

EXP. 48

SULFA DRUGS: PREPARATION OF SULFANILAMIDE

LEARNING OBJECTIVES: To illustrate some key concepts of organic synthesis and mechanisms. These concepts are the following.

1. MULTISTEP SYNTHESIS
2. PROTECTING GROUPS
3. THE SULFONIC ACID FUNCTIONAL GROUP AND ITS DERIVATIVES
4. ELECTROPHILIC AROMATIC SUBSTITUTION

QUIZ PREPARATION: Recitation notes and readings assigned in the syllabus.

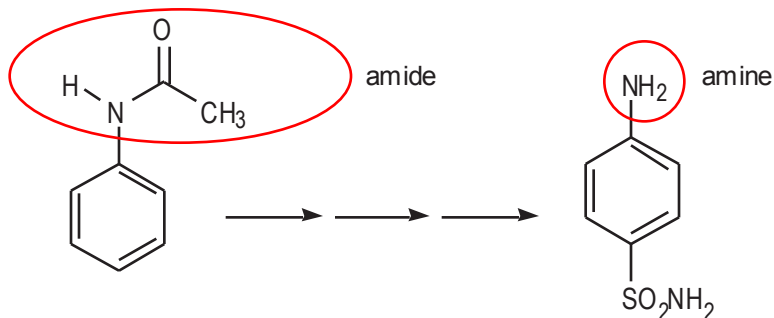
Have your textbook ready for quick reference to pages 388-396

MULTISTEP SYNTHESIS

Multistep synthesis refers to a sequence of reactions designed to produce a specific molecule as the final outcome. The sequence of reactions shown on p. 392 of your textbook is an example. The starting material is acetanilide. The sequence consists of three steps or reactions. Each reaction produces a product that is used in the next one, until the target molecule is obtained as the final product. The target molecule in this experiment is a sulfa drug called sulfanilamide.

PROTECTING GROUPS

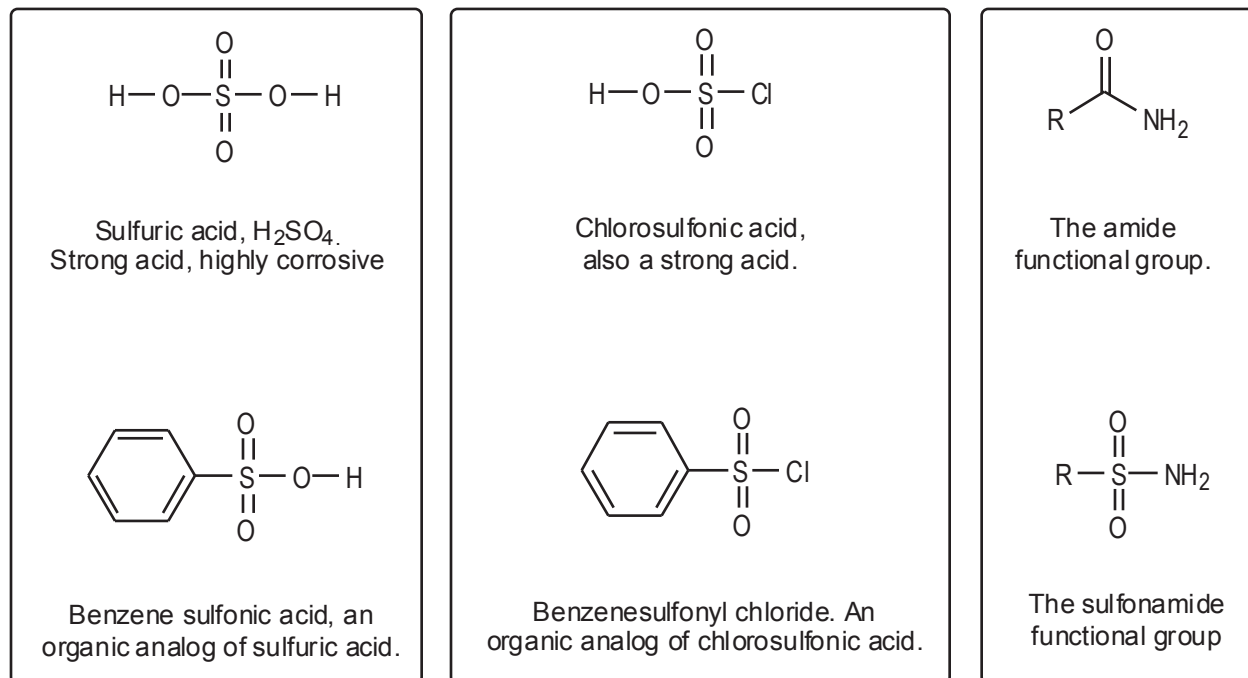
An abbreviated representation of this synthesis is shown below. Both the starting material and the product contain a benzene ring as the basic carbon skeleton. There are nitrogen-containing groups attached to both molecules. In the starting material this group is an amide. In the product it is an amine.



