JOURNAL OF CHEMICAL EDUCATION

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Laboratory Experiment

Solvent-Free *N*-Formylation: An Experimental Application of Basic Concepts and Techniques of Organic Chemistry

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Cite This: https://dx.doi.org/10.1021/acs.jchemed.9b00983

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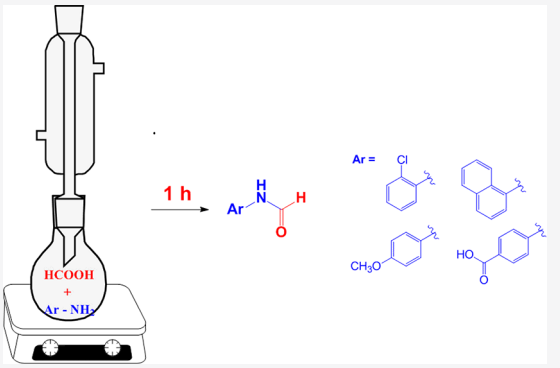
ABSTRACT: *N*-Formamides are important intermediates in the synthesis of many pharmacologically active compounds and are used as protecting groups for amines or as catalysts in different reactions. The current *N*-formylation experiment is designed as a part of an introductory organic chemistry course for undergraduate students. The experiment includes formylation of substituted aromatic amines using formic acid under solvent-free conditions. Students are introduced to laboratory safety precautions, reaction mechanism, and basic laboratory techniques such as a solvent-free reaction setup, reflux, filtration, melting point determination, yield calculation, and lab report write-up. Students synthesized four different formamides in 50−80% yield as a straightforward application of nucleophilic substitution reactions.



KEYWORDS: *Organic Chemistry, Amides, Second-Year Undergraduate*

INTRODUCTION

N-Formylation is a widely used reaction in the manufacture of key intermediates, reagents, and products for research in pharmaceuticals and synthetic industry.[1−6] For instance, *N*-formamides are important intermediates in the synthesis of pharmacologically active compounds such as antifungals,[3] antibiotics,[4] and anticancer agents.[5] They are used to synthesize organometallic compounds with semiconductor and optical characters.[6−9] *N*-Formamides have been used as protecting groups for amines in protein synthesis[10] and as catalysts in different reactions including allylations and hydrosilylations.[11] Dimethylformamide is a precursor for cyanation, aminocarbonylation, amidation, formylation, and cycloaddition.[12] Dimethylformamide dimethyl acetal can convert an active methylene group to other valuable functional groups such as enamines and amidines.[13]

Teaching acylation and nucleophilic substitution reactions is a fundamental concept in organic chemistry courses.[14−19] Nevertheless, *N*-formylation has not been published nor reported-up to our knowledge as an experiment in any chemistry laboratory course. In this paper, students prepared four different formamides using simple solvent-free procedures as a part of the introductory organic chemistry laboratory course. The reaction was chosen to demonstrate many theoretical and experimental chemical concepts as well as the intended pedagogical goals.

PEDAGOGICAL GOALS

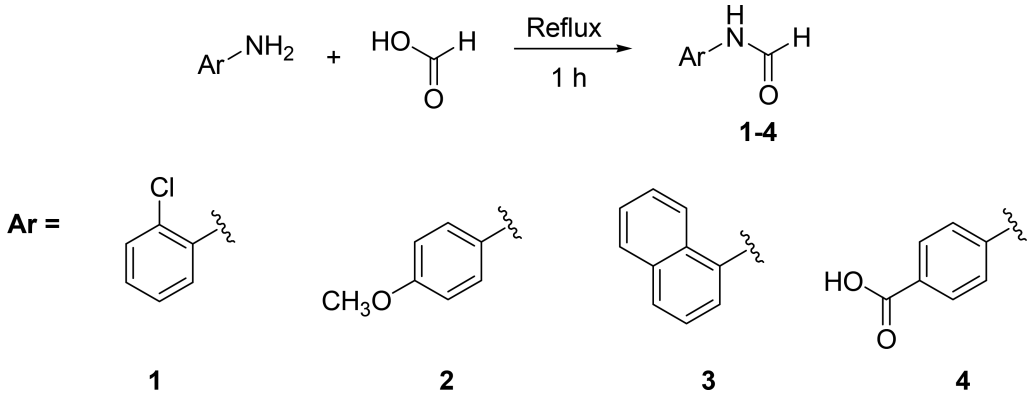
N-Formylation is an excellent example to introduce the nucleophilic substitution reaction as a basic concept in any organic chemistry course.

