

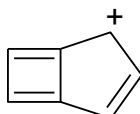


Sample: Organic Chemistry - Organic and Medical Chemistry

ORGANIC AND MEDICINAL CHEMISTRY

INSTRUCTIONS: Answer all questions directly on the original sheets provided here using chemical drawing softwares (copy and paste schemes on this sheet as necessary).

1. Explain whether the ion (1) shown below is aromatic or not (you can assume it is planar *if* it satisfies all the other requirements for aromaticity):

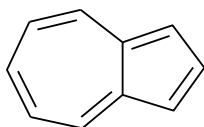


(1)

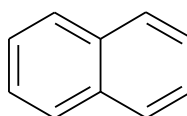
(3 marks)

The ion (1) is aromatic, because it is planar, has a delocalized conjugated π system (arrangement of alternating single and double bonds) and obeys Hückel's Rule – number of π delocalized electrons is 6 (according to Hückel's Rule, number of π electrons must be $4n + 2$, where $n=0, 1, 2, 3, \dots$ for a substance to be aromatic)

2. Compound 2 is an isomer of naphthalene. Compound 2 is found to have a high dipole moment compared to naphthalene, which has no dipole moment. Both compounds are regarded as being aromatic:



(2)



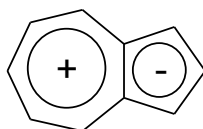
naphthalene

- (a) Explain why compound 2 is aromatic and has a high dipole moment.

(5 marks)

The compound 2 is aromatic, because it is planar, has a delocalized conjugated π system (arrangement of alternating single and double bonds) and obeys Hückel's Rule – number of π delocalized electrons is 10.

The compound 2 has a high dipole moment, because it may be regarded as the fusion of the aromatic 6 π -electron cyclopentadienyl anion and aromatic 6 π -electron tropylium cation:



In order to achieve the stable aromatic sextet in both rings, one electron from the seven-membered ring is transferred to the five-membered ring.

- (b) If compound **2** were treated with $\text{Br}_2/\text{FeBr}_3$, which ring would undergo bromination? You do not need to give the specific site of bromination – only the ring in which it occurs and a brief explanation why.

(2 marks)

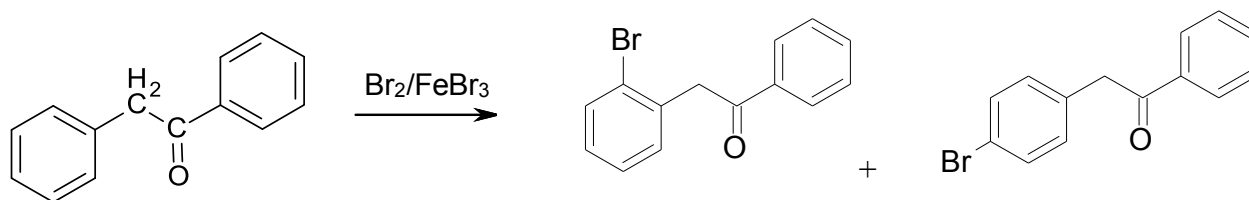
Since compound **2** may be regarded as the fusion of the aromatic 6 π -electron cyclopentadienyl anion and aromatic 6 π -electron tropylium cation, the seven-membered ring is electrophilic and the five-membered ring is nucleophilic. Bromination catalyzed by FeBr_3 is electrophilic substitution, that is why the five-membered ring would undergo bromination.

3. Predict the outcomes of the following reactions. A brief explanation of your answer in each case must be given. It is not enough just to state the answer, though full, detailed discussion involving Wheland intermediates is not required:

(3 x 5 marks)

Before start considering every particular case I'd like to note that all three reactions are electrophilic substitution reactions (S_E). That is why an electrophyl will substitute the site with the highest nucleophilicity (i.e. highest partial negative charge). Electron-acceptor substituents deactivate benzene ring in S_E reaction, orientating substituents to m-position. Electron donor substituents activate benzene ring in S_E reaction, orienting substituents to o- and p-site.

