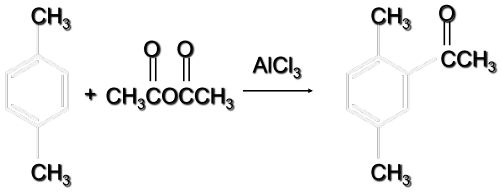
Electrophilic Aromatic Substitution

Multiple Substituent Effects:

Activation-Deactivation / Direction (Regio-selectivity)

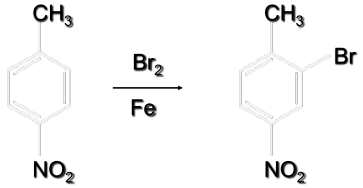
The Simplest Case

Activation & all possible sites are equivalent



99%

Another Straightforward Case



86-90%

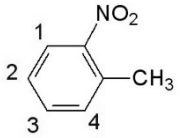
directing effects of substituents reinforce each other; substitution takes place ortho to the methyl group and meta to the nitro group

Generalization

regioselectivity is controlled by the most activating substituent

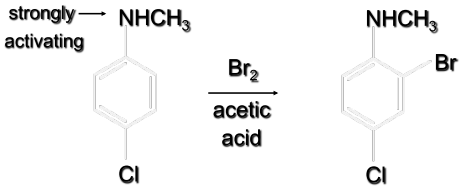
Question

- Which positions are activated for chlorination on the compound shown below?



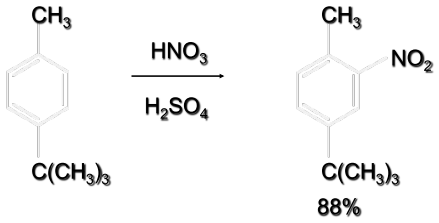
- A) 2 and 3
- B) 1 and 3
- C) 2 and 4
- D) 1 and 4

Example



87%

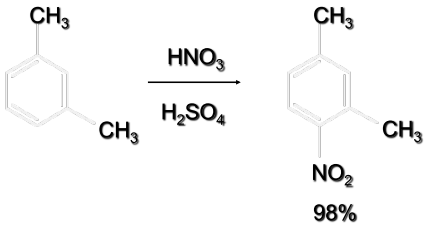
When activating effects are similar...



88%

substitution occurs ortho to the smaller group

Steric effects control regioselectivity when electronic effects are similar

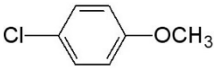


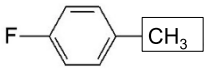
98%

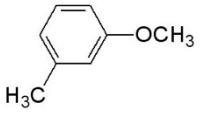
position between two substituents is last position to be substituted

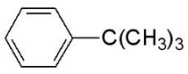
Question

- Which compound undergoes electrophilic aromatic substitution with $(CH_3)_3CCl$ and $AlCl_3$ at the slowest rate (or not at all)?

- A) 

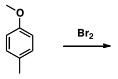
B) 

- C) 

D) 

Question

What is the major product of the following reaction?



A. 

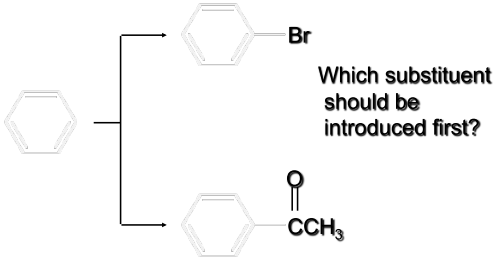
B. 

C. 

D. 

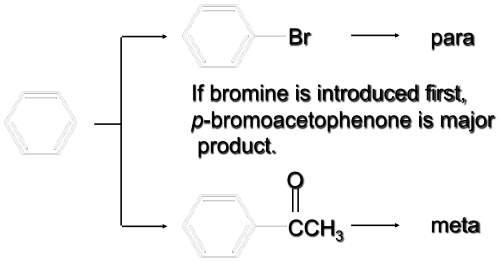
Regioselective Synthesis of Disubstituted Aromatic Compounds

Synthesis of m-Bromoacetophenone

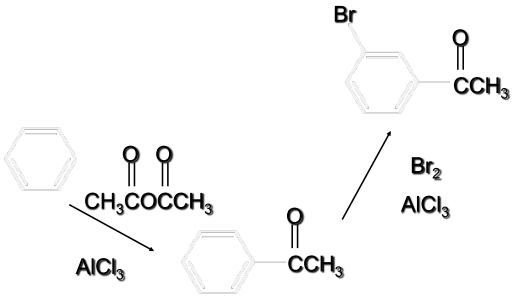


Which substituent should be introduced first?

