Chemistry of Benzene: Nucleophilic Aromatic Substitution

Part C

B. Pharm. Semester-1
Course Code: 0510210; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to explain

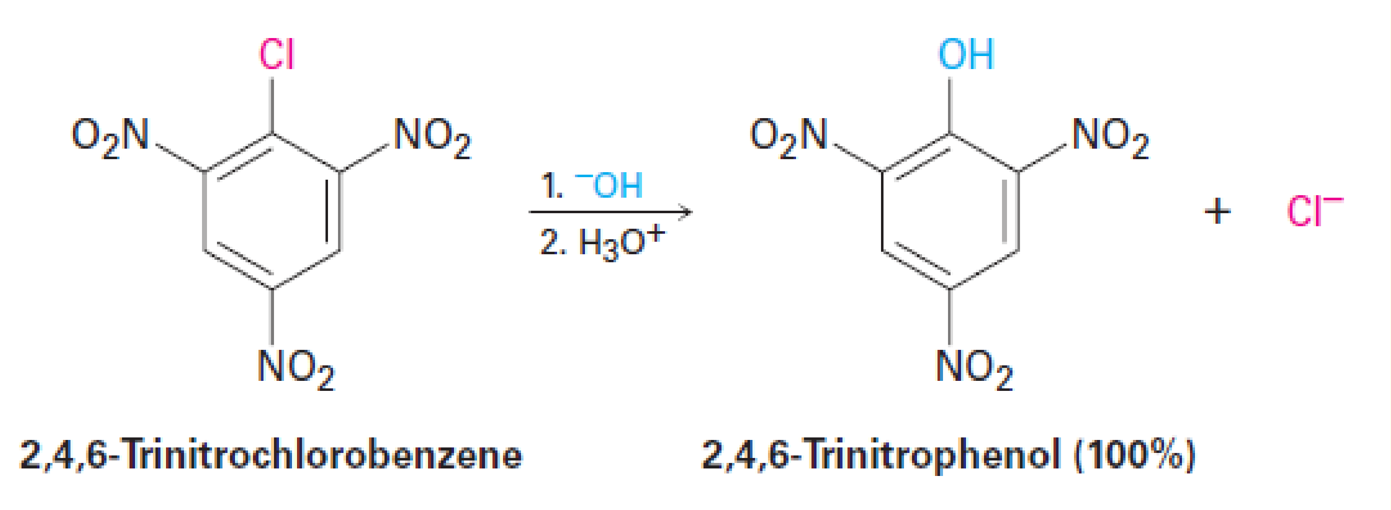
- **Nucleophilic aromatic substitution and its mechanisms**
- **Benzyne and it structure**
- **Oxidation of Aromatic compounds**
- **Bromination of Alkylbenzene side chains**
- **Reduction of Aromatic Compounds**
- **Reduction of Aralkyl Ketones**
- **Synthesis of Trisubstituted Benzenes with 2 examples**

Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

Nucleophilic Aromatic Substitution

- Although aromatic substitution reactions usually occur by an electrophilic mechanism, **aryl halides** that have **electron-withdrawing substituents** can also undergo a nucleophilic aromatic substitution reaction.
- For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. The nucleophile OH^- has substituted for Cl^-.



Nucleophilic Aromatic Substitution: Pathways

In general, nucleophilic aromatic substitution reaction, may follow two different pathways:-

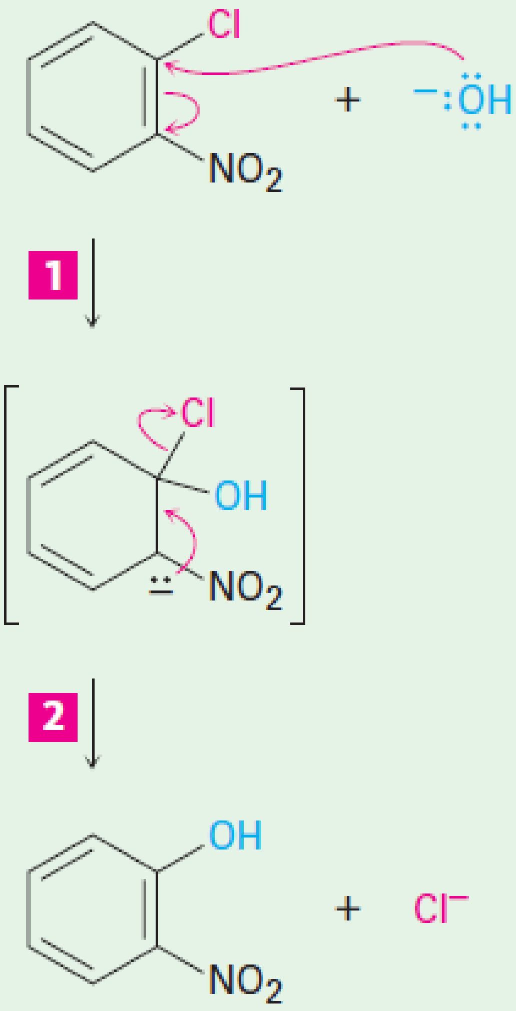
(1) Bimolecular displacement mechanism

(2) Elimination-addition mechanism involving the intermediate compound *Benzyne*

Nucleophilic Aromatic Substitution: Mechanism

1 Nucleophilic addition of hydroxide ion to the electron-poor aromatic ring takes place, yielding a stabilized carbanion intermediate.

