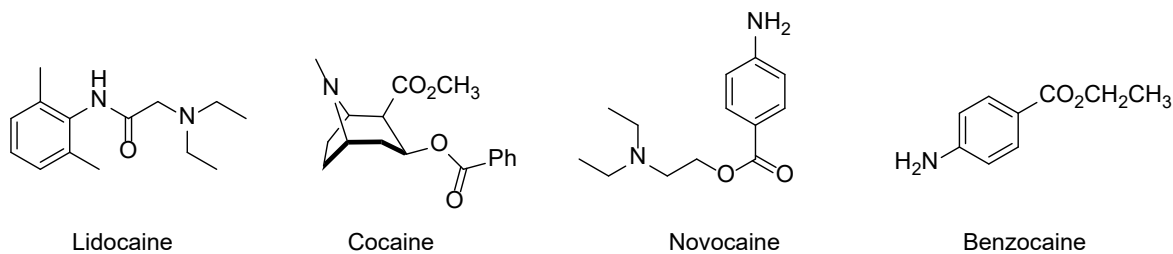


The 2-Step Synthesis of Lidocaine

Review: You should review SN2 reactions. You also need to do some on your own reading of section 20-15 in Wade. Make sure you are familiar with macroscale recrystallization and macroscale separation using a separatory funnel.

Introduction: Lidocaine is a member of the Caine family of pharmaceutical local anesthetics. Figure 1 below shows the chemical structure of Lidocaine as well as three other members of this important family of numbing agents.

Figure 1. Well-known compounds in the Caine family of local anesthetics



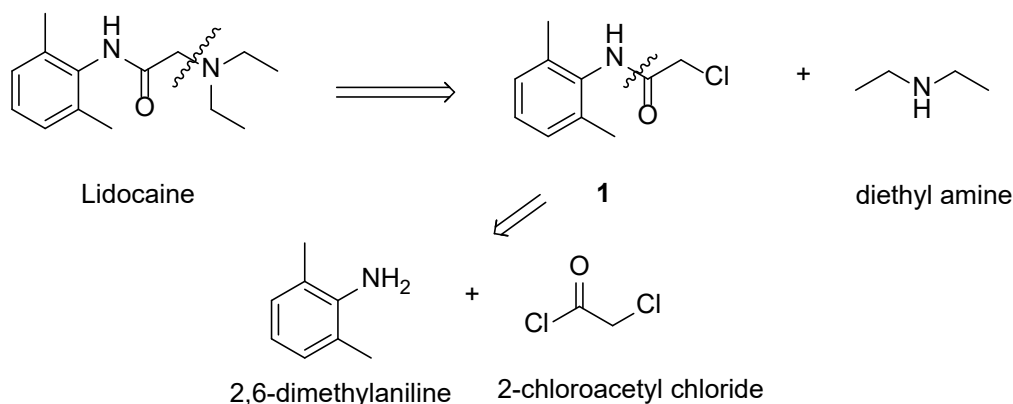
When used correctly, these compounds are very effective at providing local anesthesia, or the numbing feeling you get when you go to the dentist for a filling, for example. These compounds are administered topically, orally, or injected, depending on the situation. Topical creams and ointments that are available over the counter (OTC) generally contain Lidocaine and sometimes Benzocaine. Of the four compounds in Figure 1, Cocaine is not available OTC (hopefully this is obvious) and is not commonly used among the medical community due to its extremely addictive nature.

Local anesthetics prevent us from experiencing pain in a small portion of the body, i.e., wherever it is applied. When a local anesthetic is injected directly into the spinal fluid, our entire lower body goes numb. An example of the latter is an epidural given to a woman in labor, most commonly Bupivacaine (structure not shown). A common example of a local anesthetic is the use of Benzocaine in teething gel (Orajel®) for infants. The gel is applied to the affected area and numbs the gums temporarily.

These compounds are classified together because they show the same, or similar, mechanisms of action. Most members of the Caine family inhibit the sensation of pain by blocking the transduction of sodium ions across the cell membrane. We experience pain when our nerve endings are stimulated. When this stimulation occurs, the nerve cell (neuron) is depolarized by the influx of sodium ions. This causes a drastic change in the electric action potential (AP) and is then transferred down the nerve, directly to the central nervous system (CNS). The CNS construes this AP as pain. In short, the blocking of the "sodium gate" prevents this depolarization and pain is not experienced.

