Organic Chemistry – Exercise 7

Distribution: November 13, 2025

Help: December 11, 2025

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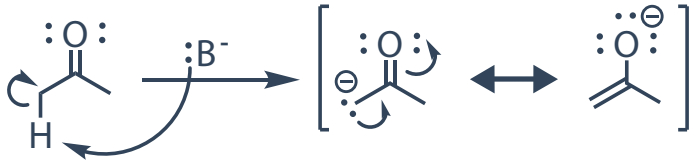
1. The aldol condensation is one of the very frequently used strategies for creating C–C bonds. It is a two-step process, where the first step is called aldol addition, and the second step is an elimination. Aldol reactions can be carried out in both acidic and basic media.

   Carbon atoms next to a carbonyl (or carboxylic) groups are called α carbons. If a proton is bonded to an α carbon it is called α proton, and it is more acidic than "normal" C–H protons.

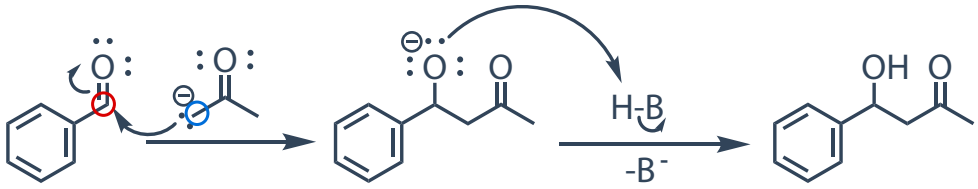
   Benzaldehyde and acetone can react in an aldol addition reaction to yield dibenzylidene acetone in basic medium.

   a. The first step is deprotonation of acetone in α position. On the example of acetone (propanone), explain the acidity of α proton by showing the resonance structures of the anion that is formed after deprotonation (use base :B$^-$ for deprotonation).



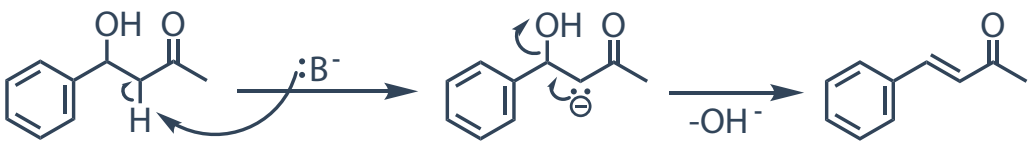
As the electron pair in the formed anion is stabilized by conjugation to a –M substituent, the carbonyl group, the α proton is acidic.

   b. The second step is the reaction of this anion with benzaldehyde to form a compound that has one carbonyl and one hydroxyl group. Show the mechanism of this step. Label the nucleophile and electrophile in this reaction.



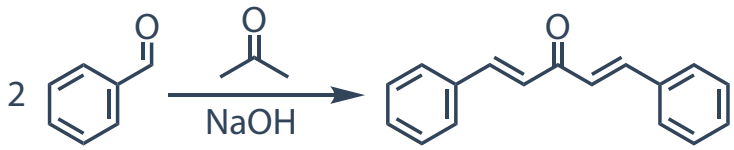
The carbonyl C atom labeled in red is acting as an electrophile and the carbon atom labeled in blue is acting as a nucleophile.

   c. The third step starts by another deprotonation of the α carbon that reacted in the previous step. It is usually performed at elevated temperatures. The product of this step is a conjugated compound ($C_{10}H_{10}O$). Show the mechanism of this step. What type of reaction is this precisely?



This step occurs via E1$_{cb}$ mechanism.

d. If the available amount of benzaldehyde is at least two times higher than the amount of acetone and there is enough base, this reaction continues. Write down the net reaction (no detailed mechanism) if there is 1 mol of acetone, 2 mol of benzaldehyde, and an excess of sodium hydroxide in the system.



As there are protons on two different α carbon atoms in acetone, the latter can react with two benzaldehyde molecules, and with the excess base, also a two-fold elimination is possible, to yield dibenzylidene acetone.

e. What is a potential side reaction that can happen in this system?

As there is an electrophilic carbonyl C atom in acetone also, the side reaction that could occur is aldol condensation between two acetone molecules.

f. Briefly note whether, and why the reaction would be faster or slower if:

i. *p*-nitrobenzaldehyde is used instead of benzaldehyde;

Since a nitro group in *para* position has an electron-withdrawing (–M and –I) effect, the carbonyl C atom will be more electrophilic, so the reaction will be faster.

ii. *p*-ethoxybenzaldehyde is used instead of benzaldehyde;

Since ethoxy group in *para* position has an electron-donating (+M) effect, the carbonyl C atom will be less electrophilic, so the reaction will be slower.

iii. formaldehyde is used instead of benzaldehyde;

As the carbonyl C atom in benzaldehyde is less electrophilic in comparison with the carbonyl C atom in formaldehyde, due to +M effect of the benzene ring, the reaction will be faster with formaldehyde.

