JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

pubs.acs.org/jchemeduc

Azeotropic Preparation of a *C*-Phenyl *N*-Aryl Imine: An Introductory Undergraduate Organic Chemistry Laboratory Experiment

Lee J. Silverberg* and David J. Coyle

Pennsylvania State University, Schuylkill Campus, 200 University Drive, Schuylkill Haven, Pennsylvania 17972, United States

Kevin C. Cannon

Pennsylvania State University, Abington Campus, 1600 Woodland Road, Abington, Pennsylvania 19001, United States

Robert T. Mathers and Jeffrey A. Richards

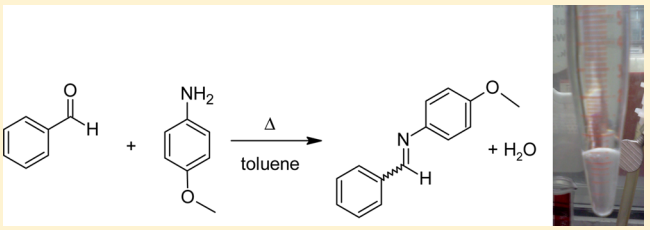
Pennsylvania State University, New Kensington Campus, 3550 Seventh Street Road, New Kensington, Pennsylvania 15068, United States

John Tierney

Pennsylvania State University, Brandywine Campus, 25 Yearsley Mill Road, Media, Pennsylvania 19063, United States

Supporting Information

ABSTRACT: Imines are important in biological chemistry and as intermediates in organic synthesis. An experiment for introductory undergraduate organic chemistry is presented in which benzaldehyde was condensed with *p*-methoxyaniline in toluene to give 4-methoxy-*N*-(phenylmethylene)benzenamine. Water was removed by azeotropic distillation using a Dean–Stark trap. The reaction was readily performed in one 3 h laboratory period, gave a crystalline product, and was easily followed visually by the amount of water collected. It demonstrated important concepts from second-year undergraduate organic chemistry, including equilibrium processes, condensation reactions, and imine formation. The experiment also gave students exposure to important laboratory techniques including azeotropic distillation, use of a water trap, and mixed-solvent recrystallization.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Aldehydes/Ketones, Amines/Ammonium Compounds, Equilibrium, Reactions*

INTRODUCTION

Imines, sometimes called Schiff bases, are the nitrogen analogues of aldehydes and ketones. They are important intermediates in biological chemistry, including the pentose phosphate pathway that produces NADPH, breakdown of glycogen to produce glucose 6-phosphate, degradation of amino acids, assimilation of amines from nitrogen fixation into glutamine and glutamate, synthesis of other amino acids, and absorption of visible light by rhodopsin in retinal rod cells.[1] Imines also serve as important synthetic intermediates,[2] particularly in synthesis of nitrogen heterocycles[2,3] and chiral amines.[4]

The synthesis of imines is addressed in second-year undergraduate organic chemistry textbooks, but is mostly absent from laboratory textbooks and this *Journal*.[5] An issue with preparation of imines is that many are not stable.[6] Only five experiments are reported in this *Journal*.[5,7−10] Enamine syntheses are similarly absent from laboratory textbooks; one experiment has been published for the synthesis of an enamine.[11]

The syntheses of imines and enamines are equilibrium processes in which water is formed.[12] Removal of water can be used to shift the equilibrium toward the products, a demonstration of Le Châtelier's Principle and a concept that students typically learn in first-year undergraduate chemistry courses. In the preparation of an imine from *p*-methoxyaniline and ethyl glyoxalate,[5] molecular sieves were used to remove the water formed over the course of 1 week at room temperature. The imine was isolated as a liquid.[5] In the reaction of cyclohexanone and pyrrolidine,[11] water was removed over 1.5 h