During this experiment, students should

- Learn how to undergo experimental risk assessment using available MSDSs for reactants, solvents, and reagents.
- Develop laboratory skills and experimental techniques including setting up reflux, ice bath, and solvent-free reactions; performing reaction workup; and writing-up experimental reports.
- Assess the purity of the product by measuring the melting point.
- Understand the nucleophilic substitution reaction and identify its components as nucleophile, electrophile, catalyst, and leaving group.
- Describe the pattern of each step of the reaction mechanism using curved arrows.
- Identify the order of activity for different electrophiles and nucleophiles.

Received: October 27, 2019
Revised: February 2, 2020

Scheme 1. *N*-Formylation of Primary Aromatic Amines



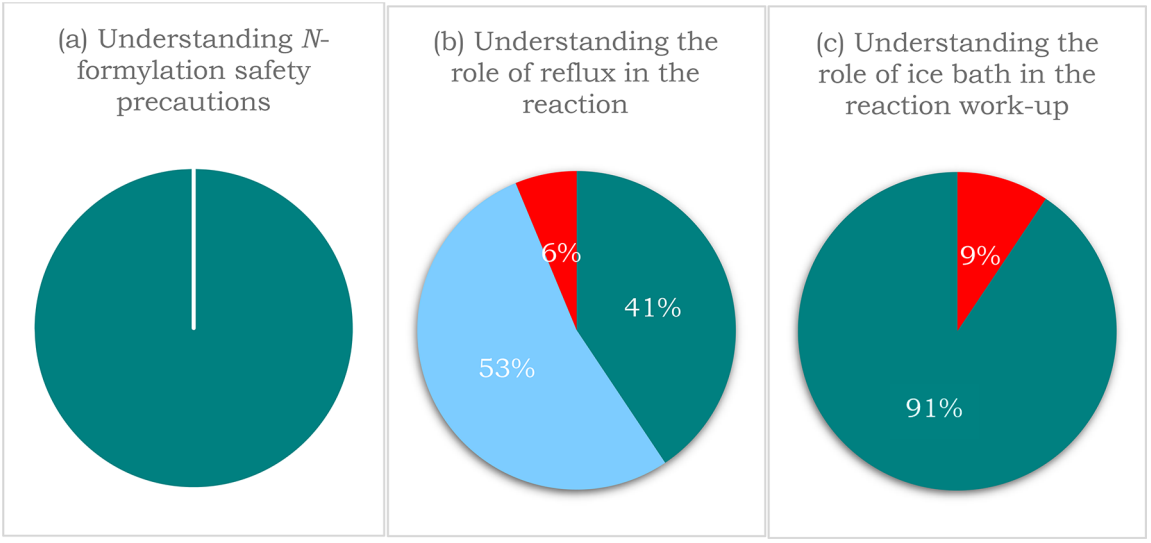


Figure 1. Assessment of *N*-formylation experiment pedagogical goals.

EXPERIMENTAL PROCEDURES

The experiment was performed in a 3 h lab period including a short prelab presentation as a part of the experimental organic chemistry course for second-year undergraduate pharmacy students. *N*-Formylation is performed by a reaction of formic acid with different aromatic amines under solvent-free conditions.[20] In the current experiment, four different aromatic amines were used to prepare four different *N*-formamides (Scheme 1). Students added the proper aromatic amine (10 mmol) to 2 equiv of formic acid (20 mmol, 0.75 mL) in a dry round bottom flask, and the mixture was stirred for 5 min followed by a 1 h reflux. It is advisible to measure the required formic acid by volume and not by weight to avoid any exposure of students to formic acid vapors. After reflux, the flask was cooled at room temperature, and then, 5 mL of ethanol was added. The mixture was poured into a beaker containing crushed ice, and the crude product was filtered while any unreacted amine or formic acid remained in the filtrate. The product was dried in an oven at 50 °C. The melting point of the collected product was measured, and the reaction yield % was calculated.

Pre- and postlab questions were designed to assess the ability of students to understand the target concepts including questions such as "write the pattern of the reaction mechanism" or "what is the role of reflux or ice bath in the experiment" or "which one of the following reagents is more reactive as a formylating agent: acetic acid, formic acid, or ethyl formate", and their answers were examined.

HAZARDS

Students took the standard laboratory safety procedures such as wearing lab coats, eye goggles, and nitrile gloves when they were handling chemicals. Before the experiment they were asked to examine MSDSs of all chemicals. The stirring and reflux were performed under fume hood. Ethanol is inflammable and an irritant in the case of skin and eye contact as well as inhalation. Formic acid is inflammable, corrosive, and irritating to the eyes, skin, and respiratory tract, and students with chest diseases must avoid exposure to formic acid fumes!