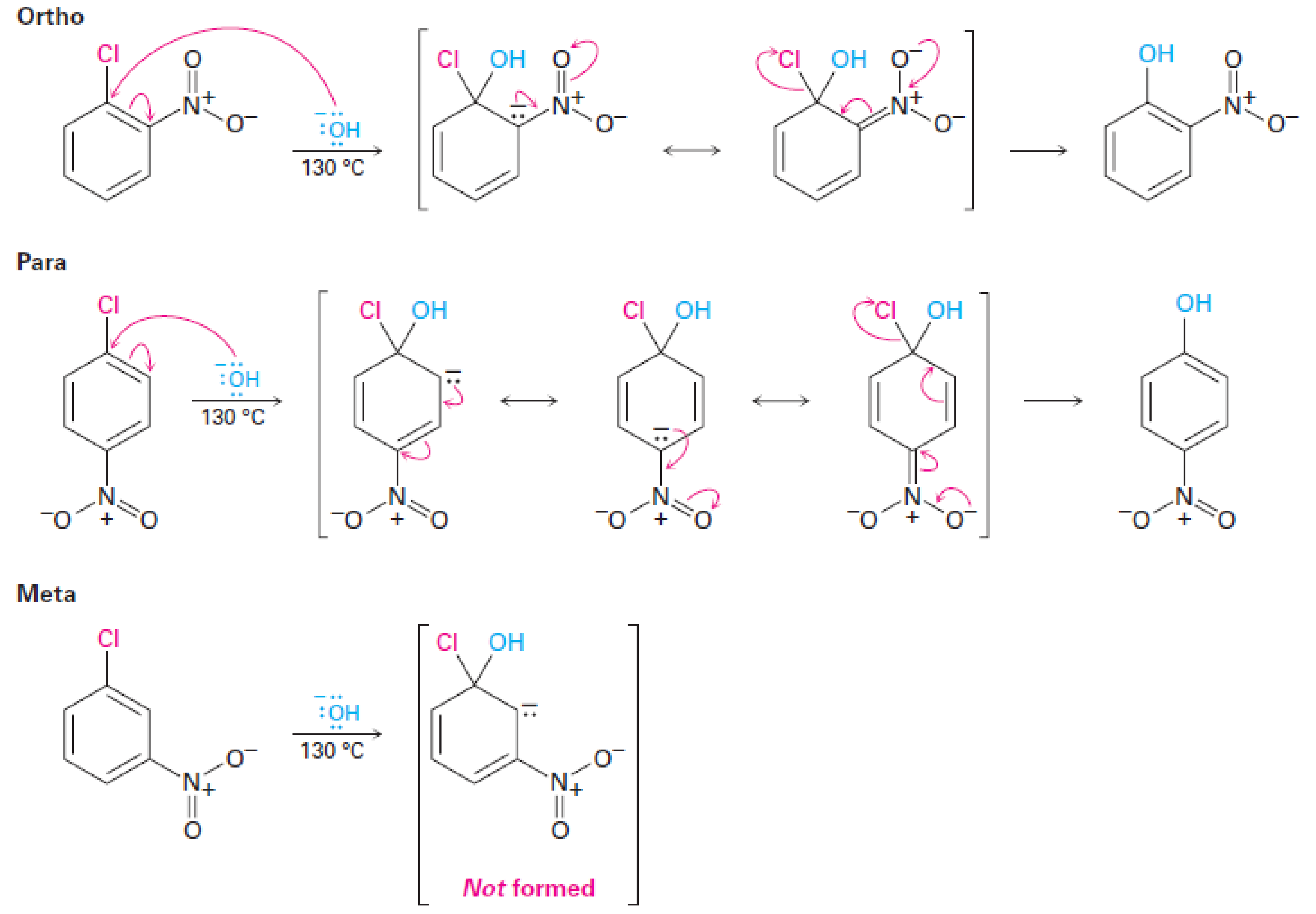
2 The carbanion intermediate undergoes elimination of chloride ion in a second step to give the substitution product.



Nucleophilic Aromatic Substitution: Mechanism

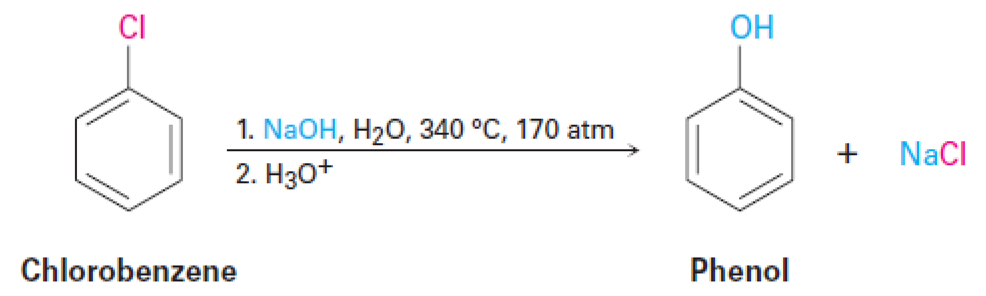
- Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance.
- A meta substituent offers no such resonance stabilization.
- Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH^-.

