Development of a Multistep Organic Synthesis Route for Undergraduate Chemistry II Laboratory

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Background

- Laboratory has been shown to be an essential component of chemistry education and provides a unique medium for teaching that cannot be done through lecture alone.
- Undergraduate laboratories are often the first connection between theory and practice students experience. However, current laboratory courses consist of separate, distinct experiments and syntheses whose purpose is only to demonstrate and illustrate concepts.
- Academic and industrial research both have many interconnected experiments with a final goal, in stark contrast to what is taught. This illustrates a disconnect between students' education and what is expected of them after graduation.

Motivation and Hypothesis

- To prepare students for future careers it is necessary to employ new methods of teaching laboratory courses to provide a better analogue to academic or industrial research. To this end this work sought to develop a multistep laboratory project with each experiment contributing directly to the next.
- This approach will now only give students exposure to a realistic research environment but may also garner a better sense of purpose for students by creating a sense of investment and responsibility towards the experiment.
- As illustrated in **Figure 1** the multistep synthesis consists of six steps, each illustrating crucial concepts essential for Organic Chemistry II.

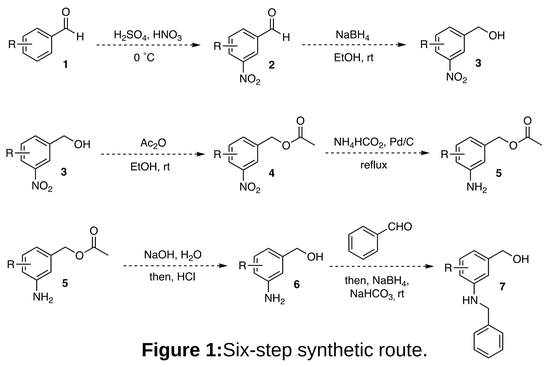


Figure 1: Six-step synthetic route.

- Due to time restraints work focused on optimizing the first step (**Scheme 1**)**,** the nitration of benzaldehyde **1** to 3-nitro-benzaldehyde **2**. This reaction is well studied and similar to a lab currently conducted in Organic Chemistry II, although not on the scale conducted here.
- **Hypothesis:** By optimizing the nitration reaction a pure product will be produced at a scale large enough to carry the product through five further reactions.

General Procedure

1. Cool sulfuric acid to 0˚C and add benzaldehyde, measuring using syringes.
2. Remove flask and add nitric acid. Stir at rt for 5 minutes.
3. Pour solution into a beaker with ice and filter.

- Alterations to the procedure were made, including mixing the acids first and then adding benzaldehyde, stirring at lower temperatures and changing the stir time, described in **Tables 1-4**.

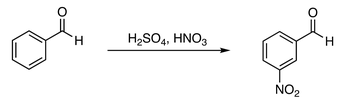
Synthetic Scheme and Reactions Conducted

Experiment #	Stir Temperature (˚C)	Stir Time (minutes)	Mix Acids Before Adding Benzaldehyde?	Percent Yield
1.1.1 (Standard)*	rt	5	No	31.08
1.11.1	0	5	No	13.18
1.8.4	0	5	Yes	71.96
1.5.2	-10	5	Yes	66.89
1.8.2	-10	20	Yes	78.38

Table 1: Effect of mixing the acids on percent yield, demonstrating the increased yield when mixing the acids first.
*Done without syringes

Experiment #	Stir Temperature (˚C)	Stir Time (minutes)	Equivalents Compared to Standard	Percent Yield
1.1.1 (Standard)*	rt	5	1	31.08
1.3.2	rt	5	2	18.92
1.5.2	-10	5	1	66.89
1.8.1	-10	5	2	73.65

Table 2: Effect of reaction scaling on percent yield, demonstrating a similar percent yield at optimal conditions even at double equivalents compared to standard.
*Done without syringes



Benzaldehyde 3-Nitrobenzaldehyde

Scheme 1: Nitration of benzaldehyde to 3-nitro-benzaldehyde

Experiment #	Stir Temperature (˚C)	Stir Time (minutes)	Percent Acid Used Compared to Standard	Percent Yield
1.1.1 (Standard)*	rt	5	100	31.08
1.7.1	rt	5	50	Trace
1.7.3	rt	10	50	Trace
1.7.4	rt	30	50	0.34
1.7.2	rt	5	25	Trace

Table 3: Effect of lowering the amount of acid on percent yield, demonstrating the effect lowering the amount of acid has on decreasing the percent yield.
*Done without syringes

Experiment #	Stir Temperature (˚C)	Stir Time (minutes)	Percent Yield
1.1.1 (Standard)*	rt	5	31.08
1.4.1	rt	20	50.00
1.8.4	0	5	71.96
1.10.4	0	10	4.73
1.8.1	-10	5	73.65
1.8.3	-10	20	76.35

