

Weak Nucleophile/Base (and strong acid) Conditions (H₂O and ROH) with Carbonyl Compounds and Epoxide Compounds

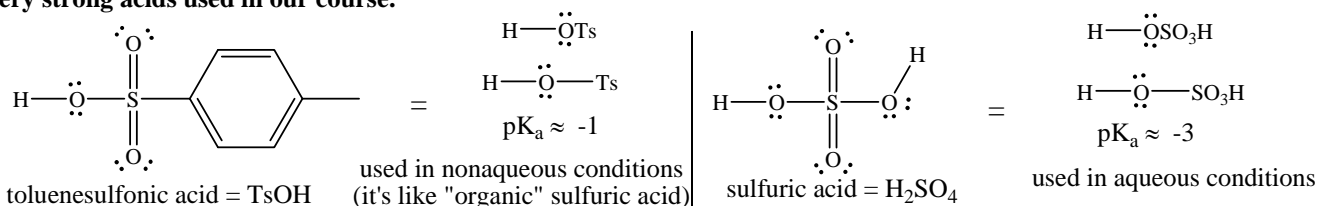
Weak nucleophiles (water, H₂O and alcohols, ROH in our course) react with secondary and tertiary RX compounds (S_N1 > E1 reactions). Also, methyl and primary alcohols react under strong HX acid conditions via S_N2, while secondary, and tertiary alcohols react under strong HX acid conditions via S_N1 (HX = HCl, HBr, HI). All alcohols react via E1 reactions with H₂SO₄/Δ. Rearrangements are always a possibility in carbocation chemistry.

Weakly electrophilic carbonyl, nitrile and epoxide compounds also become strongly electrophilic in strong acid and protic solvents. We will only use limited examples (H₂O, ROH and amines) to introduce these reactions. In weak base/nucleophile reactions (strong acid) the order of events is usually 1. Add a proton, 2. add weak nucleophile and 3. lose extra proton). Because the acidic conditions are usually strong protic acid, the solvents used are typically protic (H₂O/H₂SO₄ = H₃O⁺/H₂O or ROH/TsOH = RO⁺H₂/ROH).

Carbonyl reactions with water and alcohols often have products and reactants in equilibrium with one another, while with epoxide reactions are irreversible, due to the release of large ring strain. Writing mechanisms in acid is often longer (than base) because there is an initial protonation step, sometimes intermediate resonance structures, and a final deprotonation step required.

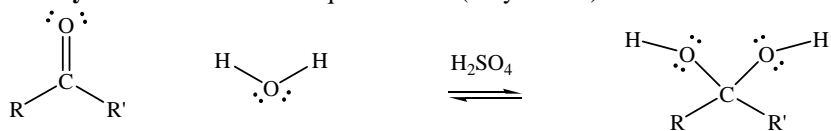
One final point is that water is often used to shift the equilibrium, in acid, to one side or the other by adding water (hydration) or removing water (dehydration). The acid we will use when water is the solvent will be sulfuric acid (H₂SO₄) and the acid we will use when an alcohol is the solvent (nonaqueous) will be toluenesulfonic acid (TsOH). You can think of TsOH as 'organic' sulfuric acid. Other acids are possible, but not discussed here.

Very strong acids used in our course.

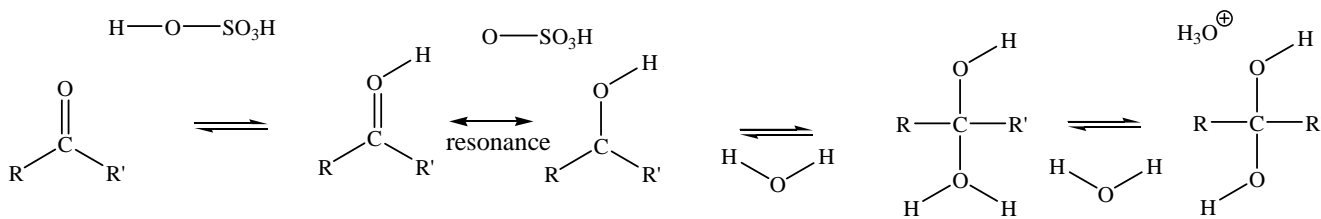


Generic Carbonyl Addition Reactions of Aldehydes and Ketones in Aqueous Acid (= hydration)

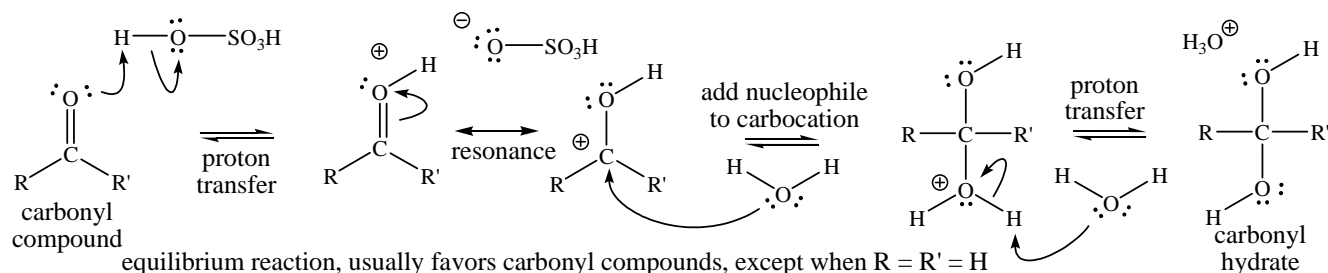
Write a step-by-step mechanism for the addition of water to an aldehyde or ketone = carbonyl hydrates. This is a reversible reaction that favors the C=O side of the equilibrium.



Possible mechanism without details (you add those)

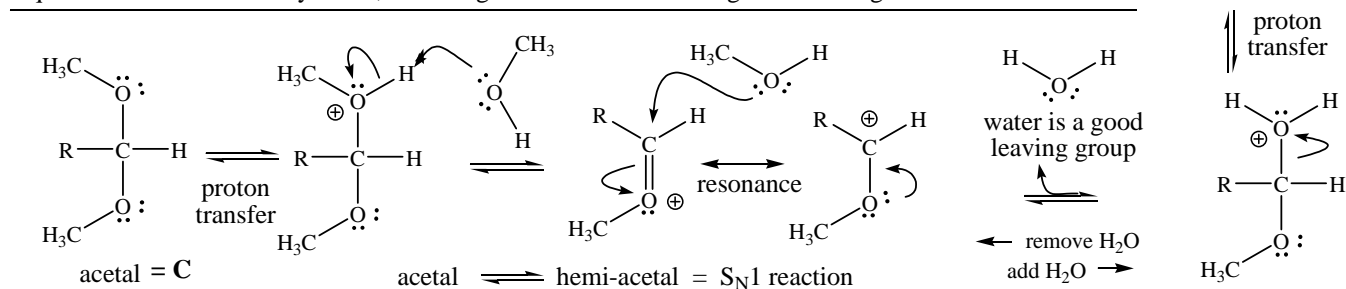
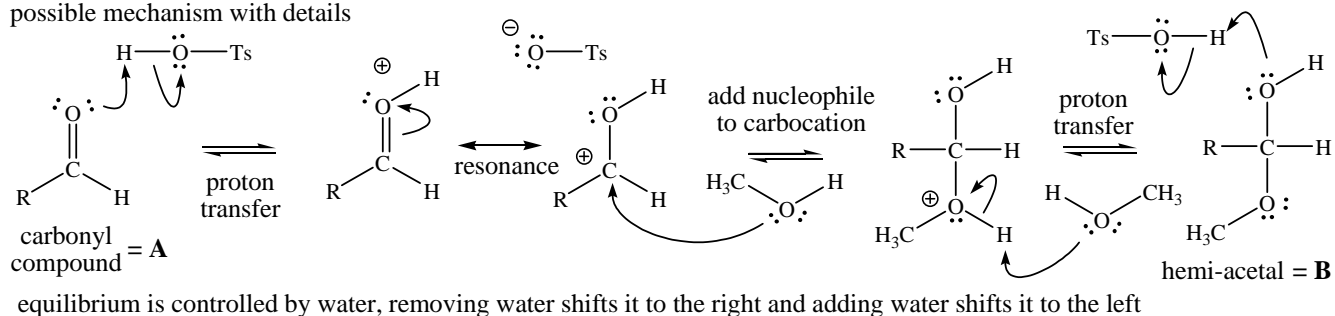


Possible mechanism with details.

