

Wittig Reactions In An Aqueous Medium Using Aromatic Aldehydes And Benzyl Triphenylphosphonium Chloride

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Abstract

Wittig reactions typically involve the use of standardized organic solvents that are expensive, hazardous to human health, and harmful to the environment. Whether or not a green alternative exists is still up for debate; however, recent reports suggest that many organic reactions (including Wittig) may generate similar or better yields if performed through a more sustainable solvent such as water. To test this theory, undergraduate chemistry students at Franklin College developed an experimental procedure to obtain comparable yields of stilbenes (alkene products) with reasonable purity from a Wittig reaction conducted in an aqueous medium. A mixture of an aromatic aldehyde and benzyltriphenyl phosphonium chloride was placed in a 10% sodium hydroxide solution and refluxed for two hours, resulting in a 30% yield. Microwave heating was then applied to increase this value to 40%, an amount equivalent to percent yields acquired when the reaction proceeds in traditional organic media. Spectroscopic methods were subsequently used to verify and characterize the purity of the resulting three stilbenes: *trans*-4-methylstilbene, *trans*-4-methoxystilbene, and *trans*-4-bromostilbene. In order to gauge effectiveness, two separate methods were evaluated on their ability to form the desired stilbene.

Keywords: Wittig Reaction, Stilbene, Aqueous Medium

1. Background

Wittig reactions play a pivotal role in the field of organic chemistry as an ideal mechanism for the synthesis of alkenes. Discovered in 1954 by German chemist Dr. Georg Wittig (who received the Nobel Prize in Chemistry in 1979 for his work), these reactions typically require the presence of organic or halogenated solvents such as tetrahydrofuran, dimethylsulfoxide and dichloromethane. Despite the detrimental health and environmental effects of these substances, little research has been done to determine the effectiveness of performing Wittig reactions in a more sustainable (“green”) aqueous-based medium. Substituting water in place of organic solvents serves as a safer, more cost-effective method for obtaining the desired stilbene product, thereby eliminating the need for other potentially damaging alternatives.

However, only a handful of studies^{1,2,3} have been conducted to investigate the formation of various compounds via the Wittig reaction using green solvents. Most recently, *Bergdahl et. al* have developed an efficient method for the synthesis of compounds known as α,β -unsaturated esters using the Wittig reaction² that generated products which were subsequently isolated in moderate to good yields. Undergraduate students in the project-oriented organic chemistry laboratory course at Franklin College have done exploratory work on Wittig reactions in altered environments by either carrying out the experiments in an aqueous medium and heating products in a Thermowell heating mantle or microwave oven.^{4,5}

This study compares the yields obtained from Wittig reactions conducted in aqueous medium using microwave radiation with those of heating it in Thermowell heating mantle. For a “green” Wittig reaction to occur, a phosphorus ylide was generated in situ by deprotonation of benzyl triphenylphosphonium chloride in presence of

sodium hydroxide. During the first step of this reaction, the nucleophilic carbon of the phosphorus ylide attaches to the electrophilic carbon of the carbonyl group of an aldehyde. The electrons from the carbon-oxygen pi bond then form a sigma bond with the positively charged phosphorous atom, generating a cyclic intermediate known as an oxaphosphetane. The second step of the reaction involves cleavage of the carbon-phosphorus and carbon-oxygen bonds, leading to the formation of the carbon-carbon and phosphorus-oxygen double bonds present in the stilbene product and the accompanying triphenylphosphine oxide, respectively. The reaction scheme is illustrated in Figure 1.

