Fonction et réaction organiques II

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1. Aromatic Chemistry

1.1. Aromaticity
  - 1.1.1. Hückel theory
  - 1.1.2. Frost-Musulin cycle
  - 1.1.3. Polycyclic aromatic compounds

1.2. Electrophilic Aromatic Substitution S_EAr
  - 1.2.1. General principles
  - 1.2.2. Important S_EAr reactions
    - 1.2.2.1. Nitration
    - 1.2.2.2. Halogenation: bromination / chlorination
    - 1.2.2.3. Friedel-Crafts reaction
    - 1.2.2.4. Sulfonation
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    - 1.2.2.6. Deuteration by ipso-substitution
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    - 1.2.2.9. Hydroxy methylation
    - 1.2.2.10. Chloro methylation
    - 1.2.2.11. Diazo-coupling
  - 1.2.3. Secondary substitution on the benzene ring
  - 1.2.4. Introducing a 3rd substituent

1. Aromatic Chemistry

1.3. Quantitative substitution Effects

1.4. Reactions proceeding by arenium cations

1.5. Reversibility in S_EAr reactions
    1.5.1. Reactivity of condensed aromatic substrates

1.6. Nucleophilic Aromatic Substitution S_NAr

1.7. Reactions of diazonium salts

1.8. Substitution by the aryne mechanism

1.9. Reduction of the aromatic ring

1.10. Construction of the aromatic ring: metal-catalyzed [2+2+2]-cyclization

2. Heterocycles

2.1. Nomenclature
  - 2.1.1. Trivial names
  - 2.1.2. The Hantsch-Widman system

2.2. Aromaticity and reactivity of heteroaromatics
  - 2.2.1. Comparison between pyrrole and pyridine
  - 2.2.2. Reactivity of electron rich heteroaromatics
  - 2.2.3. Reactivity of electron poor heteroaromatics
  - 2.2.4. The Tschitschibabin reaction

2.3. Syntheses of five-membered ring heteroaromatics
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  - 2.3.2. Thiophene syntheses
  - 2.3.3. Pyrrole syntheses
  - 2.3.4. Indole syntheses
  - 2.3.5. Oxazole syntheses
  - 2.3.6. Pyrazole and isoxazole syntheses
  - 2.3.7. Thiazole syntheses
  - 2.3.8. Imidazole syntheses

2.4. Syntheses of six- membered ring heteroaromatics
  - 2.4.1. Pyridine synthesis
  - 2.4.2. Quinoline synthesis
  - 2.4.3. Isoquinoline synthesis

3. Diels-Alder Cycloaddition

3.1. Diels-Alder Cycloadditions
    3.1.1. General reaction principle
    3.1.2. The nature of the diene
    3.1.3. The nature of the dienophile

3.2. Mechanism and stereochemical implications
    3.2.1. Diene and dienophile conformation
    3.2.2. Exo/Endo selectivity

3.3. Regioselectivity in the Diels-Alder cycloaddition

3.4. Additional examples of Diels-Alder cycloadditions
    3.4.1. Extented polycyclic aromatics as diene component
    3.4.2. Benzyne as dienophile
    3.4.3. Intramolecular Diels-Alder reactions (IMDA)
    3.4.4. Retro-Diels-Alder reaction

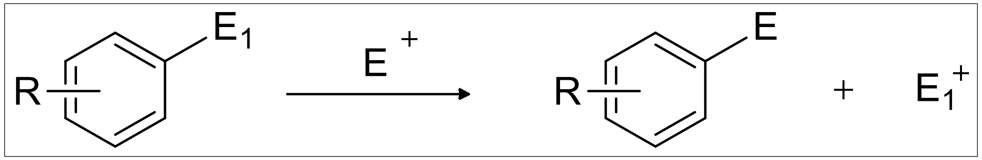
4. 1,3-dipolar cycloaddition and concerted molecular rearrangements

4.1. 1,3-dipolar cycloadditions
    4.1.1. Ozonolysis
    4.1.2. Huisgen azide-alkyne cycloaddition, Click chemistry
    4.1.3. Nitrile-oxide cycloaddition

4.2. Pericyclic reactions; concerted molecular rearrangements
    4.2.1. Cope rearrangement
    4.2.2. Claisen rearrangement
    4.2.3. Ene reactions