Table 4: Effect of stir temperature on percent yield, demonstrating the increased yield at -10˚C compared to rt and 0˚C.
*Done without syringes

Spectra of Compounds

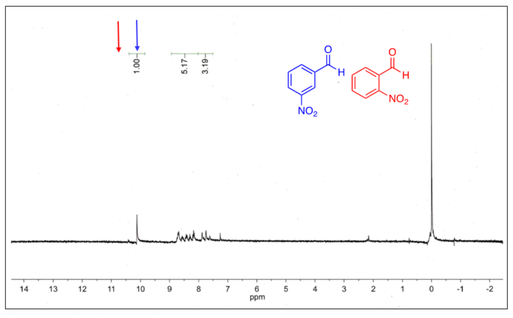


Figure 2: ^{1}H NMR spectrum of 3-nitro-benzaldehyde (blue) and 2-nitro-benzaldehyde side product (red) from 1.1.1 (Standard), stirred at rt for 5 minutes.

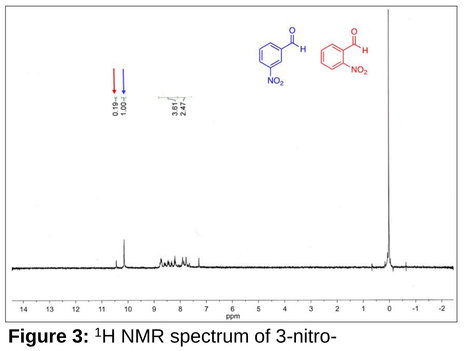


Figure 3: ^{1}H NMR spectrum of 3-nitro-benzaldehyde (blue) and 2-nitro-benzaldehyde side product (red) from 1.8.4, stirred at 0˚C for 5 minutes.

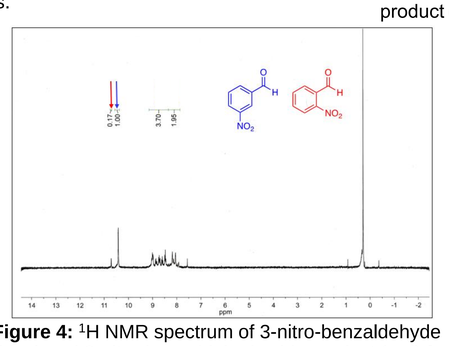


Figure 4: ^{1}H NMR spectrum of 3-nitro-benzaldehyde (blue) and 2-nitro-benzaldehyde side product (red) from 1.8.1, stirred at -10˚C for 5 minutes.

Characterization

- After synthesis, complexes were filtered using vacuum filtration and dried in laboratory cabinets for several days before characterization.
- ^{1}H NMR data was collected on complexes using an Anasazi 60MHz NMR spectrometer.

Conclusions and Future Directions

- Synthesis of the 3-nitro-benzaldehyde complex was confirmed through ^{1}H NMR. The spectra for the standard run, **Figure 2**, show there is a side product in addition to the product, likely ortho- and meta- products. These side products are present in all runs and the ratio of side product to product does not appear to vary, at approximately 1 to 5.9 even with cooling such as in **Figure 3** and **Figure 4**.
- The reaction's percent yield appears to depend upon a variety of factors:
  - Mixing the acids before adding the benzaldehyde to the reaction vessel appears to increase yield by several times over not mixing.
  - Decreasing the volume of acid added to the reaction has a strong negative impact on yields even when reaction times are greatly increased.
  - An ideal stir temperature and time was observed at temperature of -10˚C and a stir time of 5 minutes as demonstrated in Experiment 1.8.1 (**Figure 4**).
  - Increasing stir time to 20 minutes does have a minor impact on yield, however the 4x increase in time also decreases the efficiency with which the lab can be conducted in an undergraduate setting.
- Further testing is required to examine benzaldehyde derivatives, such as in **Figure 5**. Such derivatives would add variety to the results students would obtain as well as promoting the meta product while minimizing the ortho side product.

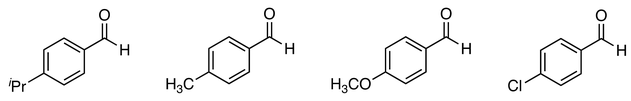


Figure 5: Benzaldehyde derivatives for use as starting material in further testing.

- Future work will focus on the next step, reducing 3-nitro-benzaldehyde to 3-nitro-benzylalcohol and optimizing the conditions.

References

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(2) Laali, K. K.; Koser, G. F.; Subramanyam, S.; Forsyth, D. A. Substituent Control of Intramolecular Hydrogen Bonding in Formyl-Protonated o-Anisaldehydes: A Stable Ion and Semiempirical MO Investigation. The Journal of Organic Chemistry 1993, 58 (6), 1385–1392. https://doi.org/10.1021/jo00058a018.

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