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Laboratory Experiment

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Saccharin Derivative Synthesis via [1,3] Thermal Sigmatropic Rearrangement: A Multistep Organic Chemistry Experiment for Undergraduate Students

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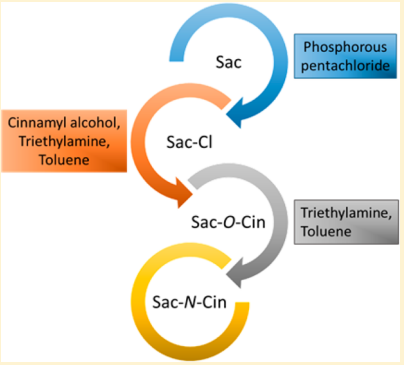
Supporting Information

ABSTRACT: Saccharin (1,2-benzisothiazole-3-one 1,1-dioxide) is an artificial sweetener used in the food industry. It is a cheap and easily available organic compound that may be used in organic chemistry laboratory classes for the synthesis of related heterocyclic compounds and as a derivatizing agent. In this work, saccharin is used as a starting material in a sequential synthesis designed for completion in three laboratory periods of 4 h each. This synthesis includes two nucleophilic substitutions, namely, the transformation of saccharin into saccharyl chloride and the addition of cinnamyl alcohol to saccharyl chloride (3-chloro-1,2-benzisothiazole 1,1-dioxide) to yield *O*-cinnamylsaccharin [(*E*)-3-(3-phenylprop-2-enoxy)-1,2-benzisothiazole 1,1-dioxide]. The third reaction is the isomerization of *O*-cinnamylsaccharin into *N*-cinnamylsaccharin [2-(3-phenyl-2(*E*)-propen-1-yl)]-1,2-benzisothiazole-3(2*H*)-one 1,1-dioxide], a [1,3] sigmatropic rearrangement. The products are characterized using melting point, IR, and ^{1}H NMR spectroscopy. These experiments allow students to acquire experience in a multistep synthesis, practice the most typical laboratory scale synthesis, isolation, purification, and analytical methods, and think through and discuss the mechanisms of the intervening reactions.

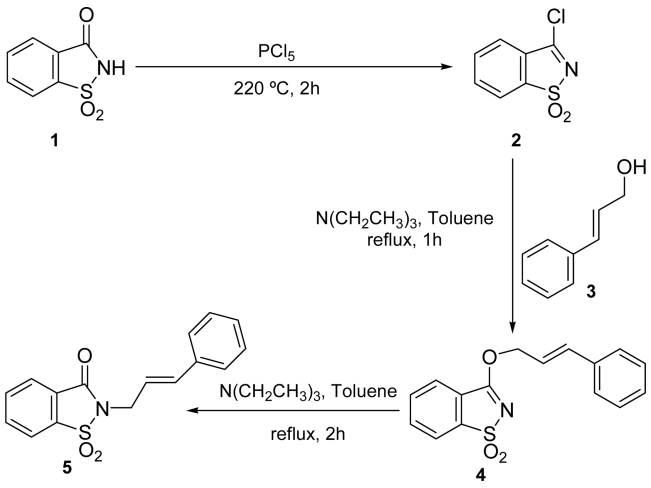


KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Synthesis, Heterocycles, Mechanisms of Reactions, Laboratory Instruction, Hands-on Learning/Manipulatives*

INTRODUCTION

Saccharin (1,2-benzisothiazole-3-one 1,1-dioxide, **1**, Scheme 1) is used in food chemistry as an artificial sweetener.[1] Saccharin derivatives are used in several domains such as agriculture,[2] medicine,[3] and pharmacy.[4] Saccharin is a cheap and easily available compound to work with, thus it may be used in laboratory experiments for teaching chemistry. In analytical experiments, sweeteners such as saccharin are quantified to teach spectrophotometric methods,[5] HPLC,[6,7] capillary electrophoresis,[7] and TLC.[8] In an organic chemistry laboratory, saccharin may be used as a reagent in synthesizing useful derivatives.[9] Students have the opportunity to learn the techniques and concepts used in the research laboratories working in this area.