Nucleophilic Aromatic Substitution: Mechanism

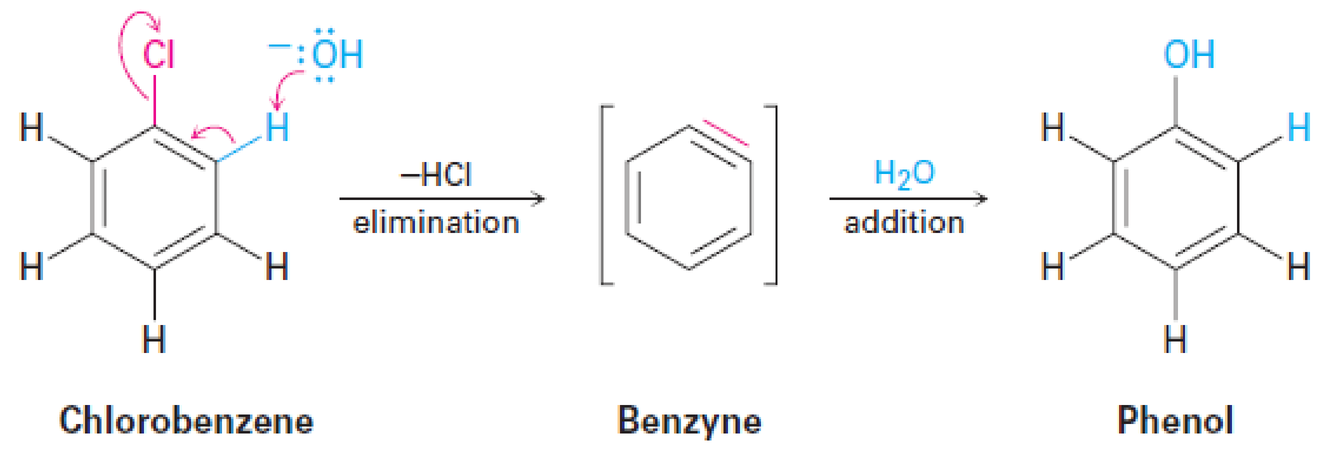


Benzyne

- Phenol could be prepared by treatment of chlorobenzene with dilute aqueous NaOH at 340 °C under 170 atm pressure.

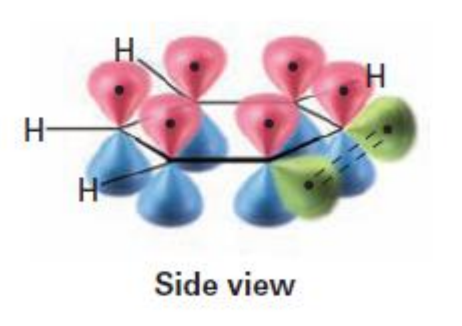


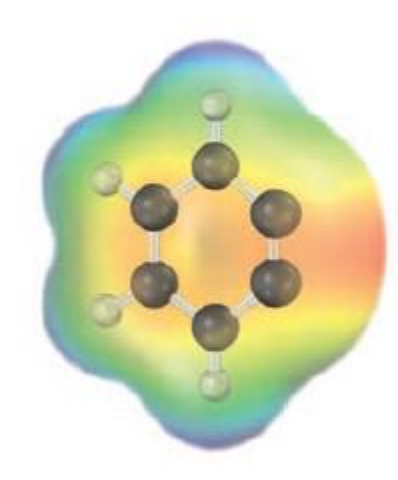
- Mechanism



Benzyne: Structure

The electronic structure of Benzyne is distorted alkyne. Although a typical alkyne triple bond uses sp-hybridized carbon atoms, the benzyne triple bond uses sp2-hybridized carbons.

