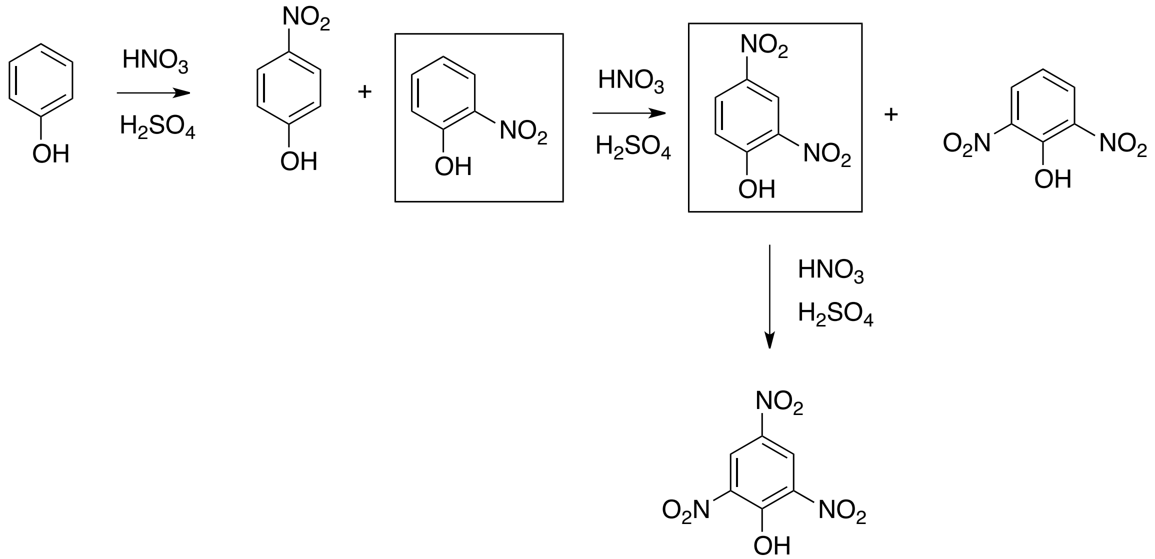
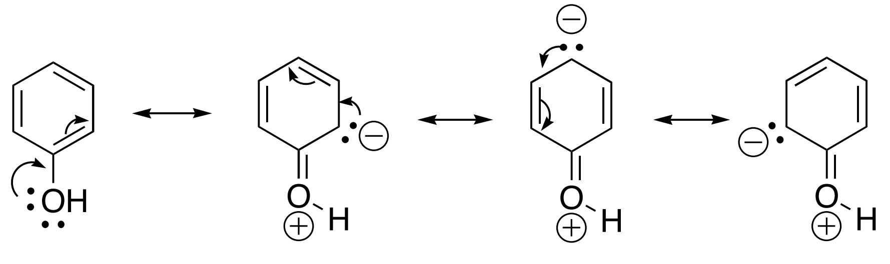
How to determine position and reactivity: Examples

The strongest donating group wins:

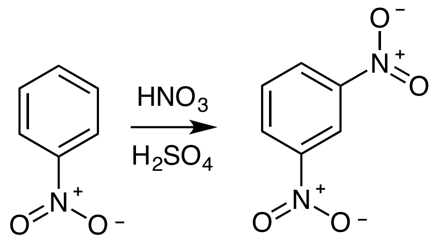


2,4,6-trinitrophenol
picric acid

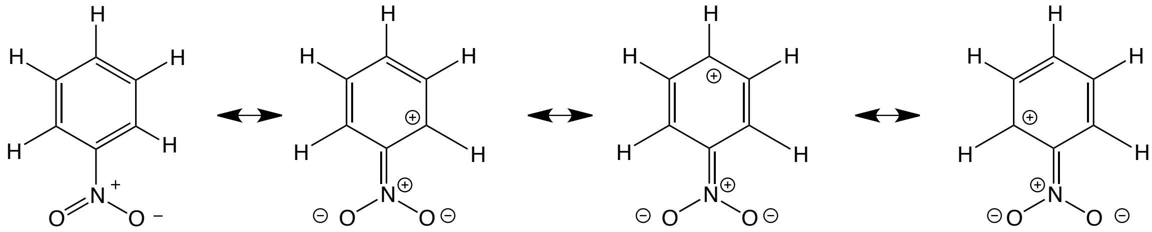
This reactivity can be explained by the following resonance forms:



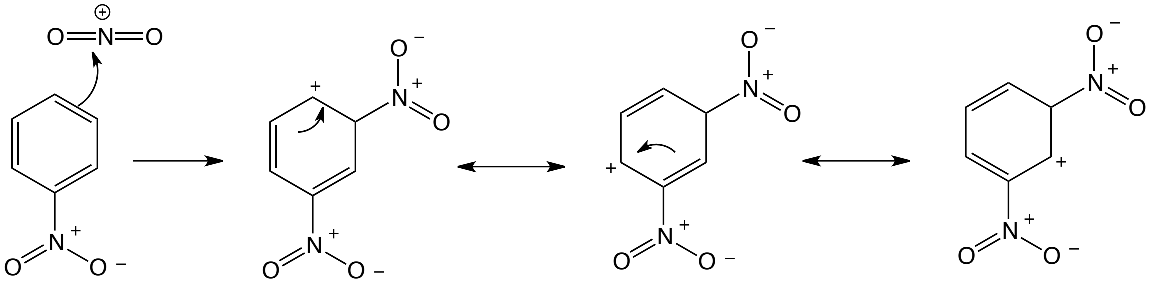
Meta-director example:



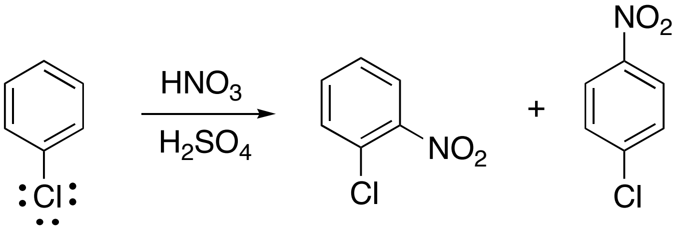
This reactivity can be explained by the following resonance forms:



The electrophile is positive and reacts at sites that are not positive (ortho para) but at those that are more negative (meta) as shown below



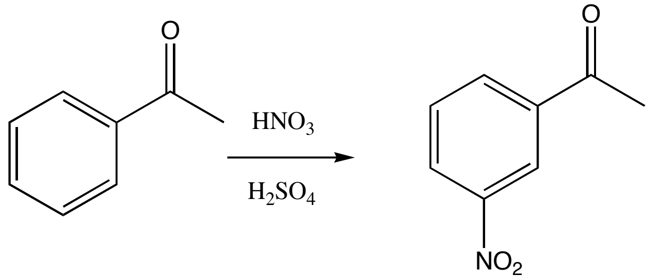
A Different Example :

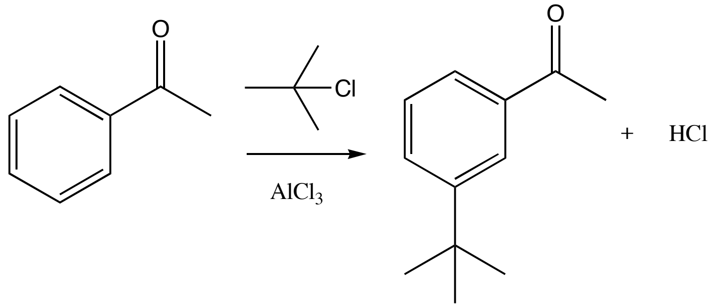


In this reaction, chlorobenzene has a chloro (-Cl) group attached on the benzene ring. When we perform nitration, only *ortho* and *para* substitution occurs. The chloro group is an electron withdrawing group **inductively**, however, the lone pairs of electrons are conjugated to the benzene ring through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

