**Lab 4: Multi-Step Synthesis of Lidocaine**

[Adapted from http://www.ux1.eiu.edu/~cfthb/classes/2845/lidocaine.pdf]


**Introduction:**

Pain relief is big business, with billions of tablets and millions of injections of pain relievers used annually. Local anesthetics are an important and well-studied class of drugs. Most anesthetics are synthetic drugs that have been developed to avoid the narcotic effects of natural products, such as cocaine.

In this experiment the local anesthetic lidocaine will be synthesized as the free tertiary amine. (The water soluble hydrochloride salt is generally used in medicine, but is more difficult to purify.) Lidocaine is sold under various trade names, the most common of which is Xylocaine. It is noted for its relatively high anesthetic activity when applied to the skin or injected into nerves, and it has a low toxicity and incidence of side effects. The two-step reaction sequence illustrated below starts with 2,6-dimethylaniline. The synthesis involves acylation of this aniline using chloroacetyl chloride, a highly reactive acid chloride, followed by an S_N2 displacement using diethylamine.

**Safety Notes:**

Handle all chemicals with care - avoid inhaling vapors or contact with skin. Flush affected areas with water if any of these come in contact with your skin:

<table>
<thead>
<tr>
<th>Step #1</th>
<th>2,6-dimethylaniline (carcinogenic) / glacial (100%) acetic acid chloroacetyl chloride (lachrymator; keep under the hood) bp 108°C</th>
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</thead>
<tbody>
<tr>
<td>Step #2</td>
<td>3 M HCl / 3 M NaOH / diethylamine (keep under the hood) bp 56°C</td>
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**Reaction Scheme**

![Reaction Scheme Diagram]

- **2,6-dimethylaniline**
- **chloroacetyl chloride**
- **α-chloro 2,6-dimethylanilide**
- **diethylamine**
- **lidocaine**
EXPERIMENTAL PROCEDURE

**Step #1 - Preparation of a-Chloro-2,6-dimethylacetanilide**

In a clean, dry 125-mL Erlenmeyer flask, mix 6.0 g (6.2 mL; 50 mmol) 2,6-dimethylaniline, 30 mL glacial acetic acid, and 5.6 g (4.0 mL; 50 mmol) chloroacetyl chloride in that order, under the fume hood. Mildly warm this mixture on a hot plate with swirling for 4 minutes, remove from the heat, and add a solution of 8 g (60 mmol) sodium acetate trihydrate dissolved in 60 mL of distilled water.

Cool the mixture in an ice bath and collect the solid product by vacuum filtration (Büchner Funnel). Rinse the solid with small portions of cold (D.I) water and draw air through it to aid drying. Dry the solid in the Büchner Funnel through high vacuum for 15 minutes. While this solid is drying under vacuum for 15 min, prepare for Step #2. When sufficiently dry determine its weight of the whitish chalky solid, measure the m.p. and collect the IR. Calculate your first-step percent yield (show all your work in the lab notebook).

**Intermediate:**

2-Chloro-N-(2,6-dimethylphenyl)acetamide  
C\textsubscript{10}H\textsubscript{12}ClNO  
(CH\textsubscript{3})\textsubscript{2}C\textsubscript{6}H\textsubscript{3}NHC(=O)CH\textsubscript{2}Cl  
F.W. 197.66  
Melting Point 143-148  
EINECS 214-460-7  
TSCA

**Step #2 - Preparation of Lidocaine**

Weigh your sample from the previous step in a clean, dry 100-mL round bottom flask. Add 50 mL of toluene, 15.6 mL (11 g, 150 mmol) diethylamine, and a stirring bar. Secure a water-cooled condenser on top of the reaction vessel and heat to a vigorous reflux with stirring for 45 minutes.

Cool the reaction mixture to room temperature (At this point I asked the students to use the house vacuum to evaporate some of the excess low bp diethylamine so it is easier to crystallize the lidocaine). Next, carefully transfer the mixture in the Rb-flask, by pipette, to a large seperatory funnel. An additional 5-10 mL of toluene can be used to complete the transfer. Wash the toluene solution with four 10-mL portions of water to remove diethylamine hydrochloride (Et\textsubscript{2}N•HCl) and excess diethylamine. Extract the organic layer with three 20-mL portions of 3 M HCl [if you see white solid form in your seperatory funnel, then you will need to add more toluene to the funnel. You may also need to do the extraction in portions. Do not shake vigorously! Vigorous...
shaking will cause emulsions in this lab!].

Combine the aqueous extracts in a 125-mL Erlenmeyer flask [or a large beaker, depending on the volume of extractions], cool the flask or beaker in an ice/salt bath, and neutralize the acidic solution by addition of 3 M NaOH in 5-mL portions [After the first 5-ml portion, then use pipette and add ~0.5ml at a time] with stirring while maintaining the temperature below 20 °C (check with pH paper). Collect the lidocaine precipitate by vacuum filtration. Rinse the solid with small portions of cold (D.I.) water and draw air through it to aid drying (Use high vacuum). Allow this sample to air dry in your drawer until the next lab. Determine the product’s melting point, Take an IR of your product and then submit your lidocaine sample for evaluation by H¹-NMR (CDCl₃ solvent).

Calculate the final yield of your product.