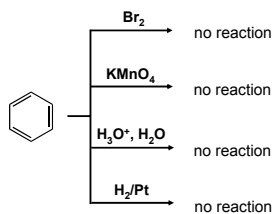


Chapter 16

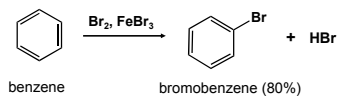
Chemistry of Benzene: Electrophilic Aromatic Substitution

Reactivity of Benzene

- stabilization due to aromaticity makes benzene significantly less reactive than isolated alkenes

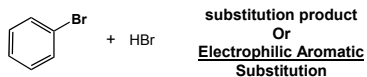
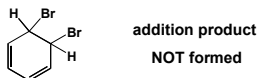
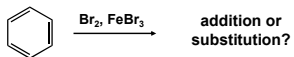


- however:



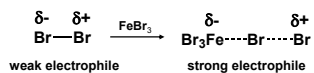
- substitution, not addition product. Why?

Answer: Addition product would not be aromatic



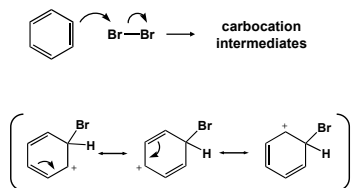
Mechanism

- goes by way of mechanism that permits product to retain aromaticity

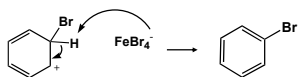


- interaction with FeBr_3 makes Br_2 more electrophilic

- polarized Br_2 is then attacked by the π electron system of the nucleophilic benzene ring (rate-limiting step) to yield a nonaromatic carbocation intermediate that is stabilized by resonance

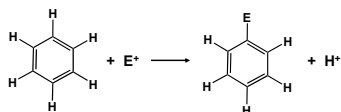


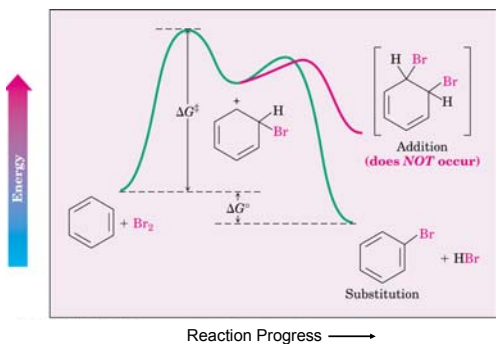
- carbocation intermediate then loses H^+ from the bromine-bearing carbon to give a substitution product



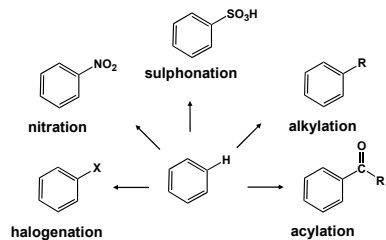
- step is similar to the second step of an $E1$ reaction

- net effect is substitution of H^+ with Br^- ; aromaticity is retained





Usefulness of Reaction



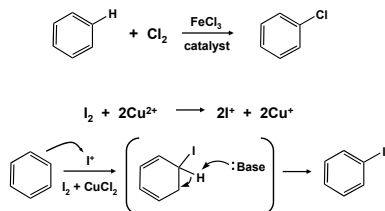
Applications:

- 1) pharmaceuticals
- 2) dyes
- 3) precursors for further reactions

Substitutions

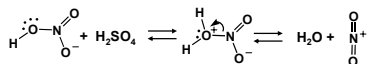
Aromatic Halogenation

- works for Cl and I, F is too reactive with poor yields
- electrophile is generated by way of a mechanism similar to bromination

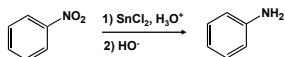


Aromatic Nitration

- electrophile is nitronium ion which is generated in a mixture of concentrated nitric and sulfuric acids

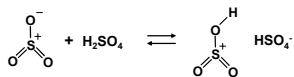


- nitro-substituted product can be reduced to yield an arylamine, useful precursors in dye production