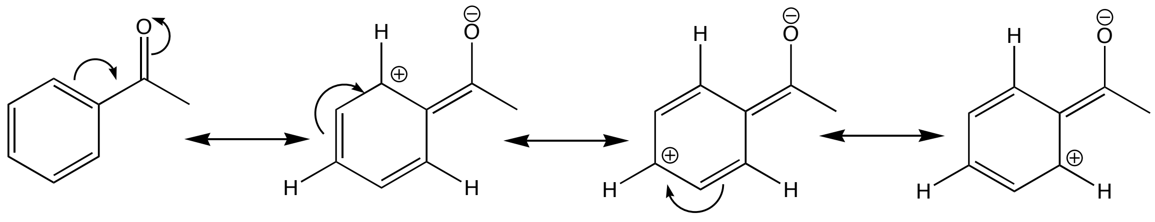
Example:

Acetophenone is meta directing

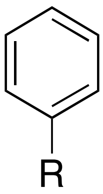




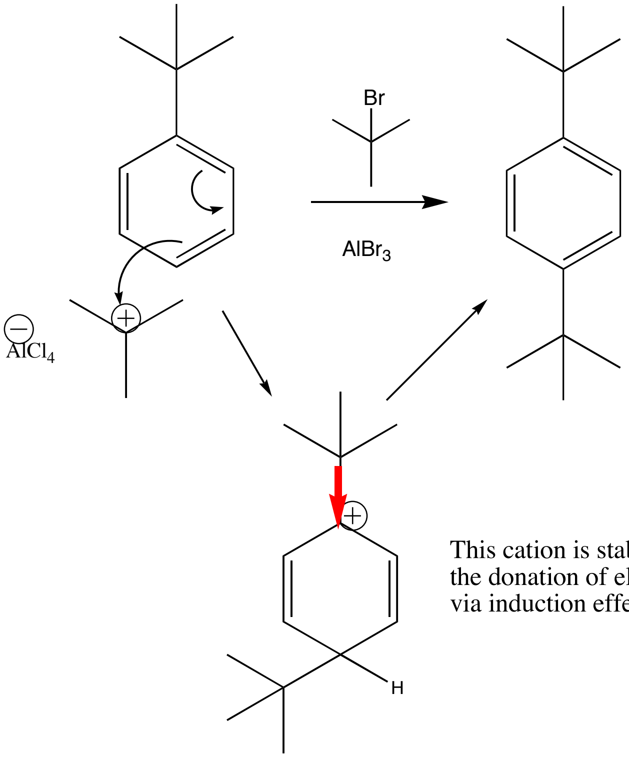
When the electrophile attacks, it avoids the partial positive charges on the *ortho* and *para* positions:



Aromatic compounds with an alkyl chain are considered inductively donating (weak) and will direct substitution to the *ortho* or *para* positions.



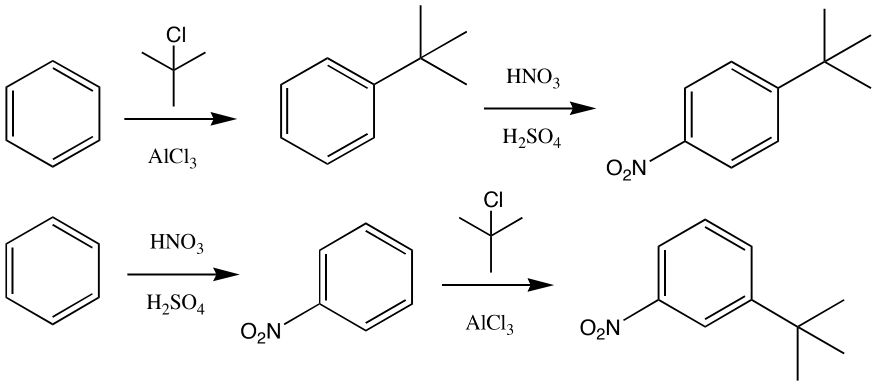
Example:



This cation is stabilized by resonance as well as the donation of electrons from the *t*-Bu group via induction effects (shown by the red arrow)

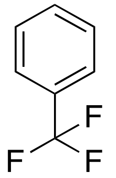
The reaction occurs at the *para* position instead of the *ortho* position due to sterics.

