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Laboratory Experiment

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Synthesis and Characterization of 1,4-Dihydro-3,1-benzoxazines and 1,2,3,4-Tetrahydroquinazolines: An Unknown Structure Determination Experiment

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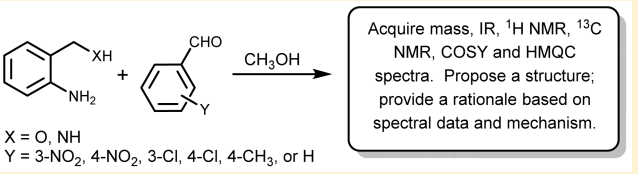
Supporting Information

ABSTRACT: In this experiment for an upper-division course in organic structure determination, each student prepares an unknown compound and characterizes the product using multiple spectroscopic techniques. The unknowns, 2-aryl-substituted 1,4-dihydro-3,1-benzoxazines and 1,2,3,4-tetrahydroquinazolines, are prepared in a single step by the condensation of commercially available aryl aldehydes with 2-aminobenzyl alcohol or 2-aminobenzylamine, respectively. The products are purified by recrystallization and characterized by their mass, IR, ^{1}H NMR, ^{13}C NMR, COSY, and HMQC spectra. Pre- and postlab assignments encourage students to use both mechanistic reasoning and information from multiple spectroscopic techniques for structure elucidation.



KEYWORDS: *Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Heterocycles, NMR Spectroscopy, IR Spectroscopy*

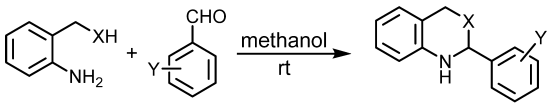
INTRODUCTION

In our upper-division course on organic structure determination, we endeavor to include experiments that model situations that are encountered by practicing chemists. Optimally, these are experiments that require students to draw upon their knowledge of chemical reactivity and information from multiple spectroscopic techniques to determine the structure of an unknown compound.[1] Although a variety of structural elucidation experiments are reported in the literature,[2] there is value in having a menu of options. Namely, this limits the repetition of experiments and the potential leakage of information from one class to the next.

The lecture portion of the course examines the use of mass spectrometry, infrared spectroscopy and 1- and 2-D NMR spectroscopy for small organic molecule structure determination. The course is populated by upper division chemistry majors and minors and, for most, this is their first advanced course in organic chemistry. Our goals for the laboratory portion of the course, and for the experiment presented herein, are 3-fold: (1) to provide students with hands-on experience with the techniques discussed in class; (2) to use information from multiple spectroscopic techniques to arrive at a structure and to assign the spectra; and (3) to integrate mechanistic reasoning into the structure elucidation process. In our experience, this third point is often neglected by students, yet for synthetic chemists, structure determination rarely occurs in a vacuum. Instead, the synthetic chemist knows the structures of the reagents and can reasonably anticipate how the compounds will react.

We anticipated that 2-aryl-1,4-dihydro-3,1-benzoxazines and 2-aryl-1,2,3,4-tetrahydroquinazolines would be good candidates for such an experiment. These compounds are prepared in a single step from commercially available starting materials (Scheme 1), are readily purified by recrystallization, and provide well-resolved ^{1}H NMR spectra. Students who have completed one year of organic chemistry are unlikely to be familiar with the dihydrobenzoxazine or tetrahydroquinazoline ring systems but will have studied reactions that involve the nucleophilic addition of alcohols or amines to aldehydes, such as acetal and imine formation. Therefore, it is reasonable to expect that students will be able to use mechanistic reasoning, along with spectroscopic data, for structure determination.

Scheme 1. Synthesis of Title Compounds



The dihydrobenzoxazine[3] and tetrahydroquinazoline[4−6] compounds are prepared by the condensation of aryl aldehydes with 2-aminobenzyl alcohol or 2-aminobenzylamine, respectively. The reaction proceeds readily in ethanol or methanol solvent at ambient temperature. A few procedures call for the use of an acid catalyst[7] or azeotropic removal of water[8] from a

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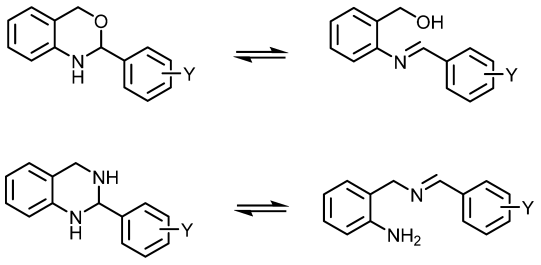
benzene solution of the reagents, but these conditions do not result in a significant improvement in reaction times or yields.

