

Water Mediated Wittig Reactions of Aldehydes in the Teaching Laboratory: Using Sodium Bicarbonate for the *in Situ* Formation of Stabilized Ylides

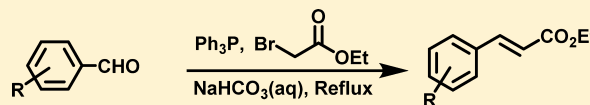
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S Supporting Information

ABSTRACT: The synthesis of alkenes using the Wittig reaction is a traditional part of many undergraduate organic chemistry teaching laboratory curricula. The aqueous medium version of the Wittig reaction presented is a reliable adaptation of this alkene formation reaction as a very safe alternative in the introductory organic chemistry laboratory. The specific aqueous Wittig reactions discussed use a *one-pot* reagent setup and *greener* methods that the students can complete within 30 min with partial workup in one laboratory period. The aqueous Wittig reactions presented have been implemented to various aldehydes and take advantage of dilute sodium bicarbonate (“baking soda”) as the only base needed for in the *in situ* formation of stabilized ylides. Outcomes from the implementation of the proposed aqueous Wittig procedure into the organic chemistry teaching laboratory curriculum are presented. Described also are reaction workup, purification, and analysis of products using ^1H NMR and IR spectroscopy.

KEYWORDS: Second-Year Undergraduate, Aqueous Solution Chemistry, Organic Chemistry, Alkenes, Synthesis, Water/Water Chemistry, Green Chemistry, Hands-On Learning/Manipulatives, Laboratory Instruction



Ever since the first report of alkene synthesis from aldehydes in the 1950s by Wittig,¹ the reaction has remained a powerful tool in the organic chemistry community for the construction of unsaturated carbon–carbon bonds. Since then the Wittig reaction has become one of the most commonly used instruments in synthetic organic chemistry to generate excess of either the *E*- or *Z*-geometrical isomers of alkenes, and even though the reaction has been known for over six decades, it is still under intense mechanistic investigation.² Conventional reaction conditions for the selective formation of *E*-alkenes use stabilized ylides and aldehydes, most of the time paired with organic solvents like toluene, DMF, or DMSO.

As a consequence of its wide use, the Wittig methodology has been included in the organic chemistry curriculum for quite some time,³ but unfortunately the Wittig protocol has historically involved dangerous reagents and relatively complicated procedures less suitable for a teaching laboratory. However, with modern laboratory techniques, the chemistry can be made much easier and safer, while still demonstrating to students the important concepts of the reaction, especially the formation of the ylide and its characteristic reaction with aldehydes to form unsaturated carbon–carbon bonds.^{3k,4}

In the early 1980s, Breslow⁵ and Grieco⁶ disclosed that the interaction of hydrophobic moieties in aqueous media can have a tremendous effect on the rate of organic reactions. However, it was not until relatively recently that the prospect of water as a medium for organic reactions gained widespread attention,⁷ and significant advances have been made in achieving organic reactions in water by utilizing this favorable hydrophobic interaction of the reactants.⁸ Such a “hydrophobic effect”⁹ fits well with the concepts learned early in the chemistry

curriculum, and is especially well-designed for the organic chemistry laboratory where chemistry experiments commonly are conducted using conventional organic solvents.

In order to increase yield or selectivity in the Wittig reaction, many modified condition alternatives have been reported, such as increasing temperature¹⁰ or pressure,¹¹ using additives,¹² sonication,¹³ silica gel,¹⁴ ionic solvents,¹⁵ irradiation with microwaves¹⁶ or light,¹⁷ and quite recently neat water.^{4a,b} Some reports describing the influence of aqueous LiCl¹⁸ and surfactant¹⁹ on the Wittig reaction have also emerged. Advances also include the *in situ* formation of the phosphorus ylide in solid state reactions employing the corresponding phosphonium salt with anhydrous K₂CO₃, and then subsequent Wittig reaction in a solvent-free setting.²⁰

The experiment disclosed is intended to expose students to alkene synthesis via the aqueous Wittig reaction conducted under very mild basic aqueous conditions, and in this way teach a novel version of an important class of reactions in organic chemistry experimentally. Instrumental analysis and group discussions are then integrated for assessment of the laboratory experience. Since water is inexpensive and extremely easy to handle and represents few environmental concerns, the illustrated laboratory experiment should help students see water as a possible medium for organic reactions, and its potential for wider adoption.

