BioE 11 Midterm 1: Spring 2023
ANSWER KEY

Last Name: _____

First Name: _____

Student ID No. (SID): _____

Instructions: This exam is 9 pages and consists of 18 multiple choice questions. A response sheet will be provided separately. Please record all your final answers on this sheet before you turn in your exam. Write your answers legibly using capital letters. Do not remove any sheets from this exam. You may use any blank space on the exam, except for the answer sheet, for scratch work.

Time allowance: 50 minutes

Resources allowed: one double-sided page of notes, pKa reference table, scratch paper, and calculator

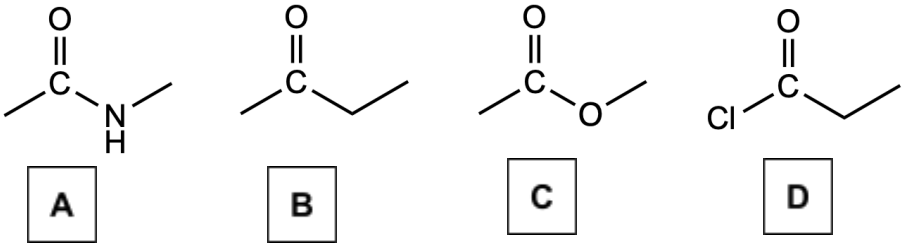
Points: 300 points

BioE 11 Midterm 1 Answer Key

Your exam will be graded based on the answers you record below. Please write legibly and use capital letters.

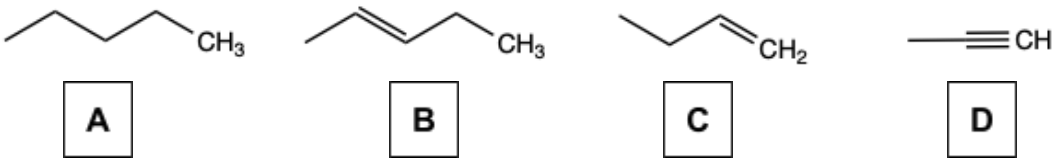
1. __D___
2. __D___
3. __C___
4. __D___
5. __D___
6. __A___
7. __B___
8. __B___
9. __C___
10. __C___
11. __C___
12. __D___
13. __I___
14. __B___
15. __B___
16. __D___
17. __G___
18. __C___

Topic: electrophilicity and nucleophilicity (answer is D)
1. Which of the following molecules will serve as the **best electrophile and acylate an alcohol?** (12 pts)



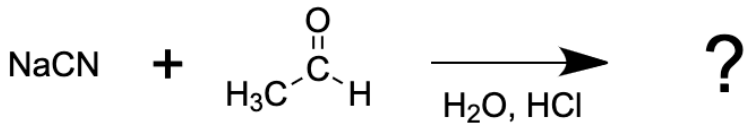
Solution: In general, carbonyls serve as good electrophiles, but this question requires an understanding of what makes a relatively better electrophile. The **answer is D** because a chlorine substituent on the carbonyl leads to a heavy electron withdrawing effect that makes the carbonyl carbon more electrophilic. Additionally, because chlorine makes for a good leaving group following carbonyl attack (Cl^-), this molecule is most likely to acylate (attach a carbonyl group to an alcohol). Answer choices A and C, while containing electronegative atoms that impart an inductive effect, also contain atoms have electron-donating properties which reduces the electrophilicity of the carbonyl. Source: Topic explored in Homework 1 (problems 1 and 2).