Synthesis of m-Bromoacetophenone



Synthesis of m-Bromoacetophenone

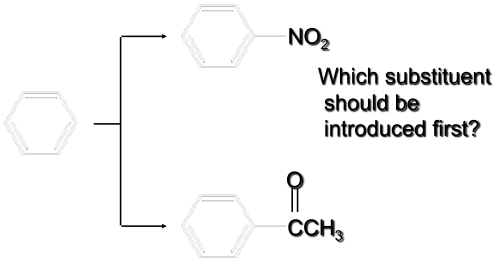


Factors to Consider

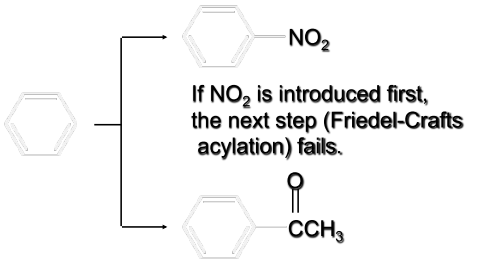
order of introduction of substituents to ensure correct orientation

Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

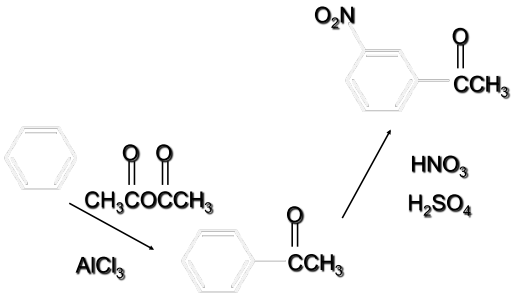
Synthesis of m-Nitroacetophenone



Synthesis of m-Nitroacetophenone



Synthesis of m-Nitroacetophenone



Factors to Consider

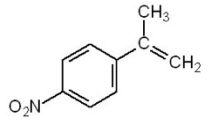
order of introduction of substituents to ensure correct orientation

Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

sometimes electrophilic aromatic substitution must be combined with a functional group transformation

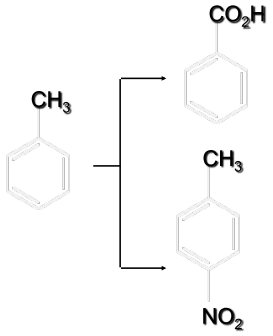
Question

- Which of the following is the most reasonable way to begin an effective synthesis of the compound shown?



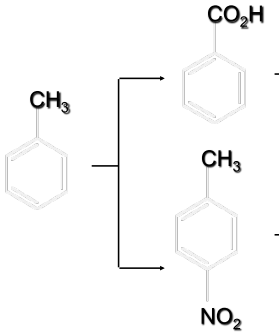
- A) Treat benzene with isopropyl chloride and $AlCl_3$.
- B) Treat chlorobenzene with propene and $AlCl_3$.
- C) Treat benzene with 2-chloropropene and $AlCl_3$.
- D) Treat benzene with 3-chloropropene and $AlCl_3$.

Synthesis of p-Nitrobenzoic Acid from Toluene



Which first? (oxidation of methyl group or nitration of ring)

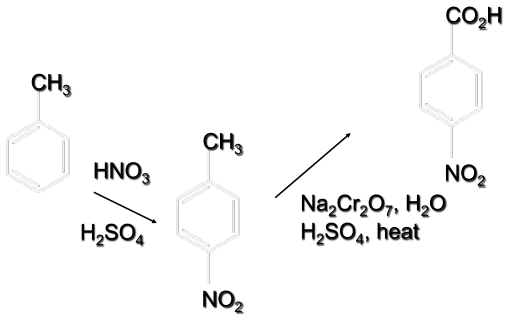
Synthesis of p-Nitrobenzoic Acid from Toluene



nitration gives *m*-nitrobenzoic acid

oxidation gives *p*-nitrobenzoic acid

Synthesis of p-Nitrobenzoic Acid from Toluene



Question

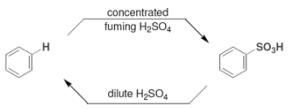
A. HNO_3/H_2SO_4
B. $Br_2/AlBr_3$
C. $CH_3Cl/AlCl_3$
D. Fuming H_2SO_4
E. $Cl_2/AlCl_3$
F. $CH_3COCl/AlCl_3$
G. Zn [Hg], HCl, heat
H. 1) $KMnO_4$, NaOH, heat 2) H_3O^+
I. NBS/heat
J. $CH_3CH_2Cl/AlCl_3$
K. $CH_3CH_2COCl/AlCl_3$
L. Dilute H_2SO_4

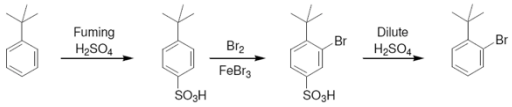
What is the correct order of reagents on the left to complete the synthesis of the following bromide?

A. B
B. D, B
C. D, B, L
D. L, B
E. L, B, D

Synthetic Applications

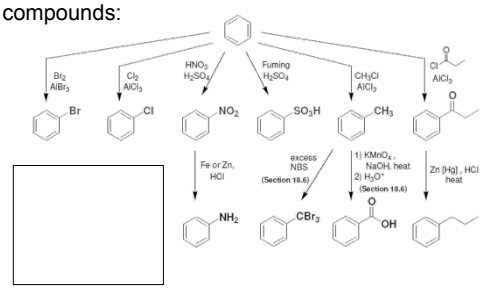
- EAS SULFONYLATION is reversible, Therefore, it can be used as a temporary blocking group.





Synthetic Strategies

- Reagents for monosubstituted aromatic compounds:



Synthetic Strategies

GROUP CONVERSIONS THAT CHANGE DIRECTING EFFECTS