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THE AQUEOUS WITTIG REACTION

Water has previously been used as a solvent for Wittig reactions utilizing modified water-soluble phosphonium salts,²¹ but the application of water as a crucial medium for conducting Wittig reactions employing poorly water-soluble stabilized ylides is limited. In this paper we present suitable solutions from our original report^{4b} on aqueous promoted Wittig reactions fitting for a second semester organic chemistry laboratory experiment. Apart from the application of the illustrated student experiments to *greener chemistry*,²² these proposed reactions contribute a valuable methodology for carbon-carbon double bond creation in water in synthetic organic chemistry.

The *in situ* formation of ylides during the Wittig reaction employing water as a medium and sodium bicarbonate as a base along with triphenylphosphine and α -bromo esters recently has been a particularly fruitful area of study. We have had seven of these aqueous Wittig reactions tailor-made and adopted in the organic teaching laboratories for over two years, during which they have been tested by a total of roughly 500 students during a three week laboratory period. The first week incorporates the examination of the importance of water as a medium in various types of organic reactions, the reaction setup and execution, and the partial workup of the Wittig product. The second week includes purification and isolation of the Wittig product using silica gel column chromatography or recrystallization and the use of a rotary evaporator. The third week is used for analysis with a discussion around the product structure and completion of ¹H NMR and IR spectroscopy.²³

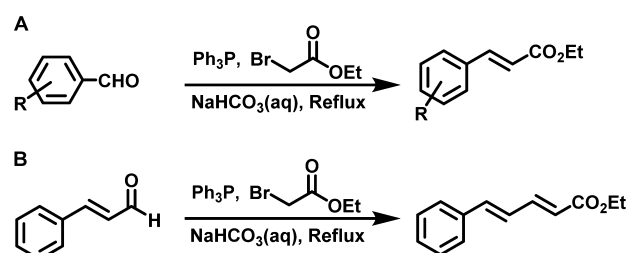
THE LABORATORY EXPERIMENTS

The aqueous Wittig reactions presented herein demonstrate optimized examples of laboratory experiments that can be adopted in second semester organic chemistry laboratory course. The aqueous Wittig reactions exemplified are simple, safe, and an example of a *greener one-pot* setup that the students can complete within 30 min with partial workup in one laboratory period. They take advantage of dilute sodium bicarbonate as the only base needed for in the *in situ* formation of stabilized ylides required for alkene formation.

Examples of the reaction are found in general organic chemistry textbooks²⁴ and in numerous published synthetic procedures,¹⁻²² and, therefore, the reaction is often covered specifically in introductory organic chemistry classes and their corresponding laboratories. Many of the literature procedures reported for conducting a Wittig reaction use problematic or hazardous reagents which make them unsuitable in an organic chemistry teaching laboratory. To circumvent such problems *greener* alternatives to the traditional Wittig reaction have been reported^{3k} using semistabilized ylide substrates and the use of sodium bicarbonate as a base.^{4b} Greener chemistry is an increasingly important lesson for young scientists for the critical analysis and simplification of laboratory procedures. The Wittig reactions described herein are summarized in Scheme 1.

While several stabilized ylides are commercially available, many can easily be prepared in the teaching laboratory *in situ* during the Wittig reaction using the less expensive reagents triphenylphosphine, ethyl bromoacetate, and sodium bicarbonate. Implementing a more contemporary aqueous Wittig reaction in the organic chemistry teaching laboratory creates a constructive experience and provides an opportunity for group discussions for the students when comparing the reaction to the classic Wittig reaction developed many years ago. An

Scheme 1. Aqueous Wittig Reactions with Ethyl Bromoacetate and Triphenylphosphine to Substituted Benzaldehydes (A) and Cinnamaldehyde (B)



organic solvent is not used in the aqueous Wittig reaction itself but is required in the workup procedure and during the purification step using either a semi-microscale silica gel column chromatography technique or recrystallization. The students will also learn how to use a rotary evaporator in order to quickly remove solvent from their product. The learning experience is also enhanced by the characterization of the Wittig products using ¹H NMR and IR spectroscopy.

