Fonction et réaction organiques II

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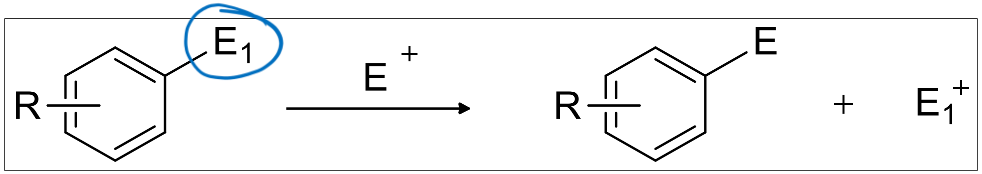
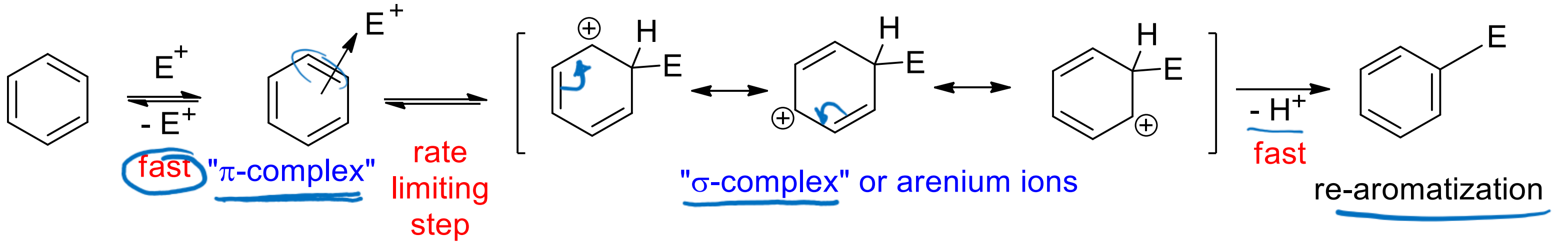
1.2. Electrophilic aromatic substitution S_EAr

- General reaction:

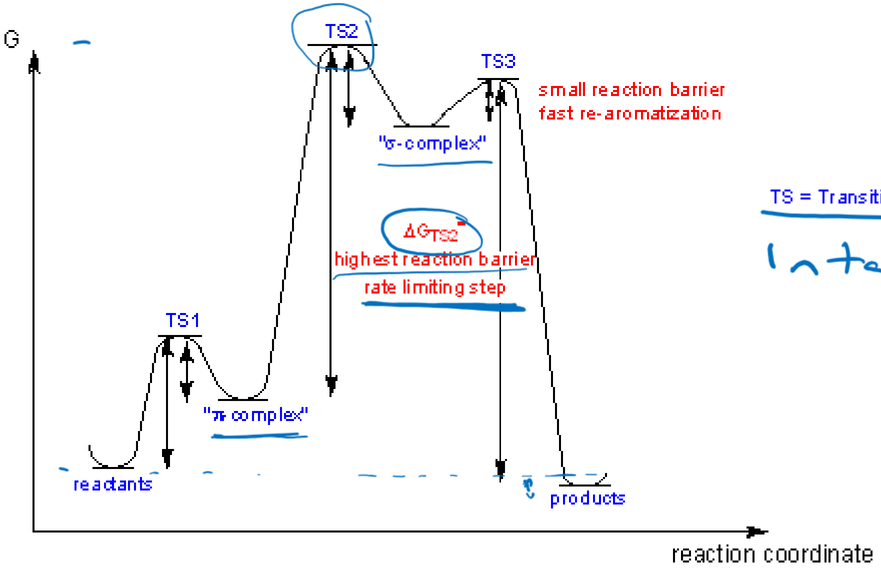


- $E_1 = H$
- Rare cases where $E_1 = SiR_3$, tBu, SO_3H is then called ipso-substitution

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



1.2.1. General principles



TS = Transition State

Intermediates = I

- Polanyi-Hammond postulate:

  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:

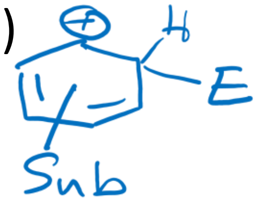
Sub

- 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$_2$, -$\bar{N}$H$_2$, -OH, -OR

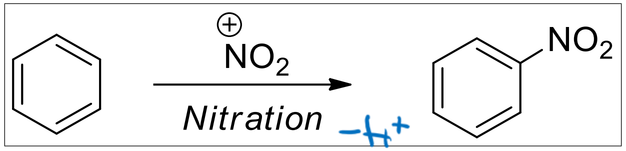
EDG with +I effect: -Alkyl, -SiR$_3$ → C_{sp^3}

EWG with –M effect: -NO$_2$, -COOR, -COR, -CHO, -CN, -SO$_3$H, -SO$_2$R

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%

$$2HNO_3 \rightleftharpoons \overset{+}{NO_2} + H_2O + NO_3^-$$

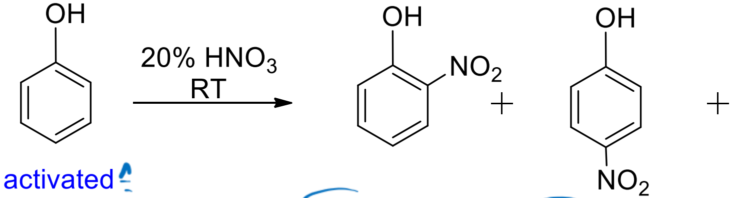
  - More forcing conditions: mixture of concentrated HNO_3 + concentrated H_2SO_4 (nitrosulfuric acid)

$$HNO_3 + 2H_2SO_4 \rightleftharpoons \overset{+}{NO_2} + H_3O^+ + 2HSO_4^-$$

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

- Examples for activated substrates: mild conditions are used

|-OH = very good EDG

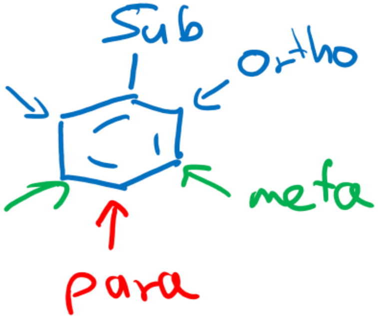


dinitro compounds

activated substrate electron rich

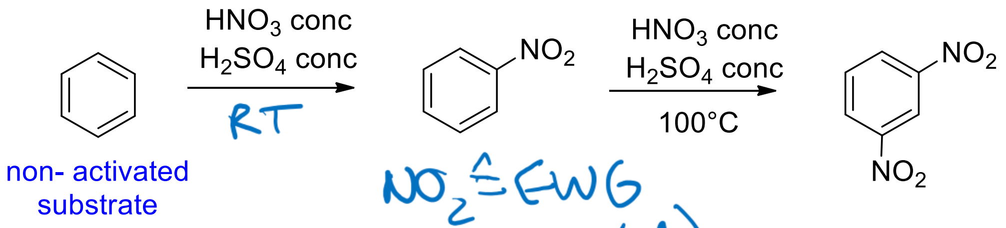
ortho nitrophenol 40%

para nitrophenol 15%



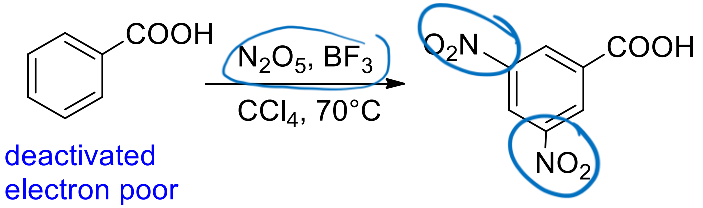
1.2.2.1. Nitration

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

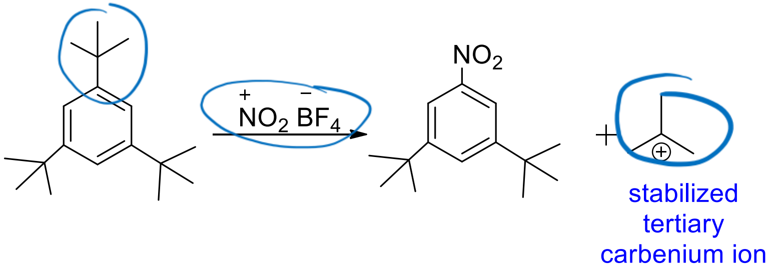


NO$_2$ ≙ EWG (deactivated)