Alternatively, the condensation reaction can be performed in the absence of organic solvents. Aqueous slurries of 2-aminobenzylamine and aromatic aldehydes provide tetrahydroquinazolines; however, the products can be difficult to isolate and purify.[9] Solvent-free protocols require elevated temperatures to form a melt phase,[9,10] prolonged grinding of the reagents,[9] or large amounts (>30 mol %) of acetic acid catalyst.[11] The title compounds are obtained in >90% yield after a 30 min reaction time when 8-ethyl-1,8-diazobicyclo-[5,4,0]-7-undecenium trifluoromethanesulfonate is used as the reaction medium.[12] However, this ionic liquid is not commercially available.

One potentially complicating factor in the characterization of the products is the solution-phase equilibrium between the heterocycle and its imine tautomer, which has been well studied for both the dihydrobenzoxazine[3,13,14] and tetrahydroquinazoline[4,15,16] systems (Scheme 2). When Y is a strong electron donor such as an alkoxy or amino group, resonance stabilization of the imine tautomer is increased and significant amounts of both tautomers are present at equilibrium. For the experiment reported herein, aldehyde reagents were selected such that the cyclic tautomer of the product would be the predominant species in solution (>90:10 heterocycle to imine ratio).[14]

Scheme 2. Equilibrium between Cyclic and Imine Tautomers



EXPERIMENTAL OVERVIEW

This experiment has been part of the laboratory curriculum in the two most recent offerings of our upper-division course on organic structure determination. Most of the experimental work was completed during three 4 h lab meetings. The 19 students who completed the experiment (12 in Fall 2013 and 7 in Fall 2015) worked individually, each preparing his or her own unknown compound and acquiring the spectra. Students were, however, encouraged to compare their spectra and discuss their interpretation of the spectral data.

The first week of the experiment was dedicated to the synthesis and purification of the unknown compounds. A portion of one class period was used to set up the reactions, which were stirred at ambient temperature overnight. Isolation and purification of the products were accomplished during the regular lab period on the following day. However, we and others[3,5] have found that the reactions are complete in less than 2 h, thus the synthesis and purification of the products could be completed in a single lab period (see Supporting Information). Characterization was completed during weeks two and three of the experiment.

EXPERIMENTAL PROCEDURE

A methanol (10 mL) solution of 2-aminobenzyl alcohol or 2-aminobenzylamine (0.400 g) and an equimolar amount of the aryl aldehyde was stirred overnight at room temperature. The solvent was removed via rotary evaporation and the crude products recrystallized from ethanol or methanol and dried in vacuo.

At the subsequent lab meetings, the students measured the melting points of their products, ran IR spectra, and acquired mass spectra on an autosampler-equipped GC-MS. Half of the class ran ^{1}H, COSY, and HMQC NMR experiments (acquisition times of 2, 4, and 15 min, respectively) at each of the two lab meetings that were dedicated to characterization. ^{13}C NMR spectra, run during overnight blocks throughout the three-week long experiment, were processed and printed during the lab meetings.

HAZARDS

All compounds should be treated as potentially hazardous and exposure via inhalation or by absorption through the skin should be avoided. All chemical manipulations should be performed in a fume hood. Eye protection, gloves, and clothing that completely covers the body should be worn. The aryl aldehydes, 2-aminobenzyl alcohol, 2-aminobenzylamine, and chloroform-*d* are eye, skin, and respiratory irritants. Chloroform-*d* is a possible carcinogen and can cause central nervous system impairment, liver damage, or infertility. Methanol is toxic and may damage the kidneys, liver or eyes. Methanol, ethanol, acetone, benzaldehyde, and 4-tolualdehyde are flammable. As the hazards associated with the dihydrobenzoxazine and tetrahydroquinazoline products are not as well-documented, care should be taken to minimize exposure.