Notice that the amide group is carried all the way through the synthesis. It is not modified into amine until the very end, when the final step is reached. The question then is, why not start the synthesis with an amine group in the first place? The amide group can be thought of as a protected amine. Amines are very reactive, whereas amides are not. The amide group is preferred because there is less probability of side reactions through the synthesis with a less reactive group than with a more reactive one. The CH₃CO portion of the amide (called acetyl group) can be thought of as a protective group for the amine that keeps it from undergoing side reactions. Protecting groups are widely used in organic synthesis for better control during the intermediate steps. They are typically removed at the end of the synthesis when they are no longer needed.

THE SULFONIC ACID GROUP AND ITS DERIVATIVES

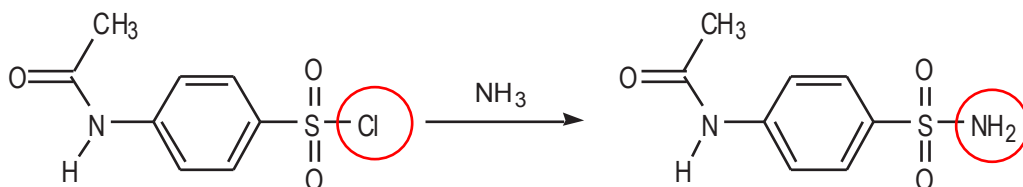
Sulfonic acids are organic analogs of sulfuric acid, an inorganic compound that is a very strong acid. Like sulfuric acid, sulfonic acids are highly corrosive, they react vigorously with water, and can cause skin burns.



Because they are highly reactive towards water, some of these substances are also lachrymators. They react with water in the eye to produce hydrochloric acid (HCl), another corrosive and irritant substance.

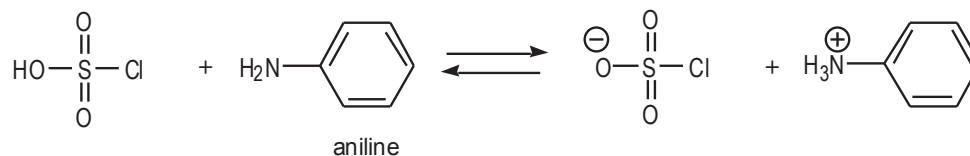
**HANDLE ALL OF THESE SUBSTANCES WITH CARE AND IN THE HOOD.
ALWAYS WEAR GLOVES AND SAFETY GLASSES.**

Sulfonyl chlorides contain a good leaving group (Cl). That is what makes them highly reactive towards water and other nucleophiles such as ammonia (NH_3). These reactions are used in this synthesis, but they can also cause problems. For example, the second step of the synthesis transforms p-acetamidobenzenesulfonyl chloride into p-acetamidobenzenesulfonamide by reaction with ammonia.

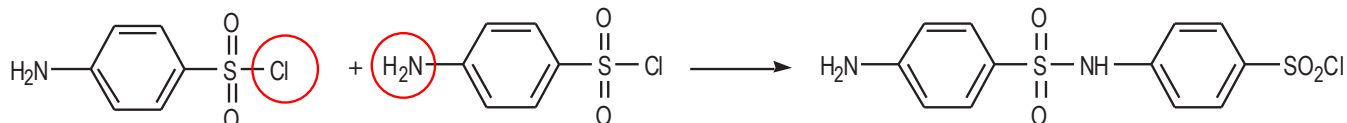


Likewise, on p. 395 at the top, the textbook recommends that the organic sulfonyl chloride be handled expeditiously after pouring it into ice to avoid the slow decomposition that results from contact with water.

