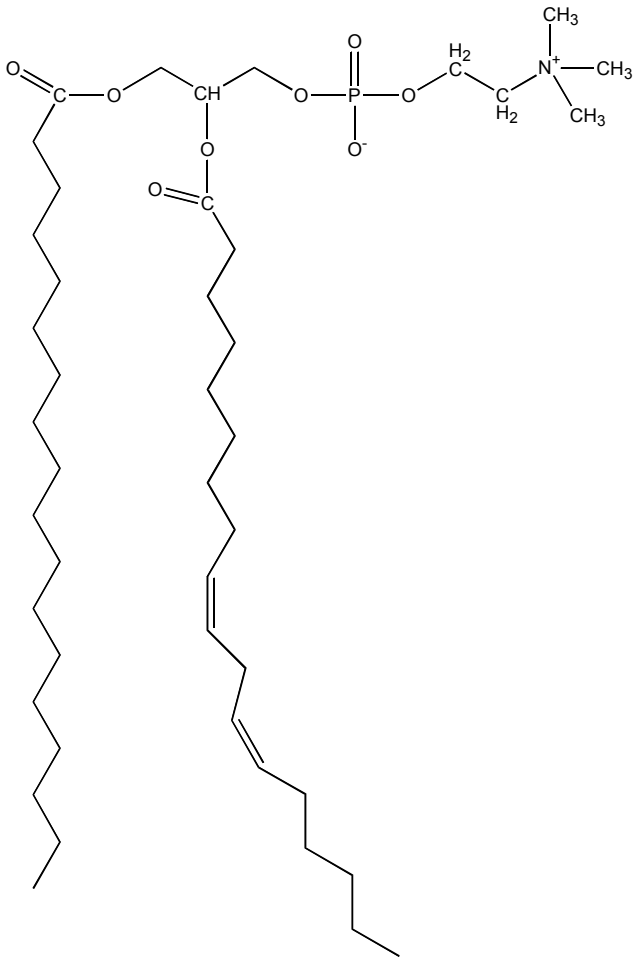
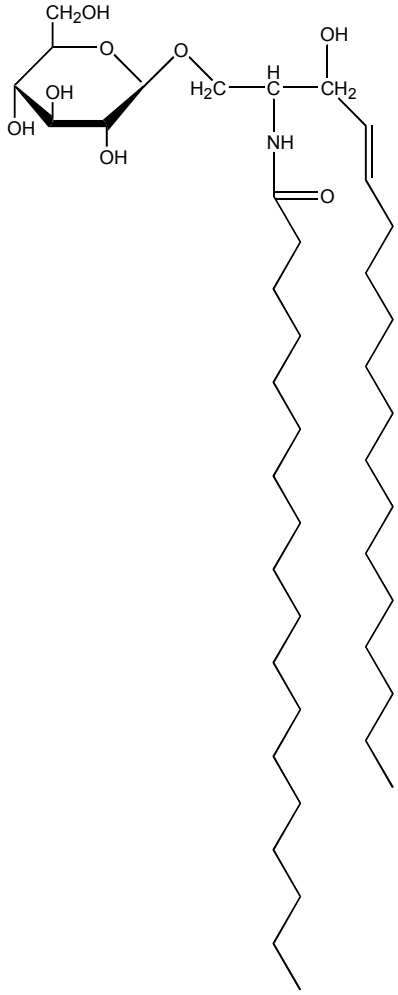
Problem 19: Lipids

Lipids are important components of our nutrition, and they fulfill a variety of important roles in the body - although we do not always want to be reminded of their presence!
Lipids can be classified according to their hydrophobicity: apolar or neutral lipids with overall hydrophobic structures store energy in our fat cells, whereas polar lipids, which contain a polar “head group” and one or more apolar “tails”, are found in the membranes around each cell of our body.
In addition to the common phospholipids like lecithin, other polar lipids like cerebroside are present in membranes surrounding human cells.



Lecithin (phosphatidyl choline)



Cerebroside

19.1 Name the building blocks of lecithin.
Indicate the head and tail structures of both lipids in the structure above.

Lipids are substances that are soluble in organic solvents like chloroform, but hardly soluble in water.