RESULTS AND DISCUSSION

Prelab Assignment

In the most recent iteration of the experiment, each student was asked to predict the product of the reaction for his or her assigned set of reagents (2-aminobenzyl alcohol or 2-aminobenzylamine, a benzaldehyde derivative, and methanol) and provide a mechanism for its formation. Students were also asked to anticipate how the IR, ^{1}H NMR, and ^{13}C NMR spectra of the proposed product would differ from that of the starting materials. It should be noted that although MS, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy had been covered in class prior to the start of this experiment, two-dimensional techniques, such as COSY and HMQC, were introduced while this experiment was in progress and therefore were not addressed in the prelab assignment.

The majority of the students (four out of seven) predicted that the product would be an imine, formed from nucleophilic attack of the arylamine of 2-aminobenzyl alcohol or the alkylamine of 2-aminobenzylamine on the aldehyde (see Scheme 2 for structures). The students cited a ^{13}C NMR signal at 160 ppm and a ^{1}H NMR signal at approximately 8.0 ppm as key evidence that would indicate the formation of an imine from a primary amine. Students likewise noted that a C═N stretching absorbance would be expected in the IR spectrum between 1690 and 1640 cm^{-1}, although they did not universally account for the effect of conjugation with the aryl ring. The absence of characteristic aldehyde signals in the IR, ^{1}H NMR, and ^{13}C NMR spectra were also commonly cited as evidence that would support the proposed structures. Finally,

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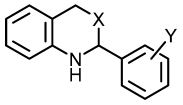
the students expected that the N—H stretches in the IR spectrum due to the reacting primary amine would be absent from the spectrum of the product but that signals due to the unreacted primary amine, in the case of imines derived from 2-aminobenzyl amine, or the alcohol, in the case of 2-aminobenzyl alcohol, would appear in the same region.

All of the students who had been assigned 2-aminobenzylamine as a reagent predicted that the product would be an imine. However, only one of the four students assigned 2-aminobenzylalcohol proposed an imine product. Other predicted structures included an aminal (one student) and a hemiacetal (two students).

Synthesis and Characterization

The dihydrobenzoxazine and tetrahydroquinazoline products were obtained in essentially quantitative crude yields (later examination of crude products by ^{1}H NMR spectroscopy revealed the presence of only trace amounts of starting materials). The products were recrystallized with an emphasis on purity over yield. Thus, second crops of crystals were not collected. The crystalline products were obtained in moderate purified yields (Table 1).

Table 1. Dihydrobenzoxazine and Tetrahydroquinazoline Products



Compound	X	Y	Yield, %[a]
1	O	3-NO_2	50
2	O	4-NO_2	46
3	O	3-Cl	58
4	O	4-Cl	59
5	O	4-CH_3	48
6	O	H	70
7	NH	3-NO_2	57
8	NH	4-NO_2	51
9	NH	4-CH_3	82
10	NH	H	63

[a]Each yield is the average of two student-run experiments with the exception of **7**, which is from a single experiment.

Each student acquired the mass, IR, ^{1}H NMR, ^{13}C NMR, COSY, and HMQC spectra (representative student spectra are included with the Supporting Information). All ten compounds provided well-resolved ^{1}H NMR spectra. Signals due to the imine tautomer were observed in the ^{1}H NMR spectra of compounds **3**, **4**, **5**, **9**, and **10** but did not interfere with the interpretation of these spectra as the imine tautomer accounted for no more than 5% of the product mixture, as determined by integration of the ^{1}H NMR spectra.

Structure Determination

The postlab report form was designed to provide a guided approach to spectral interpretation. Students were prompted to use the spectra to determine which functional groups from the reactants had participated in the reaction and which were still present. For example, students who prepared 1,4-dihydro-2-(3-nitrophenyl)-2*H*-3,1-benzoxazine, **1**, concluded that the aldehyde functionality of 3-nitrobenzaldehyde must have reacted as the carbonyl C═O stretch was not present in the IR spectrum of the product. The existence of a single band at 3310 cm^{-1} indicated that the primary amine was no longer present; however, students were initially unsure whether to attribute this signal to a secondary amine or an alcohol. The presence of the nitro group was supported by strong absorption bands at 1532 and 1349 cm^{-1}. The ^{1}H NMR (Figure 1) and COSY spectra confirmed the existence of two distinct aromatic spin systems. Integration of the aromatic region of the ^{1}H NMR spectrum revealed the presence of eight aromatic protons, which—coupled with the mild and nonacidic reaction conditions—suggested that electrophilic substitution on the aromatic rings had not occurred.

