A Green Multicomponent Reaction for the Organic Chemistry Laboratory: The Aqueous Passerini Reaction

Developed by Matthew M. Hooper and Brenton DeBoef, Department of Chemistry, University of Rhode Island. Modified by Angela King, Wake Forest University, 2012.

PURPOSE OF THE EXPERIMENT
Demonstrate the benefits of Green Chemistry by performing a Passerini reaction in water; isolate the product and purify via recrystallization; and characterize it using modern spectroscopic techniques.

BACKGROUND REQUIRED
You should be familiar with extraction, recrystallization, IR, and NMR spectroscopy. This exercise will teach you how to set up simple reactions and demonstrate the fundamentals of Green Chemistry.

BACKGROUND INFORMATION
Mario Passerini of the University of Florence discovered the first example of the reaction that now bears his name in 1921.¹ This was the first example of a family of reactions called isocyanide-based multicomponent reactions (MCRs).² Specifically, the Passerini reaction is a three component reaction (3-MCR) that involves the use of an isocyanide, a carboxylic acid, and an aldehyde.

![Scheme 1. Example of a Passerini reaction](image)

MCRs, like the Passerini, have been used extensively in the field of combinatorial chemistry,² which seeks to synthesize large libraries of similar molecules in a parallel fashion. For example, a combinatorial array of reactions can be envisioned using 10 isocyanides, 10 carboxylic acids and 10 aldehydes to create a 1000 (10³)-member library of compounds. Assuming that each of these reactions is straight-forward and high-yielding, the process could be automated, allowing larger libraries to be readily accessed.

α-Hydroxyamides, the hydrolyzed products of Passerini reactions, are common organic building blocks for natural products and drugs. Additionally, a relative of the Passerini reaction that uses imines instead of aldehydes, called the Ugi reaction, was investigated by process chemists at Merck as a method for synthesizing the antiretroviral drug, Crixivan® (Scheme 2). It is interesting to note than no examples of the catalytic asymmetric Ugi reaction have been reported, and only recently have asymmetric versions of the Passerini reaction been developed (asymmetric reactions enhance the production of either the R or S isomer

— the Ugi produces a racemic mixture. Consequently, Merck’s synthetic process involved elimination at the racemic center (*) to form an olefin and subsequent asymmetric hydrogenation using a rhodium-based catalyst to correctly set the stereocenter.

Scheme 2. Merck’s synthesis of Crixivan® via the Ugi 4-MCR.

Mechanism of the Passerini Reaction

The mechanism of the Passerini involves the attack of an aldehyde by the nucleophilic carbon of an isocyanide. [Note the interesting chemistry of the isocyanide moiety: it is both a nucleophile (C⁻) and an electrophile (N⁺).] The resulting nitrilium intermediate is attacked by the carboxylate followed by acyl transfer to form the acylated α-hydroxyamide product (Scheme 3).

Scheme 3. Mechanism of the Passerini reaction in polar solvents.

Green Chemistry

The Passerini reaction is also interesting because it is has 100% atom-economy. This means that every atom in the starting materials is incorporated in the product. Consequently, there is no intrinsic chemical waste associated with the reaction. This feature is present in very few reactions (The Diels-Alder is another example of 100% atom efficiency, while the cleavage of a t-butyldimethylsilyl ether to produce an unprotected alcohol is the epitome of poor atom-efficiency). This reaction definitely meets one of the goals of the Green Chemistry movement:


Typically, Passerini reactions are performed in non-coordinating solvents like CH$_2$Cl$_2$. However, Michael Pirrung (then at Duke, now at UC Riverside) has shown that both Ugi and Passerini reactions may be performed in water. The reactions are biphasic, so water is not a traditional solvent in these processes. Pirrung not only reports very high yields (all $>$90%) at room temperature; he also reports a 50-fold rate enhancement for the Ugi and Passerini reactions. The increase in the rate of heterogeneous aqueous reactions has been studied by many well-known chemists (e.g. Breslow, Jorgensen and Sharpless) but it is still not well understood. Due to the use of water as the “solvent”, this new procedure is very “green”:

*The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used [5th Principle of Green Chemistry].*

*Energy requirements should be recognized for the environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure [6th Principle of Green Chemistry].*

**Objective**

The purpose of the following experiment is to perform a Passerini reaction in an aqueous medium, to purify the product via crystallization from ethanol—also a green solvent (from a renewable feedstock), and to characterize the product by modern spectroscopic methods.

**PROCEDURE**

Add approximately 20mL of deionized water to a 50mL Erlenmeyer flask. Using a 5 mmol scale (for all chemicals), weigh out 0.61 g of benzoic acid and add it to the flask. Using a 1mL syringe add 0.51 mL of benzaldehyde and 0.57mL of $t$-butyl isocyanide (this should all be done in a fume hood as this chemical has a strong, unpleasant odor). Add a stir bar and cap the flask with a septum or cork. Place the flask on a magnetic stirrer using a clamp to hold it secure, and set the stirring speed as high as possible. Let the reaction proceed at room temperature for 20 – 25 minutes. White solid should form on the sides of the flask as the reaction proceeds. After the reaction is complete, uncap the flask and filter the reaction mixture using a Buchner funnel, being sure to collect all of the solid material (it is your unpurified product).

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Recrystallize the product by placing it in a small Erlenmeyer flask, dissolving it in a minimal amount of ethanol and then slowly adding distilled water until crystals start to form. Allow the cloudy mixture to stand in the freezer for 30-60 minutes for maximum yield.

After the crystals have completely formed, isolate your purified product by filtration through a Buchner funnel, and allow them to dry while pulling vacuum through the funnel for approximately 10 minutes. Weigh your product, and use this value to calculate percent yield. Analyze your product by measuring its melting point and collecting IR and NMR spectra.

SAFETY

t-Butyl isocyanide should be handled in a fume hood. It is dangerous to inhale. Handle all of the chemicals with proper personal protection including safety glasses and gloves.

Place disposable needles in the designated sharps container after use.

POST LAB QUESTIONS

1. Why is this reaction “greener” than a typical Passerini reaction?
2. Calculate the percent yield of your reaction.
3. Identify peaks in the $^1$H spectrum that correspond to the t-butyl group, the phenyl groups, and the proton that is α-to the carbonyl. Do the same for the $^{13}$C-NMR spectrum, if one was collected.
4. Identify the frequency of both carbonyl stretches in your IR. Which one corresponds to the benzyl ester?
5. What impurities were apparent in the IR and/or NMR spectra?