RESULTS AND DISCUSSION

This experiment is a part of an organic chemistry course intended for second-year pharmacy undergraduates with a total of 500 students. The lab period was a standard 3 h session including a short prelab presentation of the experiment steps given by lab instructors. The experiment, results write-up, and pre- and postlab questions took 2.5 h. Students were divided into four laboratories with each lab accommodating 28−33 students. In each lab, students worked in groups of 3−5 each. Each group was provided with a different amine, and students

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J. Chem. Educ. XXXX, XXX, XXX−XXX

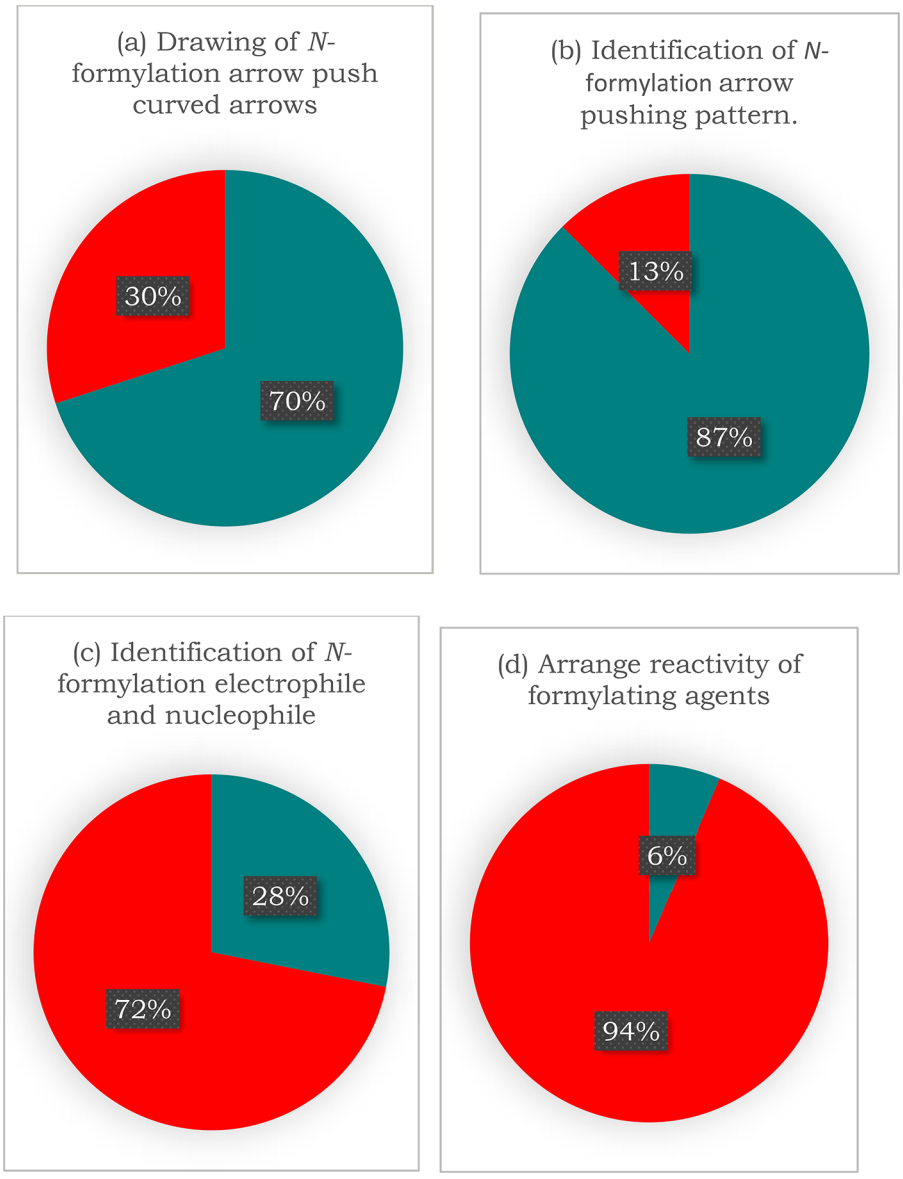

Figure 2. Assessment of *N*-formylation experiment pedagogical goals.

were encouraged to exchange results after reporting to the lab instructors for comparison. Melting points and yield % of all formamide products were reported by students (see details in Supporting Information).