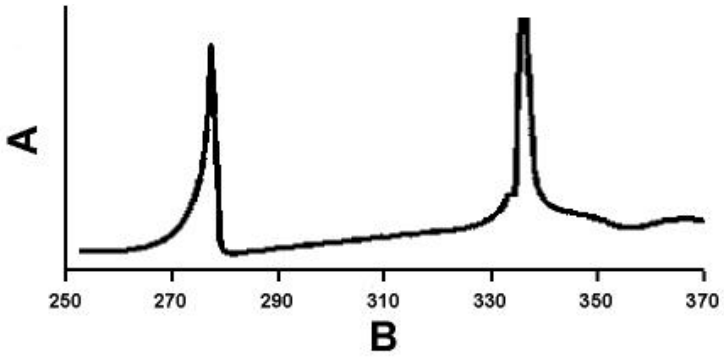
19.2 If lipids are mixed with water, what aggregates can they form? Describe two characteristic superstructures which are commonly found in biological systems, including our food. How are the lipid head groups oriented towards the water? Which factor determines the superstructure formed by a lipid?

Together with other lipids cerebrosides are found on the surface of human cells. In contrast to the head group of cholesterol which points to the inside as well as to the outside, the head group of cerebrosides is found exclusively pointing to the outer surface of human cells.

19.3 Why does this arrangement not dissipate into the entropically favoured arrangement with the head groups of the cerebrosides pointing to the inside and outside?

The differential scanning calorimetry plot below refers to a mixture of 60% disteaoryl phosphatidyl choline and 40% water.

A: heat uptake (rel. units) **B: temperature (K)**



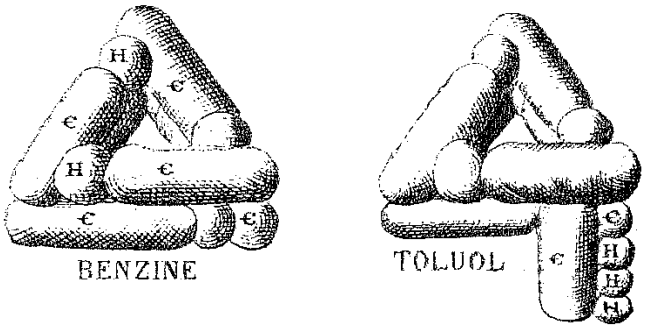
19.4 Explain the two peaks in the diagram. How can a living cell control the position of the second peak to adapt the properties of its membrane to the demands of life?

In blood, lipids are transported in the form of lipoproteins, which consist of polar and apolar lipids, as well as proteins with hydrophilic and hydrophobic surfaces.
In western countries lipoprotein levels are elevated in the blood of many people due to a high fat diet. Especially high amounts of cholesterol and cholesterol-esters in some lipoproteins lead to modifications of blood vessels and lipid deposition (atherosclerosis). This can finally result in a blockage of the blood flow in the arteries supplying the heart with oxygen: a heart attack occurs, one of the most common causes of death.

19.5 How could lipids and proteins form lipoproteins, stable superstructures which can be easily transported in blood? How would
a) cholesterol
b) esters of cholesterol with fatty acids
be incorporated into lipoproteins?

Problem 20: Kekulé, Benzene and the Problem of Aromaticity

In 1865, the german chemist August Kekulé proposed a cyclic structure for benzene, an aromatic-smelling hydrocarbon with the empirical formula C_6H_6, that was discovered in 1825 by Michael Faraday. Kekulé proposed that carbon has four valences and that it can form carbon-carbon single bonds ($^1/_4$ overlap) or double bonds ($^2/_4$ overlap). In his model, benzene has alternating single and double bonds. The remaining 6 valences are saturated with bonds to the six hydrogen atoms. These are copies of his original work:

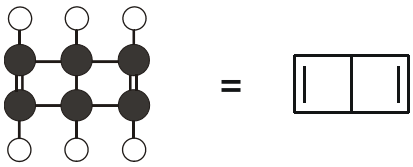


However, at that time it was already known that there is only one isomer of *ortho* di-substituted benzenes. If benzene had alternating single and double bonds there would be two isomers, one with a double bond between the substituents and one with a single bond. Kekulé solved this contradiction by assuming that the single and double bonds in benzene are "somehow combined in a common benzene nucleus".
Now, we know that benzene is a planar, regular hexagon with all the C-C bonds of equal lengths and that its chemical reactivity is different from that of a normal olefin.

20.1 Draw resonance structures that explain the electronic structure of benzene.

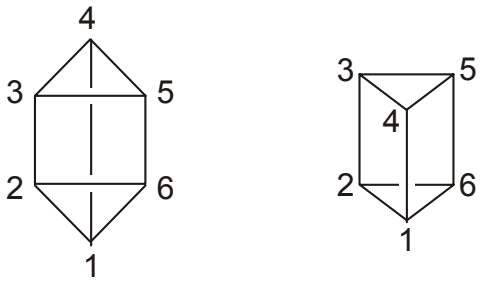
20.2 Draw the structures of all conceivable disubstituted benzene isomers bearing two identical substituents ($C_6H_4R_2$).