Received: January 22, 2016
Revised: February 18, 2016

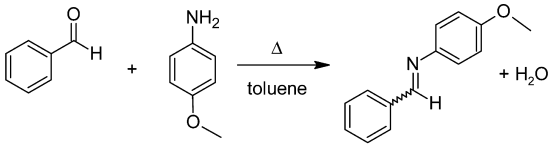
DOI: 10.1021/acs.jchemed.6b00056
J. Chem. Educ. XXXX, XXX, XXX−XXX

from a refluxing benzene solution using a Dean–Stark trap; the enamine was a liquid that could be purified by vacuum distillation, but had to be used in the same period or stored under nitrogen at 0 °C.[11] Two solvent-free reactions that yielded solid imines which were subsequently reduced to the amines have been reported;[7,8] neither experiment addressed equilibrium. In another report, an imine was generated in situ for reduction to the amine.[9] A four-step synthesis of a cyclic imine was described for graduate organic chemistry laboratory classes.[10]

Oximes and hydrazones are often prepared as derivatives in qualitative analysis laboratories; in these experiments, the focus is not on the synthesis, but on the identification of an unknown. The reactions are expected to form crystals without removal of water from the reaction.[13]

An experiment for second-year undergraduate organic chemistry is presented in which benzaldehyde (**1**) is condensed with *p*-methoxyaniline (*p*-anisidine) (**2**) in toluene to give 4-methoxy-*N*-(phenylmethylene)benzenamine (**3**), an imine (Scheme 1). Water is removed by azeotropic distillation using

Scheme 1. Reaction of Benzaldehyde (1) with *p*-Methoxyaniline (2)



a Dean–Stark trap, where the reaction can be monitored by watching water collect in the trap as it separates from toluene and sinks to the bottom of the trap. Although Dean–Stark traps purchased commercially can be expensive, methods for building a trap from common laboratory glassware have been published.[11,14−16] An additional method for a noncommercial trap is presented here. The reaction and workup are conveniently completed in one 3-h laboratory period, and a stable crystalline product is obtained.

The preparation of imines by azeotropic distillation of water is a common method,[17] and **3** has been previously synthesized in benzene,[18,19] but not by azeotropic distillation of toluene, which is a safer solvent.[20] Among the many other preparations of **3** reported, use of magnesium sulfate[21−28] or molecular sieves[29−31] in CH_2Cl_2 appears to be most commonly used. Although these and other methods may be simpler for a researcher, from a pedagogical viewpoint the ability to observe the water as it forms enables students to follow the reaction progress in real time and on a macroscopic scale, which makes the chemistry and the concept of equilibrium less abstract and more interesting.

The imine is isolated by merely adding hexanes to the room temperature product mixture, inducing crystallization. This illustrates the use of an "antisolvent" to reduce solubility, and this type of direct crystallization from a reaction mixture is desirable and frequently used by process chemists in industry.[32,33]

Pedagogical goals for this experiment were thus an introduction to imine synthesis, use of Le Châtelier's Principle to drive an equilibrium reaction to completion, use of azeotropic distillation, and use of mixed-solvent recrystallization.[13]

EXPERIMENT

Students may work alone or with a lab partner. Equimolar amounts of **1** and **2** are dissolved in toluene and heated to reflux. The water formed is collected in a Dean–Stark trap. A Dean–Stark trap constructed from a stillhead and a 5 mL round-bottom flask (Figure 1) can be used. When water stops

Figure 1. Dean–Stark trap, constructed from a stillhead and a 5 mL round-bottom flask, used at Abington campus.

accumulating (approximately 30 min or less), the reaction is cooled to room temperature. Hexanes, twice the volume of toluene present, are added, and the reaction is cooled in an ice bath to crystallize the product. Crystallization is often rapid and dramatic. The imine is collected by vacuum filtration and washed with cold hexanes to give tan/gray crystals of **3**. After drying, the product is characterized by melting point. ^{1}H NMR spectroscopy can be used, if available. If desired, recrystallization of **3** from isopropyl alcohol (IPA) gives off-white crystals. Details of the experiment are in the Supporting Information.

