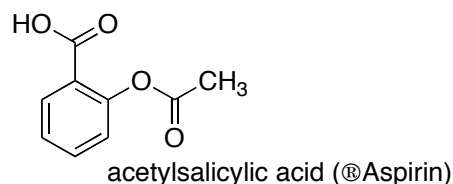
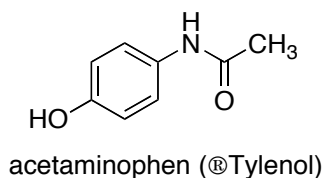
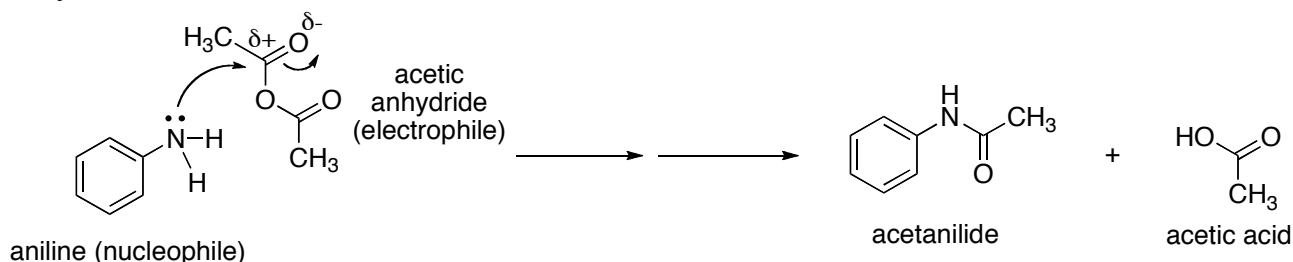


Experiment 1: Synthesis of Acetamides from Aniline and Substituted Anilines

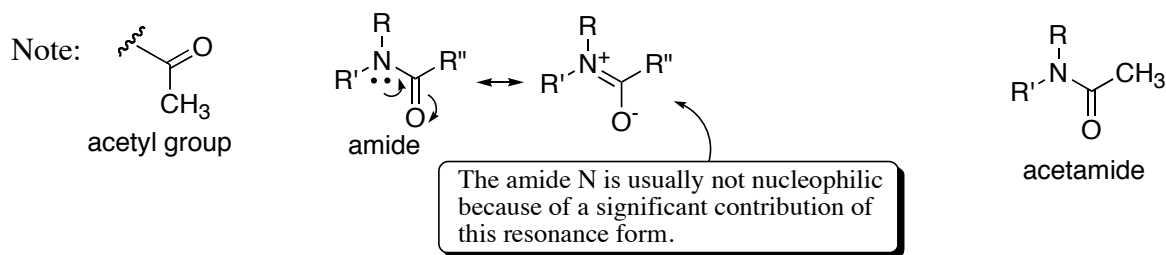
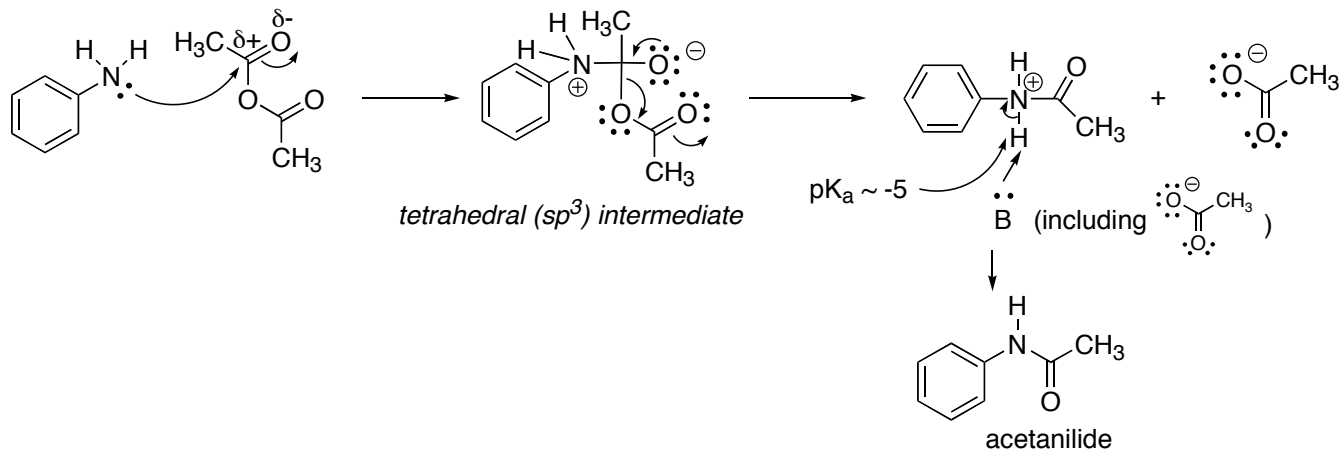
Many of the acetylated $[\text{CH}_3\text{-C(=O)-}]$ derivatives of aromatic amines (aka anilines) and phenols are pharmacologically important compounds. Some of these exhibit distinct analgesic activity. Two of the most representative examples are:



The reaction to be carried out in this experiment is:

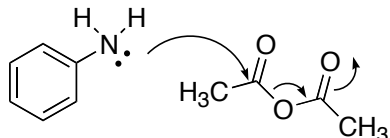
Acetylation of aniline

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.

**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.

Erlenmeyer flask
 Don't use a beaker!

aniline
 H₂O

add 1 mol equiv of conc HCl

PhNH₃⁺Cl⁻
 (all dissolved)
 H₂O
 homogeneous solution

add 1 mol equiv of acetic anhydride

PhNH₃⁺Cl⁻, acetic anhydride
 (still all dissolved in H₂O)
 H₂O
 no reaction yet!

add 1.2 mol equiv of
 H₃C(=O)O⁻ Na⁺
 (sodium acetate)
 - weak base

NaCl, acetic acid and
 CH₃C(=O)O⁻ dissolved
 in H₂O

By the action of sodium acetate,
 a small amount of free
 aniline (PhNH₂)
 is regenerated.

Free aniline has virtually no water solubility.
 But before aniline comes out of the H₂O solution,
 it quickly collides (i.e., reacts) with acetic
 anhydride dissolved in H₂O. As soon as the
 acetamide product (acetanilide) is formed,
 it will precipitate out of the H₂O solution and
 more PhNH₃⁺ gets converted to free aniline....

acetanilide as white
 precipitates (collect by
 suction filtration)

Mostly PhNH₃⁺
 and NaCl, acetic anhydride, and
 CH₃C(=O)O⁻
 (dissolved in H₂O)

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 pK_a of the conjugate acid of *p*-nitroaniline is 1.00 (see the note on pK_a).