- Examples for deactivated substrates:



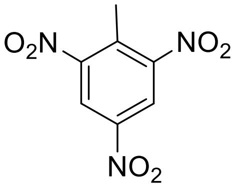
- Example for an ipso-substitution :



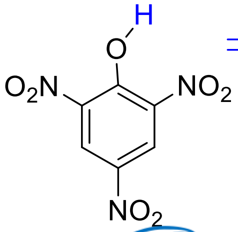
1.2.2.1. Nitration

- Nitro groups are important synthetic intermediates

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



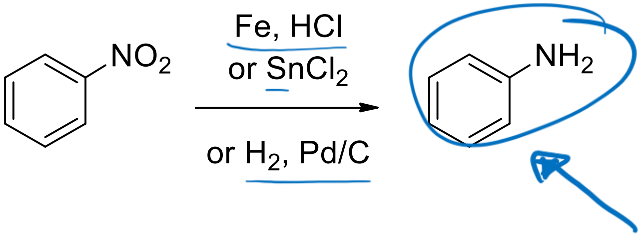
TNT



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



BASF
Aniline

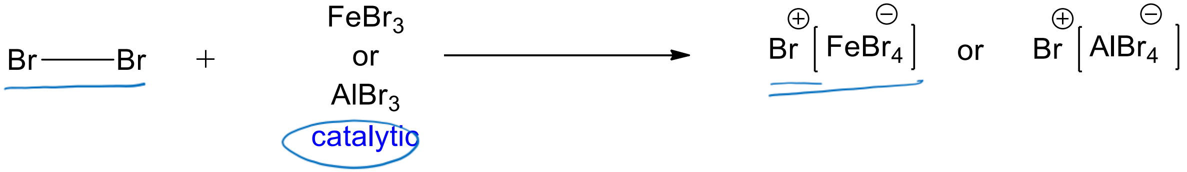
1.2.2.2. Halogenation: bromination / chlorination

- Electrophile = Br^+ / Cl^+

  Hal^+ no

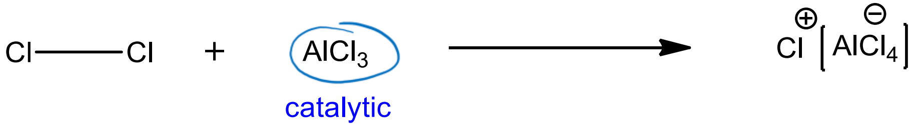
  - Fluorination: not controlable
  - Iodination: requires promoters

- Practical methods to generate the electrophile:
  - Bromination:



$$Br{-}Br + \underset{\text{catalytic}}{FeBr_3 \text{ or } AlBr_3} \longrightarrow \overset{\oplus}{Br}\,[FeBr_4]^{\ominus} \text{ or } \overset{\oplus}{Br}\,[AlBr_4]^{\ominus}$$

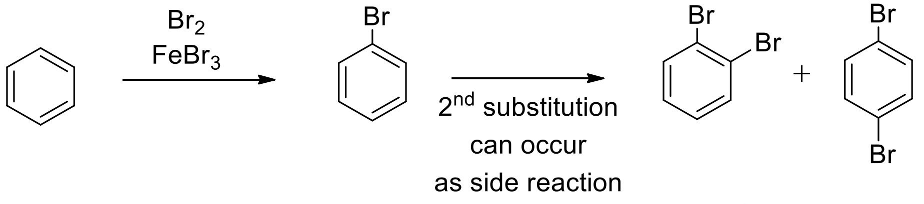
  - Chlorination:



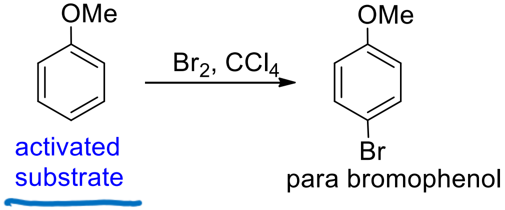
$$Cl{-}Cl + \underset{\text{catalytic}}{AlCl_3} \longrightarrow \overset{\oplus}{Cl}\,[AlCl_4]^{\ominus}$$

- Typical examples:

"neutral" reactivity

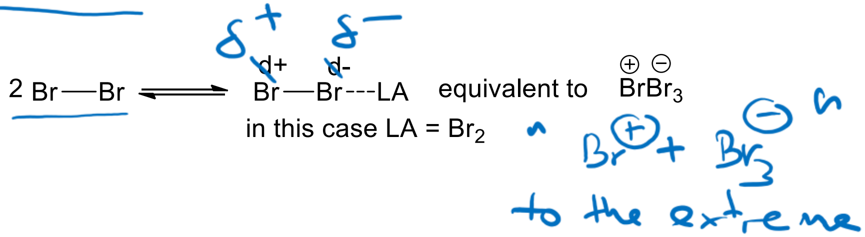


good EDG: OMe



activated substrate

para bromophenol



$$2\,Br{-}Br \rightleftharpoons \overset{\delta+}{\overset{d+}{Br}}{-}\overset{\delta-}{\overset{d-}{Br}}{---}LA \quad \text{equivalent to} \quad \overset{\oplus\ \ominus}{BrBr_3}$$

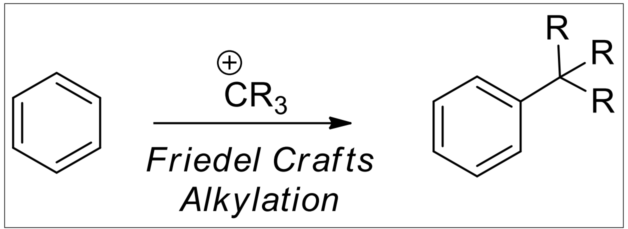
in this case LA = Br_2

"$Br^{\oplus} + Br_3^{\ominus}$" to the extreme

1.2.2.3. Friedel-Crafts reaction FC-reaction

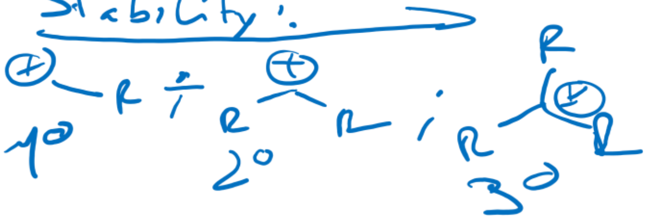
- Friedel-Crafts alkylation: $E^+ = R_3C^+$ (carbenium ion, R=H,alkyl)
- Friedel-Crafts acylation: $E^+ = RCO^+$ (acylium cation, R=alkyl,aryl)

1.2.4.1. Friedel-Crafts alkylation

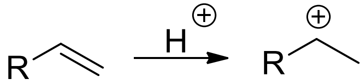


recall:

Stability:

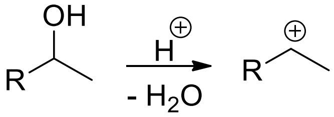


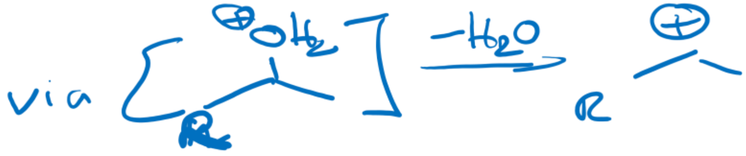
- Practical methods to generate the electrophile:
  - From protonation of alkenes: the selectivities of the carbenium ion apply