HAZARDS

Hexanes, toluene, and benzaldehyde (**1**) are flammable. *n*-Hexane, the major isomer in the mixture of hexanes, is a neurotoxin. Benzaldehyde (**1**) is harmful if swallowed or contacted with skin. 4-Methoxyaniline (**2**) is very toxic if ingested, inhaled, or contacted by skin. 4-Methoxy-*N*-(phenylmethylene)benzenamine (**3**) is harmful if swallowed. The MSDS for each compound should be consulted for further detail. All work should be performed in fume hoods. Students should wear nitrile gloves along with standard personal protective equipment, such as a lab coat and goggles.

DISCUSSION

The experiment has been performed over several years by students in introductory undergraduate organic chemistry laboratory classes at the Abington, New Kensington, and Schuylkill campuses of Pennsylvania State University. In earlier versions of the procedure, an equal volume of hexanes was added to the toluene solution, and the filtered product was rinsed with cold hexanes/toluenes (50:50 v/v). Although this worked well in the hands of the instructors, the students were frequently getting low yields due to loss of product to the mother liquor. In this updated version (see above), performed at Abington in the Fall 2015 semester, yields were consistently better due to addition of a higher proportion of hexanes.

DOI: 10.1021/acs.jchemed.6b00056
J. Chem. Educ. XXXX, XXX, XXX−XXX

In the most recent runs at the Abington campus, 15 students organized into 8 groups ran the experiment using a Dean−Stark trap constructed from a stillhead and a 5 mL round-bottom flask (Figure 1). On average, students required approximately 2 h to complete the experiment to the point of allowing the crystals to dry. After drying, the average yield of **3** (without IPA recrystallization) ranged from 53.4 to 82% with an average of 69%, and melting points ranged from 61.1−62.5 °C to 66.3−68.3 °C for an average of 63−65 °C (literature melting point 70−70.5 °C[34]).

On the basis of postlaboratory questions, all of the students understood the mechanism of the reaction, how the equilibrium was driven toward product formation, and that crystallization was induced by lowering the temperature and adding an antisolvent. Also, 93% of students could define an azeotrope and understood that toluene and water formed an azeotrope in this experiment. Lab report grades ranged from 93 to 98% and averaged 94%, which is higher than typically seen with other experiments.

Students over the course of a number of semesters answered survey questions about the experiment. Students were asked whether they found the experiment "instructive"; they almost unanimously responded "yes". Students were also asked what they liked best about the experiment. The two most common answers were use of the Dean−Stark trap and watching the product crystallize. Additional comments provided by students included, "the best lab yet", and "clear" and "easy to follow" the procedure.

An extension of this lab can be done in which the rate of collection of water is used to compare the reaction rates of 2−4 imine formation reactions in which the electronic effects of the substituents ($-OCH_3$ and $-NO_2$) are the same, but the steric effects are different. Details are in the Supporting Information.

SUMMARY

A laboratory experiment for second-year undergraduate organic chemistry was developed. The experiment was straightforward, interesting to students, and achieved its pedagogical goals: covering several important lab techniques, visualization of an equilibrium process, and an introduction to synthesis of imines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00056.

Handout for students containing a detailed discussion and experiment instructions, and separate notes for instructors; questionnaires that were given to students and lab report templates that were given to students at Abington; and an extension in which kinetic measurements based on the amount of water collected are used to study steric effects (PDF, DOC)

AUTHOR INFORMATION

Corresponding Author

*E-mail: ljs43@psu.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the students who performed the experiments and provided thoughtful feedback. R.T.M. thanks the National Science Foundation (CHE-MSN and DMR-Polymers) for support under Grant No. CHE 1308247. L.J.S. thanks SP Controls, Inc. for summer support of D.J.C. and Penn State Schuylkill for financial support.

REFERENCES

(1) Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 5th ed.; W. H. Freeman: New York, NY, 2002.

(2) Choudhury, L. H.; Parvin, T. Recent advances in the chemistry of imine-based multicomponent reactions (MCRs). *Tetrahedron* **2011**, *67* (43), 8213−8228.