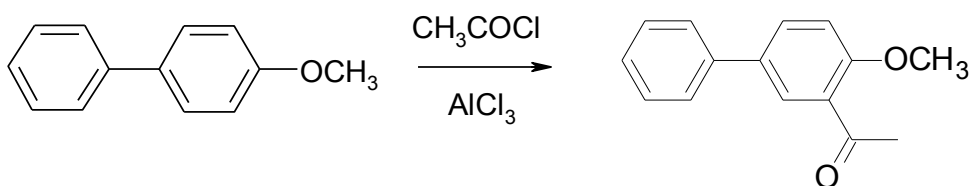
- (a) bromination of phenyl benzyl ketone:



The right ring is deactivated because carbonyl group draws electron density to itself (-M effect). Alkyl groups have weak electron donor effect (+I and +M effects). Since the methylene ($-\text{CH}_2-$) group is adjacent to the carbonyl, it has weaker electron donor effect, but anyway it activates the left ring. That is why bromination occurs into o- and p-site of the benzyl fragment (left ring).

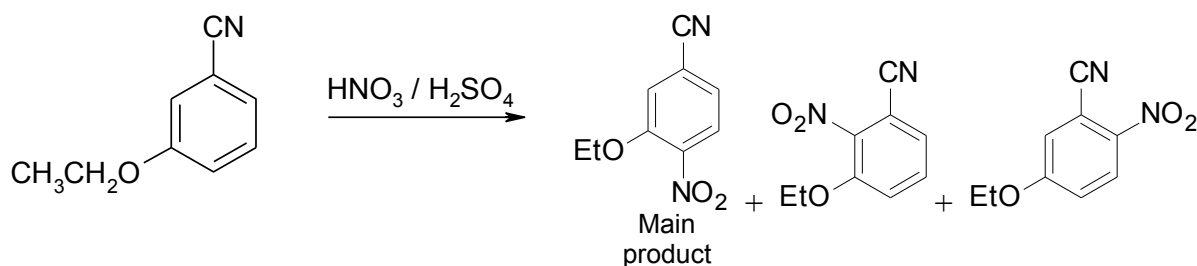


(b) acetylation of 4-methoxybiphenyl:



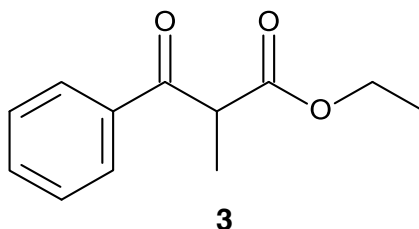
Left ring has one substituent – 4-methoxyphenyl, the right ring has two substituents: phenyl and methoxy group. All three substituents are electron donor and activate benzene rings. The $-OCH_3$ has much stronger effect (+M) compared to phenyl and 4-methoxyphenyl. That is why the left ring is much less reactive in S_E reaction and acetylation occurs into the o-site of the right ring.

(c) nitration of 3-ethoxybenzonitrile:



The CN group is an electron-acceptor (-I and -M effect), deactivating the ring and orienting the substituent into the m-position. EtO group is electron-donor (+M effect), activating the ring and orienting the substituent into the o- and p-sites. So, the substituents have opposite effect. In such case the electron-donor substituent has decisive influence. So, nitration occurs into o- and p-sites relative to EtO group. All three isomers are formed, but the first of them – 3-ethoxy-4-nitrobenzonitrile, considerably prevails, because o-sites relative to EtO group are more activated than p-position and the o-sites relative to CN group are more deactivated than the p-site.

4. Compound **3** racemises in a basic solution. Identify why this might be and propose and draw a mechanism for the racemisation of **3** using appropriate diagrams and reaction schemes.

