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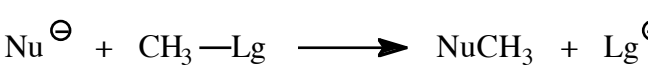
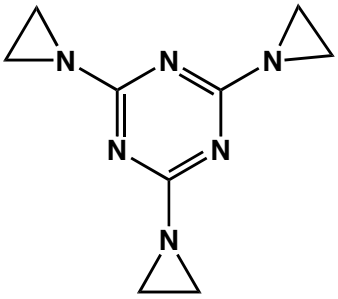
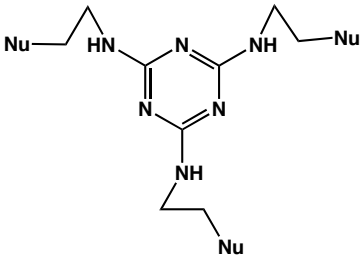
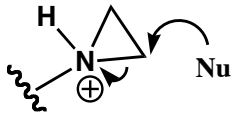
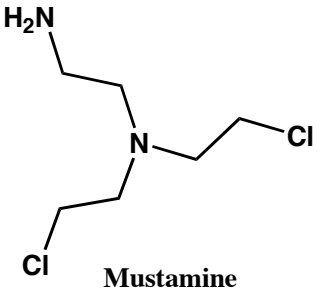
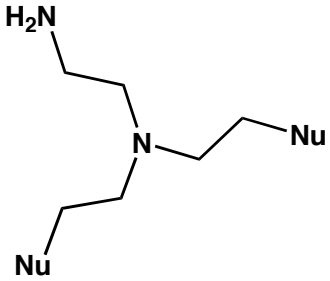
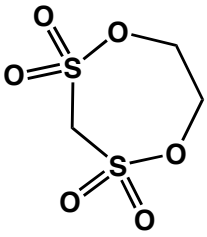
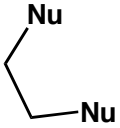
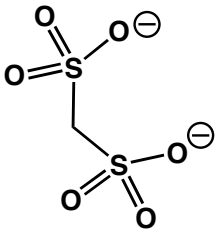
PROBLEM SET #3
CHM 333
November 13, 2008

1. The following antitumor agents are under investigation at the National Cancer Institute. For each compound show the structure of the nucleophile substitution product using "Nu⁻" as your generic nucleophile.

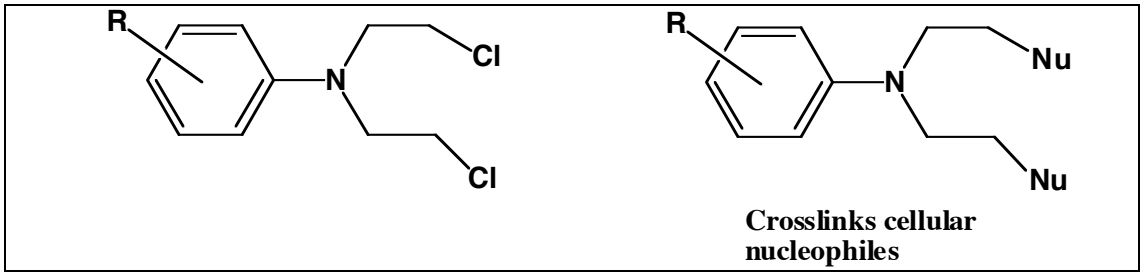
example



Note that some agents may react with a nucleophile more than once; show the product resulting from nucleophilic reaction at all possible sites. Also show the structure of the leaving group(s) resulting from these reactions.

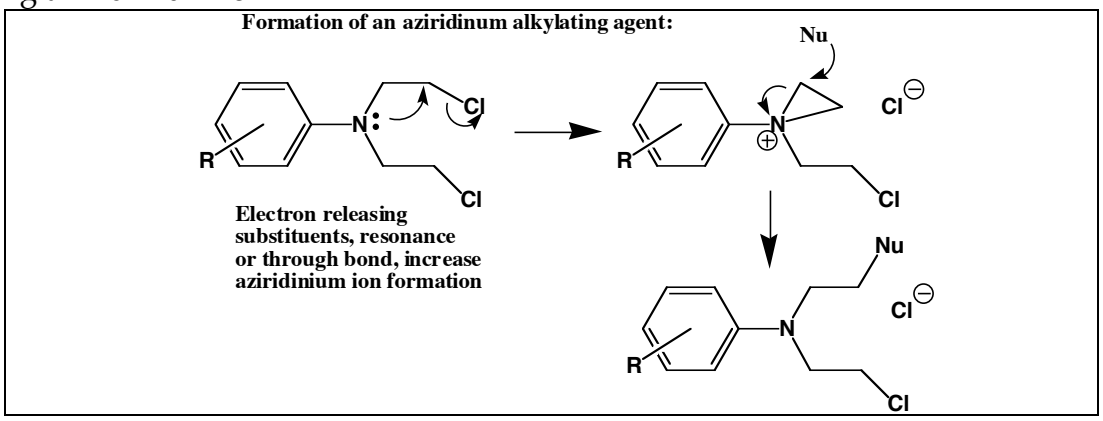
Antitumor Agent	Nucleophile Substitution Product	Leaving Group(s)
 **Triethylenemelamine**		 Protonated nitrogen is the leaving group
 **Mustamine**		
 **Cyclodisone**		

2. Substituent effects applied to drug action. The nitrogen mustard shown below inhibits the growth of hamster ovary cells by a crosslinking alkylation reaction.

