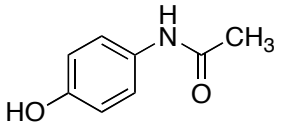
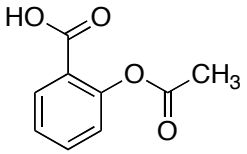
Experiment 1: Synthesis of Acetamides from Aniline and Substituted Anilines

Many of the acetylated [CH_3–C(=O)-] derivatives of aromatic amines (aka anilines) and phenols are pharmacologically important compounds. Some of these exhibit distinct analgesic activity. Two of the most representative examples are:



acetaminophen (®Tylenol)



acetylsalicylic acid (®Aspirin)

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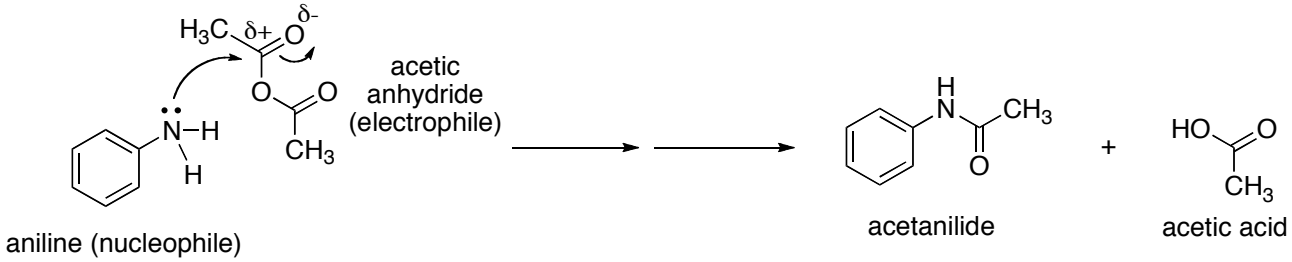
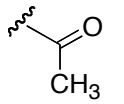
The reaction to be carried out in this experiment is:

Acetylation of aniline

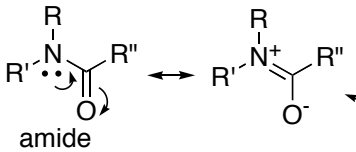


Both aniline and acetic anhydride are somewhat viscous liquids. So, simply mixing them together does not result in the efficient formation of acetanilide. Therefore, a solvent (in this case water) is used to dissolve and evenly disperse two reactants in it.

Note:

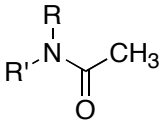


acetyl group



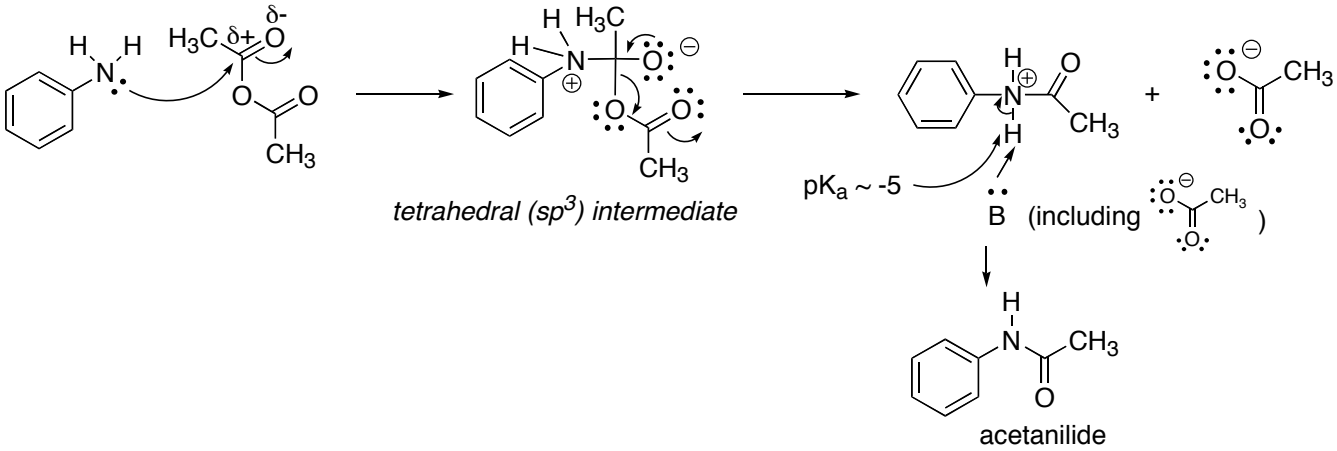
amide

The amide N is usually not nucleophilic because of a significant contribution of this resonance form.