An alternative benzene structure was proposed by Staedeler. Nowadays it is known as the Dewar benzene structure:

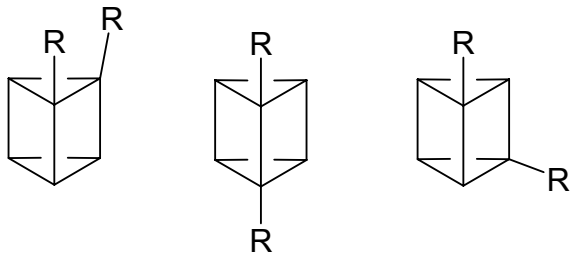


20.3 How many isomers of Dewar benzene will be conceivable if it is substituted with two identical substituents? Draw the structures.

Shortly after, A. Ladenburg, who used to be Professor for Organic Chemistry here in Kiel, proposed the so-called Ladenburg benzene structure (now called prisman):



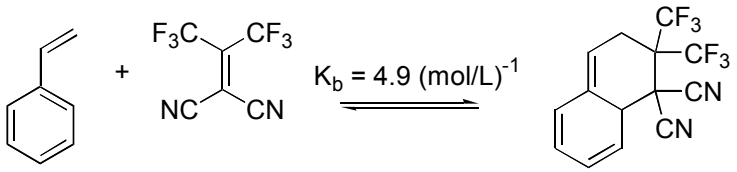
According to Prof. Ladenburg, the benzene model is in agreement with the fact that there are three disubstituted benzene isomers:

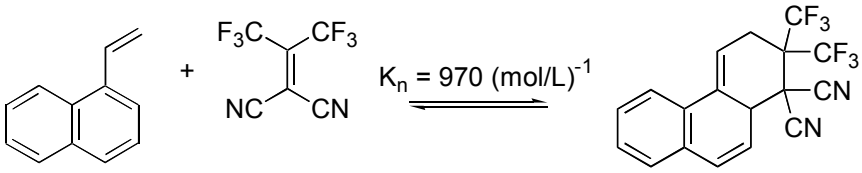


Ladenburg was wrong. The list above is not complete.

20.4 There is a 4th isomer. What does it look like?

Aromatic compounds are more stable than their non-aromatic counterparts. There are different ways to measure the so-called aromatic stabilization energy. The following experiment was performed to compare the stabilization energy of benzene with naphthalene:





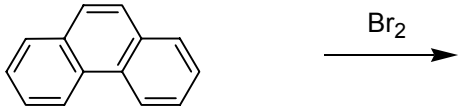
The equilibrium constants K_b and K_n were measured for both reactions at 300 K.

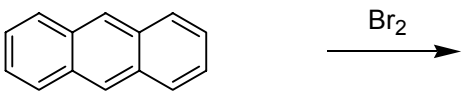
20.5 Calculate the free enthalpies of reaction $\Delta_r G$ for both reactions.

20.6 Calculate the enthalpy of reaction $\Delta_r H$ for each reaction assuming that for both reactions ΔS is -125 J mol^{-1} K^{-1} and the temperature is 300 K.

20.7 Why is the second reaction more exothermic than the first?
Write down all resonance structures of the starting materials and products and count those having favourable benzene resonances.

What do you think are the products of the following reactions (use the same arguments)?





20.8 Fill in the structures of the reaction products.

Problem 21: Benzene and Cyclohexane

21.1 How can the enthalpy of the hydrogenation of benzene be calculated from its enthalpy of combustion and the enthalpies of combustion of cyclohexane and hydrogen? Make use of Hess's law.

C_6H_6	+ 7.5 O_2	⟶ 6 CO_2 + 3 H_2O	$\Delta_r H$ = - 3268 kJ mol^{-1}
C_6H_{12}	+ 9 O_2	⟶ 6 CO_2 + 6 H_2O	$\Delta_r H$ = - 3920 kJ mol^{-1}
H_2	+ 0.5 O_2	⟶ H_2O	$\Delta_r H$ = - 289 kJ mol^{-1}

The energy difference between the formula proposed by Kekulé and the real bonding situation can be estimated by comparing the theoretically estimated and experimentally found enthalpies of hydrogenation for benzene. The enthalpy of hydrogenation of cyclohexene is 120 kJ mol^{-1}. This value is the energy of hydrogenation of a double bond.