(3) Martin, S. F. Recent applications of imines as key intermediates in the synthesis of alkaloids and novel nitrogen heterocycles. *Pure Appl. Chem.* **2009**, *81* (2), 195−204.

(4) Nugent, T. C.; El-Shazlya, M. Chiral Amine Synthesis − Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. *Adv. Synth. Catal.* **2010**, *352* (5), 753−819.

(5) Bennett, J.; Meldi, K.; Kimmell, C., II Synthesis and Analysis of a Versatile Imine For the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2006**, *83* (8), 1221−1224.

(6) Dal Colle, M.; Distefano, G.; Jones, D.; Guerrino, A.; Seconi, G.; Modelli, A. Ultraviolet photoelectron, electron transmission and *ab initio* study of the factors determining the stability of imines. *J. Chem. Soc., Perkin Trans. 2* **1994**, No. 4, 789−793.

(7) Touchette, K. M. Reductive Amination: A Remarkable Experiment for the Organic Laboratory. *J. Chem. Educ.* **2006**, *83* (6), 929−930.

(8) Goldstein, S. W.; Cross, A. V. Solvent-Free Reductive Amination: An Organic Chemistry Experiment. *J. Chem. Educ.* **2015**, *92* (7), 1214−1216.

(9) Carlson, M. W.; Ciszewski, J. T.; Bhatti, M. M.; Swanson, W. F.; Wilson, A. M. A Simple Secondary Amine Synthesis: Reductive Amination Using Sodium Triacetoxyborohydride. *J. Chem. Educ.* **2000**, *77* (2), 270−271.

(10) Amigoni, S.; Penverne, C.; Nugier-Chauvin, C.; Le Floc'h, Y. Chemistry of Natural α-Amino Acids: A Surprising "One-Pot Four-Step" Conversion of Polyfunctional Enones into Cyclic Imines. *J. Chem. Educ.* **1999**, *76* (9), 1247−1250.

(11) Darling, S. D. Enamine reactions for the undergraduate organic laboratory: A student water separator. *J. Chem. Educ.* **1966**, *43* (12), 665−666.

(12) Belowich, M. E.; Stoddart, J. F. Dynamic imine chemistry. *Chem. Soc. Rev.* **2012**, *41* (6), 2003−2024.

(13) For example: Lehman, J. W. *Multiscale Operational Organic Chemistry*, 2nd ed.; Prentice Hall: Hoboken, NJ, 2009; pp 601−602.

(14) Puterbaugh, W. H.; Vanselow, C. H.; Nelson, K.; Shrawder, E. J. Esterification for the Introductory Organic Laboratory Course: A modified Dean-Stark trap. *J. Chem. Educ.* **1963**, *40* (7), 349−350.

(15) Lee, A. W. M. An Easily Constructed Water Separator. *J. Chem. Educ.* **1983**, *60* (7), 595.

(16) Smith, W. B. A Student Preparation of Butyl Ether. *J. Chem. Educ.* **1962**, *39* (5), 212.

(17) Layer, R. W. The Chemistry of Imines. *Chem. Rev.* **1963**, *40* (3), 489−510.

(18) Zhou, Y.; Jia, X.; Li, R.; Han, B.; Wu, L. Synthesis of furano[3,2-c]- and pyrano[3,2-c]quinolines upon imino Diels-Alder reactions initiated by nitrosonium (NO^+). *Chin. J. Chem.* **2007**, *25* (3), 422−425.

(19) Sobanov, A. A.; Zolotukhin, A. V.; Galkina, I. V.; Galkin, V. I.; Cherkasov, R. A. Kinetics and mechanism of the Pudovik reaction in the azomethine series: III. Acid-catalyzed hydrophosphorylation of imines. *Russ. J. Gen. Chem.* **2006**, *76* (3), 421−429.