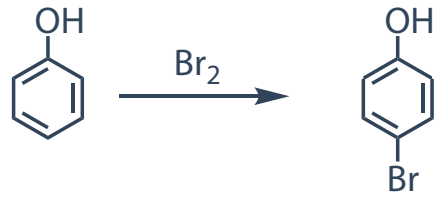
iv. 3-pentanone is used instead of acetone;

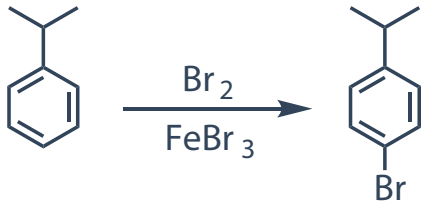
As more substituted carbanions are less stable (secondary in this case and primary in case of acetone) the reaction will be slower.

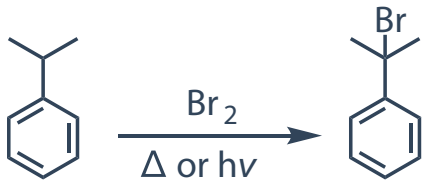
v. sodium carbonate is used instead of sodium hydroxide?

Sodium carbonate is weaker base, so the reaction will be slower.

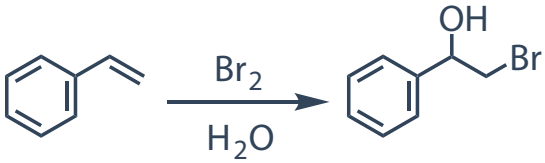
2. Bromine can react with organic compounds in many different ways depending on the reaction conditions. Consider the following reactions of aromatic compounds with bromine (there is 1 equivalent of bromine in each case). Give the structure of the major product (the product obtained in the highest yield) and state what is the type of the reaction that led to that product. Comment on regioselectivity where relevant (you don't have to comment on stereochemistry).

a) 

b) 

c) 

d) 

e) 

f) 

In a) the reaction is an electrophilic aromatic substitution S_EAr As the aromatic ring is highly activated by a hydroxyl group, the reaction proceeds even without the catalyst. Hydroxyl group is +M substituent, so the reaction occurs in *para* position.

In b) the reaction is an electrophilic aromatic substitution S_EAr in the presence of a Lewis acid as a catalyst. The isopropyl group is directing to *ortho* and *para* positions, but due to steric hindrance, the reaction occurs in *para* position.

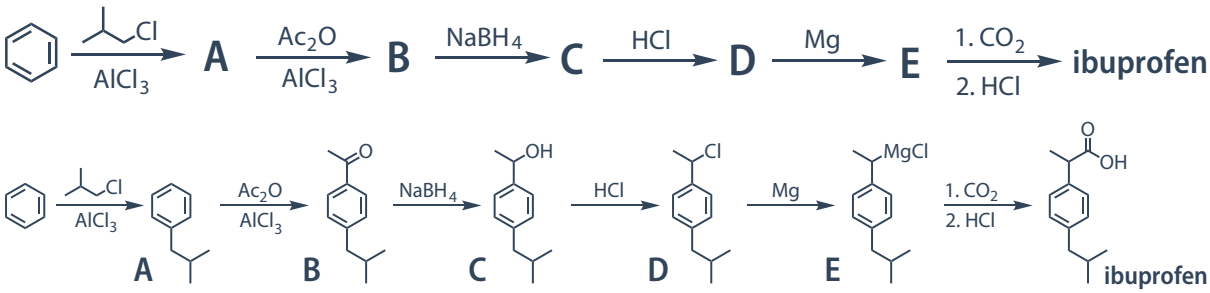
In c) the reaction is radical substitution on an aliphatic carbon. As the most stable radical that can be formed in the system is the tertiary one (which is simultaneously benzyl), the substitution occurs in that position.

In d) the reaction is an electrophilic addition A_E to the double bond.

In e) the reaction is an electrophilic addition A_E to the double bond. First the bromonium ion is formed and then it is opened by water present in the system (always from the more substituted side).

In f) there is no reaction in the system. The benzene ring is not activated, so without a proper catalyst (Lewis acid), no reaction occurs.

3. Ibuprofen is an anti-inflammatory drug used to relieve pain, fever and inflammation. It is widely used because it is usually available without prescription. Ibuprofen can be synthesized in many different ways and one of them is going to be analyzed in this exercise.