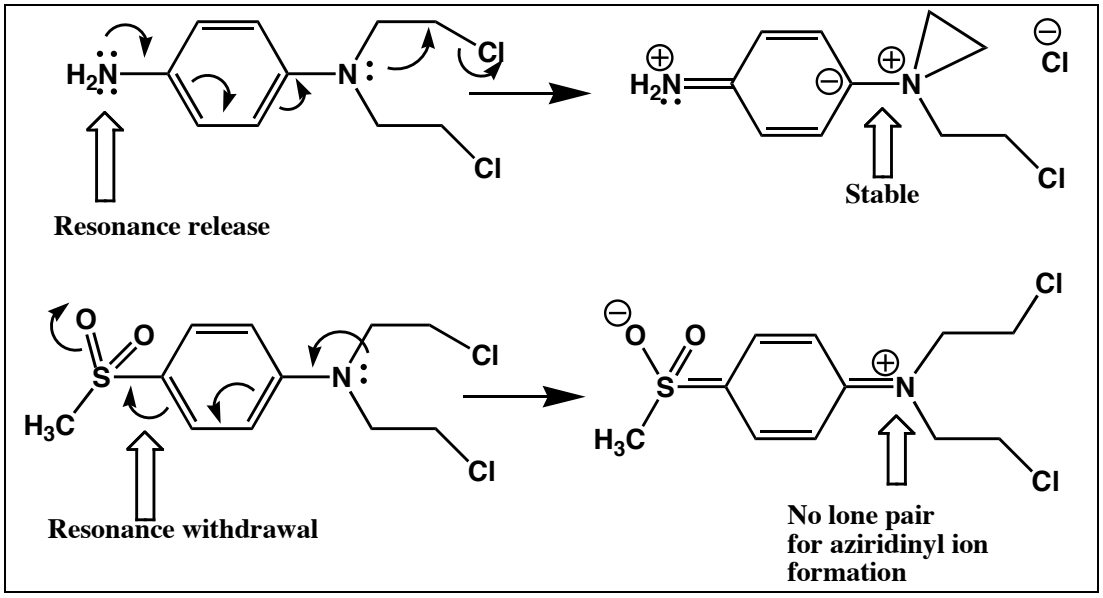


The most active analogue has a *p*-amino substituent and the least active analogue (2450-fold less active) has a p-SO_2Me substituent**.** Explain by providing an alkylation mechanism and resonance structures.

A mechanism that explains these results involves utilization of the nitrogen lone pair to form an alkylating aziridinium ion:

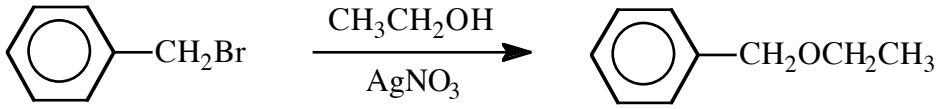


An analogue possessing an electron releasing substituent, such as p-amino, will be more active because aziridinium ion formation is favored.

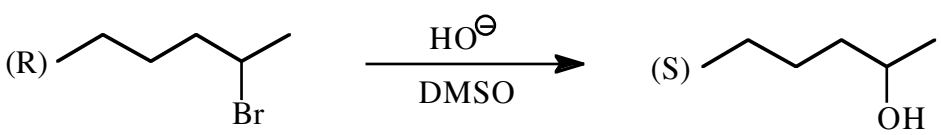


3. Predict the major organic product of the following reactions. If there is no reaction, write "NR" as your answer. Show stereochemistry of the product if appropriate.

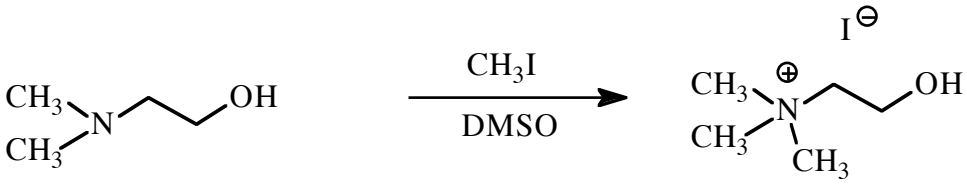
(a)



(b)

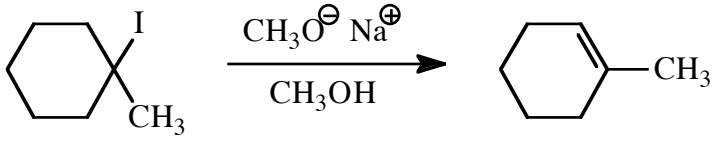


(c)

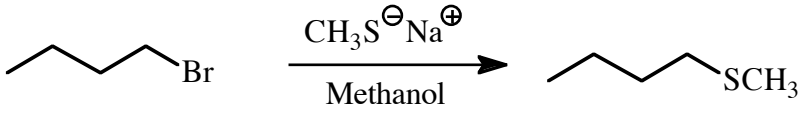


Note that nitrogen is more nucleophilic than oxygen

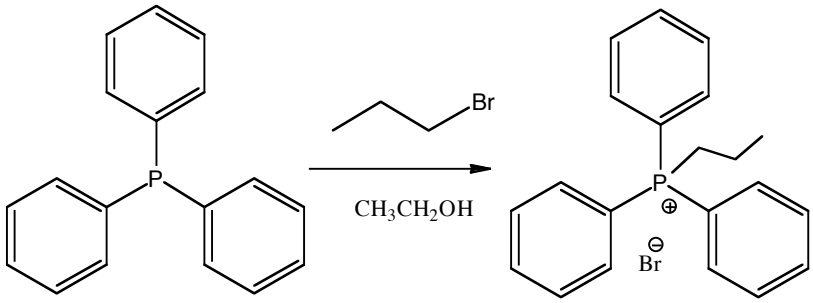
(d)



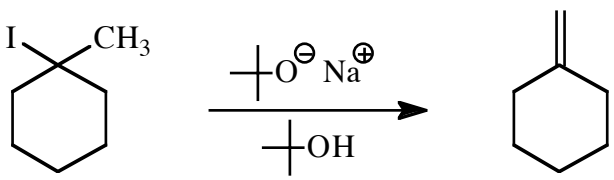
(e)



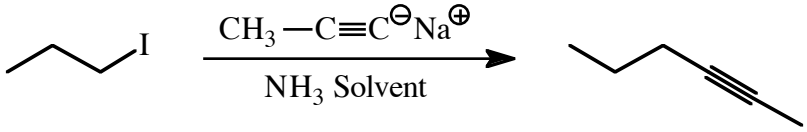
(f)