DOI: 10.1021/acs.jchemed.6b00056
J. Chem. Educ. XXXX, XXX, XXX−XXX

(20) McCann, M. *Health Hazards of Solvents*. https://www.uic.edu/sph/glakes/harts1/HARTS_library/solventhazards.txt, accessed Jan 17, 2016.
(21) Rodriguez-Solla, H.; Concellón, C.; Alvaredo, N.; Soengas, R. G. The use of samarium or sodium iodide salts as an alternative for the aza-Henry reaction. *Tetrahedron* **2012**, *68* (6), 1736−1744.
(22) Shaghafi, M. B.; Grote, R. E.; Jarvo, E. R. Oxazolidine Synthesis by Complementary Stereospecific and Stereoconvergent Methods. *Org. Lett.* **2011**, *13* (19), 5188−5191.
(23) Vatmurge, N. S.; Hazra, B. G.; Pore, V. S.; Shirazi, F.; Chavan, P. S.; Deshpande, M. V. Synthesis and antimicrobial activity of β-lactam-bile acid conjugates linked via triazole. *Bioorg. Med. Chem. Lett.* **2008**, *18* (6), 2043−2047.
(24) Wang, J.; Yuan-Xiu, L.; Pei-Yu, K.; Gau, Y.; Yang, D. Synthesis and characterization of [1]benzopyrano[4,3-d][1,3]benzooxazocin-13-one and its derivatives. *Synlett* **2006**, *2006* (17), 2791−2794.
(25) Ojima, I.; Fumero-Oderda, C. L.; Kuduk, S. D.; Ma, Z.; Kirikae, F.; Kirikae, T. Structure-activity relationship study of taxoids for their ability to activate murine macrophages as well as inhibit the growth of macrophage-like cells. *Bioorg. Med. Chem.* **2003**, *11* (13), 2867−2888.
(26) Danheiser, R. L.; Okamoto, I.; Lawlor, M. D.; Lee, T. W. Generation and [2 + 2] cycloadditions of thiosubstituted ketenes: *trans*-1-(4-methoxyphenyl)-4-phenyl-3-(phenylthio)-2-azetidinone. *Org. Syn* **2003**, *80*, 160−171.
(27) Hughes, M.; Boultwood, T.; Zeppetelli, G.; Bull, J. A. Palladium-Catalyzed Cross-Coupling of Aziridinylmetal Species, Generated by Sulfinyl-Magnesium Exchange, with Aryl Bromides: Reaction Optimization, Scope, and Kinetic Investigations. *J. Org. Chem.* **2013**, *78* (3), 844−854.
(28) Naidu, R. Novel Taxanes and Methods Related To Use and Preparation Thereof. PCT Int. Appl., 2004033442, 2004.
(29) Seayad, A. M.; Ramalingam, B.; Yoshinaga, K.; Nagata, T.; Chai, C. L. L. Highly Enantioselective Titanium-Catalyzed Cyanation of Imines at Room Temperature. *Org. Lett.* **2010**, *12* (1), 264−267.
(30) Aspinall, H. C.; Greeves, N.; Hin, S. L. F. A new Yb^{3+}-catalyzed pinacol and imine coupling reaction. *Tetrahedron Lett.* **2010**, *51* (12), 1558−1561.
(31) Keinicke, L.; Fristrup, P.; Norrby, P.; Madsen, R. Nonradical Zinc-Barbier Reaction for Diastereoselective Synthesis of Vicinal Amino Alcohols. *J. Am. Chem. Soc.* **2005**, *127* (45), 15756−15761.
(32) Myerson, A. S. *Handbook of Industrial Crystallization*, 2nd ed.; Butterworth-Heinemann: Boston, MA, 2002; pp 14−15.
(33) Anderson, N. G. *Practical Process Research & Development*; Academic Press: New York, NY, 2000; pp 226−236.
(34) Denmark, S. E.; Nakajima, N.; Stiff, C. M.; Nicaise, O. J.-C.; Kranz, M. Studies on the bisoxazoline- and (−)-sparteine-mediated enantioselective addition of organolithium reagents to imines. *Adv. Synth. Catal.* **2008**, *350* (7−8), 1023−1045.

DOI: 10.1021/acs.jchemed.6b00056
J. Chem. Educ. XXXX, XXX, XXX−XXX