The aqueous medium is mild, inexpensive, and especially safe for conducting the Wittig reaction in the teaching laboratory. The laboratory experiment can be completed in two lab periods (generally, one lab period for the reaction and one lab period for the purification), and a third week can be used for analysis with a discussion around the product structure and completion of ¹H NMR and IR spectroscopy.

EXPERIMENTAL OVERVIEW

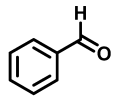
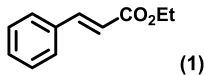
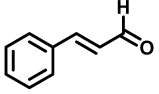
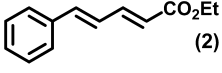
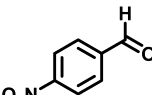
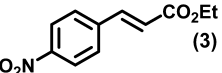
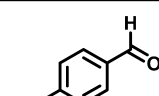
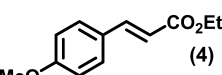
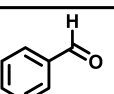
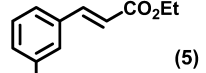
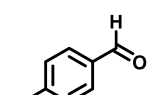
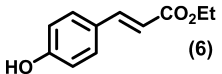
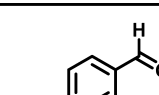
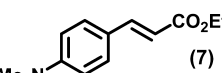
The students work individually and can choose or be assigned any of the seven suggested aldehydes (see Table 1). Alternatively the aldehydes can be provided as “unknowns” for students and they can determine the structure of their original aldehyde from the ¹H NMR spectra obtained of their product after conducting the Wittig reaction.

The aldehydes used in the experiment are benzaldehyde, cinnamaldehyde, *p*-nitrobenzaldehyde, *p*-methoxybenzaldehyde, *m*-benzyloxybenzaldehyde, *p*-hydroxybenzaldehyde, and *p*-dimethylaminobenzaldehyde. Each student mixes the appropriate aldehyde (1 equiv), triphenylphosphine (1.5 equiv), ethyl bromoacetate (2 equiv), and saturated sodium bicarbonate (20 mL) in a 100 mL single-neck round-bottom flask fitted with a reflux condenser. The heterogeneous solution is refluxed with rapid stirring for 30 min. After cooling, the solution is extracted with 4–5 portions of ethyl acetate (total solvent volume: 20–30 mL). The organic solvent is evaporated to give a mixture of the product and triphenylphosphine oxide byproduct. The product is either a white to yellow solid or oil that is purified by a simple recrystallization or by silica gel chromatography. The product is characterized by IR and ¹H NMR spectroscopy and by melting point if the product is crystalline. Detailed instructions can be found in the Supporting Information.

HAZARDS

Ethyl bromoacetate is a potent lachrymator and should be used with caution in a ventilated hood. Each of the aldehydes and triphenylphosphine are irritants and should be used with caution. Do not inhale silica dust; use with caution in a well-ventilated hood. Both the olefin products and 10% aqueous sodium bisulfite are harmful if swallowed. The products are considered skin and eye irritants and should not be swallowed.