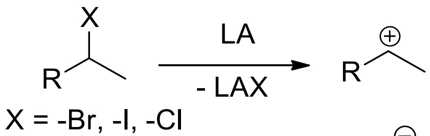
- secondary carbenium ion preferentially formed

  - From alcohols and acid:

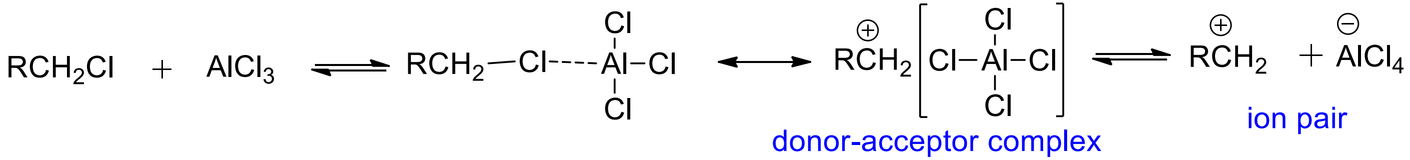




  - From alkyl halides and a Lewis acid:



stoichiometric LA



1.2.2.3. Friedel-Crafts reaction

Caution: all aspects of carbenium ions apply:

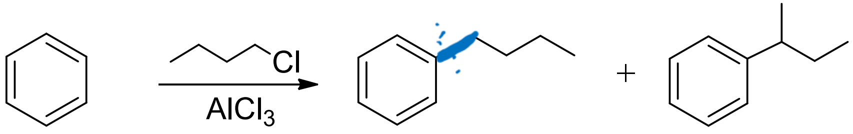
Stability: Benzylic ≥ allylic > tertiary > secondary > primary > methyl

First issue:

Wagner-Meerwein type rearrangements prone to isomerization

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

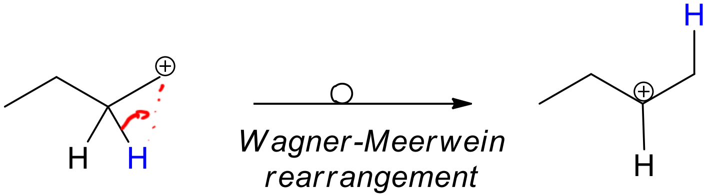
For example:



at 0°C 34% 1 : 2 66%

at 80°C 20% 1 : 4 80%

proceeding via



secondary carbenium ion
more stable

1° carbenium ion

Q:

Subst = Me

Me = EDG

+I effect

⇓

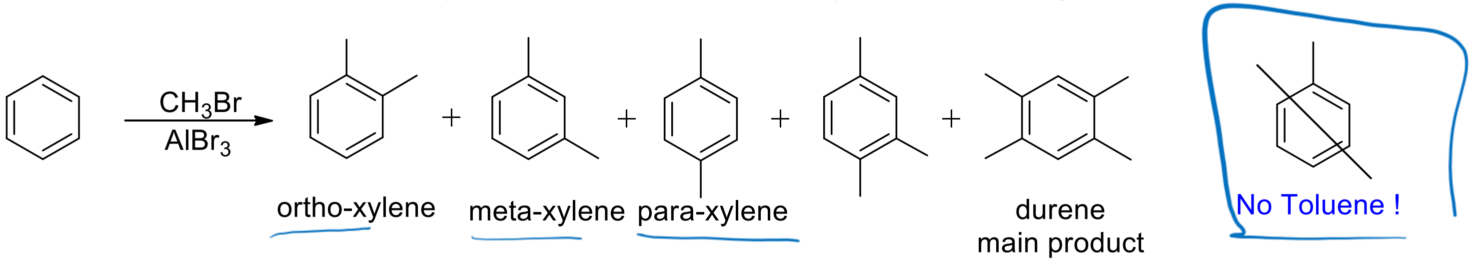
renders substrate more reactive

1.2.2.3. Friedel-Crafts reaction

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

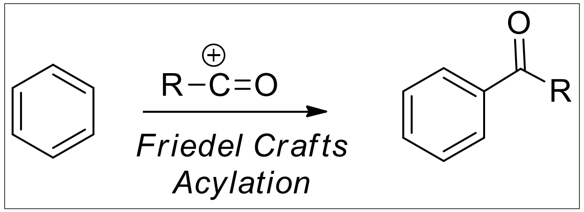
→ The product is more reactive than the starting material and therefore the reaction is difficult to stop at the mono-alkylation stage

