JOURNAL OF CHEMICAL EDUCATION

Communication

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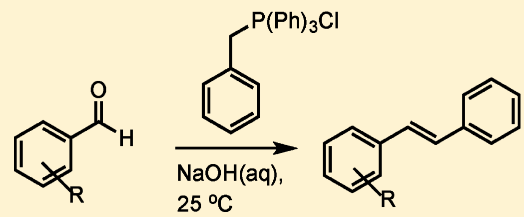
Green Aqueous Wittig Reaction: Teaching Green Chemistry in Organic Teaching Laboratories

Layne A. Morsch,* Leanne Deak, Dyllan Tiburzi, Harrison Schuster, and Brittney Meyer

Department of Chemistry, University of Illinois Springfield, Springfield, Illinois, 62703 United States

Ⓢ *Supporting Information*

ABSTRACT: Green experiments in the organic teaching lab are a vital part of training a new generation of scientists. Not only do they make the lab experience safer and produce less costly waste, they allow students an opportunity to examine and consider potentially hazardous chemical methodologies and develop alternatives. The work discussed here focuses on a series of Wittig reactions that are carried out in aqueous conditions, at room temperature, and in less than one hour. The reactions have been applied to a variety of starting aldehydes. Results for this work and strategies for implementing a green chemistry case study into the laboratory curriculum are presented.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Green Chemistry, Aldehydes, Aqueous Solution Chemistry, Reactions*

There has been much interest in green organic chemistry as the chemical community searches for more environmentally friendly processes. These types of reactions are perfect for inclusion in the undergraduate curriculum, as many chemistry educators are looking for ways to train students to challenge traditional chemical thinking and to consider how to bring green chemistry to bear on problems they may face in their careers.[1] This experiment is designed to give students experience with green chemistry, while directing them to analyze the conversion of a standard reaction to a greener version of that reaction.

The Wittig reaction has been an important reaction for exact placement of an alkene within a molecule since it was first published in 1954.[2] It has been well represented with examples in the undergraduate organic laboratory curriculum.[3−8] Examples include using stabilized ylides,[9−13] hand milling in a solvent-free environment,[14] alumina support without solvent,[15] and others accomplished via microwave-assisted reactions.[16,17] There has been much interest in aqueous examples of the Wittig reaction;[12,18−20] therefore, a broadly applicable version was sought that could be completed successfully during a three-hour organic chemistry lab period. The approach was planned to teach principles of green chemistry, reduce hazardous waste, and teach structure determination by integrating it into a case study-based learning module. This experiment has been tested for two years by 83 students as a three-week project in a second-semester undergraduate organic chemistry laboratory. The first week includes discussion of green chemistry, running a green Wittig reaction, and a comparison of the standard Wittig reaction with the green aqueous Wittig reaction with respect to each of the twelve principles of green chemistry.[21] The second week of lab allows students time to repeat the same reaction to improve their overall skills and have an opportunity for an increased yield while also having time to begin instrumental analysis of the first product. The third week is used for instrumental analysis and discussion of the product structure.

■ THE WITTIG REACTION

In the original Wittig reaction, a triphenylphosphonium halide was added to a solution of *n*-butyllithium in diethyl ether. Once the ylide had formed, the carbonyl compound was added and heated to reflux overnight. The resulting alkene was isolated via several extractions using diethyl ether, followed by column chromatography.[2] Modifications have been published that show that a milder base can be used with benzyltriphenylphosphonium chloride to form the ylide,[3] *N*,*N*-dimethylformamide (DMF) can replace diethyl ether or methylene chloride as the reaction solvent, and the extraction can be replaced by precipitating the alkene from the reaction mixture.[8]

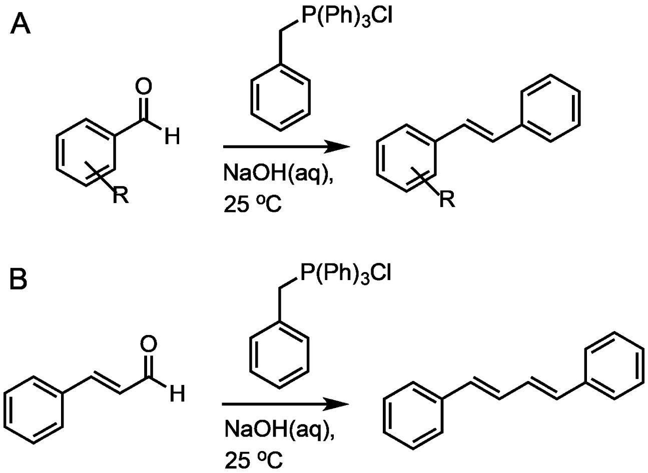
The Wittig reaction has been modified to enhance green aspects of the reaction that is applicable to a broad array of aromatic aldehydes. An aromatic aldehyde is added to an ylide formed in situ by reacting benzyltriphenylphosphonium chloride with sodium hydroxide (Scheme 1). The reaction is effective for a wide variety of aromatic aldehydes but only works with aliphatic aldehydes or ketones by heating during a thirty-minute reaction time.

