Organic Chemistry
Notes Part 38

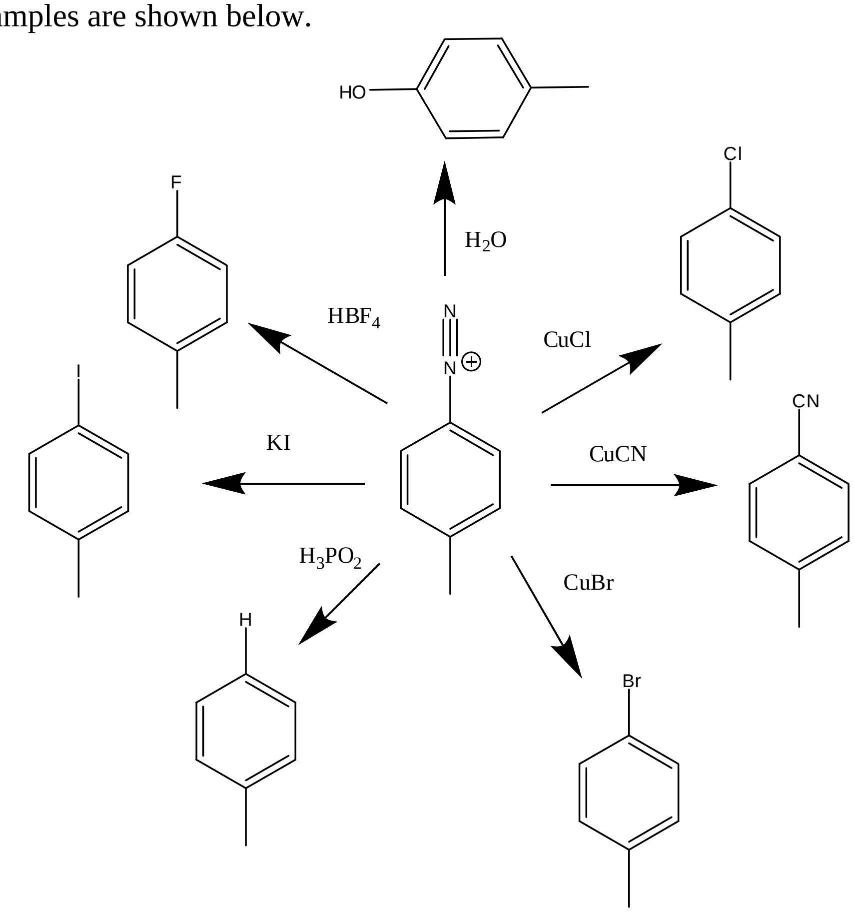
Aromatic Diazonium Salt Reactions (6th edition, Chapter 22.17, Figure 22.5, 7th edition, same)

We saw in the last notes that primary aromatic amines and nitrous acid forms the diazonium salt. The diazonium salt can be converted into many different functional groups.

Remember what you say when you first realize you have been caught for speeding (or anything else illegal). (Repeat in Queen's English.)

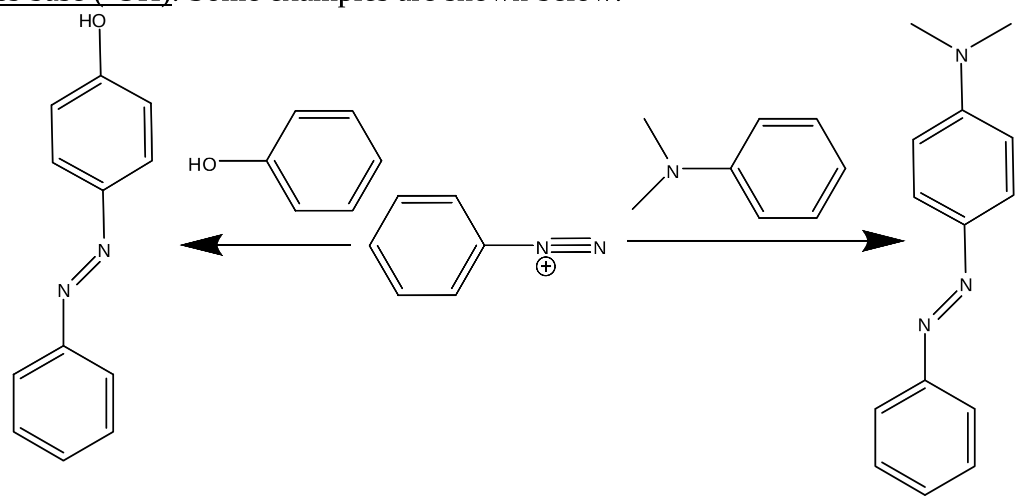
HONO!, The copper!!!

Three reagents used for the conversion of the diazonium salt are copper (I) chloride, copper (I) bromide, and copper (I) cyanide. These copper reagents are called Sandmeyer reactions. Reaction with hypophosphorus acid, H_3PO_2, converts the diazonium salt to a hydrogen. Treatment with KI converts the diazonium salt to the iodide. Conversion of the diazonium salt to the fluoride is accomplished with HBF_4 and heat and is called the Schiemann reaction. Finally, addition of water will convert the diazonium salt to an OH group. Examples are shown below.



Azo coupling (6th edition, Chapter 22.18, 7th edition, same)

Diazonium salts can also react with highly activated aromatic rings to form an azo compound. The two highly activated rings we will study in this class are phenols with a hydroxyl group and a tertiary aromatic amine with an amino group. The pH of the reaction is very important. For aniline, the pH needs to be between 5 –7. At low pH, the reaction does not take place. Why? The amine is protonated and makes the aromatic ring not reactive enough for the diazonium salt. For phenol, the pH needs to be at pH 7 – 10. At high pH, the reaction does not take place. Why? The diazonium salt reacts with the excess base (-OH). Some examples are shown below.