Example:

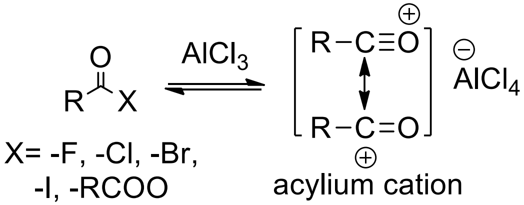


Mono substitution

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 ($AlCl_3$)

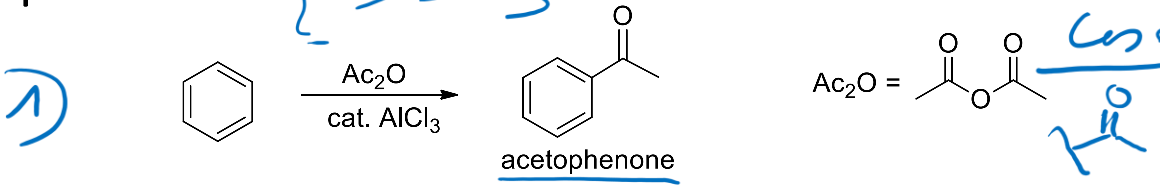


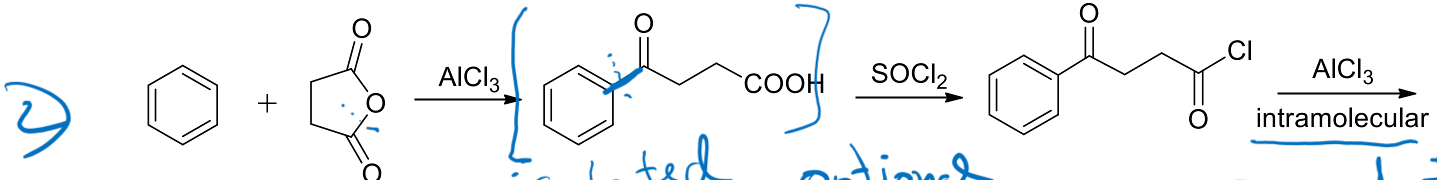
1.2.2.3. Friedel-Crafts reaction

Typical examples:

$[-\equiv^{\oplus}]$

product is less reactive





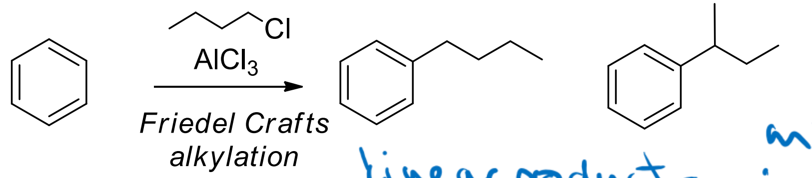
isolated   optional   second FC-acylation

only intramolecular!

- 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)

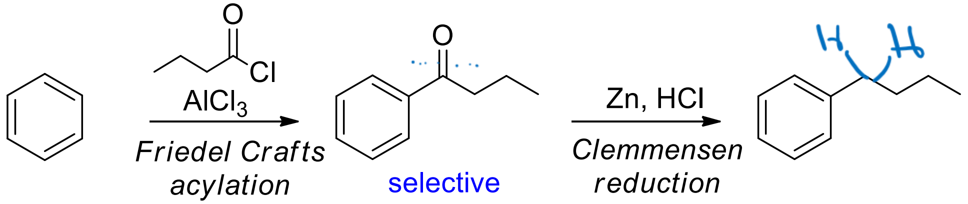


Not selective !

mixture of isomers

linear product = minor

alternative 2 steps procedure:



selective
mono acylation
no isomerization