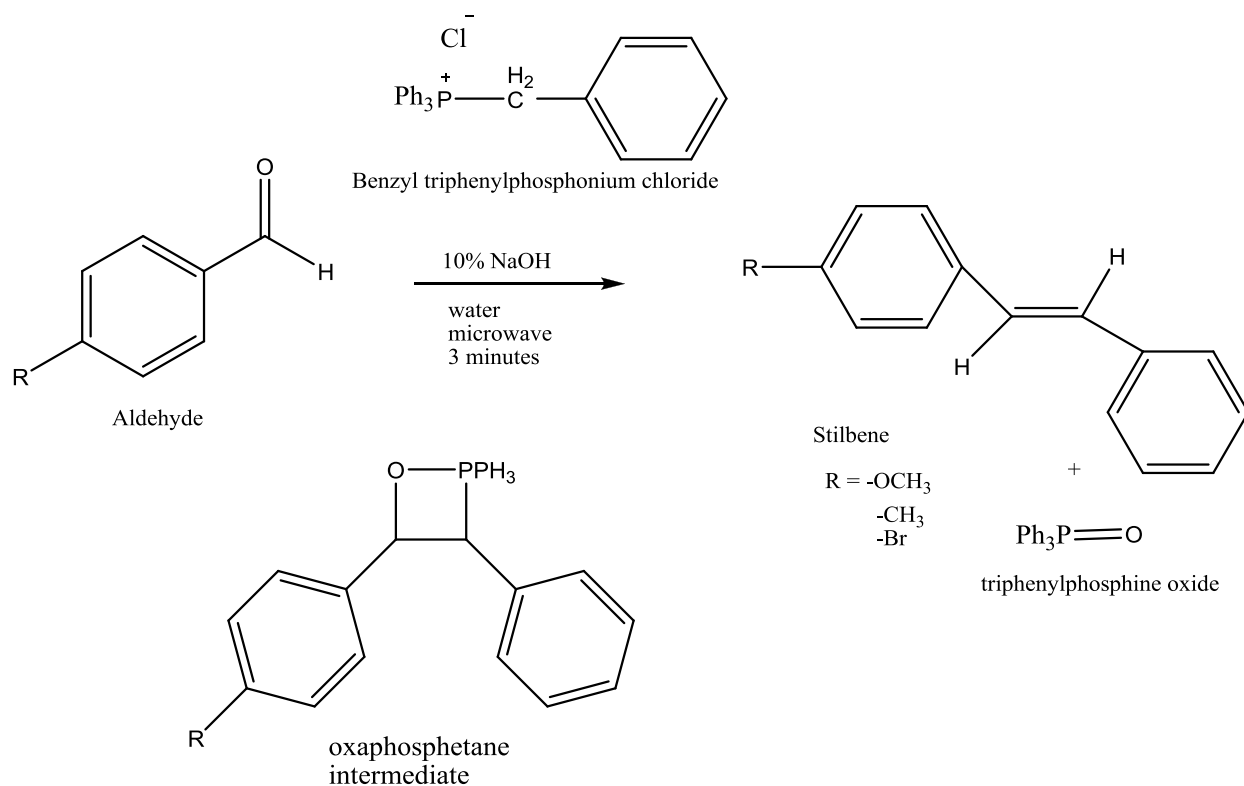


Figure 1: Reaction scheme

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2. Methodology

Several techniques were incorporated into this experiment in order to increase percent yield. First, Wittig reactions were carried out by heating in aqueous mediums using variable times (30 minutes - two hours). Merrifield resin⁷ was used to remove the triphenylphosphine oxide byproduct, in an attempt to improve overall purity. A second approach involved microwave heating of the reaction mixture for three minutes to gauge effect on product yields.

The NMR spectra were taken on 60 MHz Anasazi Instrument. The FT-IR spectra were taken on Nicolet iS10 and the mass spectra were taken on HP 5890 Series II with Mass detector 5972.

2.1. Wittig reaction in an aqueous medium using Thermowell Heating Mantle

A mixture of 0.490 g (4.078 mmole) of p-tolualdehyde and 2.146 g (5.518 mmole) of benzyl triphenylphosphonium chloride was added to a 2.5 mL of 10% NaOH and 2.5 mL of water in a centrifuge tube and refluxed for 2 hours on Thermowell heating mantle. After cooling the solution for 10 minutes, a mixture of trans-4-methylstilbene product and triphenylphosphine oxide byproduct was collected via vacuum filtration. This mixture was transferred to a test

tube, and combined with 2 mL of methanol to dissolve the nonessential triphenylphosphine oxide. The resultant solution was again cooled and product was collected via vacuum filtration, followed by rinse on the Hirsh funnel with 2 mL of ice-cold methanol. The isolated *trans*-4-methylstilbene was dried over phosphorus pentoxide for 48 hours to give 235 mg (29.7% yield) of white crystalline product, mp 110°C-116°C, lit mp 118-122°C.⁸

A mixture of 0.508 g (3.721 mmole) of p-anisaldehyde and 2.144 g (5.513 mmole) of benzyltriphenyl phosphonium chloride in 5.4 mL of 5% NaOH in a centrifuge tube was refluxed for 2 hours. The same procedure as described above was used to isolate *trans*-4-methoxystilbene, generating 236 mg (30.2 % yield) of white crystalline product, mp 131-133, lit mp: 136-138 °C.⁹

