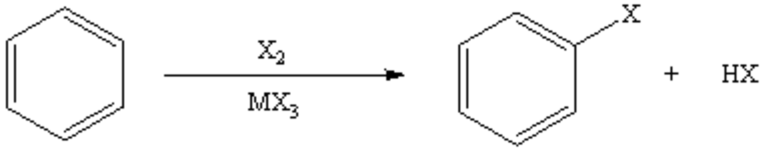
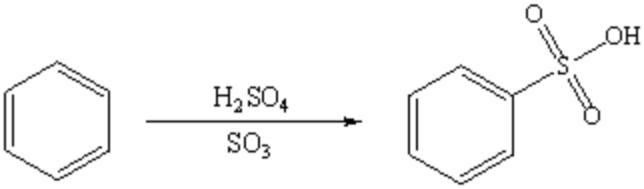
Chem 263 **Oct 1, 2009**

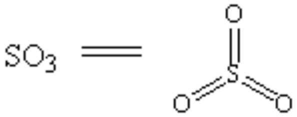
Halogenation (Review from last lecture)



Where X = halogen (Cl, Br)
M = metal Fe, B, or Al

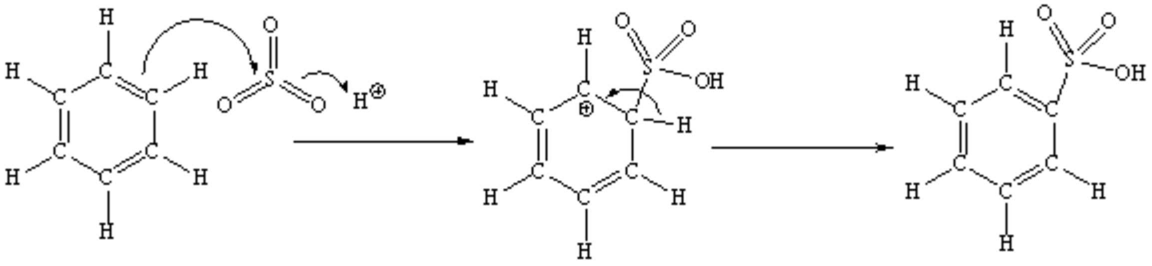
Sulfonation





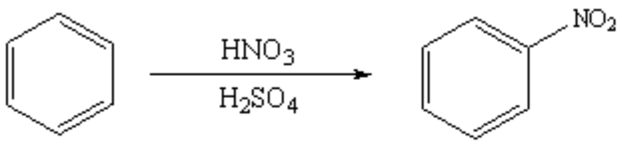
In this reaction, SO_3 is the electrophile.

Mechanism:



This reaction of SO_3 is followed by loss of proton from the conjugated cation intermediate (similar to the one we saw in halogenation).

Nitration

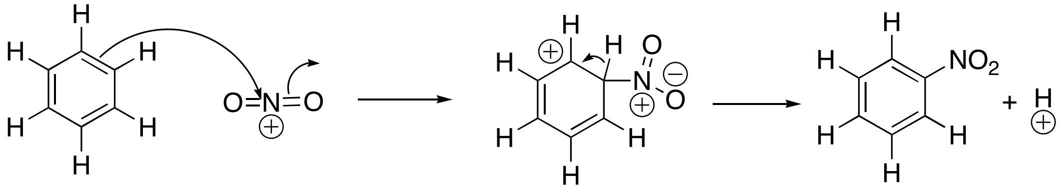


Mechanism:

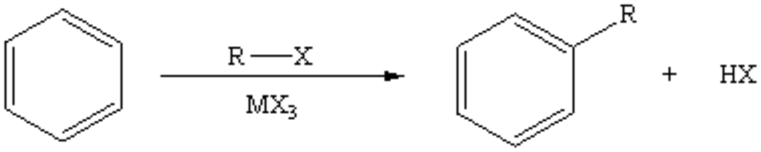
In strong acid, nitric acid is protonated to give $H_2NO_3^+$. Loss of water generates the nitronium ion that acts as electrophile.