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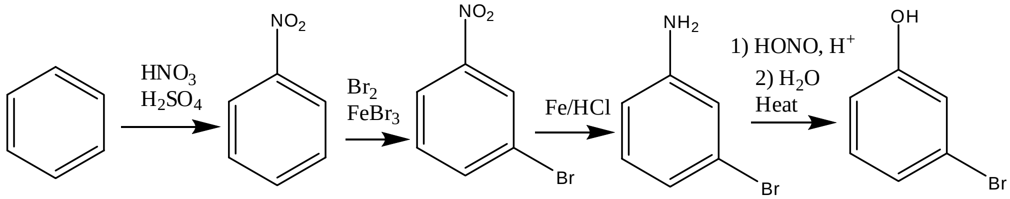
Nitro groups as directing groups (6th edition, Chapter 22.17, 7th edition, same)

Nitro groups can be used as directing groups and then removed as a diazonium salt. Some examples are shown below.

(6th edition, Problem 22.18, 7th edition, 7th edition, same) Design a synthesis of m-bromophenol from benzene.

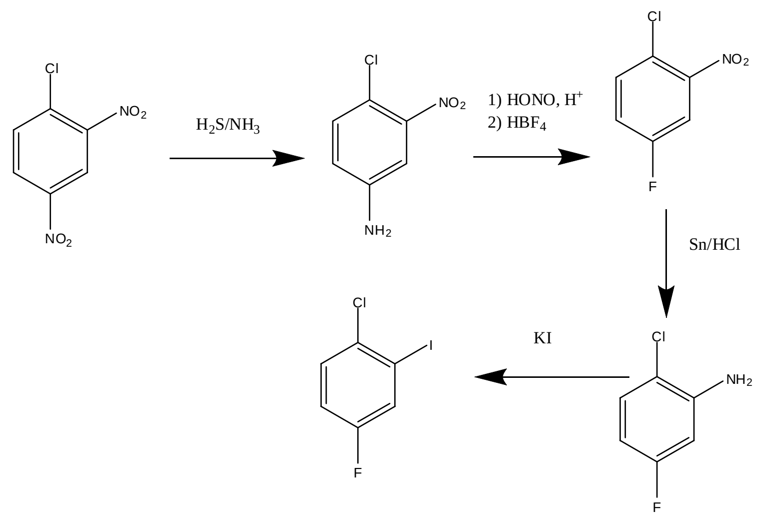


(6th edition, Problem 22.20, 7th edition, same) Show the proper sequence of synthetic transformations in the conversion of benzene to ethyl m-fluorophenyl ketone.

1) Acylation with propanoyl chloride/$AlCl_3$ to form propiophenone.
2) Nitration with nitric acid/sulfuric acid to give m-nitration.
3) Reduction with Fe/HCl to give the m-amine.
4) Reaction with 1) HONO, H+ followed by 2) a) HBF_4, b)heat)

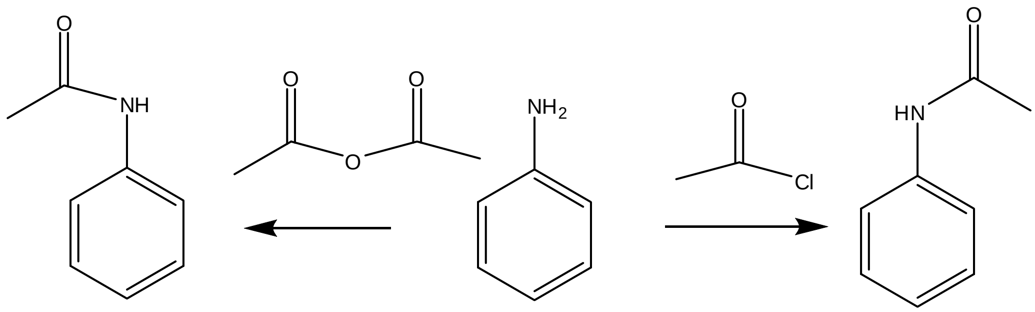
Reduction of the nitro group needed (Notes 37, pg. 4)

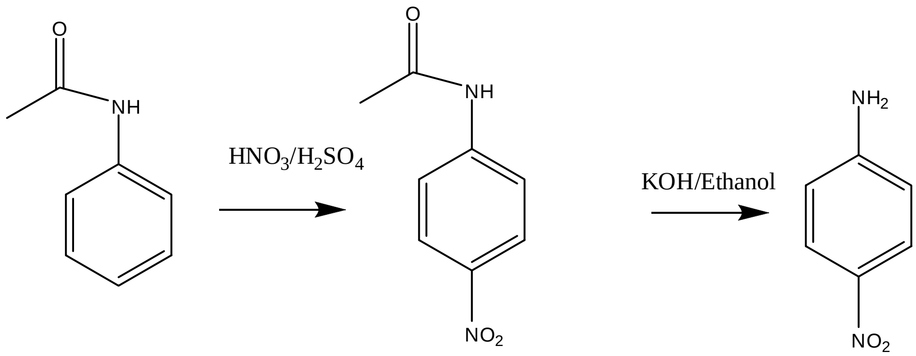
As stated earlier, H_2S/NH_3 will reduce one nitro group in preference to another nitro group. It is not known before the reaction is which nitro group will be reduced but it will be assumed in here that the desired nitro group is reduced. An example is shown below.