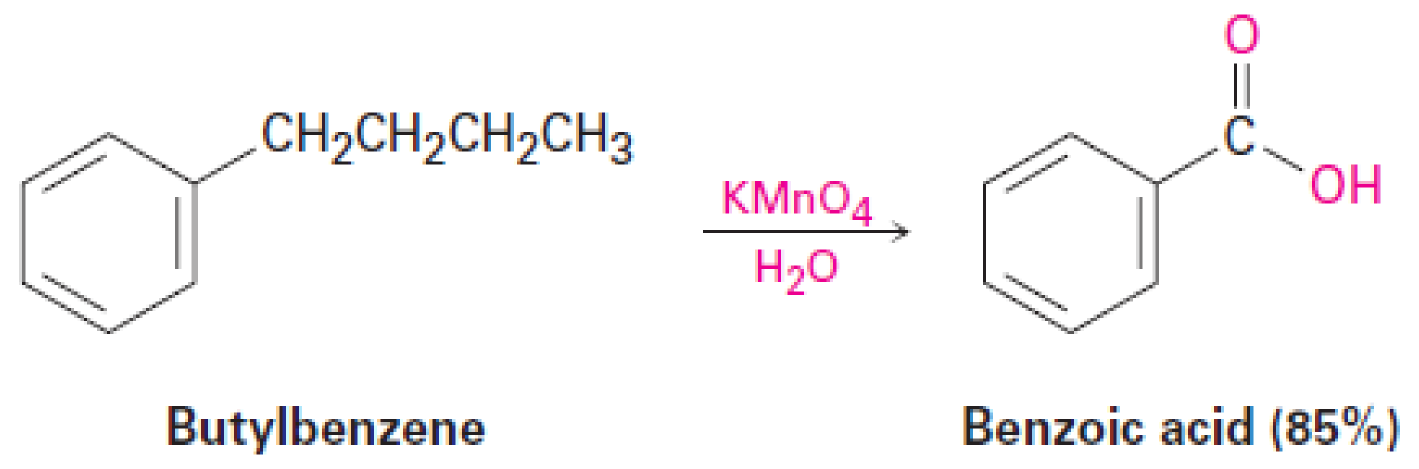




Electrostatic Potential Map

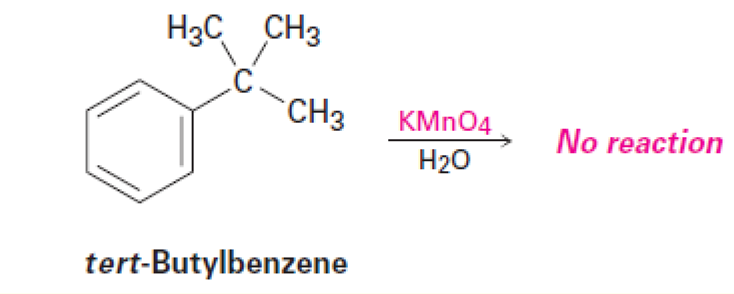
Oxidation of Aromatic compounds

- Alkyl side chains react rapidly with oxidizing agents and are converted into carboxyl groups,] CO_2H.
- The net effect is conversion of an alkylbenzene into a benzoic acid, Ar-R$\longrightarrow$ Ar-COOH.
- Butylbenzene is oxidized by aqueous $KMnO_4$ to give benzoic acid



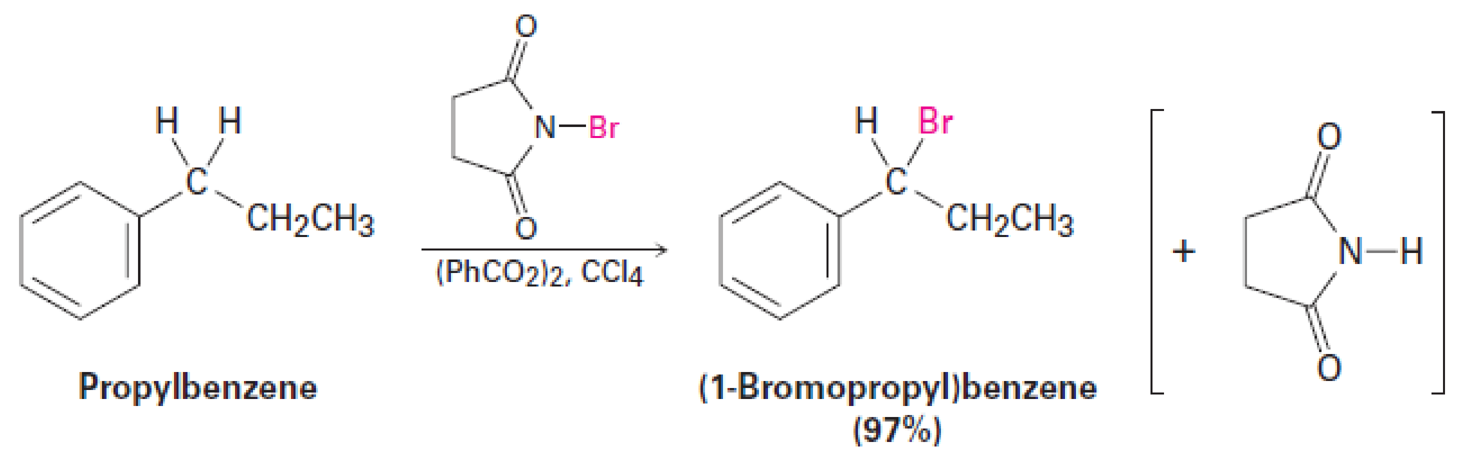
Oxidation of Aromatic compounds

But, *tert*-Butylbenzene has no benzylic hydrogens, so no oxidation takes place.



Bromination of Alkylbenzene side chains

Side-chain bromination at the benzylic position occurs when an alkylbenzene is treated with *N*-bromosuccinimide (NBS). For example, propylbenzene gives (1-bromopropyl) benzene in 97% yield on reaction with NBS in the presence of benzoyl peroxide, $(PhCO_2)_2$, as a radical initiator. Bromination occurs exclusively in the benzylic position next to the aromatic ring and does not give a mixture of products.