Scheme 1. Synthesis of Saccharyl Chloride 2 (30−60% Yield), *O*-Cinnamylsaccharin 4 (40−60% Yield), and *N*-Cinnamylsaccharin 5 (90−98% Yield)



The present work appears to be the first student laboratory experiment involving the synthesis of a saccharyl derivative and one of the few experiments describing a [1,3] sigmatropic rearrangement reported in this journal. Sigmatropic rearrangements are one of the main classes of pericyclic reactions, along with cycloadditions and electrocyclic reactions, which are now included in virtually every introductory textbook on organic chemistry. However, there are only a few publications describing [1,3] sigmatropic rearrangements in undergraduate laboratory experiments.[10]

The proposed three-step sequential synthesis requires three 4 h laboratory periods in an undergraduate organic laboratory: (1) Synthesis of saccharyl chloride (3-chloro-1,2-benzisothia-

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zole 1,1-dioxide) (**2**, Scheme 1); (2) synthesis of *O*-cinnamylsaccharin [(*E*)-3-(3-phenylprop-2-enoxy)-1,2-benzisothiazole 1,1-dioxide] (**4**, Scheme 1); (3) isomerization of *O*-cinnamylsaccharin into *N*-cinnamylsaccharin [2-(3-phenyl-2(*E*)-propen-1-yl)]-1,2-benzisothiazole-3(2*H*)-one 1,1-dioxide] (**5**, Scheme 1) in a thermal [1,3] sigmatropic rearrangement.

The first goal of these experiments is to experimentally illustrate the theoretical concepts explored in the curriculum of the second year of undergraduate organic chemistry (e.g., nucleophilic substitution); the second goal is to reinforce a range of techniques (refluxing, distillation, extraction, etc.) in typical laboratory scale synthesis, along with isolation and purification of the synthesized compounds and to use spectroscopic methods (IR and ^{1}H NMR) and melting points in order to identify them. Finally, the students acquire the encouraging experience of completing a multistep transformation, preparing them for their future capstone project. These three goals are obtained using the synthesis of an allyl saccharyl derivative.

BACKGROUND

Saccharyl chloride (**2**, Scheme 1) is the product of the first reaction in our synthesis. This reaction is a nucleophilic substitution, where an intermediate formed results from the isothiazole ring opening (Supporting Information). The isothiazole ring recloses at the high temperature of the reaction (220 °C for 2 h), and saccharyl chloride is formed.[11]

The second reaction is the transformation of this saccharyl chloride into *O*-cinnamylsaccharin (**4**, Scheme 1). This reaction also occurs by a nucleophilic substitution mechanism, although here the starting compound, saccharyl chloride, is a typical vinyl halide. The reactivity of the latter in a substitution reaction is enabled by the electron-withdrawing SO_2 group, in position 3 of the isothiazole ring (Supporting Information).

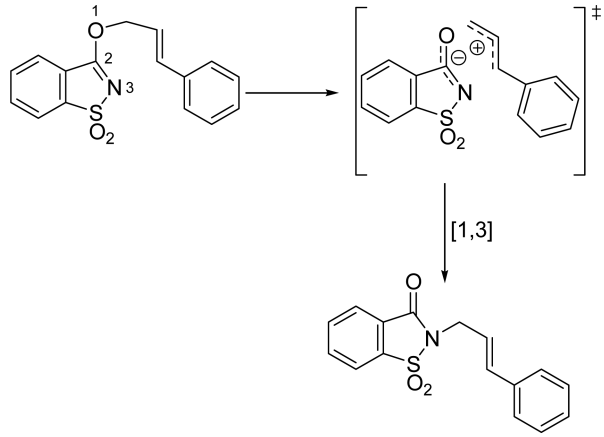
The third step is a [1,3] sigmatropic rearrangement (Scheme 1). This reaction involves breaking the ($-O-CH_2-$) and migration of a σ bond (migration of the cinnamyl group connected by a σ bond) over the π electron system and formation of a new σ bond ($-N-CH_2-$) with concomitant reorganization of the π system. This is a rare process, forbidden according to Woodward–Hoffmann rules;[12] however, it still occurs with benzisothiazolyl derivatives such as *O*-cinnamylsaccharin. This reaction has a concerted mechanism with an ionic transition state (Scheme 2). This is a favored pathway as it is less energy demanding, given the negative ionic character of the nitrogen atom and the steric hindrance induced by the bulky SO_2 group, in experimental conditions of pH and temperature.[13]