2.2. Microwave Method

2.2.1. preparation of *trans*-4-methyl stilbene

A mixture of 0.515 g (4.286 mmole) of p-tolualdehyde and 2.433 g (6.256 mmole) of benzyl triphenylphosphonium chloride was added to a 2.5 mL of 10% NaOH and 2.5 mL of water. The solution was then placed in centrifuge tube set in a beaker containing some ice. Following this process, the reaction mixture was heated for three minutes in a kitchen microwave using 2 - 3 seconds pulses and subsequently cooled in an ice bath and collected by vacuum filtration. The resulting grayish-white crystals were washed with two portions of 1 mL of methanol in order to remove triphenylphosphine oxide. This purified sample was again collected via vacuum filtration, and rinsed on the Hirsh funnel with 1 mL of ice-cold methanol. Product purity was affirmed using spectroscopic methods. The isolated *trans*-4-methylstilbene was dried over phosphorus pentoxide for 48 hours to give 307 mg, 36.9% yield, of white crystalline product, mp 108°C-110°C, lit mp 118- 122°C.⁸

2.2.2. preparation of *trans*-4-methoxystilbene

A mixture of 0.501 g (4.67 mmole) of p-anisaldehyde, 2.142 g (5.505 mmole) of benzyltriphenyl phosphonium chloride in 2.5 mL of 10% NaOH, and 2.5 mL of water was taken in the centrifuge tube. A similar approach as described above was used for heating the reaction mixture. The solution was then placed in a sand bath for 10 minutes until it started to boil, followed by immediate cooling in an ice-bath and filtration. The crude product was mixed with 2 mL of ice-cold methanol to dissolve the byproduct, and the purified sample collected via vacuum filtration to produce shiny, plate-like crystals. The isolated *trans*-4-methoxystilbene was dried in a vacuum over phosphorus pentoxide, and generated 276 mg (39 % yields) of white crystalline product, mp 130-133, lit mp: 135-138 °C.⁹

2.2.3. preparation of *trans*-4-bromostilbene

A mixture of 0.508 g (2.75 mmole) of p-bromostilbene, 1.582 g (4.068 mmole) of benzyl triphenyl phosphonium chloride in 2.5 mL of 10% NaOH, and 2.5 mL of water in a centrifuge tube was heated in a microwave oven for three minutes using 2-3 seconds pulses. The same procedure was applied to purify and isolate *trans*-4-bromostilbene as was in the case 4-methoxystilbene. This reaction produced 276 mg (39 % yields) of white crystalline product, mp 135-137, lit mp 138-142°C.¹⁰

3. Results

The first experiment carried out using p-anisaldehyde resulted in only a 10% yield of *trans*-4-methoxystilbene after the reaction mixture had been heated for a period of 30 minutes. *para*-tolylaldehyde was then used to generate *trans*-4-methylstilbene by heating for 30 minutes, also producing low yields. In attempts to obtain more products, the heating period was extended to two hours, increasing percent yield for this reaction. The same course of action and outcomes were applied to the *trans*-4-methoxystilbene as well. However, additional heating only prompted average yields of 22-30 percent. This amount is still markedly less than when the same reaction is conducted using organic solvents.

To address this issue, the original heating process was carried out using kitchen microwave, which gave the best results for the formation of *trans*-4-methylstilbene, *trans*-4-methoxystilbene, and *trans*-4-bromostilbene. All were synthesized in 37- 40% yield. The reactions were carried out in water and the isolated products were deemed pure based off of the spectral analyses gathered in all experiments. The spectra of these compounds are discussed in 3.1 and 3.2. It should be noted that during the first experiment using the microwave, some of the mixture boiled over. This problem was avoided in subsequent trials by adding ice to beaker containing the centrifuge tube to absorb excess heat and allow the procedure to proceed appropriately.

While initially Merrifield resin was intended to remove the byproduct triphenylphosphine oxide, the use of this resin did not improve percent yield and frustrated attempts to isolate a pure stilbene product. The reaction mixture was turned brownish due to the formation of iodine from sodium iodide and the filtration procedure took much longer. As such, the use of Merrifield resin was discontinued, and replaced with washing the crude product with methanol.

