|}}{C}OR$	
		$-\overset{\overset{O}{\|}}{C}NH_2$	$-SO_3H$	$-C{\equiv}N$		
	Strongly deactivating	$-NO_2$	$-NH_3^+$	$-CF_3$	$-CCl_3$	

Di- and Polysubstitution

the order of steps is important:



Theory of Directing Effects

- The rate of EAS is limited by the slowest step in the reaction
- For almost every EAS, **the rate-determining step is attack of E^+** on the aromatic ring to give a resonance-stabilized cation intermediate
- The **more stable this cation intermediate, the faster the rate-determining step** and the faster the overall reaction

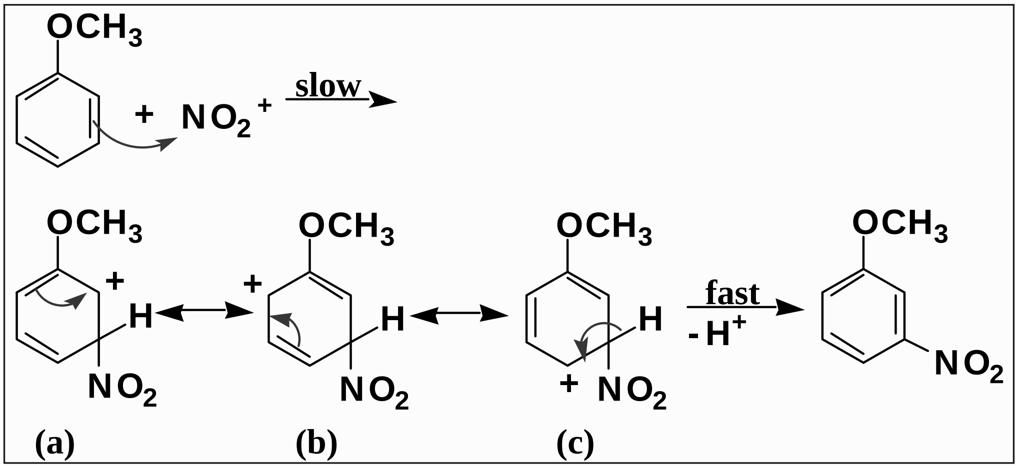
Theory of Directing Effects

- For ortho-para directors, ortho-para attack forms a more stable cation than meta attack
  - ortho-para products are formed faster than meta products
- For meta directors, meta attack forms a more stable cation than ortho-para attack
  - meta products are formed faster than ortho-para products

Theory of Directing Effects

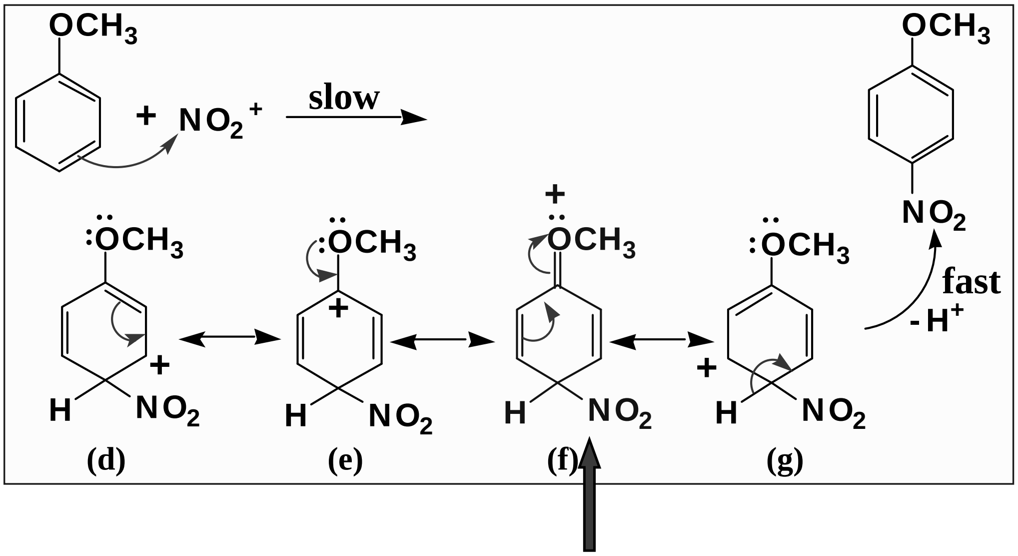
Nitration of anisole

-OCH_3; examine the meta attack:



Nitration of anisole

-OCH_3: examine the ortho-para attack:

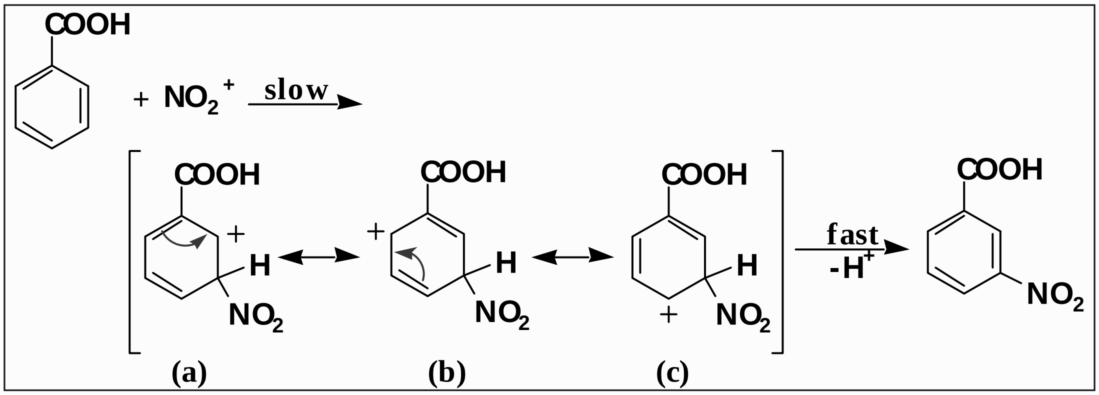


This resonance structure accounts for the selectivity

Theory of Directing Effects

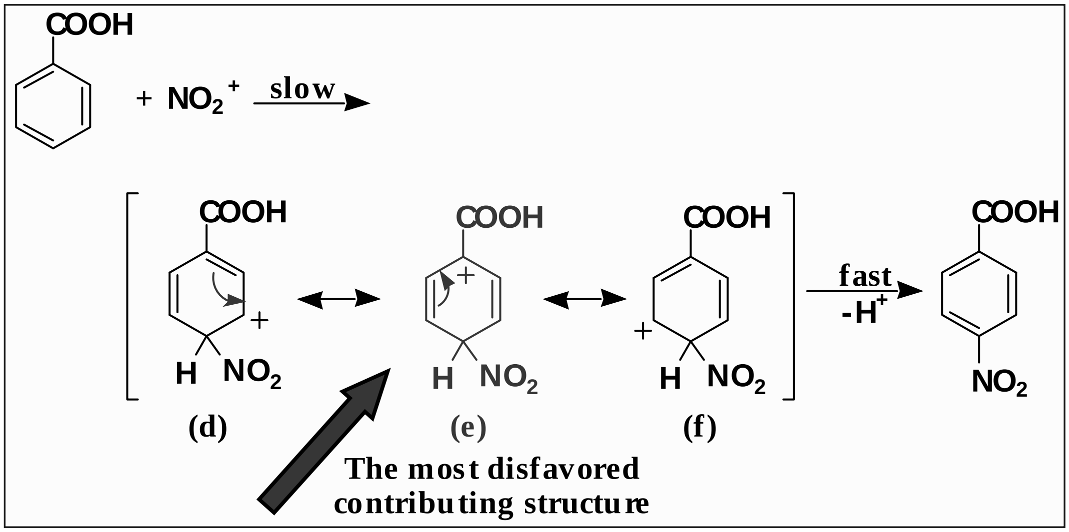
Nitration of benzoic acid

-NO_2; examine the meta attack:



Nitration of benzoic acid

-NO_2: assume ortho-para attack:



This resonance structure accounts for the selectivity

Activating-Deactivating

- Any resonance effect, such as that of -NH_2, -OH, and -OR, that delocalizes the positive charge on the cation intermediate lowers the activation energy for its formation, and has an **activating** effect toward further EAS
- Any resonance effect, such as that of -NO_2, -CN, -CO, and -SO_3H, that decreases electron density on the ring **deactivates** the ring toward further EAS

