Synthesis of \(N,N\)-Diethyl-\(m\)-Toluamide: The Insect Repellent "OFF"

Adapted by R. Minard and Sridhar Varadarajan from Introduction to Organic Laboratory Techniques: A Microscale Approach, Pavia, Lampman, Kriz & Engel (1989). Revised 10/10/00

Introduction:

**NOTE:** One lab before you plan to run this reaction, you should place a clean reaction tube containing a 1/2-inch stir bar, a 20-mL vial (but not the cap!), and a graduated 1-mL pipet into the oven so that they will be thoroughly dry by the next period. The reaction will be harmed by even the slightest traces of moisture.

In this experiment, you will synthesize the active ingredient of the insect repellent "OFF", \(N,N\)-diethyl-\(m\)-toluamide. The main functional group in this molecule is an amide. Amides can be unsubstituted, as in \(I\), monosubstituted, as in \(2\), or disubstituted, as in \(3\), shown below.

\[
\begin{align*}
\text{1:} & \quad \text{R}^\text{N} \quad \text{O} \\
\text{2:} & \quad \text{R}^\text{N} \quad \text{O} \\
\text{3:} & \quad \text{R}^\text{N} \quad \text{O}
\end{align*}
\]

The amide product from this synthesis is a disubstituted one, with structure \(3\) in which both \(R'\) and \(R''\) are ethyl groups.

Amides cannot be prepared directly by mixing a carboxylic acid with an amine. If an acid and an amine are mixed, an acid-base reaction occurs. The acidic proton is abstracted by the basic nitrogen lone pair resulting in the amine salt (ammonium salt) of the carboxylic acid, which will not react further:

However, if the water is removed from the ammonium carboxylate solution and the resulting solid heated strongly, water will be eliminated and the amide will be formed:

However, the high temperatures required for this reaction also leads to considerable thermal degradation of both the salt and product and therefore very low yields.

Amides are more commonly prepared via the acid chloride, as in this experiment. The acid chloride has a very electrophilic carbonyl and the chlorine is readily displaced by nucleophiles such as amines. In Step 1 of this reaction, the acid chloride of \(m\)-toluic acid is prepared using thionyl chloride (SOCl\(_2\)). Atmospheric moisture must be carefully avoided because the acid chloride reacts vigorously with \(H_2O\) to yield starting acid and HCl. To minimize contact with air, the acid chloride is not isolated or purified, but reacted directly with
diethylamine in Step 2. The hydrogen chloride formed in this step also reacts with the diethylamine and therefore two equivalents of diethylamine are added.

**Prelaboratory Exercise:**
The final reaction mixture contains the desired product, some unreacted acid chloride, and some diethylamine hydrochloride. 1) What reactions will occur when aqueous NaOH is added to this mixture? 2) Draw a flow chart describing in which layer, ether or water, the products and by-products are in after extraction with (a) 1M NaOH and then (b) 5% HCl?

**Cautions:**
Thionyl chloride must be dispensed in a hood. Do not breathe the vapors of this noxious and corrosive chemical. Use dry equipment when handling this material as it reacts violently with water. Do not get it on your skin.

Diethylamine is also noxious and corrosive. It should also be dispensed in a hood. In addition, it is quite volatile (bp = 56°C). Open the bottle carefully.

Wear gloves when handling thionyl chloride and diethylamine.

Use anhydrous ether in those sections in which you are directed to do so. For liquid/liquid extraction the wet ether can be used.

**Synthesis:**

**A. Formation of the Acid Chloride:**

In the hood, atop a magnetic stirrer, set up a sandbath with only 1/4 inch of sand in the bottom. Set the Varistat to 30.

Assemble a septum and Teflon tubing as shown below.

Remove the reaction tubes, stir bar and pipet from the oven where they have been drying since the previous period. Allow to cool. Weigh out 150 mg of m-toluic acid into the reaction tube containing the stir bar. In a hood, use the dry 1-mL graduated pipet to measure out 0.15 mL thionyl chloride and transfer this to the reaction tube containing the m-toluic acid. You will find a pipette suction bulb in the hooded shelf near the thionyl chloride and this should be used for drawing liquid up into the pipet. Cap with the septum & tubing.
assembly and place the open end of the teflon tube into an empty non-oven-dried reaction tube and push a piece of dampened cotton around the tube at the top of the tube. This provides a simple gas trap for catching the emitted HCl vapors. Stir and heat at a gentle reflux on the sand bath for about 15 minutes. While the reaction is refluxing, prepare a solution of 0.4 mL of diethylamine and 0.7 mL of anhydrous ether in your oven-dried vial. Obtain the ether from a septum-capped bottle (on the hooded shelf in a dessicator jar) using a 2.5-mL syringe and needle. Cap this solution until your ready to use it.