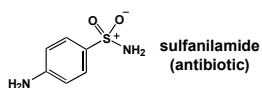


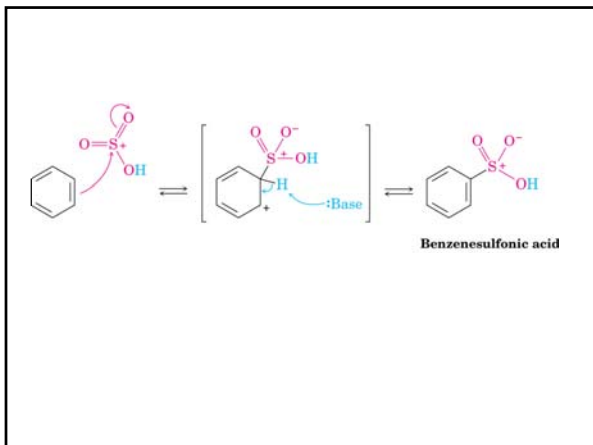
Aromatic Sulphonation

- reaction is effected in fuming sulfuric acid (H2SO4 and SO3)
- electrophile is either HSO3+ or neutral SO3



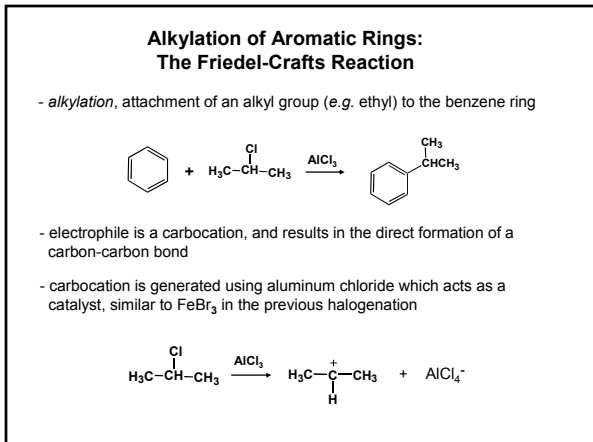
- sulphonation is reversible such that it may go forward or backward depending on reaction conditions
- useful reaction for production of sulpha drugs for treatment of meningitis and urinary-tract infections





Problem:

How many products may be formed on chlorination of *o*-xylene, *m*-xylene, and *p*-xylene?



Mechanism

Limitations of the Friedel-Crafts Reaction

1) Only alkyl halides can be used; aryl and vinylic halides are unreactive



aryl halide



vinylic halide

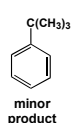
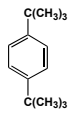
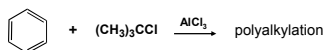
2) If strongly electron-withdrawing groups or amino groups are present on the benzene ring, then poor yields are encountered



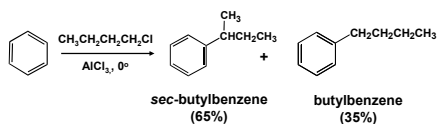
Y = nitro, amino, carbonyl

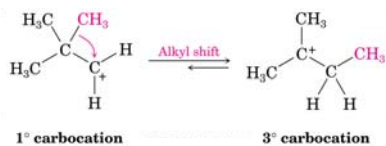
- limitations hinder usefulness and scope of reaction

3) It is often difficult to stop the reaction once a single substitution has occurred, which leads to multiple substitutions or *polyalkylations*



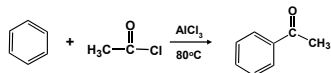
4) Carbocation rearrangements (e.g. hydride shift) occur and lead to mixtures of products



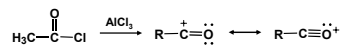


Acylation

- acyl group (-COR) is introduced onto a benzene ring by way of a reaction with a carboxylic acid chloride



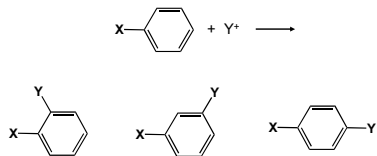
- mechanism is similar to that of alkylation; carbocation is stabilized by resonance involving an oxygen atom



- acylations never occur more than once since the product is less reactive than the nonacylated starting material

Substituent Effects in Substituted Aromatic Rings

- what happens if we carry out a reaction on an aromatic ring that already has a substituent?



Result: single product? mixture?
no reaction?