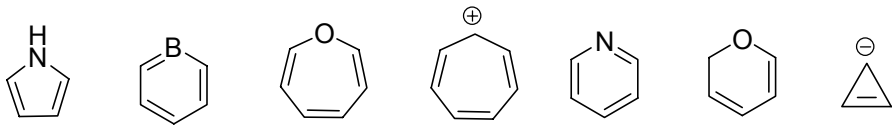
21.2 Calculate the expected enthalpy of hydrogenation of a six-membered ring with three double bonds and compare it with the value obtained in 74.1. What is the reason for this difference?

Problem 22: Non-Benzoid Aromatic Systems

Since the discovery of benzene, a lot of compounds have been identified that behave similarly. They all have some common features. According to Hückel's rule, an aromatic system must have the following properties:

- cyclic
- fully conjugated
- planar
- 4n+2 π electrons

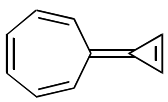
22.1 Write down the number of π-electrons in each of the compounds shown below.

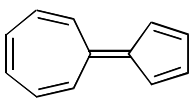


22.2 Which compounds are aromatic?

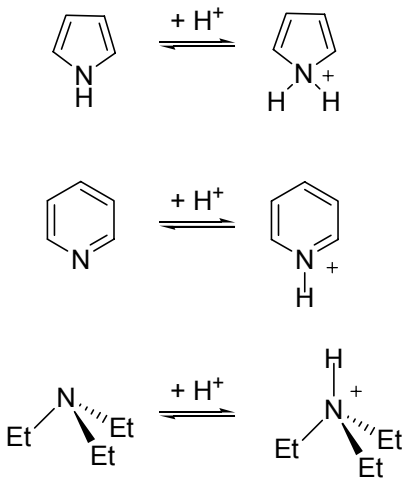
Let us now consider some examples of how aromaticity influences the chemical properties of molecules.

22.3 Which of the following two compounds would you expect to have a greater dipole moment? Support your answer by writing the corresponding (plausible) resonance structures.

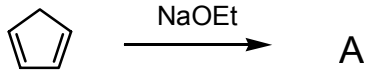
a) 

b) 

22.4 Which of the following three compounds can be protonated more easily? Assign the three pK_b values (8.8, 13.5, 3.1) to these three compounds:



Cyclopentadiene (C_5H_6) is not an aromatic compound because it is not completely conjugated. However, in contrast to acyclic dienes, it can quite easily react with a strong base such as sodium ethoxide to form a crystalline salt.

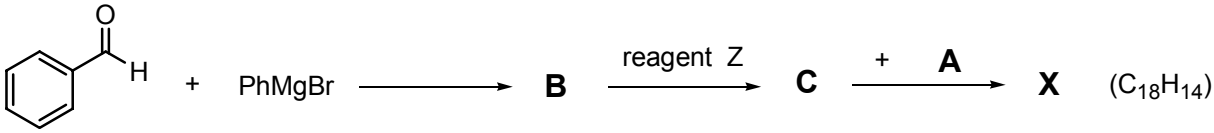


22.5 Write down a structure for compound A.

22.6 Is A aromatic according to Hückels-rule?

22.7 How many signals in the ^{1}H NMR do you expect for A?

If **A** reacts in the following sequence, a stable, deep red compound **X** will form:



Hint: **C** has the following elemental composition: C 85.69 %, H 5.53 %.

22.8 Write down structures for the compounds B, C and X.

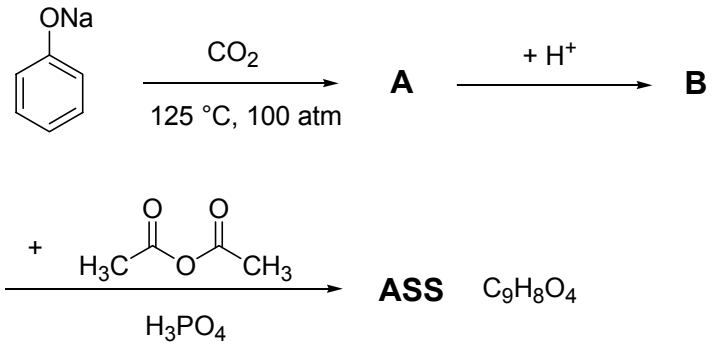
22.9 Suggest a plausible reagent Z.

