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# A Simple S<sub>N</sub>2 Reaction for the Undergraduate Organic Laboratory

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Nucleophilic substitution reactions are among some of the first reactions covered in an introductory organic course (1, 2). The S<sub>N</sub>1 and S<sub>N</sub>2 reactions introduce the fundamentals of organic reactivity, which includes the concepts of nucleophilicity and electrophilicity, acidity, competing reactions, solvent effects, and synthesis. Typically, these reactions are the first introduction to reaction mechanisms and the effect of certain factors on the mechanism of a reaction. For example, the substitution pattern of the substrate, the nucleophilicity of the nucleophile, and the solvent can all cause the rate-limiting step of the substitution mechanism to be bimolecular or unimolecular.

The substitution experiment previously utilized in the organic laboratory at this university was an S<sub>N</sub>2 displacement of benzyl chloride with sodium naphthoxide in ethanol to generate benzyl naphthyl ether (3). Although the students routinely isolated high yields of a crystalline product, the reaction involved the use of a lachrymator (benzyl chloride) that proved to be irritating to faculty and students. Thus, a new S<sub>N</sub>2 reaction was designed for the introductory organic laboratory.

The majority of the first-semester organic laboratory curriculum at this university involves teaching students how to perform basic organic techniques. Students also distinguish why particular techniques have advantages in various circumstances. Because the students have not yet been exposed to NMR or IR analysis of products, most of the experiments utilize the melting point for product confirmation. Substitution reactions are introduced early in the organic curriculum and the organic laboratory, so the primary purpose of the experiment is to address how the reaction is done and why it is performed a particular way. Any new experiment implemented in the organic laboratory should meet several of the following requirements: possess an easy-to-follow procedure; use relatively benign reagents (no lachrymators); have few competing reactions; utilize green, or greener, solvents; proceed in short reaction times (to allow students to complete the experiment) with high yields; and produce solid products for melting point analysis.

## Background

Organic laboratory textbooks typically have an experiment that compares the S<sub>N</sub>1 and S<sub>N</sub>2 reactions on the basis of rate (4). For example, substrates ranging from primary alkyl chlorides and bromides to tertiary halides and aromatic halides are treated with NaI in acetone at both room temperature and 50 °C until a precipitate forms. The student measures the time it takes for the precipitation to occur for each reaction then compares it to the other substrates to draw conclusions about the effect of substrate on the rate of the reactions. This is an excellent experiment that enables students to make conclusions about what factors affect the substitution mechanism, but requires the use of lachrymators in the laboratory and does not employ product isolation.

An alternative substitution experiment was reported by Pace and Regmi that focuses on the kinetics of the substitution

reaction (5). The rate is determined by conductivity, which allows for an important kinetic lesson. We are more interested that our students isolate and quantify the products of their reactions early in the organic sequence.

Other textbook procedures utilize alcohols as substrates for the generation of alkyl halides (4, 6). These procedures suffer from the need to use a strong acid to generate a good leaving group for substitution to occur. The analysis of these products is challenging as many of the products are low-boiling liquids and must be analyzed by techniques that may not have been covered in the course. Refractive index is sometimes used, but students typically have difficulty determining refractive indices owing to poor purity or presence of additional solvent, which changes the refractive properties of the liquid (7).

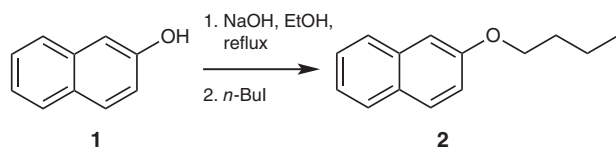
Shepherd and Stenzel contributed a procedure to this *Journal* for the synthesis of unsymmetrical alkynes by an S<sub>N</sub>2 reaction (8). Although this is a superb experiment utilizing the discovery process and engaging students, it was too involved for us to reasonably conduct in 12 different laboratory sections. In addition, the analysis required techniques (e.g., <sup>1</sup>H NMR and GC-MS) that are not covered in our first-semester course when the substitution reaction is typically introduced. The hazardous nature of some of the reagents in this experiment makes it impractical for inexperienced first-semester organic students.

An elegant synthesis of bupropion, which uses an S<sub>N</sub>2 reaction in the second step of the synthesis, was reported by Perrine and coworkers (9). This reaction is more suited to the second semester of our organic sequence based on the advanced analysis of the product. In addition, a lachrymator is formed as an intermediate in the reaction. A synthesis of butyl acetate or hexyl acetate by an S<sub>N</sub>2 reaction is described by Clennan and Clennan, but the procedure uses DMF, a toxic solvent that is also fairly water soluble (10). Another procedure worth mentioning is the alkylation of salicylaldehyde in acetone with two different bases (11). This procedure gives liquid products that are isolated by kugelrohr distillation and the use of potassium hydroxide provides a competing aldol reaction product. Although this experiment involves an S<sub>N</sub>2 reaction, it is conducted in an advanced organic laboratory course.

## Rationale

As previously shown, many of the recently published examples of nucleophilic substitution reactions in this *Journal* serve a dual purpose. There are substitution reactions imbedded in experiments designed to mimic multistep synthesis where the substitution reactions are designed to make specific targets, so the experiment itself is not oriented towards teaching the fundamentals of substitution reactions. Likewise, many discovery-based or problem-based experiments address the substitution reactions and are supplanting more traditional experiments because of the view that they can provide a better learning experience for the students.