Activating-Deactivating

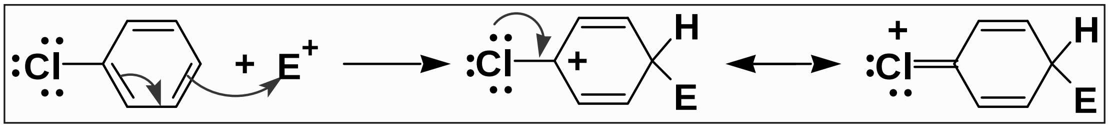
- Any inductive effect, such as that of -CH_3 or other alkyl group, that releases electron density toward the ring **activates** the ring toward further EAS
- Any inductive effect, such as that of halogen, -NR_3^+, -CCl_3, or -CF_3, that decreases electron density on the ring **deactivates** the ring toward further EAS

Di- and Polysubstitution

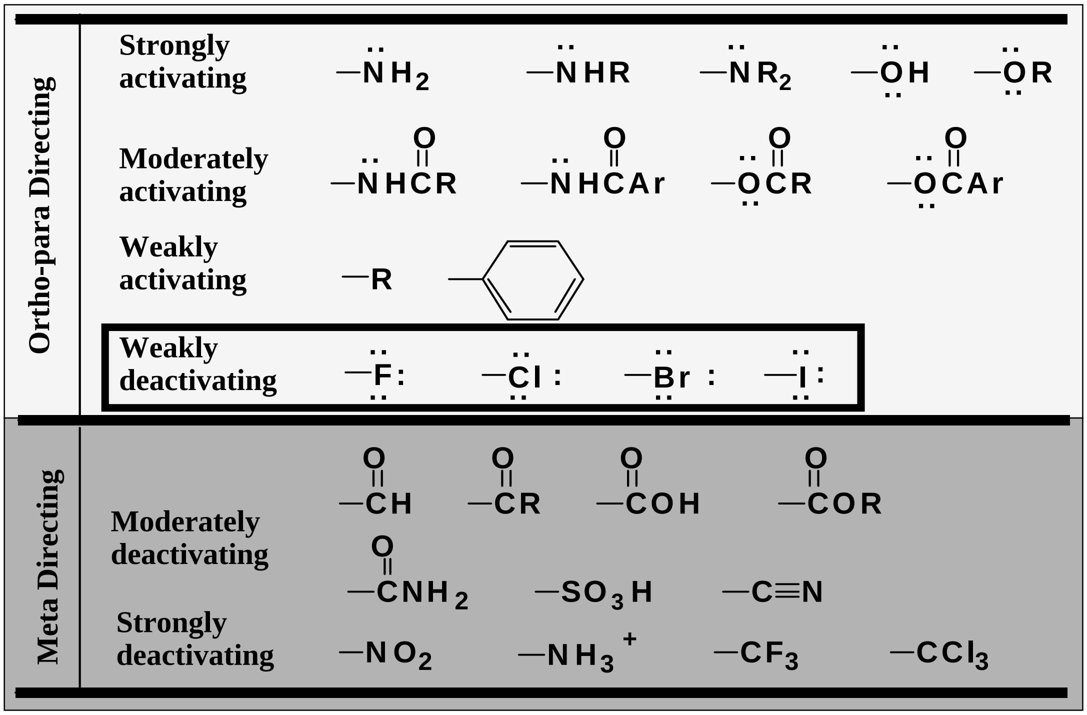
- **Generalizations:**
  - alkyl, phenyl, and all other substituents in which the atom bonded to the ring has an unshared pair of electrons are ortho-para directing; all other substituents are meta directing
  - all ortho-para directing groups except the halogens are activating toward further substitution;
  - the halogens are weakly deactivating

Activating-Deactivating

- for the **halogens**, the inductive and resonance effects run counter to each other, but the former is somewhat stronger
- **the net effect is that halogens are deactivating but ortho-para directing**

