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Identifying Passerini Products Using a Green, Guided-Inquiry, Collaborative Approach Combined with Spectroscopic Lab Techniques

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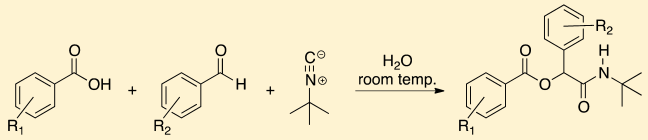
Supporting Information

ABSTRACT: The Passerini multicomponent reaction is a chemical reaction in which a carboxylic acid, an aldehyde, and an isocyanide react to form an α-acyloxy amide. The Passerini reaction can be carried out in water instead of traditional organic solvents, such as methylene chloride or MeOH, and the rate of this reaction is accelerated when carried out in water. A green, guided-inquiry, collaborative experiment has been developed for the teaching lab where a series of Passerini reactions have been conducted in water while varying electron donating and withdrawing substituents on benzoic acids and benzaldehydes. The various combinations of reactants offer a valuable and environmentally friendly way to allow students in an undergraduate chemistry lab course to identify Passerini products through various spectroscopic techniques. The lab has been designed to be a guided-inquiry, puzzle experiment that students may work on in teams.



KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Inquiry-Based/Discovery Learning, Aqueous Solution Chemistry, Green Chemistry, Collaborative/Cooperative Learning, Aromatic Compounds, Hands-On Learning/Manipulatives, NMR Spectroscopy*

The Passerini reaction is a multicomponent (MCR) reaction in which an aldehyde, an isocyanide, and a carboxylic acid react to form an ester of an α-acyloxy amide. This multicomponent reaction is the oldest MCR in which isocyanides were successfully used.[1] Another MCR that uses isocyanides is the Ugi reaction,[2] wherein ammonia or a primary amine is added to the reaction mixture. Passerini and Ugi reactions play an important role in combinatorial chemistry, high-throughput screening, and assembling pharmacologically important structures. They are typically carried out in organic solvents, such as methylene chloride or methanol.

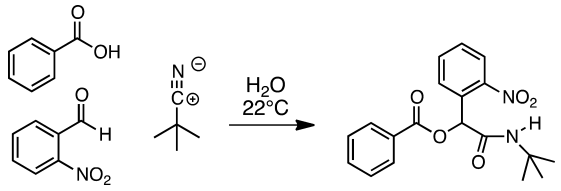
In an effort to develop green[3] versions of the Ugi and Passerini reactions, Pirrung and Sarma demonstrated that these reactions can be done in water, with the added benefit that the reaction rates are accelerated.[4] In an even more green version, it has been shown that Passerini reactions can be performed without any solvent.[5] It has been suggested that these solventless organic transformations actually occur in a liquid melt.[6] Building on the work of Pirrung and Sarma, Hooper and DeBoef developed an aqueous Passerini reaction for use in the undergraduate organic chemistry lab.[7]

Recent examples of Passerini[7] and Ugi[8] reactions have been reported in this *Journal* and are great examples of green MCRs, but they lacked a puzzle aspect. Guided-inquiry experiments[9] and structure elucidation exercises[10] can be very useful when trying to teach students problem-solving and critical thinking skills.[11] A green, guided-inquiry Passerini experiment for use in a second-year and an upper-level undergraduate organic chemistry laboratory program was developed involving the synthesis of a series of α-acyloxy amides.

EXPERIMENTAL OVERVIEW

Being a multicomponent reaction, the Passerini reaction (Scheme 1) offers numerous combinations of aldehydes, acids, and isocyanides. In order to make the experiment guided-inquiry, only combinations that resulted in products whose identity could be readily determined by NMR spectroscopy, IR spectroscopy, and mass spectrometry are used. To keep the experiment green, the only combinations used are ones that form products (a) that form quickly at room temperature, (b) that are solids, (c) that are easily precipitated out of the aqueous reaction mixture, and (d) that require no purification or only a simple recrystallization from ethanol. Nine combinations using (1) benzoic acid or 3-methoxybenzoic acid, (2) benzaldehyde or 2-nitro-, 3-nitro-, 2-chloro-, 4-bromo-, or 4-nitrobenzaldehyde, and (3) *tert*-butyl isocyanide satisfy the constraints.

Scheme 1. Example of a Passerini Reaction



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J. Chem. Educ. XXXX, XXX, XXX−XXX