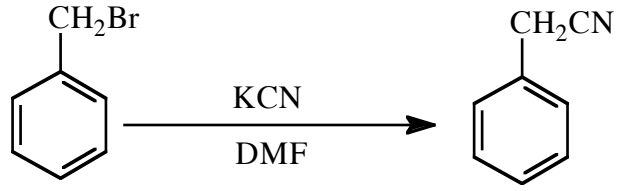
(g)



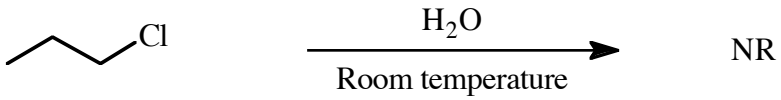
(h)



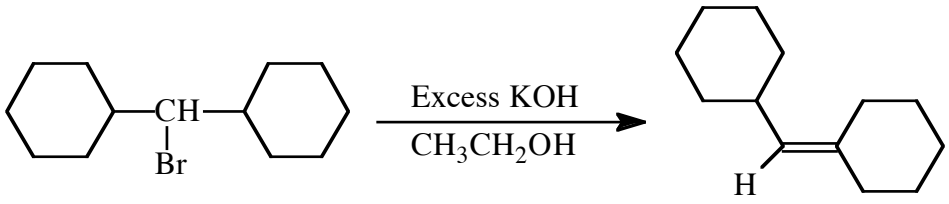
(i)


CH2Br
KCN
DMF
CH2CN

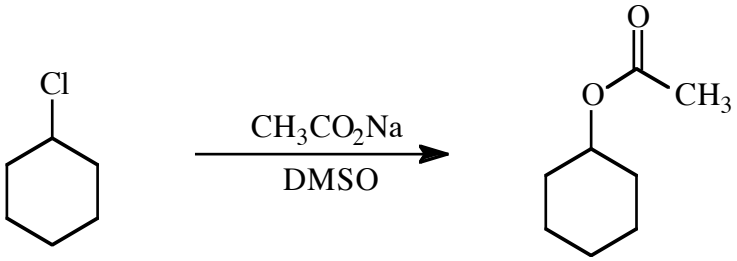
(j)


Cl
H2O
Room temperature
NR

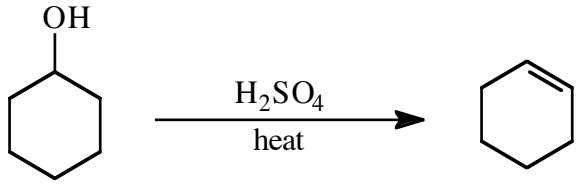
(k)


CH
Br
Excess KOH
CH3CH2OH
H

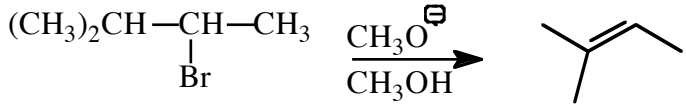
(l)


Cl
CH3CO2Na
DMSO
O
O
CH3

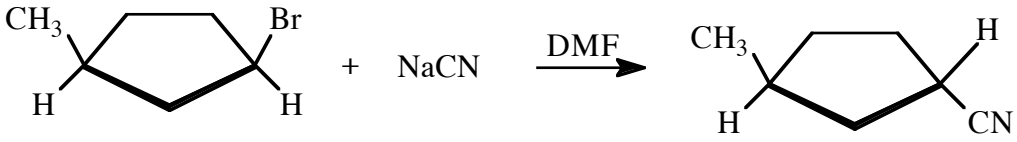
(m)


OH
H2SO4
heat

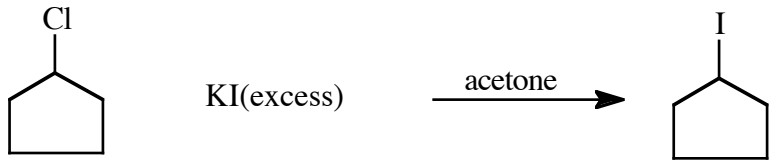
(n)

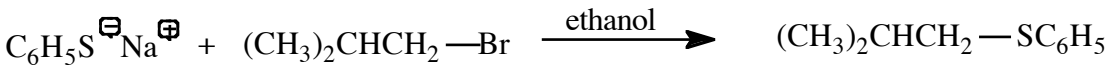

(CH3)2CH—CH—CH3
Br
CH3O⊖
CH3OH

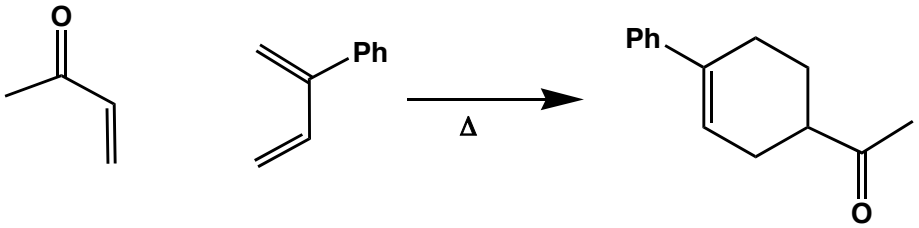
(o)

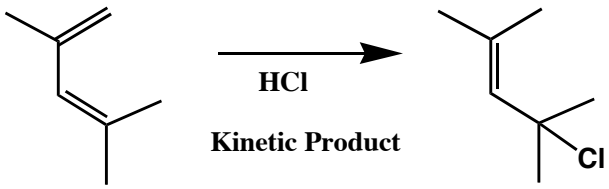

CH3
Br
H
H
+
NaCN
DMF
CH3
H
H
CN

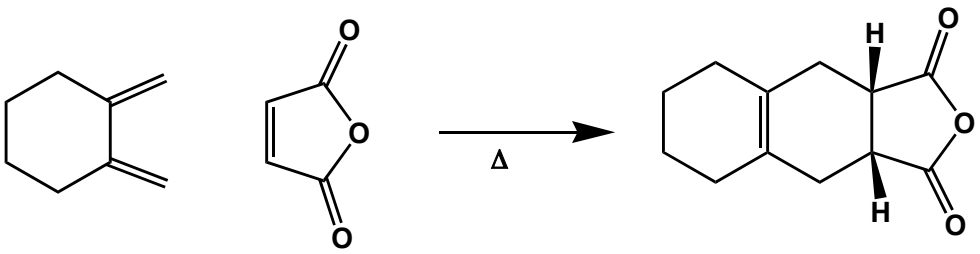
(p)