EXPERIMENTAL SECTION

Three sequential reactions are required to produce *N*-cinnamylsaccharin, **5** (Scheme 1). Students have three laboratory periods, 4 h each, to execute the sequence.

In the first step, the synthesis of saccharyl chloride **2** (Scheme 1) results from a neat reaction between saccharin and phosphorus pentachloride. The hydrochloric acid formed in this reaction escapes through a calcium chloride drying tube mounted on top of the condenser. After the reaction is run for 2 h, phosphorus(V) oxychloride ($POCl_3$) formed as a byproduct is distilled off at low pressure and saccharyl chloride solidifies. The product is recrystallized from toluene and characterized by IR spectroscopy, ^{1}H NMR spectroscopy, and melting point.

Scheme 2. Reaction Mechanism for the Rearrangement of *O*-Cinnamylsaccharin to *N*-Cinnamylsaccharin



In the second laboratory session, saccharyl chloride, **2** (Scheme 1), produced in the first step of this sequence, reacts with cinnamyl alcohol, **3**, in toluene and triethylamine at room temperature for 1 h. *O*-Cinnamylsaccharin is isolated by filtration and extraction and recrystallized from ethyl acetate[13b] and characterized by IR and ^{1}H NMR spectroscopy and melting point.

In the final laboratory session, the saccharin derivative, *O*-cinnamylsaccharin, is refluxed in toluene and triethylamine for 2 h. After solvent evaporation and recrystallization with methanol, *N*-cinnamylsaccharin is collected as small white crystals, characterized by IR and ^{1}H NMR spectroscopy and melting point.

The details of the experiment are described in the Supporting Information.

HAZARDS AND DISPOSAL

All of the reagents and chemicals in this experiment are commonly used in organic chemistry laboratories. Proper safety considerations include the standard procedures of wearing safety goggles and gloves, working under a fumehood, and avoiding contact of the chemicals with skin and eyes and inhalation of vapors. Phosphorus pentachloride may be fatal if inhaled and may cause damage to organs through prolonged or repeated exposure; it is also harmful if swallowed and causes severe skin burns and eye damage, and it reacts violently with water. Toluene is a highly flammable liquid and may be fatal if swallowed or if it enters the airways. It causes skin irritation and may cause drowsiness or dizziness. Triethylamine is a highly flammable liquid. It is harmful if swallowed and causes respiratory irritation if inhaled; it causes severe burns in contact with skin and damage in contact with eyes. Cinnamyl alcohol is harmful if swallowed, may cause an allergic skin reaction, and causes serious eye irritation. Phosphorus(V) oxychloride may be fatal if swallowed or inhaled; it causes severe skin burns and eye and organ damage after prolonged or repeated exposure. Is also reacts violently with water. Hydrochloric acid is corrosive and an irritant permeator and lung sensitizer. Deuterated chloroform is harmful if swallowed, causes skin and eye irritation, is toxic if inhaled and suspected of causing cancer. In the case of the reaction products, saccharyl

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chloride, *O*-cinnamylsaccharin, and *N*-cinnamylsaccharin, students should assume they are toxic if swallowed or inhaled.

The reaction between saccharin and phosphorus pentachloride occurs at 220 °C, which requires special attention from the instructor and the students. The hot paraffin bath can ignite if it comes into contact with other substances.

The reaction waste may be separated into halogenated and nonhalogenated organic and aqueous components.

