Green Chemistry

edited by
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ACS Education Division
Washington, DC 20036

A Green, Guided-Inquiry Based Electrophilic Aromatic Substitution for the Organic Chemistry Laboratory

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While minimizing the use of hazardous reagents and reducing such wastes has been a longstanding concern for those teaching organic chemistry laboratories, recent years have witnessed an increased focus on the "greening" of the organic chemistry teaching lab as evidenced by the wide variety of such experiments published in this *Journal (1)*. Two commercially published laboratory manuals focused on the use of green experiments in organic chemistry are also available *(2)*.

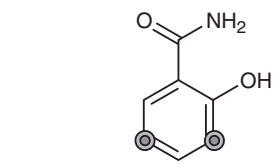
Faced with increased demand and high enrollments in organic chemistry, the faculty at this university have been intentionally working to reduce the hazardous materials used and wastes generated by our organic lab to make the lab safer for our students and to reduce the costs associated with waste disposal. The initially targeted experiment for this effort was the electrophilic aromatic substitution (EAS) laboratory. In this lab, we have traditionally carried out a multistep procedure utilizing aniline (toxic, irritant, flammable), acetic anhydride (corrosive, irritant, flammable), and a mixture of nitric and sulfuric acids (toxic, oxidizer, corrosive) to produce *p*-nitroaniline. Given that a couple of our current labs utilize common analgesics as starting materials or compounds for study, we decided to investigate these compounds as potential starting materials to develop a greener EAS lab.

Our longstanding *p*-nitroaniline experiment was a traditional multistep synthesis lab focused on helping students develop their lab technique. As part of updating this experiment, we wanted to make it more investigative without losing the technique development. Our goal was to provide students the opportunity to collect and analyze chemical data and to develop their critical thinking skills while learning the techniques common to the organic laboratory. Guided by the model proposed by Mohrig, et al. *(3),* we sought to develop a lab built around a question or problem that required students to translate their classroom experiences to predict the outcome of the experiment and, after completing the experiment, to interpret their results to answer the question and solve the problem. As suggested in Mohrig's model, the technique development aspects of the lab, while not the focus, are imbedded in the experiment. The result of our efforts is a guided-inquiry based, green electrophilic aromatic iodination of salicylamide.

Description of the Experiment

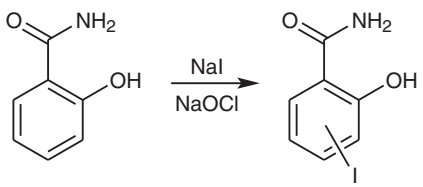
Given the analgesic "theme" of our lab, we considered a variety of analgesics and settled on salicylamide, a component of the popular analgesic BC Powder, as the starting material for the EAS reaction. While this choice was thematic, salicylamide was chosen because the directing effects of the substituents on the ring complement each other (directing to the same sites as shown in Figure 1), but leave the students with a choice of two possible sites at which the substitution could occur. We felt that the complementarity of the directing effects would enhance our students' chances for success in predicting the orientation of the substitution since they would not be forced to decipher the strength of competing groups' directing effects, yet would still leave them with the reasonable "dilemma" of having to predict which site would be more likely for substitution. To take advantage of this "dilemma", we begin the lab by asking students to predict the orientation of the substitution. Once they have grappled with this and recorded a prediction, we have them run the EAS reaction and characterize the product to test their prediction.

To eliminate the toxic reagents typically associated with an electrophilic aromatic nitration, we opted to investigate the iodination conditions originally developed by Edgar and Falling *(4)* and subsequently adapted by Gilbertson, et al. *(5).* These reaction conditions utilize household bleach and sodium iodide to generate the iodine electrophile. As detailed in the online materials, we successfully adapted these conditions for the salicylamide starting material. The reaction is shown in Scheme I.



—$CONH_2$ directs to these positions
—OH directs to these positions

Figure 1. EAS directing effects of the substituents on salicylamide.



Scheme I. Iodination of salicylamide.