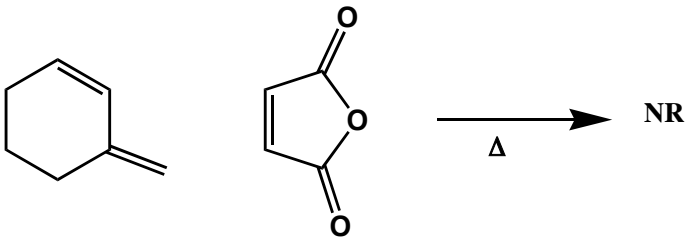

Cl
KI(excess)
acetone
I

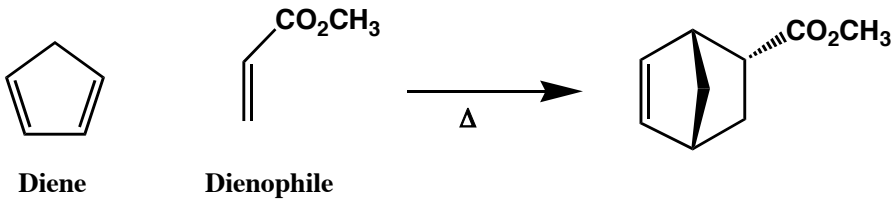
(q) 
$C_6H_5S^{\ominus}Na^{\oplus}$ + $(CH_3)_2CHCH_2$—Br
ethanol
$(CH_3)_2CHCH_2$—SC_6H_5

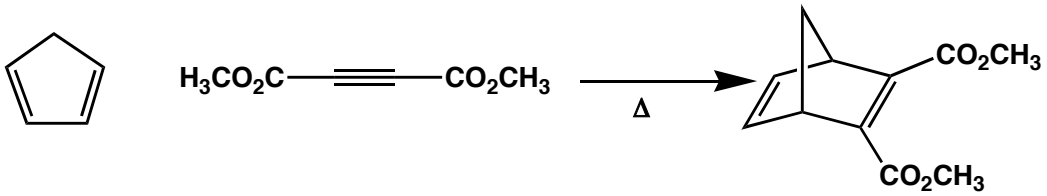
(r) 
O
Ph
Δ
Ph
O

(s) 
HCl
Kinetic Product
Cl

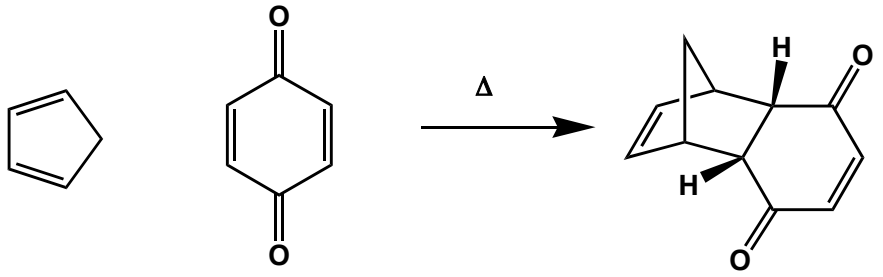
(t) 
O
O
O
Δ
H
O
O
H
O

(u) 
O
O
O
Δ
NR

(v) 
CO_2CH_3
Δ
CO_2CH_3
Diene
Dienophile

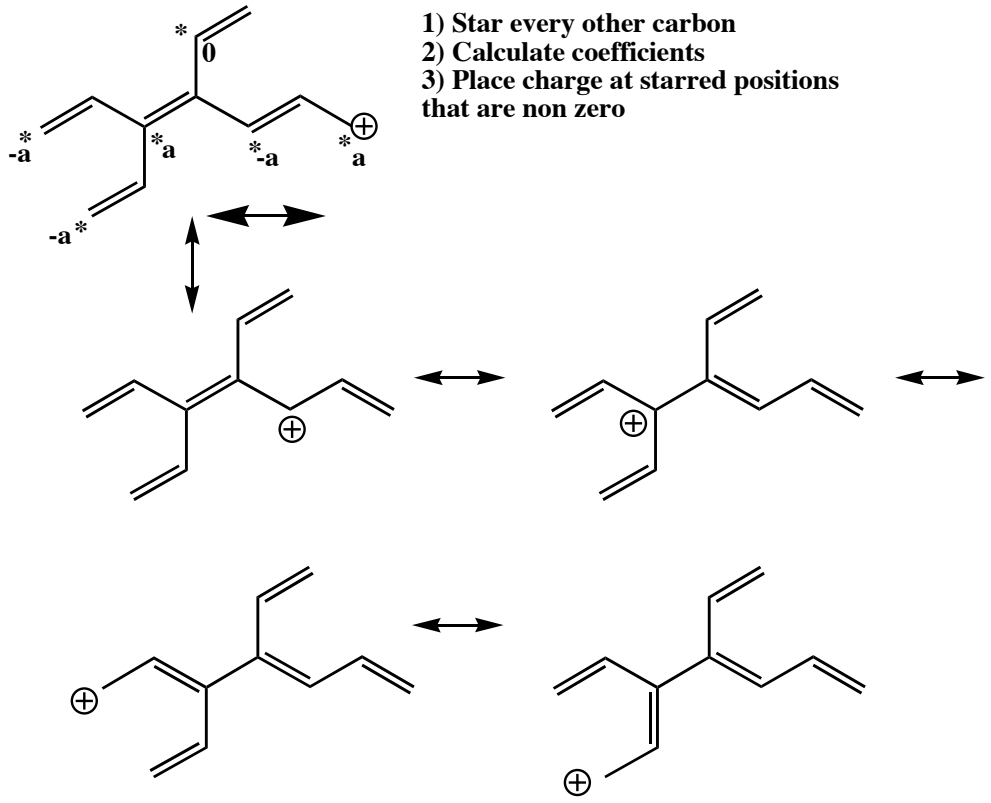
(w) 
H_3CO_2C—CO_2CH_3
Δ
CO_2CH_3
CO_2CH_3

