An Introduction to Organic Synthesis: Polysubstituted Benzenes

There are many reasons for carrying out laboratory synthesis of an organic molecule

- In the pharmaceutical industry, new molecules are designed and synthesized in the hope that some might be useful drugs
- In the chemistry industry, syntheses are done to devise more economical routes to known compounds
- In biochemistry laboratories molecules synthesized to probe enzyme mechanisms

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Planning a successful multistep synthesis of a complex molecule requires knowledge of the uses and limitations of numerous organic reactions

The trick to planning an organic synthesis is to *work backward*, often referred to as the *retrosynthetic* direction

- Keep starting material in mind and work backward to it
- Look at the final product and determine possible immediate precursors of that product
- Work backward one step at a time

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An Introduction to Organic Synthesis: Polysubstituted Benzenes

Examples of synthetic planning using polysubstituted aromatic compounds as the targets

- Electrophilic substitution on a disubstituted benzene ring is governed by the same resonance and inductive effects that affect monosubstituted rings
  - Must consider the additive effects of two groups

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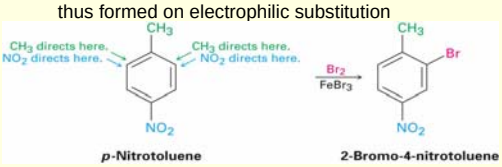
An Introduction to Organic Synthesis: Polysubstituted Benzenes

1. If the directing effects of the two groups reinforces each other, the situation is straightforward
   - In *p*-nitrotoluene both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution



p-Nitrotoluene — 2-Bromo-4-nitrotoluene

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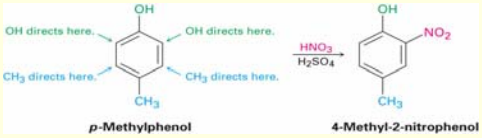
2. If the directing effects of the two main groups oppose each other, the more powerful activating group has the dominant influence
   - Nitration of *p*-methylphenol yields primarily 4-methyl-2-nitrophenol because –OH is a more powerful activator than $–CH_3$



p-Methylphenol — 4-Methyl-2-nitrophenol

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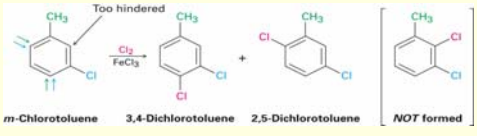
3. Further substitution rarely occurs between the two groups in a meta-disubstituted compound because this site is too hindered
   - Aromatic rings with three adjacent substituents must therefore be prepared by some other route
     - The substitution of an ortho-disubstituted compound



m-Chlorotoluene — 3,4-Dichlorotoluene — 2,5-Dichlorotoluene — *NOT* formed

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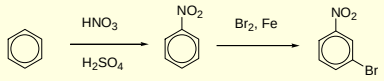
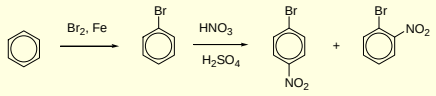
Orientation and synthesis. Order is important!

Synthesis of *m*-bromonitrobenzene from benzene:



Synthesis of *p*-bromonitrobenzene from benzene:



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Synthesizing a Polysubstituted Benzene Example 2

Propose a synthesis of 4-bromo-2-nitrotoluene from benzene.

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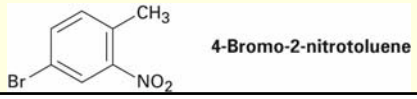
Synthesizing a Polysubstituted Benzene Example 1

Strategy

1. Draw the target molecule
2. Identify the substituents
   - The three substituents on the ring are a bromine, a methyl group, and a nitro group
3. Recall how each group can be introduced separately
   - A bromine can be introduced by bromination with $Br_2/FeBr_3$,
   - a methyl group can be introduced by Friedel-Crafts alkylation with $CH_3Cl/ AlCl_3$, a nitro group can be introduced by nitration with HNO_3/H_2SO_4
4. Then plan retrosynthetically



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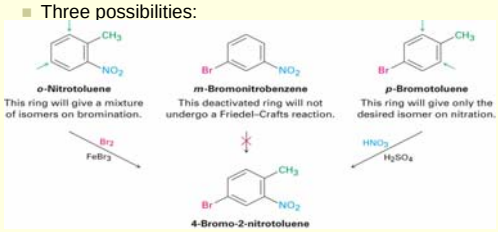
Synthesizing a Polysubstituted Benzene Example 1

Solution

- The final step will involve introduction of one of the three groups – bromine, methyl, or nitro
  - Three possibilities:



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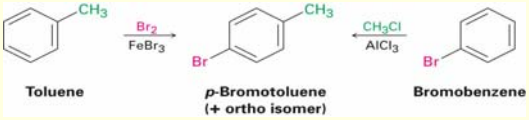
Synthesizing a Polysubstituted Benzene Example 1

- Immediate precursors of *p*-bromotoluene
  - Toluene
    - Because the methyl group would direct bromination to the ortho and para positions
  - Bromobenzene
    - Because Friedel-Crafts methylation would yield a mixture of ortho and para products



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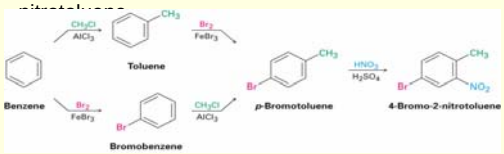
Synthesizing a Polysubstituted Benzene Example 1

- The immediate precursor of toluene
  - Benzene, which could be methylated in a Friedel-Crafts reaction
- The immediate precursor of bromobenzene
  - Benzene, which could be brominated
- Two valid routes possible from benzene to 4-bromo-2-nitrotoluene



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Synthesizing a Polysubstituted Benzene Example 2

Propose a synthesis of 4-chloro-2-propylbenzenesulfonic acid from benzene.

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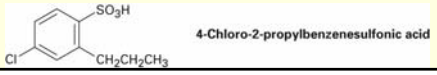
Synthesizing a Polysubstituted Benzene Example 2

Strategy

1. Draw the target molecule
2. Identify the substituents
   - The three substituents on the ring are chlorine, a propyl group, and a sulfonic acid group
3. Recall how each of the three can be introduced
   - A chlorine can be introduced by chlorination using $Cl_2/FeCl_3$, a propyl group can be introduced by Friedel-Crafts acylation with $CH_3CH_2COCl/ AlCl_3$ followed by reduction with H_2/Pd, and a sulfonic acid group can be introduced by sulfonation with SO_3/H_2SO_4
4. Then plan retrosynthetically



4-Chloro-2-propylbenzenesulfonic acid

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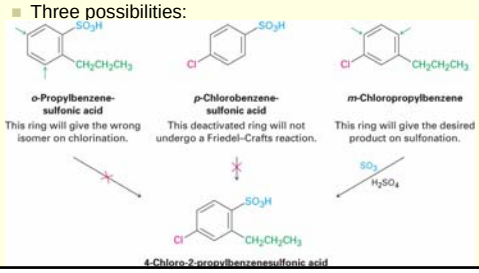
Synthesizing a Polysubstituted Benzene Example 2

Solution

- The final step will involve introduction of one of the three groups – chlorine, propyl, or sulfonic acid
  - Three possibilities:



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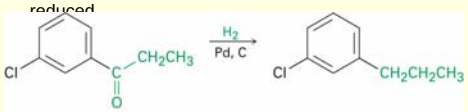
Synthesizing a Polysubstituted Benzene Example 2

- The immediate precursors to *m*-chloropropylbenzene
  - Because the two substituents have a meta relationship, the first substituent placed on the ring must be a meta director so that the second substitution will take place at the proper position
  - Because primary alkyl groups such as propyl cannot be introduced directly by Friedel-Crafts alkylation, the precursor of *m*-chloropropylbenzene is probably *m*-chloropropiophenone, which could be catalytically reduced



m-Chloropropiophenone *m*-Chloropropylbenzene

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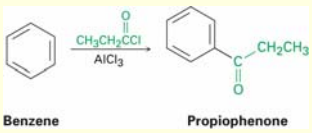
Synthesizing a Polysubstituted Benzene Example 2

- The immediate precursor of *m*-chloropropiophenone
  - Propiophenone, which could be chlorinated in the meta position

Propiophenone *m*-Chloropropiophenone

- The immediate precursor of propiophenone
  - Benzene which could undergo Friedel-Crafts acylation with propanoyl chloride and $AlCl_3$



Benzene Propiophenone

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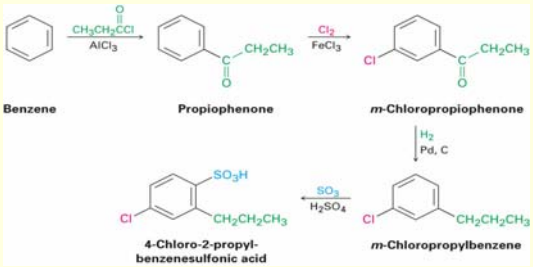
Synthesizing a Polysubstituted Benzene Example 2

- The final synthesis is a four-step route from benzene:



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