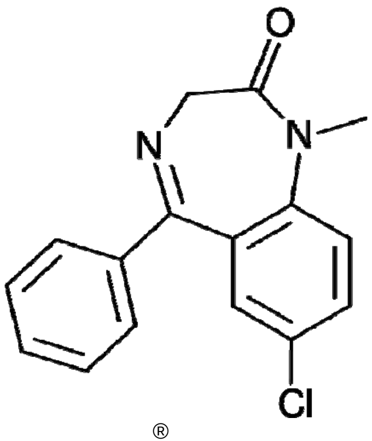


Di- and Polysubstitution



Ortho-para Directing	Strongly activating	$-\ddot{N}H_2$	$-\ddot{N}HR$	$-\ddot{N}R_2$	$-\ddot{O}H$	$-\ddot{O}R$
	Moderately activating	$-\ddot{N}H\overset{O}{\overset{\|}{C}}R$	$-\ddot{N}H\overset{O}{\overset{\|}{C}}Ar$	$-\ddot{O}\overset{O}{\overset{\|}{C}}R$	$-\ddot{O}\overset{O}{\overset{\|}{C}}Ar$	
	Weakly activating	$-R$				
	Weakly deactivating	$-\ddot{F}:$	$-\ddot{Cl}:$	$-\ddot{Br}:$	$-\ddot{I}:$	
Meta Directing	Moderately deactivating	$-\overset{O}{\overset{\|}{C}}H$	$-\overset{O}{\overset{\|}{C}}R$	$-\overset{O}{\overset{\|}{C}}OH$	$-\overset{O}{\overset{\|}{C}}OR$	
		$-\overset{O}{\overset{\|}{C}}NH_2$	$-SO_3H$	$-C\equiv N$		
	Strongly deactivating	$-NO_2$	$-NH_3^+$	$-CF_3$	$-CCl_3$	