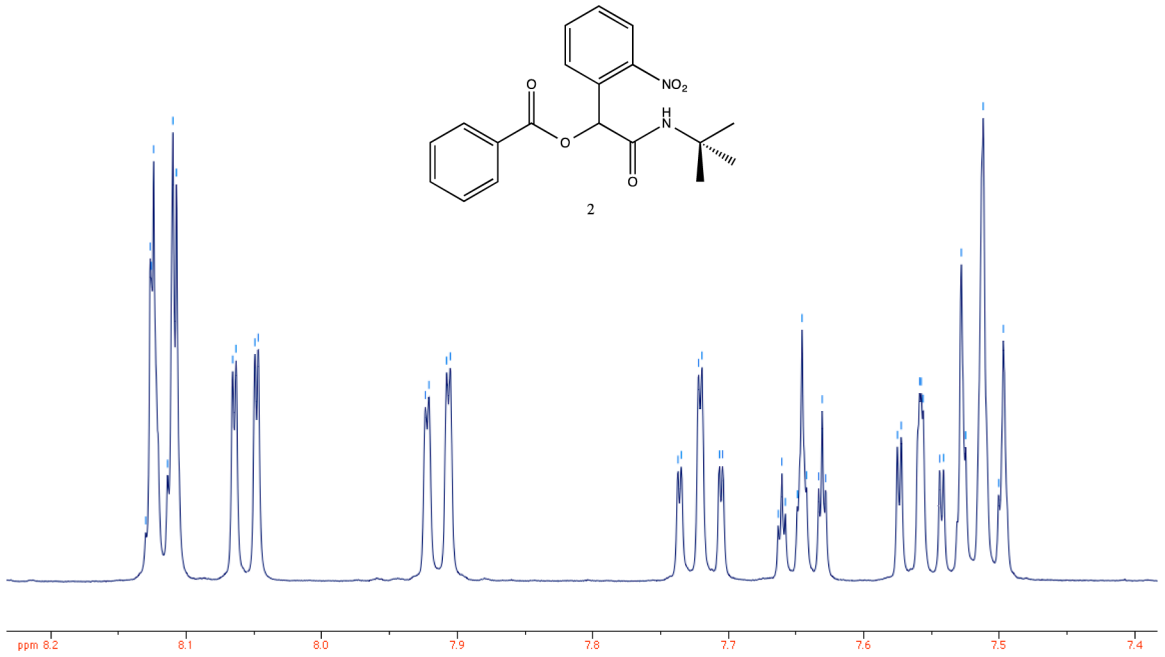

Figure 1. Expansion of the aromatic region of the ^{1}H NMR spectrum at 500 MHz for the Passerini product **2** showing the desired separation of interpretable peaks.

EXPERIMENTAL PROCEDURE

Students work in pairs. There are two versions of the experiment: in version A, students know the identities of the benzoic acid and the benzaldehyde; in version B, students do not know the identities of the benzoic acid and the benzaldehyde. Version A requires one 3 h laboratory period, and version B requires two 3 h laboratory periods. Students add (unknown) benzoic acid (2.2 mmol) to water (20 mL), followed by (unknown) benzaldehyde (2.9 mmol) and *tert*-butyl isocyanide (2.7 mmol). The mixture is stirred vigorously at room temperature for 25 min. An α-acyloxy amide precipitates. The white solid is collected by vacuum filtration and recrystallized from hot ethanol by addition of water. The product is characterized by melting point, ^{1}H NMR spectroscopy, IR spectroscopy, and mass spectrometry. From these data, in version A students identify the product of the reaction, and in version B students also identify the unknown benzoic acid and unknown benzaldehyde used in the reaction. A complete set of experimental descriptions and spectroscopic data for the compounds is in the Supporting Information.

HAZARDS

Aromatic aldehydes cause eye and skin irritation and are harmful if swallowed or inhaled. Benzoic acids are harmful to the eyes. *tert*-Butyl isocyanide is flammable and toxic. All of the products are stable, crystalline solids. They present no known hazards, but should be handled with care and should not be ingested. Appropriate personal protective equipment should be worn at all times, and all chemistry should be performed in a well-ventilated hood.

RESULTS AND DISCUSSION

This green, puzzle experiment has been run in 20 different lab sections over a four-year period a number of times at different levels with an approximate total of two hundred undergraduate organic chemistry students. Students performed version A during two of those years and version B during the other two. In all cases and in both versions of the lab, the products were easily synthesized and isolated and there has never been a reported case of the reaction not working. The challenge was in the identification of the products and, in version B, starting materials. The starting materials were almost always correctly identified, and the Passerini products were correctly identified ~85% of the time. Because the product identities were unknown, in order for students to be able to elucidate their product's structure, it was necessary to have clean, interpretable spectroscopic data. Substituents on the aromatic rings were chosen such that the aromatic protons become magnetically nonequivalent and easily distinguishable from one another. The expansion of the aromatic region of the ^{1}H NMR spectrum for the product from the reaction of benzoic acid and 2-nitrobenzaldehyde is shown in Figure 1; the structure of the α-acyloxy amide product is shown in the figure. From ^{1}H NMR data, IR data, and MS data, students identified the product of the reaction. In rare instances when a student had difficulty obtaining clean data on the product, data were provided, and, in such cases, a 15% penalty was imposed during the scoring of the student's lab report. Students who performed version A knew the identities of their starting materials, which were used by some students to guess the identity of the product before they had even done the lab. These students were almost 100% successful in identifying the structure of their product. It is for this reason that the identities of the starting materials were concealed when version B was developed. Version B, where students did not know the identities of their starting materials *or* their products, was done as an end-of-quarter capstone project; students worked in teams of two and were allowed 2 weeks for the project. While they were informed that one of their starting materials was *tert*-butyl isocyanide, they were not provided with information about the other two starting materials. Having molecular weights and fragmentation patterns from MS data proved to be far more important in version B than in version A. This more challenging version was

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J. Chem. Educ. XXXX, XXX, XXX−XXX

performed by chemistry majors, who were remarkably successful at correctly identifying their starting materials as well as their α-acyloxy amide products better than 85% of the time.

CONCLUSION

A green, guided-inquiry Passerini experiment was developed. The reaction occurred rapidly in water at room temperature, required minimal workup and purification, and yielded spectroscopic data that was clean and interpretable. Students experienced many of the principles of green chemistry discussed in class. Students have expressed that, while challenging, they enjoyed the puzzle aspect of the project.

ASSOCIATED CONTENT

Supporting Information

A full experimental section with detailed instructions for students and instructor notes; list of required reagents with CAS numbers; IR, MS, and NMR spectra for all nine compounds in the library. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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J. Chem. Educ. XXXX, XXX, XXX−XXX