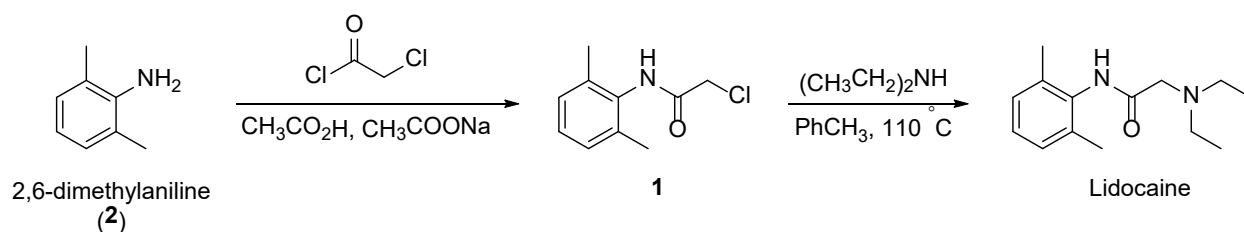
Retrosynthetic Analysis: Recall that retrosynthesis is working backwards from the desired compound and putting it together, piecewise, with known reactions. The synthesis of Lidocaine may be envisioned as outlined in the retrosynthesis in Figure 2 below. The indicated carbon-nitrogen bond (a wavy line through the bond) in Lidocaine can be formed via the SN2 reaction between commercially available diethyl amine and synthetic intermediate α -chloro amide **1**. Intermediate **1** is obtained via the commercially available compounds 2-chloroacetyl chloride and 2,6-dimethylaniline. There are other reagents involved in the synthesis of Lidocaine, however, they are generally omitted in a retrosynthetic analysis. Only the key bond formations are discussed. The detail is outlined in the explanation of each forward step.

Figure 2. Retrosynthesis of Lidocaine



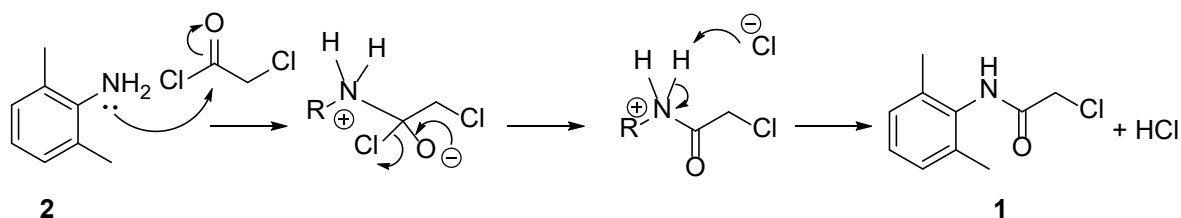
The Reaction, the mechanism and Background: The forward synthesis of Lidocaine is outlined in Figure 3.

Figure 3. The synthesis of Lidocaine



In step 1 of the reaction, 2,6-dimethylaniline is treated with α -chloroacetyl chloride in acetic acid in the presence of sodium acetate. Selective substitution at the acyl carbon (C=O) atom in this step is a reflection of the substantially greater reactivity of nucleophiles with acid chlorides (electrophile) relative to alkyl chlorides because of their electronic differences. Of the acid chloride, the chlorine and oxygen both pull electron density away from the carbon atom, which enhances its electrophilicity 10-fold. The mechanism is outlined in Figure 4 and is classified as an addition-elimination, very similar to the trimyristin saponification mechanism.

Figure 4. Mechanism of the formation of 1 from 2



Acetic acid (AA) is the solvent for this first step; the sodium salt of its conjugate base (sodium acetate) is also used, and their roles together are very important. Because acetic acid is chosen, an equilibrium is setup between itself and 2,6-dimethylaniline (Figure 5) to yield the ammonium acetate salt 3. The conversion of 2 to 1 (Figure 4) also liberates hydrochloric acid, and upon its generation, equilibrium is setup between itself and unreacted compound 2 to yield the ammonium chloride salt 4 (Figure 5). These two salts may appear to be the same, and they are with respect to the cationic portion. The difference is

2. What is the theoretical yield of Lidocaine? Base calculations on 2,6-dimethylaniline.
3. How many molar equivalents of diethyl amine are used in step 2?

Safety: 2,6-dimethylaniline is toxic and readily absorbed through the skin. You must wear gloves when handling this and any chemical during this experiment. 2-chloroacetyl chloride is toxic, corrosive and is a lachrymator (makes you cry); again wear gloves. **Diethyl amine is toxic and is very foul smelling.** The diethyl amine is to be dispensed by your TA. Follow the procedure exactly. Pardon the cliché, but it must be followed "to a T."