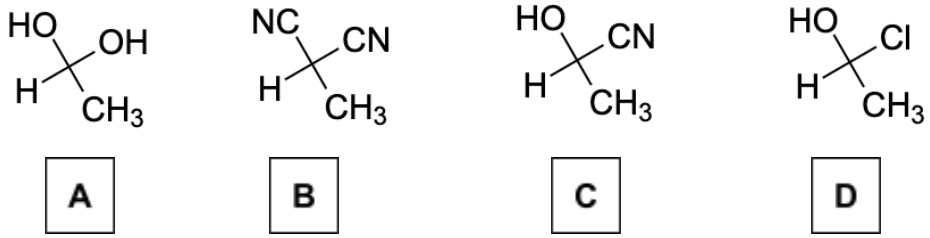
Topic: effect of orbital hybridization on acidity (answer is D)
2. Which of the following molecules is most acidic? (12 pts)



Solution: The answer is D because the alkyne is sp-hybridized. Atoms with hybrid orbitals of higher s character generally yield more acidic molecules because orbitals with more s character are more electronegative and can better stabilize the conjugate base. Source: February 6, 2023 Lecture slides (pgs. 26-27).

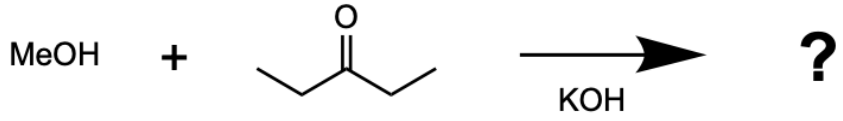
Topic: nucleophilic addition at the carbonyl (answer is C)
3. What is the product of the reaction described below? Small amounts of HCl are used in this reaction (just enough to protonate an ionized alcohol). (12 pts)

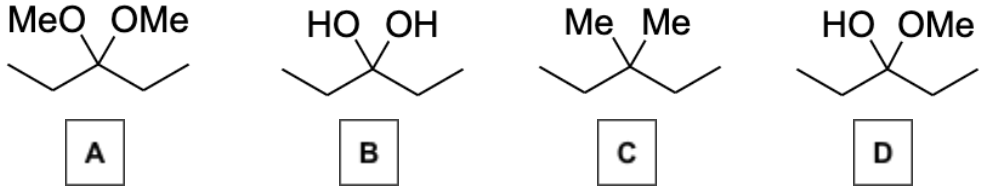




Solution: The product is C through a nucleophilic attack of the cyanide ion on the electrophilic carbonyl. In acidic conditions, the resulting alkoxide ion will quickly be protonated to form an alcohol. Source: January 20 Lecture (page 35).

Topic: base-catalyzed hemiacetal formation (answer is D)
4. What is the product of the reaction described below? This reaction is done under basic conditions. (12 pts)

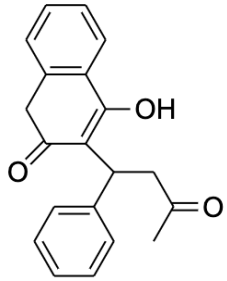




Solution: The answer is D because the reactants included describe ones that generally form acetals or hemiacetals. Because the reaction is performed under basic conditions, only hemiacetals and not acetals are formed. Recall that acid-catalyzed reactions between alcohols and ketones form acetals, but base-catalyzed reactions can only form hemiacetals because the resulting alcohol cannot be protonated to form a good leaving group under basic conditions. Source: Lecture January 25+27 Slides (page 17).

Topic: identifying aromaticity (answer is D)

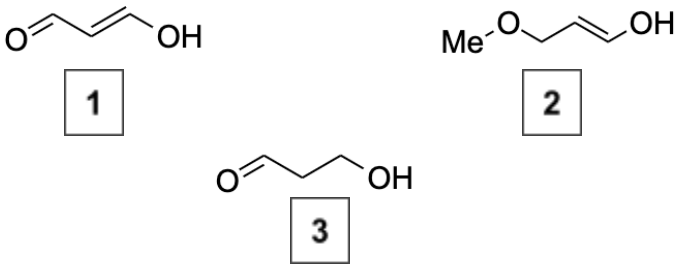
5. How many electrons are in the largest aromatic system in the compound below? (18 pts)
   a) 22
   b) 14
   c) 10
   d) 6



Solution: The answer is D because the largest aromatic system in the compound is a benzene ring which contains 6 electrons. Note the difference between counting electrons in a pi conjugated system vs in an aromatic system. Also, recall the requirements for aromaticity (i.e. molecule must be cyclic, planar, fully pi conjugated, and contain 4n+2 pi electrons). Source: This topic was explored in Homework 2 (problems 5-6).