This makes it apparent why aniline cannot be used as the starting material in the synthesis. The amino group of aniline is a strong electrophile. This would cause undesirable side reactions in the first and second steps because the molecule would tend to react as a base or as a nucleophile to form undesirable products.



Aniline is a strong base. It can react with chlorosulfonic acid in a proton exchange in the first step.



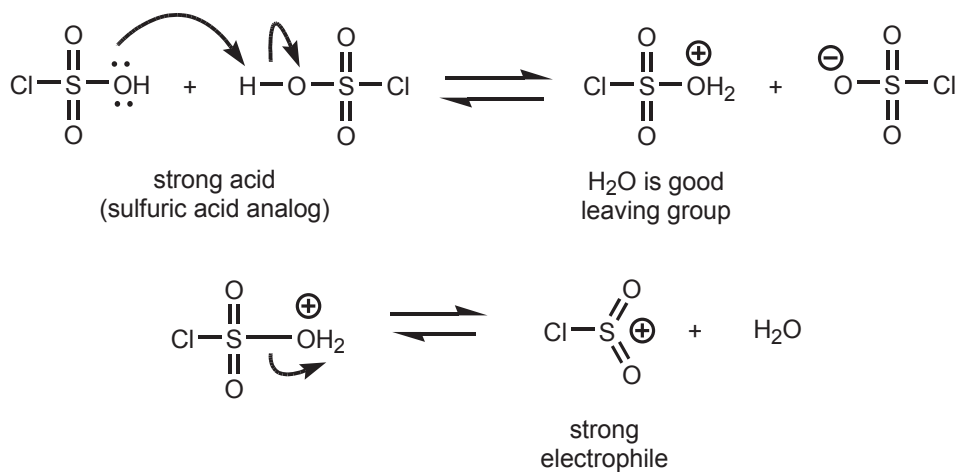
Even if this product could be prepared in the first step, it would react with itself in the second one as a nucleophile.

ELECTROPHILIC AROMATIC SUBSTITUTION

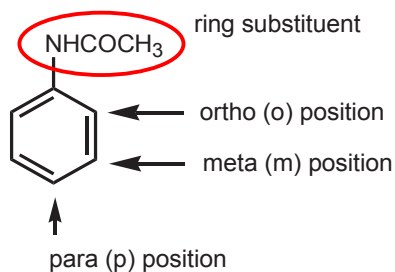
The first reaction in this sequence is an electrophilic aromatic substitution (EAS). This reaction is used to place the second group (SO₂Cl) on the benzene ring. This is not intended to be a full discussion of EAS mechanisms. For a comprehensive treatment please consult your organic chemistry textbook.

The most important steps in the mechanism are presented below.