Table 1. Summary of Product Yields and NMR Data

Aldehyde	Product ^{a,b} (1-7)	Yield Range ^c , %	¹ H NMR ^d , CDCl ₃
	 liquid (1)	60 - 93	7.68 (d, <i>J</i> = 16.0 Hz, 1H), 7.52-7.46 (m, 2H), 7.37-7.33 (m, 3H), 6.43 (d, <i>J</i> = 16.0 Hz, 1H), 4.25 (q, <i>J</i> = 7.1 Hz, 2H), 1.32 (t, <i>J</i> = 7.1 Hz, 3H)
	 mp 25-26 °C (2)	60 - 88	7.55-7.25 (m, 6H), 6.92-6.80 (m, 2H), 5.99 (d, <i>J</i> = 15.3 Hz, 1H), 4.23 (q, <i>J</i> = 7.1 Hz, 2H), 1.31 (t, <i>J</i> = 7.1 Hz, 3H)
	 mp 136-137 °C (3)	40 - 94 ^e	8.25 (m, 2H), 7.70 (d, <i>J</i> = 15.4 Hz, 1H), 7.66 (m, 2H), 6.55 (d, <i>J</i> = 15.4 Hz, 1H), 4.30 (q, <i>J</i> = 7.1 Hz, 2H), 1.35 (t, <i>J</i> = 7.1 Hz, 3H)
	 mp 48-51 °C (4)	50 - 94	7.62 (d, <i>J</i> = 16.0 Hz, 1H), 7.44 (m, 2H), 6.88 (m, 2H), 6.29 (d, <i>J</i> = 16.0 Hz, 1H), 4.18 (q, <i>J</i> = 7.1 Hz, 2H), 3.80 (s, CH ₃ CO, 3H), 1.29 (t, <i>J</i> = 7.1 Hz, 3H)
	 mp 39-40 °C (5)	60 - 90	7.64 (d, <i>J</i> = 16.0 Hz, 1H), 7.45-7.25 (m, 6H), 7.15-7.11 (m, 2H), 7.00 (m, 1H), 6.40 (d, <i>J</i> = 16.0 Hz, 1H), 5.09 (s, 2H), 4.25 (q, <i>J</i> = 7.0 Hz, 2H), 1.37 (t, <i>J</i> = 7.0 Hz, 3H)
	 mp 73-74 °C (6)	44 - 64	7.64 (d, <i>J</i> = 16.0 Hz, 1H), 7.42 (m, 2H), 6.86 (m, 2H), 6.29 (d, <i>J</i> = 16.0 Hz, 1H), 6.25 (bs, 1H), 4.26 (q, <i>J</i> = 7.0 Hz, 2H), 1.34 (t, <i>J</i> = 7.0 Hz, 3H)
	 mp 74-76 °C (7)	36 - 64	7.62 (d, <i>J</i> = 16.0 Hz, 1H), 7.42 (m, 2H), 6.66 (m, 2H), 6.22 (d, <i>J</i> = 16.0 Hz, 1H), 4.24 (q, <i>J</i> = 7.0 Hz, 2H), 3.02 (s, 6H), 1.32 (t, <i>J</i> = 7.0 Hz, 3H)

^aMajor *E*-isomer. ^bLiterature mp for the pure *E*-isomer. ^cYield range of major *E*-isomer after column chromatography purification. ^d400 MHz NMR data of major *E*-isomer. ^eHighest yield was obtained from simple recrystallization from 95% ethanol.

Ethyl acetate is an eye irritant and is highly flammable. Hexanes are highly flammable and a neurotoxin. Deuterated chloroform is an irritant, is harmful if swallowed, and is a suspected carcinogen. Consult safety data sheets for all reagents prior to conducting the laboratory experiment.

RESULTS AND DISCUSSION

The aqueous Wittig laboratory experiment has been completed during five consecutive semesters by roughly 500 second year undergraduate students enrolled in a second semester organic chemistry course. A typical student product yield was 36% to 80% depending on the aldehyde the student used. In general, the product yield is quite high, but it is dependent on how well the student accomplishes the recrystallization and the column chromatography. Typically, students obtained a solid Wittig product after purification (except for products 1 and 2) and the melting point was determined as a way to check for relative purity and compare it to the reported literature melting point (see Table 1). It is expected that a decrease in melting point will occur as a consequence of a low *E/Z* ratio. For instance, Wittig product 2 never solidified even though the pure *E,E*-isomer has been reported as a low melting point solid. The corresponding *E*-isomer is the major constitutional isomer relative to the minor *Z*-isomer (Figure 1).

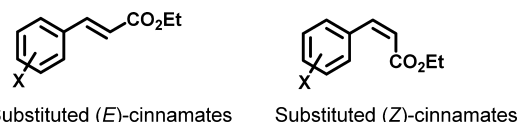


Figure 1. Illustration of *E* and *Z* isomers that form.

