



Research in the Teaching Laboratory: Improving the Synthesis of Lidocaine

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Abstract:

The multi-step synthesis of Lidocaine is traditionally a low-yielding reaction mainly due to its second step, formation of α -chloro-2,6-dimethylacetanilide. Students often question the use of an acid (acetic acid) as the solvent for the reaction of a base (2,6-dimethylaniline, **1**) with the acyl chloride (α -chloroacetyl chloride, **2**), (**Reaction Scheme**) but they follow the procedure as directed.

Students, if treated as scientists in training, should be able to form a hypothesis before an experiment, design experiments to test the given hypothesis, and evaluate the results. A typical laboratory class was assigned to synthesize α -chloro-2,6-dimethylacetanilide using the procedure in the textbook, with acetic acid. This allowed everyone to learn from mistakes and correct their technique. A post-lab discussion including mechanistic evaluation (**Mechanism: Equation 1**) required the students to form a hypothesis and develop a series of experiments that could test it. If the problem was the acidity of the solvent, a less acidic solvent (ethanol) (**Mechanism: Equation 2**) was chosen to test this hypothesis. Acetone, ethyl acetate, and tetrahydrofuran (THF) were chosen to represent aprotic solvents to test the hypothesis that an aprotic solvent would work better than the protic solvents.

The second experiment was done similarly, with the students assigned to use one of the five solvents by drawing cards from a hat. The amount of solvent was consistent (2 mL) with each experiment. Each procedure used a fifteen minute reaction time prior to quenching the reaction in 2 equivalence of sodium acetate in 10 mL of water. The resulting mixture was cooled in an ice water bath for 10 minutes prior to collecting the white solid by vacuum filtration. The resulting white solid was dried to determine the percent yield, melting point, and obtain NMR samples. Verification was conducted by performing the experiment once more with students using a different solvent than before.

Results:

The conclusion of the class was both ethyl acetate and THF produced higher yields than the standard acetic acid solvent, but solvent interactions with ethanol and acetone produced byproducts that lowered the yield. While THF was initially deemed better than ethyl acetate, the observed product in the filter flask showed the inclusion of a second filtration step. When melting point and NMR analysis showed this was identical to product **3**, the second filtration product was combined with the first, increasing the yield to 90-95%. Therefore, the class concluded that ethyl acetate was the best solvent if two filtration steps are employed.

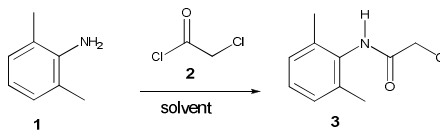
With the conclusion determined, the next assignment was proposing a hypothesis for why ethyl acetate was better than THF. This required the observations from the student notebooks. Students noted the formation of the salt **5** (**Mechanism: Equation 1**) immediately in ethyl acetate, while the salt was formed more slowly or was more soluble in THF. If salt **5** is not soluble in ethyl acetate, aniline **1** would not be protonated (**Mechanism: Equation 3**) and be available to act as a nucleophile with acyl chloride **2**.

While the student reports provided experimental detail and discussion portion of the laboratory, a survey was used to determine what the students liked most or liked least about this lab experience. The comments were extremely positive even though the class noted the elevated difficulty level of the lab. Many comments stated this was the first time an experiment was repeated, which lead to an increased level of understanding about the topic. Most appreciated the 'learning procedure' where technique was not evaluated during the initial experiment, allowing the student to learn without fear of grade penalty. Nearly everyone complained about the difficulty of the lab report, but appreciated the evaluated draft offering suggested improvements.

Funding Provided By:

- > SFASU Department of Chemistry
- > Robert A. Welch Foundation (Grant Number: AN-0008)

Reaction Scheme



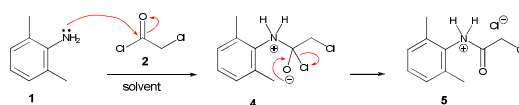
Reaction Procedure

Compound	Micro Scale	Equiv.
2,6-dimethylaniline, 1	0.300 g (2.48 mmol)	1.00
Solvent	2 mL (20-34 mmol)	8-14
α -chloroacetyl chloride, 2	0.300 g (2.66 mmol)	1.07

- > 15 minute reaction time
- > quenched with 2 eq. NaOAc in 10 mL water
- > cooled in ice-water bath (10 min.)
- > collected solid by vacuum filtration

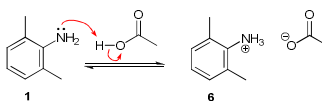
Mechanism: Desired nucleophilic addition followed by elimination.

Equation 1

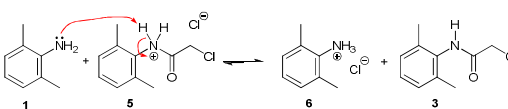


Mechanism: Competition of 2,6-dimethylaniline acting as a base.

Equation 2



Equation 3



Reaction Results

Solvent	Yield(%)	Melting pt.(°C)	Results
AcOH	60-66	138-145	This control was the baseline for comparison and the NMR and melting points were compared to this value.
EtOH	30-60	139-143	Low yield due to ester formation from solvent interaction. Product obtained has decent NMR and melting point.
Acetone	45-68 *	118-132	Messy NMR and imperfect melting points are caused by imine and enamine products from solvent interaction.
EtOAc	58-74 **	141-144	Very clean NMR product with nearly perfect melting point. Yield increased to 90-95% after two filtration steps.
THF	76-90	140-144	Very clean NMR product with nearly perfect melting point. Most yields range near 85% yield.