Two Important Effects

1) Reactivity

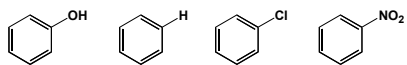
A substituent affects the *reactivity* of the aromatic ring

Substituents may either activate or deactivate the benzene ring relative to benzene

2) Orientation

The three possible disubstituted products (*i.e.* ortho, meta, para) are usually not formed in equal amounts

The nature of the substituent already present on the benzene ring determines the position of the second substituent



Relative rate of nitration

1000

1

0.033

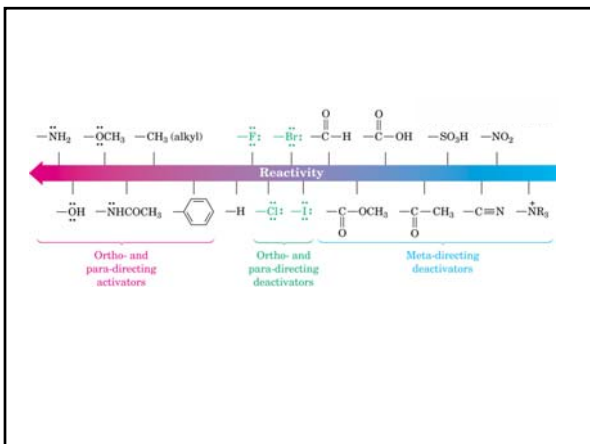
6×10^{-6}



Classification of Substituents

Three Types of Substituents:

- 1) ortho- and para- directing activators
- 2) ortho- and para- directing deactivators
- 3) meta- directing deactivators



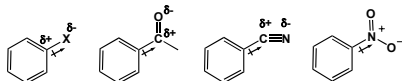
Control of Reactivity and Orientation

- interplay of *inductive effects* and *resonance effects*

- **inductive effect:**

- withdrawal or donation of electrons through a σ bond due to electronegativity and the polarity of bonds in functional groups

- withdrawal of electrons:



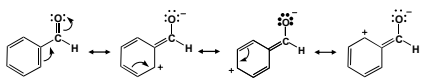
- donation of electrons:



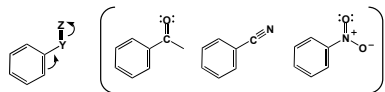
- resonance effect:

- withdrawal or donation of electrons through a π bond due to overlap of a p orbital on the substituent with a p orbital on the aromatic ring

- withdrawal of electrons:

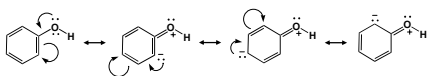


- effect is greatest at the ortho and para positions, creating a build-up of positive charge

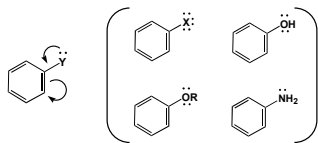


- general structure $-Y=Z$, where Z is more electronegative atom (e.g. $-\text{COR}$, $-\text{CN}$, $-\text{NO}_2$)

- donation of electrons:



- effect is greatest at the ortho and para positions, creating a build-up of negative charge



- general structure $-Y$, where Z atom has a lone pair of electrons available for donation (e.g. $-\text{OH}$, $-\text{OR}$, $-\text{NH}_2$)

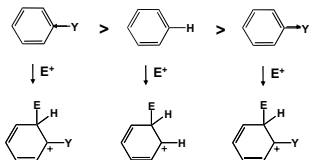
Problem:

What are the major products of the following reactions?

- mononitration of bromobenzene
- monobromination of aniline

Explanation of Substituent Effects

- must consider stability of the carbocation intermediate that forms upon *ortho*-, *meta*-, and *para*-substitution

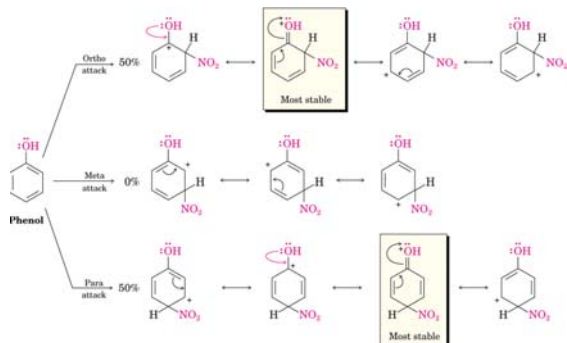


- activating groups donate electrons to the ring, thereby stabilizing the carbocation intermediate and causing it to form faster
- deactivating groups withdraw electrons from the ring, thereby destabilizing the carbocation intermediate and causing it to form more slowly