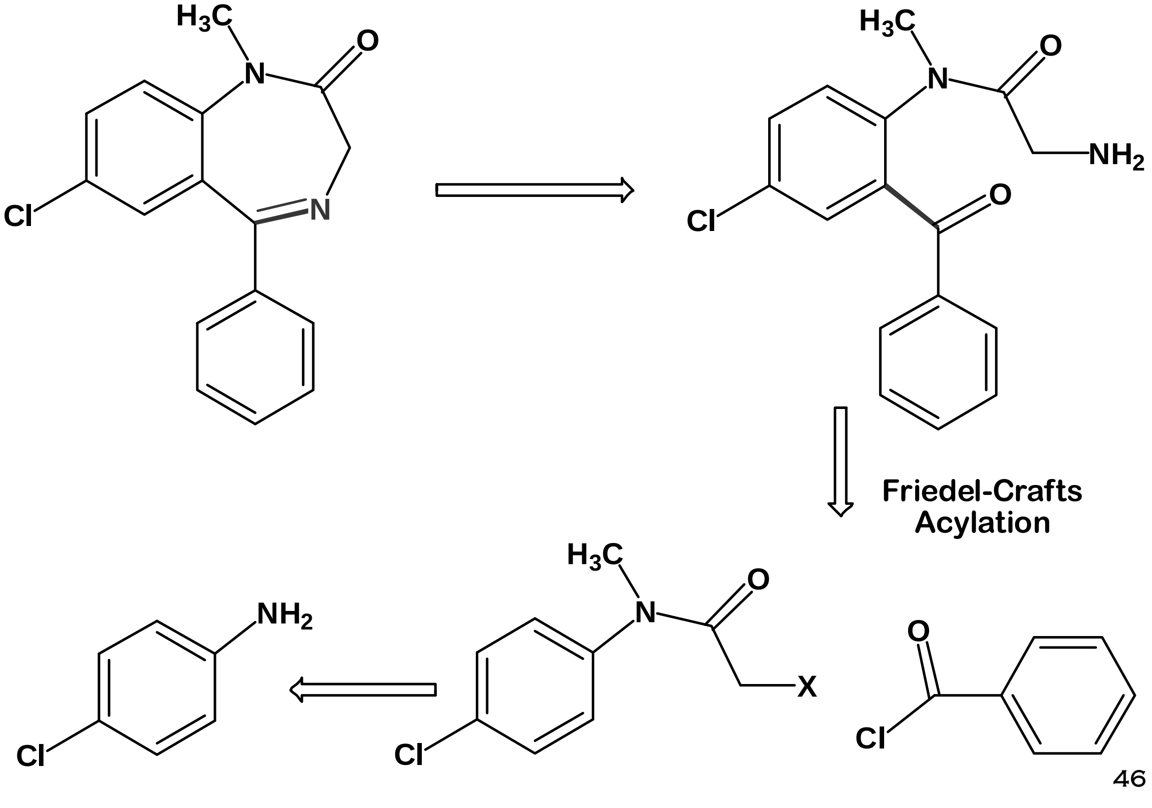
Benzodiazepins



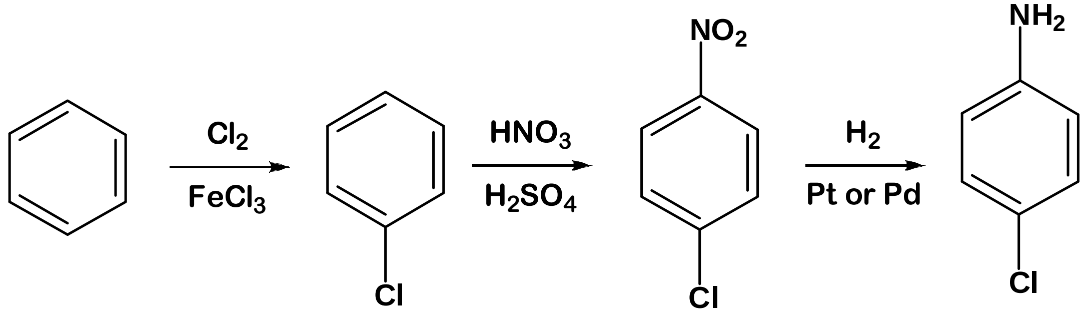
Valium®

1) Sedative-hypnotic
2) Anticonvulsant
3) Muscle relaxant
4) Anxiolytic

Retrosynthetic Analysis

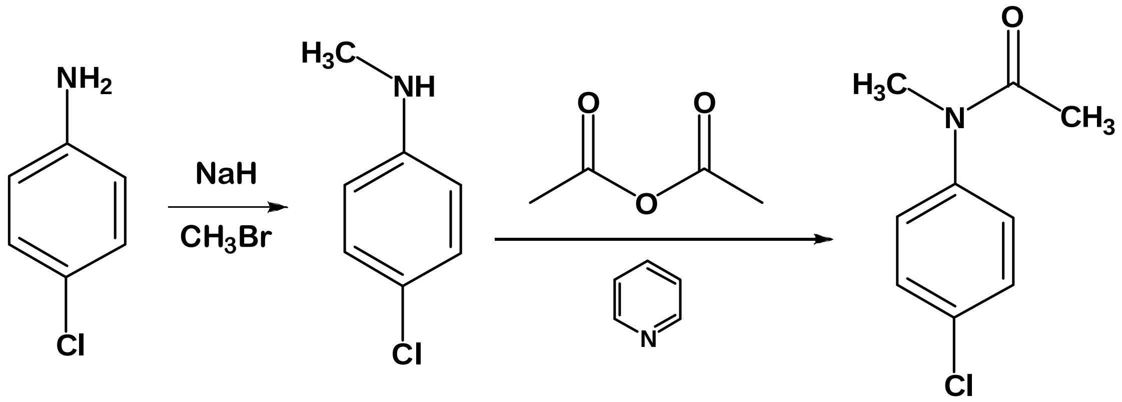


Short Problem Using EAS: the synthesis of p-Aminochlorobenzene

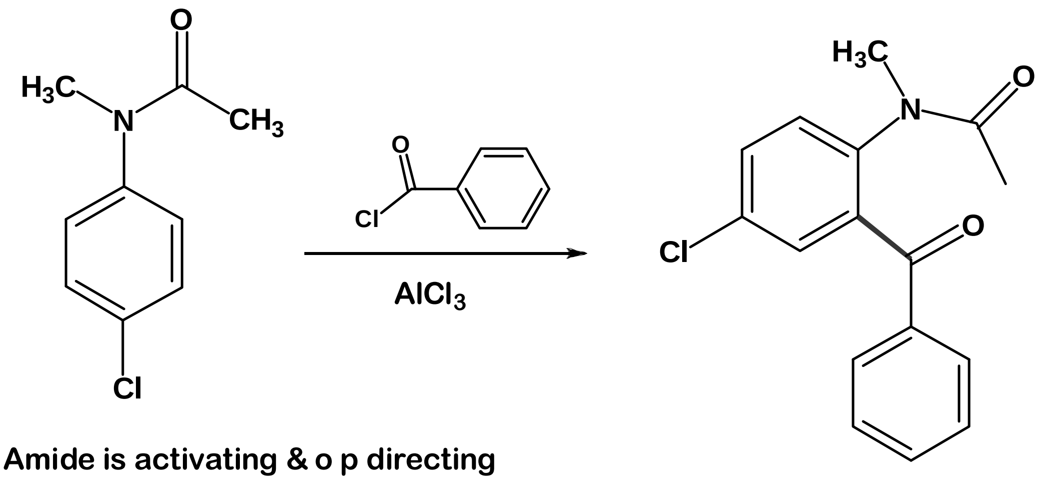


Separate o from p

