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Microwave-Assisted Synthesis of *N*-Phenylsuccinimide

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Abstract

A microwave-assisted synthesis of *N*-phenylsuccinimide has been developed for the second-semester organic teaching laboratory. Utilizing this procedure, *N*-phenylsuccinimide can be synthesized by heating a mixture of aniline and succinic anhydride in a domestic microwave oven for four minutes in moderate yields (40–60%). This technique reduces the reaction time as compared to the traditional synthesis by several hours, which allows the preparation to be achieved in a single organic chemistry laboratory period. This reaction is performed in the absence of solvent, is energy efficient, and is atom economical; therefore, it represents a “greener” preparation than the traditional synthesis of *N*-phenylsuccinimide.

Keywords

Second-Year Undergraduate; Laboratory Instruction; Organic Chemistry; Hands-On Learning / Manipulatives; Inquiry-Based / Discovery Learning; Amines / Ammonium Compounds; Green Chemistry; Nucleophilic Substitution; NMR Spectroscopy

Microwave-assisted organic synthesis (MAOS) has garnered considerable attention and is becoming more common in synthetic laboratories.^{1,2} For example, MAOS plays an important role in modern drug discovery.² Therefore, it is important for students to understand this emerging technology.³ The major advantage of MAOS is that it enables reactions to proceed more rapidly than many classical techniques. Although modern synthetic laboratories utilize single-mode microwave systems, which can be prohibitively expensive for some educators, undergraduate students can be exposed to MAOS at a reasonable cost by using a domestic microwave oven.

An example of such a reaction is the microwave-assisted synthesis of *N*-phenylsuccinimide from aniline and succinic anhydride. *N*-Phenylsuccinimides and the structurally related *N*-phenylmaleimides are important classes of heterocyclic compounds because of their function as pesticides.⁴ Traditionally, *N*-phenylsuccinimides are synthesized from a succinic anhydride and an aniline in a three step sequence: reaction of the amine with the anhydride to form the amidoacid, conversion of the carboxylic acid into an acid anhydride, and cyclization to the imide.⁵ Two microwave-assisted preparations of *N*-phenylsuccinimides have been reported. One preparation allows succinic anhydride to react with aniline in the presence of microwaves and tantalum pentachloride-silicon dioxide,⁶ whereas another preparation utilizes succinic acid and anilines.⁷

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Supporting Information. Instructions for students, notes for the instructor and a ¹H NMR spectrum. This material is available via the Internet at <http://pubs.acs.org>.

A MAOS of *N*-phenylsuccinimide from succinic anhydride and aniline as starting materials was developed using a domestic microwave oven and standard glassware (Scheme 1). The reaction time for this synthesis is minutes, whereas the traditional synthesis of *N*-phenylsuccinimides requires several hours. Because of the shorter reaction time, *N*-phenylsuccinimide can be prepared and purified in a single organic laboratory class.

This MAOS is more environmentally friendly than the traditional synthesis of *N*-phenylsuccinimide, which allows instructors to introduce the topics of green chemistry and MAOS using the same laboratory experiment. A few minutes of heating using a microwave oven is more energy efficient than several hours of heating with a hot plate. In addition, this experiment is performed without solvent, which reduces waste. Moreover, the reaction represents a good example of atom economy because the atoms of a water molecule are the only atoms of the starting materials that are not incorporated into the desired product.

Experimental Design

This experiment is designed for incorporation into a second-semester organic laboratory course and represents a nice complement to the topic of carbonyl chemistry, particularly nucleophilic acyl substitution, which is covered in the lecture portion of the course. This experiment allows the topics of green and microwave chemistry to be presented with one experiment. Students gain an understanding of how green chemistry attenuates chemical pollution on the environment. In addition students gain a basic understanding of how microwaves affect chemical reactions and the advantages that the use of microwave chemistry in organic synthesis poses over traditional methods.

Each student is given a general reaction procedure and is instructed on the proper use of the microwave in the chemistry lab. These reactions are run at miniscale rather than microscale. After purification of the products by recrystallization, the students take a melting point and ^1H NMR of their sample to prove its identity. Some of the results obtained by students are presented in Table 1 along with a comparison to the classic route to *N*-phenylsuccinimide, including number of steps, reaction times, and purification method.

Although aniline is used in this experiment, a variety of different anilines could be utilized such that a variety of *N*-substituted succinimides could be synthesized throughout a laboratory section. This provides an individualized experiment that is a good exercise for the student because suitable purification conditions would need to be determined for each product.

Hazards

Both aniline and succinic anhydride are eye, skin, and respiratory irritants. Aniline should be handled with care because it may be fatal if swallowed, inhaled, or absorbed through skin. Goggles and gloves should be worn at all times. Laboratory grade microwaves (such as CEM) should be utilized; domestic ovens do not have the safety and control capabilities of laboratory-grade microwaves. All experiments should be performed under a ventilated hood.

Results and Discussion

The experimental goal was to develop a microwave-assisted synthesis of *N*-phenylsuccinimide that could be performed in a domestic microwave oven that is a faster, greener alternative to the traditional synthesis. Students in a second-semester organic chemistry laboratory are able to synthesize *N*-phenylsuccinimide and purify the product by recrystallization from an ethanol:water solution in a single laboratory session.

The preparation of *N*-phenylsuccinimide occurs in two reaction steps (Scheme 2). The first step is the reaction of aniline with succinic anhydride to form an amidoacid. The amide nitrogen intramolecularly attacks the carboxylic acid resulting in cyclization to form the imide. The second step requires a significant quantity of energy due to the poor nucleophilicity of the amide nitrogen. The microwave provides this energy by heating the mixture to high temperatures. Instructors can work through the electron–pushing mechanism with their students to show that the amide nitrogen is weakly nucleophilic due to resonance effects, which is why this reaction requires high temperatures.

Summary

This microwave-assisted synthesis of *N*-phenylsuccinimide is well-suited for use in a second-semester organic chemistry laboratory course because it is facile and utilizes inexpensive equipment. Using this single experiment an instructor can generate discussions on several topics, such as microwave chemistry, green chemistry, nucleophilic acyl substitutions, and resonance effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
MAOS of *N*-Phenylsuccinimide

Scheme 2.

Reaction Steps for the Formation of *N*-Phenylsuccinimide

Table 1Comparison of Student MAOS to Traditional Synthetic Route To Prepare *N*-Phenylsuccinimide

Metric	MAOS	Traditional ^a
Time	4 min	10 h ^a
Synthetic Steps	1	2
Solvent	None	Dichloromethane
Purification	Recrystallization	Extraction, Column Chromatography
Yield	40–60%	80% ^b

^aTotal reaction time for two synthetic steps (5).^bOverall yield for two synthetic steps