Saccharin derivative synthesis and [1,3] thermal rearrangement: a multistep organic chemistry experiment for undergraduate students

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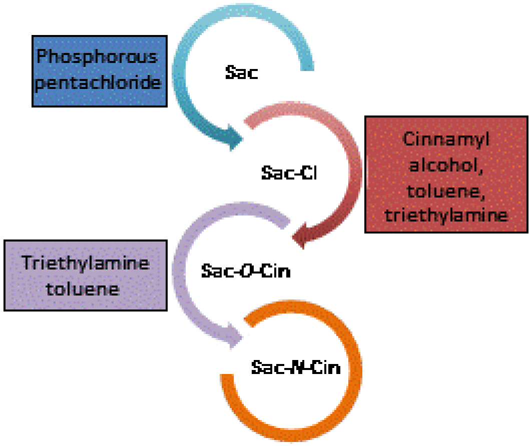
ABSTRACT

Saccharin (2,3-dihydroxy-1,2-benzisothiazol-3-one-1,1-dioxide) is an artificial sweetener used in food industry. It is a cheap and easily available organic compound, which may be used in organic chemistry laboratory classes for synthesis of related heterocyclic compounds and as a derivatizing agent. In this work saccharin is used as starting material to synthesize an allyl derivative, *O*-cinnamylsaccharin [3-(3-phenylprop-2-enyloxy)-1,2-benzisothiazole-1,1-dioxide]. This is done in two steps, using procedures that can be performed in separate 3-hour laboratory periods. The process includes nucleophilic chloride substitution to transform saccharin into saccharyl chloride (3-chloro-1,2-benzisothiazole-1,1-dioxide) and addition of cinnamyl alcohol to saccharyl chloride to yield *O*-cinnamylsaccharin. After full characterization using melting point, IR spectroscopy and ^{1}H NMR spectroscopy, the compound is isomerized and an unusual [1,3] thermal sigmatropic rearrangement occurs, with *N*-cinnamylsaccharin [2-(3-phenylprop-2-enyloxy)-1,2-benzisothiazole-1,1-dioxide] being formed.

ABSTRACT GRAPHIC

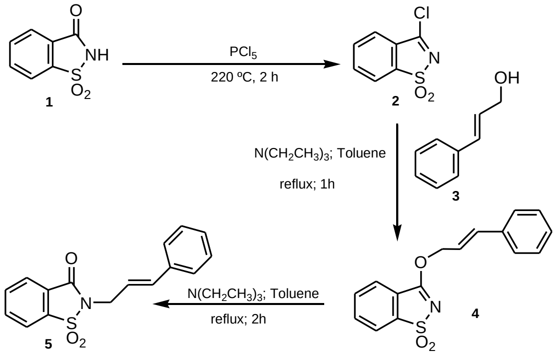


KEYWORDS

Undergraduate experiment; organic chemistry; saccharin; heterocycles; synthesis; sigmatropic rearrangement, mechanisms of reactions.

Saccharin (2,3-dihydroxy-1,2-benzisothiazol-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 cheap, easy available and a safe compound to work with, thus can be used in laboratory experiments in perspective of teaching chemistry. The analytical experiments quantify sweeteners, such as saccharin, to teach spectrophotometric methods,[5] HPLC,[6] capillary electrophoresis[7] and TLC.[8] In organic chemistry laboratory, saccharin can be used as a reagent in synthesis, to obtain useful derivatives, and students which perform these experiments have the opportunity to learn techniques and concepts found in research laboratories of this scientific field. 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. A three-step sequential synthesis, is completed in three classes of 3-h laboratory periods in an undergraduate organic laboratory: 1-synthesis of saccharyl chloride (3-chloro-1,2-benzisothiazole-1,1-dioxide), (**2**, Scheme 1); 2- synthesis of *O*-cinnamylsaccharin [3-(3-phenyl-prop-2-enyloxy)-1,2-benzisothiazole-1,1-dioxide], (**4**, Scheme 1), which, after spectroscopic characterization is isomerized to *N*-cinnamylsaccharin [2-(3-phenylprop-2-enyloxy)-1,2-benzisothiazole-1,1-dioxide], (**5**, Scheme 1) in a thermal [1,3] sigmatropic rearrangement.

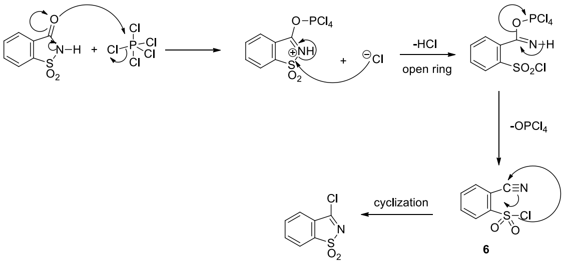
Scheme 1. Synthesis of *O*-cinnamylsaccharin,4 and thermal [1,3] rearrangement to *N*-cinnamylsaccharin, 5.