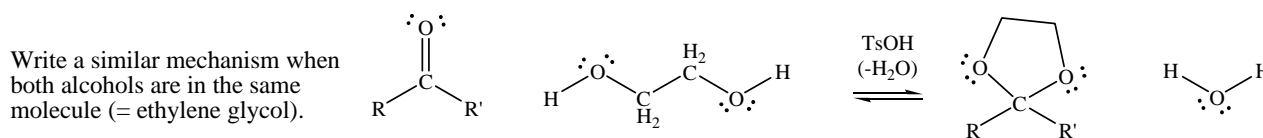


Write a mechanism for the reverse reaction = dehydration of carbonyl hydrate to carbonyl and water.

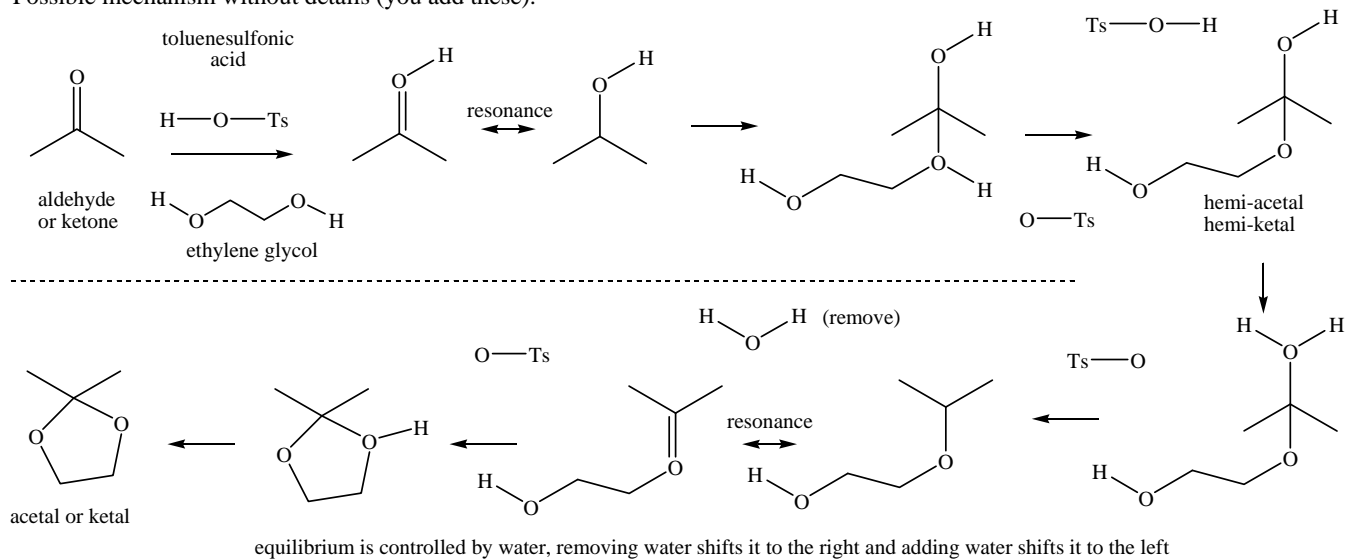
possible mechanism with details



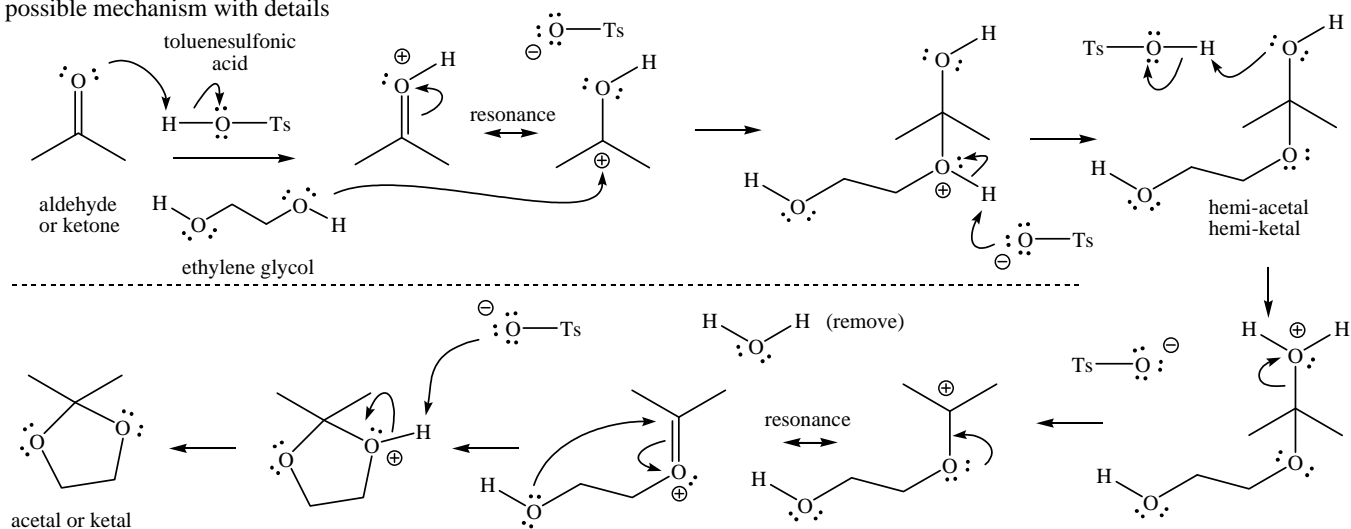
Similar mechanisms with a diol = ethylene glycol (protection of a C=O, aldehydes and ketones)



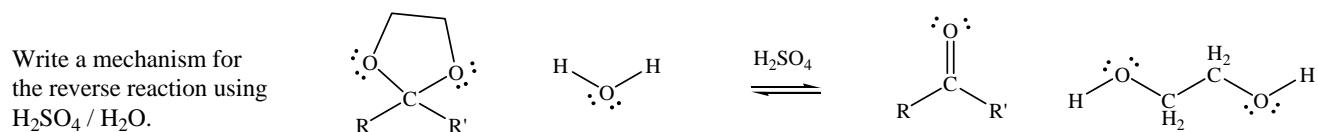
Possible mechanism without details (you add these).