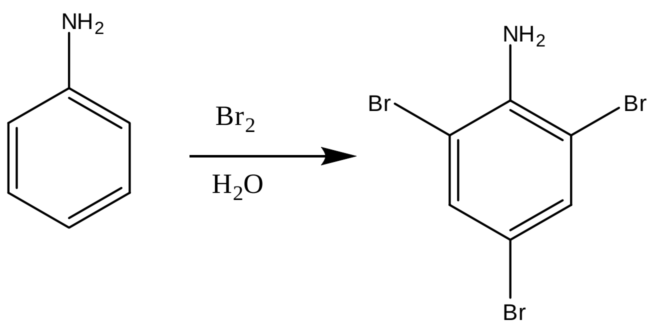
Amino groups and Electrophilic Aromatic Substitution (6th edition, Chapter 22.14, 7th edition, same)

Aniline has a NH_2 group present on the aromatic ring. N-methyl and N,N-dimethylaniline have one and two methyl groups on the aromatic nitrogen group respectively. These three groups are strong activators for EAS and usually result in "black tars" when subjected to oxidizing EAS conditions. (6th edition, pg. 970, 7th edition, pg. 933). Therefore, the nitrogen is protected as the amide group before the ring undergoes oxidation conditions with EAS. Once the amine is protected, the oxidation reaction can be carried out followed by removal of the protecting group.





Aniline can be brominated, for example, without protecting the NH_2 group but all three positions are replaced. A metal Lewis acid catalyst is not needed. An example is shown below.



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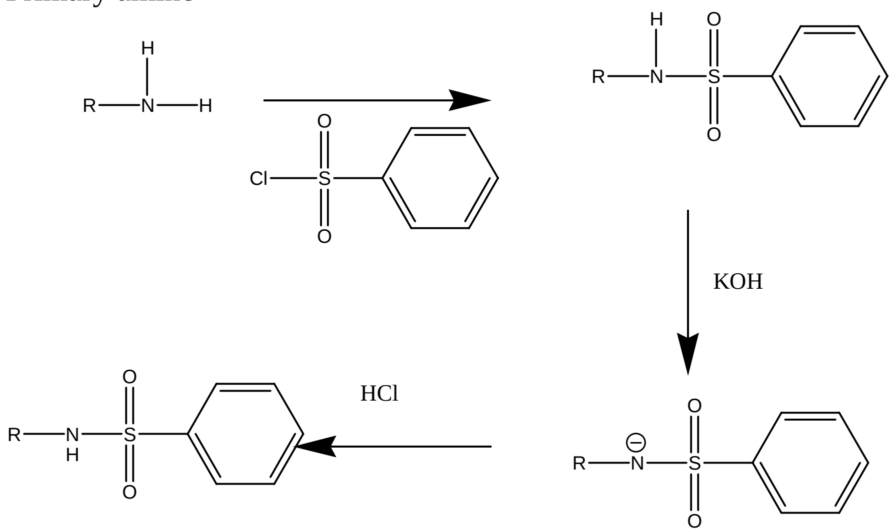
The Hinsberg test (Not in your book.)

The Hinsberg test allows for the determination of whether an amine is primary, secondary, or tertiary and involves two steps. The Hinsberg test involves formation of sulfonamides and involves shaking with excess sodium hydroxide in the first step. The second step requires acidification of the mixture. The results for the different types of amines allows a determination to be made.

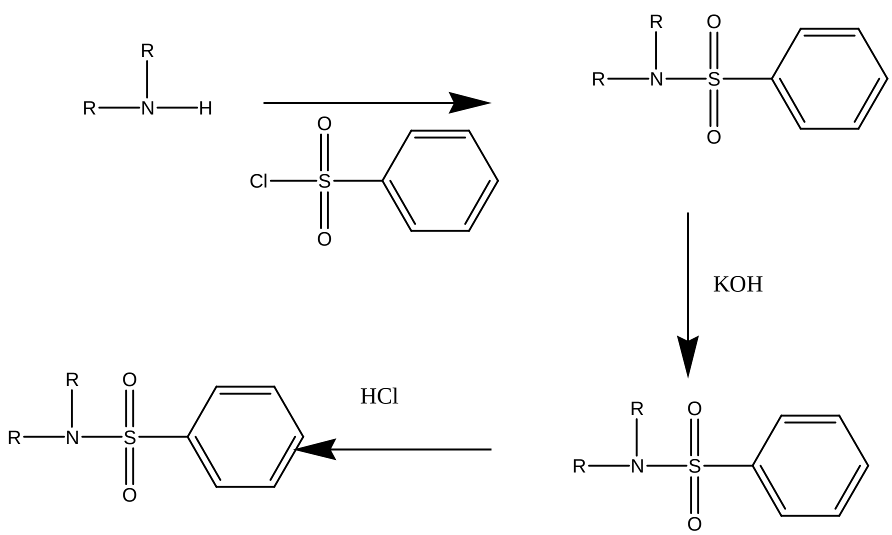
Primary amine



Water insoluble
(Precipitate)

Water soluble
(clear solution)

Secondary amine



Insoluble
(Precipitate)