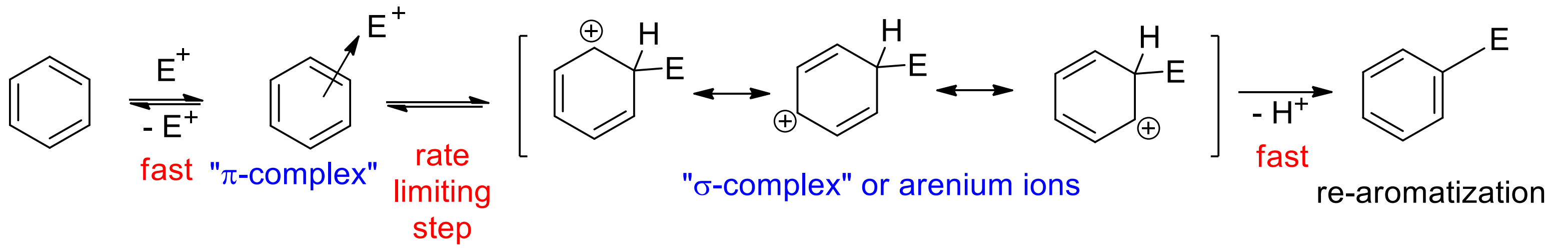
1.2. Electrophilic aromatic substitution S_EAr

- General reaction:

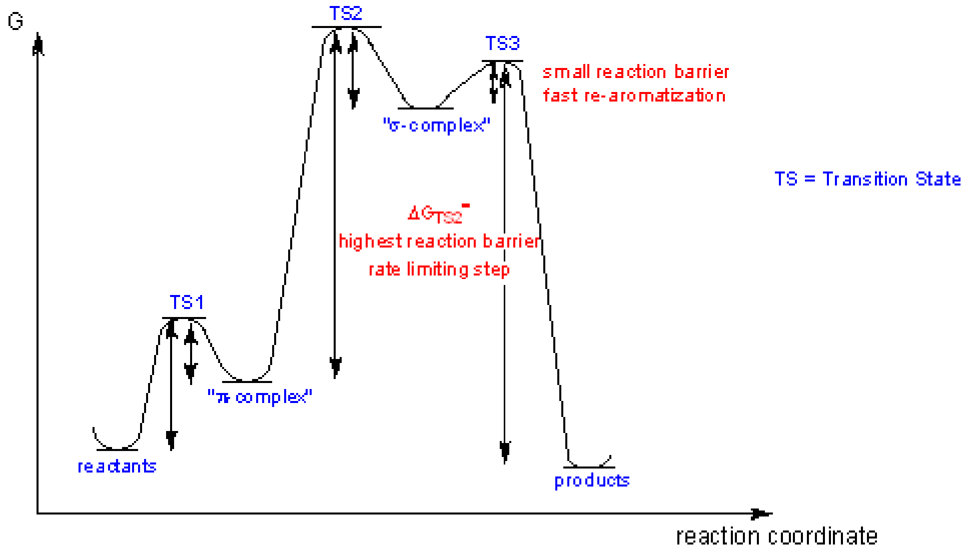


- E_1 = H
- Rare cases where E_1 = SiR_3, tBu, SO_3H is then called ipso-substitution

- Formally, the reaction is the substitution of H^+ by an electrophile E^+
- Mechanistically, it is an addition / elimination process



1.2.1. General principles



- <u>Polanyi-Hammond postulate</u>:

  When two neighboring species on the reaction coordinate are related in their energy, they are as well in their structure.

  TS2 much closer to the σ–complex than to the π-complex

- Applications:

→ Lowering the activation barrier makes a reaction faster

→ For S_EAr: TS2 looks rather similar to the σ-complex

→ Everything stabilizing the σ-complex accelerates the reaction rate

→ Everything destabilizing the σ-complex decrease the reaction rate

1.2.1. General principles

- How can one speed up the reaction? How are the substituents chosen?