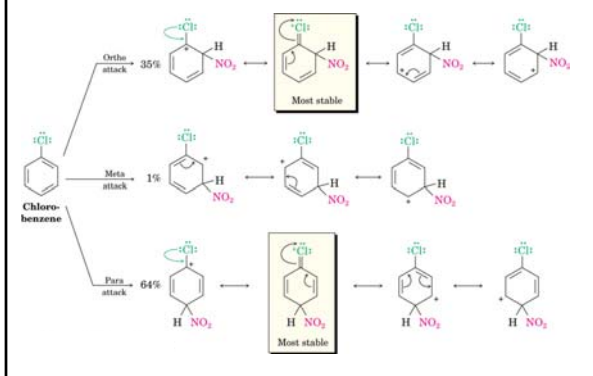
Nitration of Toluene

Mechanism

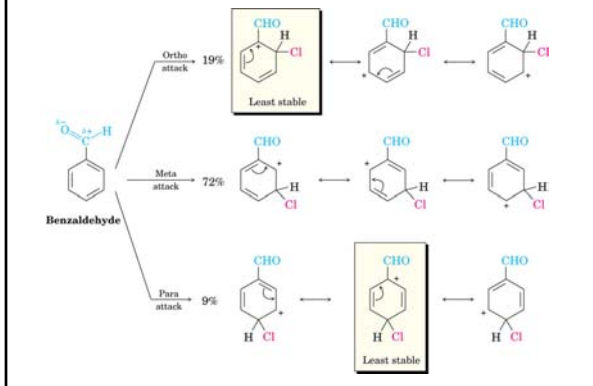
Nitration of Phenol



Nitration of Chlorobenzene



Chlorination of Benzaldehyde



Trisubstituted Benzenes

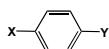
- further electrophilic substitution of a disubstituted benzene is governed by the same resonance and inductive effects



ortho-



meta-

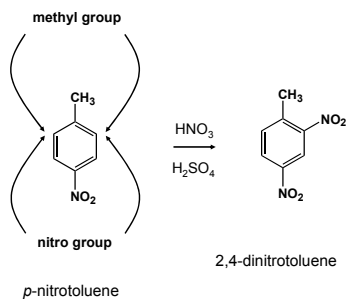


para-

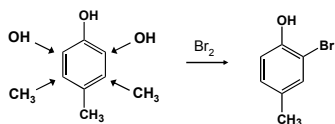
- must consider additive effects of the two groups on the ring

Three rules to follow:

1) Directing effects can reinforce each other

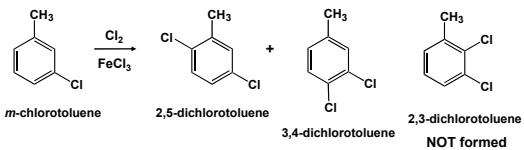


2) If the directing effects oppose each other, the more powerful activating group has the dominant influence

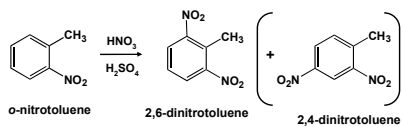


- Note: mixtures of products often result -

3) Substitution between two groups in a meta-disubstituted compound rarely occurs because the site is too hindered



- must find alternative way to synthesize such compounds

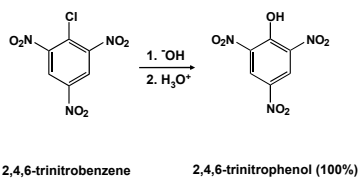


Problem:

What product would you expect from bromination of *p*-methylbenzoic acid?

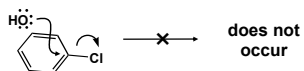
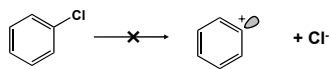
Nucleophilic Aromatic Substitution (NAS)

- aryl halides with an electron-withdrawing substituent can undergo nucleophilic aromatic substitution



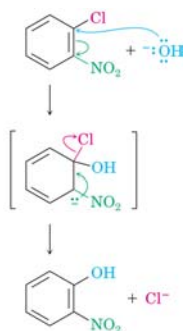
Mechanism of Reaction?