Topic: effect of resonance stabilization on acidity (answer is A)

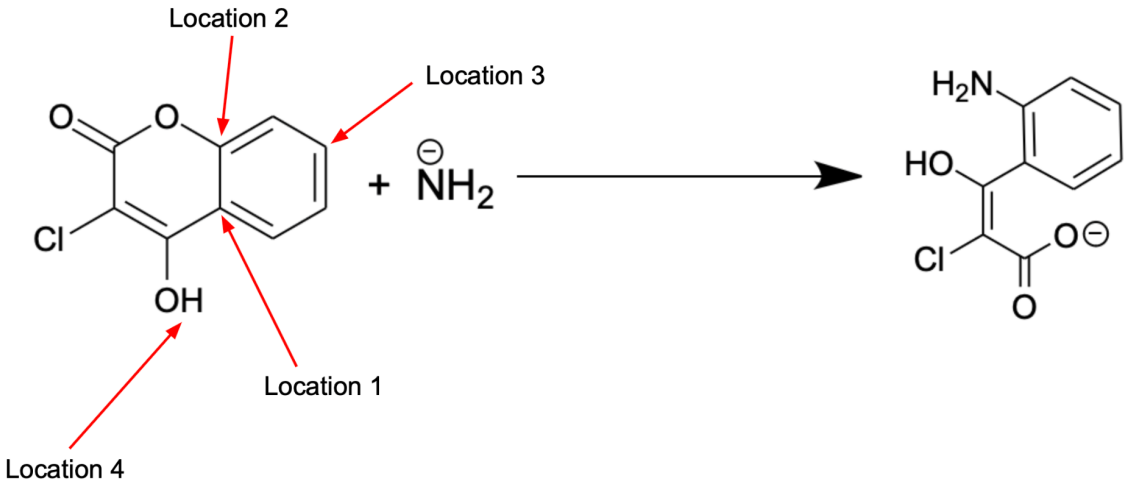
6. Rank the molecules shown below in order of decreasing acidity of the OH bond. (18 pts)
   a) 1 > 2 > 3
   b) 2 > 3 > 1
   c) 3 > 2 > 1
   d) 2 > 1 > 3



Solution: The answer is A because of the role that stabilization of the conjugate base plays in determining the strength of acidity. Answer choice 1 has the longest pi conjugated system for resonance stabilization, followed by answer choice 2, and answer choice 3. Source: Lecture Slides February 6 (page 18).

Topic: electrophilicity and nucleophilicity (answer is B)
7. Where will NH_2- attack in molecule A in order to form molecule B? *Hint: there will be 1 intermediate between the starting and final molecule)* (18 pts)

a) Location 1
b) Location 2
c) Location 3
d) Location 4



Solution: The answer is B because attacking at this location will lead to the breaking of the left ring of the molecule and result in a carboxylate ion, as shown in the product. Attacking any of the other locations will not lead to the product molecule. Source: Topic was explored in Homework 1 (problems 3-4).

Topic: biological application- lipid nanoparticles (answer is B)
8. Which factor most affects how well a lipid nanoparticle disrupts endosomes as a drug delivery mechanism? (18 pts)

a) Number of different lipids in the lipid nanoparticle
b) pKa of the ionizable lipid
c) pKa of the PEG-lipid
d) Sequence of the mRNA

Solution: The answer is B because the restructuring of the ionizable lipid in a nanoparticle leads to endosomal destabilization and rupture. The pKa of the ionizable lipid determines the conditions in which this event happens. Source: February 13 2023 Lecture Slides (page 23)

Topic: effect of hybridization on acidity (answer is C)