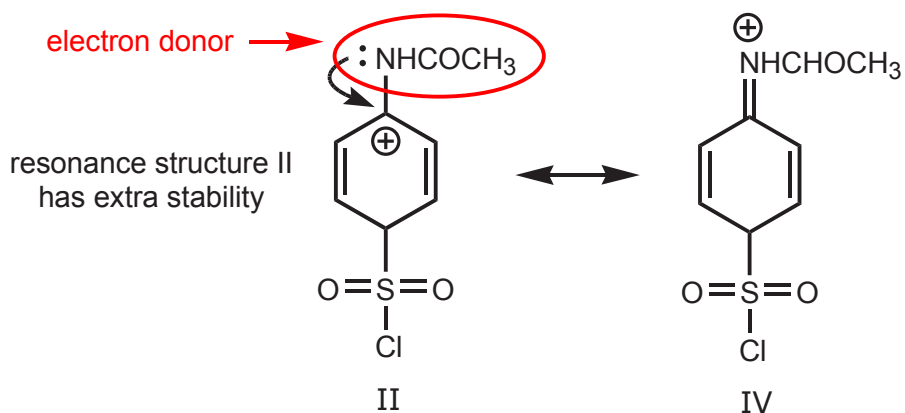
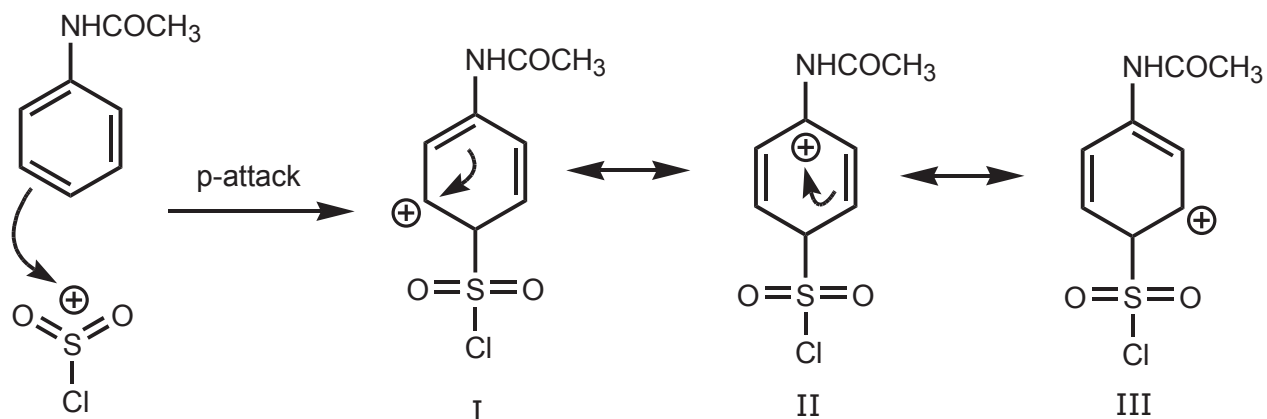
1. GENERATION OF THE ELECTROPHILE



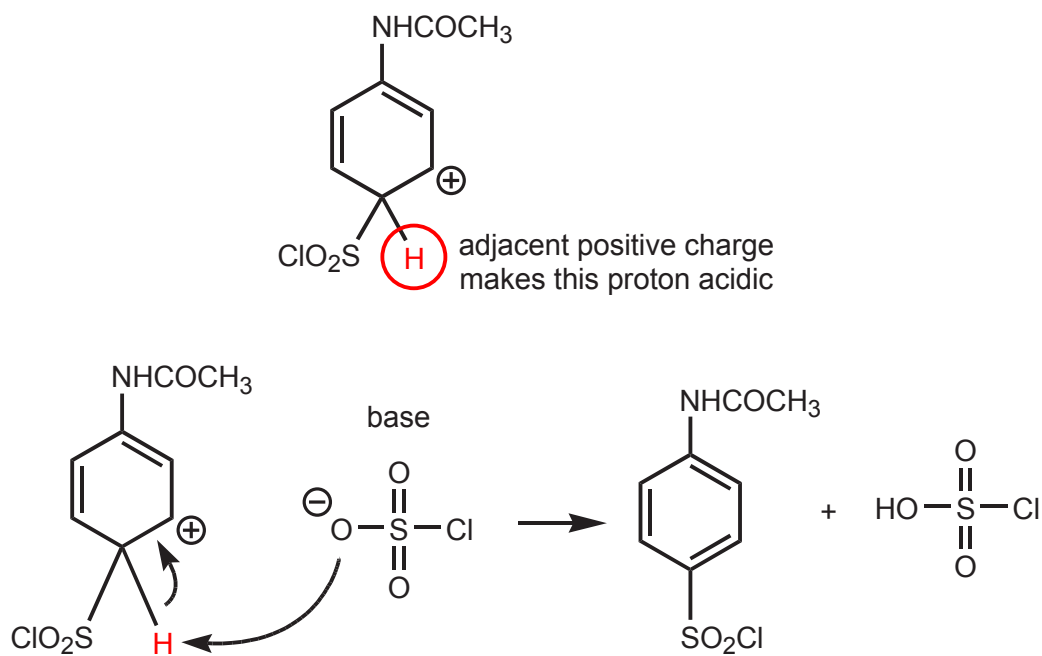
2. POSSIBLE SITES FOR ELECTROPHILIC ATTACK ON THE BENZENE RING