BACKGROUND

In terms of mechanisms of reactions, there is one common nucleophilic substitution, in a reaction synthesis of *O*-cinnamylsaccharin, **4** (Scheme1), and two with unusual features: 1- in reaction synthesis of saccharyl chloride from saccharin, it is formed an open ring intermediate (Scheme 2); 2- in reaction synthesis of *N*-cinnamylsaccharin, **5** (Scheme 1) from *O*-cinnamylsaccharin, it occurred [1,3] sigmatropic rearrangement (Scheme 3).

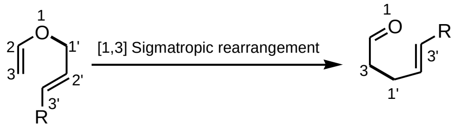
Scheme 2. Mechanism of reaction in synthesis of saccharyl chloride.



Sigmatropic rearrangements is one of the main classes of pericyclic reactions, along with cycloadditions and electrocyclic reactions. Such processes are subject to orbital symmetry control and governed by Woodward-Hoffmann Rules.[9] These topics are now included in virtually every introductory textbook of organic chemistry, despites such attention in classroom, however, there are a few literature references about [1,3] sigmatropic rearrangements in undergraduate laboratory experiments.[10]

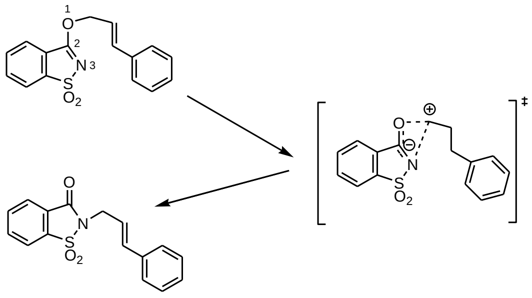
The term sigmatropic rearrangements means the migration of a sigma bond. In Scheme 3**,** it is possible visualize general [1,3] sigmatropic shift.

Scheme 3. Sigmatropic [1,3] rearrangement.



In case of *O*-cinnamylsaccharin (**4**, Scheme 1), is the experimental conditions, pH and temperature, that determinates this rearrangement. It is an unusual reaction, but occurs with benzisothiazol derivatives compounds, due to the ionic negative character of nitrogen and the steric hindrance induced by the bulky SO_2 group and the mechanism is *via pseudo*pericyclic transition state (Scheme 4). [11]

Scheme 4. Reaction mechanism for the rearrangement of *O*-cinnamylsaccharin to *N*-cinnamylsaccharin

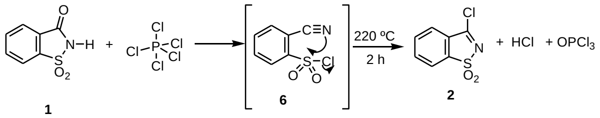


This article describes a reaction sequence which covers three important mechanisms with emphasis to the unusual [1,3] sigmatropic rearrangement; the use of saccharin in an organic laboratory synthesis experiment, while reinforcing skills in organic chemistry procedures (reflux, distillation, recrystallization, filtration) and interpretation the spectra obtained (IR e ^{1}H NMR spectra).

EXPERIMENTAL OVERVIEW

Three different reactions were required in the synthesis of *N*-cinnamylsaccharin, **5** (Scheme1). Students had three laboratory periods, 3 hours each, to complete the sequence. In the first step, the synthesis of saccharyl chloride results from a neat reaction between saccharin and phosphorous pentachloride. The reaction runs at 220 ºC for 2 hours. At a lower reaction temperature an intermediate compound is formed, **6** (Scheme 5). This intermediate has a ciano and a sulphonyl chloride groups as *orto* substituents in the benzene ring and results from isothiazole open ring. At high temperature, 220 ºC, for 2 hours the isothiazole ring closes, forming the isomer saccharyl chloride.[12] The hydrochloric acid formed during the reaction escapes through a calcium chloride drying tower used on top of the condenser. At the end of 2 hours reaction time, phosphorus (V) oxychloride ($OPCl_3$), also formed as a by-product, and it is distilled at low pressure.

Scheme 5. Reaction for the synthesis of saccharyl chloride.



In the second laboratory session saccharyl chloride, **2** (Scheme 1), produced from the first step of this sequence, was reacted with cinnamyl alcohol, **3** (Scheme 1), in toluene and triethylamine [$N(CH_2CH_3)_3$], to yield *O*-cinnamylsaccharin, **4** (Scheme 1).[13]

In the final laboratory session, the saccharin derivative, *O*-cinnamylsaccharin, was refluxed in toluene and triethylamine for 2 hours, and the isomer *N*-cinnamylsaccharin was formed. [6]

EXPERIMENT

Saccharyl chloride, *O*-cinnamylsaccharin and *N*-cinnamylsaccharin were the compounds produced in each class session.

In the first laboratory period, students synthesized saccharyl chloride, using a reflux with a calcium chloride drying tower on top. It was crucial to make the reaction in a fume hood to remove the hydrochloric acid formed as a gas. The product was purified removing $OPCl_3$ using low-pressure distillation and then recrystallized from toluene. The product was characterized by IR spectroscopy, ^1H NMR spectroscopy and melting point. The details of the experiment are described in the Supporting Information.