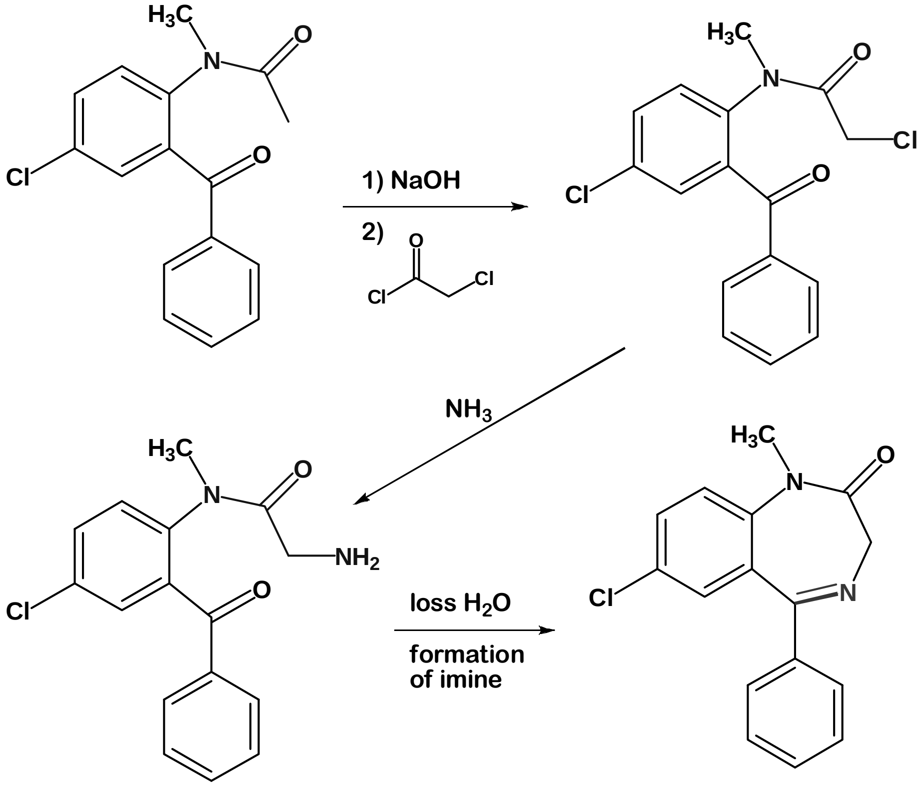
The Synthesis of the amide section:



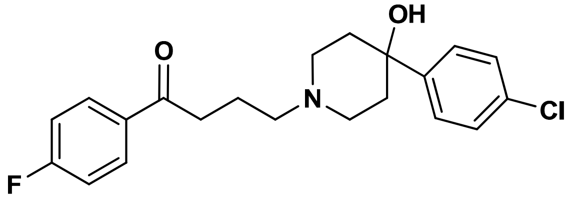
Friedel Crafts Acylation:



Amide is activating & o p directing

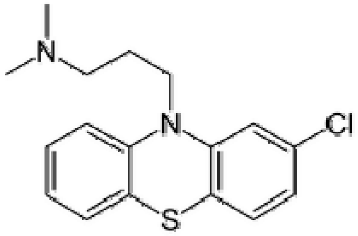


Medicinal Chemistry



Haloperidol

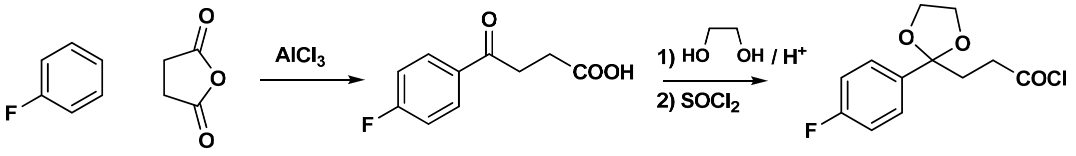
treatment of schizophrenia and acute psychotic states and delirium.

