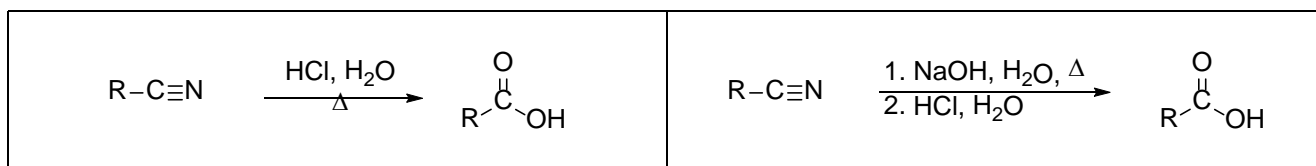


Mechanistic Assignment
CHEM 4000A – Medicinal Chemistry
Due at 3pm on Friday, February 27, 2015

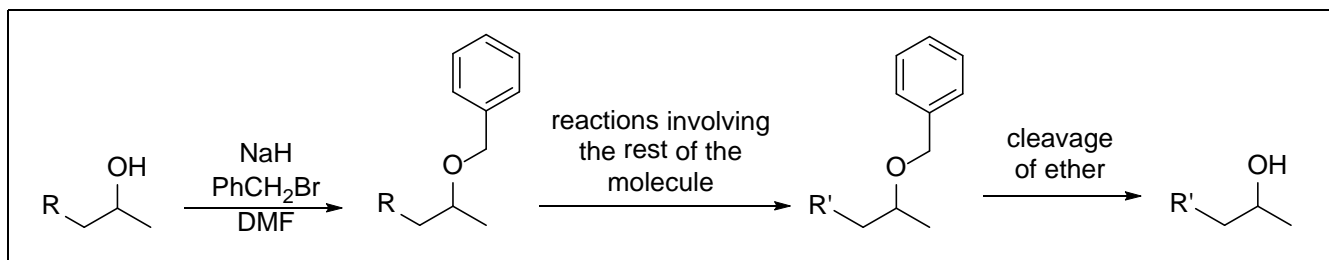
You will likely find it easiest to draw your mechanisms by hand (though you can use a program like ChemDraw if you like). The written parts of your answers can either be hand written or typed. As long as I can read them. ☺

Do not take “short cuts” showing protonation or deprotonation steps that can’t actually happen because the basic site can’t reach the acidic hydrogen. (Be warned that some textbooks, etc. have this very bad habit because it saves them space.)

1. Like esters, nitriles can be used as masked carboxylic acids in reaction in which the acidic hydrogen of the carboxylic acid group would prove problematic. They can be hydrolyzed to the corresponding carboxylic acid in the presence of either aqueous acid or aqueous base (followed by acidic work-up). These reactions are typically refluxed.



- (a) Propose a reasonable mechanism for the acid-catalyzed hydrolysis of a nitrile.
- (b) Propose a reasonable mechanism for the base-catalyzed hydrolysis of a nitrile. *You must show everything that happens before the acid is added and clearly indicate when the acid is added.*
- (c) Give an example of a molecule containing a nitrile in which it would be better to use an acid-catalyzed hydrolysis (instead of a base-catalyzed hydrolysis). Briefly explain your choice.
- (d) Give an example of a molecule containing a nitrile in which it would be better to use a base-catalyzed hydrolysis (instead of an acid-catalyzed hydrolysis). Briefly explain your choice.
2. Benzyl ethers can be used as protecting groups for alcohols:

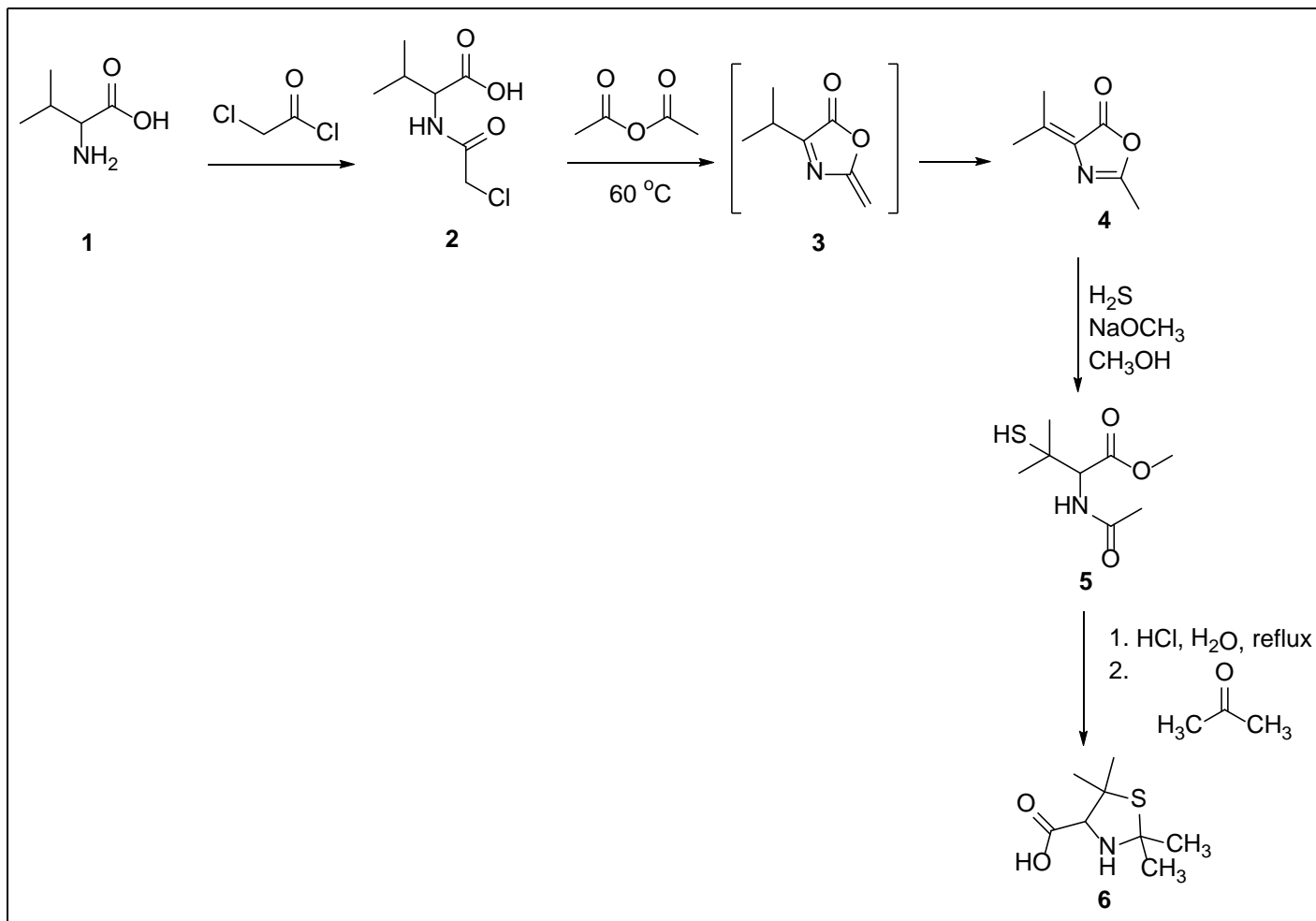


There are many different methods for cleaving the benzyl ether. The earliest reported methods included hydrogenolysis and reductive cleavage; however, those methods cause side reactions in molecules containing alkenes, alkynes and some other functional groups.

One of the first alternative methods for cleaving a benzyl ether involved the use of a Lewis acid (such as BF_3) and a nucleophile (such as $\text{CH}_3\text{CH}_2\text{SH}$).

- (a) What side reaction(s) would you expect to see if you used hydrogenolysis to cleave a benzyl ether in a molecule containing an alkene?
- (b) Propose a reasonable mechanism for the cleavage of a benzyl ether using BF_3 and $\text{CH}_3\text{CH}_2\text{SH}$.
- (c) $\text{CH}_3\text{CH}_2\text{SH}$ is a good Lewis base. Why doesn't it just react with the Lewis acid (BF_3)?
You will likely want to refer to your mechanism to explain why that is a better reaction path.

3. There have been many syntheses of penicillins over the years because they are challenging and interesting target molecules (even though many of them can be made in much larger quantities by culturing fungus). One synthesis of a penicillin started by reacting (\pm)-valine (**1**) with chloroacetyl chloride. The product of that reaction (**2**) was then reacted with acetic anhydride to give cyclic compound **3** which isomerized to cyclic compound **4**. A conjugate addition of HS^- followed by reaction with CH_3O^- opened up the ring to give compound **5**. Acid-catalyzed hydrolysis of both amide and ester followed by addition of acetone resulted in compound **6**, an important intermediate in this synthesis.



- (a) Propose a reasonable mechanism for the reaction of **1** with chloroacetyl chloride to give **2**. You can assume that weak aqueous base (e.g. $\text{NaHCO}_3(\text{aq})$) was added during the work-up.
- (b) Propose a reasonable mechanism for the reaction of **2** with acetic anhydride to give **4** (via formation of **3**).
- Hint: It is likely that you will need to use one more equivalent of acetate anion (CH_3CO_2^-) than you appear to have produced from the acetic anhydride in this reaction. Presumably, another species in solution reacts with it to give you the extra acetate anion you need.*
- Hint: The ring forms while the chlorine atom is still part of the molecule.*
- (c) Propose a reasonable mechanism for the reaction of **4** with H_2S and NaOCH_3 (in CH_3OH) to give **5**.
- (d) Propose a reasonable mechanism for the reaction of **5** with $\text{HCl}(\text{aq})$ then with acetone to give **6**.