Experimental Procedure – Preparation of *N*-(2,6-Dimethylphenyl)chloroacetamide 1. First, get ~ 100 mL of water cooling in an ice-bath. You will use it soon. Wearing gloves, measure out 3.0 mL of 2,6-dimethylaniline into a 10-mL graduated cylinder and set aside in your hood. Using a larger graduated cylinder that your TA will have for you on the common bench, measure out 15-mL of glacial (concentrated) acetic acid (be very careful as it is corrosive) and add it to a 125 mL Erlenmeyer flask. Immediately *rinse the graduated cylinder that held the acetic acid with acetone a few times and allow to air dry. You will use it again soon.* Add the amine, via a Pasteur pipet, to the acetic acid in the Erlenmeyer flask. Rinse out your 10-mL graduated cylinder with acetone a few times and dry with the air jet. In this cylinder, measure out 2 mL of 2-chloroacetyl chloride and transfer to the Erlenmeyer flask containing acetic acid and 2,6-dimethylaniline. Add your thermometer to the Erlenmeyer. Using the larger graduated cylinder that you cleaned out a moment ago, measure out 25 mL of 0.333 M aqueous sodium acetate. Add this directly to the Erlenmeyer. *Note any observations and temperature changes!* Next, remove the thermometer and rinse it into the flask with the cold water you previously prepared and add 60 mL directly to the flask (reserve the remaining cold water for use soon), stir thoroughly for 10 minutes using your glass stir rod. Isolate the product via vacuum filtration using a Buchner funnel on the common bench. Rinse with a few portions of the remaining cold water. Press as dry as possible with another piece of filter paper.

Preparation of Lidocaine, AKA: 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide – To a *pre-weighed* 50-mL round bottomed flask, add the pressed-dry amide **1** and re-weigh the flask to get an exact amount of amide **1** used (record this mass). Sequentially add 7.5 mL diethylamine, 25 mL toluene and a few boiling stones. **Special Note: The TA will add your diethyl amine for you from the reagent bottle to minimize the stench in the lab.** Attach a water-cooled reflux condenser to the round bottomed flask (see section above for the proper hook-up of a water-cooled condenser). **Turn water on very slowly. Your water going to the drain should just trickle out,** not flow like white-water rapids! Lower assembly close to the hot plate and reflux for 90 minutes (note any and all observations). Cool to room temperature, unaided. Transfer to a separatory funnel and wash the organic layer with 3x50 mL portions of water. Extract the organic layer with 3M HCl (2x20 mL). Remove aqueous layer into a new Erlenmeyer and wash organic layer in sep funnel with water (1x20 mL). Drain aqueous layer into the acidic extract just performed. Cool this flask in an ice-bath and add a thermometer to the solution. When it has reached 10 °C, add a small portion of 3M NaOH. Continue to add 3M NaOH, in portions, while keeping the temperature below 20 °C until the solution is strongly basic (green by pH paper). Note observations upon additions of base. Isolate via vacuum filtration on a Buchner funnel and let air pass through as long as possible. *Stop here for the first period.*

Characterization and Purification – Recrystallize your Lidocaine from hexanes (follow the macroscale procedure on pages 65-66 of your lab manual. Run a TLC using 3:1 EtOAc:hexanes. Spot the plate as indicated in the picture below.

This method of co-spotting allows one to determine how the compounds will run together. Sometimes compounds interact with one another.

Circle your spots and turn your plate in with your report. You will notice that Lidocaine streaks on the TLC plate at any concentration. This is completely normal and you should not worry about it. Circle the darkest region of the streak.



Lane 1: 2,6-dimethylaniline

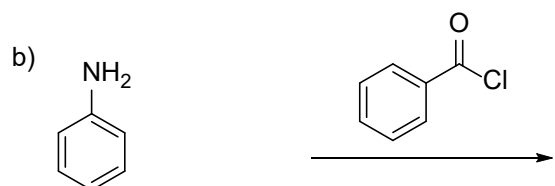
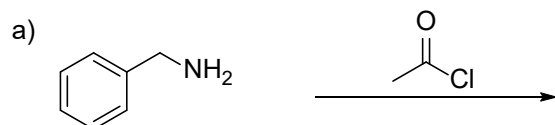
Lane 2: Co-spot of recrystallized lidocaine and 2,6-dimethylaniline

Lane 3: Authentic Lidocaine Sample

Obtain a melting point. You will run a GC/MS on your sample that will, in addition to a GC, read out a molecular mass (called mass spectrometry) in the physical chemistry labs on the third floor. Your report should discuss how you know that you have synthesized Lidocaine. Comment on all aspects, MP, TLC, mass of compound, etc.

Post-Lab Questions:

1. What is the theoretical product that would arise from 2,6-dimethylaniline reacting at the alkyl chloride carbon instead of the acyl carbon of 2-chloroacetyl chloride?
2. In the second step, toluene was employed as the solvent in the SN2 reaction. Could diethyl ether also be used? Hint: among other things, what increases the rate of a reaction?
3. In the use of a reflux condenser, why does water go in the bottom and out the top?
4. Predict the major organic product of the following reactions (you should do some reading in Wade, section 20-15 to help you answer this question):



5. In pre-lab question 3 you calculated the molar equivalents of diethyl amine. You should have obtained a number greater than 1. What is the purpose of excess diethyl amine? Refer to section 20-15 in Wade for assistance.

6. Provide a mechanism for the formation of the ESTER below from the following reaction between an acid chloride and an alcohol. Show all steps and charges. Refer to section 20-15 in Wade for assistance.