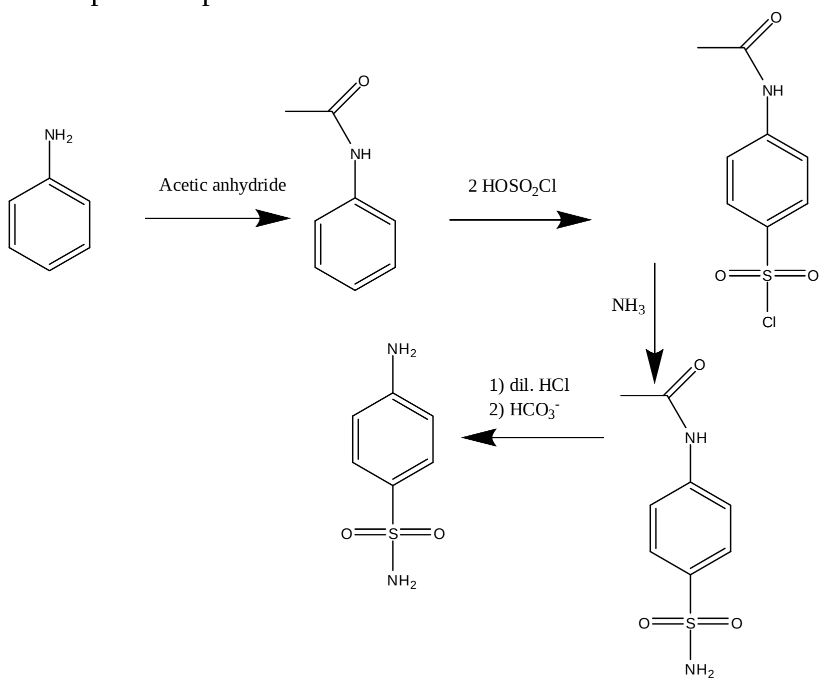
Insoluble
(Precipitate)

Tertiary amine

A tertiary amine does not react with a sulfonyl chloride to form a sulfanamide. If the amine is insoluble in water, it starts off as insoluble in the first step. The second step involves protonation of the unreacted amine which will be soluble.

Sulfa drugs (6th edition, pg. 980, 7th edition, pg. 943)

Sulfa drugs are used to kill infections. Sulfa drugs are made by the reaction scheme below. Protection of the amine is required because nitration of aniline will form decomposition products.



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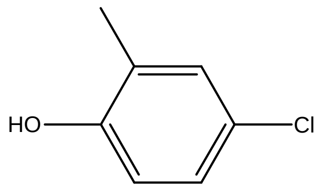
Phenols (6th edition, Chapter 24, 7th edition, same)

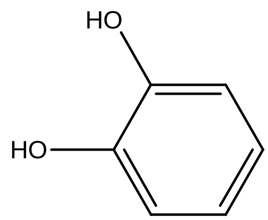
Phenols are defined by Carey as a “family of compounds characterized by a hydroxyl substitutent on an aromatic ring as in ArOH. Phenol is also the name of the parent compound, C_6H_5OH.” We will start with the nomenclature of phenols.

Nomenclature (6th edition, Chapter 24.1, 7th edition, same)

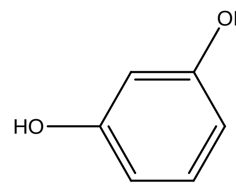
As mentioned above, the parent compound is called phenol. Addition of a methyl group to the phenolic ring forms cresol and cresol can be named as ortho, meta or para. Addition of more than two substituents does not allow one to use the ortho, meta, or para nomeclature and the phenol carbon is given number one. The aromatic diols are shown below. Carboxyl and acyl groups are given a lower number than hydroxyl groups on a benzene ring.



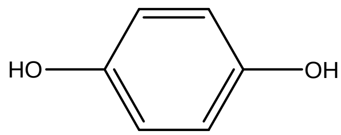
4-Chloro-2-methylphenol



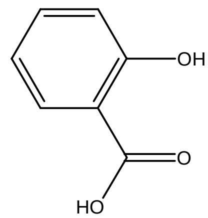
Catechol



Resorcinol



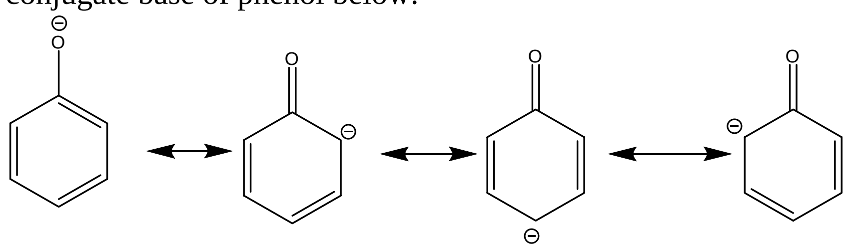
Hydroquinone



2-Hydroxybenzoic acid

Phenols and Acidity (6th edition, Chapter 24.4, 7th edition, same)

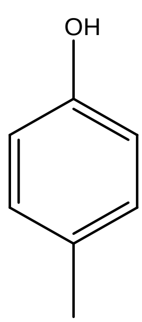
Phenols have a pKa around 10. Alcohols that are attached to an sp^3-hybridized carbon have a pKa around 16. Why are phenols more acidic than sp^3-hybridized alcohols? Resonance and induction. The inductive effect is due to the sp^2 hybridized atom being more electronegative than the sp^3 hybridized atom. The resonance effect can be explained by the conjugate base of the phenol. Give resonance structures for the conjugate base of phenol below.



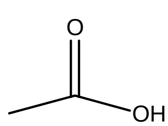
Electron withdrawing groups present on the benzene ring of the phenol helps to stabilize the negative charge on the phenoxide and makes the phenol more acidic. Put the following molecules in order of acidity from least acidic (= 6) to most acidic (=1).