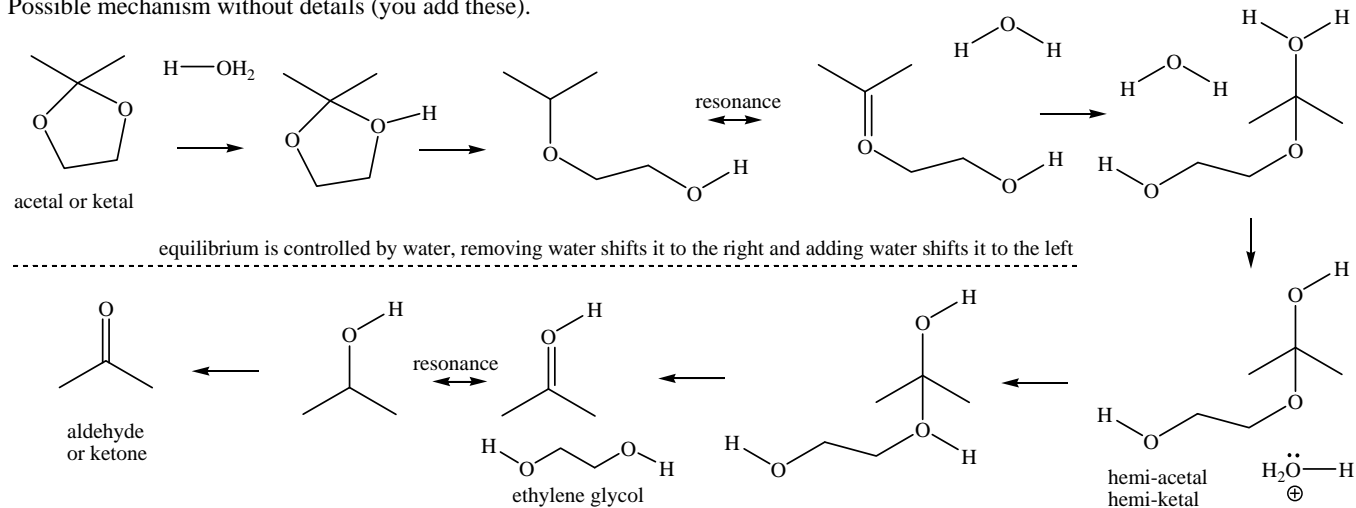
possible mechanism with details



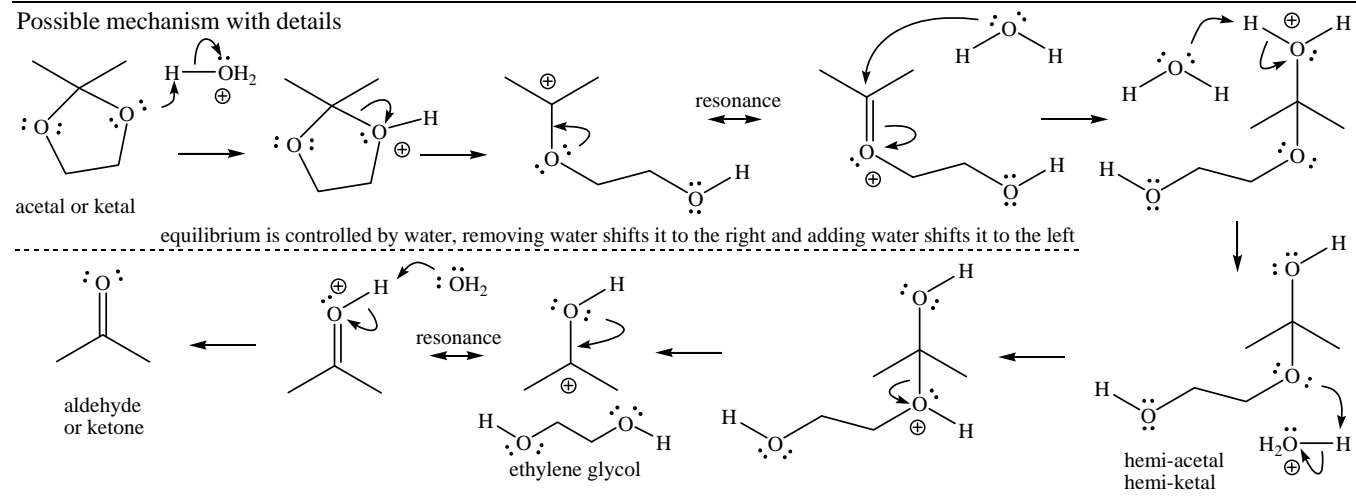
Write a mechanism for the reverse reaction (deprotection of a carbonyl).

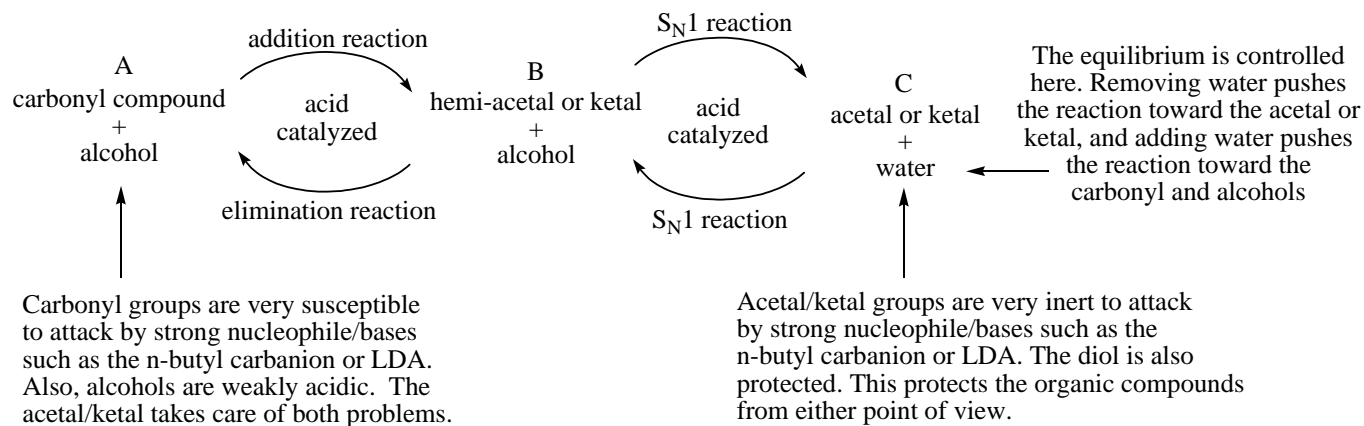


Possible mechanism without details (you add these).



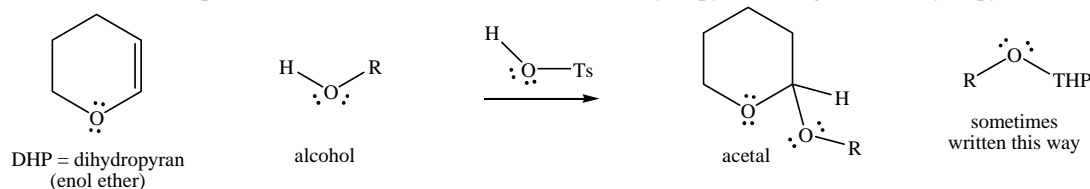
Possible mechanism with details



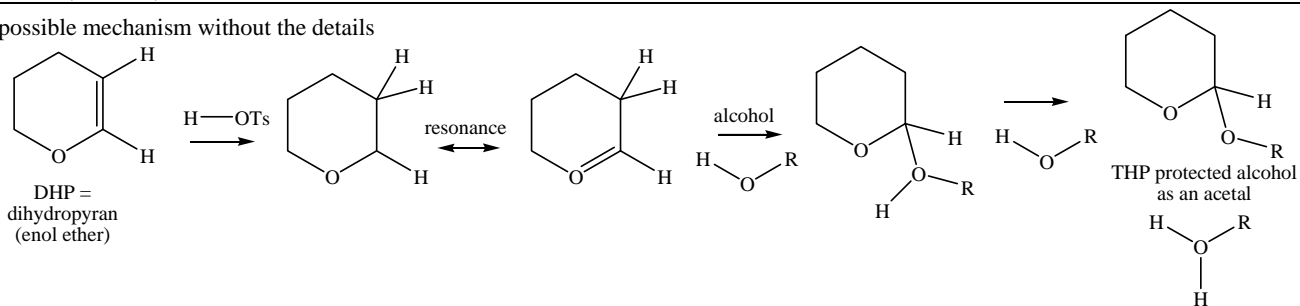


Formation of a THP protected alcohol. DHP is an enol ether, which a condensation of an aldehyde and a single alcohol. When a second alcohol is added to DHP in the presence of an acid catalyst (TsOH) and acetal forms, which protects the alcohol (instead of the carbonyl group). A similar strategy is used, but protects a different functionality (the alcohol).