■ PROCESS OF GREENING THE REACTION

This modified reaction can be used as a case study to teach the valuable concepts of green chemistry.[21] Previously published reactions already began to incorporate “less hazardous chemical syntheses” by replacing flammable alkyllithium base with aqueous sodium hydroxide.[3] The first notable change to previous versions of the Wittig reaction was replacement of reaction solvent (diethyl ether,[2] dichloromethane,[3,4] or DMF[8])

Published: February 18, 2014

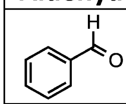
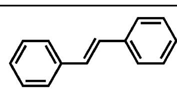
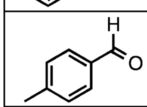
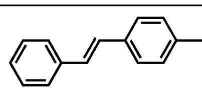
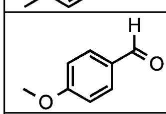
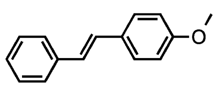
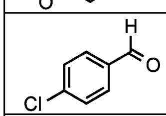
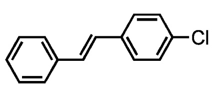
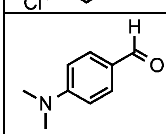
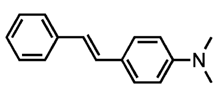
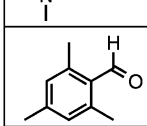
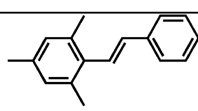
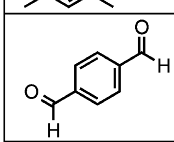
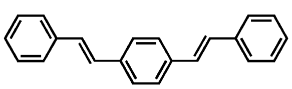
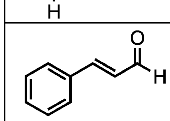
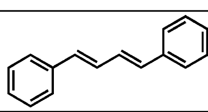
Scheme 1. Reaction Scheme for Wittig Reactions of (A) Substituted Benzaldehydes and (B) Cinnamaldehyde



with water. This clearly demonstrates the concept of "using safer solvents" by using water instead of organic solvents. Another advantage to carrying out the reaction in water is that there is no need to extract product from the solution upon completion of the reaction as the product alkenes are not water-soluble. This also reduces solvent waste. The second area of improvement was to replace propanol[7] with ethanol as the recrystallization solvent. Shifting from propanol to ethanol for the recrystallization addresses the "use of renewable feedstocks" principle as ethanol is often produced from grains rather than from petroleum products, which is the most common source of propanol. Isolating the product by recrystallization greatly reduces the volume of solvent waste from typical organic reactions that require liquid−liquid extraction or column chromatography. Because the reaction is carried out at room temperature (without heating), it also exemplifies "design for energy efficiency". The entire process addresses the idea that it is better to "prevent waste" than to clean it up following a reaction, as well as the fact that "inherently safer chemistry" reduces the potential for lab incidents. In reviewing all aspects of this reaction, students can see that six of the twelve principles of green chemistry have been addressed.[21]

It is important when discussing green chemistry that students realize that there are no perfect reactions; so, whereas several principles of green chemistry are addressed by this example of an aqueous Wittig reaction, there are other principles that are not addressed. The most obvious of these is atom economy with the triphenylphosphine oxide byproduct accounting for most of the wasted atoms. This has been addressed by some research groups but was not explored in the experiment as an option for this study.[20] In addition, this is not a catalyzed reaction. All reagents are required in stoichiometric quantities. There is also no place for in-process monitoring in this experiment. These should not be considered as drawbacks to

Table 1. Summary of Product Yields and GC−MS Data

Aldehyde	Product	% Yield Range (*E* only)	Predicted Molecular Ion (*m*/*z*)	MS of Product (*m*/*z*)
		2–36	180	180, 165, 152
		8–31	194	194, 179, 165, 152
		5–39	210	210, 195, 179, 167, 165, 152
		11–35	214	216, 214, 179, 152
		45	223	223, 207, 178
		73	222	222, 207, 192, 179, 165
		22	282	282, 265, 203, 191, 178
		13–72	206	206, 191, 178, 165

the reaction but as a part of educating students to think about all potential aspects of green chemistry before deciding which ones can be applied to a particular situation. A complete green analysis of a reaction models for students how to analyze other reactions they will encounter in the future.

■ EXPERIMENTAL OVERVIEW

Each pair of students in lab chose one of eight aldehydes (see Table 1). Benzyltriphenylphosphonium chloride is added to the aldehyde with stirring. Sodium hydroxide (10 N) is added to the mixture and the reaction is stirred at room temperature for 30 min. The reaction mixture is filtered and washed with water until the filtrate is no longer basic. The solid is recrystallized from a minimum of boiling 95% ethanol, cooled in an ice bath, and vacuum filtered to yield the crystalline product. The product was analyzed by thin-layer chromatography (TLC), GC−MS, ^{1}H NMR, and IR spectrometry. Experimental details are in the Supporting Information.