HCl

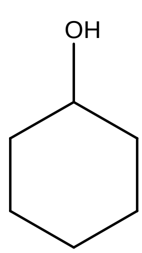
1



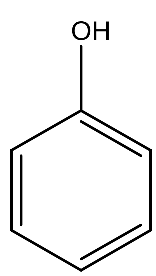
5



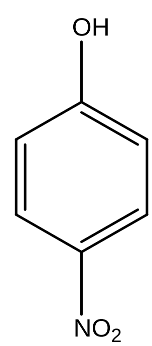
2



6



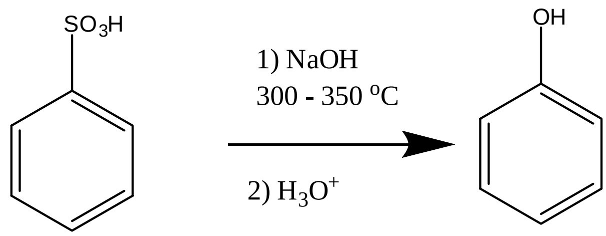
4

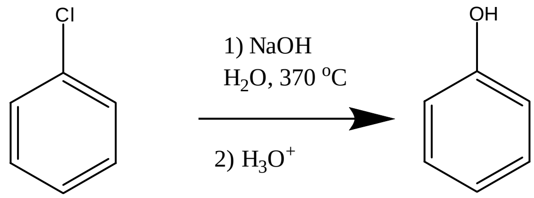


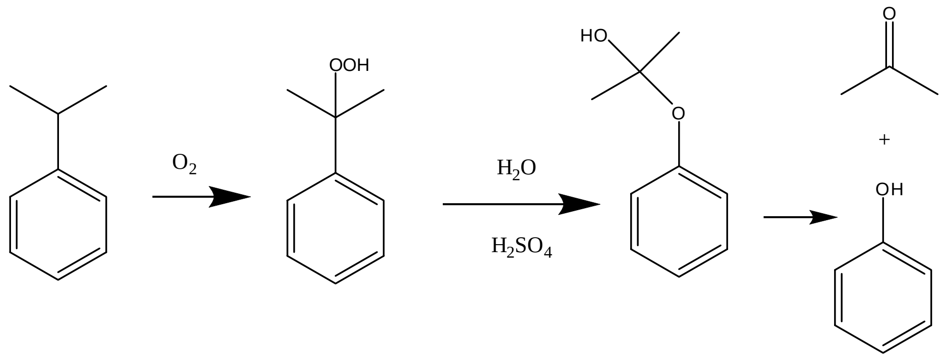
2

Synthesis of phenols (6th edition, Table 24.3, 7th edition, same)

Phenols can be synthesized by the methods given in Table 24.3. These methods are shown below.







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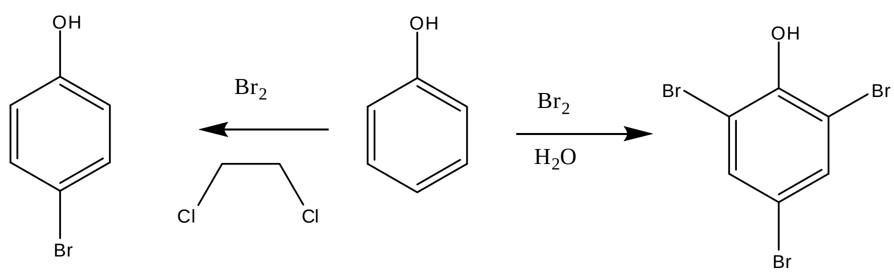
Reactions of Phenols (6th edition, Chapter 24.8, 7th edition, same)

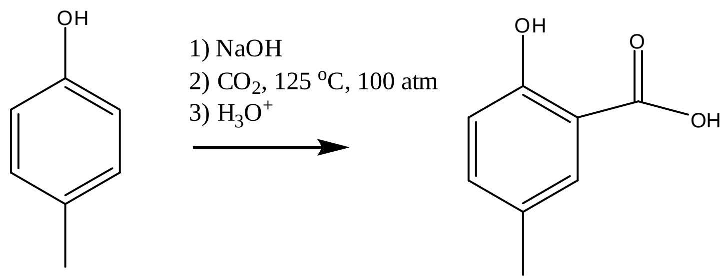
EAS – (6th edition, Table 24.4, 7th edition, same)

As seen with primary aromatic amines, phenols can add more than one substitutent. Polar solvents like water cause multiple substitutions while non-polar solvents cause monosubstitution. An example is shown below.



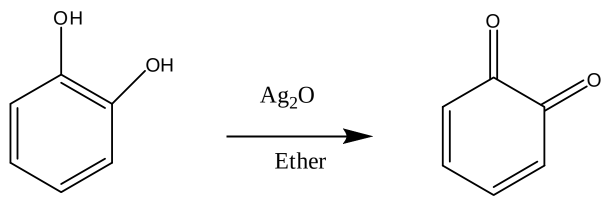
Kolbe – Schmitt Reaction (6th edition, Chapter 24.10, 7th edition, same

The Kolbe – Schmitt reaction is the reaction of the phenoxide ion with carbon dioxide. The CO_2 preferentially adds to the ortho position because the reaction is under thermodynamic control. A reaction always forms the weakest acid (or base) and the salicylate anion is the weakest base. An example is shown below.

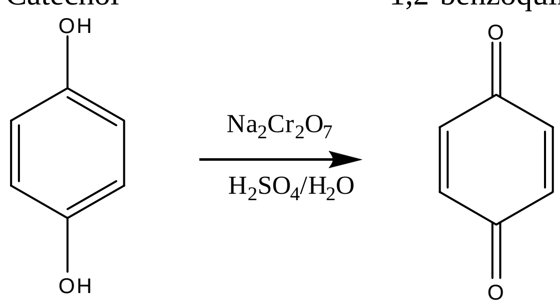


Oxidation of Phenols (6th edition, Chapter 24.14, 7th edition, same)

Catechol and hydroquinone can be oxidized to quinones with silver oxide and chromic acid, respectively. Examples are given below.