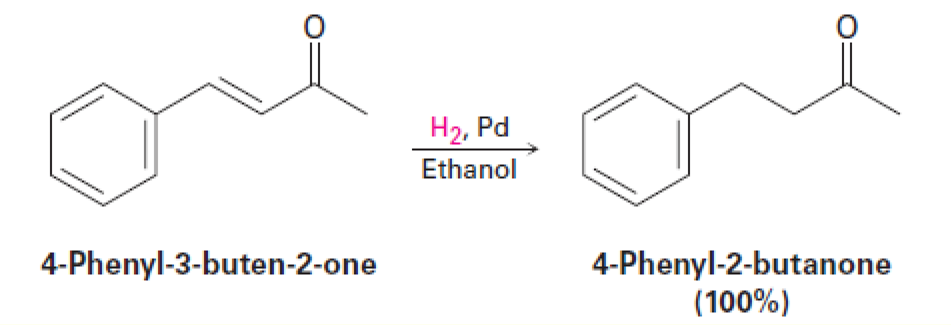
Reduction of Aromatic Compounds

Catalytic Hydrogenation of Aromatic Rings

1. The reduction of an alkene double bond selectively in the presence of an aromatic ring can takes place.

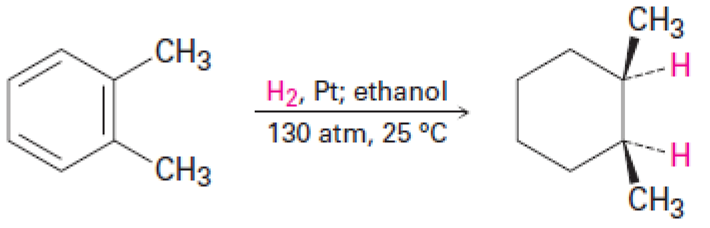
   Example: 4-phenyl-3-buten-2-one is reduced to 4-phenyl-2-butanone using a palladium catalyst at room temperature and atmospheric pressure.

2. Neither the benzene ring nor the ketone carbonyl group is affected.



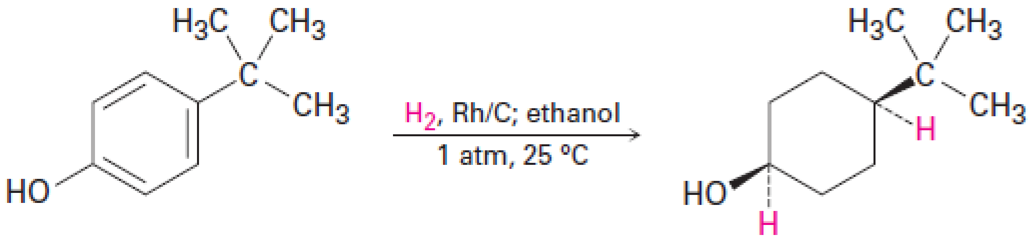
Reduction of Aromatic Compounds

To hydrogenate an aromatic ring, it’s necessary either to use a platinum catalyst with hydrogen gas at several hundred atmospheres pressure or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes.