In the current paper, we reported the most frequently used *N*-formylation reactions in our laboratories including two aniline derivatives with electron withdrawing groups (Cl and COOH), one aniline derivative with an electron donating group (OCH_3), and naphthyl amine. This reaction is reproducible with other anilines, and a scale range of 2, 5, 10, and 20 mmol of formic acid with different anilines (1, 2.5, 5, and 10 mmol, respectively) was screened prior to applying the method in our laboratories. We found that a 5−20 mmol scale of formic acid was more practical in terms of ease of handling, yield, and availability of proper glassware for undergraduates.

Students starting with 2-chloro-aniline obtained formamide **1** in 50−70% yield. Excessive washing of this product with ethanol during the reaction workup may have partially dissolved some of the product and lowered the yield for some student groups. Melting point values of crude formamide **1** were in the ranges 70−75 °C and 77−82 °C, comparable to the reported melting points which are 76−78 °C and 81−82 °C.[21] Similarly, student groups using 4-methoxyaniline prepared formamide **2** in 59−79% yield. The literature values for melting points of **2** were 77−80 °C[22] and 80−82 °C.[23] Melting points for student preparations of **2** ranged from 70 to 82 °C. The difference in melting point ranges was attributed to insufficient drying of student products. The measured melting point of crude **3** was 130−144 °C which is close to the reported value, 131−135 °C.[5] The melting point of crude **4** was 260−264 °C which has not been previously reported. Structural elucidation and the purity of formamide products were confirmed by TLC, as demonstrations by lab instructors, and IR spectroscopy.

Pre- and postlab questions were designed to measure students' understanding of target pedagogical goals (see details in Supporting Information) (Figures 1 and 2). One of the important concepts was focused on teaching students safe handling of chemicals. All students were asked to check the

https://dx.doi.org/10.1021/acs.jchemed.9b00983
J. Chem. Educ. XXXX, XXX, XXX−XXX

MSDSs of chemicals used in the reaction, and their knowledge was assessed using prelab questions. In two prelab questions, all students were able to correctly explain the health hazards of formic acid (Figure 1a, for more details see Supporting Information). It is worth noting that formic acid is an irritant chemical. Direct inhalation of formic acid fumes must be avoided, especially by students who are asthmatic or have chest problems!

The *N*-formylation experiment includes two basic experimental techniques, namely, the use of reflux during reaction and the use of an ice bath during workup. Two questions were assigned to evaluate students' understanding of the effect of these experimental techniques on the formation of formamide products. Almost 90% of students achieved the target concepts (Figure 1b,c).

The current experiment represents an application of nucleophilic substitution reactions introduced in the prelab lecture. The experiment was chosen to teach students the driving force of the reaction and how to use arrow pushing stepwise mechanism to interpret the formation of the products. Four lab questions were used to assess these target concepts. While most students were able to recognize the driving force of the reaction (see Supporting Information), only 28% of students could identify the electrophile and nucleophile in the reaction (Figure 2c). Students were also asked to compare the reactivity of acetic acid, formic acid, and ethyl formate as formylating agents which assesses their ability to anticipate the electrophilic strength of the formylating agent's carbonyl group. The results demonstrated that this concept seems hard, and only 6% of the students were able to answer its relevant questions correctly (Figure 2d). With regard to the reaction mechanism, 87% were able to identify the *N*-formylation arrow pushing reaction pattern, and 70% were able to correctly draw reaction pushing curved arrows (Figure 2a,b). Collectively, the *N*-formylation experiment was used as a simple experiment which facilitates understanding of the solvent-free nucleophilic substitution reaction for undergraduate students. The experiment helps students to develop their laboratory safety and experimental skills. It also demonstrates diversity among students regarding their understanding of the reaction mechanism.

CONCLUSIONS

Solvent-free *N*-formylation is a simple, straightforward, and low cost reaction to demonstrate basic organic chemistry principles to undergraduate students. The current experiment can be easily implemented in any introductory organic chemistry course, especially in institutions with limited resources.

The experiment is designed to teach students basic safety rules, a solvent-free reaction setup, and nucleophilic substitution. In the context of the experiment, students learned how to apply experimental risk assessments and laboratory skills and identify electrophiles, nucleophiles, and reaction mechanism patterns.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.9b00983.

Experimentally measured melting points, yield %, and IR chart of the synthesized formamides (PDF, DOCX)

Pre- and postlab questions, pedagogical goals, students answer, and statistics (PDF, DOCX)

Presentation from the prelab lecture given to students before the experiment (PDF)

Picture description of the experiment procedures (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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