Substituents are generally divided in two groups:

  - EDG (Electron Donating Group) e.g. –OMe, having +M / +I effect
  - EWG (Electron Withdrawing Group) e.g. –COOMe, having -M / -I effect

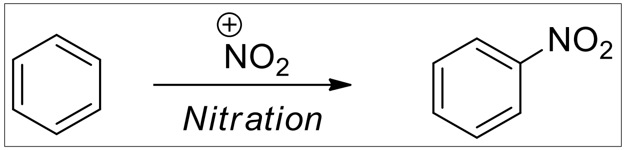
EDG stabilizes the σ-complex making the reaction faster
EWG destabilizes the σ-complex making the reaction slower
(how much faster/slower is depending on the substituent properties)

- Examples of EDG / EWG:

EDG with +M effect: $-NR_2$, $-NH_2$, -OH, -OR
EDG with +I effect: -Alkyl, $-SiR_3$
EWG with –M effect: $-NO_2$, -COOR, -COR, -CHO, -CN, $-SO_3H$, $-SO_2R$
EWG with –I effect: $-NH_3^+$, $-NR_3^+$, $-CF_3$

1.2.2.1. Nitration

- Electrophile = NO_2^+, nitronium ion $O=\overset{+}{N}=O$



- Practical methods to generate the electrophile:
  - Mild: autoprotolysis of nitric acid, in concentrated HNO_3 (68%) the amount of NO_2^+ is 3-4%

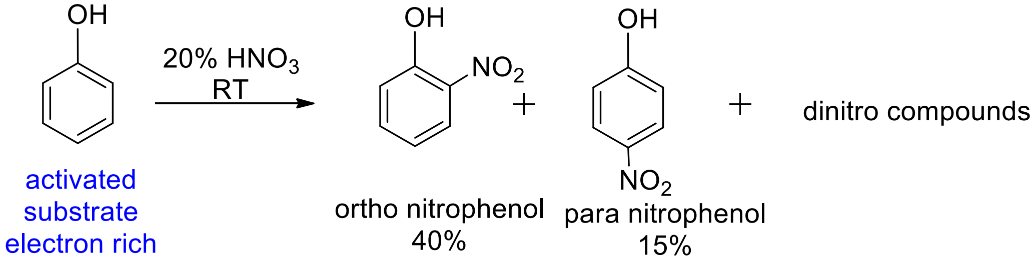
$$2HNO_3 \rightleftharpoons \overset{+}{N}O_2 + H_2O + NO_3^-$$

  - More forcing conditions: mixture of concentrated HNO_3 + concentrated H_2SO_4 (nitrosulfuric acid)

$$HNO_3 + 2H_2SO_4 \rightleftharpoons \overset{+}{N}O_2 + H_3\overset{+}{O} + 2HSO_4^-$$

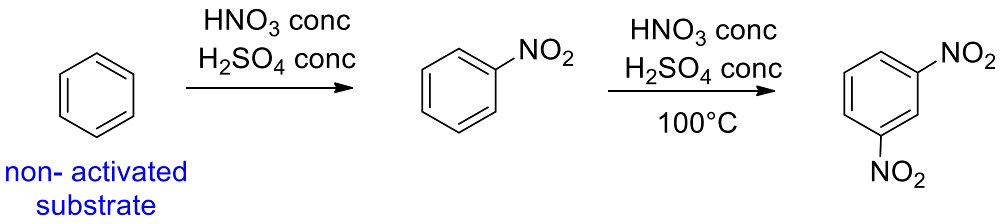
  - Strongest conditions: nitroniumtetrafluoroborat salt $NO_2^+\,BF_4^-$

- Examples for activated substrates: mild conditions are used

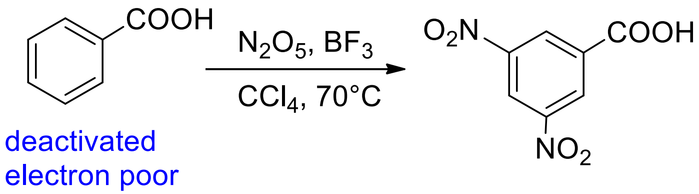


1.2.2.1. Nitration

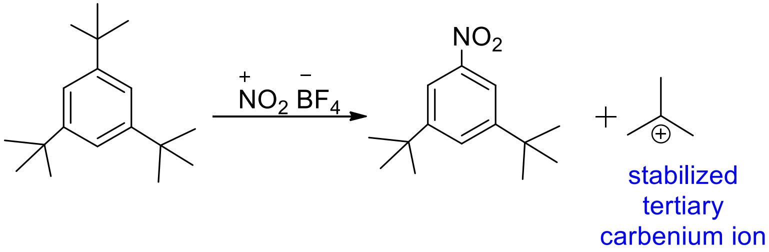
- Examples for non-activated substrates: more forcing conditions are required



- Examples for deactivated substrates:



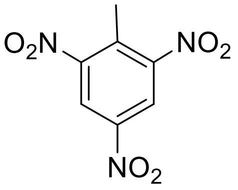
- Example for an ipso-substitution :



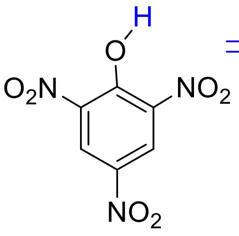
1.2.2.1. Nitration

- Nitro groups are important synthetic intermediates

Application for dyes, explosives (TNT, picric acid) and basic industrial processes



TNT

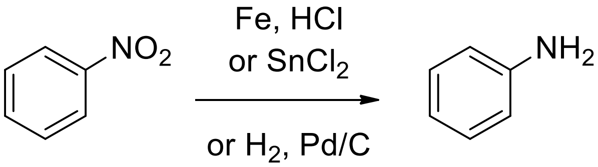


Picric Acid

very acidic due to 3EWG -NO_2 groups

⟹ cristalline salts are formed very easily but these can be explosives !

Most important follow-up reaction: reduction of the nitro group to an aniline with a variety of reducing reagents

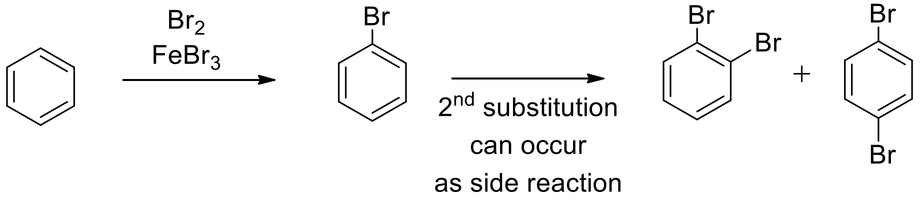


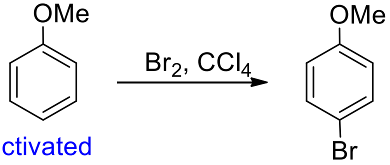
1.2.2.2. Halogenation: bromination / chlorination

- Electrophile = Br^+ / Cl^+
  - Fluorination: not controlable
  - Iodination: requires promoters

- Practical methods to generate the electrophile:
  - Bromination: $Br{-}Br \;+\; \underset{\text{catalytic}}{FeBr_3 \text{ or } AlBr_3} \longrightarrow \overset{\oplus}{Br}\,[FeBr_4]^{\ominus} \text{ or } \overset{\oplus}{Br}\,[AlBr_4]^{\ominus}$
  - Chlorination: $Cl{-}Cl \;+\; \underset{\text{catalytic}}{AlCl_3} \longrightarrow \overset{\oplus}{Cl}\,[AlCl_4]^{\ominus}$

- Typical examples:





activated substrate

para bromophenol

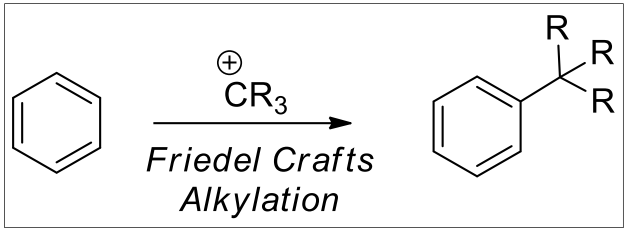
$2\,Br{-}Br \rightleftharpoons \overset{d+}{Br}{-}\overset{d-}{Br}{-}{-}{-}LA$ equivalent to $\overset{\oplus}{Br}\overset{\ominus}{Br_3}$

in this case LA = Br_2

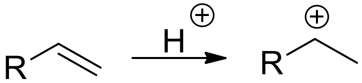
1.2.2.3. Friedel-Crafts reaction

- Friedel-Crafts alkylation: $E^+ = R_3C^+$ (carbenium ion, R=H,alkyl)
- Friedel-Crafts acylation: $E^+ = RCO^+$ (acylium cation, R=alkyl,aryl)

1.2.4.1. Friedel-Crafts alkylation

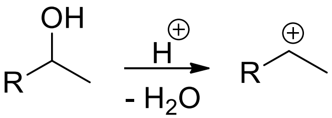


- Practical methods to generate the electrophile:
  - From protonation of alkenes: the selectivities of the carbenium ion apply