Compound **1** exhibited a prominent M+ ion (at m/z = 256 for compound **1**) in the EI mass spectrum as did all of the products. Comparison of the presumed molecular weight of **1** (256 g/mol) to the combined masses of the two reactants (274 g/mol) revealed a difference of 18 mass units, which the students readily attributed to the loss of water. From this information, the molecular formula of the product, $C_{14}H_{12}N_2O_3$, and the degree of unsaturation (DU = 10) could be deduced. An important clue came from the recognition that the degree of unsaturation in the product was equal to the combined values for the reactants. As the aldehyde carbonyl was no longer present, only the existence of a new π bond or a ring could account for the degree of unsaturation.

Some students initially attributed the doublet at 5.72 ppm in the ^{1}H NMR spectrum of **1** to an alkene proton, but examination of the HMQC spectrum showed that this signal correlated to a ^{13}C NMR resonance at 83.8 ppm. Thus, the doublet at 5.72 ppm was assigned to a methine with two

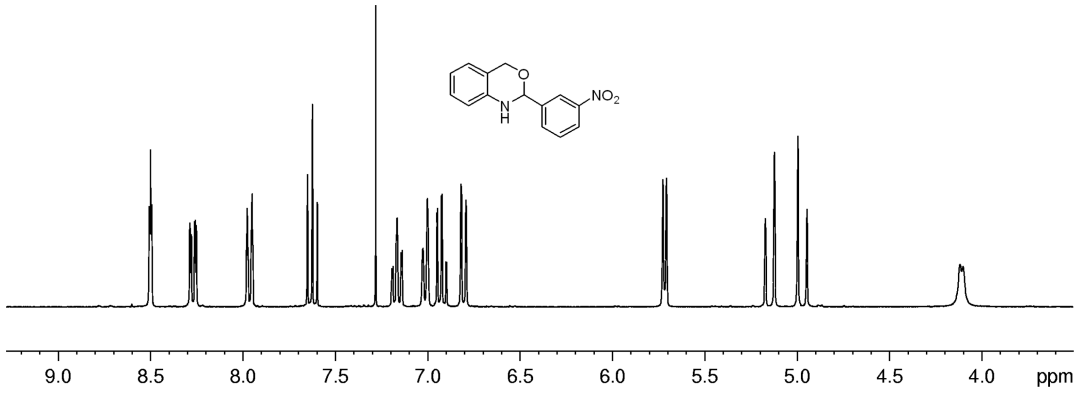


Figure 1. Representative student ^{1}H NMR spectrum of 1,4-dihydro-2-(3-nitrophenyl)-2*H*-3,1-benzoxazine.

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attached heteroatoms. The COSY spectrum of **1** revealed that this signal was coupled to the N−H signal at 4.11 ppm. The pair of doublets at 5.15 and 4.97 ppm, more precisely described as an AB quartet, was initially perplexing to the students. The signal was ultimately attributed to diastereotopic geminal hydrogen atoms, based on the coupling constant (J = −14.7 Hz) or the correlation of the two ^{1}H NMR signals to a single carbon signal in the HMQC spectrum. This information led to the identification of a —NH—CH(Ar)—O—CH_2— fragment and confirmed the presence of a ring. From this point, determination of the overall structure of the product was straightforward.

Determination of the structure of compounds **2**−**6** proceeded along similar lines. In the case of the tetrahdyroquinazoline products, **7**−**10**, there was one key difference that had the effect of increasing the difficulty of the structure determination: coupling between the aryl NH and the neighboring methine hydrogen atom was not observed in either the ^{1}H NMR or COSY spectra (a weak correlation was observed, however, in the COSY spectrum of compound **8**).