o-Xylene

cis-1,2-Dimethylcyclohexane

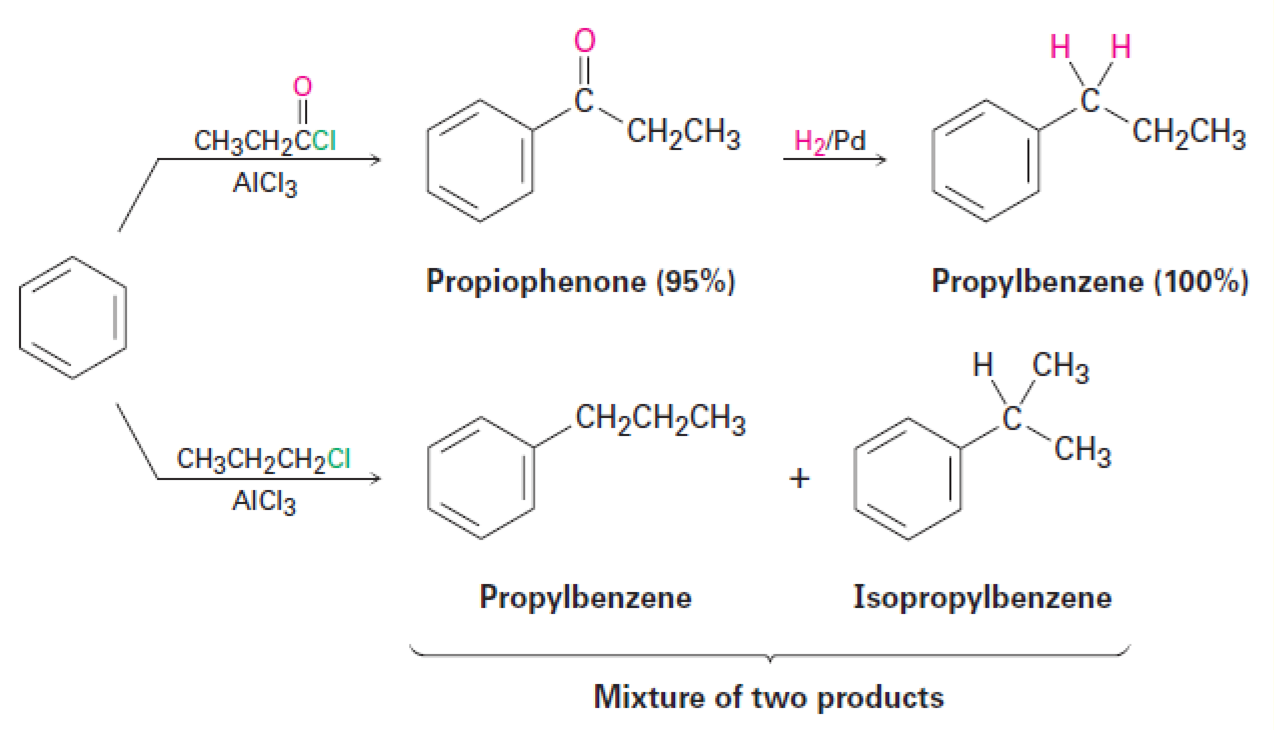


4-*tert*-Butylphenol

cis-4-*tert*-Butylcyclohexane

Reduction of Aralkyl Ketones

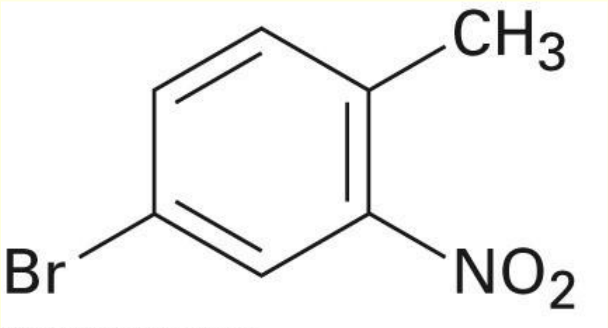
An aryl alkyl ketone prepared by Friedel–Crafts acylation of an aromatic ring can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst.

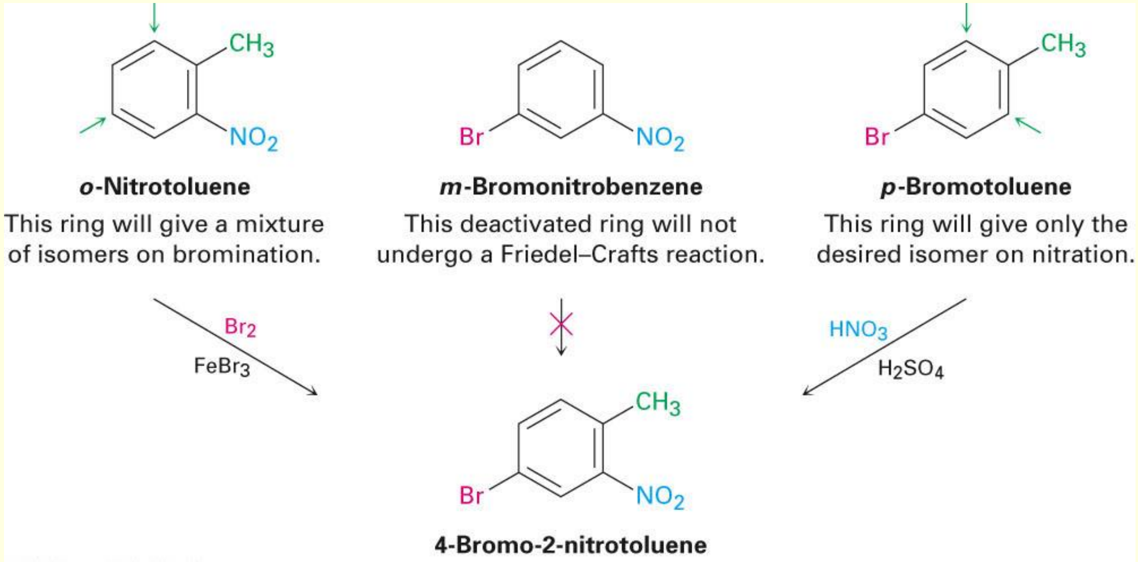


Synthesis of Trisubstituted Benzenes

These syntheses require planning and consideration of alternative routes. Ability to plan a sequence of reactions in right order is valuable to synthesis of substituted aromatic rings.

Target Compound is 4-Bromo-2-nitro-toluene **(Example 1)**





***o*-Nitrotoluene**
This ring will give a mixture of isomers on bromination.

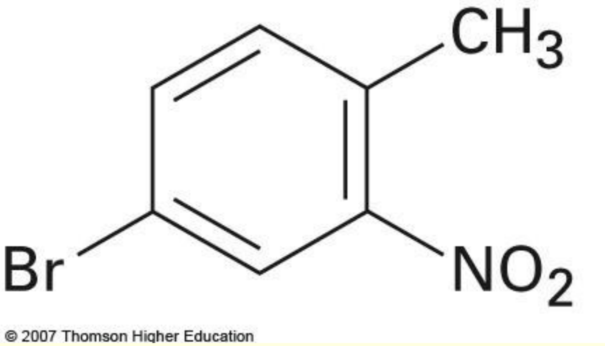
***m*-Bromonitrobenzene**
This deactivated ring will not undergo a Friedel–Crafts reaction.