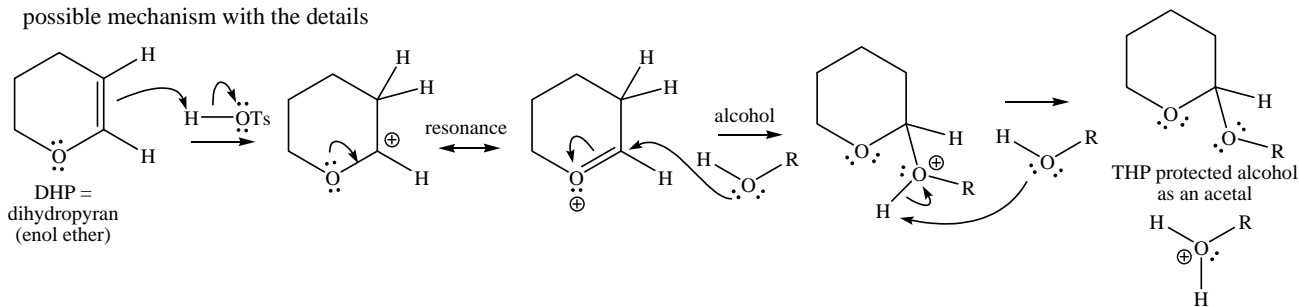
overall mechanism for protection of an alcohols as a THP ether (tetrahydropyran, using DHP = dihydropyran and TsOH)



possible mechanism without the details

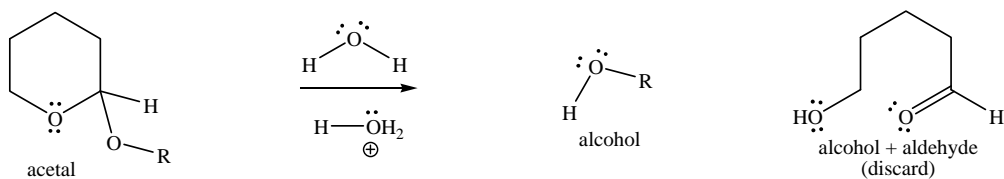


possible mechanism with the details

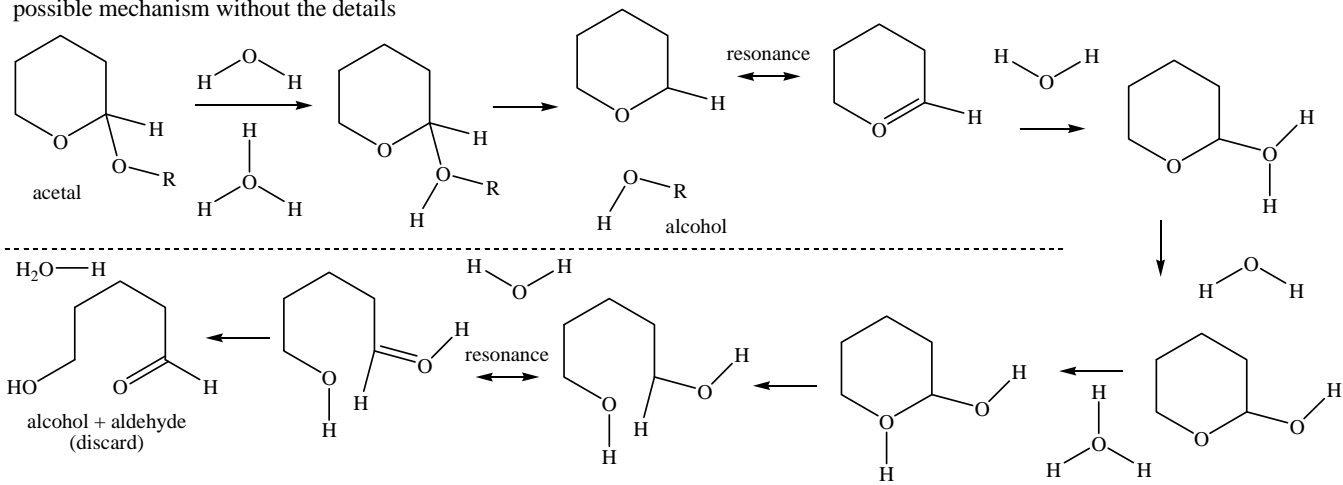


Deprotection of a THP protected alcohol

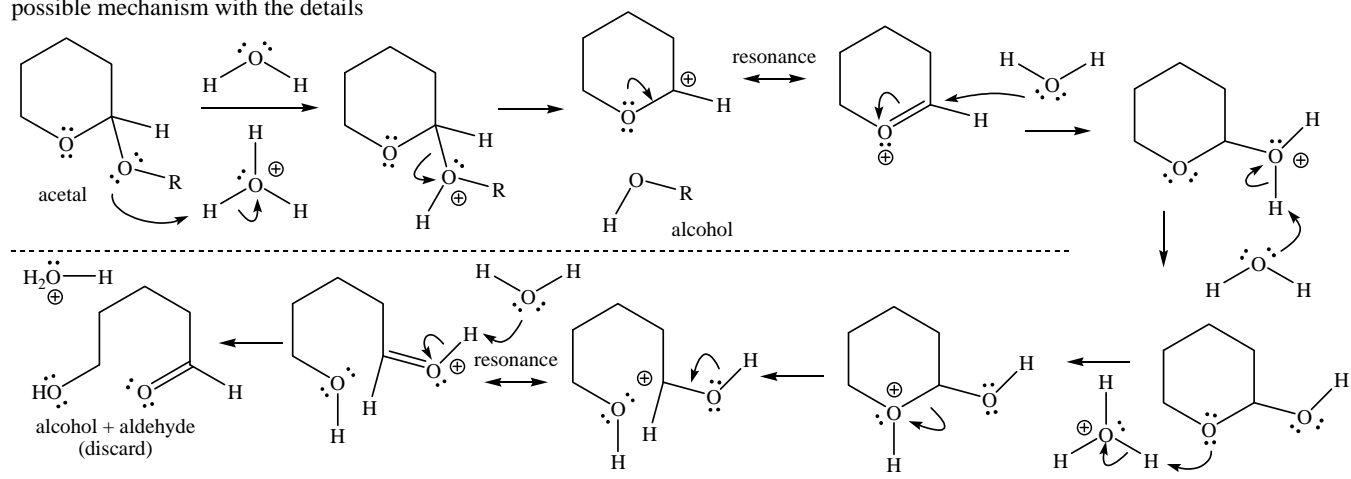
overall mechanism for protection of an alcohols as a THP ether (tetrahydropyran, using DHP = dihydropyran and TsOH)



possible mechanism without the details

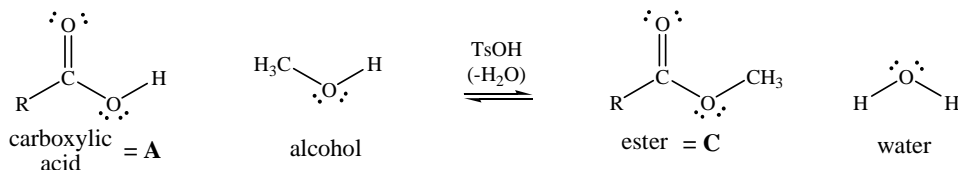


possible mechanism with the details

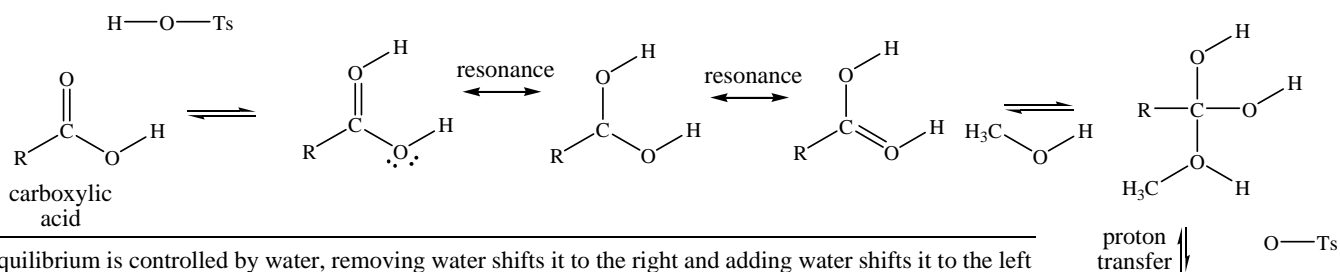


Fischer Ester Synthesis Reaction - In a closely related series of steps it turns out that carboxylic acids and alcohols can form esters and water (which is removed) using catalytic toluene sulfonic acid. Using aqueous sulfuric acid and lots of water will hydrolyze the ester back to the carboxylic acid and the alcohol. This is again an equilibrium controlled by the removal or addition of water. If you can write a mechanism from the overall reaction. If you need help, use the reactions mechanism written without the details. If you need more help, study the proposed mechanism and then try the other approaches.