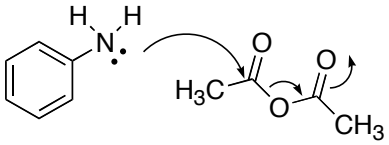


acetamide

Reaction mechanism:



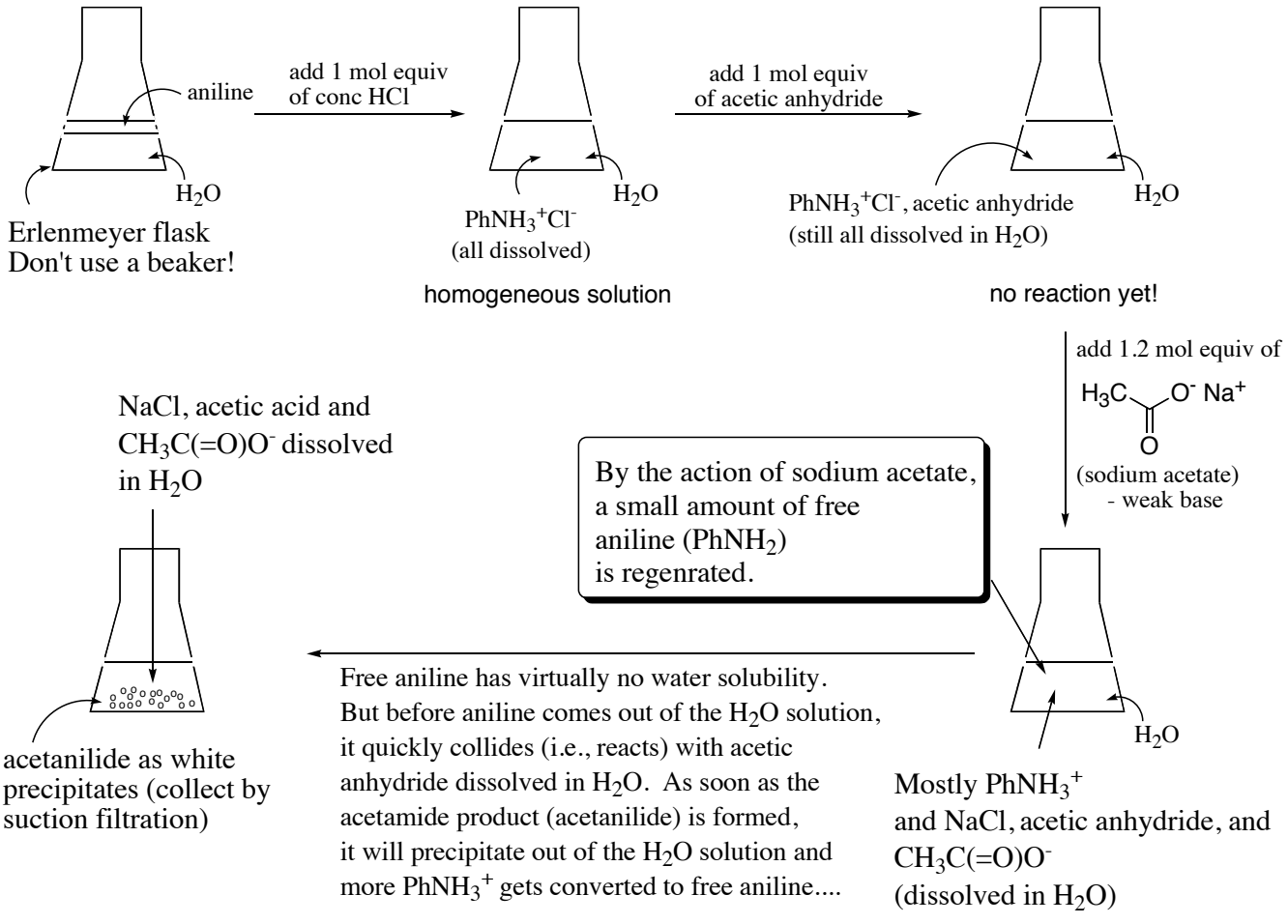
Additional comments on the reaction mechanism:
1. Aniline is a strong nucleophile (much stronger than water).
2. Acetic anhydride is a relatively unstable reagent, but does not react with water that easily.
3.



A direct substitution process at the C=O carbon does not take place. No direct S_N2 reaction at the C=O carbon is known. This is not feasible on the basis of the orbital consideration.

Experimental procedure:

Aniline is not soluble in water; so 1 mol. equiv of conc. HCl (37% HCl by weight in water) is added in order to dissolve the aniline in water.



Questions:
(1) What would happen if the order of additions of acetic anhydride and sodium acetate is reversed?
(2) What would be the outcome if 1 mol equiv of NaOH is used instead of sodium acetate?
(3) What would you have to do in order to dissolve *p*-nitroaniline into water by adding conc. HCl? The pKa of the conjugate acid of *p*-nitroaniline is 1.00 (see the note on pKa).