$$HNO_3 + H^{\oplus} \longrightarrow H_2\overset{\oplus}{O}{-}NO_2 + H_2O \rightleftharpoons \underset{\text{nitronium ion}}{{}^{\oplus}NO_2} + H_2O$$

$$^{\oplus}NO_2 = O{=}\overset{\oplus}{N}{=}O$$

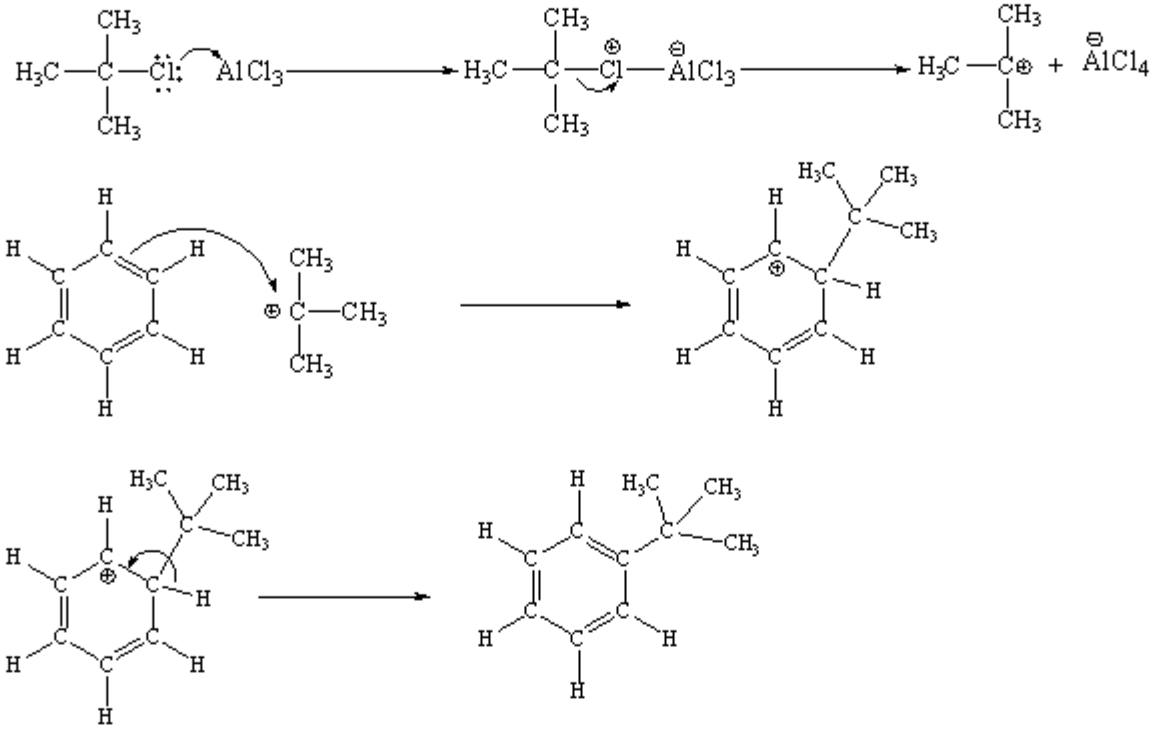


Alkylation



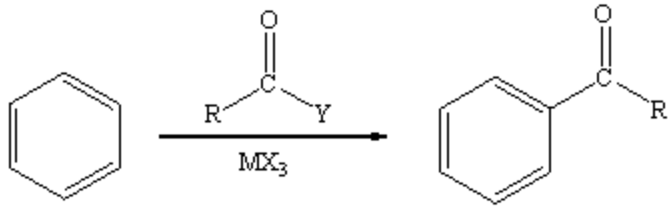
Where R = alkyl (methyl, ethyl, isopropyl, *tert*-butyl, etc)
X = halogen (Cl, Br, and I)
M = metal Fe, B, or Al

Mechanism:

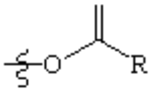


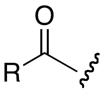
$$\overset{\oplus}{H} + \overset{\ominus}{Al}Cl_4 \longrightarrow HCl + AlCl_3$$

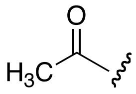
Acylation (Friedel-Crafts)

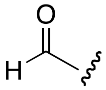


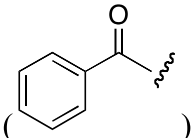
Where R = alkyl (methyl, ethyl, *tert*-butyl, etc)

Y = halogen (Cl, Br, and I), or  (an anhydride functionality)
M = metal Fe, B, or Al
X = halogen