Assignment of ^{1}H and ^{13}C NMR Spectra

Assignment of the ^{1}H NMR spectra was accomplished using chemical shift, coupling, and integration data along with the correlations from the COSY spectrum. The aryl protons of the dihydrobenzoxazine and tetrahydroquinazoline rings exhibit first order coupling and their assignment is straightforward. The second order AA′BB′ coupling pattern, characteristic of a 1,4-disubstituted aryl ring, is clearly evident in the ^{1}H NMR spectra for compounds **2**, **4**, **5**, **8**, and **9**. This coupling pattern was used, along with the chemical shift and integration of each signal, to assign these aryl proton signals. COSY correlations were of particular value in assigning the second order signals observed for the monosubstituted aromatic rings in compounds **6** and **10** and for the 1,3-disubstituted ring of compound **3**. The HMQC spectrum was used to assign ^{13}C NMR resonances due to carbon atoms with attached protons. Assignment of the remaining carbon signals was based on chemical shift, and chemical shift calculations proved to be a useful tool for this task.[17] Full assignments of the ^{1}H and ^{13}C NMR spectra are reported in the Supporting Information.

Assessment

Conversations with the students as they worked to solve the structures indicated that they found the structure determination to be a challenge. In spite of the perceived high level of difficulty, 18 of the 19 students proposed the correct structures for their unknowns. One student proposed the imine tautomer as the structure of compound **8**. The average grade on the final report was 85%, with the grades ranging from 70% to 93%.

As part of their final reports, students were asked to describe the strategy that they used and to reference specific pieces of information that led them to the final structure. In the first iteration of the experiment, the students tended to exclusively cite spectral data as evidence for the proposed structure, and we were unable to assess the extent to which the students used their knowledge of chemical reactivity and mechanism to aid in the structure determination.

Two changes were therefore made for the second offering of this experiment. First, a prelab assignment (described above) was developed to encourage the students to use their knowledge of chemical reactivity and mechanism to anticipate the product of the reaction. Second, the postlab assignment was revised such that students were specifically asked to address how their knowledge of mechanism and reactivity informed their structural elucidation efforts. The students universally noted that, as predicted in the prelab assignment, the aldehyde had reacted as evidenced by the absence of both the C═O stretch in the IR spectrum and the characteristic aldehyde ^{1}H NMR signal. Students concluded that the product was not the predicted imine, based on the lack of an imine C═N stretch in the IR spectrum or a ^{13}C NMR signal that could be attributed to an imine carbon atom. In their postlab reports, five of the seven students reasoned that intramolecular attack of the alcohol or amine on the electrophilic imine carbon atom would produce the dihydrobenzoxazine or tetrahydroquinazoline ring, respectively. The absence of the alcohol O−H stretch (for compounds **1**−**6**) or the primary aryl amine N−H stretch (for compounds **7**−**10**) from the IR spectrum was cited as evidence that these functional groups must have reacted.

Of the 18 students who arrived at the correct structure, 11 assigned their ^{1}H NMR spectra without any errors. The most common errors involved the misassignment of the protons on the amine-substituted aryl ring. The students found the COSY spectrum to be helpful in this regard, but still had to rely upon their knowledge of substituent effects on aromatic proton chemical shifts to unambiguously assign the aryl protons.

Assignment of ^{13}C NMR signals due to carbon atoms with attached protons was accomplished using the correlations observed in the HMQC spectrum. Provided the ^{1}H NMR spectrum was assigned correctly, assignment of the ^{13}C resonances due to carbon atoms with attached protons was straightforward. Only a few minor errors in HMQC interpretation were observed, usually in cases where signals were less-than-perfectly resolved. By far, the most common source of error was the incorrect attribution of signals to substituted aryl carbon atoms. Assignment of these signals is not trivial even with the aid of chemical shift calculations, and therefore, only minor deductions were taken for these errors.

In conclusion, this experiment proved to be a challenging yet reasonable structure elucidation problem for the students in an upper-level undergraduate course on organic structure determination. The unknown compounds were readily prepared in a single step. The products provided well-resolved, appropriately complex spectra. Students were encouraged to use mechanistic reasoning to assist in structure determination. No single spectral technique provided sufficient information to solve the structure. Instead, evidence from several NMR experiments as well as from the IR and mass spectra had to be pieced together to arrive at a final, reasonable structure. Likewise, students had to draw from multiple sources of information to assign the ^{1}H NMR (chemical shift, COSY correlations, and first- and second-order coupling data) and ^{13}C NMR spectra (chemical shift, chemical shift calculations, and HMQC correlations).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00155.

Student handouts and instructor notes. (PDF)

Student handouts and instructor notes. (DOCX)

Representative student spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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