The starting compound in this sequence is benzene. In the first step it is treated with one equivalent of isobutyl chloride in presence of aluminium chloride to yield compound **A**. Compound **A** is then treated with acetanhydride in presence of aluminium chloride to yield compound **B**.

a. Show the structures of compounds **A** and **B**. What are the reaction mechanisms (just give the acronyms, no detailed mechanism) through which these two compounds were obtained? Comment on the regiochemistry where relevant.

The structures are given in the main scheme. Both A and B are obtained via electrophilic aromatic substitutions. As alkyl groups are *ortho* and *para* directing and isobutyl group is bulky, B is *para* product.

Sodium borohydride ($NaBH_4$) is a reagent widely used in chemistry for reducing various compounds. One of the most common applications of sodium borohydride is for reduction of carbonyl compounds to yield the corresponding alcohols.

b. Knowing that the role of sodium borohydride in this sequence is to provide a "hydride anion" (H^-) precursor that acts as a nucleophile, give the structure of compound **C** (do not pay attention to stereochemistry).

The structure is given in the main scheme.

Compound **C** is treated with concentrated hydrochloric acid to yield compound **D** at low temperature. Compound **D** is then heated with elementary magnesium in an inert solvent to yield compound **E**.

c. Give the structures of compounds **D** and **E**. What is the mechanistic pathway through which compound **D** is obtained? Explain your answer.

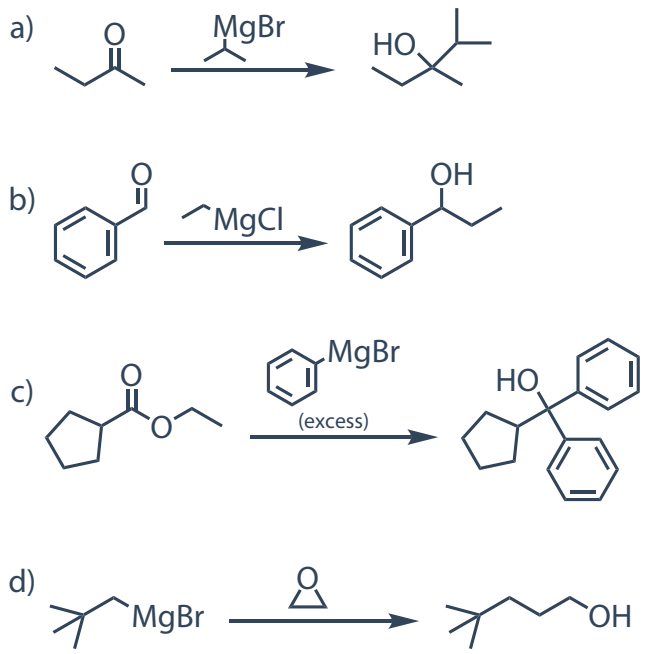
D is obtained from C via a monomolecular nucleophilic substitution S_N1. After the protonation of hydroxyl group and elimination of water a secondary and benzyl carbocation is formed, which is stabilized by resonance. Elimination is suppressed by carrying out the reaction at a lower temperature.

Finally, compound **E** is treated with carbon dioxide. After workup with hydrochloric acid, **ibuprofen** is obtained.

d. Draw the structure of **ibuprofen**. What is type of reaction through which this compound is obtained? What is the role of hydrochloric acid during the workup?

Ibuprofen is obtained via a nucleophilic addition of the Grignard reagent to the carbonyl group of CO_2. The role of hydrochloric acid is to protonate the formed carboxylate ion.

4. Give the structures and IUPAC names of the major products of the following reactions with Grignard's reagents. Consider that there is an acidic aqueous workup after each reaction.



Product of a) is 2,3-dimethylpentan-2-ol.

Product of b) is 1-phenylpropan-1-ol.

Product of c) is cyclopentyldiphenylmethanol.

Product of d) is 4,4-dimethylpentan-1-ol.

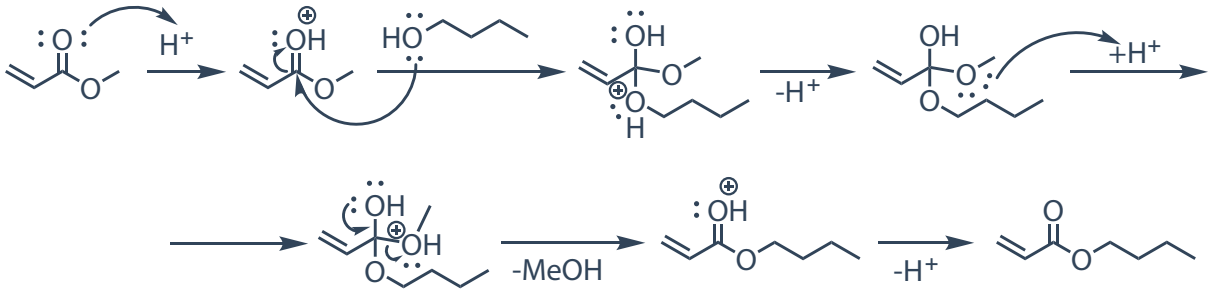
5. Transesterification is the reaction of an ester with an alcohol. This reaction is very useful in various organic synthetic strategies. It is especially useful in synthesis of polyesters (this will be discussed in much greater detail during the last chapter of the course). Transesterification is going to be discussed on the example of reaction of methyl acrylate (propenoate) and 1-butanol.