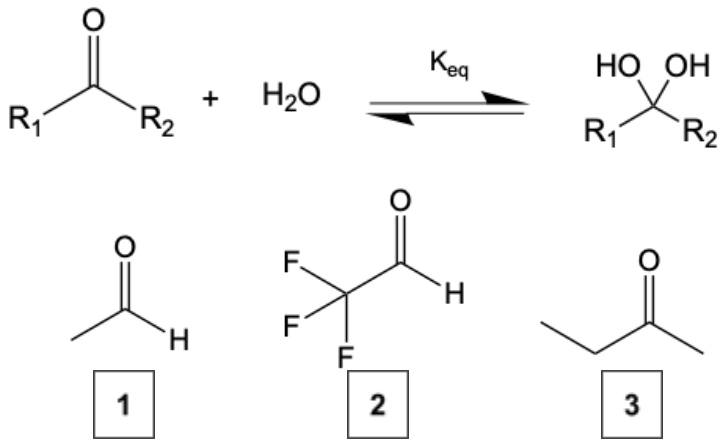
9. The pka of an alkyne is 25, whereas the pKa of an alkene is 43 and the pKa of an alkane is around 50. Choose the best explanation for this. (18 pts)

a) Alkynes have two pi bonds that are conjugated to each other, leading to greater resonance structures in the conjugate base anion than in alkenes and alkanes.
b) There are less hydrogens connected to carbons in alkynes and alkenes.
c) The hybridization of an alkyne is sp, an alkene is sp2, and an alkane is sp3; decreasing s character in hybrid orbitals is associated with decreasing electronegativity.
d) The negative charge in the conjugate base formed in an alkyne after deprotonation can delocalize into both of the pi bonds of an alkyne, whereas this is not possible in the alkene and alkane.

Solution: The answer is C because orbital hybridization determines stability of the conjugate base (and in effect acidic strength) by its effect on electronegativity. Alkynes do not allow for delocalization of electrons into pi bonds (ruling out A and D). The number of hydrogens connected to carbons does not have a significant effect on acidity (ruling out B). Source: February 6 2023 Lecture Slides (page 25).

Topic: steric and inductive effects on hydration reaction (answer is C)

10. Shown below is a general schematic for an aldehyde hydration reaction, as well as three possible substitutions for the generic R groups. Rank the possible reactants in order from lowest to highest K_{eq}. (18 pts)



a. 1 < 3 < 2
b. 2 < 3 < 1
c. 3 < 1 < 2
d. 3 < 2 < 1

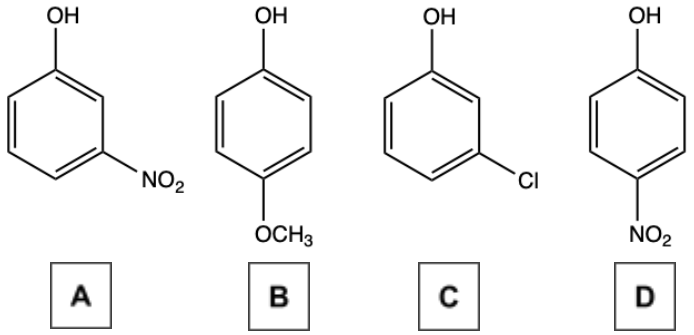
Solution: The answer is C. The two main effects to consider on K_{eq} of this reaction are (1) steric hindrance and (2) inductive effects. Molecule 3 experiences a lot of steric hindrance in the tetrahedral intermediate from two relatively bulky R groups that neighbor each other. This steric hindrance is not as presence in Molecules 1 and 2 since one substituent is simply a hydrogen. Molecule 2 contains a strong inductive effect that make the carbonyl much more electrophilic than in Molecule 1. For these reasons, K_{eq} is lowest for Molecule 3 and highest for Molecule 2. Source: January 23 2023 Lecture Slides (page 20)

Topic: biological application- imaging using fluorescent dyes (answer is C)
11. Why do fluorescent dyes for biological applications need to absorb at wavelengths greater than 600 nm? (18 pts)

a. Current imaging technologies for detecting fluorescent emissions have the highest quantum yield with dyes absorbing in that range.
b. Photons at wavelengths higher than 600 nm have more energy than photons at wavelengths lower than 600 nm.
c. Most biological tissues absorb light at wavelengths lower than 600 nm and this causes background fluorescence during imaging.
d. All of the above

Solution: The answer is C. Hemoglobin, a protein that is a major component of blood, absorbs light very well below the 600 nm range. Answer B is false; photons with higher wavelengths have lower energy. Answer choice A is false, and quantum yield of fluorescent dyes was also not a topic discussed in this course. Source: February 3 Lecture Slides (page 19).