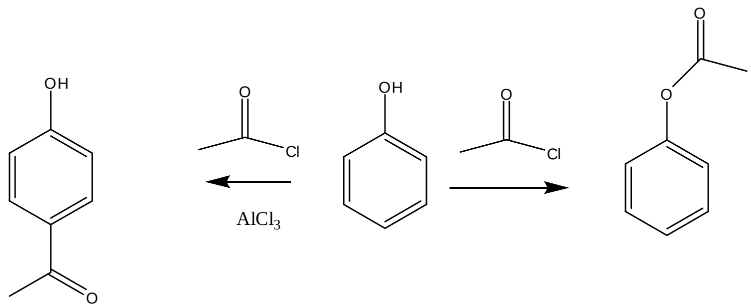
Catechol 1,2-benzoquinone



Hydroquinone p-Benzoquinone

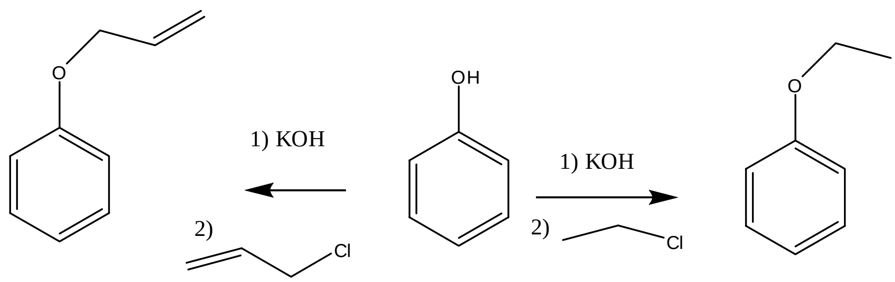
Acylation of phenols (6th edition, Chapter 24.9, 7th edition, same)

Phenols react with acylating agents differently depending upon reaction conditions. Acyl groups can be added at the oxygen and the products are called O-acylation products. Acyl groups add at the oxygen under kinetic control. Acyl groups can also be added at carbon and the products are called C-acylation products. Acyl groups add at the carbon under thermodynamic control. Addition of aluminum chloride gives C-acylation products. Some examples are given below.



Alkylation of phenols (6th edition, Chapter 24.11, 7th edition, same)

Phenols can be alkylated to form ethers under basic conditions which is called Williamson etherification. The Williamson is an SN_2 reaction so works well only for methyl, primary and some secondary halides. Some examples are shown below.



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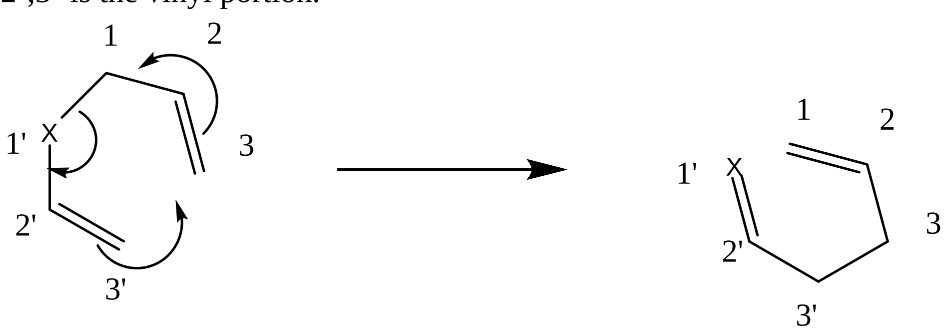
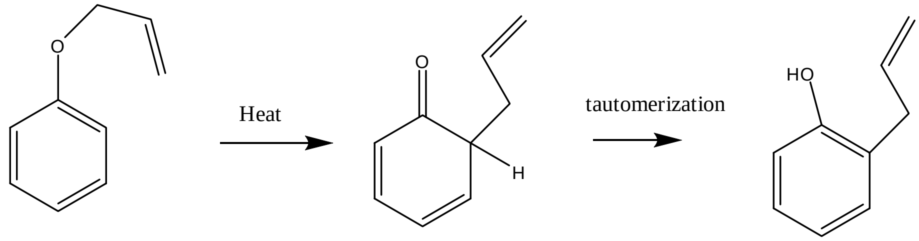
Rearrangements

There are three similar rearrangements shown below. What is required? X must be bound to a vinyl group and an allyl group. Changing X makes a differently named reaction but the arrangements are similar. These rearrangements are [3,3]-sigmatropic rearrangements. They are called 3,3 rearrangements because the bond between 1 and 1’ is broken and reformed 2 atoms away on the 3 and 3’ position. 1,2,3 is the allyl portion and 2’,3’ is the vinyl portion.



Claisen rearrangement (6th edition, Chapter 24.13, 7th edition, same)

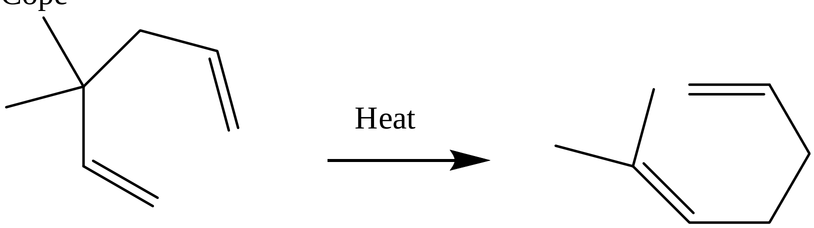
Given below is the Claisen rearrangement that substitutes oxygen for X above. A benzene ring may or may not be present but a carbonyl is generated. If benzene is present, tautomerization takes place to generate the phenol. An example is given below.