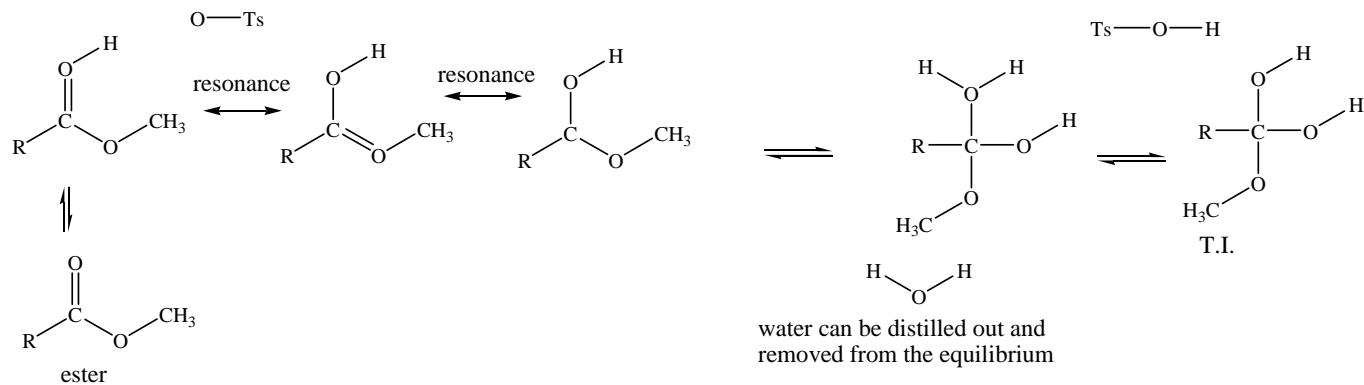
overall mechanism for Fischer esterification



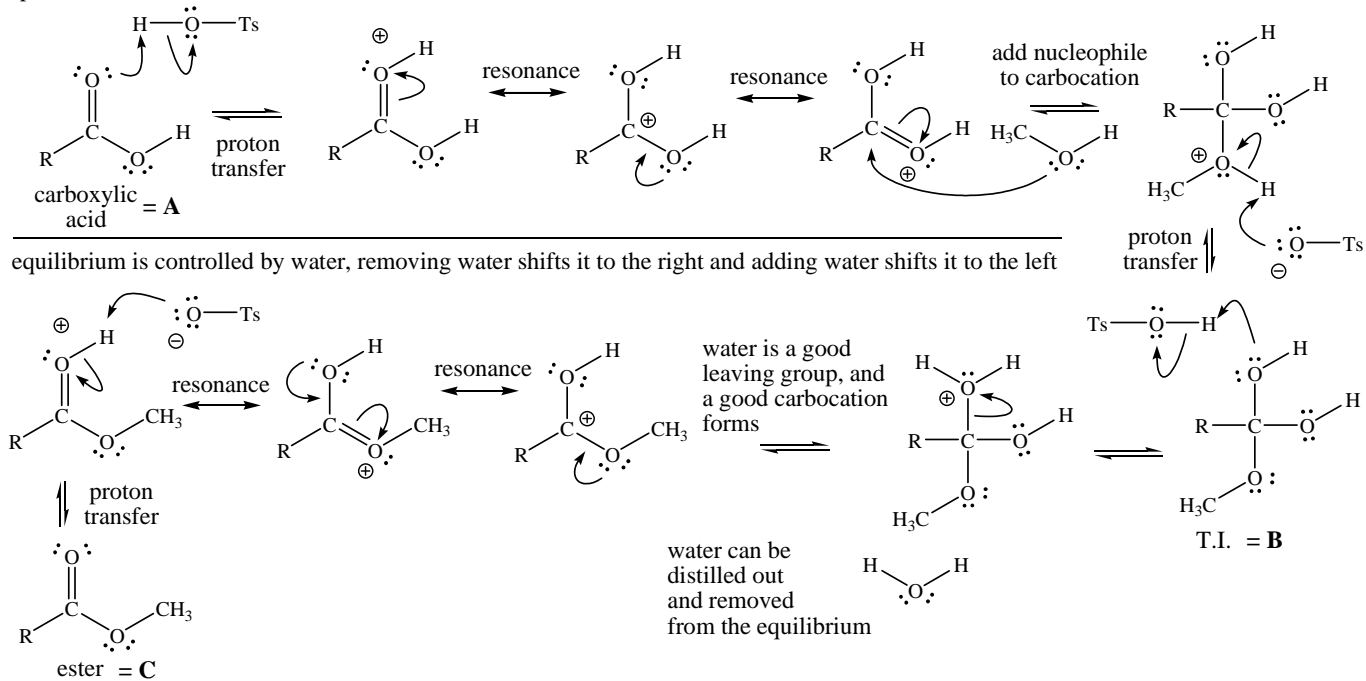
possible mechanism without the details



equilibrium is controlled by water, removing water shifts it to the right and adding water shifts it to the left

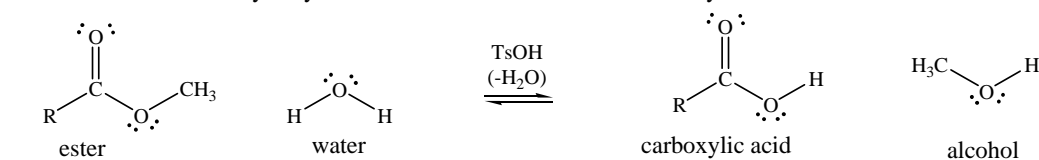


possible mechanism with the details

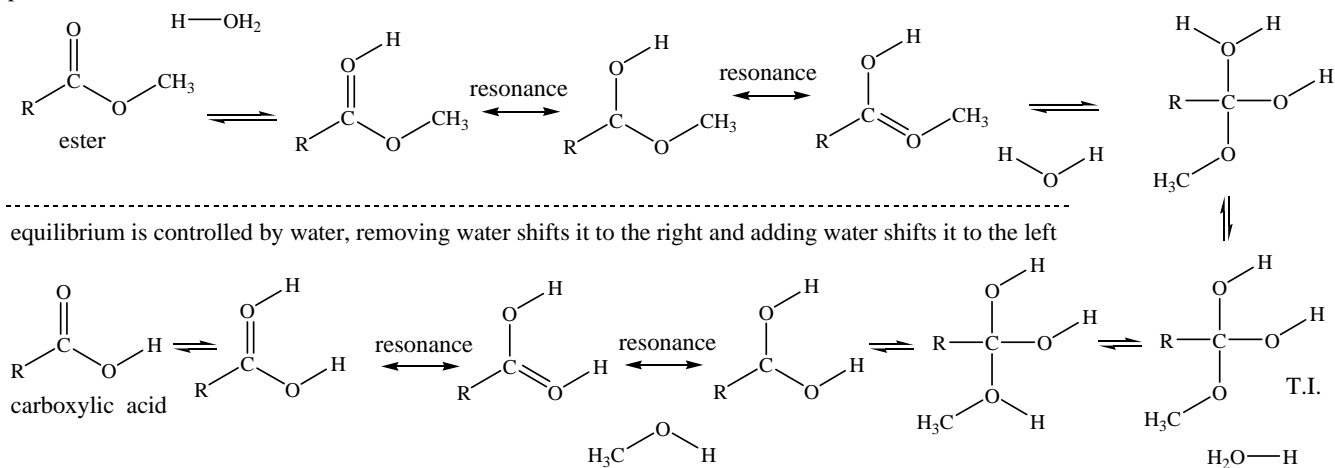


Propose a mechanism for the reverse reaction: acid hydrolysis of an ester.