22.10 Cyclopentadiene has to be freshly distilled before use in the above synthesis,because it dimerizes upon prolonged standing. Suggest a structure for this dimer.

Problem 23: Pain Reliefers

Aspirin:

Probably the most commonly used drug of all time is acetylsalicylic acid (ASS), which was released on the market as a pain reliefer under the trade name Aspirin® by a German company in 1899. Now, billions of tablets are sold each year. Acetylsalicylic acid can be synthesized according to the following scheme:



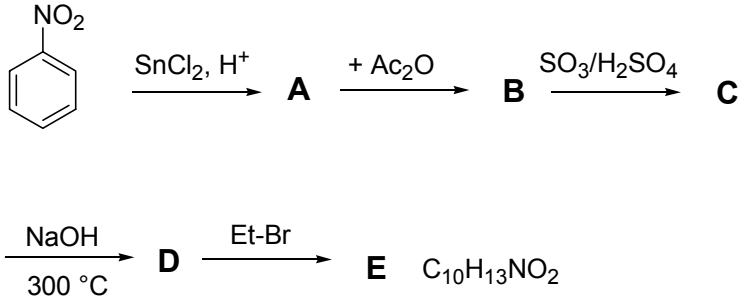
23.1 Give structural formulas for A, B and ASS.

23.2 Decide whether the following statements concerning acetylsalicylic acid are true, false or whether no decision is possible.

	true	false	no decision possible
ASS is more soluble in water at a pH of 2 than at a pH of 9.	☐	☐	☐
A further electrophilic substitution will occur ortho to the COOH group.	☐	☐	☐
The conjugate base is less water soluble than the acid.	☐	☐	☐
The NMR spectrum shows only two CH signals in the aromatic region.	☐	☐	☐
The ^{1}H NMR in D_2O/DMSO mixtures shows 5 signals.	☐	☐	☐

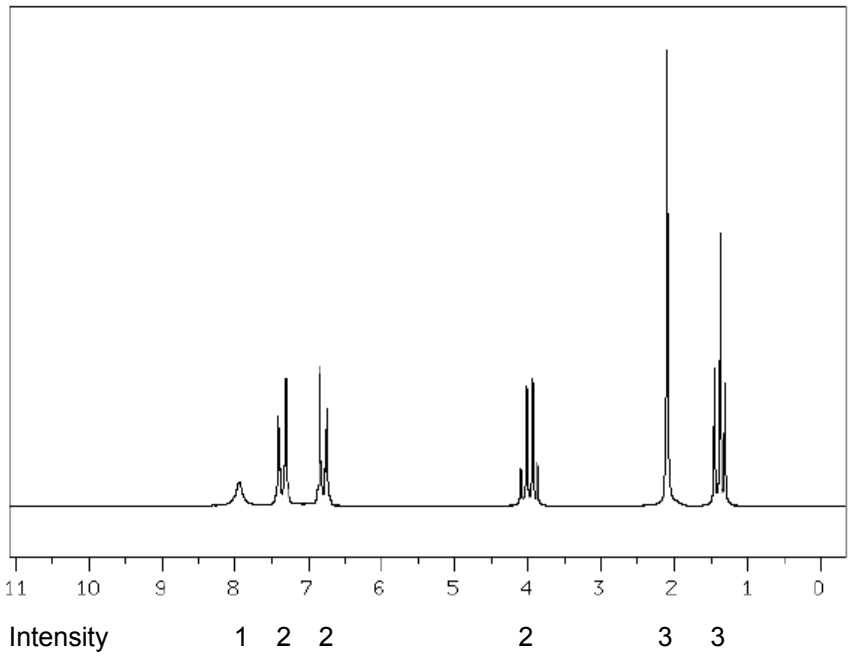
Phenacetin:

One of the first synthetic drugs, that has been commercially available since 1888, is Phenacetin, a mild analgesic. Due to side effects, it was removed from the market in 1986. Phenacetin **E** can be synthesized according to the following scheme:



The ^{1}H NMR spectrum of **E** is shown on the next page.