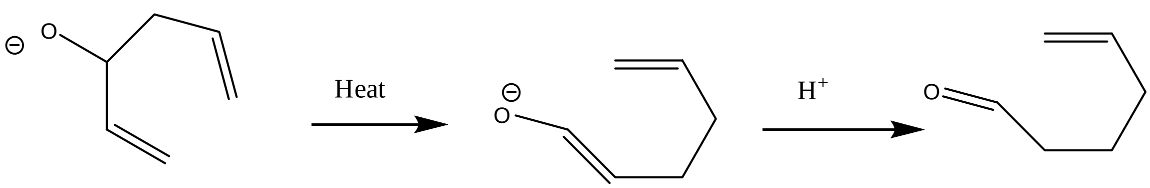
Cope and Oxy-Cope

The URL for the Cope and Oxy-Cope is http://www.organic-chemistry.org/namedreactions/cope-rearrangement.shtm. The Cope and Oxy-Cope rearrangement are similar with the X above being replaced with carbon (Cope) or with a carbon bearing a hydroxyl group. An example of each is below.

Cope-

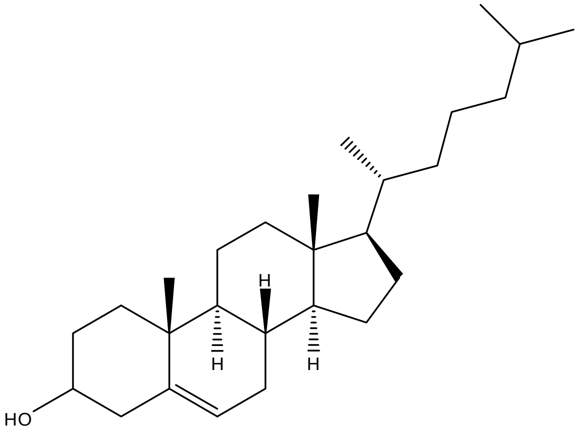


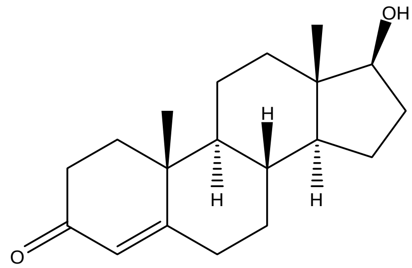
Oxy-Cope



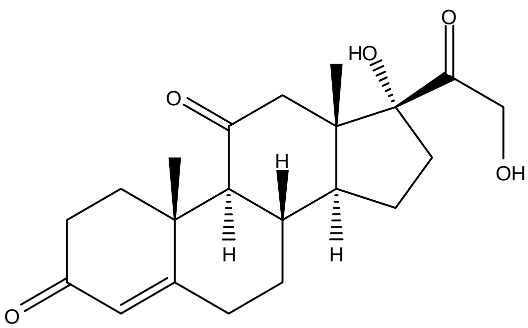
Steroids (6th edition, Chapters 26.11 - 15, 7th edition, same)

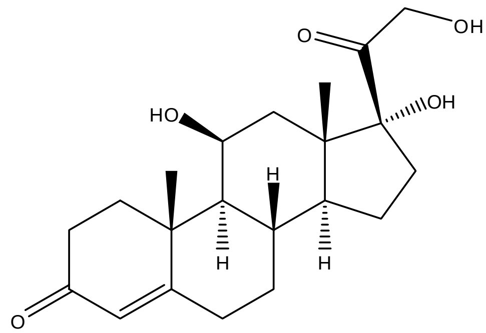
The URL for steroids is http://en.wikipedia.org/wiki/Steroid. Steroids can be broken down into animal, plant or fungus. The animal steroids can also be broken down into insect and vertebrate. The vertebrate steroids can be broken down into steroid hormones and cholesterol. Finally, the vertebrate steroids can be broken down into sex steroids, corticosteroids, and anabolic steroids. All steroids have the 6-6-6-5 ring assembly and an example of each type above is given below. Testosterone is used for a sex hormone and androstenedione is an anabolic steroid.



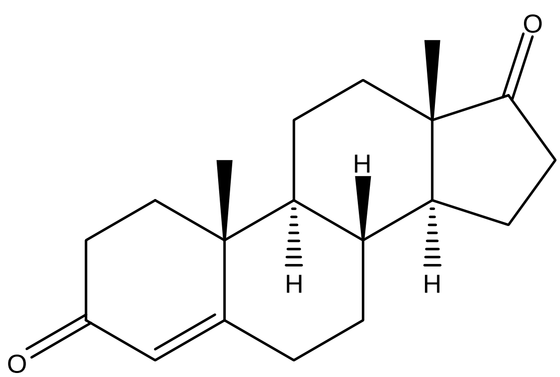


Cholesterol Testosterone





Cortisone Cortisol



Androstenedione

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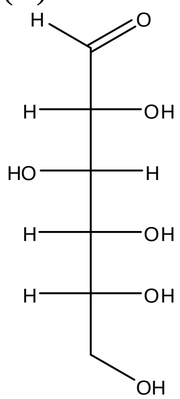
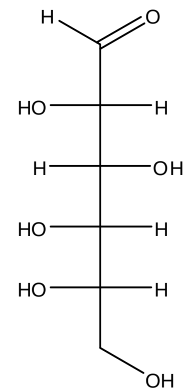
Sugars (6th edition, Chapter 25, 7th edition, same)

Sugar is described as a combination of sweet and sand. Sugars can also be called carbohydrates. Carbohydrates are defined as a polyhydroxy aldehyde or a polyhydroxy ketone. Saccharide is from the Latin for sugar and saccharides are defined as monosaccharides, disaccharides, oligosaccharides, or polysaccharides. D and L are used for whether the OH of the highest numbered stereocenter on sugars is on the right side (D) with the carbonyl group on top or on the left side (L).