In the experiment, salicylamide and sodium iodide are dissolved in ethanol and the resulting homogeneous solution is cooled to 0 °C in an ice bath. The reaction vessel is removed from the ice bath and a solution of 6% sodium hypochlorite (ultra strength household bleach) is added. The initially colorless solution quickly turns to a dark red–brown and then gradually fades to a pale yellow (almost colorless). The initial reaction typically takes less than 5 minutes. After a short waiting period, 10% sodium thiosulfate is added to remove any remaining iodine. Next, 10% hydrochloric acid is added to acidify the reaction solution and to precipitate the product. The product, a white solid, is collected by vacuum filtration and recrystallized from 95% ethanol. The entire procedure typically takes less than an hour. Finally, the product is characterized by FT-IR spectroscopy. (We use an attenuated total reflectance accessory on our instrument, which is a ThermoNicolet Avatar 370, but have obtained similar results using a KBr pellet.)

Hazards

Salicylamide and sodium iodide are irritants. Sodium hypochlorite and hydrochloric acid are irritants and corrosive. Always wear gloves and appropriate eye protection when handling these compounds.

Discussion

The characterization of the product provides students with the opportunity to interpret signals in the fingerprint region of the infrared spectrum. In modern synthetic chemistry, infrared spectroscopy has largely been relegated to functional group identification because of the wide variety of instrumental techniques available. However, infrared spectroscopy was once considered, and still is, an excellent method for determining substitution patterns on aromatic rings.

We provide the students with a table (see student handout in online materials) of characteristic aromatic bending frequencies, which occur in the 700–900 cm^{-1} region of the spectrum. In the post-lab questions, the students are given the infrared spectrum of salicylamide and asked to use the table to correlate the spectrum to the structure of the compound and to specifically identify the peak in the fingerprint region indicative of the 1,2-substitution pattern of salicylamide, which appears as a strong peak at 750 cm^{-1}. When they analyze the spectrum of their product, the students note the disappearance of the peak at 750 cm^{-1} and the presence of a new, strong peak at 816 cm^{-1}, which is characteristic of the 1,2,4-substitution pattern of the product, 5-iodosalicylamide. The only other peaks below 1000 cm^{-1} in the spectrum are either too small to be significant or are outside of the prescribed 700–900 cm^{-1} region. A typical student spectrum is shown in Figure 2.

Of the two possible iodinated products (3-iodo and 5-iodo), only 5-iodosalicylamide is a known compound *(6)*. We opted not to have students take a melting point since any data provided for comparison would have only one of the possible products and, thus, make the exercise of identifying the product a trivial one. (During our development of the lab, we confirmed the identity of the product by its melting point.)

When asked to predict the orientation of the iodination, most of our students ascertain (with a little help from a table of substituent directing effects found in any second-year organic chemistry textbook) the complementarity of the directing effects and recognize that there are two potential products. We require them to choose one of these products and to explain their choice. Working through the problem, students typically come around to the fact that the size of the iodine atom must play a role in where it can "fit" on the benzene ring. Invoking an argument based on sterics, they predict that 5-iodosalicylamide will be the preferred product. The fact that 3,5-diiodosalicylamide is a known compound indicates that sterics may not be the entire explanation, but the size of the iodine must play a role. Again, we have chosen not to make the latter information available, but it does have potential for use as an added challenge for advanced students.

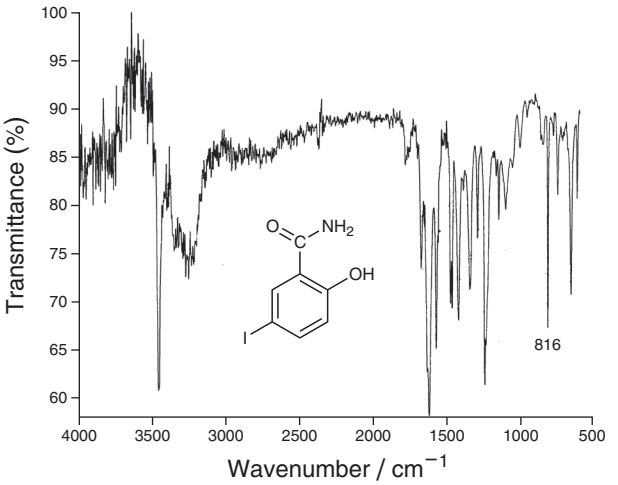


Figure 2. Typical student-collected infrared spectrum of iodination product.

Acknowledgments

We are indebted to our colleague Mark Morvant (now at the University of Oklahoma) for guiding us to the iodination procedure that we used to develop this lab. We are also grateful to Karen Welch who assisted with the literature searching.

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