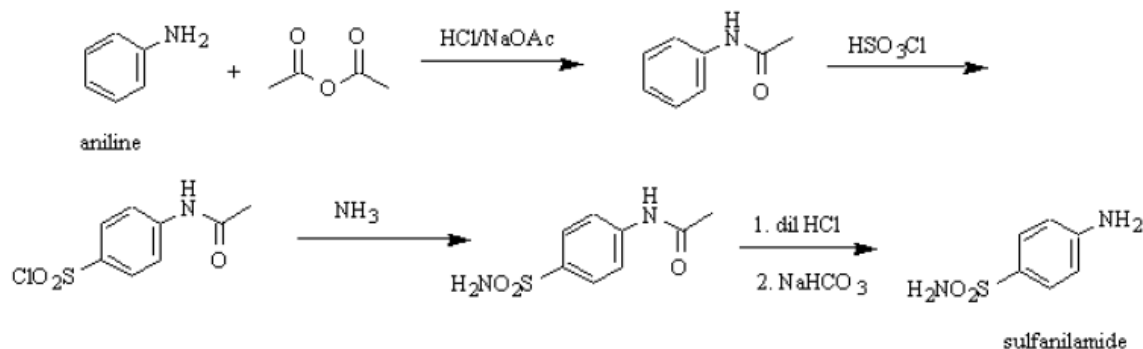


Synthesis 2: Synthesis of Sulfanilamide from Aniline

[Williamson, K.L. *Macroscale and Microscale Organic Experiments*;
Heath: Lexington, MA, 1994; pp 541-557]



Introduction.

Sulfa drugs were discovered in the early 1900's and found to be active anti-bacterial agents. Sulfanilamide inhibits the formation of folic acid in bacteria, thus preventing its further growth. Sulfanilamide is easily synthesized from aniline in four steps. You have seen the mechanisms for all of the steps, although some of the reagents may be unfamiliar.

Experimental

PART 1

Acetanilide: Dissolve 2 g of aniline in 60 mL water and 2 mL conc. HCl in a 125 mL Erlenmeyer flask. If the solution is colored, vacuum filter it through a pad of decolorizing Carbon (charcoal). Measure out 2.4 mL of acetic anhydride and prepare a solution of 2 g of sodium acetate in 12 mL of water. Add the acetic anhydride to the solution of aniline with stirring, and **at once** add the sodium acetate solution. Stir the mixture for ~ 5 mins, cool it in ice, and collect the product acetanilide. This material needs to be completely dry before the next step. Characterize the acetanilide (fluffy white crystals). **[Please note:- If crystals are not soluble in dichloromethane, then take the IR in mineral oil]**

PART 2

***p*-Acetamidobenzenesulfonyl chloride:** Place 2 g of dry acetanilide in a dry 25-mL Erlenmeyer flask. Add 5 mL of chlorosulfonic acid (corrosive and reacts violently with water) a few drops at a time using a Pasteur pipet (no metal needles!). After ~10 min the reaction should subside and almost all of the acetanilide will have dissolved. Heat the mixture in a hot water bath for ~10 min to complete the reaction. Pipet the mixture slowly with stirring into 24 mL of ice water in another 125-mL Erlenmeyer flask (use extreme caution). Rinse the reaction flask with cold water and stir the product until an even suspension of white solid is obtained. Vacuum filter the *p*-acetamidobenzenesulfonyl chloride (Chalky-white solid) and wash it with water. **[Please note:- If crystals are not soluble in dichloromethane, then take the IR in mineral oil]**

p-Acetamidobenzenesulfonamide: Transfer the moist solid to the rinsed 125-mL Erlenmeyer and add 9 mL of concentrated ammonia (ammonium hydroxide) and 9 mL of water. Heat the mixture to just below the boiling point on a hot plate with occasional swirling for 5 min. Cool the mixture in an ice bath and collect the p-acetamidobenzenesulfonamide (very small white needle like crystals) by suction filtration and allow it to drain thoroughly. [Please note:- If crystals are not soluble in dichloromethane, then take the IR in mineral oil]

Sulfanilamide: Transfer the moist solid to a 125-mL erlenmeyer, add 3 mL of con HCl and 6 mL of water. Boil the mixture gently until the solid dissolves and then continue heating at the boiling point for ~10 min longer (do not evaporate to dryness). Cool the solution to room temperature. No solid should deposit (v. light beige colored clear solution). If solid is seen, continue heating for awhile longer. To the cool solution (on ice), add a saturated aqueous solution of 2 g of sodium bicarbonate until the solution is neutral to pH paper (still keeping the flask on ice). Cool the resulting solid on ice and vacuum filter the sulfanilamide.

Recrystallize the sulfanilamide from minimum amount of water. Characterize sulfanilamide (white product) with H^1 -NMR (in DMSO solvent), IR, and melting point. Assign all characteristic data points of the material and comment on changes in the spectra through each step from starting material through product. [Please note:- If crystals are not soluble in dichloromethane, then take the IR in mineral oil]