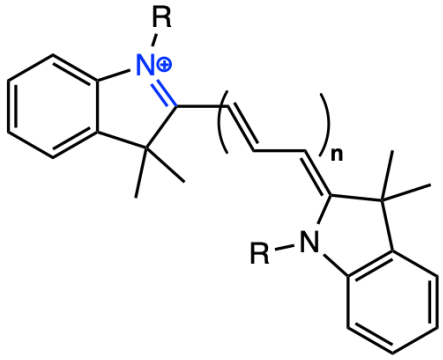
Topic: *substituent effects on phenolic pKa* (answer is D)
12. Which of the following molecules has the lowest pKa? (18 pts)



Solution: The answer is D. We are looking for the most acidic molecule, which is the one with the most stabilized conjugate base. Different substituents have different effects on acidity, with the main two effects to consider being resonance stabilization and inductive effects. The methoxy ($-OCH_3$) substituent on molecule B has electron donating properties, which destabilizes the conjugate base and makes it a poorer acid/higher pKa. The nitro ($-NO_2$) and chlorine (Cl) substituents are both electron withdrawing groups, with the chlorine operating only through inductive effects, and the nitro group operating through both inductive effects and resonance stabilization. In general, resonance delocalization offers more stabilization than the inductive effect. Only molecule D allows for a phenolate ion that is resonance stabilized through the nitro substituent, making it the most acidic molecule (lowest pKa). Source: February 3 Lecture Slides (pages 20-21). Concept also explored in Homework 3.

Topic: biological application- imaging using fluorescent dyes (answer is I)

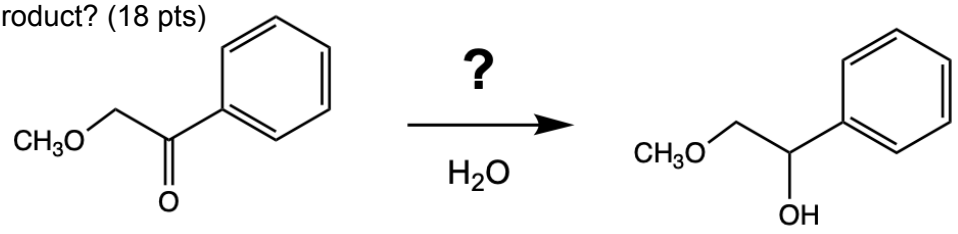
13. Reduction of the cyanine dye shown above with sodium borohydride transforms the carbon nitrogen double bond into a carbon nitrogen single bond. What effect does this have on the properties of the resulting molecule? (18 pts)



a. Reduction of the carbon nitrogen double bond will increase the absorption wavelength.
b. Reduction of the carbon nitrogen double bond will increase the water solubility of this molecule.
c. Reduction of the carbon nitrogen double bond will decrease the absorption wavelength of this molecule.
d. Reduction of the carbon nitrogen double bond will decrease the number of positive charges on this molecule.
e. All of the above
f. None of the above
g. A , B and C
h. A and C
i. C and D

Solution: The answer is I. First, let's go through what reduction means. When the Nitrogen marked in blue is reduced, an H will attack the attached double bond pushing the electrons back onto N making it neutral charged. The consequence of this is that N becomes sp^3 again and loses its double bond. If we reduce the number of double bonds in this molecule by 1, the absorption wavelength will be decreased since there is less electron distribution in the molecule. Secondly, reducing the double bond puts electrons back onto N, so it becomes neutral. Hence, C and D are correct. Source: February 3rd lecture slides (pages 24-26, 43). This concept was also explored in Homework 2 (Questions 8-9).