■ HAZARDS

Eye protection and protective gloves should be worn during this experiment. All work should be done in a fume hood, and no open flames should be used in the lab. All starting aldehydes and products are considered eye and skin irritants and should not be ingested. Benzaldehyde is a respiratory and skin sensitizer. *p*-Tolualdehyde is combustible. Benzyltriphenylphosphonium chloride is highly toxic by ingestion. Heptane is highly flammable and may be fatal if swallowed or if it enters airways. Deuterochloroform causes irritation of the skin and respiratory system, may cause chemical burns, and is a possible carcinogen. Ethanol and ethyl acetate are highly flammable and toxic by ingestion. Sodium hydroxide (10 N) is extremely damaging to the eyes and skin.

■ REPRESENTATIVE RESULTS

The modified reaction has proven effective for a variety of aromatic aldehyde reactants. Student yields after recrystallization varied from 22% to 72% depending on the aldehyde chosen. The crude yield of alkenes was significantly higher (before recrystallization) for most products as there is a mixture of *E* and *Z* isomers that form (Figure 1). This was clearly seen if the crude products were analyzed by TLC or GCMS. Typical products had an R_f of around 0.3; it is possible to detect two product spots since there is an R_f difference of about 0.1.

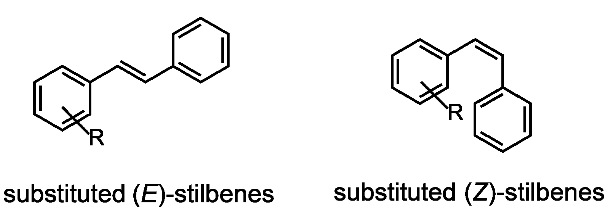


Figure 1. Example of *E* and *Z* isomers that form.

Because the reaction took only 30 min to carry out, it was possible for students to perform the reaction, isolate their product, and prepare a sample for analysis in one 3-hour class period. This experiment can be used to enhance students' ability to interpret IR, NMR, TLC, and/or GC−MS. With IR, the loss of the aldehyde carbonyl peak at ∼1696 cm^{-1} was confirmatory evidence for reaction. There will be several additional peaks in the IR due to the second phenyl group and the newly formed alkene; therefore, it is not trivial for students to assign the alkene peak formed via the Wittig reaction.

With ^{1}H NMR, the loss of the aldehyde peak that appears between 9.68 and 10.55 ppm clearly showed loss of the reactant. In addition, the presence of the alkene peaks and the additional aromatic peaks from the new phenyl group confirmed product formation.

Using GC−MS, the presence of the anticipated molecular ion and lack of aldehyde starting material showed not only the success of the reaction but also the purity of the product after recrystallization. Yields and GC−MS data in Table 1 show that the expected products were formed. It was also instructive to have students submit a crude sample of their solid before recrystallization for GC−MS analysis. This allowed students to quantify the mix of *E* and *Z* isomers in the crude product mixture. (The *Z* peak elutes earlier than the *E* by about 2 min, as one would expect, due to greater van der Waals forces in the *E* isomers.) The *E*:*Z* ratio varied as the reaction was repeated by various groups of students. For example, with *p*-tolualdehyde as reactant, the ratio varied from 65:34 to 36:64 in the crude product. Following recrystallization, the product was mostly pure *E* isomer with typical results of 99.3:0.7 ratio.

The scope of analysis will dictate whether samples can be analyzed during the same lab period or if a second lab period is required for the desired instrumental procedures. There are several advantages to this reaction for instructors with differing levels of available instrumentation or different pedagogical desires.

■ DISCUSSION

The modified reaction proved to be useful for teaching green chemistry principles while being quite broad in scope of analysis. The products were readily identifiable from the reactants by several common techniques. The loss of an aldehyde proton in the ^{1}H NMR spectrum and loss of a carbonyl stretch in IR was indicative of reactant conversion, and the appearance of the molecular ion in GC−MS (as well as identifiable fragments) were also indicative of product formation. This experiment can be used in conjunction with several types of instrumental techniques as desired to give students more experience in structural analysis or to be used as a summary project that includes all of the analyses.

■ CONCLUSIONS

A green Wittig reaction was successfully designed that works with a variety of aromatic aldehydes in aqueous solution at room temperature in less than one hour. The products were simple to isolate and were purified by recrystallization from ethanol. Students, after engaging in this case study, were able to explain incorporation of green modifications to an experiment while generating products that required them to use spectral interpretation skills for structural identification.

■ ASSOCIATED CONTENT

Supporting Information

Detailed instructions for the students; instructor notes, including detailed spectral analyses. This material is available via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*L. A. Morsch. E-mail: lmorsc1@uis.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank the University of Illinois Springfield Natural Science Division for funding and support of this work. We would also like to thank the students from Organic Chemistry 2 laboratories at the University of Illinois Springfield from 2011–2013 for testing this experiment as a course project.

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