(x)



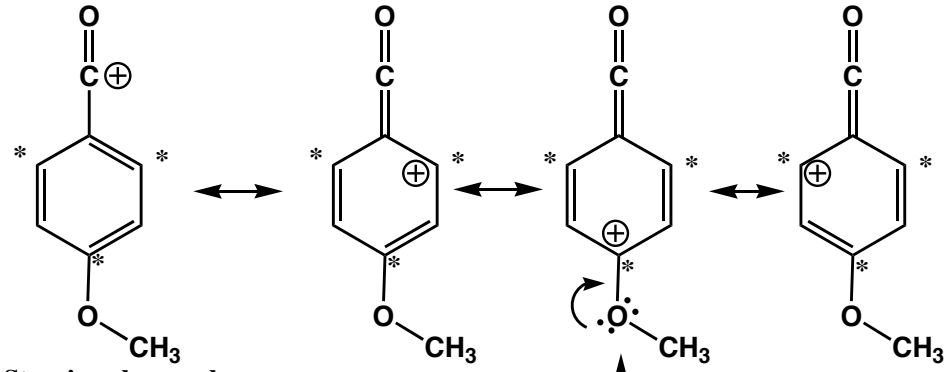
4. Show all charge delocalization structures for the following charged species. Include all degenerate structures.

a)

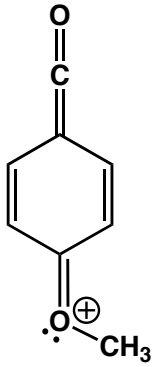


1) Star every other carbon
2) Calculate coefficients
3) Place charge at starred positions that are non zero

b)

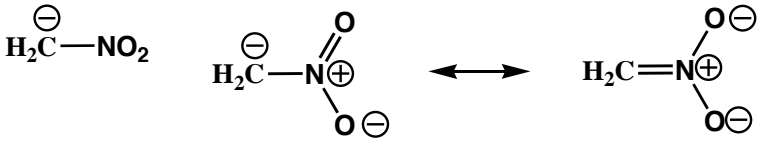


Starring shows where charge is distributed in the ring



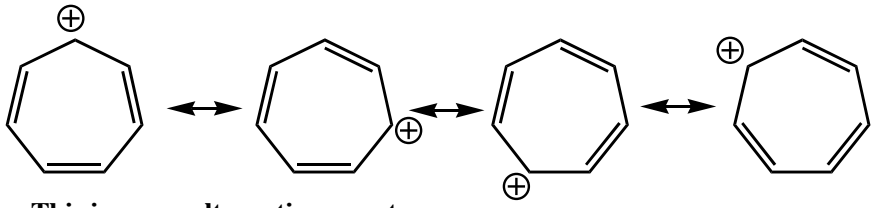
Methoxy group stabilizes the carbocation by through resonance

c)

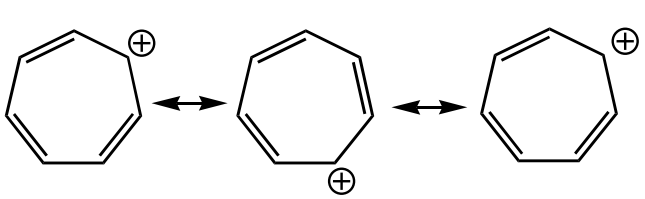


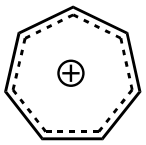
The charge-separated structure of nitro must be drawn out to answer this question

d)



This is a non-alternating π system and the charge is at every position

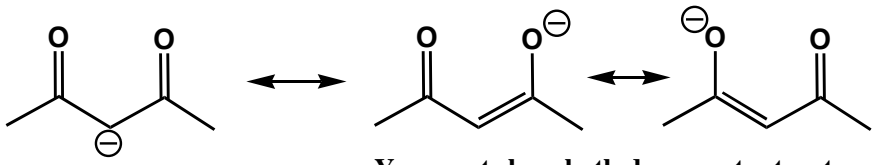




The summation of all resonance structures

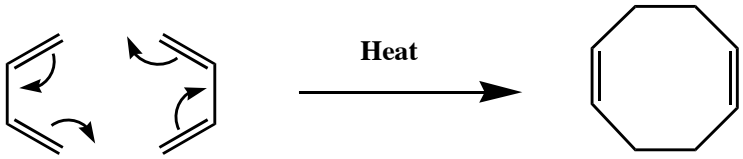
This is the tropilium ion, a common species seen in mass spectrographs

e)

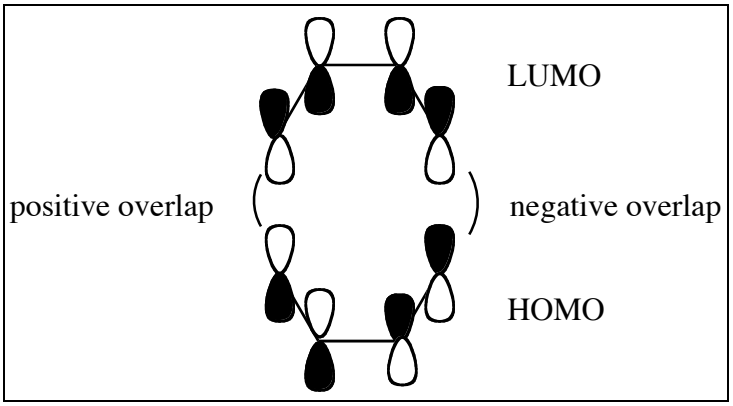


You must show both degenerate structures

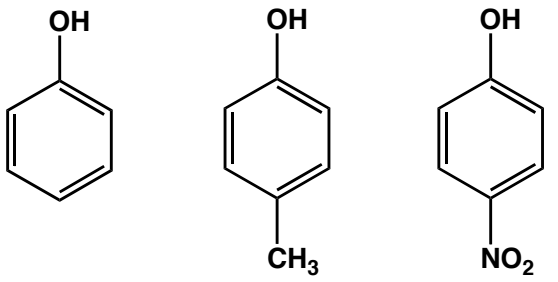
5. The following 4+4 cycloaddition does not occur thermally. Provide two explanations referring to the aromaticity of the transition state and HOMO-LUMO interactions.



