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

Matthew M. Hooper and Brenton DeBoef*
Department of Chemistry, University of Rhode Island, 51 Lower College Road, Kingston, RI 02881
bdeboef@chm.uri.edu

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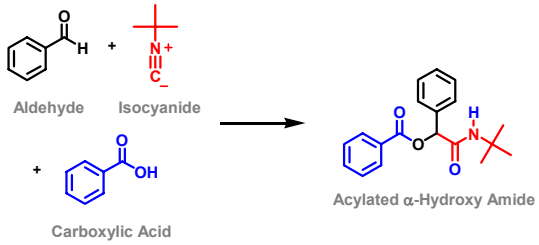
Abstract

Water is the ideal green solvent for organic reactions. However, most organic molecules are insoluble in it. Herein, we report a laboratory module that takes advantage of this property. The Passerini reaction, a three component coupling involving an isocyanide, aldehyde and carboxylic acid, typically requires ~ 24 hr reaction times in organic solvents, but produces a quantitative conversion and yield in < 30 min when performed *on water* [Pirrung, M.C. and Das Sarma, K. *J. Am. Chem. Soc.* **2003,** *126,* 444-445]. This rate enhancement allows the Passerini reaction to be easily adapted for use in a sophomore-level organic laboratory course. Additionally, the incorporation of this laboratory module facilitates discussions of both green chemistry and combinatorial chemistry in the sophomore-level curriculum.

The chemical literature is filled with many excellent chemical transformations that have pedagogical value but are not amenable to implementation in a teaching laboratory due to hazardous reagents or long reaction times. Herein, we report a new exercise that has not been incorporated in mainstream texts for the organic teaching laboratory, the Passerini reaction *(1)*.

The Passerini multicomponent reaction (3-MCR) employs three reagents—isocyanides, carboxylic acids and aldehydes—to form acylated α-hydroxyamides, important intermediates for chemical synthesis (Scheme 1) *(2)*. Multicomponent reactions, like the Passerini, are often used by medicinal chemists, particularly those working in the subfield of combinatorial chemistry because large libraries of compounds can be easily synthesized from the commercial pool of staring materials *(3)*. The imine derivative of the Passerini reaction, the Ugi reaction (4-MCR), was also explored by process chemists at Merck as a potential route to the blockbuster anti-HIV drug Crixivan® *(4)*.



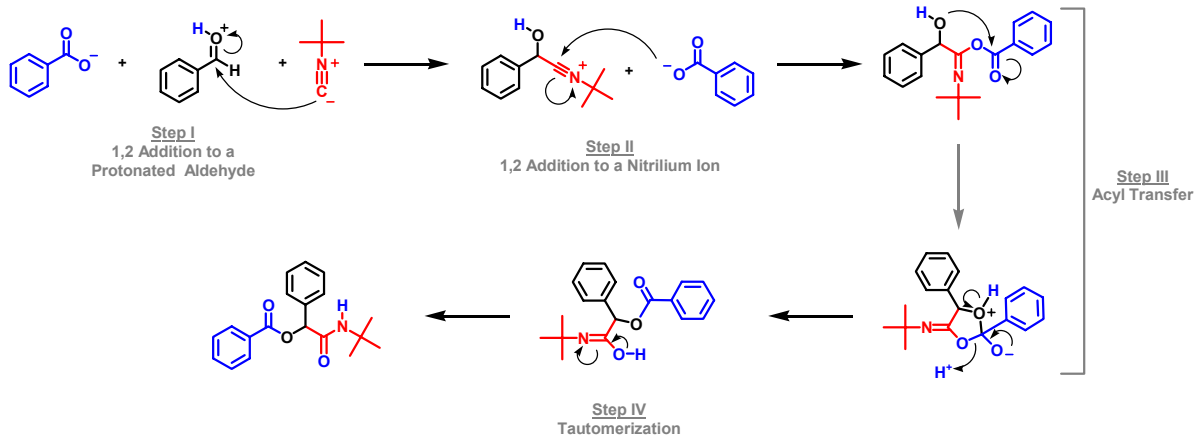
Scheme 1. Representative Passerini Reaction

The Passerini reaction is generally performed in an organic solvent such as CH_2Cl_2 or MeOH, and reaction times of 24 hrs are often required, thus making it impractical for use in a typical three hour laboratory course. Recently, Pirrung and Das Sarma reported a dramatic rate enhancement for both the Passerini and Ugi reactions when the organic solvent was replaced

with water *(5)*. In aqueous media, Passerini reactions completed in ~ 15 min, and excellent yields were observed. This method is significantly greener than the prior art because a non-toxic, innocuous solvent has been employed, and energy has been saved by both the shorter reaction times and the absence of temperature control *(6)*. Interestingly, the rate enhancement is proportional to the cohesive density of the water, in that rates increase as the temperature decreases, or as solutes (LiCl or glucose) are added to the water. This phenomenon has been observed with other aqueous organic reactions, and indicates that the process likely takes place *on water* rather than *in water (7)*.

Pedagogic Value

The mechanism of the Passerini reaction is consistent with the concepts taught in a typical sophomore-level organic chemistry course. It involves the 1,2-addition of an isocyanide (whose Lewis structure is a great question for a first semester organic chemistry exam) to a protonated aldehyde (Step I). This addition forms a nitrilium ion, which is attacked by the carboxylate (Step II). An intramolecular acyl transfer (Step III), followed by amide tautomerization (Step IV), completes the process. At URI, we teach the concepts of carbonyl additions and acylations late in the second semester organic course, so we have chosen to perform the Passerini module in a single laboratory session near the end of the semester, but the technical simplicity of the experiment allows it to be implemented at an earlier point in the curriculum, if desired.