   a. Show the equation of the overall reaction between methyl acrylate and butanol. Give the IUPAC names of both products.

The products are butyl acrylate (propenoate) and methanol.

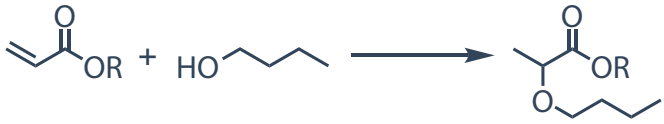
Transesterification is usually performed in presence of a catalyst. This process can be both acid- and base-catalyzed.

b. Show the mechanism if the reaction is catalyzed with a Brønsted acid (that delivers H^+). What is the role of the mineral acid in this case?



The mineral acid makes the ester carbon a better electrophile. Additionally, it protonates the oxygen of the methoxy group and thus creates a better leaving group (methanol).

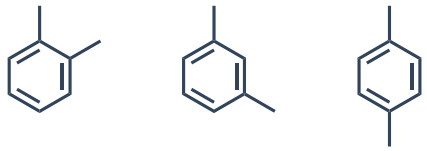
c. What is the potential side reaction that can occur if transesterification of *these* compounds is carried out in presence of mineral acid? Comment on why this is a side reaction and transesterification is the main one.



A potential side reaction is electrophilic addition of butanol to the double bond of acrylic acid. The intermediate carbocation is formed in α position to the electron deficient carboxylic C atom, so it is not particularly stable, which is why this is not the main reaction that occurs in the system.

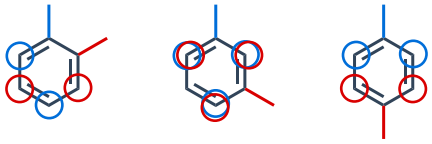
6. Xylene is a trivial name for dimethyl benzene. There are three isomers of xylene.

a. Draw structures of three isomers of xylene. What type of isomerism is this?



These are positional isomers.

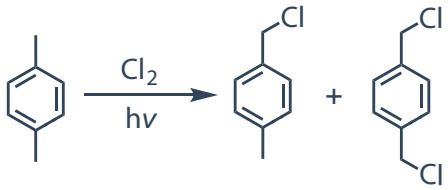
b. These isomers significantly differ in reactivity in electrophilic aromatic substitution. If a mixture of **one** mol of each of these three isomers is treated with **one** mole of chlorine in presence of $AlCl_3$, only one compound reacts. Which isomer reacts and why?



Methyl groups are directing the electrophilic aromatic substitution to occur in *ortho* or *para* positions. One of the two methyl groups is labeled blue and the other is labeled red and the corresponding positions in which they direct are labeled in the same color. It is clear that only in case of *meta*-xylene both groups direct to the same positions, which is why these positions are

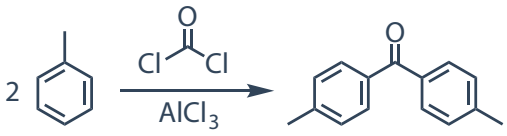
significantly more activated than in the other cases. Due to this, *meta*-xylene is the only one that reacts in this case.

c. How would the outcome differ if the same reaction was done with only *para*-xylene (1,4-dimethylbenzene) in absence of $AlCl_3$ and with constant irradiation of reaction mixture with UV light? Draw the structures of the product(s) and explain your answer.



In this case radical substitution on methyl groups would take place. A mixture of monochlorinated and dichlorinated products will be obtained.

d. Show the overall reaction of phosgene ($COCl_2$) with an excess of toluene in presence of $AlCl_3$.



Reading Suggestions:

Clayden, Greeves, Warren, *Oxford University Press*, **2012**.

Organic Chemistry, John McMurry, *Thomson Brooks/Cole*, **2008**.

Chimie Organique, Les Grands Principes, John McMurry, *Dunod Editeur*, **2009**.

Chimie Organique, Paul Arnaud, *Dunod Editeur*, **2009**.