3.1. Spectral analysis of *trans*-4-methoxystilbene

In Figure 2 ^1H NMR spectrum for *trans*-4-methoxystilbene, aromatic and vinylic hydrogens are present in the region of 6.81-7.52 ppm, and a methoxy hydrogen peak can be observed at 3.79 ppm. In Figure 2B, ^{13}C -NMR of *trans*-4-methoxystilbene, vinylic and aromatic carbons are present in the region of 114.0-137 ppm, the aromatic carbon attached to methoxy group was observed downfield at 159 ppm and methoxy carbon signal was at 55.2 ppm.

In Figure 3, the IR spectrum of *trans*-4-methoxystilbene show similar absorptions as were listed in the spectral database.¹¹ In Figure 4, the mass spectrum of *trans*-4-methoxystilbene, the molecular ion, M^+ peak was observed at m/z 210, which correlates to the molecular weight of *trans*-4-methoxystilbene. Another major peak at 195 m/z was due to the loss of $-\text{CH}_3$ group, while a peak at 179 m/z showed loss of $-\text{OCH}_3$ group. This mass spectrum is identical to the one reported in the spectral database.¹¹

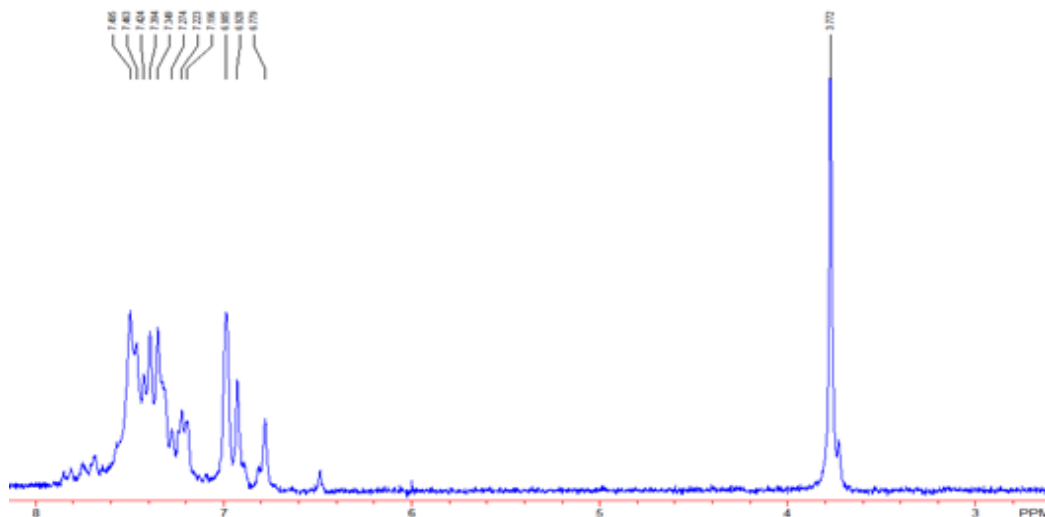


Figure 2: ^1H NMR spectrum of *trans*-4-methoxystilbene in CDCl_3

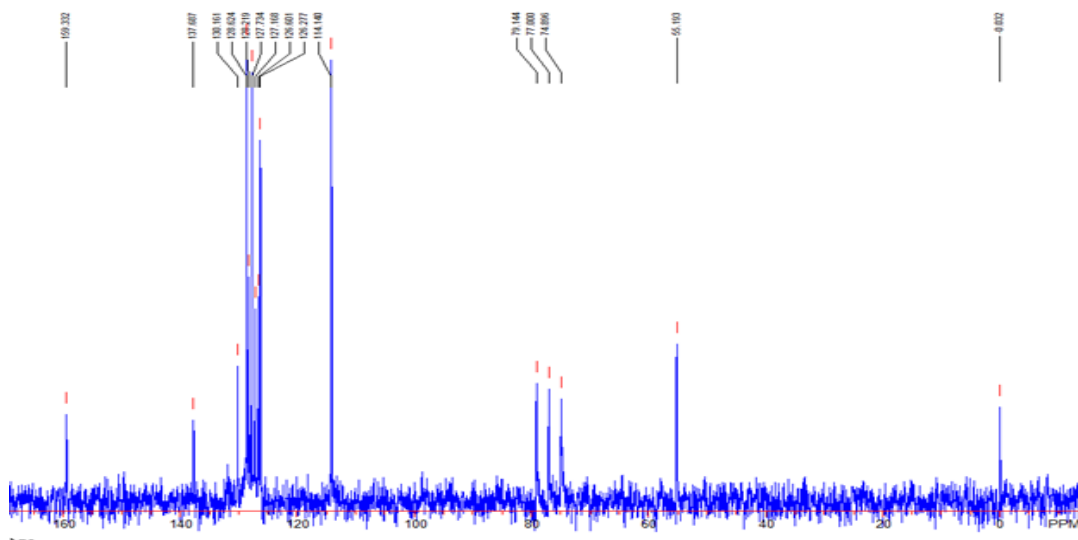


Figure 2B: ^{13}C spectrum of *trans* 4-methoxystilbene

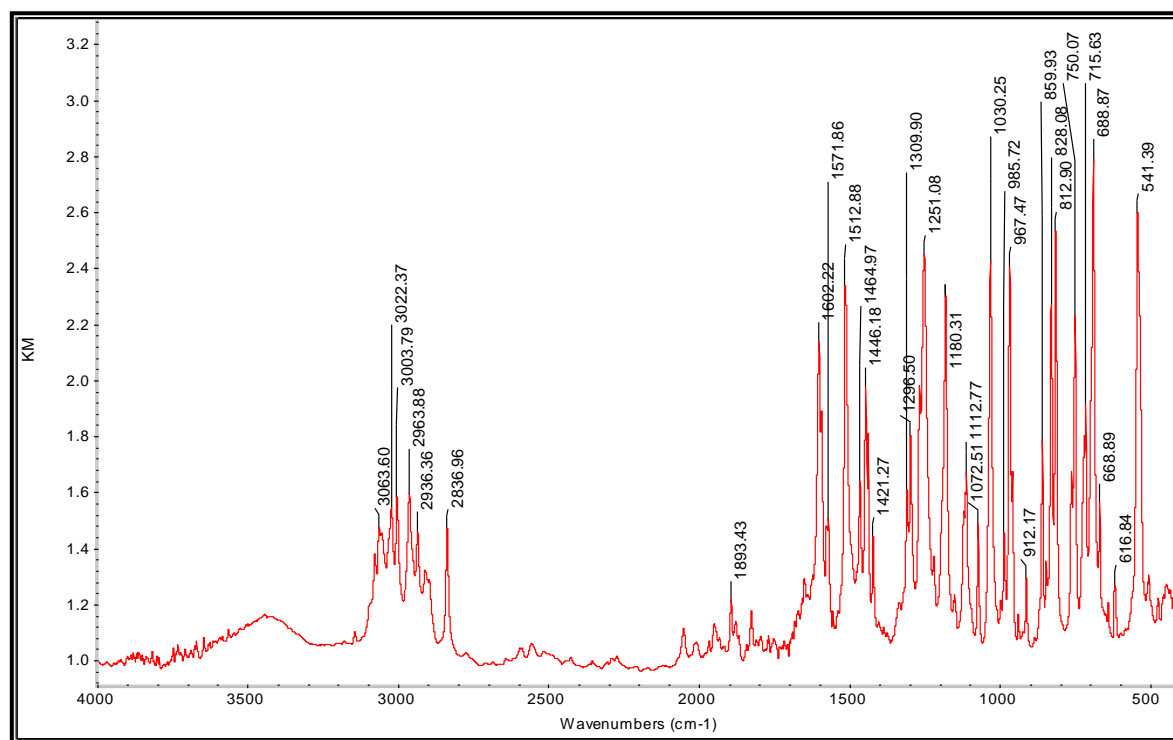


Figure 3: Infrared spectrum of *trans*-4-methoxystilbene

File : C:\HPCHEM\1\DATA\032812\ESTER3.D
 Operator : Nazir, 2012 March 28
 Acquired : 28 Mar 2012 5:42 pm using AcqMethod ESTER
 Instrument : 5972
 Sample Name: Methoxystilbene 2012 Mar 28
 Misc Info : Methoxystilbene 2012 March 28
 Vial Number: 3