An acyl group = 

. When R=CH$_3$, the group is called acetyl (

), when R=H, the group is called formyl (

), when R=benzene ring, the group is called benzoyl (

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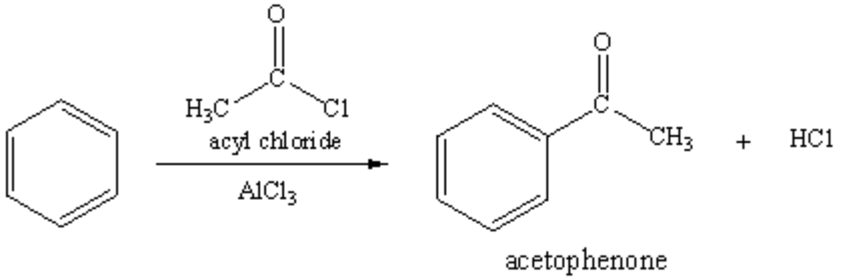
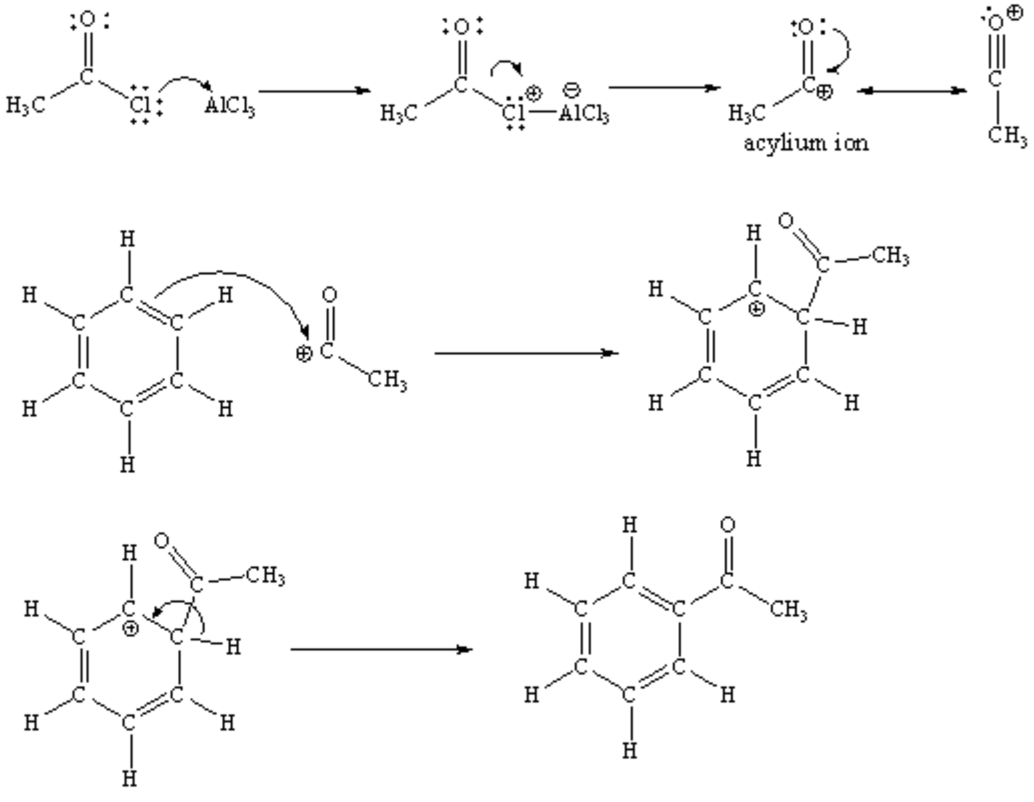
Example:

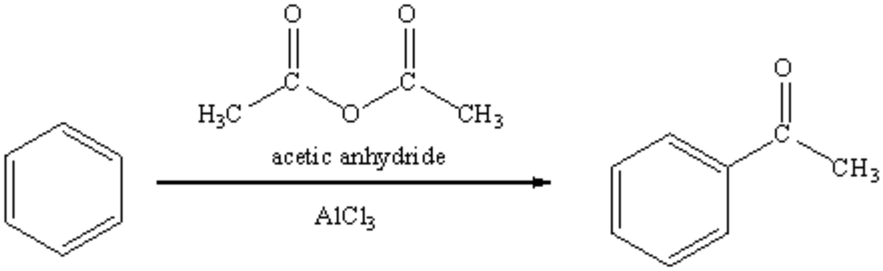


Mechanism:



$$\overset{\oplus}{H} + \overset{\ominus}{AlCl_4} \longrightarrow HCl + AlCl_3$$

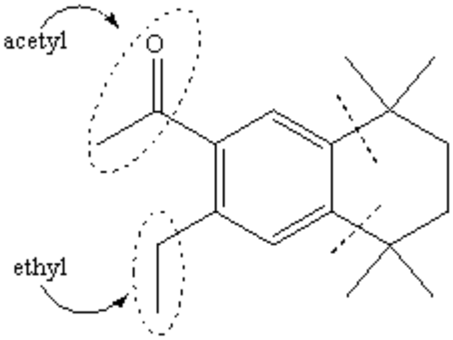
Example:



Similar to the above example, this reaction also proceeds through the acylium ion. However, we need one full equivalent of Lewis acid for this reaction. When the acyloxy group (acyl group with another oxygen) reacts with the Lewis acid, the reaction is essentially irreversible and the Lewis acid cannot be regenerated.

Now, let's look at a couple of molecules and try to analyze how to make them

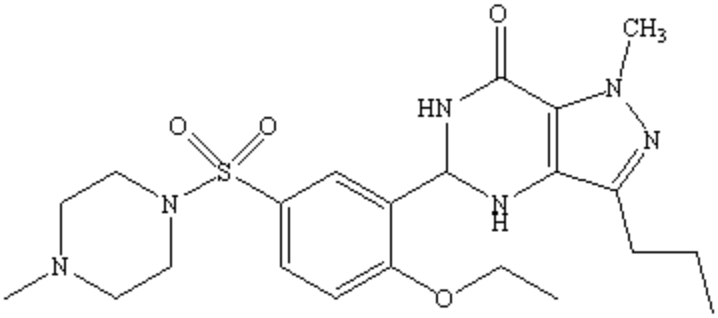
Example:



Versalide

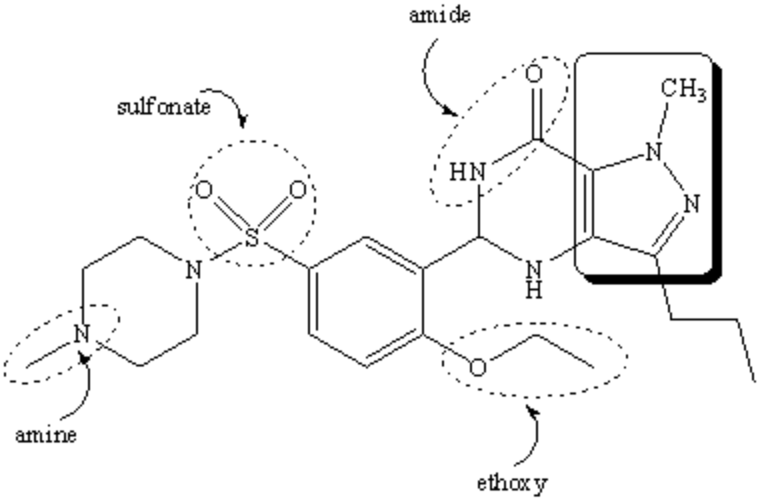
This molecule has an acetyl, ethyl, and an apparent cyclohexyl group attached to the benzene group. From what you had just learned, you should be able to analyze the synthesis of this molecule: the acetyl group can be made through Friedel-Crafts **Acylation**; the ethyl group can be attached through akylation, and similarly, the cyclohexyl ring can be made by **alkylation** twice.

Example:



The molecule shown is **Viagra**. It generates more than $ 2.7 billion U.S. per year.

Can you recognize its functional groups?



Is the ring highlighted in rectangle aromatic?

Answer: Yes. It is. Think back to last lecture on heterocycles and criteria for aromaticity. The 5 member ring is cyclic, it has two double bonds (4 pi electrons) that are conjugated, and it is planar. The methyl substituted nitrogen donates its lone pair into the 5 member ring to fit the 4n+2 rule. The other nitrogen has lone pair in *sp*^{2} orbital perpendicular to the pi (π) system.

If given a molecule, know how to analyze its parts and functional groups on the exam.

Electrophilic Aromatic Substitution for Substituted Benzenes (handout)

Substituents already present on the benzene ring determine the position of reaction and the reactivity of the system.