***p*-Bromotoluene**
This ring will give only the desired isomer on nitration.

4-Bromo-2-nitrotoluene

Synthesis of Trisubstituted Benzenes: Alternate Route

Target Compound is 4-Bromo-2-nitro-toluene **(Example 1**)



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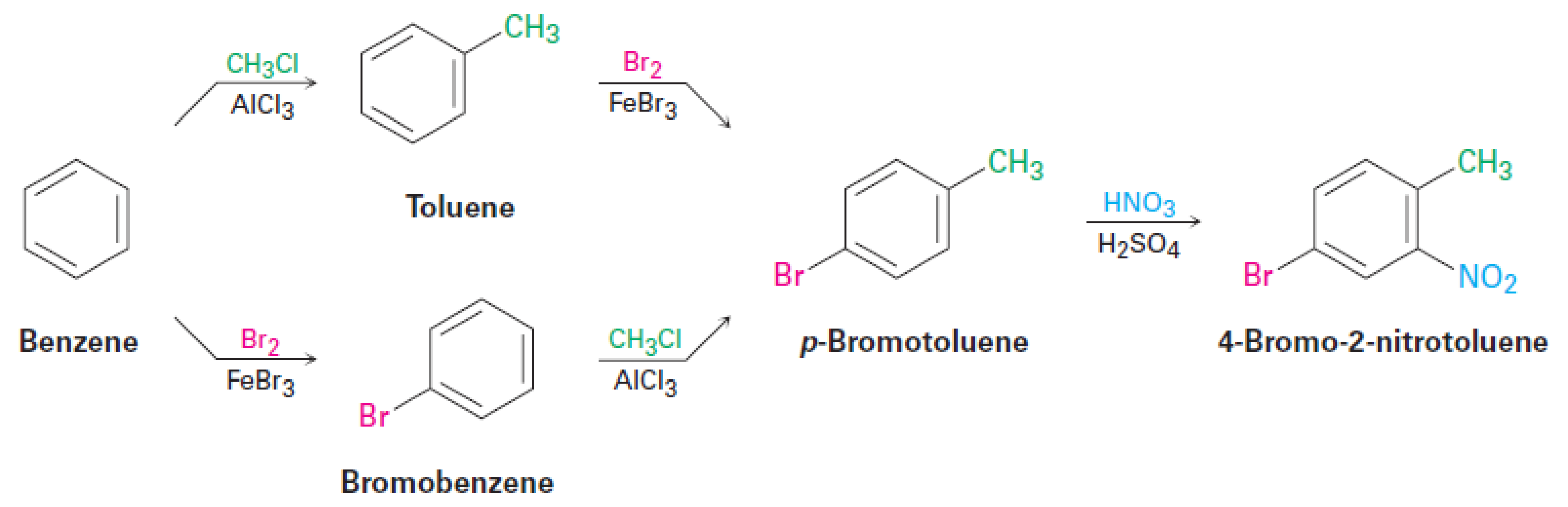
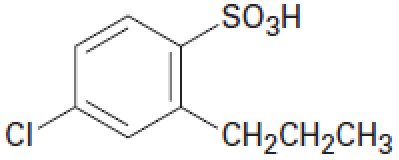
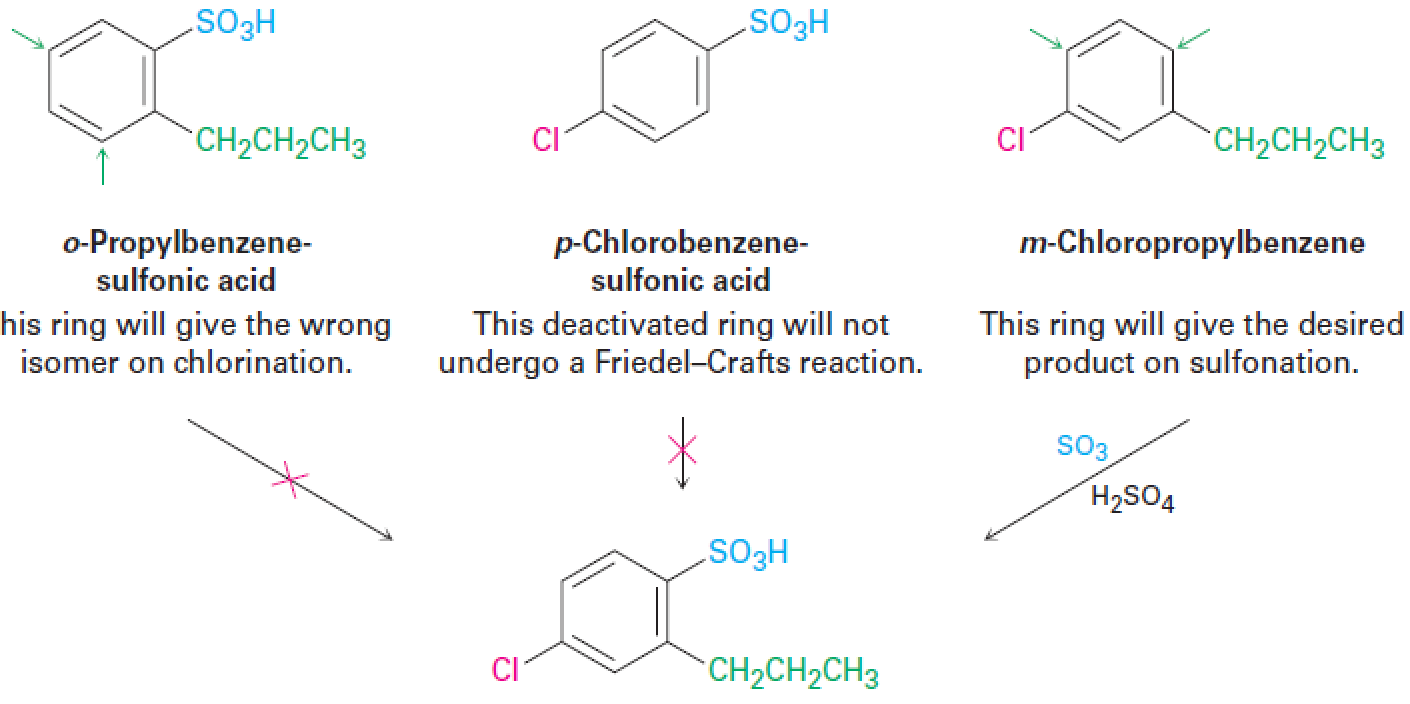


Synthesis of Trisubstituted Benzenes

4-Chloro-2-propylbenzenesulfonic acid (**Example 2**)



4-Chloro-2-propylbenzenesulfonic acid



***o*-Propylbenzenesulfonic acid**

This ring will give the wrong isomer on chlorination.