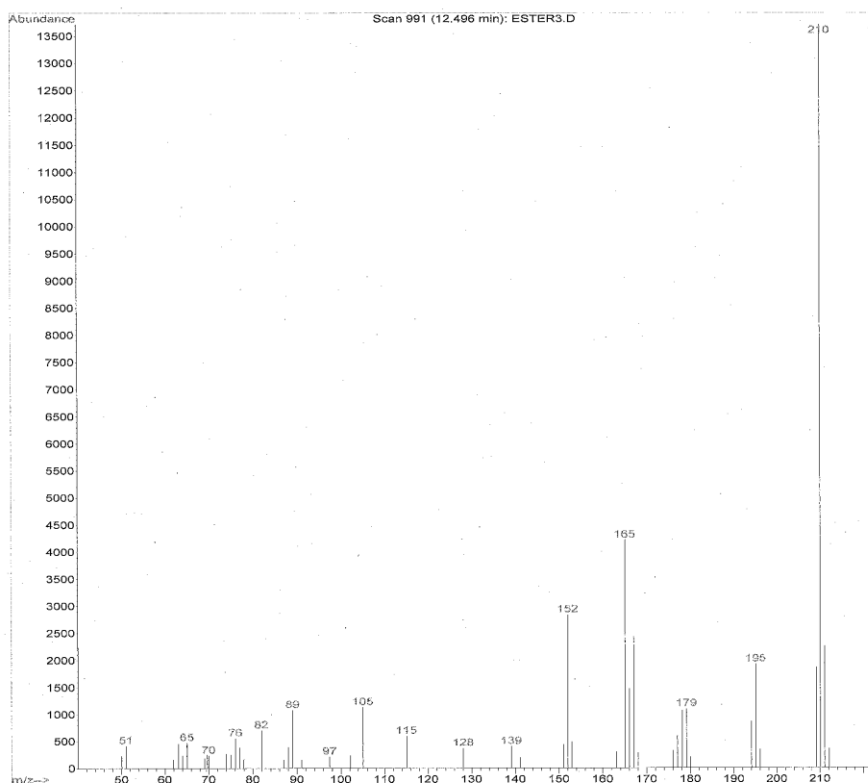


Figure 4: Mass spectrum of *trans* 4-methoxystilbene

3.2. Spectral analysis of *trans*-4-bromostilbene

In the ^1H NMR spectrum of *trans*-4-bromostilbene, aromatic hydrogens are present in the region of 7.19-7.42 ppm and vinylic hydrogens peak shows up at 6.997 ppm. The GC/mass spectrum of *trans*-4-bromostilbene showed only single peak, thereby indicating the purity of the resulting product. In the mass spectrum of *trans*-4-bromostilbene, the molecular ion peak was observed at m/z 258, which is the molecular weight of *trans*-4-bromostilbene. Another major peak at m/z 178 was due to the loss of bromo group. All spectra, the NMR, FT-IR and GC/mass spectrum of *trans*-4-bromostilbene are similar to the ones reported in the spectral database.¹¹

All spectra of *trans*-4-methylstilbene are also in agreement with the reported values.¹¹