**B. Reaction of the Acid Chloride with Diethylamine:**

Allow the tube containing the acid chloride to cool. Using your 2.5-mL syringe and needle, add 1.5 mL of anhydrous ether obtained from a septum-capped bottle (on the hooded shelf in a dessicator jar). Stir at room temperature until a homogeneous solution is obtained. Using the same syringe and needle, inject the diethyamine/ether solution dropwise, through the septum, to the acid chloride solution while mixing at room temperature. Do NOT remove the gas trap tubing from the septum. This must be in place to release pressure. As the diethylamine is added, a thick white precipitate of diethylamine hydrochloride will form in the tube. Since the magnetic stirrer is ineffective in stirring this thick slurry, agitate this mixture by using your 1-inch magnetic stir bar on the outside of the reaction tube to drag the 1/2-inch stir bar on the inside up and down through the mixture. When the addition of the diethylamine is complete, let the reaction continue for ten minutes at room temperature with occasional agitation.

**Isolation and Purification:**

Remove the septum and add 1 mL of 1M sodium hydroxide (approx. 5%) and mix as described above for about three minutes. During this time the sodium hydroxide converts any remaining acid chloride to the sodium salt of \( m \)-toluic acid. This salt is soluble in the aqueous layer. Diethylamine hydrochloride is also soluble. Any remaining thionyl chloride is destroyed by the water. The desired amide is soluble in the ether. Remove the 2-inch stir bar by using your 1-inch stir bar on the outside of the tube to "magnetically drag" the smaller stir bar up and out of the top opening. Draw off the lower aqueous layer with a Pasteur pipet and discard. Add another 1-mL portion of 5% sodium hydroxide, seal with a #0 cork, and shake well to extract any remaining unreacted \( m \)-toluic acid. Allow the layers to separate and withdraw the lower aqueous layer and discard it. Add additional ether to replace any that is lost by evaporation during these extractions.

Now extract the ether layer with a 1-mL portion of 5% or 10% HCl to remove the resulting diethylamine as its hydrochloride salt. Finally, extract the ether with a 1-mL portion of saturated sodium chloride solution. Each time, cork and shake the tube vigorously, allow time for the phases to separate, and remove the lower aqueous layer with a pipet. Discard all of the aqueous phases, but keep the ether layer.

If necessary, add sufficient ether so that the total ether volume is 2 to 2.5 mL. Then add enough anhydrous sodium sulfate to fill the tube to about the 0.5 mL mark. Cork and shake the tube occasionally for about ten minutes. The anhydrous sodium sulfate absorbs residual water in the ether solution and "dries" it. The ether contains the product, \( N,N \)-diethyl-\( m \)-toluamide, and minor impurities in solution. Pipet filter the ether solution of the product from the solid sodium sulfate with a Pasteur pipet and transfer to a clean, dry, tared reaction tube. Leave the tube open in your locker until the next lab period, by which time the ether should have evaporated, leaving your product as a viscous, high-boiling liquid (bp 160°C at 11 mm). Apply vacuum to reaction tube to ascertain that all the ether has been removed. Traces of ether will effect the usefulness of NMR and IR spectra.

**Flash Chromatography:**

Determine the weight of your crude product. Determine the number of components in the crude mixture using TLC. Put together a chromatography column as pictured in Ch 8 of the Lab Guide, but only fill the column to a depth of 2 inches with alumina. Carry out flash chromatography. Flash chromatography is carried out identical to column chromatography with the exception that the entire process is speeded up by applying nitrogen or air pressure at the top of the column using a plastic "T". Use a suitable combination of ethyl acetate and hexane (as determined by TLC) as eluant to run the column. Analyze the sample according to the method on your experimental assignment sheet. How many spots do you see by TLC? What do you think each component is?

**Final Report:**

Interpret the spectra and answer the following questions:

1. Give the reaction that would take place if the acid chloride of \( m \)-toluic acid were mixed with
   a. water   b. ethanol
2. Compare the reactivity of the carboxylic acids, acid anhydrides, acid chlorides, and esters with respect to reactions with nucleophiles such as diethylamine.

3. Give the structure of the intermediate formed from the initial reaction of \(m\)-toluic acid and thionyl chloride.

Hint: The initial reaction of water and thionyl chloride is:

\[
\text{Cl}_2\text{S}_2\text{Cl}_2 + \text{H}_2\text{O} \rightarrow \text{Cl}_2\text{SO}_2\text{OH} + \text{HCl}
\]