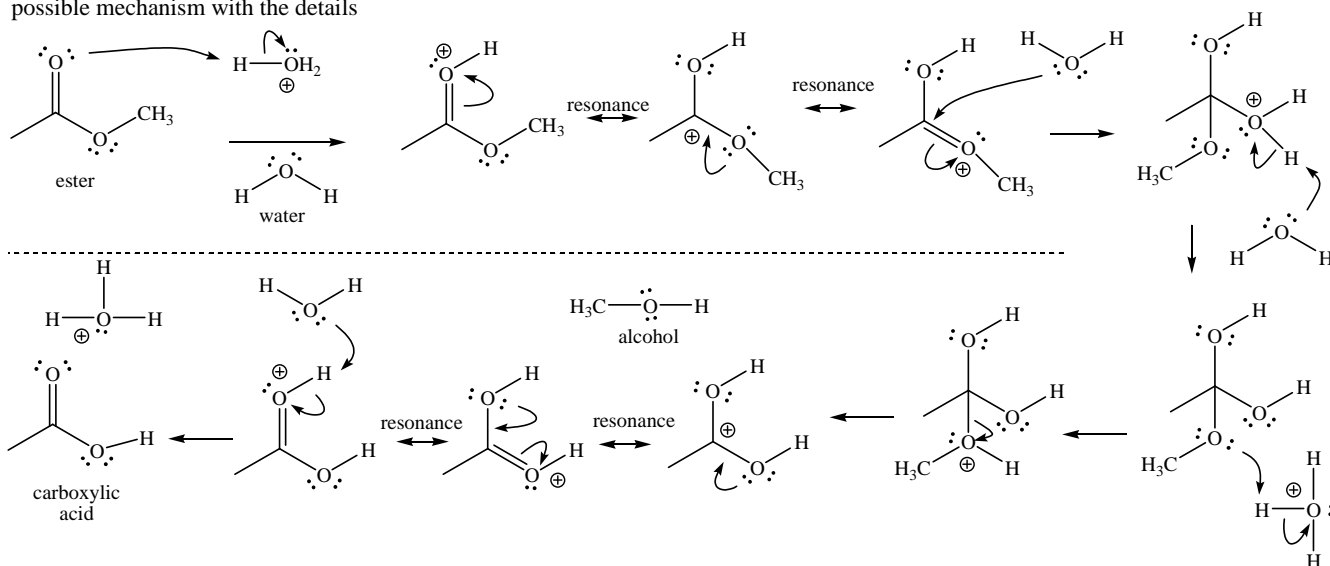
overall mechanism for hydrolysis of an ester to an alcohols and carboxylic acid



possible mechanism without the details

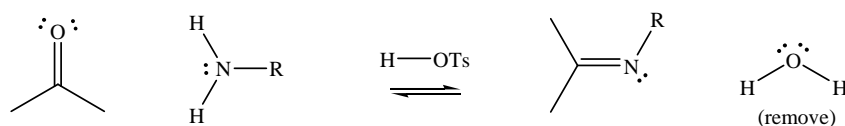


possible mechanism with the details

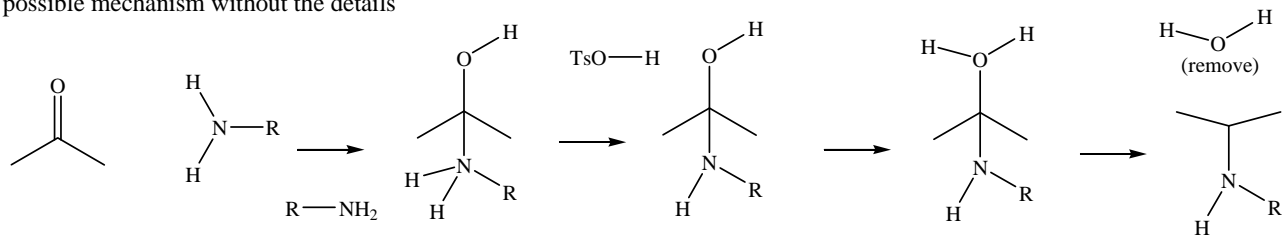


There are many examples of carbonyl groups reacting with primary RNH_2 . The following reaction shows the formation of simple imines with carbonyl groups. Reaction with hydrazine (H_2NNH_2) is similar.

Write a mechanism for imine formation using TsOH ($-\text{H}_2\text{O}$). Neutral nitrogen is a good enough nucleophile to attack without protonating the carbonyl group.



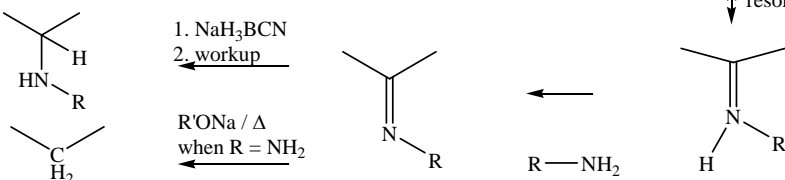
possible mechanism without the details



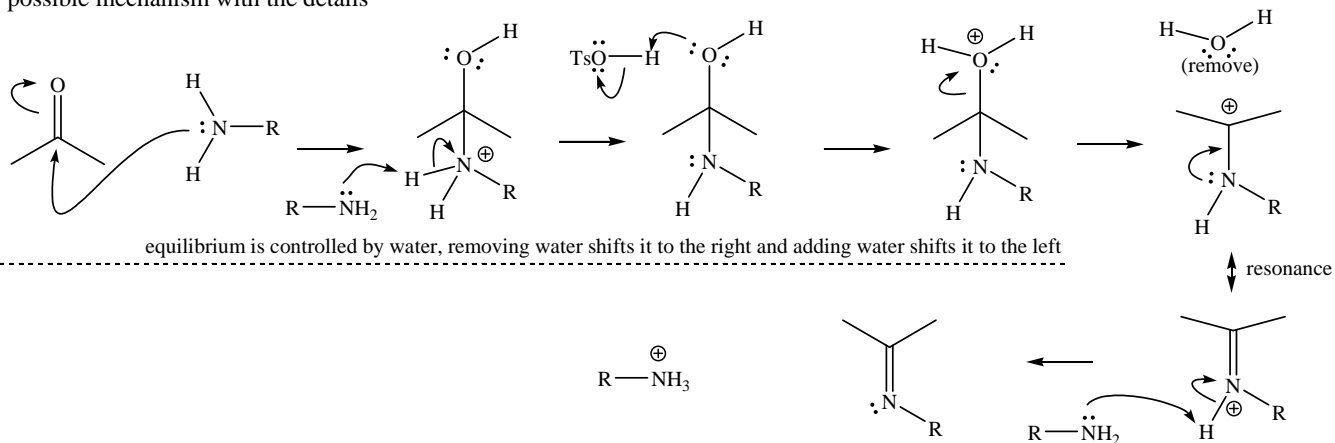
equilibrium is controlled by water, removing water shifts it to the right and adding water shifts it to the left

Imines can be made into amines using sodium cyanoborohydride (NaH_3BCN), followed by workup.

Reaction with hydrazine, followed by strong base and heat can reduce the $\text{C}=\text{O}$ to a C_2H_2 . This reaction is called the Wolff-Kishner reduction.

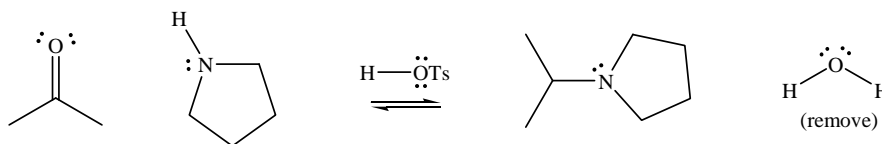


possible mechanism with the details

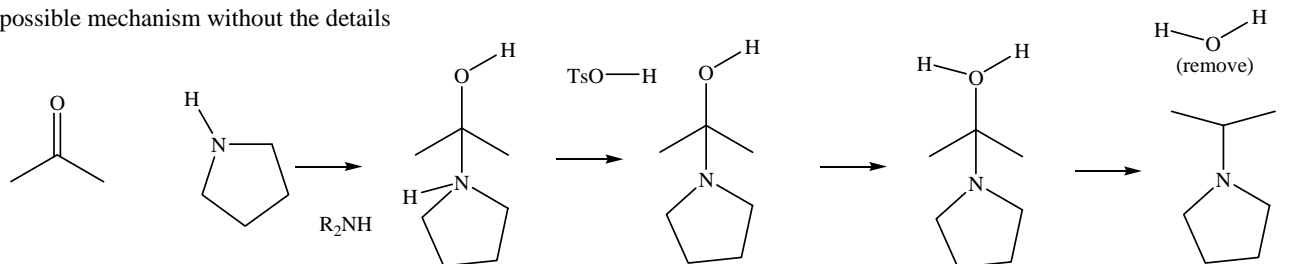


When carbonyl groups react with secondary amines, R_2NH , enamines form. Enamines are nucleophilic on the second carbon of the $C=C$ double bond. They are neutral versions of enolate chemistry in reactions with common electrophiles, and very similar to biochemical examples in nature. The following reaction shows the formation of simple enamines with carbonyl groups. After reaction with an electrophile they can be hydrolyzed back to a carbonyl group.