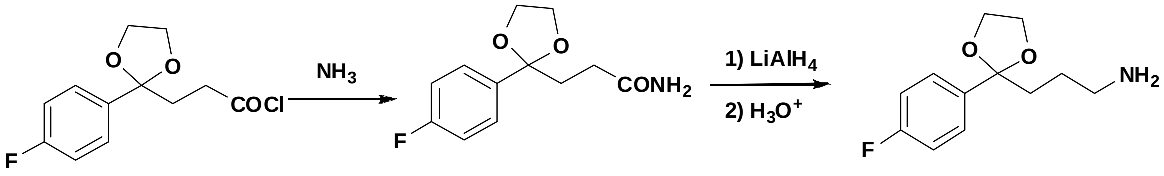


Chlorpromazine
(Thorazine)

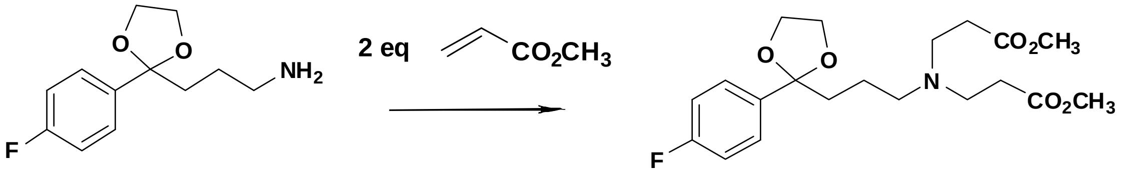
The introduction (1950) of chlorpromazine into clinical use has been described as the single greatest advance in psychiatric care, dramatically improving the prognosis of patients in psychiatric hospitals worldwide the availability of antipsychotic drugs curtailed indiscriminate use of electroconvulsive therapy and psychosurgery, and was one of the driving forces behind the deinstitutionalization movement.

Medicinal Chemistry

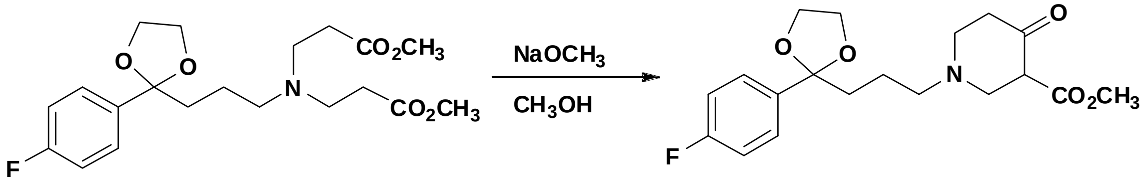


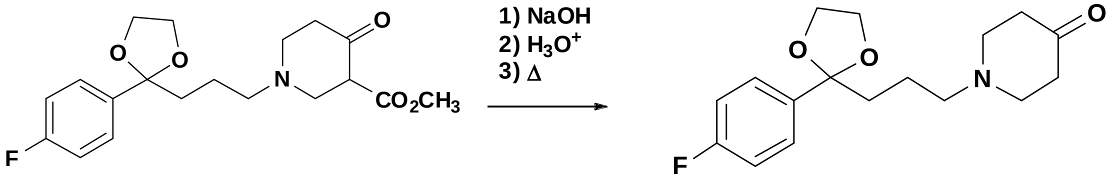


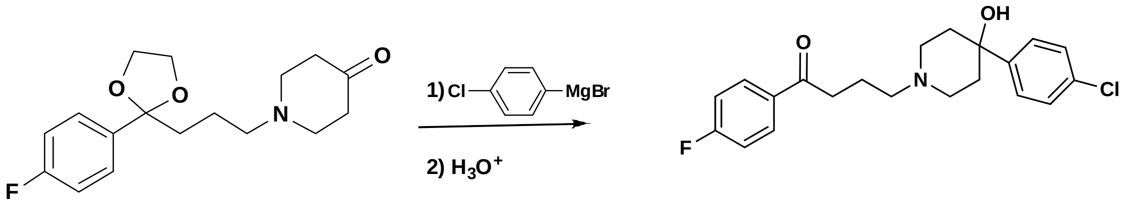
Michael Reaction in Context



Dieckmann Condensation in Context







Haloperidol