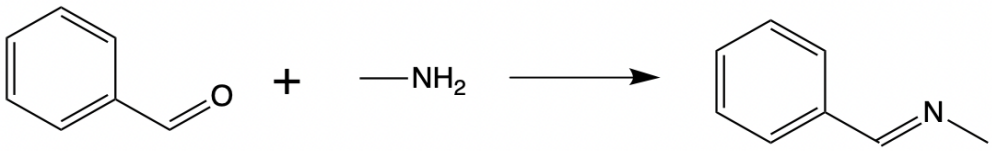
Topic: Using sodium borohydride to reduce ketones (answer is B)
14. In the reaction shown below, what missing reagent would best allow the formation of the specified product? (18 pts)



a. HCl
b. $NaBH_4$
c. NaOH
d. MeOH

Solution: The answer is B because only the sodium borohydride anion (BH_4^-) is capable of reducing ketones to alcohols. Answer choice A and B are an acid and base, respectively, which, if anything, would lead to a hydration reaction that would fully hydrate the ketone, forming a geminal diol (two alcohols on the same carbon). Since the specified product only has one alcohol group, these are incorrect. Answer choice D may lead to the formation of a hemiacetal or acetal (with -OMe or -OH groups replacing the ketone). The specified product is neither an acetal or hemiacetal, so answer choice D is incorrect. Source: January 30 2023 lecture slides (page 7). Also explored in Homework 1.

Topic: Le Chatelier's principle during imine formation (answer is B)
15. Shown below is an imine formation reaction. Which of the following strategies best enables the highest yield of the imine product? (18 pts)



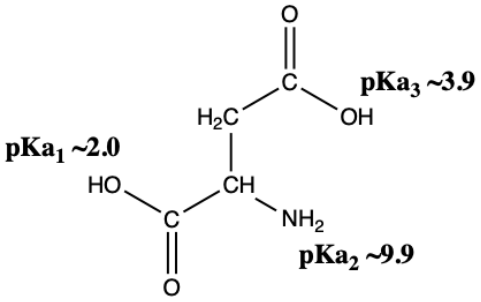
a. Conducting the reaction in the presence of a strong base
b. Removing water from the products throughout the reaction
c. Adding a protecting group to the benzaldehyde
d. Lowering the concentration of primary amine in the reactants

Solution: The answer is B. Water is a byproduct of this reaction (not explicitly shown), so removing it from the reaction will shift the equilibrium to the right and drive the reaction forward, according to Le Chatelier's principle. Answer A is incorrect because adding base would not affect the equilibrium yield of the reaction. Even if the reaction is catalyzed by acid or base, in general, adding a catalyst affects kinetics, but not equilibrium thermodynamics of a reaction. Answer C is incorrect because adding a protecting group would not aid the reaction moving forward. If anything, changing the aldehyde group on the molecule would prevent the imine formation reaction from occurring. Answer D is incorrect because lowering the concentration of primary amine in the reactants would shift the equilibrium towards the

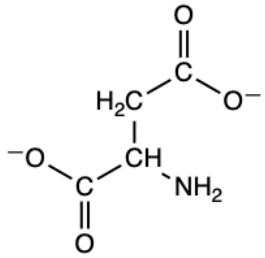
reactants (driving the reaction backward), according to Le Chatelier's principle. Source: February 15 and 17th 2023 Lecture Slides (Slide 6) and February 17th 2023 Lecture Slides (Slide 22)

Topic: protonation/deprotonation of acids/bases (answer is D)

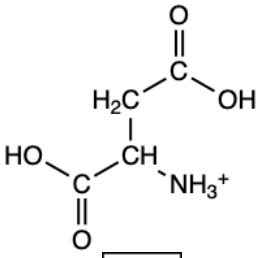
16. The structure of aspartic acid (an amino acid) and its pKa's, are shown below in the molecule's neutral, uncharged form. What form of this molecule would be most prevalent at pH 7? (18 pts)