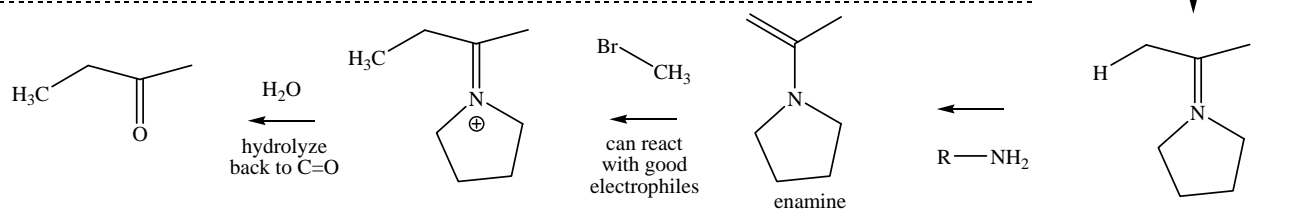
Write a mechanism for enamine formation using 2° amines and TsOH ($-H_2O$). Neutral nitrogen is a good enough nucleophile to attack without protonating the carbonyl group.



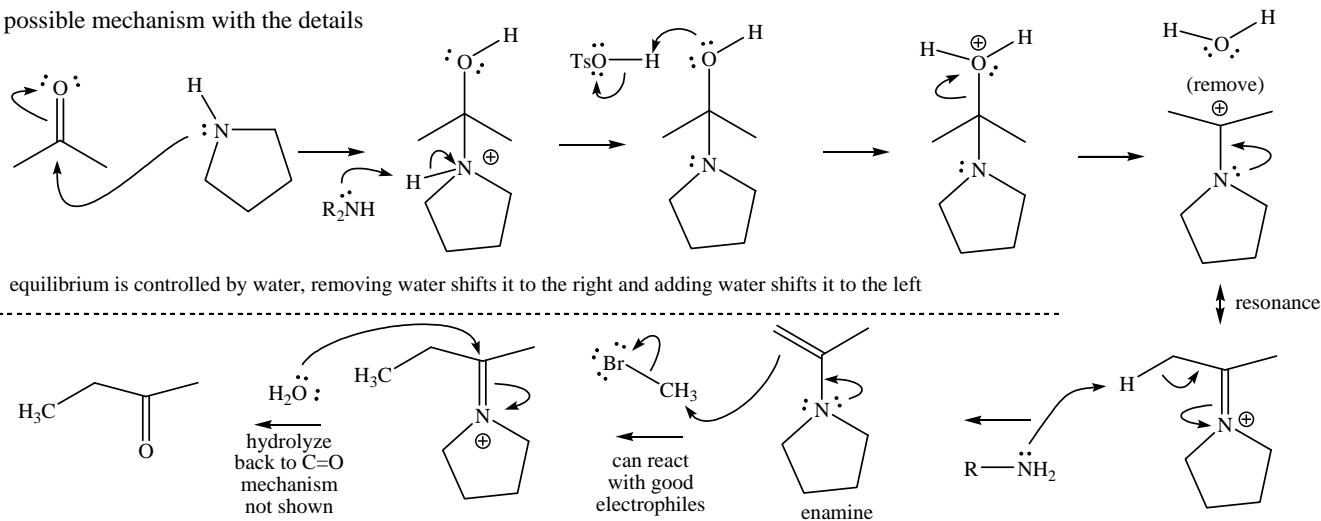
possible mechanism without the details



equilibrium is controlled by water, removing water shifts it to the right and adding water shifts it to the left

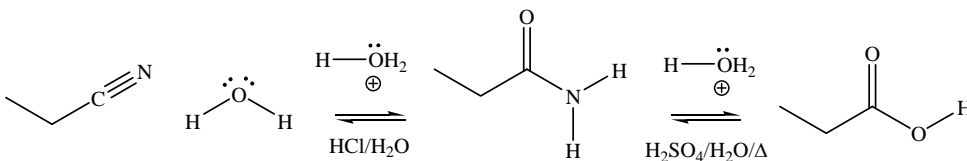


possible mechanism with the details

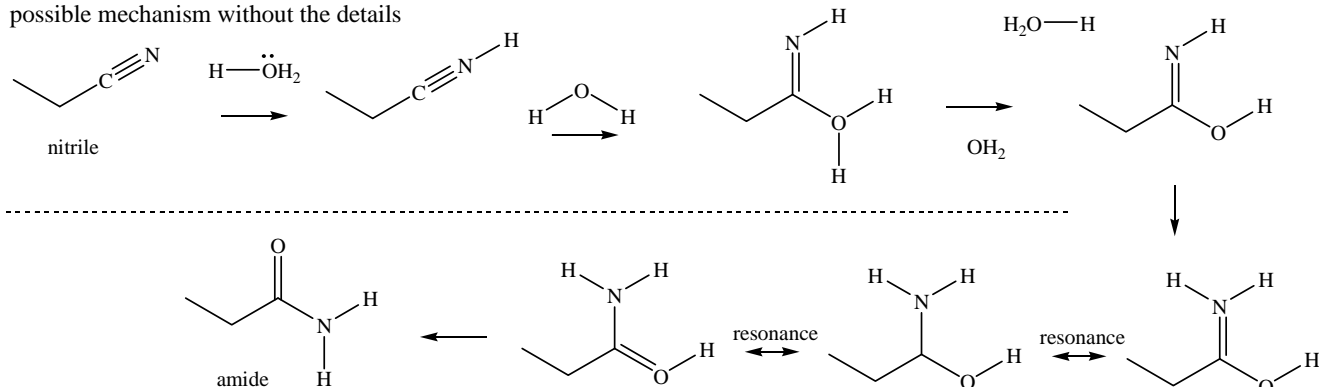


Nitriles can be hydrolyzed in milder acid (HCl/H₂O) to primary amides and in stronger acid (H₂SO₄/H₂O/Δ) to carboxylic acids.

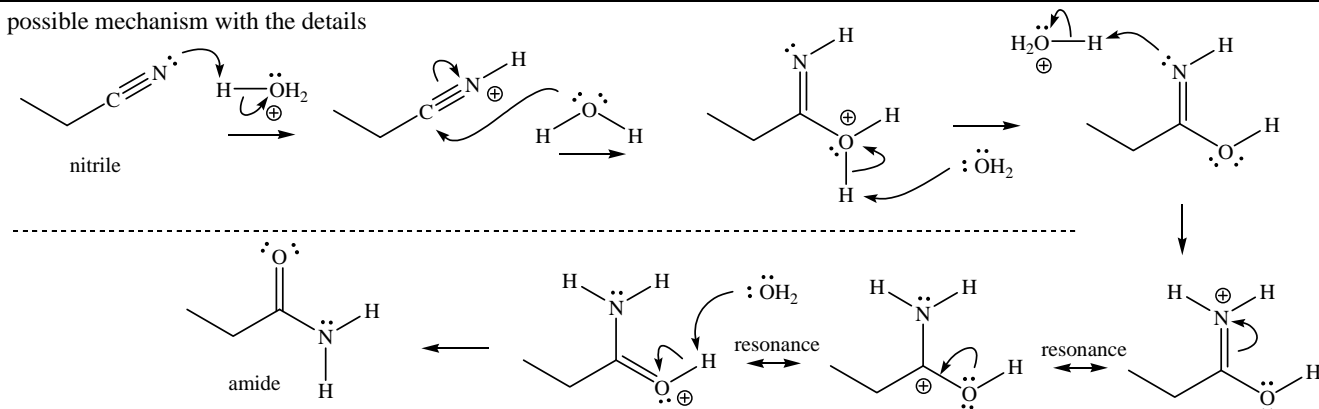
Write a mechanism for an acid hydrolysis of a nitrile group to a primary amide in HCl/H₂O or a carboxylic acid in H₂SO₄/H₂O/Δ (harsher conditions).