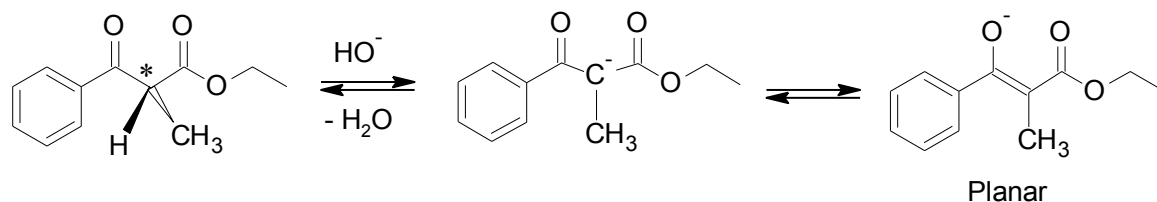


(6 marks)

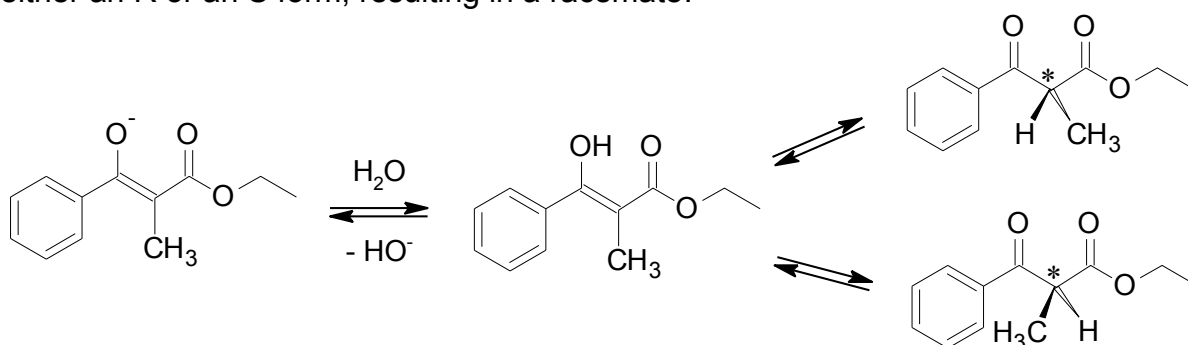
The racemization occurs by way of an intermediate enol form in which the former stereocenter becomes planar and hence achiral.



In particular case of compound **3** the chiral atom (marked with *) is bound with highly acidic hydrogen atom. This atom is eliminated when interacting with a base, resulting in planar intermediate enol form.



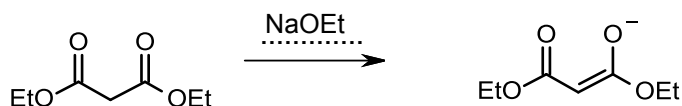
An incoming reactant (e.g. water) can approach from either side of the plane, so there is an equal probability that protonation back to the chiral compound will produce either an R or an S form, resulting in a racemate.



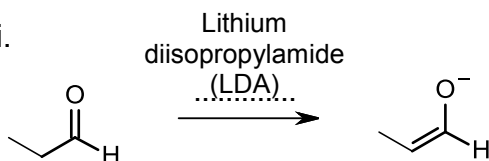
5. Answer all of the following questions

a. Identify a suitable base for the formation of the enolate for the following species and write this on top of the arrows:

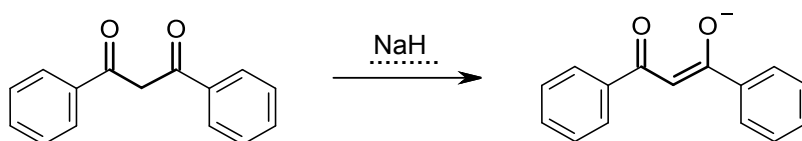
i.



ii.

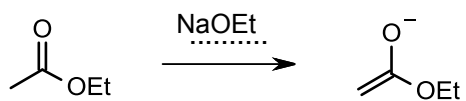


iii.