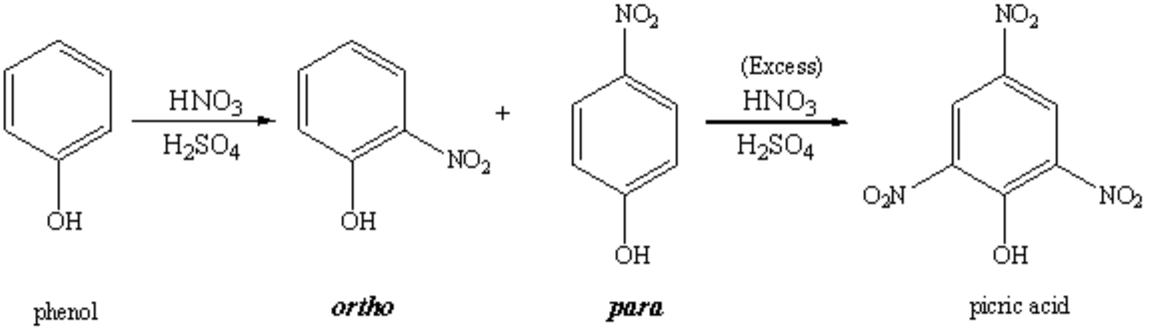
Resonance and Inductive Effects

A substituent can donate or withdraw electrons from the aromatic ring in two ways: by inductive effects and by resonance effects.

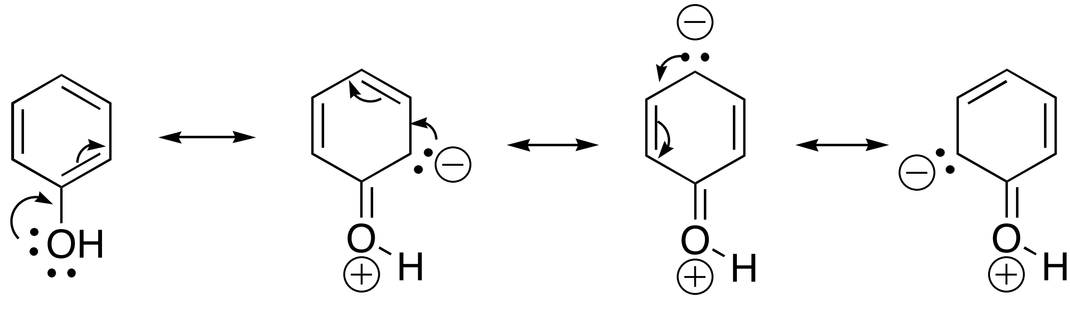
Inductive effects are due to the intrinsic electronegativity of the atoms and to bond polarity in functional groups. These effects operate by donating or withdrawing electrons through the sigma (σ) bonds. An **electron donating group** will direct to the **ortho/para** position while an **electron withdrawing group** will direct to the **meta** position. This effect is considered **weak** compared to resonance effects.

Resonance effects operate by donating or withdrawing electrons through the pi (π) bonds by overlap of the p atomic orbital on the substituent with the p atomic orbitals (π molecular orbital system) on the aromatic ring. An **electron donating group** will direct to the **ortho/para** position while an **electron withdrawing group** will direct to the **meta** position. This effect is considered **strong** compared to inductive effects.

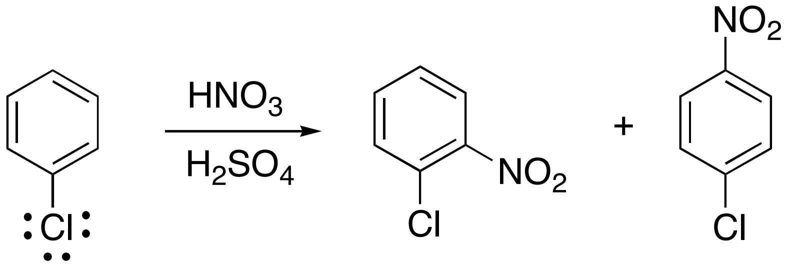
Example:



In this reaction, phenol already has a hydroxyl (-OH) group attached. When we perform nitration, only *ortho* and *para* substitution occurs. Even when we subject the reaction to excess condition, still only the *ortho* and *para* position reacts.



Example:



In this reaction, chlorobenzene has a chloro (-Cl) group attached on the benzene ring. When we perform nitration, only *ortho* and *para* substitution occurs. Chloro group is an electron withdraw group inductively, however, the lone pairs of electrons are conjugated to the benzene ring through resonance as electron donating group. As result, resonance beats inductive effect, which gives ortho, and *para* substitution products.