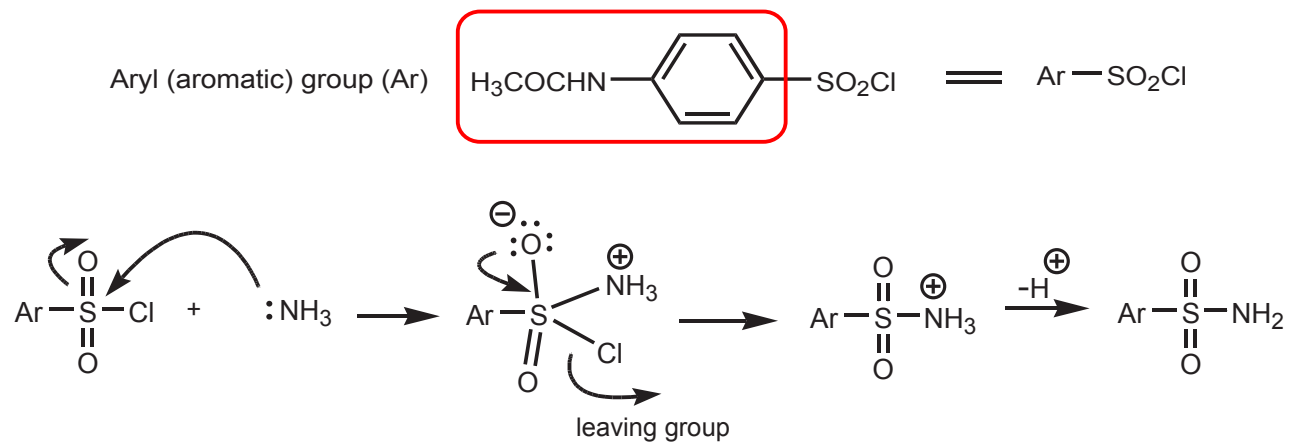
3. FORMATION OF THE "ACTIVATED σ -COMPLEX," A RESONANCE-STABILIZED REACTION INTERMEDIATE (structures I-IV).