The transition state has 8 electrons in a loop. Such 4n or antiaromatic transition states are not allowed. We call reactions of this type forbidden.
Showing the HOMO-LUMO interaction will reveal no net overlap. This means that the reaction will not occur.



6. Rank each of the following groups of compounds as instructed. Provide an explanation for your ranking along with supporting resonance structures.

a) 

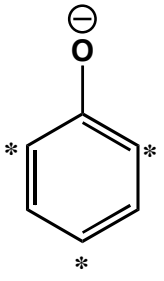
A **B** **C**

Rank by acidity of the hydroxyl group.

C > A > B

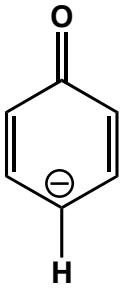
Strongest acid — Weakest Acid

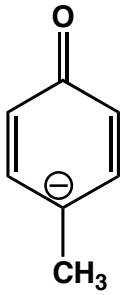
To answer this problem show the distribution of the phenolate anion using stars. The influence of the substituent on the anion can then be assessed. The more stable the phenolate anion, the stronger the acid.



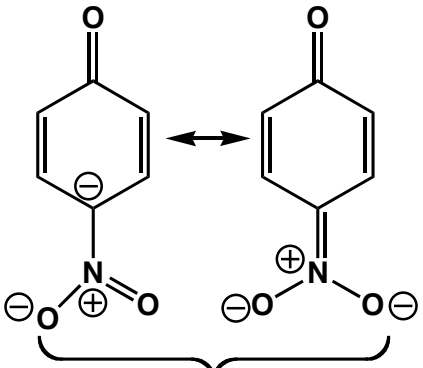
Phenolate anion with stars showing charge distribution

Since substituents are located in the para position, show the resonance form with anion in the para position.

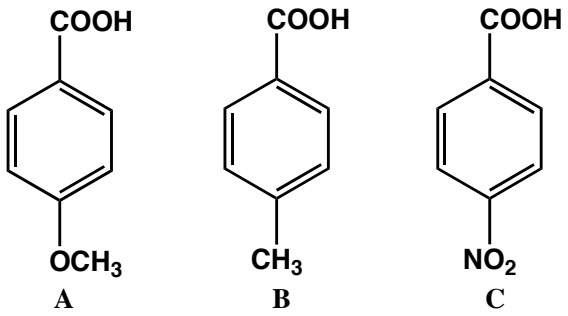




Anion destabilized by hyperconjugation



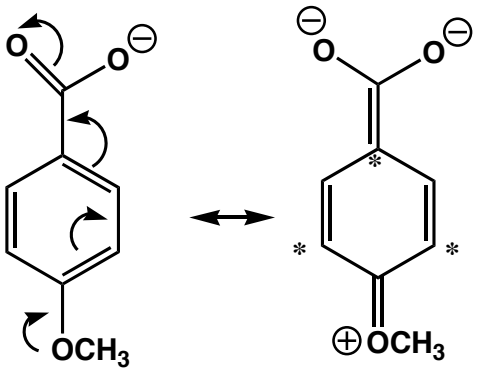
Through resonance of anion into nitro group, anion most stable.

b) 

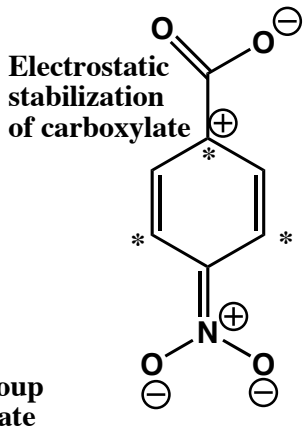
Rank by acidity of the carboxyl group.

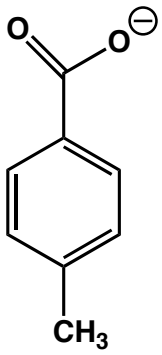
C (Strongest acid) > B > A (Weakest Acid)

To answer this problem show the influence of the substituent on the carboxylate anion using resonance and starring. The more stable the carboxylate anion, the stronger the acid.



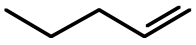
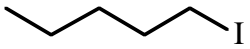
Resonance release by the methoxy group into the carboxylate group. Carboxylate anion destabilized

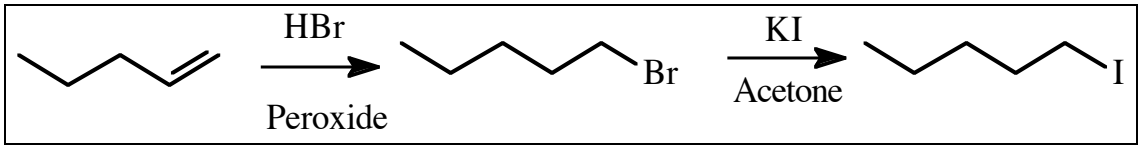




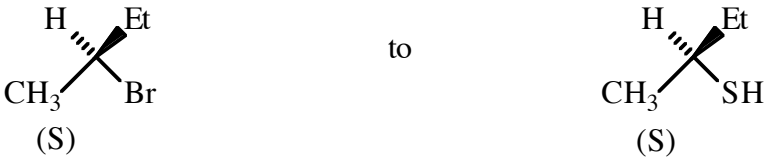
Only capable of hyperconjugation, minimal effect on carboxylate anion

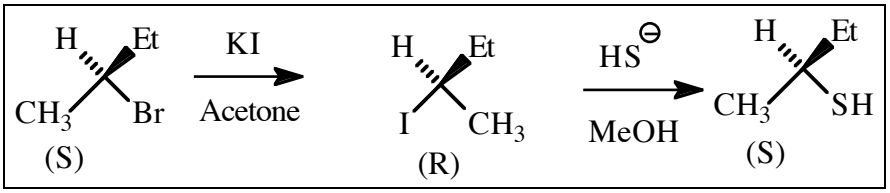
7. Show how the starting material on the left could be converted to the product on the right. Show intermediate compounds along with all necessary reagents and conditions.