Right side
D

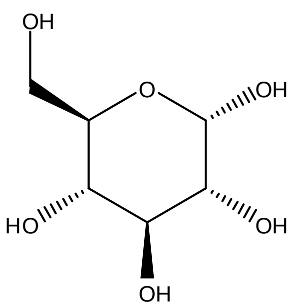
Left side
L



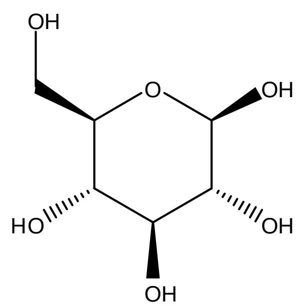
D-glucose

L-glucose

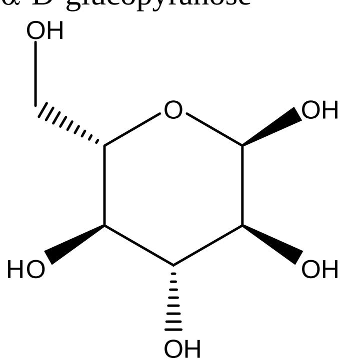
Sugars exist in their hemiacetal forms. Cyclization of an alcohol can form a five or six membered ring. A five membered ring is called a furanose. A six-membered ring is called a pyranose. Greek letters are used to describe the diasteromers that form. If the OH group on the hemiacetal carbon is down, it is called alpha. If the OH group on the hemiacetal carbon is up, it is called beta. Given below are a few examples. Haworth projections are used to show structures. Haworth projections below are labeled.



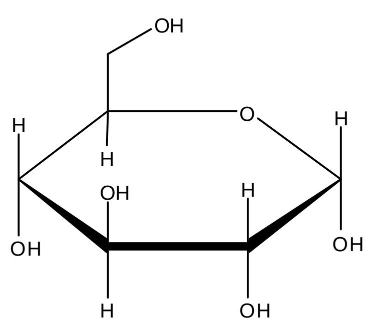
α-D-glucopyranose



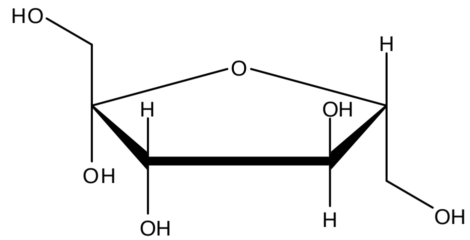
β-D-glucopyranose



α-L-glucopyranose



Haworth projection (α-D-glucopyranose)

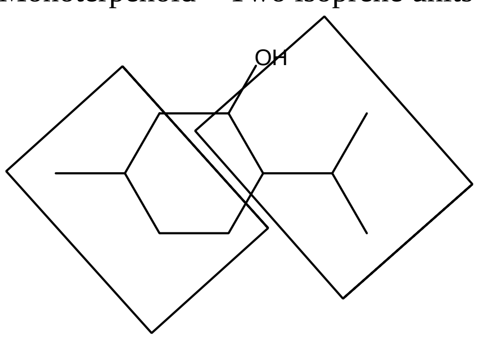


(2*S*,3*R*,4*R*,5*R*)-2,5-bis(hydroxymethyl)tetrahydrofuran-2,3,4-triol (what Chemdraw named it!)
Haworth projection (β-D-fructofuranose)

Terpenes (6th edition, Chapter 26.7, 7th edition, same)

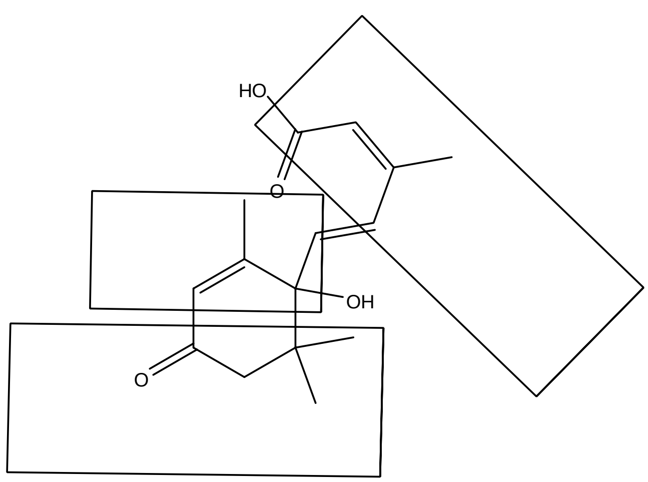
Terpenes contain isoprene units. Isoprene is 2-methyl-1,3-butadiene. Terpenoids are terpenes that have something else besides carbon and hydrogen. The terpenes are identified depending on how many isoprene units are present. It is possible to identify isoprene units in each terpene. Do you have to have double bonds like isoprene to be defined as an isoprene unit? No, all you need is 2-methylbutane in your isoprene unit. Isoprene units are in boxes below.

Monoterpenoid – Two isoprene units



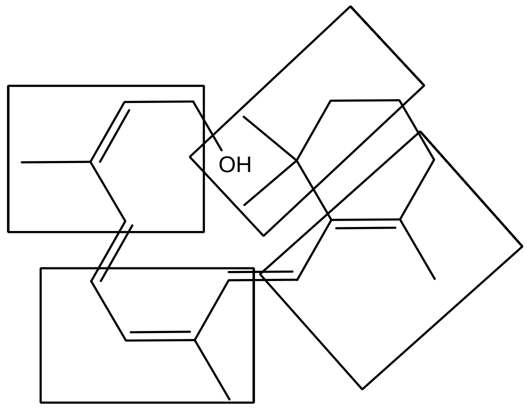
Menthol

Sesquiterpenoids – Three isoprene units



Abscisic acid

Diterpenoids – Four isoprene units



Retinol