In the second 3-hour laboratory session, purified saccharyl chloride and cinnamyl alcohol were refluxed during two hours in toluene and triethylamine. The reaction was monitored by TLC (Thin Layer Chromatography). The salt formed, triethylamine hydrogen chloride, was removed by vacuum filtration, and the filtrate was washed with 1M hydrogen chloride (3 x 20 mL), saturated sodium hydrogen carbonate (3 x 20 mL) and water (3 x 20 mL), and the combined organic phase dried with sodium sulphate ($N_{a2}SO_4$). After filtration and the solvent evaporated, *O*-cinnamylsaccharin was obtained, which was recrystallized from toluene. The product was characterized by IR spectroscopy, ^1H NMR spectroscopy and melting point.

The third laboratory class was devoted to rearrangement of *O*-cinnamiloxysaccharin into *N*-cinnamiloxysaccharin, the reaction took place in toluene and triethylamine for 2 hours at 160 °C. After evaporated the solvents under vacuum it was obtained a solid, *N*-cinnamylsaccharin. Recrystallization from ethyl acetate, yields the compound as small white crystals. The product was characterized by IR spectroscopy, ^1H NMR spectroscopy and melting point.

HAZARDS AND DISPOSAL

All reagents and chemicals in this experiment are commonly used in organic chemistry laboratories. Proper safety considerations include standard procedures of wearing safety glasses, working under a fume hood, and avoiding contact of the chemicals with skin and eyes. Inhalation of vapour is to be avoided. Phosphorus pentachloride is 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; reacts violently with water. Toluene is a highly-flammable liquid and vapour, may be fatal if swallowed or if enters airways. It causes skin irritation; may cause drowsiness or dizziness. Triethylamine is a highly flammable liquid and vapour. It is harmful if swallowed, toxic in contact with skin or if inhaled, causes severe skin burns and eye damage and may cause respiratory irritation. Cinnamyl alcohol is harmful if swallowed, may cause an allergic skin reaction and causes serious eye irritation. Phosphorus (V) oxychloride is fatal if swallowed or inhaled; causes severe skin burns and eye and organs damage after prolonged or repeated exposure. Is also reacts violently with water. Hydrochloric acid is corrosive and an irritant permeator and lung sensitizer.

The reaction waste may be separated into organic and aqueous components if required.

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 made 8 groups in 3 classes. The reagents used in experiments were relatively inexpensive and commercially available. The starting material, saccharin, besides being used as a sweetener, in investigation was used in mechanistic studies of catalysis, [14] and for the first time was used in synthesis work done by students.

The mechanisms of reactions performed should be included into organic chemistry theoretical lectures, beyond the laboratory practical constituted an excellent opportunity for to increase student skills in doing reflux, TLC analysis, purification techniques as distillation, extraction, recrystallization and characterization/identification of compounds by spectroscopic methods (IR, ^{1}H NMR) and melting point.

The synthesis of saccharyl chloride required reflux, distillation and recrystallization. Student yields, for successful conversions, were typically in the range from 30 to 60%. Melting point analysis using slightly damp samples of saccharyl chloride in unsealed melting point tubes produces melting points ranging within 1−2 degrees of literature reports. This narrow interval indicates good purity of the compound. The presence of C-

Cl band (692 cm^{-1}) in the IR spectrum and the absence of C=O band (1725 cm^{-1}) confirms saccharin conversion.

The synthesis of *O*-cinnamylsaccharin required reflux of two reagents, saccharyl chloride and cinnamyl alcohol in toluene and triethylamine, and after vacuum evaporation of solvents, the product was recrystallized. Again, students were able to show the reaction had occurred by band changes in the IR and ^{1}H NMR spectra. IR spectrum shows disappearance of the band at 692 cm^{-1} (C-Cl band) and the ^{1}H NMR shows peaks at δ (chemical shift) 6.85, 6.5 ppm (-CH=CH-) and δ 5.25 ppm (-CH_2-) and the aromatic multiplet at δ 7.5-7.25 ppm, besides the signals of benzisothiazole protons at δ 7-9-7.7 ppm.

The *O*-cinnamylsaccharin rearrangement into the *N*-cinnamylsaccharin isomer occurred in a basic medium (toluene and triethylamine) and was monitored using IR spectra. The appearance of C=O band (1750 cm^{-1}) in the IR spectrum indicated that isomerization had occurred. The chemical shifts in the ^{1}H RMN spectra of both *O*- and *N*-cinnamylsaccharin compounds were very similar. Therefore, ^{1}H NMR cannot be used to follow the reaction. The allyl part of the compound (-CH_2-CH=CH-C_6H_5) was maintained, while a carbonyl group appears in the IR spectrum, thus the isomerization occurred *via* [1,3] sigmatropic rearrangement.

Our students successfully performed this multistep synthesis of *N*-cinnamylsaccharin in organic laboratory classes, which improves their confidence in executing synthetic procedures and provided an excellent application for the theoretical knowledge obtained in organic lectures.

ASSOCIATED CONTENT

Supporting Information

List of chemicals supplies and equipment; notes for the instructor; handouts for students and sample spectra from the student samples. This material is available via the Internet at http://pubs.acs.org.

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