Notice how the order that reactions are done affect the following two examples:

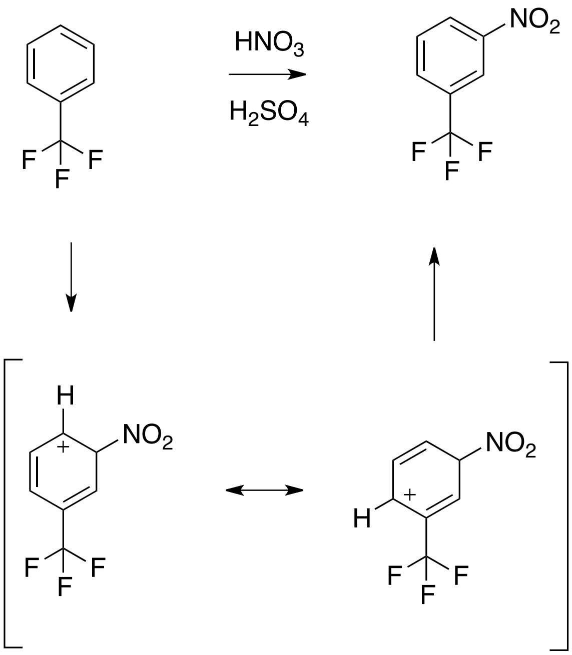


The products of the above two reactions are structural (or constitutional) isomers.

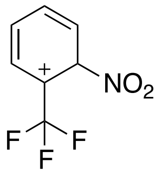
Aromatic compounds that have an electron-withdrawing group attached but that do not fall into the above categories (e.g. CF_3) are inductively withdrawing and direct substitution to the *meta* position.



Example:



If *ortho*:



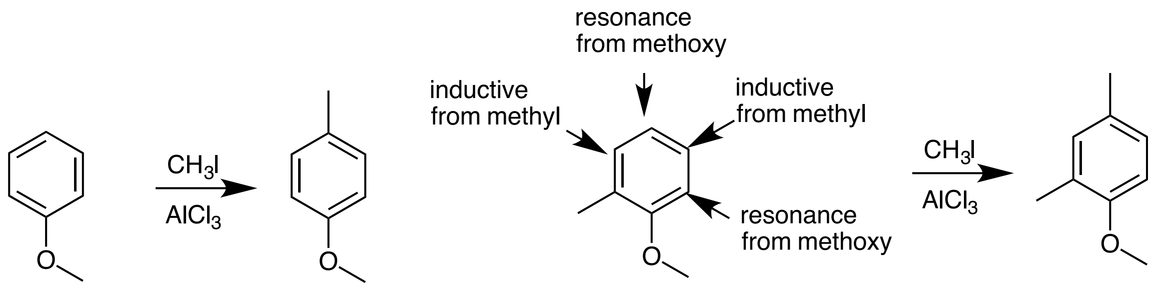
disfavored (not observed)

$-CF_3$ is electron-withdrawing and does not want to withdraw electrons from a carbon that is already positively-charged.

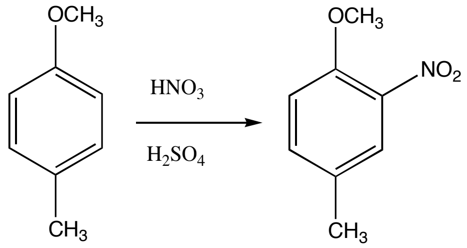
Multiple Substitution

If there is more than one group on an aromatic ring, electrophilic aromatic substitution is controlled by the **strongest donating group**.