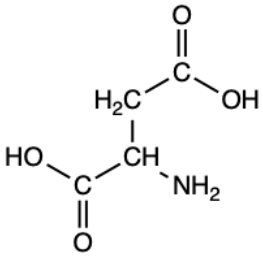
Aspartic acid



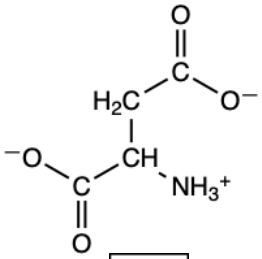
A



B



C

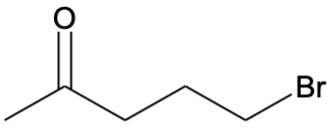


D

Solution: The answer is D. At pH 7, the pH is higher than the pKa's of the alcohol and carboxylic acid (pKa_1 and pKa_3, respectively). At pH 7, the pH is lower the pKa of the primary amine (pKa_2). This means that the alcohol and carboxylic acid will be deprotonated, and the primary amine will be protonated. Answer choice D describes this ionization state. Remember that the unprotonated form (pH > pKa) of the primary amine is R-NH_2 and the protonated form (pH < pKa) is R-NH_3^+. Source: February 8th Lecture Slides (pg. 9), explored in Homework 3 (problem 5).

Topic: power of protecting groups (answer is G)

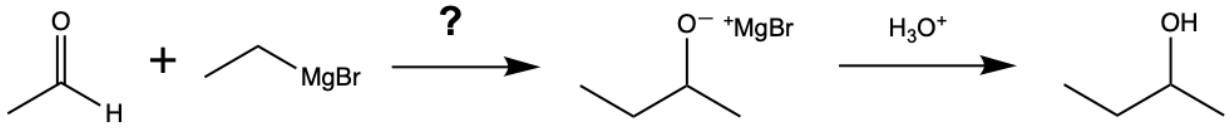
17. Suppose we have the molecule shown below. We want to make a Grignard reagent using this molecule by converting the bromine-bonded carbon into a nucleophile. Which statement(s) best describe this reaction and any problems associated with it? (18 pts)



a) It will be impossible to isolate the resulting Grignard reagent because it will self react in its present form without modifications.
b) There is no problem with this reaction, it will proceed smoothly.
c) There is a chance for self reactivity, but that can be avoided by converting the ketone into a carbon nitrogen double bond (Schiff base).
d) The self reactivity of the resulting Grignard reagent is a major problem, but that can be solved by converting the ketone into a ketal or acetal.
e) None of the above
f) A and C
g) A and D

Solution: The answer is G. The Grignard reagent is MgBr which is super reactive. If we add Mg to this molecule to form MgBr, the overall molecule will become super unstable and will self react since there are no protecting groups at the carbonyl. The resultant electronegative carbon adjacent to MgBr could attack the carbonyl or deprotonate the hydrogen at the carbon alpha to the carbonyl due to its favorable pKa (~20). To solve this issue, we can add a protecting group at the carbonyl in the form of a ketal or acetal, which will cause the electrophilicity at that carbon to be dramatically reduced. This will result in low self-reactivity. Hence, options A and D are correct. Source: Feb 22nd lecture slides (page 11).

Topic: Grignard reagent reactions (Answer is C)
18.



To form the reaction product, which solvent (indicated by the **?**) needs to be used for this reaction? (18 pts)

a. Water
b. Methanol
c. Anhydrous (no water) ether (CH_3-CH_2-O-CH_2-CH_3)
d. EtOH
e. None of the above
f. Any of the above

Solution: The answer is C because this reaction involves Grignard reagents. The Grignard reagent reaction cannot occur in any solvents that have weakly acidic properties, because the reagent will simply deprotonate the solvent instead of performing a nucleophilic attack on the carbonyl. For this reason, anhydrous ether must be used. Source: Concept was explored in Homework 1 (problem 11) and Homework 3 (problem 6).