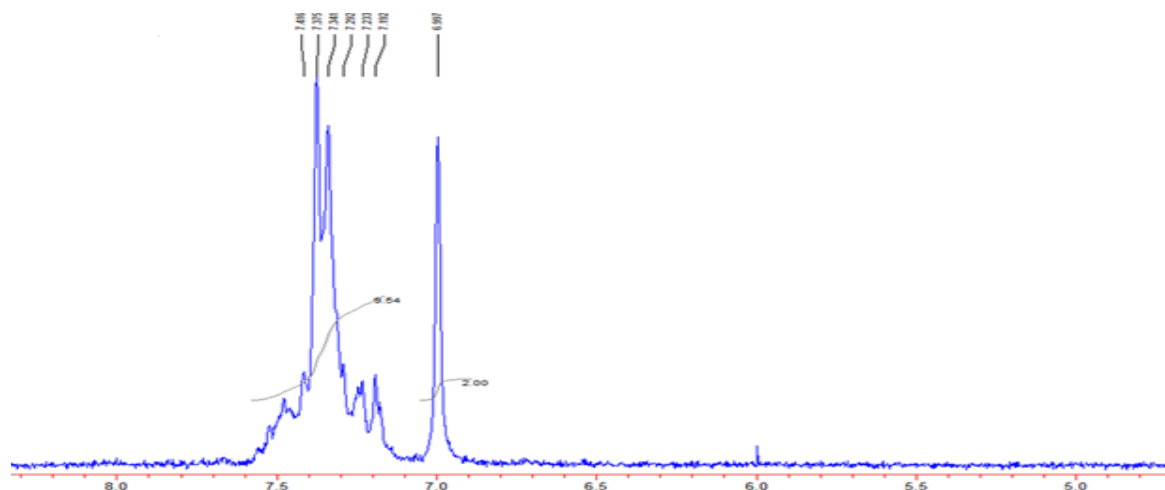


Figure 5: ^1H NMR spectrum of *trans*-4-bromostilbene in CDCl_3

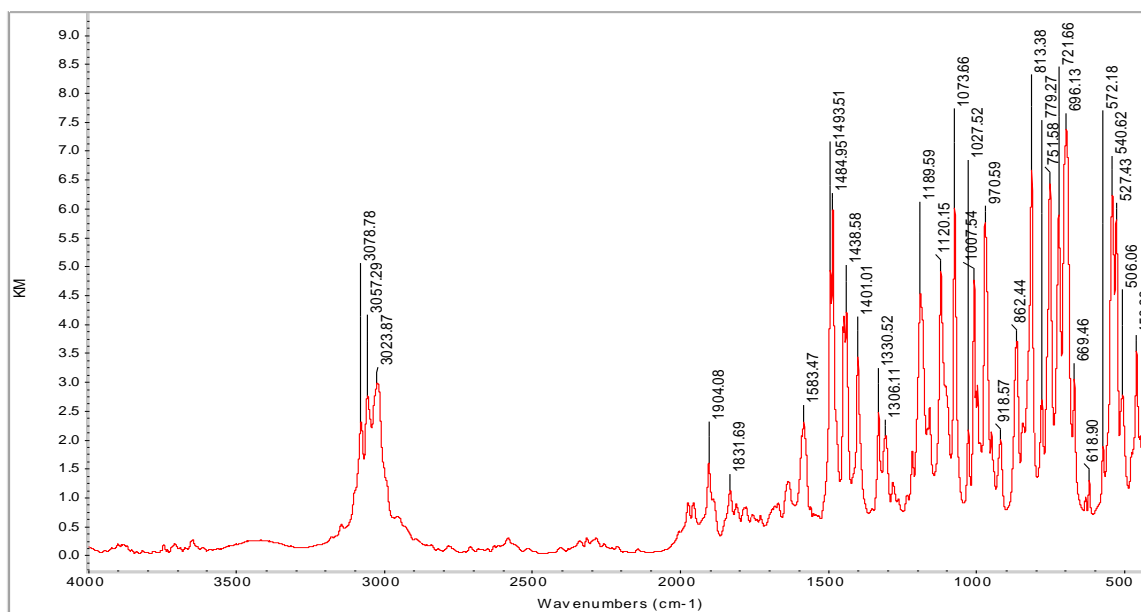


Figure 6: IR spectrum of *trans*-4-bromostilbene

4. Conclusion

This study involved the use of p-tolualdehyde, p-anisaldehyde, and p-bromobenzaldehyde in a “green” aqueous medium to synthesize stilbene derivatives from the corresponding aldehydes and benzyl triphenylphosphonium chloride. It was revealed that the solubility of benzyl triphenylphosphine oxide makes it difficult to remove completely from the reaction mixture because of its polarity, thereby affecting both purity and yield. While the mixture which was refluxed for one-half hour, just ended up giving only a 10% yield. Merrifield Resin was also used to efficiently remove the byproduct triphenylphosphine oxide⁷. However, it did not work well and gave only 14% yield of the product. Ultimately, this investigation found that heating the Wittig reaction mixture in a microwave oven achieved optimal results in comparison to all other “green” methods tested. Furthermore, this

technique produced stilbene derivatives in 37-40 percent yields, an amount comparable to when the same reaction is conducted using chlorinated solvents. This only serves to reinforce trials of a two-year project-oriented lab experiments currently being used by a group of second-semester organic chemistry students at Franklin College. Using the microwave method, these individuals have obtained product yields in the range of 37-40% as well.

5. Future Work

Drawing from the results of this experiment, it has been determined that microwave heating provides ideal conditions for Wittig reactions to proceed. Due to the fact that second semester students of organic chemistry frequently use this procedure in testing for research in their project-oriented studies, a proposal is currently being developed to obtain funds for the purchase of a laboratory-grade microwave oven at Franklin College. This upgraded instrument will not only serve as a key asset in allowing the Franklin students to more effectively synthesize organic compounds, but also contribute towards the campus' continuing green initiatives.

6. Acknowledgements

The authors gratefully acknowledge the support of Mildred M. Hoover Dean's grant and Franklin College Undergraduate Research Fund, and would also like to thank Ms. Elizabeth Shores and Students of Organic Chemistry II at Franklin College, 2012-2013.

7. References

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