(a)  To 

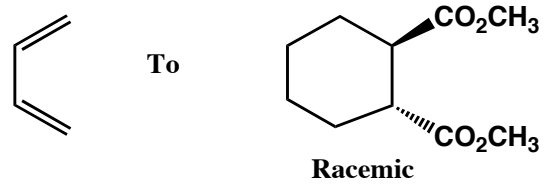


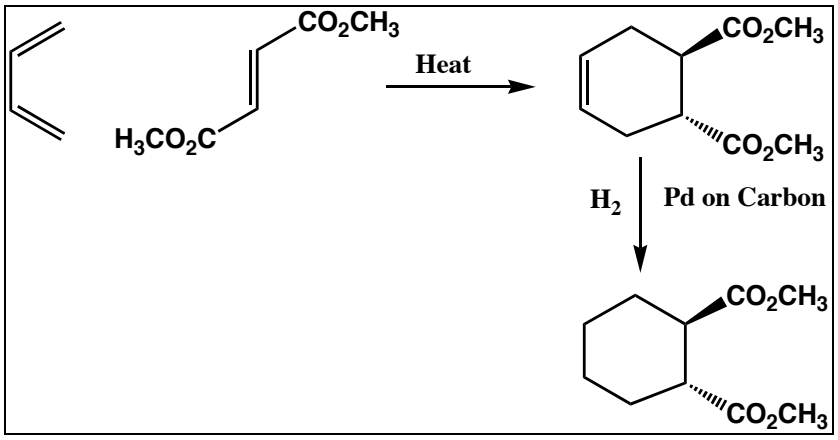
(b)


H
Et
CH3
Br
(S)
to
H
Et
CH3
SH
(S)

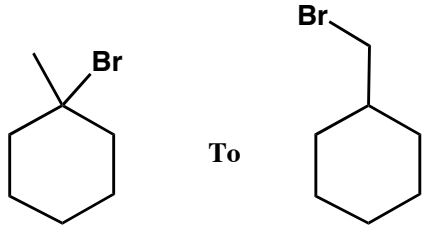

H
Et
CH3
Br
(S)
KI
Acetone
H
Et
I
CH3
(R)
HS⊖
MeOH
H
Et
CH3
SH
(S)

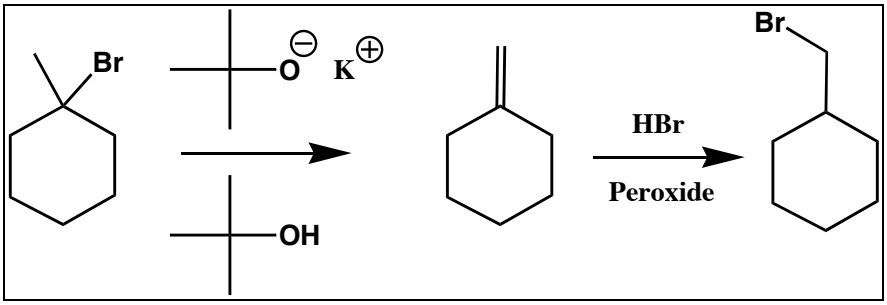
(c)


To
CO2CH3
CO2CH3
Racemic


CO2CH3
H3CO2C
Heat
CO2CH3
CO2CH3
H2
Pd on Carbon
CO2CH3
CO2CH3

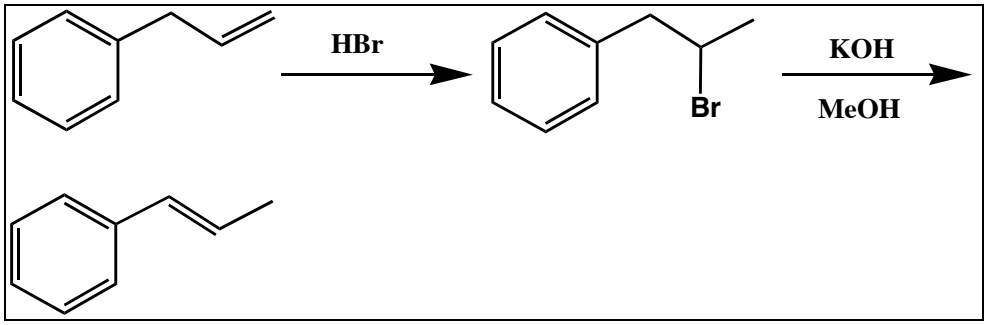
(d)


Br
To
Br

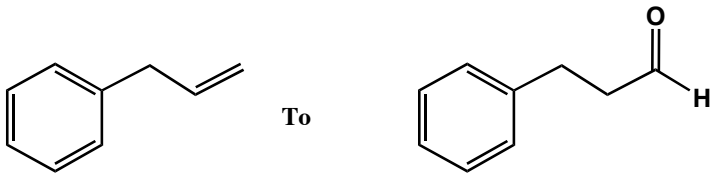

Br
O
K
OH
HBr
Peroxide
Br

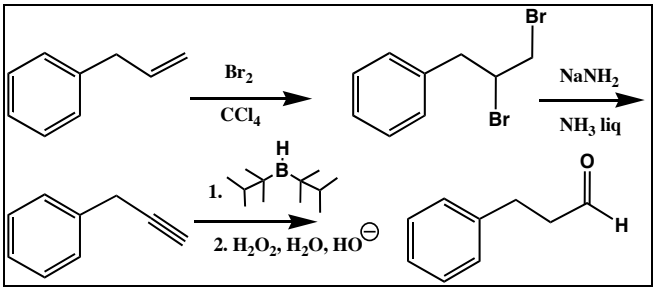
(e)