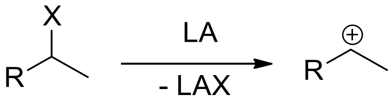


secondary carbenium ion
preferentially formed

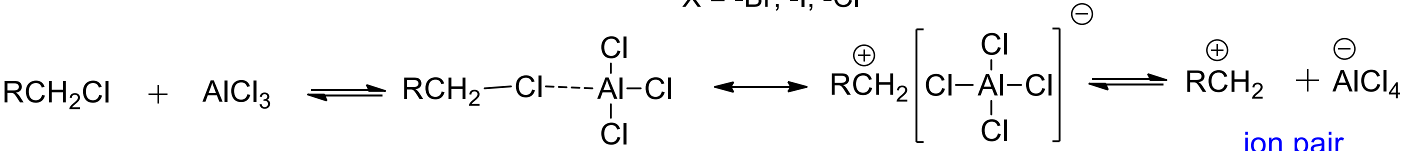
  - From alcohols and acid:



  - From alkyl halides and a Lewis acid:



X = -Br, -I, -Cl



donor-acceptor complex

ion pair

1.2.2.3. Friedel-Crafts reaction

Caution: all aspects of carbenium ions apply:

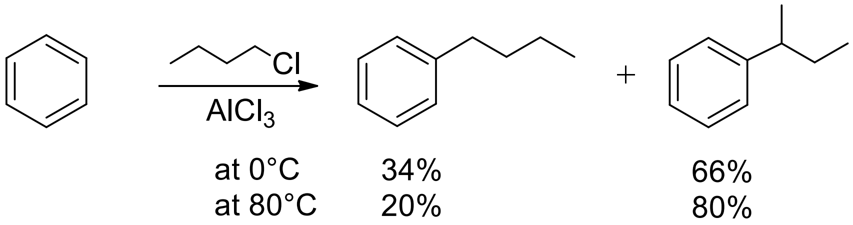
Stability: Benzylic > allylic > tertiary > secondary > primary methyl

First issue:

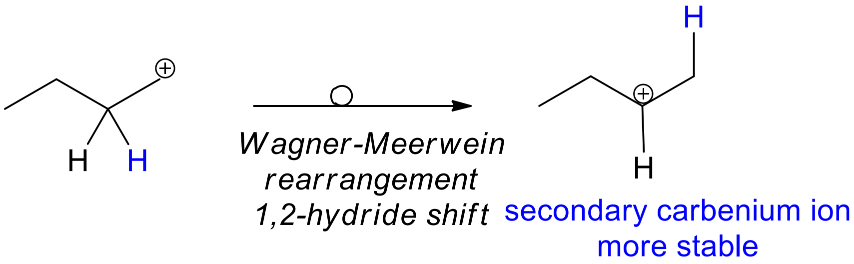
Wagner-Meerwein type rearrangements prone to isomerization

It is difficult to make primary alkyl chains under Wagner-Meerwein

For example:



proceeding via

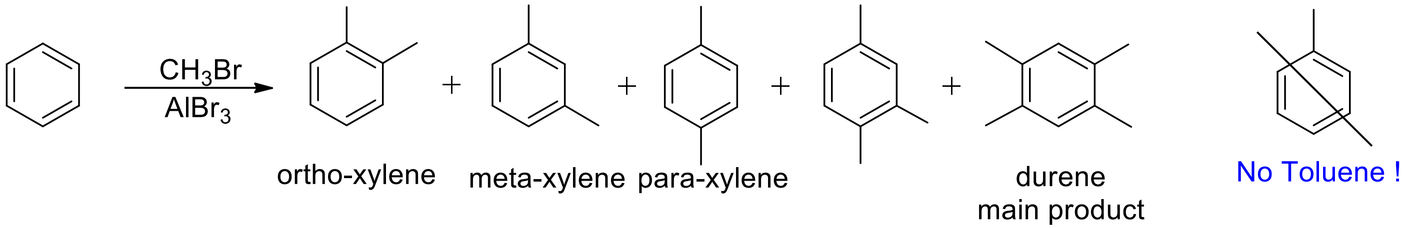


1.2.2.3. Friedel-Crafts reaction

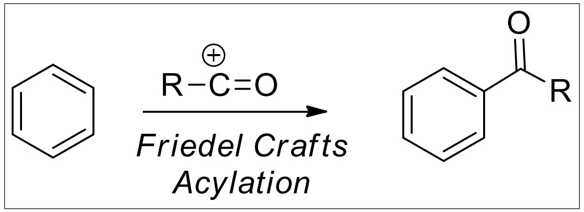
Second issue: alkyl groups are σ-donors which means:

→ The product is more reactive than the starting material and therefore the reaction is difficult to stop at the mono-alkylation stage

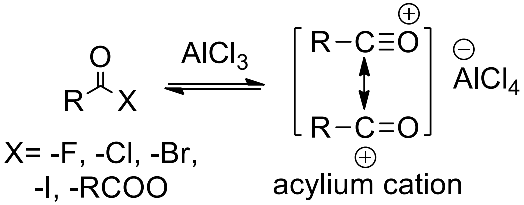
Example:



1.2.4.2. Friedel-Crafts acylation

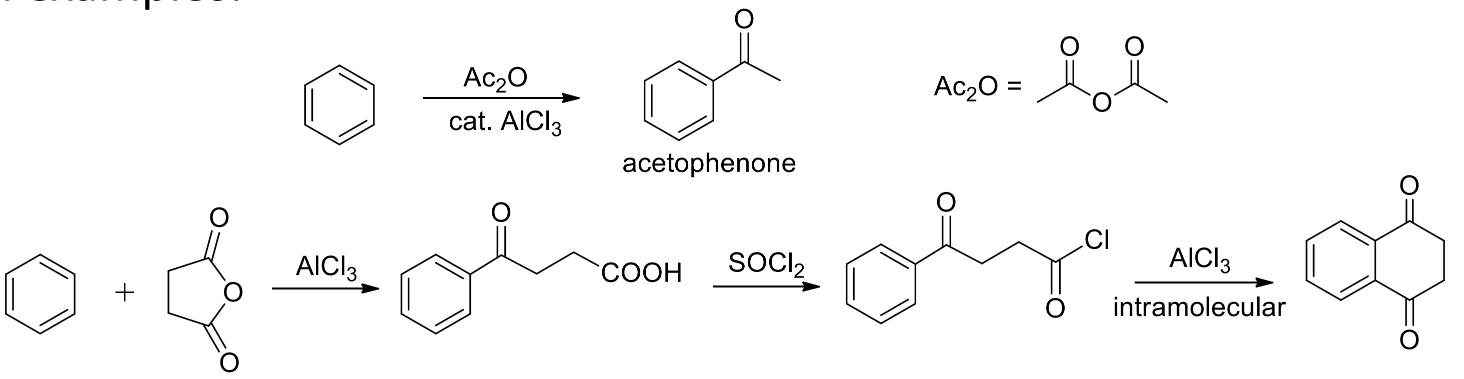


- Practical methods to generate the electrophile: from acid halogenide (acid chloride or anhydride) and a catalytic amount of a Lewis acid ($AlCl_3$)



1.2.2.3. Friedel-Crafts reaction

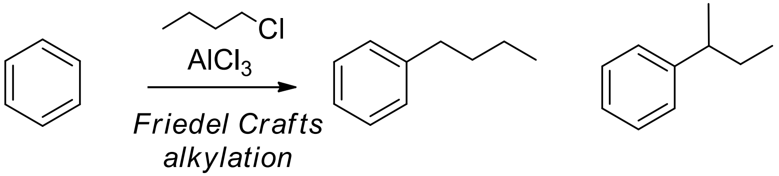
Typical examples:



- Important characteristics compared to Friedel-Crafts alkylation:

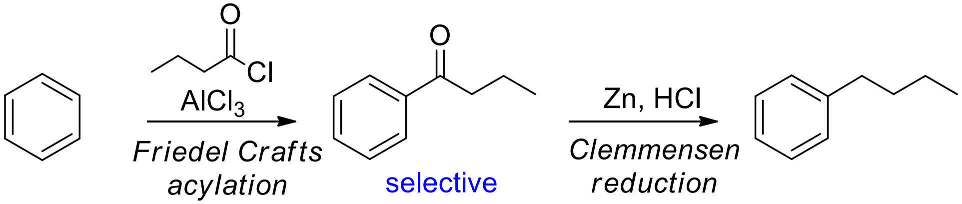
→ The introduction of a carbonyl group (EWG) decreases the reactivity

→ It prevents the risk of double acylation (however possible for intramolecular reactions)



Not selective !

alternative 2 steps procedure:



selective
mono acylation
no isomerization