Scheme 2. Mechanism of the Paserini Reaction

In addition to the pedagogic value of the Passerini reaction's mechanism, its presence in our curriculum has enabled us to introduce the topics of combinatorial chemistry and green chemistry, both of which have been extensively discussed in this *Journal* (*8,9*).

This laboratory module was first developed by an undergraduate Chemistry Education major at URI (M.M.H). It was then tested in two advanced laboratory course consisting of juniors and seniors. It was incorporated into URI's sophomore-level organic laboratory course containing 17 chemistry majors last year. Students often comment that the Passerini reaction is their favorite laboratory exercise because it works quickly and reliably provides excellent yields. Only the cost of the isocyanide has prevented us from implementing the module in our non-majors organic laboratory courses (annual enrollment ~ 400), and we are currently working on an inexpensive synthesis of sweet-smelling isocyanides to ameliorate this issue *(10,11)*.

Experimental Overview

To a 50 mL Erlenmeyer flask containing 20 mL water, benzoic acid (0.61 g, 0.50 mmol), benzaldehyde (0.51 mL, 0.50 mmol) and *tert*-butyl isocyanide (0.57 mL, 0.50 mmol) are added. The mixture is vigorously stirred for 25 minutes. The resultant white solid is collected by vacuum filtration. The crude solid is dissolved in hot ethanol and is precipitated by addition of water, yielding a white powder that is analytically pure. Typical yields range from 85 to 95%. mp: 151-153 ºC (lit. 151-153 ºC, ref *12*). LRMS (EI) [M+] calc'd for $C_{19}H_{21}NO_3$ 311.15, found 311.16 m/z. IR (neat, 25 ^{o}C) 3286.7, 1721.5, 1643.6, 1552.9, 1450.1, 1114.8 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 25 ºC): δ 8.09 (d, *J* = 8 Hz, 2H); 7.60 (t, *J* = 8 Hz, 1H); 7.53-7.46 (m, 4H); 7.41-7.35 (m, 3H); 6.22 (s, 1H); 5.98 (s, br, 1H); 1.37 (s, 9H). ^{13}C-NMR ($CDCl_3$, 25 ºC): δ 136.1, 133.7, 129.8, 129.4, 129.0, 128.9, 128.7, 127.5, 76.1, 51.6, 28.7.

Hazards

Benzoic acid [CAS# 65-85-0] is harmful to the eyes, and benzaldehyde [CAS# 100-52-7] is harmful if ingested. *tert*-Butylisocyanide [CAS# 7188-38-7] is flammable and foul smelling. It is harmful if inhaled, ingested or splashed on the skin or eyes. Appropriate personal protective equipment should be used at all times, and the reagents should only be handled in a well-ventilated fume hood. MSDS sheets are freely available from the vendor at http://www.sigmaaldrich.com.

Conclusion

The aqueous Passerini reaction is a simple and robust laboratory module. It reinforces the concepts of carbonyl addition reactions that are often taught in a second-semester organic

chemistry course. It's incorporation in our laboratory curriculum has assisted in the teaching of combinatorial synthesis strategies and has demonstrated both the scientific and environmental benefits of green chemistry.

Acknowledgements

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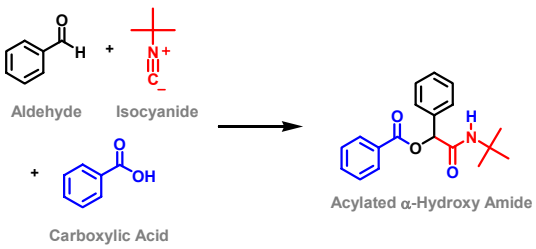
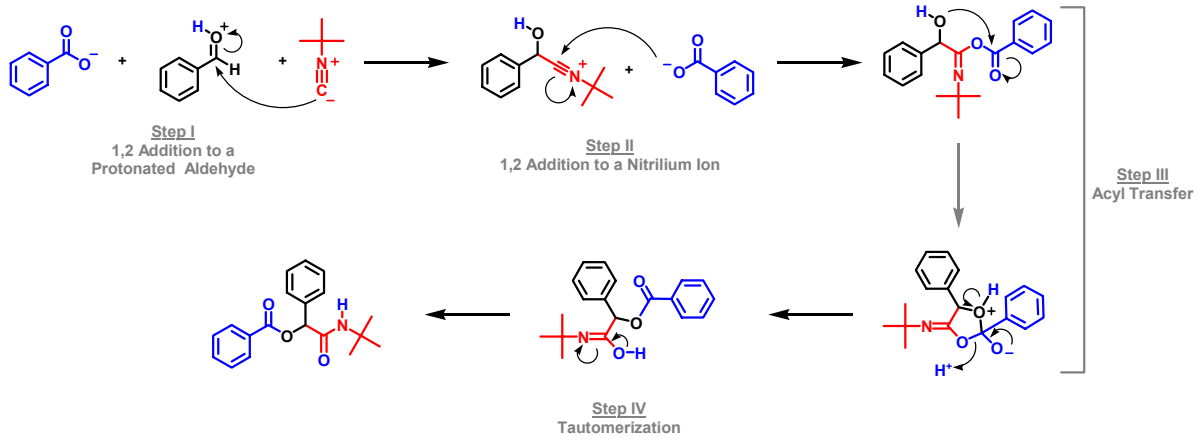
Scheme 1 (one-column)



Scheme 1. Representative Passerini Reaction

Scheme 2 (two-column)



Scheme 2. Mechanism of the Passerini Reaction