To

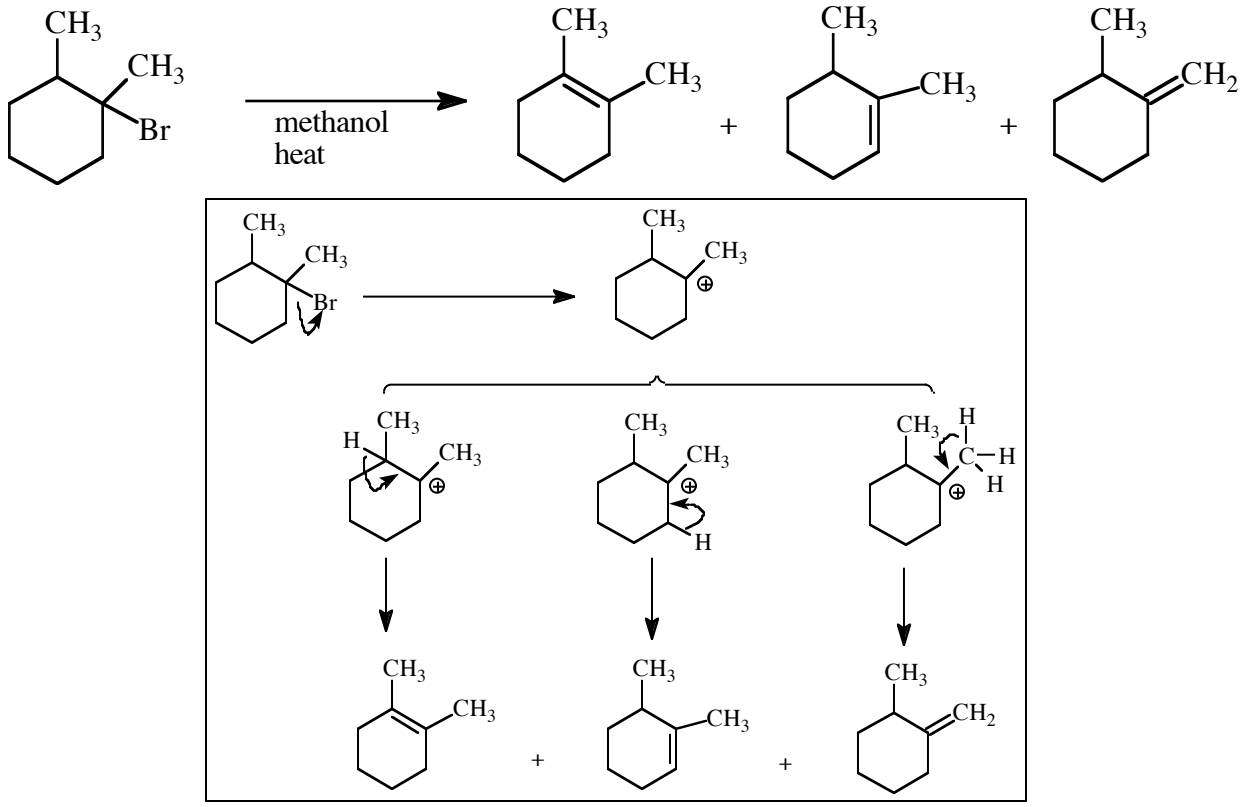

HBr
Br
KOH
MeOH

(f)

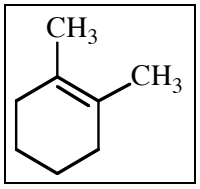

To
O
H


Br2
CCl4
Br
Br
NaNH2
NH3 liq
H
B
1.
2. H2O2, H2O, HO
O
H

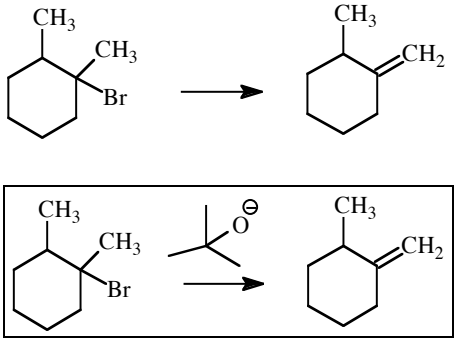
8. Provide a mechanism, which explains the formation of the solvolysis products shown below.



Which of the above alkenes is the major solvolysis product?

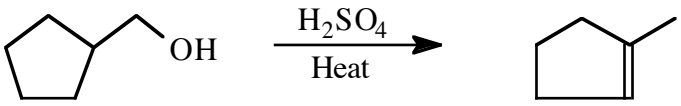


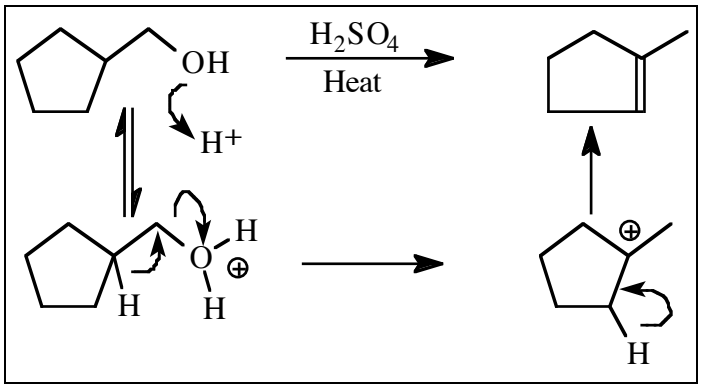
Suppose you wanted to carry out the transformation shown below in high yield. How would you do it?



9. Mechanisms. Provide a mechanism for the following reactions. Show intermediates persent in the reaction along with curved arrows and proton transfers.

(a)





(b)