- how does reaction occur? Neither $\text{S}_{\text{N}}1$ nor $\text{S}_{\text{N}}2$

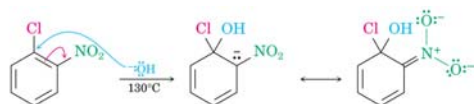


- instead, proceeds by *addition/elimination* mechanism

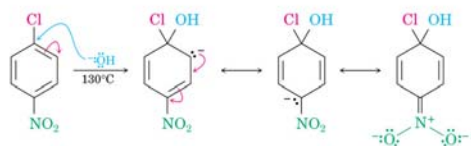
Mechanism



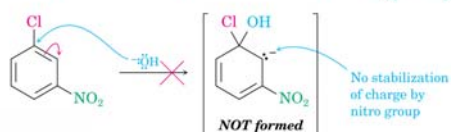
Ortho



Para



Meta



Differences Between EAS and NAS

Electrophilic Aromatic Substitution

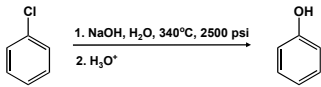
- favored by electron-donating substituents which stabilize the carbocation intermediate
- electron-withdrawing groups deactivate
- electron-withdrawing groups are meta directors

Nucleophilic Aromatic Substitution

- favored by electron-withdrawing substituents which stabilize the carbanion intermediate
- electron-withdrawing groups activate
- electron-withdrawing groups are ortho- and para- directors

Benzyne

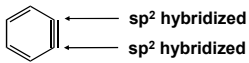
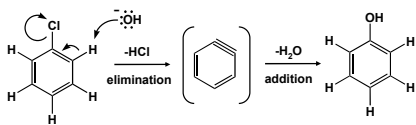
- at high temperature and pressure, chlorobenzene can be forced to react to form phenol



- phenol synthesis takes place by way of an *elimination/addition* mechanism rather than addition/elimination

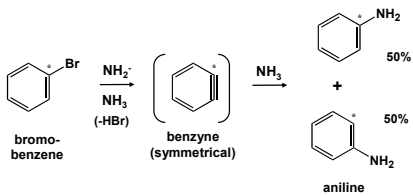
- proceeds through a reactive *benzyne* intermediate

Benzyne Intermediate

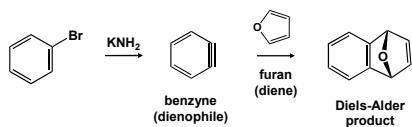


Evidence for Benzyne Intermediate

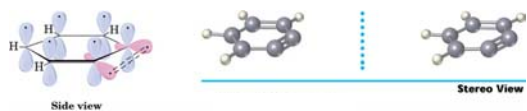
- radioactive ^{14}C labeling experiments:



- reactivity experiments involving benzyne:

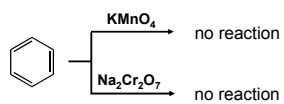


Orbital Picture of Benzyne



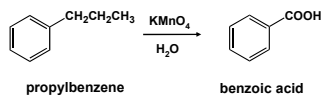
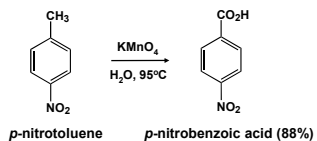
Oxidation of Aromatic Compounds

- benzene ring itself is inert to strong oxidizing agents (e.g. KMnO_4 , $\text{Na}_2\text{Cr}_2\text{O}_7$), which cleave alkene C-C bonds



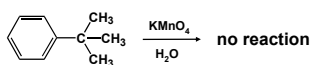
Oxidation of Alkyl-Groups

- alkyl-group side chains are readily attacked by oxidizing agents, being converted to carboxyl groups (-COOH)



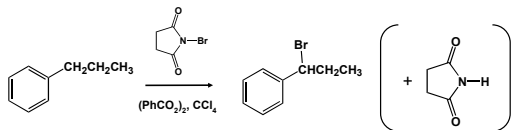
- mechanism requires C-H bond at the position next to the aromatic ring to produce benzylic radicals