RESULTS AND DISCUSSION

This multistep sequential synthesis was performed by undergraduate students in the second semester organic chemistry course, in groups of three; it was performed by 8 groups in the 3 classes in academic years from 2012 to 2015. The reagents used in the experiments were relatively inexpensive and commercially available. The starting material, saccharin, besides being used as a sweetener, was used in an organic synthesis for the first time by undergraduate students.

The mechanisms of the reactions performed in the experiments were included in the organic chemistry theoretical lectures as examples of nucleophilic substitution in substrates with different structural characteristics, and in case of the rearrangement, additionally the topic of sigmatropic rearrangement was introduced. Besides, this laboratory practical constituted an excellent opportunity for the students to improve their skills in performing reflux, isolation techniques such as distillation, extraction, and recrystallization, along with characterization/identification of products by spectroscopic methods (IR and ^{1}H NMR) and the melting point. Representative student IR and ^{1}H NMR spectra are in Supporting Information. The interpretative discussion of the results obtained stimulated students to consolidate their skills in the interpretation of the IR and ^{1}H NMR spectra.

The synthesis of saccharyl chloride required reflux, distillation, and recrystallization. The students' yields in a successful conversion were typically in the range from 30 to 60%. The melting point analysis using slightly damp samples of saccharyl chloride in unsealed melting point tubes produced melting points ranges within 1−2 °C of that in literature reports. The narrow interval indicated good purity of the compound. The presence of the C−Cl band (692 cm^{-1}) in the IR spectrum confirms the saccharin conversion.

The synthesis of *O*-cinnamylsaccharin occurred by stirring saccharyl chloride and cinnamyl alcohol in toluene and trimethylamine at room temperature. The isolated and purified product was characterized using melting point, IR, and ^{1}H NMR analysis. Again, students were able to confirm that the reaction was successful by the band changes in the IR and ^{1}H NMR chemical shifts. The IR spectrum shows the disappearance of the band at 692 cm^{-1} (C−Cl band), and the ^{1}H NMR spectrum shows the peaks at δ (chemical shift) 6.38 and 6.77 ppm (−CH═CH−); 5.15 ppm (−CH_2−); the aromatic multiplet at 7.38−7.21 ppm, and the signals of the benzisothiazole protons at 7.81−7.60 ppm.

The *O*-cinnamylsaccharin rearrangement into the product *N*-cinnamylsaccharin isomer occurred in a basic medium by addition of trimethylamine to the reaction mixture. The appearance of the C═O band (1732 cm^{-1}) in the IR spectrum indicated that the isomerization was successful. Comparing the ^{1}H NMR spectra of the two isomers, they revealed a small difference in the chemical shifts of methylene protons estimated at 0.64 ppm, a result of switching from oxygen to nitrogen. The signal splitting pattern and the integrated areas remain equal in both spectra. This led us to conclude that the hydrocarbon structure of both compounds was the same, confirming the [1,3] sigmatropic rearrangement.

CONCLUSION

The first goal of this experiment is to experimentally illustrate theoretical concepts such as the nucleophilic substitution reaction mechanism, in this case, with two different substrates: acid−base chemistry and sigmatropic rearrangement. The second goal is to reinforce the students' practical skills in fundamental laboratory techniques and chemical calculations. Thus, they had to perform mole and weight calculations, distillations, filtrations under vacuum, rotary evaporation, recrystallizations, and melting point analysis. In addition, they had to use IR and NMR instrumentation and interpreted characterization data. As the final result, our students successfully performed the multistep synthesis of *N*-cinnamylsaccharin in organic chemistry laboratory classes, achieving the third goal. Importantly, these achievements improved the students' confidence in executing the synthetic procedures and provided an excellent application for the theoretical knowledge obtained in the organic chemistry lectures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00046.

Lists of the chemicals supplies and equipment; instructor notes; the student handouts and recorded spectra of the student samples (PDF, DOCX)

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Notes

The author declares no competing financial interest.

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