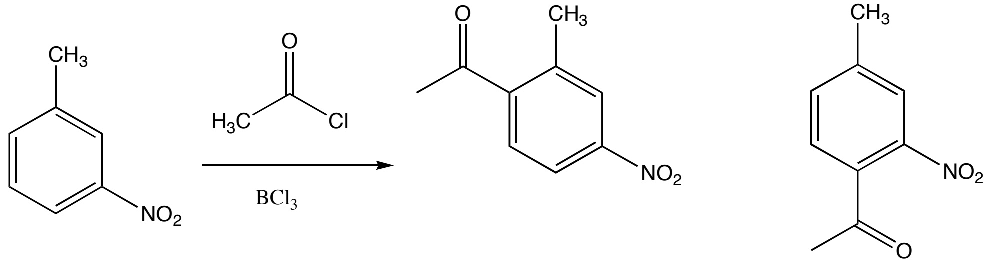
An example is the dialkylation of methoxybenzene with methyl iodide by Friedel-Crafts alkylation. Since the methoxy group is an electron-donating group (resonance donator), it will direct the first alkylation to the *ortho* and *para* positions. The second alkylation is also directed to the *ortho* and para positions relative to the methoxy group because it is a stronger director (resonance donator) than the methyl group (inductive donator). The second alkylation will go *ortho* to the methoxy rather than *ortho* to the methyl.



Similarly, nitration occurs at the *ortho* position for the following example:



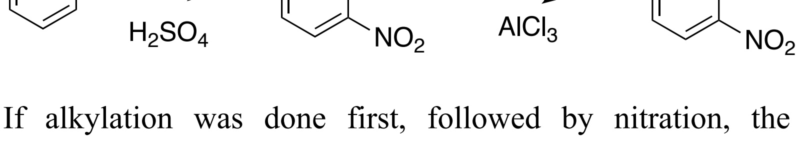
In the following case the nitro group is an electron-withdrawing group, so the methyl group is the strongest donating group and takes precedence in directing where the acetyl group will go.



In this last example, the position between the two *meta* substituents is too sterically hindered. Therefore, substitution in that position is not observed.

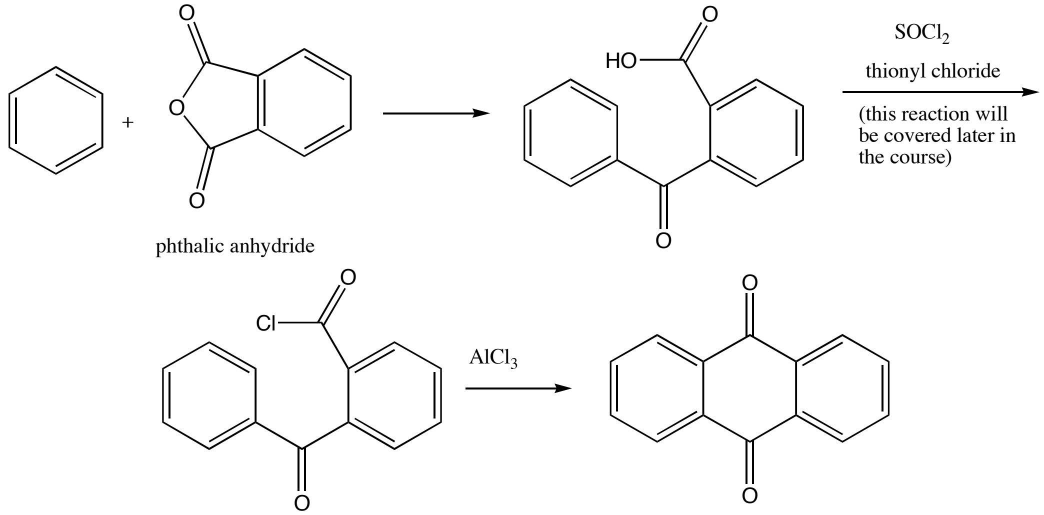
Follow-up: How do you synthesize the starting material in the previous reaction?

Answer:



If alkylation was done first, followed by nitration, the *meta*-substituted aromatic compound could not be obtained, since the methyl group is an *ortho/para*-directing group.