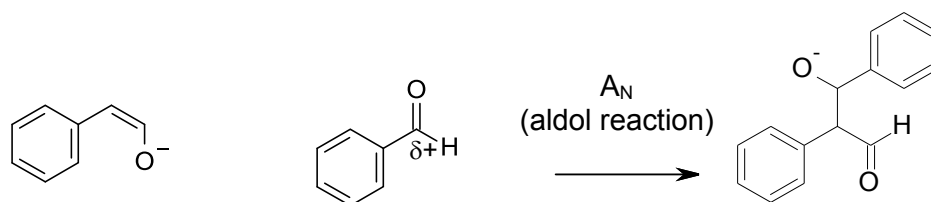
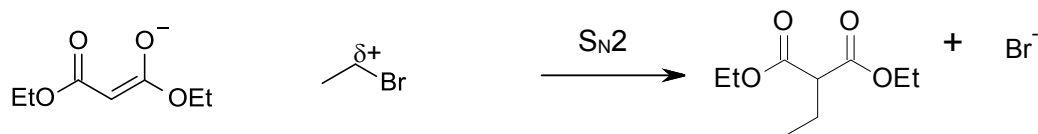


iv.

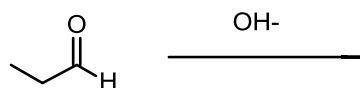
**(4 X 1 mark)**



- b. Write the product of the reaction between the following enolates (i.e. nucleophiles) and the electrophile pairs. Clearly show the electrophilic atom by writing δ^+ on it and state what type of reaction it is (e.g.: N_A ; S_NAc , S_N1 , S_N2 , elimination etc) above the arrow. (3 X 3 marks)

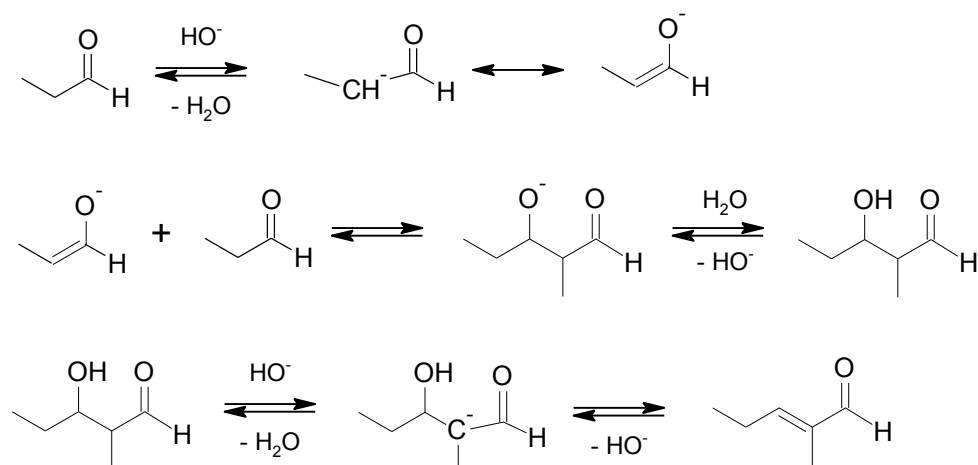


- c. write the name and draw the full mechanism of the following reaction with the use of appropriate diagrams.



(6 marks)

The reaction name is crotonic condensation. Its full mechanism may be represented as follows

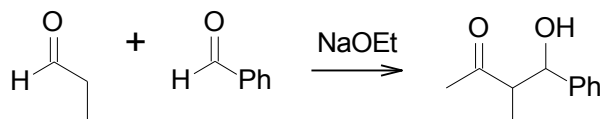




- d. draw an example of a Cross Aldol reaction that gives selectively one product and justify your answer. Please note: your example should be different from the one discussed in class during workshops. Please note also that you should write the equation only, a full mechanism is not requested in this case.

(6 marks)

If only one of the reactants has acidic α hydrogens, only this molecule forms the enolate. For example, the addition of propionic aldehyde into benzaldehyde would produce only one product:



Only the acetaldehyde has α hydrogens, so it is the nucleophilic partner, whereas the non-enolizable benzaldehyde can only be the electrophile.