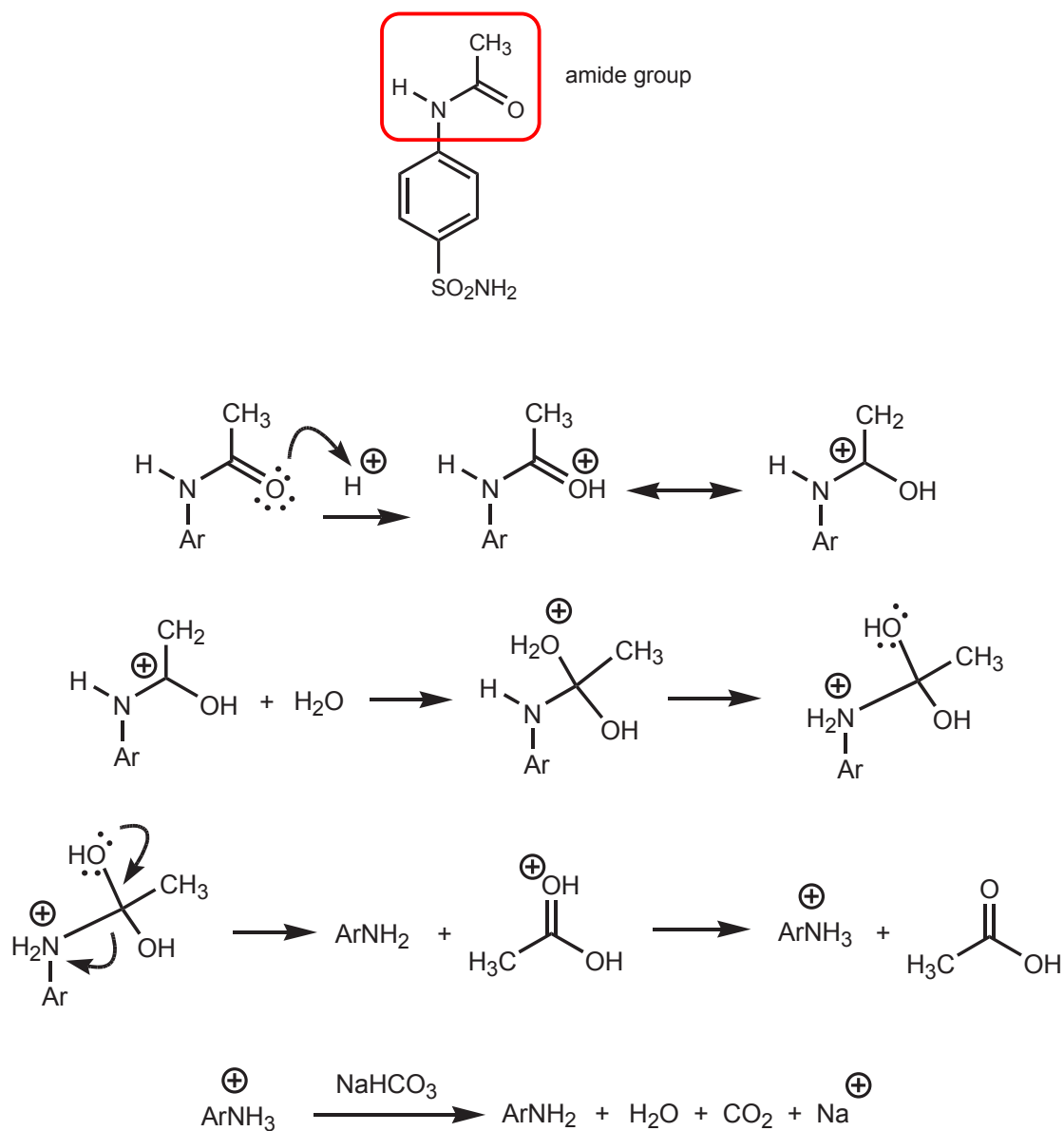
4. REGENERATION OF THE AROMATIC BENZENE RING.



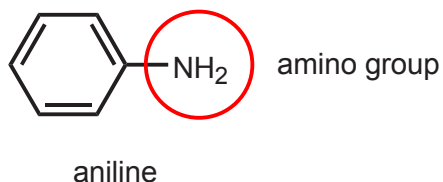
5. REACTION OF SULFONYL CHLORIDE GROUP WITH A NUCLEOPHILE (AMMONIA).



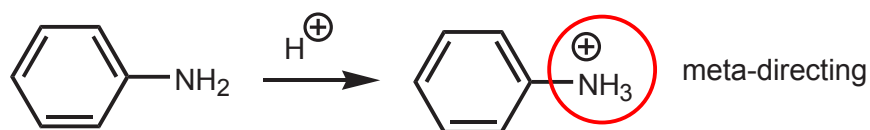
6. HYDROLYSIS OF THE AMIDE GROUP.



7. PROTECTING GROUP STRATEGY - Acetanilide is used as the starting material in these reactions, but at the end the amide group gets hydrolyzed into an amine group. Why not start the reaction sequence with aniline (below) rather than acetanilide, and save the last step? The answer is that the amino group in aniline is too reactive and it can react at several stages in the course of the reaction sequence.



For example, the amine can react in step 5 (reaction of the sulfonyl chloride group with ammonia), just like ammonia does, since they are both nucleophiles of similar structure. At the beginning of the reaction, the free amino group would get protonated by the strong acid (chlorosulfonic acid) to become a meta-directing group, rather than a para-directing group.



By using the amide, instead of the free amine, the nucleophilic properties of the nitrogen get reduced by resonance stabilization of the lone pair of electrons. In addition, the bulk of the amide group in acetanilide favors para-substitution over ortho-substitution due to steric hindrance.