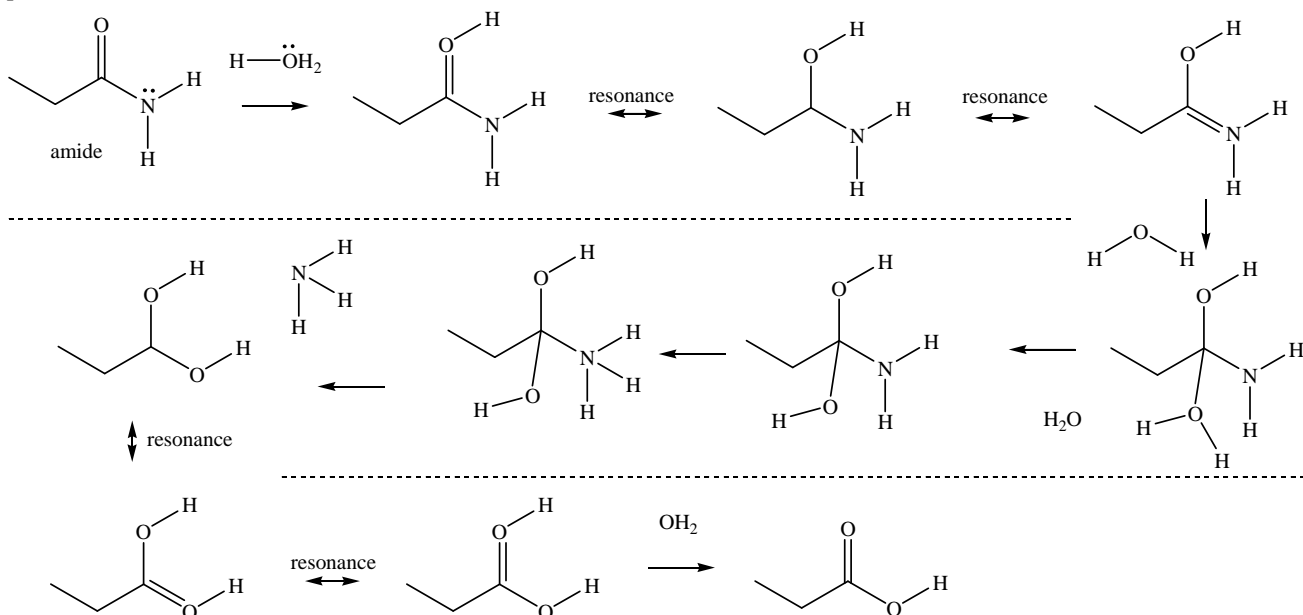
possible mechanism without the details



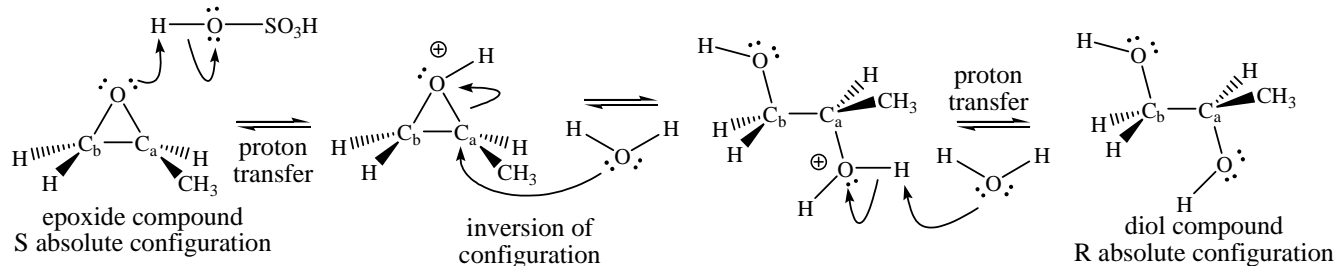
possible mechanism with the details



possible mechanism without the details

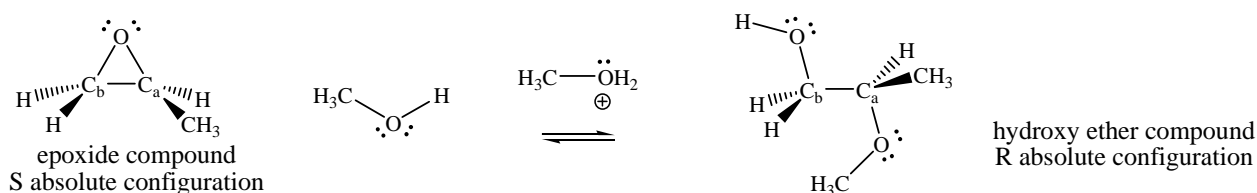


possible mechanism with the details

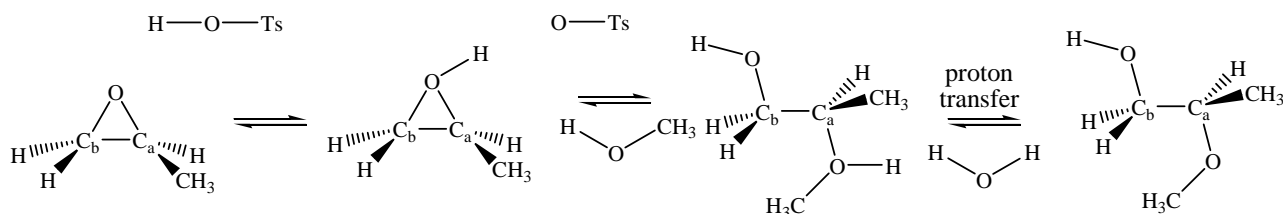


C_a has greater partial positive charge than C_b because it is more substituted, so the weak nucleophile attacks it faster. Notice that a different carbon of the unsymmetrical epoxide was attacked than was the case in strong nucleophile/base conditions. Because that carbon is chiral in this example, we can see the inversion of configuration (from S to R), even though there is an "OH" on both carbon atoms.

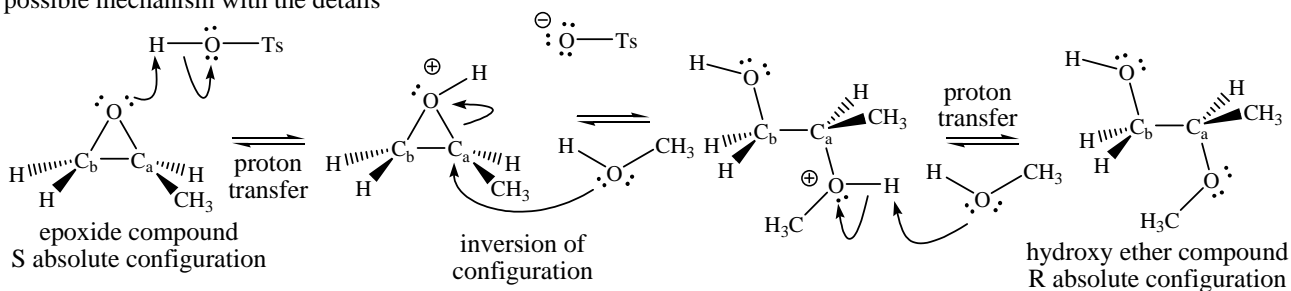
overall mechanism for epoxides in alcoholic acid (TsOH / ROH)



possible mechanism without the details



possible mechanism with the details



C_a has greater partial positive charge than C_b because it is more substituted, so the weak nucleophile attacks it faster. Notice that a different carbon of the unsymmetrical epoxide was attacked than was the case in strong nucleophile/base conditions. This is easy to see in this example because "methoxy = $-OCH_3$ " (from the attacking weak nucleophile) is different than "hydroxy = $-OH$ " (from the epoxide oxygen).