Importance of Benzylic Radical



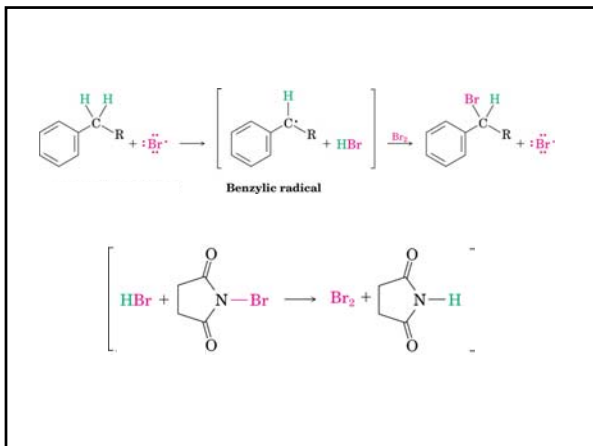
Bromination of Alkylbenzene Side Chains

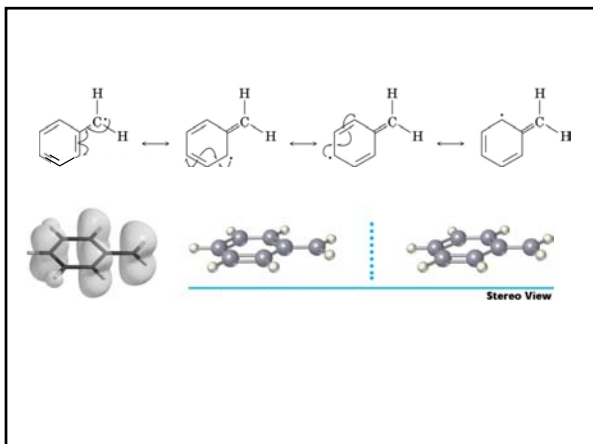
- treatment of an alkylbenzene with *N*-bromosuccinimide results in side-chain bromination at the benzylic position



- mechanism is similar to allylic bromination of alkenes

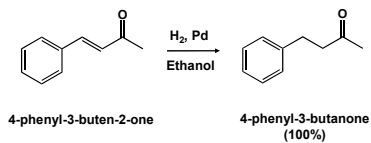
- involves a benzylic radical stabilized by resonance





Reduction of Aromatic Compounds

- benzene rings are also inert to oxidation under most conditions
- inert to catalytic hydrogenation under conditions that reduce typical alkenes
- it is therefore possible to selectively reduce double bonds in the presence of an aromatic ring

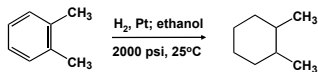


Hydrogenation of Benzene

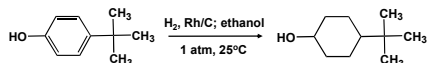
- to hydrogenate benzene, harsh reaction conditions are necessary

Examples

- platinum catalyst under several hundred atmospheres of pressure



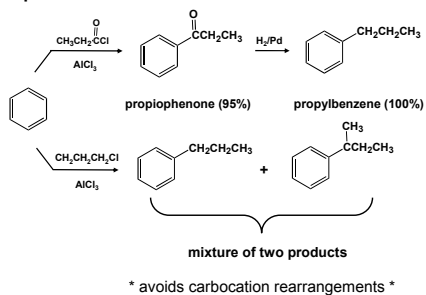
- rhodium catalyst on carbon



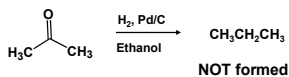
Reduction of Aryl Alkyl Ketones

- aromatic ring activates a neighboring carbonyl group toward reduction

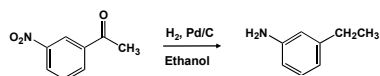
Example



- dialkyl ketones are not hydrogenated under these conditions

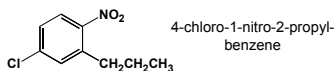


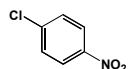
- $-\text{NO}_2$ groups are reduced to an amino group under these conditions



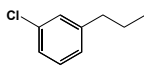
Synthesis of Trisubstituted Benzenes

- a successful multistep synthesis of a complex molecule requires a working knowledge of many organic reactions
- you need to know which reactions are available and when to use them
- such a working knowledge may be developed in the synthesis of trisubstituted benzenes since the introduction of new substituents is strongly affected by directing effects of other substituents

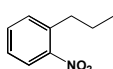




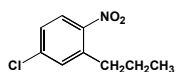
p-chloronitrobenzene



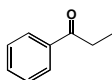
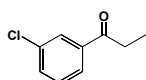
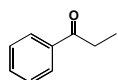
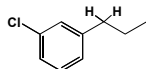
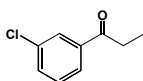
m-chloropropylbenzene



o-nitropropylbenzene



4-chloro-1-nitro-2-propylbenzene



"Total Synthesis"