23.3 Write down structural formulas for A to E. Assign the NMR signals in the figure (see next page) to the corresponding protons in the structure of E. Explain the splitting pattern of the signals. *(table of ^{1}H-NMR chemical shifts on page 24)*

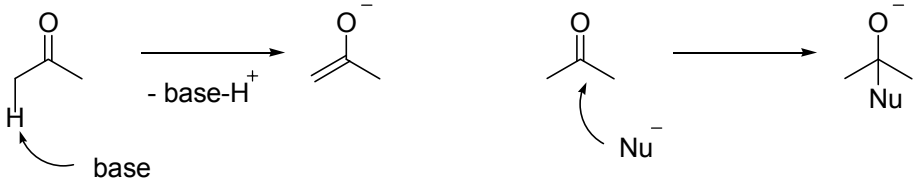


23.4 If you compare acetylsalicylic acid (ASS) and phenacetin (E), which of the following statements are true, false or can not be evaluated?

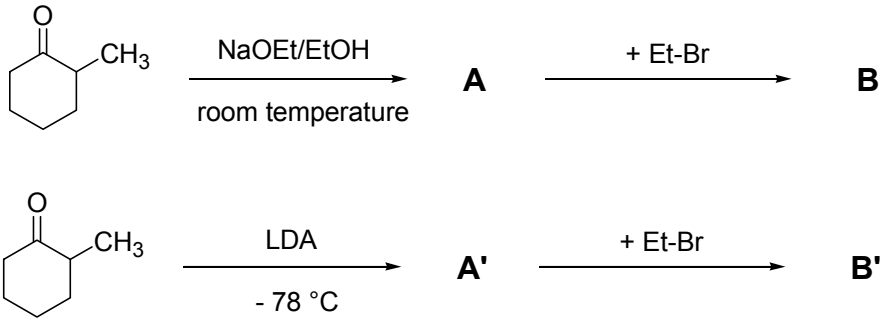
	true	false	no decision possible
At pH = 9 phenacetin is more polar than acetyl salicylic acid	☐	☐	☐
Both compounds can be deprotonated by $NaHCO_3$	☐	☐	☐
The aromatic ring in phenacetin is more electron- rich than in acetylsalicylic acid	☐	☐	☐
None of them is chiral	☐	☐	☐
On a silica gel TLC plate, developed with 5% acetic acid in ethyl acetate, the Rf value for phenacetin is larger than for acetylsalicylic acid	☐	☐	☐

Problem 24: Carbonyl Chemistry

The carbonyl group C=O is a very versatile functional group in organic chemistry as it allows a wide range of chemical reactions among them some very useful C-C-bond forming reactions. The deprotonation in the α position to form an enolate and the attack of a nucleophile on the carbonyl C-atom are the two most important ways in which a C=O can react:



A lot of stereo- and regiochemical issues are associated with both these reactions, especially when the carbonyl compound is not symmetrical. Have a look, for example, at the following regioselective alkylation of 2-methyl-cyclohexanone (only mono-alkylation shall be considered):

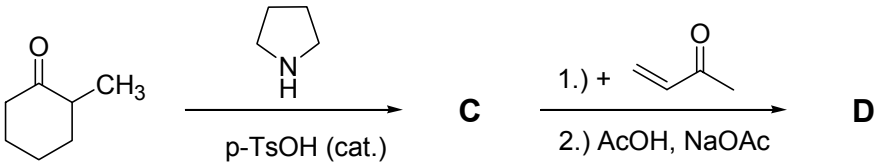


LDA: lithium diisopropyl amide, Pr_2NLi, a strong non-nucleophilic base

24.1 Write down the structures of A, A', B and B' (ignore stereochemistry here) and explain the different results of the two reactions with regard to the reaction conditions.

24.2 Why can butyllithium (BuLi) not be used for deprotonation?

The direct alkylation of enolates is often not very efficient for a preparative synthesis due to problems with further di- or tri-alkylation. Hence, enamines are sometimes used as an alternative.

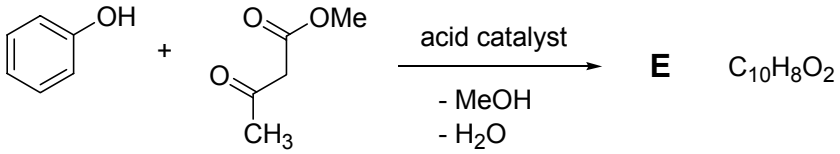


24.3 Write down the mechanism of the formation of enamine C. What about regiochemistry here?

24.4 Explain with appropriate resonance structures why enamines react with electrophiles.

24.5 Write down the structure of the reaction product D (ignore stereochemistry here).

Consider the following reaction sequence for the synthesis of a coumarin derivative (nowadays solid phase bound acids such as Nafion H or Amberlyst are used as acid catalysts).



24.6 Write down the structure of E and explain its formation.