How to determine position and reactivity: 6 & 5 membered rings are favoured

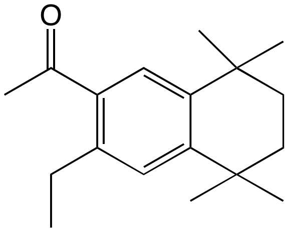


anthraquinone

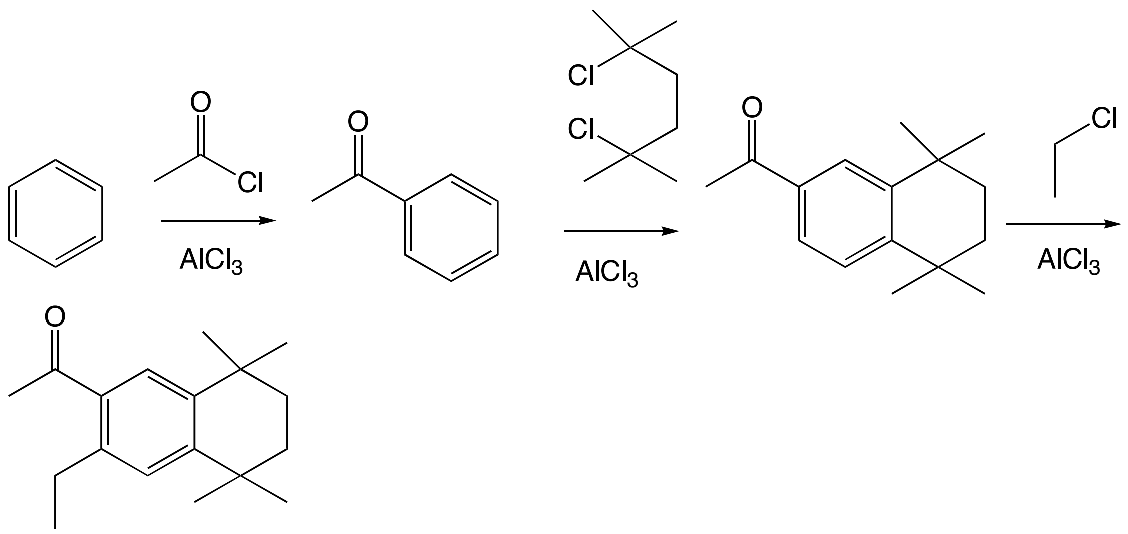
After the first two reactions, the substituent (a ketone) would normally direct the second acylation to the *meta* position as a resonance withdrawer. This does not occur, as this would produce a very strained structure. In this example, the second acylation goes to the *ortho* position to relieve the strain to produce anthraquinone. 6-rings are favoured, as are intramolecular reactions.

Synthesis Example: The sequence of steps is critical

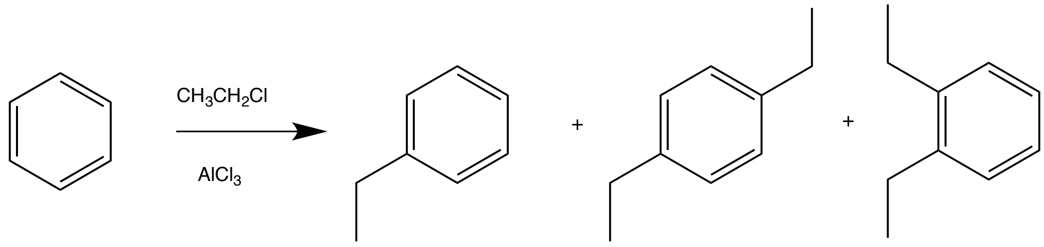
How to make versalide, shown below, from benzene?



The answer is below. Be able to rationalize this sequence.



If you start to add ethyl group first, polyalkylation happens:



Alkylation must also be last because the acetyl group will direct to the meta position.