***p*-Chlorobenzenesulfonic acid**

This deactivated ring will not undergo a Friedel–Crafts reaction.

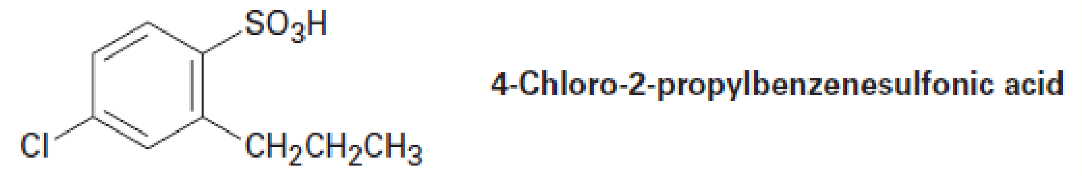
***m*-Chloropropylbenzene**

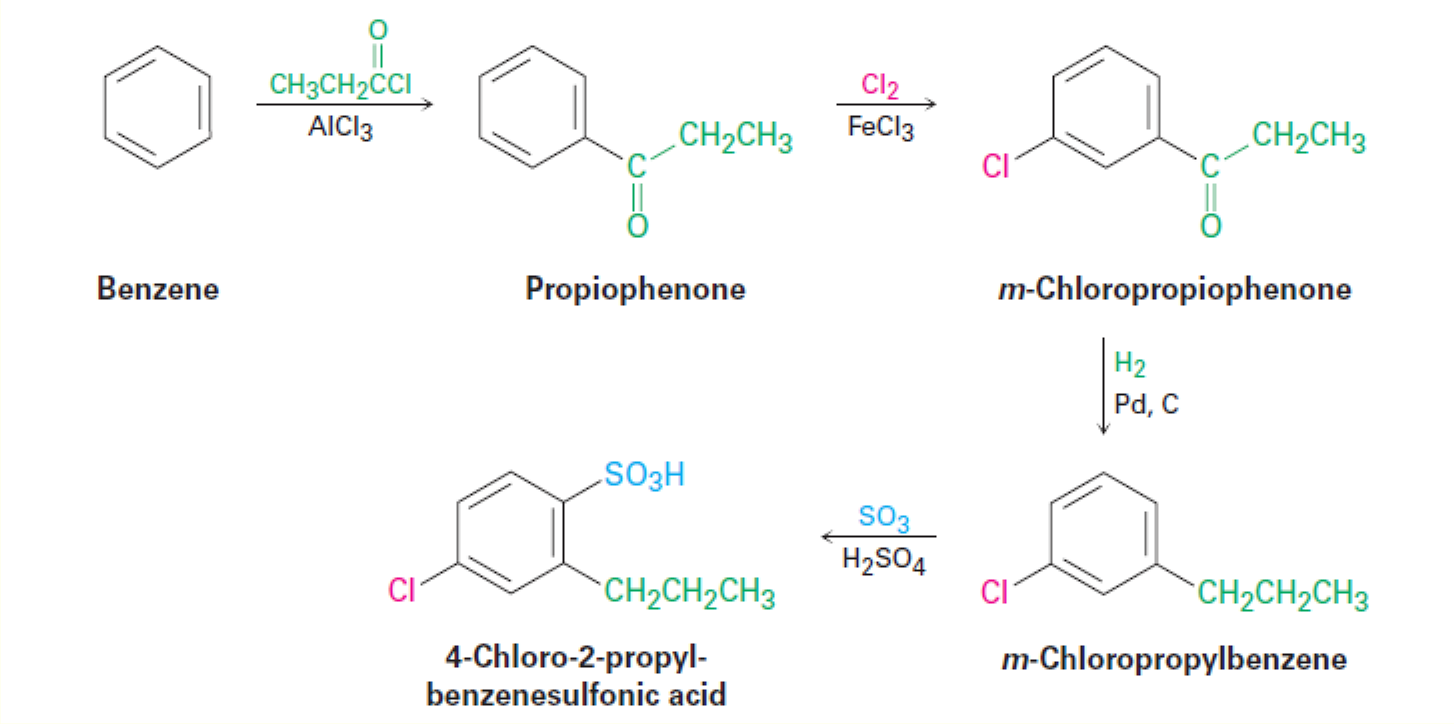
This ring will give the desired product on sulfonation.

4-Chloro-2-propylbenzenesulfonic acid

Synthesis of Trisubstituted Benzenes: Alternate Route

4-Chloro-2-propylbenzenesulfonic acid (**Example 2**)





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