Based on our use of naphthol in our previous experiment and the ease of isolation of benzyl naphthyl ether, a different naphthyl ether was pursued. Alkyl naphthyl ethers were attractive because most naphthyl ethers with alkyl chains containing four carbons or greater are solids. Primary alkyl halides were chosen to highlight the optimal case for an  $S_N2$  reaction. In addition, because 2-naphthol is soluble in ethanol and to minimize the use of highly volatile organic solvents, ethanol was the preferred solvent. To generate a better nucleophile, it was necessary to initially deprotonate the 2-naphthol with hydroxide. The desired product is 2-butoxynaphthalene,



which is a flavoring agent that has a strong fruity taste reminiscent of raspberry and strawberry (12). In addition, 2-butoxynaphthalene is a precursor to photoacid generators, which are compounds that absorb photons and then release protons (13).

## Experiment

The students add sodium hydroxide (14 mmol) to a solution of 2-naphthol (6.9 mmol) in ethanol and heat the solution to reflux. Once both the sodium hydroxide and the 2-naphthol go into solution, the alkyl halide (8.8 mmol) is added slowly. The students use 1-iodobutane, but 1-iodooctane also can be used. After 15 minutes, the reaction can be checked by thin-layer chromatography (TLC). Then, the reaction mixture is poured over ice water and the product crystallizes. The product is collected by suction filtration. The product is dried until the next laboratory period before recording the melting point.<sup>1</sup>

## Hazards

2-Naphthol and 1-iodobutane are irritants and are harmful to the environment. In addition, 1-iodobutane is flammable. Sodium hydroxide is corrosive. Ethanol causes eye and respiratory tract irritation and is flammable.

## Results and Discussion

In this reaction, an excess of the 1-iodobutane was used to ensure that only the product 2-butoxynaphthalene was isolated during crystallization and not a mixture of the product and the solid starting material, 2-naphthol, which is sparingly soluble in cold ethanol. In the student handout, the students were given reagent quantities in grams and milliliters to provide the students with practice doing conversions between grams, milliliters, and moles.

This experiment was efficient and worked well for the undergraduate students in the laboratory. The students had no trouble carrying out this reaction. The reaction was run in refluxing ethanol (13). The solution was cooled only slightly before the 1-iodobutane was added. TLC indicated the appearance of product, but not the complete disappearance of the 2-naphthol.

Owing to the high UV activity of 2-naphthol, trace quantities were visible by TLC. Product isolation was facile; crystallization occurred rapidly for most of the students when the reaction mixture was poured over ice. To maximize yields, the solution was kept in the ice bath for several minutes after crystallization began. The students needed to thoroughly cool the water used to rinse the solid product. Melting points for the products were most accurate when the solid was allowed to dry until the next laboratory period. The melting point range for the products was 29 to 34 °C, while the literature melting point is 33–35 °C. Further purification was not necessary as there was no improvement in melting point with recrystallization. Typical yields during the development of the procedure ranged from 95 to 100%. Student recovery of the product ranged from 7% to 95% and the median recovery was around 31%. Many students did not cool their solutions adequately to maximize crystallization, did not wash their crystals with ice cold water, and had product crystallize in the filtrate, but did not filter a second time to collect the remainder of the product. The procedure has been revised to require a second filtration.

This experiment is conducted before the introduction of spectroscopic structure determination. However, for those programs that introduce spectroscopy early in the organic sequence, <sup>1</sup>H NMR can be used to verify product formation. The <sup>1</sup>H NMR spectrum is clean, but students may have difficulty interpreting the aromatic region of the spectrum owing to the similar nature of the protons on the naphthalene ring. Integration is useful to identify the seven protons in the aromatic region; however, the splitting is difficult to interpret. The protons associated with the butyl chain have easily distinguishable chemical shifts and splitting. Because recrystallization occurs in ice water, the use of IR spectroscopy to distinguish the product from the starting material is difficult if the product is not sufficiently dried.

This laboratory is intended to teach students that the ideal conditions given in lecture for a reaction may not always be the conditions chosen. For example, this experiment is run in ethanol, whereas the students are typically taught that polar aprotic solvents are optimal for  $S_N2$  reactions. The understanding of acidity is fundamental to the understanding of reactivity. In this case, the students must learn why the deprotonation of 2-naphthol is more facile than the deprotonation of the solvent for the reaction. In addition, the need for deprotonation of the 2-naphthol to generate a better nucleophile reinforces the understanding of trends in nucleophile strength.

## Conclusion

This article describes an easy, safe, preparative procedure demonstrating an  $S_N2$  reaction. Product isolation in the laboratory is straightforward. A solid product is formed in the reaction, which enables the students to manipulate the product easily and determine whether they made a small or large amount of product. This laboratory reinforces lecture material about the ability of a primary alkyl halide to undergo  $S_N2$  reaction despite the atypical polar protic solvent.

## Acknowledgments

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## Note

1. For optimal product yields, it is important for students to sufficiently cool the product in ice water prior to isolation by suction filtration. Likewise, the students need to wash the product with ice cold water. The isolation of a second crop of crystals from the filtrate may be necessary.

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Student handout including pre- and postlaboratory questions

Instructor notes including answers to the pre- and postlaboratory questions and NMR spectra