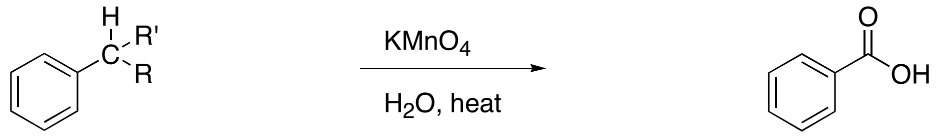
Reaction of Side Chains of Aromatic Compounds:

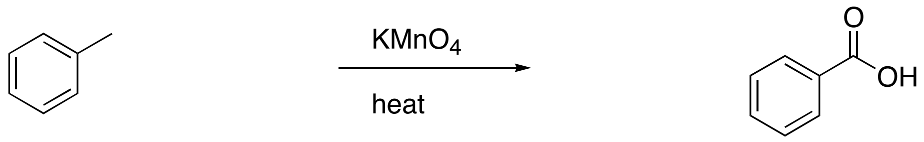
1) Alkyl Side Chain Oxidation
2) Clemmensen Reduction
3) Nitro Reduction
4) Amino Diazotization
5) Diazo Replacement + Coupling

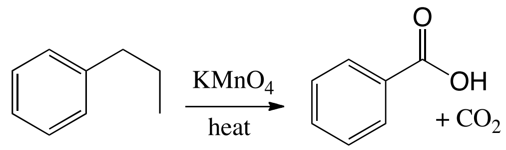
Alkyl Side Chain Oxidation Reaction

If the carbon directly attached to the aromatic ring has ≥ 1 hydrogen attached to it, it can be oxidized to the corresponding carboxylic acid using hot aqueous potassium permanganate ($KMnO_4$) as shown below.

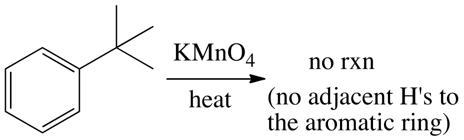
Carbon dioxide (CO_2) is one of the side products

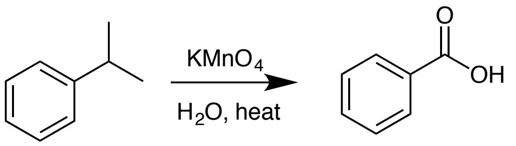




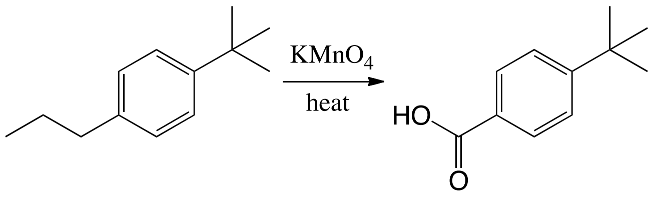


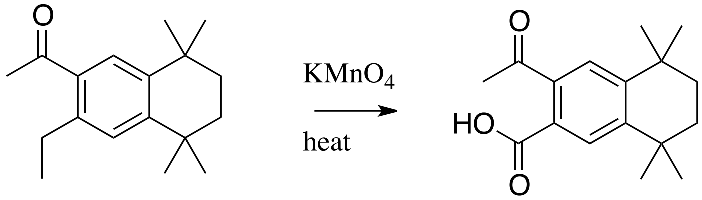
propyl benzene



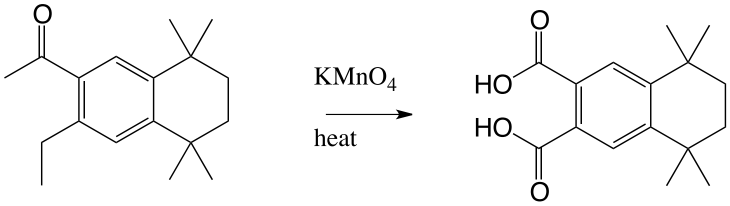


More examples of alkyl side chain oxidation:

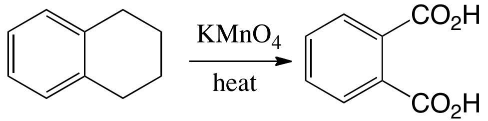




The above answer is accepted as it fits the rule given, but in reality, the methyl group of the ketone is also oxidized to a carboxylic acid (special case)



Another example



tetralin

(phthalic acid)