Even though the ratio of the *E*- and *Z*-isomers is clearly visible in the ¹H NMR spectrum, the students need to have a firm knowledge of NMR spectroscopy in order to interpret the data fully, for example by identifying the coupling constants for the *E*- and the *Z*-isomers. However, the students can still accomplish a simple analysis of their Wittig products with less ¹H NMR comprehension, for instance by the identification the alkene protons in the ¹H NMR spectrum and the determination of the *E/Z* ratio.

The students' NMR spectra were obtained by the students themselves using our 80 MHz picoSpin NMR spectrometer located on the benchtop in the laboratory. Even with this relatively low field strength instrument, sufficient spectroscopic information can be obtained in order to characterize the Wittig products. At 80 MHz it is possible to determine the coupling constant for the alkene protons. The product composition was also analyzed by 400 MHz ¹H NMR spectroscopy (see Supporting Information). In this case, the students did not

collect the NMR data themselves but instead an autosampler with the Varian 400 MHz NMR spectrometer was used, which allowed for 20 students' NMR samples to be collected overnight. Although an error analysis of the spectroscopic data can be done, it was not introduced as a requirement in the laboratory course. If the students are able to obtain a low resolution NMR (80 MHz), they will be able to compare these data with the 400 MHz spectra found in the [Supporting Information](#) and thereby analyze the difference between high and low field resolution. The students analyzed the NMR spectra and measured the *E/Z* ratio by comparing the integration of the olefin peaks for each isomer of the Wittig products, and relating the different coupling constants of alkene protons. The *E*-isomer was the major product at a ratio greater than 5:1, though the exact ratio varies by aldehyde. The loss of the aldehyde signal in the ^1H NMR spectrum (usually found at 9.5–10.5 ppm) is one indication of the consumption of the starting material. Students can compare their product NMR spectra with the spectra of the starting material (see [Supporting Information](#)). Remaining triphenylphosphine is the only major contaminant in the product after column chromatography, but made up <1% of the product. It is expected that the triphenylphosphine contamination will affect a slight decrease in melting point of the Wittig product. The student yield ranges and NMR data for the *E*-isomer of each product are summarized in [Table 1](#).

The students also used the IR spectrometer as a tool to confirm the chemical structure of the products, with the shift of the carbonyl peak from the aldehyde range to the ester range, the appearance of the ester C–O stretches, and the appearance of alkene and phenyl groups (see [Supporting Information](#)).

The reaction takes roughly 30 min to conduct, but the majority of the time in lab was spent on reaction setup, workup, and the purification followed by the evaporation of the solvent. Thus, it is recommended to conduct at least the spectroscopic analysis during a different 3 h laboratory session. The students will then have additional time available to analyze and compare their individual spectra with the ^1H NMR and IR spectra ([Supporting Information](#)). The scope of analysis is dependent on time available in the laboratory session and the instrumentation accessible. There are several benefits to the proposed instructional water based Wittig reaction with various levels of instrumentation or various academic goals.

CONCLUSION

A mild aqueous sodium bicarbonate based Wittig reaction that works with different aldehydes has been created as a suitable experiment for a second semester organic chemistry laboratory. The simple procedures included allow for simple reaction setup, purification, and characterization of products using ^1H NMR and IR spectroscopy. The large number of students who participated in this study were exposed to a number of laboratory and spectroscopic techniques required for analysis of their products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: [10.1021/acs.jchemed.6b00206](https://doi.org/10.1021/acs.jchemed.6b00206).

Laboratory materials ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using *m*-benzyloxybenzaldehyde ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using *p*-(dimethylamino)-benzaldehyde ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using *p*-anisaldehyde ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using *p*-nitrobenzaldehyde ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using cinnamaldehyde ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using benzaldehyde ([PDF](#), [DOCX](#))

Student instructions, instructor notes, and IR and ^1H NMR spectra for reaction using *p*-hydroxybenzaldehyde ([PDF](#), [DOCX](#))

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Notes

The authors declare no competing financial interest.

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